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NEW INSIGHTS IN PULMONARY HYPERTENSION

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Clinical impact of supraventricular tachycardias in patients with pulmonary hypertension

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Purpose: Supraventricular tachycardias (SVT) are frequently observed in patients with pulmonary hypertension (PH). Their prevalence and impact on prognosis of patients are not known.

Methods: We retrospectively studied the prevalence of SVT and survival in 998 patients with PH (aged 59±16 years; 451 males).

Results: SVT was observed in 234 (23%) patients. Atrial fibrillation (AF) was the most prevalent (n=168), followed by atrial flutter (AFL) (n=52), other atrial tachycardias (AT) (n=18), and AV nodal re-entrant tachycardia (AVNRT) (n=3). Prevalence of SVT in main PH classes is shown in Table. Excessive prevalence of SVT was observed in patients with PH associated with congenital heart disease (p<0.05). Other differences did not reach significance. Patients with permanent SVT were in higher NYHA functional class compared to the rest of population (3.2±0.9 vs. 2.7±1.3; p<0.05). Total of 416 (42%) patients died during mean follow-up of 8.7±9.1 years. Presence of any type of SVT was not associated with the mortality.

Prevalence of SVT according to clinical

PH class	AF	AFL	AVNRT	Other AT	Σ
Idiopathic/hereditary (n=271)	54 (20%)	17 (6%)	1 (0.4%)	3 (1%)	75 (28%)
Associated with connective tissue disease (n=73)	17 (23%)	3 (4%)	0	0	20 (27%)
Associated with congenital heart disease (n=65)	22 (34%)	6 (9%)	2 (3%)	3 (4.5%)	33 (51%)
Lung disease/hypoxia (n=188)	24 (13%)	3 (1.6%)	0	3 (1.6%)	30 (16%)
Chronic thromboembolic PH (n=361)	47 (13%)	23 (6%)	0	7 (2%)	77 (21%)
Other (n=40)	4 (10%)	0	0	2 (5%)	6 (15%)

Conclusion: Patients with PH had high prevalence of SVTs. Permanent SVTs were associated with worsening of functional class. Occurrence of atrial arrhythmias had no mortality impact in total PH population.

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Current era survival in patients with pediatric pulmonary arterial hypertension

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Background: Pulmonary arterial hypertension (PAH) is a rare disease characterized by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death. Epidemiological data are scarce, particularly in the pediatric population. Objectives: the aim of the present study was to assess prospectively the current era survival of pediatric PAH patients (P-PAH) and to compare it with the survival of adult PAH (A-PAH) patients with similar etiologies.

Methods: We included in the study consecutive PAH patients aged ≤18 years (Pediatric) and PAH patients aged >18 years (Adult) referred to a single center from February 1992 to October 2013. Due to the epidemiology of pediatric PAH we included only idiopathic PAH (IPAH) and Hereditary PAH (HPAH). Patients were treated with approved PAH drugs including combination therapy according with recent guidelines and irrespective of the age. Survival data were assessed by Kaplan-Meier curves and compared by Log-rank test.

Results: 42 pediatric PAH patients (aged 9±5 years, 83% with IPAH, 17% with HPAH) and 364 adult PAH patients (mean age 51±6 y, 83% with IPAH, 17% with HPAH) were included. Forty-three % of pediatric patients and 51% of adult patients were treated with monotherapy and the remaining with combination therapy with PAH approved drugs. Kaplan-Meier survival rate at 1, 3, 5 and 10 years after the diagnostic right heart catheterization was 93%, 79%, 76%, 64% and 92%, 79%, 68%, 52% for P-PAH and A-PAH, respectively (Log-rank test p-value at 10 years: 0.321). Hemodynamics at time of referral to our centre was, in P-PAH and A-PAH, respectively: right atrial pressure 6 (3-8) mmHg and 7 (4-11) mmHg [p-value: 0.011], mean pulmonary arterial pressure 64 (52-82) mmHg and 52 (43-62) mmHg [p-value <0.001], cardiac index 3.1 (2.3-3.7) l/min/m² and 2.3 (1.9-2.9) l/min/m² [p-value <0.001], pulmonary vascular resistance 16 (9-31) W.U. and 11 (7-15) W.U. [p-value <0.001], pulmonary vascular resistance index 18 (12-29) W.U.m² and 19 (14-25) W.U.m² [p-value: 0.972], mixed venous oxygen saturation 70 (60-74) % and 63 (56-70) % [p-value: 0.006].

Conclusions: In the current era of approved PAH medications the survival of IPAH and HPAH patients is similar in the adult and in the pediatric population.

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Prognostic value of right ventricular remodeling models based on echocardiographic parameters

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Background: Right ventricular (RV) failure is the leading cause of death in patients with pulmonary arterial hypertension (PAH) and it depends on the ability of the RV to face the afterload increase.

Aim: To define the relationship between RV remodelling models, based on echocardiographic parameters, and survival in 3 different subgroups of PAH: idiopathic+hereditary+drug and toxic-induced (PAH-IHD), associated with connective tissue disease (PAH-CTD) and associated with congenital heart disease (PAH-CHD).

Materials and methods: From September 2000 to December 2012, 530 PAH patients underwent echocardiographic study. According to 2 variables (Right ventricular End Diastolic Area Index – RVED Area I and severity of tricuspid regurgitation – TR) we defined three different models of RV response: adaptive (A) [RVED Area I ≤18 cm²/m² and no or mild TR], maladaptive (MA) [RVED Area I 19-21 cm²/m² and moderate TR], and severe dysfunction (SD) [RVED Area I >22 cm²/m² and severe TR]. All patients were treated with PAH approved drugs according to current European Guidelines (goal oriented treatment strategy). Kaplan-Meier curves were used to estimate the survival.

Results: Two hundred-ninety patients were included in the PAH-IHD subgroup, 135 in the PAH-CTD subgroup and 105 in the PAH-CHD subgroup. As far as survival at 5 years is concerned, there were no statistically significant differences among patients allocated in the A and MA models in all the three clinical subgroups (PAH-IHD: 69% in A model and 76% in MA model; PAH-CHD: 81% in A and 87% in MA; PAH-CTD: 33% in A and 34% in MA); nevertheless, in all the three clinical subgroups, 5 years survival was significantly worse in patients allocated to SD model: 56% in PAH-IHD (vs A: p=0.003; vs MA=0.008), 74% in PAH-CHD (vs A: p=0.093, vs M: 0.075) and 9% in PAH-CTD (vs A: 0.007; vs MA: 0.021); within each model of RV dysfunction, survival was significantly worse (p<0.001) in PAH-CTD subgroup versus both PAH-IHD and PAH-CHD subgroups.

Conclusions: RV models based on RVED area I and on the severity of TR are able to differentiate populations with different prognosis in PAH-IHD, PAH-CTD and PAH-CHD patients. Within each model of RV dysfunction, survival is related to the PAH type and is significantly worse in PAH-CTD patients.

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Six-minute walk-test in childhood pulmonary arterial hypertension: walking distance and decrease in oxygen saturation provide additional prognostic information

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Background: Data on the prognostic value of the 6-minute-walk-distance (6-MWD) in paediatric pulmonary arterial hypertension (PAH) is limited and it is unknown whether transcutaneous saturation (tcSO₂) and heart rate (HR) during the 6-minute walk-test (6-MWT) can improve its prognostic value.

Methods: At the national referral centre for paediatric PAH in our country, 47 paediatric PAH patients aged >7 years performed an extended 6-MWT, which includes 6-MWD and tcSO₂ and HR before ("baseline"), during ("exercise") and 5 minutes after ("recovery") 6-MWT.

Results: The 6-MWD, either in meters or in sex- and age-corrected z-scores, was associated with transplant-free survival, independent from sex, age, and the presence of a shunt-defect. Furthermore, shorter 6-MWD correlated with higher WHO-functional class and NT-pro-BNP serum levels. tcSO₂-decrease during 6-MWT, and tcSO₂-exercise were also associated with transplant-free survival, independent from 6-MWD. tcSO₂-decrease combined with the 6-MWD provided the strongest prognostic model. In patients with either a high or a low 6-MWD (> or ≤352 meters, median), a large tcSO₂-decrease during 6-MWT (> 19% for patients with and >5% for patients without a shunt defect) identified patients with worse transplant-free survival. HR during 6-MWT did not provide additional prognostic value.

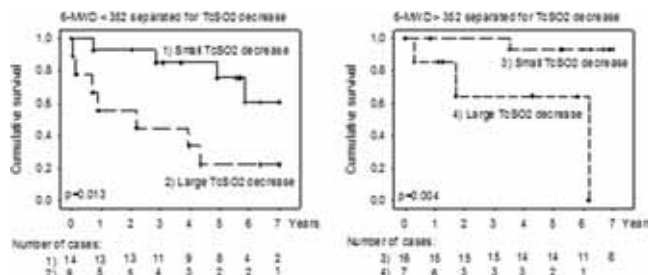


Figure 1. Transplant-free survival.

Conclusion: The 6-MWD is an independent predictor of prognosis in paediatric PAH, that reflects disease severity and clinically relevant exercise-tolerance and therefore qualifies as a treatment target. A large decrease in tcSO_2 during 6-MWT, adjusted for the presence of a shunt, indicates an additional risk factor for worse prognosis in children with PAH.

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Increase in tricuspid regurgitation severity impairs outcome in patients with pulmonary hypertension

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Purpose: Patients with pulmonary hypertension (PH) often present with tricuspid valve regurgitation (TR). We aimed (1) to establish the impact of increasing TR severity and (2) to evaluate impact of new significant TR on outcome in patients with PH.

Methods: Files from patients included in the institutional PH database between July 1989 and August 2012 were reviewed. Patients were stratified into patients with mild $\text{TR} \leq 2/4$ and significant $\text{TR} > 2/4$ at inclusion. Patients who developed significant TR in follow-up were analysed separately. Survival analysis was performed on the patient cohort. Outcome was defined as all-cause mortality.

Results: Data were available for 653 patients, 64% female, aged $60 \text{ yrs} \pm 15$. Pulmonary hypertension was idiopathic PAH in 37.8% of patients, due to left heart disease in 20.2%, due to lung disease in 5.2%, chronic thrombo-embolic PH in 32.9% and of unclear origin in 3.4%. During a mean follow-up time of 4.2 years, 256 events occurred. Univariable analysis showed Age, BSA, RA pressure, TR severity and TAPSE to be related to worse outcome. Multivariable analysis including also gender, mean PAP, PCW, RA and RV diameter and LV ejection fraction revealed age ($p < 0.001$; $\text{HR} = 1.036$ (1.019-1.054)) and TR severity ($p = 0.010$; $\text{HR} = 1.466$ (1.097-1.960)) as independent predictors of worse outcome (Fig. 1A) When patients developed significant TR, outcome was impaired compared to patients with $\text{TR} \leq 2/4$ but didn't differ significantly from patients with significant TR at first presentation.

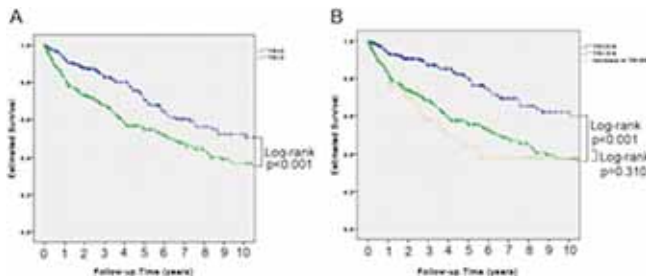


Figure 1

Conclusions: TR severity is independently related to worse outcome in patients with a pressure-loaded ventricle. Furthermore, survival is impaired if patients develop significant TR during follow-up. The development of significant TR should alert for possible disease progression.

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Right ventricular echocardiographic indices predict high altitude pulmonary pressure increment in lowlanders

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Background: The determinants of high altitude pulmonary edema (HAPE) remain ill defined. Increased hypoxia-related pulmonary artery pressure (PAP) is recognized as a key component. No validated parameter exists to predict the development of HAPE in recreational climbers. We aimed to assess whether baseline right ventricular (RV) echocardiographic indices were predictive of an increased hypoxic PAP response.

Methods: 14 lowlander subjects (8 men; ages 27-65) were assessed by echocardiography at sea level (Montreal), 3450m (Namche Bazaar) and 4730m (Chukkung) during an expedition Nepal. Baseline RV performance parameters were compared to the systolic PAP (sPAP) increment at high altitude; correlation coefficient (r) and coefficient of determination (r^2) were calculated.

Results: At high altitude, none of the subjects had clinical criteria for HAPE, although all except one had ultrasound signs of interstitial lung water. sPAP increased in all between Montreal and Chukkung (mean PAP $27.4 \pm 5.4 \text{ mmHg}$ vs. $39.3 \pm 7.7 \text{ mmHg}$ respectively; $p < 0.001$). Sea level RV Tei index by tissue doppler was moderately correlated to the sPAP increment ($r = 0.37$), as was the S' velocity ($r = 0.27$). Baseline TAPSE strongly correlated with the sPAP increment (Fig. 1). RV longitudinal strain baseline value did not correlate with sPAP increment ($r = 0.05$), but strain increment between Montreal and Chukkung was moderately correlated to the sPAP reached at the 4730m ($r = 0.39$).

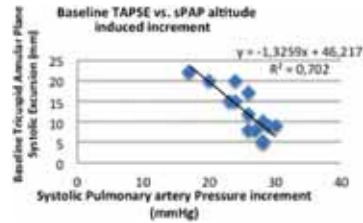


Figure 1

Conclusions: RV TAPSE, S' and Tei index at sea level correlate with the sPAP altitude induced increment in lowlanders. These findings reinforce the role of RV function in the development of HAPE and, should they be confirmed on a larger population, suggest that these indices could help counsel lowlanders before attempting high-altitude climbs.

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Pulmonary artery occlusion waveform analysis for the assessment of pulmonary vascular disease in pulmonary hypertension due to left heart disease

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Purpose: Pulmonary hypertension (PH) due to left heart disease (LHD) is the most common subset of PH. It is defined by an increase of mean pulmonary artery pressure (mPAP) $\geq 25 \text{ mmHg}$ in the presence of a mean pulmonary arterial wedge pressure (mPAWP) $> 15 \text{ mmHg}$. In the 5th World Symposium on Pulmonary Hypertension in Nice, PH due to LHD (post-capillary PH) was subdivided into two hemodynamic phenotypes, "isolated" post-capillary PH (IPCPH, diastolic pulmonary vascular pressure gradient [DPG] $< 7 \text{ mmHg}$) and "combined" pre-capillary and post-capillary PH (CPCPH, $\text{DPG} \geq 7 \text{ mmHg}$). Recent data have shown that patients with post-capillary PH and a $\text{DPG} \geq 7 \text{ mmHg}$ have an increased mortality and significant pulmonary vascular disease. Pulmonary artery occlusion technique assesses the decay from pulmonary artery pressure to PAWP to approximate the pressure in pre-capillary small pulmonary arteries (POCCL). With POCCL, pulmonary vascular resistance can be partitioned into larger arterial (upstream, $\text{Rup}\%$) and small arterial plus venous (downstream) components. The aim of the present study was to assess the accuracy of pulmonary artery occlusion waveform analysis (PAOWA) in patients with CPCPH.

Methods: PAOWA was performed in 37 patients undergoing right and left heart catheterizations at rest and after inhalation of 40ppm nitric oxide (NO). 10 patients were classified as IPCPH with a transpulmonary gradient $> 12 \text{ mmHg}$, 20 as CPCPH and 7 as idiopathic pulmonary arterial hypertension (iPAH).

Results: The lowest $\text{Rup}\%$ was observed in patients with iPAH ($67.1 \pm 12.1\%$) and CPCPH ($74.56 \pm 13.7\%$; $p = 0.57$), while patients with IPCPH showed higher $\text{Rup}\%$ ($94.5 \pm 5.3\%$). While iPAH patients (0.52 ± 11.5 , $p = 0.91$) did not show a change in $\text{Rup}\%$ upon NO, an increase in $\text{Rup}\%$ could be observed in patients with CPCPH ($6.6 \pm 7.35\%$, $p = 0.054$). A significant correlation between DPG and $\text{Rup}\%$ was observed ($r = -0.41$; $p = 0.011$).

Conclusion: PAOWA confirms that patients with PH due to LHD and a $\text{DPG} \geq 7 \text{ mmHg}$ (CPCPH) have pulmonary vascular disease similar to iPAH. In contrast to iPAH, a proportion of patients with CPCPH show a significant increase in $\text{Rup}\%$ upon NO, which might be due to reactive vasoconstriction in this condition.

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Epidemiology of combined pre-and post-capillary pulmonary hypertension in patients with heart failure

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Purpose: Heart failure (HF) is an increasingly important cause of morbidity and mortality. Right ventricular (RV) function and the presence of pulmonary hypertension (PH) have been shown to be of prognostic relevance in HF. In the 5th World Symposium on PH in Nice, PH due to left heart disease (post-capillary PH) was subdivided into two phenotypes, "isolated" post-capillary PH (IPCPH, diastolic pulmonary vascular pressure gradient [DPG] $< 7 \text{ mmHg}$) and "combined" pre-capillary and post-capillary PH (CPCPH, $\text{DPG} \geq 7 \text{ mmHg}$). Recent data have shown that patients with post-capillary PH and a $\text{DPG} \geq 7 \text{ mmHg}$ have an increased mortality and significant pulmonary vascular disease. We sought to study epidemiology, RV function and non-invasive predictors of CPCPH in HF.

Methods: A retrospective data set of 3107 all-comers undergoing first diagnostic right and left heart catheterizations at rest was analyzed. 1063 patients were identified as having HF (664 patients with systolic heart failure [SHF] and 399 with diastolic heart failure [DHF]). A prospective sample of 800 consecutive patients, comprising 391 patients with HF (172 patients with SHF and 219 patients with DHF), was utilized to validate the results of the retrospective data set.

Results: In the retrospective data set CPCPH was observed in 80 patients with SHF (12%) and 49 patients with DHF (12%). Similar results were found in the prospective database showing CPCPH in 24 patients with SHF (14%) and 26 patients with DHF (12%). Right to left ventricular ratio on echocardiography was higher in patients with CPCPH in DHF (1 ± 0.2) compared to those with SHF (0.7 ± 0.1 ; $p<0.001$). Multivariate analysis revealed COPD ($p=0.031$; Odds ratio: 4.111 [1.135;14.896]) as an independent risk factor for CPCPH in SHF. In contrast, VHD ($p=0.013$; Odds ratio: 5.877 [1.463;23.610]) and tricuspid regurgitation jet velocity ($p=0.012$; Odds ratio: 3.449 [1.317;9.028]) were predictive for CPCPH in DHF.

Conclusion: The data indicate that patients with CPCPH in DHF show more signs of right ventricular overload than those with CPCPH in SHF. Mechanisms of increased RV afterload may differ in DHF versus SHF.

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Correlation between the severity of pulmonary hypertension and vascular remodeling in chronic obstructive pulmonary disease and diffuse parenchymal lung disease awaiting lung transplantation

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Purpose: Pulmonary hypertension (PH) is well recognized complication of chronic obstructive pulmonary disease (COPD) and diffuse parenchymal lung disease (DPLD). Local pulmonary arterial stiffness indexes correlated with hemodynamic severity in idiopathic PAH (IPAH). We analyzed the relation between the severity of PH and vascular remodeling in COPD and DPLD awaiting lung transplantation (LTx).

Methods: We studied 134 patients (p), 106 pre-LTx, NYHA 3-4, 41 COPD (58 ± 5 years, 9 females), 65 DPLD (60 ± 7 years, 19 females), 18 IPAH (51 ± 16 years, 11 females), and 10 healthy controls (51 ± 1.8 years, 6 females). All patients were submitted to left and right heart catheterization, and intravascular ultrasound (IVUS) in medium sized pulmonary arteries (PAs). We assessed the mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), aortic pressure, cardiac index (CI), pulmonary vascular resistance (PVR), and capacitance (Cp), time constant (τ : $PVR\times Cp$), R-C relation, and local pulmonary arterial elastic modulus (EM: diastolic lumen area $\times$ pulse pressure/(systolic-diastolic lumen area)). We discarded p with PCWP ≥ 15 mm Hg.

Results: 48% (15/31) and 43% (25/58) of COPD p and DPLD p had precapillary PH, respectively. Both, Cp ($r=0.66$) and PVR ($r=0.43$) were significantly correlated with EM in COPD. On the contrary, in DPLD p, only PVR correlated with EM ($r=0.38$). DPLD p showed higher EM beyond mPAP, associated with a downward shift of the RC relationship.

	Control (n=10)	COPD (n=31)	DPLD (n=58)	IPAH (n=18)
mPAP, mm Hg	15 $\pm$ 10	26 $\pm$ 8*	21 $\pm$ 3*	52 $\pm$ 17**
pPAP, mm Hg	11 $\pm$ 3	16 $\pm$ 8*	24 $\pm$ 12*	49 $\pm$ 21**
CI, l/min/m ²	2.6 $\pm$ 0.1	2.3 $\pm$ 0.7	2.5 $\pm$ 0.6	2.3 $\pm$ 0.7
HR, bpm	73 $\pm$ 4	73 $\pm$ 19	79 $\pm$ 18	76 $\pm$ 13
PVR, Wood units	3.0 $\pm$ 0.6	3.5 $\pm$ 1.8	3.8 $\pm$ 1.8	12.0 $\pm$ 7.1**
Cp, ml/mm Hg	6.2 $\pm$ 1.2	4.0 $\pm$ 1.6*	2.9 $\pm$ 1.3*	1.2 $\pm$ 0.8**
τ , sec	1.1 $\pm$ 0.4	0.8 $\pm$ 0.3*	0.6 $\pm$ 0.2*	0.7 $\pm$ 0.2*
EM, mm Hg	21 $\pm$ 6	64 $\pm$ 30*	105 $\pm$ 50*	185 $\pm$ 107**

* $p<0.05$ vs. Control; * $p<0.05$ vs. COPD; * $p<0.05$ vs. DPLD.

Conclusions: The hemodynamic severity was correlated with vascular remodeling in pre-LTx COPD p. This was associated with a more preserved Cp and tau. DPLD p showed a worse vascular remodeling with lower tau and downward shift of the RC relationship.

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Optical coherence tomography evaluation of pulmonary arterial vasculopathy in patients with systemic sclerosis

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Purpose: Our understanding of the pathophysiology of pulmonary vascular disease is incomplete as smaller pulmonary vessels are difficult to access in vivo. There has been no description of in-vivo data about pulmonary vasculature of patients with Systemic Sclerosis (SSc) with and without PAH (pulmonary arterial hypertension). We used optical coherence tomography (OCT) to depict pulmonary arteries of less than 2mm in diameter during right heart catheterization (RHC).

Methods: In this ongoing study 18 stable SSc-patients with and without PAH underwent OCT of the pulmonary arteries. 14 patients met criteria for PAH (mean pulmonary artery pressure (PAM) at diagnosis 45 ± 12.6 mmHg). 4 patients had no evidence for PAH on RHC (controls). OCT was performed using a Light-Lab imaging wire with an outer diameter of 470 μ m. After delivery balloon was wedged and the distal vessel filled with a 50/50 contrast saline mixture during pullback.

Results: We obtained 82 runs in total, 4.5 mean per patient. 36 runs were not

analysed due to vessel size >2 mm (23 runs) and artefacts (13 runs). We were able to image pulmonary arteries <2 mm in diameter in 17 out of 18 patients. The ratio of Intima media thickness area (IMT-A) as compared to total vessel area was highly significantly increased in the PAH group at the level of 2 mm vessels ($29\pm 5.8\%$ vs. $21\pm 1\%$, $p=0.001$) but not significant at 1.5mm vessel level ($30\pm 8\%$ vs. $26\pm 6.9\%$). IMT-A correlated significantly with PAM at diagnosis ($p=0.002$). Runs of 10 SSc-PAH patients and 3 controls were screened for side branches $<300\mu$ m. In 4 SSc-PAH patients in whom afterload fell dramatically with therapy (PVR reduction $>50\%$) we found a significant higher number of small side branches per cm vessel (5 ± 5 vs. 1.7 ± 8 ; $p=0.015$). In the whole patient group the number of side branches did not correlate with PVR, PAM or time from diagnosis. 3 patients among the PAH group (25%) showed evidence of thrombus, recanalised clots or webs which was not previously diagnosed with VQ scan or CTPA.

Conclusion: In this first series using OCT in pulmonary arteries of patients with SSc we found significant thickening of the IMT in moderate sized pulmonary arteries in patients with PAH compared to patients without PAH. Thickening was significantly associated with mean pulmonary artery pressures at diagnosis. Furthermore, the number of small side branches was significantly higher in patients who have reduced their PVR by $>50\%$ with therapy. The number of side branches might therefore predict better prognosis in PAH.

CARDIAC MAGNETIC RESONANCE T1 MAPPING: NOVEL AND IMPORTANT

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Myocardial biopsy for the validation of cardiac magnetic resonance T1 mapping for quantification of extracellular matrix

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Background: Diffuse myocardial fibrosis / extracellular matrix expansion is a landmark feature of various cardiac diseases and is associated with an unfavorable prognosis. Recently, cardiac magnetic resonance (CMR) T1-mapping has been proposed for the quantification of extracellular matrix.

Published series mainly used two T1 mapping sequences: 1. Modified Look-Locker Inversion recovery (MOLLI) T1 mapping, allowing the calculation of extracellular volume (ECV), 2. Post-contrast multiple breath-hold T1 mapping. In addition, native (pre-contrast) T1 mapping has gained increasing interest. Although CMR T1 mapping is a very promising technique and has been advertised as the new "non-invasive myocardial biopsy", validation data, particularly in heart failure patients, are sparse.

Methods: 22 heart failure patients underwent CMR T1 mapping on a 1.5-T scanner and left ventricular biopsy within 4 weeks. The population consisted of 16 HFpEF (heart failure with preserved ejection fraction) patients, 3 patients suffering from dilated cardiomyopathy and 3 amyloidosis patients. In all patients the 3 T1 mapping sequences were applied.

Left ventricular biopsies were stained with modified Trichrome and Congo-red. Extracellular matrix was quantified with TissueFAXS and HistoQuest analysis.

Results: Extracellular matrix by TissueFAXS was $43.8\pm 20.8\%$ of the region of interest, ECV as determined by MOLLI was $33.6\pm 9.9\%$. The average post-contrast T1 time by the multiple breath-hold sequence was 407 ± 85 ms and native T1 times were 1000 ± 61 ms.

The amount of extracellular matrix by TissueFAXS correlated significantly with MOLLI ECV ($r=0.583$, $p=0.011$) and with multiple breath-hold post-contrast T1 times ($r=-0.459$, $p=0.042$), but not with native T1 times ($r=0.375$, $p=0.114$).

Conclusion: In the present series, MOLLI ECV appears to be the most accurate method for the quantification of extracellular matrix expansion when validated against myocardial biopsies. Although multiple breath-hold post-contrast T1 mapping may be influenced by renal function, heart rate, and time of acquisition, it also appears useful for non-invasive measurement of extracellular matrix. Native T1 mapping showed the weakest correlation with extracellular matrix by TissueFAXS, but there was a tendency towards a significant relationship ($r=0.375$, $p=0.114$).

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In vivo comparison between myocardial fibrosis and myocardial extracellular volume (ECV) measurement by cardiovascular magnetic resonance (CMR)

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Purpose: Myocardial fibrosis is considered as the most important indicator of cardiac damage. Recently, modified Look-Locker inversion recovery (MOLLI) cardiovascular magnetic resonance (CMR) imaging allows for T1 mapping and extracellular volume (ECV) measurement with high level of intra and inter-observer agreement. The aim of the present study was to compare between % myocardial fibrosis (%F) which was harvested by endomyocardial biopsy from the inferior left ventricle and ECV measured using MOLLI.

Methods: A total 16 patients (mean age: 64.0 ± 12.4 , male: 15) with non-ischemic heart failure [left ventricular ejection fraction (LVEF) $<30\%$] were enrolled into the present study. %F was defined as fibrosis area/fibrosis area + myocardium area) using Elastica Masson-Goldner (EMG) stain (Fig. 1). A motion corrected myocardial T1 mapping was generated automatically from MOLLI and ECV was estimated from the myocardial T1 values before and after contrast with calibration by blood hematocrit.

Results: The patients were divided into two groups according to the median value of %F (median value = 5.697). Compared to low %F group ($n=8$), high %F group ($n=8$) had higher ECV at the inferior segment (median = 30.4 [25th–75th percentile: 20.0–32.5] vs. 36.5 [33.6–41.6], $p=0.016$) corresponding to the whole left ventricle (30.0 [28.4–31.3] vs. 37.0 [33.4–40.3], $p=0.001$) (Fig. 1).

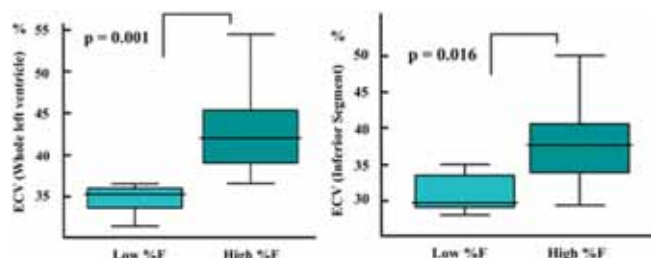


Figure 1

Conclusions: ECV measured using MOLLI CMR is related to the extent of myocardium fibrosis assessed by LV endomyocardial biopsy in patients with non-ischemic heart failure. ECV measurement can provide non-invasive and quantitative evidence of severity of myocardial fibrosis in these patients.

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T1Native as a marker for differentiation of the left ventricular hypertrophy phenotypes of hypertrophic cardiomyopathy and hypertensive cardiomyopathy

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Purpose: The differential diagnosis of hypertrophic phenotype remains challenging in clinical practice, in particular between hypertrophy cardiomyopathy (HCM) and increased left ventricular wall thickness (LVWT) due to systemic hypertension (HTN). Its importance lies in the clinical implications for patients. Diffuse myocardial fibrosis is the characteristic feature in HCM, whereas hypertensive response is underpinned by addition of myofibrils in otherwise normal myocardial tissue. Late gadolinium enhancement (LGE) imaging provided important new way of differentiation between these two entities by separating those cases with evidence of regional fibrosis. Whereas approximately 60% of patients with HCM reveal visually discernable LGE, T1 mapping is highly discriminative, irrespective of the presence of LGE.

Methods: Seventy-nine patients with diagnosis of unequivocally hypertrophic cardiomyopathy and sixty patients with hypertensive cardiomyopathy underwent routine cardiac MRI protocol including assessment of function and scar in addition to T1 mapping (3-Tesla). T1 values were measured conservatively within septal myocardium in midventricular short-axis slice prior to administration of 0.2 mmol/kg of gadobutrol.

Results: HCM group showed higher LV mass and maximum LVWT than the HTN group (HCM vs. HTN: LVmass, g/m^2 : 98.1 ± 33.6 vs. 67.2 ± 22.6 ; maximum LVWT 19.0 ± 3.9 vs. 13.2 ± 1.3 , $p<0.0001$). LGE was present in 20% ($n=10$, 4 with an ischaemic pattern) of the HTN group and in 82% ($n=48$, 2 with an ischaemic pattern) ($p<0.001$) of the HCM group). Patients with HCM showed significantly higher T1 values compared to HTN patients (HCM vs. HTN, msec: 1163 ± 46 vs. 1049 ± 31 , $p<0.0001$). Native T1 values were concordant to LVWT and LV mass ($r=0.52$ and $r=0.46$, $p<0.001$, respectively). T1 native held superior diagnostic accuracy compared to conventional functional parameters and the presence of LGE to discriminate between hypertrophic or hypertensive cardiomyopathy (AUC, T1 native=0.99, LVmass=0.82, LVWT=0.95, LGE=0.82, $p<0.001$). T1 native was identified as an independent discriminator between the two conditions.

Conclusion: We demonstrate that native T1 values can reliably discriminate between hypertrophic and hypertensive cardiomyopathy. Given its novelty and ease-of-use nature, T1 native has the immediate potential of clinical translation as a diagnostic marker between these two conditions.

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Native T1 values in discrimination of subclinical profibrotic phenotype in relatives of patients with hypertrophic cardiomyopathy

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Introduction and purpose: Hypertrophic cardiomyopathy (HCM) is associated with significant associated morbidity and mortality. Increased maximal left ven-

tricular wall thickness (LVWT) has been postulated as major risk factor of sudden death; however, relatives with normal LVWT are also at risk. Genetically driven interstitial collagenesis has been proposed as a possible mechanism of diffuse myocardial fibrosis and increased extracellular volume fractions (ECV) has been demonstrated in genotype positive subjects. T1 mapping by cardiovascular magnetic resonance (CMR) provides tissue-dependent relaxation times in line with the underlying myocardial composition. We investigated whether native T1 can also separate genotype positive subjects in the absence of increase in LVWT and how does it relate to ECV measurements.

Methods: Seventeen genotype positive first-degree relatives of HCM patients, and seventeen healthy volunteers underwent assessment of T1 mapping, function and scar by CMR at 3-Tesla scanner. T1 values were measured conservatively within the septal myocardium in a midventricular short-axis slice prior to and 15–20 minutes after administration of 0.2 mmol/kg of gadobutrol.

Results: Relatives of HCM patients were well matched for age, gender and traditional cardiovascular risk factors. The groups did not differ in the conventional LV parameters, including volumes, left and right ejection fraction or LV mass. None of the studied subjects showed late gadolinium enhancement. Compared to controls, T1 native values were increased in HCM relatives (control vs. relatives, T1 native (msec) 1045 ± 17 vs. 1104 ± 16 , $p<0.0001$), whereas T1postcontrast and lambda did not vary between groups. Native T1 was identified as the independent discriminator to differentiate between relatives of HCM patients and controls.

Conclusion: We demonstrate that T1 native values are increased in genotype positive relatives of HCM patients. We propose that T1 native may serve as an early marker of cardiomyopathy, adding valuable information to genetic testing in this increasing population, possibly without a need for a contrast CMR study.

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Cardiac amyloidosis: a T1 mapping cardiovascular magnetic resonance study

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Background: Late Gadolinium Enhancement (LGE) technique is currently used for the diagnosis of Cardiac Amyloidosis (CA) by Magnetic Resonance (MRI). Aim: to study gadolinium contrast kinetics and to quantify the myocardial extracellular volume fraction (ECV) in amyloid patients with a T1 mapping CMR technique.

Methods: Thirty-six patients with biopsy-proven systemic amyloidosis (70±9 years, 31 males, 30 immunoglobulin light chain-related, 6 transthyretin-related) and 7 patients with possible amyloidosis (64±10 years, 6 males) underwent evaluation of morphologic and functional features of CA. Conventional LGE images were acquired, with ECV estimation from pre- and post-contrast T1 mapping. Thirty healthy subjects (39±17 years, 21 males) served as controls.

Results: Patients with amyloidosis presented a concentric hypertrophy of the left ventricle (LV), associated with impaired biventricular systolic function. Among patients with definite amyloidosis, 21 (58%) presented diffuse LV post-contrast enhancement (subendocardial to transmural) and 7 (19%) focal enhancement, while 3 patients (43%) with possible amyloidosis presented focal LV enhancement. Both groups presented a higher cardiac ECV (0.43 ± 0.12 for definite, 0.34 ± 0.11 for possible amyloidosis) than controls (0.26 ± 0.04 , $p<0.05$, Fig.1) and even the patients without LGE presented an ECV significantly higher than controls (0.35 ± 0.10 , $p<0.01$). Myocardial ECV showed an area under the curve of 0.884 in discriminating patients with definite amyloidosis from controls: an ECV of 0.316, corresponding to the 95th percentile of normal subjects, yielded a 79% sensitivity and a 97% specificity.

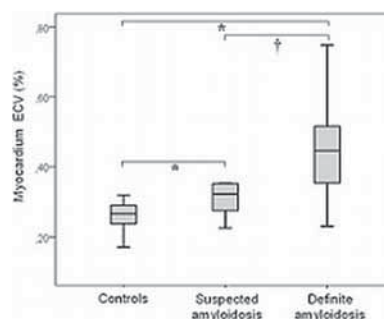


Figure 1. Myocardium ECV distribution.

Conclusions: T1 mapping ECV represents a noninvasive direct measure of the amyloid burden with potential utility in early diagnosis and disease monitoring.

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Native T1 and T2 values by cardiovascular magnetic resonance imaging in patients with systemic inflammatory conditions

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Purpose: Patients with systemic inflammatory diseases (SID) are at risk of heart failure due to sustained systemic inflammation leading to diffuse myocardial injury and left ventricular remodelling. Because native T1 and T2 values are raised in the presence of diffuse fibrosis and edema, T1 and T2 mapping by cardiac magnetic resonance (CMR) are emerging as potential tools to assess diffuse myocardial involvement. In this study, we examined native T1 and T2 values in patients with SID.

Methods: 79 patients with a clinical diagnosis of SID (systemic lupus erythematosus (SLE, n=46), rheumatoid arthritis (RA, n=17), systemic sclerosis (SS, n=9) and Wegener's granulomatosis (WG, n=7) underwent CMR study for assessment of oedema, function and scar at 3-Tesla scanner. 36 healthy subjects served as controls. Native T1 values were measured conservatively within septal myocardium of midventricular short-axis slice (mSAX). T2 values were recorded from T2 maps based on GraSE sequence. We compared regional T2 values between patients and controls, and assessed associations with native T1 values.

Results: Patients showed impaired global LV systolic function compared to controls (control vs. SLE vs. RA vs. SS vs. WG, % $\pm$ SE vs. 54 $\pm$ 12 vs. 60 $\pm$ 8 vs. 53 $\pm$ 8 vs. 56, p=0.02). The presence of LGE was variable in the groups (SLE: n=19 (41%); RA: n=2 (12%); SS: n=5 (56%); WG: n=4 (57%), which was of non-ischaemic pattern in presentation. Edema ratio was raised in all SID. Patients showed higher T1 and T2 values compared to controls (controls vs. SLE vs. RA vs. SS vs. WG, native T1 (msec): 1048 $\pm$ 26 vs. 1170 $\pm$ 52 vs. 1118 $\pm$ 52 vs. 1199 $\pm$ 81 vs. 1151 $\pm$ 57, p<0.001 and T2 (msec-average of all segments per mSAX): 48 $\pm$ 3 vs. 58 $\pm$ 7 vs. 54 $\pm$ 5 vs. 53 $\pm$ 3 vs. 57 $\pm$ 8, p<0.001). Whereas there were no T2 regional variations in controls (p>0.05 for all segments), patients showed regional differences in T2 values (range of T2 values within mSAX, maximum vs. minimum (msec): SLE: 61 $\pm$ 6 vs 54 $\pm$ 8; RA: 58 $\pm$ 6 vs. 49 $\pm$ 3, SS: 59 $\pm$ 3 vs 51 $\pm$ 3, p<0.01). There was a linear relationship between native T1 and average T2 (r=0.63, p<0.001). Quantitative native T1 and T2 values were concordant with edema ratio (r=0.56 and r=0.52 respectively, p<0.001) and the presence of LGE (r=0.28 and r=0.34 respectively, p<0.01).

Conclusion: We demonstrate that native T1 and T2 values are increased in patients with systemic inflammation compared to controls. We also demonstrate that T2 values have regional differences in the presence of diffuse involvement. Native T1 and T2 values may serve as an early marker of myocardial injury due to diffuse fibrosis and low grade of oedema.

CAROTID DISEASE AND STROKE: IMAGING THE RISK

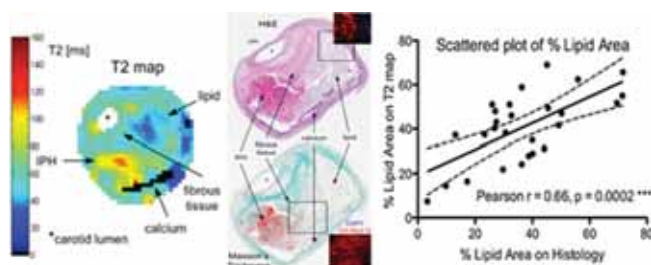
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Characterisation of carotid plaques by in-vivo quantitative T2 mapping: histological validation and lipid quantification

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Background: Multicontrast MRI has emerged as a powerful tool for plaque characterisation. While anti-lipid drugs might reduce plaque lipid measurable by MRI, the non-quantitative nature of multicontrast MRI and its need for extensive post-acquisition processing limited its clinical application. We recently reported the use of quantitative T2 mapping to measure absolute physical properties of different plaque components. Here we sought to validate, at a tissue level, the agreement between T2 mapping and histology; and to evaluate the potential of using T2 mapping in lipid quantification.

Methods: 20 patients with >70% carotid stenosis were recruited. Ethics were approved by national and local R&D committee. Black-blood cross sectional 2D images of the carotids were obtained at 3T. One reviewer classified plaque types using T2 maps with TOF images against the AHA scheme and calculated %lipid area using segmentation algorithm. An independent reviewer processed and evaluated plaque histology and lipid content.



Results: 6 of 20 patients were excluded due to motion artefacts. Of the remaining 14 plaques, 12 showed exact AHA plaque type matching. The two mismatched cases were due to difficulties in staging intraplaque haemorrhage. An average of 1.9 slices/plaque were used to evaluate lipid quantification. Estimated %Lipid Area from T2 maps was found to correlate with histology with a Pearson correlation coefficient of 0.66 (P=0.0002). The two techniques were found to have good agreement by Bland-Altman analysis with a small bias of 4.02%.

Conclusion: Our study showed the potential of in-vivo T2 mapping for plaque characterisation and its application for lipid quantification. This suggests a potential platform for evaluating the efficacy of lipid active drugs at the level of atherosclerotic plaques.

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Carotid artery stenting for vulnerable plaque detected by black-blood MRI: a study using both optimal coherence tomography and intravascular ultrasound

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Purpose: Optimal coherence tomography (OCT) is an intravascular imaging modality to assess plaque characteristics and surface of vessel in detail. The aim of this study is to evaluate vulnerable plaques in carotid stenotic lesions which are detected as high-intensity area in T1-weighted-image by MRI (Black blood technique) and tissue protrusion on the stents, using both OCT and VH-IVUS before and after carotid artery stenting (CAS).

Methods: We performed CAS in consecutive 21 patients (mean age of 77 $\pm$ 7 years) with carotid artery stenotic lesions in which MRI detected the plaque as high intensity area. We assessed plaque at the stenotic lesions by frequency-domain OCT (Illumien OCT imaging system) and by VH-IVUS (Eagle Eye) which classified plaque into four color components: fibrous, fibro-fatty, calcium and necrotic core. In analyzing OCT images, lipid rich plaque was defined as signal intensity-poor lesion covered by signal-rich bands that correspond to fibrous cap. Thin-cap fibroatheroma (TCFA) was defined as <65 μ m of cap thickness. After carotid stenting, we observed tissue prolapse through stent struts, as well as optimal stent apposition or expansion.

Results: In all cases, OCT and VH-IVUS image acquisition was successfully obtained. In VH-IVUS images, vulnerable plaque included 53.0 $\pm$ 5.2% fibrous plaque, 35.6 $\pm$ 11.3% fibrofatty plaque, 2.4 $\pm$ 1.8% calcium and 9.0 $\pm$ 7.8% necrotic core. In OCT images, lipid rich plaques are detected in all patients. Fibrous caps which covered the vulnerable plaque were detected by OCT in all cases, whereas TCFA were detected in 9 cases (42.8%) and ruptured fibrous cap were detected in 9 cases. In OCT, we observed tissue prolapse through stent struts in 6 cases (28.5%), on the other hand, IVUS, we detected that in only 2 cases (9.5%). In 6 cases of tissue prolapse observation with OCT, small debris was observed in 2 cases.

Conclusions: Even in carotid artery, OCT is effective in evaluating not only superficial lipid-rich plaques and fibrous caps especially TCFA but also tissue prolapse on the stents. OCT is more useful modality to evaluate characteristics of vulnerable plaques of carotid artery and stent positioning or tissue prolapse through stent struts compared with IVUS in procedures of CAS.

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Quantification of carotid lesion length effect on doppler velocities used routinely to determine the cross-sectional stenosis severity: an intravascular ultrasound-validated analysis

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Purpose: Doppler ultrasound is a key tool in evaluating carotid stenosis severity. Peak systolic and end-diastolic velocity (PSV; EDV) have been correlated with the angiographic cross-sectional stenosis (CS) severity, and velocity criteria for CS grading are in daily clinical use. With intravascular ultrasound (IVUS) validation, PSV and EDV thresholds for CS >50%/>75% lumen diameter/area stenosis were established, confirming that cross-sectional CS is a significant determinant of PSV and EDV.

Here, we tested the hypothesis that carotid longitudinal lesion length (LL) may also affect PSV and EDV.

Methods: Three hundred consecutive patients (age 47-83, 64.3% men) with CS>50% (63.3% symptomatic), were evaluated. Embolic protection device use for IVUS imaging (62.8%) was left to operator (filters $\approx$ %, proximal $\approx$ 1/4). In 7 (2.4%) patients IVUS was not performed as angiographic CS was considered too tight for imaging prior to lesion predilatation.

Results: Carotid LL of $\geq$ 7mm (Fig; ICA=Internal Carotid Artery) provided the best cutoff for LL effect on PSV and EDV. By regression analysis, the impact of LL on Doppler velocities was best represented by equations: PSV = 0.31*LL/MLA + 2.02 and EDV = 0.12*LL/MLA + 0.63 [m/s] (r=0.61 and r=0.54, p<0.001 for both) where MLA is minimal lumen area by IVUS [mm²]. MLA outperformed angiographic parameters of CS severity in its impact on PSV and EDV.

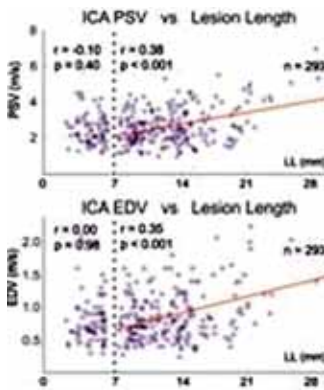


Figure 1

Conclusions: We determined the lesion length cutoff values for their non-negligible effect on PSV/EDV, and established equations that incorporate both lesion length and cross-sectional stenosis severity in routine Doppler velocities. This study provides, for the first time, systematic evidence that carotid longitudinal lesion length has a significant effect on PSV and EDV.

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Ischemic brain lesions on CT-scan related to atrial high rate episodes compatible with silent atrial fibrillation in patients with cardiac implantable electronic devices

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Background: The enhanced monitoring capabilities of cardiac implantable electronic devices (CIED) have revealed that a very large proportion of patients have unsuspected silent atrial fibrillation (AF) detected as atrial high rate episodes (AHRE). The presence of AHRE >5 min have been linked to increased risk of clinical stroke and systemic embolism. A high proportion of ischemic brain lesions could be subclinical.

Methods: We analyzed prospectively the incidence of AHRE >5 min compatible with AF in patients in sinus rhythm with dual chamber CIED and the presence of ischemic brain lesions on CT-scan.

Results: 154 patients (56% men) aged 74 ± 10 years were evaluated during a mean follow-up of 15 ± 5 months. Mean CHADS and CHADS2-VASc scores were 2.2 ± 1.2 and 3.8 ± 1.6 respectively. History of AF was present in 39 patients (25%). Cranial CT-scan was performed in 96 patients (64%), it was normal in 69 patients (72%) and it showed ischemic lesions in 27 (28%). Univariate analysis results are shown in the Table. Multivariate analysis showed that CHADS2-VASc score (OR 2.28 [1.54 - 3.38; $p < 0.001$]) and the presence of AHRE (OR 3.06 [1.01 - 9.33; $p < 0.05$]) were independent predictors of ischemic brain lesions. These results were also consistent in patients without history of previous AF (75%) where multivariate analysis showed that the presence of ischemic brain lesions was associated again to CHADS2-VASc score (OR 2.42 [1.47 - 3.98; $p < 0.001$]) and AHRE (OR 8.98 [1.86 - 43.26; $p < 0.05$]).

Table 1. Univariate analysis. Ischemic brain lesions in study population

	OR	CI	P
Age	1.10	(1.02-1.19)	<0.05
CHADS score	2.57	(1.62-4.06)	<0.001
CHADS2-VASc score	2.19	(1.49-3.20)	<0.001
History of Stroke/TIA	9.75	(3.15-30.10)	<0.001
History of AF	3.47	(1.24-9.71)	<0.05
AHRE	3.43	(1.05-11.17)	<0.05

Conclusions: CIED can accurately detect episodes of silent AF as AHRE. The presence of AHRE was associated to a higher incidence of ischemic brain lesions on CT-scan. AHRE represent a kind of silent AF where management recommendations are lacking despite the fact that a higher embolic risk is present

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A multi-biomarker strategy for predicting stroke in stable anticoagulated patients with atrial fibrillation

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Oral anticoagulation (OAC) is highly effective in preventing stroke and systemic embolism in non valvular atrial fibrillation (AF). Despite OAC, some patients still suffer from thromboembolism. Guidelines encourage the use of the CHA2DS2-VASc score, but its value in predicting thromboembolism after initiating anticoagulation remains controversial.

We tested a multi-biomarker strategy, exploring different underlying physiopathological mechanisms in order to predict thromboembolism in anticoagulated AF patients.

Methods: We studied 949 patients (50% male; median age 76) with permanent AF who were stabilised for at least 6 months on OAC (INRs 2.0-3.0). Levels of high sensitivity troponin T (hsTnT, as index of myocardial damage), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP, a marker of increased intra-ventricular pressure) and interleukin 6 (IL6, an inflammatory marker) were quantified at baseline, as was von Willebrand factor (vWf, endothelial damage marker) and fibrin monomers (a prothrombotic marker). Patients were followed-up for up to 4 years, and stroke and systemic embolism were recorded.

Results: Median follow-up was 1741 (1261-2285) days; during this period 66 patients had an adverse thromboembolic event (rate 0.03%/year). On multivariate analysis, independent predictors of thromboembolism were vWf (HR 2.36[1.42-3.90], $p = 0.001$), NT-proBNP (HR 1.97[1.19-3.27], $p = 0.008$) and CHA2DS2-VASc score (HR 1.19[1.02-1.40], $p = 0.030$).

The c-statistic for CHA2DS2-VASc predicting stroke whilst on oral anticoagulation was 0.58 ± 0.04 , $p = 0.023$ which significantly increased by adding all biomarkers to 0.66 ± 0.04 (De Long test, $p < 0.001$).

Conclusions: A multi-biomarker strategy is useful in predicting those anticoagulated patients with AF who are at risk of new thromboembolic events, even beyond the CHA2DS2-VASc score.

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Proximal occlusion versus distal filter for cerebral protection during carotid artery stenting: a meta-analysis of magnetic resonance imaging studies

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Purpose: Proximal occlusion (PO) and distal filter (DF) are used for cerebral embolic protection during carotid artery stenting (CAS). The incidence of new cerebral lesions at diffusion-weighted magnetic resonance imaging (DW-MRI) represents a surrogate endpoint for embolization in comparative studies of brain protection during CAS. We performed a meta-analysis of (DW-MRI) studies comparing PO versus DF for cerebral embolic protection during CAS.

Methods: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific session abstracts and relevant websites were searched for studies comparing PO versus DF for cerebral protection during CAS. The primary endpoint was the incidence of new cerebral lesions at DW-MRI; secondary endpoints were the incidence of new ipsilateral and new contralateral cerebral lesions at DW-MRI and death/CVA (cerebrovascular accidents).

Results: A total of 292 patients from 6 trials received protected CAS with PO (n=143) or DF (n=149). Median clinical follow-up was 90 days [30-360]. DW-MRI was performed 48 hours [24-48] after CAS. New cerebral lesions occurred in 129 patients (49%). PO versus DF did not reduce the risk of new cerebral lesions (OR [95% confidence interval] 0.74 [0.26-2.07], $P = 0.57$), neither ipsilateral (0.72 [0.24-2.16], $P = 0.55$), nor contralateral (0.55 [0.26-1.20], $P = 0.13$). PO versus DF did not reduce the risk of death/CVA (0.58 [0.18-1.90], $P = 0.37$). High-grade baseline stenosis and the presence of symptoms significantly modified the risk estimates for new cerebral lesions with PO versus DF during CAS.

Conclusions: In this meta-analysis, one half of patients receiving protected CAS developed new embolic cerebral lesions at DW-MRI, although the overwhelming majority were asymptomatic. Cerebral protection with PO versus DF did neither reduce cerebral embolization nor impact clinical outcomes. The grade of baseline stenosis and the presence of symptoms may impact the risk of cerebral embolization associated with protected CAS.

TACKLING ACUTE HEART FAILURE

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Everolimus initiation with early calcineurin inhibitor withdrawal reduced allograft vasculopathy in de-novo heart transplant recipients: results of the SCHEDULE trial

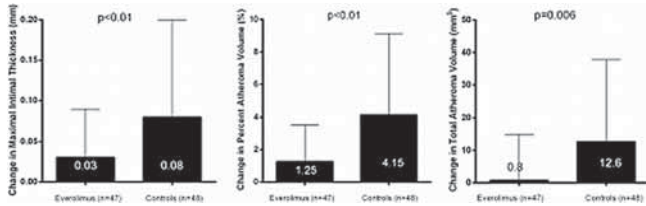
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Purpose: Early initiation of everolimus after heart transplantation (HTx) with calcineurin inhibitors (CNI) has been shown to reduce cardiac allograft vasculopathy (CAV). The SCHEDULE trial demonstrated that CNI therapy can in fact be safely withdrawn early after HTx with a beneficial effect on renal function. The effect of this strategy on CAV has not been investigated previously and was a pre-specified endpoint of the SCHEDULE trial.

Methods: The SCHEDULE trial was a 12-month multicenter Scandinavian trial where 115 de-novo HTx recipients were randomized to everolimus with complete CNI withdrawal (EVE-group) 7-11 weeks after HTx or standard CNI therapy (CNI

group). 95 (83%) patients had matched intravascular ultrasound examinations allowing change in Maximal Intimal Thickness (MIT), Percent Atheroma Volume (PAV) and Total Atheroma Volume (TAV) to be assessed along with measurement of serum inflammatory markers.

Results: Mean recipient age was 49.9 ± 13.1 yrs. The EVE group ($n=47$) demonstrated significantly reduced CAV progression as compared to CNI ($n=48$) [Δ MIT 0.03 ± 0.06 and 0.08 ± 0.12 mm, Δ PAV 1.3 ± 2.3 and $4.2 \pm 5.0\%$, Δ TAV 0.8 ± 14.1 mm³ and 12.6 ± 25.2 mm³ (all p -values < 0.01), respectively]. EVE patients had a significantly greater decline in soluble tumor necrosis factor receptor (sTNFR)-1 levels as compared to CNI ($p=0.02$) but there was no significant difference in change in levels of CRP, VCAM, VEGF, vWf, IL-8 ($p > 0.05$).



Conclusion: Everolimus initiation and CNI withdrawal early after HTx significantly reduces CAV as assessed by IVUS. This strategy appears to have some impact on systemic inflammation as reflected by a significantly greater decline in sTNFR-1. Given the dramatically beneficial effect of everolimus on CAV this novel CNI-free approach should be considered in all de-novo HTx patients.

995 | BEDSIDE

Clinical outcome and predictors of extracorporeal membrane oxygenation (ECMO) support in fulminant myocarditis

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Aims: Limited data are available on the clinical outcomes of patients with fulminant myocarditis complicated by cardiogenic shock that underwent mechanical circulatory support. We evaluated clinical outcome and predictors extracorporeal membrane oxygenation (ECMO) support in patients with biopsy proven fulminant lymphocytic myocarditis.

Methods: From August 2003 to June 2013, total 55 patients with histopathologically proven lymphocytic myocarditis were enrolled in a retrospective, single-center registry. We classified patients into ECMO group ($n=27$) and non-ECMO group ($n=28$) according to the use of ECMO for hemodynamic support during index hospitalization.

Results: Overall, patients in ECMO group were higher-risk subjects. 6 patients could not wean off ECMO support. In ECMO group, 21 patients were weaned successfully from ECMO support, 5 patients were expired during ECMO support and 1 patient use bridging ECMO for heart transplantation. In non-ECMO group, 4 patients needed for IABP support, 9 patients needed for inotropics and 15 patients recovered spontaneously. Among in-hospital survivor, there was no congestive heart failure during the follow-up period. But 1 patient in ECMO group expired due to acute myocardial infarction at 25 months. On multivariate analysis, low mean blood pressure at admission (odd ratio [OR], 18.60; 95% confidence interval [CI], 2.09-166.19, $p=0.01$) and ventricular tachycardia/fibrillation during hospitalization (OR, 43.96; 95% CI, 2.48-778.35, $p=0.01$) were predictors for requiring ECMO.

Predictor of required ECMO	Odd ratio (95% CI)	P-value
Multivariate analysis		
Heart rate	1.02 (0.98-1.06)	0.36
MAP <70mmHg	18.60 (2.09-166.19)	0.01
LVEF ≤30%	7.803 (0.92-65.99)	0.06
Pulmonary congestion on chest X-ray	13.31 (0.80-220.51)	0.07
VT/VF on ECG	43.96 (2.48-778.35)	0.01
QRS duration	1.01 (0.96-1.06)	0.64

Conclusion: In-hospital mortality remains high in patients with fulminant myocarditis needed ECMO support. Low mean blood pressure and ventricular tachycardia/fibrillation might serve as predictors for requiring ECMO.

996 | BEDSIDE

Use of heart failure pharmacotherapy and vasoactive medications in cardiogenic shock in clinical practice - observations from the CardShock study

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Purpose: To analyze real life use of heart failure (HF) pharmacotherapies and vasoactive medications in cardiogenic shock (CS).

Methods: The European multicenter CardShock study prospectively enrolled 220 patients with CS. Data on the use of vasoactive medications within the first 96 hours from inclusion were collected, focusing the analyses to the first 24 hours. In addition, the use of HF pharmacotherapies, such as beta blockers and ACE inhibitors, was analyzed until 24 hours. All-cause mortality was assessed during hospitalization and until 90 days. The data were compared between acute coronary syndrome (ACS) and non-ACS patients as well as analyzed in relation to patient characteristics and mortality. Comparisons were performed using χ^2 test and Mann-Whitney U test and survival analyses using multivariable logistic regression adjusting for potential confounders.

Results: Mean age of patients was 67 years and 26% were women. Mean blood pressure was 78/47 mmHg and average of mean arterial pressure 57 mmHg. The etiology of CS was ACS in 81% and non-ACS in 19% of patients. HF pharmacotherapies were administered to a notable proportion of patients during the first 24 hours. Intravenous furosemide was given in 65% of patients with a median cumulative dose of 120 mg at 24 hours. Overall, vasopressor or inotrope therapy was administered to 94% of patients. Noradrenaline was the most common vasopressor used (in 75% of patients) followed by dopamine (26%) and adrenaline (21%). The most common inotropes were dobutamine (49%) and levosimendan (24%). Given vasopressors were initiated within the first 24 hours from inclusion in 98% and inotropes in 94% of cases. Vasopressor and inotrope therapies were used simultaneously in 55% of patients and 30% of patients were administered more than one vasopressor. Differences in the use of HF pharmacotherapies or vasoactive medications between ACS and non-ACS patients were scarce. The use of adrenaline within the first 24 hours was independently associated with increased in-hospital (OR 3.6, 95% CI 1.1-11.5) and 90-day mortality (OR 5.1, 95% CI 1.4-18.7). Initial confusion and higher blood lactate level predicted its use and it was almost invariably used simultaneously with another vasopressor (36/39 (92%)).

Conclusions: As a rule, patients with CS are treated with vasoactive medications and frequently in combination with other vasoactive agents. However, the use of adrenaline is independently associated with increased mortality. This suggests that other treatment strategies should be considered in patients in need of this medication.

997 | BEDSIDE

A new wearable textile vest for pulmonary congestion tracking in acutely decompensated heart failure patients: a pilot study

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Purpose: To evaluate a portable wearable bioimpedance vest to track recompensation of acutely decompensated heart failure (ADHF). Pulmonary congestion, a landmark sign of ADHF, may be objectively monitored with transthoracic textile bioimpedance sensors.

Methods: Patients admitted to the cardiology ward with ADHF were screened for inclusion. The four Cole parameters were fitted to the measured bioimpedance spectra: R0 reflects extracellular fluids, R_∞ intracellular fluids, fc is tissue relaxation time, and α is tissue heterogeneity. Bioimpedance measurements and heart rate by the investigational device, body weight, New York Heart Association class, and a clinical severity score were registered on admission, on the three subsequent days, and at discharge.

Results: Twenty patients were recruited (15% female, mean age 74.7 ± 9.5 years, left ventricular ejection fraction $37.0 \pm 12.5\%$). Bioimpedance improvement was detected in 90% of patients, and relative changes in bioimpedance during hospital admission properly tracked fluid loss as measured by weight ($p < 0.001$) and clinical severity score ($p < 0.001$). Significant correlations were also found between bioimpedance and other routine parameters of HF severity, such as left ventricular ejection fraction ($r = -0.450$, $p = 0.047$) and NT-proBNP levels ($r = -0.41$, $p = 0.038$).

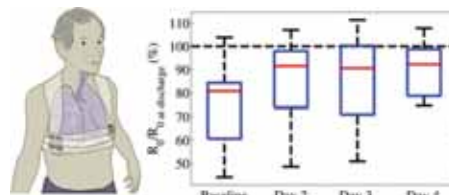


Figure 1

Clinical severity was predicted by combining bioimpedance (estimation of a dry lung), heart rate, and R_{∞} in a naïve Bayesian model with AUC=0.76, as estimated by leave-patient-out cross validation.

Conclusions: Serial monitoring of the transthoracic bioimpedance spectrum assessed by textile sensors tracked ADHF recompensation during hospital admission. Future studies will confirm whether clinical decision making in ADHF might benefit from this noninvasive, easy-to-use bioimpedance vest.

998 | BEDSIDE

Efficacy of a hospital-primary care integrated heart failure program: a population-based analysis in 56,742 patients

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Introduction and objective: Heart failure programs have proven effective in clinical studies, but its applicability in a real practice environment is more controversial. The present study evaluated the feasibility and efficacy of an integrated primary care-hospital HF management program in an integral healthcare area of 309,345 inhabitants.

Methods: The analysis included all consecutive patients hospitalized for a primary diagnosis of HF and discharged alive in all hospitals during the period 2005-2011 in which the program was implemented and compared mortality and readmissions among patients exposed to the IHFP and all patients exposed to the remaining healthcare areas of the Catalan Healthcare Service.

Results: In this study, 56,742 patients were included. There were 181,204 hospitalizations and 30,712 deaths in this period. In the adjusted analyses, the 2,083 patients exposed to the program, compared to the 54,659 patients exposed to the remaining healthcare areas, had lower risk of death (hazard ratio: 0.92 [0.86-0.97] $p=0.005$), lower risk of clinically-related readmissions (hazard ratio: 0.71 [from 0.66 to 0.76], $p<0.001$) and lower risk of readmissions for HF (hazard ratio: 0.86 [0.80-0.94] $p<0.001$). It was observed that the positive impact on morbidity and mortality was more pronounced in the consolidation period of the program.

Conclusions: The implementation of multidisciplinary heart failure programs integrating hospital and community is feasible and is associated with a significant reduction in morbidity and mortality of patients.

999 | BEDSIDE

Vasopressin receptor antagonists for the treatment of heart failure: a systematic review and meta-analysis of randomized controlled trials

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Introduction and aims: Heart Failure (HF) and hyponatremia secondary to HF is associated with impaired quality of life, more frequent hospitalizations and with an overall annual mortality rate of 10%. In the modern therapy of both acute and chronic HF, arginine vasopressin secretion could be a potentially attractive goal. Elevated vasopressin secretion may contribute to the increase in systemic vascular resistance and pulmonary capillary wedge pressure followed by a decrease in stroke volume and cardiac output via V1a receptor stimulation.

We aimed to assess benefits and harms of vasopressin receptor antagonists when compared with placebo in addition to standard care in adults with HF.

Methods: A systematic review and meta-analysis was conducted to identify randomised controlled trials without language restriction through comprehensive searches of CENTRAL and MEDLINE to January 2014. Two authors independently abstracted all data and assessed methodological quality. Meta-analysis used a random effects model, with dichotomous outcomes expressed as risk ratios (RR) and continuous outcomes as mean differences (MD) with 95% confidence intervals (CI).

All-cause and cardiovascular mortality, hospitalization for heart failure, changes in clinical assessment of HF, serum sodium concentration (Na), kidney function, quality of life and any treatment-specific side effects were the outcomes analysed.

Results: We identified 13 trials, including 5525 participants. In 10 trials, all patients with cardiac failure received standard therapy for HF, consisting of diuretic treatment, vasodilators and beta-blockers. Two of these trials used furosemide therapy with doses higher than 40 mg daily. In low-quality evidence, vasopressin receptor antagonists in patients with heart failure had no effect on all-cause mortality (RR 0.98; CI 0.88-1.08) cardiovascular mortality (RR 1.03; CI 0.91-1.16) or change in creatinine (MD -0.01; CI -0.10-0.09 mg/dL), but reduced body weight by 0.8 kg from baseline (MD -0.83; CI -1.10 to -0.55 kg) and increased Na concentration (MD 2.61; 95% C.I. 1.88-3.35 mmol/L). Compared with placebo, vasopressin receptor antagonists increased the risk of adverse events by 14% (RR 1.14; CI 1.04-1.26).

Studies were generally limited to short term follow-up.

Conclusions: Vasopressin receptor antagonist may reduce body weight and increase serum sodium concentration but do not improve all-cause mortality, cardiovascular mortality or kidney function. In addition, acceptability of long-term treatment side effects and hospitalization appear problematic.

NOVEL INSIGHTS INTO LIFESTYLE AND CARDIOVASCULAR PREVENTION

1026 | BENCH

Forty year changes in cardiovascular risk factors

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Purpose: Our country has experienced remarkable changes both in population levels of coronary heart disease (CHD) risk factors and mortality over the past decades. For the national monitoring of risk factors in major non-communicable diseases (NCDs), National FINRISK Studies have been implemented from 1972 to 2012. The purpose is to describe the 40-year changes in cardiovascular diseases risk factors.

Methods: Study population included participants aged 30 to 59 years in the series on independent random population samples. Data were collected in five-year intervals in 1972-2012. FINRISK studies so far comprised 53 589 men and women who participated in a health examination, gave a venous blood sample, and filled in questionnaires. Serum total cholesterol, systolic and diastolic blood pressure, and body mass index were measured using standardized protocol, and smoking status was recorded.

Results: Total serum cholesterol decreased remarkably until the year 2007, but after that has turned to an increase. Systolic blood pressure has continued to decline over time since 1972, while decrease in diastolic blood pressure has leveled off during last ten years. Smoking prevalence has markedly decreased. Body mass index has increased in the population, yet the significant changes occurred in the earlier survey years, not in past 10 years.

Conclusions: After three decades of favorable development, the population risk factor levels showed some increase in total cholesterol and diastolic blood pressure. This emphasizes the need for continued efforts towards national disease prevention and health promotion.

1027 | SPOTLIGHT

In Vino Veritas (IVV) Study: Randomized trial comparing long-term effects of red and white wines on markers of atherosclerosis and oxidative stress

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Background: Since the early 90s, a growing body of evidence has indicated that the mild to moderate consumption of wine, has a protective effect against cardiovascular diseases.

Methods: The IVV study is a first long-term, prospective, multicenter, randomized trial comparing the effects of red (RW) and white wine (WW) on atherosclerosis markers. 146 healthy subjects at mild to moderate risk of atherosclerosis have been randomized to a regular consumption of red wine (Pinot Noir) or white wine (Chardonnay-Pinot) /1 producer, 1 terroir/ for one year (women 0,2 l, men 0,3 l, 5 times a week, logbook for wine and other alcoholic beverages consumption). The primary endpoint is the level of HDL-cholesterol at one year, secondary endpoints are the levels of other markers of atherosclerosis (LDL-cholesterol, C-reactive protein) and oxidative stress (Lp-PLA2, Copeptin).

Results: The level of HDL significantly decreased at 6 months in WW group in comparison with baseline value (Table 1). We did not detect any differences in the levels of ALT, GGT or bilirubin.

Table 1. Change in endpoints at 6 and 12 months from the enrollment according to wine

Mean (SD)	Total	White wine	Red wine	p
N	146	74	72	
HDL				
At the enrollment	1.66 (0.58)	1.66 (0.66)	1.65 (0.50)	0.912
At 6 months	1.58 (0.48)	1.54 (0.52)	1.62 (0.43)	0.317
Difference 1	-0.09 (0.34)	-0.14 (0.41)	-0.04 (0.26)	0.074
p ²	0.002	0.005	0.231	
At 12 months	1.62 (0.49)	1.60 (0.53)	1.64 (0.46)	0.634
Difference 2	-0.04 (0.36)	-0.07 (0.42)	-0.01 (0.29)	0.362
p ²	0.180	0.171	0.718	

Conclusion: In this prospective randomized trial we did not find between long-term mild consumption of red or white wine any clinically relevant differences in the lipid profile, CRP, fasting blood glucose, other markers of atherosclerosis i.e. Lp-PLA2 or copeptin, and liver function tests. Moreover, we were unable to confirm the hypothesis coming mostly from the retrospective studies that wine drinking is associated with elevation of HDL.

The study is registered by ISRCTN under Ref. No. 54359610.

1028 | BENCH**Coffee or tea consumption: no impact on cardiovascular mortality: the IPC cohort**

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Purpose: Caffeine, antioxidants and vasodilatory compounds are present in coffee and tea. We aimed to evaluate the impact of chronic coffee or tea consumption on cardiovascular (CV) mortality and non CV mortality, taking into account a large number of metabolic parameters and lifestyle, particularly tobacco consumption, in a large French cohort.

Methods: We included 131.401 subjects (82.117 men and 49.284 women) aged 18 to 95 years who had a health checkup at the Paris IPC Preventive Medicine Center between January 2001 and December 2008. During a mean 3.55±2.2 years follow-up, we observed 95 deaths from CV and 632 from non CV causes. Coffee or tea consumption were assessed with a self-administered questionnaire and classified into three classes: none, 1 to 4, >4 cups per day. Cox multivariate regression model (HR, 95% CI) adjusted for age, gender, educational level, tobacco consumption, physical activity practice, BMI, cholesterol, triglycerides, glycaemia, perceived stress and depression scores, systolic blood pressure (SBP), and heart rate were used to evaluate mortality risks.

Results: High-volume coffee consumers (>4 cups per day) were older than non-consumers (43.7±12.4 vs 39.6±14.6 years) and had more cardiovascular risk factors except for SBP (e.g. 57% vs 17% current smokers). ECG abnormalities were less frequent than in non-consumers. Tea consumption was associated with a better CV risk profile. Lower SBP, cholesterol, BMI, glycaemia, Gamma-GT level, a lower percentage of tobacco consumption and a higher level of physical activity practice were observed among higher tea consumers compared to non-consumers. After adjustment, coffee consumption was not associated with cardiovascular [HR: 1.2 (0.7-2.2) or non CV mortality [0.90 (0.72-1.14)]. For tea consumption, there was no significant association with CV mortality [0.73 (0.44-1.19)]. By contrast, tea consumption was significantly associated with decreased non CV mortality [0.69 (0.58-0.85); p=0.0002].

Conclusion: Although coffee or tea consumptions are associated with better cardiovascular risk factors, particularly blood pressure, than non-consumers, there was no negative association with cardiovascular death. Interestingly, tea consumption was associated with low non CV mortality by comparison with non-consumers which could suggest a less risky lifestyle.

1029 | BENCH**Chronic periodontal and tooth diseases and cardiovascular mortality in France: the IPC cohort**

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Purpose: Periodontal inflammation and tooth loss are linked to cardiovascular prognosis; we aimed to evaluate the relationship between periodontal and tooth status and cardiovascular (CV) and non-cardiovascular mortality (non CV), in a large low to moderate CV risk, French cohort.

Methods: The population included 85,110 subjects: 54,346 men and 30,764 women (46.0±13.8 years) who had a standardized health check-up including a dental examination by experienced dental practitioners between January 2002 and December 2008. During a mean 3.4±2.0-year follow-up, we observed 487 deaths, 66 from CV and 421 from non-CV causes. Oral examination included presence of dental plaque, dental calculus, gingival bleeding, number of teeth lost and calculation of an index of masticatory efficiency. Risk of mortality associated with periodontal diseases was evaluated using Cox regression models (HR, 95% CI) including age, gender, educational level, tobacco consumption, glycaemia, systolic blood pressure (SBP), gamma-GT, cholesterol, body mass index (BMI), leucocyte count, coffee consumption and physical activity practice.

Results: Periodontal disease or insufficient masticatory efficiency were associated with less favorable cardiovascular risk factors: higher BMI, SBP, glycaemia, and tobacco consumption than in controls. Presence of gingival bleeding was associated with an excess risk of CV mortality [2.75 (1.03-7.37)] and non-CV mortality [1.98 (1.29-3.10)]. Dental plaque was associated with an excess risk of non-CV mortality [2.19 (1.27-3.77)] but not CV mortality [0.33 (0.03-3.47)]. Dental calculus was not associated with mortality (non CV and CV). Insufficient masticatory efficiency was not significantly associated with CV mortality [1.78 (0.78-4.06)] but was linked to non CV mortality [1.91 (1.35-2.71)]. There was no effect of tooth loss on mortality.

Conclusion: There was a distinct association between periodontal status/masticatory efficiency and CV risk factors. Independently from cardiovascular risk factors, gingival bleeding as an index of gingivitis was associated with both CV mortality and non-CV mortality. Of note, local inflammation represented by gingivitis was directly associated to CV death, independently from biological markers of systemic inflammation. In contrast, dental plaques and masticatory efficiency were only associated with non-CV mortality and therefore seem to reflect a poorer general health status, rather than represent an additional CV risk

marker. Periodontal health status should be regularly assessed, particularly in high CV risk patients.

1030 | BEDSIDE**Comparing resistant hypertension to smoking in terms of cardiovascular risk: a 3.6 year follow-up study**

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Purpose: Resistant hypertension (RHT) has gained great interest in the recent years due to its significant prevalence and need for careful diagnostic and therapeutic approach. The prognostic significance of RHT against other established risk factors such as smoking has not been investigated.

Methods: We followed 2009 treated hypertensive patients without a history of cardiovascular disease for a mean period of 3.6±1.8 years. At the baseline visit, a thorough clinical and laboratory examination was performed. Current smoking was recorded as smoking of at least one cigarette daily, and RHT as office-based uncontrolled hypertension under at least 3 drugs including a diuretic or controlled hypertension under 4 or more drugs. Based on the smoking habits and RHT status, four groups were identified: non-smokers/not having RHT (n=1073, 53% of the total population), smokers/not-having RHT (n=404, 20%), non-smokers/having RHT (n=425, 21%) and smokers/having RHT (n=107, 5%). Endpoint of interest was cardiovascular morbidity defined as the composite of coronary heart disease and stroke. The group of non-smokers/not having RHT served as reference.

Results: During follow-up, 69 events occurred (9.6 cases per 1,000 person-years). Incidence rates of cardiovascular events were 5.63 cases per 1,000 person-years in the non-smoker/not having RHT group, 13.45 cases per 1,000 person-years in the smoker/not-having RHT group, 13.95 cases per 1,000 person-years in the non-smoker/having RHT group and 15.15 cases per 1,000 person-years in the smoker/having RHT group. Unadjusted analysis showed that non-smokers/having RHT had comparable risk to smokers/not-having RHT (HR: 2.2, CI: 1.2-3.9 vs HR: 2.4, CI: 1.3-4.6, p<0.01 for both) while the smoker/having RHT group exhibited the worse prognosis (HR: 2.7, CI: 1.1-6.7, p<0.05). After adjusting for established risk factors, the significant risk of the non-smokers/having RHT group was maintained yet attenuated, while the smoker/not having RHT group exhibited now the worse prognosis.

Conclusions: Smoking and RHT exhibit a similarly significant cardiovascular risk, while, after controlling for established risk factors, the smoker status remains as the most potent predictor among the two. Concurrent risk factors strengthen the cardiovascular risk of RHT to a greater extent compared to that of smoking.

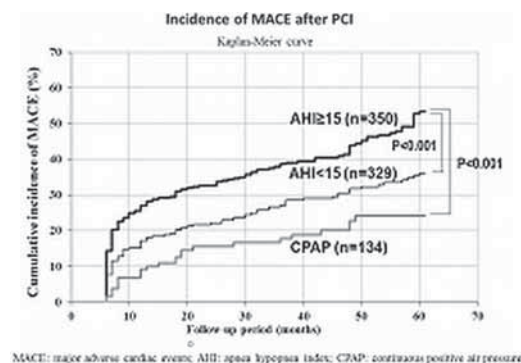
1031 | BEDSIDE**Impact of obstructive sleep apnea on secondary prevention after percutaneous coronary intervention**

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Objectives: It is well-known that Obstructive Sleep Apnea (OSA) could increase the morbidity and mortality of cardiovascular diseases. The aim of this study was to determine whether Obstructive OSA might affect long-term outcomes after percutaneous coronary intervention (PCI).

Methods: Eight-hundred-thirteen patients, who underwent successful PCI, were divided into the following three groups: those with apnea-hypopnea index (AHI) <15 (n=329), AHI >15 (n=350), and taking continuous positive airway pressure (CPAP) treatment (n=134). Among the three groups, the incidence of major adverse cardiac events (MACE) during the five years after PCI was measured. MACE was defined as cardiac death, myocardial infarction, new stenosis and restenosis.

Results: Kaplan-Meier analysis demonstrated the patients with AHI >15 had significantly higher incidence of MACE than those with AHI <15, but CPAP significantly reduced the incidence of MACE (Figure). Cox proportional hazards analysis indicated that AHI was significantly associated with the incidence of MACE (OR=1.018, 95%CI=1.010-1.027; P<0.001).



Conclusion: OSA affected the secondary prevention after PCI. However, CPAP treatment can reduce the incidence of MACE.

NEW INSIGHTS INTO THE BASIC MECHANISMS OF CARDIAC ARRHYTHMIAS

1040 | BENCH

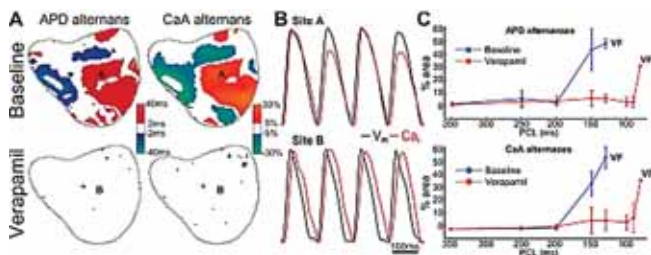
Spatiotemporal antiarrhythmic effects of verapamil on the development of APD and [Ca²⁺]_i alternans

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Introduction: The appearance of spatially discordant alternans (SDA) can lead to the initiation of ventricular fibrillation (VF). The purpose of this study is to characterize the differences that exist between the development of alternans in the onset of VF before and after verapamil administration.

Methods: Simultaneous optical mapping of voltage and calcium were recorded in four Langendorff-perfused rabbit hearts. APD and [Ca²⁺]_i amplitude (CaA) alternans were initiated using a rapid pacing protocol before and after verapamil administration, starting from a pacing cycle length (PCL) of 350 ms which was reduced until VF induction. APD and CaA alternans were defined as variations of at least 2 ms or 5%, respectively, during at least 10 consecutive beats. The percentage of mapped area that exhibited alternans was measured at each recording and presented as mean and 95% confidence interval (CI). Wilcoxon rank-sum test was used to compare the data between groups.

Results: Verapamil produced a decrease both in the PCL for VF induction (142.5±16 vs. 96.3±18.4 ms) and in the APD of 17.4±4.9 ms during fibrillation. SDA area in the ventricles increased at short PCLs both during baseline and verapamil. However, SDA area was lower during verapamil than during baseline for matched PCLs both for APD alternans (41.6% (95% CI 26.1 to 57.1) vs 5.4% (95% CI -0.5 to 11.2), p≤0.05 at PCL=150 ms) and CaA alternans (34.5% (95% CI 25.4 to 43.6) vs 6.6% (95% CI -3.1 to 16.3), p≤0.05 at PCL=150 ms), see figure.



Conclusion: Verapamil produces a reduction in appearance of discordant alternans for fast pacing rates and in the pacing cycle length required for VF induction. However, calcium alternans do appear during verapamil infusion at increased higher rates as compared to baseline.

1041 | BENCH

Increased trafficking of small-conductance Ca²⁺-activated K⁺ channels to plasma membrane modulates action potential duration in human paroxysmal atrial fibrillation

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Background: Small-conductance Ca²⁺-activated K⁺ channels (SK channels) have recently been identified in atria, and were implicated in experimental atrial fibrillation (AF). The present study explored the role of SK channels in human paroxysmal AF (pAF).

Methods: Atrial cardiomyocytes freshly isolated from right atrial appendages of sinus rhythm (SR) and pAF patients as well as HEK293 cells transiently transfected with cloned human SK channels were used for the study. Apamin was used to unmask contribution of SK channels to atrial ion currents and action potentials (voltage- and current-clamp techniques).

Results: In whole-cell voltage-clamp recordings with 0.5 μM intracellular Ca²⁺, calcium- and apamin-sensitive, voltage-independent currents (SK-channel currents, ISK) were detected in atrial cardiomyocytes from both SR and pAF patients. At +80 mV amplitude of ISK was about 3-fold larger in pAF than in SR cardiomyocytes (pAF, 2.9±0.5 pA/pF, n=10 vs. SR, 1.0±0.2 pA/pF, n=19, p<0.01). Pretreatment of pAF cardiomyocytes for 4 h with the retrograde-trafficking blocker

primaquine (120 μM) or the anterograde-trafficking blocker latrunculin A (1 μM) significantly reduced ISK by 59% and 75%, respectively. Primaquine and latrunculin A had no effect on ISK in inside-out patches excised from HEK293 cells expressing SK channels, excluding direct channel effects of both substances. These data indicate that increased trafficking of SK channels to the plasma membrane contributed to the enhancement of ISK in pAF cardiomyocytes. In whole-cell current-clamp recordings with 0.5 μM intracellular Ca²⁺, action potential duration (APD₉₀) was 30% shorter and apamin-induced prolongation of APD₉₀ was 4-fold larger in pAF than in SR cardiomyocytes, suggesting a contribution of enhanced ISK to APD shortening in pAF.

Conclusions: Our data demonstrated that ISK was enhanced in atrial cardiomyocytes from pAF compared to SR patients and contributed to APD shortening. The ISK upregulation in pAF resulted at least partially from increased trafficking of SK channels to the plasma membrane. Targeting SK channel trafficking may offer a new therapeutic option for AF treatment.

1042 | BENCH

A higher frequency and proximity of calcium sparks to the cell membrane may potentiate arrhythmogenic afterdepolarizations in atrial myocytes from patients with atrial fibrillation

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Purpose: Atrial fibrillation (AF) has been associated with increased calcium release from the sarcoplasmic reticulum (SR), but it is not known if there are concurrent changes in the distribution of local release events (calcium sparks) or in the calcium release channels (ryanodine receptors, RyRs), and the purpose of this study was to investigate whether atrial fibrillation affects the distribution of RyRs, their phosphorylation state, or the distribution of calcium sparks in human atrial myocytes.

Methods: Human atrial myocytes from patients with or without AF were loaded with the calcium indicator fluo-4. Patch-clamp technique was used to clamp the membrane potential at -80mV and measure the membrane current. Calcium sparks were visualized using resonance scanning confocal microscopy at a frame rate of 90 Hz. RyRs were visualized using antibodies against the RyR and RyRs phosphorylated at ser2808 (s2808). RyRs and calcium sparks were detected using custom-made algorithms.

Results: A total of 424 sparks were detected in myocytes from 9 patients with AF 22 and without AF. Sparks were significantly more frequent in myocytes from AF patients (53±23 vs. 8.2±2.2 events/min/cell, p<0.01), and this was due to an increased number of spark sites in AF (7.4±3.1 vs. 1.5±0.4 sites, p<0.05). Moreover the distance from the spark to the cell membrane was significantly reduced in AF (from 2.8±0.4 to 1.6±0.3 μm; p<0.05). Measurement of the SR calcium load by Integrating the transient inward current elicited by a rapid caffeine application showed no significant difference between myocytes from 24 patients with AF and 57 patients without AF (7.2±0.7 vs. 8.7±0.4 amol/pF). Furthermore, analysis of the RyR distribution revealed that there was no difference in the density of RyRs in myocytes from patients with and without AF (346 vs. 413 clusters/cell), nor were there any difference in the density of RyRs near the cell membrane (closer than 1.5 μm). However, the density of s2808 clusters increased, resulting in a significantly higher s2808/RyR ratio in myocytes from AF patients (0.56±0.03 vs. 0.33±0.04, p<0.01).

Conclusions: Increased RyR phosphorylation at ser2808 may contribute to increase the calcium spark frequency in myocytes from patients with AF and a concurrent shortening of the spark distance to the sarcolemma may contribute to promote spontaneous membrane depolarizations and increase their amplitude.

1043 | BENCH

NFAT3 gene transfer to counteract the pro-arrhythmic electrophysiological changes accompanying pathological cardiac hypertrophy

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Purpose: Besides structural remodeling, pathological cardiac hypertrophy (PCH) also results in electrical remodeling and is associated with lethal ventricular arrhythmias. We investigated in an in vitro model the possibility to counteract the pro-arrhythmic electrophysiological changes accompanying PCH by using a member of the nuclear factor of activated T cells (NFAT) family of transcription factors as they are important regulators of cardiac ion channel gene expression.

Methods: Neonatal rat ventricular cardiomyocytes (nrCMCs) were isolated from 2-day-old animals and cultured as confluent monolayers. To inhibit fibroblast proliferation, cells were treated with mitomycin-C, 1 day after cell isolation. At day 2, cells were transduced with lentiviral vectors encoding either the eGFP alone (LV:eGFP; control vector) or together with a mutant version of NFAT3 (LV:NFAT3.eGFP). Pathological hypertrophy was induced by 24-hour treatments with 100 μM phenylephrine (PE) at day 3 and 8. The pathological nature of the hypertrophy was investigated by analysis of cell surface area (CSA), total protein content and NPPA, Cx43, SERCA2A and Kv4.3 levels. Electrophysiological

properties, including conduction velocity (CV), action potential duration (APD) and APD dispersion were analysed by optical mapping.

Results: PE treatment of nrCMC cultures increased mean CSA and total protein content by ~50%. NPPA levels went up while the amounts of Cx43, SERCA2A and Kv4.3 were reduced. Local 1-Hz stimulation of the nrCMC cultures resulted in 38% arrhythmias (i.e. triggered activity) in the PE-treated nrCMCs transduced with LV.eGFP (n=56) while PE-treated nrCMCs transduced with LV.NFAT3.eGFP showed no arrhythmias (n=59). Following 1-Hz pacing, PE-treated nrCMCs transduced with LV.eGFP showed prolongation of repolarization (APD30 and APD80 = 320 and 580 vs 150 and 390 ms in PE-treated nrCMCs transduced with LV.NFAT3.eGFP; $p < 0.01$). Western blot analysis showed that Kv4.3 and Cx43 protein levels were decreased in the hypertrophic nrCMC cultures but increased by NFAT3 gene transfer. Mean CSA and total protein content did not differ between the PE-treated nrCMCs transduced with control vector or NFAT3 indicating preservation of the hypertrophic phenotype.

Conclusion: NFAT3 gene transfer can counteract the PE-induced slowing of CV (which may relate to upregulation of Cx43), lengthening of APD (which is associated with an increase in Kv4.3) and arrhythmia incidence in nrCMC cultures. NFAT3 may represent a promising target for the development of new therapies to reduce the detrimental aspects of PCH.

1044 | BENCH

The role of electrophysiological disturbance in the development of stress-induced cardiomyopathy

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Background: Stress-induced cardiomyopathy (SIC), also known as takotsubo cardiomyopathy, is characterized by transient regional myocardial akinesia involving up to 2/3 of the whole heart. This can lead to fulminant heart failure, cardiogenic shock, and literally heart rupture. Although catecholamine-mediated adrenergic overstimulation is indicated in the development of SIC, the pathophysiology leading to cardiac dysfunction of this magnitude is unknown. Excessive catecholamines cause cardiotoxicity to the heart, including electrical disturbance. Patients with SIC indeed have increased risk for electrical abnormalities i.e. Q-T segment prolongation, Torsade de Pointe, and ventricular arrhythmias. Therefore, we propose that disability of myocardial contraction in SIC is associated with catecholamine-induced electrical disturbance or electrical silence.

Method and results: We have developed SIC-like cardiac dysfunction in rats by a single high-dose injection of isoprenaline (50mg/kg). These rats developed the typical SIC pattern of apical ballooning (apical akinesia) post isoprenaline, imaged with echocardiography. In isolated, Langendorff perfused hearts, monophasic action potentials (MAPs) were simultaneously recorded from the akinetic apex and non-akinetic basal myocardium of the left ventricle. Electrical signals were not silenced in the akinetic myocardium, rather MAPs were significantly prolonged in the apex (56.3 ± 6.8 ms) of SIC hearts compared to base (45.3 ± 3.8 ms) (N=6) and to control hearts (apex 35.9 ± 3.4 ms; base 39.3 ± 1.6 ms, N=8) ($P < 0.05$). Optical mapping of the electrical activity in perfused SIC hearts using a voltage-sensitive dye showed increased dispersion of repolarization.

Conclusion: In the rats that have developed SIC-like cardiac dysfunction, electrical activation and propagation are not silenced but there are changes in the repolarization of the akinetic region that may be related to the increase risk of electrical abnormalities seen in patients. We are investigating the mechanisms associated with these changes.

1045 | BENCH

Heterocellular fusion of human ventricular scar cells with neonatal rat cardiomyocytes ameliorates pro-arrhythmia through APD shortening and MDP lowering by enhanced outward potassium current

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Purpose: Fibroblasts can be pro-arrhythmic due to their detrimental effects on cardiomyocyte electrophysiology through several mechanisms that rely on suboptimal integration into the cardiac syncytium. To force full integration of fibroblasts into the cardiac syncytium, the feasibility of heterocellular fusion between fibroblasts and cardiomyocytes as a novel anti-arrhythmic strategy was investigated.

Methods: Human ventricular scar cells (hVSCs) were isolated from patients undergoing surgical reconstruction of the left ventricle, and co-cultured with neonatal rat ventricular cardiomyocytes (CMCs). hVSCs were subsequently transduced with lentiviral vectors encoding Vesicular Stomatitis Virus-G (VSV-G; LV.VSVG.GFP⁺) or GFP (LV.GFP⁺) as control. hVSCs were co-cultured with CMCs and fusion was induced by a 3 minute exposure to pH 6.0. Cultures were analyzed by immunohistochemistry, optical mapping, species-specific RT-qPCR and patch clamp assays for effect of heterocellular fusion on electrophysiological parameters.

Results: Optical mapping experiments showed a pro-arrhythmic phenotype (7.3% occurrence of early after depolarizations (EADs) upon 1Hz electrical stimulation in CMCs vs. 50.0% in hVSC/CMC co-cultures, $p < 0.0001$). Fused co-cultures exhibited marked reduction of pro-arrhythmic features compared to control (4.6% EAD incidence in LV.VSVG.GFP⁺ co-cultures vs. 53.5% in LV.GFP⁺), which was associated with a significant decrease in action potential duration (APD; APD80 was 313.1 ± 6.2 ms vs. 510.7 ± 11.8 ms in unfused controls, $p < 0.0001$). Moreover, human-specific mRNA transcripts of KCND2 and KCND3; encoding Kv4.2 and Kv4.3 voltage-gated potassium channels were upregulated in fused co-cultures compared to unfused controls. Patch clamp experiments and functional assays with pharmacological blockade of outward potassium current confirmed these results and further substantiated their role in APD shortening and lowering of maximum diastolic potential (MDP) upon fusion.

Conclusions: Our results demonstrate that forced heterocellular fusion of hVSCs with CMCs reduced their pro-arrhythmic features, through APD shortening and MDP lowering by upregulation of voltage-gated potassium channels in hVSC nuclei, mediating stronger outward potassium current. These findings provide new mechanistic insights into anti-arrhythmic reprogramming of scar fibroblasts, which may benefit future anti-arrhythmic strategies.

ATRIAL ABLATION: TOOLS, TECHNIQUES AND OUTCOMES

P1046 | BENCH

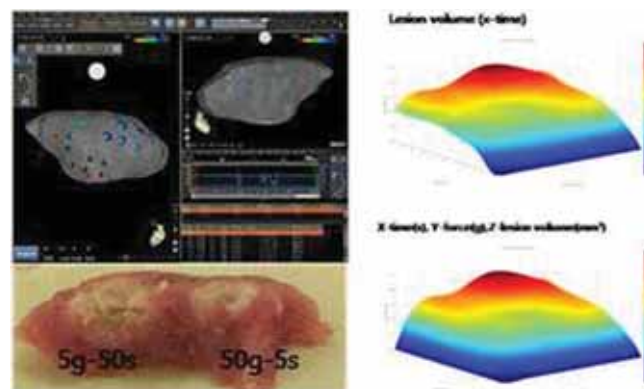
Ablation time is more important than contact force for lesion formation during radiofrequency catheter ablation in vitro model using force sensing technology

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Background: Contact-force (CF) sensing technology allows real time CF measurement during catheter ablation. Lesion size correlates linearly with contact force-time integral (FTI). This study aimed to investigate which factor is more critical for adequate lesion formation among time and CF

Methods: An open-tip irrigated CF sensing catheter was mounted perpendicularly over swine skeletal muscles and swine left ventricular endocardium. RF energy (30W, 17mL/min irrigation) was delivered during constant contact at 5g, 10g, 20g, 30g, 40g and 50g for 5 seconds (s), 10s, 20s, 30s, 40s, and 50s. We analyzed data from 108 consecutive ablation lesions by FTI.

Results: The ablation lesion depth, width, volume under the CF curve was calculated as the FTI. Lesion volume was classified into 2 groups according to the ablation time and CF. In same FTI, longer ablation time made deeper lesion depth and larger lesion volume than higher contact force (256 mm^3 vs. 68.37 mm^3 , $p < 0.001$). Lesion volume over 100 mm^3 was created by at least 20 second-ablation time with variable contact forces.



Lesino formation graph

Conclusion: Time was more important issue than contact force in same force-time integral to make adequate ablation lesion formation.

P1047 | BEDSIDE

Non PV triggers ablation in post Maze patients undergoing redo percutaneous atrial fibrillation ablation: are they important?

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Introduction: Surgical Maze is increasingly being performed for the treatment of atrial fibrillation (AF). We sought to assess the need of ablation of non pv triggers

to achieve freedom from AF at the long term follow up in patients undergoing repeat catheter ablation following a failed surgical procedure.

Methods: 113 patients undergoing redo ablation for atrial fibrillation after a failed surgical maze ablation were enrolled in this study. Besides to pulmonary vein re-isolation and CFAEs ablation, non pv triggers were elicited with isoproterenol challenge. In 61 pts (group I) non pv triggers were always ablated irrespective of their location, while in 52 pts (group II) non PV triggers were ablated with the exception of the left atrial appendage (LAA). All patients were followed up for at least one year with holter monitoring and event recorders.

Results: After the first ablation procedure, 60 (53.1%) patients were recurrence free at 12 months follow up. When stratified by LAA isolation, success rate was 69% (42/61) in Group I, and 34.6% (18/52) in Group II ($p < 0.001$). Out of the 34 patients with recurrence in Group II, 30 patients underwent repeat catheter ablation and 27 (90%) of these patients had triggers firing from the LAA, which was isolated. Overall, after LAA isolation, success rate with 1.77 procedures (1.59–1.95) was 86% after a mean of 28 ± 9 months follow up.

Conclusions: Our study demonstrate that in post Maze patients experiencing recurrence of AF, non pv triggers from the left atrial appendage are an important source of AF and their ablation is critical to achieve long term freedom from atrial arrhythmias.

P1048 | BENCH

Global contact mapping plus ablation of the left atrium for the treatment of atrial fibrillation: a novel multielectrode catheter system

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Purpose: A novel single-catheter multielectrode system (Globe) was developed for global treatment of atrial fibrillation (AF), i.e. simultaneous high-density contact mapping (e.g. voltage mapping, rotor mapping) plus radiofrequency (RF) ablation (e.g. pulmonary vein isolation (PVI), substrate modification).

Methods: The system consists of an array with 20 ribs containing up to 275 gold electrodes, which can be expanded within the body of the left atrium (LA) to a spherical, partially compliant device that contacts the atrial wall in a stable position. The system allows for continuous real-time electrophysiological and biophysical mapping of the whole atrium. RF energy can be applied simultaneously at multiple electrodes as required for the individually tailored ablation of target tissue. The tracing of the ablation sites and subsequent ablation can be done remotely in the control room. RF power output is determined by the system based on electrode contact and is regulated by varying energy application duration and temperature. The temperature sensors are located 25 μ m behind each electrode. After extensive in-vitro testing, the catheter was deployed in-vivo in 5 canines for mapping and ablation.

Results: In in-vitro studies, the mean lesion depth measured 3.2 ± 0.4 , 3.7 ± 0.4 , 4.1 ± 0.4 , 4.8 ± 0.3 , and 5.1 ± 0.3 mm, respectively, depending on the temperature set point of 53, 55, 57, 59, and 61 °C. In in-vivo studies, ablation lesion creation parameters ranged in temperature from 52–59 °C with application times of 60–180 seconds. Successful isolation was achieved in all 5 animals, even when adenosine testing was used. Continuous “wave mapping” allowed for on-line observation of LA activation spread during ablation and for on-line confirmation of PVI or isolation of other targets (e.g. “box” isolation). Two animals were sacrificed immediately after the procedure while the other three were survived up to 68 days. Contiguity of lesion lines and lesion transmural was confirmed by histology.

Conclusions: The Globe array is a completely new catheter concept permitting simultaneous high-density multielectrode contact mapping of the entire LA plus RF ablation for both PVI and substrate targets (e.g. rotors) with a single device. The lesions created with the system in the animals caused acute PVI. Chronically, the lesions were shown to be contiguous, transmural and durable.

P1049 | BEDSIDE

Who will be free from antiarrhythmic drug therapy one-year after catheter ablation of atrial fibrillation - J-CARAF

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Purpose: The Japanese Heart Rhythm Society (JHRS) conducted a nationwide survey of catheter ablation of atrial fibrillation (AF) to obtain a perspective view of the performance and safety of the treatment in Japan. To know the mid-term performance of the therapy and to elucidate the factors related with antiarrhythmic drug (AAD)-free survival, we analyzed one-year outcome of registered patients.

Methods: JHRS requested electrophysiology centers to register patients who underwent AF ablation in September 2011 or March 2012. In 2013, one-year follow-up data of registered patients were collected.

Results: Data of 1193 patients from 119 centers (61.9 ± 10.8 years) were accumulated. One or more AAD were given to 621 patients (52.1%) at the time of discharge. Within one year, 159 patients experienced re-ablation. One-year after index AF ablation, 776 of the remaining 1034 patients (65.0% of 1193) were free from AAD treatment. Univariate analysis showed that none of age, sex, previous AF ablation, lone AF, CHA2DS2-VASc score, and use of 3D imaging system was related with AAD-free survival. AAD, statin, renin-angiotensin-aldosterone system blockade, and beta blockade prescribed at the time of discharge failed to show favorable effect on the outcome, while paroxysmal AF (PAF/ 68.4% vs. 56.6%, $p = 0.000$), history of prior AAD therapy (76.9% vs. 81.1%, $p = 0.020$), left atrial (LA) diameter (40.1 ± 6.8 mm vs. 41.5 vs. 6.7 mm, $p < 0.001$), procedure time (3.37 ± 1.11 h vs. 3.72 ± 1.30 h, $p = 0.000$), lack of CFAE ablation (10.1% vs. 16.3%, $p = 0.002$) or LA linear ablation (19.6% vs. 27.1%, $p < 0.005$), and elimination of inducible AF (46.4% vs. 37.4%, $p = 0.000$) were significantly associated with AAD-free survival. In multivariate logistic regression analysis, only PAF (OR 1.35 [1.02–1.79], $p < 0.05$) and procedure time (OR 0.81 [0.73–0.90], $p = 0.000$) were significant predictors of AAD-free survival.

Conclusions: One-year after AF ablation, two-thirds of patients were free from AAD without re-ablation. No pharmacological treatment at the time of discharge showed appreciably favorable effect on mid-term outcome. PAF and shorter procedure time were independent predictors of AAD-free survival.

P1050 | BEDSIDE

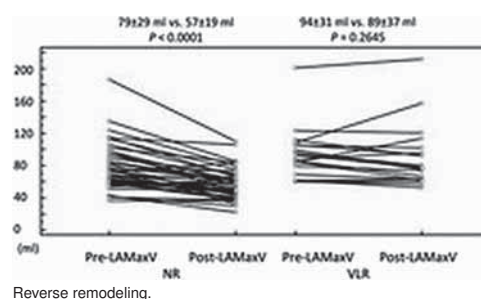
Can we predict very late recurrence after catheter ablation for nonparoxysmal atrial fibrillation? Analysis of left atrial function with multi-detector computed tomography

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Purpose: Some patients receiving catheter ablation for atrial fibrillation (AF) suffer from very late recurrence (VLR; initial recurrence >12 months after AF ablation), but its pathophysiology has not been fully elucidated. We analyzed the left atrial function of nonparoxysmal AF patients who underwent catheter ablation by multi-detector computed tomography (MDCT).

Methods: We retrospectively evaluated 63 patients who underwent initial ablation for drug-refractory persistent or longstanding-persistent AF and had no recurrence in the initial year after ablation. We followed them for average 3.2 ± 1.5 years and divided them into 2 groups based on the presence of VLR (VLR-group and NR-group). All patients were submitted to 256-slice MDCT scan before and 3 months after ablation, and estimated LA volume including maximum and minimum volume during cardiac cycle (LAMaxV, LAMinV) and LA emptying fraction.

Results: Out of 63 study subjects (60 ± 10 years, 52 males), 21 patients experienced VLR. There was no significant difference between the groups in the preoperative demographic data. The reduction rate of LAMaxV after ablation was significantly better in NR-group than in VLR-group ($25 \pm 19\%$ vs. $5 \pm 18\%$, $P = 0.0002$). Higher post-LAMinV was associated with higher risk of VLR. (Hazard ratio = 1.0168 [95%CI: 1.0074–1.0263], $P = 0.0005$).



Conclusion: Poor reverse remodeling after ablation was a risk factor of VLR. Improvement of left atrial function may be an important marker to evaluate the effectiveness of catheter ablation.

P1051 | SPOTLIGHT

Botulinum toxin injection in epicardial fat pads can prevent recurrences of atrial fibrillation after cardiac surgery: results of a randomized pilot study

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Background: Animal models suggest that botulinum toxin injection into the epicardial fat pads suppressed atrial fibrillation (AF) inducibility. The aim of this

prospective randomized double-blind study was to compare the efficacy and safety of botulinum toxin injection into epicardial fat pads for preventing atrial tachyarrhythmias in patients with paroxysmal atrial fibrillation undergoing CABG surgery.

Methods and results: Patients were randomized to botulinum toxin (Xeomin, Germany; n=30) or 0.9% normal saline (control; n=30) injection into epicardial fat pads. Patients were followed for 30 days to assess maintenance of sinus rhythm. There were no significant differences between the groups in the median time until extubation, or intervals from end of surgery to eligibility for and to actual discharge from the ICU (all $P>0.05$). There were no significant differences in CK-MB levels in the postoperative period. Postoperative AF occurred in 2 (7%) of 30 patients in the botulinum toxin group and in 9 (30%) of 30 patients in the placebo group (log-rank test $P=0.024$). There was no significant difference in the postoperative hospital length of stay between groups ($P=0.12$), with a median (25th–75th percentile) length of stay of 6 (5–8) days in the botulinum toxin group versus 6 (4–8) days in the placebo group. Other postoperative complications, including death, were similar between groups (all $P>0.05$).

Conclusion: Botulinum toxin injection in epicardial fat pads provided atrial tachyarrhythmia suppression after cardiac surgery without any serious adverse events.

P1052 | BEDSIDE

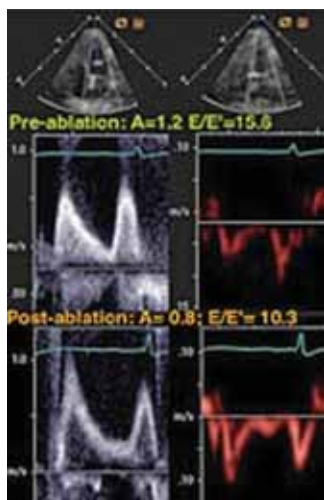
Improvement in left ventricular diastolic parameters following catheter ablation of atrial fibrillation

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Introduction: Atrial fibrillation (AF) is commonly associated with impaired ventricular relaxation and heart failure with preserved ejection fraction. We studied the relationship of atrial size and LV diastology before and after ablation and hypothesized that atrial size and LV filling parameters will improve after catheter ablation of AF.

Methods: Patients presenting for catheter ablation of AF were included in this study. Baseline atrial volume was obtained from pre-procedural CT or MR imaging while LV filling parameters, including mitral valve inflow velocities and tissue Doppler, were assessed using transthoracic echocardiography. The same measures were repeated 3 months following catheter ablation.

Results: Two hundred and ninety three patients (60.8% male) were included in the study. 178 patients (60.7%) had paroxysmal AF. The mean LV ejection fraction was $58\pm12\%$. At baseline, the mean LA volume was 94 ± 38 ml and the estimated mean LV filling pressure (E/E') was 9.5 ± 3.9 . Ventricular relaxation pattern was identified as normal in 86 patients (52.1%), impaired in 36 (21.8%), pseudo-normal in 29 (17.6%) and restrictive in 14 (8.5%). Post ablation, the mean LA volume significantly decreased (94 ± 38 ml to 84 ± 34 ml; $p<0.01$). Mitral inflow A waves decreased from 0.70 ± 0.23 to 0.38 ± 0.31 post ablation ($p<0.01$) and E/E' decreased from 9.5 ± 3.9 to 5.6 ± 5.1 ($p<0.05$). Post ablation, LV relaxation patterns were identified as normal in 122 patients (55.0%), impaired in 27 (12.2%), pseudo-normal in 60 (27.0%) and restrictive in 13 (5.9%). A total of 41 patients (27.2%) were determined to have improved diastolic filling patterns post ablation.



Conclusion: Catheter ablation of atrial fibrillation is associated with decreased LA volumes and improved LV filling pressures and diastolic relaxation pattern.

IMPORTANT ISSUES BELOW THE SURFACE

P1053 | BEDSIDE

New algorithm of OptiVol 2.0 can discriminate false positive events from OptiVol 1.0 alert events

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Background: A major cause of heart failure related hospitalizations is fluid accumulation. Recent studies have suggested that intrathoracic impedance (ITI) may be a useful parameter to track daily changes in pulmonary fluid status. OptiVol alert, which is a fluid status algorithm calculated from ITI, can detect impending fluid accumulation at an early stage. However, the algorithm of OptiVol 1.0 was reported to have a lot of false positive events. New algorithm of OptiVol 2.0 was improved to reduce false positive OptiVol alert events. Then, we examined if the algorithm of OptiVol 2.0 can reduce false positive OptiVol alert events in a simulation.

Methods: Patients who suffered from ischemic or non-ischemic heart disease and who had been implanted with a high energy device with an OptiVol feature were included in this study. The patients underwent various examinations, including body weight, chest X-ray, electrocardiogram, a blood sample such as serum BNP levels and echocardiography, at enrolment and following an OptiVol alert. All patients were followed by a wireless remote monitoring system and were asked to visit hospitals after OptiVol alert events. We defined that primary endpoint was the difference of log BNP between OptiVol alert and baseline. We calculated OptiVol 2.0 index from raw data of ITI, and we examined if calculated OptiVol 2.0 index in a simulation also reached threshold as with OptiVol 1.0 alert events.

Results: From 2010 to 2011, 197 patients in 12 institutes were enrolled in the present study. Mean age was 66 ± 11 years, mean ejection fraction was $44\pm14\%$ and mean log BNP was 2.2 ± 0.5 . During a median follow-up period of 24.0 months, we could calculate OptiVol 2.0 index from the raw data of ITI in 308 of 651 OptiVol alert events. In these 308 OptiVol 1.0 alert events, 221 log BNP values were measured, and there was no significant difference in log BNP between OptiVol alert and baseline (2.28 ± 0.46 vs 2.17 ± 0.53 , $p=0.1955$). In 90 of 221 OptiVol 1.0 alert events, OptiVol 2.0 index also reached threshold of 60. In these 90 events, log BNP was significantly higher in OptiVol alert than that at baseline (2.36 ± 0.44 vs 2.17 ± 0.53 , $p=0.0127$). However, in 131 of 221 OptiVol 1.0 alert events, OptiVol 2.0 index did not reach threshold of 60. In these 131 events, there was no significant difference in log BNP between OptiVol alert and baseline (2.23 ± 0.46 vs 2.17 ± 0.53 , $p=0.5904$).

Conclusion: New algorithm of OptiVol 2.0 can discriminate false positive events from OptiVol 1.0 alert events.

P1054 | BEDSIDE

Subclinical left ventricular dysfunction in chronic asymptomatic alcoholics

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Background: The purpose of the study was to use speckle tracking echocardiography (STE) to identify subclinical global systolic function abnormalities in chronic asymptomatic alcoholics with normal ejection fraction.

Methods: We studied 30 healthy subject and 75 asymptomatic alcoholics divided into two groups, group I (TLDE <15 kg ethanol/kg body weight) and II (TLDE ≥ 15 kg ethanol/kg body weight), according to total lifetime dose of ethanol (TLDE) Left ventricular (LV) wall thickness, dimensions, LV mass index and ejection fraction were determined. In the 2D-STE analysis, LV global longitudinal strain (G-LS), longitudinal global strain rate in systole (G-SRs), longitudinal global strain rate in early diastole (G-SRearly) and longitudinal global strain rate in late diastole (G-SRlate) values were obtained.

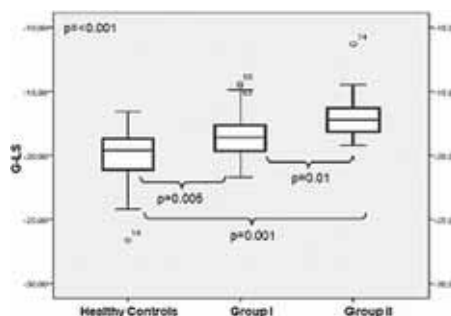


Figure 1.

Results: The alcoholics had larger end-systolic and end-diastolic dimension, thicker interventricular septal and posterior wall and higher LV mass index. However, there were no differences in end-systolic and end-diastolic dimension, and LV mass index among alcoholics. Ejection fraction did not differ between groups. G-LS was lower in alcoholics ($p < 0.001$) (figure). We found that G-LS was significantly lower among alcoholics while LV mass index and LV dimensions remained unchanged. While G-SRsys was lower in the alcoholics than in the control group ($p = 0.03$), there were no differences in G-SRearly and G-SRlate values. There was a significant correlation between G-LS values and TLDE ($r = 0.49$, $p < 0.001$).

Conclusions: This study is the first demonstrating, by 2D-STE, the presence of early functional abnormalities of longitudinal systolic function in chronic alcoholic patients. These functional abnormalities have a parallel development with the increase alcohol consumption.

P1055 | BEDSIDE

Characterisation of the octogenarians presenting to the incident heart failure clinic

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Purpose: The prevalence of heart failure (HF) rises with advancing age, and peaks amongst the octogenarians. We investigated the characteristics of the patients aged 80-89 years presenting to the incident HF clinic.

Methods: We interrogated the incident heart failure clinic data-base serving a city with 550,000 inhabitants. Patients with suspected HF whose natriuretic peptides (NTproBNP) is > 400 pg/ml (ng/l) receive an echocardiogram and a clinical assessment by a heart failure cardiologist. We collected data on the patients seen between 14th of April 2012 and 31st of January 2014. We concentrated on the patients aged 80-89 years, and classified the patients according to the rise of NTproBNP, the New York Heart Association (NYHA) functional class, the co-morbidities, the diagnostic findings and the likelihood of management changes.

Results: We saw 1269 patients, of whom 522 patients (41%) were octogenarians. The male:female ratio is 1:1.3. There are 332 patients (64%) with NYHA classes II-IV. The co-morbidities were: Chronic kidney disease (CKD stage III-IV) (42%), systemic hypertension (37%), atrial fibrillation (AF) (34%), diabetes mellitus (12%), chronic obstructive pulmonary disease (8%), cerebrovascular accidents (7%) and dementia (3%). The diagnoses were: 110 patients (21%) did not have HF, 191 patients (37%) had HF due to left ventricular systolic dysfunction (HF-LVSD), 156 patients (30%) had HF with preserved left ventricular ejection fraction (HFPEF), 38 patients (7%) had HF due to pulmonary hypertension, and 27 patients (5%) had HF due to valvular disease. The management of the patients was changed in 394 patients (75%) as a result of their attendance at the incident HF clinic, and 13% of them were followed up by the cardiologists. It appears that NYHA class rather than the rise in NTproBNP or the number of co-morbidities dictated the frequency of changes in the management being offered.

Conclusions: HF-LVSD, and not HFPEF, is the most common HF diagnosis amongst octogenarians with raised NTproBNP presenting to the incident heart failure clinic. Their NYHA functional class is the main determinant of the frequency of changes made to their management.

P1056 | BEDSIDE

Lung ultrasound in the outpatient management of heart failure patients without signs of pulmonary congestion and low NT-proBNP values: subgroup analysis of a multicenter prospective randomized study

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Purpose: Lung ultrasound (LUS) helps in detecting pulmonary interstitial and alveolar fluid through its sonographic evidence of B-lines. This time-saving bedside tool gives immediate information about the extent of pulmonary congestion. We investigated whether LUS is able to provide additional information regarding therapeutic management of outpatients with chronic heart failure (HF) with low NT-proBNP values and no signs of pulmonary congestion on physical examination.

Methods: Amongst 95 patients enrolled in a multicenter randomized study, we performed a subgroup analysis of 30 patients without signs of pulmonary congestion on physical examination and NT-proBNP value < 1000 pg/mL. Patients were prospectively enrolled according to the following criteria: (1) history of HF for at least 6 months, (2) left ventricular ejection fraction (LVEF) $< 45\%$, (3) adequate medical therapy for at least 2 months. Patients were randomized into two groups: A who underwent to LUS, B who underwent to physical examination only. Therapy was modified according to the presence and extent of B-lines in group A and physical examination in group B. The ultrasound examination was performed with a handheld echocardiography device. Patients were evaluated at baseline and after 3 months. The primary end-point was a significant reduction of hospitalizations for acute decompensated heart failure (ADHF) in group A during follow-up. The secondary end-points were changes of NT-proBNP values, quality of life test (QLT) score and cardiac mortality.

Results: Amongst the 30 patients evaluated (mean age 68 ± 11 years, mean NTpro-BNP value 513.6 ± 260.2 pg/mL), 17 were enrolled in group A and 13 in group B; the 2 groups are similar for age, LVEF, NYHA class. B-lines were iden-

tified in 10 patients (59%) of group A. The 3-month hospitalization rate for ADHF was 0% in group A and 23% in group B (OR: 0.76, 95% CI: 0.57-1.0; $p = 0.03$). In group A, mean NT-proBNP values did not differ significantly between baseline and at 3 months (565 ± 255 pg/mL vs 535 ± 215 pg/mL, $p = 0.38$), while in group B an increasing trend was observed (287 ± 101.4 pg/mL vs 323.3 ± 114.3 pg/mL, $p = 0.015$). Mean QLT scores in group A were 12.4 ± 9.1 at baseline and 11.3 ± 8.7 at 3 months ($p = 0.2$), 13.7 ± 7.7 vs 14.1 ± 8.6 in group B ($p = 0.7$). No deaths occurred. The NYHA class in group A was 2.1 ± 0.4 at baseline and 2.0 ± 0.3 at 3 months ($p = 0.2$), 2.1 ± 0.3 vs 2.1 ± 0.3 in group B ($p = 0.3$).

Conclusions: The therapeutic management of outpatients according to LUS data proved to reduce the hospitalization rate for ADHF in chronic HF patients without clinical signs of pulmonary congestion and low values of NT-proBNP.

P1057 | BEDSIDE

Elevated lipoprotein(a) levels, LPA risk genotypes, and increased risk of heart failure - a general population study in 98 097 individuals

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Purpose: Elevated lipoprotein(a) levels represent a genetically determined risk factor for myocardial infarction and aortic valve stenosis. We aimed to determine whether elevated lipoprotein(a) levels and corresponding LPA risk genotypes (rs10455872, rs3798220, kringle IV type 2 repeat polymorphism) are associated with increased risk of heart failure, which is presently unknown.

Methods: We combined data from two general population studies (1991-2013; N=10855) (2003-2013; N=87242), including a total of 98097 participants of whom 4122 were diagnosed with heart failure. We conducted observational and genetic instrumental variable analyses in a Mendelian randomization study design to assess evidence of causality.

Results: Elevated lipoprotein(a) levels were associated with multivariable adjusted hazard ratios for heart failure of 1.10 (95% confidence interval: 0.97-1.25) for 34th to 66th percentile levels (8-19 mg/dL), 1.24 (1.08-1.42) for 67th to 90th percentile levels (20-67 mg/dL), 1.57 (1.32-1.87) for 91st to 99th percentile levels (68-153 mg/dL), and 1.79 (1.18-2.73) for levels > 99 th percentile (> 153 mg/dL), versus levels < 34 th percentile (< 8 mg/dL) (trend, $p < 0.001$). Lipoprotein(a) levels were elevated among carriers of rs10455872 and rs3798220 minor alleles, and of low number of KIV-2 repeats (trend, all $p < 0.001$). Combining all genotypes, instrumental variable analysis yielded a genetic relative risk for heart failure of 1.18 (95% CI, 1.04-1.34) for a 10-fold lipoprotein(a) increase, comparable to the corresponding observational hazard ratio of 1.22 (1.11-1.35). Upon exclusion of participants diagnosed with myocardial infarction or aortic valve stenosis, risk estimates were attenuated.

Conclusions: Elevated lipoprotein(a) levels associate with increased risk of heart failure with genetic evidence of causality. The association appears mediated, at least partly, via increased risk of myocardial infarction and aortic valve stenosis.

P1058 | SPOTLIGHT

Prognostic role of new parameters derived from cardiopulmonary exercise test beyond the oxygen consumption

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Purpose: To assess the prognostic value of two new cardiopulmonary exercise test (CPET)-derived variables in patients with chronic heart failure (CHF): peak circulatory power (PCP) and peak oxygen uptake efficiency (POUE)

Methods: We retrospectively studied 325 consecutive CHF pts, referred to our outpatient clinic: M/F=266/59, aged 52.7 ± 11.6 years, ischemic etiology: 115 patients (35%), NYHA III-IV: 78 (24%), mean LVEF: $32.92 \pm 10.61\%$, in sinus rhythm: 250 (77%), receiving beta blockers: 298 (91.7%) and ACE inhibitors: 233 (71.6%).

All patients underwent clinical examination, blood sampling for assessment of NT-pro-BNP plasma levels, 2D echocardiogram, six-minutes walking test and performed symptom-limited CPET at cycle ergometer using an incremental symptom-limited protocol. We divided our study population into four groups according to the median value of PCP (group A and B: with PCP $<$ and > 1939 mmHg/ml/kg/min, respectively) and the median value of peak OUE (group C and D: with peak OUE $<$ and > 0.72 , respectively).

Results: Compared to group B, patients of group A (162/325) had worse functional and clinical status, exercise capacity and ventilator efficiency than (LVEF % 30.68 ± 8.74 vs 35.67 ± 12.30 $p < 0.0001$; NYHA III/IV 55 vs 23 $p < 0.0001$; NT Pro BNP values 1076 ± 1491.97 vs 478.04 ± 524.54 pg/ml $p < 0.0001$; Watt max (%), $36.92 \pm 19.66\%$ vs $47.54 \pm 11.56\%$ $p < 0.0001$; HR%, $63.58 \pm 16.46\%$ vs $70.95 \pm 15.39\%$ $p < 0.001$; Slope VE/VCO2 30.26 ± 7.73 vs 26.68 ± 5.97 $p < 0.0001$). Furthermore, PCP was able to predict major adverse events (i.e. heart transplantation or enrollment in waiting list 22 vs 8 $p < 0.006$, acute HF 26 vs 12 $p < 0.02$, exitus 10 vs 3 $p < 0.04$). On the other hand, POUE failed to predict poor outcome, even if group C (163/325) was significantly associated with more impaired clinical and functional status compared to group D (LVEF % 31.11 ± 9.87 vs 35.35 ± 11.14 , $p < 0.0003$; NYHA III/IV 56 vs 22, $p < 0.0001$; Watt max %

38,97±20,13 vs 45,14±12,46, $p<0,001$; HR %64,62±17,10 vs 69,88±15,04, $p<0,003$, total meters at 6-minutes walking test 328,8±89,50 vs 364,18±95,98, $p<0,0007$; SlopeVE/VCO₂ 30,64±7,2 vs 26,29±6,32, $p<0,0001$; NT Pro BNP values 1014,86±1455,07 vs 565,72±745,53 pg/ml, $p<0,0005$.
Conclusions: Although both PCP and POUe are able to identify, in CHF patients, those with poorer clinical and functional status, only PCP showed a strong predictive value for major adverse events in this subsets of patients.

P1059 | BEDSIDE
How objective is NYHA classification? A literature review comparing NYHA class with cardiopulmonary exercise testing

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Purpose: The New York Heart Association (NYHA) classification is commonly used by physicians and studies all over the world. However, it is open to interpretation by both physicians and patients, which can influence its reliability. We aim to review the literature on all studies done with NYHA class and its corresponding cardiopulmonary exercise testing (CPET) results, and thus assess the objectiveness of NYHA in assessing functional class in heart failure patients.

Methods: We ran a PubMed search of "Comparison of NYHA to CPET", "NYHA and CPET", and "heart failure and CPET" - yielding 321 papers. 39 studies comparing CPET results in each NYHA class were included. 282 papers were excluded, with 81 studies describing CPET values in combined NYHA classes and 201 studies failing to compare NYHA to CPET. In the majority of studies, only the peak oxygen consumption (VO₂) data was complete and was thus the main variable we included for analysis. We then obtained the mean and standard deviation of peak VO₂ for each NYHA class for each paper and compared them across.

Results: A total of 37 studies were included (6 USA, 22 Europe, 7 Asia, 2 South America), with a total of 3454 patients (1633 males, mean age 57.4±9.0yrs old). The mean peak VO₂ was 23.7±4.7 mL/(kg·min) in NYHA I patients, 17.4±2.5 mL/(kg·min) in NYHA II patients, 12.9±2.3 mL/(kg·min) in NYHA III patients and 11.9±2.1 mL/(kg·min) in NYHA IV patients. There was substantial overlap between peak VO₂ values in each NYHA class (see Fig. 1), especially between Class II, III and IV.

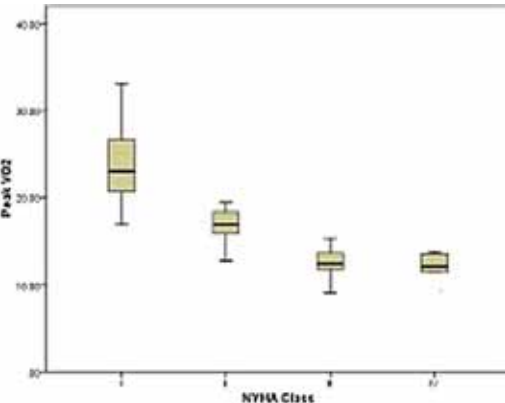


Figure 1. Distribution of peak VO₂ results in each NYHA class.

Conclusion: The NYHA classification is intrinsically subjective which is dependant on the patient's reported symptoms and the evaluator's interpretation. More objective measurements like CPET may be used additionally to better assess patients.

ADVANCES IN IMAGING OF CONGENITAL HEART DISEASE

P1060 | BEDSIDE
Aortic root asymmetry in Marfan syndrome implies significant disparities between echo and MRI measurements

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Purpose: We aim to evaluate the presence of aortic root asymmetry in Marfan syndrome and its impact on the correlation between echo and MRI measurements
Methods: MRI and echocardiographic studies were performed in 127 non-operated Marfan patients. Mean time between studies was 9.1±16.2days. Aortic root diameter was measured by echocardiography using the leading-edge to leading-edge approach at end-diastole. The three cusp-to-commissure aortic root diameters were measured at end-diastole from the axial cine-MRI images and av-

eraged (ARav). Asymmetry was defined as a difference ≥3mm among the three aortic root diameters by MRI.

Results: 127 Marfan patients were included (age: 26.2±13.7yrs; 76 females, 59.8%). Mean aortic root by echocardiography (ARecho) was 35.2±6.2mm. The mean averaged aortic root diameter (ARav) by MR was 34.9±5.8mm and maximum (ARmax) was 35.9±6.1mm.

Asymmetry was present in 30 patients (23.6%). In these, the greatest aortic root diameter was LC in 12 (40.0%), NC in 11 (36.7%) and RC in 7 (23.3%). Asymmetry was present in 13 (52.0%) patients with ARecho ≥42mm (n=25) compared to 17 (16.7%) with ARecho <42mm ($p=0.001$).

ARecho was highly correlated with ARav by MRI ($r=0.966$, $p<0.001$) and with ARmax ($r=0.964$, $p<0.001$).

Mean difference between ARecho and ARmax was 1.4±1.7mm in the asymmetric and 0.6±1.6mm in the non-asymmetric patients ($p=0.018$). Among patients with an asymmetric aortic root, 5 (16.7%) had a difference ≥3mm between ARmax and ARecho.

	Asymmetric aortic root n=30	Non-asymmetric aortic root n=97	p
Age, yrs	31.4±14.8	23.9±12.9	0.009
Gender, female	19 (63.3%)	57 (58.8%)	0.832
Aortic root by echo, mm (ARecho)	38.5±6.2	34.1±5.9	0.001
Averaged aortic root by MRI, mm (ARav)	38.0±5.9	34.0±5.5	0.001
Maximum aortic root by MRI, mm (ARmax)	39.9±6.1	34.7±5.6	<0.001
Difference ARmax minus ARecho, mm	1.4±1.7	0.6±1.6	0.018

Conclusions: Aortic root asymmetry is common in Marfan patients. In the presence of aortic dilatation, aortic asymmetry is more frequent and implies a marked difference between echo and MRI aortic root measurements. Therefore, in the presence of aortic dilatation, MRI should be performed to rule out aortic root asymmetry and determine the best imaging technique for aortic root enlargement follow-up.

P1061 | BEDSIDE
Delayed enhancement cardiac MRI identifies ventricular dysfunction and impaired regional myocardial mechanics in univentricular heart diseases

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Background: The impact of myocardial fibrosis on cardiac performance and clinical outcomes in patients with a functional single ventricle before stage-3 (Fontan) is unknown. Objective- The purpose of this study is to evaluate the relationship between myocardial fibrosis identified by cardiac magnetic resonance imaging (cMRI) and ventricular performance in patients before Fontan operation.

Methods: Seven-teen patients with functional single ventricle who are undergoing Fontan operation had cMRI study with the myocardial delayed enhancement imaging were prospectively examined from May 2013 to January 2014. Late gadolinium enhancement (LGE) was quantified by the percent LGE of ventricular mass. To identify regional wall motion abnormalities, ventricle circumferential strain (CS) was assessed using commercially available zisostation2 (Ziosoft).

Results: Of 17 patients (mean age at study was 3.2±0.8 years), 5 (29%) had positive LGE (LGE+) in the ventricular myocardium, median percent LGE was 3.0% (IQR 3.0% to 9.0%). Pre-Fontan cMRI revealed that patients with LGE had increased end-diastolic volume index (145.0±30.6 ml/BSA vs. 112.6±19.9 ml/BSA, $P=0.02$), increased end-systolic volume index (105.2±34.1 ml/BSA vs. 70.5±20.7 ml/BSA, $P=0.02$) compared with those without LGE (LGE-). Patients with LGE have shown to have lower ventricular CS compared with the area without LGE (basal: -1.9±1.9% vs. -4.0±3.0%, $P=0.046$; mid: -3.9±2.1% vs. -8.0±3.9%, $P=0.007$; apical: -3.9±2.4% vs. -8.2±2.8%, $P=0.004$). Compared with LGE- group, LGE+ group had decreased ventricular ejection fraction (28.7±9.4% vs. 38.1±9.9%, $P=0.04$) as well as higher levels of BNP (112.2±90.3 pg/ml vs. 30.7±47.6 pg/ml, $P=0.03$). In addition, patients with LGE+ had higher score of Ross classification (2.4±0.55 vs. 2.0±0, $P=0.02$) and New York University Pediatric Heart Failure Index (11.4±3.8 vs. 7.9±1.3, $P=0.01$) than in LGE- group. Age at stage-2 palliation was significantly older in patients with LGE+ group than LGE- subjects (18.5±15 months vs. 8.5±3.4 months, $P=0.045$). Post-operative course was not significantly changed between LGE+ and LGE- groups (ICU stay: 6.2±2.5 days vs. 8.1±1.8 days, $P=0.11$; hospital stay: 36.2±10.1 days vs. 36.7±18.4 days, $P=0.96$).

Conclusion: In this pre-Fontan cMRI study, the age to stage-2 palliation may attribute to substantial myocardial fibrosis. The area of LGE was associated with impaired regional CS as well as disturbed ventricular performance. Further studies are needed to examine the possible specificity of LGE as a predictor of heart failure and latent myocardial dysfunction in long-term outcome.

P1062 | BEDSIDE**Quantitative assessment of systolic right ventricular function using longitudinal strain in patients with a systemic right ventricle**

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Purpose: Late systolic dysfunction of the systemic right ventricle (RV) in patients with transposition of the great arteries (TGA) after Mustard operation (TGA-Mustard) and in patients with congenitally corrected TGA (cc-TGA) is of major concern. We evaluated RV peak systolic longitudinal strain (LS) in these patients, compared it to healthy controls and assessed its relationship with conventional echocardiography, electrocardiography and NT-proBNP.

Methods: Echocardiography, electrocardiography and NT-proBNP measurement were performed on the same day in patients with TGA-Mustard or cc-TGA. Echocardiography was also performed in healthy controls. LS was analyzed with use of speckle-tracking echocardiography.

Results: We included 66 subjects: 40 patients with a systemic RV with a mean age of 36 ± 7 years, and 73% male (31 TGA-Mustard patients (34 ± 4 years after corrective surgery) and 9 cc-TGA patients), and 26 age- and gender-matched controls. LS of the RV lateral wall was significantly lower in patients with TGA-Mustard ($-15.5 \pm 3.5\%$) or cc-TGA ($-16.1 \pm 3.6\%$) than in healthy controls ($-26.4 \pm 4.5\%$, $p < 0.001$), as was the LS per RV segment (Fig. 1). LS of the RV lateral wall was lower in patients in NYHA class II than class I, and correlated with RV apex-base diameter ($r = 0.54$, $p = 0.001$), RV fractional area change ($r = -0.36$, $p = 0.039$), QRS duration (0.43 , $p = 0.012$) and NT-proBNP ($r = 0.53$, $p < 0.001$).

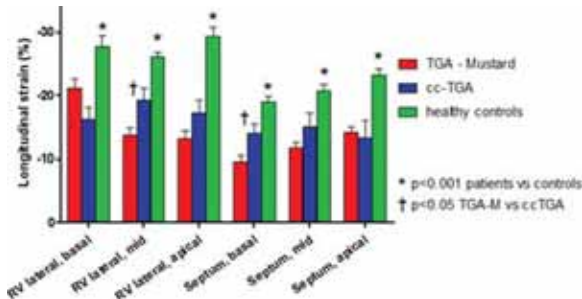


Figure 1. Segmental systolic longitudinal strain.

Conclusions: RV LS is lower in patients with a systemic RV than in healthy controls, especially in the RV apical segment. Since RV LS correlates with RV function and dimensions, future use of LS as a more quantitative tool to measure RV function could be implemented. The correlation between RV LS and NT-proBNP indicates a potential prognostic value of strain in patients with a systemic RV.

P1063 | BEDSIDE**Two-dimensional longitudinal strain is a useful index to identify subclinical right ventricular dysfunction at long-term follow up of corrected Tetralogy of Fallot by trans-atrial approach**

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Purpose: Late right ventricular (RV) dysfunction remains the main burden of corrected Tetralogy of Fallot (cToF), even after RV-sparing surgical approach (trans-atrial approach, TAA). This study aimed to assess the presence and extent of subclinical RV dysfunction at long-term follow-up in cToF pts who underwent surgical correction by TAA.

Methods: We performed 2D and 3D echo in 25 asymptomatic cToF pts (17 ± 4 yrs, 15M) with > 10 years follow-up (mean 16 ± 3 yrs) and compared RV function indexes with those obtained in 18 healthy subjects, matched for age- gender- and body size (C).

Results: cToF pts had RV volume overload (RV EDV 94 ± 23 ml/m² vs 53 ± 23 ml/m² in C, $p < 0.001$) due to significant pulmonary regurgitation (PR index $75 \pm 11\%$). In cToF pts, all RV systolic function indices were impaired in comparison to C: fractional area change (FAC) (38 ± 6 vs $45 \pm 8\%$, $p = 0.01$), TAPSE

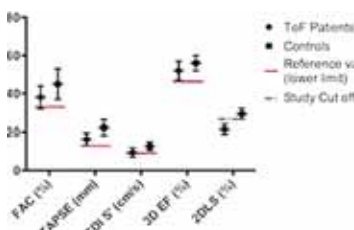


Figure 1. RV systolic parameters comparison.

(1.63 ± 0.33 vs 2.23 ± 0.41 cm, $p < 0.001$), TDI S' wave (1.01 ± 0.22 vs 1.37 ± 0.24 cm/s, $p < 0.001$), 2D global longitudinal strain (RVLS) (21.5 ± 2.5 vs $29.4 \pm 2.8\%$, $p < 0.001$) and 3DEF (52 ± 5 vs $56 \pm 4\%$, $p = 0.01$). At ROC curve analysis, RVLS had the greatest predictive power (AUC=0.98, optimal cut-off= -24%), with 87% sensitivity and 100% specificity to separate cToF pts from C. FAC had the lowest discriminative power (AUC=0.72), while TAPSE, TDI S' wave and 3DEF had intermediate AUC values (0.91, 0.87 and 0.73, respectively). However, if compared with normative values recommended by guidelines, RV systolic function would have been classified as normal in most of ToF pts (Fig. 1): 71% by FAC, 67% by TAPSE, 59% by TDI S' and 96% by 3DEF. Conversely, only 4 pts (16%) had RVLS $< -24\%$.

Conclusions: In the presence of RV volume overload, RVLS emerged as the most sensitive marker of subclinical RV myocardial dysfunction in cToF corrected by TAA.

P1064 | BEDSIDE**Main pulmonary artery area limits exercise capacity in patients long-term after arterial switch operation (ASO) for transposition of the great arteries**

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Background: Despite excellent contemporary surgical results, exercise capacity is decreased in patients after ASO. This study compared right ventricular (RV) function, outflow tract area, distensibility and pulmonary blood flow (PBF) distribution of ASO patients to controls and correlated these measurements to exercise capacity.

Methods: Participants underwent cardiac magnetic resonance imaging including angiography and flow measurements and cardio-pulmonary exercise testing. RV function, smallest cross-sectional area of the main (MPA), left (LPA) and right pulmonary artery (RPA), LPA and RPA distensibility (relative area change), PBF distribution and percentage of predicted peak oxygen uptake (VO_{2peak}/kg%) were measured.

Results: Sixty-five patients were included (72% male, mean VO_{2peak}/kg% $86.8 \pm 19.6\%$). The table compares ASO patients to controls and shows correlation coefficients to VO_{2peak}/kg% for ASO patients. MPA area indexed for BSA was smaller in patients aged > 18 yrs (170.9 ± 76.5 compared to 228.5 ± 49.1 mm²/m², $p < 0.01$).

ASO patients compared to controls

	ASO (n=65)	Healthy (n=21)	VO _{2peak} /kg% (r)
Age (years) [#]	19.9 [14.4–25.4]**	26.4 [23.3–29.9]	–0.324**
RV EDV (ml/m ²)	93.2 (13.9)**	103.5 (17.4)	0.266*
RV SV (ml/m ²)	51.7 (8.1)	54.0 (8.5)	0.368**
RV EF (%)	55.7 (5.3)*	52.5 (4.2)	0.201
RV mass (gr/m ²)	30.8 (6.4)**	22.2 (3.8)	0.140
MPA area (mm ² /m ²)	192.5 (72.8)**	278.8 (60.4)	0.391**
			(age > 18 : 0.454**)
LPA area (mm ² /m ²) [#]	59.4 [41.0–90.2]**	156.5 [140.0–185.7]	0.044
RPA area (mm ² /m ²) [#]	98.0 [65.6–148.1]**	139.3 [123.4–174.8]	0.051
LPA, RPA distensibility (%)	30.5 (10.0), 35.1 (9.3)	30.0 (5.4), 34.7 (5.2)	–0.156, –0.121
LPA : RPA flow (%)	45.1 : 54.9 (7.6)	44.9 : 55.1 (3.8)	0.080

[#]Median [interquartile range] and Mann-Whitney U test or Spearman's correlation; other mean ($\pm$ SD) and Student T-test or Pearson's correlation; * $p < 0.05$, ** $p < 0.01$.

Conclusion: In ASO patients MPA, LPA and RPA areas were smaller compared to controls and VO_{2peak} was reduced compared to reference values, while distensibility and PBF distribution remained within normal range. MPA area was strongly correlated to VO_{2peak}/kg%, suggesting that MPA area - rather than branch stenosis - limits oxygen transport in ASO patients.

P1065 | BEDSIDE**Accuracy of flow measurements by cardiac magnetic resonance in peripheral and main pulmonary arteries in different clinical settings**

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Objectives: Accuracy of flow measurements by phase-velocity magnetic resonance (PV-MR) is sensible to the presence of regurgitation, stenosis, through plane motion or complex anatomy.

This study compares the accuracy of PV-MR in determination of pulmonary blood flow in the main pulmonary artery (MPA) and in both peripheral pulmonary arteries (PPA) in different clinical pathologies.

Method: Three groups of patients were compared: Healthy individuals (H, n=54), patients with tetralogy of Fallot with significant pulmonary regurgitation and without pulmonary or right ventricular outflow tract stenosis (PR, n=50) and patients with RV outflow tract or pulmonary stenosis (PS, n=50). Pulmonary stroke volume was determined by PV-MR in PPA and MPA and compared to aortic stroke volume in the ascending aorta (AO). No patient had significant atrial or ventricular shunting.

Results: Median age was not different between groups: 23 (range 7-69) vs. 21 (range 7-50) vs. 20 (range 8-52) years, $p=0.3$. Bland-Altman analyses revealed for all groups a higher bias for PV-MR of MPA than PPA in comparison to AO flow measurements (table).

Bias was more important in groups with PR and PS than in H. However F-test analyses did not reveal significant differences of the variances (table).

Table 1

	Healthy individuals		Pulmonary regurgitation		Pulmonary stenosis	
	MPA vs. Aorta	PPA vs. Aorta	MPA vs. Aorta	PPA vs. Aorta	MPA vs. Aorta	PPA vs. Aorta
Bias $\pm$ SD (ml)	2.894 $\pm$ 29.2	-0.575 $\pm$ 27.9	5.24 $\pm$ 11.9	-1.18 $\pm$ 8.61	5.0 $\pm$ 18.21	1.0 $\pm$ 12.6
Limits of agreement	-54.4; 60.2	-55.3; 54.2	-18.1; 28.6	-18.1; 15.7	-30.7; 40.7	-23.6; 25.6
Variance ($\%^2$)	574	489	492	350	708	401
F-test; p value		1.4		1.7		1.9

MPA, main pulmonary artery; PPA, peripheral pulmonary arteries.

Conclusions: In all groups, determination of pulmonary stroke volume by PV-MR of peripheral pulmonary arteries showed less bias than of main pulmonary artery, however the variances did not differ significantly. We therefore propose to confirm in selected patients pulmonary blood flow measurements of the main pulmonary artery by flow measurements of the peripheral pulmonary arteries.

P1066 | BEDSIDE

Three-dimensional speckle tracking echocardiographic evaluation of right atrial function in corrected tetralogy of Fallot

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Introduction: Tetralogy of Fallot (TOF) is one of the most frequently diagnosed congenital cardiac abnormalities. It is known that in TOF patients with right ventricular dilation, abnormal biatrial function and biventricular diastolic dysfunction are common. Three-dimensional speckle tracking echocardiography (3DSTE) seems to be a promising non-invasive imaging tool for accurate evaluation of global and regional volumes and function of heart chambers. The present study was designed to assess right atrial (RA) volumes and functional properties in patients with corrected TOF by 3DSTE.

Methods: The study comprised 18 consecutive TOF patients (48.2 $\pm$ 11.8 years, 6 males). Their results were compared to 18 age- and gender-matched healthy controls (50.3 $\pm$ 15.6 years, 10 males). Complete two-dimensional Doppler echocardiography and 3DSTE have been performed in all cases.

Results: Calculated RA maximum (74.1 $\pm$ 51.5 ml vs. 37.8 $\pm$ 10.1 ml, $p=0.006$) and RA minimum (58.2 $\pm$ 48.6 ml vs. 23.1 $\pm$ 7.9 ml, $p=0.005$) volumes and RA volume before atrial contraction (67.9 $\pm$ 51.3 ml vs. 30.2 $\pm$ 8.9 ml, $p=0.004$) were significantly increased in TOF patients. Total (25.7 $\pm$ 12.5% vs. 39.1 $\pm$ 8.8%, $p=0.0007$) and passive (10.0 $\pm$ 7.0% vs. 19.8 $\pm$ 9.0%, $p=0.001$) RA emptying fractions proved to be decreased in TOF. Global radial (-9.5 $\pm$ 5.6% vs. -15.0 $\pm$ 9.9%, $p=0.05$), longitudinal (16.9 $\pm$ 10.9% vs. 30.8 $\pm$ 11.2%, $p=0.0007$) and area (20.2 $\pm$ 18.8% vs. 40.9 $\pm$ 19.8%, $p=0.003$) strains were significantly reduced in TOF patients as compared to matched controls.

Conclusions: Significant alterations in RA volumes and functional properties could be demonstrated in patients with corrected TOF by 3DSTE.

REFINING ANTITHROMBOTIC THERAPY IN CORONARY ARTERY DISEASE

P1067 | BEDSIDE

Analysis of the bleeding and thromboembolic risk with concomitant use of antiplatelet treatment in the AMPLIFY trial

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Purpose: The AMPLIFY trial compared apixaban with conventional anticoagulation consisting of enoxaparin followed by warfarin in patients with acute venous thromboembolism (VTE). In this analysis, we examined the impact of concomitant antiplatelet therapy on the risk of major bleeding, the primary safety endpoint, and

recurrent VTE or VTE-related mortality, the primary efficacy endpoint, in patients enrolled in the trial.

Methods: Patients who reported concomitant use of antiplatelet treatment at any time during the clinical trial were identified, and rates for the adjudicated primary safety and efficacy endpoints in these patients were compared with those in patients not taking antiplatelet drugs.

Results: Of the 2676 patients treated with apixaban and 2689 treated with conventional therapy, 402 (15%) and 411 (15%), respectively, reported concomitant antiplatelet drug use; primarily with aspirin. In patients taking concomitant antiplatelet therapy, major bleeds occurred in 5 patients in the apixaban group and in 17 patients in the conventional treatment group (relative risk, 0.30; 95% confidence interval, 0.11 to 0.81). In patients randomized to apixaban, the rate of major bleeding in those taking concomitant antiplatelet drugs was 3-fold higher than in those not taking these agents (1.2% and 0.4%, respectively), whereas in those randomized to conventional treatment, the rate of major bleeding in patients taking concomitant antiplatelet drugs was 2.9-fold higher than in those not taking these agents (4.1% and 1.4%, respectively). Rates of VTE or VTE-related death were similar in those taking or not taking concomitant antiplatelet drugs in both the apixaban group (3.6% and 2.0%, respectively) and the warfarin group (3.0% and 2.6%, respectively).

Conclusions: Although concomitant administration of antiplatelet drugs produced a proportionally similar increase in the risk of major bleeding in patients randomized to apixaban or conventional treatment, there were fewer major bleeds with apixaban. Thus, the overall safety benefit of apixaban over conventional treatment was maintained in patients taking concomitant antiplatelet drugs. Concomitant administration of these drugs did not appear to influence the rates of VTE or VTE-related death.

P1068 | BEDSIDE

A meta-analysis of non-compliance or planned discontinuation of aspirin and the risk of mortality and non-fatal myocardial infarction in patients with established or at risk of coronary artery disease

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Purpose: Aspirin for prolonged duration is commonly prescribed to patients with a history of or at increased risk of occlusive vascular events (secondary prevention) due to its proven role in reducing mortality and non-fatal myocardial infarction (MI). Non-adherence due to poor compliance; adverse effects or discontinuation due to medical reasons may deteriorate outcomes among such patients.

Methods: PubMed and Embase were searched to identify the studies that report discontinuation or non-adherence of aspirin. Studies reporting the hazardous outcomes (all-cause mortality and non-fatal myocardial infarction) were included in the review. Two reviewers independently performed the literature search and data abstraction using a structured template. Effect size in terms of odds ratios were pooled by random effects method. Quality assessment was done as per Cochrane Collaboration's tool for ascertainment of bias and a funnel plot was constructed to determine the publication bias.

Results: A total of 856 titles were screened, after which 11 observational studies met the inclusion criteria (103,759 patients). 3 studies evaluated aspirin adherence in acute coronary syndrome (ACS), 3 on the discontinuation in peri-operative period (coronary artery bypass graft (CABG) and valvular replacement, 3 in aspirin adherence in drug eluting stents (DES) and 2 on aspirin non-compliance in coronary artery disease (CAD). Pooled overall estimates suggest that aspirin discontinuation/non-adherence is associated with significantly increased risk of death and MI (Hazard Ratio=1.64, 95% CI= 1.19-2.25). The risk was highest with DES (HR=3.33, CI=2.41-4.66) followed by ACS (HR=2.00, CI=1.47-2.65) and CABG (HR=1.73, CI=1.3-2.3). Graphical representation delineating temporal trends showed that the risk is present regardless of the duration of therapy.

Conclusion: Aspirin non-adherence is strongly linked with increased mortality and risk of MI among patients with a history of ACS, CAD, DES implantation and peri-operative patients. Efforts should be undertaken to improve the compliance of aspirin in patients at risk of cardiovascular events and controlled clinical trials should be conducted to identify evidence based strategies of improving outcomes in non-complaint patients. Our findings are limited by variable duration of follow up and significant heterogeneity among the included studies.

P1069 | BEDSIDE

Effects of systolic blood pressure levels on risk for strokes in coronary artery disease patients receiving anti-thrombotic combination therapy: JCAD study

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Purpose: There is increasing concern that aggressive anti-thrombotic therapy would increase the risk of stroke in patients with coronary artery disease (CAD),

particularly in those having elevated systolic blood pressure (SBP). Thus, we investigated the effects of anti-thrombotic therapy and SBP levels on the incidence of stroke in CAD patients registered in JCAD study.

Methods and results: In 12,936 angiographically documented CAD patients, the incidences of ischemic and hemorrhagic strokes were 4.2 and 1.1 per 1,000 patients-year, respectively. Ischemic stroke was increased with SBP elevation in patients not receiving anti-platelet therapy (APT) or warfarin (Fig. 1). APT, particularly dual APT (DAPT), reduced ischemic stroke in patients with SBP >140 mmHg, whereas the incidence of ischemic stroke was similar among patients receiving warfarin, irrespectively of APT and SBP levels. Hemorrhagic stroke was increased in patients receiving warfarin+DAPT with SBP >140 mmHg, whereas other treatment regimens had the incidences similar to no anti-thrombotic therapy.

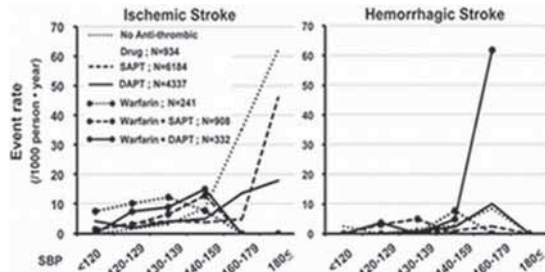


Figure 1. SBP and risks of strokes.

Conclusions: APT, particularly DAPT, was useful for prevention of ischemic stroke in CAD patients, especially hypertensive ones. Warfarin+DAPT increased hemorrhagic, but not ischemic, stroke with elevated SBP in CAD patients. Therefore, strict SBP control is recommended in CAD patients receiving warfarin+DAPT.

P1070 | BEDSIDE

Platelet reactivity and circulating platelet-derived microvesicles in patients with acute coronary syndrome following dual antiplatelet treatment

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Purpose: Dual antiplatelet therapy (DAT) with aspirin and P2Y₁₂ receptor inhibitors is the treatment of choice in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Platelets and platelet-derived microvesicles (PMVs) play a crucial role in the arterial thrombotic process. Measuring platelet function is methodologically demanding and measurement of PMVs could therefore offer an additional method to assess platelet function in previously frozen and stored samples from large biobanks. In the present study we investigated how platelet function measured with multiplate and PMVs measured by flow cytometry were affected by clopidogrel treatment in patients with ACS and PCI.

Methods: 200 patients with ACS who underwent PCI were included in the study and venous blood samples were obtained at discharge. All patients were loaded with 600 mg clopidogrel before PCI. Platelets were activated with ADP (6.4 mM) and analysed by whole blood impedance aggregometry (WBA; Multiplate™). Aggregation ≥ 47 U (WBA) defined low responders to DAT.

PMVs were measured by flow cytometry (Beckman Gallios) in samples prepared from stored platelet poor plasma (2000g, 20 min in room temperature). Twenty μ l of sample were incubated with lactadherin-FITC and CD42a-PE (platelet antigen GPIIb/IIIa) and CD62P-APC (P-selectin).

Results: Platelet function measured with WBA revealed that 35 of 180 patients (19%) were low responders and 148 (81%) patients were normal responders with clopidogrel treatment. Levels of PMVs were almost two fold higher in the low responder group compared to patient that responded well to treatment (for both CD42a and CD62P, positive PMVs, $p < 0.005$ and $p < 0.004$ respectively).

Conclusions: Patients with high on clopidogrel treatment platelet reactivity have elevated levels of circulating PMVs, indicating ongoing platelet activation despite DAT. PMVs can be used as biomarkers to assess platelet function in plasma samples from large prospective clinical studies.

P1071 | BEDSIDE

Prospective evaluation of ischemic and bleeding events in patients with PCI and oral anticoagulation and a matched control group. The LASER registry of the WG of Thrombosis of the ESC

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Background: The optimal antithrombotic regimen in patients with an indication for oral anticoagulation undergoing stent implantation still has to be defined. We sought to evaluate current practice in these patients and prospectively collect data in patients with OAC and a matched control group without the indication for OAC.

Methods and results: The LASER included prospectively 482 patients with OAC and stent implantation and a matched group (matched for age, gender and indication for PCI) without OAC. The indication for PCI was STEMI in 9.3%, NSTEMI in 31.1% and unstable angina or stable CAD in 59.6%. The predominant indication for oral anticoagulation was atrial fibrillation (79.8%). Triple therapy with vitamin K antagonists (VKA), aspirin and clopidogrel was used in 95.6%, VKA plus clopidogrel in 3.6% and VKA plus aspirin in 0.8%. Compared to the matched control group without the indication for OAC DES were used less often in the OAC group (64% vs. 31%). In-hospital ischemic and bleeding events were not different between the groups. After 3 months only 42% of patients were still treated with triple therapy while 41% were on OAC alone and 16% on dual antiplatelet therapy. Clinical follow-up at 3 and 12 months revealed higher mortality in the OAC group (table).

Clinical events in the patients with OAC and the matched control group with dual antiplatelet therapy (DAPT)

	OAC	DAPT	P-value
Death	10.1%	3.6%	< 0.001
Stroke	3.7%	2.7%	0.4
Myocardial infarction	6.0%	6.9%	0.8
Bleeding	16.6%	15.0%	0.8

Conclusion: Triple-therapy is the most widely used antithrombotic regimen in patients with OAC undergoing stent implantation. DES are less frequent used in patients with OAC. In patients with OAC mortality but not bleeding is significantly increased at 1-year follow-up.

P1072 | BEDSIDE

Direct and indirect comparison of ticagrelor and prasugrel pharmacodynamic effects: a systematic review and network meta-analysis

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Background: A large number of studies have linked on-treatment platelet reactivity to adverse clinical outcomes, particularly coronary ischemic events and stent thrombosis. Since novel P2Y₁₂ inhibitors (prasugrel and ticagrelor) have been predominantly tested against clopidogrel, data on pharmacodynamic comparisons between these two drugs are scarce. We therefore directly and indirectly compared ticagrelor with prasugrel in a network meta-analysis.

Methods: PubMed, Cochrane, and EMBASE were searched for studies assessing platelet reactivity in coronary artery disease patients treated with ticagrelor and/or prasugrel standard maintenance doses for more than 6 days. All randomized trials and observational studies using prasugrel and/or ticagrelor and providing biological data using VerifyNow P2Y₁₂ Reaction Units (PRU), Platelet Reactivity Index vasodilator-stimulated phosphoprotein phosphorylation (PRI-VASP) or maximal platelet aggregation (MPA) from light transmission aggregometry (LTA) were considered eligible. Summary effect estimates were generated with random-effects modeling to indirectly compare ticagrelor with prasugrel.

Results: Data were extracted from 28 studies (7 articles regarding direct comparison and 21 articles regarding indirect comparison) which included 4119 patients. Mean age was 62 $\pm$ 9 years, 75.47% were male. Compared with clopidogrel, both ticagrelor and prasugrel were associated with a decrease in platelet reactivity using VerifyNow (mean PRU difference -2.17 [-2.84 -1.49] and -1.72 [-2.10 -1.35] respectively), VASP (mean PRI difference -1.83 [-2.13, -1.53] and -1.24 [-1.61 -0.86] respectively) and LTA (mean MPA difference -1.41 [-1.94, -0.88] and -0.86 [-0.98, -0.73] respectively).

Direct comparison showed higher platelet inhibition was obtained with ticagrelor compared with prasugrel according to VerifyNow (mean PRU difference -0.96 [-1.30, -0.62], $p < 0.00001$), VASP (mean PRI difference -0.59 [-0.88, -0.29] $p < 0.00001$) and LTA (mean MPA difference -1.03 [-1.46, -0.61] $p < 0.00001$). Indirect comparison found that ticagrelor pharmacodynamic effect was significantly greater than prasugrel according to VASP ($p = 0.02$). A similar, but non-significant trend was found according to VerifyNow and LTA.

Conclusions: Our current meta-analysis suggests that after indirect and direct comparison between ticagrelor and prasugrel, ticagrelor achieved superior platelet inhibition compared with prasugrel.

P1073 | BEDSIDE

A tailored antiplatelet strategy in STEMI patients based on CYP2C19 genotyping is feasible in daily practice - POPular Genetics study

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Rationale: Treatment with dual antiplatelet therapy (aspirin plus clopidogrel, pra-

sugrel or ticagrelor) is essential to prevent atherothrombotic events in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI). Although ticagrelor and prasugrel reduce thrombotic events compared to clopidogrel, they increase bleeding risk and costs. Clopidogrel effectiveness varies between patients, partially according to differences in CYP2C19 drug metabolism, but in the subset of CYP2C19 *1/*1 (extensive metabolizer) patients clopidogrel seems equally effective than the newer drugs, with less costs and possibly less bleeding events. The POPular Genetics study tests the hypothesis that CYP2C19 genotype guided antiplatelet is non-inferior to the use of ticagrelor or prasugrel, for the combined endpoint of death, myocardial infarction, stroke, stent thrombosis and TIMI major bleeding. However, it is questioned if routine genotyping shortly after pPCI is feasible in daily practice.

Methods: All patients randomized to the genotyping arm of the ongoing open label, multicenter POPular Genetics study (NCT01761786) were included in this analysis. For every patient a buccal swab or blood sample was obtained during or shortly after pPCI to perform genotyping, using the SPARTAN RX point-of-care device, a validated in-house TaqMan StepOnePlus assay or shipment to a study site with genotyping equipment. P2Y12 inhibitors were prescribed according to local protocol and subsequently adjusted according to the genotyping results: clopidogrel in CYP2C19 *1/*1 patients and ticagrelor or prasugrel in patients carrying 1 or more *2 or *3 (loss-of-function) alleles.

Results: A total of 669 patients were included in 4 study sites until November 2013. Of those patients, 331 were randomized to the genotyping group, with CYP2C19 *1/*1 in 232 (70.1%), *1/*2 in 91 (27.5%), *1/*3 in 1 (0.3%) and *2/*2 in 7 (2.1%) patients, resp. The time between pPCI and the genotyping result was on average 20:44 hours (range 1:50–168:49 hours), with 77.4% of results available within 24 hours after pPCI and 92.4% within 48 hours. The P2Y12 inhibitor was switched according to genotyping result in 47.4% of patients, 28x to ticagrelor or prasugrel and 129x to clopidogrel.

Conclusion: The ongoing POPular Genetics study shows that it is feasible to tailor antiplatelet treatment in STEMI patients within 24–48 hours after pPCI according to CYP2C19 metabolizer status in the vast majority of patients. The efficacy, safety and cost-effectiveness of a tailored antiplatelet strategy are under evaluation.

PCI COMPLICATIONS AND PATIENT SUBSETS

P1074 | BEDSIDE

Long-term clinical outcomes after polytetrafluoroethylene-covered stent implantation for coronary perforation

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Purpose: Polytetrafluoroethylene-covered stents (PCS) have improved the in-hospital clinical outcomes of patients with coronary perforation. However, there are a few reports regarding their long-term outcomes.

Methods: We analyzed data that was retrospectively collected from 19270 patients who underwent percutaneous coronary intervention in our hospital between January 2004 and December 2013. The study endpoints were major adverse cardiac events (MACEs), defined as cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). Furthermore, individual parameters were evaluated. Additionally, Cox regression analysis was performed to determine the independent predictors of MACEs including all-cause death.

Results: Among the 258 patients with coronary perforation, 42 (16.3%) were treated with PCS. The median follow-up period was 1090 days; interquartile range, 394–1882 days. The MACE rates were 22%, 25% and 36% at 1, 2 and 3 years, respectively. The TLR rates including in-stent occlusion detected by coronary angiography (CAG) were 17.6%, 17.6% and 22% at 1, 2 and 3 years, respectively.

On the Cox regression model, the independent predictors of MACE were dyslipidemia (HR 0.35, [95% CI, 0.13–0.95]; $P=0.04$) and chronic total occlusion (HR 0.21, [95% CI, 0.06–0.67]; $P=0.01$).

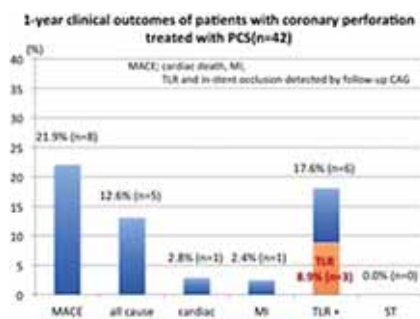


Figure 1. 1 year clinical outcomes

Conclusions: However the 1-year MACE was relatively high, TLR and other long-term outcomes were feasible after 1 year. Furthermore, PCS implantation for coronary perforation in CTO lesions did not worsen MACEs, which indicates

that coronary perforation during PCI for CTO lesion is not a serious consequence although PCI for CTO has higher risk of coronary perforation.

P1075 | BEDSIDE

Temporal trends in treatment and outcome in octogenarians and nonagenarians with acute coronary syndrome

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Purpose: Although many elderly patients are commonly encountered in daily clinical practice, they are usually excluded from the clinical trials and when these patients are hospitalized for acute coronary syndromes (ACS) they are less likely to receive guideline-recommended therapies and have worse outcomes. This study aimed to evaluate temporal trends in the presentation, treatment and outcomes of elderly ACS patients.

Methods: This analysis from the AMIS Plus registry investigated all ACS patients above 70 years enrolled from 2001 to 2012. Characteristics of presentation, treatment and outcomes were analyzed according to three age groups (reference group 70–79 years; octogenarians 80–89 years; nonagenarians ≥ 90 years) and three 4-year periods (period 1: 2001–2004, period 2: 2005–2008 and period 3: 2009–2012).

Results: From a total of 13,652 patients, 7974 were in the reference group, 5009 were octogenarians, and 679 were nonagenarians. STEMI was equally prevalent in all 3 groups (50.4%, 50.1% and 50.8%, respectively). Delay from symptom onset to admission was similar across all age groups. Resuscitation use prior to admission decreased with increasing age (reference group 3%, octogenarians 2% and nonagenarians 0.5%; $p<0.001$). Nonagenarians more frequently presented with worse cardiac function (Killip class ≥ 2 was 8.3% in the reference group, 11.8% in octogenarians and 16.6% in nonagenarians; $p<0.001$), more comorbidities, in particular more renal diseases (reference group 9.1%, octogenarians 18.7%, nonagenarians 27.8%; $p<0.001$) and heart failure (reference group 4.9%, octogenarians 9.0%, nonagenarians 14.0%; $p<0.001$). During the 3 periods use of PCI significantly increased in all age groups: in the reference group from 56.9% to 79.0% to 84.0%, in octogenarians from 24.1% to 44.5% to 57.2%, in nonagenarians from 6.2% to 9.1% to 18.1%; all $p<0.001$). In hospital mortality decreased during the 3 periods: in the reference group from 8.1% to 7.0% to 6.9% ($p=0.23$), in octogenarians from 16.3% to 12.9% to 12.6% ($p=0.007$) and in nonagenarians from 26.5% to 24.7% to 23.0% ($p=0.74$). In all age groups, Killip class ≥ 2 was the most important independent predictor but in nonagenarians it was the only independent predictor of in-hospital mortality.

Conclusion: In very old ACS patients, PCI use showed a marked increased over the past 12 years and in-hospital mortality slightly decreased at the same time. An impaired cardiac function at admission was associated with a worse outcome in all groups, particularly in nonagenarians.

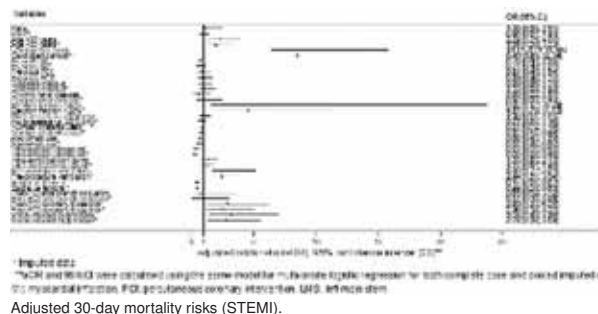
P1076 | BEDSIDE

Comparative outcomes after unprotected left main stem PCI: a national linked cohort study of 5,065 acute and elective cases from the british cardiovascular intervention society (BCIS) database

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Purpose: To report outcomes from PCI to an unprotected left main stem (ULMS) stenosis according to presenting syndrome, including ST-elevation myocardial infarction (STEMI), non ST-elevation acute coronary syndrome (NSTEMI) and chronic stable angina (CSA).

Methods: Prospective population-based linked cohort study using data from the BCIS database, 1st Jan 2005 through 31st Dec 2010.



Results: There were 784 (15.5%) STEMI, 2,381 (47.0%) NSTEMI and 1,900 (37.5%) CSA. Overall, mean (SD) age was 70.2 (12.3) years and there were 3,483 (69.5%) males. 323 (41.2%) STEMI and 222 (9.3%) NSTEMI had cardiogenic shock. 148 (44.3%) of STEMI, 318 (19.5%) NSTEMI, 118 (9.1%) CSA had a left ventricular ejection fraction <30%. Crude 30-day and 1-year mortality rates were: STEMI 28.3% & 37.6%, NSTEMI 8.9% & 19.5%, CSA 1.4% & 7.0%. Unadjusted in-hospital major adverse cardiovascular & cerebrovascular event rates were: STEMI 26.6%, NSTEMI 6.6%, CSA 3.3%. Risk of 30-day mortality was greater for STEMI and NSTEMI than CSA (adjusted odds ratio (aOR), 95% confidence interval (CI) STEMI: 29.45, 19.37 to 44.80, NSTEMI: 6.45, 4.27 to 9.76). Over 40% of patients presenting with STEMI had cardiogenic shock, in whom mortality was higher than in STEMI without shock (30-days: 52.0% vs. 11.7%, 1-year: 61.1% vs. 20.9%). Radial, compared with the femoral approach, was associated with lower of 30-day mortality (STEMI: aOR, 95% CI: 0.37, 0.21 to 0.62; NSTEMI: 0.66, 0.45 to 0.97).

Conclusions: Over half of the UPLMS PCI was non-elective and these patients had worse outcomes than elective cases. Cardiogenic shock was present in 40% of STEMI, of whom 52% died at 30-days. The radial approach was associated with lower early mortality in acute cases compared with femoral.

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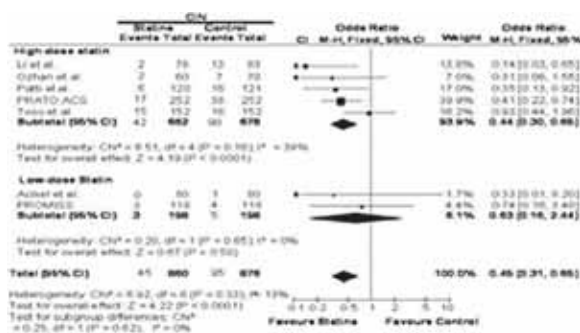
Do statins prevent contrast induced nephropathy in patients undergoing coronary angiography or percutaneous intervention? A meta-analysis of 7 randomized trials

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Purpose: Contrast Induced Nephropathy (CIN) is a complication of procedures that foresee the use of contrast media, mediated by endothelial dysfunction, cellular toxicity from the contrast agent and tubular apoptosis. Statins have been shown to possess pleiotropic effects (anti-oxidant, anti-inflammatory and antithrombotic properties). Aim of this meta-analysis is to evaluate the efficacy of short-term statins for the prevention of CIN in patients undergoing coronary angiography/PCI.

Methods: We performed formal searches of PubMed, EMBASE, Cochrane central register of controlled trials and major international scientific session abstracts from 1990 to 2013 of trials which compares short-term statins versus Placebo for the prevention of CIN in patients undergoing coronary angiography/PCI. Data regarding study design, statin dose, inclusion and exclusion criteria, number of patients, and clinical outcome was extracted by 2 investigators. Disagreements were resolved by consensus.

Results: A total of 7 trials were included. CIN occurred in 5.2% (45/860) of patients treated with statins versus 10% (95/876) of the placebo group (OR [95%CI]=0.45 [0.31-0.65], $p<0.0001$; $\text{phet}=0.33$). The benefits were mostly observed with high-dose short-term statin therapy (OR[95%CI]=0.44 [0.30-0.65], $p<0.0001$; $\text{phet}=0.16$), but not with low-dose statin therapy, (OR[95%CI]=0.63 [0.16-2.44], $p=0.50$; $\text{phet}=0.65$). By meta-regression analysis, no significant relationship was observed between benefits from statin therapy and patient's risk profile, LDL cholesterol, contrast volume or diabetes rate.



Conclusions: Among patients undergoing coronary angiography/PCI the use of short-term statins reduces the incidence of CIN, and therefore are highly recommended even in patients with LDL cholesterol below the recommended threshold.

P1078 | BEDSIDE

Differences in coronary artery disease (CAD) among patients infected with human immune deficiency virus (HIV) undergoing percutaneous coronary intervention (PCI): results from a single-center registry

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Purpose: Premature CAD is a known complication in HIV patients. However, the angiographic features or CAD burden in HIV patients has not been well described.

Methods: We compared HIV positive (n=97) patients who underwent PCI over a 9-year period to HIV negative (n=92) patients matched for age, gender, dia-

betes and year of PCI. Quantitative coronary angiography (QCA) analysis was performed blinded to HIV status. We also determined the 1-year rate of major adverse cardiac events (MACE) including death, myocardial infarction (MI), and urgent revascularization.

Results: The mean age was 57 years. HIV patients had lower body mass index, worse lipid profile, and presented more frequently with MI (28% vs. 11%, $p=0.003$). While CAD burden was similar in the two groups (Syntax score, 13 ± 8 vs. 11.7 ± 7 , $p=0.15$), HIV patients had more proximal disease with worse calcification (Table). Post-PCI, the residual diameter stenosis was worse among HIV patients (19 ± 8.3 vs. 16.6 ± 8.3 , $p=0.02$). 1-year MACE was high in both groups (16.5% vs. 13%, $p=0.50$).

Angiographic characteristics according to HIV status (lesion-level analysis)

	HIV (n=145)	Non HIV (n=139)	p-value
Lesion length (mm)	16.9±10.9	15.1±8	0.12
Reference vessel diameter (mm)	2.65±0.70	2.34±0.63	0.0001
Minimal lumen diameter (mm)	0.86±0.53	0.68±0.44	0.0003
Diameter Stenosis (%)	67±15.3	71.2±16.5	0.027
Lesion location:			
LAD (vs LCx, RCA)	59 (40%)	58 (43%)	0.45*
Proximal (vs mid, distal)	57 (40%)	36 (27.1%)	0.01*
Heavy calcification (vs no/mild, moderate)	25 (18.1%)	11 (8.1%)	0.009*
TIMI flow grade 3 (vs 0, 1, 2)	108 (76.6%)	88 (63.3%)	0.01*
True Bifurcation (x,x,1)	32 (22%)	26 (18.7%)	0.45

*p values for >2 group comparisons (comparison groups listed). Abbreviations, LAD: Left anterior descending artery; LCx: Left circumflex artery; RCA: Right coronary artery.

Conclusion: In this first HIV QCA study, HIV patients were more likely to present with acute MI, and displayed multiple angiographic differences in lesion characteristics compared to matched controls. These findings suggest that atherosclerosis and its progression are altered in the setting of HIV.

P1079 | BEDSIDE

Glycemic control for kidney injury prevention after PCI: preliminary results from EUGlycemia for Renal Impairment Prevention after contrast-medium Exposure (EURIPE) randomized study

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Purpose: Contrast Induced-Acute Kidney Injury (CI-AKI) is one of the most recurring adverse events after percutaneous coronary intervention (PCI), leading to high morbidity and mortality incidence. Patients affected by diabetes mellitus and/or chronic renal impairment are at higher risk of this complication. Up-to-date, the gold standard for CI-AKI prevention is hydration with isotonic saline solution (ISS) before and after exposure of contrast medium. The role of several protective agents, such as N-Acetyl-Cysteine (NAC) has been largely discussed, with conflicting results. Moreover, poor glycemic control before PCI has been associated with increased incidence of CI-AKI. We sought to evaluate the efficacy of glucose-insulin-potassium (GIK) and NAC, in addition to ISS, for the prevention of CI-AKI in patients undergoing PCI.

Methods: 102 diabetic and/or with chronic renal failure patients has been randomized to 3 different protocols: ISS-GIK-NAC (group 1), ISS-GIK (group 2), ISS (group 3). ISS infusion started 12 hours before PCI and maintained up to 24 hours after the procedure. GIK infusion was administered from 12 hours before up to 12 hours after the procedure. NAC was given as oral doses of 1200 mg 12 hours and 1 hour before PCI. Blood samples were collected before and 24 hours after PCI to evaluate serum creatinine (sCr). CI-AKI was defined, according to the RIFLE criteria, as an increase of sCr $\geq 25\%$ from baseline within 48 hours after contrast administration.

Results: We observed a significant reduction of mean sCr after PCI in the overall population (1.02 mg/dl versus 0.99 mg/dl, $p=0.03$). In detail, this reduction was observed in group 1 and 2, whereas, a slight increase was found in group 3 (-4% in group 1 and 2 and +3% in group 3) (group 1 vs group 3, $p=0.01$; group 2 vs group 3, $p=0.01$; p for trend = 0.01). The overall incidence of CI-AKI was 4%, with all the 4 cases in the group 3. The percentage of patients who developed any post-PCI sCr increase from baseline was higher in group 3 compared to other two groups (54% vs 42% in group 2 vs 29% in group 1; p for trend = 0.04).

Conclusions: The results of this study showed an absolute and percentage significant reduction of sCr after PCI in patients with GIK infusion and NAC administration, in addition to ISS. Our hypothesis is that maintaining a peri-procedural euglycemic state, jointly with the protective action of insulin on kidney metabolism, may play a favorable role in preventing contrast-induced renal impairment in diabetic and with chronic renal failure patients undergoing PCI.

P1080 | BEDSIDE

Prevention of contrast-induced nephropathy with single bolus erythropoietin in diabetic patients with chronic kidney disease undergoing coronary interventions - a randomized controlled trial

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Purpose: Contrast-induced nephropathy (CIN) is associated with poor outcomes, thus prevention of CIN may be of clinical value. Erythropoietin has been shown

to be tissue-protective in experimental models and in few clinical studies of acute kidney injury. We therefore evaluated the effectiveness of a single bolus of erythropoietin for prevention of CIN after coronary angiography (CA) and/or percutaneous coronary intervention (PCI) in consecutive diabetic patients with chronic kidney disease who are at high-risk of developing CIN.

Methods: A prospective, randomized, controlled trial was carried out in 120 diabetic patients with eGFR <60 ml/min/1.73m² who underwent non-urgent CA with or without PCI. Patients received a subcutaneous single dose of 50,000U of erythropoietin or standard preventive protocol (normal saline + N-Acetyl-Cysteine) before CA. CIN was defined as an increase in serum creatinine level, compared to basal value, of at least 0.5 mg/dl during the first 2 days after exposure to contrast media. Primary outcome was the incidence of CIN. Secondary outcomes were the sensitivity and positive predictive value (PPV) of cystatin C CC and Neutrophil gelatinase-associated lipocalin (NGAL) for diagnosis of CIN.

Results: The observed incidence of CIN in our study (6%) was significantly lower than the expected for such high risk population. The administration of EPO prior to CA resulted in a trend (yet non-statistically significant) for reduction in CIN (8.3% vs. 4%, $p=0.31$). The results were independent of basal kidney function, contrast media type or volume, gender and type of procedure. Cystatin C and NGAL demonstrated a low sensitivity (16.6%) and low PPV (6.7 and 33.3% respectively) for detecting CIN.

Conclusion: The administration of a single dose of erythropoietin prior to CA or PCI resulted in trend toward reduction in the incidence of CIN; however, the low incidence of CIN among non-urgent patients in our study probably masked the potential reno-protective effect of erythropoietin.

ADDRESSING THE CHALLENGES IN CARDIAC REHABILITATION

P1081 | BEDSIDE

Impact of a hospital-based multidimensional educational program early after acute coronary syndromes: A multicentric Swiss prospective trial

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Introduction: Medical societies recommend the development of national programmes to improve secondary prevention in patients with acute coronary syndromes (ACS). We tested the impact of a hospital-based intensive multidimensional educational program (ELIPS) used as add-on to the recommended process of care (standard care) for patients hospitalized with ACS.

Methods: The ELIPS (multi-dimensional prevention Program after acute coronary Syndrome) programme was implemented in 4 main academic hospitals in Switzerland. The ELIPS intervention comprises a number of actions added to standard care and coordinated by designated leaders at each hospital: (1) a patient-centered educational program making use of interactive tools (film, discharge card, informational cards, website, wall chart for motivational interviewing [MI] sessions); (2) training courses for care-providers on MI and cardiovascular health education. In a before-after prospective design, we compared the standard care group (2009-2010) to the ELIPS group (2011-2012) for 1-year adherence to evidence-based therapies (aspirin, beta-blockers, statins, angiotensin-converting enzyme [ACE] inhibitors or angiotensin-receptor blockers [ARB]), attendance to cardiac rehabilitation (CR) and achievement of recommended targets of cardiovascular risk factors (CVRF), adjusting for differences in baseline characteristics.

Results: Overall 2732 patients were included, 1335 in the standard care group, and 1397 in the ELIPS group. Mean age of patients (61 vs 64 years), no differences were found in evidence-based therapy at discharge. A greater proportion of ELIPS patients attended to a CR program compared (73.3% vs 66.3%, $p=0.02$) to the standard group. At 1-year, the use of beta-blockers was higher in the ELIPS group (80.0% vs 75.4%, $p=0.01$), with similar use of aspirin (97.5% vs 96.8%), statins (92.0% vs 94.2%) and ACE inhibitors/ARB (81.4% vs. 80.6%) in the two groups. 1-year control of LDL-C <100 mg/dl was significantly better in the ELIPS group (74.1% vs 69.4%, $p=0.01$). No significant differences were observed for other CVRF targets.

Conclusions: The implementation of a hospital-based intensive multidimensional educational program early after an ACS (phase I of CR) improved attendance to CR (phase II of CR) and had the potential to improve long-term adherence to secondary preventive targets. Early in-hospital educational initiatives should be systematically implemented and covered by hospital payment system.

P1082 | BEDSIDE

Impact of a cardiac rehabilitation program on systolic and diastolic function after acute myocardial infarction: a randomized trial

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Purpose: After acute myocardial infarction (AMI), cardiac rehabilitation (CR) re-

duces major adverse cardiac events and improves quality of life. However, its effects on cardiac systolic and diastolic function are controversial. The aim of this study was to evaluate the short-term effect of a CR program on cardiac structure and function, in patients after AMI.

Methods: One month after AMI, 225 patients were randomized to be included in a CR program ($n=124$; 54.7 ± 11.0 years) versus a control group with standard care ($n=101$; 55.7 ± 10.8 years). Patients in the CR group performed a 8-week training program, under clinic supervision, with 60 minutes sessions (including 30-minutes with an intensity of 70-85% of maximum heart rate), held three times a week. At the start and at the end of the program, all patients were submitted to detailed transthoracic echocardiography (including mitral flow analysis, pulmonary vein flow analysis, tissue-Doppler velocities and 2D and 3D ejection fraction) and cardiopulmonary exercise test (determination of peak VO₂, VO₂ at anaerobic threshold (AT) and duration of exercise).

Results: There was a significant improvement in functional capacity in the CR group, as determined by peak VO₂ and VO₂ at AT (1.46 ± 3.93 mL/kg/min increase). In the control group, there was no significant change in peak VO₂, VO₂ at AT or duration of the exercise ($p>0.05$).

There was no significant variation in diastolic function parameters in CR group: E'septal variation: -0.05 ± 1.20 cm/s; E' lateral: 0.16 ± 1.91 cm/s; mean E/E': -0.29 ± 2.72 cm/s, $p>0.05$; E/A ratio: -0.10 ± 0.48 ; deceleration time: -5.00 ms (IQR 61.00ms), $p>0.05$.

Left ventricular systolic function parameters did not change significantly after the CR program (2D ejection fraction variation $-1.21 \pm 7.82\%$, $p>0.05$; S' septal -1.00 ± 1.72 cm/s, $p>0.05$; S' lateral -0.03 ± 1.25 cm/s, $p>0.05$).

Conclusion: In this group of patients after AMI, an 8-week CR program led to a significant improvement of exercise capacity. However, the CR program failed to improve cardiac systolic or diastolic function, even when those were assessed by sensitive cardiac function evaluation parameters.

P1083 | BEDSIDE

Exercise based cardiac rehabilitation in heart failure patients: an updated meta-analysis demonstrating benefits in hospital admission and exercise capacity

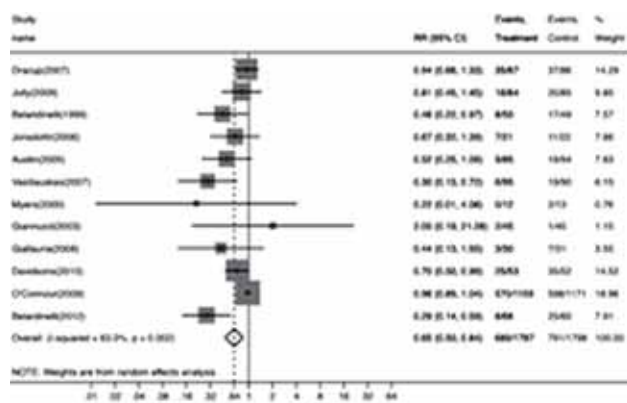
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Background: Guidelines recommend exercise-based cardiac rehabilitation (EBCR) for patients with heart failure (HF). However, research to date has not investigated the longer-term outcomes including mortality and hospitalisation in light of the contemporary management of HF.

Methods: Systematic review including a meta-analysis of EBCR on all-cause mortality, hospital admission, and standardized exercise capacity using four separate exercise tests in patients with heart failure (HF) over a minimum follow-up of 6-months from January 1999 until January 2013. Electronic searches were performed in the databases: Medline, CENTRAL, EMBASE, CINAHL, and PsycINFO constrained to randomized controlled trials (RCTs).

Results: A total of 46 separate RCTs qualified for the meta-analysis, which employed the methods of Mantel and Haenszel or DerSimonian (binary data) or Cohen (continuous data). The relative risk (RR) ratio for hospital admission was significantly reduced (RR ratio, 0.65; 95% confidence interval [CI], 0.50 to 0.84; $P \leq 0.001$), but mortality was not (RR ratio, 0.88; 95% CI, 0.77 to 1.02; $P=0.13$).

The standardised exercise capacity after EBCR showed a standardised mean difference (SMD) in favour of the exercise group as compared with the controls (SMD, 0.98, 95% CI, 0.59 to 1.37; $P<0.001$). Women and elderly people were less frequently enrolled in the RCTs independent of the outcomes. Heterogeneity was moderate to high in the analysis of hospital admission and the standardised exercise capacity.



Outcome of hospital admission

Conclusions: EBCR in patients with HF is associated with significant improve-

ments in exercise capacity and hospital admission over a minimum of 6 months follow-up, but not in all-cause mortality.

P1084 | BEDSIDE

Compliance with cardiac rehabilitation guideline in the Netherlands

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Purpose: In 2010 the Health Inspectorate conducted a survey on all institutions that offer cardiac rehabilitation (CR) programs in the Netherlands. The number of patients enrolled in a program was too low. Also patients were insufficiently supported in lifestyle changes. The investigation was repeated in 2012. The aim of this investigation was to determine if all institutions that offer a CR program comply with the guideline.

Methods: Follow-up was performed between December 2012 and June 2013. All 90 hospitals and 9 rehabilitation centres submitted questionnaires about their program; 14 hospitals without cardiac rehabilitation were questioned about their referral rates. All institutions assessed their CR program using a previous constructed framework of 19 indicators based on the Dutch guideline Cardiac Rehabilitation (2004, updated in 2010). The criteria used were based on the guideline and defined in cooperation with the Netherlands Society of Cardiology.

Results: The response rate was 100%. The 76 hospitals increased their intake of patients with a myocardial infarction from 57% in 2009 to 64% in 2012. The referral rates of the 14 hospitals without a CR program rose from 66% in 2010 to 70% in 2012. Registration of individual lifestyle information and data collection at aggregated level improved evidently compared to 2010. However, patient participation in smoking cessation and weight loss programs had not sufficiently increased. Less than half of the institutions had an adequate score. Also the number of patients offered to partake in the lifestyle information program was low, not all institutions offered this program.

Performance on 19 indicators of CR

	Hospitals with CR	CR centre	Hospitals without CR	Order inspectorate
19 indicators	14	1	—	None
18–15 indicators	43	6	—	Improve inadequate indicators
<14 indicators	9	2	—	Improve inadequate indicators and report improvement
Intake/referral rates 2012 (%)	64	—	70	—

N=99 (76 hospitals with CR program, 9 CR centres, 14 hospitals without CR program).

Conclusion: The current referral rate to CR programs has improved but is still too low.

The compliance with the guideline had improved in almost all institutions and was sufficient in 15 institutions.

The support to a healthy lifestyle was inadequate in more than 50% of the institutions.

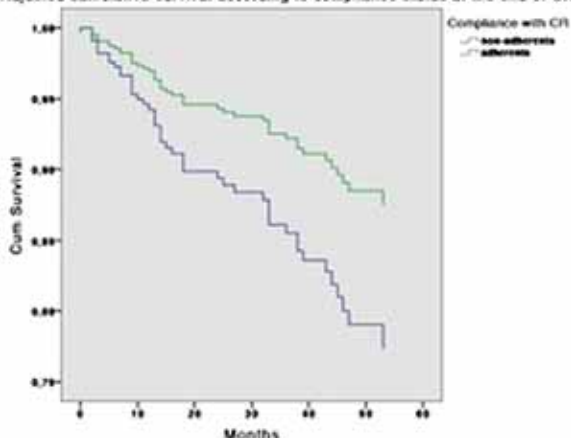
P1085 | BEDSIDE

Cardiac rehabilitation adherence as a determinant of cardiovascular disease burden after ACS

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Background: Cardiac rehabilitation (CR) after acute coronary syndromes (ACS) exerts positive effects over functional capacity, CV risk factors and cardiovascular morbidity and mortality. We evaluated prognostic impact of CR non-compliance over CV morbidity and mortality.

Adjusted cumulative survival according to compliance status at the end of CR



Methods: 505 patients referred to CR after ACS were enrolled. Sociodemographic, clinical and functional data were collected. Non-adherence to CR was defined as completing less than 30% of exercise sessions.

Data on mortality and morbidity was collected from hospital records and primary care and other institution's electronic records by nationwide health data platform. Composite outcome (all cause mortality, new hospital admission for ACS, stroke and CHF and/or revascularization procedures) was used for survival analysis by cox-proportional hazards model.

Results: 56 (11.1%) NA, attending 6.4±4.3 exercise sessions. NA was more common in women (NA: 21.4% vs A: 12.0%, p=0.04), those living alone (32.1% vs 12.7%, p<0.01) and those unemployed (27.3% vs 16.3%, p<0.01). Except for previous ACS history (34.5% vs 14.5%, p<0.01) and functional capacity [8.5±2.5 MET vs 9.4±2.1 MET, p=0.01], there were no between-group differences regarding cardiovascular risk factors, ACS characteristics, left-ventricular function, coronary vessel involvement or quality of life. Mean follow-up time was 29.6±18.1 months with 46 events. CR adherence status predicted an adverse outcome on univariate analysis (HR 2.4, 95%CI 1.2-4.8) and after adjustment for relevant covariates (HR 1.9, 95%CI 1.1-4.4).

Conclusions: CR non-adherence associates with higher risk of cardiovascular morbidity and mortality after ACS. Strategies to promote patient's referral and adherence to CR programs should be implemented to minimize burden of coronary heart disease.

P1086 | BEDSIDE

Learning and coping strategies improves attendance in cardiac rehabilitation

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Background: Cardiac rehabilitation (CR) in ischemic heart disease (IHD) and heart failure (HF) has a potential to reduce mortality and morbidity and improve quality of life. However, far from all patients complete CR or succeed with last-lifestyle improvements. Patient education programs which can enhance attendance in CR are needed. A new patient education; learning and coping strategies (LC), was developed.

Objective: Aim of this study was to measure the effect of LC strategies on attendance in CR.

Methods: The study was designed as an open 1:1 randomised controlled trial with LC strategies applied to standard CR as one of the arms versus standard CR as the control arm. Key points in the LC strategies were: Situated and reflexive education, individual clarifying interviews before and after the program and participation of expert patients in the sessions. The CR program in both arms consisted of eight weeks with training three times a week and education once a week. All sessions lasted one and a half hour. Both arms were initiated and finished with an exercise test on a bicycle and follow up exercise test was performed three month after.

Results: In total 827 patients over 18 years admitted with IHD or HF were included. Two patients were excluded. Out of the 825 patients 413 were randomised to the LC group (mean age 63 years, 76% male, 79% with IHD, 21% with HF) and 412 to the control group (mean age 63 years, 76% male, 78% with IHD, 22% with HF). No significant baseline differences between the groups were found. In total 816 (99%) patients attended the initial exercise test. Out of these 816 patients 652 (80%) attended the CR program, defined as completion of the second exercise test at the end of the program. In the LC group 340 (83.3%) attended the CR program compared to 312 (76.5%) in the control group (p=0.018). At three month follow up 313 (76.7%) patients in the LC group completed the exercise test compared to 287 (70.3%) in the control group (p=0.039). Thus attendance was significantly higher (9%) for patients in the LC group. In total all patients attended on average in 19.1 out of the 24 planned training sessions. In the LC group 80% attended at least 18 sessions which was significantly higher than the patients in the control group where 73% attended 18 sessions or more (p=0.023). On average all patients attended 6.3 out of the 8 planned education sessions. In the LC group the patients attended on average 6.6 education sessions which was significantly more than 6.0 in the control group (p=0.04).

Conclusion: LC strategies applied in CR improves attendance.

P1087 | BEDSIDE

Non adherence to cardiovascular preventive guidelines is associated with all-cause and cardiovascular mortality

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Background: Cardiovascular (CV) disease remains the first cause of pre-ma-

ture death in European countries. Control of CV risk factors is thus mandatory. The purpose of this study was to know the real impact of the non-observance of lifestyle and dietary rules on mortality in primary prevention.

Methods: Our study population consisted in patients, both women and men, who had consulted from 1995 to 2011 to the Department of Preventive Cardiology (DPC) of a Southwestern University Hospital. We excluded patients whose age was less than 30 year-old and all patients with established history of ischemic heart disease (International Classification of Disease, 9th revision, codes 410.0-414.9). Questionnaires collecting data on socio-economic level, knowledge of lifestyle and dietary rules, previous medical history, drugs intake, observance and cardiovascular risk factors were recorded by a trained medical staff. Vital status (causes and date of death) was obtained for each participant through the national database. Multivariable predictive relationships with total mortality were evaluated with the use of a Cox proportional hazards model.

Results: 4885 patients were included. 56% were men and the mean age was 53. After a mean follow up of 8.6 years, 129 deaths including 31 CV deaths were recorded. After adjustment for age and gender, ignorance of lifestyle and dietary preventive CV rules was significantly associated with all-cause mortality (Hazard Ratio (HR)=2.16, $p<0.001$, 95% CI [1.51-3.09]) and with CV mortality (HR=2.28, $p=0.020$, 95% CI [1.14-4.61]). After adjustment for age and gender, non compliance to anti-hypertensive diet (HR=1.62, $p=0.01$, 95% CI [1.12-2.33]), anti-diabetic diet (HR=1.78, $p=0.034$, 95% CI [1.04-3.04]) were significantly associated with all-cause mortality. Non compliance to lipid lowering diet was not significantly associated with all-cause mortality (HR=1.40, $p=0.25$, 95% CI [0.79-2.48]). In multivariate analysis, after adjusting for age, gender, smoking status, diabetes, hypertension and socio-economic status, ignorance of lifestyle and dietary preventive CV rules remained significantly associated with all-cause mortality (HR=1.66, $p=0.015$, 95% CI [1.10-2.50]). Non compliance to anti-diabetic diet did not remain associated with all-cause mortality (HR=1.75, $p=0.065$, 95% CI [0.97-3.17]) in the full adjusted model.

Conclusions: Ignorance of lifestyle and dietary preventive CV rules was associated with all-cause mortality in primary prevention stressing the potential impact of lifestyle on long-term mortality.

CARDIAC AND ARTERIAL REMODELLING IN HYPERTENSION

P1088 | BEDSIDE

Free androgen index as a predictor of central hemodynamics and arterial stiffness in postmenopausal women

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Background: Androgenicity may be involved in arterial stiffening in menopause. We hypothesized that free androgen index (FAI), a more accurate marker of androgenicity compared with total circulating testosterone, is a predictor of changes in central hemodynamics and arterial stiffness in postmenopausal women.

Methods: We evaluated FAI as a predictor of changes in endothelial function, central hemodynamics, localized and systemic arterial stiffness in 158 postmenopausal women followed for 1 year. HeartScore was used as a measure of estimated total CV risk. We also aimed to compare FAI versus testosterone alone, for the above end-points.

Results: FAI significantly correlated with pulse-wave velocity (PWV), flow-mediated dilatation (FMD), stiffness index and aortic and peripheral pulse pressure at baseline ($p<0.05$ for all). Also, FAI was significantly associated with changes at follow-up in PWV, aortic systolic and pulse pressure, carotid stiffness index (SI), and HeartScore. After adjustment for age, changes in systolic blood pressure, HOMA and BMI which significantly changed over follow-up, FAI remained an independent predictor of changes in PWV ($p=0.023$), aortic pulse pressure ($p=0.009$) and SI ($p=0.044$). After adjustment for circulating testosterone levels, most of the observed univariate associations with FAI (PWV and central hemodynamic parameters) remained significant while testosterone lost its significance.

Conclusions: In healthy postmenopausal women, FAI is an independent predictor of short-term changes in central hemodynamics and arterial stiffening. When compared with circulating testosterone levels, FAI is more profoundly associated with these parameters.

P1089 | BEDSIDE

Increased circulating mesenchymal stem cells in patients with essential hypertension and left ventricular hypertrophy

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Purpose: Stem and progenitor cells are implicated in ventricular remodelling and have great clinical significance in many cardiovascular diseases. However, there

are limited data regarding the involvement of mesenchymal stem cells (MSCs) in the pathophysiology of arterial hypertension. The aim of this study was to investigate the circulation of MSCs in patients with essential hypertension.

Methods: We included 24 patients with untreated essential hypertension and 19 healthy individuals. All subjects underwent a complete echocardiographic study. In addition, peripheral blood samples from all participants were immunostained with antibodies against the cell surface markers CD34, CD45 and CD90. Using flow cytometry, we measured MSCs as a population of CD45-/CD34-/CD90+ cells and also as a population of CD45-/CD34-/CD105+ cells. The resulting counts were translated into the % percentage of MSCs in the total cells of peripheral blood.

Results: Hypertensive patients were shown to have increased circulating CD45-/CD34-/CD90+ compared to controls ($0.0069\pm0.012\%$ compared to $0.0085\pm0.0015\%$, respectively, $p=0.039$). No statistically significant difference in circulating CD45-/CD34-/CD105+ cells was found between hypertensives' and normotensives' peripheral blood ($0.018\pm0.013\%$ compared to $0.015\pm0.014\%$, respectively, $p=0.53$). Notably, CD45-/CD34-/CD90+ circulating cells were positively correlated with left ventricular mass index (LVMI) ($r=0.516$, $p<0.001$).

Conclusions: Patients with essential hypertension have increased circulating MSCs compared to normotensives, and the number of MSCs is correlated with LVMI. Our findings contribute to the understanding of the pathophysiology of hypertension and might suggest a future therapeutic target.

P1090 | BEDSIDE

The association of left ventricular hypertrophy with intraventricular dyssynchrony at diastolic phase during exercise in hypertensive patients

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Background: We previously demonstrated that left ventricular hypertrophy (LVH) is associated with intraventricular dyssynchrony at rest and systolic phase during exercise in hypertensive patients. However, dyspnea on exertion is much more correlated with diastolic phase. Therefore, in this study, we investigated whether LVH is also associated with diastolic dyssynchrony during exercise or not.

Methods: A total of 90 patients with hypertension who having exertional dyspnea and LVH and 30 control individuals were enrolled. Exercise stress echocardiography was performed using a symptom limited, multistage supine bicycle test. To evaluate the diastolic dyssynchrony of LV, we used tissue Doppler image. We calculated the standard deviation (SD) of the averaged time from Q wave to myocardial early diastolic velocity at 12 segments (TPe-SD, ms). Diastolic dyssynchrony index was defined as SD of TPe. Also at exercise, modified SD (SD/heart rate) was applied.

Results: TPe-SD was significantly higher in patients with LVH at rest (27 ± 11.0 vs. 18.7 ± 7.4 ms, $p<0.005$) with exaggeration of the degree at peak exercise (42.0 ± 10.6 vs. 30.6 ± 12.4 ms, $p<0.001$). When applying modified SD, the difference is much more increased (80.0 ± 17.6 vs. 49.0 ± 21.3 ms, $p<0.001$). Multiple regression analysis showed LV mass index ($\beta=0.515$, $P=0.001$) and E/E' at peak exercise ($\beta=-0.253$, $P=0.025$) were independently associated with LV dyssynchrony during diastolic phase.

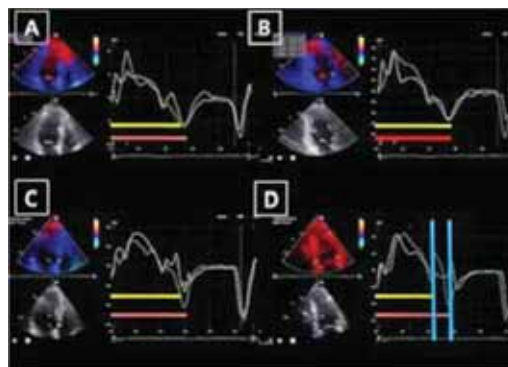


Figure 1. A, B: Non-LVH. C, D: LVH at rest and exercise.

Conclusion: Intraventricular diastolic dyssynchrony during exercise is significantly associated with the degree of LVH in hypertensive patients. And exaggerated diastolic dyssynchrony during exercise can deteriorate diastolic function and this result might explain the exertional dyspnea in hypertensive patients with LVH.

P1091 | BEDSIDE**Relationship between biochemical markers of cardiac remodelling and postexercise elevation of left ventricular filling pressure in arterial hypertension**

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Purpose: Recent studies have demonstrated the usefulness of multi-marker approach for risk stratification of patients with arterial hypertension. The biological markers reflecting cardiac hypertrophy, fibrosis and apoptosis correlate with systolic and diastolic function of left ventricle (LV). The tissue Doppler E/e' ratio at rest is a powerful predictor of cardiac events in a hypertensive population. Exercise-induced elevation of E/e' is an important contributor to the development of heart failure. Our objective was to compare blood markers of cardiac remodelling among hypertensive patients with normal and elevated postexercise E/e'.

Methods: The study group was composed of 227 untreated hypertensive males (aged 51±8 years). All the patients underwent 24-hour ambulatory blood pressure monitoring and conventional two-dimensional echocardiography. The E/e' ratio measurement was performed before starting exercise and immediately after symptom-limited treadmill test according to the Bruce protocol. The postexercise E/e' > 13 was considered to denote patients with elevated LV filling pressure. Plasma carboxy-terminal propeptide of procollagen type I (PICP, a marker of cardiac fibrosis), cardiotrophin-1 (CT-1, a marker of cardiac hypertrophy) and annexin V (a marker of apoptosis) were measured by ELISA.

Results: All the patients had E/e' < 8 at rest. Fourteen patients (6.2%) presented postexercise elevation of LV filling pressure. These patients had reduced exercise capacity compared to subjects with normal postexercise E/e' (7.5±2.8 vs. 9.1±2.2 MET; p=0.008). We found that annexin V levels are similar in both groups - 0.77 (0.44; 1.17) ng/ml in subjects with postexercise E/e' > 13 vs. 0.89 (0.6; 1.25) ng/ml in patients with postexercise E/e' < 13, p=0.4. The difference in CT-1 level wasn't statistically significant - 282.2 (142; 813.1) pg/ml in patients with elevated LV pressure after exercise vs. 471 (111.7; 941.9) pg/ml in patients with normal postexercise LV filling pressure, p=0.59. However, PICP level was significantly higher in patients with elevated postexercise E/e' (263.3 (102; 438.5) pg/ml vs. 103.5 (52.6; 192.3) pg/ml, p=0.047). Receiver operating characteristics curve showed that a cut-off value of 140.8 pg/ml for the PICP provided 68% specificity and 75% sensitivity for the predicting of elevated postexercise E/e'.

Conclusions: Baseline plasma PICP level had a good predictive value for the development of elevated postexercise E/e' in patients with arterial hypertension. However, there was no relationship between CT-1 and annexin V levels with augmented LV filling pressure after exercise.

P1092 | BEDSIDE**Arterial stiffness is a better predictor of left ventricular hypertrophy than the Framingham Risk Score and central hemodynamics: insights from 1,141 never-treated hypertensives**

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Purpose: Left ventricular hypertrophy (LVH) heralds target organ damage and calls for aggressive therapeutic approaches. We investigated the predictive ability of arterial stiffness, central hemodynamic indices and the Framingham Risk Score for detecting LVH.

Methods: 1,141 newly diagnosed, never-treated hypertensives were recruited. Carotid-femoral pulse wave velocity (cfPWV), central (aortic) blood pressures, augmentation index (AIx) and left ventricular mass index (LVMI) were measured. The 10-year risk for cardiovascular disease (CVD) was calculated using the Framingham Risk Score (FRS). Correlation coefficients, regression after controlling for confounders and ROC curves were calculated.

Results: The cohort had mild-moderate hypertension (systolic BP: 151±18 mmHg, diastolic BP: 90±11 mmHg). LVH was detected in 43% of patients; 10-year CVD risk was 16.1±9.7%. LVMI had a stronger correlation with cfPWV (r=0.39, p<0.001) compared to aortic systolic BP (r=0.33, p<0.001), pulse pres-

sure (r=0.306, p<0.001) and AIx (r=0.121, p<0.001). After adjusting for diabetes mellitus presence, eGFR, aortic systolic BP, total cholesterol and 10-year CVD risk, cfPWV remained an independent predictor of LVMI levels (R²=0.243, B=1.60, p<0.001). In ROC analysis, cfPWV emerged as a better predictor of LVH (AUC: 0.735, p<0.001) compared to the FRS (AUC: 0.727, p<0.001), aortic systolic BP (AUC: 0.687, p<0.001), aortic pulse pressure (AUC: 0.705, p<0.001) and AIx (AUC: 0.649, p<0.001).

Conclusions: Aortic stiffness is independently associated with LVMI and is a better predictor of LVH than the FRS, aortic BPs and wave reflections. Elevated levels of cfPWV signify target organ damage, which extends beyond large artery stiffness and herald LVH. This has implications for risk stratification and choice of therapy.

P1093 | BEDSIDE**Visceral fat volume is associated with diastolic dysfunction in patients with resistant hypertension - Resist-POL Study**

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Purpose: To evaluate the impact of obstructive sleep apnea and metabolic syndrome on left ventricle diastolic function in patients with resistant hypertension (RHT).

Methods: We analyzed data from 155 patients (92M, 63F). All patients underwent thorough examination including: biochemical evaluations (MS was defined by The Adult Treatment Panel (ATP) III), ambulatory blood pressure monitoring (ABPM), polysomnography (OSA was defined as apnea/hypopnea index > 15/h) and echocardiography. Left ventricular mass index (LVMI) and diastolic parameters were obtained. Additionally intra-abdominal visceral fat volume (VFV) were measured at L4-L5 disc space level using a computed tomography scan.

Results: Patients were divided into 4 groups based on presence of MS and OSA: group 1) OSA(-), MS(-) [n=42]; group 2) OSA(+), MS(-) [n=14]; group 3) OSA(-), MS(+) [n=46] and group 4) OSA(+), MS(+) [n=53]. There were no differences in LVMI and 24h SBP/DBP values between these groups. Table 1 shows variable of E/e' and VFV. Both LVMI (r=0.36; p<0.0001) and VFV (r=0.40; p=0.002) correlated with E/e'. In a multivariate linear model including age, gender, AHI, 24-h SBP, 24-h DBP, LVMI and MS, MS and AHI were not independently associated with E/e'. In a multivariate linear model including age, gender, AHI, 24-h SBP, 24-h DBP, LVMI and VFV independently associated with E/e' were LVMI (beta=0.42, p<0.001) and VFV (beta=0.37, p<0.003).

Table 1

Variables	OSA(-) MS(-) Group 1 (n=42)	OSA(+) MS(-) Group 2 (n=14)	OSA(-) MS(+) Group 3 (n=46)	OSA(+) MS(+) Group 4 (n=53)	p
VFV	12.96±7.4	19.19±6.1*	17.52±6.3†	23.67±6.1*	<0.0001
E/e'	7.02±1.8	8.85±1.9	8.24±2.8	8.98±3.2‡	0.009

*Group 1 vs. Group 2, †Group 1 vs. Group 3, ‡Group 1 vs. Group 4.

Conclusions: Among factors characterizing metabolic abnormalities the volume of visceral fat is most closely related with LV diastolic dysfunction in patients with true RHT.

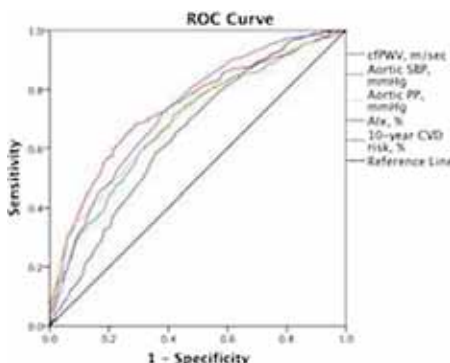
P1094 | BEDSIDE**Development of LV hypertrophy in treated hypertensive patients: the Campania-Salute Network (CSN)**

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Purpose: Left ventricular (LV) hypertrophy (LVH) is the hallmark of hypertensive target organ damage and predictor of major cardiovascular (CV) events. In a population-based cohort, antihypertensive therapy might be less efficacious for regression of LVH than indicated by results in clinical trials, independently of blood pressure (BP) control. We assessed whether both LVH develops during antihypertensive treatment and a phenotype at risk is identifiable in a large cohort of treated hypertensive patients without LVH, referred to our tertiary care center.

Methods: From the Campania-Salute Network (CSN), we evaluated 2889 consecutive hypertensive patients (age 50±11 years, males 60%, baseline systolic BP (SBP) 142±15 mmHg and diastolic BP (DBP) 90±10 mmHg), without echocardiographic LVH and prevalent CV disease, with glomerular filtration rate (GFR) > 30 mL/min/1.73m², a follow-up of at least 1 year and a validated follow-up echocardiogram. Evaluation for LVH was done at the time of the last visit. LVH was identified at LV mass index (LVMI) ≥ 50g/m^{2.7} in male patients and ≥ 47g/m^{2.7} in women.

Results: After a median follow-up of 56 months (inter-quartile range: 36-99), 450 patients (16%) had developed LVH. They were older, more often diabetic, with longer history of hypertension and more extended follow-up period (all p<0.001). They also exhibited higher baseline BMI and SBP, thicker carotid intima-media complex (IMT) and greater LVMI than patients without follow-up LVH (all p<0.001). SBP and DBP at the time of the last control were also higher in patients developing LVH (both p<0.0001). No sex-difference was observed. During follow-up, patients developing LVH were prescribed more antihypertensive medications, and specifically more diuretics and Ca++-channel blockers (both



ROC curves.

$p < 0.001$). Multivariable logistic regression, including all covariates significantly different, indicates that incident LVH was independently associated with older age (OR=1.03/year, 1.01–1.05, $p < 0.0001$), higher baseline LVMI (OR=1.26/ $\text{g} \times \text{m}^{2.7}$, 1.21–1.32, $p < 0.0001$), BMI (OR=1.09/ $\text{kg} \times \text{m}^{-2}$, 1.05–1.14, $p < 0.0001$), and number of medications (OR=1.24, 1.03–1.46, $p < 0.02$) as well as with higher SBP at the time of last control (OR=1.02/ mmHg , 1.01–1.04, $p < 0.0001$).

Conclusion: We demonstrated that LVH develops during antihypertensive therapy, despite more aggressive antihypertensive treatment. We identified a phenotype of hypertensive patient at high risk to develop LVH: elderly, overweight patients with values of LVMI close to cut-points and uncontrolled SBP despite more aggressive therapy are likely to increase their LVMI over time to level of clear-cut LVH.

VASCULAR REMODELLING

P1095 | BENCH

The role of B cells in pathogenesis of abdominal aortic aneurysm

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Abdominal aortic aneurysm (AAA) is a common and fatal disease. While most of AAA tissues are associated with atherosclerosis, recent studies have demonstrated that the pathogenesis of AAA may be quite different from that of atherosclerosis. Human AAA walls contain large amount of B cells and immunoglobulins that participate in the pathogenesis of atherosclerosis. However, the significance of B cells and immunoglobulins in the pathogenesis of AAA has been uncertain. In this study, we first examined human AAA tissue and found that B cells are making clusters with other inflammatory cells, including macrophages and T cells, suggesting the involvement of B cells in AAA pathogenesis. We next examined the role of B cells in the atherosclerosis-independent model of AAA in mice that was induced by periaortic application of CaCl_2 . B cells were found in mouse AAA walls, but not in normal aortic walls, throughout the 6 weeks of observation period. IgM and IgG deposition was also observed with the peak at 1 week after CaCl_2 treatment. We then compared the AAA model between wild type (WT) and B cell-deficient mice (mu-MT). The AAA size in mu-MT was significantly smaller than those in WT, indicating that the presence of B cells promotes AAA development. The suppression of AAA development in mu-MT mice was associated with the reduction in the expressions of matrix metalloproteinase-9 (MMP-9) and MMP-2 one week after the CaCl_2 treatment, indicating that B cells promote the destructive inflammatory response at this time point. Furthermore, treatment of human AAA tissue in culture with polyclonal human immunoglobulins significantly increased secretion of proinflammatory IL-6. These findings suggest that B cells may promote AAA progression independent of atherosclerosis, partly through the proinflammatory effect of immunoglobulins. Elucidation of the role of B cells would provide a new insight into the AAA pathogenesis that may lead to the development of novel diagnostic and therapeutic strategies.

P1096 | BENCH

Critical role of PDGF-induced PI3 kinase and PLC γ signaling in human and experimental pulmonary hypertension

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Purpose: Pulmonary vascular remodeling is a critical pathogenic response in pulmonary hypertension (PH). Targeting of this process by imatinib is effective in experimental and human PH. While the β platelet-derived growth factor receptor (β PDGFR) is an important target of imatinib, the compound is non-specific and inhibits multiple other kinases. Thus, the role of β PDGF signaling in PH is not clear from these data. We analyzed material from human idiopathic PAH (IPAH) and utilized a genetic mouse model to provide definitive evidence for the role of β PDGF signaling in PH.

Methods and results: Analyzing expression and activation state of the β PDGFR in IPAH (western blot analyses and immunohistochemistry), we found overexpression of the receptor and increased phosphorylation of Y751 and Y1021, binding sites for PI3 kinase (PI3K) and PLC γ . Next, we assessed the role of these molecules in vitro. Using pharmacological inhibitors, we identified PI3K and PLC γ as the critical mediators of β PDGFR-mediated proliferation (BrdU incorporation assays) and migration (modified Boyden chamber assays) in murine pulmonary arterial smooth muscle cells (mPASMC). As these processes are critical for vascular remodeling, we studied β PDGFR-F3/F3 mice, harboring genetic ablation of PI3K and PLC γ binding to the β PDGFR. Co-immunoprecipitation experiments revealed that, while binding of PI3K and PLC γ was blocked, association of other signaling molecules to the β PDGFR and overall receptor phosphorylation were not impaired. Importantly, PDGF-induced proliferation and migration were abolished in mPASMC isolated from F3/F3 mice, and PDGF-mediated protection from apoptosis was also lost in these cells. In line with these observations, PDGF-induced phosphorylation of Akt and Erk 1/2, as well as expression of cyclin D1 were sig-

nificantly impaired in F3/F3-cells. In vivo, PH was induced by exposure of mice to hypoxia (10%) for 3 weeks. Vascular remodeling (morphometric analyses and assessment of the degree of medial hypertrophy) was completely blunted in F3/F3 mice, as compared to WT littermates. Heterozygous F3/+ mice exhibited an intermediary phenotype. Consequently, F3/F3 mice, and to a lesser extent heterozygous F3/+ mice, were protected from hypoxia-induced PH and right ventricular hypertrophy, with no effects on the systemic circulation.

Conclusion: These data from a genetic mouse model and from human IPAH provide definitive evidence for the crucial role of PDGF-dependent PI3 kinase and PLC γ signaling in PH. Thus, anti-remodeling strategies targeting on the PDGF pathway represent a promising therapeutic tool.

P1097 | BENCH

Muscle atrophy F-box (MAFbx) regulates neointimal formation during vascular remodeling in mice

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Purpose: Muscle atrophy F-box (MAFbx), also known as FBXO32, F-box protein 32 and atrogin-1, is an E3 ubiquitin ligase expressed only in muscle. MAFbx was originally identified as a critical mediator of skeletal muscle atrophy, and endogenous MAFbx plays an essential role in mediating pathological cardiac hypertrophy in response to pressure overload, in part through nuclear activation of NF- κ B. Tumor necrosis factor (TNF)- α is a proinflammatory cytokine involved in many features of inflammation that promotes atherosclerosis and neointima formations after vascular injury. TNF- α stimulates the expression of MAFbx in skeletal muscle cells. Recently, the expression of MAFbx in vascular smooth muscle cells has been reported, but the role of endogenous MAFbx during vascular remodeling remains unknown. In this study, we investigated the association between TNF- α and MAFbx and revealed the role of MAFbx in mediating a pathological form of vascular neointimal hyperplasia.

Methods and results: Mice were subjected to carotid artery ligation. After 4 weeks, expression levels of MAFbx mRNA were increased in the carotid artery. In cultured mouse vascular smooth muscle cells (MVSM), expression levels of MAFbx mRNA were confirmed and increased by TNF- α -stimulation. TNF- α also induced cell proliferation and migration in MVSM obtained from WT mice. Interestingly, these increases were significantly inhibited in MVSMs obtained from MAFbx knockout (MAFbx-KO) mice. To evaluate the role of endogenous MAFbx during vascular remodeling, MAFbx-KO and WT mice were subjected to carotid artery ligation. After 4 weeks following this intervention, the intima/media ratio was significantly higher in WT mice than in MAF-KO mice (0.84 ± 0.40 vs. 0.34 ± 0.14 , $P < 0.05$). The expression levels of I κ B- α were reduced by TNF- α for 30 min in MVSMs obtained from WT mice. TNF- α -induced attenuation of I κ B- α was less in MVSMs obtained from MAFbx-KO compared to those obtained from WT mice. TNF- α also induced upregulation of IL-6, a downstream target of NF- κ B, in MVSMs obtained from WT mice. These increases were significantly reduced in MVSMs obtained from MAFbx-KO mice.

Conclusions: MAFbx is expressed in vascular smooth muscle cells and regulates neointimal formation during vascular remodeling through the NF- κ B pathway. Inhibition of MAFbx might be a therapeutic target for preventing atherosclerosis and arterial restenosis after angioplasty.

P1098 | BENCH

Factor VII activating protease (FSAP) deficiency promotes neointima formation by enhancing leukocyte accumulation and activity of matrix metalloproteinase-2 and -9

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Purpose: The factor VII activating protease (FSAP) is a multifunctional circulating plasma serine protease that also activates pro-urokinase. The Marburg I single nucleotide polymorphism (MI-SNP) in the FSAP-encoding gene is characterized by low proteolytic activity and represents a risk factor for atherogenesis in humans. The aim of this study was to determine the function of FSAP in vascular remodeling processes using mice lacking this gene.

Methods: Wire-induced injury of the femoral artery was performed to induce neointima formation in FSAP-/- mice on a C57BL/6 background and WT controls. Vessels were harvested 14 days after injury and were analysed by immunohistochemistry (IHC), qPCR, western blotting and quantitative zymography. In vivo microscopy was performed on the mouse cremaster muscle to analyse leukocyte trafficking to the perivascular tissue upon 4 hours of stimulation with chemokine (C-C motif) ligand 2.

Results: The neointimal lesion size and the proliferation of vascular smooth muscle cells were significantly enhanced in FSAP-/- mice compared to WT controls

(neointima/media ratio 2.46 ± 0.34 vs. 1.69 ± 0.09 , $n=7$, $***p<0.001$). This was associated with increased numbers of accumulating CD45+ leukocytes and CD68+ macrophages within the lesions of FSAP-/- mice. Using in vivo microscopy, we found that FSAP deficiency significantly promoted the intravascular adherence and the subsequent transmigration of leukocytes to the perivascular tissue ($n=4$, $*p<0.05$). As assessed by quantitative zymography of tissue lysates, there was a significantly enhanced activity of matrix metalloproteinase (MMP)-2 and MMP-9 but not urokinase within the neointimal lesions of FSAP-/- mice compared to controls. IHC showed a co-staining of MMP in particular with accumulating leukocytes. Moreover, expression of platelet-derived growth factor-BB, known as a specific FSAP substrate and inducer of chemokine production and proliferation of smooth muscle cells, was enhanced in FSAP-/- mice, as assessed by IHC but not by qPCR.

Conclusions: Whereas carriers of the loss-of-function MI-SNP are at high risk for vascular diseases, our data on vascular remodeling processes in mice indicate that FSAP deficiency promotes the inflammatory response and alters vascular proteolysis by post-translational regulation or altered turnover but not by transcriptional changes. Thus, these novel cellular effects of FSAP provide a direct mechanistic explanation for the observations in human disease.

P1099 | BENCH

Cell-specific off-target effects of ticagrelor but not clopidogrel-active metabolite in endothelial dysfunction

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Background: Anti-platelet drugs targeting the P2Y12 receptor have shown different beneficial effects in clinical trials; particularly, ticagrelor has been reported to reduce mortality in ACS patients compared to clopidogrel. However, P2Y12 receptors are not only found on platelets but also on other cell types; therefore, some of the beneficial effects may be mediated in a platelet- or even P2Y12 receptor-independent manner.

Methods: To investigate potential endothelium dependent effects of P2Y12 antagonists, primary human aortic- (HAECs), brain microvascular- (HBMVECs) and cardiac microvascular-endothelial cells (HCMVECs) were stimulated with TNF α (10 ng/ml) and treated with increasing concentrations of clopidogrel-active metabolite (CAM) (1.5×10^{-8} M– 1.5×10^{-6} M), which binds to the P2Y12 receptor after CYP 450 activation or ticagrelor (10^{-7} M– 10^{-5} M). Effects of anti-platelet drugs on endothelial activation was determined by expression of pro-coagulant tissue factor (TF) and its counter-player TF pathway inhibitor (TFPI), expression and activity of eNOS, expression of COX-1, COX-2 and the adhesion molecules VCAM-1 and ICAM-1 by western blotting. Additionally, underlying signal transduction pathways were assessed. The expression of P2Y12 receptors was investigated by qRT-PCR and possible role for adenosine receptor activation were examined using A1, A2a, A2b and A3 receptor antagonists.

Results: Ticagrelor, unlike CAM showed anti-coagulant properties by reducing TF expression in a concentration-dependent manner in HAECs and HBMVECs but not HCMVECs. The observed effect was mediated via PI3 and p70S6 kinase. Further, activation of eNOS by phosphorylation (Ser1177) was increased by ticagrelor via PI3 kinase in HAECs but not in microvascular ECs, whereas total eNOS levels were not altered. CAM treatment did not affect eNOS activation in either cell type. Ticagrelor compared to CAM decreased VCAM-1 expression and augmented COX-2 protein levels via the MAP Kinase p38 at the highest concentration tested (10^{-5} M). No effect was observed on COX-1 and ICAM-1 protein levels. Surprisingly, P2Y12 receptor mRNA was not detected in endothelial cells. Furthermore, pre-incubation of cells using specific adenosine receptor antagonists did not alter the effects of ticagrelor.

Conclusions: Ticagrelor, unlike CAM displays 1) an anti-coagulant and anti-inflammatory profile and 2) enhances activation of eNOS. The effects were observed to be cell-specific and appeared to be mediated independently of P2Y12 or adenosine receptors. These findings may have additional implications for ticagrelor in cardiovascular disease.

P1100 | BENCH

A monoclonal antibody against the interferon-alpha/beta receptor subunit 1 stimulates arteriogenesis in a murine hindlimb-ischemia model without affecting atherosclerosis

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Background: Increased interferon-beta (IFN β) signaling was shown in patients with insufficient coronary collateral growth (i.e. arteriogenesis). Furthermore, mice treated with IFN β demonstrate inhibition of arteriogenesis. Interestingly, type I interferons have been identified as proatherosclerotic cytokines and in mouse

models of atherosclerosis, IFN β treatment accelerated lesion formation and increased accumulation of macrophages in plaques. We hypothesized that monoclonal antibodies inhibiting IFN β signaling will stimulate arteriogenesis and at the same time attenuate atherosclerosis.

Methods: In a murine hindlimb-ischemia model, atherosclerotic apolipoprotein E (APOE) -/- and low density lipoprotein receptor (LDLR) -/- mice were treated respectively during a 1- and 4-week period with blocking monoclonal antibodies (MAbs) specific for mouse Interferon- α/β Receptor subunit 1 (IFNAR1) or murine IgG isotype as control. The arteriogenic response was quantified using laser Doppler perfusion imaging (LDPI) as well as immunohistology. Effects on atherosclerosis were determined by quantification of plaque area and composition analysis by immunohistochemistry. Several downstream targets of IFN β were assessed by real time polymerase chain reaction (RT-PCR), both in the aortic arch as well as in hindlimb tissue.

Results: Hindlimb perfusion restoration after femoral artery ligation was improved in mice treated with anti-IFNAR1 compared to controls as assessed by LDPI. This was accompanied by a decrease in CXCL10 expression in the IFNAR1 MAb treated group. Anti-IFNAR1 treatment reduced plaque apoptosis without affecting total plaque area or other general plaque composition parameters.

Conclusion: Blocking IFNAR1 using monoclonal antibodies during 1- and 4-week treatment periods stimulates collateral artery growth in mice without exacerbating atherosclerosis. This is the first reported successful strategy using monoclonal antibodies to stimulate arteriogenesis.

P1101 | BENCH

Long-term performance of autologous tissue ultra-small-caliber vascular grafts (biotubes) in a rat abdominal aorta replacement model

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Objective: There are practically no small-caliber synthetic vascular grafts (<6 mm) with acceptable patency rate for the use of coronary bypass or peripheral vascular repair below the knee. We have developed autologous small-caliber vascular grafts, named "biotubes", by simple, safe and economical "in-body tissue architecture technology", which is a novel concept of regenerative medicine and one of the in vivo tissue engineering. In this study, we evaluated the long-term (more than 1 year) results of ultra-small-caliber biotubes using a rat abdominal aorta replacement model.

Methods: Silicone rod molds (diameter: 1.5 mm, length: 20mm) ($n=12$) were placed into subcutaneous pouches of rats, and after 1 month the implants with their surrounded connective tissues were removed. Biotubes with internal diameter of 1.5 mm were obtained as tubular connective tissues from the implants after pulling out the impregnated molds. After anti-thrombogenic coating, they were auto-implanted to the infrarenal abdominal aorta using an end-to-end anastomosis. At over 1 year (14-18 months, median 16 months), graft status was evaluated by ultrasonography, 7-tesla magnetic resonance angiography (MRA) and histology.

Results: High patency rate of 83% (10/12) was obtained. During observation period, ultrasonography and MRA showed little stenosis, no aneurismal dilation in biotubes, and no anastomotic intimal hyperplasia. Their luminal surface was smooth and completely covered with endothelial monolayer.

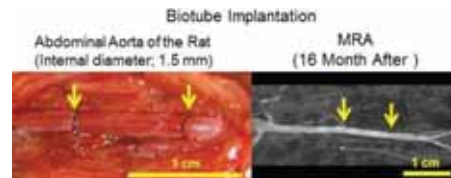


Figure 1. Biotube implantation.

Conclusion: Long-term implantation results of ultra-small caliber biotubes were firstly reported. The biotubes performed as excellent vascular grafts with high patency and regeneration activity including complete endothelialization without aneurismal formation, stenosis.

IMAGING BEFORE OR AFTER NON CORONARY INTERVENTIONS

P1102 | BEDSIDE

Usefulness of cardiac computed tomography for assessing of atrial septum defect in adult compared with transesophageal and transthoracic echocardiography and invasive catheterization

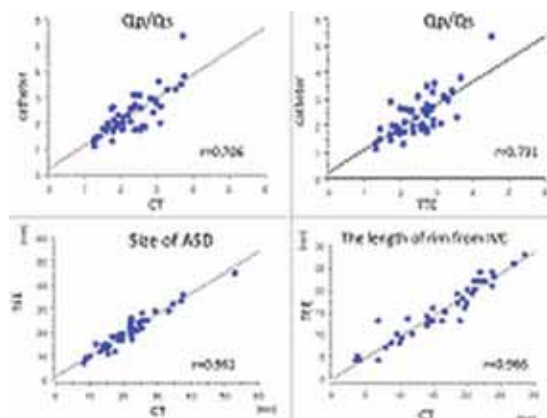
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Background: Atrial septum defect (ASD) is one of the common form of congenital

heart disease in adult. Cardiac computed tomography (CT) is known as an excellent tool for evaluating congenital heart disease including ASD. The purpose of this study was to investigate the usefulness of cardiac CT in evaluating the morphology and hemodynamics of secundum ASD in adult using a new software, compared with transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) and invasive catheterization.

Methods: A total of 50 patients (60 ± 14 years old, 64% female) with secundum ASD were enrolled. Cardiac CT was performed, followed by 3D reconstruction of ASD for determination of the defect size, the length of rims from the circumference of ASD and the pulmonary to systemic blood flow ratio (Qp/Qs) in the Siemens-workstation (syngo.CT Cardiac Function and RVA-Right Ventricular Volumetry), results were compared among TEE, TTE, invasive catheter and CT measurement.

Results: Cardiac CT was comparable with TTE and TEE in evaluating Qp/Qs as a reference standard of invasive catheterization ($r=0.786$; $p<0.001$, $r=0.731$; $p<0.001$, respectively). A linear association was observed between cardiac CT and TEE in evaluating ASD size ($r=0.961$; $p<0.001$). The length of rims from the circumference of ASD evaluated with cardiac CT were also comparable with those with TEE, the rim length from aortic valve ($r=0.925$; $p<0.001$), mitral valve ($r=0.916$; $p<0.001$), tricuspid valve ($r=0.867$; $p<0.001$), inferior vena cava ($r=0.966$; $p<0.001$) and posterior of atrium ($r=0.884$; $p<0.001$).



Cardiac CT measurements in evaluating ASD.

Conclusion: Cardiac CT is of use in evaluating the Qp/Qs, size of ASD and the length of rims from the circumference of ASD. Cardiac CT could be informative modality for optimizing clinical management for ASD patients.

P1103 | BEDSIDE

Computed-tomographic assessment of membranous septal anatomy for risk prediction of atrioventricular block associated with transcatheter aortic balloon expandable valve implantation

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Objectives: To assess the risk of conduction system abnormalities requiring permanent pacemaker (PPM) implantation following transcatheter aortic valve implantation (TAVI) with balloon expandable valve.

Background: The membranous septum (MS) length serves as an anatomic surrogate of the distance between aortic annulus and bundle of His and thus may show an inverse relation to risk of conduction system abnormalities.

Methods: Fifty two consecutive patients (80.6 ± 7.4 years) with symptomatic severe aortic stenosis underwent a native and contrast-enhanced 256-slice computed tomography (CT) with iterative reconstruction technique before TAVI. The contrast-enhanced CT-data was reconstructed at 10% increments of the RR-interval and the (non-reformatted) standard coronal view in the systolic phase (40% of RR interval) was used for MS length measurement.

Results: Eighteen patients (35%) required PPM implantation after the procedure due to high degree atrioventricular block ($n=12$), new-onset bundle branch block with PR prolongation ($n=3$), and slow atrial fibrillation ($n=3$). Pre-procedural multivariable logistic regression model revealed MS length as the most powerful independent predictors of PPM implantation with an odds ratio of 1.3 (CI: 1.04–1.62; $P=0.02$). In the post-procedural analysis MS length minus implantation depth was the most powerful independent predictors of PPM implantation in patients undergoing TAVI with an odds ratio of 1.33 (CI: 1.6–1.12; $P=0.001$).

Conclusion: MS length as assessed by CT imaging is the most powerful pre-procedural predictor for pacemaker following TAVI, while the difference between MS length and implantation depth is the most powerful post-procedural predictor as well as the most powerful independent predictor in general.

P1104 | BEDSIDE

CT sizing of left atrial appendage prior to percutaneous closure using watchman device: feasibility and initial experience

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Purpose: Percutaneous interventional closure of the left atrial appendage (LAA) using the Watchman device (Boston scientific, Natick, Massachusetts) has emerged as an alternative therapy for reduction of embolic stroke in patients with non-valvular atrial fibrillation and contraindications to oral anticoagulation. Device sizing is based on TEE as well as angiographic measurements. Computed tomography (CT) provides complete volumetric evaluation of the LAA. We assessed the feasibility of CT sizing of the LAA prior to closure using the Watchman device.

Methods: 13 patients referred for interventional LAA closure were examined using Dual Source CT prior to the interventional procedure. Data sets were acquired using prospectively ECG-triggered high pitch spiral acquisitions triggered at 60% of the cardiac cycle. Multiplanar reconstructions were aligned with the plane of the LAA ostium and measurements were performed in a cross-sectional plane orthogonal to the long axis of the LAA at the level of the left circumflex coronary artery. Three measurements were performed: mean diameter (maximum + minimum diameter/2), effective diameter from area measurement ($\sqrt{[\text{area}/\pi] \times 2}$) and effective diameter from perimeter measurement (perimeter/ π). LAA dimensions determined by CT were compared to intraprocedural sizing, which was based on angiographic and TEE assessment

Results: Mean patient age was 76 ± 7 years (8 males). LAA closure was successfully performed in all 13 patients with no relevant leak (2×33 mm, 5×27 mm, 4×24 mm and 3×21 mm device). In one patient 2 devices (1×33 mm and 1×21 mm) were used due to a very wide LAA ostium. Mean diameter, perimeter derived effective diameter and area derived effective diameter as determined by CT were not significantly different (23 ± 5 cm, 23 ± 5 cm and 22 ± 5 cm, respectively, $p=0.9$). Agreement between CT sizing and initial intra-procedural sizing was slightly better for mean diameter and perimeter derived effective diameter (8/13) compared to area derived effective diameter (7/13). Initial intraprocedural sizing was changed in 3 patients due to failed implantation (upgraded in 2 patients and downgraded in 1 patient). In patients with disagreement between intraprocedural sizing and the 3 CT-based measurements, CT recommended a smaller device in 3 patients and a larger device in 1 patient, and the device was implanted according to the intraprocedural sizing.

Conclusions: CT sizing of the LAA prior to interventional closure is feasible. Whether CT-based sizing would correlate to better interventional or clinical outcomes needs to be further evaluated.

P1105 | BEDSIDE

Feasibility of an ultra low dose CT for left atrium and pulmonary veins imaging using a new model-based iterative reconstruction

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Purpose: To evaluate the feasibility of ultra low dose CT for left atrium and pulmonary veins imaging using new model-based iterative reconstruction

Materials and methods: 200 patients, with persistent or intermittent atrial fibrillation, scheduled for catheter ablation were enrolled in this study and randomized into two groups: Group 1 (100 patients, MDCT with VEO, no ECG triggering, tube voltage and tube current of 100kV and 60 mA, respectively, regardless of patient's BMI) and Group 2 (100 patients, MDCT with adaptive statistical iterative reconstruction algorithm (ASIR) rather than MBIR, no ECG-triggering and, kV and mA tailored on patient BMI). The image quality, the CT-attenuation, image noise, signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR) of left atrium and every pulmonary vein branch and Effective Dose (ED) were evaluated for each exam and compared between two groups.

Results: No differences between two groups in terms of population characteristics and image quality score. Statistically significant differences were found between Group 1 and Group 2 in mean attenuation, SNR, and CNR of left atrium. Significant lower values of noise were found in Group 1 vs Group 2 in the quantitative analysis of pulmonary veins. Group 1 showed a significantly lower mean ED in comparison with Group 2 (0.49 ± 0.03 versus 6.01 ± 2.2 mSv).

Conclusions: The CT for left atrium and pulmonary veins imaging using VEO is feasible and allows to perform examinations with very low radiation exposure without loss of image quality

P1106 | BEDSIDE

Pre-procedural planning for percutaneous left atrial appendage occlusion using 3-dimensional patient-specific models obtained by 3D printing: a proof-of-concept analysis

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Background: Most cerebrovascular events related to atrial fibrillation result from

thromboemboli arising from the morphologically diverse left atrial appendage (LAA). We demonstrate the feasibility of a priori LAA 3-D model analysis using cardiac CT and cost-effective commercially available 3D printing for pre-procedural modeling of the LAA.

Methods: The 320-slice cardiac CT exams of six random patients were selected to serve as source data. CT DICOM data was converted to stereolithography (STL) files (Simpleware, LTD). The MakerBot Replicator 2™ was employed as the consumer level 3D printer and compared with Stratasys™ Objet500 Connex which served as the reference professional-grade printer. The MakerBot prints were created using poly lactic acid (PLA) filament. The Stratasys prints were created using proprietary material.

Results: Six different LAA replicas were produced using each printer. The prints from both models were equivalent in fidelity of reproduction, level of detail, and quality of print. Print times were similar, averaging between 90–120 minutes. The cost of the Stratasys (over \$100,000) and TangoPlus® (approximately \$2/inch²) is substantially greater than the MakerBot Replicator 2 (\$2,500) and PLA filament (less than \$0.10 per model). Using the TangoPlus material and Stratasys produced rubber-like prints which are more amenable to simulation of surgical procedures and for training purposes. The firm characteristics of the PLA prints are more durable and suited for making measurements to size LAA occlusion devices. The biggest hurdle in the process was learning how to use the software. After the initial learning curve, DICOM images could be transformed into 3D models within about 1 hour.

Conclusion: This proof-of-concept analysis has demonstrated the feasibility of using cost-effective and readily available commercial-grade 3D printing technology to accurately recreate the LA and LAA prior to intervention. We believe that safety, efficiency, and patient education regarding LAA occlusion procedures will be aided by pre-procedural visualization, tactile manipulation, measurement, and sizing of equipment using 3D printing.

P1107 | SPOTLIGHT

Patterns in deformation and contact force of implanted aortic valve stents

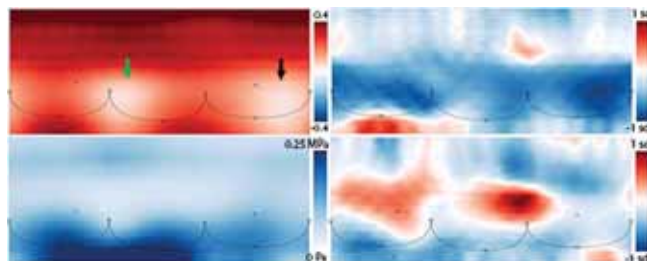
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Purpose: Stent deployment in TAVI results in a stent shape, which is controlled by a force equilibrium between the stent and the surrounding tissues. These forces are required to secure the stent against embolization and to seal it against paravalvular leaks (PVL). We aim at a method to predict PVL from the force and deformation patterns of implanted stents.

Methods: We analyze CT images acquired after TAVI from 30 patients. The shape of the implanted stent is extracted and a mechanical model is employed to estimate the radial forces. The distribution of the radial forces and deformations are presented on 2D maps depicting the area of the unrolled stent.

Results: The mean stent deformation over all 30 patients (upper left image) shows an elliptic pattern in the sinus portion: In the white areas near the aortic sinus (green arrow) and the left coronary sinus (black arrow), the stent radius is almost unchanged to the original radius. The compression in the dark red regions reaches 40%. The mean force distribution (lower left image) shows a force concentration at the right coronary sinus, close to the membranous septum. We compared the mean deformation and the mean force between two groups of patients with no or mild PVL (group 1) vs. moderate PVL (group 2) and detected distinct patterns for each group. The images on the right show for both groups the difference of the group's mean radial force to the mean of the whole population. In group 2 (bottom), the force distribution is less homogeneous than in group 1 (top), with strong forces (and deformations) in the middle section of the stent, and lower radial forces at the ventricular margin.



Deformation and force distribution.

Conclusion: Our findings show that distinct force and deformation patterns exist for TAVI stents with and without leakage.

P1108 | BEDSIDE

Diagnostic performance of cardiac CT in detecting left atrial thrombus

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Purpose: The exclusion of left atrial thrombus is essential before the electrical- or pharmacological cardioversion in patients with atrial fibrillation. In clinical practice transoesophageal echocardiography (TEE) is the reference standard method to diagnose left atrial thrombus. We aimed to evaluate the diagnostic performance of cardiac computed tomography angiography (CTA) regarding the detection of left atrial thrombus compared to the gold standard TEE.

Methods: In total 444 patients were referred to left atrial angiography before atrial fibrillation ablation procedure (149 women, 295 men, mean age 56y) between February 2011 and January 2014. We have investigated the patients who subsequently underwent TEE (n=201).

Results: CTA excluded left atrial thrombi in 178 cases. In all negative CTA cases were confirmed by TEE (true negatives). In 23 cases CTA showed incomplete contrast filling in the left appendage: 19 false positives and 4 true positives. According to our results sensitivity of cardiac CT is 100% [95% CI: 40.2%-100%], specificity was 90.4% [95% CI: 85.4%-94.1%], negative predictive value was 100% [95% CI: 97.9%-100%] and positive predictive value was 17.4% [95% CI: 5.1%-38.8%].

Conclusion: Cardiac CT is a very sensitive modality diagnosing left atrial thrombus, the negative predictive value proved to be 100%. In patients where cardiac CTA excludes left appendage thrombus subsequent TEE examination may be unnecessary.

PROGNOSIS IN HEART FAILURE: SCIENCE AND UNCERTAINTIES

1124 | BEDSIDE

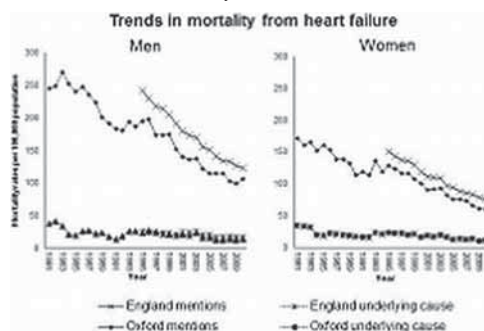
Steep decline in mortality from heart failure over three decades

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Purpose: The proportion of deaths due to heart failure (HF) reflects both its prevalence and survival. Prevalence of HF is increasing, but survival is longer. Selection rules for assigning the underlying cause of death discourage the selection of HF as a cause of death if other causes are certified on the same death certificate. We sought to define trends in population mortality attributable to HF in a national population and a large regional population, using all certified causes of death, not just underlying cause.

Methods: We analysed death registration data for multiple-cause coded causes of death for all deaths occurring in England, 1995–2010, population 52 million, and in a regional population, 1981–2010, population 2.5 million, for which data on all causes of death were available from a much earlier date.

Results: HF was mentioned as a factor contributing to death in 310,594 cases between 2001–10 in England. Mortality rates based on underlying cause alone underestimated the impact of HF on overall population mortality (compared to those based on all recorded causes of death) by a factor of six. Analysing all mentions of heart failure, we found that mortality rates from HF have declined dramatically over the last 30 years. Considering all ages and both sexes combined, age- and sex-standardised mortality measured as all recorded causes of death in 2008–10 were only 40% of those in 1981–83.



Trends in heart failure mortality.

Conclusion: Mortality rates based on underlying cause are a more sensitive marker of the contribution of HF to overall population mortality. There have been very substantial declines in the population mortality of HF, with the decline beginning well before the introduction of modern medical and device therapy for the condition.

1125 | BEDSIDE

Is there a heart rate paradox in acute heart failure?

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Background: Higher heart rate (HR) associates with higher mortality in chronic heart failure (HF). The impact of HR in acute HF is not established. We studied the prognostic impact of admission HR in patients hospitalized due to acute HF and analyzed if prognostic implications differed between patients admitted in sinus rhythm (SR) and those in atrial fibrillation (AF).

Methods: Patients admitted with acute HF were prospectively included. Clinical data, laboratory parameters and co-morbidities were recorded. An echocardiogram was performed. Physicians were aware of the ongoing registry. Primary endpoint was all-cause death. Follow-up was 6 months. We used a Cox regression analysis to study the association of HR with 6-month all cause mortality. HR was analyzed both as a continuous variable and as a categorical variable: <100 and ≥ 100 beats per minute (bpm). Analysis was stratified according to admission rhythm. Multivariate models were built. Cross classification was made attending to admission (cut-off 100 bpm) and discharge (cut-off 80 bpm) HR and association with outcome determined.

Results: We analyzed 577 patients. Median age was 78 years, and 56.6% had left ventricular systolic dysfunction. Median emergency department HR was 86 (72-101) bpm, 258 were in AF. During follow-up 112 patients died. Death risk increased steadily with lower admission HR. The association of HR with mortality was significant only in patients in SR. Patients with an admission HR <100 bpm had a hazard ratio (95% CI) of death at 6 months of 4.76 (1.71-13.21) when in SR and 1.56 (0.87-2.79) when in AF. Association was independent of systolic blood pressure, New York Heart Association class, B-type natriuretic peptide, age, ischaemic aetiology, systolic dysfunction, prognostic modifying therapy and haemoglobin. The multivariate adjusted hazard ratio of 6-month death in patients in SR with HR <100 bpm was 2.92 (1.02-8.34). Per each 10 bpm increase in HR the multivariate adjusted hazard ratio was 0.82 (0.68-0.98). Ninety-three patients had admission HR ≥ 100 and discharge HR <80bpm; 78 admission HR ≥ 100 and discharge HR ≥ 80 bpm; 286 admission HR <100 and discharge HR <80 bpm and 120 admission HR <100 and discharge HR ≥ 80 bpm; mortality rates at 6-month were 8.6%, 14.1%, 21.4% and 26.7%, $p=0.004$.

Conclusions: In acute HF patients in SR, those presenting with tachycardia have a better prognosis. Per each 10bpm increase in admission HR there is a 18% decrease in 6-month death risk. This association with prognosis is not observed in AF. Patients presenting with tachycardia and discharged with controlled HR have the better outcome.

1126 | BEDSIDE

Benefit of positive airway pressure (PAP) therapy in patients with sleep apnoea (SA) in Germany: a retrospective comparative cohort analysis based on a statutory health insurance (SHI) database

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Purpose: SA is relatively common, occurring in about 20% of adult males and 10% of females. This study investigated the effects of PAP therapy on morbidity (including comorbid disease), all-cause and disease-specific mortality, and costs in patients with SA in Germany from a SHI perspective.

Methods: Outcomes for a total of >4 million individuals covered by the SHI database were analysed (approximately 5% of the German SHI population). PAP therapy was initiated in 4068 patients with SA. Propensity score was used to define a control group of 4068 SA patients matched for age, sex, risk factors/etiology, region and medication who received usual care (no PAP). Patients were followed over three years after initiation of PAP.

Results: Mean patient age was 60 years, and 80% of patients were male. Baseline patient characteristics were similar in the PAP and no PAP groups, except for obesity (significantly more common in the PAP group, 33.84% vs 27.11%; $p<0.0001$). The three-year mortality rate was significantly lower in patients treated with PAP compared with the no PAP group (4.5% vs 7.2%, 37.5% reduction; $p<0.0001$). Three-year rates for coronary heart disease mortality (4.5% vs 7.2%, 37.9% reduction; $p=0.0002$) and heart failure mortality (14.7% vs 21.4%, 31.6% reduction; $p<0.0001$) were also significantly lower in the PAP vs no PAP group.

Conclusion: PAP therapy for patients with SA significantly reduced three-year mortality compared with usual care.

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Atrial fibrillation and the risk of incident heart failure in community-dwelling older adults: findings from a propensity-matched cohort of a prospective population study

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Background: Atrial fibrillation (AF) is common in older patients with heart failure (HF) and is considered a risk factor for HF. However, to what extent this association is independent remains unclear. The objective of the current analysis was to examine the impact of AF on incident HF in a propensity-matched cohort from a community-dwelling population of older adults without HF.

Methods: Of the 5795 community-dwelling adults aged ≥ 65 years in the Cardiovascular Health Study (CHS), 5521 were free of prevalent HF at baseline, of which 116 had ECG-documented AF at baseline. Propensity scores for AF, calculated for each participant, were used to assemble 114 pairs of those with and without AF who were balanced on 30 baseline characteristics. Cox regression models were used to estimate association of AF with centrally adjudicated HF over 13 years of follow-up.

Results: Participants ($n=228$) had a mean ($\pm$ SD) age of 75 (± 6) years, 41% were women, and 6% were African American. Incident HF occurred in 45% and 24% of matched participants with and without AF, respectively during 13 years of follow-up (HR, 2.13; 95% CI, 1.36–3.46; $p=0.001$; Figure 1). Baseline AF had no association with all-cause mortality (HR, 1.07; 95% CI, 0.77–1.48; $p=0.687$)

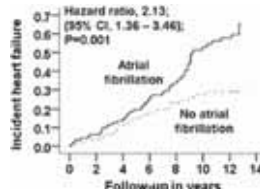


Figure 1. KM plots for incident heart failure by atrial fibrillation.

Conclusion: Among community-dwelling older adults, baseline AF is an independent risk factor for incident HF but had no independent association with mortality.

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Efficacy and safety of ticagrelor in patients with acute coronary syndrome and heart failure - insights from the platelet inhibition and patient outcomes (PLATO) trial

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Purpose: Heart Failure (HF) is a frequent complication of patients with acute coronary syndromes (ACS). We examined the efficacy and safety of ticagrelor in patients with ACS and HF as well as evaluated baseline predictors of post-discharge HF in ACS patients.

Methods: We classified all 18,624 patients with ACS in the PLATO trial in two

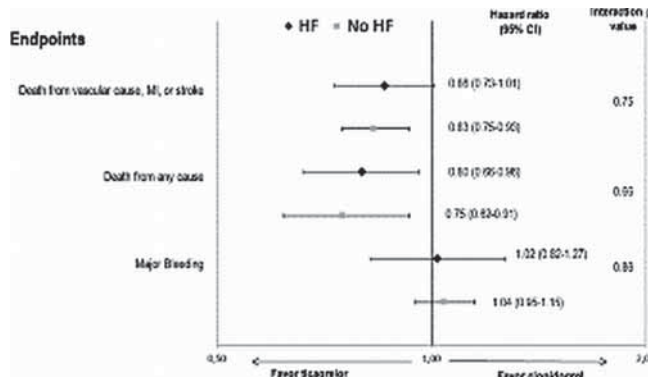


Figure 1

groups; no HF and HF based on the presence of clinical signs of HF (on admission, in-hospital or post-discharge), NT-proBNP >2500 pmol/mL, or Killip class II or III on admission. We used Cox-regression models with HF as a time-dependent variable to evaluate efficacy of ticagrelor versus clopidogrel on clinical endpoints and safety. In patients without prior HF at the time of hospital discharge, a multi-variable Cox regression model was used to assess predictors of post-discharge HF.

Results: Overall, a total of 3324 (17.8%) patients experienced HF following the ACS index event. Patients with HF were older, more often female and with significantly more co-morbidities than patients without HF. Patients randomized to ticagrelor, compared to clopidogrel, experienced lower risk of efficacy clinical events regardless of the presence of HF. The risk of bleeding was similar between the two groups. A total of 990 patients experienced HF after hospital discharge (2.24% at 3 months, 3.0% at 6 months, and 3.96% at 12 months). Predictors of developing post-discharge HF were: higher heart rate, higher NT-proBNP, troponin I >0.08 µg/mL, hypertension, chronic obstructive pulmonary disease and older age. **Conclusion:** We found clinical predictors for post-discharge HF that may guide treatment strategies in patients with ACS. Ticagrelor significantly decreased mortality in ACS patients, without causing more major bleedings, compared with clopidogrel regardless the presence of HF.

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Myocardial fibrosis in patients with non-ischemic cardiomyopathy compared to established prognostic factors

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Purpose: The study sought to compare the prognostic value of myocardial fibrosis to other clinical, laboratory, electrocardiographic and echocardiographic findings in patients with non-ischemic cardiomyopathy (NICM).

Methods: 283 NICM patients referred to a tertiary Centre underwent clinical examination, plasma N-terminal fragment of probrain natriuretic peptide (NT-proBNP) assay, electrocardiography, echocardiography, Holter monitoring and cardiac magnetic resonance for late gadolinium enhancement (LGE) detection and quantification. All patients were then followed-up for a 32-month median period (interquartile range 18-50) for a composite end-point including cardiac death, hospitalization for heart failure and aborted sudden cardiac death.

Results: LGE was detected in 135 (48%) patients. 91 (32%) patients achieved the study end-point. At multivariate analysis, higher NT-proBNP concentrations (HR: 1.267 [1.012-1.585], P:0.039) and LGE presence (HR: 2.035 [1.212-3.414], P: 0.007) or greater extent (HR: 1.092 [1.012-1.179], P: 0.024) were associated with high likelihood of achieving the combined end-point, independently of other prognostic determinants, including New York Heart Association (NYHA) functional class, left ventricular ejection fraction (EF), right ventricular EF, left atrial area, mitral regurgitation, and non-sustained ventricular tachycardia episodes at Holter monitoring.

Conclusions: In NICM patients, myocardial fibrosis is a strong and independent predictor of adverse outcome, when compared to other established prognostic markers.

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Frailty is related with decreased survival in elderly patients hospitalized with heart failure

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Purpose: To evaluate the frailty phenotype influence on survival of elderly patients hospitalized with heart failure and representative of daily clinical practice.

Methods: One-year follow-up prospective study of 431 consecutive patients. We included patients older than 74 years with high comorbidity who were admitted with a main diagnosis of decompensated heart failure. Clinical characteristics, including geriatric assessment, were recorded during index admission; post-discharge outpatient follow-up included frailty assessment by Fried et al criteria (grip strength, gait speed, physical activity, fatigue and unintentional weight loss). The relationship among frailty status and survival was analysed through Kaplan-Meier survival curves in frail and non-frail patients and Cox regression analysis adjusting for covariates.

Results: Mean age was 85±5 years, 59.7% were females, mean Charlson comorbidity index was 3.1±1.8, basal NYHA functional class III-IV was present in 28.7% of patients. Forty three percent of patients had had a previous admission due to heart failure and 59.3% showed atrial fibrillation on admission. Left ventricle ejection fraction was lower than 45% in 20.2% of patients. Treatment on discharge included ACEI or ARB in 58.6% and beta-blocker in 34%. Dependence in any ADL was present in 43.7% of patients and 41% fulfilled frailty criteria.

One-year mortality was 27% in frail patients and 15% in non-frail patients (p<0.03). Frailty non-adjusted HR for mortality was 1.99 (95% CI 1.25-3.17).

On a multivariate parsimonious model (Cox regression), frailty (HR 1.74, 95% CI 1.08-2.79), age (HR 1.07 per year, 95% CI 1.02-1.12), dementia (HR 3.08, 95% CI 1.56-6.06), serum creatinine (HR 1.43 per mg/dl, 95% CI 1.04-1.96), preserved ejection fraction (HR 0.52, 95% CI 0.32-0.85) were independently related with mortality. On a multivariate non-parsimonious model (Cox regression), including previous variables and gender, beta-blocker treatment, ACEI-ARB treatment and potassium-sparing agents treatment, frailty (HR 1.64, 95% CI 1.01-2.68) was independently related with mortality.

Conclusions: Frailty phenotype is independently related with one-survival in elderly patients admitted with heart failure. Identification of frailty should be included in these patients' assessments as can identify high risk cases that deserve more extended geriatric interventions. Frailty is also relevant in patients recruited in clinical trials since can determine survival as a covariate. Simple measures of frailty, such as gait speed or grip strength should be evaluated as clinical practice tools in cardiology.

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A potential linkage between mitochondrial function of the heart and leg muscle in patients with heart failure

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Purposes: Congestive heart failure (CHF) often accompanies cachexia, namely body wasting, which is a potential target of therapeutic intervention in cases of CHF. To gain insight into the mechanism of cardiac cachexia, we hypothesized that patients with chronic heart failure (CHF) would show the impairment in mitochondrial function of legs along with the decrease of muscle power and cardiopulmonary exercise parameters. Technetium-99m sestamibi (99mTc-MIBI) has been reported to show slow clearance in proportion to mitochondrial membrane potential in cultured cardiomyocytes. We reported that there was a correlation between the washout rate of 99mTc-MIBI and the mitochondrial function in vivo.

Methods: We enrolled 45 patients with chronic heart failure after the treatment of acute exacerbation. After administration of 99mTc-MIBI, they were examined by collecting signals from the heart and bilateral legs in early (20 minutes after the injection) and delayed phases (3 hours), in which washout rates were calculated. We tested the correlation between the washout rate and ejection fraction (EF) on echocardiography, brain natriuretic peptides (BNP), and other clinical values along with the parameters of an exercise tolerance test, muscle power, and the length of circumflex of the thighs.

Results: Patients characteristics were as follows: 62.2% were male; 37% had dilated cardiomyopathy; 55% had hypertension and 24% had diabetes; the age was 68±15.2 years (mean±SD); the mean ejection fraction was 41±14%; and the mean washout rate was 46.8±9.1%. The 99mTc-MIBI washout rate of the heart was positively correlated with BNP levels (r=0.61, p<0.005) and the 99mTc-MIBI washout rate of the leg (r=0.427, p<0.005), but was not correlated with EF. Peak oxygen consumption was negatively correlated with the 99mTc-MIBI washout rate of the legs (r=0.66, p=0.018) and mildly correlated with the length of the circumflex of the thigh (r=0.44, p=0.05), indicating that mitochondrial function of leg muscle, along with the muscle volume, may limit the exercise capacity in patients with chronic heart failure.

Conclusion: The 99mTc-MIBI washout rate of the heart is one of the likely markers of myocardial damage or dysfunction. The mitochondrial function of the leg muscles may limit the exercise capacity and there is an association between mitochondrial function of the heart and peripheral muscle in patients with heart failure

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Lower activation of renin-aldosterone and sympathetic nervous systems in overweight patients with acute heart failure and its association with favorable short-term prognosis

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Background: Previous studies have demonstrated that higher body mass index (BMI) was associated with better prognosis in the setting of heart failure, so called "obesity paradox". The underlying mechanisms of the obesity paradox have not yet been determined, but hormonal response to haemodynamic alteration could be an influencing factor since fat tissue is considered as a hormone-producing organ. We prospectively enrolled patients admitted for acutely decompensated heart failure (ADHF), and sought to examine activation of renin-aldosterone and sympathetic nervous systems in overweight patients in association with their short-term clinical outcome.

Methods and results: A total of 281 consecutive ADHF patients (183 men; mean age 76±12 years) admitted to our hospital was studied. Patients were divided into two groups according to BMI; overweight patients, BMI ≥25kg/m²; lean patients, BMI <25kg/m². Those patients were followed up to a mean period of 161 days. Adverse events were defined as all-cause death and unplanned readmission for heart failure. Plasma renin activity, plasma aldosterone concentration, and plasma norepinephrine concentration were measured both on admission and

before discharge. Overweight patients were associated with younger age, higher serum Na level, lower plasma BNP level, and higher hemoglobin level. Medications including ACE inhibitors/ARB, β -blockers, and aldosterone antagonists were not different between overweight and lean subjects. Despite that systolic blood pressure on admission was greater (140 ± 27 vs. 131 ± 30 mmHg, $p=0.028$), the overweight group, as compared with the lean group, had lower plasma renin activity (4.1 ± 5.7 vs. 7.1 ± 12 ng/mL/hr, $p=0.049$), plasma aldosterone concentration (83 ± 57 vs. 126 ± 140 pg/mL, $p=0.016$), and plasma noradrenaline level (568 ± 368 vs. 801 ± 922 pg/mL, $p=0.049$) on admission. However, those values were comparable in both groups before discharge. Multivariate Cox proportional hazard regression analysis showed BMI ≥ 25 kg/m² was independently associated with a lower adverse events (OR: 0.15, $p<0.01$) among variables including sex, age, history of hypertension and diabetes mellitus, serum Na and creatinine levels, plasma BNP level, and left ventricular ejection fraction.

Conclusions: Overweight patients showed better short-term prognosis compared to lean patients. Lower activation of renin-aldosterone and sympathetic nervous systems at acute phase of decompensation was shown in overweight patients, suggesting one of the underlying mechanisms for the obesity paradox.

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Prognostic impact of metabolic syndrome in patients with chronic heart failure: data from GISSI-HF trial

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Purpose: Prognostic role of Metabolic Syndrome (METS) in unselected populations and in patients with CHD has been defined previously. We evaluated the impact of METS on prognosis in chronic heart failure (HF).

Methods: International Diabetes Federation criteria were used for METS. Adjusted Cox's regression models with total mortality and death for HF worsening as outcomes were fitted in 6,648 patients (pts) enrolled in GISSI-HF trial with no missing values for the variables of interest. Impact of each component of METS on prognosis was also assessed.

Results: See Table. METS compared to no METS was significantly associated with risk of total and HF death. As compared with pts with no METS and no type 2 DM, the risks of total and HF death were significantly lower in patients with METS and no DM, whereas they were significantly increased in pts with DM and no METS. Pts with METS and DM showed no difference as to risk of total and HF death compared with pts with no METS and no DM. Risk of total and HF death were lower in pts with BMI ≥ 30 or hypertension (SBP ≥ 130 /DBP ≥ 85 mmHg or previously diagnosed/treated hypertension), whereas they were increased in patients with glycaemia ≥ 100 or DM or low HDL-C (<40 mg/dl in males and <50 mg/dl in females). No association was found between METS and triglycerides (≥ 150 mg/dl).

Conclusions: In HF, METS is associated with lower total and HF death. Such findings are likely due to reverse epidemiology.

NOVEL BIOMARKERS IN PREDICTING CARDIOVASCULAR DISEASES

1134 | SPOTLIGHT

The biomarker tissue inhibitor of metalloproteinase-1 (TIMP-1) is an independent predictor of all-cause mortality in the AGES-Reykjavik study

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Purpose: Biomarkers matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of metalloproteinase-1 (TIMP-1), relate to remodeling of the extracellular matrix.

In some disease states, the imbalance of these proteins leads to tissue destruction, proteolysis, and synthesis of cytokines and inflammation. Two intermediate-sized studies indicated that TIMP-1 predicts prognosis. We investigated TIMP-1 levels to predict all-cause mortality in the AGES-Reykjavik Study.

Methods: Participants in this study represent 5721 of the 5764 community-dwelling men and women characterized by the AGES-Reykjavik Study and followed by the Icelandic Heart Association since 1967. We measured TIMP-1 using an ELISA assay in citrate plasma drawn in 2002-2006 in participants and related results to all cause mortality.

Results: At the time of blood sampling, the mean age was 77 years (range 66-98); 58% were female; hypertension was treated in 64%, diabetes was present in 13%, and 12% were active smokers. Of the 5721 participants in the study, 39% died with a median follow-up of 8 years.

Kaplan Meier survival analysis showed higher quartiles of TIMP-1 were associated with all-cause mortality (Fig.1 1). Both Kaplan Meier and Cox analyses suggested a potential threshold effect where mortality risk elevates after TIMP-1 levels surpass a threshold. Cox multivariable regression analysis adjusted for the cardiovascular risk factors: age, gender, hypertension, smoking status and diabetes found TIMP-1 had the second highest Wald Chi-square score (after age) in the adjusted model.

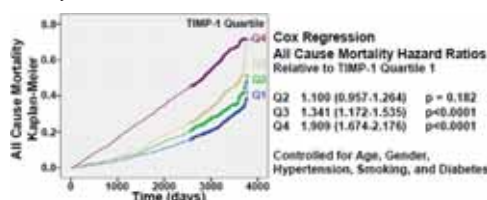


Figure 1

Conclusion: The biomarker, TIMP-1, is a strong predictor of all-cause mortality in older community dwelling subjects even after adjusting for cardiovascular risk factors.

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Ultra-sensitive troponin I strongly predicts incident coronary heart disease in the general population. Results from the MONICA/KORA Augsburg Case-Cohort study

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Background: High-sensitive (hs) troponin T and I assays as well as ultrasensitive (us) troponin I enable measurement of troponins in 65% to 98% of the general population. We prospectively investigated whether increased concentrations of us-troponin I are associated with an increased risk of coronary heart disease (CHD) after controlling for traditional risk factors.

Methods: We conducted a population-based case cohort study in middle-aged healthy men and women within the MONICA/KORA Augsburg studies. Serum levels of us-troponin I (Single Molecule Counting technology, Singulex) were available in 2,745 men and women including 803 incident CHD cases. Geometric mean us-troponin I was 1.56 ng/L. Mean (SD) follow-up was 16.0 (5.8) years.

Results: Baseline concentrations of us-troponin I were higher in cases compared to non-cases (geometric mean 2.56 vs. 1.49 ng/L, $p<0.0001$) and in men compared to women (geometric mean 1.93 vs. 1.27 ng/L, $p<0.0001$). After adjustment for variables of the Framingham Risk Score (FRS), the hazard ratio (HR) with 95% confidence interval (CI) for a CHD event in the top quartile compared to the bottom quartile was 2.71 (95% CI, 1.83-4.01). After additional adjustment for alcohol intake, physical activity, and body mass index, hazard ratios remained essentially unchanged. The AUC for the base model including FRS variables only was 0.836 (95% CI, 0.821-0.854) and increased modestly to 0.848 (95% CI, 0.833-0.867) for the model including additionally us-troponin I. Reclassification metrics (IDI and NRI) comparing the two models were 0.0193 (95% CI, 0.0085-0.0361) and 0.0477 (95% CI, -0.0089-0.1240), respectively.

Abstract 1133 – Table 1

(No pts, %)	All-cause mortality			Death for HF worsening		
	No. (%)	HR (95% CI)	P	No. (%)	HR (95% CI)	P
METS+ (1,212 pts, 18.2%)	261 (21.5)	0.83 (0.72–0.95)	0.005	73 (6.0)	0.76 (0.59–0.98)	0.031
METS– (5,436 pts, 81.8%)	1613 (29.7)	1.00 (ref.)		546 (10.0)	1.00 (ref.)	
METS– DM+ (1,651 pts, 24.8%)	619 (37.5)	1.34 (1.21–1.48)	<0.0001	222 (13.4)	1.44 (1.21–1.72)	<0.0001
METS+ DM+ (665 pts, 10%)	170 (25.6)	1.03 (0.87–1.21)	0.762	50 (7.5)	0.99 (0.73–1.35)	0.963
METS+ DM– (547 pts, 8.2%)	91 (16.6)	0.76 (0.62–0.95)	0.015	23 (4.2)	0.65 (0.42–0.99)	0.046
METS– DM– (3,785 pts, 56.9%)	994 (26.3)	1.00 (ref.)	324	(8.6)	1.00 (ref.)	
BMI ≥ 30 (1,492 pts, 22.4%)	331 (22.2)	0.85 (0.76–0.96)	0.011	97 (6.5)	0.82 (0.65–1.02)	0.071
Glycaemia ≥ 100 or DM (4,092 pts, 61.5%)	1,205 (29.4)	1.08 (0.98–1.18)	0.136	401 (9.8)	1.12 (0.95–1.33)	0.170
Hypertension (4,742 pts, 71.3%)	1,297 (27.4)	0.80 (0.72–0.88)	<0.0001	396 (8.4)	0.71 (0.60–0.84)	<0.0001
Low HDL-C (2,412 pts, 36.3%)	710 (29.4)	1.08 (0.99–1.19)	0.097	254 (10.5)	1.20 (1.02–1.41)	0.027
High triglycerides (2,298 pts, 34.6%)	612 (26.6)	0.96 (0.87–1.06)	0.425	193 (8.4)	0.90 (0.76–1.07)	0.230

Conclusions: Troponin I measured by an us-assay was detectable in almost all subjects. This is the first population-based prospective study with long-term follow-up showing that even modestly increased concentrations of us troponin I are strongly associated with incident CHD independently of a variety of traditional risk factors.

1136 | BEDSIDE

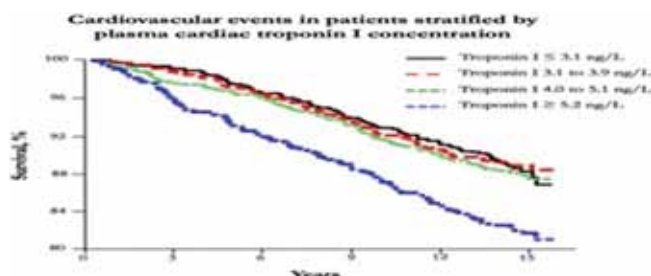
High-sensitivity cardiac troponin i predicts long-term cardiovascular outcomes in the west of Scotland coronary prevention study

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Background: The West of Scotland Coronary Prevention Study compared pravastatin versus placebo in middle-aged men without a history of myocardial infarction. We evaluated the association between baseline troponin concentration and cardiovascular events over 15 years follow-up, and the impact of statin therapy on troponin at 1 year.

Methods: Plasma cardiac troponin I concentration was measured with a high-sensitivity assay (Abbott Diagnostics) at baseline and 1 year following randomisation to 40 mg of pravastatin or placebo in 3,278 participants. Hospitalization for myocardial infarction or death from coronary heart disease was recorded with a median follow up of 15 years.

Results: Troponin concentration at baseline was an independent predictor of myocardial infarction or death from coronary heart disease ($p < 0.001$, Figure). Compared to the first quarter (≤ 3.1 ng/L), patients in the top quarter (≥ 5.2 ng/L) were at highest risk after adjustment for other risk factors (Hazard Ratio 1.52, 95% Confidence Interval [CI] 1.15 to 1.99, $p = 0.003$). Troponin concentration at 1 year was reduced in patients on pravastatin (-11.4% , 95%CI -7.4% to -15.2%), but increased in those on placebo (10.5% , 95%CI 5.1% to 16.2% ; $p < 0.001$ between groups).



Conclusion: Cardiac troponin I concentration is an independent predictor for cardiovascular events and is reduced by statin therapy. This biomarker has major potential for cardiovascular risk stratification and for use in clinical efficacy or safety trials.

1137 | BEDSIDE

The soluble interleukin 6 receptor and its natural antagonist, sgp130 and the risk of myocardial infarction

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Aim: To investigate the association of soluble Interleukin 6 receptor (sIL6R) levels with the risk of myocardial infarction (MI) in a large population based case-control study, the Stockholm Heart Epidemiology Program (SHEEP) and to explore whether circulating levels of the soluble gp130 (sgp130), a natural antagonist of the sIL6R, might modify this association.

Methods: 1213 non-fatal MI and 1561 age, sex and residential matched controls from the SHEEP study were investigated. sIL6R (ng/mL) were measured in the available serum samples from 682 cases and 1103 controls. Sgp130 (ng/mL) concentrations were measured in participants exposed to low sIL6R (value < 25 th, Q1) ($n = 424$) and to high sIL6R (value > 75 th, Q4) ($n = 438$) levels. MI risk was calculated by unconditional logistic regression models and expressed as odds ratio (OR) with 95% confidence intervals (CI). Risk estimates were adjusted for the matching variables (crude) and for hypertension, diabetes, hypercholesterolemia, body mass index, smoking and non-steroid anti-inflammatory drugs (adjusted model).

Results: sIL6R median and interquartile ranges (IQR) values were higher in cases 43 (32-65) than in controls 41 (32-54), $p = 0.0016$. High (> 75 th = 54.5) sIL6R levels were associated with an increased risk of MI, with an OR of 1.6 (95% CI 1.3-2.0) (crude model) and an OR of 1.4 (95% CI, 1.1-1.8) at adjusted analysis, as compared to sIL6R < 25 th. Median (IQR) sgp130 levels did not differ between individuals exposed to low (Q1) and high (Q4) sIL6R ($p = 0.83$). Compared to low sIL6R (Q1), exposure to Q4 sIL6R increased the MI risk [OR 1.4 (95% CI, 1.0-1.9)] at the crude and at the adjusted analysis [1.2 (95% CI, 0.9-1.7)]. Inclusion of sgp130 in the crude model did not modify this association OR to

1.4 (95% CI, 1.0-1.9). A secondary analysis was performed to investigate the effect of sgp130 on the MI risk associated with sIL6R levels within the highest (Q4) sIL6R quartile. In this stratum, when compared to the lowest quartile, participants in the highest quartile had a risk of MI of 2.3 (95% CI, 1.2-4.2). We then analyzed the MI risk in this group (Q4) according to serum sgp130 levels. In the presence of sgp130 higher than the median value, comparing Q4 with Q1, we observed a reduction in the OR associated with high sIL6R [OR 1.0 (95% CI, 0.3-2.8), an effect modification not observed in the presence of sgp130 levels below the median value [OR 2.9 (95% CI, 1.7-7.2)].

Conclusions: Elevated circulating levels of sIL6R are associated with an increased risk of MI. In the presence of high serum sIL6R levels, circulating sgp130 levels seem to modify this association.

1138 | BEDSIDE

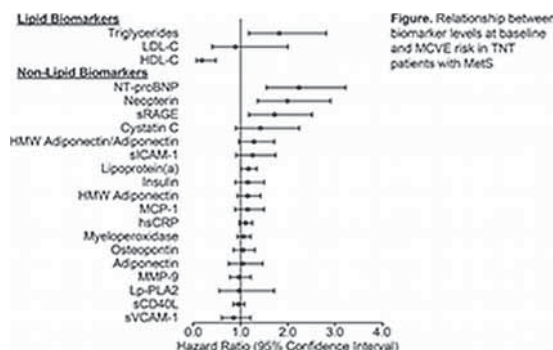
Relationship of major cardiovascular events and 18 non-lipid biomarkers among patients with stable coronary disease and metabolic syndrome: a subanalysis of the treating to new targets trial

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Purpose: Non-lipid biomarkers have attracted much interest due to their potential use in predicting adverse cardiovascular (CV) outcomes and identifying individuals at high CV risk. New risk predictors may be particularly useful in patients with metabolic syndrome (MetS). In the Treating to New Targets (TNT) trial, 10,001 coronary patients were randomized to atorvastatin (ATV) 10 or 80 mg and followed for a median of 4.9 years. In the 5584 MetS patients, relative risk of major CV events (MCVE) was reduced by 29% with ATV 80 vs 10 mg ($P < 0.0001$). This subanalysis evaluated the predictive value of biomarkers on MCVE risk in statin-treated coronary patients with MetS.

Methods: Biomarkers were measured after an 8-week run-in period on ATV 10 mg (baseline) and after 1-year treatment with ATV 10 or 80 mg. The predictive value of LDL-C, HDL-C, triglycerides and 18 non-lipid biomarkers on risk of MCVE (cardiac death, myocardial infarction, stroke or resuscitated cardiac arrest) was evaluated by Cox proportional hazards model adjusted for age, sex and treatment. Hazard ratios were for each doubling of biomarker concentration.

Results: In 612 MetS patients included in the analysis, baseline levels of triglycerides, HDL-C, Lp(a), NT-proBNP, neopterin and sRAGE were highly predictive of future MCVE (Figure). After 1 year of treatment, only neopterin and NT-proBNP remained predictive of MCVE. Changes in LDL-C, triglyceride, hsCRP, insulin, Lp-PLA2, NT-proBNP, sICAM-1 and sVCAM-1 levels at Year 1 were significantly different between treatment groups.



Conclusions: In statin-treated coronary patients with MetS, baseline levels of triglycerides and HDL-C were the lipids predictive of MCVE; of the 18 non-lipid biomarkers assessed, Lp(a), NT-proBNP, neopterin and sRAGE were associated with future CV events.

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Plasma chemerin is a strong and independent predictor of cardiovascular event risk

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Purpose: Associations of the adipokine chemerin with the metabolic syndrome (MetS) and with chronic kidney disease (CKD), two important indicators of in-

creased cardiovascular event risk, have been described. However, the power of chemerin to predict cardiovascular events has not been investigated so far and is addressed in the present study.

Methods: We measured plasma chemerin in a high-risk cohort of 495 patients undergoing coronary angiography for the evaluation of suspected or established coronary artery disease (CAD) in which cardiovascular events were prospectively recorded over 3.5 ± 1.1 years. Significant baseline CAD was diagnosed in the presence of coronary artery stenoses $\geq 50\%$.

Results: At baseline, plasma chemerin was significantly higher in patients with the MetS as defined by the current harmonized consensus definition ($n=147$) than in non-MetS subjects (201 ± 71 ng/ml vs. 163 ± 62 ng/ml $p < 0.001$) and was inversely correlated with estimated glomerular filtration rate (eGFR; $r = -0.33$, $p < 0.001$). During follow-up, chemerin significantly predicted cardiovascular events ($n=82$) univariately, after adjustment for age, gender, BMI, and eGFR, and also after additional adjustment for the presence of significant baseline CAD, with standardized hazard ratios of 1.83 [1.19-2.83], $p=0.006$; 1.77 [1.12-2.80], $p=0.015$; and 1.69 [1.07-2.67], $p=0.024$, respectively.

Conclusions: From this first prospective evaluation of the cardiovascular event risk associated with chemerin we conclude that chemerin is strongly predictive of cardiovascular events independently from standard risk factors, from the MetS, and from the baseline presence of CAD.

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Progression of kidney disease in non-diabetic patients with hypertension: Predictive role of circulating visfatin

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Purpose: Declining renal function, estimated by the glomerular filtration rate (GFR), is an independent risk factor for all-cause mortality and poorer outcomes in cardiovascular disease (CVD). Previous evidence showed endothelial dysfunction and systolic blood pressure (SBP) were associated with GFR loss after adjustment for other CV risk factors and antihypertensive treatment. Patients with increased serum visfatin levels are negatively correlated with GFR, but whether these changes are related to a subsequent decline in GFR with extended follow-up period remain unclear.

Methods: Totally, 200 non-diabetic hypertensive out-patients with initial serum creatinine level < 1.5 mg/dL and GFR ≥ 50 mL/min/1.73 m² (baseline GFR 80.6 ± 25.2 mL/min/1.73 m²) were enrolled. Endothelial function was assessed by flow-mediated dilatation (FMD), and visfatin levels were determined in study subjects. The study end points are the occurrence of renal events including doubling of serum creatinine from baseline values, 25% loss of GFR from baseline values, and the occurrence of end-stage renal disease during follow-up period.

Results: The mean annual rate of GFR decline (Δ GFR/y) was -1.26 ± 2.76 mL/min/1.73 m² per year during the follow-up period (103 $\pm$ 30 months). The Δ GFR/y was correlated with the visfatin level, baseline GFR, FMD, SBP, and fasting blood glucose (FBG). Multivariate analysis indicated that increased visfatin ($r = -0.331$, $p < 0.001$), baseline GFR ($r = -0.234$, $p = 0.001$), FMD ($r = -0.163$, $p = 0.015$), and FBG ($r = -0.160$, $p = 0.015$) are independent predictors of Δ eGFR/y. When we divided the patients into 4 groups according to the visfatin levels, there was an association between the visfatin level and the Δ GFR/y (mean Δ GFR/y: -0.34 ± 1.95 vs. -0.68 ± 2.06 vs. -1.54 ± 2.35 vs. -2.48 ± 3.82 , $p < 0.001$). Cox proportional hazard regression model analysis showed that visfatin levels (HR, 1.08; 95% CI, 1.04-1.12, $p < 0.001$), FMD (HR, 0.87; 95% CI, 0.77-0.98, $p = 0.026$) and FBG (HR, 1.01; 95% CI, 1.00-1.02, $p = 0.005$) were independently associated with the risk of developing future renal composite events after adjustment.

Conclusions: Increased serum visfatin levels and endothelial dysfunction are associated with subsequent decline in GFR in hypertensive patients. Serum visfatin levels provide incremental information regarding risk for incident CKD beyond traditional risk factors.

1141 | SPOTLIGHT

Circulating toll-like receptor 4-responsive microRNA panel is a biomarker for coronary artery disease: results from a randomized study of treatment with renin-angiotensin system blockades

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Background: The extracellular microRNAs (miRNAs) circulate in the blood-stream and may serve as novel diagnostic and therapeutic biomarkers. The aim of this study was to investigate circulating miRNA expression in patients with coronary artery disease (CAD), and to examine the effects of renin-angiotensin system (RAS) blockades on miRNA levels.

Methods: This study included 41 patients with CAD (mean age, 66.4 ± 13.2 ; %male, 85%) and 20 subjects without CAD (non-CAD) (mean age, 61.6 ± 12.5 ; %male, 85%). Plasma miRNA profiling was analyzed using microarray assay for 1,700 human miRNAs. The candidate miRNAs were verified with real-time PCR. The amount of Toll-like receptor 4 (TLR4) and CD14 on peripheral blood mononuclear cells (PBMCs) cell surfaces was measured by FACS. Patients with CAD were randomized to 12 months of combined treatment with either telmisartan (ARB) or enalapril (ACEI). Plasma samples and PBMCs were obtained from peripheral blood at baseline and after 12 months.

Results: The microarray assay showed significant differences in 22 miRNAs between the CAD and non-CAD groups ($P < 0.05$). Real-time PCR verified that the 4 TLR4-responsive miRNAs were among the 22 miRNAs that were significantly down-regulated in the CAD group versus the non-CAD group (miR-31; 1.56 ± 0.74 vs. 2.78 ± 0.92 ; miR-181a; 1.51 ± 1.05 vs. 3.69 ± 2.21 ; miR-16; 1.78 ± 0.55 vs. 3.51 ± 1.85 ; miR-145; 1.69 ± 0.29 vs. 2.47 ± 0.90 : CAD group vs. non-CAD group, all $P < 0.05$). Levels of TLR4 were higher in the CAD group than in the non-CAD group ($P < 0.01$) and were negatively correlated with levels of TLR4-responsive microRNAs (TLR4 MFI vs. miR-31; $r = -0.47$, $P < 0.01$; TLR4 MFI vs. miR-181a; $r = -0.26$, $P < 0.05$; TLR4 MFI vs. miR-16; $r = -0.26$, $P < 0.05$; TLR4 MFI vs. miR-145; $r = -0.28$, $P < 0.05$). ROC curve analysis showed that a panel of these four circulating miRNAs has substantial diagnostic potential with an AUC of 0.93 (95% CI = 0.87-0.99) for the detection of CAD. Both ARB and ACEI groups showed increased TLR4-responsive miRNAs and diminished levels of TLR4 protein (all $P < 0.01$). Changes in miRNAs and TLR4 levels were greater in the ARB group than in the ACEI group ($P < 0.05$).

Conclusion: In conclusion, circulating TLR4-responsive miRNA panel may be novel diagnostic and therapeutic biomarker for patients with CAD.

1142 | BENCH

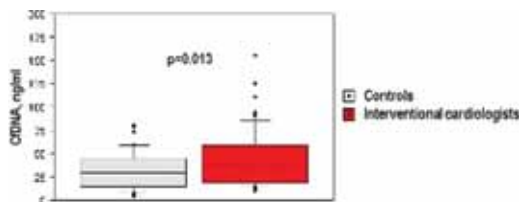
Elevated levels of circulating cell-free DNA in interventional cardiologists occupationally exposed to low levels of ionizing radiation

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Purpose: Circulating cell-free DNA (cf-DNA) is a marker of cell death and tissue damage in several disorders, including cancer, myocardial infarction, stroke and hematologic disorders. Aim of the study was to investigate the impact of chronic low-dose radiation exposure on serum cf-DNA levels in interventional cardiologists working in high-volume cardiac catheterization laboratory and exposed to chronic doses of ionizing radiation.

Methods: We enrolled 50 interventional cardiologists (26 males; age= 48.4 ± 10 years) and 50 age- and gender-matched unexposed controls (27 males; age= 47.6 ± 8.3 years). Quant-iTTM dsDNA High-Sensitivity assay was used to measure circulating cf-DNA isolated from serum samples.

Results: There was no statistically significant difference in clinical characteristics between exposed and control subjects. No significant relationships were found between cf-DNA and age, gender, smoking and other clinical parameters. Cf-DNA levels were significantly higher in interventional cardiologists compared to the non-exposed group (44.2 ± 31.1 vs. 30.6 ± 19.2 ng/ml, $p = 0.013$). The exposed group with > 10 years of work showed significantly increased serum concentrations of cf-DNA (49.2 ± 33.8 vs. 30.8 ± 18.1 ng/ml, $p = 0.04$).



Conclusions: Our data show increased levels of cf-DNA in interventional cardiologists than in controls, providing evidence for its potential role of relevant biomarker to monitor the cellular damage induced by exposure to chronic low-dose radiation.

IMAGING IN MYOCARDIAL DISEASE AND THROMBOEMBOLIC PULMONARY HYPERTENSION

1147 | BEDSIDE

Disease-specific differences of left ventricular rotational mechanics between cardiac amyloidosis and hypertrophic cardiomyopathy: a feature-tracking magnetic resonance study

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Purpose: Left ventricular twist (LVT) and untwisting (LVUT) rate are global and thorough parameters of LV function. Aim of the present study was to investigate the differences in LV rotational mechanics between patients with cardiac amyloidosis (CA) and hypertrophic cardiomyopathy (HCM).

Methods: 20 consecutive patients with CA, 20 consecutive patients with HCM and 20 consecutive subjects without evidence of structural heart disease were included. Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE) imaging was performed using a 1.5 Tesla scanner to evaluate biventricular

function, LV mass index and presence/extent of LGE. Feature-tracking analysis was applied to LV basal and apical short-axis images to determine peak basal and apical rotation, peak LVT, time to peak LVT, peak LVUT rate and time to peak LVUT rate.

Results: Peak LVT in CA patients was significantly impaired compared to control subjects ($11.3 \pm 4.0^\circ$ vs. $15.0 \pm 1.6^\circ$; $p < 0.05$), due to an impairment of peak basal rotation ($-2.9 \pm 2.5^\circ$ vs. $-7.0 \pm 0.7^\circ$; $p < 0.001$). Conversely, peak LVT in HCM patients was significantly higher compared to control subjects ($18.9 \pm 6.7^\circ$ vs. $15.0 \pm 1.6^\circ$; $p < 0.05$), due to an increase in peak apical rotation ($12.9 \pm 5.5^\circ$ vs. $8.3 \pm 1.4^\circ$; $p < 0.01$). Peak LVUT rate was significantly impaired in CA patients compared to control subjects ($-83 \pm 42^\circ/\text{sec}$ vs. $-112 \pm 26^\circ/\text{sec}$; $p < 0.05$), while it was preserved in HCM patients ($-107 \pm 37^\circ/\text{sec}$ vs. $-112 \pm 26^\circ/\text{sec}$; $p > 0.05$). Time to peak LVUT rate was significantly prolonged in both CA and HCM patients compared to control subjects ($146 \pm 30\%$ of LV systole vs. $133 \pm 23\%$ vs. $113 \pm 6\%$; ANOVA $p < 0.001$). At ROC curve analysis, peak basal rotation $> -5.9^\circ$, peak LVT $\leq 13.8^\circ$ and peak LVUT rate $> -81^\circ/\text{sec}$ had the highest sensitivity and specificity for identification of patients with CA (100% and 83%, 75% and 80% and 55% and 95%, respectively); peak apical rotation $> 11^\circ$ and peak LVT $> 17^\circ$ had the highest sensitivity and specificity for identification of patients with HCM (75% and 83% and 65% and 100%, respectively). At multivariate analysis, age ($p = 0.007$), LV ejection fraction ($p = 0.035$) and extent of LGE ($p < 0.001$) were independently related to peak LVT; LV mass index ($p = 0.015$) and extent of LGE ($p = 0.004$) were independently related to peak LVUT rate, while extent of LGE ($p < 0.001$) was the only variable independently related to time to peak LVUT rate.

Conclusions: CA and HCM have specific behavior of LV rotational mechanics. The extent of LGE significantly influences the LV rotational mechanics.

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Pericardiectomy improves right ventricular echocardiographic mechanics in patients with constrictive pericarditis without history of radiotherapy or previous cardiac surgery

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Background: Complete pericardial resection is the definitive treatment for patients with constrictive pericarditis (CP). Two-dimensional speckle tracking echocardiography (2D-STE) has not routinely been used to assess right ventricular (RV) function in CP patients. The aim of this study was to evaluate RV mechanics using 2D-STE in patients with CP undergoing pericardiectomy.

Methods: One hundred and fourteen CP patients (mean age 62 years, 65% male) were included in this study. All echocardiographic images were prospectively analyzed offline using 2D-STE technology. Patients were divided into 3 groups: radiotherapy as the primary cause of CP, ($n = 31$); non-radiation-induced CP with history of cardiac surgery (S-NR-CP, $n = 48$) and non-radiation-induced CP without history of cardiac surgery (NS-NR-CP, $n = 35$). Results were analyzed using the student t-test, Pearson correlation coefficient (r), univariate and multivariate linear regression.

Results: Pericardiectomy significantly improved RV free wall strain in the NS-NR-CP group ($p = 0.021$) but not in the S-NR-CP or R-CP groups. Patients with the lowest quartile pre-operative RV strain values (-8 to -12) improved the most ($p < 0.001$). History of coronary bypass graft surgery or pre-operative tricuspid regurgitation severity did not significantly affect strain improvement post-pericardiectomy among the three groups. After adjusting for age, sex, body mass index, body surface area and pulmonary arterial systolic pressure, lower pre-operative RV free wall strain (-8 to -12) predicted post-operative RV strain improvement ($p < 0.0001$).

Conclusion: Pericardiectomy improves RV mechanics in patients with constrictive pericarditis without history of radiotherapy or previous cardiac surgery.

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Cardiac involvement detected by magnetic resonance imaging in systemic sclerosis

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Purpose: Cardiac involvement in systemic sclerosis (SSc) affects the prognosis of the disease. Myocardial fibrosis is the pathological hallmark of this complication, reported in $> 50\%$ of cases at necropsy. Delayed gadolinium enhancement (DE) cardiac magnetic resonance (CMR) is the gold-standard for myocardial fibrosis assessment. Our aim was to evaluate the added value of DE-CMR in SSc patients and its clinical correlations.

Methods: After a thorough clinical evaluation, 208 SSc pts (age = 51 ± 14 yrs, 90% females) were referred to DE-CMR. On the same day they underwent a comprehensive echocardiogram.

Results: Five pts were not able to undergo DE-CMR and in 8 pts gadolinium was not injected due to lack of a peripheral vascular access. Echocardiography showed normal systolic function in 94.5% of pts, whereas DE-CMR showed a

pattern of non-ischaemic myocardial fibrosis in 22.5% pts. In 2% pts, T2-weighted CMR showed myocardial oedema. Among clinical characteristics, only a Scl-70 autoantibodies positivity (HR 2.04; 95% CI 1.03-4.08) and a history of ulcers (HR 2.14; 95% CI 1.08-4.24) were independent predictors of the presence of myocardial fibrosis. Among imaging (echo and CMR) data, right ventricular function parameters were independent predictors of myocardial fibrosis.

	no DE (151, 77.5%)	DE (44, 22.5%)	P
CMR LV Ejection fraction (%)	68 ± 7	67 ± 9	ns
CMR RV Ejection fraction (%)	67 ± 7	63 ± 9	<.05
LA volume indexed (ml/m ²)	25 ± 8	26 ± 8	ns
E/e'	8.5 ± 2.7	8.3 ± 3.3	ns
TDI S' LV (cm/sec)	9.4 ± 2.0	9.2 ± 2.2	ns
TDI S' RV (cm/sec)	13.5 ± 3.1	12.8 ± 2.6	ns
TAPSE (mm)	22.8 ± 4.2	19.6 ± 5.5	<.01
PASP (mmHg)	28 ± 8	26 ± 9	ns

LA = left atrium; LV = left ventricle; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; PASP = pulmonary arterial systolic pressure

Conclusions: CMR can detect patterns of reversible (by T2-weighted) and irreversible (by DE) cardiac involvement in a significant percentage of SSc patients, often without overt systolic or diastolic left ventricular dysfunction on echocardiography. The association between a history of ulcers and myocardial fibrosis may suggest a similar pathological substrate of abnormal vascular function, underlying cutaneous and cardiac complications.

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Clinical and instrumental characterization and the long-term prognosis of Mildly Dilated Cardiomyopathy

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Purpose: To define the clinical and instrumental characterization and the long-term prognosis of Mildly Dilated Cardiomyopathy (MDCM). MDCM is a subgroup of idiopathic dilated cardiomyopathy (IDCM) characterized by slightly dilated left ventricle and presenting systolic dysfunction. The long-term evolution and the prognosis of the disease is unknown in the current treatment and clinical management era of IDCM.

Methods: From 1988 to 2008 we enrolled 659 patients with IDCM; MDCM was considered in presence of LVEF $< 50\%$ and LV end-diastolic volume index (LVEDVI) $< 86 \text{ ml/m}^2$ at echocardiographic evaluation.

Results: 252 patients (38%) fulfill the pre-specified criteria for MDCM. At baseline evaluation MDCM patients were less symptomatic than IDCM patients (NYHA III-IV 15% vs 30% respectively, $p < 0.001$) and had a slightly higher LVEF (36 ± 8 vs $30 \pm 12\%$, $p < 0.001$). Interestingly MDCM patients initially improved under optimal therapy, then were stable at mid-term, followed by a progression in the long term approaching the condition of other IDCM patients. At 10 years follow up mortality for all causes death was 21% in MDCM and 39% in IDCM ($p < 0.001$); heart failure death/HTx and sudden death/malignant ventricular tachycardia rates were 10% vs 18% ($p = 0.002$) and 12 vs 20% ($p = 0.005$) in MDCM and IDCM patients respectively. MDCM with baseline LVEF $\leq 35\%$, compared to the other MDCM patients, presented lower survival rates ($p = 0.001$) but similar rates of long-term sudden death and malignant ventricular arrhythmias ($p = 0.6$).

Conclusions: MDCM identifies a consistent subgroup of IDCMs discovered in an early phase rather than a specific disease and it presents benign long-term outcome. Initially it is characterized by a less adverse evolution, however it presents a long term progression approaching the other IDCM. Baseline LVEF cut-off of 35% is not helpful in predicting the risk of major arrhythmic events in MDCM.

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Long term follow up after refined balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension

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(background)Chronic thromboembolic pulmonary hypertension (CTEPH) is known as a serious disease with poor prognosis. Although pulmonary endarterectomy (PEA) can cure some patients, not all patients can undergo PEA because of technical limitations. Recently, we reported our initial experience with balloon pulmonary angioplasty (BPA) for 68 inoperable patients with CTEPH. In this report, exercise capacity and hemodynamics were remarkably improved with low mortality. However, long term outcome of BPA, especially the cumulative survival rate was not yet investigated.

(method)211 patients (male 16, mean age 62.3) with inoperable CTEPH who underwent BPA (1015 procedures) between November 2004 and February 2014 in our hospital were enrolled. 103 patients were completed BPA procedures and 89 patients were followed up more than 6 months. We investigated exercise capacity and hemodynamics at baseline, immediate after BPA and follow up. In addition, cumulative survival rate of them was analyzed using Kaplan-Meier method.

(result)There were 5 in-hospital deaths and in-hospital mortality was 2.4%. Exercise capacity and hemodynamics were significantly improved. At follow up (av-

eraged 16.0 months), none of them experienced restenosis or recurrence of pulmonary hypertension even after the discontinuation of pulmonary hypertension specific drugs. Exercise capacity at follow up were unchanged, whereas hemodynamics were additionally improved compared to that at immediate after BPA. The long term favorable effect of BPA on hemodynamics resulted in good survival rate of our patients treated with BPA. Cumulative survival rate at 1-, 2-, 3- and 5-year was 96, 96, 95 and 90%, respectively.

Outcome of BPA

	Pre BPA	Immediate after BPA	Follow up (N=89)
WHO FC	3±0.36	2±0.37	2±0.43
6MWD (m)	266.0±129.0	356.0±137.4	394.5±111.6
mPAP (mmHg)	42.1±10.6	26.0±4.8	22.0±5.1
PVR (dynes·cm ⁻⁵)	694.7±520.3	362.5±117.2	292.7±116.1

(conclusion) Refined BPA could improve exercise capacity and hemodynamics of inoperable patients with CTEPH. Additional improvement of hemodynamics after long term follow up resulted in good survival rate of them treated with BPA. Refined BPA would be a better alternative to medicinal treatment for inoperable patients with CTEPH.

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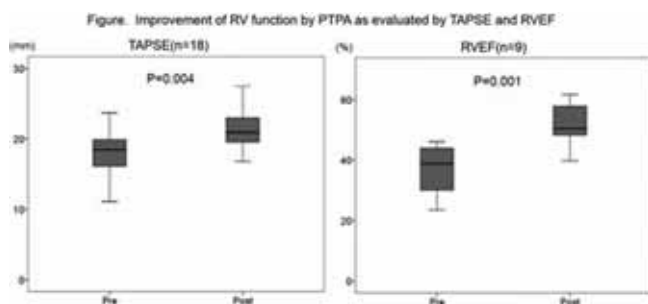
Percutaneous transluminal pulmonary angioplasty improves right ventricular function in patients with inoperable chronic thromboembolic pulmonary hypertension

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Purpose: Recent studies have demonstrated that percutaneous transluminal pulmonary angioplasty (PTPA) improves pulmonary hemodynamics in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). In this study, we examined whether PTPA also improves right ventricular (RV) dysfunction in those patients.

Methods: We performed a total of 232 PTPA procedures (median 4.5 procedures per patient) for 48 consecutive patients with inoperable CTEPH (median age 64 yrs, 77.1% female). Before PTPA, we treated all patients with optimal medical treatment and performed right heart catheterization before and after PTPA. RV function was evaluated by tricuspid annular plane systolic excursion (TAPSE) on echocardiogram (n=18, 37.5%) and RV ejection fraction (RVEF) on cardiac magnetic resonance imaging (n=9, 19%) before and after PTPA.

Results: No patient died during the PTPA procedure or during a mean follow-up period of 8.5 months. Comparisons before and after PTPA showed significant hemodynamic improvements for mean pulmonary artery pressure (41.1 ± 10.4 to 25.7 ± 5.4 mmHg, $P < 0.001$), cardiac index (2.2 ± 0.5 to 2.7 ± 0.6 L/min·m², $P < 0.001$) and PVR (738 ± 345 to 283 ± 97 dyn·sec·cm⁵, $P < 0.001$). Furthermore, RV function was also significantly improved for both TAPSE (18.3 ± 3.3 to 21.6 ± 2.8 mm, $P = 0.004$) and RVEF (36.9 ± 8.8 to $52.1 \pm 7.3\%$, $P = 0.001$) (figure).



Conclusions: PTPA improves not only pulmonary hemodynamics but also RV function in patients with inoperable CTEPH.

1153 | BEDSIDE

Either balloon pulmonary angioplasty or surgical pulmonary endarterectomy can cover most of patients with chronic thromboembolic pulmonary hypertension as treatment option

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Aims: Pulmonary endarterectomy (PEA) is the standard therapy for chronic thromboembolic pulmonary hypertension (CTEPH); however, up to 40% of patients are non-operable. Recently, the efficacy of balloon pulmonary angioplasty (BPA) for non-operable patients has been reported, as the procedure becomes more refined. We evaluated the efficacy and safety of BPA for non-operable CTEPH patients as well as those of surgical PEA in operable CTEPH.

Methods: Consecutive 60 CTEPH patients were reviewed retrospectively. Twenty-five operable patients underwent PEA (57.2±13.6 years old, San-Diego type I: 11, II: 3, III: 11, IV: 0), and 32 non-operable patients underwent BPA

(67.4±11.5 years old, San-Diego type I: 0, II: 4, III: 20, IV: 8). BPA was repeated in 1 to 6 sessions to every patient depending on their severity. Three patients did not consent with any invasive procedure because of advanced age.

Results: Although proportion of San Diego classification was different between PEA and BPA group, both PEA and BPA significantly improved hemodynamics and symptoms similarly, such as a significant increase in cardiac output (CO) and decrease in mPAP and pulmonary vascular resistance (PVR) (Table). Reperfusion pulmonary injury occurred in 3 patients (12.0%) after PEA, and in 27 sessions (28.4%) after BPA with 3 sessions required emergent intubation. The mortality rates of PEA and BPA were 8.0% and 3.1%, respectively ($P = \text{NS}$).

Table 1

		Baseline	Post procedure	P value
BPA (n=32)	CO (L/min)	3.50±0.86	4.25±1.13	<0.001
	mPAP (mmHg)	38.9±7.1	21.1±5.7	<0.001
	PVR (dynes/cm ⁵)	761±333	285±137	<0.001
	WHO Fc (I/II/III/IV)	(0/4/20/8)	(12/16/3/0)	<0.001
PEA (n=25)	CO (L/min)	3.36±1.08	4.41±1.54	0.006
	mPAP (mmHg)	43.9±11.0	21.7±6.5	<0.001
	PVR (dynes/cm ⁵)	772±273	262±123	<0.001
	WHO Fc (I/II/III/IV)	(0/3/14/8)	(13/8/2/0)	<0.001

Conclusion: The efficacy and safety of BPA for non-operable cases were similar to those of PEA for operable cases. Most CTEPH patients can be satisfactorily treated by BPA or PEA.

1154 | BEDSIDE

A randomized open label study comparing first-line treatment with bosentan or sildenafil in chronic thromboembolic pulmonary hypertension (CTEPH)

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Background: Phosphodiesterase type-5 inhibitors (PDE-5 I) and endothelin receptor antagonists (ERA) are oral drugs effective in patients with idiopathic pulmonary arterial hypertension (PAH) and PAH associated with connective tissue diseases. We assessed the effects of these two classes of drugs in patients with CTEPH.

Objectives: To compare first-line sildenafil (S) treatment (20 mg tid) with first-line bosentan (B) treatment (125 mg bid) in patients with operable and not operable CTEPH.

Methods: Consecutive naïve patients with CTEPH were randomized to receive B or S. Evaluation was performed by clinical assessment, 6-minute walk test [6MWT] and right-heart catheterization [RHC] at baseline and after 3-4 months of therapy. Statistical analysis: T-test and Wilcoxon-Mann-Whitney test.

Results: 114 CTEPH patients were randomized: 58 to the B group (mean age 64±16; Female/Male: 37/21) and 56 to the S group (mean age 61±17; Female/Male: 26/30). Four patients (6.9%) in the B group and 3 (5.4%) in the S group did not complete the short term evaluation because of death, pulmonary endarterectomy (PEA) before the re-evaluation, adverse events. 54 patients in the B group and 53 in the S group completed the study (mean treatment period: 4.0±1.5 months). Twenty-three patients in B group and 33 patients in S group underwent PEA after the treatment period. No differences in the effects were observed between S and B and between operable and not operable patients.

Effects of therapies

	6MWT (m)	RAP (mmHg)	mPAP (mmHg)	CI (L/min/m ²)	PVR (WU)	MVO2 (%)
Baseline	372±141	8±4	44±10	2.6±0.7	8.3±3.9	63±8
Bosentan	418±139	7±4	40±9	2.9±0.8	6.3±3.0	65±7
p	<0.001	0.79	<0.001	<0.001	<0.001	0.04
Baseline	406±134	8±5	49±11	2.6±0.8	8.6±3.8	64±9
Sildenafil	461±144	7±3	42±8	2.8±0.6	6.5±2.4	67±7
p	<0.001	0.007	<0.001	<0.001	<0.001	<0.001

RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance, MVO2: mixed venous oxygen saturation.

Conclusion: Treatment with S or B are associated with similar improvements in exercise capacity and hemodynamics in patients with operable and not operable CTEPH

1155 | BEDSIDE

Sildenafil increases stroke volume during exercise in patients with chronic thromboembolic pulmonary hypertension

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Introduction: Stroke volume (SVi) is an important prognostic factor in patients with pulmonary hypertension and is typically assessed at rest. We sought to eval-

uate whether a single dose of oral sildenafil can influence the SVi response to exercise in patients with chronic thromboembolic pulmonary hypertension (CTEPH). **Methods:** Fourteen CTEPH patients and 8 healthy controls underwent cardiac magnetic resonance (CMR) imaging at rest and during incremental supine bicycle exercise to near-maximal exertion with simultaneous invasive hemodynamic monitoring. During real-time exercise and free-breathing, left and right ventricular (LV and RV) volumes were derived from real-time cine imaging and registered with simultaneous invasive measures of mean pulmonary artery pressure (mPAP). Exercise was performed at baseline and then following administration of 50mg oral sildenafil.

Results: As illustrated in Figure 1, CTEPH patients had a greater increase in mPAP relative to cardiac output (CO) than controls at baseline (8.6 ± 1.9 vs. 1.5 ± 0.3 mmHg/l/min; $P=0.002$). In addition, SVi and RV ejection fraction (RVEF) increased during exercise in controls, but not in CTEPH patients (interaction group*workload $P<0.0001$). Sildenafil decreased the slope of the mPAP/CO relationship both in CTEPH patients ($P=0.02$) and in controls ($P=0.09$). However, this was associated with an increased SVi in CTEPH patients ($P<0.05$), but not in controls. Within the CTEPH cohort, the increase in SVi following sildenafil was greater during near-maximal exercise-intensity than at rest ($P=0.02$).

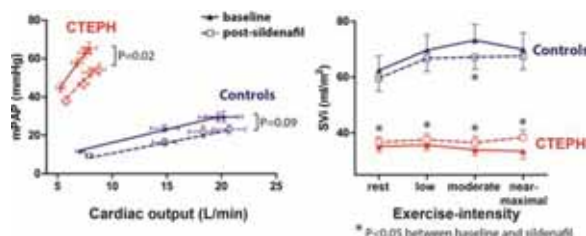


Figure 1

Conclusion: Sildenafil improves RV function and stroke volume during exercise in patients with CTEPH, but not in healthy subjects.

CLINICAL PHENOTYPES AND OUTCOMES IN CARDIOMYOPATHIES

1193 | BEDSIDE

Structural myocardial substrate is a prerequisite for malignant ventricular arrhythmias and sudden death in carriers of ARVC-causing desmosomal gene mutations

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Background: Experimental studies raised the hypothesis that mutations of genes encoding for desmosomal (DS) proteins may "per se" induce electrical ventricular instability and life-threatening arrhythmias, independently of development of a structural myocardial substrate. This study assessed whether the occurrence of malignant arrhythmic events among carriers of DS-gene-mutations depends on phenotypic expression of arrhythmogenic right ventricular cardiomyopathy (ARVC).

Methods: The study population included 123 DS-gene mutation carriers (62 males; median age 29 (15–47) years) with no history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) at the time of first clinical evaluation. The cumulative probability of experiencing VT/VF or SCD was evaluated prospectively during a long-term follow-up and stratified by presence and severity of the ARVC phenotype. ARVC was classified as "definite" or "borderline" according to the 2010 International Task Force (ITF) criteria and its phenotypic expression graded as mild or severe on the basis of presence of epsilon waves, extent of negative T-wave and severity of RV dilatation/dysfunction.

Results: At the time of first clinical evaluation, 69 of 123 (56%) subjects fulfilled the ITC diagnostic criteria for ARVC (genotype +/phenotype +), either "definite" (N=51; 41%) or "borderline" (N=18; 15%), while 54 (44%) did not (genotype +/phenotype -). During a median follow-up of 7 (5–12) years, 11 subjects had arrhythmic events such as sustained VT (N=9), appropriate ICD shock on VF (N=1) and SCD (N=1). All patients who reached the arrhythmic end-point had a diagnosis of "definite" ARVC, whereas genotype +/phenotype - subjects and "borderline" ARVC patients had an uneventful long-term outcome ($p<0.001$). Among patients with "definite" ARVC, a severe phenotype was associated with a significantly higher rate of arrhythmic events than that of a mild phenotype (38% vs 4%; $p=0.002$).

Conclusions: The study results suggest that the development of a structural myocardial substrate is a prerequisite for malignant ventricular arrhythmias and SCD in carriers of ARVC-causing desmosomal gene mutations. These findings have significant implications for clinical monitoring and risk assessment of ARVC genotype +/phenotype - subjects.

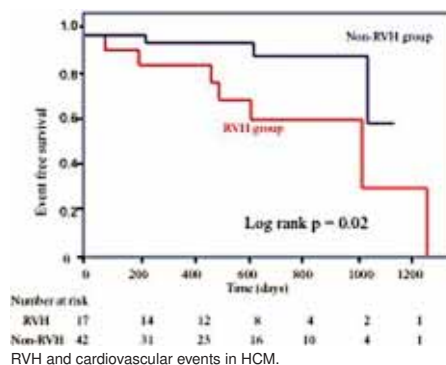
1194 | BEDSIDE

Right ventricular hypertrophy as a determinant for clinical severity in hypertrophic cardiomyopathy: evidence from magnetic resonance imaging

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Background: Although left ventricular (LV) morphology and function have been well studied in hypertrophic cardiomyopathy (HCM), few data exist regarding right ventricular (RV) ones. Therefore, we studied impact of RV morphology and function on cardiovascular events in HCM using cardiac magnetic resonance imaging (CMR).

Methods and results: We examined 59 HCM patients (36 men, age 60.5 ± 15.0 years) who underwent CMR exhibiting maximal LV thickness >13 mm and asymmetrical septal hypertrophy. RV hypertrophy (RVH), defined as RV maximal wall thickness >5 mm, was observed in 17 of 59 patients (RVH group). The RVH group showed higher prevalence of heart failure (64.7% vs. 11.9%, $p<0.0001$) associated with higher brain natriuretic peptide levels (387.7 ± 287.4 vs. 226.1 ± 217.3 pg/ml, $p=0.02$) than those in the non-RVH group. The RVH group showed reduced RV end diastolic volume index (48.7 ± 16.0 ml/m² vs. 64.4 ± 13.9 ml/m², $p=0.001$) in accordance with greater LV mass index (110.4 ± 21.6 g/m² vs. 75.6 ± 21.4 g/m², $p<0.0001$). Interestingly, the RVH group was highly associated with RV-late gadolinium enhancement in comparison with the non-RVH group (29.4% vs. 0%, $p<0.0001$). During follow up period, the RVH group had higher incidence of cardiovascular events such as heart failure admission, ventricular tachyarrhythmia/fibrillation, stroke and sudden cardiac death than that in the non-RVH group (log-rank $p=0.02$). Under these conditions, multivariable analysis revealed that only RV maximal wall thickness was independent predictor of cardiovascular events ($p=0.03$).



RVH and cardiovascular events in HCM.

Conclusion: These results demonstrate that HCM with RVH determined by CMR can be associated with the higher incidence of cardiovascular events than non-RVH patients.

1195 | BEDSIDE

Prognostic impact of quantification of late gadolinium enhancement in cardiac magnetic resonance on mortality and morbidity in hypertrophic cardiomyopathy with systolic dysfunction

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Purpose: A subset of patients with hypertrophic cardiomyopathy (HCM) develop systolic dysfunction so-called end-stage phase. Reduced left ventricular (LV) ejection fraction (EF) reflects poor prognosis. Late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) detecting myocardial fibrosis is associated with major adverse cardiac events (MACE) in general HCM population. Inverse relationship is present between LGE and LVEF in HCM, however, which of LGE or LVEF predicts mortality and morbidity more precisely in HCM with systolic dysfunction remains unclear.

Methods: We assessed the extent of LGE with a threshold of 6 SD expressed as a percentage of the total LV mass (%LGE) in 47 consecutive HCM patients with systolic dysfunction defined as LVEF $<50\%$ (average $34 \pm 13\%$) who underwent CMR (36 males, mean age 59 ± 14 years) and followed them over 4.5 ± 1.6 years. The primary composite end point was MACE such as all-cause death, lethal arrhythmia, LV assist device implantation, heart transplantation or stroke due to cardiac emboli. Two separate secondary end points were defined, heart failure (HF) end point including unplanned heart failure hospitalization (UPHFH) and HF death and arrhythmic end point including lethal arrhythmia and sudden cardiac death.

Results: LGE was detected in all patients with an extent of $30 \pm 15\%$ of LV mass. During the follow up, 19 of 47 patients developed primary end point of MACE. On the other hand, 23 of 47 patients had secondary HF end point and 11 of 47 patients reached secondary arrhythmic end point. Multivariable analysis revealed %LGE as the only independent predictor of both primary and secondary HF end points. These risks increased as %LGE increased (hazard ratio [HR]: 2.89 /10%, 95% confidence interval [CI] = 1.39 to 7.82, $p=0.003$ and HR: 3.48 / 10%, 95% CI = 1.62 to 10.0, $p<0.001$, respectively). LVEF was inversely related to %LGE ($r = -$

0.46; $p < 0.001$) and was a predictor of both primary and secondary HF end points in univariate analysis, but not an independent predictor in multivariate analysis. The number of recurrent UPHFH per patient was related to not LVEF but %LGE ($r = 0.49$; $p < 0.02$). Neither %LGE nor EF was a predictor of secondary arrhythmic end point in univariate analysis.

Conclusion: %LGE is the only independent predictor of MACE and HF end point and reflects mortality and morbidity more precisely than LVEF in HCM with systolic dysfunction. Quantification of LGE is useful for predicting MACE and HF events and can contribute to further risk stratification in HCM with systolic dysfunction.

1196 | BEDSIDE

Independent validation of the novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD)

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Purpose: Current risk stratification models for sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM) are suboptimal. The recent HCM Risk-SCD study (O'Mahony et al. Eur Heart J, 2013) proposed a novel risk prediction model to improve decision-making for prophylactic ICD implantation in individual HCM patients. This study is an external and independent validation of this new risk prediction model.

Methods: The study population consisted of a consecutive cohort of 706 HCM patients without prior SCD event, from 2 tertiary referral centers. Primary endpoint was a composite of SCD and appropriate ICD therapy, identical to the HCM Risk-SCD endpoint. The 5-year SCD risk was calculated using the HCM Risk-SCD formula. Receiver operating characteristic (ROC) curves and C-statistics were calculated for the HCM Risk-SCD score, and the 2003 ACC/ESC guidelines and 2011 ACCF/AHA guidelines.

Results: During follow-up (7.7 ± 5.3 years), SCD occurred in 42 (5.9%) of 706 patients (age 49 ± 16 years, 34% female). The C-statistic of the new model was 0.71 (95% CI 0.60–0.81, $p = 0.002$) which performed significantly better than the conventional risk factor models based on the 2003 guidelines (C-statistic of 0.63; 95% CI 0.51–0.74, $p = 0.05$) and 2011 guidelines (C-statistic of 0.60; 95% CI 0.47–0.73, $p = 0.1$). Figure 1 shows the ROC curves for the novel risk prediction model and the current guidelines.

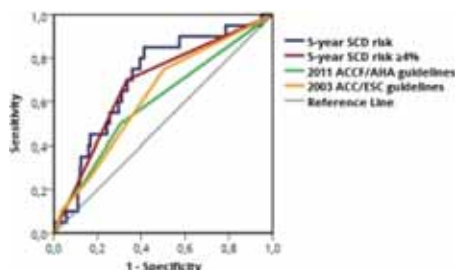


Figure 1

Conclusion: The recently developed HCM Risk-SCD score significantly improves the risk stratification of individual HCM patients, as compared to the existing risk stratification methods.

1197 | BEDSIDE

Prevalence and age distribution of hypertrophic cardiomyopathy phenocopies: data from a single center including both adults and children

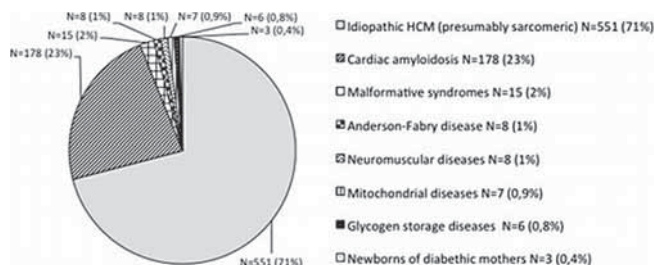
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Purpose: We evaluated the prevalence and age distribution of hypertrophic car-

diomyopathy (HCM) phenocopies in a large population including both children and adults.

Methods: Aetiological diagnosis was made in 776 HCM phenotype patients (0–94 yrs) on the basis of clinical/instrumental features, molecular biology, enzymatic dosages, biopsy, magnetic resonance imaging and 99mTc-DPD scintigraphy.

Results: The prevalence of the different phenocopies is reported in the figure. The distribution of aetiologies according to age decades is shown in the table and was strongly age-dependent.



Prevalence of different aetiologies.

Conclusions: This is the first study that provides data on the prevalence of the different HCM phenocopies in a referral centre, treating both adults and children.

PERCUTANEOUS AORTIC AND MITRAL VALVE REPAIR

1206 | BEDSIDE

Self-expandable versus balloon-expandable devices in patients with mixed aortic valve stenosis undergoing transcatheter aortic valve implantation: results from a single-center registry

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Objectives: The aim of this study was to compare outcomes in patients with mixed aortic stenosis (MAS), undergoing transcatheter aortic valve implantation (TAVI) via a transfemoral (TF) approach with the Medtronic CoreValve (MCV) versus Edward-SAPIEN or SAPIEN XT Valve (ESV).

Background: Prevalence of MAS in patients undergoing TAVI is unclear. Due to the particular pathophysiology of this condition, these patients could represent a high-risk group with regards to device malpositioning, post-procedural aortic regurgitation and other complications. To date no study has evaluated the performance of the commercially available MCV and ESV in this particular subgroup of patients.

Methods: From November 2007 to September 2013 all patients with a documented baseline MAS condition that underwent transfemoral (TF) TAVI either with MCV or ESV, were included in this analysis. MAS patients were defined by the presence of at least moderate aortic stenosis (AS) associated with moderate or severe aortic regurgitation (AR). Outcomes were assessed according to valvular academic research consortium (VARC-2) criteria at 30 days, 1 and 2 years.

Results: Among 472 patients in whom a baseline echocardiographic data were available, 295 (62.4%) had a pure aortic stenosis (PAS) while 177 had MAS (37.6%). Of 177 MAS patients, 59 (33.3%) were treated with MCV and 83 (46.8%) with ESV through a TF approach. At 30 days there were no differences in all-cause mortality (5.2% vs. 2.4%; $p = 0.391$), cardiovascular mortality (3.4% vs. 2.4%; $p = 0.724$), device success (58.6% vs. 67.5%; $p = 0.282$) or early safety endpoint (34.5% vs. 25.3%; $p = 0.237$). However, a greater incidence of valve embolization (7.5% vs. 0%; $p = 0.013$), need for a second valve (9.4% vs. 0%; $p = 0.005$), permanent pacemaker implantation (28.8% vs. 9.8%; $p = 0.010$) and moderate to severe peri-prosthetic AR (PPAR; 12.1% vs. 0%; $p = 0.001$) was found in the MCV group.

Finally, at 1 year there were no differences in all-cause and cardiovascular mortality (15.5% vs. 12.2%; $p = 0.572$, and 12.1% vs. 4.9%; $p = 0.119$). Conversely, at 2 years, a greater all-cause (29.3% vs. 14.6%; $p = 0.035$) and cardiovascular mortality (21.1% vs. 4.9%; $p = 0.001$) was found in the MCV group.

Conclusions: MCV was associated with a greater incidence of moderate-to-severe PPAR and other intra- and peri-procedural complications in MAS patients that underwent TAVI. No significant differences were found in mortality at 30 days

Abstract 1197 – Table 1. Distribution of the different aetiologies according to age decades

Phenocopies	0–10 yrs N=69	10–20 yrs N=38	20–30 yrs N=52	30–40 yrs N=75	40–50 yrs N=134	50–60 yrs N=138	60–70 yrs N=153	70–80 yrs N=88	80–90 yrs N=28	90–100 yrs N=1
Idiopathic HCM (presumably sarcomeric)	44 (64)	34 (89)	46 (88)	69 (92)	108 (81)	102 (74)	90 (59)	46 (52)	11 (39)	1 (100)
Wild type TTR amyloidosis	0	0	2 (4)	5 (7)	12 (9)	15 (11)	17 (11)	9 (10)	1 (4)	0
AL amyloidosis	0	0	0	0	11 (8)	14 (10)	36 (24)	18 (20)	3 (11)	0
Mutant TTR amyloidosis	0	0	0	0	0	1 (1)	6 (4)	15 (17)	13 (46)	0
Malformative syndromes	8 (12)	2 (5)	1 (2)	1 (1)	1 (1)	1 (1)	1 (1)	0	0	0
Anderson-Fabry disease	0	0	1 (2)	0	1 (1)	3 (2)	3 (2)	0	0	0
Neuromuscular diseases	5 (7)	2 (5)	1 (2)	0	0	0	0	0	0	0
Mitochondrial diseases	5 (7)	0	0	0	1 (1)	1 (1)	0	0	0	0
Glycogen storage diseases	4 (6)	0	1 (2)	0	0	1 (1)	0	0	0	0
Newborns of diabetic mothers	3 (4)	0	0	0	0	0	0	0	0	0

and 1 year between the 2 valve groups. However a greater all-cause and cardiovascular mortality was found in patients treated with the MCV at 2 year follow-up.

1207 | SPOTLIGHT

Effective orifice area and hemodynamic performance of the 14Fr transcatheter colibri heart valve compared with the SAPIEN and Corevalve TAVI

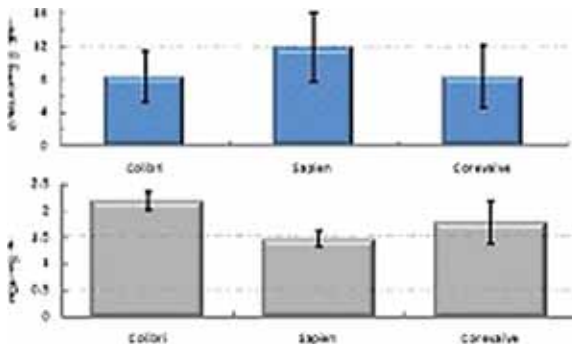
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Background: Transcatheter heart valve implantation has emerged as a technology to replace the aortic valve of patient with high surgical risk. Current available technology approved includes the Sapien and the corevalve that have shown better hemodynamics than the surgical valves. In November 2012, the first in human series of the Colibri heart valve were implanted in our center. The Colibri Heart Valve is the first pre-package, pre-mounted, low profile, dry valve that is ready to be used from its 14Fr introducer to the patient.

We sought to compare the Effective Orifice Area (EOA) and hemodynamic performance of these three devices within the first 30 days following implantation.

Methods: Doppler hemodynamics were performed before and after implantation of the Colibri Heart Valve (CHV) in five consecutive patients. Gradient across the valve was assessed using continuous Doppler. EOA was calculated using the left ventricular outflow tract (LVOT) area multiply by ratio of the time velocity integral (TVI) of the LVOT measured with pulse Doppler and the TVI across the Colibri Heart Valve recorded with continuous Doppler. These findings were compared using t-test and ANOVA with published data for the Sapien 23mm valve (n16) and the 26mm Corevalve (n40).

Results: The mean gradient of the 23mm internal diameter CHV was 8.4 + 3.4mmHg versus 11.9 + 4.2 of the 23mm Edward's Sapien and 8.4 + 3.8 for the 26mm CoreValve. The EOA of the CHV was 2.18cm² + 0.17 versus 1.47cm² + 0.14 for the 23mm Sapien (p=0.0001) and 1.78cm² + 0.4 for the 26mm Corevalve (p=0.0169).



Conclusion: Colibri Heart Valve showed lower gradients and statistically significantly higher EOA than the 23mm Sapien and the 26mm Corevalve when measured within the first 30 days post implantation.

1208 | BEDSIDE

Hemodynamic assessment of percutaneous versus surgical bioprostheses for aortic stenosis during exercise: a pilot study

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Background: Poor hemodynamic performance as assessed by transprosthetic gradient (TG) after aortic bioprosthesis implantation is associated with less symptomatic improvement and worse prognosis. This effect is magnified in smaller valves. Transcatheter aortic valve implantation (TAVI) has been associated with lower TG when compared to surgical aortic valve replacement (SAVR) in previous studies. However, no data are available on the hemodynamic response to exercise in this population.

Aim: To assess the hemodynamic performance of TAVI versus SAVR in small sized valves at rest and exercise

Methods: Twenty patients (P) were prospectively assessed, consisting of 10 P submitted to TAVI with the Corevalve prosthesis (23 & 26) and 10 age-matched SAVR controls with similar valve dimensions, who had been submitted to valve implantation within a similar interval. A symptom-limited treadmill exercise protocol (EP) modified for frail/elderly patients was used. Echocardiographical evaluation was performed at rest and peak exercise.

Results: No significant differences between groups were found on patient age (TAVI 81.7 + 6.66 y vs SAVR 80.2 + 3.37 y), BMI (25.0 +0.9 vs 27.8 +1.15, all p=NS) or time since implantation (17.2 +3.6 vs 14.7 +5.3 months, p=NS). The logistic Euroscore was higher in TAVI patients (15.2% vs 8.7%; p 0.013).

SAVR patients were more likely to be under betablocker therapy (20% vs 70%, p=0.025), with no other differences in medication. Max heart rate during EP was 107 +10.9 vs 121 +10.4 and exercise duration was 7.21 + 1.8 vs 14.0 + 4.7 minutes (p=0.002). No differences were found on left ventricular (LV) ejection fraction (EF) (LVEF <50%: 30% vs 20%) or LV dimensions (LV end-diastolic diameter (d) 50.8 +2.3 vs 50.5 +2.6, LV end-systolic d 29.1 +1.9 vs 31.8 +2.3, p=NS). Resting TG was significantly lower in TAVI patients (Max TG 14.43 +1.79 vs 21.5 +1.15, p=0.003, mean TG 7.5 +1.0 vs 12.5 +0.8, p=0.0019). TG at peak exercise was also significantly lower in TAVI patients (Max TG 23.3 +3.1 vs 38.7 +3.6, p=0.004; mean TG 11.7 +2.1 vs 21.1 +2.3, p=0.01). Systolic pulmonary artery pressure, transmitral wave velocities and peak LVEF were similar. After multi-variate analysis of baseline clinical and echocardiographical variables, TAVI was the only independent predictor of lower max TG at rest and at peak exercise (p=0.032, p=0.023).

Conclusion: Patients submitted to TAVI have a better transprosthetic hemodynamic profile at rest and during exercise than SAVR. TAVI may be a more suitable option in AVR in patients when a small diameter bioprosthetic valve is implanted.

1209 | BEDSIDE

Impact of mitral ring remodeling after mitralclip procedure in the reduction of functional mitral regurgitation

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The Mitralclip (MC) procedure appears to reduce mitral ring diameters in patients with functional etiology but is unclear whether this reduction has relation with the severity of MR postprocedure.

Our objective was to investigate if the remodeling of the mitral ring with the MC procedure has some impact in the reduction of MR in patients with functional etiology.

Methods: From October 2012 to January 2014 all patients with functional MR who were treated with a MC in our centre were included in the study. A transthoracic and transesophageal (TEE) 2D and 3D echocardiogram was performed immediately before and after placement of the device (IE33 equipment, Qlab software, Philips). The changes in mitral ring diameters measured by means of 3DTEE (intercomisural (IC) and anteroposterior (AP)) were correlated with the severity in MR evaluated by the effective regurgitant orifice (ERO).

Results: 18 consecutive patients with functional MR were included (mean age 61±16; 72% males; 66% NYHA functional class III-IV; FEVI 28%±12; pulmonary artery systolic pressure 48±10 mmHg). Immediately post procedure the ERO decreased from 0.49±0.06 to 0.20±0.10cm², p<0.0005. A significant reduction was observed in the AP-diameter of the mitral annulus (29±5 vs 26±5mm, p<0.0005) without changes in IC-diameter (42±4 vs 42±4mm, p=0.76). A significant correlation was observed between the reduction in AP-diameter and the reduction in ERO immediately postprocedure (r=0.55, p=0.017, Fig. 1).

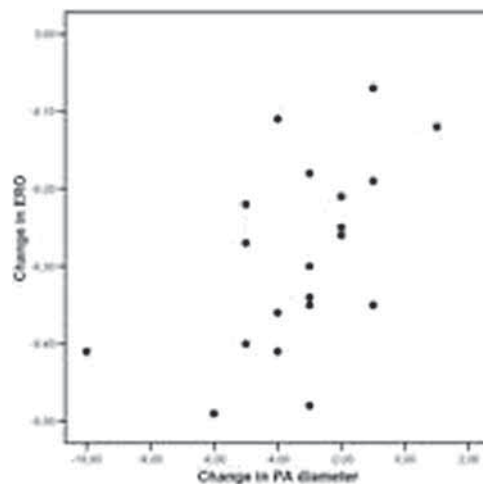


Figure 1. Correlation changes ERO-APmitral annulus.

Conclusions: The Mitralclip procedure causes an immediate reduction in AP-diameter of the mitral annulus in patients with functional MR. This remodeling is significantly associated to reduction in MR, evaluated by ERO.

1210 | BEDSIDE

Computed Tomography for the assessment of mitral valve in patients undergoing transcatheter aortic valve

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Introduction: Indication of percutaneous aortic valve implantation (TAVI) when simultaneous presence of moderate-to-severe mitral regurgitation (MR) occurs is object of debate. Albeit multidetector computed tomography (MDCT) is routinely performed to TAVI candidates in many centers, the potential usefulness of this tool to decide which patients with dual valvulopathy may benefit from isolated TAVI is unknown.

Methods: We analysed 94 patients treated with transfemoral self-expandable aortic prosthesis according to the baseline degree of their MR. All clinical and procedural variables were prospectively recorded. An off-line analysis of echocardiographic and MDCT images, including annulus and leaflets semi-quantitative analysis of calcification, was performed in order to determine predictors of MR improvement.

Results: Mean age was 81 ± 7 years, and median STS-score 5.1 [3.8-7.6]%. Patients with moderate-to-severe MR ($n=42$, 44.6%) presented worse left ventricular ejection fraction (55% vs 63%, $p=0.006$), and higher systolic pressure of pulmonary artery (51 vs 39 mmHg, $p<0.001$). In 22 pts (52.4%) MR degree improved to mild or none. MDCT independent predictors of MR improvement were: absence of leaflets calcification in 76.5% vs 23.1%, OR=1.92 [95%CI: 0.03-0.79], $p=0.026$, and mitral annulus size (34.7 ± 3.5 vs. 39.7 ± 3.8 mm), OR=2.61 [95%CI: 0.01-0.40], $p=0.003$, with 35.95 mm as the cut-off value in ROC analysis that better predicted MR improvement. Other predictors of MR improvement were: Baseline NYHA functional class ≤ 2 ; absence of calcification of mitro-aortic junction; absence of left bundle branch block; and baseline aortic regurgitation ≥ 3 as assessed by echo.

Conclusions: More than half of the patients who suffered from simultaneous moderate/severe MR and underwent TAVI had a significant reduction in the degree of MR. MDCT analysis of the mitral anatomy determined that MR improvement was not influenced by mitral annulus calcification but it was inversely related to the diameter of mitral annulus and the degree of calcification of mitral leaflets and mitro-aortic junction.

1211 | BEDSIDE

Surgical outdownd versus percutaneous access in transfemoral transcatheter aortic valve implantation: insights from the brazilian TAVI registry

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Background: Choosing the best strategy for vascular access in patients undergoing transcatheter aortic valve implantation (TAVI) is a crucial step for performing the procedure. Femoral access for TAVI is achieved by either surgical outdownd and closure or percutaneous puncture and hemostasis with closing devices. Currently, little is known about the impact of the two access approaches on clinical outcomes after transfemoral TAVI.

Methods: The Brazilian registry is a national study that prospectively and retrospectively enrolls patients treated with TAVI. Patients undergoing transfemoral TAVI were divided into two groups and compared according to the vascular access approach (percutaneous vs surgical). The choice of technique was left to the discretion of the operator and local heart teams. All-cause mortality, vascular complications, and life-threatening bleeding were analysed one year post-TAVI.

Results: Of the 402 patients enrolled, percutaneous access was performed in 182 and surgical in 220. Clinical outcomes at 30 days and 1 year is detailed in the following Table.

Percutaneous vs surgical approach

	Percutaneous approach (n=182 pts)	Surgical approach (n=220 pts)	p-value
All-cause mortality 30 days	8.8%	8.6%	0.9
All-cause mortality 1 year	25.3%	22.7%	0.7
Major vascular events	8.8%	8.2%	0.8
Life-threatening bleeding	9.3%	8.2%	0.6

Conclusion: In transfemoral TAVI, the vascular access strategy (either percutaneous or surgical) is not a major determinant of clinical outcomes one year after the procedure.

ADVANCING AGE AND ACUTE CORONARY SYNDROME

1233 | BEDSIDE

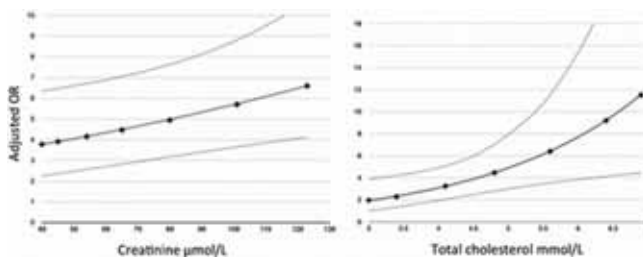
Prevalence of risk factors at presentation and early mortality in patients 80 years or older with ST-segment elevation myocardial infarction

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Purpose: Elderly patients with ST-segment elevation myocardial infarction (STEMI) are at high risk of complications and early mortality; still they are underrepresented in clinical trials and observational studies. We aimed to study risk profiles at presentation and early mortality in older (≥ 80 years) vs. younger (< 80 years) STEMI-patients.

Methods: Prospective cohort study. The study population comprised 4092 consecutive STEMI patients admitted to our university hospital during 2006 to 2010. Baseline characteristics at admission were recorded as well as in-hospital mortality. Explanatory strategy was used in the analyses.

Results: Patients ≥ 80 years ($n=536$) were more likely to be female, have prior myocardial infarction, angina and stroke, but less likely to be current smokers. The crude in-hospital mortality rate was 16.2% in patients ≥ 80 years and 3.5% in those < 80 years (crude odds ratio 5.41, 95% confidence interval, 4.0-7.3). The adjusted odds ratio for mortality for patients ≥ 80 vs. < 80 years increased with increasing levels of serum creatinine and total cholesterol (Figure). In patients with low levels of serum creatinine and total cholesterol, the odds ratio was 3.01 (95% confidence interval, 1.86-4.93; $p=0.0001$); increasing to 11.72 (95% confidence interval 5.26-26.3; $p=0.001$) in patients with high levels of both risk factors.

Adjusted OR for mortality, ≥ 80 vs < 80 yrs

Conclusion: High levels of serum cholesterol and creatinine were important risk factors for early mortality in elderly patients with STEMI. Depending on the levels of cholesterol and creatinine, in-hospital mortality in patients ≥ 80 years varied from a three-fold to an almost twelve-fold risk compared to younger patients.

1234 | BEDSIDE

Mental status at presentation as a predictor of outcome in acute coronary syndrome among elderly patients

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Purpose: To assess the impact of mental status alteration (MSA) at presentation for acute coronary syndrome (ACS) on cardiovascular events among elderly.

Methods: After exclusion of patients with unstable conditions, neurological disorders or language deficiency, we assessed MSA defined by an abnormal confusion assessment test or Mini Mental Status Evaluation (MMSE < 27) in 101 consecutive patients ≥ 75 years old.

3-month follow-up was completed in all patients. Mortality, the primary endpoint of the study was assessed using a cox model adjusted on age, gender, heart rate, Killip class and troponin rise.

Results: MSA was identified in 49 (49%) patients. Patients with MSA were older (84 ± 5 vs 81 ± 5 , $p=0.006$), had lower body index mass (25 ± 4 vs 27 ± 4 , $p=0.02$), lower education level (primary only in 89 vs 67%, $p=0.01$), higher rates of carotid artery surgery (12 vs 2% $p=0.04$) and higher rates of Killip Class ≥ 2 (47 vs 35%, $p=0.03$). The invasive management and medical therapy were similar between patients with or without MSA.

Rates of in-hospital and 3 months mortality were higher in MSA patients (14.3 vs 2%, $p=0.02$ and 20.4 vs 2%, $p=0.003$). Rates of any or cardiovascular hospitalization were high and similar between the groups (32.6 vs 27% and 14.3 vs 11.5%).

The adjusted cox model identified MSA and MMSE as independent predictors of 3-month mortality (HR 13.4, 95%CI 1.7-105 and HR 0.86, 95%CI 0.8-0.9 respectively).

Conclusions: MSA is detected in almost half of patients ≥ 75 years old presenting with ACS using simple clinical tests. Despite similar management the rates of in-hospital and 3 months mortality are dramatically increased in such patients. Studies are needed to assess the mechanisms of the disease and the impact of specific management among such high risk patients.

1235 | BEDSIDE

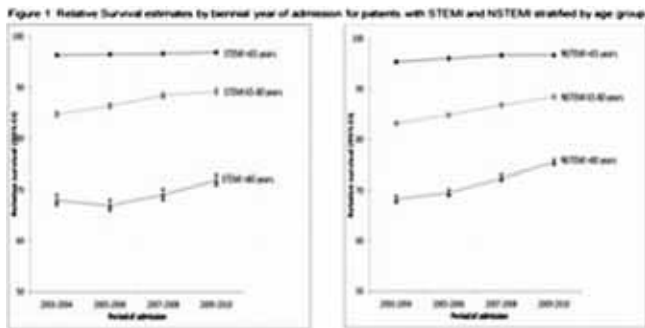
Age-dependent improvements in survival after hospitalisation with acute myocardial infarction: An analysis of the Myocardial Ischemia National Audit Project (MINAP)

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Purpose: Our aim was to investigate age-dependent improvements in survival after hospitalisation with Acute Myocardial Infarction (AMI).

Methods: A total of 583,466 patients with AMI admitted to 247 hospitals between January 1, 2003 and December 31, 2010. Six month relative survival (RS) was calculated using an age, sex and biennial year matched population from the Office for National Statistics. Risk adjusted mortality rates (RMAR) were estimated using shared frailty regression. Evidence-based medications were computed as five-drug treatment with aspirin, clopidogrel, beta-blockers, statin and ACE inhibitors.

Results: Older patients compared with the younger patients presented more frequently with co-morbid conditions, including Chronic Heart Failure (11.1% vs 1.6%), Chronic Renal Failure (7.8% vs 1.7%) and previous AMI (30.8% vs 15.8%). Older patients were less likely to be admitted to a Coronary Care Unit (39.1% vs 64.0%), be under the care of a Consultant Cardiologist (30.1% vs 51.1%) and less frequently received Evidence-Based Medications after hospital discharge (73.7% vs 85.5%). For STEMI, there was an increase in RS for patients aged 65 to 80 ys (84.8% vs 89.2%) and those over 80 ys (68.0% vs 71.8%), but not for patients aged 18 to <65 ys (96.4% vs 96.9%). For NSTEMI patients aged 18 to <65 ys RS was higher, but stable (95.5% vs 96.8%) and improved for patients aged 65 to 80 ys (83.2% vs 88.5%) and patients aged >80 ys (68.3% vs 75.5%). Likewise, RMAR improved for patients aged ≥65 ys, were stable and higher for patients <65 ys.



Conclusions: There were significant improvements in survival after hospitalisation with AMI in the older but not younger patients. The scope for further reductions in mortality is likely to be much greater for older than younger patients with AMI.

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Outcome of patients admitted with acute coronary syndrome and given only palliative treatment

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Purpose: At a time when compliance with guidelines is increasingly used to benchmark the quality of hospital care, very little is known about patients admitted with acute coronary syndromes (ACS) who are treated palliatively. This study aimed to evaluate the baseline characteristics and outcomes of these patients.

Methods: Using the data of ACS patients enrolled in the AMIS Plus Registry from 1997-2012, characteristics at presentation and outcomes were analysed according to 3 treatment groups: palliative treatment, defined as use of aspirin and analgesics only (no other antithrombotics [anticoagulants or antiplatelets, heparins, P2Y12 inhibitors, GPlIb/IIIa] and no reperfusion); conservative treatment, defined as any treatment except pharmacological or mechanical reperfusion; and reperfusion treatment (thrombolysis and/or percutaneous coronary intervention during the index admission).

Results: Among 39,401 ACS patients, 1367 (3.4%) were treated palliatively, 10,865 (27.6%) conservatively and 27,169 (69.0%) underwent reperfusion therapy. In 1997, 6% of all patients were treated palliatively and 60% conservatively. This continuously decreased to below 3% and 17%, respectively in 2012. In comparison with conservatively treated patients and those who underwent reperfusion, palliative patients were older (77y vs 72y vs 63.3y; $p<0.001$), predominantly female (42% vs 35% vs 23%; $p<0.001$), and suffered more frequently from hypertension (72% vs 65% vs 56%; $p<0.001$), diabetes (31% vs 25% vs 16%; $p<0.001$), heart failure (15% vs 8% vs 2%; $p<0.001$), cerebrovascular diseases (15% vs 11% vs 4%; $p<0.001$), renal disease (22% vs 15% vs 4%; $p<0.001$), and dementia (9% vs 6% vs 0.5%; $p<0.001$). They more frequently required resuscitation prior admission (6% vs 4% vs 4%; $p=0.012$) and were more often in Killip class III/IV at admission (19% vs 11% vs 5%; $p<0.001$). Patients treated

palliatively had more complications, such as cardiogenic shock after admission (18% vs 8% vs 4%; $p<0.001$), stroke (1.7% vs 1.2% vs 0.8%; $p<0.001$) and had a higher hospital mortality than patients treated conservatively or with reperfusion (27.1% vs 11.4% vs 3.5%; $p<0.001$).

Conclusion: ACS patients treated palliatively were older, sicker, with more heart failure at admission and suffered a very high in-hospital mortality. While refraining from more active therapy may often constitute the most humane and appropriate approach, a consensus should be reached on whether such patients should be included in the overall evaluation of ACS patient outcomes.

1237 | BEDSIDE

Mortality and neurological outcome in target temperature management at 33 or 36 degrees in the elderly after out-of-hospital cardiac arrest

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Purpose: Age remains an important determinant of outcome in most cardiac diseases, but the effects of target temperature management (TTM) in elderly survivors of out of hospital cardiac arrest (OHCA) are not well established. We aimed to determine mortality and neurological outcome in elderly comatose OHCA survivors and if age modifies the effect of level of TTM.

Methods: This study is a predefined post-hoc analysis of the TTM-trial randomizing 950 patients to 24 h of TTM at 33 or 36 C, which showed no difference in mortality or Cerebral Performance Category (CPC) and modified Rankin Scale (mRS) between the two groups. We analyzed the effect of older age in relation to long term survival and neurological outcome assessed by CPC and mRS after 180 days, dividing patients into 5 age groups: <65 (median), 66-70, 71-75, 76-80 and >80 years of age.

Results: Elderly patients (≤65 vs >65) more often had non-shockable rhythm ($p=0.01$), while bystander CPR ($p=0.04$) and ST-segment elevation ECG were less prevalent ($p<0.01$). Other pre-hospital characteristics, incl. OHCA location, time to ROSC, witnessed arrest and bystander defibrillation were similar.

Increasing age was significantly associated with a lower survival rate (Fig. 1), corresponding to an adjusted hazard ratio (HR) of 1.04 per year of age, 95% CI = 1.04-1.06, $p<0.001$). As a result, CPC and mRS was higher with increasing age. Focusing on survivors, a trend towards worse neurological outcome (CPC>2 or mRS>3) in higher age groups was found ($p=0.04$, $p=0.001$, resp.) The effect of level of TTM was not modified by age, Pinteraction=0.94.

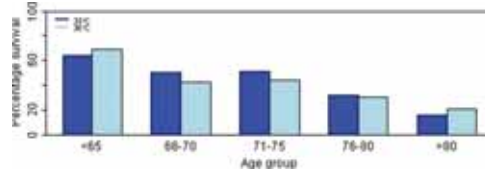


Figure 1. 180 day survival in the 5 age groups

Conclusions: Increasing age is associated with increased mortality and adverse neurological outcome in comatose survivors of OHCA. There was no difference in outcome between 33 and 36 in any of the age groups.

1238 | BEDSIDE

Resuscitating octogenarians with out-of-hospital cardiac arrest, is it worth it?

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Background: Out-of-hospital cardiac arrest (OHCA) is associated with a poor prognosis and as co-morbidity and susceptibility to critical illness increases with age ethical dilemmas may arise when OHCA occur in the very old.

Methods: During 2002-2011 consecutive patients with OHCA were treated by the physician-based EMS-system. Pre-hospital data based on Utstein-criteria and data on post-resuscitation care were collected.

Results: A total of 5,329 patients with OHCA were recorded, and 24% (n=1,279) were octogenarians. Treatment was more often terminated in the pre-hospital setting in octogenarians (76% vs. 61%, $p<0.001$), but 218 (16%) octogenarians were successfully resuscitated. Mean age was 85±4 vs. 61±12, octogenarians were less often male (54% vs. 74%, $p<0.001$), whereas non-shockable rhythm (59% vs. 46%, $p<0.001$) and OHCA in a private setting (73% vs. 61%, $p=0.001$) were more common. Octogenarians were less often treated with therapeutic hypothermia (27% vs. 53%, $p<0.001$), but cardiac etiology of the OHCA had similar

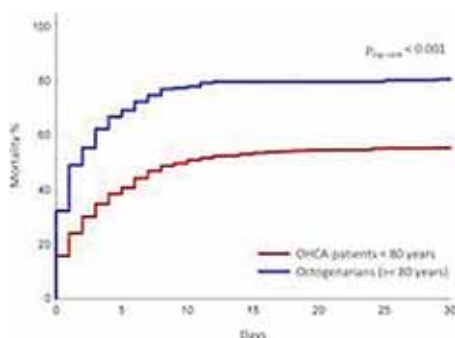


Figure 1

prevalence (82% vs. 81%, $p=0.8$). 30-day mortality in successfully resuscitated patients was 81% vs. 55% ($p<0.001$), Fig.1, which remained significant after adjustment for known confounders (HR=1.68 (95%CI: 1.34-2.10), $p<0.001$). A favorable neurological outcome (cerebral performance category 1 or 2) was found in 72% ($n=33$) of octogenarians compared to 85% ($p=0.02$) corresponding to an adjusted OR 0.29 (0.11-0.75), $p=0.01$.

Conclusion: OHCA in octogenarians was associated with a significantly higher mortality rate even after adjustment for other prognostic factors, including comorbidity. However the majority of octogenarian survivors were discharged with a good neurological outcome, and thus refraining from resuscitating the old in general does not seem justified.

MORE THAN DISEASE MANAGEMENT: DILEMMA IN CARDIOVASCULAR CONDITIONS

1248 | SPOTLIGHT

The significance of knowledge and skills of close relatives to patients with LVAD

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Background: Close relatives to patients with LVAD are often burdened by anxiety regarding malfunction of the LVAD. In order to provide knowledge and skills, an education- and training program has been established at our institution.

The aim of this study was to explore the subjective significance of knowledge and skills of close relatives to LVAD patients in order to optimize their training. No similar studies have been identified.

Methods: Qualitative semistructured interviews with close relatives, living with LVAD patients. All close relatives to patients who had a LVAD between sep. 2011 – mar. 2013 were included, ($n=15$). Relatives of patients who died, were under the age of 18 or those who were transplanted were subsequently excluded ($n=7$). The interviews were recorded and transcribed. Data was divided into two areas; the significance of: "when the close relatives had knowledge and skills" and "when they did not have knowledge and skills".

Both areas was inductively analysed using U. H. Graneheim and B. Lundman's approach to thematised qualitative content analysis, where data are condensed into codes and divided into categories, that gather and provide some overarching themes.

Results: Out of eight possible participants, six ($n=6$) female spouses participated. The mean age was 56 years (range: 42-63). At the time of the interviews, the patients had in mean had their LVAD for 371 days (range: 43-877).

Where knowledge and skills existed, the data analysis revealed themes which described sense of security, empowerment and psychological well being, but also that the strive for knowledge could become overwhelming.

Insufficient knowledge and skills resulted in a feeling of lack of control and experience of negative physiological- and psychological affect. Five of the participants had a desire to know more.

Conclusion: Data analysis revealed that knowledge and skills in relation to the LVAD were of importance to the close relatives. Education and training enhance sense of security, empowerment and add a psychological well being.

Follow-up education and training after hospital discharge is of paramount importance.

1249 | BEDSIDE

Health locus of control and self-care and their role in clinical outcomes in patients with heart failure

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Purpose: Patients perception of internal locus control (i.e. the belief that health can be improved by one's own efforts) might be an important factor improving

self-care behaviors and clinical outcomes, however only a few studies have focused on it so far in patients with heart failure (HF). We aimed at (1) assessing associations of health locus of control with HF patient's self-care behaviors and clinical outcomes, and (2) exploring factors associated with the health locus of control in HF patients.

Methods: A total of 107 outpatients with HF (mean age 64, 74% male, 80% NYHA I-II) were followed for 2 years. Health locus of control was assessed with the Japanese health locus of control scale (range: 14-56, a higher score indicates having more internal locus of control). Self-care behaviors were evaluated using the HF self-care risk score (range: 0-6), which was calculated from the European Heart Failure Self-Care Behavior Scale. Depressive symptoms were assessed with the center for epidemiological studies depression scale (CES-D) (range: 0-60). Clinical and demographic data was also collected from the medical chart. Pearson's product moment correlation coefficient and Cox regression analysis were used to assess the relationship of locus of control with self-care behaviors and clinical outcomes. Multiple regression analysis was used to explore factors associated with the health locus of control.

Results: The total health locus of control score was 39.4 ± 5.6 . Approximately 20% had a relatively low internal locus of control score of <35 . HF self-care risk score and the CES-D score was 3.3 ± 1.6 and 13.1 ± 8.1 , respectively. A higher HF self-care risk score, indicating poorer self-care behaviors, was significantly correlated with a lower locus of control score ($\rho=-0.23$, $p=0.02$). During the follow-up, 17% were hospitalized for HF or died. In the Cox regression analysis, even after adjustment for clinical variables including age, B-type natriuretic peptide level (BNP), and medications such as beta-blocker, lower health locus of control score was associated with the poorer outcomes (hazard ratio =0.96, 95% confidential interval =0.83-0.99, $p=0.03$). Multivariate analysis adjusted for age and BNP showed that having more depressive symptoms was an independent risk factor for lower locus of control ($\beta=-0.16$, $p=0.03$). Ischemic etiology and education history were not related to health locus of control.

Conclusions: Health locus of control is associated with HF patient's self-care behaviors and clinical outcomes. Depressive symptoms are important factors influencing patient's locus of control.

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An educational intervention nursing at discharge from the emergency department reduces admissions for heart failure in the short term in patients with atrial fibrillation

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Introduction: Atrial fibrillation (AF) is common in the emergency department and has a high morbidity and mortality. An educational nursing intervention can promote self-management for patients and improve their prognosis.

Objectives: To determine whether an educational nursing intervention at discharge from the emergency department in patients with AF can increase the level of knowledge about the arrhythmia and its treatment, and decrease admissions and complications associated with AF.

Material and methods: Clinical, prospective, randomized, blinded and controlled study in AF patients discharged from the emergency department of a tertiary hospital. Period: one year. Randomization into two groups: 1) Intervention: instruction on AF, treatment, warning signs and pulse control, and delivery of individualized information leaflet, and 2) Control. At 30 days and 3 months, phone monitoring and review of the clinical history of all patients to assess knowledge about the arrhythmia, presence of complications and readmission rates.

Results: 240 patients, 116 in the intervention group and 124 in the control group, were included. Age 76 ± 11 years, 138 (58%) women. At 30 days, patients in the intervention group were more aware of the precautions of treatment ($p=0.028$) and warning signs of AF ($p=0.023$), required less admissions for heart failure ($p=0.023$), and had fewer complications at 30 days and at 3 months (without significant differences). Of the patients with a first episode of AF, patients in the intervention group required a lower rate of emergency room visits at 30 days ($p=0.045$) and 3 months ($p=0.022$), and less admissions for any cause at 3 months ($p=0.019$).

Conclusion: A nursing intervention at discharge from the emergency department increases the degree of knowledge of patients about AF and reduces admissions for heart failure in the short term. Patients with a new diagnosis of AF are most benefited.

1251 | BEDSIDE

Why do nurses discuss prognosis with the heart failure patient, and why not?

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Purpose: The trajectory of HF is often unpredictable and it might be relevant to initiate discussions about prognosis with the HF patient by HF nurses. This study aims to describe which subjects Swedish and Dutch HF nurses discuss with their

patients and their reasons for discussing prognosis or not with their patients at nurse-led HF clinics.

Methods: A survey was conducted targeting nurses at outpatient HF clinics in Sweden (n=81) and in The Netherlands (n=81). The nurses (n=278) completed a registration form for every HF patient they met in their practice a pre-specified week. They registered which subjects were discussed during the patients' visits, including prognosis. The reasons for discussing prognosis or not were collected by open-ended questions.

Results: The nurses completed registration forms in 1 809 HF patients (mean age 71 ± 12 , 61% males, 80% in NYHA class II-III). Topics that were most often discussed during the outpatient visit included HF symptoms (94%), symptom monitoring (90%) and adherence to treatment (87%). With 38% of the patients, prognosis was discussed during the visit. In total, 33% of the nurses reported that they discussed prognosis because a change in the condition of the patient occurred, 23% reported that it was discussed to point out the seriousness of HF and 17% had discussed prognosis because the patients themselves had initiated the conversation. Major reasons for not discussing prognosis included that other problems and issues were found to be more important (22%), prognosis had already been discussed (20%) or because the nurses did not find it relevant to discuss (18%).

Conclusions: During a HF clinic visit, discussing prognosis occurs less often than discussing other topics such as HF symptoms or adherence. Prognosis is not always seen as the most important subject to discuss. A change in patient condition is an important reason for nurses to discuss prognosis. This information can be used to help nurses find an optimal time and opportunity to discuss prognosis with HF patients.

1252 | BEDSIDE

Sleep quality and quantity: association with quality of life and function in patients with pulmonary hypertension

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Aim: Although sleep apnoea is prevalent in patients with pulmonary hypertension (PH), few studies have evaluated sleep quality and quantity and its effect on patient well-being. The aim of this analysis was to determine the effect of sleep on quality of life, fatigue and function in patients with PH.

Methods: As part of a longitudinal study the following baseline data were collected: demographic and clinical information, 6 minute walk distance (6MWD), functional class (FC) rated by clinician and patient, and questionnaires: MOS Sleep, EmPHasis-10 a PH specific quality of life measure, and Fatigue Severity Scale (FSS).

Results: 179 patients with PH: mean age 56 (SD13) years, female 68%, FC II 42%, FC III 49%; idiopathic aetiology 37%, congenital aetiology 19%, were recruited from 9 centres in the UK and Ireland. Mean 6MWD was 348 (SD175.5) metres, and mean sleep quantity was 6.9 (SD 1.7) hours (range 2–13 hours). Somnolence and Sleep Problems Index (SPI) subscales of the MOS Sleep had small to moderate correlations with EmPHasis-10, FSS, patient and clinician rated FC, and 6MWD (table). Sleep quantity had weaker correlations with EmPHasis-10, 6MWD and FC than quality of sleep. Patients in the poorest quintiles for somnolence and SPI subscales reported fewer hours of sleep, more fatigue and worse quality of life, and were more likely to be in FC III/IV compared to patients with better scores. Those in the worst SPI quintile also were more likely to use oxygen and tended to have shorter 6MWD. Scores did not differ by gender or age.

Correlations

	Sleep quantity	SPI	Somnolence	FC (patient)	FC (clinician)	6MWD	FSS
EmPHasis-10	-0.202**	-0.578**	-0.587**	0.608**	0.514**	-0.391**	0.727**
FSS	-0.113	-0.488**	-0.575**	0.555**	0.416**	-0.248**	
6MWD	0.261**	0.308**	0.233**	-0.474**	-0.568**		
FC (clinician)	-0.063	-0.374**	-0.346**	0.514**			
FC (patient)	-0.218**	-0.414**	-0.432**				

**p<0.01.

Conclusions: Sleep quality had stronger associations than sleep quantity with quality of life, fatigue and patient function. Use of sleep questionnaires may be a simple method to identify patient difficulties and highlight patients who need further investigation. Subsequent studies should incorporate sleep monitors to enhance understanding of sleep and its effects on well-being in patients with PH.

1253 | BEDSIDE

Erectile function in ICD patients

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Purpose: This study aimed to investigate the prevalence of erectile dysfunction

in cardiovascular patients with implantable cardioverter defibrillator.

Methods: This descriptive cross-sectional study included male patients with implantable cardioverter defibrillator. Inclusion criteria were NYHA I-III without diseases in the urinary tract. Exclusion criteria were no partner. Participants filled out the International Index of Erectile Function questionnaire that concerns sexual function and consists of five domains. The International Index of Erectile Function meets psychometric criteria for test reliability and validity. The study was conducted as a postal survey. Questionnaires were mailed out to 597 patients from two university hospitals.

Results: Two hundred forty patients responded, 14 questionnaires came back blank and 21 patients did not have a partner. Data from 205 patients (response rate 34.3%) were analyzed. Mean age of patients was 62.1 ± 11.6 . International Index of Erectile Function total mean score was 41.7 ± 24.3 (scale range 5 to 75). Erectile Function domains mean score was 16.3 ± 11.7 (Scale range 1 to 30). Erectile Function domain was distributed between 41.4% having severe erectile dysfunction (Score range 6 to 10), 6.8% moderate erectile dysfunction (Score range 11 to 16), 7.9% moderate to mild erectile dysfunction (Score range 17 to 21), 7.9 mild erectile dysfunction (Score range 22 to 25) and 36.1 having no erectile dysfunction (Score range 26 to 30). Mean score for Orgasmic Function domain was 6.2 ± 4.2 (Score range 0 to 10), Sexual Desire domain was 6.3 ± 2.5 (Score range 2 to 10), and Intercourse Satisfaction domain was 6.4 ± 5.6 (Score range 0 to 15) and Overall Satisfaction domain was 6.3 ± 2.6 (Score range 2 to 10).

Conclusions: Erectile dysfunction was present in more than 60% of male patients with implantable cardioverter defibrillator and more than 40% had severe erectile dysfunction. Also intercourse satisfaction was affected. All though this is not conclusive, results indicates that sexual function needs to be addressed in patients with implantable cardioverter defibrillator.

INNOVATIONS IN CARDIAC PACING

1263 | BEDSIDE

A paced QRS duration could predict the new-onset congestive heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricle

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Purpose: The right ventricular (RV) apical pacing results in progressive left ventricular (LV) dysfunction and contributes to the development of heart failure (HF). In MOST and DAVID trials, increased heart failure hospitalization was associated with the prevalence of more than 40% RV pacing. This study aimed to investigate the prevalence and clinical predictors for the development of the new-onset congestive heart failure (CHF) after long-term RV apical pacing in patients with acquired atrioventricular (AV) block who require permanent pacing.

Methods: We studied the clinical outcomes after long-term (>90% ventricular pacing during more than 1 year) RV apical pacing for acquired AV block in 233 patients without a LV systolic dysfunction (ejection fraction (EF) >50%). We compared age, sex, history of diabetes, hypertension and coronary artery disease, paced QRS duration and echocardiographic parameters between LV systolic dysfunction and normal LV systolic function. The CHF was defined as elevated serum pro-BNP level (more than 700 pg/dL) or CHF hospitalization.

Results: The mean follow up duration was 76 months. The permanent RV apical pacing was associated with the new-onset CHF in 42 patients (18%) with high degree AV block. In multivariate analysis, after adjusting age, sex, LV EF, the history of hypertension and CAD, pacing duration, and medication, a paced QRS duration could independently predict the new-onset CHF. A paced QRS duration more than 162 msec might help us to predict the new onset CHF.

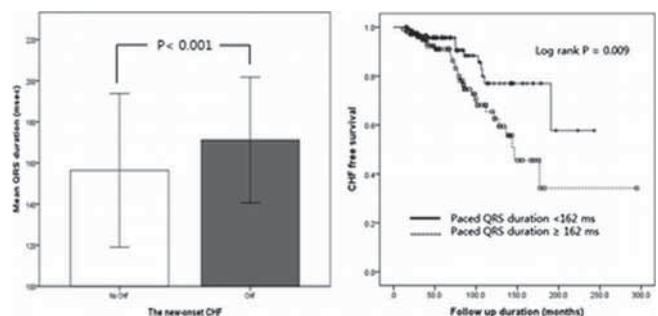


Figure 1

Conclusions: A paced QRS duration might be associated with the new-onset CHF after permanent RV apical pacing in patients with high degree AV block. So, we try to decrease the paced QRS duration in permanent RV apical pacing.

1264 | BEDSIDE

Left anterior descending coronary artery flow impaired by right ventricular apical pacing and its relevance to pacing-induced systolic dyssynchrony

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Introduction: Although right ventricular apical (RVA) pacing may affect the coronary blood flow; however, there is no prospective study to address. We aimed to assess coronary blood flow changes after RVA pacing and the role of systolic dyssynchrony.

Methods: Seventy patients with sinus node dysfunction were prospectively enrolled. Coronary flow was evaluated by diastolic velocity time integral (VTI) at the distal-portion of left anterior descending coronary artery (LAD) with transthoracic echocardiography at baseline and follow-up. Systolic dyssynchrony was assessed with tissue Doppler imaging by time standard deviation to peak systolic velocity of 12 left ventricular segments (cutoff value ≥ 33 ms).

Results: Sixty-five patients were finally analyzed. At follow-up (mean time: 127 ± 45 days), LAD velocity-time integral (LAD-VTI: 12.1 ± 4.2 vs. 10.7 ± 4.6 cm, $p < 0.001$) were decreased together with left ventricular systolic deterioration (ejection fraction: $65 \pm 7\%$ vs. $62 \pm 7\%$, $p < 0.05$). However, these changes were only detected in those with pacing induced systolic dyssynchrony (Table). Significant LAD-VTI reduction (defined as $\geq 5\%$) occurred in 34 (52%) patients which was more prevalent in pacing-induced systolic dyssynchrony group (85.3% vs. 16.1%, $\chi^2 = 31.1$, $p < 0.001$). Though similar at baseline, LAD-VTI was significantly lower in dyssynchrony group at follow up ($p < 0.001$). Cox-regression analysis showed that pacing-inducing systolic dyssynchrony [hazard ratio (HR): 3.62, $p = 0.009$] and accumulative pacing percentage $\geq 40\%$ (HR: 3.32, $p = 0.027$) were associated with reduction of LAD-VTI. In multiple analysis, only pacing-inducing systolic dyssynchrony was the associated factor (HR: 2.93, $p = 0.045$).

Parameters	Without systolic dyssynchrony (n=31)			With systolic dyssynchrony (n=34)		
	Baseline	Follow up	P value	Baseline	Follow up	P value
Left ventricular end-diastolic volume, ml	57 ± 17	61 ± 19	0.162	58 ± 15	62 ± 12	0.072
Left ventricular end-systolic volume, ml	20 ± 8	22 ± 9	0.080	21 ± 7	$25 \pm 6^*$	0.003
Left ventricular ejection fraction, %	66 ± 6	64 ± 7	0.258	64 ± 8	$60 \pm 6^*$	0.017
LAD-VTI, cm	12.9 ± 4.8	13.0 ± 4.9	0.640	11.4 ± 3.3	$8.7 \pm 3.3^*$	< 0.001

* $P < 0.05$ vs. the corresponding column of no systolic dyssynchrony group.

Conclusions: RVA pacing disturbs coronary flow, which might be related to the development of systolic dyssynchrony. This may provide additional evidence of the deleterious effect of RVA pacing.

1265 | SPOTLIGHT

Clinical utility and effects on patients outcome of pacemaker remote follow-up: single centre experience of 2000 patients

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Introduction: In spite of the fact that several studies have demonstrated the feasibility and technical reliability of pacemaker (PM) remote follow-up, Physicians are still reluctant to use it as the method of choice for PM follow-up. In this study we report our 6 years experience in PM remote follow-up and the impact of using this technology on patient medical care and health resource utilization.

Patients and methods: Two thousands patients with PM were included in the remote follow-up clinic between February 2008 and February 2014. The clinic was managed by 2 pacing expert nurses, 2 physicians and the head of the unit. Fifty minutes/week for the nurse and 15 min/week for the physician were spent for remote follow-up data analysis.

After the third month post PM implant, the patients were completely followed-up by the remote follow-up clinic.

Results: 164 (8.2%) transmission problems were reported, the majority were corrected by phone calls (95%), and the rest, with a visit to the PM follow-up clinic. In 5 (0.3%) patients, the monitor had to be replaced due to dysfunction. 99.8% of patients were completely satisfied with the remote follow-up of their pacemakers according to a survey that was conducted to all the patients and only 4 (0.2%) were switched to regular out-patient visits due to personal demand.

Arrhythmia (atrial fibrillation and/or atrial tachycardia) was the most frequent alert (14%). In 66 patients new onset atrial fibrillation was diagnosed. There were 22 (1.1%) alerts for ventricular tachycardia; only in 2 cases were proved to be true. Thirty alerts for lead dysfunction were received, 53% of which were due to lead impedance changes. Fourteen cases of lead displacement were diagnosed and one case of rupture of lead insulation.

The PM remote follow-up unit in our department reduced the workload on our out-patient PM clinic by 46%.

Conclusions: This study confirms that PM remote follow-up is feasible and reliable. It helps in early detection of lead problems and arrhythmias and plays a role in the optimization of health-care resource allocation.

1266 | BEDSIDE

A leadless pacing device, first in-human data on feasibility and safety

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Purpose: Leadless pacing devices have recently been developed to overcome the limitations of conventional pacemakers with respect to lead and device pocket associated complications. We report initial clinical experiences of the first 5 patients implanted at our hospital.

Methods: From November 2013 until January 2014, 5 patients with conventional 1-chamber-pacemaker indication underwent implantation of a leadless pacing device. Device implantation was performed with a minimally invasive approach using the right femoral vein for vascular access. Procedural data, device performance and complications during as well as after the implantation procedure were assessed.

Results: The device could be implanted successfully in all patients (mean age 78.4 ± 6.0 years) in the apicoseptal region of the right ventricle. In 4/5 patients sensing and pacing values were acceptable at the first implantation site, while in one patient the device had to be repositioned once due to impaired sensing values. Two periprocedural complications occurred with one patient with pre-existing LBBB experiencing temporary complete atrioventricular block during manipulation with the catheter delivery system and one patient suffering from a pseudoaneurysm of the right arteria femoralis profunda that could be treated with thrombin injection. Device parameters at discharge were stable in all patients.

Procedural data

Patient	Procedure time (min)	Fluoroscopy time (min)	Radiation dose (cGy/cm ²)	Periprocedural complications
1	150	26.6	5610	Temporary AVB III°
2	50	9.0	1429	—
3	50	10.5	5076	—
4	80	16.5	1352	—
5	40	7.2	807	Pseudoaneurysm of the right femoral artery

Conclusion: In this small patient series implantation of a leadless pacing device was successful in all patients with good sensing and pacing values. Lack of a subcutaneous device pocket and permanent leads is particularly attractive due to a potential reduction of device and lead associated complications. Data on long-term performance and safety are needed.

1267 | BEDSIDE

A leadless cardiac pacemaker: single center 18 months follow-up results

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Purpose: Transvenous and epicardial leads have been the standard for patients with pacemaker systems for over 50 years. A novel completely self-contained Leadless Cardiac Pacemaker (LCP) has been introduced to reduce complications associated with lead placement, lead performance and the subcutaneous pulse generator. We evaluated the clinical performance of this device in patients with a minimum of 1-year follow-up.

Methods: Patients with an indication for VVI-pacing were considered for enrolment. Eligible patients were implanted with a LCP. Under fluoroscopic guidance the LCP was inserted through the femoral vein using an 18Fr delivery catheter. The LCP was positioned in the right ventricular apex, fixated using a screw-in helix, and released after obtaining satisfactory electrical measurements. All consecutive patients with a LCP implanted in our center between Dec 2012 and Mar 2013 were included.

Results: A total of 8 patients (82 ± 9 years, 75% male) were implanted with a LCP. The implant success rate was 100% with a mean procedure time of 41 ± 17 minutes (range, 24 to 67 minutes). In patients enrolled the complication-free rate was 100%. One patient did not complete follow-up due to the need for ICD-implantation and successful LCP retrieval. The pacing performance results at implant, discharge, 3 and 9 months follow up were respectively: mean threshold at 0.4 ms pulse width; 0.79 ± 0.49 V, 0.39 ± 0.13 V, 0.43 ± 0.19 V, 0.41 ± 0.17 V, R-wave amplitude; 7.3 ± 3.6 mV, 8.4 ± 2.8 mV, 9.3 ± 3.1 mV, 9.7 ± 3.0 mV, and impedance; 873 ± 281 Ohms, 824 ± 158 Ohms, 739 ± 207 Ohms, 690 ± 188 Ohms. There were no late complications. At the time of this data set compilation, 14 Feb 2014, not all subjects have had their 18 months post-implant follow-up visit to allow us to evaluate the clinical performance of the LCP at 18 months. Performance and safety results at 18 months will be updated later and added to this analysis.

Conclusions: In our center this novel Leadless Cardiac Pacemaker demonstrates very stable performance and safety results during follow-up. We here present the longest follow-up results of the performance of the LCP to date. Our results support the use of the LCP as a safe and reliable alternative to conventional pacemaker systems. Continued evaluation is warranted to further characterize this system.

1268 | BENCH

A batteryless cardiac pacemaker powered by cardiac motion

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Introduction: The battery is one of the most limiting factors of modern pacemaker designs. Battery replacements require repeated surgical interventions with associated morbidity and costs. Alternative power sources not relying on stored energy become essential to improve a patient's quality of life. Harvesting cardiac energy might provide a continuous energy source to power batteryless pacemakers. A possible mechanism to convert cardiac motion into electrical energy can be found in the automatic wristwatch: the movement of a person's wrist accelerates an eccentric mass in the clock housing. An integrated generator converts the rotation into electrical energy.

Methods: A harvesting device was derived from the clockwork of an automatic wristwatch. The harvester was then anchored on the heart thanks to a custom-made housing (total mass 16.7 g, figure). For an in-vivo study with a 60 kg domestic pig, a sternotomy was performed to suture the prototype onto the anteroapical part of the left ventricle. The harvesting device was connected to a custom-built single-chamber pacemaker. Finally, an epicardial bipolar pacing wire was used to deliver the pacemaker stimulus.

Results: The energy harvesting device supplied the pacemaker with enough energy to perform continuous VVI pacing (pacing threshold 1.0 V/0.5 ms, sensing 9.8 mV, impedance 1279 Ω) at 130 bpm (pacing output 1.6 V/0.8 ms). Simultaneously, the harvesting device generated a mean output power of 52 μ W over an additional load resistor of 1 k Ω .



Conclusion: We demonstrated the feasibility of pacing the heart using its own mechanical activity. The harvested energy exceeded the power requirement of a modern pacemaker (~10 μ W). Furthermore, we expect to increase the performance by optimising this first-generation prototype.

Poster Session 2

LIPOPROTEINS IN CARDIOVASCULAR PREVENTION

P1270 | BEDSIDE

Triglycerides are independent risk predictors in stable coronary artery disease

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Objective: Risk prediction with fasting compared to postprandial serum triglycerides (TG) in patients with cardiovascular disease remains unclear, especially in patients who are treated with a statin. The aim of this prospective study was to analyze the role of fasting and postprandial serum triglycerides (TG) as risk modifiers in patients with coronary artery disease (CAD).

Methods: A sequential oral triglyceride (OTT, 75g cream fat) and glucose tolerance test (OGT, 75g glucose) was applied to obtain standardized measurements of postprandial TG glucose kinetics in patients with stable CAD confirmed by angiography. Lipid and glucose parameters were measured at fasting, 3, 4, and 5 hours after the OTT/OGT. The primary outcome was the composite endpoint of death and hospitalization for acute coronary syndrome or hospitalization for unplanned, symptom-induced coronary angiography and revascularization within 48 months follow-up.

Results: N=514 patients with angiographically confirmed, clinically stable CAD were enrolled. Median age was 68 years, 83% were male, 95% were treated with statins and median LDL-cholesterol concentration was 105mg/dl.

Fasting TG were strongly associated with the area under the curve (AUC) of the postprandial TG increase ($R=0.93$, $p<0.0001$). Patients were stratified by TG tertiles for statistical comparisons of baseline variables and time-to-event analyses. Compared to the lowest tertile of fasting TG (<106mg/dl), patients in the highest tertile (>150mg/dl) were younger, more obese, more were smoking, they had a higher blood pressure and pulse, lower HDL- and higher LDL-cholesterol and more had glucose intolerance or a metabolic syndrome. A similar association was observed with the AUC tertiles.

Follow-up at was 100% complete. Both fasting and postprandial TG predicted the primary outcome (fasting TG >150mg/dl vs. <106mg/dl: HR 1.79, 95%-CI 1.31-2.45, $p=0.0001$; AUC >1120mg/dl vs. <750mg/dl: HR 1.78, 95%-CI 1.29-2.45,

$p=0.0003$). Postprandial TG parameters did not improve risk prediction compared to fasting TG. The number of cardiovascular deaths and myocardial infarctions was higher in the upper tertile of fasting TG >150mg/dl (HR 1.79, 95%-CI 1.04-3.09, $p=0.03$). Risk prediction by TG was independent of traditional risk factors, medication, glucose metabolism, LDL- and HDL-cholesterol.

Conclusions: Fasting serum triglycerides >150 mg/dl independently predict cardiovascular events in patients with coronary artery disease on guideline-recommended medication. Assessment of postprandial TG does not improve risk prediction compared to fasting TG in these patients.

P1271 | BEDSIDE

Impact of statin therapy on low-density lipoprotein cholesterol and triglyceride levels in patients with hypertriglyceridaemia: a VOYAGER meta-analysis

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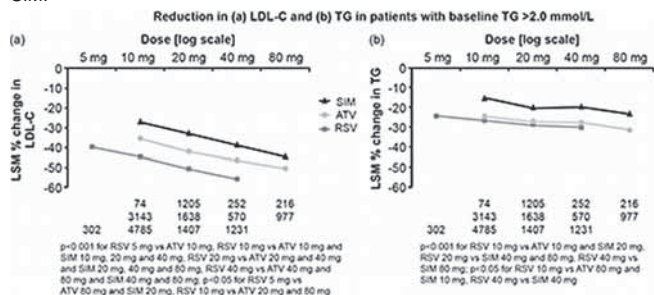
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Background: Several studies have indicated a causal role for triglycerides (TG) in the development of coronary artery disease. Recently published guidelines from the European Atherosclerosis Society (EAS) Consensus Panel define mild-to-moderate hypertriglyceridaemia as a TG level of 2.0–10.0 mmol/L and recommend a TG level <1.7 mmol/L as desirable; however, the primary treatment goal in these patients remains the LDL-C goal. Individual patient data ($n=32,258$) from the VOYAGER meta-analysis of 37 studies were used to analyse LDL-C and TG reduction in patients with baseline TG >2.0 mmol/L.

Methods: The least-squares mean (LSM) % change from baseline in LDL-C and TG was compared during 15,800 patient exposures to rosuvastatin (RSV) 5, 10, 20 and 40 mg, atorvastatin (ATV) 10, 20, 40 and 80 mg, and simvastatin (SIM) 10, 20, 40 and 80 mg in patients with baseline TG >2 mmol/L. Comparisons were made using a single mixed-effects model using only data from studies directly comparing treatments by randomised design.

Results: LSM % reductions in LDL-C and TG are shown in the figure. Reductions in LDL-C with RSV 10–40 mg doses were significantly greater than for equal or double doses of ATV and SIM (all $p<0.05$). RSV 10 mg produced a significantly greater ($p<0.05$) reduction in TG than ATV 10 mg, but reductions with RSV 20 and 40 mg were similar to equal doses of ATV. Doses of RSV 10–40 mg resulted in significantly greater ($p<0.05$) reductions in TG than equal or double doses of SIM.



Conclusions: In patients with hypertriglyceridemia, LDL-C reduction, the primary treatment goal, was substantial and dependent on the choice and dose of statin. The reduction in TG was numerically less than for LDL-C, and additional therapy may be considered to potentially further reduce residual cardiovascular risk.

P1272 | BEDSIDE

Association of high serum apolipoprotein B-48 level with increased proteinuria and reduced estimated glomerular filtration rate (eGFR)

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Postprandial hypertriglyceridemia (PHTG) is one of residual risk factors for coronary heart disease (CHD) and caused by the impaired clearance of chylomicron remnants (CM-R), which directly influence the progression of atherosclerotic plaque. We developed ELISA and CLEIA system for measuring serum apolipoprotein (apo) B-48 for evaluating the accumulation of CM-R. In our former study, we found that high fasting apoB-48 level significantly correlated with the prevalence of CHD. Proteinuria and reduced estimated glomerular filtration rate (eGFR) are independent risk factors for cardiovascular events and renal dysfunction. In the present study, we have investigated whether serum apoB-48 levels are associated with renal dysfunction.

Methods: A total of 264 patients in our hospital were enrolled. Biochemical markers for lipid metabolism including serum apoB-48, TG, LDL-C, HDL-C and proteinuria were measured. Subjects were classified into 4 groups by eGFR and proteinuria: high eGFR (>60 mL/min/1.73 m²) without proteinuria ($\geq 1+$ by urine dipstick) (n=50); high eGFR with proteinuria (n=75); low eGFR (>60 mL/min/1.73 m²) without proteinuria (n=74); and low eGFR with proteinuria (n=65). ApoB-48 level and apoB-48/TG ratio were compared among these groups and multiple regression analysis was done using these parameters.

Results: Serum log-apoB-48 and log-apoB-48/TG levels were significantly higher in patients with high eGFR with proteinuria, low eGFR with proteinuria and low eGFR without proteinuria than in those with high eGFR without proteinuria. eGFR was significantly correlated with log-apoB-48 and log-apoB-48/TG levels, but urine protein level was significantly correlated only with the log-apoB-48 level. Multiple regression analysis indicated that log-apoB-48/TG levels were a significant determinant of reduced eGFR, suggesting that increased serum apoB-48 concentrations partly contributed to an increased risk of CKD.

Conclusion: Both low eGFR (<60) and proteinuria ($\geq 1+$) were independent determinants of high apoB-48 levels. Taken together, the present results suggest that increased serum apoB-48 concentrations may contribute to an increased risk of cardiovascular events.

P1273 | BENCH

Precise non invasive diagnosis of subclinical and mild coronary artery disease promotes the rationale use of statins and very low outcomes in hypercholesterolemic patients

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Background: Statin therapy is one of the cornerstones of prevention of cardiovascular (CV) events in patients (P) with hypercholesterolemia (HC). It is controversial the impact of the diagnosis of subclinical and mild coronary artery disease (CHD) in the prescribing propensity of a statin and subsequent outcomes in P with HC.

Aim: To analyze changes in statin use and outcomes after the non invasive diagnosis of subclinical and mil CHD in P with previously known HC.

Methods: Prospective and observational study of a cohort of 400 P screened between 2007 and 2009, without cardiovascular history and submitted to diagnose CHD by means of non invasive coronary angiography using 64-rows multidetector CT (MDCT). Current Appropriateness Criteria and Guidelines for the diagnosis of CHD and the performance of MDCT were strictly observed, including blinded CT review. Main variables included were age, sex, major risk factors, CHD status (normal coronary arteries or mild CHD with luminal stenosis <50%), drugs (statin, aspirin, ACE inhibitor, ARB, Calcium channel antagonists, diuretic and betablocker) and outcome (total mortality, cardiovascular mortality, non fatal MI, unstable angina, PCI or CABG). The follow up, CV outcomes collection and prescribing propensity was accomplished through historic controls from Euroaspire Survey and medical records and data collected from a wide Community Database jointly managed by care centers and general practitioners. The MDCT report did not add advices or recommendations over any drug prescription.

Results: After a median of 4.6 years, a total of one hundred and forty six P completed the survey: mean age 63 $\pm$ 13 yo; M/F ratio 45/55. Prevalence of HC previous MDCT was 29%. Subclinical and mild CHD was diagnosed in 49%. After the follow up, in HC group, statin prescription was 50% when the diagnosis was of normal coronary arteries, increasing to 84% when the diagnosis was subclinical and mild CHD (Odds Ratio 5.3; 95% CI 1.2-23.1; p=0.02). Hence, the prescription propensity after MDCT resulted in 5 vs. 3 additional treatments with statin per 100 patients-years compared with hypercholesterolemic P and normal coronary arteries. Outcomes were very low and similar to P with normal coronary arteries (0.3 vs. 0.6 major events per 100 patients-years).

Conclusion: Non Invasive diagnosis of subclinical and mild CHD: 1) increase the prescription of a statin in hypercholesterolemia; 2) enhancing the adherence to evidence based preventive therapies resulted in a very low incidence of major CV events at long term follow up.

P1274 | BENCH

Anti-TNF therapy improves endothelial protective functions of HDL in patients with rheumatoid arthritis

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Purpose: Recent studies suggest that HDL may adopt a pro-atherogenic pheno-

type in patients with rheumatoid arthritis (RA). However, the effects of common anti-inflammatory treatments on HDL function are not yet known. In this study we investigated the impact of infliximab + methotrexate (MTX) versus placebo + MTX on HDL functionality in patients with early RA.

Methods: Eighteen patients 55.58 (12.45) years with erosive early RA receiving MTX were randomised to infliximab (5mg/kg) or placebo infusions. At week 54 and thereafter, all patients received infliximab. HDL function was measured at baseline, 54 weeks and 110 weeks. The impact of HDL on cultured endothelial cells was assayed using ESR Spectroscopy for nitric oxide bioavailability (NO) and Superoxide Production (SO). HDL-associated Paraoxonase-1 (PON-1) activity was measured by spectrophotometry. HDL-mediated cholesterol efflux was measured in J774 macrophages, pre-treated with cAMP.

Results: Combination of infliximab and MTX treatment at 54 weeks resulted in marginally improved HDL endothelial properties compared to MTX alone. At 110 weeks, following two years treatment with Infliximab and MTX all endothelial HDL properties including NO, SO and PON-1 were significantly improved (p>0.01) (Fig. 1). HDLs cholesterol efflux capacity remained unchanged at 54 and 110 weeks of treatment.

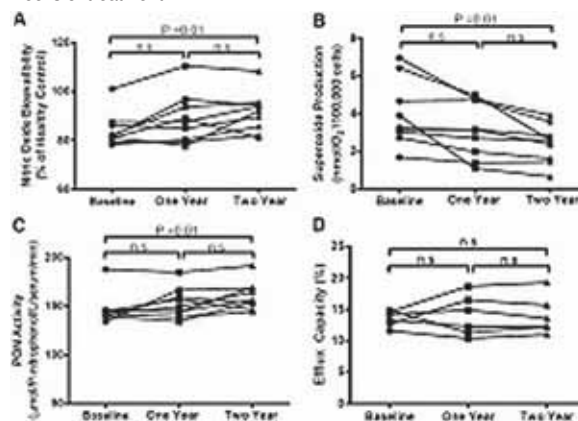


Figure 1. HDL function with 2 years infliximab.

Conclusion: In this study we demonstrated, for the first time in patients with RA that two years treatment with infliximab has a significant beneficial effect on HDL endothelial properties of these patients. These findings suggest that targeting anti-TNF alpha pathway might be a novel treatment option to improve HDL functionality in patients with chronic inflammatory conditions.

P1275 | BEDSIDE

Antisense inhibitor of apoC-III produces significant decreases in apoC-III and triglycerides and increases in HDL-C as a single agent or in combination with fibrates in hypertriglyceridemic patients

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Background: ApoC-III is a 79 amino acid glycoprotein, synthesized principally by the liver, which associates with apoB-containing lipoproteins and HDL. It plays a pivotal role in regulating plasma triglyceride (TG) levels by inhibiting hydrolysis of TG-rich lipoproteins as well as receptor-mediated uptake of lipoprotein remnants by the liver and is recognized as a CV risk factor. ISIS-APOCIIIrx selectively inhibits apoC-III protein synthesis in the liver.

Purpose: To assess the change from baseline in fasting lipids and lipoproteins following 13 weeks of treatment with ISIS-APOCIIIrx as a single agent or in combination with fibrates in patients with hypertriglyceridemia (HTG).

Methods: Patients ≥ 18 years were enrolled in double-blind Phase 2 studies to receive ISIS-APOCIIIrx (up to 300 mg) or placebo as weekly SC injections for 13 weeks. Populations studied were: (1) HTG patients with type 2 diabetes on ≥ 1 g/day stable metformin and not on TG-lowering medication (2) HTG patients not on TG-lowering medication and (3) HTG patients on a stable background of fibrate. Baseline and end-of-treatment fasting serum samples were analyzed for lipids and lipoproteins.

Results: Treatment with ISIS-APOCIIIrx resulted in consistent and significant

Table 1

Fasting lipid (mg/dL)	Mean % (SD) change from baseline		
	Single agent in diabetics (N=7)	Single agent (N=11)	Add on to stable fibrate (N=10)
Mean baseline TG	259 mg/dL	Mean baseline TG 559 mg/dL	Mean baseline TG 394 mg/dL
Range	187–356 mg/dL	291–952 mg/dL	224–932 mg/dL
ApoC-III	-88% (6.0)*	-80% (9.3)***	-71% (13.0)**
Triglycerides	-72% (8.3)*	-71% (14.1)***	-64% (8.9)**
HDL-C	+40% (19.8)*	+46% (24.0)***	+52% (23.7)**
Non-HDL-C	-28% (16.4)	-11% (38.3)	-19% (28.8)

*p<0.05, **p<0.01, ***p<0.001.

dose-dependent decreases in apoC-III and TG, and increases in HDL-C, with no significant change in non-HDL-C whether administered as a single agent or in combination with fibrates. Comparison of the effects of the 300 mg/week dose of ISIS-APOCIII_{Rx} (i.e. the dose studied in all groups of patients) is shown (Table 1). ISIS-APOCIII_{Rx} treatment in these Phase 2 studies was generally safe and well tolerated. There were no clinically meaningful changes in liver tests or other laboratory values.

Conclusions: Overall, we believe that treatment with ISIS-APOCIII_{Rx} results in an improved atherogenic profile in HTG patients whether administered as a single agent or when used in combination with fibrates.

P1276 | BEDSIDE

Systematic study of the effects of lowering low-density lipoprotein-cholesterol on regression of coronary artery diseases using intravascular ultrasound

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Objective: Conflicting results currently exist on the effects of LDL-C levels on coronary atherosclerotic plaque, and the target level of LDL-C resulting in the regression of the coronary atherosclerotic plaques (CAP) has not been settled.

Methods: PubMed, EMBASE, and Cochrane databases were searched from Jan. 2000 to Nov. 2013 for randomized controlled or blinded end-points trials assessing the effects of LDL-C lowering therapy on regression of coronary atherosclerotic plaque in patients coronary heart disease by intravascular ultrasound. Data concerning the study design, patient characteristics, and outcomes were extracted. The significance of plaques regression was assessed by computing standardized mean difference (SMD) between the baseline and follow-up. SMD were calculated using fixed or random effects models.

Results: Twenty trials including 5910 patients with coronary heart disease were identified. Lowering LDL-C by >45.4% and to level ≤ 66.8 mg/dL in the baseline LDL-C >120<130 mg/dL; lowering LDL-C by >40.4% and to level ≤ 77.8 mg/dL in baseline LDL-C >130 mg/dL could significantly reduce the volume of CAP at follow up (SMD -0.108 mm³, 95% CI -0.176~-0.040, $p=0.002$; SMD -0.139 mm³, 95% CI -0.193~-0.084, $p=0.000$; SMD -0.123 mm³, 95% CI -0.199~-0.048, $p=0.001$; SMD -0.199 mm³, 95% CI -0.314~-0.085, $p=0.001$; respectively). The mean duration of follow up was from 17.4~19.4 months.

Conclusions: Intensive lowering LDL-C with >18 months of duration could lead to the regression of coronary atherosclerotic plaque, LDL-C level should be reduced by >40% or to a target level <78 mg/dL for regressing CAP.

P1277 | BEDSIDE

Phytosterol and oxysterol levels in plasma and aortic valve cusps in patients with severe aortic stenosis

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Background: We hypothesized that in patients with severe aortic stenosis phytosterol and oxysterol concentrations in serum and aortic valve cusps correlate with each other, independent of statin treatment.

Methods and results: We included 104 consecutive patients (68/36; m/f) between 40 and 87 years (mean 69.8 yrs.) who were admitted to our hospital for elective aortic valve replacement due to severe aortic stenosis. Study participants were assessed for established cardiovascular risk factors and concomitant statin treatment (no statins: 36/statins: 68). Venous blood samples were drawn one day prior valve surgery and the aortic valve cusps were analyzed to determine non-cholesterols (cholestanol, lathosterol, lanosterol and desmosterol) and oxysterols (7 α -OH, 7 β -OH, 7 keto-campesterol, -sitosterol) by gas chromatography-flame ionization/ mass spectrometry. As expected, there were significantly lower absolute and cholesterol corrected serum concentrations of cholesterol precursors (lathosterol, lanosterol and desmosterol) in statin treated patients. The concentration of the two most common plant sterols (sitosterol and campesterol) strongly correlated with each other in plasma ($r=0.911$; $p=0.000$) and aortic valve cusps ($r=0.945$; $p=0.000$) as well as between the two groups ($r=0.488$; $p=0.000$ campesterol; $r=0.350$; $p=0.000$ sitosterol). We found a significant correlation between plant sterols and their oxidized forms in aortic valve cusps ($r=0.712$; $p=0.000$ campesterol to sum oxycampesterol; $r=0.706$; $p=0.000$ sitosterol to sum oxysitosterol), but not in serum ($r=0.243$; $p=0.014$ campesterol to sum oxycampesterol, $r=0.317$; $p=0.001$ sitosterol to oxysitosterol). Furthermore, there was a significant correlation between 7 α -hydroxy-, 7 β -hydroxy-, and 7 keto-campesterol/sitosterol in aortic valve tissues, irrespective of statin treatment.

Conclusion: In patients with severe aortic stenosis phytosterols and their respective oxidized forms correlate significantly in aortic valve tissue, but not in serum. Moreover, there is no correlation of oxysterols in serum with their respective concentrations in aortic valve cusps. These data suggest that sterol oxidation in cardiovascular tissue is a local process that is independent of statin treatment.

P1278 | BEDSIDE

The influence of statin intake on the progression of coronary artery calcium: the Heinz Nixdorf Recall study

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Purpose: Statin intake is regarded to stabilize coronary artery plaques. We aimed to determine, whether this influences the progression of coronary artery calcification (CAC).

Methods: Participants from the Heinz Nixdorf Recall Study (age 45 to 75 years) without known cardiovascular disease were included. CAC-Score (CACS) was assessed using electron beam computed tomography at baseline and after five years and quantified by the Agatston-Score. Regression analysis was used to determine the association of CAC progression with statin intake with Log-transformation of CAC to normalize for its distribution. CAC progression was defined as difference of log-transformed CAC ($\log(\text{CAC}[t1]+1) - \log(\text{CAC}[t0]+1)$). Effect size was depicted as % change in CAC+1.

Results: Overall, 3483 subjects (mean age 59 years, 47% male) were included. Subjects with statin intake had higher CACS at baseline (median [Q1; Q3]: 58.8 [2.6; 273.3] vs. 5.9 [0; 80.2], $p<0.0001$) and higher absolute CAC progression over 5 years (median [Q1; Q3]: 57.1 [4.6; 256.0] vs. 7.7 [0; 83.3], $p<0.0001$). In unadjusted regression analysis, statin intake was associated with higher CAC progression (Estimate (95% confidential Interval): 39 (20-62)%, $p<0.0001$) with the similar effect size when adjusting for cardiovascular risk factors including cholesterol levels (31 (12-52)%, $p=0.0006$). Subjects with higher CAC at baseline showed no relevant association of statin intake with CAC progression, while CAC progression was significantly higher for subjects with statin intake, when CACS was low at baseline ($\text{CAC}\geq 100$: 4 (-6-15)%, $p=0.5$ vs. $\text{CAC}<100$: 75 (40-120)%, $p<0.0001$). The results were confirmed in a case-controlled design subanalysis, matching subjects with statin intake with controls by age, gender, risk factors, and CAC category at baseline (overall: 38 (15-67)%, $p=0.0007$; $\text{CAC}<100$: 62 (21-116)%, $p=0.001$; $\text{CAC}\geq 100$: 7 (-5-21)%, $p=0.2$). To further confirm our results for the overall cohort, we assessed the association of statin intake with CACS at follow-up adjusted for CACS at baseline and found that statin intake was associated with higher CACS at follow-up: 41 (21-65)%, $p<0.0001$.

Conclusion: Within 5 years of follow-up, statin therapy is associated with increased progression of CAC in the general population without known cardiovascular diseases despite their lipid lowering effect, confirming the trend, suggested in previous randomized clinical trials. Notwithstanding other explanations like bias by indication, our results may support the hypothesis of a plaque stabilizing effect of statins, which might be reflected by an increase in CAC.

P1279 | BEDSIDE

High LDL cholesterol decreases life expectancy in primary prevention

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Background: The 2012 ESC guidelines recommend a LDL-cholesterol (LDL-C) lower than 3 mmol/L for subjects at low or moderate risk with a class I/A and a strong grade. According to ESC, statins should be used as the drugs of first choice. However, statins in primary prevention cause controversy in some European countries. The aim of this study was to assess the association between elevated LDL-C with total and cardiovascular (CV) mortality in primary prevention.

Methods: Our study population consisted in patients who had been admitted from 1995 to 2011 in a preventive cardiology unit of a large university hospital. We excluded patients whose age was less than 30 and all patients with previous ischemic heart disease. A 12h-fast lipid panel was obtained in all subjects the same day of the visit and in the same laboratory. Vital status in 2011 (causes and date of death) was checked through the death national database. Multivariable relationships with total and CV mortality were evaluated with a Cox proportional hazards model.

Results: 4885 patients were included (59% men; mean age 53 ± 10). After a mean follow-up of 8.6 years, 129 deaths, including 31 CV deaths, were recorded. The mean LDL-C was 3.98 ± 1.18 mmol/L (3.90 mmol/L in men and 4.11 mmol/L in women). Among these 4885 patients, 2648 (54.2%) had LDL-C levels lower than 4 mmol/L, 1890 (38.7%) had LDL-C between 4 and 6 mmol/L, 347 (7.1%) had LDL-C higher than 6 mmol/L, and 1833 (37.5%) were on current lipid-lowering treatment. After adjustment for age, gender, smoking, hypertension and diabetes, an increased LDL-C >4 mmol/L was significantly associated with all cause mortality (hazard ratio (HR) 2.06; 95% confidence interval (CI) [1.42-3.00], $p=0.001$) and with CV mortality (HR 2.18; 95% CI [1.04-4.57], $p=0.04$). After adjustment for these classical risk factors and for lipid-lowering treatment, LDL-C remained significantly associated with an increasing risk of all cause mortality; with LDL-C <4 mmol/L as a reference class, LDL-C levels between 4 and 6 mmol/L were

associated with an increased all cause mortality (HR 1.72; 95% CI [1.17-2.54], $p=0.006$) as well as LDL-C >6 mmol/L (HR 2.60; 95% CI [1.49-4.85], $p=0.001$).

Conclusions: LDL-C levels higher than 4 mmol/L were significantly associated with all-cause and cardiovascular mortality in primary prevention. The observation of a gradient of risk associated with elevated LDL-C supports causality in this low risk population. The 2012 ESC LDL-C target seems to be appropriate in Southern Europe.

P1280 | BEDSIDE

Association of a polymorphism of the zinc finger protein 259 gene (ZNF259) with dyslipidemia in Japanese individuals

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Purpose: Various loci and genes that confer susceptibility to coronary heart disease (CHD) have been identified for Caucasian populations by genome-wide association studies (GWASs). Given that dyslipidemia is a major risk factor for CHD, we hypothesized that some polymorphisms might contribute to the genetic susceptibility to CHD through affecting the susceptibility to dyslipidemia. The purpose of the present study was to examine a possible association of dyslipidemia (hypertriglyceridemia, hypo-HDL-cholesterolemia, or hyper-LDL-cholesterolemia) in Japanese individuals with 15 polymorphisms identified as susceptibility loci for CHD in the previously GWASs.

Methods: Study subjects comprised 5460 Japanese (2354 subjects with dyslipidemia, 3106 controls) who visited the participating hospitals between 2002 and 2012. Dyslipidemia was defined as a serum triglyceride of ≥ 1.65 mmol/L, a serum HDL-cholesterol of <1.04 mmol/L, or a serum LDL-cholesterol of ≥ 3.64 mmol/L. To compensate for multiple comparisons, we adopted the criterion of a false discovery rate (FDR) for statistical significance of association.

Results: Comparisons of allele frequencies by the chi-square test revealed that the rs964184 of the zinc finger protein 259 gene (ZNF259) was significantly ($P=0.0006$, FDR=0.0094) associated with dyslipidemia. Multivariable logistic regression analysis with adjustment for age, sex, and body mass index revealed that the rs964184 of ZNF259 was significantly associated with dyslipidemia ($P=0.0029$; odds ratio, 1.18; dominant model), with the minor C allele representing a risk for this condition. Examination of each lipid profile revealed that rs964184 ($P=7.1 \times 10^{-9}$, FDR=1.1 $\times 10^{-7}$), rs46522 of the ubiquitin-conjugating enzyme E2Z gene (UBE2Z) ($P=0.0025$, FDR=0.0165), and rs4845625 of the interleukin 6 receptor gene (IL6R) ($P=0.0033$, FDR=0.0165) were significantly associated with hypertriglyceridemia. Multivariable logistic regression analysis with adjustment for age, sex, and body mass index revealed that the rs964184 of ZNF259 ($P=5.1 \times 10^{-9}$; odds ratio, 1.38; dominant model), rs46522 of UBE2Z ($P=0.0039$, odds ratio, 1.20; dominant model), and rs4845625 of IL6R ($P=0.0020$, odds ratio, 1.25; dominant model) were significantly associated with hypertriglyceridemia. Serum concentrations of triglycerides significantly ($P=5.1 \times 10^{-13}$) differed among ZNF259 genotypes (GG, 3.52 ± 2.43 mmol/L; GC, 3.91 ± 2.82 mmol/L; CC, 4.57 ± 3.12 mmol/L; means $\pm$ SD).

Conclusions: ZNF259, UBE2Z, and IL6R may be susceptibility loci for hypertriglyceridemia in Japanese individuals.

P1281 | BEDSIDE

Lipoprotein (a) is a strong predictor of cardiovascular and all-cause mortality in 4885 subjects in primary prevention

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Background: Lipoprotein(a) [Lp(a)] has been considered a cardiovascular (CV) risk factor (RF) for many years. Most of the studies, often published before 2000, have analysed the association of elevated Lp(a) with CV diseases after adjustment only for age and sex. The aim of this study was to assess the long-term

association of elevated Lp(a) with all-cause and CV mortality in a healthy cohort in primary prevention.

Methods: Our population consisted in subjects who were examined between 1995 and 2011 in the Department of Preventive Cardiology (DPC) in a large university hospital. We excluded patients whose age was less than 30 years as well as patients with established ischemic heart disease (International Classification of Disease, 9th revision, codes 410.0-414.9). Lp(a) was measured by an immunoassay in the same laboratory and in all subjects on fresh plasma the same day of the visit. Information on vital status (causes and date of death) was obtained for each participant through the national death database. Multivariate predictive relationships of Lp(a) with CV and total mortality were evaluated with a Cox proportional hazards model.

Results: 4885 patients were included. 56% were men and the mean age was 53. After a mean follow-up of 8.6 years, 129 deaths, including 31 CV deaths, were recorded. The mean Lp(a) was 36 mg/dl (31 mg/dl in men and 42 mg/dl in women). Classical parameters such as age, gender, diabetes, hypertension and elevated LDL-cholesterol were confirmed as independent CV RF. In multivariate analysis and after adjustment for the above parameters, Lp(a) was statistically and significantly associated with total and CV mortality. There were significant adjusted associations between levels of Lp(a) greater than 50 mg/dl and total mortality (hazard ratio: 1.50; 95% CI: 1.01-2.24, $p=0.046$) and CV mortality (hazard ratio: 2.73; 95% CI: 1.33-5.64, $p=0.006$).

Conclusions: Elevated Lp(a) levels, especially above the threshold of 50 mg/dl defined by the European Atherosclerosis Society Consensus Panel, were associated with all-cause and CV mortality in this long-term cohort study. Therefore, Lp(a) should be measured nowadays in order to assess global CV risk.

NOVEL BIOMARKERS PART I

P1283 | BEDSIDE

Soluble ST2 to identify the risk of new-onset reduced versus preserved ejection fraction heart failure in community dwelling older adults

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Purpose: Soluble ST2 (sST2) is a sensitive marker of cardiac stress, but is not cardiac specific. Prior studies have shown sST2 identifies risk of new-onset heart failure (HF) in low- to intermediate- risk asymptomatic individuals. We sought to determine if sST2 could further differentiate the risk of HF with reduced ejection fraction (HFrEF) versus HF with preserved EF (HFpEF) in older adults with no history of HF.

Methods: Using the Cardiovascular Health Study, a cohort of community dwelling adults ≥ 65 years, sST2 was measured using the Presage assay in 2141 participants without a prior HF or MI and with a baseline echocardiogram. Participants were followed-up for a median of 13.1 years for incident HF. EF within 30 days of HF was documented when available. HF was adjudicated by a central committee. HFrEF was defined as EF $<45\%$. sST2 was analyzed across tertiles, as a continuous variable (log transformed), and at its approved cut-off of 35 ng/mL.

Results: There were 592 HF events (139 HFrEF, 196 HFpEF and 257 unknown EF) in the study population who had a mean age of 72 ± 5 , 35% male, 85% Caucasian, 1.3% baseline EF $<45\%$. Progressively higher sST2 concentrations were predictive of incident HFrEF, but not HFpEF after adjustment for clinical and echocardiographic risk factors (Table).

Conclusions: sST2 in older adults differentiates risk for future HFrEF suggesting levels may identify a preclinical phenotype of patients that could benefit from specific available therapies to reduce progression to symptomatic HF.

P1284 | BEDSIDE

Elevated levels of soluble ST2 independently predict total mortality but not subsequent cardiovascular events in stable coronary heart disease patients: 10-year follow-up of the STABLE study

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Purpose: Soluble (s) ST2, a member of the interleukin-1 family has been sug-

Abstract P1283 – Table 1. sST2 level and incident HFrEF or HFpEF

N=2141	HFrEF N=139 events			HFpEF N=196 events		
	Incident rate (per 100 pt yrs)	Unadjusted	Adjusted*	Incident rate (per 100 pt yrs)	Unadjusted	Adjusted*
sST2 tertile						
T1	0.39 (0.28, 0.54)	Reference	Reference	0.73 (0.57, 0.92)	Reference	Reference
T2	0.53 (0.40, 0.71)	1.36 (0.88, 2.10)	1.21 (0.78, 1.88)	0.69 (0.53, 0.88)	0.98 (0.69, 1.39)	0.85 (0.59, 1.21)
T3	0.74 (0.57, 0.95)	1.90 (1.25, 2.88)	1.59 (1.04, 2.45)	0.89 (0.70, 1.12)	1.32 (0.94, 1.85)	1.07 (0.76, 1.50)
Test for trend		$P=0.002$	$P=0.03$		$P=0.1$	$P=0.01$
Ln(sST2)		3.20 (1.97, 5.18)	2.00 (1.18, 3.37)		1.41 (0.90, 2.20)	1.11 (0.71, 1.75)
sST2 >35 ng/ml (11.1%)		2.84 (1.89, 4.26)	1.88 (1.29, 3.03)		1.43 (0.94, 2.17)	1.22 (0.78, 1.94)

*Adjusted for age, race, gender, DM, HTN, CHD, BMI, eGFR <60 , smoking, LVEF $<45\%$ (HFrEF only), relative wall thickness, and LV mass.

gested to play an important role in cardiac remodelling, hypertrophy, immune response and inflammatory signalling. Yet data on its potential clinical relevance as a predictor for cardiovascular disease (CVD) events and mortality are controversial. Thus, we assessed the predictive value of sST2 for subsequent CVD events and total mortality in stable coronary heart disease (CHD) patients, simultaneously controlling for a large number of potential confounders.

Methods: Plasma concentrations of sST2 (ELISA, Critical Diagnostics) were measured at baseline in a cohort of 1,073 patients aged 30-70 years with stable CHD. The Cox proportional hazards model was used to determine the prognostic value of sST2 on a combined CVD endpoint after adjustment for covariates.

Results: The median sST2 level was 28.9 ng/mL (IQR 23.8, 35.1). Elevated sST2 levels were associated with male gender, and left-ventricular dysfunction but not with age, history of hypertension, and heart failure. Furthermore, sST2 was significantly correlated with GDF-15 ($R=0.22$), NT-proBNP ($R=0.17$), MRproANP ($R=0.16$), cystatin C, hsTn I and T (all $R=0.12$), as well as CRP ($R=0.11$), and sPLA2 ($R=0.16$), respectively (all p -values <0.0001). During a median follow-up of 10.0 years, 205 patients (19.0%) experienced a fatal- or non-fatal subsequent CVD event. In an age and sex adjusted model, sST2 was associated with a hazard ratio (HR) for secondary CVD events of 1.51 (95% CI, 1.03-2.22) when extreme quartiles (Q4 vs Q1) were compared. However, further adjustment for clinical factors attenuated the association (HR 1.39; 95% CI 0.94-2.06). By contrast, a statistically significant association was still seen with total mortality ($N=173$ deaths) in multivariable analyses comparing Q4 vs Q1 with a HR of 1.71 (95% CI 1.11-2.65) after adjustment for clinical factors. Further adjustment for cystatin C, NT-proBNP, and CRP attenuated the association and it became non-significant (HR 1.36; 95% CI 0.87-2.11). In analyses using sST2 as a continuous variable it was still clearly associated with mortality, even after inclusion of emerging biomarkers (HR per unit increase 1.67 (95% CI 1.02-2.72)).

Conclusions: Elevated levels of sST2 in stable CHD patients did not independently predict subsequent CVD events but overall mortality in a secondary prevention cohort with long-term follow-up.

P1285 | BEDSIDE

A comparison of soluble ST2 and high sensitivity C-reactive protein for prediction of cardiovascular mortality in the Electricity Generating Authority of Thailand cohort study

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Background: Soluble ST2 (sST2) is increased by cardiomyocyte stretch and inflammation. It has been studied in select community-based Western cohorts. This is the first study to evaluate if sST2 is an independent predictor of cardiovascular mortality in the Thai population and how it compares to highly sensitive C-reactive protein (hsCRP) for this application.

Methods: Concentrations of sST2 and hsCRP were measured in 2,058 employees of the Electricity Generating Authority of Thailand (EGAT Cohort Study) from sera stored in 2002. Participants' baseline characteristics were reviewed and covariates associated with sST2 and hsCRP identified; participants were then categorized by quartiles of sST2 and hsCRP concentration. Association with all-cause mortality, cardiovascular and non-cardiovascular mortality in 2012 was assessed.

Results: In 2,058 participants (mean age 59 years, 75.8% male), the median of sST2 was 18.39 ng/ml and the median of hsCRP was 1.47 mg/L. Male sex, prior stroke, fasting plasma glucose, and serum creatinine were associated with higher sST2 levels. The cut-point of sST2 and hsCRP in 4th quartiles were 23 ng/ml and 3.1 mg/L, respectively. There was no correlation between these two markers (Spearman's $\rho=0.007$). During the 10-year follow-up, 192 (9.3%) died; 106 participants (5.2%) underwent coronary angiography; and 95 participants (4.6%) required revascularization. sST2 in 4th quartile group was associated with increased all-cause mortality (OR=2.75; 95% CI=1.77-4.25; $p<0.001$). Cardiovascular mortality also increased significantly across sST2 categories from 8.3% in the 1st quartile to 44.4% in the 4th quartiles (OR=5.47; 95% CI=1.56-18.90; $p=0.01$). After adjusted with other cardiovascular risk factors, sST2 >23 ng/ml showed a strong predictor of cardiovascular death (HR=4.19; 95% CI=1.10-16.90; $p=0.04$). hsCRP only predicted all-cause mortality ($p=0.01$).

Conclusions: In this worker-based Thai cohort, sST2 strongly predicted cardiovascular and all-cause mortality, and was superior to hsCRP for this application.

P1286 | BEDSIDE

Predictive role of ST2 for mortality in anticoagulated patients with atrial fibrillation

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Background: Atrial fibrillation (AF) is associated with high morbidity and mortality. For assessing prognosis in AF, clinical risk scores are recommended for initiating oral anticoagulation (OAC) reduces the risk of stroke and death. How-

ever the risk of total and cardiovascular mortality remains high in this type of patients, even under OAC. It has been observed that rates of mortality, heart failure, myocardial infarction and stroke increase with older age and risk scores. Biomarkers may add significant information regarding mortality. ST2 is a member of the interleukin-1 receptor family. Patient's risk of mortality and morbidity increases with ST2 levels >30 ng/mL in patients with heart failure or acute coronary syndrome. We assessed the predictive value of ST2 levels in an unselected "real world" cohort of anticoagulated AF patients seen in everyday clinical practice.

Methods: We studied 562 patients (49% male; median age 77 [IQR: 71-82]) with permanent AF who were stable (for at least 6 months) on OAC (INRs 2.0-3.0). ST2 levels were quantified by a quantitative sandwich monoclonal ELISA. Patients were followed-up for up to 4 years, and adverse events of all cause mortality were recorded. A Cox regression analysis was performed using ST2 levels as a continuous variable.

Results: Median (IQR) of ST2 levels were 51.23 (39.09-67.40) ng/mL. Median follow-up was 1587 days [IQR 1482-1617] days, and during this period, 91 patients died (3.72%/year). The c-statistic for ST2 was 0.58; $p=0.033$. On multivariate analysis, age [1.09 (1.05-1.13); $p<0.001$], diabetes mellitus [1.76 (1.08-2.88); $p=0.023$], previous stroke [2.16 (1.29-3.60); $p=0.003$], and ST2 levels [1.008 (1.002-1.14); $p=0.008$] were the variables which remained associated with mortality. Levels of ST2 were also significantly associated with the risk of mortality even after adjusting for the CHA2DS2-VASc score [HR: 1.007 (1.001-1.013); $p=0.014$].

Conclusion: In a "real world" anticoagulated AF patient's cohort, ST2 levels are an independent predictive factor of all-cause mortality. ST2 levels could be a biomarker used to improve clinical risk assessment in anticoagulated AF patients.

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P1287 | BEDSIDE

Long-term predictive value of soluble ST2 concentrations and left ventricular remodeling: the EGAT study

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Background: Soluble ST2 (sST2) is a strong predictor for cardiovascular events, including mortality and new-onset heart failure (HF). Cross-sectional associations have been reported between sST2 and left ventricular (LV) remodeling in patients with established HF, however it is not known if elevated sST2 concentrations would predict long-term cardiac remodeling in general populations.

Methods: In our study, we used stored serum collected in 2002 from a cohort study (Electricity Generating Authority of Thailand [EGAT] study) to assess predictive value of sST2 concentrations (Critical Diagnostics, CA, USA) for LV remodeling. Echocardiography was performed in 2012; LV quantification, systolic and diastolic function were analyzed for their association with log-transformed baseline sST2 concentrations from using adjusted linear regression analysis.

Results: 565 participants were enrolled; the majority were male (71.7%) with an average age of 58.3 years. After adjustment for age, sex, body-mass index, low and high density lipoprotein cholesterol, prevalent diabetes mellitus, renal function, C-reactive protein, and mean blood pressure, sST2 was significantly correlated with numerous important echocardiographic parameters of LV size and function (Table).

Association between sST2 and Echo

	Multivariate* (log sST2)		
	β Coefficient	95% CI	p-value
Transmitral peak inflow velocity of early diastolic filling (Mitral E), cm/s	15.077	5.138, 25.016	0.003
Intraventricular septal thickness during diastole (IVSd), mm	-1.752	-2.815, -0.690	0.001
LV end diastolic dimension (LVEDd), mm	4.046	1.007, 7.086	0.009
Posterior wall thickness during diastole (PWTd), mm	-0.893	-1.959, 0.173	0.101
Left ventricular ejection fraction (LVEF), %	-2.155	-6.655, 2.344	0.347
Relative wall thickness (RWT)	-0.080	-0.142, -0.018	0.012
LV end diastolic dimension index (LVEDd index), mm/m ²	3.105	1.232, 4.978	0.001

Conclusions: Among a general population cohort followed for 10 years, higher baseline concentrations of sST2 were correlated with parameters of myocardial remodeling including more dilated LV and thinner myocardium. Future studies are needed to better understand mechanisms of sST2-mediated LV remodeling, the links between sST2 and risk for HF events, and whether therapeutic strategies may be employed to lower such risks.

P1288 | BEDSIDE

Impact of serum omentin-1 levels on cardiac prognosis in patients with heart failure

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Background: Various adipokines are reported to be associated with develop-

ment of heart failure (HF) through insulin resistance and chronic inflammation. Omentin-1 is a novel adipokine and associated with incident coronary artery disease. However, it remains unclear whether serum omentin-1 levels are associated with cardiac prognosis in patients with HF.

Methods: We measured serum omentin-1 levels at admission in 156 consecutive patients with HF and 20 control subjects without signs of significant heart diseases. We prospectively followed patients with HF for the end points of cardiac death or re-hospitalization for worsening HF.

Results: Serum omentin-1 levels were significantly lower in patients with HF compared with control subjects. Furthermore, serum omentin-1 levels were markedly lower in HF patients with cardiac events compared with those without. Serum omentin-1 levels were decreased with advancing New York Heart Association (NYHA) functional class, whereas serum omentin-1 levels did not correlate with serum brain natriuretic peptide levels ($r=0.217$). Then we divided the patients into 2 groups based on the median serum omentin-1 level. Kaplan-Meier analysis revealed that significantly higher cardiac event rates were observed in low omentin-1 group compared with high omentin-1 group (log-rank test $p<0.001$). Cox hazard analysis showed that decreased serum omentin-1 level (hazard ratio 1.76, 95% CI 1.43-3.56) was independently associated with cardiac events after adjustment of predictors that were significant by univariate analysis.

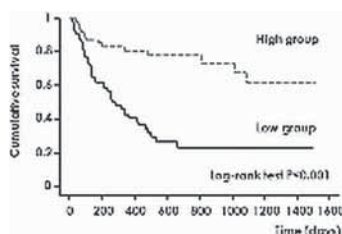


Figure 1. Cumulative survival.

Conclusion: Decreased serum omentin-1 levels were associated with poor cardiac prognosis in patients with HF.

P1289 | BEDSIDE

Plasma omentin significantly predicts cardiovascular events independently from the presence and extent of angiographically determined baseline coronary artery disease

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Purpose: No prospective data on the power of the new adipocytokine omentin to predict cardiovascular events are available. We therefore aimed at investigating i) the association of plasma omentin with cardiometabolic risk markers, ii) its association with angiographically determined coronary atherosclerosis, and iii) the power of plasma omentin to predict cardiovascular events.

Methods: We measured plasma omentin in a series of 295 patients undergoing coronary angiography for the evaluation of established or suspected stable CAD; presence of baseline CAD was defined as the presence of any lumen irregularities at angiography; the extent of baseline CAD was defined as the number of significant coronary stenoses $\geq 50\%$; prospectively cardiovascular events were recorded over a mean follow-up period of 3.5 years.

Results: During this period, 17.6% of our patients suffered cardiovascular events, corresponding to an annual event rate of 5.3%. Plasma omentin did not differ significantly between patients with and subjects without significant CAD ($p=0.783$), but prospectively omentin significantly predicted cardiovascular events after adjustment for age, gender, BMI, diabetes, hypertension, LDL cholesterol, HDL cholesterol and smoking with a standardized adjusted hazard ratio (HR) of 1.41 [95% CI 1.16-1.72], $p<0.001$, as well as after additional adjustment for the presence and extent of CAD at the baseline angiography (HR 1.52 [95%CI 1.23-1.86], $p<0.001$).

Conclusions: From this first prospective evaluation of the cardiovascular risk associated with plasma omentin we conclude that elevated omentin is a strong predictor of cardiovascular events independently from the presence of baseline CAD.

P1290 | BEDSIDE

Combining NT-pro-BNP with a novel restitution based biomarker substantially improves prediction of sudden cardiac death risk

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Purpose: The Regional Restitution Instability Index (R2I2) is a promising new

ECG based biomarker of sudden cardiac death (SCD). This abstract explores the potential of a combined R2I2 and NT-pro-BNP SCD risk marker in an ischaemic cardiomyopathy cohort.

Methods: Blinded prospective observational study. Study group: 55 ischaemic cardiomyopathy patients undergoing risk stratification for implantable cardioverter defibrillator (ICD). The R2I2 technique has been described previously: an EP study is performed and ECG surrogates for action potential duration and diastolic interval are used to measure restitution heterogeneity. Plasma samples obtained on the day of the ICD procedure were assayed for NT-pro-BNP.

Results: During median follow up of 22 months, 15 patients experienced ventricular arrhythmia (VA)/SCD. R2I2 was significantly higher in patients experiencing VA/SCD than those not (mean $\pm$ SEM: 1.12 ± 0.05 vs 0.84 ± 0.09 , $p=0.004$). R2I2 was independent of log NT-pro-BNP and left ventricular ejection fraction in prediction of endpoint (Cox model, $p=0.001$). Partitioning patients using a log NT-pro-BNP ≥ 2.65 gave a significantly higher rate of VA/SCD in those with high versus low log NT-pro-BNP (38% vs. 6%, $p=0.01$). Patients with R2I2 ≥ 1.03 and log NT-pro-BNP ≥ 2.65 had a hazard ratio for VA/SCD 17 times that of patients negative for both (Cox model, $p<0.007$). Kaplan Meier analysis (Figure 1) showed significant separation in rates of VA/SCD in patients stratified by R2I2 ≥ 1.03 and log NT-pro-BNP ≥ 2.65 (log-rank, $p<0.0001$).

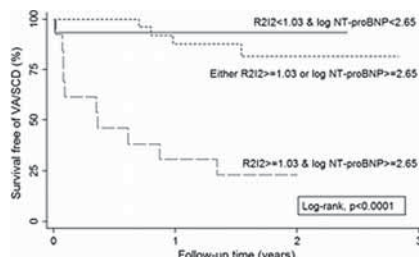


Figure 1. Kaplan Meier analysis

Conclusion: Combined R2I2+NT-pro-BNP identify patients with particularly high risk of ventricular arrhythmia/SCD. These patients might benefit from careful treatment optimisation. R2I2+NT-pro-BNP might retain sufficient positive predictive value for application to lower risk cohorts.

P1291 | SPOTLIGHT

SDMA and L-arginine correlate with subclinical atherosclerosis in a large population cohort

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Circulating levels of arginine derivatives can predict cardiovascular mortality. However, their role as atherosclerotic biomarkers is unclear. Asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) may contribute to subclinical atherosclerosis by inhibition of endothelial nitric oxide (NO) synthase and cellular L-arginine (ARG) uptake, respectively. ARG up-regulates endothelial NO production and thus maybe atheroprotective. Therefore, we tested if ADMA, SDMA and the sum of both (DMA) are positively, while ARG is inversely correlated with carotid inter-media thickness (IMT) and presence of atherosclerotic plaque. Cross-sectional data of 2007 subjects (48.2% φ , age: 45 – 81 years) from the Study of Health in Pomerania (SHIP-0) was used. All adjusted models were corrected for sex, age, smoking status, waist-to-hip ratio and glomerular filtration rate. An adjusted ANOVA was fitted to ADMA, SDMA, DMA, and ARG plasma concentration tertiles with continuous log-corrected IMT. Associations between plasma arginine derivative concentrations and increased IMT, defined as above the 75th sex- and age-specific quartile, as well as the presence of atherosclerotic plaque were calculated using logistic regression models.

Increased IMT was found in 517 subjects (25.7%). SDMA plasma concentration tertiles were significantly associated with IMT, while ADMA, DMA, and ARG were not. Post-hoc analysis identified a positive correlation and significant differences between medium and high plasma SDMA concentrations [<33 rd: 0.816 (0.789; 0.845), 33rd–66th: 0.778 (0.755; 0.802), >66 th: 0.824 (0.796; 0.853)]. High SDMA and DMA concentrations were related to higher odds of increased IMT in the adjusted [SDMA OR 1.371; 95% CI (1.068; 1.760) and DMA OR 1.310 (1.024; 1.676)] and unadjusted model. A total of 1413 subjects (70.4%) had carotid atherosclerotic plaques. Non-adjusted logistic regression models identified a significant positive association for the presence of atherosclerotic plaque with ADMA, SDMA, and ARG. After adjustment only ARG remained significant, demonstrating increased odds for atherosclerotic plaques with high ARG concentrations in the non-adjusted and adjusted model [OR 1.367; 95% CI (1.040; 1.799)].

In conclusion, as hypothesized high SDMA and DMA concentrations correlate with an increased IMT. Unexpectedly, increased plasma ARG levels were positively related to atherosclerotic plaques, thus, not linked with less subclinical

atherosclerosis. Therefore, whether arginine derivatives may serve as atherosclerotic biomarkers deserves further research.

P1292 | BEDSIDE

Impact of indoxyl sulfate on coronary plaques in patients on hemodialysis; IS-HD study

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Background: Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease (CVD). Indoxyl sulfate (IS) is a uremic toxin (UT) that is associated with CVD and mortality in CKD patients. However, an impact of serum IS level on coronary plaque burden (CPB) or coronary artery calcium (CAC) is unknown. Therefore, the aim of this study is to investigate the relationship between serum IS level and CPB or CAC in patients on hemodialysis.

Methods and results: The study is prospective observational study and registered with university hospital medical information network (UMIN) clinical trial registration: UMIN000009500. We enrolled 30 patients (19 men, 67.4±10.7 years) on hemodialysis who underwent coronary computed tomographic angiography (CCTA) with 320-rows (Aquilion ONE) for suspected CVD between December 2012 and November 2013. The patients with prior coronary artery bypass grafting, prior pacemaker implantation, and severe heart failure (New York Heart Association Classification III - IV) were excluded. CCTA with 320-rows was performed on a dialysis-free day and blood samples were collected on the same morning before CCTA. Serum IS level and various oxidative and inflammatory markers, such as 8-OHdG, ADMA, pentaxin3, TGF- β , E-selectin, ICAM-1, were examined. Cardiac and carotid echography was performed within $\pm$ 30 days of CCTA. The non-enhanced scans were used to evaluate the total amount of CAC according to the agatston approach. The plaque quantification was performed using dedicated quantitative software with a 3D registration algorithm (QAngio CT 2.0.5, Medis medical imaging systems, Leiden, the Netherlands). By univariate analysis, CPB was significantly correlated with serum IS level ($r=0.533$, $p=0.002$). Good correlations for CAC were observed for HbA1c ($r=0.403$, $p=0.027$), serum potassium ($r=0.429$, $p=0.020$), right carotid artery intima-media thickness ($r=0.386$, $p=0.039$), and serum ICAM-1 ($r=-0.366$, $p=0.047$). Furthermore, CPB was significantly higher in patients with hyperuricemia ($p=0.014$), and CAC was significantly higher in those with vitamin D preparation ($p=0.004$). Multivariate analysis identified serum IS level and hyperuricemia as predictive factors of greater CPB after controlling for all evaluated variables. In contrast, no significant predictive factors were identified for CAC.

Conclusions: We are able to correlate, for the first time, serum IS level and CPB in patients on hemodialysis. Our findings provide a critically important link between UT and atherogenic CVD in hemodialysis patients.

P1293 | BENCH

Profiling of circulating microRNAs in interventional cardiologists occupationally exposed to chronic ionizing radiation

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Background: Aberrant expression of circulating microRNA (miRNAs) is related to various diseases, including cancers and cardiovascular disease. However, it is unknown whether dysregulation of miRNAs may occur following exposure to chronic ionizing radiation exposure. Aim of this study was to investigate the plasma miRNA profile in interventional cardiologists working in cath laboratory.

Methods: Global miRNA expression was performed in 10 interventional male car-

diologists (age = 54±5.4 years) and 10 healthy subjects (age = 53.2±5.5 years). RNA was isolated from plasma using the miRNeasy Kit (Qiagen) and hybridized on Agilent MicroRNA 60K array containing probes for 2006 human miRNAs. Highly deregulated miRNAs were validated using qRT-PCR. Target genes and biological pathways were determined with DAVID (<http://david.abcc.ncifcrf.gov/>) and the interactions were visualized with Cytoscape (<http://cytoscape.org/>).

Results: Microarray analysis revealed a significant decrease of hsa-miR-134 ($p=0.00045$), hsa-miR-575 ($p=0.00023$), hsa-miR-1275 ($p=0.000027$) and hsa-miR-2392 ($p=0.00011$) in exposed when compared to controls. The relative fold changes of the qRT-PCR validation were in line with the microarray data. Bioinformatic analysis revealed 928 predicted target genes, most of which are involved in DNA repair, apoptosis, neuronal brain function, control of spermatogenesis and metabolic process (figure). Deregulated miRNAs were also previously reported to be potential biomarkers of disease (cancer and neuropsychiatric disorders), suggesting the possibility that radiation exposure might interfere with the health risk.

Conclusion: These findings showed dysregulation of specific miRNA profiles, giving clues for better understanding the health risk from exposure to low dose ionizing radiation.

P1294 | BEDSIDE

Circulating miRNA and the severity of coronary artery disease

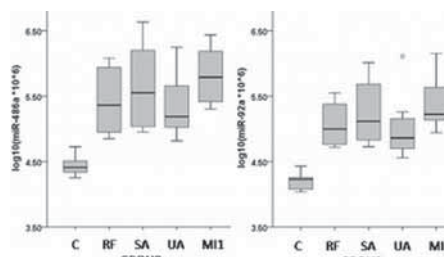
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Background: The individual risk of a patient with coronary artery disease (CAD) for developing an acute coronary syndrome (ACS) is currently difficult to estimate. To date, there is no specific marker able to predict the risk for ACS.

Objectives: We aimed to identify such a biomarker by studying the distribution of miRNA in 4 groups of patients: SA (stable angina, $n=22$), UA (unstable angina, $n=21$), MI1 (patients 1 month after myocardial infarction, $n=11$), RF (subjects with CAD risk factors, but no significant CAD, $n=10$), compared to C (healthy subjects, $n=10$).

Methods: MiRNA were isolated from pooled sera of SA, UA, MI1, RF and C individuals and following, a screening for 84 miRNA was performed. Fold change (FC) values of analyzed miRNA were expressed relative to C group. MiR-125a, miR-146a, miR-33a (known to be associated with dyslipidemia, endothelial dysfunction and inflammation) were selected for validation in each patient's serum using reverse transcription miRNA with stem loop specific primers and real time quantitative PCR with specific TaqMan primers.

Results: Screening analysis showed that miR-122a (FC 63.07), miR-486a (FC 52.89), miR-92a (FC 51.19) had the highest values compared to C. All miRNA had higher serum levels in SA, UA, RF, MI1 groups, compared to C ($p<0.05$ for all). MiR-486a and miR-92a had higher levels in patients with MI1 than UA. MiR-125a, miR-146a, and miR-33a did not differ between groups.



Circulating mRNA and the severity of CAD.

Conclusions: In the analysed cohort the selected miRNA failed to discriminate between SA and UA. However, in more severe forms of CAD (ie MI1), levels of miR-486a and miR-92a were increased compared to UA.

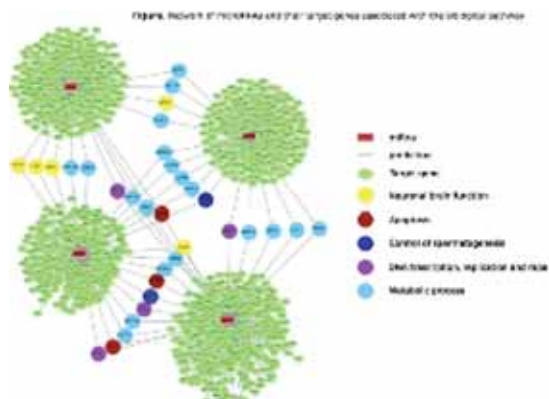
GENDER, FAMILY AND CARDIOVASCULAR RISK

P1296 | SPOTLIGHT

Sex differences in the prognostic impact of left ventricular hypertrophy in members of a cohort with high prevalence of obesity and diabetes: the Strong Heart Study

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Purpose: In the Strong Heart Study (SHS) cohort, women exhibit higher left ventricular (LV) mass index (LVMI) than men, a characteristic associated with central adiposity. There is no information on whether LV hypertrophy (LVH)-associated outcome is different in men and women, in relation to adiposity.



Methods: We studied 2520 participants to 2nd SHS exam, free of prevalent cardiovascular (CV) disease (59±8 years, 64% women, 54% obese, 45% diabetic). LVH was assessed by echocardiographic LVM, using SHS-specific cut-point, maximizing the population risk attributable to LVH ($\geq 47.2 \text{ g/m}^2$), and excess of LVM (by ratio of observed LVM to the value predicted by sex, stroke work and height). The association of LVH with incident CV events (combined fatal and non-fatal heart failure, coronary artery and cerebrovascular disease) was evaluated by sex-specific Cox models (median follow-up=14 yrs), adjusting for variables that were significantly different between men and women: age, pulse pressure (PP), waist/hip ratio, adipose body mass (by bioelectric impedance), diabetes, smoking status, HDL cholesterol and concentric LV geometry (relative wall thickness ≥ 0.43). Attention was paid to avoid substantial multicollinearity among covariates (variance inflation factor <2).

Results: Compared to men, women had higher prevalences of obesity (58 vs. 45%), diabetes (48 vs. 40%), LVH (23 vs. 14%, all $p < 0.001$), but not of hypertension (41 vs. 43%). During follow-up, 651 CV events occurred. After adjusting for confounders, LVH increased CV risk quantitatively more in women (HR=1.42 [95% CI 1.09-1.84], $p=0.009$) than in men (HR=1.25 [0.86-1.83]). The difference between men and women was proven to be statistically significant by sex×LVH interaction term (HR=1.21, [1.07-1.37], $p < 0.002$). In women, the effect of LVH was independent of significant association with age (HR=1.02/year, [1.00-1.04]), PP (HR=1.02/mmHg, [1.01-1.02]), diabetes (HR=2.53, [1.95-3.30]), smoking (HR=1.49, [1.13-1.96]), HDL-cholesterol (HR=0.99/mg×dL, [0.98-1.00]) and concentric LV geometry (HR=1.84, [1.19-2.84], all $p < 0.05$), without significant impact for anthropometrics. When, excess of LV mass was added to the previous model, observed/predicted LVM was significantly associated with CV outcome in women (HR=1.11/10% [1.01-1.17], $p=0.02$) but not in men (HR=1.00/10%, [0.90-1.10], $p=0.9$), independent of LVH and the other covariates.

Conclusions: In a population with high prevalence of obesity and diabetes, after adjusting for potential confounders including central adiposity, LVH and excess of LVM were associated with higher risk of CV events in women than in men.

P1297 | BEDSIDE

Impact of gender on the risk of coronary atherosclerosis and cardiovascular events conferred by HbA1c in subjects without known diabetes

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Purpose: Diabetes confers a larger increase in the relative risk of cardiovascular events among women than among men. Whether gender also affects the association of HbA1c with coronary atherosclerosis and cardiovascular events among subjects without known diabetes is unknown and is addressed in the present study.

Methods: We enrolled a large consecutive series of 1479 patients undergoing coronary angiography for the evaluation of established or suspected coronary artery disease (CAD), including 495 women and 984 men who did not have previously known diabetes. Significant CAD was diagnosed in the presence of significant coronary stenoses $\geq 50\%$. Prospectively, we recorded cardiovascular events over 4.4±1.2 years.

Results: Among women, 36.4%, 56.2%, and 7.4% and among men 44.2%, 46.6%, and 9.1% had HbA1c values of <5.7% (normal according to ADA criteria), 5.7-6.4% (at risk of diabetes according to ADA criteria), and $\geq 6.5\%$ (diabetes according to ADA criteria), respectively. The prevalence of angiographically diagnosed significant CAD in these HbA1c categories was 31.2%, 38.2%, and 47.2% among women ($p_{\text{trend}} = 0.041$) and 63.2%, 65.3% and 64.8% among men ($p_{\text{trend}} = 0.589$). An interaction term gender × HbA1c was statistically significant ($p < 0.001$), indicating that the association of HbA1c with CAD was significantly stronger among women than among men. During follow-up, the incidence of cardiovascular events was 21.5% in women and 28.5% in men ($p=0.002$). Among women, HbA1c strongly and significantly predicted cardiovascular events (adjusted OR for a 1% increase in HbA1c HR 2.08 [1.24-3.03]; $p < 0.001$), but not among men (HR 1.12 [0.94-1.53]; $p=0.145$). An interaction term gender × HbA1c again was statistically significant ($p=0.011$), indicating that HbA1c was a significantly stronger predictor of cardiovascular events among women than among men.

Conclusions: We conclude that gender significantly modulates the risk of coronary atherosclerosis and cardiovascular events conferred by HbA1c in subjects without known diabetes.

P1298 | BEDSIDE

Women with acute myocardial infarction are less invasively treated compared to men in durres population

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Background and aim: Many studies have showed that women with acute myocardial infarction (AMI) have worse outcomes compared to men and also un-

dergo less diagnostic tests and interventions. The aim of this study was to evaluate the differences in treatment and in hospital mortality between men (M) and women (W) in the pts with AMI in Durres population.

Methods: 259 pts consecutive with AMI, admitted in the Cardiology, between January 2011 to October 2013 were included in the study. Demographic, diagnostic, therapeutic, and clinical data were collected from hospital medical records. The CCU application of various diagnostic and therapeutic procedures was also recorded, including coronary angiography and reperfusion procedures. Continuous variables are presented as means ($\pm$ standard deviation) and categorical variables as percentages. Gender differences were assessed by the chi-square test for categorical variables and by Student's t-test for continuous variables.

Results: Of 259 pts with AMI, 183 (70.6%) males and 76 (29.4%) females. W were significantly older than the M (72±8.7 vs 63±11) $p < 0.001$. A significantly higher percentage of W compare to M had DM (31.6% vs. 29.0%), HTN (77.6% vs 64.5%), obesity (57.9% vs 48.6%) but a lower percentage had a history of smoking (19.7% vs 68.7%), previous AMI (10.5% vs 14.8%) positive family history (46.8% vs 39.5%), dyslipidemia (81.9% vs 72.4%). The W more frequently had an AMI of anterior localization (46.1% vs 36.1%), while M presented more with inferior localization (47.0% vs 31.6%). W had a significantly higher Killip class at admission (Killip IV; 18.4% vs 10.9%), compared with the M. W received almost the same pharmacologic treatment like M. A significant proportion of M compared to W underwent coronary angiography (41.0% vs 25.0%) $P < 0.015$. W were less likely to undergo invasive procedure, even after correcting for age (OR, 1.27; 95% CI, 0.58-2.57; $P=0.05$). Mortality in CCU was significantly higher in women, 10 (5.46% vs 8 (10.5%). $P=0.05$.

Conclusions: W less frequently received coronary angiography, PCI, or revascularization surgery compared to M, but receive already the same pharmacological treatment like men. W have a worse prognosis after an AMI largely as a function of clinical factors. W with AMI were older and had a higher incidence of HTN, obesity and DM than M.

P1299 | BEDSIDE

Gender specific differences of adherence to treatment in patients after acute coronary syndromes

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Purpose: Low adherence to evidence based secondary prevention medicines in patients after acute coronary syndromes (ACS) may result in a lower general well-being and worse prognosis. The aim was to study gender differences of adherence to therapy in post-ACS patients on long-term follow-up.

Methods: 190 consecutive patients (aged 36-80, mean age 62.3±10.4 years) were interviewed at 21 months after ACS. Patients were asked to provide comments on their medicine-taking behavior. Quality of life has been measured by means of the SF-12v2 questionnaire.

Table 1

	All patients, %	Men, %	Women, %
Forget to take medicines			
Never	73.9	73.5	75.0
Seldom	21.3	20.5	23.2*
Often	3.2	3.8	1.8*
Always	1.6	2.3	0.0
Changed doses of medicines			
Never	57.8	61.1	50.0*
Seldom	34.8	32.1	41.2*
Often	6.4	5.3	8.9*
Always	1.1	1.5	0.0

* $p < 0.01$.

Results: The medicine-taking behavior of post-ACS patients is presented in table 1. Three-quarters of patients reported that they never forget to take medicines and 58% - that they never change the doses of prescribed medicines. Women were less likely to forget taking their medicines, although women were less adherent to the recommended doses: every second woman sometimes changed the doses of medicines. Low adherent (to prescribed medicines and their regimen) patients were less satisfied with their therapy, general well-being, health-care professionals and had lower quality of life. These findings should be taken into consideration when planning activities to increase adherence to ACS treatment.

P1300

ABSTRACT WITHDRAWN

ABSTRACT WITHDRAWN

P1301 | BEDSIDE**Impact of gender, co-morbidity and social factors on labour market affiliation after first admission for acute coronary syndrome**

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Background: Over the last decades survival after acute coronary syndrome (ACS) has improved, leading to an increasing number of patients returning to work, but little is known about factors that may influence their labour market affiliation. This study examines the impact of gender, co-morbidity and socio-economic position on subsequent labour market affiliation in patients admitted for the first time with ACS.

Methods: From 2001 to 2009 all first-time hospitalisations for ACS were identified in the Danish National Patient Registry (n=79,714). Data on sick leave, unemployment and retirement were obtained from an administrative register covering all citizens. The 21,926 patients, aged 18–63 years, who had survived 30 days and were part of the workforce at the time of diagnosis were included in the analyses where subsequent transition between the above labour market states was examined using Cox proportional hazards models.

Findings: A total of 37% of patients were in work 30 days after first ACS diagnosis, while 55% were on sick leave and 8% were unemployed. Table 1 shows that the proportion in work increased, while the proportion on sick leave decreased during follow-up. Seventy-nine per cent returned to work once during follow-up. This probability was highest among males, those below 50 years, living with a partner, the highest educated, with higher occupations, having NSTEMI or percutaneous coronary intervention and with no co-morbidity. During five years follow-up, 43% retired due to disability or voluntary early pension. Female gender, low education, basic occupation, co-morbidity and having an invasive procedure and receiving sickness benefits or being unemployed 30 days after admission were associated with increased probability of early retirement.

Table 1. Workforce participation

	30 days after time of diagnosis N (%)	1 year after diagnosis N (%)	2 years after diagnosis N (%)	5 years after diagnosis N (%)
Part of the workforce	21926 (100)	21869 (99.7)	19664 (98.4)	15468 (88.0)
In work	8150 (37.2)	8777 (40.1)	8856 (45.0)	10,079 (65.2)
Unemployed	1743 (8.0)	1850 (8.5)	1936 (9.9)	2878 (18.6)
Sick leave	12033 (54.9)	11220 (51.4)	8852 (45.0)	2511 (16.2)

Conclusion: About half of patients with first-time ACS are in work shortly after the event. Women, the socially disadvantaged, those with presumed severer events and co-morbidity have lower rates of return.

P1302 | BEDSIDE**Psychosocial gender differences in coronary artery disease and effect of a psychosocial intervention on vital exhaustion findings from the SPIRR-CAD trial**

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Introduction: Men and women with coronary artery disease (CAD) differ psychosocially. Vital Exhaustion (VE) and other psychiatric symptoms are higher in

women and stronger predictors for an unfavorable outcome. Therapeutic activities are traditionally focused upon physical exercise, especially in men, but try also to attenuate psychological symptoms. Few studies have systematically tested effects in both men and women. The Stepwise Psychotherapy for Reducing Risk in CAD study (SPIRR-CAD) offered the possibility to examine psychological differences between men and women and their changes over time.

Methods: In this trial, 450 men (78.9%) and 120 women (21.1%) with CAD (age below 75 y), who had mild to moderate depression (scoring 8 or higher on the Hospital Anxiety and Depression Scale (HADS)), were randomized to a psychosocial intervention program. Psychosocial measures of depression, exhaustion, and coping (HADS, VE, SF36, FKV) were collected at baseline and 18 months follow up.

Results: Men had more severe heart disease (EF, history of MI, CABG; $p < 0.05$), whereas women had higher psychosocial burden: They were more likely to live alone (w 57%, m 32%), had lower education and employment rates ($p < 0.05$) and higher anxiety ($p = 0.005$), depression ($p = 0.03$) and exhaustion ($p = 0.001$). The psychosocial intervention showed a significant gender effect: women reduced VE significantly more than men in the TG compared to the CG (F 4.02; $p = 0.046$). Patients with depressive coping (FKV) showed a lower decrease of VE ($\beta = 0.12$; $p = 0.02$).

Conclusion: Women showed higher psychosocial impairment than men, but a better response to the intervention. VE was recently found to accelerate progression of CAD in women, so foci and strategies in psychosocial interventions may need to differ between men and women with CAD. Intervention programs specifically tailored to women's or men's psychological and biological needs may be most effective.

P1303 | BEDSIDE**A family history of premature cardiovascular disease is independently associated with increased carotid intima-media thickness**

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Background: Measurement of carotid intima-media thickness (IMT) has been shown to be beneficial in pts. at increased CV risk. However, with the exception of the Reynolds score, risk scores for cardiovascular disease (CVD) do not take into account family history of premature atherosclerosis. We therefore sought the association of family history of premature CVD with subclinical atherosclerosis as evidenced by increased IMT.

Methods: We studied 2124 primary prevention pts. (967 men; age 53 ± 9) Clinical data was obtained by pt. history and Framingham 10-year risk was calculated from risk data. IMT was acquired and measured offline by an experienced sonographer in the far wall in three planes of the common carotid artery within 2cm of the bifurcation. Age and gender-corrected values for the 75% CI from normal were used as a cut-off for analysis.

Results: 1573 pts. had low risk, 387 intermediate risk and 164 were high risk. BMI was increased (29 ± 7) and there was a moderate incidence of smoking (41%) and HTN (44%). Total cholesterol (TC) was 5.2 ± 1.1 mmol/L, HDL was 1.4 ± 0.04 mmol/L, and there were 486 (23%) pts. with DM. IMT in the pt. cohort was 0.65 ± 0.13 mm and 942 (44%) pts. had increased age-corrected IMT. 1240 (58%) pts. had a family history of CVD. Age-corrected IMT was increased in 50% of pts. with a family history vs. 36% of those without. Pts. with a family history were younger, less obese and had much lower risk (4% vs. 14%) but had significantly higher SBP, DBP and TC (all $p < 0.0001$), however there was no significant difference in IMT between those with and without a family history (0.66 ± 0.13 vs. 0.65 ± 0.13). In a multiple logistic regression age (OR 0.93; $p < 0.0001$), gender (OR 1.09; $p = 0.004$), SBP (OR 1.02; $p < 0.0001$), DBP (OR 0.97; $p < 0.0001$), being overweight (OR 1.25; $p < 0.0001$) and family history of CVD (OR 0.45; $p < 0.0001$) were independently associated with increased age-corrected IMT. (Model $\chi^2 = 194.61$; $p < 0.0001$). Framingham risk was not associated with increased IMT.

Conclusions: Pts. with a family history of premature CVD have a significant incidence of increased IMT. Positive family history may be useful in risk stratifying these pts. who are at increased cardiovascular risk, and early treatment and intervention may benefit them. Further longitudinal studies are needed to confirm this.

P1304 | SPOTLIGHT**Family history is not associated by itself with better lifestyle choices: the heart age tool experience**

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Purpose: The Heart Age tool has been proven to be effective in communicating the relevance of lifetime risk of CVD and motivate people to lower their risk. Users of the Heart Age tool who report a family history of CVD may be sensitized to their CVD risk and already more likely to have a healthier lifestyle than other users. We therefore characterised the profile of users of the heart age tool with a self reported family history of CVD to better understand the relationship between family history, heart age and current lifestyle behaviours.

Methods: Heart Age is freely available via an open access website. Data from 188,139 registered users aged 21–80 years with no prior heart disease was anal-

ysed. These users self-reported demographic (including age, gender and self-reported family history of CVD) and classic CVD risk factor information (blood pressure, diabetes, total and HDL cholesterol, BMI, smoking). Based on these data, an individual's estimated 10 year CVD-risk was calculated according Framingham CVD risk models and translated into a Heart Age. Subjects included in the analyses were: free from CVD, aged between 21 and 80 years and self reported information on CVD risk factors, fruit and vegetable consumption, physical activity, weight and waist circumference.

Results: 39% of users reported a family history of CVD in at least one parent and 13% of users reported a family history of premature CVD (father younger than 55 years of age; mother younger than 65 years of age). Heart age scores were higher in those with a family history of CVD (+5.8 years > real age) than those without (+4.3 years > real age) and this was more marked in those reporting two parents with CVD (+6.9 years > real age). Those users reporting a family history were more likely to report a known cholesterol level (39-48%) than those without a family history (27%). They were also more likely to report a known blood pressure value (65% -70%) than those without (56%). On the other hand minimal differences existed in lifestyle behaviours between those reporting a family history of CVD and no family history.

Conclusions: These analyses suggest that those with a family history of CVD had higher heart ages than those who did not. Nevertheless, whilst awareness of cholesterol and blood pressure levels were greater in those with a family history of CVD, there were no differences in healthy lifestyle behaviours. This suggests that raising awareness of family history alone is unlikely to be sufficient to lead to lifestyle changes.

P1305 | BEDSIDE

Spousal concordance for cardiovascular health in a primary care based sample

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Purpose: Previous research has demonstrated spousal concordance for cardiovascular (CV) risk factors. However, there is a dearth of research on overall CV health among couples. The American Heart Association devised definitions for poor, intermediate and ideal CV health based on 7 health metrics; smoking, BMI, physical activity, diet, blood pressure, cholesterol and glucose. Our aim was to examine these metrics and concordance levels for CV health among couples from a community based sample and to examine if the CV health status of an individual is associated with that of their spouse.

Methods: The Mitchelstown Study was established to examine CV risk factors and diabetes in a middle-aged Irish sample. For the present study, potential couples were identified as 2 study participants living at the same address with the same telephone number. This list was cross-referenced with reported marital status by questionnaire and the electronic patient record. Information on the individual CV health metrics was collected using standardised methods. All participants were categorised into ideal, intermediate and poor categories for each of the individual metrics and for overall CV health. The prevalence of each category was calculated. The 0-7 point and 0-14 point CV health metrics scores were computed and compared within couples using linear regression.

Results: Of 2047 participants, 191 potential couples were identified. We excluded 6 sibling pairs, 1 divorced couple and 3 other couples who did not report being married in the baseline questionnaire. Analysis was carried out on 181 couples. The mean age for husbands was 61 years and for wives was 60 years. There were significant associations between husbands and wives for smoking status ($p < 0.05$), diet ($p < 0.05$), blood pressure ($p < 0.05$), total cholesterol ($p < 0.05$) and glucose ($p < 0.05$). No couple had ideal CV health (i.e. both spouses with 7 ideal health metrics). The majority of couples ($n=127$, 69%) were concordant for poor CV health. There was a significant relationship between spouses for both CV health metrics scores ($p < 0.05$).

Conclusion: The majority of couples had poor CV health. Our results suggest that an individual's overall CV health status is associated with that of their spouse. Therefore interventions targeting couples and families offer an opportunity to optimise the effect of preventative strategies. The CV health metric system could also potentially be used as a way of communicating CV risk status to couples as achieving a greater number of ideal health metrics is associated with a lower risk of CV mortality.

NOVEL BIOMARKERS PART II

P1307 | BEDSIDE

Growth differentiation factor 15 is independently associated with cardiovascular events and total mortality in patients with stable coronary heart disease: 10-year follow-up of the KAROLA Study

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Purpose: Growth differentiation factor 15 (GDF-15) belongs to the transforming

growth factor β superfamily and is involved in inflammatory and apoptotic pathways. It has been proposed as a predictor of mortality and disease progression in patients with cardiovascular (CV) disease. We evaluated if baseline GDF-15 levels were associated with subsequent CV events and total mortality in patients with stable coronary heart disease.

Methods: GDF-15 serum concentrations were measured at baseline in 1073 subjects aged 30-70 years participating in an in-patient cardiac rehabilitation program (median follow-up 10 years). Cox-proportional hazard models were used to evaluate the association of log-transformed (ln) GDF-15 baseline levels as a continuous variable and by quartiles (using the bottom quartile as reference) with the onset of subsequent CV events (myocardial infarction, stroke, cardiovascular death) and total mortality adjusting for age, sex, body mass index, left ventricular function, smoking, total and HDL-Cholesterol, renal function, diabetes, hypertension, use of statins, diuretics and angiotensin-converting-enzyme inhibitors.

Results: In our study sample (84.3% men, mean age 59 years) there were a total of 172 CV events and 152 deaths. The median GDF-15 levels were 1233.0 pg/mL (IQR 917.0, 1703.0) at baseline. A one unit increment of ln GDF-15 was associated with a hazard ratio (HR) of 2.19 [95% CI 1.67, 2.87] for a subsequent CV event, and with a HR of 2.65 [95% CI 2.03, 3.47] for death adjusting for age and sex. Respective hazards ratios in multivariable analyses were 1.57 [95% CI 1.09, 2.26] for a subsequent CV event, and 2.02 [95% CI 1.40, 2.92] for death. Comparing extreme quartiles, patients in the top quartile had a HR of 2.62 for a CV event [95% CI 1.60, 4.28] after adjustment for age and sex. In multivariable analysis this association was attenuated and non-significant. However, the trend test showed a p -value=0.028 with the following hazard ratios: 2nd quartile 0.84 [95% CI 0.49, 1.44], 3rd quartile 1.06 [95% CI 0.62, 1.82], and 4th quartile 1.59 [95% CI 0.93, 2.71]. Using total mortality as an endpoint, in age and sex adjusted analysis a HR of 5.28 [95% CI 2.72, 10.24] was seen for those in the top quartile. After further adjustment this association remained statistically significant with a HR of 2.85 [95% CI 1.42, 5.70].

Conclusions: Baseline levels of GDF-15 measured after an acute event were associated with subsequent CV events as well as 10-year total mortality in patients with stable coronary heart disease.

P1308 | BEDSIDE

Soluble urokinase plasminogen activator receptor is in contrast to high sensitive C-reactive protein associated to coronary artery calcifications in healthy middle-aged subjects

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Purpose: To study the association between two markers of low-grade inflammation, soluble urokinase plasminogen activator receptor (suPAR) and high sensitive C-reactive protein (hs-CRP), and coronary artery calcification (CAC), and to investigate whether these markers can be used to refine traditional cardiovascular risk assessment.

Methods: The study is a population based cross sectional study of 1159 randomly sampled men and women aged 50 or 60 years from our country, free of cardiovascular disease and diabetes. CAC was measured by a non-contrast cardiac CT scan and total 10-year cardiovascular mortality risk was estimated using SCORE. Plasma samples were analysed for suPAR and hs-CRP. The association between suPAR, hs-CRP and CAC was evaluated by multivariable ordinal logistic regression analyses adjusted for SCORE. The additive effect of suPAR to SCORE was evaluated by comparing area under curve (AUC) and net reclassification index (NRI) in relation to dichotomous outcome of CAC (<100 U vs. ≥ 100 U).

Results: The odds of being in a higher CAC category, i.e. having more severe CAC, increased 16% (odds ratio (OR) 1.16, 95% confidence interval (CI) 1.03-1.30, $p=0.02$) when plasma suPAR concentration increased 1 ng/l. Gender-specific analyses showed that this association was more pronounced in women (OR 1.30, 95%CI 1.05-1.61, $p=0.01$) than in men (OR 1.15, 95%CI 1.00-1.33, $p=0.05$). In comparison, hs-CRP did not affect the CAC category (OR 1.00, 95%CI 0.98-1.03, $p=0.90$). When adding suPAR to SCORE, AUC increased from 0.66 (95%CI 0.59-0.72) to 0.70 (0.63-0.78) in women ($p=0.04$), and from 0.65 (95%CI 0.60-0.70) to 0.68 (95%CI 0.63-0.74) in men ($p=0.03$). In women with CAC > 100U the overall proportion of correctly reclassified was 36%, whereas in women with CAC < 100U overall 15% were incorrectly reclassified, giving a NRI of 21% ($p < 0.001$). In men with CAC > 100U overall 7% were incorrectly reclassified, while in men with CAC < 100U overall 26% were correctly reclassified, giving a NRI of 19% ($p < 0.001$). The difference in NRI between men and women was not statistically significant.

Conclusions: suPAR, but not hs-CRP, appears to be associated with CAC independently of SCORE. The association is strongest in women. By adding suPAR to SCORE the prediction of CAC improved slightly in both genders.

P1309 | BEDSIDE**Serum levels of soluble Flt-1 are associated with cardiovascular events in patients with chronic kidney disease**

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Background: Since chronic kidney disease (CKD) is highly prevalent, it is necessary to efficiently extract a high-risk population from CKD patients. Vascular endothelial growth factor (VEGF) plays a role in endothelial integrity. The soluble VEGF receptor-1 (sFlt-1) is an endogenous inhibitor of VEGF. A previous cross-sectional study demonstrated that increased sFlt-1 levels are associated with endothelial dysfunction in CKD. However, it is unknown whether sFlt-1 levels predict cardiovascular events among patients with CKD.

Methods and results: To examine the prognostic value of serum sFlt-1 levels in comparison with Framingham risk score (FRS), cystatin C, N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), high-sensitivity Troponin-I (hsTrop-I), and neutrophil gelatinase-associated lipocalin (NGAL), we performed a prospective cohort study. Serum levels of sFlt-1, cystatin C, NT-proBNP, hsCRP, hsTrop-I, and NGAL were measured employing specific enzyme-linked immunosorbent assays. A total of 94 stable outpatients with CKD (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m²) were followed up over 3 years. The primary outcome was major adverse cardiac events (MACEs). During the median follow-up period of 772 (interquartile range: 341-1,080) days, MACEs developed in a total of 20 patients (21%). Time-dependent, survival receiver operating characteristic curve analyses revealed that the area under the curve of sFlt-1 (0.72) was superior to those of FRS (0.54), cystatin C (0.56), NT-proBNP (0.52), hsCRP (0.55), hsTrop-I (0.71), and NGAL (0.58) at 1 year. Stepwise multivariate Cox proportional hazard analysis, including FRS, these biomarkers, and proteinuria, revealed that the sFlt-1 level, but not other parameters, was independently associated with MACEs (hazard ratio, 1.7 for 1-SD increase; 95% CI, 1.1-2.8; P=0.019).

Conclusions: We first demonstrated that serum levels of sFlt-1 were significantly and closely associated with MACEs among stable outpatients with CKD. An increased sFlt-1 value may serve as a predictor of cardiovascular events in CKD.

P1310 | BEDSIDE**The association between resistin concentrations and the occurrence of cardiovascular disease in older persons: the health, aging and body composition (Health ABC) study**

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Background: Serum resistin is implicated in promoting insulin resistance and inflammation. Prospective data regarding the association between resistin levels and cardiovascular (CVD) outcomes are sparse.

Methods: We studied 3044 older adults aged 70-79 years at baseline from the Health, Aging, and Body Composition Study. Using Cox regression model, we assessed hazard ratio (HR) according to quartiles of serum resistin concentrations for the risk of "hard" coronary heart disease (CHD) events, "hard CHD" events plus hospitalization for angina or coronary revascularization (total CHD events), stroke, and total CVD events (CHD and stroke events). We adjusted the association for the age, gender, race, total and HDL-cholesterol, triglycerides, fasting glucose, systolic blood pressure, smoking, body mass index, creatinine, and history of CVD, diabetes, and hypertension. We further adjusted for biomarkers of inflammation and insulin resistance (HbA1c, insulin, leptin, adiponectin, C reactive protein, interleukin-6 and tumor necrosis factors- α).

Results: During a median follow-up of 11.5 years, 884 participants developed CHD events (559 "hard" events), 333 stroke events and 1106 CVD events; all these events were associated with resistin concentrations. In clinical variables adjusted model, HRs of resistin (highest -24.31 ng/mL- vs. lowest quartile-14.01 ng/mL-) were 1.38 (95%CI 1.14-1.67) for CHD events (P=0.002 for trend), 1.47 (95%CI 1.16-1.87) for "hard" CHD events (P=0.001 for trend) and 1.33 (95%CI 1.11-1.58) for CVD events (P=0.003 for trend), but was not significant for stroke 1.27 (95%CI 0.93-1.73; P=0.13 for trend). After further adjustment for biomarkers of inflammation and insulin resistance, these associations were attenuated; 1.17 (95% CI 0.94-1.47) for CHD events, 1.22 (95% CI 0.92-1.60) for "hard" CHD events and 1.07 (95% CI 0.88-1.31) for CVD events.

Conclusions: Among older adults, higher resistin levels were associated with an

increased risk of CHD and CVD events independently of clinical variables. The association is partially interdependent with biomarkers of insulin resistance and inflammation.

P1311 | BEDSIDE**Urinary proteomics for the identification of disease-specific biomarkers in heart failure with reduced ejection fraction**

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Purpose: An "ideal" biomarker for overt heart failure with reduced ejection fraction (HFrEF) is still lacking. Proteome analysis in urine has provided highly accurate biomarkers of renal dysfunction, coronary artery disease and hypertension, but has not yet been investigated in HFrEF. We sought to identify HFrEF-specific biomarkers using urinary proteomics.

Methods and results: Urinary proteome was analysed using capillary electrophoresis mass spectrometry in 64 HFrEF patients (aged 66±11 years, left ventricular ejection fraction 28±6%) and 53 healthy controls. To identify potentially discriminating biomarkers for HFrEF, data from a training set of 24 patients were compared to 53 controls. A total of 79 peptides were identified, achieving 96% sensitivity and 98% specificity for HF detection (1/24 cases and 1/53 controls were misclassified). Identified peptides were used to build 4 novel biomarker sets, which were successfully applied to a blinded validation set of 40 patients and 9 controls. Sequencing of 21 of the identified peptides revealed that 71% of them were collagen alpha-1 (I) fragments, which were down-regulated in HFrEF patients compared to controls. Collagen alpha-1 (III) and (XVIII) fragments, uromodulin, ProSAS peptide and membrane-associated progesterone receptor component 1 peptides were also found.

Conclusion: Urinary proteomic analysis was able to identify a set of HFrEF-specific urine peptides that may serve as potential biomarkers of the syndrome. Most of the identified peptides were associated with extracellular matrix remodelling.

P1312 | BEDSIDE**Prime mover or fellow traveller: 25-hydroxy vitamin D's seasonal variation, cardiovascular disease, and death in the Scottish Heart Health Extended Cohort (SHHEC)**

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Aims: Alleged causal links in temperate countries between seasonal variation in sunlight, hypovitaminosis D, and winter peaking of cardiovascular disease and death imply a natural experiment deserving further investigation. We explored vitamin D, seasonality, and disease in a study at high latitudes.

Methods and results: We tested three postulates on 13,224 Scottish Heart Health Extended Cohort (SHHEC) participants followed 22 years, using archived recruitment serum to assay 25-hydroxyvitamin D (25OHD):

1. Endpoints (First Cardiovascular Event, All Death, Cardiovascular Death), enumerated by calendar month of occurrence inversely reflect fluctuations in 25OHD.
2. Endpoint seasonality is exaggerated in those with low 25OHD.
3. Low 25OHD predicts endpoints, independent of other risk factors.

Baseline 25OHD levels in 13,224 participants were low: median 38.1 nmol/L, interquartile range 28.9-50.3, but March levels were half those in August. There was no seasonal variation in First Cardiovascular Event (n=3307). Highs and lows for All Death (n=2987) and Cardiovascular Death (n=1350) occurred months earlier than extremes of 25OHD. Seasonal endpoint variation showed no significant difference between participants above and below the median for 25OHD. Cox model hazard ratios for endpoints, with population ranking by decreasing 25OHD increased quasi-linearly, with no threshold. Multiple adjustment reduced this excess by 60%, and to non-significance in women. 25OHD made no independent contribution to cardiovascular discrimination and reclassification.

Conclusion: In this natural experiment involving two-fold annual fluctuation, 25OHD failed two causal postulates, and was equivocal for the third. The results question low vitamin D's alleged role as prime mover of cardiovascular disease and death.

P1313 | BEDSIDE**The alpha1-antitrypsin/LDL complex level is associated with the SYNTAX score of complexity and severity of coronary artery disease**

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Background: Oxidatively modified LDL-cholesterol (oxLDL) is involved in the progression of atherosclerosis. Recently, two novel oxLDL, serum-amyloid-A/LDL complex (SAA-LDL) and α 1-antitrypsin/LDL complex (AT-LDL) were identified. The SYNTAX score is a lesion-based angiographic scoring system originally de-

vised to grade the complexity of coronary artery disease (CAD). The SYNTAX score was able to stratify risk for very long-term adverse clinical outcomes. However, the relationships of these two markers with the complexity and severity of CAD assessed with the SYNTAX score are unknown.

Method and results: We enrolled a total of 357 consecutive patients who electively underwent coronary artery angiography (CAG). Pre-procedural serum levels of high-sensitivity C-reactive protein (hsCRP), SAA-LDL, and AT-LDL were measured by specific enzyme-linked immunosorbent assays. The SYNTAX score was calculated according to CAG results. The mean age was 70 ± 11 (SD) years, and the rate of male gender was 61%. The prevalence of hypertension, diabetes, dyslipidemia, and a history of smoking habit were 80, 45, 63, and 60%, respectively. Patients were divided into 2 groups according to the SYNTAX score: those with low- (≤ 22 , $n=333$) and intermediate/high-risk (> 22 , $n=24$) groups. There was no significant difference in age, the rate of male gender, body mass index, lipid and metabolic profiles, and the prevalence of hypertension, dyslipidemia, diabetes and history of smoking habit between the two groups. However, serum levels of AT-LDL ($P=0.012$), but not hsCRP ($P=0.4$) or SAA-LDL ($P=0.11$), were significantly higher in the intermediate/high- compared with the low-risk group. In simple regression analyses, there was significant positive correlation of AT-LDL ($P=0.004$), but not hsCRP and SAA-LDL, with the SYNTAX score. Stepwise regression analysis, including data on age, a male gender, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, diabetes, history of smoking, hsCRP, SAA-LDL, and AT-LDL, revealed that AT-LDL ($P=0.004$), but not hsCRP or SAA-LDL, was an independent predictor of the SYNTAX score. Finally, we performed multivariate logistic regression analysis for the intermediate/high-risk group. The AT-LDL level was significantly associated with intermediate/high-risk group, even after adjusting for established risk factors (OR, 1.6; 95%CI, 1.1-2.4 for 1-SD increase; $P=0.015$).

Conclusion: We first demonstrated that serum levels of AT-LDL were independently associated with the intermediate/high-SYNTAX score. The AT-LDL level may serve as an indicator of the complexity and severity of CAD.

P1314 | BEDSIDE

Thyroid-stimulating hormone and premature atrial contractions in a young population

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Purpose: Thyroid disorders increase the risk for atrial fibrillation. However, the underlying mechanism of this association remains poorly understood. We therefore assessed the relationship between levels of thyroid-stimulating hormone (TSH) and frequency of premature atrial contractions (PACs).

Method: A population-based cohort of healthy adults without prevalent cardiovascular disease, diabetes or body mass index $> 35 \text{ kg/m}^2$ aged 25-41 years was investigated. The number of PACs per participant was obtained using a validated 24-hour electrocardiography (ECG) device. TSH was quantified from fasting venous blood samples. Multivariable negative binomial regression models were used to assess the relationship between TSH levels and the number of PACs.

Results: 2049 participants (median age 37 years) were included in this analysis, of which 46.9% were men. The median TSH (interquartile range (IQR)) was 1.84 (1.35; 2.52). Overall, 6.7% of the participants had a TSH $\geq 4 \text{ mU/L}$ (reflecting subclinical hypothyroidism) and 4.5% had a TSH $\leq 0.8 \text{ mU/L}$ (reflecting subclinical hyperthyroidism), respectively. The median (IQR) PAC count per hour was 0.13 (0.04; 0.29). Results of the multivariable regression analysis are shown in the table. Risk ratios for the relationship between PAC count and TSH levels were lowest in quartile 2 and 3, assuming a U-shaped association. Both subclinical hypothyroidism (risk ratio (95% confidence interval (95%CI)) 1.88 (1.38; 2.56), $p < 0.0001$) and subclinical hyperthyroidism (risk ratio (95%CI) 1.82 (1.26; 2.64), $p = 0.002$) were independently associated with PAC count.

Thyroid-stimulating hormone and PACcount

	Quartile 1 (n=519)	Quartile 2 (n=515)	Quartile 3 (n=506)	Quartile 4 (n=509)
Sex/age adjusted	Reference	0.54 (0.43; 0.67)	0.67 (0.54; 0.84)	0.70 (0.57; 0.88)
Fully adjusted	Reference	0.61 (0.49; 0.77)	0.76 (0.59; 0.97)	0.94 (0.76; 1.19)

Data are risk ratios. Fully adjusted model was adjusted for sex, age, body mass index, current smoking, hypertension, high- and low density lipoprotein, creatinine, high-sensitivity C-reactive protein, haemoglobin A1c, physical activity and alcohol consumption.

Conclusion: A U-shaped relationship between TSH level and PAC count was seen in our young and healthy study population, suggesting that both hypo- and hyperthyroidism are related to the frequency of PAC occurrence.

P1315 | BEDSIDE

Genetic factors as predictors of late cardiovascular mortality in coronary patients

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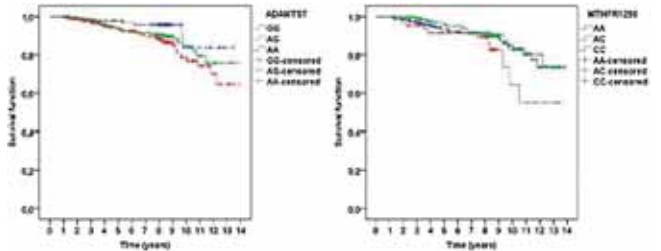
Several studies have attempted to associate genetic profiles with the development

of Coronary Artery Disease (CAD). However, few studies have evaluated genetic profiles associated to the cardiovascular mortality.

Objective: Our aim is to identify the genetic variants associated to the late cardiovascular mortality.

Methods: A case-control study with a total of 1032 coronary patients, 81 cases (patients who died of cardiovascular death) and 951 controls (coronary patients who survived) was performed during a follow-up period of 5.7 ± 3.7 years, to evaluate the cardiovascular mortality. The clinical, biochemical and genetic profiles were analyzed. The genetic variants analyzed were: ACE I>D, AGT174, AGT235, ATIR, APO E1 e E2, MTHFR 677, MTHFR1298, locus 9p21.3, GJA4, PCSK9, KIF 6, IGF2BP2, PON192, PON55, CDKN2B, ADAMTS7 and IGF2BP2. Univariate analysis was performed and OR and 95% CI were determined. P-values less than 0.05 were considered significant. A Cox regression was performed to estimate the independent variables associated to mortality and the survival curves were constructed using the Kaplan-Meier method.

Results: After a follow-up period of 5.7 ± 3.7 years, coronary patients showed a cardiovascular mortality of 7.8%. There were significant differences in the gene variants, namely MTHFR 1298 CC (OR=2.11; $p=0.029$) and ADAMTS7 AA (OR=1.55; $p=0.055$), as well as in age, diabetes, platelets and homocysteine levels.



Survival curves: ADAMTS7 and MTHFR1298

Conclusions: Our study showed that MTHFR1298 CC and ADAMTS 7 AA increased the risk of late cardiovascular mortality. Since these genes are linked to the endothelial dysfunction and inflammatory cellular processes, carriers of these 2 variants should have a particularly careful secondary prevention, which may justify a search for new therapeutic approaches.

BIOMARKERS: TROPONIN AND MORE

P1317 | BEDSIDE

Cardiac specific biomarkers and LVH identify differential risk of new-onset reduced versus preserved ejection fraction heart failure in older adults

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Purpose: To determine whether biomarkers of subclinical myocardial injury (high sensitive [hs] cTnT) and stress (NT-proBNP) differentiate risk of HFref vs. HFpEF among older asymptomatic adults with LVH.

Methods: NT-proBNP and hs cTnT were measured in older adults without HF or prior MI in the Cardiovascular Health Study. LVH was determined by echo. HF events were adjudicated over a median 13.1 years as HFref (EF<45%) or HFpEF. The risk of each HF type by LVH and age/sex-stratified tertiles of each biomarker was adjusted for demographics, CV risk factors, and LV relative wall thickness.

Results: Among 2347 participants there were 643 incident HF events (215 [33.4%] HFpEF, 150 [23.3%] HFref, and 278 [43%] without documented EF). Risk of HFref was 5-fold (NT-proBNP) and 7.8-fold (hs cTnT) greater among those with LVH and the highest biomarker tertile vs. those without LVH and lowest biomarkers (Table 1). In contrast, these groups had 3.1-fold and 2.6-fold greater risks of HFpEF (Table 1). There was an interaction ($p=.02$) between LVH and NT-proBNP for risk of HFref but not HFpEF.

Table 1

LVH by echo	Tertile of NT-proBNP	Heart failure reduced EF		Heart failure preserved EF	
		Unadjusted	Adjusted	Unadjusted	Adjusted
None (n=2053)	1	1.0	1.0	1.0	1.0
	2	1.0 (0.6, 1.7)	1.0 (0.6, 1.6)	1.0 (0.6, 1.4)	1.0 (0.7, 1.4)
	3	1.7 (1.1, 2.2)	1.7 (1.1, 2.6)	1.7 (1.1, 2.3)	1.6 (1.1, 2.3)
Yes (n=294)	1	1.0 (0.6, 1.7)	0.9 (0.3, 3.0)	1.2 (0.5, 2.8)	1.1 (0.5, 2.6)
	2	3.5 (1.7, 7.1)	2.9 (1.4, 6.0)	1.8 (0.9, 3.8)	1.5 (0.7, 3.2)
	3	6.5 (3.8, 11.0)	5.1 (2.9, 8.9)	3.3 (2.0, 5.7)	3.1 (1.8, 5.4)
None	Tertile of hs cTnT				
	1	1.0	1.0	1.0	1.0
	2	2.3 (1.4, 3.7)	1.8 (1.1, 2.9)	1.4 (0.9, 1.9)	1.2 (0.8, 1.7)
Yes	3	3.6 (2.3, 5.8)	2.6 (1.6, 4.2)	2.4 (1.7, 3.3)	1.8 (1.3, 2.6)
	1	2.7 (1.1, 6.5)	2.2 (0.9, 5.3)	2.5 (1.3, 4.5)	2.3 (1.3, 4.3)
	2	3.4 (1.4, 8.1)	2.7 (1.1, 6.5)	1.6 (0.7, 3.6)	1.2 (0.5, 2.8)
	3	12.9 (7.5, 22.2)	7.8 (4.4, 13.8)	3.7 (2.1, 6.6)	2.6 (1.4, 4.8)

Conclusion: Older adults with elevated hs cTnT or NT-proBNP and LVH are at markedly greater risk for incident HF, especially HFREF.

P1318 | BEDSIDE

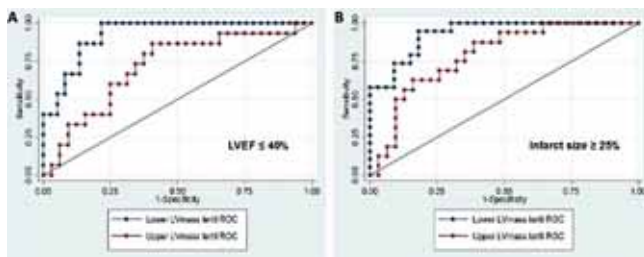
Quantification of troponin shows worse discriminatory capacity in the prediction of both large infarct size and poor left ventricular ejection fraction in the presence of ventricular hypertrophy

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Introduction and purpose: Infarct size estimation using biomarkers - creatine kinase (CK) and troponin (cTn) - is currently being evaluated as endpoint in many clinical trials. We recently described for the first time in a retrospective study that peak of cTnI could overestimate infarct size in presence of left ventricular hypertrophy (LVH). Prospective evidence regarding this hypothesis is needed and focuses the purpose of the present work.

Methods: A cohort of 140 patients with anterior ST-segment elevation acute myocardial infarction was prospectively recruited. A full cardiac magnetic resonance (CMR) study was performed 5-7 days after myocardial infarction, and CK and cTnI systemic values were serially measured. The cohort was categorized in tertiles according to indexed LV mass in CMR. Analysis of ROC curves were performed to study the discriminatory capacity of AUC of TnI vs. AUC of CK in predicting LVEF less than 40% and infarct size greater than 25%, in the lower vs. upper tertile.

Results: Discriminatory capacity of AUC of TnI in predicting poor LVEF and large infarct size was significantly worse for the upper tertile vs. lower tertile of indexed LV mass: 0.7146 vs. 0.9261 ($p=0.02$, Figure A) and 0.7903 vs. 0.9330 ($p=0.05$, Figure B), respectively. No significant differences were found regarding discriminatory capacity of AUC of CK for neither of the studied parameters.



Conclusions: Quantification of released cardiac troponin offers lower discriminatory capacity in the prediction of both large infarct size and poor left ventricular ejection fraction in the presence of ventricular hypertrophy. Left ventricular hypertrophy should be taken into consideration when infarct size and ejection fraction is estimated or predicted by troponin release.

P1319 | BEDSIDE

High-sensitivity troponin t and troponin i in the prediction of subsequent cardiovascular disease events in stable coronary heart disease patients: 10-year follow-up of the karola study

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Purpose: There is increasing evidence that even slightly elevated circulating troponin levels in patients with stable coronary heart disease (CHD) several weeks after an acute event are associated with adverse outcome. Since initial studies have indicated that there may be differences between troponins concerning their kinetics and other properties, we assessed the predictive value of two new high-sensitivity (hs) troponin assays for subsequent cardiovascular disease (CVD) events in stable CHD patients, simultaneously controlling for a large number of potential confounders.

Methods: Plasma concentrations of hsTnT (Roche Elecsys) and hsTnI (Abbott ARCHITECT) were measured at baseline in a cohort of 1,039 patients aged 30-70 years with CHD. A Cox proportional hazards model was used to determine the prognostic value of hsTnT compared to hsTnI on a combined CVD endpoint (cardiac death, non-fatal MI and stroke) after adjustment for established risk factors (i.e. age, gender, school duration, smoking, diabetes, number of affected vessels, initial management of CHD, HDL- and LDL-cholesterol) and additionally, for other emerging biomarkers.

Results: Median levels of hsTnT and hsTnI were 14.1 ng/L (IQR 9.1-22.2) and 14.6 ng/L (IQR 9.6-24.2), respectively with all values above the level of detection. The age and gender adjusted Spearman partial correlation coefficient between both troponins was 0.66 ($p<0.0001$). Levels of both troponins were associated with higher age, body mass index, a higher number of affected vessels,

and decreased left-ventricular function. During a median follow-up of 10 years, 200 patients (19.2%) experienced an adverse CVD event. In a multivariate model adjusted for established risk factors and including both troponins, hsTnT was associated with a hazard ratio (HR) of subsequent CVD events of 2.21 (95% CI, 1.19-4.09) when extreme quartiles were compared. The respective HR for hsTnI was 2.00 (95% CI, 1.11-3.62). However, further adjustment for NT-proBNP and GDF-15 attenuated the associations and they became non-significant.

Conclusions: Slightly elevated levels of hsTnT and hsTnI each add independent information if considered simultaneously to established risk factors and seem to have a similar long-term predictive value for subsequent CVD events in stable CHD patients.

P1320 | BEDSIDE

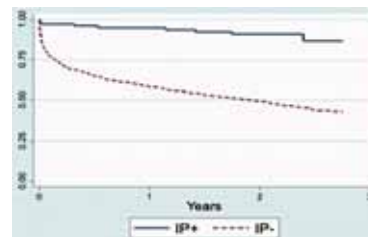
Troponin elevations following unselected invasive cardiac procedures: mortality in patients without myocardial infarction

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Purpose: A wide range of disease entities have been known to cause cardiac troponin elevations without myocardial infarction (MI). Yet no studies have investigated the prognostic implications of this condition in unselected pts undergoing invasive cardiac procedures. In this study we set out to assess the mortality risk in these pts.

Methods: We conducted a 1-year prospective study in unselected pts admitted to a university hospital. All pts who had cTnI measured because of a suspected MI were included. The decision limit for the diagnosis of MI was >0.03 ug/L. Pts with elevated cTnI, but who did not fulfill the criteria of the universal definition for MI, were categorized according to the underlying disease mechanisms.

Results: From January 2010 to January 2011 a total of 3762 pts qualified for inclusion. 1577 pts had cTnI elevations, of whom 488 had a MI. In 78 (7%) of the remaining 1089 pts, the elevations were caused by an invasive cardiac procedure (IP+). The 3 most common procedures were CABG, aortic valve replacement and radiofrequency ablation (68/78). In 1011 non-MI pts, cTnI elevations were due to other conditions than invasive cardiac procedures (IP-). Median cTnI levels were 8.8 ug/L (IQR 3.8-16.1) for IP+ and 0.09 ug/L (IQR 0.05-0.20) for IP- pts ($p<0.0001$). During a median follow-up of 2.1 years, 550 pts died. Mortality differed between the groups: IP+ pts 10.3% and IP- pts 53.6% ($p<0.0001$) (figure). In a multivariate Cox regression analysis the hazard ratio for IP- pts was 2.0 (95% CI 1.5-2.6) compared with IP+ pts.



Conclusion: Pts with cTnI elevations caused by unselected invasive cardiac procedures, but without fulfilling the MI diagnosis, have a low long-term mortality, despite very high cTnI levels.

P1321 | BEDSIDE

The role of renal extraction in determining cardiac troponin T levels in chronic conditions and after acute myocardial injury

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Background: Cardiac troponin T (cTnT) in blood plays a pivotal role in the diagnosis of MI. Asymptomatic patients with a spectrum of renal function have been reported to have elevated levels of cTnT, when measured by a high sensitive (hs) assay, which has prognostic implications. Whether cTnT elevation is due to increased subclinical myocardial injury or decreased renal cTnT clearance is incompletely understood. Therefore, we sought to investigate the fractional renal extraction and cardiac production of cTnT at low baseline levels and after acute myocardial injury.

Methods: Ten men and 6 women undergoing electrophysiology ablation procedures were enrolled in this study. 15 patients had pulmonary vein ablation for atrial fibrillation and 1 patient had ablation for ventricular tachycardia. hs cTnT was measured in samples obtained from the renal vein, radial artery and coronary sinus pre- and 43±34 minutes post last ablation.

Results: The mean creatinine and eGFR was 0.95 ± 0.22 mg/dL and 84.7 ± 25.3 ml/min/1.73m², respectively. Post-procedural values for cTnT were greater than

20-fold higher compared to pre-procedural baseline values (Table 1). Cardiac production with minimal renal extraction of cTnT was noted both before and after acute myocardial injury.

Table 1. hs cTnT levels pre- and post-acute myocardial injury

Parameters	Pre-procedure*	Post-procedure
Renal vein (RV) (ng/L)	18.8±31.1	414±192.8
Radial artery (RA) (ng/L)	20.9±35.4	454.4±227.9
Coronary sinus (CS) (ng/L)	30.4±49.3	525.1±213.1
Fractional cardiac production of cTnT ^a	0.49±0.65	0.19±0.19
Fractional renal excretion of cTnT ^a	0.06±0.22	0.076±0.07

*10 patients had one or more values <3.0 ng/L and were excluded from the analysis ^aRenal extraction = (RA-RV)/RA; ^aCardiac production = (CS-RA)/CS.

Conclusion: Our study shows renal extraction in this group of patients with normal renal function is negligible at both low and high systemic levels of cTnT suggesting that decreased renal extraction is likely not the reason for increased cTnT levels in patients with chronic kidney disease.

P1322 | BEDSIDE

Is cardiac troponin I the predictor for in-hospital mortality in patients undergoing liver transplantation?

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Background: Troponin is a specific marker of myocardial damage. The clinical significance of the troponin elevation after LTx is unknown.

Aim: To assess the significance of the cardiac troponin I elevation in patients after LTx.

Patients and methods: We retrospectively estimated data of 80 patients [54M, age 52.0±7.4 yrs] undergoing urgent or elective LTx. Plasma cTnI concentration was measured before surgery and 24, 48, 72 hours after. To assess the significance of TnI elevation the following factors were analysed: age, dialysis before LTx, pre-surgery parameters: MELD, creatinine, hemoglobin, fibrinogen and albumin concentrations, platelets count, INR; parameters related to surgery: surgery duration and anhepatic phase, cardiac output, pulmonary artery pressure, pulmonary artery wedge pressure, hemoglobin concentration.

Results: During in-hospital period 9 (11.25%) patients died. In 41 pts increased level of cTnI after surgery was observed. There was no patient with electrocardiographic signs of myocardial ischemia in the first 24 hours after surgery. Patient's death was significantly related to higher maximal cTnI concentration (median 0.09 vs 1.85, $p<0.01$). cTnI correlated with MELD ($r=0.166$, $p<0.05$), surgery duration ($r=0.346$, $p<0.001$), time of anhepatic phase ($r=0.278$, $p<0.001$), pre-surgery cardiac output ($r=0.154$, $p<0.05$), minimal hemoglobin concentration ($r=-0.198$, $p<0.05$).

Conclusions: In studied group the elevation of cardiac troponin I seems to be a predictor for in-hospital mortality after liver transplantation. We have found some selected clinical, biochemical and hemodynamic parameters to be correlated with the elevation of cTnI.

P1323 | BEDSIDE

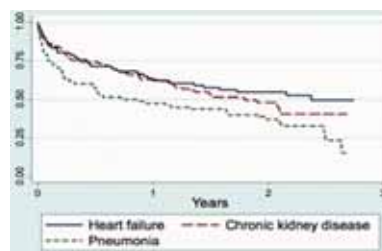
Most prevalent conditions causing troponin elevations in an unselected hospital cohort without myocardial infarction

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Purpose: To identify and characterize the most prevalent conditions causing troponin elevation in unselected hospitalized pts, in whom an acute myocardial infarction (MI) has been ruled out.

Methods: During a one-year period we prospectively studied unselected pts admitted to a university hospital. All pts having troponin I (cTnI) measured were considered. The MI diagnosis was according to the universal definition, and a cTnI value >30 ng/L was the decision limit for a MI. In non-MI pts with cTnI >30 ng/L a diagnosis-committee decided the cause of cTnI elevation. Pts were followed for at least one year with mortality as end-point.

Results: In 2010 a total of 3762 pts had cTnI measured. Of these 1089 had cTnI >30 ng/L but did not fulfill the MI diagnosis. Totally, 81 different conditions causing cTnI elevations were identified. The three most prevalent causes were: Chronic kidney disease ($n=97$), pneumonia ($n=80$) and heart failure ($n=66$). The mean age ($\pm$ SD) did not differ between the groups: 78 (11), 79 (11) and 75 (11) yrs old ($p=0.092$). Also, the median peak cTnI values were similar: 70 (40-130), 70 (50-140), and 70 (50-110) ng/L ($p=0.80$). Leucocytes and CRP values were significantly higher in pneumonia pts. During median 2.1 yrs of follow-up 142 of the 243 pts in the 3 groups died. Mortality was highest in pneumonia pts, 69% (55/80), followed by chronic kidney disease 57% (55/97) and heart failure pts 49% (32/66)



Survival rate in different diseases.

($p<0.0001$; figure). In multivariate Cox regression analysis the hazard ratio for pts with pneumonia was 2.1 (95% CI 1.2-3.5) compared with heart failure pts.

Conclusion: Chronic kidney disease is the most prevalent condition causing cTnI elevations in unselected hospitalized pts without MI. Pneumonia comes second and is associated with a nearly 70% two-year mortality.

P1324 | BEDSIDE

Head-to-head comparison of MR-proANP and NT-proBNP in patients with stable coronary heart disease followed over 8 years

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Background: Pathophysiological studies suggest that A-type natriuretic peptides might provide valuable information beyond B-type natriuretic peptides about cardiac dysfunction in patients with CHD. The clinical performance of elevated circulating MR-proANP in a head-to-head comparison to NT-proBNP in unselected patients with stable CHD has not been evaluated.

Methods: Plasma concentrations of MR-proANP and NT-proBNP were measured at baseline in a cohort of 1,048 patients aged 30-70 years with CHD, and participating in an in-hospital rehabilitation program. Main outcome measures were cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke.

Results: During a median follow-up of 8.1 years, 150 patients (incidence 21.1 pro 1,000 patient-years) experienced a secondary CVD event. MR-proANP was associated with a hazard ratio (HR) of 1.89 (95% CI 1.01-3.57) when the top quartile was compared to the bottom quartile in the fully adjusted model (p for trend 0.011). For NT-proBNP the respective HR was 2.22 (95% CI 1.19-4.14) with a p for trend of 0.0012. Finally, on top of a multivariate model including hs-troponin T, MR-proANP improved various model performance measures including c-statistics, and reclassification metrics, but without being superior to NT-proBNP.

Conclusions: MR-proANP and NT-proBNP show similar prognostic value in stable CHD.

P1325 | BEDSIDE

ProANP, changes in adiponectin during STEMI and prognosis

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Background: Natriuretic peptides (NP) have been suggested to regulate adipocyte metabolism including adiponectin. In patients with HF, infusion of ANP increased plasma adiponectin. However, this has not been studied in a clinical setting or in myocardial infarction. Accordingly, we investigated the interplay between proANP and adiponectin and the prognostic implications in patients with STEMI.

Methods: We prospectively included 760 patients with STEMI treated with primary-PCI, from September 2006 to March 2011. Blood samples were drawn immediately before PCI, and in a subgroup ($n=80$) additionally three times. Plasma adiponectin and proANP were measured in all blood-samples. Endpoints were all-cause mortality ($n=137$) and the combined endpoint ($n=188$) of major adverse cardiovascular events (MACE).

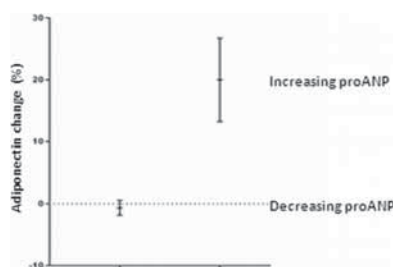


Figure 1. Changes in adiponectin during STEMI

Results: Plasma adiponectin and proANP were strongly associated at admission ($p < 0.001$). In patients with increasing proANP during STEMI, adiponectin also increased (1.3 ± 0.4 vs. 0.0 ± 0.1 , $p < 0.001$).

Patients with higher adiponectin had increased risk of both all-cause mortality and MACE (both, $p < 0.001$). After adjustment for confounding risk factors by Cox-regression analysis, adiponectin remained an independent predictor of both all-cause mortality and MACE: hazard ratio for each doubling of adiponectin: 1.44 (95% CI 1.10-1.88; $p = 0.007$) and 1.38 (95% CI 1.11-1.71; $p = 0.004$) respectively. However, the association vanished when proANP was included in the analysis (both, $p > 0.10$).

Conclusion: Adiponectin increases subsequently to proANP during STEMI. Increasing adiponectin is associated with increased risk of both all-cause mortality and MACE. However, the concomitantly elevated proANP levels appear to explain the positive association between adiponectin and worsened outcome.

P1326 | BEDSIDE

Brain natriuretic peptide (BNP) as a prognostic parameter for cardiovascular events and death in HIV-infected patients

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Background: HIV-infected patients exhibit an increased rate of cardiac diseases, due to an elevated rate of cardiac risk factors and side effects of antiretroviral therapy. The aim of the present study was to analyze the impact of B-type natriuretic peptide (BNP) as a prognostic parameter for cardiovascular events and death in HIV-infected individuals.

Methods: This prospective multicentre observational Cohort study elucidates cardiovascular disease prevalence by standardised non-invasive cardiovascular screening program and laboratory tests including BNP in 842 HIV-infected patients from four specialised outpatient clinics in Germany between 2004 and 2011. The follow-up period was 60 month. The impact of BNP on the incidence of cardiovascular events and all-cause mortality were assessed using multivariate Cox regression analysis.

Results: At baseline, 84% of the 842 patients were male, 89% Caucasians, 60% MSM, 31% were CDC-categorised C and 47% immunological stage 3. In mean, HIV Infection was diagnosed for 7.8 ± 5.6 years at baseline (IQR 2.8–11.6 years). The mean age was 44 ± 10 (IQR 37–50, range 20–75) years and the mean measured CD4 cell counts were 507 ± 298 (IQR 301–650, range 4–1984) cells/ μ l. 728 (87%) patients underwent antiretroviral treatment, of whom 65% had an HIV-RNA < 50 copies/ml. 111/801 patients (13%) had BNP values ≥ 35 pg/ml and 31/842 (4%) patients had BNP values ≥ 100 pg/ml. Subjects with high BNP levels had increased frequency of coronary events and death (coronary events/mortality: 20% for BNP > 35 pg/ml vs. 6% for BNP ≤ 35 pg/ml, and 48% for BNP > 100 pg/ml vs. 6% for BNP ≤ 100 pg/ml, respectively). In unadjusted univariate model, BNP ≥ 35 pg/ml and BNP ≥ 100 pg/ml were associated with a 3.3 [95%-CI 2.3–4.8]-fold and a 5.2 [95%-CI 3.2–8.7]-fold risk, respectively, for all-cause mortality and CV-events. After further adjustment for traditional cardiovascular risk factors supplied over the grouped scores (Framingham Risk resp. CVD from d'Agostino) and HIV related variables (HIV Stadium C = AIDS) and CD4 Cells, BNP was still predictive in the model using the Framingham risk score (1.6 [1.1–2.5] for BNP > 35 pg/ml and 1.9 [1.1–3.3] for BNP > 100 pg/ml), respectively.

Conclusions: According to our data, BNP values higher than 35 pg/ml and 100 pg/ml are both an independent predictor for an increased overall risk in HIV-infected individuals. Therefore, BNP could be an appropriate tool for a screening program for HIV-associated disorders in this patient population.

RENAL DENERVATION PART II

P1328 | BEDSIDE

Effect of renal denervation on glucose metabolism after 12 months follow-up

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Background: Renal denervation is invasive endovascular procedure using radiofrequency ablation to the renal arteries and decrease renal sympathetic activity. The effect of renal denervation on glucose metabolism is recently studied.

Methods: We summarized 40 patients. From this group were 15 women and 25 men. 20 patients had diabetes mellitus 2.type. Mean age was 59 years. Fasting glucose, glycated hemoglobin, microalbuminuria and C-peptide were measured.

Results: In all patients ($n=40$) increased fasting glucose, 7.1 ± 1.6 to 7.5 ± 2.3 ($p=0.039$). Glycated hemoglobin without significant changes, 4.6 ± 0.9 to 4.6 ± 1.1 ($p=0.148$). Microalbuminuria decreased, 38 ± 96.7 to 24.7 ± 46.6 ($p=0.024$). C-peptide increased, 1235 ± 744 to 1274 ± 588 ($p=0.49$). In group of patients with diabetes ($n=20$) fasting glucose increased, 8.3 ± 1.5 to 9.0 ± 2.5 ($p=0.035$), gly-

cated hemoglobin increased 5.2 ± 0.9 to 5.3 ± 1.1 ($p=0.113$), microalbuminuria decreased, 64 ± 132 to 18 ± 26 ($p=0.124$) and C-peptide increased, 1439 ± 976 to 1503 ± 724 ($p=0.426$). In patients without diabetes there were no significant changes in all parameters.

Conclusions: We did not prove any improvement of insulin sensitivity and glucose metabolism after 12 months follow-up. Our results do not correlate with results which were up to now published. The reason can be bad compliance diabetic regimen in patients with diabetes. We found quite high level of non compliance to the antihypertensive medication, man could suppose the same with peroral antidiabetics. It will be necessary to perform other studies with more patients in the future.

P1329 | BEDSIDE

The impact of renal sympathetic denervation on office and ambulatory blood pressure levels in patients with true resistant hypertension and obstructive sleep apnea-the interim analysis

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Purpose: The aim of our ongoing study is to investigate the clinical utility of renal denervation (RDN) for the treatment of resistant hypertension (RHTN) coexisting with obstructive sleep apnea (OSA). Here we report an interim analysis of the primary end point - blood pressure reduction at 3 months.

Methods: 35 patients (27M, 8F, mean age 55.4 ± 7.9 , range:32-69ys) with true RHTN (office systolic [SBP] $\geq 140/90$ mmHg and daytime SBP average ≥ 135 mmHg on ≥ 3 antihypertensive drugs including a diuretic) coexisting with moderate-to-severe OSA (apnea/hypopnea index ≥ 15) were allocated to two groups: in 19 patients (14M, 5F, mean age 54.2 ± 9.6 , range: 32-69 ys) RDN was performed and 16 patients (13M, 3F, mean age 57.1 ± 4.6 , range:50-65ys) were assigned to control group. At baseline and at three months follow-up all patients underwent evaluation of office blood pressure (OBP) an ambulatory blood pressure levels (ABP) by ABPM.

Results: The treatment and control groups were well matched in regard to baseline characteristics. At 3 months OBP levels in the RDN group reduced by $26/17$ mm Hg ($p < 0.001/p < 0.001$), whereas they did not differ significantly from baseline in the control group (change of $2/-3$ mmHg, $p=0.369/p=0.132$). Between-group differences in OBP change were significant at $p < 0.01$ for both systolic and diastolic OBP respectively. At 3 months systolic OBP < 140 mmHg was noted in 14 patients in the RDN group and in 2 patients in the control group (73.7% vs. 12.5%, $p < 0.001$). In ABPM 24h, daytime and nighttime ABP levels were reduced by $-13/-9$ mmHg ($p < 0.01/p < 0.01$), $-15/-9$ mmHg ($p < 0.01/p < 0.01$) and $-11/-8$ mmHg ($p < 0.01/p < 0.01$) in RDN group. In the control group no significant changes in 24h, daytime and nighttime ABP levels were observed. Between-group differences in ABP were significant for daytime systolic and diastolic ABP levels ($p=0.02$ and $p=0.019$, respectively) and for 24h systolic and diastolic ABP levels ($p=0.019$ and $p=0.033$, respectively), but not for nighttime ABP levels.

Conclusions: The interim analysis of the on-going study designed to evaluate the clinical utility of renal denervation in true resistant hypertension coexisting with moderate-to-severe OSA showed improvements in office and ambulatory blood pressure levels 3 months after the procedure.

P1330 | BEDSIDE

The risk to fail in RDN- the unfavourable role of accessory renal arteries

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Purpose: Among patients with drug resistant arterial hypertension (DRAH) renal artery variations are common in MRI prior to renal denervation (RDN). Furthermore bilateral denervation should be done to interrupt the spinally interfered renal cross talk in hypertension regulation. In contrast to concomitant main branches, performing RDN in pole arteries is not recommended due to their small vessel diameter. We thought to investigate whether the absence of radiofrequency ablation (RF) in accessory arteries is a predictor for RDN success after 6 months.

Methods: We performed RDN (RF catheter system, Simplicity, Medtronic Co.) in 110 patients (58,1% male, mean age 65.0 ± 10.2 years, BMI 32.1 , 48,4% DM II, 6.0 ± 1.2 antihypertensive drugs). After 6 months 62 patients underwent a 24h ABDM to assess the RDN success related to their anatomically driven completeness of RF ablation.

Results: Prior RDN the entire study group possessed a mean office BP (OBP) $163 \pm 14/87 \pm 10$ mmHg and a mean ABDM $154 \pm 10/85 \pm 9$ mmHg. 12 of 62 patients (19,4%) offered accessory concomitant main or pole arteries which were not completely ablated. In comparison patients without anatomical anomalies showed a drop off in 24h OBP of $-18 \pm 4/-5 \pm 2$ mmHg, whereas those with aberrant arteries decreased by $-12 \pm 8/3 \pm 4$ mmHg in OBP ($p=0.67$). Thus, based on a decline of 10mmHg in OBP 42 of all patients (67,7%) responded to RDN, 34 (54,8%) with anatomically normal renal artery constitution vs. 8 (12,9%) with double branches or pole arteries. The relative risk of patients with accessory vessels and incomplete ablation procedure to fail in RDN was 1,83 ($p=0.19$). Regarding

the RDN success no differences could be observed in capacity of applied power or number of ablation points between anatomic groups.

Conclusion: At RDN screening, accessory renal arteries are a common phenomenon in patients presenting with DRAH. However, to fail to ablate these vessels caused by small diameter or anatomical challenges is associated with an increased risk of an absent success of RDN after 6 months.

P1331 | BENCH
Evaluation of lesion and thermodynamic characteristics of Symplicity and EnligHTN renal denervation systems in a phantom renal artery model

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Purpose: Radiofrequency renal artery denervation has been used effectively to treat resistant hypertension. However, comparison of lesion and thermodynamic characteristics for different systems has not been previously described. We aimed to assess spatiotemporal lesion growth and ablation characteristics of Symplicity and EnligHTN systems.

Methods: A total of 39 ablations were performed in a phantom renal artery model using Symplicity (n=17) and EnligHTN (n=22). The phantom model consisted of a hollowed gel block surrounding a thermochromic liquid crystal (TLC) film, exhibiting temperature sensitivity of 50-78 °C. Flow was simulated using 37 °C normal saline with impedance equal to blood. Radiofrequency ablations with each system were delivered with direct electrode tip contact to the TLC.

Results: Lesion size was interpreted from the TLC as the maximum dimensions of the 51 °C isotherm. Mean lesion depth was 3.82mm ±0.04 versus 3.44mm ±0.03 (p<0.001) for Symplicity and EnligHTN respectively. Mean width was 7.17mm ±0.08 versus 6.23mm ±0.07 (p<0.001), respectively. With EnligHTN, steady state temperature was achieved 20 sec earlier, and was 15 °C higher than Symplicity.

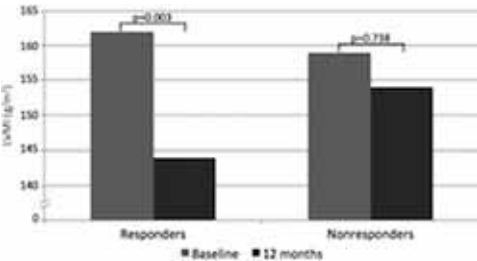
Conclusion: In this phantom model, Symplicity formed larger lesions compared to EnligHTN with lower catheter-tip temperature. The clinical significance of our findings needs to be further explored.

P1332 | BEDSIDE
Effects of renal sympathetic denervation on left ventricular structure and function: 1-year follow-up

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Background: Catheter-based sympathetic renal denervation (RDN) is an emergent therapeutical option for patients with resistant hypertension. However, the impact of RDN in left ventricular (LV) performance is yet to be established. Our aim was to evaluate the effects of RDN on LV structure and function (systolic and diastolic) in patients with resistant hypertension.

Methods and results: From a prospective registry of 49 consecutive patients with resistant hypertension submitted to RDN between July-2011 and February-2014, all of them, by protocol, underwent an echocardiogram before and one year after RDN. The results are presented for patients with at least 1-year fup (n=24). Mean age was 63±7 years, 54% were men, the majority had hypertension lasting for more than 10 years (88%) and the median number of anti-hypertensive agents was 6. Left ventricular hypertrophy was present in all but 1 of these 24 pts. At 1-year, there was a significant decrease on both systolic (181±25 to 152±12mmHg, p<0.001) and diastolic blood pressure (BP) (90±15 to 79±9mmHg, p=0.001). Regarding the 1-year echocardiogram, there was significant reduction in LV mass: 162±36 to 146±38g/m² (p=0.007) with no significant difference on the other evaluated parameters (LV ejection fraction, E/e' ratio, E wave deceleration time and left atrial volume index). Reduction in LV mass achieved statistical significance



Abstract P1335 – Table 1. Systolic 24h BP, β (95% CI)

	Continuous (n=1508) [†]	Quartile 1 (n=377)	Quartile 2 (n=377)	Quartile 3 (n=377)	Quartile 4 (n=77)	P for trend [‡]
Fully adjusted	1.98 (0.98; 2.97)**	Ref.	1.06 (-0.23; 2.36)	1.75 (0.45; 3.05)	2.82 (1.51; 4.13)	<0.0001
Fully adjusted with HOMA	1.70 (0.69; 2.71)**	Ref.	0.91 (-0.39; 2.20)	1.54 (0.23; 2.84)	2.47 (1.14; 3.80)	0.0002

Coefficients were adjusted for sex, age, body mass index, high-sensitivity C-reactive protein, physical activity, low density lipoprotein, high density lipoprotein, medication for hypertension, hemoglobin A1c, smoking, alcohol, body composition and education. Ref., Reference; HOMA, homeostatic model assessment insulin resistance. **p-value <0.01; [†]GLP-1 was log-transformed; [‡]p for trend across quartiles GLP-1.

only in BP responders (defined as a >10mmHg decrease in office systolic BP): n=19, 162±40 to 144±41g/m², p=0.003, vs 159±23 to 153±28 g/m², for nonresponders; n=5, p=ns (figure).

Conclusions: In this population of patients with resistant hypertension submitted to RDN, blood pressure reduction was associated with a significant reduction in indexed left ventricular mass.

P1333 | BEDSIDE
Response or no response to renal sympathetic denervation - are there answers in exercise tolerance?

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Renal sympathetic denervation (RSD) in patients with drug resistant hypertension is a feasible procedure to strongly reduce office blood pressure as well as sinus rhythm heart rate at rest. Furthermore, studies have shown long term effects in exercise tolerance assessed in ergospirometry (CPET) in those patients who underwent RSD compared to non denervated hypertensive patients. However, it is still unknown whether differences exist between responders and none responding patients concerning their exercise tolerance.

Our study aim was to investigate whether exist differences in CPET parameters among RSD patients related to their RR response after 6 months.

Methods: Among a RSD cohort of 62 patients who underwent CPET at baseline and after 6 months we selected 40 patients (60% male, 65±9 years of age, 5,8±1,5 antihypertensive drugs [AHD]) divided in group 1 with 20 patients with the strongest response (in 24h ABDM) and in a group 2 with 20 patients without any response to RSD.

Results: Both groups presented comparable baseline parameters regarding medical history, number of AHD (group 1: 5,4±0,4; group 2: 6,1±0,3) and baseline office RR (OBP 161±5/88±3 vs. 170±7/84±4). After 6 months, responders showed a decline in blood pressure at rest by -24±6/-8±3 mmHg, while OBP in none responders increased by 12±3/10±4 mmHg (p<0,001). Furthermore, responders tended to were more efficient (117±22 vs. 110±20 Watts), to have lower exercise RR (186±8/95±6 vs. 198±10/100±11mmHg), a better peak oxygen uptake (19,8±5,7 vs. 18,7±6,7 ml/kg*min) and a lower pulse pressure at rest and during exertion (p=0,6). At recovery after 1 minute, the systolic blood pressure decline was more pronounced in group 1 vs. group 2 (-25±8 vs. -19±9; p=0,13). Moreover, responders exhibited an improvement in heart rate recovery compared with patients who did not respond to RSD (p=0,06).

Conclusion: Patients successfully ablated by radiofrequency showed an improvement in their exercise capacity and exertional blood pressure rise accompanied by a favourable impact on prognostic parameters in drug resistant hypertension like heart rate recovery and pulse pressure. Disappointing, the most of the CPET variables assessed showed still a tendency in favour of responders after RSD.

HUMORAL REGULATION OF BLOOD PRESSURE

P1335 | BEDSIDE
Glucagon-like peptide-1 and blood pressure in young, healthy adults: a population-based study

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Purpose: Glucagon-like peptide 1 (GLP-1) not only plays an important role in the pathophysiology of impaired glucose tolerance, but is also correlated with blood pressure (BP) in experimental studies. The aim of this study was to assess the relationship of GLP-1 plasma levels and BP in young and healthy adults.

Methods: Healthy adults between 25 and 41 years of age without cardiovascular disease, diabetes or a body mass index >35 kg/m² were enrolled in a population-based study in the Principality of Liechtenstein. Total GLP-1, determined with research-use-only Single Molecule Counting technology assay, and ambulatory BP data were available in 1508 participants. Ambulatory BP monitoring was performed over 24h hours using a validated device. Multivariable linear regression models were constructed to assess the relationship of GLP-1 with ambulatory BP.

Results: Median age of our population was 38 years. Median (interquartile range) GLP-1 levels across GLP-1 quartiles were 20.3 (16.6; 22.4), 27.6 (26.3; 29.8), 37.4 (34.8; 40.4) and 55.9 (50.0; 65.4) ng/L for men and 19.7 (16.2; 21.8), 28.2

(26.0; 29.7), 36.5 (34.2; 40.1) and 53.2 (47.7; 65.5) ng/L for women. Results of the multivariable linear regression models are shown in the table. There was a significant linear relationship of GLP-1 with both systolic and diastolic (not shown) 24h BP after multivariable adjustment. Inclusion of homeostatic model assessment insulin resistance into the model attenuated this relationship, but all associations remained statistically significant. In separate analyses, GLP-1 was significantly related to both daytime (β per 1 log-unit increase in GLP-1 2.01; 95% confidence interval (CI) 0.97, 3.05; $p=0.0002$ for systolic and 1.17; 95%CI 0.37, 1.98; $p=0.0044$ for diastolic BP) and nighttime BP (β per 1 log-unit increase in GLP-1 1.33; 95%CI 0.25, 2.42; $p=0.0155$ for nighttime systolic BP and 1.02; 95%CI 0.23, 1.80; $p=0.0113$ for nighttime diastolic BP).

Conclusion: Plasma levels of GLP-1 are significantly associated with both systolic and diastolic ambulatory BP levels. Part of this relationship seems to be mediated by insulin resistance.

P1336 | BEDSIDE

In hypertensive women, both the results of the screening for hyperaldosteronism and of the evaluation of insulin resistance depend on the timing of assessment in relation to the ovarian cycle

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We have reported that in low-renin hypertensive women the increment of plasma aldosterone that occurs in the luteal compared to the follicular phase of the ovarian cycle markedly increases the positivity for suspected primary hyperaldosteronism; it has also been reported that aldosteronism is associated with insulin resistance (IR) (Garg J.Clin.Endocrinol.Metab, 2010) and that IR slightly but significantly increases in the luteal phase in normotensive women (Yeung J.Clin.Endocrinol.Metab, 2010). We here report the results of a study on 31 women in the fertile age evaluated because of arterial hypertension in whom both aldosterone and HOMA-IR index (glucose*insulin/405) levels were investigated during the ovarian cycle.

All measures (plasma aldosterone, PRA, insulin, glucose and progesterone levels) were done at the 5-7th (follicular phase) and 21-25th (luteal phase) day of the menstrual cycle, without hypotensive therapy or with doxazosin 4mg per day. All women reported a regular cycle, age: 41.7 ± 8.4 [mean $\pm$ SD] (range: 19-53) years, BMI 25.1 ± 4.6 (19.3-35.8) kg/m².

Compared to the follicular phase, in the luteal phase plasma progesterone (P), aldosterone (ALDO), renin activity (PRA), insulin (I) and HOMA-IR all increased significantly: P from 0.6 ± 0.3 to 8.7 ± 4.1 ng/mL ($p < .0001$, t-paired); ALDO from 13.6 ± 8.3 to 21.1 ± 8.3 ng/dL ($p < .0001$); PRA from 0.42 ± 0.40 to 0.69 ± 0.87 ng/mL/hr ($p < .02$); I from 6.23 ± 2.96 to 8.67 ± 4.11 mU/L ($p < .0001$); HOMA-IR from 1.39 ± 0.8 to 2.01 ± 1.21 ($p < .0001$). For example, the proportion of ALDO > 15 ng/dL with ALDO/PRA > 40 increased from 7/31 (23%) to 16/31 (52%); the proportion of HOMA-IR > 2.5 increased from 3/22 (14%) to 6/22 (27%).

Multiple regression analysis demonstrated that P - but not ALDO - and BMI were strong positive independent predictors of plasma insulin and HOMA-IR: univariate analysis 1.) I vs P $p=0.016$; vs BMI $p < 0.0001$; 2.) HOMA-IR vs P $p=0.065$; vs BMI $p < 0.0001$; multivariate analysis 1.) I vs P ($p < 0.002$) + BMI ($p < 0.0001$); 2.) HOMA-IR vs P ($p < 0.02$) + BMI ($p < 0.0001$).

These results in hypertensive women confirm that plasma aldosterone may greatly increase during the luteal phase of the ovarian cycle and suggest that also insulin resistance may increase to a greater extent than in normotensive women. The ovarian cycle is thus a source of variability of plasma aldosterone and of insulin resistance in hypertensive women in fertile age, with potential relevance in the diagnostic workup and pathophysiology of hypertension.

P1337 | BENCH

EPAC1 plays an important role in regulation of renin and AQP2 expression in the kidney of mice

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Objectives: Cyclic AMP (cAMP) signaling plays pivotal roles in the regulation of hemodynamics. Main therapeutic targets for heart failure, including β -adrenergic receptor (β -AR) mediated signaling, renin-angiotensin system and the regulation of body fluid volumes are also controlled by cAMP mediated signaling. Protein kinase A has been the most common downstream mediator of cAMP. Recently, exchange protein directly activated by cAMP (EPAC) was identified as a novel direct target of cAMP. Our recent studies demonstrated that chronic β -AR stimulation-induced cardiac dysfunction, apoptosis and fibrosis were attenuated by EPAC1 deficiency. In this study, we examine the role of EPAC1 in regulation of renin and aquaporin-2 (AQP2) expression in kidney using EPAC1 knockout (EPAC1KO) mice. These molecules play important role in regulation of hemodynamics and their expression levels are known to be modulated by cAMP signaling.

Methods and results: The renin mRNA levels in renal cortex of EPAC1KO mice were significantly lower than that in wild type (WT) mice both at basal conditions ($\sim 53\%$, $P < 0.01$, $N=8$) and after 18 hours water restriction ($\sim 33\%$, $P < 0.01$, $N=7-8$). These results imply that inhibition of EPAC1 may lead to suppression of the renin-angiotensin system. In addition, AQP2 mRNA levels both in renal cortex and medulla were lower in EPAC1KO mice than that in WT mice (cortex: $\sim 41\%$

lower, $P < 0.01$, outer medulla: $\sim 44\%$ lower, $P < 0.01$, inner medulla: $\sim 41\%$ lower, $P < 0.05$, $N=8$). Consistently, water intake was significantly increased in EPAC1KO mice (~ 1.3 fold, $P < 0.05$, $N=9$), indicating that water reabsorption through AQP2 may be inhibited by EPAC1 deficiency.

Conclusions: EPAC1 plays important role in maintaining the expression of renin and AQP2 in the kidney of mice, suggesting that inhibition of EPAC1 may possibly suppress the renin-angiotensin system and cause diuretic effect. Taken together with the results of our previous studies on the roles of EPAC1 in the heart, these findings imply that EPAC1 may be a novel effective therapeutic target for heart failure therapy.

P1338 | SPOTLIGHT

Sarcoidosis is associated with non-dipper blood pressure pattern

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Objectives: Cardiovascular complications are responsible for the majority of deaths in sarcoidosis patients. Autonomic dysfunction (AD) is frequent in sarcoidosis and considered as a result of small fiber neuropathy. Non-dipper blood pressure (BP) pattern, which is also linked to AD, is associated with increased risk of cardiovascular and renal diseases. The aim of the present study was to evaluate non-dipping BP pattern in normotensive patients with pulmonary sarcoidosis (PS).

Methods: Sixty-three normotensive patients with PS (group 1) and 49 healthy subjects (group 2) were prospectively enrolled. Ambulatory BP monitoring was performed in all participants over a 24-h period.

Results: The non-dipping BP pattern was significantly more frequent in patients with PS as compared to control group (80% vs. 53%, respectively, $p=0.002$). More advanced PS (grade 2) was an independent predictor of non-dipper BP pattern (odds ratio: 10.4, 95% confidence interval: 1.1-95.4, $P=0.03$). Masked hypertension and body mass index were also found as other predictors of non-dipping BP pattern.

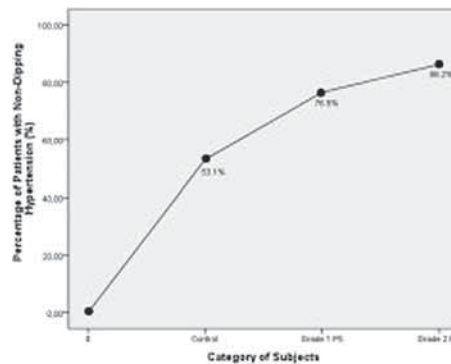


Figure 1

Conclusions: The present study showed that non-dipping BP pattern is frequently observed in normotensive patients with PS. The probable mechanism underlying the non-dipping BP in PS is autonomous nervous system dysfunction. This study calls attention to the importance of ambulatory BP monitoring in patients with PS. PS represents an independent risk factor for non-dipping BP and these patients have increased cardiovascular risk.

P1339 | BEDSIDE

Acetazolamide prevents periodic breathing during sleep in hypoxic conditions at high altitude by interacting with gender-related differences in chemoreflex sensing

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Purpose: Acute high-altitude exposure induces in healthy subjects a blood pressure (BP) rise, particularly evident at night. Periodic breathing during sleep (PBS) is a common finding during acute exposure to high-altitude, and its occurrence may affect autonomic cardiovascular control and BP through cyclic deoxygenations and re-oxygenations. At high-altitude PBS is more frequent in males, although the mechanisms accounting for this gender-related difference are not completely understood. Acetazolamide has proved useful in preventing PBS as well as to counteract blood pressure (BP) rise at high-altitude.

We aimed at investigating PBS pathophysiology at high-altitude, focusing on gender-related differences in chemosensitivity and by assessing the modifications of chemoreflex control induced by acetazolamide.

Methods: 44 healthy lowlanders (21 females), randomized to acetazolamide/placebo, underwent polysomnography at sea-level and at 4559 m a.s.l. Hypoxic and hypercapnic chemoreflex sensitivities were assessed at sea-level.

Results: Males exhibited increased hypoxic chemosensitivity even after ventilation was normalized for body height (0.10 ± 0.02 vs 0.08 ± 0.02 L/min/%SpO₂/m, $p < 0.001$), and displayed PBS at altitude more frequently than females (40.9 ± 27.8 vs 7.3 ± 4.0 events/hour, $p = 0.008$). Ventilation increased from sea-level to high-altitude ($+4.6 \pm 2.1$ L/min, $p < 0.001$), irrespectively of gender and treatment. Acetazolamide leftward-shifted the CO₂ set-point without gender-related differences and, at altitude, it improved oxygen saturation ($p < 0.001$) during daytime (85.2 ± 3.8 vs $77.1 \pm 6.6\%$) and nighttime (78.2 ± 2.6 vs $71.4 \pm 4.3\%$) compared to placebo. The reduction ($p < 0.001$) of end-tidal CO₂ pressure from sea-level to high-altitude was more marked on acetazolamide than placebo (24.9 ± 2.7 vs 29.9 ± 3.0 mmHg, $p = 0.041$). Acetazolamide at high-altitude resulted in less PBS in males (3.8 ± 3.8 events/hour, $p = 0.002$) and in females (2.9 ± 3.5 events/hour, $p = 0.069$), abolishing between-gender differences.

Conclusions: The greater severity of PBS displayed by males at high-altitude could be attributed to their higher chemosensitivity to hypoxia, promoter of ventilatory instability in context of hyperventilation-induced hypocapnia. Acetazolamide may attenuate BP-increase associated to altitude exposure by influencing the two sides of chemoreflex loop (modifying apneic threshold and improving oxygenation) and thus counteracting the occurrence of PBS in both genders.

P1340 | BEDSIDE

Plasma renase deficiency is associated with presence of arterial hypertension in patients after surgical repair of coarctation of aorta

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Purpose: The purpose of the study was to evaluate plasma renase level (REN), a novel catecholamine-metabolising enzyme, in patients after surgical repair of coarctation of aorta (CoA) and among control volunteers in the context of underlying arterial hypertension (HA).

Methods: This case-control study comprised 50 consecutive patients after Dacron patch CoA repair (31 men (62%); aged 33 (26;40) years; HA present in 21 (42%)) matched in terms of age and gender with control group consisting of 50 patients (31 men, 62%; aged 29 (24;37) years; HA in 29 (58%)). Both groups were stratified depending on the presence of HA. Plasma REN, C-reactive protein (CRP) and carotid intima-media thickness (IMT) were acquired in both groups, while ultrasound and tonometric markers of vascular remodeling in the study group exclusively.

Results: REN was lower in study than in control group (5825.1 vs. 6592.7 ng/ml; $p = 0.041$), lower among hypertensive than normotensive CoA subjects (4946 vs. 6461 ng/ml, $p = 0.027$) and lower in hypertensive than normotensive controls (5165.0 vs. 8564.3 ng/ml; $p < 0.0001$). REN inversely correlated with serum creatinine ($r = -0.36$) and arterial blood pressure in the whole population, and with central systolic ($r = -0.29$) and diastolic pressure ($r = -0.35$) in the study group. A trend for negative correlation with flow-mediated dilation ($r = -0.24$, $p = 0.098$) and pulse-wave velocity ($r = -0.23$, $p = 0.11$) and no correlation with CRP and IMT were observed in the study group. Multivariate regression analysis indicated creatinine and pulse pressure as independent predictors of REN in the whole population. REN level < 4958 ng/ml was a potent predictor of HA in CoA patients (OR=3.8; 95%CI: 1.1-12.8).

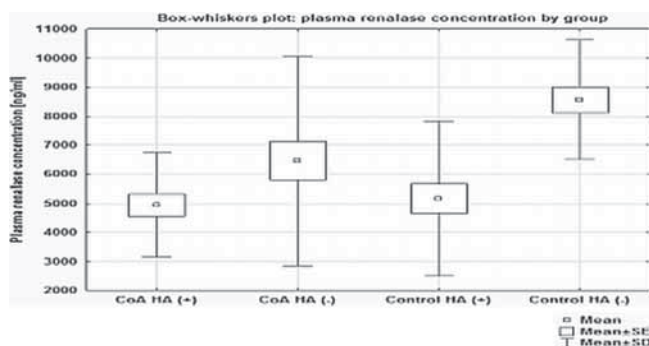


Figure 1. Box-whiskers chart

Conclusions: REN deficiency is associated with the presence of HA in both post-CoA patients and healthy controls.

P1341 | BEDSIDE

Role of sympathetic overactivity and it's relationship with diastolic parameters in resistant hypertension

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Purpose: Sympathetic overactivity plays an important role in development of hypertension. In recent years, interventional therapies which targets the sympathetic system becomes popular for resistant hypertension. However; the effect of sympathetic predominance in resistant hypertension is not very clear. In our study; we aim to evaluate the impact of sympathetic overactivity on resistant hypertension and its relationship with diastolic dysfunction.

Method: Among 218 patients enrolled; 57 were resistant hypertensives, 83 were controlled hypertensives and 78 were normotensives. Mean heart rate and time domain heart rate variability (HRV) values (Standart deviation of NN intervals (SDNN), standart deviation of all 5 minute NN intervals (SDANN), root mean square of successive differences (RMSSD), Triangular index) which reflects sympathetic overactivity were obtained from 24 hour ECG recordings. Transthoracic echocardiography was performed and diastolic parameters (left ventricular (LV) mass, LV mass index, left atrial (LA) volume index) were assessed. HRV values were compared between groups. Association between HRV values and diastolic parameters was researched in resistant hypertensives.

Results: In resistant hypertensive group; mean heart rate (86.4 ± 9 vs 71.9 ± 9.1 ; $p < 0.001$) was significantly higher; SDNN (114.4 ± 10.3 vs 159.7 ± 38.4 ; $p < 0.001$), SDANN (107.4 ± 50.7 vs 147.5 ± 47.8 ; $p < 0.001$) RMSSD (33.6 ± 16.2 vs 47.8 ± 21.7 ; $p < 0.001$) and Triangular Index (29.7 ± 10.2 vs 43.6 ± 13.5 ; $p < 0.001$) were significantly lower than normotensive group; mean heart rate (86.4 ± 9 vs 74.1 ± 10.6 ; $p < 0.001$) was significantly higher; SDNN (114.4 ± 10.3 vs 137.3 ± 37.1 ; $p < 0.002$) and Triangular Index (29.7 ± 10.2 vs 36 ± 10.9 ; $p < 0.006$) were significantly lower than controlled hypertensive group. These results reflect clear sympathetic predominance in resistant hypertension compared to both normotensive and controlled hypertensive state.

In controlled hypertensive group; SDNN (137.3 ± 37.1 vs 159.7 ± 38.4 ; $p < 0.001$), SDANN (124.1 ± 37.6 vs 147.5 ± 47.8 ; $p < 0.004$) and Triangular Index (36 ± 10.9 vs 43.6 ± 13.5 ; $p < 0.001$) values were significantly lower than normotensive group. Among resistant hypertensives; LV mass, LV mass index and LA volume index were significantly negatively correlated with SDNN and Triangular index.

Conclusion: Our study showed that sympathetic overactivity exists in hypertensive patients and this effect is much more prominent in resistant hypertensives. There is also a distinct correlation between sympathetic overactivity and diastolic dysfunction in resistant hypertension.

P1342 | BEDSIDE

Impact of obstructive sleep apnea syndrome on plasma fibrin clot properties in patients with hypertension at high cardiovascular risk

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Purpose: Formation of dense and poorly lysable plasma fibrin clots is observed clinical settings with high cardiovascular risk. Recently, it has been reported that in patients with obstructive sleep apnea (OSA), clot lysis time is prolonged. The aim of the present study was to investigate plasma fibrin clot properties in high-risk patients with arterial hypertension with and without OSA but without clinically overt cardiovascular disease.

Methods: We studied 87 hypertensive patients at high cardiovascular risk (according to the 2007 ESH/ESC criteria) suspected of OSA. Patients with previously diagnosed atherosclerotic cardiovascular disease were excluded. Fibrin clot properties including clot permeability (Ks), clot lysis time (CLT), and turbidimetric parameters of clot formation (the lag phase of fibrin formation and maximum absorbancy (Δ Absmax) at 405 nm) were determined at the day of polysomnography.

Results: There were 49 patients (aged 49.9 ± 8.8 years, 38M, 11F) with OSA (apnea/hypopnea index > 15 events/h) and 38 control patients (mean age 47.1 ± 9.1 years, 22M, 16F) who did not differ with regard to age, sex, BMI and blood pressure. Patients with OSA had lower Ks (59 ± 0.9 vs $75.5 \pm 1.20 \cdot 10^{-9}$ cm²; $p < 0.001$) and longer CLT (106.8 ± 13.4 vs 90.5 ± 15.1 min; $p < 0.001$). In OSA patients clots tended to be formed faster (lag phase, 41.1 ± 4.2 vs 43.2 ± 5.6 s; $p = 0.061$) and had higher Δ Absmax (0.86 ± 0.05 vs 0.84 ± 0.08 ; $p = 0.11$). Ks and CLT correlated with AHI ($r = -0.58$; $p = 0.001$, and $r = 0.47$; $P = 0.001$, respectively) and mean saturation ($r = 0.53$; $P = 0.001$, and $r = -0.30$; $P = 0.006$, respectively). In 14 patients with OSA fibrin clot properties who were evaluated before and after 3 months of CPAP treatment, an increase in Ks (6.1 ± 1.1 vs $7.7 \pm 0.1 \cdot 10^{-9}$ cm²; $p < 0.01$), shorter CLT (106.1 ± 10.8 vs 86.4 ± 14.2 ; $p < 0.01$), longer lag phase of fibrin formation (40.2 ± 3.8 vs 44.7 ± 4.0 s; $p = 0.009$), and lower Δ Absmax (0.86 ± 0.05 vs 0.82 ± 0.07 ; $p = 0.061$) were observed.

Conclusions: In hypertensive patients with high cardiovascular risk, the presence of OSA was associated with unfavorable, prothrombotic changes in the structure and function of fibrin clots which significantly improve after CPAP treatment. The study suggest a novel prothrombotic mechanism in OSA which can be revers by CPAP treatment.

P1343 | SPOTLIGHT**Relationship of vascular stiffness and sympathetic vascular tone with beat-to-beat systolic blood pressure variability in the elderly**

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Purpose: To investigate the relationship of beat-to-beat Systolic Blood Pressure Variability (SBPV) with vascular stiffness, sympathetic vascular tone, and baroreflex sensitivity in elderly subjects aged 60-79 years old in orthostatic position.

Methods: Cross-sectional study, smoke- and diabetes-free elderly subjects (n=62) with and without hypertension (HTN), aged 60-79 years, female=34 (55%), HTN=42 (68%), without other comorbidities or use of chronotropic drugs. Blood pressure (BP) was measured in a sitting position (clinic SBP); then it was continuously measured by photoplethysmography in supine position for 15 minutes at rest and during a 10-minute head-up tilt test. Supine and orthostatic autonomic modulation of systolic BP were assessed through spectral analysis of SBPV in the low (0.04-0.15 Hz) and high frequency (0.15-0.40 Hz) bands. SBPV was estimated by the standard deviation (SD) of beat-to-beat SBP values during 10 minute head-up tilt. Sympathetic vascular tone was estimated by LF-SBPV index. Vascular stiffness was assessed through applanation tonometry on the radial artery. After computed generation of transfer function, augmentation index (Aix) was used to estimate vascular stiffness.

Results: Orthostatic SBPV was positively correlated with resting clinic SBP (r=0.221, p=0.042), Aix (r=0.308, p=0.007) and LF-SBPV (r=0.325, p=0.005), whereas there was a negative correlation with BRS LF (r=-0.290, p=0.01). Additionally, clinic SBP, Aix, LF-SBPV were positive independent predictors of orthostatic SBPV (B=0.04±0.02, p=0.03, R²=0.08; B=0.08±0.03, p=0.02, R²=0.18; B=0.06±0.03, p=0.04, R²=0.28, respectively) after adjusting for age (table 1).

Table 1. Summary of regression analysis

Parameters	B (±SD)	Beta	p-value	p-model	R ²
Age (ys)	-0.095±0.050	-0.224	0.060	0.313	0.017
Clinic SBP (mmHg)	0.038±0.017	0.257	0.030	0.084	0.080
Aix	0.080±0.033	0.279	0.019	0.010	0.177
LF-SBPV (Hz)	0.059±0.028	0.255	0.037	0.001	0.277
LF BRS (ms/mmHg)	-0.269±0.154	-0.206	0.088	0.001	0.314

Conclusion: Clinic SBP, vascular stiffness, and sympathetic vascular tone are associated with increased beat-to-beat SBPV in normotensive and hypertensive subjects aged 60-79 years old. These factors should be considered in elderly patients with increased orthostatic SBPV.

P1344 | BEDSIDE**Rapid blood pressure increase in young middle age predicts decreased autonomic function at 60-64 years in the British 1946 birth cohort study**

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Purpose: Decreased vagal function and increased sympathetic function, reflecting a disturbance in the autonomic nervous system, have been associated with increased CV mortality in both healthy adults and in those with prevailing CV disease. The mechanisms for these autonomic disturbances are less known, but humoral, central nervous factors, as well as afferent effects via baroreceptors which can influence blood pressure regulation might be implicated. In this study we set out to assess whether blood pressure change at a particular period during adult life may predict later autonomic dysfunction.

Methods: Data from 951 adults who underwent HRV measurements at 60-64 years from the MRC National Survey of Health and Development (NSHD), also known as the British 1946 birth cohort, were analysed.

Blood pressure was measured repeatedly during adulthood, at 36, 43, 53 and 60-64 years of age. Heart rate variability (HRV) was measured at 60-64 years by a 12-minute recording of resting ECG. For assessment of autonomic function, spectral analysis of R-R-intervals was used. The power spectrum analysis for low frequency (LF) and high frequency (HF) was normalized to total power, which allows a more reliable measurement of sympathetic and parasympathetic tone. HF power was used as a measure of cardiac parasympathetic modulation or vagal tone, and LF power was used as a measurement of sympathetic tone, or, possibly more accurately, baroreflex outflow. The LF/HF ratio was used to reflect the sympathetic/parasympathetic balance. The change in systolic blood pressure (SBP) between the consecutive time points was assessed, and a regression analysis of conditional change in SBP was performed.

Results: Greater increase in SBP between 36-43 years was associated with decreased HF power (vagal tone) (β = -0.11 (CI -0.22 to -0.01), p=0.037), increased LF power (sympathetic tone) (β = 0.12 (CI 0.02 to 0.22), p=0.028) and increased LF/HF power ratio (β = 0.01 (CI 0.001 to 0.01), p=0.036) at 60-64 years of age. Blood pressure change later in life and current SBP were not associated with these HRV measurements. The associations were not altered after adjusting for sex, BMI or measures of physical activity.

Conclusions: Blood pressure change in early midlife predicts autonomic dys-

function at 60-64 years, and is more closely associated with autonomic dysfunction than blood pressure change later in life, or even with current blood pressure. This stresses the importance of early prevention of blood pressure increase, and indicates that early middle-age SBP screening might be important for assessment of future CV risk.

ADVANCES IN CONGENITAL HEART DISEASE**P1346 | BENCH****3'UTR SNPs and haplotypes in GATA4 gene contribute to the genetic risk for congenital heart disease**

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Background: Single nucleotide polymorphisms (SNPs) in 3' untranslated region (3'UTR) of GATA4 gene may contribute to the pathogenesis of congenital heart disease (CHD) by altering miRNA gene regulation. We analyzed the association between SNPs and haplotypes in the 3'UTR region of the GATA4 gene and CHD risk.

Methods: SNPs located within the 3'UTR of GATA4 gene were analysed for putative miRNA-binding sites using bioinformatics algorithms, calculating the difference in Free Energy of hybridization (ΔFE, kcal/mol) for each wild-type versus variant allele. The sum of all |ΔFE| (|ΔFEtot|) was calculated in order to predict the biological importance of SNPs binding more miRNAs. The selected SNPs were genotyped in a case-control association study of 150 CHD patients and 250 healthy subjects. The haplotypes were evaluated by using SNPAnalyzer (<http://snp.istech21.com/snpalyzer/2.0/>) and SNPStats (<http://bioinfo.iconcologia.net/SNPstats>).

Results: Bioinformatics analysis indicated 4 SNPs (+1158 C>T, +1256 A>T, +1355 G>A, +1521 C>G) with a |ΔFEtot| = 9.91, 14.85, 11.03, 21.66 respectively. Two SNPs (+1158 C>T and 1521 C>G) were found to be significantly associated with CHD risk (p=0.011 and 0.009 respectively). Haplotype analysis showed that the more common haplotype CAGC (Figure) increased the risk of CHD (p=0.014). Conversely, the TTGC haplotype (more uncommon in CHDs) was associated with a significantly decreased risk of developing CHD (p=0.035, see Table). Computational analysis showed that the presence of +1158 T can potentially create a binding site for putative miR-3162-3p, while the presence of +1256 T can destroy the binding site for putative miR-365-5p.

Table. 3'UTR GATA4 haplotypes and association with CHD

Haplotype association with response (n=400, crude analysis)

	C	T	G	A	Ref	OR (95% CI)	p-value
1	C	A	G	C	1.000		
2	C	A	G	T	0.2226	0.86 (0.55 - 1.35)	0.23
3	C	T	G	C	0.1825	0.99 (0.66 - 1.48)	0.96
4	T	T	G	C	0.1166	0.69 (0.36 - 1.34)	0.019
5	C	A	A	G	0.0572	0.52 (0.25 - 1.09)	0.063
6	C	T	G	T	0.013	0.09 (0.01 - 0.97)	0.04
7	C	A	A	T	0.011	0.31 (0.03 - 2.23)	0.29
8	T	T	A	T	0.0002	0.08 (0.01 - 0.97)	0.04

Global haplotype association p-value: 0.0013

Conclusion: 3'UTR SNPs and haplotypes in GATA4 gene are new genetic factors for CHD, likely by altering miRNA gene regulation.

P1347 | BENCH**Persistent vascular remodeling related to development of arteriosclerosis or atherosclerosis in Kawasaki disease - Immunohistochemical study using an animal model**

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Background: Atherosclerotic coronary heart disease has recently emerged as a clinical issue among young individuals with a history of Kawasaki disease (KD), which is a systemic vasculitis unique to children. However, whether or not and how KD promotes arteriosclerosis remains unclear. We hypothesized that, analogous to the pathogenesis of arteriosclerosis or atherosclerosis, endothelial injury and the resultant intimal thickening are induced in coronary arteries after attenuation of vasculitis.

Methods: We used a rabbit model of KD developed by Onouchi and performed histopathological analysis of the coronary arteries at acute (1, 3, 5, and 7 days) and chronic (3 months) phases of the disease.

Results: In these rabbit models, a pan-arteritis with significant intimal cellular hypertrophy was histologically detected in the acute phase, and arterial intimal thickening was observed during the chronic phase. Immunohistochemical analysis of the coronary arteries revealed that the thickened intimal lesions observed during the chronic phase comprised abundant α-smooth muscle actin (α-SMA)-positive cells, most of which concomitantly expressed vascular cell adhesion molecule-1 and nuclear factor-κB. Although macrophages positive for RAM11 were barely detected, macrophage colony stimulating factor was strongly expressed in migrating smooth muscle cells in the intimal layer. In addition, the accumulation of proteoglycan as extracellular matrix was distinctly visible in the thickened intima,

indicating progressive accumulation of lipids and proliferation of smooth muscle cells within the lesion.

Conclusions: These findings suggest that, in KD-associated vasculitis, the migration of α -SMA-positive cells into the thickened intima might induce continuous vascular inflammation and remodelling, which might progress to coronary atherosclerosis or atherosclerosis.

P1348 | BEDSIDE

Constantly changing biological reactions and biomarkers during exercise in Fontan circulation

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Background: Haemodynamics after the Fontan procedure is very different compared with that in healthy individuals, but in many cases, the procedure poses no hindrance to daily lifestyle. Exercise tolerance after the Fontan procedure differs according to the type of the operative procedure, with total cavopulmonary connection (TCPC) resulting in a better exercise tolerance than atriopulmonary connection (APC). However, few detailed studies have examined how biological reactions change over the course of exercise.

Methods: The subject comprised 4 patients who had undergone the Fontan procedure (2 patients each for APC and TCPC) and 2 healthy volunteers. Subjects performed a 15-minute exercise test on an ergometer and were assessed at rest. Assessment items included heart rate (HR), blood pressure (BP), SpO₂, cardiac function [cardiac index (CI) and cardiac contractile force coefficient (ICON)] using a non-invasive cardiac output monitor and biomarkers (NT-proBNP, ANP and aldosterone).

Results: HR, BP, CI and ICON increased in all subjects during exercise, but the rate of increase was lowest in case of APC patients. ANP was increased through exercise in all subjects, and peak values were highest in APC patients. In addition, values returned to those at rest after 1 hour in all subjects except for APC patients, who showed no recovery (Fig. 1A). Aldosterone was increased after exercise in healthy controls and APC patients, but no change in TCPC patients (Fig. 1B).

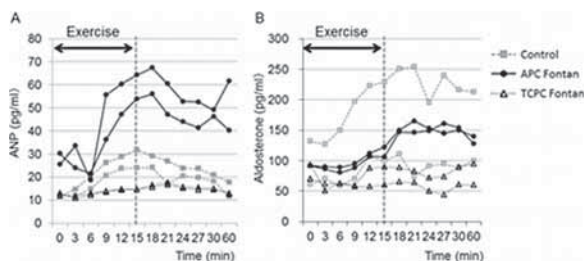


Figure 1. Changing biomarkers during exercise.

Conclusion: When changes in biological reaction and biomarkers were compared during exercise, patients who had undergone TCPC had better Fontan haemodynamics than APC patients and TCPC in particular showed temporal changes comparable with those of healthy individuals.

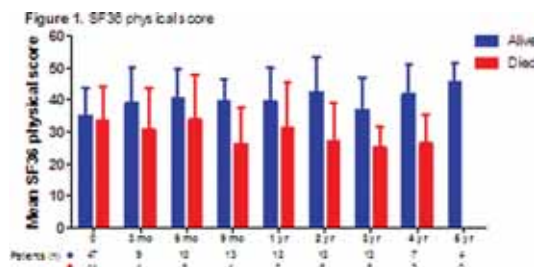
P1349 | BEDSIDE

Longitudinal changes in quality of life predict mortality in adult patients with pulmonary arterial hypertension due to congenital heart disease

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Purpose: Patients with pulmonary arterial hypertension due to congenital heart defects (PAH-CHD) have high morbidity and mortality rates, affecting their quality of life (QoL). Most studies on QoL lack longitudinal follow-up. This study aimed to assess quality of life over time and to determine its predictive value for mortality.

Methods: This prospective study on QoL was conducted since 2005 in a cohort of adult PAH-CHD patients, starting advanced therapy treatment. Short-form QoL health surveys (SF36) were recorded at baseline and at follow-up visits (median



4 years). We investigated the association between QoL, divided in a physical and mental score, and mortality using logistic regression. Change in QoL was calculated as the difference between first and last available SF36 score.

Results: In total 196 questionnaires were analyzed from 61 patients with PAH-CHD (mean age 43±13 years, 43% male, 34% Down syndrome). Fourteen patients died (23%). The mean standardized SF36 physical score was decreased (35 vs 50 in a standardized healthy US population), in contrast to the mean mental score (51 vs 50). Patients who died showed declining physical (-4.3) as well as mental scores (-5.8). In univariate regression decline in SF36 physical score was a determinant for mortality (OR 7.3; 95%CI 1.3-40.4, p=0.02).

Conclusion: Decline in longitudinal course of SF36 physical scores are predictive for mortality.

P1350 | BEDSIDE

Emergencies due to unrecognised aortic coarctation in adults

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Objective: Data on the extremely rare cohort (survivors in whom adulthood was emergently complicated due to unrecognised coarctation of the aorta (CoA)) are missing.

Methods: The study=retrospective, cross-sectional, descriptive. The cohort = all adults with the CoA who were (2000-2012) under the care in the university cardiovascular centre with the special view on emergencies in adults due to unrecognised (EAU) CoA. Data collection (database + interview) = 1. emergencies-type, age, resolution, repetition; 2. potential risks-residues, foreign metallic cardiovascular material; 3. others.

Results: The whole group (Fig. 1): 54 adults (35±15 (18-83) years; 60% men). In 26% (14/54 pts) the diagnosis of CoA was made in adulthood-importantly in 64% (9/14 pts) emergently (34±19 years). Description of this EAU CoA subgroup (9 pts): emergencies occurred once per 6±7 years sooner in men (25±8 years) when comparing women (46±23 years). Emergencies were: acute heart failure (33%; both genders), spinal complications (33%; men), aortic complications (11%; man), hypertensive crisis (22%; women). Except one woman refusing any interventions, other emergencies (8/9 pts) were resolved surgically. In this EAU CoAo subgroup the second emergencies were in 44% (4/9 pts; follow-up 20±16y ears): cardiac arrest, aortic dissection, acute heart failure). In the EAU CoA subgroup there were also in 33% (3/9 pts) non-surgically treated complications (endocarditis, systolic dysfunction) and 75% (3/4) of EAU CoA women became a mother-prior the diagnosis of CoA.

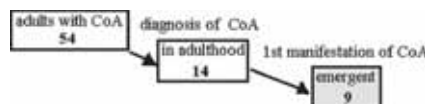


Figure 1

Conclusions: Except case reports and necropsies, this is the first cohort based study on emergencies in adults due to unrecognised CoA. Clinicians in the general cardiovascular centre for adults may see emergencies in adults due to unrecognised CoA once per 6 years.

P1351 | BEDSIDE

Prevalence of coronary artery anomalies in patients undergoing coronary artery angiography: a review of 16768 patients

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Objectives: In our study, prevalence of CAAs in coronary artery angiography (CAG) performed patient group is aimed to be detected by investigating images in our hospital which is a tertiary healthcare provider.

Background: Coronary artery anomalies (CAAs) existing as of birth and they are coincidentally detected most of the time.

Methods: Images of 16.768 CAG performed patients in our hospital were evaluated regarding CAAs.

Result: CAAs were detected in 120 cases (0.7%). Anomalies of origination and course was observed in 86 cases (70.1%). Absence of LMCA was spotted in 59 cases (49.9%) as the most frequent anomaly in subgroup analysis of these cases. Anomalous location of coronary ostium with normal coronary sinus was observed in 7 cases (5.8%). Anomalous location of coronary ostium outside normal coronary sinuses was determined in 20 cases (16.6%). In analysis of these 20 cases; arising Cx from right sinus of valsalva was observed in 8 cases (6.6%) as the most frequent abnormal exit anomaly. Arising Cx from RCA was seen in 6 events (5%), arising RCA from left sinus of valsalva was seen in 4 events (3.3%) and arising LMCA from right sinus of valsalva was seen in 2 events (1.6%) constituted other exit anomalies.

Conclusions: In our study, absence of LMCA was the most frequently encountered

Table 1. Prevalence data according to the basic classification in angiography and anomaly population

	Patients (n)	Prevalence of angiography population (n: 16,768)	Prevalence of anomaly population (n: 120)
Anomalies of origination and course	86	0.006%	71.6%
Anomalies of intrinsic coronary arterial anatomy	18	0.001%	15.0%
Anomalies of coronary termination	16	0.090%	13.3%
Anomalous anastomotic vessels	0	0.00%	0.0%

tered anomaly. Although CAAs are rare cases, they can cause difficulties in CAG interventions and surgical operations. In our study, frequencies of CAAs are presented in CAG performed patients.

P1352 | BEDSIDE

Adults with congenital heart disease have lower habitual physical activity level compared to healthy age and gender matched controls

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Background: Most adult patients with congenital heart disease have reduced aerobic exercise capacity. Their habitual physical activity level is however less studied. The aim of this study was to investigate habitual physical activity level in a cohort of adults with congenital heart disease (CHD) compared to healthy controls.

Material and methods: Eighty-three adults (34 women, mean age 37.0±15.0) with CHD, classed as either "complex" (n=42) or "simple" (n=41), and 41 age and gender matched healthy controls (16 women, mean age 37.0±15.1) were studied with a combined uniaxial accelerometer and heart rate monitor that was applied on the chest and worn during 5 consecutive days. They were encouraged to proceed with their usual activities. A validated algorithm based on individual age, gender, height and weight converted data into time spent in different metabolic equivalent (MET) levels during an average monitored day. Based on the national recommendations on physical activity of at least 150 min/week (0.36 hours/day) at moderate intensity (3-6 MET), this recommendation was considered as a cut off between low vs. moderate/high activity levels. Respiratory muscle function (maximum expiratory pressure, MEP, and maximum inspiratory pressure, MIP) as well as muscle function in shoulder- and calve muscles was tested. Health related quality of life (HRQoL) was evaluated using EQ-5D-3L questionnaire. The questionnaire data was indexed and dichotomized into EQ-5Dindex=1 (best possible HRQoL), and EQ5Dindex<1 (any degree of impaired HRQoL).

Results: Adults with complex CHD were less physically active at moderate intensity (3-6 MET) compared to healthy controls (0.57±0.59 vs. 0.99±0.68 MET hours, p=0.015). Fifty percent (n=21) of the patients with a complex lesion did not reach the national recommendations of physical activity, compared to 22% (n=9, p=0.024) in patients with simple lesions and 14.6% (n=6, p=0.003) in healthy controls. In a multivariate logistic regression model higher MEP (p<0.001; OR 1.04; 95%CI 1.02-1.06) and EQ-5Dindex=1 (p=0.001; OR 6.97; 95%CI 2.11-23.08) were independently associated with physical activity above the recommended level.

Conclusion: Many adults with complex CHD have low habitual physical activity level and are thereby exposed to an increased risk of acquired cardiovascular disease related to a sedentary lifestyle. Furthermore, low physical activity level was associated with lower HRQoL that generally is related to impaired health. Rehabilitation aiming to increase physical activity is indicated, especially for patients with complex CHD.

P1353 | BEDSIDE

Multicenter registration for fetal echocardiography in Japan

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Background: Nation wide multicenter registration for fetal echocardiography leading definitive diagnosis, not screening, was started in September 2004 in Japan. Japanese Society of Fetal Cardiology endorsed the registration and performs a key role for understanding and investigation of the current situations.

Subjects and method: Totally 15,923 on-line registrations for the definitive diagnosis using fetal echocardiography enrolled from 1 October 2004 to 25 December 2013. We investigated the ratio of the registrations in accordance with the annual changes of registrations, the number of registrations in each prefecture and classification of diseases.

Result: The number of registrations increased year by year. There were only 1,400 registrations until 2009, which increased to more than 2,000 registrations after the year. As for the classification of diseases, 7,233 cases were reported as a congenital heart defect, which accounted for 46%. For the rest, 37% showed normal conditions, and 7% caused an arrhythmia and some extracardiac abnormalities. The percentages remained almost unchanged throughout the years. By prefecture, there were 2,677, 2,384, 2001 and 1,561 registrations in Osaka,

Tokyo, Kyoto and Nagano, respectively. Less than 50 registrations, however, had been made for the 9 years in 18 prefectures. The congenital heart defect reports consisted of 1,271 cases of VSD (8%), 329 cases of SRV, 94 cases of SLV, 678 cases of DORV, 618 cases of HLHS, 618 cases of AVSD and 563 cases of TOF; thus, many of the abnormalities tended to be found on the four-chamber view. A minority of cases included 352 cases of dTGA (2.2%), 447 cases of CoA, 104 cases of IAA. In particular, only 33 cases of TAPVC were reported and those were 1% of all. Regarding the arrhythmia, there were 408 cases of PAC (2.6%), 130 cases of complete atrioventricular block, 102 cases of PVC, 68 cases of PSVT, 59 cases of Af&AF and 40 cases of VT.

Conclusion: Nowadays, the number of registrations tended to increase, and finally 15,000 registrations were achieved. Many of the diseases, which could be detected on the four chamber view easily by screening, were diagnosed definitely. It is essential that Japanese Society of Fetal Cardiology, as a key player, disseminates the registration through improvement of the gap between the regions.

P1354 | BEDSIDE

Echocardiographic screening for congenital heart disease in infants and preschool children: 12 years experience in a civic event for children care

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Background: Fetal echocardiography has been performed for the early prenatal diagnosis of major congenital heart disease (CHD) and cardiac screening for neonates and infants are usually performed by auscultation. However, CHD can be diagnosed in school age or adulthood sometimes in advanced stage. We had chance to perform echocardiography screening for infants and preschool children in a civic event for children care which our prefecture held once a year for their healthy life.

Methods: Subjects consisted of 8819 infants and preschool children (1 month to 6 year-old) underwent echocardiography in the public event from 2001 to 2013. Children with known CHD were excluded. The event opens 2 days in every year except 2010 for an epidemic of a severe acute respiratory syndrome.

Results: We performed echocardiographic screening on 735±144 children in each event. In totally 12 events, subjects consisted of 3175 0-year-old (36%), 2292 1-year-old (26%), 1058 2-year-old (12%), 794 3-year-old (9%), and others. In all subjects for 12 events, we could identify echocardiographic abnormality in 137 children (1.6%), which included 31 atrial septal defect, 21 patent ductus arteriosus, 8 ventricular septal defect and so on (Table). A serious case of Bland-White-Garland syndrome was detected and immediately send to hospital.

Prevalence of abnormality

Atrial septal defect	31	Coronary-PA fistula	2
Patent ductus arteriosus	21	Quadracuspid aortic valve	2
Ventricular septal defect	8	Atrioventricular septal defect	1
Pulmonary artery stenosis	8	LV-RA communication	1
Aortic bicuspid valve	5	Bland-White-Garland syndrome	1
Moderate mitral regurgitation	4	Supravalvular aortic stenosis	1
LV hypertrophy	4	Cor triatrium	1
mild aortic regurgitation	2	Dextrocardia	1

Conclusions: Cardiac abnormality, which could not be pointed out by prenatal echocardiography and neonatal auscultation, could be identified in substantial number of neonates and infants by echocardiographic screening. Echocardiographic screening in infants may be useful for early diagnosis of CHD in the country where its birthrate is declining.

P1355 | BEDSIDE

Impact of early initiation of intravenous prostanoid therapy in patients with congenital heart disease-related pulmonary arterial hypertension

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Purpose: Pulmonary vascular disease can complicate large intracardiac shunt lesions, precluding the possibility for surgical repair. Advanced oral therapy (AOT) is safe and effective in these patients. Intravenous therapy is less utilized due to fears of infection and paradoxical embolism; the impact of this choice is uncertain.

Methods: We compared outcomes of patients with congenital heart disease-related pulmonary arterial hypertension (CHD-PAH) initially treated with AOT (endothelin receptor antagonists and phosphodiesterase-5-inhibitors) to those initiated on intravenous prostanoids (IP). We identified 51 patients with CHD-PAH from a prospectively collected database of over 800 patients with PAH presenting between 1998-2010 to a tertiary referral center, including 21 ASDs, 25 VSDs, 2 AV canal defects and 3 PDAs. 32 patients received AOT and 19 patients IP.

Results: Patients on AOT and IP were of similar age (45±16 years), sex (75% women), race, body mass index and comorbidities. Baseline 6 minute walk distance (330±138 vs. 292±149 meters) and WHO function class were also similar (III or IV in 53% vs 52%), though mean pulmonary artery pressure (50±23 vs. 68±19 mmHg, p=0.006) and pulmonary vascular resistance (8.4±8.2 vs. 15.6±10.6, p=0.009) were higher in the IP patients. Use of additional therapies

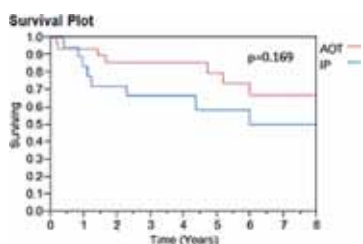


Figure 1. Mortality in CHD-PAH by initial therapy.

was similar in both groups, though warfarin use was expectedly higher in IP patients (47% vs. 84%, $p=0.008$). Neither group had paradoxical embolisms or life-threatening infections. Survival, however, did not appear to be favorably impacted by IP therapy (Fig. 1).

Conclusion: Early initiation of IV prostanoïd therapy in patients with CHD-PAH appears to be safe, but may not provide significant mortality benefit above what advanced oral therapy already provides.

P1356 | BEDSIDE

Mortality is predicted by small area of common chamber at birth in asplenia patients with total anomalous pulmonary venous connection

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Introduction: We know asplenia patients with total anomalous pulmonary venous connection (TAPVC) have worse prognosis if they have small common chamber. This study assessed whether mortality was estimated by preoperative area of common chamber (Pre-CC) for asplenia with TAPVC before 1st palliation.

Methods: The medical records of 14 asplenia with TAPVC were reviewed. They underwent high-resolution computed tomography (HRCT) before 1st palliation between 2004 and 2011. Pre-CC was calculated as ellipsoid between upper and lower pulmonary veins. The area under a receiving operating characteristics (ROC) curve was calculated to determine the best discriminating Pre-CC for predicting mortality. Each index was calculated for predicting mortality. Next, we examined whether 2nd PreCC before 1st palliation was associated with mortality.

Results: HRCT were performed at median 0 day. Pre-CC was between 3.6mm² and 23.6mm². Eight died eventually. Descriptive features at birth which were turned up by means of daily clinical practice, such as level of oxygen saturation, cardiothoracic ratio, and degree of pulmonary congestion, were not different between mortality group and non-mortality group. In addition, the ratio of mortality was not related to morphological and functional differences: TAPVC type; pulmonary artery morphology; degree of atrio-ventricular valve regurgitation; existence of ventricular dysfunction. Only small Pre-CC was associated with mortality (10.6mm² vs. 21.6mm², $p=0.014$). The area under ROC curves of Pre-CC for predicting mortality was 0.85 ($p=0.028$). ROC curve analysis confirmed 16.3mm² as the best diagnostic cut-off value. Sensitivity of small Pre-CC (≤ 16.3 mm²) for predicting mortality was 88%; specificity 83%; negative predictive value 83%; positive predictive value (PPV) 88%. Seven patients had 2nd HRCT before 1st operation. Three patients had Pre-CC under 16.3mm² at 1st time. Although two of them had Pre-CC over 16.3mm² at 2nd time, they all died. Four patients had PreCC over 16.3mm² at 1st time. Although two of them had Pre-CC under 16.3mm² at 2nd time, they all survived.

Conclusions: Our study showed there were no significant factors other than Pre-CC which predict mortality in asplenia patients with TAPVC before 1st palliation. PreCC at 2nd time did not reflect prognosis in asplenia. Small Pre-CC must be firmly attributed to obstructive lesions of pulmonary vascular bed in fatal life. Modification of obstructive lesion would be only temporal after birth. We might estimate mortality in asplenia patients with TAPVC by Pre-CC.

P1357 | BEDSIDE

Grown-up congenital heart disease intensive care admissions: an 8-year experience

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In response to reduced health funding due to the current economic crisis, in 2013 NHS England began to reorganise cardiac services in the London region to pool clinical expertise and reduce costs. This approach is likely to be rolled out throughout the remainder of the UK and abroad. As increasing numbers of congenital heart disease patients survive until adulthood, there will be an increase in hospital admissions with pressure on general intensive care units (ICU) to care for these patients with no onsite grown-up congenital heart disease (GUCH) team. To assess the ICU need of GUCH patients, we reviewed admissions to the ICU at our tertiary centre.

Coded data was used to identify patients with congenital heart disease who had been admitted to the intensive care from 2005 to 2013 who were under the care of the grown-up congenital heart disease team. The electronic database was then reviewed to identify age, sex, admission duration, reason for admission and complications.

513 ICU admissions were identified from 501 patients, 434 (85%) were following elective or emergency cardiac surgery and as such were not looked at further, these patients would continue to be operated on at a specialist centre. Of the remaining 79 (15%) admissions, 37 (7%) were admitted to the general ICU, 22 as an emergency, 11 following elective non-cardiac surgery and 4 were transferred from the cardiac ICU for prolonged respiratory weaning. 42 (8%) patients were admitted to the cardiac ICU, 26 as an emergency, and 16 following elective non-cardiac surgery. Mean age of the admissions was 37years, (standard deviation (SD) 14), 49% were female. Mean ICU stay was 7.9days (SD 13.7), mean hospital stay 25.8days (SD 30.5). The most common diagnoses were tetralogy of Fallot (13, 16%) and transposition of the great arteries (12, 15%), aortic stenosis, atrial septal defects, coarctation and pulmonary atresia accounted for 4 (5%) patients each. 14 (22%) patients died during their admission, 4 (6%) were transferred to further units for ongoing care and complications occurred in 39 (62%) patients. The most common were cardiac arrest (15, 19%), acute kidney injury (12, 15%) and pneumonia (8, 10%).

Despite the majority of GUCH patients being admitted to a cardiac ICU following elective cardiac surgery, a considerable portion of our GUCH patients would have required admission to a general ICU. These patients are intensive users of health facilities. Clinical leads will have to plan for this change in service provision as general ICUs may see a larger number of GUCH patients unless a dedicated referrals system exists for these patients.

ACUTE PULMONARY EMBOLISM AND BASIC SCIENCE IN PULMONARY ARTERIAL HYPERTENSION

P1359 | BEDSIDE

TIMI Risk Index calculated at hospital admission predicts both in hospital mortality and all cause mortality at follow-up in acute pulmonary embolism

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Introduction: TIMI Risk Index (TRI) is a friendly user prognostic assessment tool that is used to predict 30 day mortality in patients with STEMI and NSTEMI. It is based on simple clinical and demographic data: age, heart rate and systolic blood pressure. It is known that these three variables are also independent prognostic factors in other cardiovascular acute diseases like acute pulmonary embolism (APE). TRI has not yet been tested to assess prognosis in APE.

Objective: This study aims to assess the prognostic impact of TRI calculated at hospital admission on both in-hospital and after discharge prognosis in patients with APE.

Methods: Retrospective, observational study that included all patients with APE diagnosed during emergency room stay by MDCT between January 2010 and December 2011. The primary endpoint was all cause in-hospital mortality and the secondary endpoint was all cause death after discharge. A receiver operating characteristics (ROC) curve was used to test TRI as a predictor of the primary endpoint and to obtain the best cut-off value. Regression analysis were done to assess strength of prediction.

Results: Between January/2010 and December/2011, 436 patients (205 males, mean age 72 years) were diagnosed with APE. 46 (10.6%) patients died during hospital stay. Means of TRI were significantly different between patients that died during hospital stay (TRI mean 51.46, sd 23.00) and patients that survived (TRI mean 37.78, sd 17.45) ($p<0.001$). For the outcome of in-hospital mortality, area under the curve (AUC) was 0.683 ($p<0.01$), yielding moderate discriminative power. We considered the best cut off point to be a TRI of 34. A TRI greater than 34 was strongly associated with a worse in-hospital prognosis (unadjusted OR 6.64, 95% CI 2.30-19.18, $p<0.01$). Only TRI greater than 34 significantly contributed to the prediction model (TRI greater than 34 adjusted OR 18.572 (95% CI 2.457-140.400), $p=0.005$, troponin level adjusted OR 1.723 (95% CI 0.989-3.001), $p=0.055$). During follow-up, of 260 patients 50 died (11.5%). Means of TRI were also statistically different between patients that died during follow-up after discharge (TRI mean 43.58, sd 15.84) and patients that were still alive (TRI mean 36.24, sd 17.78), $p=0.012$. A value of TRI higher than 34 was found to be associated with a lower event free survival (hazard ratio 2.257 (95% CI 1.195-4.261) $p=0.012$).

Conclusion: TRI is a predictor of both in hospital mortality and all cause mortality at follow-up after APE.

P1360 | BEDSIDE

Local fibrinolysis, rotational thrombus fragmentation and thrombus aspiration in patients with massive pulmonary embolism

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Background: In patients with massive pulmonary embolism the treatment choices are systemic fibrinolysis and surgical embolectomy as both methods are proved to reverse right ventricular failure and cardiogenic shock. A feasible alternative of those treatments are percutaneous catheter techniques. In our institution

for the period December 2012 - August 2013, 14 patients with acute pulmonary embolism and hemodynamic instability were treated with local fibrinolysis, rotational thrombus fragmentation and thrombus aspiration.

Methods: All 14 patients were with PE and hemodynamic instability and echocardiographic evidence for RV dysfunction. The mean time from the beginning of symptoms was 3 ± 2 days. One patient died before the procedure and was excluded from analysis. The procedure in all patients was performed in the first 12 hours from hospitalization. We used right or left common femoral vein for access site with insertion of 8 Fr sheath. After insertion of 5 Fr Pigtail catheter a selective pulmonary angiography was made. Then consecutively in the right and left main branch a local administration of alteplase 25 mg was performed through the Pigtail catheter. With 0.035 inch guidewire through the pigtail a rotational thrombus fragmentation was performed. Then a precise selective angiography was made with a 8 Fr guiding catheter JR in all segmental branches of the pulmonary artery with diameter above 6 mm. A meticulous thrombus aspiration was then performed in all segmental branches that were involved through the same catheter.

Results: From the analyzed 13 patients 66.7% were male with a mean age of 57 years. The in-hospital survival was 92.7% as only one patients died due to lung infection. We also evaluated the 24 hours effect from the procedure. There was an increase in both O₂ saturation (92,18% vs 97,6%, $p=0.008$) and pO₂ (67,8 vs. 114,5 mm Hg, $p=0.002$). The right ventricular basal diameter decreased (49 mm vs. 38 mm, $p=0.009$) and the systolic function (tricuspid annular plane systolic excursion) was increased (13 mm vs. 18 mm $p=0.011$). The systolic (82 mmHg vs. 62 mmHg $p=0.03$) and mean (51 mmHg vs. 41 mmHg, $p=0.034$) PA pressure also decreased. At 8-12 months follow-up all patients were alive with sustained clinical and echocardiographic result with no residual pulmonary hypertension.

Conclusion: Our experience showed that the described manual technique is a feasible, effective and save method for treatment of high risk patients with pulmonary embolism. Our method permits decrease of overall used dose of lytic agent combined with effective mechanical removal of thrombus material.

P1361 | BEDSIDE

Atrial fibrillation prognostic score CHA2DS2-VASC may be used to assess prognosis after discharge in acute pulmonary embolism

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Introduction: A recent retrospective cohort study of patients with acute pulmonary embolism (APE) has showed that the atrial fibrillation score CHA2DS2-VASC was also a valid tool to assess long term prognosis in APE patients.

Objective: This study aims to assess the prognostic impact of CHA2DS2-VASC calculated at hospital admission on after discharge prognosis in patients with APE diagnosed by (MDCT) during emergency room stay.

Methods: Retrospective, observational study that included all patients with APE diagnosed during emergency room stay by MDCT between January 2010 and December 2011. The primary endpoint was all cause death after discharge. We used the non parametric test Mann-Whitney to compare the distribution of score between patients that died during follow up after discharge and patients that did not die. A receiver operating characteristics (ROC) curve was used to test CHA2DS2-VASC as a predictor of the primary endpoint and to obtain the best cut-off value. Then we transformed CHA2DS2-VASC into a categorical variable with 2 groups: patients with a CHA2DS2-VASC score equal or below 2 (group 1); patients with a CHA2DS2-VASC score equal or above 3 (group 2). Finally we test the strength of prediction with a Cox regression survival model.

Results: Between January 2010 and December 2011, 436 patients (205 males, mean age 72 years) were diagnosed with APE. 46 (10.6%) patients died during hospital stay. During follow-up, of 260 patients 50 died (11.5%). 190 patients had reliable data enabling the calculation of CHA2DS2-VASC score. Of these 60 died during hospital stay. Distributions of CHA2DS2-VASC score were statically different between patients who died at follow up and patients who did not die ($p=0.002$). Area under the curve (AUC) was 0,714 ($p=0.002$), yielding moderate discriminative power. We considered the best cut off point to be a CHA2DS2-VASC score of 3. 48 patients with a CHA2DS2-VASC score equal or below 2 (group 1) and 82 patients with a CHA2DS2-VASC score equal or above 3 (group 2) were followed up after discharge. Mortality at follow up was statically different between group 1 and group 2 (6,2% vs 20,7%, $p=0.042$). A value of CHA2DS2-VASC score equal or higher than 3 was found to be associated with a lower event free survival (HR 3,459 (95% CI 1,013 – 11,814) $p=0.048$).

Conclusion: A value of CHA2DS2-VASC score equal or higher than 3 is associated associated with a worse prognosis after discharge in APE.

P1362 | BEDSIDE

Acute pulmonary embolism complicating hospitalization for other reason has a dismal prognosis

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Introduction: Acute pulmonary embolism (APE) is a known complication of hospitalization. There is scarce literature concerning the prognosis of patients in which APE is a complication of other disease status that motivated hospital ad-

mission. We aimed to compare both 30-day mortality and mortality at follow-up between patients in which APE is a complication of hospitalization and patients in which APE is the single entity that motivated hospital admission.

Methods: Retrospective, observational study that included all patients with APE diagnosed by MDCT between January 2010 and December 2011. The primary endpoint was 30 day all-cause mortality and the secondary endpoint was all cause mortality at follow-up. APE patients were divided into two groups: 1) patients admitted to a hospital ward for a reason other than APE and that were diagnosed APE >72 h after admission; 2) patients admitted to a hospital ward because of APE diagnosed in emergency room stay or patients admitted to a hospital ward with no diagnosis in which APE was diagnosed <72 h after admission.

Results: 528 patients (247 males, mean age 72 years) were diagnosed with APE. Group 2 had 436 patients (82,3%) and group 1 only 65 (12,3%) patients. Group 1 patients had higher opacification or consolidation areas on pulmonary parenchyma (59,4% vs 43,6%, $p=0,022$). The localization of thrombi in pulmonary vasculature was also different between groups, with group 1 patients having less thrombi on pulmonary trunk and main pulmonary arteries (27,0% vs 41,7%, $p=0,028$). Group 1 patients had higher troponin I ($1,81\pm 6,05$ vs. $0,30\pm 1,00$, $p<0,001$), higher PCR ($9,94\pm 9,19$ vs $6,47\pm 6,80$, $p=0,023$), higher D-dimer ($24,47\pm 54,38$ vs $8,79\pm 11,82$, $p<0,001$) and lower hemoglobin ($11,67\pm 2,19$ vs $13,02\pm 1,95$, $p=0,001$). 30-day mortality was significantly different between group 1 and group 2 [46,7% vs. 14,9%, unadjusted OR=5,00 (95% CI: 2,30–10,90), $p<0,001$]. When we considered belonging to group 1 and troponin level together, they significantly predicted 30-day mortality ($\chi^2=23,624$, $df=2$, $n=246$, $p<0,001$). Both variables significantly contributed to the prediction model (belonging to group 1 adjusted OR=8,57 (95% CI: 2,65–27,72), $p<0,001$, troponin level adjusted OR 1,60 (95% CI: 1,06–2,42), $p=0,026$). During follow-up, all cause mortality was significantly higher for group 1 patients (hazard rate 4,02 (95% CI: 1,89–8,55, $p<0,001$).

Conclusion: Patients admitted to a hospital ward for a reason other than APE and that were diagnosed APE >72 h after admission have a dismal prognosis both on the first month after diagnosis and afterwards.

P1363 | BEDSIDE

Accuracy of ct-assessed rvd in predicting short term mortality in patients with acute PE: a systematic review and a meta-analysis of the literature

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Background: In patients with acute pulmonary embolism (PE), rapid and accurate risk assessment is crucial to predict the clinical course and to select the most appropriate treatment strategy.

Contrast-enhanced chest computed tomography (CT) is increasingly used as the first-line PE imaging test for diagnosis, having at the same time the ability to identify right ventricular dysfunction (RVD).

In recent years, several studies with limited number of patients and using various cut off for RVD have investigated the prognostic role of RVD assessed by CT in predicting short-term mortality, showing discordant results.

Methods: Studies evaluating the prognostic accuracy of the CT-assessed RVD as predictor of short term (<1 month) all-cause and of PE-related death, in both hemodynamically stable and unstable patients with acute PE, were systematically searched in the MEDLINE and EMBASE databases (up to November 2013). Search strategy was supplemented searching in the abstract book of International Society of Thrombosis and Haemostasis meetings (2003-2013). Weighted mean sensitivity (WMS) and specificity (WMSp) with 95% confidence intervals (CIs) were calculated using a bivariate random-effects regression approach.

Results: Twenty-four studies, for a total of 4817 patients, were included; 20 of the 24 studies used a cut off for Right ventricular/left ventricular ratio between >0.9 and >1.1. CT-assessed RVD had a WMS of 70.6% (95% CI 62.3, 77.8%) and WMSp of 52.6% (95% CI 44.8, 60.2%) in predicting short-term all-cause mortality. When we considered only normotensive patients (eleven studies for a total of 2767 patients) we had a WMS of 65.5% (95% CI 56.8, 73.5%) and a WMSp of 50.6% (95% CI 42.8, 58.3%) for this outcome. The seven studies (2771 patients) evaluating PE-related mortality resulted in a WMS of 91.2% (95% CI 78.1–96.8) and in WMSp of 39.9 (95%CI 33.7-46.5).

Conclusions: CT-assessed RVD appeared to have a limited role in predicting all-cause mortality in patients with acute PE. Conversely, this test had a good sensitivity in predicting PE-related mortality.

P1364 | BENCH

Phosphodiesterase-5 inhibition by vardenafil protects the right ventricle against ischemia

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Purpose: To investigate if phosphodiesterase-5 (PDE5) inhibition by vardenafil protects the right ventricle against ischemia.

Materials and methods: Hearts from male Wistar rats (n=39) were isolated and perfused in a pressure controlled modified Langendorff setup. The hearts

were randomised to control (CON), ischemic preconditioning (IPC, 2 x 5 min of global ischemia), or addition of the PDE5 inhibitor vardenafil (VAR, 66nM), the cGMP-dependent protein kinase (PKG) blocker KT 5823 (1uM) or vardenafil plus KT 5823. Drugs were added to the perfusion buffer five minutes prior to global ischemia. The interventions were followed by 40 min of global ischemia and 120 min of reperfusion in all groups. The effects of IPC on the right ventricle were evaluated by measurement of the infarct size/area-at-risk ratio (IS/AAR).

Results: Ischemic preconditioning reduced infarct size in the RV. A cardioprotective effect similar to ischemic preconditioning was seen for the PDE5 inhibitor vardenafil. The PKG blocker KT 5823 abolished the cardioprotective effect of vardenafil. KT 5823 alone did not have any effect on infarct size. (Fig.1).

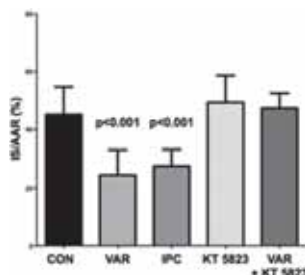


Figure 1. Infarct size/area at risk (IS/AAR).

Conclusion: PDE5 inhibition by vardenafil protects the right ventricle against ischemia. This effect is abolished by blockade of PKG suggesting that PKG is a key mediator of the cardioprotective effects of vardenafil in the right ventricle.

P1365 | BENCH

Echocardiographic prediction of pre- versus post-capillary pulmonary hypertension

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Background: The differential diagnosis between pre- and post-capillary pulmonary hypertension (PH) is of major therapeutic relevance, and thus requires an optimal clinical probability assessment with use of echocardiography.

Methods: We reviewed the medical records of 152 consecutive patients referred to a PH center over a 1-year period of time and who underwent quasi simultaneous (within 1 hr) echocardiography and right heart catheterization. Echocardiography was performed as usually recommended for the assessment of PH and left heart conditions. PH was defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. Post-capillary PH was diagnosed on the basis of a wedged PAP (PAWP) > 15 mmHg.

Results: Ten/152 patients (7%) had no PH, 81/152 (53%) had pre-capillary PH and 61/152 (40%) had post-capillary PH. The following echocardiographic variables predicted pre-capillary PH: right greater than left heart chambers surface area at end-diastole ($p=0.0018$), left ventricle eccentricity index ≥ 1.1 ($p=0.0039$), dilated inferior vena cava (IVC) with no inspiratory collapsibility ($p=0.0076$), E/e' ratio < 10 ($p=0.00001$), right ventricle forming the heart apex ($p=0.0144$). β coefficients from multiple logistic regression were significant for dilated IVC with no inspiratory collapsibility ($p=0.0464$) and E/e' < 10 ($p=0.0002$). A score based on β coefficients, ranging from 3 to 34 points gave an optimal discrimination at > 5 , with a positive predictive value of 68% and a negative predictive value of 78% for pre-capillary PH.

Conclusion: Echocardiography allows for a clinically satisfactory differential diagnosis between pre- and post-capillary PH.

P1366 | BENCH

Myocardial extracellular volume fraction quantified by cardiac magnetic resonance as an early marker of right ventricular dysfunction in chronic pulmonary hypertension

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Purpose: Early detection of right ventricular (RV) dysfunction in pulmonary hypertension (PH) is essential due to prognostic implications. Our aim was to assess the association between myocardial extracellular volume fraction (ECV) quantified by cardiac magnetic resonance (CMR) and hemodynamics and RV performance in chronic PH.

Methods: Experimental chronic PH was generated by pulmonary vein banding in 38 pigs whereas 6 pigs underwent sham operation. Right heart catheterization and immediate CMR were performed 2 months after the intervention. T1 mapping imaging (Modified Look-Locker Inversion-recovery [MOLLI]) was acquired before

contrast administration and after equilibrium in a short-axis view at the level of the papillary muscles. A region of interest was placed at the anterior and inferior RV insertion points to quantify ECV.

Results: Banded animals (mean PAP=38 $\pm$ 13 mmHg) showed higher ECV values at the anterior and inferior RV insertion points as compared to sham controls (35 $\pm$ 8 vs. 25 $\pm$ 5%, $p=0.016$ and 37 $\pm$ 7 vs. 25 $\pm$ 3%, $p<0.001$, respectively). ECV at the anterior and inferior RV insertion points significantly correlated with pulmonary hemodynamics, RV-arterial coupling, RV dimensions and ejection fraction (Fig. 1A, B). Eleven (30%) banded animals presented RV dysfunction whereas 27 (70%) still showed preserved RV function (RVEF $>50\%$). Animals with PH and preserved RVEF already showed significantly higher ECV at the RV insertion point as compared with sham controls (Fig. 1C).

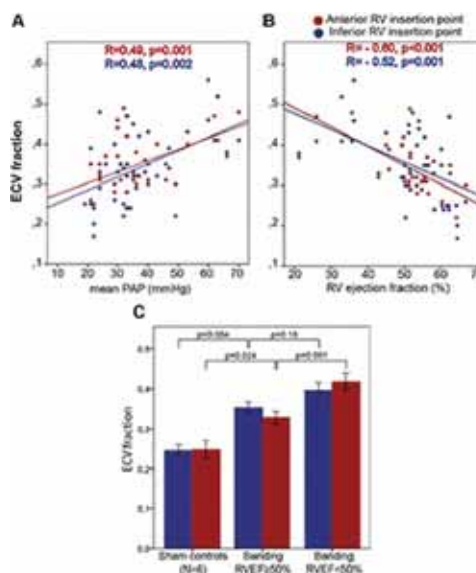


Figure 1. Association between ECV, mPAP and RVEF/

Conclusions: CMR-measured ECV at the RV insertion points increases in early phases of chronic PH and correlates with hemodynamic and RV performance in an experimental porcine model of chronic PH. ECV emerges as a potential parameter for early detection and monitoring of RV dysfunction.

P1367 | BENCH

Pulmonary vascular remodeling in the Fontan circulation

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Purpose: The Fontan circulation is a definitive palliation for patients with a univentricular heart in which systemic venous return flows directly into the pulmonary circulation without support of a subpulmonary ventricle. The Fontan circulation is characterized by a gradual attrition over time, that has been contributed to the un-physiologic pre- and afterload of the single ventricle, the chronically increased systemic venous pressures and recently, to chronic non-pulsatile flow in the pulmonary vascular bed. A gradual increase of the pulmonary vascular resistance could be a key factor in the long-term failure of the Fontan circulation, although its mechanism is insufficiently explained. We hypothesized that chronic non-pulsatile flow, present in the Fontan circulation, is associated with adverse pulmonary vascular remodeling in small pulmonary vessels.

Methods: Pulmonary vascular histomorphometric analysis and immunohistochemistry were performed in lung tissue obtained at autopsy from 12 Fontan patients and 24 age-matched controls. The Fontan patients were assigned to either an "acute" group A (death < 15 days after the Fontan operation; $n=5$) or a "chronic" group B (death > 5 years after the Fontan operation; $n=7$). Two age-matched control groups ($n=10$ and $n=14$ respectively) were included.

Results: The intima thickness ($p=0.002$) is significant increased and the media ($p=0.028$) is significant smaller in intra-acinar pulmonary vessels of the older Fontan patients ($n=7$) compared with age-matched controls ($n=14$). The age at death ($r=0.964$; $p<0.001$) and the duration of the Fontan circulation ($r=0.714$; $p=0.036$) are both significantly positive correlated with intima thickness in the older Fontan group ($n=7$). Immunohistochemistry showed media attenuation and severe intimal thickening of the intra-acinar pulmonary vessel wall, the composition of this intimal thickening is acellular fibrosis with collagen deposition.

Conclusion: This study shows significant adverse pulmonary vascular remodeling of the intra-acinar pulmonary vessels in the Fontan circulation associated with chronic non-pulsatile flow, consisting of involution of medial smooth muscle

cells and the presence of eccentric intimal fibrosis with collagen deposition. This pattern of pulmonary vascular remodeling is strikingly different from vascular remodeling known to occur in pulmonary arterial hypertension.

P1368 | BENCH

Apolipoprotein E deficiency is a novel risk factor for pulmonary arterial hypertension (PAH) independently of insulin resistance and dyslipidemia

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Apolipoprotein E (ApoE) is expressed in and secreted from human pulmonary artery smooth muscle cells (HPASMC), downregulated in lungs from PAH patients, and a transcriptional target downstream of bone morphogenetic protein receptor II (BMP-RII), i.e. the receptor that is dysfunctional in many forms of PAH.

Purpose: To determine whether normoxic ApoE $-/-$ mice – in the absence of high fat diet and IR – develop PAH, right ventricular hypertrophy and enhanced peripheral pulmonary artery (PA) muscularization with age.

Design and methods: Male ApoE $-/-$ mice and controls (n=4-8) were fed regular chow for 15 weeks or 1 year. A 1.4F catheter was inserted via the right jugular vein for assessment of right ventricular systolic pressure (RVSP). Systemic BP, LV fractional shortening and cardiac output (CO) were determined by tail-cuff method and echocardiography. For assessment of right (RVH) and left (LVH) ventricular hypertrophy, we calculated the mass ratios of RV to LV+septum (RV/LV+S), and LV+S/BW. Peripheral PA (PPA) muscularization was determined by PA morphometry at alveolar wall level and calculation of the ratio: partially and fully muscularized peripheral PA / total number of peripheral PA. Fasting blood glucose, plasma insulin and adiponectin were measured with a glucometer and RIA. We further investigated the growth-inhibitory effect of recombinant ApoE (10 μ g/ml) on PDGF-BB-induced HPASMC proliferation by cell count and MTT assay, and RV/LV ApoE mRNA expression by qPCR. Statistics: One-way ANOVA/Bonferroni posthoc test.

Results: 15-wk old ApoE $-/-$ mice did not differ from controls in terms of RVSP (23.2 vs. 20.6 mmHg), RV/LV+S (0.30 vs. 0.26), PPA muscularization (8.14 vs. 2.32%), CO and BP. However, when compared to age-matched controls, 1yr-old ApoE $-/-$ mice developed PAH (RVSP 29.5 vs. 22.8 mmHg), RVH (RV/LV+S 0.40 vs. 0.23) and increased PPA muscularization (30.9 vs. 11.3%, n=4-10; p<0.001) in the absence of IR, as indicated by similar glucose, insulin and adiponectin levels. One year old ApoE $-/-$ mice had lower plasma cholesterol and triglyceride levels than their younger counterparts. LV function, LV/BW, CO, BP and HCT were similar at 1 year of age. Preliminary qPCR analysis shows abundant ApoE mRNA expression in the murine RV and LV. Recombinant ApoE protein blocked PDGF-BB-induced proliferation of HPASMC.

Conclusions: ApoE deficiency in itself appears to be a novel risk factor for PAH independently of IR and dyslipidemia.

P1369 | BENCH

Specific targeting of activated platelets allows detection of pulmonary embolism with a single-chain antibody functionalized for MR imaging

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Introduction: Pulmonary embolism is a major source of morbidity and mortality worldwide. Currently used techniques for the detection of pulmonary embolism, as contrast enhanced computed tomography or nuclear imaging, still bear the challenge of persistent exposure to radiation. However, standard radiation-free magnetic resonance imaging (MRI) struggles to provide sensitive imaging information of the lung.

In this study, we investigate a molecular imaging approach using a functionalized single-chain antibody selectively targeting ligand induced binding sites of activated platelets (LIBS) to detect pulmonary thromboemboli using MRI.

Methods and results: Murine pulmonary embolism was induced by injecting 5% thrombin via a tail vein catheter. Immunohistochemistry confirmed the presence of large, platelet rich thromboemboli in pulmonary arteries of injected animals (thrombin 5%: 4.3 $\pm$ 0.3 emboli per pulmonary lobe vs. saline: 0.4 $\pm$ 0.2, p<0.01). After induction of pulmonary embolism, we then injected LIBS molecular probe functionalized with microparticles of iron oxide (LIBS-MPIO). LIBS target binding was first analyzed ex vivo by immunohistochemistry: LIBS-MPIO selectively bound to activated platelets on pulmonary thromboemboli (LIBS-MPIO: 9.8 $\pm$ 5.3 MPIO/ FOV vs. Control-MPIO: 0.45 $\pm$ 0.17 MPIO/ FOV, p<0.01) when compared to an unspecific control-antibody or saline injection. Moving towards in vivo molecular MRI, we performed repetitive T2* weighted MRI scans of the lung before and after thrombin injection. In areas with thromboemboli, we detected local parenchymal edema, most probably due to vessel obstruction. We thus exploited this increased signal intensity for the use of iron oxide particles for targeted imaging. Compared to pre-injection control, LIBS-MPIO induced a circumscribed signal void within the edematous area. Ex vivo, LIBS-MPIO labeled thromboemboli could be correlated histologically to the area of the signal void.

Conclusions: In this study, we demonstrate delivery and binding of a molecular MRI imaging probe targeting activated platelets in pulmonary thromboembolism. Interestingly, we were not only able to image activated platelets from the thrombus, but also an edema caused by this pathology. As a perspective, this murine molecular imaging approach could provide exciting new opportunities for increasing sensitivity of standard MRI for detection of pulmonary embolism with important implications for clinical translation.

P1370 | BENCH

Synchrotron radiation pulmonary micro-angiography to visualize pulmonary micro-vasculature in monocrotaline induced pulmonary arterial hypertension rats

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Purpose: Pulmonary arterial hypertension (PAH) is a progressive disease with increased vascular constriction and resistance. Visualization of the micro-vasculature would provide insights regarding the vascular remodeling due to PAH. Previously, we have established a method for synchrotron radiation pulmonary micro-angiography (SRPA) in an in-vivo rat model. High spatial resolution is achieved by Synchrotron radiation derived X-rays because of higher photon density. In this study, we aimed to visualize micro-vasculature in monocrotaline (MCT) induced PAH rats and validate SRPA reliability by comparing with echocardiographic data.

Method: MCT induced PAH were made by a single subcutaneous injection of 60 mg/kg MCT to 4 week-old SD rat. After 2 weeks, echocardiography was performed to evaluate the peak pulmonary blood flow (PBF) velocity and cardiac function. SRPA was performed at the Photon Factory of the High Energy Accelerator Research Organization.

Result: SRPA visualized decreased pulmonary micro-vasculature in PAH compared with the control (Fig. 1). The minimum identified pulmonary arteriole diameter was 100 μ m. The Peak PBF velocity measured by echocardiography was significantly decreased in PAH compared with the control (827.9 $\pm$ 80.3 vs 1237.6 $\pm$ 77.3mm/sec, p<0.01). The left ventricular ejection fraction was not different in PAH (81.2 $\pm$ 3.5 vs 73.7 $\pm$ 2.7%), but the left ventricular systolic diameter was significantly decreased in PAH (5.4 $\pm$ 0.3 vs 6.4 $\pm$ 0.2mm).

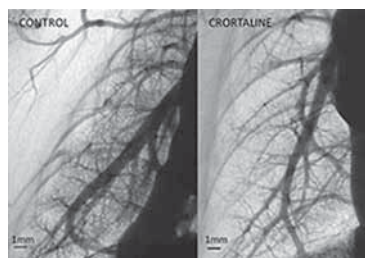


Figure 1

Conclusion: SRPA was useful to visualize micro-vasculature remodeling in PAH. Decreased pulmonary micro-vasculature in PAF was accompanied by decreased PBF velocity detected by echocardiography. This newly developed SRPA technology may help to investigate the mechanism of vascular remodeling associated with PAH.

VALVE DISEASE: MISCELLANEOUS

P1372 | BEDSIDE

Anatomy, function and family pattern of bicuspid aortic valve: what does the addition of aortic coarctation add?

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Background: Frequent coexistence of bicuspid aortic valve (BAV) and aortic coarctation (AoC) suggest a common underlying developmental defect. Familial aggregation in both conditions supports the existence of a genetic basis. Our aim was to compare familial aggregation, phenotypic concordance and the prevalence of valvular and aortic complications in individuals with BAV, with AoC and without AoC (BAVNC).

Methods: We studied 90 consecutive families of patients with an echocardiographic diagnosis of BAV (mean age: 45.9 $\pm$ 16.3 years; 72.2% males), of whom 23.3% had associated AoC. First-degree relatives (FDR) underwent a transthoracic echocardiogram for assessment of valve anatomy, function and degeneration, as well as aortic diameters at different levels (sinus of Valsalva-SV, ascending aorta-AA).

Results: BAV phenotype in probands was anteroposterior in 75.4%. AoC showed a tendency to have BAV without raphe in a higher proportion than BAVNC. Indexed diameters of AA, valve degeneration and the presence of aortic regurgitation were significantly more frequent in BAVNC, even after adjusting for age,

sex, body surface and valvular function. One BAVNC patient suffered an aortic dissection. No differences were observed regarding BAV prevalence or opening valve configuration in FDR. Global prevalence of BAV in FDR was 6.5%, higher than in the general population (0.5-1%). BAV phenotype was not constant among probands and FDR, with no differences observed for this discordance between groups (Table).

BAV with or without coarctation

	BAVNC	BAV + AoC	P
No. probands/No. of FDR	69/217	21/76	
- AP configuration n (%)	53 (75.4)	16 (76.2)	p=0.938
- SV $\geq 21\text{mm/m}^2$ n (%)	29 (42.0)	7 (33.3)	p=0.476
- AA $\geq 21\text{mm/m}^2$ n (%)	50 (72.5)	7 (33.3)	p=0.001
- Aortic dissection n (%)	1 (1.4)	0 (0.0)	p=1.000
BAV prevalence in FDR n (%)	14 (6.5)	5 (6.6)	p=1.000
Family prevalence of BAV n (%)	11 (15.9)	5 (23.8)	p=0.515
Phenotypic discordance in FDR (%)	54.5	40.0	p=0.361

Conclusion: The prevalence of BAV was similar in FDR of patients with and without AoC, although a high percentage of phenotypic discordance was found within the same family. The population with isolated BAV had higher rates of AA dilation, valve degeneration and aortic regurgitation compared to that with combined BAV and AoC.

P1373 | BENCH

The content of CD14++CD16+ monocytes and the extend of monocyte activation before TAVI is associated with death after

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Purpose: A systemic inflammatory syndrome (SIRS) often occurs after TAVI and is known to be a strong predictor of mortality. Mechanism for initiating SIRS after TAVI are not yet known. The proinflammatory CD14++CD16+ monocyte subset has been associated with cardiovascular events and death in patients with chronic kidney disease. As these monocytes with a CD14++CD16+ phenotype are known to be active producers of inflammatory cytokines, like $\text{TNF}\alpha$ we hypothesize that the level of these monocyte subset has an impact on the development of inflammatory reactions after TAVI. Further, we hypothesize that the content of CD14++CD16+ monocytes and the extend of activation of monocytes overall predict a worse outcome after TAVI.

Methods: 102 patients (mean age: 81.6 ± 5.4 years) with symptomatic severe aortic stenosis underwent TAVI with a transfemoral approach. In all patients Flow-cytometric quantification analyses of peripheral blood were done on the day before the procedure and on day 1 and day 7 after TAVI. The content of "proinflammatory" monocytes was detected by co-expression of the monocyte specific lipopolysaccharide receptor CD14 and the Fc γ III receptor CD 16. The extend of activation of monocytes was determined by quantification of the cell adhesion molecule MAC-1 (CD11b). Additionally, proinflammatory cytokines such as C-reactive protein (CRP) were measured at baseline and the days after TAVI.

Results: Initially, all patients received TAVI successfully. 3 months after TAVI 15 patients of all 102 patients died, predominantly without a dysfunction of the implanted aortic valve. No differences in EURO-Score, comorbidities like diabetes, obesity, hypertension and CAD were found between survivors and patients who died during follow up. A high content of CD14++CD16+ monocytes before TAVI (13.8% vs. 8.4%, $p < 0.001$) and on day one after TAVI (18.8% vs. 10.5%, $p = 0.01$) was independently associated with death at 3 months after TAVI. A high expression of CD11b before and after TAVI, which represent a high extend of activation of monocytes was also associated with death ($p = 0.03$). The expression of CD11b on all monocytes before TAVI and the absolute number of CD14++CD16+ monocytes before TAVI, but not of CD14++CD16- monocytes were associated with an increase of CRP ($p < 0.001$), in the first two days after TAVI.

Conclusions: The number of CD14++CD16+ monocytes and the extend of monocyte activation before TAVI is independently associated with death in the intermediate follow up period after TAVI. These cells may act as initiators of systemic inflammatory processes shortly after TAVI.

P1374 | BEDSIDE

Tricuspid regurgitation and clinical outcomes in patients with heart failure

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Background: Hemodynamically significant tricuspid regurgitation (TR) is common in patients with heart failure (HF) and has been reported to portend poor prognosis. However, it is still unknown whether TR is a surrogate marker of advanced myocardial and valvular heart disease or a mediator of disease progression.

Methods: We studied 542 patients admitted for HF. TR severity was assessed by echocardiography according to ESC guidelines. Congestion was assessed with a 10-point scale. The study endpoint was all cause mortality with a median follow-up of 2 years.

Results: Higher TR grade was associated with several clinically significant cardiac abnormalities including LVEF $< 45\%$, moderate or severe mitral regurgitation, RV dysfunction and pulmonary artery systolic pressure (PASP) > 50 mm Hg (All $P < 0.001$). The median PASP was 38, 47, 55 and 60 mm Hg in patients with none/trivial, mild, moderate and severe TR, respectively ($P < 0.001$). There was a graded increase in the number of signs of congestion with increasing TR severity ($P < 0.001$). In addition, higher TR grade was associated with higher BNP, worse renal function and abnormal liver function tests.

Kaplan-Meier analysis showed a graded increased probability of mortality during follow up with increasing TR severity (Fig. 1). However, in a multivariable Cox model adjusting for clinical and echocardiographic parameters, TR was not associated with increased mortality risk. Compared with patients with none/trivial TR, the adjusted hazard ratio for mortality was 1.04 (95% CI 0.71-1.52), 1.32 (95% CI 0.85-2.06) and 1.44 (95% CI 0.85-2.06) in patients with mild, moderate and severe TR, respectively.

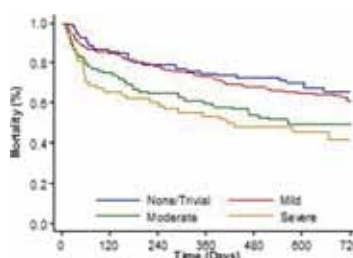


Figure 1. KM curves according to TR severity.

Conclusion: In patients with HF, the association between TR and mortality can be explained by associated co-morbidities.

P1375 | BEDSIDE

Clinical characteristics and actual managements of severe isolated tricuspid regurgitation associated with atrial fibrillation without structural heart diseases

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Objectives: Tricuspid regurgitation (TR) is commonly due to left-sided heart disease and/or pulmonary hypertension. However, patients with atrial fibrillation (AF) without structural heart diseases, that is to say "lone AF", sometimes show severe TR, especially among aged people. Although severe TR associated with lone AF is common in clinical settings, there are few reports about treatment and prognosis of this disease. The purpose of this study is to clarify the clinical characteristics and actual managements of patients with severe isolated TR associated with lone AF.

Methods: We retrospectively investigated 103648 consecutive transthoracic echocardiographic (TTE) examinations between 1999 and 2011 in our hospital, and examined the incidence and etiology of severe TR, and actual managements and prognosis of patients with severe isolated TR associated with lone AF.

Results: Among 103648 TTE examinations, 1955 examinations (1.9%), 850 patients, showed severe TR. Among these 850 patients, 183 patients (21.5%) (67 male, median age: 77 years) were diagnosed as severe isolated TR associated with lone AF. Among these 183 patients, no follow-up TTE was performed in 63 patients (34%), severe TR disappeared at follow-up TTE in 47 patients (26%), and severe TR was followed up for more than one year in 73 patients (40%). Among these 73 patients, survival rate at 10 years after development of severe TR was 80% and 29 patients (40%) were hospitalized due to right heart failure during follow-up. Most of hospitalizations occurred more than 5 years after development of severe TR, and 13 patients experienced multiple hospitalizations. Four patients died of right heart failure within 5 years after first admission and they had experienced multiple hospitalizations. Only two patients underwent isolated tricuspid valve surgery.

Conclusions: Severe isolated TR associated with lone AF is common among aged people, but has not been followed up systematically. Incidence of hospitalization due to right heart failure is high during a long term follow-up period and prognosis of patients with multiple hospitalizations was poor, however, tricuspid valve surgery has rarely been performed.

P1376 | SPOTLIGHT

The value of D-dimer in predicting prosthetic valve thrombosis in patient undergoing valve surgery

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Purpose: Nowadays, plasma D-dimer level has been considered to be a diagnostic marker for predicting cardiac thrombotic events appearance. The goal of this prospective study was to investigate the diagnostic value of plasma D-dimer levels in predicting prosthetic valve thrombosis (PVT).

Methods: The study group comprised 95 consecutive patients (59 women and 36 men; mean age, 44.39 ± 1.16 years) with prosthetic heart valves that were referred

to our echocardiography laboratory from after prosthetic valve surgery. D-dimer levels were determined by quantitative D-dimer, micro-latex immunoassay.

Results: Transesophageal echocardiography demonstrated the presence of a distinct mobile echo interpreted as a local thrombus on the atrial surface of the mitral prosthesis in 47 asymptomatic patients (32 patients with MVR, 21 patients with AVR, and 10 patients with AVR + MVR).

Analysis of variance also revealed a higher plasma D-dimer level in PVT group compared with non-PVT group ($1378.79 \pm 181.54 \mu\text{g/L}$ vs. $369.52 \pm 181.42 \mu\text{g/L}$, $p < 0.001$). Multiple linear regression analysis identified D-dimer levels as the significant independent factor for PVT formation (OR = 1.011, $P < 0.001$). According to the ROS curve analysis, plasma D-dimer level had a high value for discriminating PVT from non-PVT condition ($c = 0.951$, 95% CI = 0.901 – 0.999). A cutoff D-dimer value of 890 $\mu\text{g/L}$ was determined for discriminating between the patient with and without PVT, yielding a sensitivity of 80.9% and a specificity of 97.9%.

Conclusion: High plasma D-dimer levels were identified as a predictive marker of thromboembolic events in patients with prosthetic valves.

P1377 | BEDSIDE

Cardiac transplantation in patients with predominantly rheumatic valvular heart disease: experience of 28 years

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Purpose: Heart transplantation is a treatment option for patients with end-stage heart failure. International records indicate that only 2.6% of transplant patients have valvular heart disease. The indications in this subgroup of patients are limited, mainly due to the lack of large studies. The objective of this study was to evaluate the epidemiological and clinical profile of the patients with valvular heart disease undergoing heart transplantation.

Methods: In the period from 1985 to 2013, 569 heart transplants were performed at our institution and 20 (3.51%) had valvular heart disease as the initial disorder. We analyzed clinical profile, laboratory, echocardiographic and histopathological and related outcomes (mortality and rejection). The variables were analyzed using Student's t-test and Fisher's exact test.

Results: Mean age was 39.5 ± 15.2 years, 65% men, 90% with rheumatic etiology, 5% congenital and 5% bicuspid aortic valve. About 85% had undergone previous valve surgery, 45% had more than one surgery and 95% had normal functioning valve prosthesis at the time of transplantation. Atrial fibrillation was present in 35%, systemic arterial hypertension in 10%, diabetes in 5% and 45% had dyspnea NYHA functional class IV, while 40% were in functional class III. The indication for cardiac transplantation was refractory heart failure in dependence of inotropic and / or drugs for circulatory support in 35% and persistent class III / IV in 50%. The mean ejection fraction of left ventricle was $26.6 \pm 7.9\%$. The 1-year mortality was 20%. An important aspect was that, after histological examination of the receptors hearts, 27.7% of patients had reactivated rheumatic myocarditis (presence of Aschoff bodies) without prior diagnosis. Univariate analysis showed that age, sex, ejection fraction, rheumatic activity and rejection were not associated with mortality at 1 year.

Conclusion: In this cohort, rheumatic heart disease was the leading cause of heart transplantation and a significant portion of these patients had reactivated myocarditis, diagnosed in histological analyses. This indicates that before proposing surgical treatment modalities, as heart transplantation, is valid to investigate the existence of rheumatic activity, especially in valvular cardiomyopathy with severe systolic dysfunction.

P1378 | BEDSIDE

Imaging characteristics of prosthetic heart valves acquired with MDCT six weeks post implant: the IMPACT study

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Purpose: Multidetector-row computed tomography (MDCT) is a promising technique complementary to echocardiography to identify the morphological substrate of suspected prosthetic heart valve (PHV) dysfunction. We provide the first prospective study to establish normal postoperative MDCT reference images and image quality and the incidence of unexpected pathology.

Methods: Patients were included prospectively and 256-slice retrospectively ECG-gated contrast-enhanced MDCT was acquired six weeks after uncomplicated PHV implantation. Two observers assessed PHV abnormalities, leaflet motion and surrounding anatomy. Overall image quality was scored in best systolic and diastolic phases (1=non-diagnostic, 2=moderate, 3=good, 4=excellent).

Results: Forty-six patients were included with 33 mechanical and 16 biological PHVs. Mechanical PHV leaflet motion was symmetrical in all PHVs. Minor findings were moderate pericardial effusion (3/46 patients), periaortic/pericardial

hematoma (3/46 patients), slight PHV angulation (3/40 aortic PHVs) and fuzziness of periaortic fat (33/40 aortic PHVs). MDCT detected unexpected pathology in three patients. One showed pseudoaneurysms with severe PHV dehiscence requiring reoperation. Two cases required follow-up; one concerned aspecific sub-prosthetic tissue, the other a supraprosthetic pseudoaneurysm and unexpected coronary anomaly. Overall median (range) image quality for PHVs was 3.0 (2.5-4.0) Perimount; 2.5 (2.0-2.5) Mitroflow; 3.0 (2.0-4.0) St-Jude; 3.0 (2.0-4.0) Caromedics; 2.5 (2.5-3.0) Sorin; 3.0 (3.0-3.5) ON-X.

Conclusion: MDCT performed after PHV implantation showed symmetrical leaflet motion in mechanical PHVs and overall good image quality for both biological and mechanical PHVs. MDCT detected three cases of unexpected pathology requiring reoperation or follow-up.

P1379 | BEDSIDE

Evaluation of direct current cardioversion following percutaneous transmitral commissurotomy in rheumatic mitral stenosis patients with atrial fibrillation for maintaining long term sinus rhythm

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Purpose: In patients with rheumatic mitral stenosis (MS), atrial fibrillation (AF) is associated with unfavourable prognosis. High risk of thromboembolism renders restoration of sinus rhythm (SR) a preferred strategy over rate control. Percutaneous transvenous mitral commissurotomy (PTMC) is effective in improving hemodynamics, but may not be enough to restore SR.

Methods: Prospective randomized study aimed at evaluating efficacy of cardioversion for rhythm control in patients with long standing AF in rheumatic MS, after successful PTMC. Primary endpoint was maintenance of SR after 09 months. Secondary end points were functional capacity, embolic episodes, drug side effects and mortality.

Results: Thirty five patients were studied in 02 groups -Group 1 (n=20) only PTMC, Group 2 (n=15) PTMC + Direct Current cardioversion (DCC) + Amiodarone for 06 weeks. In group 2 all patients had successful cardioversion to SR. At the end of follow up (09-13 months), 95% in group 1 were in AF, while 5% reverted to SR spontaneously. In Group 02, 87% patients were in SR and 13% had reverted to AF. Difference in rate of SR was 0.82 (95% CI 0.2, 1.01) ($p=0.001$), with a relative risk of 7.1 (1.95, 25.9, 95% CI, $P=0.001$) for patients to be in AF who undergo only PTMC. There was significant improvement in quality of life (SF36) score in group 2 ($p=0.001-0.004$), with no deaths, stroke or adverse drug effects in either group.

Conclusion: In patients with rheumatic MS and AF, DCC following successful PTMC, may be a reasonable strategy to attain long term SR.

P1380 | BEDSIDE

Left atrial strain for prognosis prediction of patients with moderate mitral valve regurgitation

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Background: Left atrial (LA) function assessed by 2D Speckle Tracking Echocardiography (2D-STE), has been demonstrated to be a marker of early cardiovascular risk, empowering standard LA functional evaluation. The present study applied LA functional analysis to patients with moderate mitral regurgitation (MR) for prediction of adverse cardiovascular outcomes.

Methods: This prospective study included 247 patients (mean age 67 ± 10 years, 47% men) with moderate MR who referred to echocardiographic laboratory for a general medical consultation. This population was followed for development of atrial fibrillation (AF), hospitalization for heart failure (HF), stroke, transient ischemic attack and cardiovascular death. Left atrial assessment was based on parameters such as LA area, LA volume, LA diameter, LA ejection fraction. 2D-STE was used for LA functional analysis, measuring Global peak atrial longitudinal strain (PALS) by averaging all atrial segments.

Results: Of 247 subjects at baseline, 99 had 115 new events during a mean follow-up of 3.1 ± 1.5 years. All LA parameters, traditional parameters, and parameters derived by speckle tracking echocardiography were independently predictive of combined outcomes ($p < 0.0001$ for all comparisons). Overall performance for prediction of cardiovascular events was greatest for global PALS (area under receiver operator characteristic curve: global PALS 0.86, indexed LA volume 0.72, LA ejection fraction 0.65, LA area 0.60, LA diameter 0.57). A graded association between degree of LA dysfunction and risk of cardiovascular events was evident only for global PALS.

Conclusions: This study demonstrated a strong and independent association between global PALS and adverse cardiovascular events that appears to be superior to the other conventional parameters of LA analysis in patients with moderate MR, underlining the potential additional power of this technique to better stratify patients with mitral valve regurgitation.

P1381 | BEDSIDE**Left atrial appendage function after percutaneous mitral commissurotomy**

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Background: The left atrial appendage (LAA) is a common site of thrombus formation and is the source of systemic thromboembolism in patients with rheumatic mitral stenosis. LAA contractile dysfunction is a common finding in these patients. The aim of this study was to assess immediate and 6-month follow-up LAA function by transesophageal Doppler echocardiography in patients who underwent percutaneous mitral commissurotomy (PMC).

Methods: 56 consecutive patients with symptomatic critical mitral stenosis who underwent PMC were enrolled. All had underwent transthoracic and transesophageal echocardiography before, 24 hours after, and 6 months after PTMC. Pulse Doppler velocities of the LAA were measured, including peak early diastolic (E wave), peak late diastolic (A wave), and peak systolic (S wave). The corresponding tissue Doppler velocities of the LAA, including peak early diastolic (E(LAA)), peak late diastolic (A(LAA)), and peak systolic (S(LAA)), were also measured. LAA ejection fraction was measured using the modified Simpson's method.

Results: The mean age of the 56 enrolled patients was 36.4 ± 7 years. 45% were in sinus rhythm. PMC was successful in all patients. The pulse Doppler velocities of the LAA at baseline, after PMC, and at 6-month follow-up were as follows: for the E wave, 16.7 ± 3 , 16.05 ± 2.1 and 16.88 ± 2.35 cm/s, respectively ($P < 0.001$); for the A wave 25.25 ± 6.81 , 24.19 ± 3.61 , and 26.3 ± 5.51 cm/s, respectively ($P < 0.001$); and for the S wave, 27.32 ± 5.37 , 33.12 ± 6.41 , and 36.16 ± 6.99 cm/sec, respectively ($P < 0.001$). The corresponding tissue Doppler velocities of LAA were as follows: for E(LAA), 5.35 ± 0.71 , 5.88 ± 0.65 , and 6.20 ± 0.74 cm/s, respectively ($P < 0.001$); for A(LAA), 7.67 ± 1.72 , 7.87 ± 1.57 , and 8.78 ± 1.33 cm/s, respectively ($P < 0.001$); and for S(LAA), 4.77 ± 1.42 , 6.22 ± 1.23 , 7.02 ± 1.31 cm/sec, respectively ($P < 0.001$). There was a nonsignificant increase in LAA ejection fraction ($49.57 \pm 10.14\%$ vs $51.3 \pm 10.76\%$ vs $52.41 \pm 12.3\%$, respectively, $P = 0.052$). On patients in sinus rhythm a significant difference for LAA EF was observed ($48.57 \pm 10.14\%$ vs $53.2 \pm 11.3\%$ vs $54.11 \pm 11.2\%$, respectively, $P = 0.005$). Very good intraclass correlation of the LAA parameters was also observed with LV longitudinal function.

Conclusions: The present study shows contractile dysfunction of the LAA in patients with mitral stenosis, which significantly improved after PMC, and a further improvement was observed at 6-month follow-up. Favorable 6-month improvements in LAA parameters suggest

P1382 | BEDSIDE**Left ventricular vortex formation time index in mitral valve stenosis**

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Background: Left ventricular (LV) vortex formation time index (VFT) is a measure of intraventricular blood flow efficiency. We have previously demonstrated attenuation of VFT in LV dysfunction and LV outflow obstruction. We aim to study VFT in mitral valve stenosis (MS).

Methods: Echocardiography was performed in 20 healthy controls and 50 cases of different severity of rheumatic MS. Presence of atrial fibrillation, LV ejection fraction $< 50\%$ or presence of other valvular heart disease was excluded. Mitral valve leaflet separation (MLS) index was averaged from mitral leaflet separation diameter in diastole from parasternal long axis and apical 4-chamber views. VFT was quantitated as a dimensionless ratio of diastolic transmitral stroke distance (L) to MLS index (D). VFT was correlated to MS severity and left atrial (LA) volume and function derived using the biplane area length method.

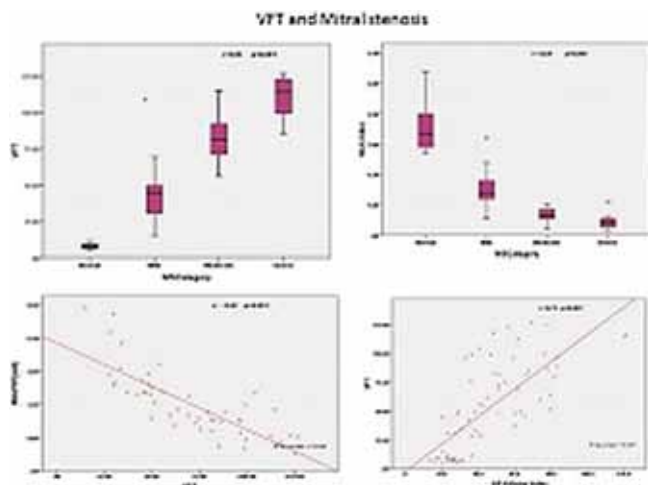


Figure 1

Results: In controls optimal VFT was found to be 7.8 ± 1.8 and was proportionately higher with increasing severity of mitral stenosis (Table 1).

VFT correlated strongly and negatively with mitral valve area ($r = -0.8$, $p < 0.001$) and total LA emptying fraction ($r = -0.73$, $p < 0.001$) and positively with LA volume index ($r = 0.73$, $p < 0.001$) (Fig. 1)

Conclusion: LV VFT was suboptimal with MS. It becomes more out-of-range with increasing severity of MS and correlate with increasing LA size and worsening emptying function. LA emptying function and degree of mitral valve opening appears to be determinants of LV flow propagation.

P1383 | BEDSIDE**Treatment preferences assessed with standard gamble in patients referred for aortic valve replacement**

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Introduction: Symptomatic aortic stenosis (AS) is a condition with increased mortality, morbidity and rapid worsening of patient's health. Aortic valve replacement (AVR) is the only curable treatment. AVR should only be performed in motivated patients. Patients referred for surgery are increasingly old and frail with little known about their preferences for surgery and evaluation of health. Standard gamble (SG) assesses preferences by identifying the highest risk for treatment mortality patients are willing to take. The perioperative risk and uncertainty relating to the procedure lends the SG relevance for evaluating preferences in this condition.

Methods: Cross-sectional study of 505 patients with severe AS referred for AVR. The SG was interviewer-administered, other assessments included clinical variables, echocardiography with assessment of aortic valve severity and myocardial function, EQ-5D, Short Form-36 (SF-36) and self-reported questionnaire of AS-related symptoms. Patient's preferences were postulated to be more highly associated with assessments of health and AS related symptoms than with objective measures of disease severity. Patients with poorer self-assessed health and symptoms were hypothesized to have lower SG scores and hence willing to take more operative risk.

Results: 439 completed the SG interview with mean (SD) age 75 (11) years, 44% women. Patients had a median SG score of 0.75 (interquartile range 0.50-0.95). SG scores were independent of sociodemographic variables, clinical variables, and hemodynamic valve parameters. In multiple logistic regression SF-36 mental health [OR 1.02 (1.00 - 1.03), $p = 0.02$], EQ-VAS [OR: 1.03 (1.02 - 1.05), $p < 0.001$], SF-36 health transition in last year [OR: 0.99 (0.98 - 1.00), $p = 0.05$] and number of AS-related symptoms during last week [OR: 1.40 (1.14 - 1.72), $p = 0.001$] were associated with SG score < 0.75 . The model accounted for 17 - 23% of the total variance (pseudo R square).

Conclusions: Preferences for operation in patients with severe AS are not associated with clinical or echocardiographic assessment of the AS but with patient's assessment of their health, change in health and AS-related symptoms. This highlights the importance of assessing patient preferences as a means of informing clinical decision making. However, only a small amount of variation in SG-score is accounted for, emphasizing the importance of actually measuring preferences in pre-operative assessment of patients with severe AS.

IMAGING IN VALVE DISEASE**P1385 | BEDSIDE****Impact of proximal versus distal left ventricular outflow tract measurements on stroke volume in normal subjects**

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Purpose: Left ventricle (LV) stroke volume (SV) assessment with Doppler echocardiography to characterize the "flow state" has gained importance during the last few years in valvular heart disease, particularly in aortic stenosis. Current ESC guidelines recommend measuring the LV outflow tract (LVOT) diameter 0.5-1 cm to the aortic valve (AV), whereas nowadays some authors suggest measuring at the level of the hinge points of the AV annulus. Previous studies from CT and RT3DE have demonstrated the frequent non-circular morphology of the LVOT with an underestimation of the LVOT cross sectional area when using the LVOT diameter. We aim to report the differences between both measurements and their impact on SV in normal subjects.

Methods: The NORRE study is a multi-centre study involving accredited echocardiography laboratories of the European Association of Cardiovascular Imaging (EACVI) studying echocardiographic parameters according to recommended approaches in a large cohort of healthy population ($n = 734$; 45.8 ± 13.3 years; 43.6% of male). LVOT diameter was measured at the level of the hinge points of the AV annulus (distal LVOT) and 0.5-1 cm from the AV (proximal LVOT). The LVOT velocity time integral was measured with the pulse Doppler sample volume just proximal to the AV. Stroke volume index (SVI) was reported after normalization by the body surface area. "Low flow" (LF) was defined as a SVI < 35 ml/m² according to current knowledge.

Results: Distal LVOT diameters were significantly larger than proximal LVOT di-

ameters (20.7 vs. 20.1 mm; $p < 0.001$). SVi was also higher in the group of distal LVOT diameter than in the proximal LVOT (41.6 vs. 39.4 ml/m²; $p < 0.001$). There was a strong correlation between both SVi ($r = 0.881$; $p < 0.001$), however when we classified the patients according to the flow, there was a higher proportion of LF patients in the proximal LVOT group (24.7 vs. 16.9%; $p < 0.001$), with discordances in the classification of 10% of the patients. No differences were found in the percentage of patients with LF according to age (older or younger than 50 years) in both measurements and nor according to gender in the distal LVOT group. Nonetheless, there was a higher proportion of LF in male patients in the proximal LVOT group (27.0 vs. 9.6%; $p = 0.044$).

Conclusions: Carefully evaluation of LVOT diameter is crucial in the evaluation of SV and AV area. Both methods of measurement provide significant differences in the LVOT diameters, with a larger distal LVOT diameter. These differences are translated into a higher SV and a different proportion of LF patients when using the distal LVOT diameter.

P1386 | BEDSIDE

Prognostic value of tricuspid annular dilatation assessed by three-dimensional transesophageal echocardiography

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Background: This study aimed to evaluate the relationship between tricuspid annular dilatation (TAD) and tricuspid regurgitation (TR), and the prognostic value of TAD using three-dimensional transesophageal echocardiography (3D TEE).

Methods: Tricuspid annular area (TAA) was measured in 116 patients using 3D TEE. Patients were classified into three groups (mild TR: $n = 77$, moderate TR: $n = 26$, severe TR: $n = 13$). Moreover, patients were classified into two groups based on rehospitalization for heart failure (HF); HF (+) group ($n = 18$) and HF (-) group ($n = 98$).

Results: TAA in the severe TR group was significantly larger than that in the mild and moderate TR groups (18.4 ± 3.8 cm² vs. 11.7 ± 3.2 cm², 12.3 ± 3.4 cm², $p < 0.05$). TAA in the HF (+) group was significantly larger than that in the HF (-) group (16.8 ± 4.3 cm² vs. 11.8 ± 3.3 cm², $p < 0.001$). In receiver operating characteristics curve assessing the ability of TAA to predict hospitalization for HF, the area under the curve was 0.84. $TAA \geq 15$ cm² best predicted hospitalization for HF with 77.8% sensitivity and 84.6% specificity. The incidence of hospitalization for HF during 3 years was significantly higher in the TAD (+) group ($TAA \geq 15$ cm²) than the TAD (-) group (48.3% vs 4.6%, $p < 0.001$, Figure).

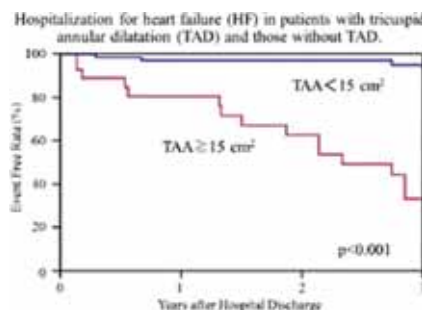


Figure 1

Conclusions: The results of this study suggested a possible association between TAD and the TR severity. TAD estimated using 3D TEE may predict hospitalization for prospective HF.

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Evaluation of the tricuspid annulus size: clinical implications from comparison between 2D-transsthoracic and 3D-transesophageal echocardiography

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Background: Tricuspid annuloplasty is recommended during left-heart valve surgery when tricuspid annulus (TA) is dilated, independently of the degree of tricuspid regurgitation, but the methodology to measure TA and thresholds are not clearly defined. We aimed to compare TA diameter (TAD) measurements performed using bi-dimensional transthoracic echocardiography (2D-TTE) in the 4 different views to three-dimensional measurements performed during transesophageal echocardiography (3D-TEE) and to define thresholds of TA enlargement for routine practice.

Methods: 2D-TTE measurement of the TAD was performed in parasternal long-axis view of the right ventricle inflow, parasternal short-axis, apical 4-chamber (A4C) and sub-costal views in 184 prospectively enrolled patients and 66 healthy volunteers. 3D dynamic volumetric data of the TA were also acquired by TEE

using a matrix array transducer (X7-2t, Philips) in the 184 patients. Multiplanar reconstructions were performed offline using dedicated software (QLab7, Philips) to measure the long-axis (LA) of the TA.

Results: In the 184 patients, TAD measurements were not different between the 4 TTE views ($P = 0.13$), but A4C was the most feasible and the most reproducible method (Table). TAD measurement in A4C view by TTE (3.90 ± 0.62 cm) was well correlated ($r = 0.84$, $p < 0.0001$) to LA by 3D-TEE (4.33 ± 0.63 cm), but with a systematic 4 mm underestimation. In the healthy volunteers, mean value of TAD in A4C was 3.2 ± 0.4 cm or 1.8 ± 0.23 cm/m² and the upper limit of 95% confidence interval was 4.2 cm or 2.3 cm/m².

Tricuspid annulus diameter by 2D-TTE

2D-TTE views	TA diameters measurements (cm)	Feasibility (%)	Reproducibility	
			Intra-observer (cm)	Inter-observer (cm)
Parasternal long-axis view of				
the right ventricle inflow	3.77 ± 0.53	76	0.03 ± 0.21	0.07 ± 0.25
Parasternal short-axis	3.80 ± 0.56	65	0.02 ± 0.22	0.11 ± 0.28
Apical 4-chamber	3.90 ± 0.62	92	0.04 ± 0.14	0.05 ± 0.22
Sub-costal	3.86 ± 0.61	73	0.06 ± 0.25	0.12 ± 0.31

Conclusion: TAD measurement in A4C view by 2D-TTE was highly feasible, reproducible and accurately reflected TA size, even if it was systematically underestimating its maximal diameter. Based on measurements in healthy volunteers, we suggest to consider tricuspid annuloplasty during left-heart valve surgery when TA is more than 2.3 cm/m² or 4.2 cm in A4C.

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Leaflet adaptation as a determinant of tricuspid regurgitation severity in patients with pulmonary hypertension

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Purpose: Tricuspid regurgitation (TR) is a risk factor for mortality and morbidity in pulmonary hypertension (PH). TR severity varies among patients with comparable degrees of PH and right ventricular (RV) remodeling. The contribution of tricuspid leaflet adaptation to the pathophysiology of functional TR has yet to be examined. We hypothesized that tricuspid leaflet growth occurs in PH, and that its adequacy relative to RV remodeling is a determinant of TR severity.

Methods: A prospective cohort of 255 patients with PH from pre- and post-capillary etiologies was assembled at two hospitals. Those with pacemakers or organic TR were excluded. Patients underwent a 3-D echocardiogram focused on the tricuspid apparatus. TR severity was quantified by the vena contracta. Tricuspid leaflet area was traced by blinded readers using the Omni 4D custom software package. Tricuspid closure area, a measure of annular area and tethering, was similarly traced. The ratio of leaflet area to closure area was calculated, reflecting the adaptation (i.e. growth) of the valve leaflets to occlude the closure area and thus maintain valvular competency. Regression and ROC analyses were employed to test the effect of leaflet-to-closure area on TR severity.

Results: Functional TR was mild in 116 (45.5%), moderate in 86 (33.7%), and severe in 53 (20.8%). PH patients had a twofold increase in RV volumes, 70% increase in annular area, and 47% increase in leaflet area compared with normal controls. Those with severe TR had an inadequate increase in leaflet area relative to closure area, such that the ratio of leaflet-to-closure area < 1.8 was highly predictive of severe TR (odds ratio 68.7; 95% CI 16.2, 292.7). Leaflet area and closure area demonstrated additive effects in predicting TR severity: the median vena contracta was 8.5 mm in the group with small leaflet area and large closure area ($N = 48$), 4.8 mm in the group with small leaflet area and large closure area ($N = 85$), 3.3 mm in the group with small leaflet area and small closure area ($N = 76$), and 3.0 mm in the group with large leaflet area and small closure area ($N = 46$).

Conclusions: Leaflet adaptation plays a significant role in defining which PH patients are affected by severe functional TR. The ratio of leaflet-to-closure area is a powerful indicator of TR severity that reflects the adequacy of leaflet adaptation relative to RV remodeling. The therapeutic impact of these findings may be to guide surgical repair of functional TR by identifying which patients stand to benefit from a tricuspid leaflet augmentation procedure.

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Accuracy of two- and three-dimensional echocardiography to diagnose congenitally bicuspid aortic valves: a surgical pathology validation study

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Background: Bicuspid aortic valve (BAV) is the most common congenital heart valve abnormality, which often leads to severe aortic stenosis (AS) or insufficiency (AR) and ascending aorta dilatation. Preoperative recognition of BAV, commonly by echocardiography, is crucial to properly select and plan therapeutic proce-

dures. However, the relative accuracy of two (2DTEE) and three-dimensional (3DTEE) transesophageal echocardiography in diagnosing BAV remains to be clarified.

Methods: Single center, prospective study. From January to May 2013, 40 consecutive patients (67 years, range 19–82 years; 53% males) had aortic valve surgery at our Institution: 18 (45%) AS; 8 (20%) pure AR; and 14 (35%) combined AS and AR. All patients underwent 2DTEE and 3DTEE in the operating room to assess aortic valve morphology before surgery. All echocardiograms were reviewed blindly by the same investigator, and the aortic valve morphology was categorized as bicuspid, tricuspid, or indeterminate. Echo findings were compared with surgical pathology analysis (gold standard) (Table). Sensitivity, specificity, negative (NPV) and positive (PPV) predictive value of 2DTEE and 3DTEE were calculated.

Results: Compared with surgical pathology analysis, 3DTEE (Sens=100%; Spec=96%; NPV=100%; PPV=93%) was significantly more accurate than 2DTEE (Sens=36%; Spec=100%; NPV=75%; PPV=100%) in the overall study population (Table). In the subgroup of 8 patients with isolated AR, 3DTEE and 2DTEE showed similar accuracy (Sens 100%, Spec 98%, NPV= 100%, PPV= 96%).

Table 1. Diagnostic accuracy of 2DTEE and 3DTEE versus surgical pathology analysis

	Surgical pathology analysis (n=40)	
	BAV+ (n=14)	BAV- (n=26)
3DTEE+	14	1
3DTEE-	0	25
2DTEE+	5	0
2DTEE-	9	26

Conclusions: When compared with gold standard pathological anatomy, 3DTEE proved to be a highly accurate imaging technique for the diagnosis of BAV. In pts with AS, the possibility to visualize the valve from the aortic perspective by 3DTEE adds significant diagnostic value in comparison with standard 2DTEE.

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Three-dimensional changes of the mitral annulus geometry and dynamics in patients with functional mitral regurgitation: insights for mitral valve repair

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Background: Current three-dimensional transthoracic echo (3DTEE) allows quantitative assessment of mitral annulus (MA) geometry and function comparable with transesophageal approach.

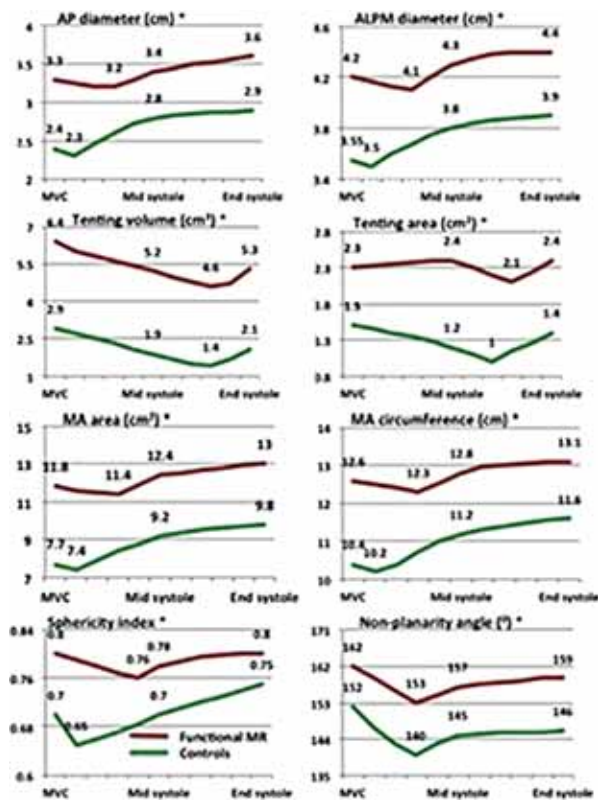


Figure 1. MA parameters in dynamic in FMR vs C.

Objectives: To provide better insights into the pathophysiology of functional mitral regurgitation (FMR) using 3DTEE.

Methods: 56 pts with mild to severe FMR due to ischemic cardiomyopathy (58±17 yrs, 42 men) and 52 age- and gender-matched controls (C) underwent 3D full-volume acquisition of the mitral valve (MV). MA geometry was analyzed using prototype software package (MV assessment 2.3, TomTec, D). MA parameters were recorded at 4 reference frames: mitral valve closure (MVC), mid- and end-systole, and the frame of minimum value. Time from MVC to minimum value was recorded as % of systole duration.

Results: FMR pts presented larger antero-posterior (AP) and anterolateral-posteromedial (ALPM) diameters, MA area (MAA) and circumference (MAC) at every reference frame (*p<0.001) (Figure). FMR pts also showed higher MA sphericity index (SI), MV tenting volume and area at every reference frame (*p<0.001). MA was flatter over the entire systole in FMR than in C (*p<0.001). In addition, FMR presented longer time to maximum MA contraction, to minimum AP (26±24% vs 11±9%) and ALPM diameters (26±24% vs 13±8%), to minimum MAA (20±16% vs 11±6%) and MAC (21±17 vs 11±6%), and to minimum SI (41±28% vs 20±18%) (all p<0.001).

MAA fractional change (15±5% vs 28±5%) and MA displacement (5±3 vs 10±2 mm) were lower in FMR than in C (p<0.001).

Conclusion: Quantitative analysis revealed altered MA geometry and dynamics in pts with FMR. Reduced and delayed MA conformational changes might explain the early occurrence of regurgitation in FMR. Our findings may be useful for planning future procedures for MV repair.

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Incremental utility of live real time three dimensional transthoracic echocardiography in the assessment of morphological abnormalities of the mitral valve in rheumatic heart disease

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Purpose: Live real time three dimensional (RT 3D) transthoracic echocardiography (TTE) was employed to objectively assess the morphological abnormalities of mitral valve associated with rheumatic heart disease (RHD) with a view to assess the limitations of two dimensional (2D) TTE, if any, in visualizing these abnormalities.

Methods: The patient group comprised of 31 adult cases of clinically diagnosed RHD and the echocardiographic studies were performed using Philips I E33 ultrasound system (Andover USA) by a single, experienced cardiologist. The diagnosis of definite RHD was made on the basis of the World Heart Federation criteria [1].

Results: Definite RHD with mitral valve involvement was confirmed by 2D TTE for all the cases. Analysis of the morphological abnormalities of the mitral valve by RT 3D TTE yielded additional following details:

- Cases of pure mitral regurgitation (MR) had greater irregularity of leaflet thickening whereas cases of mitral stenosis (MS) with or without MR had more uniformly thickened valves.
- Prolapse of the middle scallop of anterior mitral leaflet (AML) was visualized in most (25 of 31) cases; additionally prolapse of lateral scallop of AML was seen in 1 case and flail AML with, improper co-aptation of the middle scallop was visualized in 1 case.
- Diastolic doming of the middle scallop of AML into LV was visualized for a minority of cases of pure MR (2 out of 8) whereas it was visualized for almost all the cases of MS (21 of 23).
- Leaflet redundancy and chordal lengthening was not visualized for any case.
- Chordal thickening and shortening was not detected for any case of pure MR but it was visualized for all the cases of MS.

Conclusions: The irregular thickening of mitral leaflets potentially contributes to severity of MR. Uniform thickening found associated with MS is less often co-existent with MR. Prolapse of the AML is the most consistent and pathognomic morphological abnormality of RHD which can be readily differentiated by RT 3D TTE from myxomatous degeneration. This can be detected by 2D TTE and thus be included in diagnostic criteria. Irregular leaflet thickening can be easily missed by 2D TTE, especially in cases of pure MR which perhaps represent early stages of disease. Therefore, exclusion of AML prolapse and inclusion of leaflet thickening potentially compromises the specificity and sensitivity of the WHF criteria [1].

Reference:

1. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline; Nat. Rev. Cardiol. 2012;9:297–309.

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Prevalence of valvular strands during routine echocardiographic examinations

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Purpose: Valvular strands [Lambli's excrescences], have been associated with

increased embolic risk. In previous studies valvular strands have been detected by trans-esophageal echo. The current high resolution echocardiographic systems allow detection of valvular strands [Lambli's excrescences] often even by transthoracic echocardiography.

We sought to assess incidence of valvular strands [Lambli's excrescences] during routine trans-thoracic and/or trans-esophageal echocardiography and define their relation to the cardiovascular risk factors, co-morbidities and outcome.

Methods: Over 21000 echocardiographic examinations were performed at our hospital during 2008-2012 and were searched for reporting of valvular strands [Lambli's excrescences]. 150 such studies were identified and the presence of valvular strands [Lambli's excrescences] was confirmed. Clinical characteristics of these patients, co-morbidities and outcome were analyzed and compared with the same parameters of 150 age and gender matched individuals without valvular strands.

Results: Incidence of valvular strands was maximal at age 61-70 [0.94%], occurred more common in men than in women, 92 versus 58, $p < 0.00001$. Valvular strands were more common on aortic than on mitral valve 125 versus 36 respectively, $p < 0.00001$, were more often associated with thickened or calcified valve, and predominantly occupied ventricular portion of aortic valve and atrial portion of the mitral valve, $p < 0.00001$. Valvular strands were not associated with mortality, but were more frequent in patients with an embolic event 40 versus 20, $p < 0.005$.

Conclusions: Valvular strands [Lambli's excrescences] appear not to affect life expectancy, but are associated with embolic/cerebro-vascular risk, are more common in older patients, in men than in women, and are more commonly located on the aortic than on mitral valve.

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Cardiovascular outcome predictors in systemic sclerosis

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Background: Cardiovascular (CV) involvement is recognized as a poor prognostic factor in systemic sclerosis (SSc). The aim of this study was to evaluate the usefulness of nailfold video-capillaroscopy (NVC), brain natriuretic peptide (BNP) blood level and exercise echocardiography to predict the occurrence of CV events in SSc.

Methods: We prospectively enrolled 65 patients with SSc (age 54 ± 14 years, 30% female). All patients underwent a graded semi-supine exercise echocardiography. Both baseline resting pulmonary hypertension (PH) and PH during follow-up (FUPH) were defined as systolic pulmonary arterial pressure (sPAP) > 35 mmHg, and exercise-induced PH (EIPH) as sPAP > 50 mmHg during exercise.

Results: EIPH was present in 21 patients. During FU (27 ± 18 months), 13 patients developed FUPH and 9 presented CV complications (2 transient ischemic cerebro-vascular events without significant carotid stenosis, 2 symptomatic resting PH confirmed by right heart catheterization, 1 paroxysmal atrial fibrillation associated with heart failure and 4 severe peripheral vascular ischemic events leading to amputations without arterial stenosis including on death). Patients with CV events were significantly older (63 ± 14 vs. 52 ± 13 years; $p = 0.03$), presented more frequently with NVC grade > 2 (89 vs. 43%; $p = 0.009$), had higher resting and exercise sPAP (respectively: 30 ± 6 vs. 24 ± 6 ; $p = 0.007$ and 57 ± 13 vs. 44 ± 13 vs. mmHg; $p = 0.01$), and higher BNP blood level (112 ± 106 vs. 26 ± 19 pg/ml; $p = 0.0001$). After adjustment for age and gender, NVC grade > 2 ($\beta = 2.4 \pm 1.1$; $p = 0.03$), exercise sPAP ($\beta = 0.08 \pm 0.04$; $p = 0.02$), EIPH ($\beta = 2.30 \pm 1.13$; $p = 0.04$), exercise LAP ($\beta = 0.93 \pm 0.45$; $p = 0.04$), maximal resting sPAP during FU, FUPH (respectively; $\beta = 0.24 \pm 0.09$; $p = 0.01$ and $\beta = 3.52 \pm 1.16$; $p = 0.002$) and BNP ($\beta = 0.08 \pm 0.04$; $p = 0.02$) were independent predictor factors of CV events.

Conclusion: Almost one of 5 patients with SSc presented CV events during follow-up. NVC, BNP level assessment and exercise echocardiography could be useful tool to identify such SSc patients at higher risk.

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Gender differences in hypertrophic response to aortic stenosis

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Purpose: Hypertrophic response to pressure overload is gender-specific. Our aim was to evaluate gender differences in left ventricular (LV) remodeling, myocardial fibrosis and biomarkers of extracellular matrix (ECM) remodeling in isolated severe aortic stenosis (AS).

Methods: We analyzed clinical and echocardiographic parameters, at baseline and 6 months after valve replacement (AVR), in a prospective cohort of 132 severe AS patients, 77 females (58.3%). A subgroup analysis of myocardial fibrosis and baseline ECM biomarkers procollagen type I carboxy-terminal peptide (PIP), metalloproteinase (MMP) 1 and 9, and tissue inhibitor of MMP (TIMP) 1 and 2 was performed.

Results: Women had smaller LV diameters, volumes and LV mass (LVM), but these differences disappeared after indexation. When comparing the %observed

LVM/predicted LVM, women had more inappropriate LVM increase than men ($160.93 \pm 53.37\%$ vs $140.25 \pm 37.35\%$, $p = 0.031$). Six months after AVR, LVM regression was similar between genders but women had more residual hypertrophy (68.8% vs 39.6% , $p = 0.002$). Baseline %observed LVM/predicted LVM inversely correlated with 6 months LVM regression ($r = -0.330$, $p = 0.001$), and a cut-off of $> 142\%$ had a 72.5% sensibility and 68.6% specificity for predicting residual LVH at 6 months (AUC 0.732, $p > 0.001$). Baseline PIP levels tended to be higher in women (775.7 ± 250.2 vs 649.1 ± 94.1 ng/ml, $p = 0.067$) and TIMP1/MMP1 levels positively correlated with baseline LVM index ($r = 0.681$, $p = 0.003$) only in women. Moreover, women had significantly more fibrosis than men (median of 15.39% (P25-75:7.95-29.09) vs 10.04% (P25-75:6.00-14.96)). In women higher TIMP2 and TIMP1/MMP1 levels correlated with lesser 6 month LVM regression (TIMP2: $r = -0.650$, $p = 0.022$; TIMP1/MMP1: $r = -0.748$, $p = 0.005$).

Conclusions: In AS women develop more inappropriate LVM than men and have more residual hypertrophy after surgery. A gender-specific ECM remodeling, with more interstitial fibrosis in women, could explain these differences.

TAVI: REGISTRIES AND OUTCOMES

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Transaortic transcatheter aortic valve implantation - experience from the first multicenter, multinational prospective registry (ROUTE)

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Objective: Transaortic transcatheter aortic valve implantation (TAO-TAVI) is an alternative access route for patients with significant respiratory disease, poor left ventricular function, chest wall deformities and after multiple redo surgeries. ROUTE is the first multicenter, multinational prospective registry to document the course and outcomes of patients undergoing this new procedure.

Methods: ROUTE commenced in February 2013 and aims to document TAO-TAVI at up to 25 sites across Europe with about 200 patients included. The principal research objective is to determine overall mortality rates within 30 days after TAVI. Secondary objectives relate to TAVI related mortality, VARC complications and to identify predictors of adverse outcomes.

Results: As of February 2014 a total of 83 patients undergoing TAO-TAVI had been included; 68.1% would also have been eligible for the TA and 22.2% for the TF approach. The principal reason for choosing TAO was that it was the standard procedure at the site (49.3%), followed by an adverse vessel status (21.3%).

Patients had a mean age of 82.1 ± 5.3 years, 53.0% were female and 14.8% were smokers. Mean STS risk score was 11.1 ± 7.6 and the peak transvalvular gradient 70.7 ± 21.1 mmHg. The majority of patients had NYHA class III/IV heart failure (84.7%).

Ministernotomy was the default access route (100%). The procedure was completed at a mean of 118.3 ± 36.6 min and 14.6 ± 7.3 min of fluoroscopy. Most received a 26 mm valve (44.7%), followed by 29 mm (29.0%) and 23 mm (26.3%). Overall 97.4% of valves were successfully deployed and 2.6% received a second valve (in valve). One patient was converted to conventional surgery. There were no dissections, no ruptures of the aortic root, and 1 patient with major bleeding complications. 22.4% had a balloon dilation post delivery and 2.7% moderate paravalvular regurgitation (none severe). Two patients required a permanent pacemaker. After implantation, the peak transvalvular gradient was 15.8 ± 7.7 mmHg (mean 8.6 ± 4.7 mmHg).

At the 30-day follow-up, 98.1% of patients were alive (1 died), none experience stroke, and 4 patients were requiring hospitalizations for valve-related symptoms.

Conclusions: The results of this landmark registry provide important information on the procedural success rates and early mortality in patients undergoing transaortic TAVI in a large cohort of patients with aortic stenosis.

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Impact of "high" implantation of self-expandable valve in both short- and long-term outcome of patients undergoing TAVI

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Purpose: Transcatheter aortic valve implantation (TAVI) is an emerging treatment option for inoperable or high risk patients. Low implantation (over 8mm) has been frequently implicated with moderate or severe paravalvular aortic regurgitation (PVR). However, it has not been evaluated the effect of high implantation on the outcome of the procedure. The purpose of this study is to assess whether high implantation affects the short- and long-term outcome of the procedure.

Methods: Consecutive patients who underwent TAVI were evaluated. Echocardiographic parameters were recorded before the procedure, at discharge of the

patient and during one month- and one year- follow-up. Permanent pacemaker implantation (PPI), one month- as well as one year- mortality were recorded according to VARC criteria. ID was defined as the distance both from the native coronary cusp (NCC) and the left coronary cusp (LCC) to the deepest edge of the deployed bioprosthesis in the left ventricle using an offline program. The patients were separated into two groups according to the ID. Group I included all patients with normal (4-8 mm) or low implantation (>8 mm) and Group II included those with high (0-4 mm) or over the annulus implantation (distance from either LCC or NCC <0 mm).

Results: One hundred eighty six (81 ± 5.5 years, 103 males) who underwent TAVI were recorded. In Group I, peak gradient at discharge (17 ± 8 vs. 14 ± 4 mmHg, $p < 0.01$) and mean gradient at discharge (9 ± 4 vs. 7.5 ± 3.5 , $p = 0.02$) was significantly higher comparing to Group II, while there was no difference among two groups during one month- and one year- follow up. Furthermore, the percentage of patients with need for PPI after TAVI, was significantly greater in Group I comparing to Group II (45.6% vs. 2.9%, $p = 0.03$). Similarly, one year- all cause mortality was higher in Group I (13.7% vs. 0%, $p = 0.03$) while one year- cardiovascular as well as one month- and in-hospital mortality did not differ among two groups.

Conclusions: In conclusion, high implantation seems to have a positive effect on short- and long-term outcome of the procedure.

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Incremental value of left ventricular capacitance in predicting outcome in patients undergoing to percutaneous aortic valve implantation

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Purpose: To evaluate the incremental value of Left Ventricular Capacitance in predicting outcome of patients undergoing to Percutaneous Aortic Valve Implantation (TAVI) using a partial non-invasive approach.

Methods: We retrospectively evaluated 160 patients (Age 82 ± 5 years; Female 60%) with severe symptomatic aortic valve stenosis (AVA < 0.6 cm ^{2} /m ^{2}) and preserved left ventricular function (EF $> 50\%$) at high surgical risk (Log Euroscore $17.1 \pm 8.7\%$) who performed TAVI procedure with Corevalve Prosthesis. Single beat method for estimation of left ventricular end diastolic pressure volume relationship (EDPVR) was used to characterize diastolic properties of LV, on the basis of the premise that volume normalized EDPVRs share a common shape (LVEDP = $\alpha \times$ EDV $^\beta$). LVEDP was estimated invasively, before TAVI. LVEDV was evaluated non invasively by 2D echocardiography. Derived α and β indices were used to predict EDV at LVEDP 20 mmHg (EDV20). Qualitative angiographic method to grade paravalvular leak (PVL) was used according to the VARC-2 criteria. The primary end point of the study was one year death from any causes. Secondary end-point was one year death from cardiovascular causes after TAVI.

Results: After TAVI, a prosthetic regurgitation (PVL) was observed in 128 patients (80%). Moderate regurgitation was observed in 30 patients (18.7%) and severe in 4 patients (2.5%). During 1 year follow-up the primary end point (all cause mortality) was reached in 19 patients (11.8%). The secondary end point (cardiovascular mortality) occurred in 13 patients (8.1%). On Univariate Cox regression analysis several parameters were significantly associated to all cause mortality but on multivariate analysis we identified only moderate/severe PVL (HR 5, CI 2.1 to 12.5, $p = 0.0004$), NYHA functional class (HR 2.5, CI 1.2 to 5.5, $p = 0.015$) and EDV20 (HR 0.95, CI 0.94 to 0.99, $p = 0.009$) as independent risk factors for all cause mortality. EDV20 and moderate/severe PVL were also associated with Cardiovascular Mortality (Multiple Cox regression: PVL HR 5.6 IC 95% 2 to 16; $p = 0.0015$; EDV20 HR 0.96 IC95% 0.93 to 0.99; $p = 0.02$).

Conclusions: Paravalvular aortic regurgitation (PVL) after TAVI adversely affects outcome of patients. Diastolic left ventricular properties play a pivotal role in determining the response of left ventricle to the changes in haemodynamic conditions. A severely reduced left ventricular compliance is a strong independent predictor of adverse events. Partial non invasive estimation of left ventricular diastolic properties is an useful tool in predicting the outcome and in risk stratification after TAVI.

P1399 | BEDSIDE

Impact of access on TAVI procedural and midterm term follow up: a meta-analysis of 13 studies and 10468 patients

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Purpose: In most of the patients, Transcatheter Aortic Valve Implantation (TAVI) may be performed using transfemoral (TF) or transapical (TA) approach: however impact of access choice on periprocedural and mid-term results remains to be defined. Aim of our study was to evaluate the impact of access choice on short and mid-term follow-up after TAVI

Methods: Medline and Cochrane Library were searched for articles describing differences in baseline, peri-procedural and mid-term outcomes among patients undergoing TF or TA TAVI. The primary end point was all-cause mortality at mid-term follow-up, while secondary ones were 30 days mortality and in hospital com-

plications (bleeding and cerebrovascular events). The independent impact of access choice was evaluated with pooled analysis using a random-effect model.

Results: 13 studies with 10468 patients were included. TF was the most exploited strategy (69.5% vs. 30.5%). After adjusting for confounding variables, 30 days and follow-up mortality (median 365 days, range 222-400) were lower in TF patients with a pooled adjusted odds ratio of 0.81 [0.68-0.99 I2 99%] and 0.85 [0.80-0.90 I2 96%], respectively. Regarding periprocedural outcomes, TF reduced risk of bleedings and strokes (OR respectively of 0.74 [0.66-0.82 I2 95] and 0.91 [0.83-0.99] I2 86% respectively).

Conclusions: TF approach reduces mortality in TAVI patients, due to lower rates of periprocedural bleedings and strokes.

P1400 | BEDSIDE

The magnitude of aortic valve calcification does not affect the mid-term survival of patients undergoing aortic valve replacement for severe isolated aortic stenosis

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Purpose: To determine whether the magnitude of valvular calcification (AVC) which was associated with adverse outcomes in asymptomatic patients with severe AS before undergoing aortic valve replacement (AVR), has prognostic value after AVR.

Methods: Between 2010-13, of 680 pts who underwent AVR at our Institution, 465 had surgery for severe isolated AS (mean: age = 77 (9) yrs, 56% male, EF = 61 (5) %, AV area index = 0.36 (0.1) cm ^{2} /m ^{2} , 11% bicuspid AVs) and accurate clinical information was obtained in all the pts. The excised valves mean weight was 2.4 (0.9) gr. At the time of AVR, 19 pts underwent also mitral valve surgery for significant regurgitation. Mean f/u 18 (9) months. All pts underwent echocardiographic (echo) examinations before AVR and the echo studies were read off-line by one observer. All-cause mortality was extracted from the Social Security Death Index database. Independent t-test and Fisher's exact test were used as indicated, and survival analysis of the time to death was done using the Cox proportional hazards regression model.

Results: At the end of the follow-up there were 44 deaths of which 10 were within 30 days of surgery. Mean time interval between AVR-death was 7 (7) months. Clinical and echo variables including AV area were analyzed in unadjusted and highly adjusted models for age, gender, body surface area, hypertension, diabetes, renal insufficiency, hyperlipidemia, CAD, and CABG to determine their association with death and the relationship between AVW and post AVR death. AVW was not associated with early or mid-term postoperative mortality in any model. In both univariate and highly adjusted models indicated above, moderate or severe mitral regurgitation, heart failure at presentation, and age were associated with postoperative mortality (for highly adjusted models: HR=2.8, 95% CI: 1.6, 4.9; $p = 0.002$, HR=2.4, 95% CI: 1.2, 4.8; $p = 0.02$, and HR=1.1, 95% CI: 1.03, 1.1; $p = 0.001$, respectively).

Conclusions: 1. In a cohort of pts undergoing AVR for severe isolated AS, pre-operative significant mitral regurgitation uncorrected at the time of AVR, heart failure at presentation and older age are associated with postsurgical all-cause mortality. 2. AV weight, as an expression of total valvular calcium burden is not independently associated with post AVR mortality and does not add an excess risk when combined with the 3 variables found to be associated with death.

P1401 | BEDSIDE

Survival post transcatheter aortic valve implantation for aortic stenosis: the STT score. derivation and external validation

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Aims: Surgical risk scores have failed to accurately predict events after TAVI, stressing the need for a dedicated tool incorporating all clinical variables useful to discriminate risk of patients undergoing TAVI.

Methods and results: All consecutive patients undergoing TAVI at our institutions were enrolled. The primary endpoint was one year all-cause mortality (as for VARC definition), and secondary endpoint was all-cause death after 30 days. Accuracy of the score was derived, and externally validated. Net classification improvement compared to STS score was appraised. A total of 1064 patients constituted the derivation cohort, and 180 the external validation cohort. 165 patients (15%) died at one year follow up, and previous stroke (OR 1.80; 1.4-3), inverse of renal clearance (OR 8; 6-14) and systolic pulmonary arterial pressure more than 50 mmHg (OR 2.10; 1.5-3) were independently related to all-cause mortality. Area Under the Curve (AUC) of the Survival post TAVI (STT) for the primary end point was of 0.68 (0.62-0.71). At 30 days, 65 (7%) died, and AUC for them was 0.66: (0.64-0.75). On external validation cohorts, AUC curves of STT were, respectively, 0.66 (0.56-0.7) for 30 days and 0.67 (0.62-0.71) for all-cause mortality at follow-up. Net reclassification improvement (NRI), for 30 days

all-cause mortality for STT compared to STS was of 31% ($p < 0.001$), and of 14% ($p < 0.001$) for all-cause mortality at follow up.

Conclusions: STT represents an easy and accurate score to define risk of 30 days and of mid-term mortality for patients undergoing TAVI, improving STS score performance.

P1402 | BEDSIDE

Long-term performance of a nonmetallic, retrievable and repositionable aortic valve in patients with severe aortic stenosis, 5 Year Follow-Up of the 22 F-Direct Flow Medical Valve

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Background: There is limited information on 5-year outcome of patients undergoing trans-catheter aortic valve implantation. In particular, long-term results of a non-metallic inflatable valve design has never been reported. Less radial force of this device may impact its stability and hemodynamic function over time.

Aim of the study: To evaluate the 5-year clinical and echocardiographic outcome of the retrievable and repositionable first generation 22F-Direct Flow Medical Valve percutaneous aortic valve.

Methods and results: From 2007 to 2008 31 symptomatic high-risk for surgery patients (mean age 82 ± 4 y) with severe aortic stenosis and a mean logistic EuroSCORE of $29 \pm 7\%$ were the subject of this analysis. Clinical, echocardiographic and hemodynamic follow-up were obtained during 5 years. Survival rates were 81%, 69%, 60%, 54% and 54% at 1,2,3,4, 5 years, respectively. At 5 years, all surviving patients were in NYHA-class I. Echocardiography revealed a significant decrease of the mean gradient from baseline (49.1 ± 13.8 mmHg) to 30 days (19.1 ± 6.8 mmHg, $p < 0.001$), which remained stable over 5 years (15.3 ± 6.0 mmHg) ($p = \text{NS}$). At 5-year follow-up aortic regurgitation assessed by TTE was non or trace in all patients.

Conclusions: In this preliminary series, the first generation of the nonmetallic, repositionable and retrievable 22F-DFM valve was associated with acceptable clinical outcome and stable hemodynamic performance over 5 years with trace or less aortic regurgitation in all patients.

P1403 | BEDSIDE

Trends in trans-catheter aortic valve implantation between 2011 and 2012. Results from the GARY Registry

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Background: Trans-catheter aortic valve implantation (TAVI), either by a surgical access (S-TAVI) or by a percutaneous trans-vascular access (V-TAVI), has established as a routine treatment modality for older surgical high-risk patients suffering from severe symptomatic aortic stenosis. Little is known on current trends concerning patient selection as well as results in the last years.

Methods: We analysed all patients treated with TAVI between 2011 and 2012, who were included in the prospective German aortic valve replacement registry (GARY).

Results: Out of all documented aortic valve replacement therapies (also the surgical ones) the proportion of the TAVI procedures in GARY was 27.6% in 2011 (3938/14247) and 31.9% (5333/16722) in 2012 (p -value: < 0.001).

Parameter	2011 (n=3940)	2012 (n=5342)	p-value
Number of treated patients	3938	5333	—
Transvascular TAVI (Pt)	2719	3760	—
Surgical TAVI (Pt)	1186	1446	—
Age (years, mean)	80.8	81	0.190
Women (%)	56	54.6	0.190
Cardiogenic shock <48h (%)	3.2	2.4	0.024
EF <30%	8.6	8.3	0.520
Log. EuroScore (% mean)	25.4	23.6	<0.001
Intervention by "heart team" (%)	49.1	54.7	<0.001
Mean gradient before TAVI (mean)	45.4	43.9	0.001
Mean gradient after TAVI (mean)	5.8	5.8	0.109
Residual aortic insufficiency $\geq 1^{\circ}$ (%)	6.2	5.9	0.537
Conversion to surgery (%)	1.6	1.2	0.099
Duration of intervention (Min., mean)	93.8	89.5	<0.001
In-hospital stroke (%)	3.6	2.4	0.001
In-hospital death (%)	5.8	4.9	0.039

Conclusions: The GARY Registry documents an absolute increase in TAVI numbers between 2011 and 2012, as well as a relative increase out of all aortic valve replacement therapies. Patient characteristics were similar, besides a small reduction in the mean log. EuroScore. This may contribute to the observed decrease in hospital event rates.

P1404 | BEDSIDE

When and why do patients die after successful transcatheter aortic valve replacement (TAVI)?

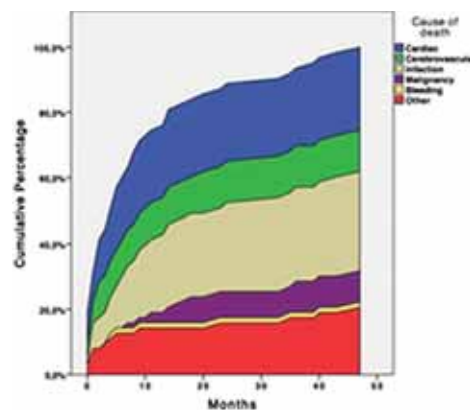
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Background: Transcatheter aortic valve replacement (TAVI) is a valuable alternative for patients suffering from severe aortic stenosis and who are not candidates for surgical valve replacement. The overall rate of death in this patient population is reported to be 34% over 24 months.

Aim: The aim of this retrospective analysis was to assess the overall long term mortality and the cause of death in patients after successful TAVI during four years follow-up.

Methods and results: Since 2007 327 TAVI procedures have been performed in our institution (210 transfemoral, 97 transapikal, 20 transaortal). The overall perioperative mortality was 4.9%. The mean annual mortality after successful TAVI was 16.75% TF, 28.57% TA and 11.76% TAo ($p < 0.05$).

The reasons for mortality after the perioperative period comprised cardiac (25.4%), infectious (30.2%), malignancy (9.5%) cerebrovascular (12.7%) bleeding (1.6%) and other reasons (20.6%). There was no significant difference between the different access routes and the causes of death observed. An overview of the timing and the causes of death are given in the graph.



TAVI - Cause of death.

Conclusion: After successful TAVI, long-term survival is favourable in the trans-femoral TAVI patient group. Despite the increased mortality in patients having undergone transapikal TAVI, no statistically significant difference was found regarding the cause of death with respect to access route. Interestingly, infection as the cause of death in the postprocedural period surpasses the number of deaths due to cardiac reasons.

P1405 | BEDSIDE

Mortality prediction using five different risk scores for cardiac surgery in patients undergoing transcatheter aortic valve implantation (TAVI): a multicenter Brazilian registry

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Background: Transcatheter aortic valve implantation (TAVI) has been established as a standard treatment in inoperable patients and an attractive alternative for surgical high-risk patients with symptomatic severe aortic stenosis. Predicting mortality in patients undergoing TAVI is still a challenge. The aim of this study was to evaluate the performance of five risk scores for cardiac surgery on predicting 30-day mortality among patients of the Brazilian Registry of TAVI.

Methods: The Brazilian Multicenter Registry prospectively enrolled 418 patients undergoing TAVI in 18 centers between 2008 and 2013. For all patients, the 30-day mortality risk was calculated using the following surgical risk scores: logistic EuroSCORE I (ESI), EuroSCORE II (ESII), STS Score (STS), Ambler Score (AS) and Guaragna Score (GS). The performance of the risk scores was evaluated in terms of their calibration (Hosmer-Lemeshow test) and discrimination [area under the receiver-operating characteristic curve (AUC)].

Results: Mean age was 81.5 ± 7.7 years. The CoreValve (Medtronic) was used in 86.1% of the cohort and transfemoral approach was used in 96.2%. The observed 30-day mortality was 9.1%. The mean 30-day mortality predicted by the scores was: ESI, $20.2 \pm 13.8\%$; ESII, $6.5 \pm 13.8\%$; STS, $14.7 \pm 4.4\%$; AS, $7.0 \pm 3.8\%$; GS, $17.3 \pm 10.8\%$. By using the AUC, none of the tested scores was able to accurately predict 30-day mortality. The AUC for the scores were: 0.57 (CI 95%: 0.48-0.66; $p = 0.11$) for the ESI; 0.52 (CI 95%: 0.43-0.62; $p = 0.63$) for the ESII; 0.55 (CI 95%: 0.46-0.64; $p = 0.26$) for the AS; 0.48 (CI 95%: 0.4-0.57; $p = 0.71$) for the STS and

0.54 (CI 95%: 0.45-0.63; $p=0.38$) for the GS. The Hosmer-Lemeshow test indicated acceptable calibration for all scores ($p>0.05$).

Conclusions: In this real world Brazilian registry, the surgical risk scores were inaccurate in predicting mortality after TAVI. Risk models specifically developed for TAVI are necessary to accurate estimation of patient prognosis.

MORE ON TAVI

P1407 | BEDSIDE

Late outcome up to 6 years after transcatheter aortic valve implantation (TAVI)

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Purpose: Few data exist on long-term results of TAVI and they are crucial for decision making. We assessed late outcome after transcatheter aortic valve implantation (TAVI), up to 6 years and analysed its predictive factors with a particular emphasis on functional status.

Methods: Between October 2006 and December 2009, 123 consecutive patients were discharged alive after TAVI in our institution. Mean age was 82 ± 8 years and 88% of patients were highly symptomatic in New York Heart Association (NYHA) class III-IV. Mean logistic EuroSCORE was $22 \pm 12\%$. Follow-up was complete in 122 patients (99%).

Results: The overall 6-year survival was $31 \pm 5\%$ (Figure 1), 56% of deaths being non-cardiac. In multivariate analysis, predictive factors of late mortality were the presence of lower limb arteritis ($p=0.04$), a higher Charlson Comorbidity Index ($p=0.049$), a lower baseline aortic valve area ($p<0.0001$), higher post-TAVI systolic pulmonary artery pressure ($p=0.015$) and post-TAVI paraprothrotic aortic regurgitation $\geq 1/4$ ($p=0.015$). Event-free survival rate according to Valve Academic Research Consortium-2 (VARC-2) criteria was $28 \pm 4\%$ at 5 years. Finally, the rate of good functional results, defined as survival in NYHA class I or II, was $32 \pm 5\%$ at 5 years. In the survivors the EQ-5D questionnaire further confirmed the benefit in terms of quality of life.

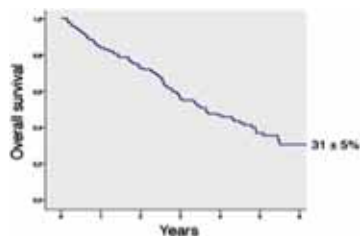


Figure 1

Conclusion: Despite a high-risk profile, one third of patients discharged alive after TAVI were still alive at 6 years. The survivors exhibited good functional results assessed by NYHA class and quality of life standardized evaluation.

P1408 | BEDSIDE

The prognostic value of Galectin-3 and NT-proBNP in patients undergoing transcatheter aortic valve implantation

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Background: Galectin-3 and N-terminal segment of B-type natriuretic peptide pro-hormone (NT-proBNP) are associated with a higher risk of death in acute and chronic heart failure patients. Furthermore, NT-proBNP provides prognostic information in patients undergoing transcatheter aortic valve implantation (TAVI). The aim of the present study was to determine the prognostic value of galectin-3 and NT-proBNP in patients undergoing TAVI within a one-year follow-up period.

Methods: A total of 184 consecutive patients with aortic stenosis undergoing elective transfemoral TAVI were included. Blood samples were collected before and 1 day after TAVI. Galectin-3 and NT-proBNP were quantified in serum using immunoassays. Patient follow-up was for 1 year.

Results: Nineteen (10.3%) patients died within 1 year after hospital discharge. There were no differences in baseline characteristics between deceased and surviving patients. Galectin-3 levels were similar at baseline in patients who died and those who survived (21.2 ng/mL [$14.2-32.8$] vs. 18.2 ng/mL [$14.3-23.8$], respectively; $P=0.09$), whereas NT-proBNP levels at baseline were higher in patients who died ($3,392.0 \text{ ng/L}$ [$1,710.0-15,118.0$] vs. $1,819.0 \text{ ng/L}$ [$817.8-4,920.5$]; $P=0.008$). Patients who died had higher galectin-3 (24.4 ng/mL [$14.5-39.2$] vs. 18.4 ng/mL [$14.4-25.0$]; $P=0.007$) and NT-proBNP ($4,608.0 \text{ ng/L}$ [$3,099.0-10,153.0$] vs. $2,520.0 \text{ ng/L}$ [$1,162.0-4,751.0$]; $P=0.003$) levels after TAVI. In par-

ticular, male patients ($n=8$) who died had higher galectin-3 levels after TAVI (25.0 ng/mL [$13.6-37.7$] vs. 36.9 ng/mL [$18.0-52.2$]; $P<0.001$). Multivariate Cox regression analysis revealed that the risk of mortality was higher if galectin-3 was increased 1 day after TAVI (hazard ratio 1.15; $P=0.001$). Compared with NT-proBNP (AUC 0.803 [95% CI 0.59-1.02; $P=0.03$]), the level of galectin-3 1 day after TAVI best predicted mortality, especially in men (AUC 0.828 [95% CI 0.55-1.11; $P=0.01$]).

Conclusion: Galectin-3 provides prognostic information predicting mortality within a 12-month period when measured 1 day after TAVI. These findings provide information about this biomarker that could be used for risk stratification in patients undergoing TAVI.

P1409 | BEDSIDE

Use of a balloon-expandable transfemoral sheath in a TAVI cohort with difficult access site

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Background: In patients undergoing transcatheter aortic valve implantation (TAVI), the high prevalence of peripheral artery disease (PAD) is limiting femoral access and increases vascular complications. Major vascular complications are known predictors of post-TAVI mortality and morbidity. To increase access site availability and to reduce major vascular complications, the use of a balloon-expandable large-bore vascular sheath has been suggested.

Methods and results: We performed a study in 245 patients undergoing TAVI between 2008 and 2012 with the Medtronic CoreValve prosthesis. Within this cohort, 31 patients underwent transfemoral TAVI with the use of a SoloPath balloon-expandable sheath. Of these patients, 61.3% were male (19/31). Mean age was 80 ± 6 years with a mean logistic EuroSCORE of $32.6 \pm 19.6\%$ and a STS score of $10.8 \pm 7.0\%$. In comparison to the conventional access sheath group, the primary composite endpoint of death at 30 days, major vascular complications, and major bleeding was not increased in the SoloPath cohort, despite a significantly higher prevalence of access-complicating PAD. No differences in VARC major vascular complications, short-, and long-term mortality were observed.

Conclusion: The use of a balloon-expandable large bore sheath is safe and feasible in a cohort with a high prevalence of PAD and at high risk for vascular complications. The benefit of such a sheath needs to be evaluated in randomized trials.

P1410 | BEDSIDE

Impact of previous acute pulmonary oedema after transcatheter aortic valve implantation: insight from FRANCE 2 Registry

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Objectives: The aim of this study was to assess the influence of previous clinical history of acute pulmonary oedema (PO) in severe aortic stenosis (AS) patients undergoing transcatheter aortic valve implantation (TAVI).

Background: The prognostic value of previous PO has not been thoroughly investigated in a large-cohort of TAVI-patients.

Methods: Data were analyzed for 3195 patients enrolled in the French national TAVI registry, FRANCE2. We compared the clinical outcome of enrolled patients divided broadly into three groups according to the frequency of previous acute PO episode; group 1: no-episode, group 2: single-episode, group 3: multiple-episodes within the year preceding TAVI.

Results: Of the 3195 patients (mean age: 82.7 ± 7.2 years, mean logistic EuroSCORE: 21.8 ± 14.3) with TAVI, 1880 (58.8%) had no-episode, 937 (29.3%) single-episode, and 378 (11.9%) multiple-episode. Both 30-day and cumulative 1-year mortality increased significantly across the 3 groups (7.7% vs. 9.2% vs. 15.9%; $p<0.001$, 14.0% vs. 19.4% vs. 24.1%; $p<0.001$, respectively). In addition, single-PO was not independently associated with an increased mortality at 30-day and 1-year compared to no-PO (HR: 1.01; 95%CI: 0.77-1.33; $p=0.935$, HR: 1.17; 95%CI: 0.96-1.42; $p=0.123$, respectively). In contrast multiple-PO was independently associated with an increased risk of both 30-day and cumulative 1-year mortality (HR: 1.60; 95%CI: 1.17-2.21; $p=0.004$, HR: 1.35; 95%CI: 1.05-1.73; $p=0.019$, respectively).

Conclusion: In conclusion, a history of previous multiple-PO within the year preceding TAVI, but not single-PO, is independently associated with increased mortality at short- and mid-term follow up. Taking previous PO history into consideration might play a crucial role in the selection process in this real-world clinical practice and might contribute as one of the major independent predictors allowing a useful risk-stratification tool for TAVI selection patients and outcome. Then, TAVI should be considered early in patients with AS, when possible, in those with no or single PO episode.

P1411 | BEDSIDE**Frailty is a determinant of survival in elderly patients with symptomatic severe aortic stenosis: a prospective study**

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Purpose: To analyze the prognostic influence of frailty in elderly patients with symptomatic severe aortic stenosis (SAS).

Methods: Two-year follow-up prospective study of 438 patients over 75 years diagnosed of symptomatic SAS. Frailty was assessed according to the Cardiovascular Health Study criteria. Patients were classified as frail and non-frail.

Results: Mean age was 83±4.7 years and 58.2% were women. Main symptoms were III-IV NYHA functional class in 35% and angina in CCS III-IV functional class in 11.5% of patients. Frailty criteria was found in 44.1% of patients and 71.5% of frail patients were women.

With a mean follow-up of 78 weeks, frail patients showed a significant higher mortality (48% in frail vs 22% in non-frail patients, $p<0.001$) and a shorter mean survival (71.5±3 weeks in frail vs 94±1.6 in non-frail patients, $p<0.001$).

Two hundred and seven patients (47.2%) received medical-conservative treatment, 157 (35.8%) surgical aortic valve replacement and 74 (16.9%) transcatheter aortic valve implantation.

Two-year mortality rate was 56% in frail vs 37% in non-frail patients under medical treatment ($p=0.001$), 13% in frail vs 8% in non-frail patients ($p<0.001$) under surgical treatment and 45% vs 12% ($p<0.001$) in patients who received percutaneous intervention.

On a treatment-stratified Cox regression analysis, and adjusted by age, LVEF, NYHA functional class, diagnosis of dementia, serum creatinine, coronary heart disease, and presence of anaemia, frailty was an independent mortality-related factor (HR 2.11 CI 95% 1.35-3.11).

Conclusion: In older-old individuals with symptomatic severe aortic stenosis, frailty is an independent two-year mortality-related factor. Frailty should be considered in treatment decision-taking on these patients.

P1412 | BEDSIDE**The predictive value of Q to peak transaortic gradient interval on improvement in left ventricular function in patients undergoing transcatheter aortic valve replacement**

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Background: The improvement of left ventricular ejection fraction (LVEF) in patients with impaired left ventricular function and severe aortic stenosis (AS) after transcatheter aortic valve replacement (TAVR) is highly variable. There is currently no baseline variable that reliably predicts the improvement of LV function in patients with LVEF <45% undergoing TAVR procedure. Time interval from the beginning of QRS to the peak of transaortic gradient (QPGI) represents the summation of electrical and mechanical coupling. The predictive value of this time interval on improvement in the LVEF in patients with impaired LV function and AS after TAVR has not been studied.

Method: Baseline ECGs and serial echocardiograms of 77 consecutive patients with LVEF<45% who underwent TAVR using Edwards-SAPIEN (94%) and Core Valve (6%) and survived to hospital discharge between 2007 and 2013 at our hospital were reviewed. The baseline median QPGI was used to divide the patients into 2 groups: QPGI<240ms and ≥240 ms.

Results: Patients with QPGI≥240ms (n=34) had average QRS duration of 161 ms, and higher incidence of left bundle branch block (26.4%), permanent right ventricular pacemaker implantation (53%) and lower incidence of intraventricular conduction delay (20.6%) as compared to those with QPGI<240ms (QRS duration of 117ms, 9.1%, 4.7% and 51.%) respectively. After a median of 13.7±13.2 months, the patients with QPGI <240ms had a significant increase of LVEF from 35 to 50% vs no significant change in those with QPGI≥240ms. By Receiver Operator Characteristic curve, the QPGI of 240ms was determined as the optimal threshold for predicting the improvement of LVEF. The probability of increasing LVEF by at least 10% was 79.1% and 20.1% for patients with QPGI < and ≥240ms respectively. The sensitivity and specificity of using QPGI <240ms as predictor for significant increase in LVEF was 83% and 73% respectively.

Conclusion: 1 Among patients with LVEF below 45% and severe AS undergoing TAVR, the baseline QPGI accurately predicts clinically significant improvement of LV function. At least a 10% improvement of LVEF in the setting of a QPGI<240ms is common.

P1413 | SPOTLIGHT**Reimbursement policies, hospital features and innovation in healthcare. the case of transcatheter aortic valve implantation in Italy**

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Purpose: Transcatheter aortic valve implantation (TAVI) use in high-risk and inoperable patients with symptomatic severe aortic stenosis is supported by increasing empirical evidence. Many factors influence its introduction into healthcare systems. We investigated the adoption and diffusion of TAVI since its introduction into the Italian market in 2007, and we identified the potential drivers of uptake and diffusion at hospital and regional levels.

Methods: Our sample consisted of all Italian hospitals that adopted TAVI since its introduction in 2007. We classified the hospitals according to funding status, ownership, type, teaching status, location and presence of a regional budget balance plan (BBP). We estimated correlation coefficients between the number of TAVIs and variables at the regional level. A nonparametric Mann-Whitney test was used to compare TAVI volumes across groups of hospitals. Last, we run several regressions to estimate the determinants of TAVI adoption in 2012 and the variation of its diffusion between 2011 and 2012.

Results: In total, 7,261 patients underwent TAVI in Italy between 2007 and 2012, corresponding to a penetration rate in 2012 of 18.1%. At the regional level, TAVI is strongly positively correlated with DRG-based funding mechanisms. At the hospital level, tariff-funded hospitals outperform capitation-funded ones; a level of tariff greater than 25,000€ favours a higher volume of implants; private hospitals outperform public hospitals; teaching and research hospitals implant more valves than do general hospitals; non-BBP hospitals perform slightly better; and southern hospitals outperform hospitals in northern and central Italy. However, none of these differences is statistically significant. The regression analysis shows that none of the control variables at the hospital level significantly explains the level of TAVI adoption in 2012, except for the presence of a regional BBP that significantly reduces TAVI adoption. The incremental TAVI adoption between 2011 and 2012 is significantly correlated with geographic area and regional health expenditure per capita.

Conclusions: The diffusion of TAVI in Italy is characterised by great variability. Major drivers of TAVI adoption and diffusion seem to be hospital type, ownership and reimbursement schemes. Our findings suggest that – although relevant – reimbursement policies are not the major driver of new technologies' adoption and that other variables would need to be further investigated (e.g., the role of referring clinicians) to better interpret wide variability of TAVI diffusion.

P1414 | BEDSIDE**Challenges of coronary angiography or intervention in patients who received prior TAVI procedure**

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Objectives: Transcatheter aortic valve implantation (TAVI) has evolved into a standard procedure for high-risk patients suffering from aortic stenosis. In these mostly elderly patients coronary artery disease may either be already present or may develop. Therefore, some patients will require coronary angiography (CA) or percutaneous coronary intervention (PCI) immediately or following TAVI. Since the beginning of the TAVI era, many different valve prostheses have entered clinical practice. While some are implanted in a fully subcoronary locus, other devices are placed partially or fully over the coronary ostia and may therefore potentially interfere with diagnostic or interventional catheters. The aim of our analysis was to evaluate the feasibility of coronary angiography or coronary intervention in patients with prior TAVI.

Methods: Over a period of several years 780 patients were treated at our center by TAVI using eight different valve prostheses (Symetis Acurate TA and Acurate TF; Medtronic CoreValve and Engager; JenaValve, SJM Portico; Edwards Lifesciences SAPIEN and SAPIEN XT). In this analysis all patients were included who underwent either CA or PCI following TAVI. CA or PCI was rated as fully feasible when coronary ostia could be fully intubated, partially feasible when coronary arteries could be visualized only unselectively, or unfeasible when coronary ostia could not be visualized.

Results: A total of 34 patients received CA or PCI after TAVI at our hospital (18=Sapien/11=CoreValve/4=Acurate/1=JenaValve). In patients with subcoronary valves (SAPIEN, SAPIEN XT, JenaValve) 19/19 had full accessibility with standard catheters, and in 2/19 CA was able to be performed using other standard catheter sizes. Out of the 19 patients 6 required PCI, which was successfully performed in all of them. In patients with valve types that were placed partly above the coronary ostia (CoreValve, Acurate TF/TA, Portico), no selective intubation of coronary arteries (LCA=3; RCA=3; both=3) was possible in 9/15 cases, even with different diagnostic catheters. Full accessibility was only present in 4/15 cases. In 2/15 cases, visualization of RCA or LCA was only feasible via aortography.

Conclusion: CA or PCI following TAVI is usually feasible; however, especially with devices that are placed partially above coronary ostia, there can be interference

with diagnostic or interventional catheters that may impede straightforward intervention. This has to be taken into account prior to TAVI implantation, especially in the treatment of younger patients suffering from coronary artery disease.

P1415 | BEDSIDE

Structured professional education in transcatheter aortic valve implantation - 5 years of experience with the SAPIEN/SAPIEN XT valve

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Objectives: Transcatheter aortic valve implantation is one of the most complex and potentially challenging cardiac interventions, requiring a well-structured institutional setting, a high level of interventional skills and a close cooperation of members of the heart team. Based on the Edwards experience in more than 10,000 patients during the early training phase of new heart teams across Europe with the SAPIEN / SAPIEN XT valves we report on the impact of this training on procedural outcomes over time.

Methods and results: The Edwards professional education program starts with a structured training program, followed by proctored sessions and subsequent procedural support by clinical specialists at the implanting institution. We report on the procedural success rate of the supported cases from 2008 to 2012, selected complications from 2010 to 2012 and the impact of renewed training during the launch of the 2nd generation SAPIEN XT valve in April 2010.

The overall procedural success rate (PSR) for all cases (n=14,760) supported by a clinical specialist increased from 95.2% in 2008 to 97.5% in 2010 and remained stable at that level between 2010 and 2012 (97.6%). There was no learning curve observed during the whole period (stable high PSR of around 98%) for transfemoral (TF) procedures, while a gradual learning curve was observed for transapical (TA) procedures (increasing from 93.5% to 97.2%).

For 10,422 cases between 2010 and 2012, 10,172 cases were reported as being successful whereas 250 cases as procedural failures (2.4%). The complication rate was below 1% for each documented complication and for any given year: ventricular valve embolization (n=43; 0.41%), moderate to severe valvular/paravalvular leakage (n=41; 0.39%), aortic valve embolization (n=35; 0.33%), cardiac tamponade (n=9; 0.09%), coronary obstruction (n=9; 0.09%) and aortic rupture (n=4; 0.04%).

The overall PSR in the 1st quarter of 2010 was 96.4% and did not change during the clinical introduction of the SAPIEN XT valve in the 2nd – 4th quarter 2010 (98.5%; 97%; 97.4% respectively). There was no change in PSR detected for both, TF and TA procedures.

Conclusions: These data illustrate the effectiveness of a comprehensive professional education program in centers, where a new TAVI-program is initiated or when a new valve is introduced. The results reinforce the concept of supporting these centers by proctoring and by the support of a clinical specialist.

P1416 | BEDSIDE

Transapical mitral valve-in-valve implantation for degenerated bioprostheses: a consecutive case series

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Purpose: Reoperations for the treatment of degenerated mitral bioprosthesis are burdened by high mortality and morbidity. Transcatheter techniques may represent an alternative therapeutic option in this setting. The aim of this study was to report the feasibility of transapical valve implantation for the treatment of degenerated mitral bioprosthesis.

Methods: Five patients (age 80±6 yrs-old) presenting with degenerated mitral bioprosthesis (range 27 and 29 mm), with baseline New York Heart Association ≥3, underwent transapical valve implantation of Edwards Sapien XT valve (26 or 29 mm) in mitral position at our institution. Degenerated mitral bioprostheses presented massive regurgitation in 2 cases, combined stenosis and regurgitation in 3 cases. Mitral bioprostheses were Edwards Perimount valve in 2 cases, Mosaic valve in 2 cases and Bio-Implant valve in one case.

Results: Transapical valve implantation was successful in all patients. Mean procedural time was 106 minutes, mean fluoroscopy time was 20 minutes. One patient had thoracic wall bleeding which required surgical revision. One patient developed an apical left ventricular false aneurysm. Pre-discharge echocardiography showed a normal functioning Edwards Sapien XT valve (trans-prosthesis gradient 4-7 mmHg) in all five patients. At follow-up New York Heart Association class improved, being ≤2 in all patients. Mean hospital length was 5 days. At 6-month follow-up all patients were alive.

Conclusions: Transapical mitral valve-in-valve implantation is a feasible option that can be considered as an alternative approach to reoperative mitral valve surgery in selected high risk patients.

ANTIARRHYTHMIC DRUGS

P1418 | BEDSIDE

Pregnancy in the congenital long-QT syndrome: efficacy and safety of beta-blocker therapy for prevention of lethal ventricular arrhythmias

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Purpose: Pregnancy is known as a considerable risk of lethal cardiac events (ventricular tachycardia and syncope) in patients with congenital long-QT syndrome (LQTS). Although β -blocker (BB) is the most effective and commonly used agents to prevent lethal ventricular arrhythmias in LQTS, the efficacy and safety of BB therapy during pregnancy in LQTS is still unclear. In this study, we investigated 1) how pregnancy increased the QT interval and arrhythmic risk of LQTS patients, 2) the efficacy and safety of BB for pregnancy in the LQTS patients and their infants.

Methods: A retrospective analysis was performed on patients with congenital LQTS who had ever been pregnant, and total 72 pregnancies in 34 LQTS patients (28±4 years old) including 23 genotype-determined (8 LQT1, 13 LQT2, 1 LQT1+3, 1 LQT7) and 11 genotype-unknown were enrolled. We evaluated clinical and electrophysiological characteristics of patients and their pregnancy outcome in presence (BB(+): n=16) or absence of BB therapy (BB(-): n=56).

Results: Nineteen (26%) LQTS patients had taken a BB therapy but 3 of them (11%) discontinued BB for pregnancy despite having ever experienced syncope and ventricular tachycardia. Follow-up ECG during pregnancy was able to be evaluated in 17 LQTS patients including 8 BB(+) and 9 BB(-). No significant difference was observed in the heart rate and QT interval before pregnancy (baseline) between the two groups. Six-month after pregnancy, the QT interval was not altered in both groups, whereas heart rate was decreased in BB(+) group (71±6 to 64±6 bpm; p=0.01) but not in BB(-) group (67±10 to 72±9 bpm; p=0.3). Thus, the QTc interval was significantly shorter in BB(+) compared to BB(-) group (467±35 ms vs. 520±50 ms; p<0.05). Although the history of cardiac events before pregnancy was extremely higher in BB(+) group compared to BB(-) group (100% vs. 43%, p=0.001), Three (9%) patients, all in BB(-) group, had lethal cardiac events during pregnancy but none in BB(+) had any cardiac events. Spontaneous abortion occurred in 8 pregnancies but its frequency was not different between two groups. In the perinatal clinical findings, the birth weight was smaller and the gestational week was shorter in BB(+) group than in BB(-) group, whereas no significant difference was observed in the fetal distress and congenital malformation between two groups.

Conclusions: BB therapy during pregnancy may be tolerated for fetus as well as decrease the risk of cardiac events in the LQTS patients suggesting that higher risk LQTS patients had better continue BB therapy even for their pregnancy.

P1419 | BENCH

Vernakalant reduces ventricular vulnerability without enhancing proarrhythmia in an experimental model of chronic heart failure

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Background: The antiarrhythmic agent vernakalant (VER) initially seemed to be a new promising option for pharmacological cardioversion of atrial fibrillation. We recently demonstrated a significant prolongation of the QT-interval induced by vernakalant. The aim of the present study was to investigate if application of vernakalant in escalating doses is safe in an arrhythmia-sensitive model of chronic heart failure.

Methods and results: 10 female rabbits received a ventricular pacing lead. CHF was induced in 10 rabbits by 4 weeks of rapid ventricular pacing (400 beats/min). All rabbits developed clinical signs of heart failure. In isolated hearts, eight endo- and epicardial monophasic action potentials and a simultaneously recorded 12-lead ECG showed a significant and dose-dependent QT prolongation after application of VER as compared with baseline in sham and failing hearts (10 μ M: +18ms, 30 μ M: +45ms, p<0.05) accompanied by an increase of action potential duration (APD90, ±13 ms with 10 μ M VER; +21ms with 30 μ M VER). Administration of VER did not affect dispersion of repolarization. Lowering of potassium concentration in bradycardic AV-blocked hearts did not provoke early afterdepolarizations (EAD) or polymorphic ventricular tachycardia despite significant QT prolongation.

The results were compared to 12 rabbits treated with sotalol (SOT, 100 μ M). SOT led to an increase in QT-interval (+78ms) and APD90 (+52ms). In contrast to VER, SOT led to an increase in dispersion of repolarization (+41ms, p<0.05) and led to the occurrence of EAD in 11 of 12 and of TdP in 9 of 12 hearts (78 episodes) after lowering of potassium concentration.

Conclusion: In the present study, application of VER or SOT led to a significant prolongation of myocardial repolarization in failing hearts. However, VER did not affect dispersion of repolarization nor induced EAD and therefore did not induce ventricular tachyarrhythmias. These results imply that application of vernakalant does not trigger proarrhythmia despite significant QT-prolongation.

P1420 | BENCH**Effects of vernakalant on refractory period and conduction velocity are preserved after electrical remodeling**

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Purpose: Vernakalant is an effective antiarrhythmic drug for cardioversion of recent onset atrial fibrillation (AF) lasting 7 days or less in nonsurgery patients and 3 days or less in postoperative AF. Like in other antiarrhythmic compounds, its efficacy declines with increasing duration of AF. The purpose of this study is to investigate the decline in efficacy of vernakalant at different stages of remodeling.

Methods: In conscious goats without electrical remodeling (NR, n=11) and after 24 hours of electrical remodeling (ER, n=8) the effects of lower and higher intravenous infusion dosages (LD, HD) of vernakalant on refractory period (RP), conduction velocity (CV) and AF cycle length (AFCL) were determined in both atria. In goats with persistent AF (AFp, 10 days, n=10) the effects on CV, AFCL and cardioversion efficacy were studied. Also the rate-dependency of the electrophysiological effects was investigated.

Results: Vernakalant caused a dose-dependent effect on RP, CV and AFCL at all stages of remodeling. Its effects on CV, RP and AFCL were preserved after ER (table) and after 10 days of AF. No rate dependent effect of vernakalant on ERP and CV was observed. The median duration of AF paroxysms in ER goats were significantly reduced from 277s (IQR: 25-462s) at baseline to 34s (IQR: 21-86s) at the higher dose. After 10 days of AF, cardioversions occurred in 5 out of 9 animals.

Conclusions: Vernakalant's antiarrhythmic effect is based on slowing of conduction and prolongation of refractory period. Only a rate dependent effect for CV was found. Unsuccessful cardioversion of persistent AF was not related to loss of effect on CV, AFCL or RP.

P1421 | BEDSIDE**Efficacy of quinidine in patients with Brugada syndrome and frequent ventricular arrhythmia episodes**

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Background: Frequent ICD discharges represent a malignant form of ventricular arrhythmias (VA) in patients with Brugada syndrome (BS). Shocks are associated with multiple consequences, such as psychologic disorders, proarrhythmia, deleterious effect on cardiac function, electromechanical dissociation, and death. Quinidine is the only oral medication that has shown efficacy in preventing VA and terminating arrhythmic storms due to recurrent ventricular fibrillation (VF) in patients with BS.

Purpose: The purpose of the present report is to describe the Spanish nationwide long-term experience regarding the use of quinidine in patients with the BS and frequent appropriate ICD shocks

Methods: All centers contributing to the nacional registry of ICD implants in Spain were contacted in order to identify patients with BS and frequent ICD shocks that were treated with quinidine.

Results: A total of 23 patients were identified, mean age 41±13 years, 19 (82%) were male. The ICD had been implanted for secondary prevention in 13 patients (57%), syncope with VA inducible during electrophysiology study in 7 (30%) and for primary prevention in 3 (13%). Quinidine administration was started due to arrhythmic storm in 6 (26%) patients, frequent ICD shocks in 17 (74%). Median time from ICD implant to quinidine administration was 21.5 months (IQR 14.5-50.5). Quinidine bisulfate was prescribed in 8 patients at a mean dose of 570±247 mgr/day, and hydroquinidine in 15 patients at a mean dose of 715±338 mgr/day. After a mean follow-up of 47±43 months under quinidine we observed a significant reduction in the median number of shocks from 5 shocks per patient (IQR 3.5-7) to a median of 0 (IQR 0-0). A total of 6 patients experienced VA (5 patients had at least 1 ICD shock, in 3 of them shocks were related to a reduction in the dose of Quinidine). Two patients had VA treated successfully with antitachycardia pacing, 2 patients required radiofrequency catheter ablation and 2 patients had recurrent arrhythmic storm. Side effects were present in 4 (17%) patients (diarrhea and cutaneous lupus eritematosus) that were managed with reduction of the doses of quinidine.

Conclusions: Quinidine administration in patients with BS and recurrent ven-

tricular arrhythmias is effective in the majority of patients and contributes to a significant reduction in the number of ICD shocks during follow-up.

P1422 | BENCH**GS-458967, a selective late sodium current inhibitor, terminates torsades de pointes arrhythmias in the chronic atrioventricular block dog model**

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Purpose: GS-458967 is a novel selective and highly potent late sodium current inhibitor (late INa). In this study, we evaluated whether GS-458967 1) affects electrophysiological parameters in normally conducted sinus rhythm (SR) dogs and 2) reduces dofetilide-induced Torsades de Pointes arrhythmias (TdP) in the sensitive chronic atrioventricular block (cAVB) dog model.

Methods: GS-458967 (0.03 and 0.1 mg/kg/5') was first tested in 6 SR dogs. In remodelled cAVB dogs (n=6), GS-458967 (0.1 mg/kg/5') was administered after TdP was induced by dofetilide (D: 25 µg/kg/5'). In both SR and cAVB dogs, monophasic action potentials (MAP) from left and right ventricles (LV-RV MAP duration) along with ECG intervals were recorded. The arrhythmic score (AS) was calculated as the average of the most 3 severe outcomes within 10': being no ectopic beat (no EB: 1 point) single (sEB: 2 points) or multiple EBs (mEB: 3-5 points), beats of TdP (6-50 points) and number of defibrillations (50-100 points).

Results: In SR dogs, only the higher dose of GS-458967 (0.1 mg/kg/5') reduced (*p<0.05 vs SR) repolarization parameters: QTc, LV MAPD and RV MAPD (from 307±10, 210±12, 188±8 to 297±10*, 199±13*, 180±8* ms, respectively), at a maximal plasma concentration of 787±265 nM. In cAVB dogs, GS-458967 (0.1 mg/kg/5') totally abolished TdP (4/6 after dofetilide vs. 0/6), and reduced AS (1.3±0.4 baseline, 31±33\$ after dofetilide and 1.9±1.0 after GS-458967; \$p<0.05 vs baseline and GS-458967). Only some sEB remained present. In addition, in the presence of dofetilide, GS-458967 did not significantly reduce repolarization parameters, such as QTc interval (620±40 ms after dofetilide vs. 594±35 ms after GS-458967).

Conclusions: This study demonstrates that selective blockade of the late sodium current 1) shortens the repolarization duration in SR dogs, and 2) is very effective in terminating dofetilide-induced TdP in cAVB dogs.

P1423 | BENCH**Effects of dronedarone on myocardial transcriptome and proteome in a porcine model of myocardial infarction**

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Purpose: Background: Dronedarone has been shown to be harmful in patients with recent decompensated heart failure. Furthermore, the PALLAS study has shown that dronedarone therapy increases mortality in patients with permanent atrial fibrillation. A pathophysiological explanation for these study results is lacking. In line with the improvement of microvascular flow during AF, dronedarone was capable of reducing the infarct size in acute models of myocardial infarction (MI). However, in our previous study dronedarone therapy did not change infarct size or left ventricular function in a chronic model of anterior MI. The aim of the present study was to elucidate the effects of dronedarone on transcriptome and proteome of healthy (RV), infarcted (LV), and border-zone (BZ) myocardium.

Methods: An anterior MI was induced in 16 pigs. Eight pigs were treated with dronedarone for four weeks after MI, the remaining pigs served as control. At day 28 tissue samples were taken from RV, LV, and BZ; microarray-based RNA profiling as well as 2D-DIGE followed by mass spectrometry were used to screen dronedarone-dependent differences in gene and protein expression. Verification of selected targets was performed by qRT-PCR or immunoblot analysis.

Results: Transcriptome analysis identified 967 or 515 unique transcripts that were affected by Dronedarone in LV or BZ, respectively. Proteome analysis revealed 53 (LV), 50 (RV), or 35 (BZ) protein spots, respectively, that were changed by Dronedarone. IPA analysis of transcriptome data identified Calcium Signaling, Protein Kinase A Signaling, Integrin Signaling, Cardiac Hypertrophy Signaling and Mitochondrial Dysfunction to be among the canonical pathways affected significantly by Dronedarone. IPA analysis of proteome data identified Cardiovascular Disease, Skeletal and Muscular System, and cardiovascular System Develop-

Abstract P1420 – Table 1. Effect of vernakalant during 250ms cycle length pacing and AF at different stages of remodeling

State of remodeling	ERP (ms)	ΔERP HD (ms)	CV (ms)	ΔCV HD (ms)	CVaf (ms)	ΔCVaf HD (ms)	AFCL (ms)	ΔAFCL HD (ms)
NR	125±4.5	23±6.3 [~]	88±6.2	-15±6.3 [~]	NA	NA	137±5.2	62±5.7 [~]
ER	87±1.7 ^{***}	28±5.2 [~]	90±6.8	-10±4.5 [~]	66±3.2	-13.4±2.5 [*]	107±2.5 ^{##}	53±4.3 [~]
AFp	NA	NA	NA	NA	65±2.6	-13.2±3.0 [*]	97±4.4 ^{##}	55±2.6 [~]

[~]p<0.05 vs. Baseline, ^{*}p<0.01 vs. Baseline, [#]p<0.05 vs. NR and ^{##}p<0.01 vs NR.

ment as significantly regulated pathways. ACADSB, ADIPOQ, COL6A1, COMP, MAPK9, MYBPC3, PDIA3 and TFBI were among the 29 targets that were equally affected at transcriptome and proteome level.

Conclusion: Dronedron therapy, although lacking significant effects on infarct size 28d post infarction, provokes significant changes in myocardial gene expression. These changes might improve LV performance in the long term.

P1424 | BENCH

Despite inhibition of IK_r vernakalant does not elicit an atrial positive inotropic effect

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Purpose: The multi ion channel blocker Vernakalant has recently become available in Europe. Among others, Vernakalant inhibits IK_r, which would lead to delayed early repolarization and potentially restore atrial contractility. The purpose of this study is to assess the positive inotropic effect of Vernakalant.

Methods: In 10 goats, the atria were instrumented with piezoelectric crystals, unipolar electrodes and a right atrial pressure catheter. In awake goats, the atrial effective refractory period (AERP) and hemodynamic parameters such as developed pressure (ΔP), fractional shortening (FS) and atrial work index (AWI) were assessed for the right atrium at baseline and at 2 clinical relevant dosages of Vernakalant. Experiments were performed in control (CTL) condition and after 24 hours of AF (24hAF). Subsequently, after 5 half-lives AF was re-induced for 24 hours and monophasic action potentials were recorded in an open chest study under anesthesia.

Results: At baseline, high dose Vernakalant increased the AERP from 136 ± 19 ms to 187 ± 26 ms ($p < 0.001$). After 24hAF AERP decreased to 53 ± 15 ms. High dose Vernakalant caused an increase in AERP comparable to CTL, to 103 ± 28 ms ($p < 0.01$). Hemodynamically, Vernakalant significantly increased atrial segment lengths by 4-8%, therefore leading to a small degree of stretch. However, Vernakalant did not affect ΔP in CTL and 24hAF. Further, no differences in FS and AWI in sinus rhythm or during 450 ms cycle length pacing were observed in CTL or in 24hAF atria. Importantly, early repolarization was not affected, indicated by the unchanged degree of repolarization within the first 50 ms of the action potential (70 ± 20 , 67 ± 12 and $56 \pm 15\%$ for baseline, low and high dose respectively).

Hemodynamic effect of vernakalant in the right atrium after 24 hours of atrial fibrillation

	Diastolic distance (mm)	Developed pressure (mmHg)	Fractional shortening	AWIsr (mm-mmHg)	AWI450 (mm-mmHg)
Baseline	21.8 ± 3.8	0.72 ± 1.12	0.14 ± 0.09	1.08 ± 0.88	1.16 ± 2.06
Low dose	$23.3 \pm 4.3^*$	0.37 ± 0.36	0.09 ± 0.05	0.88 ± 1.04	1.77 ± 1.74
High dose	$23.1 \pm 4.1^*$	0.66 ± 0.66	0.10 ± 0.06	1.99 ± 2.26	1.12 ± 1.76

In a single experiment measurements were performed at baseline and at a low and high dose of Vernakalant. * $p < 0.05$.

Conclusion: Vernakalant increases atrial stretch and prolongs AERP. However, Vernakalant does not have an atrial positive inotropic effect due to the limited effect on the early repolarization.

P1425 | BENCH

Effects of cilostazol on a canine right ventricular wedge model of Brugada syndrome

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Purpose: To date there is no recommendation of oral drugs that can be used for effective prevention of ventricular fibrillation (VF) in patients with Brugada syndrome (BS). Cilostazol, an oral phosphodiesterase type III inhibitor, is reported in cases to prevent VF in patients with BS, however, the underlying mechanism is poorly understood. We used arterially-perfused RV wedge preparations to investigate the electrophysiological effect of Cilostazol in a BS model.

Methods: BS model was created on 16 arterially-perfused canine RV wedge preparations. Pinacidil at $2 \mu\text{mol/L}$, Terfenadine at $5 \mu\text{mol/L}$ and Pilsicainide at $5 \mu\text{mol/L}$ were simultaneously perfused. Once BS model stabilized, the 16 preparations were divided into 2 groups: in one group, perfusion was continued

Table 1

	Control Group	Cilostazol Group
No. of preparations	8	8
QT (ms)	228 ± 12	274 ± 18
J point elevation (mv)	0.48 ± 0.12	$0.18 \pm 0.08^*$
Transmural dispersion of repolarization (ms)	70 ± 16	$46 \pm 18^*$
Epicardial regional dispersion of repolarization (ms)	76 ± 18	$32 \pm 16^*$
Endocardial regional dispersion of repolarization (ms)	44 ± 16	30 ± 16
VT/VF incidence (episode)	14	3 [†]
Endocardial ERP (ms)	155 ± 10	175 ± 10
Epicardial ERP (ms)	150 ± 10	170 ± 10
Dispersion of ERP (ms)	5 ± 10	5 ± 10

[†] $p < 0.05$. ERP, effective refractory period.

with the aforementioned drugs (Control group); in another group, Cilostazol at $10 \mu\text{mol/L}$ was added (Cilostazol group). Transmembrane action potential was recorded from epicardium and endocardium of the wedge preparation, as well as pseudo-ECG. Program stimulation was performed. Spontaneous or induced arrhythmia events were registered.

Results: In arterially-perfused canine RV wedge BS model, Cilostazol corrected J point elevation, decreased transmural and epicardial regional dispersion of repolarization, and was associated with less arrhythmia events (Table 1).

Conclusion: Cilostazol may prevent VF in BS by offsetting the electrophysiological abnormalities, especially the widened transmural dispersion of repolarization.

P1426 | BENCH

Mechanoelectric feedback alterations induced by the benzothiazepine derivative jtv-519

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Purpose: To analyze the effects of mechanical stretch on myocardial activation during ventricular fibrillation (VF) in an isolated and perfused rabbit heart model in order to compare the responses obtained under the influence of a drug (JTV-519) that act on the intracellular Ca²⁺ dynamics and to determine whether the electrophysiological effects of stretch are modified by this benzothiazepine derivative that inhibits ryanodine receptor opening probability and sarcoplasmic / endoplasmic reticulum Ca²⁺ ATPase pump activity.

Methods: In twenty six Langendorff-perfused rabbit hearts VF recordings were obtained using epicardial multiple electrodes on the left ventricle free wall under control conditions ($n=9$) and during perfusion of JTV-519 $1 \mu\text{mol}$ ($n=9$) or $0.1 \mu\text{mol}$ ($n=8$). VF was induced by pacing at increasing frequencies, maintaining coronary perfusion during arrhythmia. After the induction of VF, stretching was applied and maintained for ten minutes and after this period, local stretching was suppressed. VF dominant frequency (spectral techniques) was determined each minute during the study protocol.

Results: JTV-519 slowed the arrhythmia during baseline recordings (control dominant frequency = 14.3 ± 3.0 Hz vs JTV-519 $1 \mu\text{mol}$ dominant frequency = 6.6 ± 0.9 Hz, $p < 0.001$, and JTV-519 $0.1 \mu\text{mol}$ 10.8 ± 0.9 Hz, $p < 0.05$). The VF acceleration observed in the control series during stretch was abolished in the $1 \mu\text{mol}$ JTV-519 series and diminished in the $0.1 \mu\text{mol}$ JTV-519 series (41% increment in the control series, -2% increment in the $1 \mu\text{mol}$ JTV-519 series, ($p < 0.0001$ vs control) and 20% increment in the $0.1 \mu\text{mol}$ JTV-519 series). After suppressing stretch in the control series dominant frequency returned to values similar to baseline (post-stretch = 13.7 ± 2.6 Hz, ns vs baseline), while in the $1 \mu\text{mol}$ JTV-519 series there was a significant dominant frequency decrease in the post-stretch state (post-stretch = 5.9 ± 0.8 Hz, $p < 0.05$ vs baseline). No decrease was found in the $0.1 \mu\text{mol}$ JTV-519 series (post-stretch = 10.2 ± 1.0 Hz, ns vs baseline).

Conclusion: The benzothiazepine derivative JTV-519 modifies the baseline VF activation patterns slowing the arrhythmias and at the highest studied concentrations abolishes the ventricular electrophysiological modifications produced by acute myocardial stretching.

P1427 | BENCH

Therapeutic doses of ranolazine prolong ventricular action potential duration with a frequency-dependent effect without modifying calcium transient duration

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Purpose: Ranolazine is an antianginal drug that has been shown to effectively protect against atrial and ventricular arrhythmias in clinical and experimental studies. However, the mechanisms by which ranolazine exerts its antiarrhythmic effects are not completely understood. Our aim was to analyze the effects of ranolazine administration at therapeutic doses on action potential and calcium transient duration in ventricular myocardium.

Methods: We analyzed 20 Langendorff-perfused rabbit hearts using simultaneous voltage and calcium optical mapping during control conditions ($n=11$) and $5 \mu\text{M}$ ranolazine (RNZ, $n=9$) continuous perfusion. The electromechanical uncoupler blebbistatin, the voltage dye di-4-ANBDQPO and the calcium dye Rhod-2 AM were used. External stimuli (2 ms duration, twice the diastolic threshold) were applied in the outflow tract of the right ventricle by means of a bipolar electrode at a frequency of 4, 5, 6, 7 and 8 Hz. Optical movies were recorded using a 128×128 pixels EMCCD camera at 1 kHz sampling frequency. The optical action potential duration at 80% of repolarization (APD80) for the voltage signal and the [Ca²⁺]_i transient duration at 80% return to baseline (CaT80) were computed. Data are reported as mean $\pm$ SD. A mixed model ANOVA with repeated measures in one

factor (frequency) was used to assess differences between groups with a two-tailed alpha level of $P < 0.05$.

Results: Epicardial optical APD80 was not different between control and RNZ groups when the longest pacing cycle lengths (4 and 5 Hz) were used. However, when hearts were challenged with pacing at shorter cycle lengths, APD80 significantly increased in the RNZ group at 6, 7 and 8 Hz (109 ± 3 vs 104 ± 6 ms at 6 Hz, 104 ± 6 vs 95 ± 5 ms at 7 Hz and 95 ± 4 vs 88 ± 4 ms at 8 Hz; $P < 0.05$ vs control). With respect to calcium dynamics, values of CaT80 were not different between control and RNZ groups at all the pacing frequencies studied.

Conclusions: In our experimental model, ranolazine administered in a therapeutic dose ($5 \mu\text{M}$) prolongs action potential duration in ventricular myocardium at high pacing frequencies, without modifying calcium transient duration. This increase in action potential duration could be involved in the antiarrhythmic effects of ranolazine.

P1428 | BEDSIDE

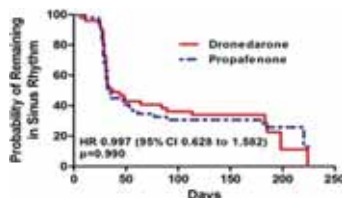
Efficacy of dronedarone versus propafenone for the maintenance of sinus rhythm in patients with atrial fibrillation after electrical cardioversion

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Introduction: The efficacy of dronedarone versus propafenone to maintain sinus rhythm in patients with atrial fibrillation is unknown.

Methods: In this single center, open label, randomized trial, we randomly assigned 98 patients who were receiving dronedarone (49 patients), 400mg twice a day or propafenone (49 patients) 150mg three times a day, then increased dose, 300mg twice a day. Follow-up clinical evaluations were conducted at the first, second, third, and sixth months. The primary end point was the time to the first recurrence of atrial fibrillation.

Results: The median times to a recurrence of atrial fibrillation were 31 days in the dronedarone group and 32 days in the propafenone group ($P = 0.817$). The median (interquartile range) ventricular rate at the first recurrence of atrial fibrillation was 76.5 (67.3-86.5) beats per minute in the dronedarone group and 83.0 (71.0-96.0) beats per minute in the propafenone group ($P = 0.059$).



Dronedarone vs propafenone.

Conclusion: Dronedarone and propafenone had similar efficacy to maintain sinus rhythm in patients with atrial fibrillation after electrical cardioversion. The ventricular rate at first recurrence of atrial fibrillation had a tendency to lower in dronedarone group compared to propafenone group.

P1429 | BEDSIDE

Correlation between colchicine effects on early atrial fibrillation recurrence after ablation and left atrium epicardial adipose tissue volume

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Background: The epicardial adipose tissue (EAT) has been shown to release activated pro-inflammatory cytokines and EAT was associated with the development of atrial fibrillation (AF). Immediate recurrence of AF after AF ablation was related with inflammatory process. Colchicine after AF ablation could suppress the inflammatory reactions and AF recurrence. We evaluated the correlation between colchicine effects on AF recurrence within 2 weeks following AF ablation and various inflammatory factors, including EAT volume surrounding left atrium (LA) (LA-EAT volume).

Methods: We studied 35 patients who received colchicine treatment with 0.5 mg/day for 2 weeks from the next day after AF ablation. The study patients underwent 256-row multi-detector computed tomography before ablation. LA-EAT was automatically identified using the threshold attenuation values of -50 to -200

	Non-AF recurrence group (n=20)	AF recurrence group (n=15)	P value
LA-EAT volume (ml)	16.0 ± 8.5	25.6 ± 14.2	0.03
hs-CRP (mg/dl)			
Pre ablation	0.21 ± 0.23	0.13 ± 0.17	0.24
2 days after ablation	1.04 ± 0.59	1.56 ± 1.70	0.29
2 weeks after ablation	0.17 ± 0.15	0.19 ± 0.31	0.82
Body temperature (°C)			
Maximum	37.3 ± 0.5	37.3 ± 0.3	0.74
At discharge	36.2 ± 0.4	36.2 ± 0.5	0.69

Hounsfield unit. LA-EAT volume was measured by semi-automatically tracing axial images from the bifurcation of the pulmonary artery to the coronary sinus. We compared LA-EAT volume, hs-CRP (pre-ablation, 2 days and 2 weeks after ablation) and body temperature during hospital between AF recurrence group (AF > 30 sec) and non-AF recurrence group within 2 weeks after AF ablation.

Results: LA-EAT volume was significantly lower in non-AF recurrence group (n=20) than in AF recurrence group while the other factors were similar. (Table).

Conclusion: Colchicine treatment after AF ablation may suppress the incidence of early AF recurrence in the patients with lower LA-EAT volume.

SYNCOPE

P1431 | BEDSIDE

A neuroendocrine basis for the underlying mechanisms of dysautonomic syndromes in syncope: the SYSTEMA cohort

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Purpose: Syncope (sudden transient loss of consciousness due to cerebral hypoperfusion with rapid recovery) affects ~40% of the population but mechanisms remain elusive. This study aimed to evaluate haemodynamics and cardiovascular biomarkers during passive orthostasis preceding syncope.

Methods: 667 consecutive patients (298M, 369F; 55 ± 21 years, range 15-93) with unexplained syncope/pre-syncope were investigated by head-up tilt testing (HUT). Blood samples during supine rest before HUT and after 3 min of 70° tilt were used for determination of plasma epinephrine, norepinephrine, renin, C-terminal-pro-arginine-vasopressin (CT-proAVP), C-terminal- endothelin-1 (CT-pro ET-1), and mid-regional-fragment of pro-atrial-natriuretic-peptide (MR-pro ANP) in both positions. Beat-to-beat blood pressure (BP) and ECG were continuously recorded for 20 min or until spontaneous syncope (Italian Protocol) yielding baseline+3 min tilt haemodynamics, systolic (SBP), diastolic (DBP) and heart rate (HR), plus maximal deviation from baseline during tilt. Multivariate-age/sex-adjusted linear regression assessed associations between baseline biomarkers, haemodynamics and HUT changes.

Results: Higher resting CT-proET-1 predicted decrease in SBP (1SD: β -coefficient = -3.72, SE=0.97mmHg; $p < 0.001$) and DBP (β -coefficient = -2.14, SE=0.48mmHg; $p < 0.00001$) during HUT. Decrease in SBP and DBP at 3 min HUT paralleled increased CT-proAVP (1SD: β -coefficient = -2.43, SE=0.69mmHg; $p < 0.001$, and β -coefficient = -1.69, SE=0.35mmHg; $p < 0.00001$, respectively). Lower resting MR-proANP predicted increase in HR at 3 min HUT (1SD: β -coefficient = -1.28, SE=0.41bpm; $p = 0.002$), maximal increase in HR during HUT paralleled increased norepinephrine (1SD: β -coefficient = 1.79, SE=0.47bpm; $p < 0.001$).

Conclusions: Elevated rest endothelin-1 occurs in orthostatic hypotension, while low resting ANP predicts tachycardia during HUT. Further, increased upright vasopressin shows possible compensation against hypotension preceding syncope, while progressive upright HR increase is paralleled by norepinephrine release, possibly compensating inadequate vasoconstriction and tachycardia.

P1432 | BEDSIDE

Influence of age on brain desaturation during head-up tilt test induced syncope in vasovagal patients

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Aim of study: Analysis of influence of age on cerebral regional oxygen saturation (rSO₂) measured by near infra-red spectroscopy (NIRS) during head-up tilt test (HUTT) in patients with vasovagal syncope (VVS).

Study population: 1134 pts (694 women), aged 17-82 yrs. (median: 40 yrs.) with VVS referred to HUTT.

Methods: All pts. underwent standard HUTT. During HUTT rSO₂ of frontal lobes of brain was measured using INVOS cerebral oximeter. Changes of rSO₂ during HUTT in relations to baseline value was expressed as a relative decrease (in%) of rSO₂ in left and right channels. Area limited by curve of rSO₂ during HUTT (rSO₂-AUC), mean (rSO₂-mean) and maximal (rSO₂-max) desaturations during HUTT were analyzed. Patients were divided into 4 groups according to quartiles of age. Measured parameters of brain saturation were compared quartiles of patients' age.

Results: HUTT was positive in 917 pts. (80,6%) Significant desaturation preceded syncope induction during HUTT in comparison to pts. with negative test (31,1 and 32,3% vs 10,4 and 10,6% $p < 0.00001$). Higher values of both mean and maximal desaturation and rSO₂-AUC were observed in the youngest (17-25 yrs.) and the oldest (60-82 yrs.) pts. in comparison to the subjects with age between 25-60 yrs. (II and III quartiles).

Parameters of cerebral saturation

Measured parameter of rSO ₂	1st quartile	1st quartile	1st quartile	IVth quartile	p value
rSO ₂ mean_L (%)	6.9	5.3	5.4	6.3	0.04
rSO ₂ mean_R (%)	6.6	5.1	5.0	6.3	0.02
rSO ₂ min_L (%)	27.3	23.6	25.9	29.4	0.03
rSO ₂ min_R (%)	29.3	25.3	27.2	31.3	0.01
rSO ₂ -AUC_L (%min)	178.3	130.9	139.3	175.6	0.02
rSO ₂ -AUC_R (%min)	172.8	131.7	136.0	175.8	0.02

Conclusions: 1. The brain saturation changes induced by syncope during HUTT are related to the age of patients with vasovagal faints. 2. The youngest and the oldest patients are more sensitive to brain hypoperfusion related to the vasovagal syncope. 3. Lower degree of desaturation induced by syncope in the middle aged pts. with vasovagal syncope may reflect the more feasible autoregulation of brain perfusion or other mechanism, i.e. kind of preconditioning.

P1433 | BEDSIDE

Features and pregnancy outcomes in women with the syndrome of postural orthostatic tachycardia

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Background: Postural orthostatic tachycardia syndrome (POTS) is characterized by the increase in heart rate over 30 beats per minute when standing up. Postural orthostatic tachycardia syndrome is much more common in women than in men. Pregnancy exacerbates POTS, however, there is not enough observation and evidence on the course and outcome of pregnancy for women with POTS.

Aim: Study the characteristics and pregnancy outcomes in women with POTS.

Methods: POTS was traced during pregnancy in 25 women (25.5±2.3 years), who also had POTS before. During pregnancy, these women were observed in the cardiac center every three months. Women were also observed within a year after delivery (after 3, 6, 9 and 12 months).

ECG monitoring, blood pressure monitoring, evolution of autonomic function at supine rest and 5 minute passive tilt (Taskforce, CNSystem, Austria) were made.

Results: POTS increased in 20 patients (80%) during pregnancy. Hypotension before pregnancy was reported in 18 women. Pregnancy-related hypotension was reported in 20 women. 12 women had reflex syncope before pregnancy, 3 of them had syncope during pregnancy. Syncope first appeared in 3 women. Increased values of spontaneous baroreflex were observed in pregnancy with significant reduction of baroreflex sensitivity during tilt. All women were recommended to wear compression elastic stockings. Compression elastic stockings were worn by 15 women (60%). They have seen an increase in diastolic and systolic blood pressure during the daytime hours ($p < 0.01$). These women also decreased the clinical symptoms of orthostatic failure.

Beta-blockers have been assigned to 10 women. Five women were wearing compression knitted fabrics as well as using beta blockers. Five women refused to use both. All women completed pregnancy successfully. All the infants were born alive. In 10 cases, infants were born underweight. Congenital anomalies did not occur. All women retained POTS symptoms postpartum.

Conclusion: Pregnancy exacerbates the POTS, however, POTS is not a contraindication to pregnancy. POTS may lead to the formation of foetuses with low body weight. Women with POTS should be observed during pregnancy. Compression elastic stockings help reduce symptoms in pregnant POTS.

P1434 | BEDSIDE

Atrial fibrillation is associated with syncope and falls in a general population cohort

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Background: Syncope is an important, but underestimated clinical problem in older persons. It is often overlooked in clinical practice or mistaken for fall incidents. Despite the fact that incidence of syncope increases exponentially in people aged 70 and older, data gathered in this population is limited. Atrial fibrillation (AF) is the most common cardiac arrhythmia, but little evidence exists regarding the association between AF, falls and syncope in the general population.

Methods: Sectional analyses within a population sample of people aged 50 and over. Five-minute electrocardiogram recordings (n=4885) were analysed to detect AF. Information on syncope and falls in the past year was gathered through computer aided personal interviews (CAPI). Self-reported comorbidities, subjective and objective health measures and medications were also recorded. Multivariate logistic regression was performed to study associations between atrial fibrillation and falls and syncope.

Results: Mean age was 62 years (range 50-91), 54% were female. Prevalence of AF was 3% with a marked age gradient to 8% in participants aged ≥75 years. Of participants, 5% (n=223) reported syncope and 20% (n=972) reported falls

in the past year. Overall, AF was significantly associated with syncope after adjustment for confounders (OR 2.1 [95% CI 1.1 – 4.2]). After stratification by age category, we found that this association was strongest and only significant in participants aged 50-64 years (OR 5.6 [2.0 – 15.5]). Stratified for age group, AF was significantly associated with falls in participants between aged 65-74 years after adjustment for confounders (OR 2.0 [1.0 – 4.0]).

Conclusions: Adults aged ≥50 with syncope, and adults aged 65-74 years with falls are twice as likely to have AF at physical examination. Early recognition of AF could potentially decrease syncope and fall risk. It could also help prevent stroke and other AF-related cardiovascular events.

P1435 | BEDSIDE

The management of syncope: Remote telemetry counseling patients with syncope in the emergency department of our region based on the guidelines of the European Society of Cardiology

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Background: Guidelines of the European Society of Cardiology (ESC) are standard for the diagnosis of syncope.

Aim: Diagnosis of syncope based on ESC recommendations in remote telemetry consultation patients in Emergency Departments (EDs) of our region.

Methods: Regional Cardiological Center performs remote telemetry consultation in 27 EDs in our region with population of 1.7 million people. Patients (pts) with syncope delivered in EDs between March, 1st, and April, 1st, 2012 were all included in a prospective observational study.

Consulting physicians have learnt diagnostic standards of ESC. EDs reported primary data (history, physical examination, blood pressure and standard electrocardiogram) to the remote telemetry office. Consultants made recommendations about pts examination and treatment if the primary examination did not reveal cause of syncope. Patients with syncope of unknown cause were hospitalized in a specialized cardiological center if necessary.

Results: 935 patient consultations were held in the remote center from our region ED during the month, there of 135 pts had syncope (14.4%, median age 73, interquartile range 18-85, 62% women). 37.0% of patients had arrhythmogenic syncope (there of 22.3% pts had bradyarrhythmias, 12.5% tachyarrhythmia and 2.2% pacemaker failure). 3.2% of pts had drug-induced syncope. Cardiovascular diseases were the cause of syncope in 15.5%. Reflex syncope was observed in 18.5% and orthostatic hypotension in 10.4% of pts. Autonomic failure due to chronic alcohol intoxication was present in 3.0% of pts. 6.6% of pts were "non-syncope". Unexplained syncope was found in 8.8% of pts.

Conclusion: Remote telemetry consultations allow diagnosis of syncope in hospitals located in rural areas in accordance with the recommendations of ESC. Arrhythmogenic syncope prevailed in connection with the specific references in EDs.

P1436 | BEDSIDE

Tilt testing results are related to the tilt table properties

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The tilt testing environment and equipment used can influence the characteristics of the evoked neurocardiogenic reflex. Various tilt tables have different lowering times. There are no unequivocal data regarding the results of tilt testing performed under such different conditions. In particular there are no clear observations of self-perpetuating asystole in the setting of persisting tilt.

The aim of the study was to compare the results of tilt testing performed with two different tilt tables.

The study group consisted of 824 patients (618 F and 206 M), aged 41.4±14.2 years, diagnosed because of syncope. Patients were divided in two groups according to the tilt table: group I (644 pts) had the tilt testing performed with the table with 47 seconds lowering time and group II (180 pts) was testing with tilt table with 10 seconds lowering time.

Results are shown in Table 1:

Table 1

	Group I	Group II	p value
VASIS I (n)	322	116	$p < 0.05$
VASIS II (n)	207	36	$p < 0.05$
VASIS III (n)	9	4	n.s.
No syncope (n)	106	24	$p < 0.05$
Duration of LOC (s)	32.1	16.4	$P < 0.001$
Pause duration (s)	12.0	10.5	n.s.

The multivariate regression revealed that the duration of loss of consciousness (dLOC) was positively related only to VASIS type of neurocardiogenic reaction and to the type of tilt table.

Conclusions: Longer lowering time during tilt testing increases the percentage of cardioinhibitory type of neurocardiogenic reaction. Longer lowering time influences duration of loss of consciousness during syncope. Duration of RR pause during cardioinhibitory type of syncope remains uninfluenced by lowering time indicating its independent mechanism.

P1437 | BEDSIDE**Remote vs. conventional follow-up of implantable loop recorders; time to diagnosis and overall diagnostic yield is similar**

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Purpose: Implantable loop recorders (ILR) are endorsed by ESC guidelines for the investigation of syncope. Remote monitoring of ILRs may improve diagnostic yield. We investigated time to diagnosis and diagnostic yield of remote monitoring compared to conventional follow-up.

Methods: Patients receiving Medtronic Reveal XT ILR were prospectively enrolled to remote monitoring (Medtronic Carelink Network). Scheduled transmissions were made weekly for 8 weeks and monthly thereafter. Patients were asked to make additional transmissions following symptoms. Comparison was made retrospectively to the previous 100 consecutive patients followed non-remotely.

Results: 25 patients were enrolled to remote monitoring, 60% were female, median age was 48.7 years with mean follow-up of 443.2±140.6 days. The conventional follow-up cohort consisted of 100 patients, 62.7% were female, median age was 54.0 years, mean follow-up 393.4±248.2 days.

In the remote group 18 of 25 patients (72%) had ≥1 symptomatic episode; a diagnosis was made in 12 patients (48%). In the control group, 61 patients had ≥1 symptomatic event resulting in a diagnosis in 37 (37%) patients (p=0.314). The types of diagnoses in the remote follow-up group were sinus node disease (SND) in 1 patient, AF in 2 patients, vasovagal syncope (VVS) in 2 patients, complete heart block (CHB) in 1 patient; 6 patients had typical symptoms without any significant arrhythmia.

In the control group, 4 patients had SND, 4 AF, 6 VVS, 2 CHB, and 2 SVT; the remaining 19 patients had typical symptoms without any arrhythmia.

Mean time to diagnosis was 257.6±188.7 days in the remote arm vs. 171.6±147.7 days in the control group (p=0.63). Time to first symptom was similar in both groups. Time from symptom onset to review of ILR data was shorter in the remote group (5.7±8.1 days vs. 23.9±37.1 days s, p<0.001). The majority of the delay in the remote group was delay in patient transmission of data.

Compliance with remote monitoring was excellent and patient satisfaction was rated highly.

Conclusions: Remote monitoring of ILRs allows rapid assessment of symptomatic events but diagnostic yield and time to diagnosis is similar to non-remote follow-up. This may be related to the greater contribution of symptomatic episodes (rather than automatically detected episodes) to diagnosis in both groups.

P1438 | BEDSIDE**Evaluation of brain desaturation during head-up tilt test in teenagers with suspected vasovagal syncope**

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Brain hypoperfusion, causing the syncope, may lead to changes in the brain tissue. The question is how differ teenagers response to the brain hypoperfusion in relation to older group of patients with syncope.

Aim of study: Analysis of changes of cerebral regional oxygen saturation (rSO2) measured by near infra-red spectroscopy (NIRS) during head-up tilt test (HUTT) in young patients with vasovagal syncope (VVS).

Study population: We observed 507 pts.: 151 young pts. (107 girls) aged 12-18yrs (Group I) and 356 adult patients (248 women) – Group II - with VVS referred to HUTT.

Methods: All pts underwent HUTT according standard Westminster protocol. During HUTT rSO2 of frontal lobes of brain was measured using INVOS cerebral oximeter in all pts. Baseline value of rSO2 was evaluated during 15 min. supine phase before HUTT. Changes of rSO2 during HUTT was expressed as a relative decrease (in%) of rSO2 in left and right channels. Area limited by curve of rSO2 and baseline level of rSO2 during HUTT (rSO2-AUC), mean (rSO2-mean) and maximal (rSO2-max) desaturation during the test was also analyzed in all patients.

Results: HUTT was positive in 131 pts. from group I (86.8%) and 285 pts. from group II (80.1%). Significant desaturation preceded syncope induction during HUTT in all pts in comparison to pts with negative test (-29.6 and -31.8% vs -11.4 and -12.1% p<0.00001). Higher values of mean desaturation and area limited by the desaturation curves were observed in teenagers in comparison to adult pts. with vasovagal syncope induced by HUTT. (rSO2-mean L 7.8% vs 5.7%; rSO2-mean R 7.7% vs 5.4%, p<0.02; rSO2-AUC 188.7 vs 153.5%min; 204.8 vs 149.5%min, p<0.015). There were no significant differences of maximal desaturation between both groups.

Conclusions: 1. Syncope induced by Head-Up Tilt Test lead to more pronounced cerebral desaturation in teenagers than in adult people. 2. Higher brain desaturations caused by hypoperfusion leading to reflex syncope in young patients might be a potential injuring factor for the nervous tissue in this group of patients.

P1439 | BEDSIDE**Age-dependent differences in tilt-testing results and RAAS activation in patients with vasovagal syncope**

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The inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) could lead to haemodynamic disturbances resulting in a syncope. The aim of the study was to assess the activation of RAAS during the tilt-induced syncope with regard to the type of a neurocardiogenic reaction and the age of studied patients. The study population consisted of 641 patients (211 M, 430 F) aged 43.7±18.4 years, with the syncope during diagnostic tilt testing. Aldosterone concentration (ALDO) was measured in a supine position before the test (ALDO 1), immediately after the syncope (ALDO 2) and 10 minutes after the syncope (ALDO 3). Patients were divided into 4 groups according to quartiles of age.

Results are shown in the table. There were no differences between the age quartiles with regard to tilt testing results according to VASIS classification. The older groups of patients showed less pronounced RAAS activation irrespective from VASIS classification.

Table 1

Age quartile/VASIS (I/II/III)	ALDO 1 (pg/ml)	ALDO 2 (pg/ml)	ALDO 3 (pg/ml)
102/59/7	105.4±78.6	219.6±189.9	266.4±166.0
89/59/2	95.3±92.0	235.4±251.9	261.3±198.1
89/55/1	64.3±34.4*	126.1±72.5*	167.8±83.9*
121/52/5	66.6±47.7*	157.1±100.0*	183.5±100.8*

*p<0.005 vs 1 and 2 quartile.

Conclusions: RAAS activation during tilt testing-induced syncope decreases with older age. This phenomenon do not influence the type of neurocardiogenic reaction. The implementation of therapeutic measures based on water and salt supply could be more effective in older patients with vasovagal syncope.

P1440 | BEDSIDE**Thoracic impedance to characterize hemodynamic changes preceding syncope**

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Purpose: Shifting of thoracic blood volume from the thorax to the lower extremity is a well known mechanism of neurally mediated syncope (NMS), a condition often resulting in falls and accidents. We previously demonstrated the feasibility of accurate prediction of NMS based on heart rate and pulse wave characteristics. The aim of the present study was to examine whether thoracic impedance (THI), a surrogate parameter of thoracic fluid content is suitable for assessment of hemodynamic changes preceding syncope.

Methods: In 44 patients with a history of unexplained syncope diagnostic 70° head-up tilt table testing (HUTT) was conducted, following current ESC guidelines. Heart rate, beat-to-beat plethysmographic blood pressure and THI were continuously recorded. THI as 30 s average during HUTT was compared among baseline (tilt up -1 min), early (tilt up +1 min) and late tilt (tilt back -1 min). ROC analysis was employed to determine predictive power in respect to occurrence of syncope.

Results: In 21 (48%) patients (57±18 years, 8 females) HUTT was positive, resulting in induction of syncope. In 15 of these patients (71%) syncope occurred following nitrate challenge. Mean time to syncope onset was 43.9±4.9 min after tilting. In both groups a consecutive rise in THI during tilting could be observed (p<0.0001), with no significant difference between groups (p=0.7991). Using the absolute difference of THI over time proved to be a robust measure of THI changes, with the development during HUTT (THI early vs. late) being the most accurate predictor of syncope occurrence. Choosing a cut-off value of 1.74Ω a sensitivity of 76.2% and a specificity of 55.0% could be achieved.

Conclusion: Thoracic impedance is useful to characterize hemodynamic changes preceding syncope during tilt table testing. As THI can be easily and reliably measured and is less prone to artifacts than measurement of pulse wave characteristics, it might improve acute syncope prediction. Further studies, integrating both methods might result in more robust algorithms and thus could foster the reliable application of this technology in ambulatory patients.

P1441 | BEDSIDE**Use of implantable loop recorder in children with long QT syndrome**

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Purpose: Prior research has demonstrated high efficiency of the implantable loop recorder (ILR) in identifying causes of syncope and palpitation in children and adults. Long-term ECG monitoring using IRL was proposed for studying a cause of syncope in children with LQTS.

Materials and methods: ILRs were implanted in 12 children with LQTS from 11 unrelated families. Mean age at implantation was 10±4 years (from 2.5 to 16), 58% were boys. Four pts had experienced syncope and all pts were treated with beta-blockers. There were no indication for ICD implantation before long-

term ECG monitoring was initiated. The ILR follow-up period was 24±8 months on average (from 4 to 35 months).

Results: After IRL implantation 5 of 12 pts experienced syncope (3) or pre-syncope (2) episodes. Two children showed episodes of sustained self-terminated ventricular fibrillation (VF) during syncope. The duration of VF was up to 67 ms. Both were implanted with ICD. The third patient was diagnosed with reflex asystolic syncope. He had two subsequent episodes of asystole lasted 5226 and 14689 ms provoked by venipuncture. As he had LQT3, the ICD was implanted. Two patients had demonstrated recurrent episodes of pre-syncope that coincided with severe bradycardia with heart rate of about 35 bpm.

Conclusion: In children with LQTS, implantable loop recorders can provide valuable information for identification of the cause of syncope. It permits to distinguish arrhythmic and vasovagal mechanisms what is important for choosing adequate strategy of treatment.

P1442 | BEDSIDE

Reduced baroreflex sensitivity during head-up tilt test in patients with vasovagal syncope

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Purpose: The evidence is conflicting regarding the role of baroreflex in patients with vasovagal syncope. The aim of the study was to measure baroreflex sensitivity (BRS) and other hemodynamic parameters during head up tilt test (HUT) with nitroglycerine stimulation.

Methods: Nitroglycerine stimulated HUT was performed in 51 patients with the history of recurrent syncope (mean age 46±19 years, 18 men, 23 women). Cardiac output (CO), stroke volume (SV), left-ventricular ejection time (LVET) and total peripheral resistance (TPR) were assessed during HUT by volume-clamp method using a beat-to-beat photoplethysmography. Spontaneous baroreflex sensitivity was computed using a sequential BRS calculation.

Results: HUT was positive in 28 patients and negative in 23 patients. Baroreflex sensitivity (expressed as proportion of baseline value) was significantly lower at the time of syncope in HUT positive group when compared to end test values in HUT negative group (0.54±0.27 vs. 0.72±0.35, p=0.03). CO was significantly lower in HUT positive patients compared to HUT negative patients (2.6±1.4 vs. 4.3±1.4 l/min, p<0.0001), similarly as SV (34.7±14.7 vs. 49.2±19 ml, p=0.005). LVET was significantly higher in syncopal patients (282.27±26.2 vs. 240.5±58.8 ms, p=0.002) and TPR did not differ between two groups of patients at the time of syncope.

Conclusion: Reduced baroreflex sensitivity may contribute to the development of the vasovagal syncope by inability to adequately counteract hypotension resulting from decreased cardiac output at the time of syncope.

MECHANISMS OF ARRHYTHMIAS

P1444 | BENCH

Cathepsin A-inhibitor reduces susceptibility to atrial tachyarrhythmias and attenuates impairment of left atrial emptying function parameters in rats with myocardial ischemia/reperfusion

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Introduction: Congestive heart failure (CHF) is known to be associated with activation of the renin-angiotensin system leading to the development of an arrhythmogenic substrate in the atria. We investigated the effect of the novel inhibitor of alternative angiotensin-generating enzyme cathepsin A (SAR) in comparison to the inhibitor of angiotensin converting enzyme (ACE) ramipril on susceptibility to atrial tachyarrhythmia (AT) and left atrial (LA) emptying function.

Method: In male Wistar rats, we investigated the effect of chronic treatment with SAR (30mg/kg/d, n=15) and ramipril (1mg/kg/d, n=15) for 3 months on atrial electrophysiology and the development of an atrial arrhythmogenic structural and contractile substrate during CHF induced by 30min of myocardial ischemia followed by reperfusion (I/R). 10 sham operated and 15 placebo treated I/R-rats served as a control. LA-emptying function (magnetic resonance imaging) and atrial electrophysiological parameters were measured before the hearts were harvested for histological and biochemical analysis.

Results: Three months after surgery I/R-rats showed increased left ventricular (LV) enddiastolic pressure, dilated LA, longer inducible AT-durations and reduced atrial contractile function. LA-cathepsin A-gene expression (2.14±0.32 vs. 1.3±0.28; p<0.01) as well as ACE-plasma activity were increased in I/R-rats compared to sham operated rats. Cathepsin A inhibition by SAR and ACE-inhibition by ramipril attenuated the effect of I/R on LA total percent emptying (47±4% and 46±3%, respectively, vs. 37±3% in I/R, p<0.01), susceptibility to LA-tachyarrhythmia (0.69±3.08s and 1.00±3.74s, respectively, vs. 25.00±8.09s in I/R, p<0.01) and total atrial activation time (11.9±0.6 ms; 12.9±0.3 ms, respectively vs. 15.2±1.7 ms in placebo, p<0.01). SAR but not ramipril treatment significantly reduced amount of total atrial fibrosis (34±1% vs. 41±2% in I/R-

rats, p<0.01), collagen1a mRNA expression (9.05±1.26 vs. 14.61±2.0 in I/R-rats, p<0.05) and connexin 43 lateralization in I/R-rats.

Conclusion: Upstream therapy by SAR attenuates the development of an atrial arrhythmogenic substrate and preserves LA-emptying function parameters in I/R-rats comparable to ramipril. Atrial fibrosis formation as well as lateralization of connexin 43 can just be affected by SAR and not by ramipril.

P1445 | BENCH

Myeloperoxidase-deficiency protects from ventricular tachycardia in a murine model of ischemic cardiomyopathy

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Background: Leukocytes have emerged as important mediators of adverse myocardial remodeling following myocardial infarction. Myeloperoxidase (MPO), a heme enzyme abundantly expressed and released by polymorphonuclear neutrophils (PMN), exerts pro-inflammatory and pro-fibrotic properties and has been identified to be causally linked to the formation and propagation of various cardiovascular disorders. We disclosed recently, that MPO critically promotes atrial fibrosis and arrhythmias. Thus, we sought to investigate whether MPO might also influence structural and electrical remodeling in ventricular myocardium.

Methods and results: Wild-type C57bl/6J (WT) and MPO-deficient (Mpo^{-/-}) mice underwent either sham surgery (n=7, 6) or ligation of the left descending coronary artery (LAD) (n=7, 5). Right ventricular electrophysiological investigations 3 weeks after LAD ligation disclosed profoundly increased vulnerability for ventricular tachycardia (VT) in infarcted WT as compared to Mpo^{-/-} mice (number of VT episodes: 6.7±1.3 vs. 1.8±0.9, p<0.01, sham: 2.0±0.4 vs. 1.7±0.8, p=0.79; total time of VT episodes: 3.67±0.88 vs. 0.88±0.36 sec, p<0.05, sham: 0.70±0.18 vs. 1.07±0.75 sec, p=0.67). Epicardial mapping analyses indicated a delayed velocity and enhanced heterogeneity of electrical conduction in WT as compared to Mpo^{-/-} mice. No differences were observed in infarct size between WT and Mpo^{-/-} mice, as assessed by hematoxylin/eosin stain of myocardial sections.

Conclusions: The current data demonstrate, that MPO increases the vulnerability for ventricular arrhythmias in a murine model of ischemic cardiomyopathy. Whereas no differences were observed in infarct size, characteristics of electrical conduction pointed to aggravated adverse electrical or structural remodeling in WT as compared to Mpo^{-/-} mice. While the underlying mechanisms still have to be elucidated, the results underline the important role of inflammatory processes in cardiac remodeling upon myocardial infarction and identify MPO as a potential therapeutic target to prevent ventricular arrhythmias in ischemic cardiomyopathy.

P1446 | BENCH

Mosaic respiratory chain deficiency due to induced mtDNA deletions in the mouse heart leads to an increase in inducible ventricular arrhythmias after myocardial infarction

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Purpose: In the heart, mitochondrial dysfunction occurs physiologically during aging as shown by a low cytochrome c oxidase activity in single scattered cells in vitro (COX⁻ cells). Recent studies have shown that few COX⁻ cells are sufficient to cause spontaneous arrhythmias in very old (18months) but not younger (12months) mice. Here, we evaluate the inducibility of arrhythmias in these younger mice with structural heart disease due to myocardial infarction, which do not exhibit spontaneous arrhythmias.

Methods: A cell-type specific knockin strategy was used to generate a mouse model that expresses a dominant-negative mitochondrial Twinkle helicase (K320E mutation; delTwinkle) in the heart (Rosa26-floxed-Stop-delTwinkle x MCK-Cre). At the age of 12 month myocardial cryo infarction was induced in all mice using a 3mm stamp to generate a structural heart disease and myocardial scar. 2 weeks after the operation we performed in vivo electrophysiological investigations using transvenous right heart catheterization to determine surface and intracardiac electrocardiogram (ECG) parameters. Ventricular extrastimulus pacing and burst stimulation maneuvers were used to evaluate ventricular vulnerability.

Results: At the age of 12 months, delTwinkle mice exhibited 5fold increased levels of mtDNA deletions (qPCR; p<0.05) but no generalized mitochondrial defect as indicated by unchanged protein levels and normal activities (spectrophotometry) of five oxidative phosphorylation complexes. COX⁻ cardiomyocytes were found in 0.17% (±0.12) in hearts of delTwinkle while such cells were never seen in control hearts. Compared to controls, no alterations in standard surface ECG parameters, atrial and ventricular refractory periods, as well as sinus-node and AV-node function were present. However, the probability of induction of ventricular tachycardias (VTs) was significantly higher in delTwinkle mice compared to controls (10.5% vs. 3.2%; p=0.04). VTs could be induced in 56% of all delTwinkle mice and in only 40% of control mice.

Conclusions: The existence of only few interspersed COX⁻ cardiomyocytes due to the accumulation of mtDNA deletions is associated with inducible ventricular arrhythmias after myocardial infarction without accompanying alterations in electrophysiological parameters. Mitochondrial DNA deletions, as found in the aging

heart, might therefore promote arrhythmias in the elderly population beyond structural heart diseases.

P1447 | BENCH

Beta-blockers do not prevent the pro-arrhythmic action of high-level sympathetic stimulation: a role for neuropeptide Y?

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Purpose: Beta-blockers (BB) are the only anti-arrhythmic drug that improve mortality in patients with ischaemic heart disease, but a significant risk of arrhythmia remains. During high-level sympathetic drive, such as during myocardial infarction, co-transmitters including neuropeptide Y (NPY) can be released with norepinephrine. NPY is a potent vasoconstrictor that can also reduce parasympathetic activity and alter cardiac electrophysiology. We hypothesised that ventricular fibrillation threshold (VFT) would still be reduced following high-level sympathetic stimulation even in the presence of a BB. We also investigated whether NPY is independently pro-arrhythmic and decreases VFT, and if this mechanism is mediated by the Y1 or Y2 receptor.

Methods: Hearts with intact stellate ganglia (SG) and sympathetic innervation were isolated from male Sprague Dawley rats (250-300g) and Langendorff perfused in constant flow mode. VFT was determined by pacing at a fixed cycle length (150ms x 20 beats) followed by a 5sec 50Hz burst at increasing current amplitude (mA) until sustained VF was induced. VF was cardioverted with 1ml of potassium chloride solution (50mmol/L). A control experiment demonstrated that VFT remained constant over 3 successive inductions (n=6). SG were stimulated at 10Hz, 1msec pulse width (above capture voltage). Drugs were perfused for 15 mins before stimulation. Electrical restitution (RT) was derived from optically mapped action potentials. All data are presented as mean±standard error.

Results: Direct right SG stimulation significantly ($p<0.05$) increased heart rate and left ventricular developed pressure (LVDP) and these changes were completely blocked by metoprolol (10 μ M/L). However, 2 mins of RSG stimulation in the presence of metoprolol still significantly reduced VFT by over 50% (2.2 ± 0.049 vs. 1.2 ± 0.026 mA, n=5). A similar result was observed following 2 mins stimulation of the left SG. Exogenous NPY (250nmol/L, n=6) also significantly reduced VFT by 50% (2.4 ± 0.15 vs 1.2 ± 0.12 mA) and increased coronary vascular resistance and LVDP. The action of NPY on VFT, CVR and LVDP were abolished by the Y1 receptor antagonist BIBO3304 (1 μ M, n=6), but not by Y2 receptor blockade with BIIE0246 (1 μ M, n=6). Preliminary analysis of RT by optical mapping is suggestive of a steepening of the curve with NPY 250nM (0.27 ± 0.04 vs NPY 0.42 ± 0.12 , n=4).

Conclusion: Prolonged sympathetic stimulation remains pro-arrhythmic in the presence of BB, implicating sympathetic co-transmitters as a novel arrhythmic trigger. NPY can directly decrease VFT via a Y1 receptor mediated mechanism and steepens the RT curve.

P1448 | BENCH

Acetylcholine-dependent potassium current determines atrial defibrillation threshold by regulating post-shock refrillation

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Purpose: Termination of atrial fibrillation (AF) by electrical cardioversion (ECV) remains the mainstay of AF treatment in symptomatic patients. Still, standard ECV attempts may be below atrial defibrillation threshold (aDFT) and hence unsuccessful in up to 20% of patients. However, increasing ECV energy in such instances causes significant tissue damage. Continuous high frequency activation, as a consequence of AF, causes remodelling of the atria, which is associated with ECV failure. Constitutive activation of the atrium-specific acetylcholine-dependent potassium current (IK,ACh) is known to be a constituent of this remodeling. However, it is unknown whether and how this current contributes to the atrial defibrillation threshold (aDFT) and the consequent ECV success rate. Therefore, we investigated the effects of IK,ACh blockade on aDFT in AF.

Methods: Neonatal rat atrial cardiomyocyte monolayers were burst paced to induce reentry-based AF and subjected to biphasic truncated exponential shocks (10-ms duration) of at 20-100V (10V increments) to determine aDFT. To study the effects of IK,ACh on the CT, cultures were treated with Tertiapin or transduced with lentiviral vectors encoding Kcnj5-specific shRNAs. Optical mapping was used to assess electrophysiological parameters prior to, during and after ECV attempts.

Results: Successful ECV depended on full synchronization of all phases around phase singularities. ECV below aDFT failed because of incomplete synchronization or post-shock refrillation. Post-shock refrillation occurred at significantly higher voltages than incomplete synchronization (58 ± 21 vs 34 ± 8 V) and depended on presence of steep repolarization gradients, which occurred at critical pre-shock diastolic intervals (6-12ms at action potential durations [APDs] of 25.8 ± 4.6 during reentry). Tertiapin significantly increased wavelength during reentry (0.48 ± 0.14 vs 0.30 ± 0.09 cm in controls), which correlated strongly with aDFT ($R^2=0.69$), in contrast to conduction velocity ($R^2=0.06$), cycle length ($R^2=0.35$), APD80 ($R^2=0.44$), and complexity ($R^2=0.50$). As a result, IK,ACh blockade significantly decreased aDFT (32 ± 11 vs 60 ± 25 V in controls). Trans-

duction with Kcnj5 shRNA containing lentiviral vectors confirmed these results.

Conclusions: These results suggest that remodeling of IK,ACh could increase aDFT by shortening of wavelength during reentry and thereby decrease ECV success rate. Hence, this study provides new mechanistic insight into failing ECV and identifies IK,ACh as a possible atrium-specific target to increase effectiveness of ECV while decreasing its harmfulness.

P1449 | BEDSIDE

Arrhythmias occurrence relations with angiotensin 2 levels in hypertensive patients

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Activity of renin-angiotensin-aldosterone system play significant role in development of cardio-vascular diseases and particularly in development of hypertension. Arrhythmias development in hypertensive patients also determined by renin-angiotensin system activity.

The purpose of our study was to evaluate the role of angiotensin 2 (AT2) activity in development of electrophysiological remodelling in hypertensive patients.

Methods: Were examined 196 patients with arterial hypertension 1-3 grade complicated by HF I-II NYHA functional class. The mean age of patients - 52.2 (6.8) years. Patients with acute myocardial infarction in history, diabetes mellitus and autoimmune diseases were excluded from the study. In all patients was performed ECG in 12 standard leads, Holter ECG monitoring, EchoCG (ASE/EAE recommendations 2005) and were evaluated plasma levels of AT2 (ng/l). AT2 levels equal to 10-30 ng/l were defined as low and AT2 levels >30 ng/l were defined as high. HF NYHA functional class was determined by using the 6MWT. Extrasystoles types were determined by Lown B. classification. Mean ejection fraction - 65.8 (5.7)%.

The comparison of frequency of arrhythmias occurrence in hypertensive patients with different levels of AT2 was performed by χ^2 test. Statistical significance was defined at the level of methods for $p<0.05$.

Results: As it can be seen from table 1. the frequency of occurrence of frequent supraventricular premature beats, frequent ventricular extrasystoles and ventricular extrasystoles 3-4 grade was statistical significant higher in patients with high levels of AT2.

AT2 levels & arrhythmias occurrence

Arrhythmias types	Angiotensin 2 levels		χ^2	p
	10-30 ng/l; n (%) n=92	>30 ng/l; n (%) n=104		
All SVPB	62 (67%)	77 (74%)	0.76	0.38
Rare SVPB	44 (48%)	43 (49%)	0.05	0.81
Frequent SVPB	18 (19%)	34 (31%)	4.3	0.03
All ventricular extrasystoles	52 (56%)	67 (64%)	1.65	0.19
Rare ventricular extrasystoles	37 (40%)	38 (36%)	0.28	0.59
Frequent ventricular extrasystoles	15 (16%)	29 (28%)	3.97	0.038
Ventricular extrasystole 3-4 grade	12 (14%)	25 (22%)	3.86	0.04

SVPB, supraventricular premature beat.

Conclusion: Thus, results of our study indicates role of high levels (>30 ng/l) of AT2 in arrhythmias development in hypertensive patients.

P1450 | BENCH

Remodeling of calcium handling proteins during atrial fibrillation complicated by tachyopathy in a porcine model

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Background: Atrial fibrillation (AF) and heart failure (HF) are two of the most frequent cardiovascular diseases. They often coexist and lead to significant morbidity and mortality. Recent evidence suggests a key role for Ca²⁺ handling abnormalities in the perpetuation and progression of AF. Despite the clinical significance of this dual epidemic, AF-associated remodeling of atrial Ca²⁺ cycling in the presence of HF has not been addressed to date.

Methods: Persistent AF was induced in domestic pigs by atrial burst pacing via an implanted cardiac pacemaker. Animals underwent electrophysiological and echocardiographic examination on day 1 and prior to euthanization (day 7). Expression of Ca²⁺ handling proteins was analyzed in right atrial tissue samples obtained from pigs with persistent AF (day 7; n=5) and compared to untreated control pigs in sinus rhythm (SR) (n=5).

Results: During AF animals displayed significantly reduced left ventricular ejection fraction (LV-EFday 1, $73\pm6\%$; LV-EFday 7, $58\pm8\%$) and prolonged atrial refractory periods. Persistent AF and HF were associated with down-regulation of Ca²⁺-calmodulin-dependent kinase II (CaMKII β) by 37% without affecting the auto-phosphorylation state of CaMKII β at Thr286. We further observed suppression of PKARII (-62%), L-type calcium channel (LTCC) subunit α_2 (-75%), phosphorylated phospholamban (Ser16, -92%; Thr17, -70%), and phosphorylated ryanodine receptor (Ser2808, -62%). Expression of NCX was increased by 400% compared to controls. In contrast, expression of Serca2a, phosphorylated ryanodine receptor at Ser2814 and LTCC α_1c was not significantly altered.

Conclusions: In conclusion, AF produces distinct remodeling of Ca²⁺ handling

proteins in the presence of tachycardia that is different from paroxysmal or persistent AF in the absence of relevant structural heart disease. These findings highlight the complexity of electrical remodeling processes and provide a starting point for more personalized understanding of AF pathophysiology and treatment efficacy in HF patients.

P1451 | BENCH

Low proarrhythmic potential of escitalopram and citalopram in contrast to haloperidol despite significant QT-prolongation

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Background: In several case reports proarrhythmic effects of citalopram and escitalopram have been reported. The aim of the present study was to investigate if application of citalopram, escitalopram or haloperidol have the potential to provoke polymorphic ventricular tachycardia in a sensitive model of proarrhythmia.

Methods and results: In 20 female rabbits, citalopram or escitalopram (2 µM and 4 µM, n=10) were infused after obtaining baseline data. Eight endo- and epicardial monophasic action potentials and a simultaneously recorded 12-lead ECG showed a significant QT prolongation after application of citalopram as compared with baseline (2 µM: +47ms, 4 µM: +56ms, $p < 0.05$) accompanied by an increase of action potential duration (APD90, ±18 ms with 2 µM citalopram; +27ms with 4 µM citalopram). Administration of citalopram also increased dispersion of repolarization (2 µM: +12ms, 4 µM: +12ms; $p = ns$). Lowering of potassium concentration in bradycardic AV-blocked hearts provoked early afterdepolarizations (EAD) in 3 of 10 hearts and polymorphic ventricular tachycardia resembling torsade de pointes in only 1 of 10 hearts (4 µM, 22 episodes). Application of escitalopram also increased QT-interval (2 µM: +8ms, 4 µM: +30ms, $p < 0.05$) and APD90 (2 µM: +5ms, 4 µM: +20ms, $p < 0.05$) without significant effects on dispersion of repolarization (2 µM: +5ms, 4 µM: +7ms, $p = ns$). No proarrhythmia was observed in this group. The results were compared to 10 rabbits treated with haloperidol (1 µM and 2 µM). Haloperidol led to an increase in QT-interval (1 µM: +51ms; 2 µM: +85ms; $p < 0.05$) and APD90 (1 µM: +30ms; 2 µM: +36ms; $p < 0.05$). In addition, haloperidol increased dispersion of repolarization (1 µM: +17ms, 2 µM: +40ms; $p < 0.05$) and led to the occurrence of EAD in 7 of 10 and of polymorphic ventricular tachycardia in 5 of 10 hearts (69 episodes) with 2 µM haloperidol after lowering of potassium concentration.

Conclusion: In the present study, application of citalopram only caused polymorphic ventricular tachycardia in 1 of 8 hearts while escitalopram did not induce proarrhythmia despite significant QT prolongation. In contrast, haloperidol led to a more marked prolongation of myocardial repolarization combined with a more marked increase of dispersion of repolarization. These results imply that application of citalopram or escitalopram is not as proarrhythmic as some case reports might suggest while haloperidol is torsadogenic.

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Herg blockade by iboga alkaloids

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Purpose: The iboga alkaloids are a class of naturally occurring and synthetic compounds, some of which modify opiate withdrawal or self-administration of abused substances in humans and/or animal models. Fatalities, and case reports describing QT prolongation and PVTs including TdP call attention to the safety of ibogaine, the prototypic iboga alkaloid. We evaluated hERG blockade by ibogaine

with purities of 94% and 99.5% derived respectively by extraction from Tabernanthe iboga and by semisynthesis via voacangine; as well as ibogaine's principal metabolite noribogaine; 18-methoxycoronaridine (18-MC), a product of rational synthesis; and voacangine.

Methods: IKr was measured using the whole-cell patch clamp technique in HEK 293 cells superfused with extracellular solution with and without drug in the same cell.

Results: We found that 94% and 99.5% ibogaine block the hERG channel with respective EC50s of 3.53 ± 0.16 µmol/L (n=11) and 4.09 ± 0.69 µmol/L (n=14). Similarly, noribogaine and voacangine block the hERG channel with respective EC50s of 2.86 ± 0.68 µmol/L (n=11) and 2.25 ± 0.34 µmol/L (n=6). hERG blockade was similar among the 4 drugs (one-way ANOVA, $p > 0.05$). 18-MC to the limit of solubility decreased IKr with an estimated EC50 between 50 µmol/L and 100 µmol/L (n=9).

Conclusion: 18-MC is possibly a safer congener and a candidate for development. The EC50s of ibogaine and noribogaine appear clinically relevant regarding levels associated with QT prolongation, PVTs, and/or fatalities observed in patients. Noribogaine, with a T1/2 in humans on the order of days may mediate delayed fatalities following the ingestion of ibogaine.

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Disparate effect of single and co-administration of clarithromycin and furosemide on cardiac gene expression (Kcnq1, Cacna1c, Myh6, Myh7 and Myh7b) in beta-adrenergically stimulated hearts

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Purpose: In presence of hypokalaemia, the use of QT-prolonging clarithromycin can lead to Torsades de Pointes (TdP). Sustained prolongation of repolarisation may affect cardiac performance that is usually under control of calcium regulating proteins as well as myosin heavy chains (MHCs). We tested levels of mRNA expression of K⁺ channel genes, intracellular Ca²⁺ regulating genes and also MHCs genes in beta-adrenergically stimulated as well as in non-stimulated hearts.

Methods: Wistar rats were treated for 7 days with clarithromycin (CLA, 200 mg/kg/d, p.o.), furosemide (FUR, 200 mg/kg/d, p.o.) or both (CLA+FUR). Controls (CON) received vehicle. ECG was monitored under basal conditions and under cumulative isoproterenol stimulation (ISO doses of 5-60 ng/min, i.v.) in anaesthetized animals. Using qRT-PCR, we examined the left ventricular expression of the following genes: Kcnh2 (RERG1), Kcnq1 (KVLQT1), Cacna1c (LTCC α1C subunit), Atp2a2 (SERCA2a), Ryr2 (ryanodine receptor 2), Myh6 (alpha-MHC), Myh7 and Myh7b (beta-MHCs).

Results: As expected, furosemide caused hypokalaemia ($P < 0.05$). Both, clarithromycin as well as furosemide administration increased QT (and QTc) duration. The co-treatment further potentiated the observed QT (and QTc) prolongation even significantly when compared to single administrations ($P < 0.05$, respectively). ISO administration caused a gradual increase in heart rate which was similar between groups. Although only in one of ten rats of CLA+FUR group, we observed a presence of TdP during ISO administration. Exclusively in CLA+FUR group, ISO stimulation significantly increased the expression Kcnq1 (KVLQT1) as compared to single treatments (by 56% against FUR and by 52% against CLA, for both $P < 0.05$, respectively) and also expression of Cacna1c as compared to all other groups (by 73% against CON, by 97% against FUR and by 75% against CLA, for all $P < 0.05$, respectively). Interestingly, we found a significant increase of all MHCs genes in stimulated CLA+FUR hearts as compared to all other groups (for all $P < 0.05$, respectively). Importantly, none of the analyzed genes was significantly changed in non-stimulated hearts of FUR, CLA or CLA+FUR rats when compared to CON.

Conclusion: The co-administration of CLA and FUR strongly increases the duration of QT and can induce beta-adrenergically triggered TdP in rat. Interestingly, the alterations in genes expression (Kcnq1, Cacna1c, MHCs genes) were present only when drugs combination occurs and only as a consequence of concomitant beta-adrenergic stimulation.

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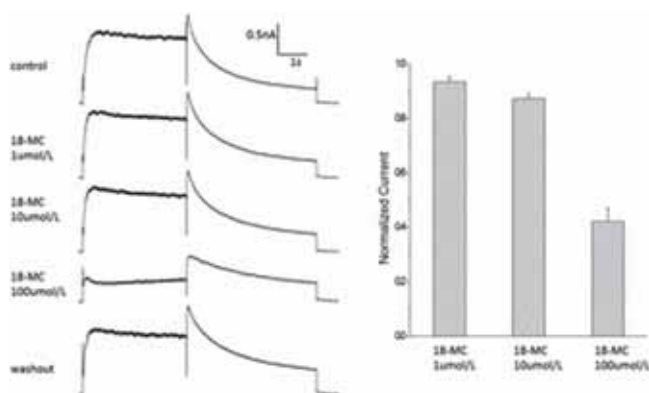
GENETIC ASPECTS OF ARRHYTHMIAS

P1455 | BEDSIDE

Ethnicity and phenotype in the SCN5A E1784K mutation

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Purpose: Long QT (LQTS) and Brugada syndromes (BrS) are arrhythmia syn-



Blocking effect of 18-MC.

dromes with highly variable penetrance. The E1784K mutation in SCN5A is the most commonly identified mutation in both LQTS and BrS and causes an overlap syndrome. Carriers within the same pedigree may exhibit LQTS phenotype, BrS phenotype or both. This international project characterized a unique cohort of E1784K carriers in order to identify associations between phenotype and ethnicity.

Methods: 133 E1784K mutation carriers belonging to 38 families from 5 different countries including Japan were included. Data was collected on age, gender, symptoms, family history and the ECG. Non-digital and digital ECG data were analysed using proprietary software. At least 2 readings were taken per variable and the mean value used. BrS was defined as a type 1 ECG pattern that was spontaneous or induced by a class 1 antiarrhythmic. Statistical significance was determined using either the 2-tailed t-test or Chi-squared test as appropriate.

Results: Among the 133 E1784K mutation carriers, spontaneous BrS and longer QTc intervals were more evident in the Japanese carriers who were more symptomatic albeit without prior aborted SCD. Drug-induced BrS phenotype was unmasked in 63% of Caucasians (34/54) who underwent a test. However, a family history of other SCD was present in 50% of Caucasian families compared to only 13.6% of Japanese families ($p=0.015$). Results are summarised in Table 1.

Table 1

	Total (n=133)	Caucasian (n=103)	Japanese (n=30)	p-value
Age (years, mean, range)	29, 1–70	30, 1–70	23, 6–62	0.0582
Sex-male (n, %)	66, 50	50, 48	16, 53	0.6443
QTc (ms, mean, range)	481, 389–579	475, 389–551	500, 430–579	0.0002
Spontaneous BrS (n, %)	8, 6	1, 1	7, 23	<0.0001
PR (ms, mean, range)	170, 128–302	171, 104–302	165, 128–191	0.5098
QRS (ms, mean, range)	94, 60–136	89, 60–120	95, 64–136	0.0531
Pre-syncope/syncope (n, %)	23, 17	11, 11	12, 40	0.0002
Aborted SCD (n, %)	4, 3	4, 4	0, 0	0.2731

Conclusions: There is significant variation in expression of E1784K between ethnicities with varying severity and prior symptomatology. This supports a strong role for genetic modifiers of phenotype and risk which deserves further study.

P1456 | BENCH

Allelic variations in hERG expression discriminates between symptomatic and asymptomatic LQTS2 patient-hiPSC derived cardiomyocytes

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Aim: We evaluated if cardiomyocytes (CMs) derived from LQTS2 patient-specific hiPSC could assist in discriminating disease phenotype between symptomatic and asymptomatic patients carrying hERG mutations.

Methods and results: Skin fibroblasts from five patients with heterozygous R366X mutations in KCNH2 gene that encodes for IKr potassium ion channel, from a single family with symptomatic and asymptomatic disease manifestations, were reprogrammed to generate transgene-free human induced pluripotent stem cells (hiPSC). These hiPSC were differentiated into cardiomyocytes for confirmational studies. Expectedly, cardiomyocytes from LQTS2 patients (asymptomatic and symptomatic, 628 ± 73 ms, $n=26$) showed delayed repolarization as compared to cardiomyocytes from control (355 ± 48 ms, $n=15$) in corrected field potential (cFPD) in our multi-electrode array analysis. Although cFPDs from cardiomyocytes of symptomatic patients showed longer cFPD (689 ± 89 ms, $n=10$) as compared to asymptomatic (601 ± 109 , $n=16$), no statistical difference was observed. Interestingly, adrenergic stimulation of these cardiomyocytes demonstrated symptomatic patients were significantly prone to irregularities in contraction rhythms as compared to asymptomatic and control group. The irregularities in symptomatic patients could be effectively prevented using beta-blockers. Our pyrosequencing results had demonstrated that hERG displayed differential allelic gene expression pattern only in LQTS2-cardiomyocytes, but not in hiPSC or fibroblast. Furthermore, 67% of the KCNH2 transcripts were dominated by the mutant allele in symptomatic patient samples, whereas both alleles showed equal dominance in undifferentiated LQTS2-iPSCs. Our results indicate that variations in allele-specific expression may provide insights in explaining the differences in symptomatic and asymptomatic LQTS2 clinical presentations.

Conclusions: Understanding the mechanisms governing subtle differences between symptomatic and asymptomatic patients would provide unparalleled insights in developing new diagnostic tools for patient management. Our study leverages the potential of reprogramming technology in disease modelling for better understanding of differential disease penetrance in LQTS2.

P1457 | BEDSIDE

Clinical and mutational spectrum of the patients with cardiac glycogenosis secondary to prkg2 mutations

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Purpose: PRKAG2 mutation is responsible for a rare autosomal dominant cardiac glycogenosis. Clinical manifestations associate ventricular pre-excitation (VPE) syndromes with hypertrophic cardiomyopathies (HCM). The evolution can be complicated with atrio-ventricular (AV) blocks, severe heart failure episodes and sudden deaths (SCD). We aimed to describe the natural history of this disease in 9 French families.

Methods: A cohort of 34 patients from 9 families was diagnosed between 2001 and 2010 in the laboratory for molecular diagnosis of HCM at Pitié-Salpêtrière Hospital. Whereas 5 families carried the recurrent p.Arg302Gln mutation, 4 families private mutations including 3 unreported. A survival study with Kaplan-Meier curves and LogRank tests allowed the calculation of the hazard ratios associated with the clinical hallmarks of the PRKAG2 syndrome at 40 years of age. We also compared clinical characteristics of p.Arg302Gln patients (21 patients, 62% of the cohort), vs newly identified mutations patients (13 patients).

Results: Hazard ratios for a 40 year old patient: VPE 70% (99%-CI: 50%-87%), HCM 66% (99%-CI: 8%-61%), AV blocks 22% (99%-CI: 9%-46%), SCD 20% (99%-CI: 8%-42%), device implantation (pacemaker or defibrillator) 25% (99%-CI: 2%-48%). Heart transplant was realised in 2 patients at 55 and 60 years of age. The median age at death was 60 years. Ablation procedures of the VPE were complicated with AV blocks in 4/6 patients, requiring a cardiac device implantation. Between patients carrying the recurrent mutation and private mutations, no significant difference was identified regarding the development of VPE, the presence of a HCM, severe heart failure, complications or death. However, a trend toward a lower risk of HCM was identified in p.Arg302Gln mutation patients compared to other mutations.

Conclusion: This is the first study to describe the clinical evolution of the PRKAG2 syndrome in a large cohort of 35 carriers issued from 9 families. Complications may occur spontaneously but AV blocks can be favoured by VPE ablation attempts. Prognosis is severe with a natural history of the disease in favour of a high risk of death in this cohort.

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Andersen-Tawil syndrome - symptomatology and prognosis in seven affected families

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Purpose: Andersen-Tawil Syndrome (ATS) is a rare genetic disease caused by a mutation in KCNJ2. It is characterized by arrhythmias, U-waves in ECG, periodic paralysis and developmental abnormalities. Diagnosis and treatment can be difficult due to varied symptomatology and unknown prognosis. Unnecessary ablations and ICD implantations are not rare. The aim of the study was to evaluate ATS symptomatology and prognosis in 7 affected families.

Methods: 7 probands with pathogenic mutations in KCNJ2 and 23 first degree relatives were examined. Clinical evaluation, ECG analysis, genetic screening, pedigree analysis and Holter studies in symptomatic carriers were performed. Group 1 included 17 mutation carriers (age 27.3 ± 14.7 , 29.4% males). Group 2 consisted of 13 unaffected relatives (age 28.8 ± 21.6 , 38.5% males).

Results: Gr.1 prevalence of dysmorphic features was: clinodactyly of fingers – 47.1%, micrognathia – 47.1%, clinodactyly of toes – 11.8%, syndactyly of toes – 11.8%, primary dentition in the 3rd decade of life – 11.8%, low-set ears – 5.9%. Clinodactyly was observed in one non-carrier (7.7%). The height and weight of adults were 158.3 ± 6.5 cm, 52.4 ± 7.7 kg in Gr.1, and 170.4 ± 8.9 cm, 74.4 ± 16.0 kg in Gr.2, ($p<0.001$ and <0.0001 , respectively). Neurological manifes-

	U-wave (% of pts)	QTc >440ms (% of pts)	QTUc >600ms (% of pts)	Median QTc (ms)	Median QTUc (ms)	U wave (ms)	T-peak- U-peak (ms)	T-peak- T-end (ms)
Carriers	94.1	23.5	88.2	427	664	186	236	145
Non-carriers	38.5	7.7	15.4	412	582	133	166	91
p	=0.0051	=0.22	=0.008	=0.04	<0.0001	=0.01	<0.0001	<0.0001

tations (41.2%) and syncope (24.9%) were observed in patients with mutations. ECG results are presented in Table. Each of 8 Holter studies revealed BrVT, VES (200–33000/24h) and PVT (120–170/min) in 7 pts. SCD was reported in 3 non-genotyped relatives: two of them in the family with the coexisting LQT2 mutation. The triad of manifestations appeared only in probands. In one family, pedigree analysis revealed a de novo mutation.

Conclusions: In our ATS cohort: 1) The most prevalent dysmorphic manifestations were clinodactyly and micrognathia; 2) The presence of giant U-wave, prolonged QTU interval, but not long QT interval, was typically observed, though it appears also in relatives without the mutations; 3) ATS could be caused by a de novo mutation; 4) SCD was rare. Decisions about ICD implantation and ablation must be done cautiously.

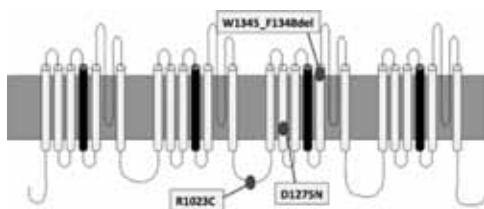
P1459 | BEDSIDE

Cardiac sodium channel gene mutations associated with dilated cardiomyopathy

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Background: Mutations in the cardiac sodium channel gene, SCN5A, cause a variety of inherited arrhythmic syndromes. However, the relationship between the SCN5A gene mutations and left ventricular (LV) dysfunction is still unclear.

Methods and results: We screened the SCN5A gene in 603 probands associated with phenotypes that indicated sodium channel loss-of-function mutations such as Brugada syndrome (BrS), cardiac conduction disease (CCD), sick sinus syndrome (SSS), idiopathic ventricular fibrillation (IVF) and atrial fibrillation (AF). In this cohort, we identified SCN5A mutations in 41 probands (21 in BrS, 14 in SSS, 4 in AF, 4 in CCD, and 3 in IVF, including overlap syndrome). Four of 41 patients were associated with decreased LV systolic function (R1023C in two patients, D1275N and W1345_F1348del in one patient, respectively). One of the R1023C mutation carrier was 46 yo male diagnosed with arrhythmogenic right ventricular cardiomyopathy with LV involvement, and the other R1023C carrier was 75 yo female associated with complete atrio-ventricular block and severe LV dysfunction. The patient with a D1275N mutation was 61 yo female suffered from AF and SSS, and her LV function was decreased. The W1345_F1348del mutation carrier was 71 yo male. He received a pacemaker implantation due to SSS, and his LVEF was decreased to 30%.



Topology of the cardiac sodium channel.

Conclusions: In this study, approximately 10% (4/41) of the patients with SCN5A mutations who presented with sodium channel loss-of-function phenotypes were associated with LV dysfunction. Further experiments will be needed to reveal the underlying mechanisms of SCN5A-related cardiomyopathy.

P1460 | BENCH

Aging-related atrial and ventricular transcriptomic changes in the rat heart. Implications for cardiac arrhythmias

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Purpose: Aging is associated with significantly increased prevalence of cardiac arrhythmias, but transcriptional events that underlie this process remain to be established.

To gain insight into molecular mechanisms of aging-related cardiac arrhythmias, we performed mRNA expression analysis comparing atrial and ventricular myocardium from healthy Wistar-Kyoto (WKY) rats of different ages.

Methods: Atrial and ventricular sampling was performed in 3 groups (n=4 each) of young (14-week-old), adult (25-week-old), and aging (47-week-old) WKY rats. mRNA expressions of 89 genes involved in cardiac arrhythmogenicity were investigated using TaqMan Low Density Array analysis.

Results: Of the 89 studied genes, 40 and 64 genes presented steady atrial and ventricular expressions, respectively. All genes differentially expressed within the atria of WKY rats were up-regulated with advancing age, mainly the genes encoding for various K⁺, Ca²⁺, Na⁺ channels, and type 6 collagen. Atrial expression levels of 19 genes were positively correlated with age. Ventricular transcriptomic analysis revealed a balance between up-regulated and down-regulated genes encoding for the same ion channels. Aging atria displayed a transcriptomic profile

consistent with higher propensity to arrhythmias, including up-regulation of genes encoding for If, ICa-L, ICa-T, INa, outward K⁺ currents, and collagen, while ventricular transcriptome did not seem to be significantly altered by aging.

Conclusions: Our results indicate the induction of an up-regulation transcriptional response in atrial but not ventricular myocytes with advancing age, suggesting that the two chambers undergo different molecular remodeling programs. Additionally, the present results could partly explain the higher propensity to atrial than ventricular arrhythmias in the elderly.

P1461 | BENCH

CaMKII inhibition prevents ventricular and supraventricular tachyarrhythmias in a murine model of recessive CPVT

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Purpose: Bidirectional ventricular tachycardias (VT) are considered a main finding for diagnosing catecholaminergic polymorphic VT (CPVT), and expose patients to sudden cardiac death. Adrenergically mediated atrial tachycardias (AT) are also common manifestations of the disease. It has been suggested that the sarcoplasmic reticulum Ca²⁺ leak induced by β -adrenergic stimulation is mediated principally by Ca²⁺/calmodulin-dependent serine-threonine protein kinase II (CaMKII). To date, no evidences of spontaneous AT in a homozygous CASQ2-R33Q^{-/-} mouse model are available.

Methods: After screening for VT, eleven CASQ2-R33Q^{-/-} mice were chosen for investigating AT. Mice were implanted with micro-osmotic pumps delivering KN-93 (30 μ mol/kg/day) and re-evaluated after 72h. Additional studies were performed in 5/11 (45%) mice after KN-93 wash-out, while another group (N=4) was treated with KN-92, an inactive congener without inhibitory effect on CaMKII signaling. AT incidence was investigated at transesophageal recording in anesthetized mice. In vitro electrophysiological analyses on atrial cardiomyocytes were performed as well.

Results: Heart rate was dramatically reduced upon KN-93 delivery in both baseline condition (408 $\pm$ 37bpm vs. 470 $\pm$ 58bpm, p<0.01) and after adrenergic drug challenge with epinephrine (epi) 2mg/kg i.p. (588 $\pm$ 80bpm vs. 659 $\pm$ 56bpm, p<0.03), while the phenomenon was reverted at wash-out (502 $\pm$ 64bpm at baseline, and 694 $\pm$ 52bpm after epi). VT occurrence was reduced by 54% (45% bidirectional VT, 5/11 p<0.003), while AT occurrence decreased by 62% (from 73%, 8/11, to 27%, 3/11, p=0.03) upon KN-93, and cardiac arrhythmias returned to baseline levels at wash-out. Since in vitro Ca²⁺ imaging studies demonstrated that CASQ2-R33Q^{-/-} atrial myocytes lack regular spontaneous Ca²⁺ events and display severe frequency dependent and isoproterenol (ISO) sensitive Ca²⁺ handling disorders, action potential evaluations in isolated atrial cells from CASQ2-R33Q^{-/-} found delayed after depolarizations (DADs) in 8/10 cells (80%), followed by triggered activity (TA) in 20% cases (2/10) upon adrenergic challenge with ISO (30nM) and pacing at 1Hz. On contrary, pretreatment with KN-93 almost abolished DADs and TA, which were found in 17% cases (1/6, p<0.05 vs. ISO). Finally, KN-92 administration did not prevent arrhythmic events neither in vitro nor in vivo.

Conclusions: CaMKII selective inhibition blunted incidence of cardiac arrhythmias through a reduction in adrenergic response in CPVT mice. Accordingly, targeting CaMKII signaling might be an additional therapeutic strategy for arrhythmia management in CPVT patients.

P1462 | BEDSIDE

A novel SCN4B intronic variant identified in patients with Brugada syndrome and idiopathic ventricular fibrillation caused an exon skipping

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Purpose: Ventricular fibrillation (VF) sometimes occurs in apparently healthy people without organic cardiac disease. Some of them showed characteristic ST-segment elevations in V1-V3 of their ECG and are diagnosed as Brugada syndrome (BrS). In contrast, others without these ECG abnormalities are regarded as idiopathic VF (IVF). It is widely known that SCN5A mutations are identified in BrS and IVF patients. There are four β subunits for Nav1.5, and three of them (SCN1B, SCN2B, SCN3B) have also been reported to be responsible for BrS. It remains unknown, however, whether mutations in SCN4B, which encodes Nav β 4, are associated with BrS or IVF.

Methods: In 234 BrS and 54 IVF patients, we screened genetic mutations in SCN4B. We extracted mRNA from leukocytes, fibroblast and cardiomyocytes

RARE DISEASES

from control samples and performed RT-PCR. To confirm the splice error, we constructed a minigene system including the variant, and it was transfected into human embryonic kidney (HEK293) cells and analyzed.

Results: We identified one SCN4B intronic variant in 6 patients (5 BrS and 1 IVF, 2% of cohort) and summarized the clinical data in Table. The variant was not seen in 240 controls and is located in intron 3, c. 463 + 3 a>t. We could obtain cDNA of SCN4B from cardiomyocytes, but not from leukocytes or fibroblast, indicating the tissue specific expression of the gene. Minigene system confirmed that the variant caused an exon 3 skipping. This would cause a deletion of 229 nucleotides and thereby a premature stop codon with frame shift (c. 235_463del, p. Leu155Trpfs*8).

Clinical characteristics of carriers

Proband	Age/Sex	Symptom	ICD	Diagnosis	Heart rate (beats/min)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
1	37/M	syncope	–	BrS	NA	160	100	400	NA
2	60/M	CPA	+	BrS	50	200	100	420	382
3	32/M	asymptom	–	BrS	80	170	80	400	462
4	19/M	CPA	–	IVF	70	170	70	380	410
5	44/M	syncope	+	BrS	72	170	80	320	351
6	63/M	syncope	–	BrS	74	180	100	380	422

M, male; CPA, cardio-pulmonary arrest; NA, not available.

Conclusion: We identified an SCN4B intronic variant, c. 463 + 3 a>t, which would result in a skipping of exon 3, thereby leading to the premature termination of Navβ4, and its decreased expression would be related to BrS or IVF occurrence. No SCN4B mRNA is expressed in leukocytes or fibroblasts.

P1463 | BENCH

Novel abnormal splicing variants identified in induced pluripotent stem cell-derived cardiomyocytes from a long-QT syndrome patient with KCNQ1-A344A

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Background: Long-QT (LQT) syndrome is an inherited arrhythmic disorder characterized by prolongation of cardiac action potentials, and an increased risk for life-threatening ventricular arrhythmias. LQT type 1 is the most common type of LQT syndrome, which is caused by mutations in the alpha-subunit of the slow component of the delayed rectifier potassium channel (IKs) gene, KCNQ1. A synonymous mutation (c.1032G>A, p.A344A) in KCNQ1 is located in the 3' end of exon 7, and reported to cause abnormal splicing. We previously reported the abnormal splicing patterns and functional characterization of KCNQ1-A344A using patient's blood lymphocytes and a heterologous mutant expression system in cultured cells.

Objectives: We aimed to recapitulate the LQT1 phenotype and investigate the disease causing mechanisms of KCNQ1-A344A carriers using human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs).

Methods and results: We generated iPSCs from peripheral blood lymphocytes obtained from an 11-year-old male carrying KCNQ1-A344A. He experienced syncope while swimming and his QTc interval was 436 ms at rest and prolonged to 527 ms during exercise. In addition to our previous findings using the blood lymphocyte's RNA, we identified novel abnormal splicing variants using patient-derived iPSC-CMs (exon 6-7 skipping, exon 6-8 skipping, and insertion of the 5' end of intron 7). Multi-electrode array (MEA) analyses revealed that isoproterenol prolonged the corrected field potential duration (cFPD) in LQT1-iPSC-CMs more than that in control CMs (the rate of change: 35% vs. 14%, p<0.01). In addition, IKr blocker, E4031, provoked early afterdepolarization-like waveforms only in LQT1-iPSC-CMs (40%, n=10 vs. control; 0%, n=8).

Conclusions: We newly identified the additional exon skipping and intron inserted mRNAs using patient-derived iPSC-CMs with KCNQ1-A344A, and the iPSC-CMs could recapitulate the LQT1 phenotype. Patient-specific iPSC-CMs are useful to understand the pathophysiology of LQT.

P1465 | BEDSIDE

Identification of latent mutations in primary inherited arrhythmia syndromes using benchtop next generation sequencer

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Purpose: The genetic analysis has been applicable for the diagnosis and the treatment in primary inherited arrhythmia syndromes. Recently, benchtop next generation sequencers (BNGS) have been available for targeting gene screening. This study aimed to search for the latent mutations in patients with inherited arrhythmias.

Methods: This study consisted of 152 patients diagnosed with inherited arrhythmias (table). They were negative for mutations in target genes of their disease, those were screened by DHPLC, HRM or direct sequencing methods. We designed amplicon primers for 47 genes which were reported as causative or suspected genes for primary inherited arrhythmia syndromes. Using TruSeq custom amplicon kit and a BNGS MiSeq system, we performed analyses for our targeted genes. Detected mutations were confirmed by direct sequence methods.

Results: We identified 86 mutations in 70 patients (table). In 62 LQTS patients, we identified 8 RYR2 mutations, which were the major cause of CPVT. Two KCNQ1 mutations identified in LQTS patients were supposed to be overlooked by conventional screening methods. In 19 BrS patients, we identified 3 desmosomal mutations, which would indicate that BrS and ARVC were overlapping. In 10 CPVT patients, we identified 3 RYR2 mutations though no mutation was identified in minor CPVT genes.

Conclusions: We unveiled latent mutations by BNGS in short time. Especially in LQTS, we elucidated the high frequency of RYR2 mutations. However, we need to distinguish the variants identified in this method are truly disease causing or not.

P1466 | BEDSIDE

High frequency of ANK2 mutations in patients with non-genotyped primary inherited arrhythmia syndromes

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Purpose: Mutations in ANK2 were reported to cause ankyrin syndrome, including long QT syndrome (LQTS) type 4. But the number of reported patients who were diagnosed as ankyrin syndrome is very small. One of the reasons is that the size of ANK2 is big to screen in conventional methods. Therefore, this study aimed to search for the ANK2 mutations using benchtop next generation sequencer (BNGS) and elucidate the clinical characteristics of the patients with ANK2 mutations.

Methods: The cohort of this study consists of 118 patients with primary inherited ventricular tachyarrhythmia. They were all negative for mutations in KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2 and CACNA1C. We analyzed genetic variants using BNGS, MiSeq (illumine) and confirmed the mutations in direct sequence methods. The nucleotide number is based on NM_020977.3.

Results: Among 118 patients, we identified 2 ANK2 mutations in 4 symptomatic patients (3.4%). The first mutation, c.4603 t>a, p.W1535R, was identified in 36-year-old female (patient 1) diagnosed as LQTS and 39-year-old male (patient 2) diagnosed as Brugada syndrome (BrS). Another mutation, c.5065 g>a, p.V1689M, was identified in 5-month-old boy (patient 3) diagnosed as LQTS and 43-year-old male (patient 4) who was recorded monomorphic ventricular tachycardia. Both mutations were judged as damaging in most prediction software and located in C-terminal domain, where many previous mutations were identified. Patient 1 admitted an emergency hospital after vomiting and QT prolongation (QTc 590 ms) and repeated TdP was recorded in ECG. The ECG of patient 2 showed coved type ST elevation and he experienced two times of syncope at night. His mother had also experienced syncope. VF was induced in his electrophysiological study. Patient 3 was a 5-month-old boy who suddenly lost consciousness with seizure after taking bath. His ECG showed QT prolongation (QTc 480 ms) and his mother suffered syncope while swimming at her teens. Patient 4 consulted a doctor due to repeated palpitation, and ventricular tachycardia was recorded, which was stopped by verapamil injection. Paroxysmal atrial fibrillations were recorded in Holter ECG in addition to frequent PVCs.

Abstract P1465 – Table 1. Number of the identified mutations

Diagnosis	Patient No.	Mutation No.	Mutation (+) Patient No.	Desmosomal genes	RYR2	SCN5A	LTCC	KCNQ1	KCNH2	ANK2	AKAP9	Other genes
LQTS	62	30	26	2	8	0	0	2	0	2	1	15
BrS	19	15	13	3	1	1	2	0	1	1	3	3
IVF	17	12	8	2	1	0	1	0	1	0	1	6
ARVC	11	1	1	0	0	0	0	0	0	0	0	1
CPVT	10	11	8	2	3	0	0	0	0	0	1	5
Others	33	17	14	2	3	2	3	0	2	1	1	3
Total	152	86	70	11	16	3	6	2	4	4	7	33

ARVC, arrhythmogenic right ventricular cardiomyopathy; BrS, Brugada syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia.

Conclusions: We identified 2 ANK2 mutations in 4 symptomatic patients with inherited tachyarrhythmia using BNGS. Although the genetic screening of ANK2 has been difficult due to the size of the gene, BNGS enables us to screen the gene in short time. Because the number of reported ANK2 mutations in inherited arrhythmias is small, we need to accumulate the patients with ANK2 mutations and explore the mechanism of ankyrin syndrome.

P1467 | BEDSIDE

Identification of novel SCN10A variants in Brugada syndrome patients

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Background: Voltage-gated sodium channels are indispensable for action-potential regulation in human heart. The expression of Nav1.8 in cardiomyocytes has been known, and a polymorphism of SCN10A which encodes Nav1.8 was reported to affect the atrioventricular conduction. In addition, a variant in SCN10A was reported to be associated with Brugada syndrome (BrS). This study aimed to investigate the frequency of SCN10A mutations in Japanese patients with BrS, and to compare the phenotypic differences between patients with other BrS-causative genes.

Methods: The subject of this study consists of 240 Japanese probands suspected as BrS. We screened SCN10A genes using high resolution melting method and direct sequencing. To achieve differentiation of rare variants identified in the healthy controls, we checked SCN10A in 250 healthy Japanese subjects. In addition, the possible impact of amino acid substitutions on the structure and function of human protein was evaluated using 3 prediction software packages. Previously, we identified 7 CACNA1C mutation carriers and 17 SCN5A mutation carriers in our BrS probands. After gene-screening, we compared the clinical characteristics among probands with gene mutations in SCN10A, CACNA1C or SCN5A.

Results: We identified 5 SCN10A variants in 6 probands (2.5%). Five probands were male. Four probands complained of symptoms; 1 deceased by sudden cardiopulmonary arrest at age of 35, 1 suffered ventricular fibrillation (VF) and 2 had recurrent syncope. An electrophysiological study induced reproducible VF in 1 syncope proband. Two probands were implanted implantable cardioverter defibrillators. Regarding their electrocardiograms, 5 probands showed saddle-back type in V2 lead, remain 1 proband showed clear coved-type ST elevation in V1-2 leads. Four probands with type2 BrS ECG were examined pilsicainide challenge test, and revealed a coved-type ST elevation in the right precordial leads. Topologically, 1 variant locates in transmembrane region, 3 locate in S5/S6 pore region and last one locates in the C-terminus. In prediction software, all variants were judged to be probably/possibly damaging. Compared with BrS patients carrying CACNA1C or SCN5A mutation, although there were no significant differences among them, symptomatic patients in SCN10A group tend to be older than those in other groups.

Conclusions: We identified 5 novel SCN10A variants in 6 BrS probands. Although the functional significance of these SCN10A variants remains unknown, most of the probands showed severe arrhythmic attacks. Therefore, we should treat these mutation carriers as deleterious clinically.

P1468 | BEDSIDE

Cardiac involvement in familial amyloidotic polyneuropathy

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Purpose: Familial Amyloidotic Polyneuropathy (FAP) is a genetic disease with multisystemic involvement, including cardiovascular (CV). The purpose of this study was to evaluate a large contemporary cohort of individuals with FAP in relation to the CV involvement: symptoms, signs of autonomic dysfunction and electrocardiographic (ECG) changes.

Method: Observational, retrospective, single-center study of 664 carriers of FAP related Transthyretin (TTR) mutations.

Results: In our sample, median age was 38 years (IQ 32-48), 56% were female, 99% were Val30Met TTR mutation carriers and 61% were symptomatic (48% in stage 1, 7% in stage 2 and 5% in stage 3, according with Coutinho staging). During a mean time of disease symptoms of 8±5.5 years, 24% started treatment with tafamidis, 27% implanted pacemaker (PM), 18% underwent liver transplantation and 4% died.

Disease onset occurred with neurological symptoms in 80% of cases and 3% with CV symptoms. Additionally, 49% of patients (pts) developed CV symptoms during follow-up, at a mean age of 42±14 years (3.5±4.4 years after disease onset). CV symptoms became more frequent with disease progression (43% in stage 1 vs 81% in stage 3, p<0.001). In men, CV symptoms appeared at a younger age (40±15 vs 44±13, p<0.001). 30% of pts had CV dysautonomia and only 6 cases showed signs of overt heart failure.

In FAP pts, 82% had sinus rhythm (SR), 16% PM rhythm, 4% Atrial fibrillation, 8% Sinoatrial Dysfunction (SAD), 26% impaired atrioventricular conduction (IAVC) - 24% 1st degree AV block, 4% 2nd degree AV block, 3% complete AV block -

and 27% impaired intraventricular conduction (IIVC) - 18% LAHB, 5% LBBB, 4% RBBB. There was low voltage QRS in 10%, Q waves in 7% and poor R wave progression in 12%. The proportion of pts without SR increased with the stage (p<0.001). There was a significant increase in PR and QRS intervals (p<0.001), as well as the prevalence of IAVC and IIVC (p<0.001) with increasing neurologic stage. Similarly, the presence of non-cardiac symptoms was associated with a higher prevalence of ECG changes.

First degree AV block was significantly associated with the presence of LAHB (28%), LBBB (19%) or RBBB (8%), as well as with SAD (16%) and advanced AVB (16%).

In asymptomatic carriers (n=258), the most frequent ECG changes were 1st degree AV block (6%) and nonspecific ventricular repolarization abnormalities (8%); only 2% had IIVC.

Conclusion: In our population, the CV events occurred in about one half of pts, at a young age, mostly with dysautonomia and conduction disturbances, and progressed with disease evolution.

P1469 | BENCH

Semiconductor next generation sequencing of the main QT interval duration genes in a cohort of long QT and Brugada Syndrome patients

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Purpose: Mutations at the KCNH1, KCNQ1, SCN5A, and KCNE1/E2 that encode cardiac channels have been associated with inherited arrhythmias and the QT-interval in the general population. We aim to analyze how Next Generation Sequencing (NGS) technologies would be of special interest to uncover the genetic variation at these genes in large cohorts of patients with Long QT and Brugada Syndrome (LQTS vs. BrS).

Methods: We developed a procedure for the NGS of the five genes through amplification of all the coding exons in only two tubes followed by semiconductor array sequencing in an Ion Torrent Personal Genome Machine (PGM). A total of 60 patients (index cases) with LQTS (29) or BrS (31) were NGS sequenced for the five genes.

Results: We identified 25 putative mutations (19 in LQTS and 6 in BrS patients) that were confirmed through Sanger sequencing of the corresponding amplicons: 8 in KCNQ1, 10 in KCNH2, and 7 in SCN5A. In addition, five patients (16%) with a clinical phenotype of BrS were carriers of a rare KCNE2 variant (p.T8A). Their clinical profile included spontaneous type I ECG in 3 cases (60%), syncope in 2 cases (40%), and male gender in 4 cases (80%). History of sudden death of first degree relatives younger than 45 years (age range 13 to 41) was documented in 3 cases (60%). No any of those patients experienced malignant arrhythmias or sudden death. Despite this KCNE2 variant has been linked to prolonged QT interval duration in the general population, we did not found it in any patient with a clinical phenotype of LQTS (p<0.01).

Conclusions: Here we show the usefulness of the NGS procedure to uncover the genetic mutations and variants related to arrhythmogenic syndromes in our cohort. The method allowed for detection of a genetic variant encoding the auxiliary β subunit KCNE2 (p.T8A) not previously reported as affecting BrS patients. It is well known how this protein interacts with the potassium transient-outward current, which plays a major role for arrhythmogenesis in BrS. Our data encourage further analysis about the electrophysiological significance of p.T8A KCNE2 variant in BrS patients.

P1470 | BEDSIDE

Prevalence of early repolarisation in paediatric relatives of sudden arrhythmic death syndrome (SADS) victims

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Background and aims: Elevation of the ECG J-point in the inferior and lateral leads (early repolarisation) has been described in survivors of VF arrest and occurs in adult first degree relatives of sudden cardiac death (SCD) probands at a frequency significantly greater than in controls, raising the possibility that this could represent an independent risk factor in the aetiology of SCD. However, data on early repolarisation in the paediatric population are lacking. This study aimed to assess the prevalence of early repolarisation in paediatric first degree relatives of sudden arrhythmic death (SADS) victims.

Methods: Paediatric relatives (aged <18 years) of SADS probands referred to the Inherited Arrhythmia Clinic at our hospital had their initial screening ECG reviewed for evidence of J-point elevation. J-point elevation was defined as ST-elevation >1mV from baseline, QRS-ST slurring or a discrete notch in two or more inferior (II, III, aVF) or lateral (I, aVL, V4, V5, V6) leads.

Results: The ECGs of 95 paediatric first degree relatives of SADS victims from 31 families were reviewed by two assessors. J-point elevation was present in 22 patients (23%) of this patient group compared to the reported prevalence of 5-13% in the general paediatric population.

Conclusions: Infero-lateral J-point elevation occurs in a substantial proportion of paediatric first degree relatives of SADS probands with a similar prevalence

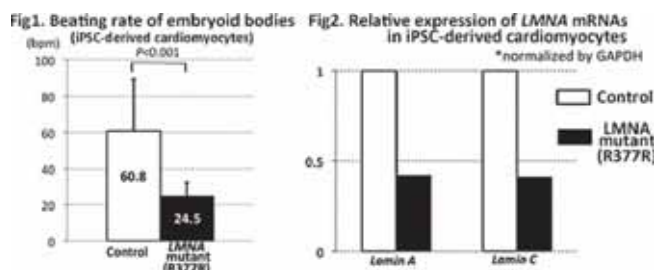
to that described in adults. This suggests that early repolarisation could be an important inherited trait when evaluating relatives of SADS victims. Prospective follow up of this group of children is important to establish the implication of this finding in future risk stratification.

P1471 | BENCH

Recapitulation of lamin A/C-related cardiomyopathy using patient-specific induced pluripotent stem cells: a novel splicing mutation in LMNA gene

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Mutations in lamin A/C gene (LMNA) are the most common cause of familial dilated cardiomyopathy (DCM) with cardiac conduction system disease (CCD). Here we report a 63-year-old male case suffered from DCM and CCD. The proband's mother, sister, and two sons were also affected with DCM and/or CCD. We identified a novel synonymous mutation, c.1131C>T, p.R377R, in exon 6 in LMNA. The results of genetic analysis with his family members were completely correlated with their clinical phenotypes. In order to analyze the association of the synonymous mutation with splicing, we used the web-based splicing site analysis tool (Berkeley Drosophila Genome Project). The prediction indicated that the LMNA-R377R mutation generates the abnormal boundary of splicing donor site adjacent to the mutated base (score for 3' splice site: 0.91). The abnormal splicing would introduce a frameshift and premature termination in the sequence. We generated induced pluripotent stem cells (iPSC) from peripheral lymphocytes and differentiated into cardiomyocytes (CMs). The beating rate of embryoid bodies from patient iPSC was significantly lower than that from control iPSC (Fig. 1). Expression levels of LMNA in patient iPSC-CMs were reduced by half (Fig. 2), which was compatible with the result of peripheral blood lymphocytes.



Beating rate and LMNA mRNAs expression.

These findings indicated that the LMNA-R377R synonymous mutation led the cryptic splicing followed by nonsense-mediated mRNA decay in iPSC-CMs from the patient. The iPSC-CMs derived from the patient with lamin A/C-related cardiomyopathy could recapitulate the disease specific phenotype, and are useful to investigate the disease causing mechanisms.

P1472 | BEDSIDE

Arrhythmias among young patients with multiple connective tissue abnormalities

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Purpose: Hereditary connective tissue diseases (Marfan syndrome, Ehlers Danlos syndrome, and etc.) are risk factors of arrhythmia and sudden cardiac death. We aimed to investigate the incidence arrhythmias among young patients with multiple connective tissue abnormalities but no signs and family history of known hereditary syndromes.

Methods: The study included 549 patients with connective tissue dysplasia (330 men, mean age 23.51±8.67). The main connective tissue abnormalities were signs of musculoskeletal system (n=549: abnormal curvature of the spine, flat feet, hyper-flexible joints, deformities of the anterior wall of the chest, dolichostenomelia and etc.), signs of cardiovascular system (n=409: prolapse of the mitral or aortic valves, aortic aneurysm, varicose veins and etc.), and signs of respiratory system (n=119, primary pneumothorax and etc.) and skin (n=169). Continuously monitoring heart activity (Holter monitor) was performed for all patients.

Results: Arrhythmias were detected in 69,95% of patients (n=384): episodes sinus tachycardia (20,95%), inappropriate sinus tachycardia (1,09%), sinus bradycardia (3,83%), sinus arrhythmia (39,89%), vegetative sinus node dysfunction (0,73 per cent), the migration of the rhythm pacemaker (8,20%), ventricular extrasystole (16,21%), supraventricular extrasystole (17,67%), paroxysmal atrial tachycardia (2,73%), atrioventricular node block (1,28%), sinoatrial node block (0,73%), infra-Hisian blocks (7,29%), WPW-syndrome (0,18%). Arrhythmia in 52,60% of cases combined with pathology of the heart valves, in 61,98% of cases (n=238; 95%CI 56,90-66,82) - with disorders of arteries and veins. Among pa-

tients with arrhythmias was significantly more men (n=253; 65,89%; $\chi^2=17,27$; p=0.000) and cases of aberrations of repolarization, diastolic dysfunction.

Conclusions: Arrhythmia increased the chance of recording aberrations of repolarization (OR 4,36, p=0.000) and diastolic dysfunction (OR of 2.23, p=0.003). Factors increasing the likelihood of arrhythmias among young patients with multiple connective tissue abnormalities are male (OR 2,21, p=0.000), pronounced manifestations of connective tissue dysplasia (OR 1,70, p=0.006), dispersion QTc- interval >50 ms (OR 8,84, p=0.000), deviations from the normal circadian index (OR 3,39, p=0.000).

P1473 | BEDSIDE

Insight into the pro-arrhythmic triggers in J wave syndrome: results of 15 year-follow up

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Purpose: Experimentally, hypokalemia increases the net repolarization current and enhances the transmural dispersion of repolarization in Brugada syndrome (BrS). On the other hand, we have recently reported recurrent ventricular fibrillation (VF) related to hypokalemia in early repolarization syndrome (ERS). Taken together, we analyzed the importance of hypokalemia in ERS and BrS patients during long-term follow up.

Method: From early 1999 to 2014, in our emergency department and after excluding patients with chronic kidney diseases, serum potassium (S.K+) at time of resuscitation of 57 VF survivors was measured, including 24 patients with J-wave syndrome (11 ERS and 13 BrS patients) and 33 VF-survivors due organic heart disease (OHD).

Results: Immediately after resuscitation, S.K+ was significantly lower in J-group than in OHD group (3.1 ± 0.4 Vs 4.9 ± 1.1 mEq/L, $P < 0.001$). Interestingly, 3 patients developed VF associated with hypokalemia shortly after starting oral steroid therapy for treatment of concomitant bronchial asthma, and they were free from any VF event after steroid discontinuation.

Furthermore, 3 patients with ERS had recurrent in-hospital electrical storms associated with hypokalemia (S.K+: 2.65 ± 0.05 mEq/L) and J-wave augmentation (J-amplitude 2.3 ± 1.1 mm). Importantly, after successful resuscitation, they were kept on anti-mineralocorticoids therapy with follow-up S.K+ of (3.72 ± 0.24 mEq/L) and significant reduction in J- amplitude (0.9 ± 0.5 mm, $P < 0.01$) and free of VF episodes during follow up of 3.5~15 years.

Conclusion: In long-term follow up, hypokalemia has clearly added a substantial pro-arrhythmic effect in J-wave augmentation and VF mechanism in J-wave syndrome and hence, strict prevention and treatment of even mild hypokalemia is crucial especially in patients with recurrent VF episodes.

P1474 | BENCH

The rs3807989 G/A polymorphism in the CAV1 gene is associated with atrial fibrillation in Chinese Han populations

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Background: A recent meta-analysis of several genome wide association studies (GWASs) identified six new susceptibility single nucleotide polymorphisms (SNPs) for atrial fibrillation (AF) in individuals of European ancestry. We aimed to replicate the association between these SNPs and AF in a Chinese Han population.

Methods: We included a total of 597 cases with AF, and a control group consisting of 996 participants in absence of AF. The 6 SNPs were genotyped by using the middle-throughput iPLEX Sequenom MassARRAY platform. All statistical analyses were performed using STATA 12.0 software.

Results: Among the SNPs analyzed in the study, the SNP rs3807989 in the CAV1 gene on chromosome 7q31 was found to be significantly associated with AF (OR = 0.76; 95% CI, 0.64 – 0.90; $P = 0.001$), with adjustment for gender and age in the additive model. When controlling for covariates of gender, age, hypertension, coronary artery disease (CAD), and diabetes, the relationship was still significant (OR = 0.75; 95% CI, 0.63 – 0.89; $P = 0.001$).

Conclusion: In conclusion, we replicated the associations of SNPs identified by a GWAS with AF in Chinese Han populations. The study results showed that the SNP rs3807989 was significantly associated with AF. This finding may promote a better understanding of AF pathogenesis, risk prediction, and stratification of treatment strategy.

CLINICAL ARRHYTHMOLOGY

P1476 | BEDSIDE

Uninterrupted warfarin therapy has less bleeding as compared to heparin bridging in patients on chronic anticoagulation undergoing cardiac rhythm device implantation: a metanalysis

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Introduction: Patients on chronic anticoagulation pose a complex clinical

dilemma when undergoing implantation of cardiac rhythm devices (Pacemaker or Automated Implantable Cardioverter-Defibrillator). Peri-procedural anticoagulation options include uninterrupted oral anticoagulation and heparin-based bridging therapy. Optimal management of peri-operative anticoagulation in these patients is not well defined.

Objective: We performed a meta-analysis of available publications in the field to compare the risk of bleeding in patients on uninterrupted warfarin versus heparin-based bridging therapy undergoing cardiac rhythm devices implantation.

Methods: Clinical trials evaluating the bleeding events in patients on anticoagulation undergoing cardiac rhythm devices implantation were considered. Studies were obtained using search words in Medline, PubMed, EMBASE, CINAHL and Cochrane databases. The odds risk across all study groups was computed using Mantel-Haenszel random effects model. Results were calculated with 95% CI and were considered statistically significant if 2-sided alpha error was <0.05 .

Results: Eleven trials were included for analysis ($n=2795$). Mean age and follow-up duration were 65.5 years and 4.1 weeks respectively. The odds ratio of bleeding in patients on uninterrupted warfarin therapy compared to patients undergoing heparin bridging therapy was computed to be 0.35 (0.25, 0.47); $p<0.00001$ (Figure 1).

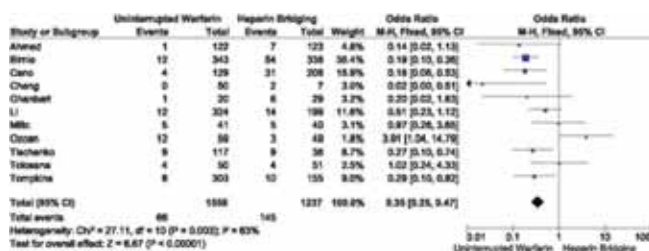


Figure 1

Conclusion: In patients undergoing cardiac rhythm devices implantation, uninterrupted warfarin therapy offers lower bleeding rates when compared to heparin bridging therapy.

P1477 | BEDSIDE

HEMORR(2)HAGES bleeding score predicts hematoma occurrence in patients with uninterrupted oral anticoagulation (OAC) undergoing cardiac device procedures

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Purpose: Uninterrupted oral anticoagulation (OAC) therapy during cardiac device procedures is associated with reduced hematoma formation as compared with bridging approach. The HASBLED score has previously shown to predict bleeding in patients undergoing cardiac and non cardiac procedures on bridging strategy. However, predictors of hematoma formation during uninterrupted OAC remain to be identified. The present study was designed to investigate whether common bleeding risk scores [HASBLED, ATRIA and HEMORR(2)HAGES] predict hematoma occurrence in patients with uninterrupted OAC undergoing cardiac device procedures.

Methods: Twenty-three patients (mean age 76.7 ± 9 years, F:M=8:15) undergoing device procedures (11 replacements, 10 ex novo implants, 2 system/pocket revisions) during uninterrupted OAC were consecutively enrolled in the study. Main bleeding scores [HASBLED, ATRIA, HEMORR(2)HAGES] were calculated in all patients based on clinical, instrumental and laboratory parameters. Hematoma was clinically described as any suffusion or ecchymosis in the pocket area. All patients signed an informed consent before entering the study.

Results: Five out of 23 patients (21.7%) developed pocket hematoma during the next 15 days after the procedure. Age (74 ± 12 vs. 76 ± 8 , $p=0.69$) and gender (F:M 1:4=7:11, $p=0.47$) were comparable among patients with and without hematoma occurrence. By contrast, patients developing pocket hematoma displayed higher INR values (2.6 ± 0.2 vs. 2.2 ± 0.3 , $p<0.05$). Among different bleeding scores, HEMORR(2)HAGES was significantly increased in patients with hematoma formation (2.6 ± 0.9 vs. 1.3 ± 0.8 , $p<0.01$). Interestingly, linear regression analysis showed that HEMORR(2)HAGES was significantly associated with hematoma occurrence, regardless of gender and INR value ($\beta=0.79$, $p<0.01$).

Conclusions: Our pilot study indicates that HEMORR(2)HAGES bleeding score may represent a reliable predictor of hematoma occurrence among patients with uninterrupted OAC. These unanticipated findings suggest that HEMORR(2)HAGES score might be useful to warrant safer INR therapeutic ranges while minimizing bleeding risk in patients with uninterrupted OAC undergoing cardiac device procedures.

P1478 | BEDSIDE

Cost effectiveness of device surgery without interruption of oral anticoagulation: results from the bridge or continue warfarin for device surgery randomized controlled trial (Bruise control)

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Background: In a recent randomized controlled trial (BRUISE CONTROL), a strategy of continuing warfarin treatment at the time of pacemaker or defibrillator surgery resulted in a reduced incidence of clinically significant hematoma as compared with bridging therapy with heparin. The objective of this sub-study was to assess the cost effectiveness of continued-warfarin as compared with bridging-heparin therapy in this group of patients.

Methods: Analysis assessed the direct health care related costs from the Canadian healthcare system perspective for continued-warfarin therapy and bridging-heparin therapy. Health care resources included the cost of anticoagulant medications, laboratory tests, hematoma and other thromboembolic related hospital stays, emergency room visits and physician visits. Indirect costs were not estimated. Resource use was weighted by appropriate unit costs. Cost effectiveness was assessed through the incremental cost per hematoma averted with uncertainty assessed through non-parametric bootstrapping. Sensitivity analyses examined the impact of both patient and surgical characteristics and the effect of alternative assumptions regarding costs on the cost effectiveness results.

Results: Clinically significant hematoma occurred in 12 of 343 (3.5%) patients in the continued warfarin arm and 54 of 338 (16.0%) patients in the bridging arm (relative risk, 0.19; 95% confidence interval, 0.10 - 0.36; $P<0.001$). Treatment with continued-warfarin was also associated with lower costs as compared with bridging-heparin therapy (\$218 versus \$2041), a cost savings of \$1823 (95% CI \$1357 to \$2490). Consequently, continued warfarin treatment is the dominant strategy being both more effective and less costly. This is driven by a marked reduction in ambulatory visits/hospitalizations and reduced drugs costs. Results were robust to detailed deterministic and probabilistic sensitivity analyses.

Conclusions: A strategy of continued warfarin markedly reduces direct cost of care in patients undergoing surgery for either a pacemaker or defibrillator compared to heparin bridging

P1479 | BEDSIDE

Permanent pacemaker implantation during anticoagulant treatment with dabigatran etexilate (single centre experience)

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Objective: The aim of present study was to assess the frequency of hemorrhagic and thrombotic complications arising after permanent pacemaker implantation in patients receiving anticoagulant therapy with dabigatran etexilate.

Methods: Prospective observational study included 16 patients with permanent or persistent atrial fibrillation (of whom 7 males) receiving dabigatran, who underwent primary pacemaker implantation between January 2013 and January 2014. The control group consisted of 70 patients with atrial fibrillation who received warfarin and underwent primary pacemaker implantation. Information about adverse events was collected during the initial hospitalization and over a period of following 30 days. Endpoints were defined as intensive intraoperative bleeding; postoperative bleeding required additional surgical intervention or cancelling of anticoagulant treatment; requirement in plasma transfusion; incidence of hematomas that did not require surgery; thromboembolic complications of any localization. Statistical analysis was performed using Statistica 7.0 programs package; Fisher exact test was used to compare event frequencies in independent groups; comparisons of continuous variables were performed using Mann-Whitney test. Data is presented as "Me [25; 75]" (Median [interquartile range]).

Results: The groups did not differ significantly by baseline parameters. All the pacemaker implantations were performed by standard protocol (with mean number of implanted leads of 1,2 in each group). The interval between the last dose of dabigatran and surgical intervention was 16 [12; 28] hours; interval before first dabigatran dose administration after pacemaker implantation ranged from 8 to 24 hours. In all patients receiving warfarin, it was not interrupted. There were no major bleeding complications in early postoperative period both in dabigatran and warfarin groups. Hematomas that not required surgical intervention occurred in 2 patients who took warfarin and in 1 patient in dabigatran group ($p=0.48$). All patients completed the extended period of observation. There were no hemorrhagic or thromboembolic complications within 30 days after discharge both in groups receiving dabigatran and warfarin.

Conclusions: In patients receiving dabigatran, pacemaker implantation did not lead to increased frequency of bleeding or thrombotic events. Further studies are required to establish the safety of continued therapy with this anticoagulant in perioperative period.

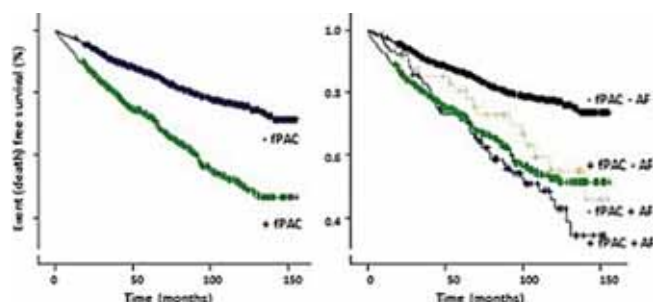
P1480 | BEDSIDE**Higher mortality seen in patients with frequent premature atrial contractions**

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Purpose: Frequent premature atrial complexes (fPACs) have been reported as a risk factor for Atrial Fibrillation (AF). Some studies have linked fPACs to high mortality. More work is needed to establish this relationship.

Methods: We analyzed Holter recordings obtained between 2000 and 2010 of 1357 patients free of AF at baseline. Holter groups with fPAC (>100/day) and infrequent PACs (<100/day) were compared. Electronic medical records and EKGs were reviewed to ascertain baseline characteristics as well as occurrence of AF and death during median follow-up of 7.5 yrs. Logistic regression and Kaplan-Meier analyses were performed.

Results: Mean age was 64 yrs with 93% men. Mean BMI, A1c, left atrial size and average HR were 31.24 kg/m², 6.42%, 42.56 mm and 73 bpm, respectively. 37.31% of patients with fPACs died during follow-up as compared to 18.87% in non-fPAC group. After adjusting for demographics, medication use, co-morbidities, lab and echo findings, multivariate regression analyses confirmed fPACs to be independently associated with higher incidence of death (OR 1.44, 95% CI 1.07-1.92, P=0.015). Furthermore, mortality rates in patients with +fPAC/+AF, -fPAC/+AF, +fPAC/-AF and -fPAC/-AF were 48.11%, 36.73%, 34.3% and 17.8% respectively (p<0.0001).



Kaplan-Meier survival curves

Conclusion: Patients with fPACs (>100/day) have higher all-cause mortality, especially when they develop subsequent AF.

P1481 | BEDSIDE**Anti-arrhythmic drugs did not reduce progression from paroxysmal to sustained atrial fibrillation: from the Fushimi AF Registry**

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Purpose: Atrial fibrillation (AF) increases the risks of thromboembolism and death, and the prevalence of AF is increasing significantly (reportedly, 0.6% of total population in Japan).

Progression from paroxysmal to sustained types (persistent or permanent) of AF is sometimes seen, but the effect of rhythm-control therapy on the progression remains elusive. We investigated the effect of anti-arrhythmic drugs (AAD) on the progression of AF.

Methods: The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all of the AF patients living in Fushimi-ku, Kyoto, which is a typical urban district of Japan with a population of 283,000. At present, we have enrolled 3,821 Japanese AF patients (1.2% of total population) from March 2011 to December 2013. We investigated 1,398 paroxysmal AF patients at baseline who completed one-year follow-up.

Results: 457 paroxysmal AF patients (32.7%) were prescribed AAD at baseline; 107 (7.7%) for Vaughan-Williams class Ia, 17 (3.7%) for Ib, 318 (22.8%) for Ic, 13 (0.9%) for amiodarone, 34 (2.4%) for bepridil. 428 patients (30.6%) were prescribed single AAD and 29 patients (2.1%) were prescribed multiple AADs. Patients receiving AAD were more often male (61.7% vs. 55.6%; p=0.03) and younger (71.1 vs. 73.4 years of age; p<0.01). Patients with AAD were less likely to have heart failure (11.2% vs. 21.0%; p<0.01), diabetes (20.1% vs. 25.6%; p=0.02) and chronic kidney disease (28.5% vs. 34.6%; p=0.02). CHADS2 score was lower in patients receiving AAD (1.63 vs. 1.97; p<0.01). HATCH score, a postulated scheme for the prediction of AF progression, was also lower in patients receiving AAD (1.56 vs. 1.97; p<0.01). During the one-year follow-up period, progression of AF occurred in 79 patients (5.7%); 27 patients receiving AAD (5.9%) and 52 patients not receiving it (5.5%), with an odds ratio for patients receiving AAD of 1.07 [95% confidence interval (CI), 0.66 to 1.72; p=0.77] using univariate analysis, and 1.07 (95% CI, 0.65 to 1.73; p=0.79) using multivariate analysis. Furthermore, investigating each class of AAD, progression of AF occurred in 6 patients for Ia (5.6%), 2 patients for Ib (11.8%), 16 patients for Ic (5.0%), 2 patients for amiodarone (15.4%) and 3 patients for bepridil (8.8%). Progression of

AF occurred in 25 patients with single AAD (5.8%) and 2 patients with multiple AADs (6.9%).

Conclusion: 5.7% of paroxysmal AF patients progressed to sustained AF in a year. Any class of AAD did not reduce progression from paroxysmal to sustained AF, during one-year follow-up of the Fushimi AF Registry in Japanese AF patients.

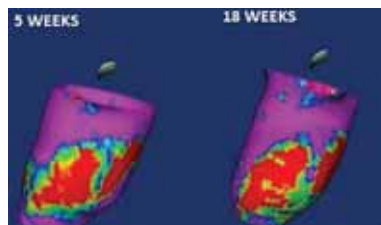
P1482 | BEDSIDE**Temporal changes in spatial characteristics of scar tissue in an experimental model of acute myocardial infarction: an MRI study**

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Background: Spatial characteristics of scar tissue including total extent of heterogeneous tissue (HT) and intrascar corridors of HT are related to cardiac mortality. However, little is known concerning evolution of scar architecture during the first months after acute myocardial infarction (AMI).

Methods: A transmural anterior AMI was created in 12 pigs. Myocardial scar was characterized 5 weeks and 18 weeks later with gadolinium ceMRI. End-diastolic and end-systolic left ventricular volumes (EDV and ESV), left ventricular mass and necrotic mass were quantified with QMASS 7.2[®] MEDIS. The ventricular wall was divided in 2 layers and the average of the subendocardium and subepicardium signal intensity (SI) was projected over 3D endocardial and epicardial shells. The SI was color coded, thus defining three different areas: 1) healthy tissue defined by SI < SI peak in normal myocardium, 2) core scar defined by SI greater than minimal SI in core scar and 3) heterogeneous tissue (HT) in between those extremes. A SI channel was defined as a corridor of HT differentiated by a lower SI from the surrounding scar.

Results: Mean EDV and ESV at 5 weeks after AMI were 114±13 cc and 77±13 cc, with a mean ejection fraction of 29±9%. Mean increase of EDV and ESV at 18 weeks was 49±15 cc and 31±17 cc. Between 5 weeks and 18 weeks, mean reduction of endocardial and epicardial scar area was 5±15 cm² and 3±15 cm². At 5 weeks, 10 endocardial and 16 epicardial SI channels were observed. At 18 weeks, 20 endocardial and 18 epicardial SI channels were identified.



Conclusions: Spatial characteristics and architecture of scar change over time in the first months after AMI. A better knowledge of patterns of evolution of scar could be relevant for risk stratification in ischemic heart disease.

P1483 | BEDSIDE**Long term prognosis of intraventricular conduction delay in patients with structurally normal heart**

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Purpose: Long-term prognosis of nonspecific intraventricular conduction delay (IVCD) remains unclear. This study was performed to elucidate long-term prognosis of IVCD in structurally normal heart.

Methods: Between 2000 and 2005, we evaluated the patients who underwent 12-lead electrocardiography. IVCD was defined QRS > 110ms without the criteria of complete or incomplete bundle-branch block. The patients were excluded if they had structural heart diseases, such as myocardial infarction, valvular heart disease, congenital heart disease and cardiomyopathy. In a matched-cohort design, 353 patients (IVCD group) (male 83.9% with a mean age of 52.2±13.3 years) were matched for age and sex with 1060 patients (no IVCD group) who had neither IVCD nor structural heart diseases.

Results: During the follow-up of 6.9±3.2 years, the cumulative incidence rates of complete atrioventricular block, heart failure, atrial fibrillation, sick sinus syndrome and all-cause mortality in the IVCD group were higher than no IVCD group (all P<0.001, except for all-cause mortality (P=0.049)). And using univariate Cox's regression analysis, only the risk of atrial fibrillation was increased in the IVCD group (hazard ratio (HR) 1.97 [95% confidence interval (CI) 1.26-3.01], p=0.002). However complete atrioventricular block (HR 0.13 [95% CI 0.12-1.53], p=0.10), heart failure (HR 1.69 [95% CI 0.75-3.80], p=0.20), sick sinus syndrome (HR 0.39 [95% CI 0.13-1.46], p=0.16) and all-cause mortality (HR 0.79 [95% CI 0.49-1.73], p=0.79) were not increased in the IVCD group.

Conclusion: In the patients with structurally normal heart, IVCD was associated with future development of atrial fibrillation. However complete atrioventricular block, heart failure, sick sinus syndrome and all-cause mortality were not increased in the patients with IVCD.

P1484 | BEDSIDE

The prognostic value of ST-segment elevation in lead aVR in patients with idiopathic pulmonary arterial hypertension

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Background and aims: We aimed to investigate the relation between the presence of ST-segment elevation in lead aVR in electrocardiography with the severity of disease assessed with clinical, hemodynamic, and neurohormonal parameters in patients with Idiopathic Pulmonary Arterial Hypertension (IPAH).

Methods: The study group comprised 28 patients with IPAH. Six-Minute Walking Distance (6MWD), plasma Brain Natriuretic Peptide (BNP), history of in-hospitalizations secondary to acute clinical worsening states and needed to escalate the treatment were used to assess the clinical, hemodynamic, and neurohormonal status of patients.

Results: There were no significant differences between distinguished groups in terms of: age, disease duration, hemoglobin levels, oxygen saturation, baseline functional NYHA class, 6MWD, cardiac output, BNP, pulmonary artery systolic pressure, right atrial pressure, pulmonary vascular resistance. Whereas patients with aVR-ST elevation had a higher heart rate (84 ± 13 vs 67 ± 5 , $p=0.017$) as compared to those not. Mean follow-up period was 27 ± 3 months after diagnosis. During this time patients with the presence of ST-segment elevation in lead aVR had higher clinical worsening states (acute deterioration (16 vs 5, $p<0.05$) and more needed to escalate the PAH specific therapy (11 vs 3, $p<0.05$) and higher mortality (5 vs 1, $p<0.05$) compared to those not.

Conclusions: IPAH patients with the presence of ST-segment elevation in lead aVR in ECG had significantly worse survival in reference to those with not. The observations presented above establish presence of aVR-ST elevation may indicate the functional impairment and may also have a prognostic potential enabling the identification of patients with higher risk of unfavourable disease course during follow-up period.

P1485 | BEDSIDE

Do patients really wear their wearable cardioverter-defibrillator?

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Introduction: Indications for the use of wearable cardioverter-defibrillator (WCD) expanded over the last years. Nevertheless, only little is known about the patient compliance with the treatment with a WCD.

Material and methods: We collected the data of all patients treated with a WCD between 2009 and 2013 in our institute and analyzed them with special regard to the wearing discipline.

Results: 26 patients (21 male, 5 female, mean age 62.4 ± 13.7 years [range 28–83 years]) were treated with a WCD over 1509.7 ± 732.3 hours [range 180.5–3063.93 hours]. There was no appropriate but one inappropriate shock and half of all patients received an implantable cardioverter – defibrillator (ICD) during follow-up. The WCD was worn 23.2 ± 1.9 hours each day [range 13.9–24.0 hours].

Discussion and conclusion: The patient's compliance with the treatment with a WCD was very good. The treatment discipline might be influenced by the choice of the right patient, the choice of the right VT threshold to avoid inappropriate shocks as well as the regular controlling of the wearing discipline.

DIAGNOSIS OF ARRHYTHMIA

P1487 | BEDSIDE

Diagnostic approach of idiopathic ventricular fibrillation: results from the FIVI-Gen study

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Background and objectives: Idiopathic Ventricular Fibrillation (IVF) is a rare entity that might be due to subclinical underlying cardiomyopathies and channelopathies of genetic origin. We aim to assess the diagnostic yield of a novel systematic protocol in patients with IVF.

Methods: IVF was defined as sustained VF episode which required external defibrillation, and with no pathological findings in basal electrocardiogram (ECG), echocardiogram, and coronary angiography. The diagnostic protocol consisted of three sequential steps: 1.- pharmacological tests with epinephrine and flecainide; 2.- first and second-degree relatives assesment with EKG and echocardiogram and 3.- genetic testing with next-generation sequencing method including 126 genes for cardiomyopathies and channelopathies.

Results: Thirty five probands (60% males, mean age 39.3 ± 14.5 years) from 9 spanish centres were assesed. Final diagnosis was obtained in 19 probands/families (54.2%). The most prevalent underlying etiology were Cathelic laminergic Polymorphic Ventricular Tachycardia (20%), Brugada Syndrome (17.1%) and Long QT syndrome (8%). The way to reach the diagnosis and a summary of the results are shown in figure 1. Relevant, but unconvulsive findings, were observed in 10 other cases (28.5%), not completely fulfilling current diagnostic criteria for the specific disease. Among these cases we found a possible arrhythmogenic right ventricular cardiomyopathy, two possible hypertrophic cardiomyopathy patients and a lamin A/C mutation with no clear phenotype in other case.

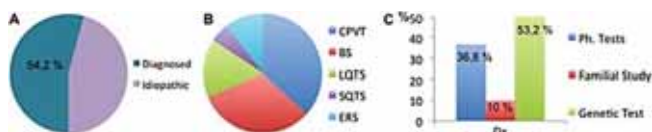


Figure 1

Conclusions: Cardiac channelopathies are the most prevalent underlying diagnosis in IVF. This novel systematic protocol achieves a definitive diagnosis in more than a half of previously "idiopathic" VF episodes.

P1488 | BENCH

Steepening of the slope of QT interval restitution is a risk factor for drug-induced arrhythmias

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Introduction: An excessively prolonged, rate-corrected QT interval (QTc) is a clinical marker of increased risk of arrhythmic sudden death. Similarly, a steep ventricular restitution curve slope has been associated with increased risk of ventricular arrhythmias (VA). In experimental studies QT interval prolonging drugs consistently steepen ventricular restitution slopes constructed by recording electrograms or action potentials. In vivo, dependence of QT on diastolic interval (DI) has been assessed via 24-h Holter recording, a method limited to spontaneous rhythms that does not analyze QT/DI slope. We used a steady state ventricular pacing (VP) protocol to study dofetilide (DOF) effects on QT restitution, hypothesizing that prolonged repolarization would be associated with steeper restitution slopes.

Methods: We performed VP in 7 anesthetized dogs at cycle lengths (CL) 5-10% < sinus CL. VP consisted of abrupt shortening of basic CL (BCL) for 1 min followed by a return to BCL. We constructed QT restitution curves using the last 10 beats preceding a return to BCL, at which time steady-state QT shortening had occurred. DOF was administered during sinus rhythm to obtain $\geq 25\%$ QTc increase (Bazett formula).

Results: DOF prolonged QTc from 378 ± 5 to 559 ± 30 ($p<0.05$) and sinus CL from

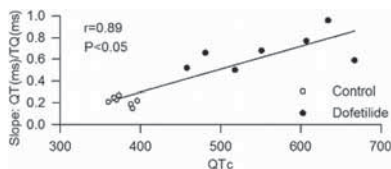


Figure 1

Abstract P1485 – Table 1

	Number	Wearing-time (hours)	First left ventricular ejection fraction	Second left ventricular ejection fraction	ICD implantation during follow-up
Cardiomyopathie	12 (46,2%)	1283,3±612,6	30,0±6,5	33,7±4,8	6 (50,0%)
Acute Myocarditis	5 (19,2%)	1936,0±423,1	40,4±12,7	51,4±7,1	0 (0,0%)
Acute myocardial infarction	4 (15,4%)	1482,0±315,6	33,0±9,0	39,8±7,1	3 (75,0%)
Endoplasmatis	3 (11,5%)	1883,4±1511,0	27,3±6,0	28,3±3,8	3 (100,0%)
Following coronary artery bypass graft	2 (7,7%)	1874,6±830,2	35,0±7,1	42,5±14,8	1 (50,0%)

598±25 to 711±44 ms ($p<0.05$). Both at baseline and after DOF, QT had a significant relationship with DI (both $p<0.05$). In the presence of DOF restitution slope increased from 0.20±0.02 to 0.67±0.06 ($p<0.05$). These slopes correlated positively with QTc (Fig. 1).

Conclusions: The slope of the QT restitution curve is directly proportional to QTc. Because the QT restitution outcome parallels that for QTc, the former can be an additional risk indicator for drug-induced proarrhythmia.

P1489 | BEDSIDE

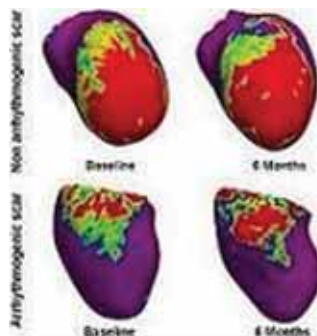
Identification of the arrhythmogenic substrate in acute phase of STEMI

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Purpose: A 3D reconstruction of the contrast enhanced-cardiac magnetic resonance (ce-CMR) allows visualization of scar and border zone (BZ) channels. BZ channels have been identified as critical isthmuses of ventricular tachycardia. We hypothesized that this arrhythmogenic substrate could be identified in the acute phase of a ST elevation myocardial infarction (STEMI).

Methods: Consecutive patients with STEMI and primary percutaneous coronary intervention were included. A 3D high-resolution 3T ce-CMR was obtained within the first 6 days and at 6 months. LV volumes and left ventricular ejection fraction (LVEF) were measured. The LV wall was segmented and characterized using a pixel signal intensity algorithm at 10 myocardial layers. A 3D color-coded shell map was obtained for each layer to depict the scar core and BZ distribution. The presence/characteristics of BZ channels were registered for each layer in both studies. Myocardial scar was classified as arrhythmogenic if BZ channels were present.

Results: 40 patients (32 male, 57.7±10.9 years) were included. LVEF improved from 48.4%±9.7 to 52.3%±10.9 ($p=0.001$) at 6 months and LV end diastolic volume tended to increase from 161.8±39.4 ml to 170.4±54.8 ml ($p=0.128$). 44 BZ channels were present baseline and 41 of them (93.1%) were present in the same segment/orientation at 6 days and 6 months (Figure 1). 26 (65%) patients were classified as having arrhythmogenic scar at baseline and 24 (92.3%) persisted at 6 months. Two (5%) patients had spontaneous sustained ventricular arrhythmias during follow-up and both had BZ channels in the acute phase.



Conclusions: Ce-CMR can identify BZ channels in acute phase of STEMI that persist visible in the healed infarction, suggesting its usefulness for sudden cardiac death risk stratification.

P1490 | BEDSIDE

Atypical atrioventricular nodal reentrant tachycardia: prevalence, electrophysiologic mechanisms, and tachycardia circuit

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Purpose: To assess the prevalence, electrophysiologic mechanisms, and tachycardia circuit of atypical atrioventricular nodal reentrant tachycardia (AVNRT).

Methods: We studied 483 consecutive patients with AVNRT in our two centers, ($n=297$ in the first one and $n=186$ for the second). AH (latest rapid deflection of atrial activation to earliest deflection of His bundle activation) and HA (end of His bundle to earliest rapid deflection of atrial activation) intervals were measured during atypical AVNRT ($AH\geq 70$ ms), and compared with measurements in 30 patients with typical (slow-fast) AVNRT ($AH<70$ ms). AH and HA intervals represent conduction times as depicted in Figure. Assuming that conduction velocity over the fast pathway is similar in the anterograde and retrograde direction, the AH during fast-slow should be smaller than the HA during slow-fast, since $A > H$, thus $(H-A) < (A-H)$, if they use the same "fast" pathway in their circuits.

Results: Twenty six patients (5.4%) had an atypical form, 17 of them fast-slow, 5 slow-slow, and 4 unclassified according to conventional criteria. In fast-slow $AH=108.9\pm 36.8$ ms (range: 55-172), in slow-fast $HA=47.2\pm 7.2$ ms (range: 37-62), $p<0.001$, and in slow-slow $HA=167.8\pm 75.3$ ms (range 127-300), $P=NS$ compared to AH during fast-slow.

Conclusion: Characteristics of anterograde pathway conduction during fast-slow AVNRT resemble those of retrograde conduction during slow-slow rather than

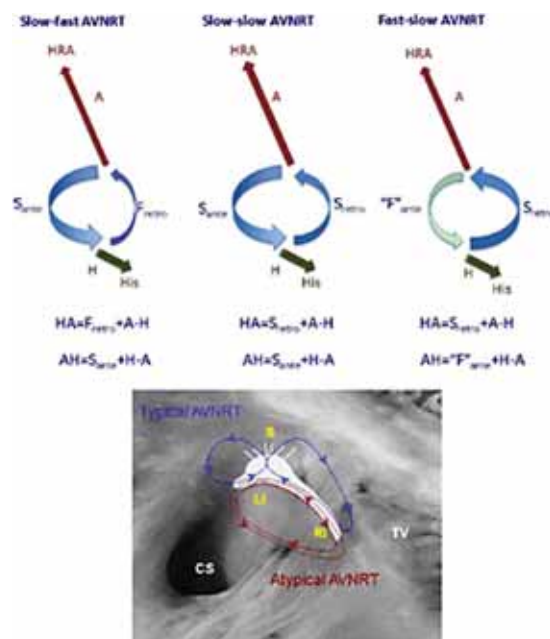


Figure 1

slow-fast form. In atypical AVNRT, the circuits use one of the inferior nodal extensions, left (LI) or right (RI) for the anterograde limb and the other extension for the retrograde limb (Figure). Classification into fast-slow or slow-slow types is meaningless.

P1491 | BEDSIDE

Strategy of early detection and active management of supraventricular arrhythmia with remote monitoring: The SETAM trial

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Purpose: Atrial fibrillation is the most commonly encountered sustained cardiac arrhythmia in medical practice and it is often associated with conduction disorders. Biotronik home monitoring (HM) technology provides relevant notifications for detection of supra-ventricular arrhythmias (SVA). The SETAM randomized, multicenter trial assessed the impact of HM on detection and treatment of SVA.

Method: Patients implanted with a dual chamber pacemaker were enrolled in the study at hospital discharge if they had a sinus rhythm at enrollment, no antiarrhythmic, anticoagulant or dual-antiplatelet therapy, and if they had a CHA2DS2-VASc score for stroke risk of 2 or more. The patients were randomly assigned to an active group, followed by HM, or a control group without HM surveillance. The time from enrollment to the management of SVA was compared between the two groups.

Results: A total of 595 patients (mean age = 79±8 y.o, 63% male, mean CHA2DS2-VASc score = 3.7±1.2) were followed during 12.8±3.3 months. There was no difference in the baseline clinical characteristics between the two groups. The most prevalent concomitant co-morbidities were hypertension (82% patients), diabetes (29%) and vascular disease (24%). Implantation indications were atrio-ventricular blocks in 77% of patients, sinus node disease in 20% and conduction disorders or others in 3%.

The global SVA incidence was 25% (29% in the active group vs 22% in the control group, $p=ns$). A therapy (drugs or ablation) was instituted for 47/291 patients (16%) in the active group versus 44/304 patients (14%) in the control group ($p=ns$). The treatment strategy was the same between the groups; anticoagulation was initiated in the majority of patients (75%), antiarrhythmic drugs in 49% of patients.

The median time from enrollment to the first therapy for SVA was 109 [44; 211] days in the active group versus 210 [66; 370] days in the control group, representing a median gain of 101-days in SVA management (48% reduction, $p=0.01$). In the active group, 93% of the notifications transmitted by HM were appropriate

for SVA detection. The remaining 7% were inappropriate for SVA (over-sensing, noise or non-sustained VT).

Among the 91 patients receiving a therapy, 58% were free of SVA at 12 months in the active group vs 22% in the control group ($p=0.003$).

Conclusion: The SETAM study provided evidence that HM allows earlier detection and treatment of SVA in patients implanted with pacemakers.

P1492 | BEDSIDE

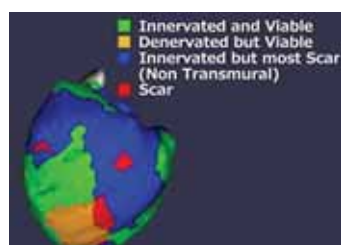
Identification of the underlying substrate in patients with ventricular arrhythmias: imaging the mismatch of perfusion and sympathetic innervation

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Introduction: Catheter ablation of ventricular arrhythmia (VA) has been greatly facilitated by 3D image integration. We described the combination of SPECT images of myocardial perfusion and the distribution of the sympathetic activity which is projected on the 3D endo- and epicardial surface of the left ventricle derived from contrast computed tomography (cCT).

Methods: Five patients (3 males, median age 63 yrs) scheduled for VA ablation were studied. Three had ischaemic heart disease, 1 hypertrophic cardiomyopathy, 1 dilated cardiomyopathy + LV non-compaction, 1 bronchiectasis. Three patients had implanted ICD. All patients underwent cCT and dual-tracer radionuclide imaging with 123I-metaiodobenzylguanidine (mIBG) for sympathetic innervation and 99mTc-methoxyisobutylisonitrile (MIBI) for viability using a solid-state camera (DSPECT, Spectrum Dynamics). Regions of mismatch between mIBG and MIBI uptake were identified. The merged images were imported into an electro-anatomical mapping system (CARTO, Biosense Webster) and were available during VA ablation.

Results: All imaging studies were performed without complication. There was good agreement between the voltage amplitude map and myocardial viability except in areas that were inaccessible to the catheter. Location and region of mismatch did vary between the substrates and were not necessarily related to scars. A 2 months follow-up demonstrated no recurrence of sustained VA and no ICD interventions.



LV dual tracer image (mIBG-MIBI mismatch).

Conclusion: The combination of anatomical and functional information on myocardial viability and innervation provides a novel type of "road map" for VA ablation. Superimposition of this multiplexed information allows for the first time to localize the region of mismatch which may be pro-arrhythmogenic. Larger prospective studies are warranted.

P1493 | BEDSIDE

The incidence of cardiac conductive disorders in hypertensive patients: the role of obstructive sleep apnea

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Objective: The data evidences the higher prevalence of cardiac conductive disorders in patients with sleep apnea. However, the results of prospective studies are not highly convincing. The objective of our study was to assess in a prospective study the role of obstructive sleep apnea (OSA) for the development of heart rhythm conductive disorders in hypertensive patients. Design and methods. Since 2002 till 2006 out of 493 screened patients we selected 279 subjects [190 (68%) males] with controlled hypertension and without known other cardiovascular diseases and diabetes mellitus. All subjects were overweight with the mean body mass index (BMI) 34.2 ± 6.5 kg/m². Based on the results of sleep study (Embletta, Iceland) the subjects were divided into 2 age- and sex-matched groups: with OSA – 204 patients, and without sleep breathing disorders – 75 subjects. Every 6 months patients were contacted by phone and once a year came for an office visit for physical and instrumental examination. The evaluated end-point included the newly onset of significant heart conductive disorders, such as pauses at Holter monitoring >2000 msec, atrioventricular block (AV) II-III degree and sinoatrial (SA) block, including the need for pacemaker implantation. Cox regression model included apnea-hypopnea index (AHI), mean saturation level, apnea duration, hypertension duration, standard risk factors (age, sex, smoking, alcohol consumption), BMI, cardiovascular therapy (beta-blockers and renin-angiotensin-aldosterone system inhibitors).

Results: The median follow-up period was 108 (67.5; 120.0) months. After 10 years since the first enrolled patient cardiac conductive disturbances have been registered in sixteen (7.8%) OSA subjects [9 cases of AV block, SA block was registered in 8 subjects; there was a combination of AV and SA conductive disturbances in 1 patient; four of them required pacemaker implantation] while none from control group developed conductive disorder ($\chi^2=6.16$; $p=0.015$). The multiple Cox-regression analysis demonstrated that the following factors were associated with the conductive disorder development: AHI ($p=0.007$), and beta-blocker use ($p=0.047$), BMI had a borderline significance ($p=0.07$). When apnea duration was included in the model it showed to be a significant predictor ($p=0.002$), while AHI became non-significant ($p=0.32$).

Conclusions: Our data suggest that OSA is associated with the development of cardiac conductive disorder in hypertensive patients, and the duration of apnea episodes is crucial. Suggesting the role of autonomic disbalance the underlying mechanisms require further investigation.

P1494 | BEDSIDE

Arrhythmias in patients with chronic kidney disease – data with implanted loop recorders

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Purpose: Patients with severe chronic kidney disease are known to have high prevalence of different arrhythmias. However, previous studies have lacked technological capacity to adequately detect rhythm disturbances over periods of months or years. This is the first study to use subcutaneously implanted loop recorders to gather reliable long-term arrhythmic data from this patient group.

Methods: The present preliminary data is based on 27 patients (62.7 ± 7.7 years [mean $\pm$ SD], range 45 to 74 years, 19 men) with more than 2 months of follow-up; the patient pool is continuously expanding. The main kidney diseases were diabetic nephropathy (11 patients), polycystic kidney disease (6) and chronic glomerulonephritis (5). All the patients had stage 4 or 5 renal failure. One patient was in the pre-dialysis stage, two received peritoneal dialysis, while the rest were treated with hemodialysis. The median time since the start of the dialysis was 2.0 years. Six patients (22%) were known to have some manifestation of atrial fibrillation (AF) prior to the implantation of the loop recorder, 3 chronic and 3 paroxysmal AF, being in line with published data.

Results: During the follow-up of 16 ± 6 months, 17 (63%) patients had documented episodes of AF. Four patients (15%) had bouts of non-sustained ventricular tachycardia; this fact was unknown before the loop recorder data. Two patients had bradycardia, revealed by the device, necessitating a pacemaker. Five patients died, two of them due to ventricular tachyarrhythmia.

Conclusions: Prevalence of several types of arrhythmia, documented with loop recorders, is essentially higher than previously thought in patients with severe kidney disease. Particularly, occurrence of AF is over twice as common as given in the literature. These findings, if confirmed with the accumulating number of patients in this investigator-initiated study, may have marked clinical implications regarding pharmaceutical as well as device therapy.

P1495 | SPOTLIGHT

New criteria during right ventricular apical entrainment to differentiate between AVNRT and ORT

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PPI-TCL during RV entrainment can help in differentiation between atrioventricular reentrant tachycardia (AVRT) and AV nodal reentrant tachycardia (AVNRT), however it has some fallacies and limitations. RV pacing during SVT produces progressive QRS fusion before the QRS morphology becomes stable. This transition zone (TZ) may differentiate AVRT from AVNRT independent of entrainment success. We thought to test atrial preexcitation (AP) & Stimulus to atrial (S-A) interval fixation in relation to TZ in identifying the mechanism of SVT.

We studied retrospectively and prospectively the effect of properly timed RVP (within 40 ms) in 118 patients on atrial timing in relation to TZ. A fixed S-A interval was defined as variation ≤ 5 ms during RVP & AP is the first change in atrial CL ≥ 10 ms. 9 patients were excluded due to cycle length oscillation > 10 ms before the onset of RVP and 6 patients had atrial tachycardia and were excluded. In the remaining 103 patients, PPI-TCL and c PPI-TCL were significantly longer in AVNRT patients but postpacing response couldn't be assessed in 11 patients showing tachycardia termination with RVP entrainments. And PPI-TCL was not diagnostic in 6 (15%) patients with ORT (> 115 ms) but all of them had cPPI-TCL < 110 ms. AP occurred during TZ in most AVRT patients and after TZ in most AVNRT patients. However, S-A fixation occurred during TZ in all AVRT patients and after TZ in all AVNRT patients. Fixation of S-A interval and AP in relation to TZ were more sensitive than either PPI-TCL or cPPI-TCL in identifying the mechanism of SVT (100%, 91.5%, 83.5% and 89.5% consecutively).

We can conclude that during RVP within 40 ms of the tachycardia cycle length, fixed S-A interval and AP in relation to FZ were superior to PPI-TCL and c PPI-TCL measurement in identifying the mechanism of SVT

P1496 | BEDSIDE**Cardiovascular magnetic resonance findings and the value of anticardiac antibodies in patients with inflammatory dilated cardiomyopathy and conduction disturbances with structurally normal heart**

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Purpose: To compare the persistence of inflammation according to endomyocardial biopsy (EMB) and cardiovascular magnetic resonance (CMR) and the level of circulating autoantibodies in inflammatory dilated cardiomyopathy (DCMi) patients (pts) and pts with conduction disturbances and structurally normal heart (CD).

Methods: 22 pts with CD and structurally normal heart (8 male, mean age 39.3 ± 11.0) and 22 pts with DCMi (10 male, mean age 40.5 ± 10.5) underwent Holter ECG monitoring with subsequent CMR with assessment of myocardial edema (ME), early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE). In serum of all pts persistence of autoantibodies to beta1-adrenergic receptor (β 1-AABs) and M2 muscarinic receptor (M2-AABs) was evaluated. In pts with DCMi endomyocardial biopsy (EMB) was performed.

Results: EMB revealed active inflammation in 14 (60.9%) of DCMi pts, that was proved by CMR only in 7 of them (≥ 2 criteria). The most frequent finding in these pts was LGE – in 12 pts (54.5%) (the volume of affected myocardium was $22.8[16.95;51.1]$ cm³), ME was found in 8 pts (36.4%), sighs of EGE in 7 pts (31.8%). 17 (77%) of DCMi pts have shown elevated level of IgG β 1-AABs. LGE positive pts were characterized by higher number of ventricular premature complexes (VPC) ($3643[255;8500]$ vs $659[64;2403]$ $p=0.04$) and higher level of β 1-AABs IgG ($1.16[0.71;2.05]$ vs $0.69[0.54;0.93]$, $p=0.019$). The amount of β 1-AABs correlated with number of non-sustained ventricular tachycardia (VT), total amount of VPC, and volume of myocardium with LGE ($r=0.71, 0.47, 0.61$ respectively) in DCMi pts. None of CD pts revealed LGE at CMR. 4 (18.2%) of them had ME, 7 (31.8%) were EGE positive, 2 (9.1%) of them had 2 positive CMR criteria. 12 (54.5%) CD pts revealed enhanced level of IgM to M2-AABs, while in DCMi group it was positive only in 8 (34.8%) of pts. The titer of M2-AABs was higher than in CD group than in DCMi pts ($0.68[0.49;1.24]$ vs $0.55[0.43;0.86]$, $p=0.04$). ROC-analyses revealed that IgM to M2-AABs had the best diagnostic value in detection of myocardial inflammation according to EMB data ($S=0.889$) in DCMi pts.

Conclusion: 77% DCMi pts revealed enhanced level of IgG to β 1-AABs which correlates with total amount of VPC, number of VT and volume of myocardium with LGE. IgM to M2-AABs revealed the best diagnostic value in detection of inflammation compared to EMB data. Their level was elevated in 54.5% of CD pts. 9.1% of CD pts had 2 positive CMR criteria. The presence of IgM to M2-AABs and CMR data might indicate the inflammatory etiology of conduction disturbances in pts with structurally normal heart.

CARDIOVASCULAR PATHOPHYSIOLOGY**P1498 | BEDSIDE****B cells within human stenotic aortic valves are associated with the severity of aortic stenosis: relation to inflammatory infiltrate and calcification within the leaflets**

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Purpose: Recent studies highlighted the importance of macrophage-B cell bidirectional interaction in the pathogenesis of atherosclerosis, which is to some extent similar to aortic stenosis (AS). Macrophage-derived BAFF protein drives B cell activation, and probably, B cells in turn regulate macrophage function, impairing the ability of macrophages to phagocytosis. A role of B cells in AS is largely unknown.

The aim of this study was to investigate the in loco presence of B cells within aortic valve leaflets and to determine its interactions with AS severity.

Methods: 37 patients with dominant AS undergoing aortic valve replacement were studied (age, 59.7 ± 10.6 years; mean gradient, 41.23 ± 12.54 mmHg). Indirect immunohistochemistry was performed on decalcified valve leaflets using antibodies against CD20, BAFF-R and CD68, after antigen retrieval. Decalcification had no effect on tissue antigenicity.

Results: The B cells, placed mostly close to neovessels, were detected within all the examined valve leaflets in 100% AS patients, and the number of B cells ranged from 5 to 31/mm² (mean 17.9 ± 11.6 /mm²). Double staining showed that $27 \pm 13.5\%$ of B cells express receptor BAFF-R. There were positive correlations between the number of B cells and macrophages ($r=0.45$, $p=0.018$) and between macrophages and B cells-associated BAFF-R expression ($r=0.66$, $p=0.002$). Moreover, the number of B cells showed a positive correlation with the degree of valve calcification ($r=0.41$, $p=0.039$) and with maximum ($r=0.63$, $p=0.02$), but not mean transvalvular gradient, and tended to correlate with aortic valve area ($r=0.45$, $p=0.054$). There were no statistically significant correlations between B cells within the leaflets and plasma CRP or fibrinogen.

Conclusions: B cells are present within aortic valve leaflets in increasing numbers when the severity of AS and valve calcification augment, which supports the

concept that dysregulated immune mechanisms like in atherosclerotic plaques may play a significant role in the pathogenesis of AS. We postulate that the interaction between B cells and macrophages, through BAFF-R receptor within aortic valve leaflets may impair the clearance of apoptotic bodies, which in turn may enhance valvular calcification and potentiate the progression of AS.

P1499 | BENCH**MiR-141: a novel plasma biomarker for calcified aortic stenosis?**

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Purpose: Calcified aortic stenosis (CAS) is a dystrophic calcification process whose pathophysiology is in relation with osteogenic proteins. Bone morphogenic protein-2 (BMP-2) is a major regulator of calcification and miR-141 is a repressor of the osteogenesis mediated by BMP-2. Recently, Yanagawa et al demonstrated a downregulation of miRNA-141 expression in patients with bicuspid aortic valve, a known condition of high risk of calcification. Our hypothesis is that plasmatic levels of miR-141 could be a plasma biomarker for valvular calcification risk.

Methods: We have enrolled 62 patients undergoing aortic valve replacement for calcified aortic stenosis without coronary disease or another valvular pathology, from March 2012 to December 2013. We obtained valvular leaflets at surgery and plasma samples. Total RNA was isolated from plasma and tissue, and miR-141 levels were determined by quantitative RT-PCR (qPCR). Levels of U6 snRNA, or 4.5S RNA when appropriated, were used to normalize samples.

Results: Plasma levels of miR-141 were low in comparison with levels in valves. However, there is a clear correlation between miR-141 and glomerular filtration rate ($p=0.028$) and treatment with warfarin (0.047). In addition, plasma levels of miR-141 had a trend to be lowered in patients with severe left ventricular hypertrophy and bicuspid valve, although without statistical significance.

Conclusions: miR-141 was almost undetectable in plasma of patients and, therefore, this miRNA would not be useful as a biomarker. On the other hand, miR-141 was associated with left ventricular hypertrophy, renal function and warfarin treatment. Our study is still open to confirm if miR-141 is a principal key in valvular calcification process and could be a novel therapeutic and preventive strategy for calcified aortic stenosis.

P1500 | BENCH**Calumenin is involved in early and late stages of arterial calcification**

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Molecular pathways involved in arterial calcification remain unclear. Gamma-carboxylation of matrix-Gla-protein (MGP) and osteocalcin (OCN) may participate during arterial calcification. Gla-MGP inhibits BMP2-dependent calcification pathway. Calumenin inhibits gamma-carboxylation and has been found in atherosclerotic and calcified tissues. A polymorphism in 3'UTR CALU (rs1043550) has been related with calcium score in non-ST-elevation acute coronary syndrome. We aimed to explore the functionality of rs1043550 polymorphism, its clinical relevance and the temporal expression pattern of calumenin in calcification cellular models including endothelial and vascular smooth muscle cells.

Methods: We explored the functionality of rs1043550 in 3'UTR CALU by luciferase assay in HUVEC and VSMC. We assayed the temporal pattern of calumenin expression during calcification in endothelial/VSMC transdifferentiation into osteoblast-like cells. In addition, we enrolled 139 stable ambulatory patients undergoing cardiac TC for evaluation of calcium score to assess the clinical impact of rs1043550 polymorphism.

Results: We found that rs1043550 reduces in 30% the mRNA stability of CALU in both HUVEC (51.93 ± 9.43 vs. 35.90 ± 4.84 RLU, $p=0.031$) and VSMC (896.76 ± 88.91 vs. 609.05 ± 46.77 , $p=0.001$). VSMC showed an overexpression of calumenin at day 3 (1.17 ± 0.17 vs. 0.51 ± 0.08 , $p=0.038$) when calcium is statistically higher compared with control (5.59 ± 0.26 vs. 0.42 ± 0.03 , $p=0.001$). After day 3, calumenin expression is lowered along the time in VSMC, similarly as occurred in HUVEC. Moreover, gene expression analyses showed that calumenin expression is lowered when B-catenin expression becomes higher together with higher expression of osteoblast phenotype markers. Thereby, we performed ICC on cell monolayers and also found a cellular calumenin staining higher in calcifying HUVEC/VSMC at day 3 which is decreasing along the time. In contrast, calumenin staining was higher in the mineralized ECM during the mineralization process. When investigating the rs1043550 polymorphism in patients, we found that presence of CALU g allele was associated to lower calcium scores (below the fourth quartile) measured by coronary TC after adjusting by clinical variables (OR: 6.19, 95%CI: 1.07-35.85; $p=0.042$).

Conclusions: Calumenin exerts direct and indirect effects on arterial calcification which are differently manifested depending on the early or late stage of the arterial calcification process. This double participation may explain the role of rs1043550 polymorphism in calcification process in patients.

P1501 | BENCH**Moderate diet restriction can reverse alterations of cardiac function induced by postnatal overfeeding in mice**

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Postnatal overfeeding (OF) in rodents induces a permanent moderate increase in body weight, metabolic disorders and progressive alterations of cardiac function. Our aim was to determine whether moderate diet restriction could restore cardiac function in mature overfed mice.

Immediately after birth, litters of C57BL/6 mice were either maintained at nine (normal-fed group, NF), or reduced to three in order to induce OF. At weaning, mice of both groups received a standard diet ad libitum (AL). At 6 months of age, half of the OF mice were assigned to a moderate 20% calorie restriction (CR, OF-CR) for one month, while NF and the other half of the OF mice continued to eat ad libitum (NF-AL, OF-AL). Cardiac function was followed using echocardiography and, at 7 months, the sensitivity to ischemia-reperfusion injury was evaluated in isolated perfused hearts.

Six-month-old OF mice weighed 22.5% more than NF mice. Left ventricular fractional shortening (LVFS) and ejection fraction (LVEF) were decreased in OF mice (25.5% vs. 30.5% for LVFS; 50% vs. 58% for LVEF, $p < 0.05$). Left ventricular internal diameter in diastole (LVIDd) and systole (LVIDs) were significantly greater in OF than NF mice. One month of moderate CR normalized body weight in OF-CR compared with OF-AL (31.1 vs. 37.4 g, $p < 0.001$). Moreover, LVEF was greater in OF-CR than OF-AL (61% vs. 52%, $p < 0.05$) and became comparable to that in NF-AL. LVIDd and LVIDs were also normalized in OF-CR. Ex vivo, after 30 min of global ischemia, hearts isolated from OFCR mice showed better functional recovery than those of the two other groups.

Our study suggests that short-term moderate diet restriction could normalize body weight gain induced by postnatal OF and, interestingly, could reverse alterations of cardiac function and susceptibility to myocardial ischemia-reperfusion injury in OF.

P1502 | BENCH**The antiplatelet effect of aspirin is influenced by a common genetic variant in the PEAR1 gene**

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Purpose: The antiplatelet effect of aspirin displays considerable inter-individual variability. It remains unclear to what extent single nucleotide polymorphisms (SNPs) determine the antiplatelet effect of aspirin. Our aim was to identify platelet-related SNPs influencing platelet aggregation during aspirin treatment. Furthermore, we explored if the influence of these SNPs was associated with cyclooxygenase-1 activity and platelet activation.

Methods: We included 985 Danish patients with stable coronary artery disease treated with aspirin 75 mg/day as antiplatelet mono-therapy. Compliance with aspirin was confirmed by serum thromboxane B2 measurements. Patients were genotyped for 16 common SNPs in platelet-related genes using TaqMan assays. Whole blood platelet aggregometry was performed using Multiplate Analyzer (agonists: arachidonic acid and collagen) and VerifyNow Aspirin. Serum thromboxane B2 and soluble P-selectin were used as markers of cyclooxygenase-1 activity and platelet activation. Platelet aggregation, cyclooxygenase-1 activity and platelet activation were compared across genotypes in adjusted analyses.

Results: The A allele of the rs12041331 variant in the platelet endothelial ag-

gregation receptor-1 (PEAR1) gene was associated with reduced platelet aggregation across platelet function tests and agonists (Figure). Carrying the PEAR1 A-allele was also associated with increased platelet activation ($p=0.05$), but not with cyclooxygenase-1 activity. Platelet aggregation was unaffected by the other SNPs analyzed.

Conclusions: A common SNP (rs12041331) in the PEAR1 gene was reproducibly associated with reduced platelet aggregation in aspirin-treated patients with coronary artery disease. The effect of this polymorphism may be related to changes in platelet activation.

P1503 | BENCH**Post-transcriptional regulation of adiponectin by microRNA-378 in adipose tissue: a novel mechanism for hypoadiponectinemia**

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Background: It is well known that hypoadiponectinemia is associated with high prevalence of cardiovascular events, but the mechanisms for hypoadiponectinemia are largely unknown. MicroRNAs (miRNAs), small non-coding RNAs that regulate gene expression post-transcriptionally, are involved in biological processes, including obesity and insulin resistance. We evaluated whether the miRNA-378 pathway is involved in adiponectin gene transcription.

Methods and results: First, we determined a putative target site for miRNA-378 in the 3' prime untranslated region (3'UTR) of the adiponectin gene by in silico analysis. The expression levels of adiponectin, PGC-1 β , and ESRRG were decreased in 3T3-L1 cells overexpressing inhibitors of miRNA-378. Luminescence activity in HEK 293 cells expressing a renilla-luciferase-adiponectin-3'UTR sequence was significantly inhibited by overexpressing mimics of miRNA-378, and the decrease was reversed by adding inhibitors of miRNA-378, indicating that post-transcriptional activity of the adiponectin 3'UTR was regulated via the miRNA-378-binding site (in vivo analysis). In conclusion, we found that intracellular levels of miRNA-378 were crucial for expression of adiponectin and that they could modulate adiponectin levels posttranscriptionally via the 3'UTR sequence-binding site.

Conclusion: Our findings warrant further investigations into the role of miRNAs in regulating the posttranscriptional activity of adiponectin. Especially, it is crucial to clarify the roles of miRNA-378 as a mechanism for hypoadiponectinemia.

P1504 | BEDSIDE**Cerebral perfusion in patients with metabolic syndrome: relationship with endothelial dysfunction and cognitive disorders**

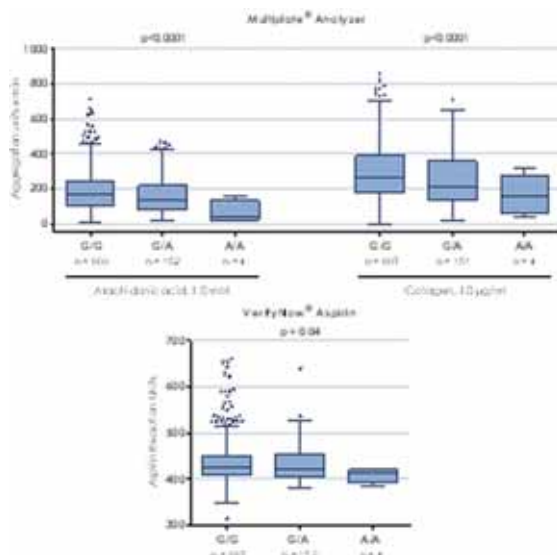
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Purpose: To estimate role of endothelial dysfunction in development cerebral perfusion disturbance and cognitive disorders in patients with metabolic syndrome (MetS).

Methods: The study involved 52 patients (mean age 52 $\pm$ 5) with MetS. Fifteen healthy volunteer were investigated as control group. All patients were investigated by perfusion brain SPECT with 99mTc-HMPAO and comprehensive neuropsychological testing. Endothelial function was assessed by flow-mediated dilation in brachial artery by vascular Doppler after pneumatic tourniquet stress at forearm according to D.Celermajor. Brain SPECT slices were divided into 14 symmetrical (right and left) regions of interest per patients: inferior and superior frontal lobes, temporal, anterior and posterior parietal, occipital lobes and cerebellar hemispheres. Regional cerebral blood flow (rCBF) (ml/100g/min) in these regions was calculated.

Results: The results of Brain SPECT showed that cerebral perfusion was significantly decreased in regions of MetS patients in comparison with control group. The regional cerebral blood flow in patients with metabolic syndrome in decrease on 7.3% ($p=0.003$), 6% ($p=0.028$), 5.9% ($p=0.024$) was revealed in right and left anterior parietal cortex, in right posterior parietal region correspondingly, as well as with decrease on 8.3% ($p=0.007$), 6.6% ($p=0.009$) and 5% ($p=0.041$) in right superior frontal cortex, in right temporal and occipital regions, correspondingly, in comparison with control patients. Cognitive dysfunction was detected in 90% MetS patients. The flow-dependent vasodilatation in MetS patients was decrease on 41.3% in comparison with control group ($p=0.021$). In addition in 32 (61%) from 52 MetS patients was observed inadequate change of brachial artery diameter in reactive hyperemia peak, in 11 (22%) patients registered constricted response on reactive hyperemia and only in 9 (17%) patients detected normal response. Relationship between rCBF, cognitive function and indices of endothelial dysfunction was found. Significant correlation was shown between flow-dependent dilatation in MetS patients and rCBF in left superior frontal region ($R^2=0.126$; $p=0.023$). The brachial artery diameter in phase of reactive hyperemia positive correlated with rCBF in left superior frontal cortex, temporal and right anterior parietal regions ($R^2=0.449$; $p=0.006$, $R^2=0.320$; $p=0.277$, $R^2=0.327$; $p=0.026$, correspondingly), as well as with visualgnosis function ($R^2=0.415$; $p=0.009$).

Conclusion: Deterioration of cognitive functions in MetS patients was associated with endothelial dysfunction and brain perfusion decreasing.



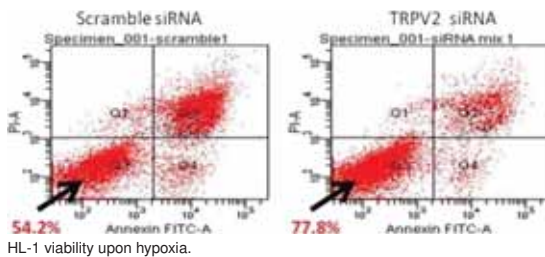
P1505 | BENCH**Upregulation of the vanilloid 2 receptor channel in HL-1 cells exposed to hypoxia may induce rapid cell death**

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Purpose: A new super-family of channels that may have a role in cardiac calcium homeostasis has recently been described. These are non-selective and non-voltage-gated transient receptor potential (TRP) channels; most of them are permeable for Ca^{2+} and gated by diverse stimuli. Published evidence suggests that dilated cardiomyopathy is associated with an accumulation of the TRP vanilloid 2 (TRPV2) channel in cardiomyocytes in various heart failure animal models as well as in patients. We sought to assess whether TRPV2 overexpression may affect cardiomyocyte cell viability following myocardial infarction.

Methods: Murine HL-1 cardiac cells were exposed to hypoxic conditions for 18 hours. TRPV2 levels on the cell membrane were tested by flow cytometry using an anti-TRPV2 antibody. Cellular viability was assessed by Annexin V-FITC-PI assay followed by flow cytometry analysis. The direct effect of TRPV2 on cell viability was studied by introducing a TRPV2 or scramble siRNA to the cells prior to the exposure to hypoxia.

Results: TRPV2 expression on the cell membrane was elevated by 60% upon exposure to hypoxia. The upregulation of this channel protein was correlated with a significant reduction in cellular viability (77.8 ± 3.1 versus 58.9 ± 4.3 percent viability in normoxic versus hypoxic cells). Interestingly, transient transfection with a TRPV2 siRNA inhibited the cell death observed in the scramble-siRNA or untransfected HL-1 cells under hypoxia. The viability of HL-1 cells grown under normoxic conditions was not affected by the siRNA.



Conclusion: TRPV2 may play an important role in mediating cardiomyocyte cell death following myocardial infarction. These data point to a potential novel therapeutic target for cardiomyocyte cell loss occurring shortly after an acute MI.

P1506 | BENCH**Prognostic value of plasma LMP in diabetic patients with acute coronary syndrome**

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Objective: Leukocyte-derived microparticle (LMP), originating from activated or apoptotic leukocytes, is increased in patients with cardiovascular risk factors. We evaluated whether LMP is an independent marker for cardiovascular events in diabetic patients with acute coronary syndrome (ACS).

Methods: 109 cases of hospitalized patients with diabetes were divided into ACS group, stable angina pectoris (SAP) group and non-CHD group. The number of plasma LMP was determined in all patients by flow cytometry at the time of admission. We established follow-up records of all patients to observe the recent occurrence of cardiovascular events, and discussed the relationship between LMP and coronary events in 12 months.

Results: LMP in ACS group was significantly higher than SAP group and non-CHD group ($P < 0.05$). LMP had higher level in SAP group than non-CHD group ($P < 0.05$). 98 cases were of successful follow-up, lost in 11 cases. 24 cases of patients had cardiovascular events within 12 months, the LMP levels were significantly higher in patients with cardiovascular events than without cardiovascular events ($P < 0.05$). COX regression analysis showed that LMP was an independent risk factor for cardiovascular events in 12 months in patients with diabetes and ACS ($P = 0.028$).

Conclusion: The level of circulating LMP is an independent risk predictor of diabetic patients with ACS in recent cardiovascular events.

P1507 | BENCH**Improvement of brain microcirculation induced by sympathetic neuromodulation in obese rats with metabolic syndrome**

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Purpose: Cardiovascular and metabolic risk factors that characterize the

metabolic syndrome (MS) are accompanied by sympathetic hyperactivity. In this study, we investigated the effects of a chronic oral treatment using centrally-acting sympatho-inhibitory drugs, clonidine or a selective I1 imidazoline agonist LNP599 on the brain microvascular function in rats under long-term high-fat diet.

Methods: Fifty male Wistar rats were maintained under normal diet (CON, $n=10$) or high-fat diet (HFD, $n=40$) during 20 weeks. Thereafter, the HFD group received oral clonidine (HFD+CLO, 0.1 mg/kg), LNP599 (HFD+LNP599, 20 mg/kg) or vehicle (HFD). Systolic blood pressure (SBP) was evaluated by photoplethysmography during the long-term treatment and the cerebral microcirculation flow was evaluated by Laser Speckle contrast Imaging (Perimed) and the brain functional capillary density and endothelial-leukocyte interaction were evaluated by intravital microscopy. All experiments were conducted in accordance with internationally accepted principles for the care and use of laboratory animals (protocol # P 0034-08).

Results: The HFD group presented a decreased blood perfusion in the brain (163 APU, arbitrary perfusion units) compared to control group (239 APU). Chronic treatment with both clonidine and LNP599 lowered SBP to control values and increased blood flow perfusion (HFD+CLO: 185 APU and HFD+LNP599: 190 APU) when compared to HFD group ($p < 0.05$). Topical administration of acetylcholine (ACh, 100 mM) on the cranial window was used to assess the brain microvascular function. Endothelial-dependent vasodilation response to ACh was significantly increased in HFD+CLO group (25% from baseline) and in HFD+LNP599 group (5% from baseline) while on the non-treated group we observed a vasoconstriction effect (-1.3% from baseline). HFD group presented a marked brain functional capillary rarefaction (117 ± 11 capillaries/mm²) which was reversed to control group values by clonidine and LNP599 treatment (326 ± 51 and 378 ± 31 capillaries/mm², respectively). Clonidine and LNP599 treatments were able to significantly reduce the number of rolling of leukocytes (HFD+CLO: 4 ± 0.5 cells/min; $p < 0.05$ or HFD+LNP599: 4.3 ± 1 cells/min; $p < 0.05$, vs. HFD group: 12 ± 0.5 cells/min).

Conclusions: These results suggest that the modulation of sympathetic activity results in a reduction of SBP accompanied by a reversion of capillary rarefaction and improvement of blood flow perfusion and endothelial function in the brain of obese rats with metabolic syndrome.

CARDIAC PATHOPHYSIOLOGY**P1509 | BENCH****X-ray phase-contrast synchrotron radiation based micro-CT to study detailed cardiac anatomy, myofiber structure and vasculature of a rodent heart**

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Purpose: Cardiac cell organization in a 3D fibre structure enables the heart to efficiently pump a large volume-fraction. Information on this complex organization is essential to understand diseases. Microscopy techniques provide sufficient detail, but 3D imaging of whole hearts often results in distortions of detailed geometry and fibres. CT/MRI resolution is usually too low to study cellular mechanics in detail. Therefore we developed a novel approach to study heart in great detail, but on the whole organ scale.

Methods: A young rat heart was formalin-fixed, ethanol-dehydrated and embedded in agarose. X-ray phase-contrast synchrotron radiation-based micro-CT was performed at 7.43 μm resolution (ESRF-ID19, 19Kev). The heart was rotated over 360°. Five acquisitions were necessary to cover the whole heart along its long axis. The series were reconstructed using state-of-the-art filtered backprojection. The reconstructed volumes were merged into a single dataset covering the whole heart.

Results: Atria, ventricles, great vessels and valves can be clearly differentiated in a longitudinal reslicing of a dataset (Fig. 1A). Details of local complexity of the walls and part of the vasculature are visible (Fig. 1B, C). Using volume rendering, the detailed architecture of the ventricles can be observed in a transverse view (Fig. 1D). Fiber orientation can be recognised and the coronary vessels tree can be segmented.

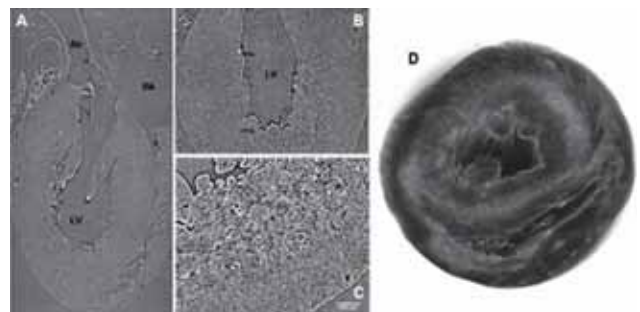


Figure 1

Conclusions: We have obtained novel, high resolution, datasets of a whole heart providing structural information on microscopic level without the need of slicing. This opens up a new range of exciting possibilities for a systems approach towards cardiac structure and function, providing fast acquisition of the whole heart.

P1510 | BENCH

Neuregulin-1 preserves right ventricular diastolic function in animal model of pulmonary arterial hypertension

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Neuregulin (NRG)-1 is involved in the preservation of left ventricular performance. Nevertheless, the role of NRG-1 in pulmonary arterial hypertension (PAH) and right ventricular (RV) diastolic stiffness is unknown. We analysed the presence and possible underlying mechanisms of RV diastolic dysfunction in an animal model of PAH and the role of NRG-1 in this context.

Wistar rats randomly received monocrotaline (MCT, 60mg/Kg,sc) or vehicle. After 14 days, rats received NRG-1 (40µg/Kg/day,ip) or vehicle. The study resulted in 4 groups: control (CTRL, n=16); CTRL+NRG (n=15); MCT (n=13); MCT+NRG (n=18). RV invasive hemodynamic studies and sample collection were performed 25-28 days after MCT administration. Isolated cardiomyocytes were stretched to measure resting tension and phosphorylation of titin isoforms was analyzed (ProQ Diamond and SYPRO Ruby protein gel stains). Only significant results ($p < 0.05$) are given.

RV diastolic stiffness (β) was increased in MCT rats (MCT vs CTRL: 0.016 ± 0.002 vs 0.008 ± 0.001). However, NRG-1 treatment attenuated this change (MCT+NRG: 0.007 ± 0.001). Histological analyses revealed increased cardiomyocyte cross-sectional areas (MCT vs CTRL: 536.67 ± 59.46 vs $375.39 \pm 47.43 \mu\text{m}^2$), indicating RV hypertrophy. In addition, the amount of RV fibrosis was enhanced in PAH tissue (MCT vs CTRL: 2.04 ± 0.17 vs $0.98 \pm 0.07\%$). NRG-1 also attenuated both changes (MCT+NRG: $409.01 \pm 19.72 \mu\text{m}^2$ and $1.00 \pm 0.17\%$, respectively). MCT-group isolated cardiomyocytes developed higher passive force when compared to CTRL-group cells at the sarcomere lengths of 2.0 (MCT vs CTRL: 1.90 ± 0.43 vs $1.43 \pm 0.29 \text{N/m}^2$), 2.2 (MCT vs CTRL: 3.66 ± 0.69 vs $2.68 \pm 0.24 \text{N/m}^2$), and $2.3 \mu\text{m}$ (MCT vs CTRL: 5.76 ± 1.15 vs $3.86 \pm 0.87 \text{N/m}^2$). NRG-1 restored passive force development to levels similar to the CTRL-group, at 2.0, 2.2, and $2.3 \mu\text{m}$ (MCT+NRG: 1.28 ± 0.25 , 3.04 ± 0.55 , and $3.63 \pm 0.89 \text{N/m}^2$, respectively). CTRL+NRG-group cells developed less passive force compared to CTRL-group (CTRL+NRG: 1.16 ± 0.31 , 2.27 ± 0.38 , and $3.05 \pm 0.54 \text{N/m}^2$, at 2.0, 2.2, and $2.3 \mu\text{m}$ respectively). Titin phosphorylation was reduced in RV tissue of MCT rats (MCT vs CTRL: 1.06 ± 0.38 vs 1.62 ± 0.85 , arbitrary units) and increased in MCT+NRG group (2.28 ± 0.61).

RV diastolic stiffness is increased in MCT rats, with important contributions from increased fibrosis and intrinsic stiffening of the RV cardiomyocyte sarcomeres. NRG-1 treatment decreases the passive force and thus myocardial stiffness, either in rats with RV hypertrophy or in healthy animals. These findings show that NRG-1 pathway regulates systolic and diastolic function at the cellular level, suggesting a potential therapeutic role of this pathway in PAH.

P1511 | BENCH

Vascular rarefaction mediates whitening of brown fat in obesity

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Brown adipose tissue (BAT) is abundant in newborn humans and small rodents. Recent studies have shown that human adults also possess active brown adipose tissue and it decreases with obesity and aging. In addition to its thermogenic function, it has been suggested that BAT contributes to systemic metabolism because of its high oxidative capacity. Several studies have demonstrated that vascularity in white adipose tissue is crucially involved in maintaining systemic metabolic homeostasis; however, the importance of vascularization in BAT is inadequately understood. Here we show that obesity causes capillary rarefaction and hypoxia in BAT that is much more robust than in WAT. This condition leads to BAT "whitening" that is associated with diminished β -adrenergic signaling, the accumulation of large lipid droplets and mitochondrial dysfunction and loss. These changes in the BAT microenvironment impair thermogenic responses and contribute to dysfunctional glucose metabolism.

Diet induced obese (DIO) model maintained on a high fat high sucrose diet exhibited a marked increase in intra-cellular lipid droplet accumulation and a reduction in mitochondria number in brown adipocytes. DIO model displayed reduced adrenergic receptors and VEGF-A expression, capillary rarefaction and evidence of hypoxia. BAT whitening was also observed by the targeted ablation of Vegfa in adipose tissue of non-obese mice, which demonstrated an impaired systemic glucose metabolism and reduction in thermogenic response. The introduction of Vegfa specifically into BAT of obese mice restored vascularity, ameliorated brown adipocyte dysfunction, and improved insulin sensitivity.

An increase in ROS production and reduction in membrane potential were detected in mitochondria isolated from BAT from obese or Vegfa ablated mice, asso-

ciated with a significant increase in autophagic responses. These changes were inhibited with the introduction of vegfa specifically into BAT.

These data show that overnutrition promotes hypoxia in BAT, causing it to whiten through mitochondrial dysfunction and loss, subsequently contributing to impaired systemic glucose metabolism.

P1512 | BENCH

In vivo silencing of mitochondrial adaptor p66Shc gene improves endothelial insulin resistance in obese mice

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Purpose: Insulin resistance is mostly driven by oxidative stress and inflammation. This condition precipitates type 2 diabetes and predicts long-term morbidity and mortality. However, the molecular link between obesity and impaired insulin signalling remains to be elucidated. Restoration of endothelial homeostasis has been recently shown to improve insulin delivery in other organs and prolong lifespan in mice. The mitochondrial adaptor p66Shc is a key source of reactive oxygen species (ROS) in the endothelium. In this study we hypothesize that p66Shc-derived ROS production mediates endothelial insulin resistance in obesity.

Methods: Twelve obese leptin-deficient mice (LepOb/Ob) and 12 wild-type littermates were used for all the experiments. In vivo gene silencing of p66Shc was performed by i.v. administration of a mix of 2 siRNAs specifically targeting p66Shc together with a cationic delivery reagent. Scrambled siRNA (scr.siRNA) was used as a control. Endothelium-dependent relaxation to insulin (10^{-12} to 10^{-6} mol/L) was assessed in aortic rings isolated from obese and control mice. Protein expression was determined by immunoblotting and mitochondrial ROS measured by ESR spectroscopy. Furthermore, knockdown of p66Shc gene was performed by siRNA technology in endothelial cells (EC) isolated from LepOb/Ob and WT mice. Data are expressed as percentage of control.

Results: Obese mice showed an impairment of vasodilatory response to insulin (27 ± 8 vs $54 \pm 6\%$, $p < 0.01$). Interestingly enough, p66Shc siRNA restored insulin-dependent relaxation as compared with scr.siRNA (40 ± 6 vs $25 \pm 6\%$, $p < 0.01$). Improved insulin signalling in siRNA-treated obese mice was explained by suppression of inhibitory Ser-636 phosphorylation of insulin receptor substrate-1 (IRS-1) and restoration of Akt/eNOS pathway. In endothelial cells isolated from LepOb/Ob mice p66Shc silencing significantly blunted ROS generation. This finding was associated with improved insulin-dependent activation of Akt and eNOS. In addition, normalization of oxidative stress following p66Shc silencing affected expression of NF- κ B and PGI2 synthase, important modulators of endothelial insulin sensitivity.

Conclusions: p66Shc-driven oxidative stress is an important determinant of endothelial insulin resistance in obese mice. Targeting p66Shc may represent a promising strategy to improve NO availability and insulin signalling and, hence, prevent adverse cardiometabolic effects in obese patients.

P1513 | BENCH

Aerobic training regulate cardiac miRNA-208a and MED13 levels preventing obesity in Zucker rats

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Aerobic exercise training (ET) has been established as an important treatment for obesity, since it counteracts aberrant cardiac metabolism and weight gain; however, underlying mechanisms remain to be further determined. MicroRNAs (miRNAs) inhibit protein expression by base-pairing with the 3' UTRs of mRNA targets. MiRNA-208a is a cardiac-specific miRNA that regulates β -MHC content and systemic energy homeostasis via MED13, a subunit of the Mediator complex. We investigated whether ET regulates the miRNA-208a and their target MED13 related with the weight loss in obese Zucker rats (OZR). OZR (n=10) and Lean (L, n=10) male rats were assigned into 4 groups: OZR, trained OZR (OZRT), L and trained L (LT). Swimming ET consisted of 60 min of duration, 1x/day/10 weeks, with 4% caudal body weight workload. OZR groups showed a significant augment in the body weight compared with L groups. However, ET was effective in reducing weight gain in OZRT (59%) compared with OZR group. In accordance, ET reduced 20% visceral fat weight in OZRT compared with OZR group. These alterations were accompanied by resting bradycardia (12%), reduction of triglycerides (57%) and low density lipoprotein (61%) and increased of high density lipoprotein (42%) and peak VO2 (21%) in the OZRT compared with OZR group. No difference was observed in blood pressure and glucose between groups. Cardiac miRNA-208a levels analyzed by real-time PCR increased 57% in OZR paralleled with a decrease of 39% in MED13 protein levels analyzed by western blot compared with L group. In contrast, ET corrected the cardiac miRNA-208a and MED13 levels in OZRT compared with L group. Furthermore, ET reduced the increased cardiac mass (13%), normalized β -MHC mRNA and protein levels and improved the loss of diastolic function caused by obesity. These results suggest that ET can prevent weight gain via increased of cardiac MED13 and pathological cardiac hypertrophy via β -MHC reduction by regulation of miRNA-208a, indicating the heart in the systemic metabolic control and the miRNA-208a as potential therapeutic target for metabolic and cardiac disorders.

P1514 | BENCH**Mechanisms of increased oxygen radical formation in alcoholic cardiomyopathy in a mouse model of acetaldehyde overload and potential therapeutic approaches**

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Background: Growing evidence suggests, that NADPH-oxidases (NOX) are involved in the pathogenesis of ethanol related organ damage. We sought to investigate the role of NADPH oxidase derived superoxide in the development of alcoholic cardiomyopathy (ACM) using ALDH2^{-/-} mice as an animal model of acetaldehyde overload and whether pharmacologic or genetic ablation of NOX2 could beneficially influence the disease model.

Methods: Male B6, ALDH2^{-/-} and ALDH2^{-/-}NOX2/gp91phox^{-/-} were fed a 2% ethanol vs. liquid control diet. After 5 weeks, cardiac function was assessed with echocardiography, malondialdehyde levels in internal organs were measured by dot blot. NOX activity in cardiac membrane fractions was quantified by chemiluminescence, while the expression of NOX2 was assessed by WB. For in vitro studies, cardiomyocytes (CMs) were isolated from B6 mice via cannulation and retrograde perfusion of the aorta. Plated CMs were incubated in culture media containing increasing concentrations of ethanol (EtOH) or acetaldehyde (MeCHO) in the presence or absence of the NOX inhibitor apocynin. Subsequently, CM mitochondrial membrane potential and mitochondrial ROS production was assessed by automated cellular imaging using the fluorescent probes TMRM+ and MitoSOX.

Results: ALDH2^{-/-} fed the 2% ethanol diet displayed a significantly decreased LV systolic function compared to ALDH2^{-/-} fed the liquid control diet and to B6 mice. Furthermore, ethanol-fed ALDH2^{-/-} mice exhibited significantly increased levels of malondialdehyde in internal organs (highest in the heart), increased heart/body and lung/body weight ratios, significantly increased cardiac NOX activity and significantly increased expression of the NOX2 subunit p67phox and the NOX2 activator Rac1 compared to control fed ALDH2^{-/-} and B6 mice. These results were corroborated by in vitro studies: cultured CMs which incubated with media containing MeCHO showed significantly increased levels of mitochondrial ROS and significantly decreased mitochondrial membrane potential. Pharmacologic ablation of NOX in CMs exposed to MeCHO lowered mitochondrial ROS and partially preserved mitochondrial membrane potential. Finally, we subjected mice double negative for ALDH2 and NOX2/gp91phox to the ethanol diet for 5 weeks. Echo revealed that the additional lack of NOX2/gp91phox protects mice from the acetaldehyde-overload induced cardiomyopathy.

Conclusions: Our results in vitro and in vivo data show that NOX derived ROS contributes to the development of ACM. We further provide evidence that ablation of NOX-2 can beneficially influence the disease in vitro and in vivo.

P1515**P1516 | BENCH****Nav1.5 N-terminus is responsible for the Nav1.5 and Kir2.x reciprocal modulation**

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Purpose: It has been demonstrated that the N-terminal domain of Nav1.5 channels (Nter), a 132 aminoacids peptide, is able to increase the Nav1.5 current (INav1.5) density. Additionally, it is known that there is a reciprocal modulation of the expression of Nav1.5 and Kir2.1 and Kir2.2 channels. Thus, we tested whether Nter is able to increase the expression of Kir2.x channels.

Methods: Currents were recorded using the patch-clamp technique in Chinese ovary cells transiently transfected with wild-type or site directed mutated Nter, Kir2.1, Kir2.2, and Nav1.5 channels.

Results: Cotransfection of Nter with Kir2.1 and Kir2.2 channels significantly increased Kir2.1 current (IKir2.1) and IKir2.2 measured at -120 mV from -126±12 to -183±18 pA/pF (n=25, P<0.05) and from -72±9 to -114±13 pA/pF (n=22, P<0.05), respectively. Conversely, cotransfection of Nter with Kir2.3 channels, which did not bind to syntrophin with a high affinity as demonstrated in immunoprecipitation experiments, did not significantly modify IKir2.3. Nter did not increase the current density generated by Nav1.5 channels lacking their C-terminal PDZ domain (Nav1.5ΔPDZ). Noteworthy, Nav1.5ΔPDZ channels still co-immunoprecipitated with syntrophin. We identified in the Nter peptide a sequence which could act as a "PDZ-like" binding domain (18-RESLA) and we tested its involvement in the Nter "chaperon" effect by site directed mutagenesis. The results demonstrated that mutants of all residues, except p.S20A Nter, increased IKir2.x. To further confirm the role of Ser20, p.S20A Nav1.5 channels were cotransfected with either Kir2.1 and Kir2.2 channels. Cotransfection of Kir2.1 channels with p.S20A Nav1.5 channels did not increase IKir2.1 as cotransfection with Nav1.5 channels did (from -126±12 to -192±16 pA/pF, n=35, p<0.05). Finally, to test the Nter chaperon effect in a cardiac model, adult rat ventricular myocytes were enzymatically dissociated, cultured, and infected with either a control adenoviral construction (Ad-GFP) or an Nter codifying adenoviral construction (Ad-Nter). Results demonstrated that myocyte infection with Ad-Nter significantly increased both the inward sodium (INa) and inward rectifier (IK1) currents.

Conclusions: The N-terminal domain of Nav1.5 channels exerts "chaperon-like" effect increasing INav1.5 and IKir2.x densities. This effect depends on the residue Ser20, which probably determines the binding to syntrophin via an "internal" PDZ binding domain.

P1517 | BENCH**Characteristics of pre-clinical models for the study of atherosclerosis and restenosis**

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Purpose: Animal models are necessary for the evaluation of new endovascular therapies. We compared relevant models of restenosis with and without atherosclerotic injury in pigs and rabbits. Our aim was to compare the characteristics and feasibility of these models.

Methods: We compared atherosclerotic lesions induced by balloon injury and atherogenic diet in pig coronary arteries (n=33) and rabbit aorta (n=12). We also studied the lesions of WHHL rabbits (n=6), which portray a familial hypercholesterolemia type phenotype and have naturally high circulating cholesterol levels. In-stent restenosis (ISR) was also evaluated in different branches of the pig coronary tree by OCT imaging (n=12). Stents were implanted in the right (RCA), the left anterior descending (LAD) and left circumflex (LCX) coronary artery.

Results: Injured rabbit aortas developed lipid rich and uniform lesions. Porcine coronary injury produced lesions with varying characteristics and creation of lipid rich lesions was difficult even with high fat diet (picture). OCT follow up revealed very different characteristics in the different coronary branches in regards to the formation of in-stent restenosis. The RCA was found most resistant to ISR (RCA 17.9±3.5% vs LAD 33.7±3.8% vs LCX 39.9±9.2%) six weeks after stent implantation.

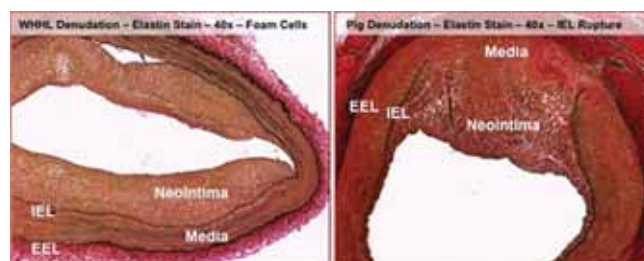


Figure 1. WHHL aorta and pig coronary histology.

Conclusions: The rabbit aorta with double injury of high cholesterol and mechanical de-endothelialization produced most atherosclerosis-like lesions. The

ABSTRACT WITHDRAWN

anatomy of the porcine coronary artery is, however, more similar to the clinical setting when evaluating devices for the treatment of coronary artery lesions. The innately different characteristics of the different coronary branches must be taken into account when designing porcine studies of restenosis.

P1518 | BENCH

ATP mediated signaling in pre-sympathetic area of the brainstem is critical for development of hypertension in spontaneously hypertensive rats

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Purpose: Increased sympathetic tone is associated with the development and progression of essential hypertension. Pharmacological studies have shown a direct stimulatory effect of ATP on bulbospinal pre-sympathetic neurons, resulting in increased sympathetic tone and BP. Here, we explored whether reduction of extracellular ATP in the rostral ventral lateral medulla oblongata (RVLM), a brainstem region containing sympathoexcitatory pre-sympathetic neurons, affects development of hypertension in spontaneously hypertensive rats (SHRs).

Methods: We developed a lentiviral vector (LVV) to drive the expression of a potent membrane-bound ectonucleotidase – transmembrane prostatic acid phosphatase (TMPAP) for facilitated breakdown of extracellular ATP. LVV-TMPAP or control LVV-GFP were injected stereotactically into the RVLM of pre-hypertensive (8-weeks-old) spontaneously hypertensive rats (SHRs) and age-matched Wistar rats. Blood pressure measurements were performed by occlusive tail cuff method. Measurements were commenced 1 week after the injections and repeated weekly for 4 weeks. Data is expressed as mean $\pm$ SEM and one-way ANOVA was used to assess statistical significance.

Results: Expression of TMPAP in the RVLM of SHRs resulted in a significant reduction in arterial blood pressure. Three weeks after the injections, SHRs transduced to express TMPAP in the RVLM had mean arterial blood pressure of 115.6 ± 8.8 mmHg ($n=7$), which was significantly ($p=0.009$) lower than that in SHRs transduced to express GFP (152.9 ± 8.4 mmHg, $n=9$). In comparison, TMPAP expression in the RVLM had no significant effect on the mean arterial blood pressure of control Wistar rats (91.4 ± 4.5 vs 92.6 ± 3.5 mmHg, $p=0.836$, $n=8$ in both groups).

Conclusion: Increased breakdown of extracellular ATP in the sympathoexcitatory circuits of the brainstem attenuated the development of hypertension in SHRs. ATP mediated signaling in the pre-sympathetic area of the brainstem appears to be critical in the development of essential hypertension.

CARDIAC BIOLOGY

P1520 | BENCH

Role of FGF21 in the control of UCP3 in the heart

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Introduction: Uncoupling protein 3 (UCP3) is a member of the mitochondrial anion carrier superfamily of proteins uncoupling mitochondrial respiration. It has been shown that UCP3 is expressed in the heart and it has been involved in the protection against heart failure by prevention of reactive oxygen species (ROS) production. We have recently shown that FGF21, an endocrine member of the FGF family, is produced by the heart and exerts protective effects preventing cardiac hypertrophy development. The aim of the study was to determine the role of FGF21 on UCP3 expression in the heart.

Methods: Studies in vivo were performed in hearts from wild-type (wt) and Fgf21-null mice. To assess the effects of the inflammatory process, mice were subjected to intraperitoneal (i.p.) injection of lipopolysaccharide (LPS) for 4 hr. To induce cardiac hypertrophy mice were subjected to isoproterenol (ISO) infusion for 7 days. Cell culture of neonatal cardiomyocytes from rats and mice were used for the in vitro studies. Cardiomyocytes in culture were treated with LPS for 24 hr in the presence or absence of FGF21.

Results: We found that treatment of FGF21 in cardiomyocytes in culture induces the expression of UCP3. Moreover, FGF21 reduces reactive oxygen species production in cardiac cells. In keeping with this, Fgf21-null mice presented reduced expression of UCP3 in response to stimulation with LPS-induced pro-inflammatory pathways or ISO-induced cardiac hypertrophy in the heart. Moreover, we showed that FGF21 is expressed in and released by cardiomyocytes in response to LPS, and its expression is under the control of the Sirt1 (sirtuin-1) pathway. Using neonatal cardiomyocytes in culture from wt and Fgf21-null mice we found that the FGF21 released by cardiomyocytes acts in an autocrine manner to protect the cells against oxidative stress.

Conclusions: Our data indicate that FGF21 regulates in an endocrine/autocrine manner UCP3 expression thus preventing reactive oxygen species production in cardiac cells. Therefore FGF21 acts in the heart as an antioxidant factor preventing pro-oxidative pathways induced by inflammatory/hypertrophic conditions.

P1521 | BENCH

Mediators of oxidative stress in atrial myocardium in Zucker Diabetic Fatty rats

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Purpose: Hyperglycemia induces the production of reactive oxygen species in cardiomyocytes. Cell death by apoptosis is the predominant damaging mechanism in diabetic cardiomyopathy. Cardiomyocyte death causes loss of contractile tissue and initiates cardiac remodelling processes. The mediators of oxidative stress and apoptosis in atrial myocardium in the presence of diabetes type 2 are not described so far.

Methods: Zucker Diabetic Fatty (ZDF) rat is an animal model that mimics human diabetes mellitus type 2 (T2DM). Left and right atrial tissue samples from male rats (obese ZDF; $n=8$) and their non-diabetic controls, lean ZDF ($n=6$), were analysed at the age of 12 weeks (onset of diabetes) and 24 weeks (advanced state). Atrial tissues were analysed at the transcriptional and protein levels. Analyses focused on the expression of indicative markers of oxidative stress, NADPH oxidases, LOX-1, and the apoptosis markers, bax, μ -calpain, and caspase 3, during the progression of T2DM severity. Moreover, the possible contribution of MAPK and canonical NF- κ B signalling was analysed by immunoblotting.

Results: The atrial tissue expresses three isoforms of catalytic subunits of NADPH oxidase: NOX1, NOX2 and NOX4. T2DM leads to an increased expression of NOX1, and NOX2 in atrial tissue. Interestingly, the expression of NOX4 was elevated at the onset of diabetes only. Increased oxidative stress facilitates the oxidation of low density lipids (LDL). As a consequence, the expression of the receptor for oxidized LDL remained continuously increased at the transcriptional (2.2 ± 0.36 ; $p=0.01$) and protein level (2.0 ± 0.19 ; $p=0.01$) atrial tissue of diabetic rats. This finding confirmed results of transcriptome analysis. In addition, T2DM-dependent oxidative stress activates pro-apoptotic mechanisms in atrial tissue. With disease progression we could detect enhanced expression of μ -calpain (mRNA 1.8 ± 0.20 ; protein 2.0 ± 0.34 ; $p<0.05$), an enzyme responsible for disintegration of sarcomere structure and initiation of apoptosis. Immunoblot analysis also showed the occurrence of active caspase 3 in atrial tissue of diabetic rats at the age of 6 months. Immunoblot analyses further revealed that the "oxidative state" in atrial tissue is not accompanied by either activation of MAP kinases, or by activation of the canonical NF- κ B.

Conclusions: Our data show that T2DM is associated with significantly elevated atrial expression of NADPH oxidase and LOX-1. The persistence of oxidative stress in atrial tissue facilitates apoptosis and induces calpains responsible for degradation of myofibrillar proteins.

P1522 | BENCH

Alterations in the interactome of serine/threonine protein phosphatase type-1 in atrial fibrillation patients

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Introduction: Altered protein phosphatome associated with global changes in serine/threonine protein phosphatase type-1 (PP1), a major phosphatase in the heart, has been implicated in the development of atrial fibrillation (AF). However, the phosphorylation status of PP1-targeted proteins in different subcellular compartments is not consistently changed in the same direction, underscoring a lack of understanding in the underlying mechanisms. Since PP1 is composed of a catalytic subunit (PP1c) and a large set of regulatory (R)-subunits that confer localization and substrate specificity to the holoenzyme, we tested the hypothesis that PP1 is dysregulated at the level of these R-subunits in patients with paroxysmal AF (pAF).

Methods: Cardiac lysates were co-immunoprecipitated (co-IP) with PP1c antibody, separated by SDS-PAGE, in-gel digested, and analyzed by mass spectrometry. Protein identification and label-free quantification were achieved using MaxQuant (1.3.0.5) while bioinformatics analyses were performed using MEME and FIMO. PP1 interactors with differential binding to PP1c between pAF and sinus rhythm (SR) patients were further studied using quantitative real time (qRT)-PCR, Western blotting (WB), immunocytochemistry (ICC), and co-IP.

Results: 78 and 135 putative PP1c interactors were captured respectively from human atria and mouse ventricles, most of which were previously unreported. Of these, 60 in human and 102 in mouse contained at least one of the 3 common PP1c-docking motifs (RVxF, MyPhoNE, and SILK), representing the most PP1c interactors ever identified from the heart. Applying this protocol to pAF and SR samples, we found increases in binding between PP1c and PPP1R7 (1.6-fold, $P=0.04$), CSDA (5.7-fold, $P=0.001$), and PDE5A (1.8-fold, $P=0.05$) in pAF patients. Since CSDA and PDE5A are novel PP1 interactors, we validated these interactions using bioinformatics, ICC and co-IP. WB showed that these upregulated associations cannot be ascribed to changes in global protein expression alone, suggesting that PP1 must be studied at the level of its interactions with R-subunits and not merely at its global level or activity.

Conclusions: We developed a simple yet powerful methodology to study the PP1 interactome and identified numerous novel interactors. Using this approach

we showed that the dysregulation of PP1 occurs at the level of its R-subunits in pAF patients, which may explain the subcellular heterogeneity in PP1 activity and downstream protein phosphatome observed in AF. This represents a novel concept in AF pathogenesis and may provide more specific drug targets for treating AF.

P1523 | BENCH

Moderate PGC-1 α 1 expression in the heart induces unique functional phenotype without metabolic remodelling

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Peroxisome proliferator-activated receptor gamma co-activator alpha (PGC-1 α) is a master regulator of cardiac metabolism activating signalling cascades through PPAR α and ERR α . It has been shown that robust, cardiac specific over expression of PGC-1 α leads to metabolic remodelling with subsequent functional complications. However, the role of moderate PGC-1 α 1 expression associated with physiological adaptations, like the one resulting from endurance training increasing the expression by 2-4-fold, is yet to be clarified. To elucidate this we have studied the phenotype of a mouse model in which PGC-1 α 1 transgene is driven by muscle creatine kinase (MCK) promoting only modest (3-4-fold) cardiac over-expression. To find out the physiologically relevant consequences of PGC-1 α 1 over expression in the heart, we have done in vivo cardiac imaging, studied the electrophysiology of transgenic hearts and done in vitro analysis of metabolism. The findings from our in vivo experiments propose, that PGC-1 α 1 TG mice have a clear dilation of the left ventricle without heart failure, whereas in vitro studies showed no metabolic remodelling or altered mitochondrial density of cardiomyocytes but increased Ca $^{2+}$ sensitivity of the contractile element and decreased expression of ryanodine receptor 2. Collectively, our data suggests that PGC-1 α 1 has unknown targets, different from those mediated by PPAR α and ERR α , that shape the functional phenotype of cardiomyocytes without interfering with metabolism.

P1524 | BEDSIDE

Insulin resistance is associated with cardiac aging and shorter leukocyte telomere length

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Purpose: Cardiac aging is an independent risk factor for cardiovascular disease. The main signs of the aged heart are a thickening of the left (LV) ventricular walls and LV diastolic dysfunction. Insulin resistance (IR) is exacerbating aging-related changes in the cardiac structure and function. One possible mechanism underlying IR-induced cardiac dysfunction with advancing age could be related to decreased telomeres length of leukocytes (LTL). Telomeres are tandem repeats of the DNA sequence at the end of chromosomes and protect DNA molecule from damage. LTL is a marker of replicative aging. Our hypothesis is that IR led to shorter telomeres and senescent phenotypes in the heart.

Methods: We investigated 118 non-obese participants aged 60 to 85 years without history of CVD, diabetes and regular drug medication. All the volunteers underwent standardized transthoracic echocardiography with the available system (iE33; Philips), had an oral glucose tolerance test. HOMA-IR was calculated as fasting insulin (mU/ml) x fasting glucose (mmol/l) / 22.5. IR was diagnosed in case of HOMA-IR elevation >2.5 based on reference. LTL was measured by real-time quantitative polymerase chain reaction. We determined the relative ratio of telomere repeat copy number (T) to single-copy gene copy number (S).

Results: In older individuals HOMA-IR was significantly positively related to LV septal wall thickness ($r=0.489$, $p<0.001$), LV posterior wall thickness ($r=0.458$, $p<0.001$), E/Em ($r=0.379$, $p<0.01$) and inversely correlated with E/A ($r=-0.320$, $p<0.01$), Em/Am ($r=-0.342$, $p<0.01$). LTL was significantly and independently associated with age ($\beta=-0.026$, $p=0.015$) and HOMA-IR ($\beta=-0.176$, $p=0.027$). Results of analysis of variance (ANOVA) showed that LTL was significantly related to diastolic function indices regardless of age ($p<0.001$). Older subjects with higher HOMA-IR had a shorter telomeres ($p=0.046$) and more expressed LV hypertrophy and diastolic dysfunction to compared to subjects with normal HOMA-IR. Individuals with IR did not significantly differ from those with normal HOMA-IR in the proportion of smokers, or levels of blood pressure and BMI.

Conclusions: These findings suggest that insulin resistance is associated with more expressed signs of the aging heart and shorter LTL. Accelerated telomere attrition appears to be the mechanism by which impaired insulin resistance develops into cardiac aging.

P1525 | BENCH

From beat rate variability in induced pluripotent stem cell-derived pacemaker cells to heart rate variability in human subjects

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Numerous studies showed that heart rate (HR) fluctuates around a mean, a phenomenon termed HR variability (HRV). A key feature of human SAN is that HRV exhibits self-similarity contributing to its complexity. We reported that networks of human embryonic stem cell-derived cardiomyocytes (CM) and iPS cell-derived CM (iPSC-CM) exhibit beat rate variability (BRV), fractality and power-law behavior resembling HRV in human SAN. To investigate whether cellular BRV is a source of HRV, we hypothesized three-levels of interaction among different cardiomyocyte entities: (1) single pacemaker cells, (2) networks of electrically coupled pacemaker cells, (3) in situ SAN. To test this hypothesis, we analyzed HRV properties in ECGs of healthy volunteers, and BRV in extracellular electrograms and action potentials of spontaneously contracting embryoid bodies (EBs) and iPSC-CM, respectively, both fabricated from volunteers' keratinocytes. We also hypothesized that disrupting intracellular Ca $^{2+}$ handling impacts on BRV. The major findings were: (1) Marked BRV/HRV were present at all three levels, reflected by Standard Deviations (STD) of inter-beat intervals (IBIs) and Poincaré plot SD1 and SD2. (2) BRV indices were >20 in single cardiomyocytes than in networks or heart, suggesting the large increase in BRV occurs in transitioning from network to single cardiomyocyte. We also compared BRV among single cells, small (~5-10 cells) and larger EBs (>10 cells): BRV indices progressively increased as cell number decreased. These findings illustrate that as more cells are included in the network, BRV decreases sharply, suggesting the higher the number of interactions among the potential pacemakers, the smaller the variability around the mean beat rate. Further, we found that BRV magnitude is similar within the group including the heart, EB and the large cluster, but are significantly ($P<0.05$) larger upon transitioning to the small cluster and a single cell. Finally, disrupting intracellular Ca $^{2+}$ handling by means of RU360 (mitochondrial Ca $^{2+}$ uptake blocker), GCP-37157 (mitochondrial Na $^{+}$ -Ca $^{2+}$ exchanger antagonist) and ryanodine, markedly augmented BRV magnitude, suggesting that intracellular mechanisms contribute to BRV/HRV and the fractal behavior of heart rhythm. The decreased BRV magnitude in transitioning from single cell to EB suggests that HRV of hearts in situ originates from summation and integration of multiple cell-based oscillators. Hence, complex interactions among multiple pacemaker cells and intracellular Ca $^{2+}$ handling mechanisms determine HRV in humans and isolated cardiomyocyte networks.

P1526 | BENCH

Morphometric characterization of intracardiac neurons modulating atrial cardiac electrophysiology

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Purpose: Neuronal modulation is a key element in the regulation of heart rate and rhythm. As has been demonstrated by anatomical studies, intrinsic cardiac neurons (ICN) on the level of the atria form a complex network. Although it is well known that ICN are involved in the pathophysiology of atrial fibrillation, detailed morphometric and functional characterization of these cells has not yet been undertaken.

Methods: Hearts were harvested from the hearts of male mice, aged between 12 and 16 weeks (C57BL6, Charles River, France). Epicardial fat at the dorsal surface of the atria and in-between the great vessels, containing the bulk of ICN, was carefully removed and enzymatically digested. ICN were then resuspended in supplemented Claycomb medium, containing glutamine and B27, and incubated on poly-L-lysine coated cover slips. For neuron-myocyte co-culture atrial myocytes (HL-1 cells) were prepared in the usual fashion and applied to the culture dish together with ICN, using a removable 2-well silicone insert. After initial incubation for 48h (37°C, 5% CO $_2$) ICN were digitally photographed and assessed for their morphology and length of axons outgrowth. FACS analysis of cultured ICN was undertaken, using immunofluorescent staining for tyrosinhydroxylase (TH), cholin-acetyltransferase (ChAT) and neurofilament light-chain (NFL).

Results: Under adapted culture conditions ICN, as well as atrial myocytes remained viable for extended periods (>72h), with myocytes exhibiting habitual proliferation and spontaneous contractility, while ICN showed axonal outgrowth. Three populations of neuronal phenotypes could be observed, which occurred in distinct distribution: 1. unipolar ICN (27.0%), 2. bipolar ICN (42.3%), 3. multipolar ICN (30.8%). Following the loss of axons during the isolation process, ICN exhibited characteristic axonal outgrowth according to their cell type, with unipo-

lar ($90.7 \pm 10.3 \mu\text{m}$) and bipolar ($73.4 \pm 10.6 \mu\text{m}$) showing typically longer axons, than the smaller multipolar ICN ($35.7 \pm 5.6 \mu\text{m}$; $p=0.0013$). In the FACS analysis ICN could be identified as a discrete population positive for TH, ChAT and NFL immunostaining.

Conclusions: Our findings demonstrate the feasibility of isolation and cultivation of adult murine ICN, exhibiting characteristic distribution of cell types and rate of axonal outgrowth. Furthermore ICN can be kept in stable co-culture with atrial myocytes. These methods enable detailed in-vitro studies looking into the complex interaction of atrial neurons and myocytes, one key mechanism in the pathophysiology of atrial fibrillation.

P1527 | BEDSIDE

Default profile of serum miRNA in patients with patent vs. occluded target vessel in acute coronary syndrome

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Circulating microRNAs (miRs) are recognized as useful cardiovascular biomarkers in acute coronary syndromes (ACS). Vessel occlusion is not always manifested with ST-elevation; no specific biomarkers have been identified to differentiate ACS with patent or occluded infarct-related coronary artery (IRA), so far. However, data indicate possibility of IRA occlusion in the absence of ST-elevation what unfortunately leads to delays in diagnosis and revascularisation therapy.

Methods: Forty-four consecutive patients (mean age 57.5 ± 9.9 years) with uncomplicated ACS and positive troponins were admitted. Patients were classified into 2 categories, with respect to patent vs. occluded IRA and those with ST-elevation or non-ST elevation MI (STEMI vs. NSTEMI). On admission, inflammatory markers (hs-CRP, fibrinogen, TNF- α and IL-6) and expression levels of selected serum cardiac and brain-ischemia induced miRNAs (miR-1, -16, -34a, -122, -124, -208b, -133a/b, -375, and -499) were analyzed.

Results: There were 17 STEMI and 27 NSTEMI. Of those, occluded IRA was found in 15 NSTEMI subjects and 13 STEMI patients, while the remaining subjects from STEMI and NSTEMI group had a patent IRA during coronary angiography. Summarizing, 16 patients were categorized to the patent and 28 to the occluded groups; consistently, STEMI vs. NSTEMI patients had significantly higher troponin T levels, lower fibrinogen concentration (3.4 ± 1.24 vs. 4.4 ± 1.78 g/L; $p=0.049$), and a 3.83-fold higher miR-134 expression ($p<0.05$). Whereas, patients with the occluded vs. patent IRA had significantly higher levels of circulating miR-133a (fold change: 7.00), miR-133b (4.57), miR-34a (5.50), miR-124 (2.55) and miR-134 (3.45), but no difference in the levels of troponin T and inflammatory markers. ROC analysis showed that predictors of IRA occlusion are: expressions of miR-124 (area under the curve; AUC: 0.787, sensitivity of 78%, specificity of 63%, $p=0.002$), miR-133b (AUC: 0.704; sensitivity of 63%, specificity of 74%, $p=0.027$) and miR-134 (AUC: 0.686, sensitivity of 63%, specificity of 69%, $p=0.043$). With respect to STEMI vs. NSTEMI group, only miR-134 showed discriminating value (AUC: 0.725, sensitivity of 75%, specificity of 63%, $p=0.015$).

Conclusions: miRs expression do not discriminate patients with STEMI and NSTEMI, with the only exception to miR-134. Surprisingly, higher expression levels of several cardiac and brain miRs were related to IRA occlusion. Discriminating value of miR-133b and miR-124 in indicating patients with IRA occlusion, thus requiring urgent coronary revascularisation, despite the lack of ST-elevation on ECG needs to be established.

P1528 | BENCH

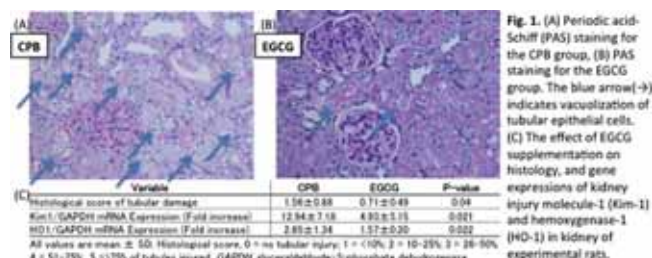
Oral pretreatment with a green tea polyphenol ameliorated renal impairment in a cardiopulmonary bypass model for diabetic rats

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Purpose: Acute kidney injury (AKI) is a common and serious postoperative complication following exposure to cardiopulmonary bypass (CPB), and diabetes mellitus is an independent risk factor for AKI after cardiac surgery. Epigallocatechin-3-gallate (EGCG), a major polyphenolic component of green tea that we reported its cardioprotective properties previously, is thought to have a renoprotective effect through its diverse biochemical activities. We investigated the effects of EGCG on renal damage in a CPB model for diabetic rats.

Methods: The Goto-Kakizaki (GK) rats, non-obese Wister substrains which develop Type2 diabetes mellitus early in life, (300-360 g) were randomly assigned to 1 of 3 groups: Sham ($n=10$), CPB (CPB alone, $n=9$), or EGCG (CPB+EGCG, $n=7$). The EGCG group was given EGCG solution orally at 1 mmol/L for 2 weeks; the Sham and CPB groups received tap water alone for 2 weeks. Subsequently, CPB was conducted for 30 min at a flow rate of 100 ml/kg/min in the CPB and EGCG groups. 24 hours after CPB, we compared renal function markers and histologic changes.

Results: Compared with the CPB group, the EGCG group exhibited limited



histological tubular injury ($P=0.04$), and reduced gene expression of kidney injury molecule-1, a biomarker for renal tubular injury (Kim-1: $P=0.021$) and hemoxygenase-1, an ubiquitous enzyme up-regulated in response to oxidant stress and inflammatory stimuli (HO-1: $P=0.022$) (Fig. 1). There was no significant difference in the level of serum tumor necrosis factor-alpha between the CPB and EGCG groups.

Conclusions: These findings suggest that oral pretreatment with EGCG alleviates the kidney damage in a CPB model for diabetes rats by its antioxidative properties.

P1529 | BENCH

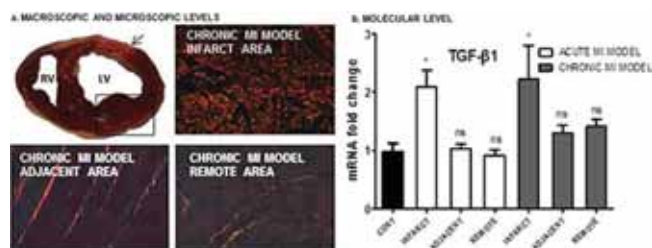
Macroscopic, microscopic and molecular characterization of myocardial fibrosis in a swine model of reperfused myocardial infarction

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Purpose: Fibrosis plays a key role in the pathophysiology of left ventricular (LV) remodeling after myocardial infarction (MI). The dynamics of this process and whether it is a localized or diffuse phenomenon has not been totally clarified. We aimed to characterize these issues in a swine model of reperfused anterior MI.

Methods: Swine were subjected by means of percutaneous balloon inflation to a transient 90-min occlusion of mid left anterior descending artery followed by 72-h (acute MI model) or 1-month (chronic MI model) reperfusion. The extent of fibrosis was macroscopically (triphenyltetrazolium staining, % of LV volume) and microscopically (Sirius red staining, % of field) quantified in the infarct, adjacent and remote areas as well as in controls. TGF- β 1, collagen1-A1, A2 and 3A1 gene expression was determined.

Results: Macroscopically, necrosis ($16 \pm 5\%$ in the acute MI model) and fibrosis ($16 \pm 4\%$ in the chronic MI model) were detected in all cases. Macroscopic fibrosis occurred in the infarct but not in the adjacent or remote areas (figure). At microscopic level, in comparison with controls, fibrosis was only significantly increased in the chronic MI model at the infarct area ($35 \pm 4\%$, $p<0.001$) but not in the acute MI model or in the adjacent and remote areas in the chronic MI model ($<4\%$ in all cases, $p=ns$, Figure). TGF- β 1 ($p<0.05$, acute and chronic MI models, figure) and collagen1-A1, A2 and 3A1 ($p<0.001$, chronic MI model) gene expression was significantly increased in the infarct but not in the adjacent or remote areas ($p=ns$).



Conclusion: In a model of anterior MI, 1-month after reperfusion, at macroscopic, microscopic and molecular levels, myocardial fibrosis appears as a localized process which mainly affects the infarct area but not the adjacent or remote regions.

EXPLORING ATRIAL FUNCTION BY ECHOCARDIOGRAPHY

P1531 | SPOTLIGHT

Left atrial strain as independent parameter to predict left ventricular end diastolic pressure

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Background: Several noninvasive measurements are widely applied to estimate left ventricular filling pressures (LVFP) and to establish a correct therapeutic strat-

egy in a lot of cardiac diseases, especially in patients with heart failure. Among these, left atrial (LA) deformation analysis by speckle tracking echocardiography (STE), has recently demonstrated to be highly accurate to estimate LVFP even in patients with advanced heart failure. The aim of this study was to examine the accuracy of LA strain in predicting LVFP, analyzing its dependency from left ventricular parameters.

Methods: A total of 87 stable patients with sinus rhythm undergoing cardiac catheterization were studied. LV end diastolic pressure (LVEDP) was obtained during cardiac catheterization; peak atrial longitudinal strain (PALS), mean E/E' ratio, left ventricular longitudinal strain (GLS) and mitral annular plane systolic excursion (MAPSE) were measured in all subjects by another independent operator. PALS values were obtained by averaging all segments (global PALS), and by separately averaging segments measured in the 4-chamber and 2-chamber views.

Results: Global PALS correlated significantly with LVEDP ($r=-0.86$; $p<0.0001$). Lower levels of correlation were found for E/E' ratio ($r=0.57$; $p=0.01$), GLS ($r=0.40$; $p=0.05$) and MAPSE ($r=-0.22$; $p=ns$). Parameters of LV systolic analysis presented lower correlation in subgroup of patients with lower LV ejection fraction. ROC analysis showed global PALS as the best predictor of increased LVEDP (AUC: 0.83). In multivariate analysis, global PALS emerged as a determinant of the LVEDP, independently on other confounding factors.

Conclusions: In comparison to E/E' ratio and LV systolic parameters, LA strain is a strong and independent parameter for non invasive prediction of LVEDP.

P1532 | BEDSIDE

Diagnosing paroxysmal atrial fibrillation in patients with ischemic strokes and transient ischemic attacks using echocardiographic measures of left atrium function

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Background: The underlying cause of ischemic strokes (IS) and transient ischemic attacks (TIA) is not identified in 25% of the cases. However, asymptomatic paroxysmal atrial fibrillation (PAF) is often suspected to be the cause of the cryptogenic IS or TIA. Therefore, the aim of this study was to examine if echocardiographic measures of left atrial (LA) function including LA emptying fraction (LA EF) and minimal LA volume (min LAV) could diagnose PAF in patients with IS and TIA.

Methods: We retrospectively included 219 patients who after acute IS or TIA underwent a transthoracic echocardiographic examination in sinus rhythm. Patients were designated as PAF-patients if they had one or more reported incidents of AF before or after their echocardiographic examination.

Results: Patients in the PAF group were significantly older (61 ± 13 vs. 51 ± 14 years, $p<0.001$) than patients without PAF. Besides age, no other baseline characteristic (sex, hypertension, diabetes, cholesterol) was associated with PAF. None of the conventional echocardiographic parameters (LV ejection fraction, LV volumes, E/A-ratio, deceleration time, maximal LAV) were significantly associated with PAF. However, the atrial measures evaluating LA function (min LA volume and the LA EF) were significantly different (LA EF: $45\%\pm10\%$ vs. $50\%\pm10\%$, $p=0.041$; min LAV: $30.2\text{ mL}\pm17.3\text{ mL}$ vs. $24.3\text{ mL}\pm9.8\text{ mL}$, $p=0.001$) in patients with PAF, even after adjusting for age and gender ($p<0.05$ for both). Using joint criteria, by combining the cut-off values of age, LA EF and min LAV (with highest sensitivity and specificity determined from the ROC-curves), the diagnostic accuracy of PAF improved, resulting in a sensitivity of 95% and negative predictive value of 97% (See Table).

Diagnostic accuracy for age/LA EF/min LAV

	Sensitivity	Specificity	PPV	NPV
Age ≥ 60 years	63.64%	70.86%	35.44%	88.57%
Age ≥ 60 years and/or LA EF $< 45\%$ and/or min LAV $> 23\text{ mL}$	95.45%	32.57%	26.25%	96.61%

LA EF, left atrium emptying fraction; min LAV, minimum left atrium volume, PPV, positive predictive value; NPV, negative predictive value.

Conclusion: In patients with IS and TIA, measures of LA function (min LAV and LA EF) are independently associated with the presence of PAF. Applying these may yield better risk stratification for PAF-presence in patients suffering cryptogenic IS and TIA.

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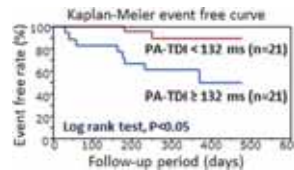
Total atrial conduction time evaluated with tissue Doppler imaging predicts cardiac prognosis in patients with chronic heart failure

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Purpose: It has been proposed that total atrial conduction time is a marker of atrial remodeling. Recently, a novel echocardiographic parameter based on tissue Doppler imaging (TDI) has been used to assess the total atrial conduction time. The aim of this study was to investigate whether total atrial conduction time predicts poor prognosis in patients with chronic heart failure (CHF).

Method: Transthoracic echocardiography was performed at discharge in 42 consecutive CHF patients with sinus rhythm (26 males, mean age 67 ± 14 years) who were hospitalized for heart failure. Total atrial conduction time was estimated by measuring the time delay between the onset of the P-wave of electrocardiogram and the peak A'-wave on the TDI of the left atrial lateral wall (PA-TDI duration).

Results: There were 11 cardiac events (26%) during a median follow-up period of 311 days. There were no significant differences in left ventricular end-diastolic dimension and ejection fraction between patients with and without cardiac events. Patients with cardiac events were significantly older and had larger left atrial volume index (LAVI) and longer PA-TDI duration (144 ms vs. 123 ms, $P<0.01$) than those without events. Multivariate Cox proportional hazard analysis showed that PA-TDI duration was an independent predictor for cardiac events (hazard ratio 4.113 (per 1 SD increase), 95% confidence interval 1.320-22.740, $P<0.05$). Kaplan-Meier analysis showed that cardiac event rates were markedly higher in patients with long PA-TDI duration than in those with short PA-TDI duration (89% vs. 50%, $P<0.05$).



Kaplan-Meier event free curve.

Conclusion: Long PA-TDI duration was associated with poor cardiac prognosis. PA-TDI duration is a feasible predictor for cardiac events in patients with CHF.

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Decreased left atrial mechanical function assessed by echocardiographic free strain in patients with uncontrolled blood pressure

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Purpose: Both uncontrolled blood pressure (BP) and left atrial (LA) enlargement are commonly observed in patients who receive antihypertensive agents, but the impact of uncontrolled BP on LA mechanical function remains unknown.

Methods: This study enrolled 279 hypertensive patients (HTgp) being treated and 42 normal controls. Patients were divided into the controlled (systolic BP <140 and diastolic $<90\text{ mmHg}$, HTgp1) and uncontrolled (HTgp2) group according to their office BP readings in the past 3 months. LA function was assessed by 2-dimensional speckle tracking free strain, including systolic (SSa), early diastolic (SEa) and late diastolic (SAa) strain.

Results: The 3 groups were matched with age and gender. Despite similar LA empty fraction, the hypertensive groups had significantly reduced SSa, SEa and SAa, in addition to larger left ventricular (LV) mass index and LA volume index. HTgp2 showed further impaired SEa than HTgp1. The impairment of SEa was observed in 113 (41%) patients with 47 (32%) in HTgp1 and 66 (50%) in HTgp2. In a multivariate logistic regression model created to identify the associated factors of the SEa impairment, the uncontrolled BP (OR 2.526, $p=0.002$) and older age (OR 1.069, $p<0.01$) appeared significant. However, the gender, presence of diabetes or hyperlipidemia, LV hypertrophy and LA volume index were not related with the SEa impairment.

Parameters	Control (n=42)	HTgp (n=279)	HTgp1 (n=146)	HTgp2 (n=133)	HTgp1 vs. HTgp2
Systolic BP, mmHg	122 $\pm$ 12	138 $\pm$ 16 [§]	127 $\pm$ 10 [†]	150 $\pm$ 12 [§]	<0.001
Diastolic BP, mmHg	76 $\pm$ 8	82 $\pm$ 10 [§]	79 $\pm$ 8	87 $\pm$ 10 [§]	<0.001
LV mass index, g/ m ²	70 $\pm$ 12	101 $\pm$ 21 [§]	94 $\pm$ 17 [§]	110 $\pm$ 19 [§]	<0.001
LA volume index, ml/m ²	31.7 $\pm$ 4.8	42.8 $\pm$ 8.0 [§]	41.0 $\pm$ 7.5 [§]	43.1 $\pm$ 8.5 [§]	<0.001
LA empty fraction, %	61.0 $\pm$ 7.0	62.0 $\pm$ 8.4	63.0 $\pm$ 7.9	63.0 $\pm$ 8.9	NS
SSa	53.1 $\pm$ 10.1	35.9 $\pm$ 8.0 [§]	36.6 $\pm$ 7.8 [§]	35.1 $\pm$ 8.3 [§]	NS
SEa	31.2 $\pm$ 7.6	18.5 $\pm$ 7.1 [§]	19.8 $\pm$ 8.3 [§]	17.2 $\pm$ 5.3 [§]	0.002
SAa	21.8 $\pm$ 5.4	17.6 $\pm$ 4.2 [§]	17.6 $\pm$ 3.9 [§]	17.9 $\pm$ 4.5 [§]	NS

[§]P<0.001, [†]P<0.01, [‡]p<0.05, compared with the control group.

Conclusions: Hypertension is associated with early impairment of LA mechanical function detected by novel echocardiographic parameters. Further decrease in LA reservoir and conduit function as reflected by SEa would be attributed to the uncontrolled BP, which might be a composite index of several adverse processes occurred in hypertension.

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Redefining the size of the left atrium: matching volume and area

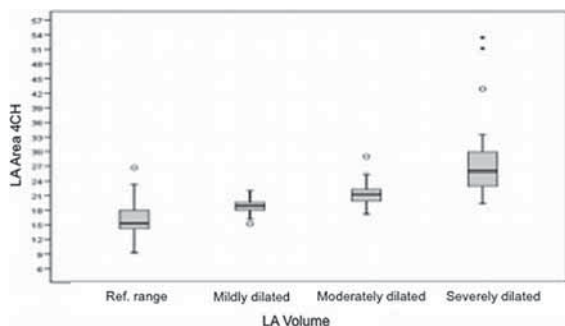
C. Cortina Camarero, M. Sarrion Catala, L. Mora Yague, V. Suberviola, J.M. Cano Moracho, C. Beltran Herrera, A. Estevez Paniagua, A. Sanchez Hernandez, D. Vaqueriza Cubillo, R. Munoz Aguilera. University Hospital Infanta Leonor, Cardiology, Madrid, Spain

Left atrium (LA) size is an important predictor of adverse events in many cardiac

diseases. To estimate the LA size, volume rather than area measurements are preferred. However, using volume and area data frequently yield different assessment of the degree of LA enlargement according to the reference values published. The aim of this study was to redefine the cut-off values of LA area based on the volume measurements as the 'gold standard'.

Methods: We prospectively enrolled 357 consecutive patients referred for an echocardiogram. The LA volume indexed to BSA was calculated with the area-length biplane technique. In 256 patients, new reference area values were obtained that better correlate to the volumetric assessment using ROC analysis. In the remaining 101 patients, these new reference values were validated.

Results: Patients age range was 16-95 years. LA volume could not be measured in 14% of the patients. An agreement study between LA volume and apical 4 chamber (A4Ch) area was performed showing (weighted kappa = 0.48, 95% CI 0.42-0.54) the inaccurate classification provided by LA area values. The new reference values obtained for LA A4Ch area were: Normal <18 cm², mildly dilated 18-20 cm² (AUC=0.85, 95%CI 0.78-0.92), moderately dilated 20-23cm² (AUC=0.81, 95%CI 0.68-0.95), severely dilated >23 cm² (AUC=0.87, 95%CI 0.79-0.96). In 101 patients, we applied these new range values for LA area and found an excellent agreement with volume measurements (weighted kappa=0.84, CI 95% 0.77-0.91).



New range values of LA area.

Conclusions: The published reference values of LA size based on area measurements poorly correlates with the volume estimations. The proposed range values of LA dilatation according to area measurements significantly improved the accuracy for defining normal size and different grades of dilatation.

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Tissue doppler imaging assessment of atrial electromechanical delay and dyssynchrony to predict non-valvular atrial fibrillation recurrence 6 month after cardioversion

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Background: There is lack of reliable tests for predicting non-valvular atrial fibrillation (AF) recurrence. Atrial electromechanical delay (AED) and atrial dyssynchrony (AD) assessed by tissue Doppler imaging (TDI) may reflect factors predisposing to AF recurrence.

Purpose: Retrospective comparison of AED and AD evaluated by TDI after cardioversion in patients with and without recurrence of AF during next 6 months.

Methods: The study included 77 patients (pts) with persistent AF (mean age [median (Me) and interquartile range (Q25-Q75)] 62 (55-68) ys; 49 men (64%) and 28 women (36%)), in whom cardioversion was performed. The evaluation of atrial electromechanical function was performed by transthoracic spectral TDI during first 24-72 hours after cardioversion. Left and right atrial electromechanical delay (LA-ED and RA-ED) parameters were assessed as periods from beginning of P-wave on single-lead electrocardiography to the peak of TDI late diastolic wave of lateral mitral and tricuspid annuli, accordingly. AD was evaluated as LA-ED and RA-ED difference. Group 1 (G1) included 33 pts (43%) without AF recurrence during 6 months follow-up, group 2 (G2) – 44 pts (57%) with AF recurrence. G1 and G2 were comparable by age, gender and clinical characteristics. Area under curve (AUC), sensitivity (Se), specificity (Sp) and relative risk (RR) were presented with 95% confidence intervals (CI).

Results: Parameters of atrial electromechanical function were significantly higher in G2 than in G1: LA-ED (171 (148-183) and 144 (139-159) ms, accordingly, p<0.001) and AD (42 (30-60) and 22 (13-32) ms, accordingly, p<0.001). On the basis of ROC-analysis, with a cut-off value of AD ≤31.5 ms, the Se and Sp to predict no recurrence of AF during 6 months were 72.7% (95% CI 57.2-85.0%) and 72.7% (95% CI 54.4-86.7%) (AUC 0.823 (95% CI 0.730-0.917)), and the RR was 3.42 (95% CI 1.91-6.10), being higher than those of LA-ED at cut-off ≤156.5 ms: Se 63.6% (95% CI 47.8-72.6%), Sp 66.7% (95% CI 48.2-82.0%), AUC 0.735 (95% CI 0.622-0.848) and the RR 1.71 (95% CI 1.12-2.60).

Conclusion: TDI-derived AD and LA-ED might be useful as predictors of AF recurrence during 6 months following cardioversion in patients with non-valvular persistent AF.

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The left atrial regional deformation analysis in the patients with atrial fibrillation: 2D speckle tracking echocardiography using CARTOSOUND

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Introduction: Global left atrial (LA) strain by transthoracic 2-dimensional speckle tracking echocardiography (STE) has been reported to be a non-invasive method for assessment of whole LA reservoir and booster pump function. However, little has been known about the regional LA wall deformation among different LA areas. Furthermore, in the patients with atrial fibrillation (AF), it is still unclear whether regional LA strain associates with the endocardial voltage information obtained by 3-dimensional anatomical and voltage mapping (EAM) for radiofrequency catheter ablation (RFCA). Recently, CARTOSOUND (C-S) enable us to visualize the intra-cardiac ultrasound image in the EAM. Accordingly, the aim of this study was to evaluate the region specific LA deformation and to assess its association with the voltage in the LA in atrial fibrillation patients.

Methods: Thirty-two patients with AF (persistent:n=12, paroxysmal:n=20, average age: 62±9 year-old) were included in this study. In persistent AF patients, AF was restored by antiarrhythmic drug and/or electrical cardioversion. All patients underwent an intra-cardiac echocardiography and endocardial voltage mapping during sinus rhythm using CARTOSOUND just before RFCA. Longitudinal strain (LS) were measured in the bottom, lateral (short-axis-view near the mitral valve annulus), posterior (vertical view between left and right pulmonary veins) and septal wall of the LA. Strain-time curve were obtained from onset of p-wave on electrocardiogram.

Results: In the bottom and lateral wall, the strain showed negative monophasic pattern (peak LS: -15±7%, -18±9%, respectively). In the posterior wall, 3 phases pattern, positive-negative-positive strain time curve was observed (peak LS: -12±9%). It seems to be the opposite of global LA strain time curve. On the other hand, peak LS was positive in the anterior or septal area (+12±6%). Furthermore, in the subjects with low voltage area (LVA: <1.0mV, >10%, n=15) in the LA, peak LS in the posterior wall was significantly smaller than those without LVA (LVA+: -8±9%, LVA-: -16±7%, p<0.05). Although peak LS in other areas tended to decrease in the subjects with LVA, it was not statistically significant.

Conclusions: The regional LA deformation may be non-uniformly-distributed over the whole LA, in which bottom and lateral wall may work as a systolic booster, septal wall as a LA reservoir, and posterior wall may passive deformation area. Furthermore, LA posterior passive deformation may get worse as LA voltage was reduced, probably reflecting endocardial fibrosis accumulation.

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Left atrial systolic and electromechanical functions after ST-elevation myocardial infarction. a tissue doppler echocardiographic imaging study

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Background: Left atrial (LA) function provides prognostic value in post-infarction patients. However, assessment of LA function remains limited with no accepted golden standard.

Aim: To evaluate the existence and determinants of LA systolic and electromechanical dysfunctions following ST-elevation myocardial infarction (STEMI) using tissue Doppler imaging (TDI).

Methodology: Thirty patients (median age: 58 years; 27 males; 8 with diabetes) in sinus rhythm with successfully reperfused STEMI were prospectively enrolled. All patients had echocardiography within 24 hours of STEMI and at Fu (median: 9 months; range: 6-12). Indexed LA maximal, minimal, and volume at onset of P wave on ECG were calculated using Simpson's rule. LA total, active, and passive emptying volumes and fractions were calculated. Using pulsed-TDI, both peak velocity and duration of regional atrial contraction (A') in all basal segments of LA walls (septal, lateral, anterior, inferior, posterior) were measured and then averaged. LA electromechanical function (time intervals from the onset of P wave on ECG to the beginning; peak; and end of A' wave) was assessed. Systolic (Sm) and diastolic TDI velocities of lateral mitral annulus were measured. LA systolic dysfunction was defined as reduction of A' velocity by ≥0.14 cm/s between baseline and Fu studies (median value of change of A' velocity in all patients).

Results: During Fu, there was significant increase in the three indexed LA volumes (p<0.05) with significant increase in both total (10 to 12.5 ml/m², p=0.016) and passive (5.3 to 7.4 ml/m², p=0.001) emptying volumes and no change in active emptying volume (4.6 to 4.3 ml/m², p=0.98). All emptying fractions showed no significant changes between baseline and Fu. Compared to baseline, A' wave at Fu showed reduced velocity (from 10.5 to 8.3 cm/s, p=0.03) and prolonged duration (from 117 to 124 msec, p=0.02). Among several baseline clinical and echocardiographic variables, only Sm velocity was reduced in patients with LA systolic dysfunction (6.7 cm/s) versus patients without (9.6 cm/s; p=0.006). Sm velocity correlated with A' velocity at baseline (r=0.51, p=0.01) but not at Fu. Indices of LA electromechanical function showed no significant changes between baseline and Fu.

Conclusion: Following STEMI, LA systolic function - as assessed by TDI - could be abnormal, even in conditions with normal LA function when assessed by pha-

sic volume changes. LA systolic dysfunction is associated with longitudinal left ventricular systolic dysfunction. No LA electromechanical abnormalities were detected among post STEMI patients.

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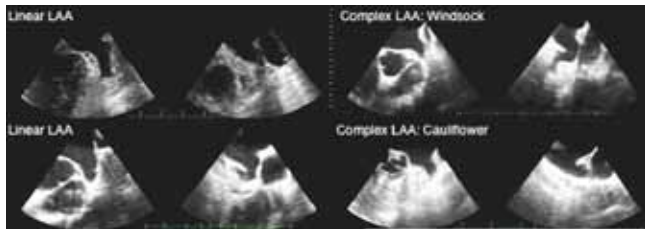
Assessment of transesophageal echocardiography to describe left atrial appendage morphology

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Purpose: Left atrial appendage (LAA) morphology, investigated by computed tomography (CT) and magnetic resonance imaging (MRI), has recently proved to relate to the risk of cerebrovascular events in patients with Atrial Fibrillation (AF). Aim of our study was to assess transesophageal echocardiography (TEE) imaging in describing LAA morphology.

Methods: Two hundred consecutive patients referred for TEE were enrolled. In the first group of 47 (23.5%) patients LAA morphology was analyzed by conventional TEE and described as Cactus, Chicken Wing, Windsock or Cauliflower. In the second group of 153 (76.5%) patients, instead, a 3D-Xplane diagnostic algorithm was performed to stratify LAA morphology as Linear (Cactus and Chicken Wing) or Complex: Windsock and Cauliflower. Interobserver variability within three independent readers was assessed in both groups of patients and stratified by operator's experience and training. In a subgroup of 19 (12.4%) patients agreement of LAA morphology description by 3D-Xplane diagnostic algorithm was compared to cardiac MRI.

Results: By conventional TEE the agreement among operators on LAA morphology classification was poor ($p < 0.13$). The 3D-XPlane diagnostic algorithm, instead, significantly increased interobserver agreement up to $\rho = 0.32$ within all readers and up to $\rho = 0.82$ among the experienced and specifically trained operators. LAA morphology description in this latter group provided very strong agreement with cardiac MRI (up to $\rho = 0.77$).



LAA morphologies as shown by 3D X-plane.

Conclusions: LAA morphology assessment is challenging by conventional TEE. To improve diagnostic accuracy the use of the 3D-Xplane technique associated with a specific diagnostic algorithm and training of the operators is fundamental.

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Determinants of discrepancies between two-dimensional echocardiographic methods for assessment of left atrial volume

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Purpose: The determinants of discrepancies among 2D echocardiographic methods for left atrial volume (LAV) assessment have been poorly investigated. Thus we aimed at identifying the determinants of differences between two-dimensional (2D) echocardiographic methods for the estimation of LAV.

Methods: LAV was measured in 613 patients (age 45 ± 20 years, 62% male, 282 healthy subjects, 180 athletes and 151 hypertensives) using the ellipsoid model (LAV-EI), and the single-plane and biplane area-length method (LAV-AL) and Simpson's rule (LAV-Simps). Based on a mathematical model, two LA geometry indexes were also tested as predictors of discrepancies in multivariable analysis: the ratio between left atrial (LA) medial-lateral diameter in the 4-chamber view (MLD) and LA anteroposterior diameter (APD); and the ratio between 4-chamber view LA area and that of an ellipse with the same diameters (deviation from ellipse [DE] coefficient).

Results: LAV-EI underestimated biplane LAV-AL and biplane LAV-Simps by an average of 35% and 26%, respectively. The MLD/APD ratio and the DE coefficient

were the strongest predictors of relative differences between biplane and the ellipsoid methods, together accounting for 76% of the difference between LAV-AL and LAV-EI and 68% of that between LAV-Simps and LAV-EI. The DE coefficient was also the only determinant of the LAV-AL/LAV-Simps difference ($\beta = 0.167$, $p < 0.0001$). Body mass index (BMI) was the strongest predictor of the differences between the single-plane and biplane approach of both area-length ($\beta = 0.427$, $p < 0.0001$) and Simpson methods ($\beta = 0.424$, $p < 0.0001$). The concordance between single-plane and biplane approaches was suboptimal in overweight-to-obese individuals.

Conclusions: LA geometry is the main determinant of inconsistencies between 2D methods for LAV estimation. BMI is the strongest determinant of differences between single-plane and biplane approaches. These findings suggest that on a single-patient basis, different 2D echocardiographic methods cannot be used interchangeably for diagnosis and follow-up, and that biplane methods should be preferred, particularly in overweight-to-obese individuals.

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Prognostic value of left atrial size and function assessed by three dimensional speckle tracking analysis

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Background: Several left atrial volume and functional indices calculated by 2 and 3-dimensional echocardiography have been proposed as predictors of future cardiac events. Prognostic value of left atrial maximum and minimum volume (LAVImax and LAVImin), left atrial emptying fraction (LAEmPF) and left atrial ejection fraction (LAEJF) measured by 3-dimensional speckle tracking analysis (3DSTA) have not assessed in large number of patients.

Methods: LAVImax/LAVImin, LAEmPF and LAEJF were measured by 2-dimensional echocardiography (2DE) and 3DSTA in 358 patients with various cardiovascular diseases. After excluding patients with atrial fibrillation / flutter and mitral valve disease, 321 subjects (male 68%, mean age: 72 ± 18 yo) were followed to record major adverse cardiovascular events (MACE). To determine the cut off values, the same indices were measured in other 80 normal subjects.

Results: During a mean follow-up of 2.3 years, MACE developed in 76 patients, including 26 cardiac deaths. The cut-off criteria of LAVImax, LAVImin and LAEmPF by 2DE and 3DSTA had significant predictive power of MACE by Kaplan-Meier survival analysis ($p < 0.001$). These six indices were still significant and independent after adjustment for clinical variables and left ventricular ejection fraction. The cut-off criteria of LAVImin and LAEmPF by 3DSTA had higher hazard ratio (HR) than other indices (HR: 2.86, 95%CI: 1.55~4.86 and HR: 2.76, 95%CI: 1.44~4.78). Both LAVImin and LAEmPF by 3DSTA had additive prognostic value for prediction of MACE over LAVImax by 3DSTA and other 2D indices.

Conclusions: LAVImin and LAEmPF by 3DSTA had strong prognostic values for future major cardiac events in patients with various cardiovascular disease.

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Prognostic value of cardiac time intervals measured by tissue Doppler imaging M-mode echocardiography in the General Population

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Purpose: The cardiac time intervals are intimately related to cardiac function and disease. Color Tissue Doppler Imaging (TDI) M-mode through the mitral leaflet is an easy, fast, and precise method to estimate the cardiac time intervals. The purpose of this study was to evaluate the prognostic value of the cardiac time intervals in predicting major cardiovascular events (MACE) in the general population.

Methods: Within the Copenhagen City Heart Study, a large community based population study, cardiac function was evaluated in 1,915 participants by both conventional echocardiography and by TDI. The cardiac time intervals, including the isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), and the ejection time (ET) were obtained by TDI M-mode through the mitral leaflet. IVCT/ET, IVRT/ET and the myocardial performance index ($MPI = (IVRT + IVCT)/ET$) were calculated.

Results: During follow-up (median 10.8 years), 383 (20%) participants reached the combined endpoint (MACE) of being admitted with ischemic heart disease (IHD), heart failure and cardiac death. All the cardiac time intervals were significant predictors of future MACE ($P < 0.001$ for all) in a competing risk Cox regression model. However, after multivariable adjustment for clinical predictors (age, gender, BMI, eGFR, Heart Rate, systolic BP, hypertension, diabetes, smoking status, atrial fibrillation, previous IHD, previous ischemic stroke) and conventional echocardiography (LVEF, LA dimension, LVMI, E/e') only the combined indexes, including information on both the systolic and diastolic performance (the IVRT/ET and the MPI), remained significant prognosticators (IVRT/ET: HR 1.16 (1.00-1.34), $P = 0.045$; MPI: HR 1.12 (1.01-1.23), $P = 0.031$). In addition, when adding the MPI to a cox model already including all other echocardiographic parameters (LVEF, E/e', E/A-ratio, Dec time, LA dimension, LVMI) resulted in a significant increase in the Harrell's c-statistics (76.2% vs. 75.8%, $P = 0.048$). Furthermore, reclassification analysis when adding the MPI to our clinical predictors and LVEF

yielded a better predicting model with a significant increase in the categorical net reclassification index of 4.694% ((95% CI 2.085-7.303%), $p < 0.001$).

Conclusion: In the general population, the combined cardiac time intervals which include information on both the systolic and diastolic function in one index (IVRT/ET and MPI) are powerful and independent predictors of future MACE. In addition, they provide prognostic information over and above clinical variables and conventional echocardiographic measures of systolic and diastolic function.

CONTRAST IMAGING AND TISSUE CHARACTERISATION

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Deformation imaging reflects myocardial histological and molecular changes in low-gradient aortic stenosis

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Purpose: Low-gradient aortic stenosis (LGAS) is associated with a worse prognosis and high operative risk compared to aortic stenosis (AS) with normal left ventricular (LV) ejection fraction (EF). We aimed to find correlations between echocardiographic parameters of regional myocardial LV function and histological and molecular markers of LGAS compared to AS with normal EF.

Methods: Intraoperative biopsies were obtained from 5 consecutive patients with LGAS (EF 31±6%) and 7 patients with AS (EF 57±7%). Preoperative echocardiography quantified LV global and regional function. The fraction of cardiac interstitial tissue, the intracellular volume fraction of myofibrils and myofiber diameters were determined by light microscopic morphometry. Expression of sarcoplasmic-endoplasmic reticulum calcium ATPase SERCA-2a and of sodium/calcium exchanger NCX-1 were assessed by immunohistochemical staining.

Results: Histologically, a significant increase in interstitial volume fraction distinguished LGAS (28.6±19.7%) from AS (10.1±7.7%, $p < 0.05$), without differences in myofiber diameters and myofibrillar volume fraction. At protein level LGAS was characterized by a decrease in SERCA-2a (1.7±0.45 for LGAS vs. 2.79±0.27 units for AS, $p < 0.05$) and a marked increase in NCX-1 (2.6±0.22 for LGAS vs. 0.36±0.38 units for AS, $p < 0.05$). Echocardiographically a typical impairment of radial LV function was found in LGAS, as shown by the values of mean LV strain (7.5±2.2% for LGAS vs. 18±5.1% for AS, $p < 0.05$) and respectively strain rate (0.6±0.2 1/s for LGAS vs. 1.5±0.4 1/s for AS, $p < 0.05$), while longitudinal function parameters were impaired in both groups. Significant linear correlations were found between SERCA-2a and both myofibrillar volume ($r = 0.71$, $p < 0.01$) and mean LV radial strain rate ($r = 0.75$, $p < 0.01$), between NCX-1 and EF ($r = 0.93$, $p < 0.001$) and between interstitial volume fraction and mean LV radial strain ($r = 0.67$, $p < 0.05$).

Conclusions: The hallmark of LGAS as compared to AS with normal EF was the decay in radial LV function due to myocardial remodeling by increased interstitial volume and compromised myocardial energetics reflected by depletion of SERCA-2a and overexpression of NCX-1. Thus, deformation imaging allows a clinically promising insight into pathogenesis of LGAS.

P1545 | BEDSIDE

Usefulness of contrast enhanced transesophageal echocardiography to guide thoracic endovascular aortic repair (TEVAR) procedure

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Background: Thoracic endovascular aortic repair (TEVAR) is commonly considered as a valid alternative to surgery. Endoleaks occurrence is one of the principal limitations of TEVAR. Transesophageal echocardiography (TEE) is often adopted in adjunct to fluoroscopy and angiography (ANGIO) during stent-graft implantation. In the present study we compare intraprocedural ANGIO, TEE, and contrast enhanced TEE (cTEE) and we also evaluate their accuracy in early endoleaks detection and characterization.

Methods and results: 54 patients with thoracic aortic disease suitable for TEVAR were prospectively enrolled in the study. After stent placement, the result of the procedure was assessed by ANGIO, TEE, and cTEE. The use of contrast (Sonovue, Bracco) significantly improved TEE quality ($p = 0.0001$). cTEE was superior in entry tears, false and true lumen and aneurysm thrombosis identification, and microtears and ulcer like projections detection before stent deployment. After stent deployment, cTEE was more accurate than TEE and ANGIO in the detection of slow flow in the false lumen and in the aneurysmal sac ($p = 0.0001$), and in the remaining flow identification ($p = 0.0001$). Notably cTEE is more accurate in the endoleaks detection ($p = 0.0001$) and in the incomplete stent expansion diagnosis and need for a further balloon inflation ($p = 0.002$), or a further stent implantation ($p = 0.006$), when compared to TEE and ANGIO.

Conclusions: TEVAR procedures are improved by complimentary use of contrast fluoroscopy, multiplane TEE with Doppler flow interrogation, and cTEE. This triple imaging approach provides decisive additional information in all phases of the procedure improving safety of stent-grafting and, thus, eventually the procedural outcomes

P1546 | BENCH

Ultrasound-enhanced thrombolysis of platelet-rich thrombi in a flow tubing system

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Background: Although diagnostic ultrasound with high mechanical indexes is able to mechanically induce clot reduction in the presence of microbubble infusion, there have been no studies of the efficacy of sonothrombolysis for the platelet-rich thrombi (white thrombus). Therefore, the aim of the study was to demonstrate the efficacy of high mechanical indexes diagnostic ultrasound with microbubbles infusion to enhanced thrombolysis of the platelet-rich thrombi inside a flow tubing system.

Methods: Platelet-rich thrombi were formed by infusing 0.4 ml of platelet-rich plasma into the tubing (diameter 5 mm). A 1.5 mm diameter needle was placed at the center of the clot and removed after thrombus formation to allow flow inside the thrombus. A total of 36 platelet-rich thrombi were randomized to 15 minutes treatments with ultrasound (Siemens Sequoia c512, MI 1.9) and 0.5% lipid-encapsulated microbubbles (flow rate 20 ml/min) (US+MB group), ultrasound alone (US alone group) or microbubble alone (MB alone group). Ultrasound monitored of the lumen diameter was observed. Percentage thrombus dissolution (% TD) was calculated by weighing the thrombi before and after treatment.

Results: HE staining confirmed the platelet-rich thrombus formation. Lumen diameters were significantly dilated with US+MB treated group than the US alone group and MB alone group (13.2±1.5 mm² vs 9.1±1.1 mm² vs 7.6±0.9 mm², respectively, $p < 0.05$). %TD was also significantly higher with US+MB treated group than the US alone group and MB alone group (47% vs 26% vs 18%, respectively, $p < 0.05$).

Conclusions: Thrombus dissolution of the platelet-rich thrombi was observed in a flow tubing system with high mechanical indexes diagnostic ultrasound and microbubbles.

P1547 | BEDSIDE

Functional and volumetric left atrial reverse remodeling after cardiac resynchronization therapy: relationship with clinical response

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Introduction: Left ventricular (LV) reverse remodeling has been used to define a favourable response to cardiac resynchronization therapy (CRT). Left atrial (LA) reverse remodeling post CRT and its relation with clinical response has not been fully studied. Objective was to evaluate functional and volumetric LA remodeling after CRT and its relationship with clinical outcomes.

Methods: 70 patients in sinus rhythm who received CRT were included. In all patients, echocardiography was performed at baseline and 12 months follow-up with LA deformation analysis during active atrial contraction by strain derived from speckle tracking (LASa: LA negative peak strain curve during atrial contraction). Patients were grouped according to LV reverse remodelling response as ECHO+ (LV end-systolic volume reduction > 15% at 12 months) or ECHO- and to clinical outcome after CRT as Clin+ (> 20% increase in the 6 minutes walking test without transplantation or death at 12 months) or Clin-. Paired and independent T-test were used.

Results: Globally, LA volume did not change and LASa increase after 12 months with CRT. These changes differed according to ECHO+ and Clin+ (Figure). Among patients with ECHO-, those with Clin+(n=15) showed larger increase of LASa and greater reduction of LA volume than patients with Clin- (Δ LASa: -1.85±1.21% vs -0.45±1.37%, $p = 0.04$; Δ volume LA: -6.5±7.6 mL vs +13.2±14.1 mL, $p = 0.01$). Patients who were ECHO+ and Clin+ showed significantly higher LASa and a significantly lower volume at baseline as compared to other groups (Fig. 1).

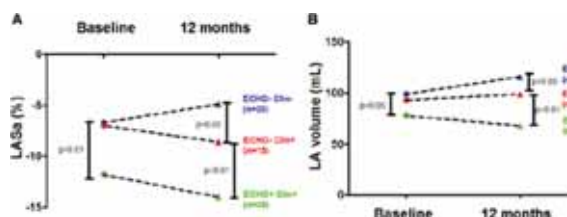


Figure 1

Conclusions: Patients without LV reverse remodeling but with clinical improvement showed LA volumetric and functional remodeling post CRT. These data suggest that CRT has also a positive impact on LA function, which in turn contributes to the improvement of symptoms.

P1548 | BEDSIDE**Prediction of contractile reserve based on neuronal network analysis of myocardial texture in resting native and contrast-enhanced echocardiographic images**

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Aim: Myocardial viability is a clinically important parameter characterizing myocardium after acute coronary syndromes. It is currently defined using imaging with inotropic stimulation (dobutamine stress, DSE) or structural imaging (late enhancement by CMR). Contractile reserve demonstrated by stress echocardiography is a valuable specific finding related to left ventricular (LV) recovery in long-term and translating onto more favorable clinical course. We aimed to apply myocardial texture analysis using neuronal networks to predict contractile reserve detected in DSE in unenhanced and contrast-enhanced myocardial images acquired 7 days after reperfused ST-elevation MI.

Methods: Apical echocardiographic views (native or contrast-enhanced with iv Sonovue injection imaged with Contrast Perfusion Sequence, CPS) were recorded in 49 pts (16 female, mean age 60±10.5) with first STEMI treated with successful primary percutaneous coronary intervention. Each pt underwent a standard low-dose DSE with doses up to 15 mcg/kg/min to identify the viability in area subtended by infarct related-artery, defined as 1 grade contractility improvement (4-grade kinesis scale, 18 segment LV model).

A custom software (MaZDa 4.77) was used for texture analysis. briefly, 299 image features were calculated for defined regions of interest in each image (including 9 features from histogram, 6 from gradient matrix, 20 from run length matrix, 220 from co-occurrence matrix, and 44 from wavelet transform). 8 most reproducible parameters were selected based on lowest intra class feature variance followed by selection of parameters that minimized 1-nearest neighbour (1-NN) classification error.

Results: Multilayer perceptron neural network (MLP neural network based) and support vector machines (SVM, using both linear and radial basis kernels) were applied to predict the presence of segmental contractile reserve in DSE. Neuronal network (MLP) correctly predicted the contractile reserve in 80% of all segments globally. In area-at-risk prediction was correct for 69% (native) and 68% (CPS, red component), better than results obtained with SVM (correct classification for 68% and 62%, resp).

Conclusions: Texture analysis with advanced computational tools including SVM and MLP allows for 70% accurate prediction of contractile reserve in DSE of infarct-related segments, a slightly less than obtained in previous research for prediction of necrosis thickness in CMR but offering an alternative for predicting this parameter in native resting echocardiogram.

P1549 | BEDSIDE**Effects of glucagon-like peptide-1 (GLP-1) on myocardial blood flow reserve diabetes: cardioprotection or not? A study in type 2 diabetes and non diabetics under controlled glycemic conditions**

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Background: We evaluated the effect of Glucagon-like peptide-1 (GLP1) on myocardial blood flow reserve (MBFR) in subjects with & without type 2 diabetes (T2D & nonT2D) under controlled glycemic conditions.

Methods: 21 subjects with no CAD [8 T2D & 13 nonT2D] underwent 2 visits (GLP1 visit: GLP1 infusion at 1.2 pmol/kg/min & Normal Saline (NS) visit: NS infusion). During each visit, 2 stage pancreatic clamp [somatostatin, glucagon and insulin] was infused, along with glucose to maintain euglycemia followed by hyperglycemia (each 2 hr stages). Blood glucose (BG) was monitored/10 min. Myocardial contrast echocardiography (MCE) was performed during final 30 min of steady glycemic state using Definity (200 ml/hr) at rest & during regadenoson stress [400 ug IV bolus]. MBFR was quantified.

Results: NonT2D[85% females, age 48±6 yrs, BMI 25±3 kg/m², fasting BG 90±5 mg/dl, HbA1C 5±.3%]. T2D[75% male, age 54±6 yrs, BMI 32±4 kg/m², fasting BG 143±22 mg/dL, HbA1C 7±.7%]. BG levels across groups (T2D-GLP1, T2D-NS, nonT2D-GLP, nonT2D-NS) during euglycemia were (94±5, 96±5, 98±3, 94±8 mg/dL, p=.236) while hyperglycemia were 231±13, 238±11, 223±11, 228±11mg/dL, p=0.055, respectively. Mean hyperglycemic MBFR was reduced vs euglycemic MBFR in T2D-NS, p=0.038 & nonT2D-NS, p=0.031, but not in T2D-

GLP1 or nonT2D -GLP1, Figure. For both glycemic stages, MBFR was lower in T2D-NS vs nonT2D-NS (euglycemia p=0.010; hyperglycemia p=0.003), but was not different in T2D-GLP1 vs nonT2D-GLP1 (euglycemia p=0.125; hyperglycemia p=0.048). T2D-NS showed trend for lower hyperglycemic MBFR vs T2D-GLP1, p=0.059.

Conclusions: MBFR is lower in euglycemic T2D than nonT2D. Hyperglycemia reduces MBFR in both diabetics and nonT2D. GLP-1 infusion appears to modulate the magnitude of MBFR reduction in diabetics suggesting a protective cardiovascular effect.

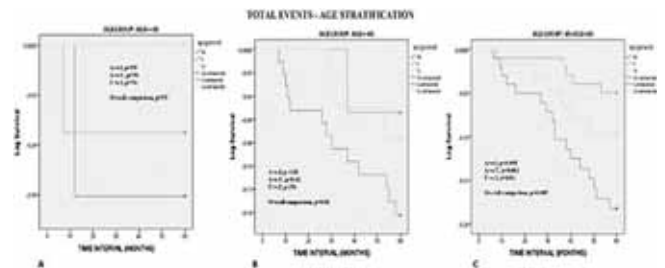
P1550 | BEDSIDE**Prognostic role of dobutamine stress contrast echo in coronary artery disease: how does age interrelate to appropriateness criteria?**

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Purpose: Dobutamine stress contrast echo (DSCE) is a valuable adjunct in clinical practice for the assessment of the presence and extent of coronary artery disease (CAD). The aim of the current study was to evaluate the prognostic role of DSCE in patients with known or suspected CAD in different age groups according to appropriateness indication.

Methods: We studied 2380 (58.8±9.9 years) consecutive patients who were referred to our department for DSCE. Patients were classified into 3 groups according to their age: young adults (age≤45yrs), middle-aged (453 months) and hospitalizations. Furthermore, they were stratified according to the 2011 appropriateness criteria as appropriate (A), uncertain (U) and inappropriate (I). Mean follow-up lasted 57.1±10.1 months. End points included all-cause mortality, cardiac death, the need for late revascularization (>3 months) and hospitalizations.

Results: Out of 2380 patients, 45.6% were classified as appropriate, 31.7% as inappropriate and 22.7% as uncertain. In (20.6%) patients, ischemic response to DSCE was illustrated. During follow-up end-points were noted in (9.9%) patients. Moreover, appropriate and uncertain setting combined was more predictive for a positive DSCE result than the inappropriate class ($\chi^2=58.8$, $p<0.05$), with the most positive response being noted in the appropriate setting (28.1%). Logistic regression analysis revealed that DSCE response was the strongest predictor for adverse outcomes (OR 51.7, $p<0.05$), especially for middle-aged patients.



kaplan-mayer curves, age stratification

Conclusion: Dobutamine stress contrast echo is a strong predictor of end points in patients with known or suspected CAD, especially for middle-aged patients with appropriate indication.

P1551 | BENCH**The NFκB binding motif promotes nuclear import of plasmid DNA and improves the efficiency of ultrasound-targeted microbubble destruction mediated gene transfection**

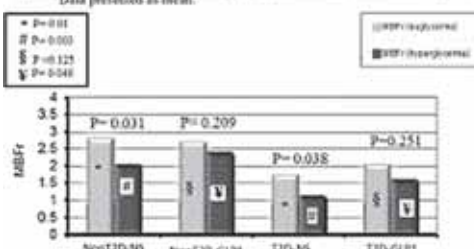
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Purpose: As a novel non-viral gene delivery system, ultrasound-targeted microbubble destruction (UTMD) appears to be a promising technology. However, the transfection efficiency was not desirable. The nuclear membrane barriers may be responsible for the inefficiency because they restrict the import of exogenous genes. So in this study we tried to improve the nuclear import of plasmid DNA using the NFκB binding motif and increase the transfection efficiency of UTMD.

Methods: Human umbilical vein endothelial cells (HUVECs) were transfected using UTMD with two different Cy3 labeled plasmids: pHSDF-1α and pHSDF-1α-NFκB. The pHSDF-1α-NFκB plasmid was constructed by inserting a specific DNA targeting sequence (five optimal repeats of the binding motif for the inducible transcription factor NFκB) into the pHSDF-1α plasmid. Cell Counting Kit-8 (CCK-8) was used to test the effect of NFκB binding motif on cell viability. The nuclear distribution of SDF-1α gene and the nuclear import efficiency were observed using fluorescence microscope. The expression level of SDF-1α gene was detected by RT-PCR, Western Blot and ELISA. The nuclear import and gene expression efficiency of pHSDF-1α-NFκB were detected and compared with those of pHSDF-1α to explore the effect of NFκB binding motif on gene transfection.

Results: The insertion of NFκB binding motif did not affect cell viability. The nuclear import and gene expression of pHSDF-1α-NFκB were significantly higher

Figure: CFR during euglycemia and hyperglycemia in T2D and nonT2D subjects. Data presented as mean.



than those of phSDF-1 α . Compared with the NF κ B-free plasmids, the amount of NF κ B plasmids in the nucleus increased 6.5-fold and the expression of SDF-1 α protein was 4.4-fold greater.

Conclusion: The NF κ B binding motif can significantly promote the nuclear import of exogenous plasmid DNA and improve the transfection efficiency of UTMd.

P1552 | BENCH

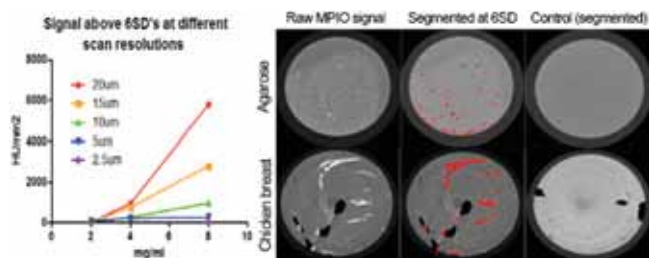
Multimeric microparticles of iron oxide (mMPIO) for dual modality molecular imaging with CT & MRI

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Background: Computed tomography (CT) is widely used in cardiovascular imaging; but it has limited scope for molecular imaging due to the challenge of delivering sufficient CT contrast payload at target tissue. We recently developed ligand-targeted micron-sized particles, derived from multiple iron oxide nanoparticles as agents for molecular MRI. The high payload of iron in these particles suggests dual potential as a CT contrast agent.

Methods: Dextran coated nanoparticles (50nm) were covalently assembled into microparticles, termed mMPIO (650-800 nm). The x-ray attenuation properties, standardised to Hounsfield units (HU), of mMPIO were characterised in phantoms using micro-CT at scan resolutions of 2.5-20 μ m and particle concentrations of 1-8 mg/ml of iron.

Results: A stringent threshold for mMPIO contrast segmentation was set 6 standard deviations (SD) above the mean signal from agarose medium, to optimise specificity and dynamic range. At 20 μ m resolution the HU was 179 $\pm$ 9 and did not vary with particle concentration. By expressing CT signal quantitatively using HU multiplied by segmented signal area (HUmm² - equivalent to Agatston units used in calcium quantification) the minimum detection limit was $\approx$ 2mg/ml (Figure) with contrast signal rapidly rising to 5790 HUmm² (8mg/ml, 20 μ m resolution). These contrast effects translated into high attenuation and excellent contrast against muscle tissue when mMPIO were injected into chicken breast tissue in vitro.



Conclusion: Using a proven platform for molecular MRI, we show that mMPIO provide conspicuous quantifiable contrast effects on CT. This suggests a potential platform as a dual-modality molecular imaging agent with potential for application in cardiovascular and inflammatory pathologies.

P1553 | SPOTLIGHT

Diagnostic value of strain echocardiography, galactin-3 and tenascin-C levels for the identification of patients with pulmonary and cardiac sarcoidosis

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Background: Cardiac involvement in sarcoidosis has been associated with poor prognosis. We evaluated myocardial contractility quantitatively in a cohort of pulmonary sarcoidosis (PS) patients with and without cardiac involvement. We also studied markers of fibrosis (tenascin-C [Tn-C] and galectin-3 [Gl-3]) as diagnostic tools for PS and cardiac sarcoidosis (CS).

Methods: Forty ambulatory patients with PS of grades 1-2, and 26 healthy subjects were prospectively enrolled. All patients with PS underwent cardiac magnetic resonance (CMR) to explore the presence of CS. The study population was divided into three groups: controls (n=26), non-CS patients (n=34), and CS patients (n=6). Speckle-tracking strain echocardiography (STE) was performed on all patients, and Gl-3 and Tn-C values measured in all patients and controls.

Results: PS patients had higher levels of Gl-3 and Tn-C than did controls, and the STE parameters of PS patients, including global longitudinal strain (GLS) and global circumferential strain (GCS), were lower than those of controls ($p < 0.001$ for all comparisons). GLS values were lower in CS patients than in the other groups ($p = 0.05$).

Conclusions: PS patients demonstrate reduced cardiac contractility, independent of CMR-proven structural cardiac lesions, while patients with structural le-



sions have more pronounced drop in strain parameters. Tn-C and Gl-3 are promising markers for the diagnosis of PS, but they are not specific for cardiac involvement.

ASSESSMENT OF LEFT VENTRICULAR FUNCTION BY 3D ECHOCARDIOGRAPHY

P1555 | BEDSIDE

Comparison of three-dimensional and two-dimensional global longitudinal strains of left ventricle in patients with acute myocardial infarction

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Background: Global longitudinal strain of left ventricle (GLSLV) is an objective parameter of global myocardial function. Three-dimensional echocardiography is a theoretically ideal in the measurement of LV mechanics. We want to compare GLSLV by 3-dimensional strain echocardiography (GLSLV-3D) and 2-dimensional strain echocardiography (GLSLV-2D) in patients with acute myocardial infarction (AMI).

Methods: From September 2011 to April 2013, all consecutive patients with first AMI were included. GLSLV were calculated with 3-D and 2-D speckle tracking with EchoPAC-PC software (GE medical systems). Mean clinical follow-up was 17 $\pm$ 6 months for checking adverse clinical events including heart failure admission, re-AMI and death.

Results: Total 142 patients (111 males, mean 61 $\pm$ 12 years old) were analyzed. Of them, 101 patients (71%) were diagnosed as ST-segment elevation myocardial infarction. GLSLV-3D had significant correlations with GLSLV-2D ($r = 0.490$, $P < 0.001$), 3-D LV ejection fraction (LVEF-3D, $r = 0.496$, $P < 0.001$), wall motion score index (WMSI, $r = 0.354$, $P < 0.001$) and NT pro-B-natriuretic peptide level ($r = 0.323$, $P < 0.001$). There were 9 major adverse clinical events (2 deaths, 6 hospitalizations for heart failure, and 1 AMI) during the follow-up period.

GLSLV-3D was associated with adverse clinical events (HR=1.335, 95% CI=1.063-1.676, $P = 0.013$). However, GLSLV-2D did not show significant result (HR=1.143, 95% CI=0.943-1.389, $P = 0.172$).

Conclusions: GLSLV-3D showed good correlations with GLSLV-2D, LVEF-3D, WMSI and serum NT pro-BNP concentration. GLSLV-3D was associated with significantly adverse long-term adverse clinical events in patients with AMI.

P1556 | BEDSIDE

Relation between left ventricular diastolic elastance and myocardial deformation indices

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Background: Diastolic elastance (Ed) which is the ratio of mitral inflow and annular velocity to stroke volume (E/e'/SV) has been proposed as a marker of ventricular diastolic properties. Our aim was to assess the relations between Ed and myocardial mechanical parameters using three dimensional speckle tracking echocardiography (3DSTE).

Methods and results: We studied 54 normal subjects (mean age 35 $\pm$ 12.3 years, 54% males, LVEF: 58.6 $\pm$ 3.1%). Arterial elastance (Ea) as approximated by the ratio of end-systolic pressure (ESP) to SV; end-systolic elastance (Ees) calculated as the ratio of ESP to end-systolic volume and ventricular-arterial coupling (VAC), the ratio of Ea/Ees were calculated. Myocardial mechanical param-

ters include longitudinal strain (LS), radial strain (RS), circumferential strain (CS), twist, rotation, torsion and three dimensional global strain (3DGS) were measured using 3DSTE. Significant relations were found between LS, apical rotation and 3DGS with age and a weak correlation was also found between twist and age ($r=0.26$, $P=0.06$). One way ANOVA linear regression analysis showed significant relations between Ed, Ea, Ees and VAC with CS ($r=0.74$, $P=0.00$ and $r=0.73$, $P=0.001$ and $r=-0.41$, $P<0.001$ and $r=-0.41$, $P<0.001$) (Fig. 1), and 3DGS ($r=-0.64$, $P=0.00$ and $r=-0.68$, $P=0.001$ and $r=0.32$, $P=0.02$ and $r=0.32$, $P=0.02$). It has also shown a weak relation between torsion and Ed ($r=-0.26$, $P=0.06$), and strong relations between torsion with Ees and VAC ($r=0.31$, $P=0.02$ and $r=-0.31$, $P=0.02$ respectively).

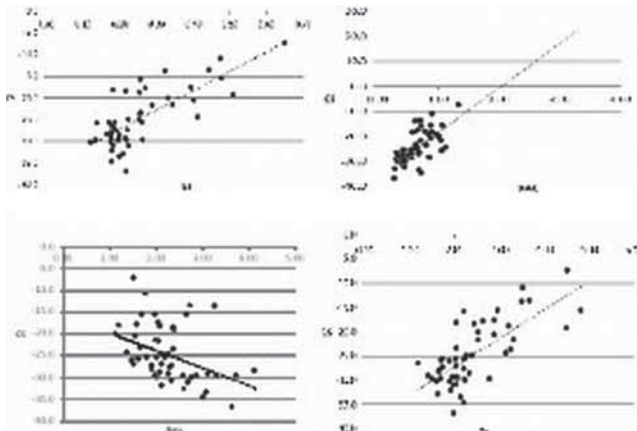


Figure 1

Conclusion: In normal subjects diastolic elastance is related to circumferential strain and three dimensional global strains.

P1557 | BEDSIDE

Left ventricular contractile function in hypertension assessed by myocardial global strain rate using novel one-beat three-dimensional speckle tracking echocardiography with high volume rate

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Background: Left ventricular (LV) systolic properties in hypertension (HTN) are impaired by pressure overload, resulting in heart failure (HF) with reduced ejection fraction (HFrEF). LV myocardial strain rate (SR) during systole evaluated by 2-dimensional speckle tracking echocardiography (2D-STE) was reported as a quantitative index of LV contractility. However, the heart is a complex organ that undergoes cyclic changes in multiple directions and the mechanics seem to be best represented by 3D strain tensor. Thus, we examined LV contractility by global SR using a novel one-beat real-time 3D-STE with high volume rate and assessed the hypothesis that LV contractility in HTN is already reduced before LVEF or stroke work (SW) appears to be decreased.

Methods: We measured global LV longitudinal, circumferential and radial strain and peak SR during systole and isovolumic contraction in HTN ($n=85$, age 69 ± 7 , 56men) and normal controls ($n=60$, age 69 ± 9 , 37men) by the 3D-STE. Patients with HTN were divided into 4 groups according to LV geometry (A: normal geometry, $n=21$. B: concentric remodeling, $n=20$. C: concentric hypertrophy, $n=24$. and D: eccentric hypertrophy, $n=20$). LVEF and SW were measured as LV systolic function and systolic performance.

Results: LV mass was increased in HTN with hypertrophy compared with control (control; 88 ± 14 , C; $133\pm26^*$ and D; $132\pm16^*$ g/m², $^*p<0.01$ vs. control). LV strain and SR were obtained by the 3D-STE with volume rate of 65 ± 5 vps within 3 minutes. LV strain in all 3 directions reduced in HTN with B, C and D compared with control (longitudinal strain: control; -19 ± 4 , A; -17 ± 4 , B; $-16\pm4^*$, C; $-15\pm5^*$, D; $-14\pm5^*$, $^*p<0.05$). LV SR during systole in all 3 directions also reduced in HTN with B, C and D compared with control (radial SR: control; 2.6 ± 0.6 , A; 2.4 ± 0.5 , B; $2.1\pm0.5^*$, C; $2.0\pm0.3^*$ and D; $1.7\pm0.3^*$ s⁻¹, $^*p<0.01$) despite no reduction in LVEF and SW among 5 groups (LVEF: control; 67 ± 6 , A; 66 ± 6 , B; 67 ± 5 , C; 68 ± 9 and D; $67\pm9\%$ and SW: control; 4.4 ± 1.0 , A; 4.4 ± 0.9 , B; 4.4 ± 1.0 , C; $5.1\pm1.2^*$ and D; $5.4\pm1.6^*$ kg $\times$ cm, $^*p<0.05$). LV SR during isovolumic contraction also reduced in HTN with hypertrophy (radial SR: control; 1.2 ± 0.4 , A; 1.1 ± 0.3 , B; 1.0 ± 0.3 , C; $0.9\pm0.3^*$, D; $0.8\pm0.3^*$ s⁻¹, $^*p<0.01$) and correlated negatively with LV mass ($r=-0.31$, $p<0.01$).

Conclusions: LV contractility in HTN with hypertrophy assessed by global myocardial SR during systole and isovolumic contraction using the novel 3D-STE already reduced without reduction in LVEF and SW. LV global SR during systole and isovolumic contraction is a sensitive marker of contractility and may be useful to detect an early phase of HFrEF.

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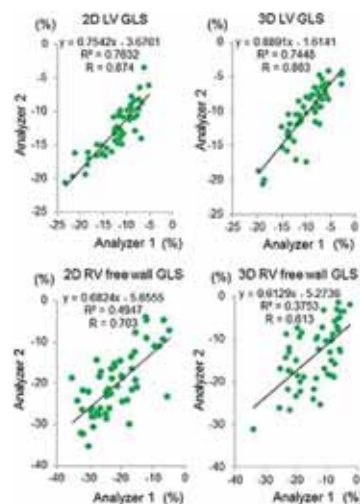
Consistencies of independent estimates of 3D TTE global longitudinal strain of both ventricles between assessors were worse than for 2D, but better than 3D ventricular EF in a population with 80% HCM

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Purpose: We evaluated the consistency of different assessors in estimating three-dimensional (3D) global longitudinal strain (GLS) of left (LV) and right ventricle (RV) using transthoracic echocardiography (TTE) for LV and RV systolic function. We compared results from two independent specialists using this approach for 3D LV and RV parameters in a population with 80% hypertrophic cardiomyopathy (HCM) subjects.

Methods: 53 subjects (43 HCM (32 male; 62 ± 15 years) and 10 controls (5 male; 57 ± 23 years)) underwent TTE (Vivid E9, GE Healthcare) to measure 2D and 3D GLS of the LV and RV using ECHOPAC and TOMTEC software by two independent specialists.

Results: Consistencies of estimates of 3D LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) between the two assessors were 0.871 (3D LV EDV, $P<0.001$), 0.800, (3D LV ESV, $P<0.001$), and 0.254 (3D LV EF, $P=0.066$). Consistencies of 2D and 3D GLS of the LV between two assessors were 0.874 (2D GLS of LV, $P<0.001$) and 0.863 (3D GLS of LV, $P<0.001$). Consistencies of estimates of 3D RV EDV, ESV, and EF between two assessors were 0.854 (3D RV EDV, $P<0.001$), 0.834 (3D RV ESV, $P<0.001$), and 0.204 (3D RV EF, $P=0.144$). Consistencies of 2D and 3D GLS of whole RV and those of RV free wall only between two assessors were 0.871 (2D GLS of whole RV, $P<0.001$), 0.636 (3D GLS of whole RV, $P<0.001$), 0.703 (2D GLS of RV free wall only, $P<0.001$), and 0.613 (3D GLS of RV free wall alone, $P<0.001$).



Conclusions: Consistencies of independent estimates of 3D GLS of the LV and RV using TTE between two assessors were worse than for 2D GLS of the LV and RV, but better than 3D LV and RV EF in a population with 80% HCM subjects.

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Accuracy and reproducibility of three-dimensional echo left ventricular volumes obtained using fully automated and manually edited endocardial border tracing algorithms

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Purpose: Fully automated algorithms to measure left ventricular (LV) volumes and ejection fraction (EF) by three-dimensional echocardiography (3DE) are attractive in order to speed-up the workflow in the lab and improve inter-observer reproducibility of measurements. However, the relative accuracy and reproducibility of fully automated and semiautomated 3DE LV endocardial border tracking algorithms remains to be clarified.

Methods: A single researcher obtained 3DE data sets of the LV in 71 patients (65% males, 47 years (95%CI 41, 55 years) with a wide range of end-diastolic volumes (from 73 ml to 330 ml) and EF (from 21% to 80%) using two different 3DE systems equipped with both fully automated and semiautomated LV volume measurement algorithms (Vivid E9, GE Vingmed, Horten, N; Acuson SC2000, Siemens, CA) during the same echo session. CMR was performed in 34 patients within 24 hours from the 3DE study. A single researcher analyzed the 3DE data sets with AutoLVQ (EchoPAC BT 13, GE Vingmed, Horten, N) and SC2000 (Siemens, CA) in row one week apart from one vendor to the other. A second researcher with comparable experience in quantitating 3D data sets performed a second set of measurements in 30 patients. CMR quantification of LV volumes

was performed by a third investigator without knowledge of the results of the 3DE analysis.

Results: Bland-Altman analysis showed that EDVs measured using semiautomated algorithms with manual editing were significantly more accurate than those measured with fully automated algorithms (bias = -16 ml, LOA $\pm$ 35 ml and bias = -31 ml, LOA $\pm$ 39 ml, $p < 0.0001$ for E9, and bias = -19 ml, LOA $\pm$ 41 ml and bias = -37 ml, LOA $\pm$ 42 ml, $p < 0.0001$ for SC 2000, respectively). Conversely, end-systolic volumes (ESV) and EF were similar with both fully automated and semiautomated algorithms. As expected, fully automated algorithms reduced the time to EF (30 ± 10 s vs 187 ± 46 s; $p < 0.0001$) and improved inter-observer reproducibility (bias $\pm$ LOA) in comparison with semiautomated algorithms with manual editing both using E9: EDV (1 ± 8 vs 1 ± 22 ml, respectively), ESV (1 ± 6 vs 2 ± 17 ml), EF (1 ± 5 vs $1 \pm 8\%$) (all $p < 0.01$); and SC 2000: EDV (1 ± 16 vs 6 ± 30 ml), ESV (0 ± 13 vs 3 ± 24 ml), EF (0 ± 4 vs $3 \pm 10\%$) (all $p < 0.01$).

Conclusions: Fully automated 3DE algorithms for LV quantification are time-saving and improve inter-observer reproducibility of LV volume measurements. However, they provide LV EDV which are significantly less accurate than semiautomated ones in comparison with CMR, therefore the LV stroke volume is underestimated using fully automated 3DE algorithms

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Noninvasive estimation of left ventricular diastolic function in hypertension by novel one-beat real-time three-dimensional speckle tracking echocardiography with high volume rate

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Background: Left ventricular (LV) pressure overload in hypertension (HTN) causes LV hypertrophy (LVH), which leads to decline of LV relaxation and increase of LV stiffness. LV myocardial strain rate (SR) during isovolumic relaxation (IVR) measured by 2-dimensional speckle tracking echocardiography (2D-STe) was reported to have a good correlation with time constant of LV pressure decline (τ). However, the heart is a complex organ that undergoes cyclic changes in multiple dimensions and the mechanics seem to be best represented by 3D strain tensor. Thus, we developed a novel one-beat real-time 3D-STe and software to measure global myocardial SR and examined LV diastolic function in HTN.

Methods: Patients with HTN ($n=85$, age 69 ± 7) and preserved ejection fraction (EF) $> 50\%$ and controls ($n=60$, age 69 ± 9) were enrolled. Patients with HTN were divided into 4 groups according to LV geometry (A: normal geometry, $n=21$; B: concentric remodeling, $n=20$; C: concentric LVH, $n=24$ and D: eccentric LVH, $n=20$). We measured LV longitudinal, circumferential and radial global SR during IVR as LV relaxation by the novel 3D-STe with high volume rate of 50-80vps. We estimated LV stiffness as LV diastolic stress / LV strain. LV stress was calculated as LV diastolic radius $\times$ PCWP / end diastolic wall thickness. PCWP was estimated as $10.7 - 12.4 \times \log$ left atrial (LA) active emptying function / minimum LA volume as we previously reported. LV strain was estimated as (end systolic thickness - end diastolic thickness) / end systolic thickness.

Results: There was no difference in LVEF among 5 groups. LV mass was increased in HTN with hypertrophy compared to control (C; $133 \pm 26^*$ and D; $132 \pm 16^*$ vs. control; 88 ± 14 g/m², $*p < 0.01$). LV radial SR during IVR in HTN was decreased even in normal geometry compared to control (control: -0.93 ± 0.56 , A; $-0.70 \pm 0.47^*$, B; $-0.65 \pm 0.32^*$, C; $-0.52 \pm 0.34^*$ and D; -0.49 ± 0.35 s⁻¹, $*p < 0.05$ vs. control) without elevation of E/e' (9.5 ± 2.1 , 10.6 ± 2.2 , $11.0 \pm 2.9^*$, $13.0 \pm 2.3^*$ and $12.5 \pm 3.0^*$, respectively). LV stiffness was increased in HTN with LVH (52 ± 25 , 55 ± 21 , 64 ± 43 , $83 \pm 41^*$ and $116 \pm 43^*$, respectively). There was a significant correlation between LV mass and SR during IVR in all directions (radial SR; $r=0.30$, $p < 0.01$).

Conclusions: LV relaxation even in HTN with normal geometry assessed by LV global myocardial SR during IVR using the novel 3D-STe was already impaired despite no reduction of LVEF and no elevation of E/e'. LV stiffness was increased in only HTN with LVH. Noninvasive evaluation of LV diastolic function using SR by 3D-STe may be useful to detect an early phase of heart failure with preserved EF.

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Intervendor consistency and accuracy of left ventricular volume measurements using three-dimensional echocardiography

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Purpose: Intervendor consistency of LV volume measurements from 3D data sets has never been tested. Then, we designed this study: i. to test the accuracy in measuring LV volumes and ejection fraction (EF) of 3 3DE systems vs. CMR; ii. to assess intervender variability of 3DE LV volume and EF measurements.

Methods: A single researcher obtained 3DE data sets of the LV in 71 patients

(65% males, 47 years (95%CI 41, 55 years) with a wide range of end-diastolic volumes (EDV, from 73 ml to 330 ml), using 3 different 3DE systems (iE33, Philips Medical System, Andover MA; Vivid E9, GE Vingmed, Horten, N; Acuson SC2000, Siemens, CA) during the same echo session. CMR was performed in 35 patients. A single researcher analyzed the 3DE data sets with QLab (Philips Medical system, Andover, MA), EchoPAC (GE Vingmed, Horten, N) and SC2000 (Siemens, CA) in row one week apart from one vendor to the others. CMR quantification of LV volumes was performed by a second investigator.

Results: All 3 3DE systems provided LV volumes which were closely correlated with CMR volumes: EDV (iE33: $r=0.92$, bias -15 ml, LOA $\pm$ 42 ml; E9: $r=0.96$, bias -16 ml, LOA $\pm$ 35 ml; SC 2000: $r=0.94$, bias -19 ml; LOA $\pm$ 41 ml), end-systolic volume (iE33: $r=0.93$, bias -11 ml, LOA $\pm$ 42 ml; E9: $r=0.98$, bias -15 ml, LOA $\pm$ 35 ml; SC 2000: $r=0.95$, bias -11 ml, LOA $\pm$ 39 ml), and EF (iE33: $r=0.86$, bias 1, LOA $\pm$ 13%; E9: $r=0.84$, bias 3, LOA $\pm$ 15%; SC 2000: $r=0.84$, bias 0, LOA $\pm$ 15%). 3DE LV volumes and EFs measured with iE33 and E9 in the 71 study patients were similar (Table). Conversely, LV EF was significantly lower when measured with SC 2000 (Table, data are summarized as median 95% CI).

LV volumes and EF among the 3 3DE system

	iE33	E9	SC2000	p value
Heart rate (bpm)	64 (59,67)	66 (61,69)	66 (62,70)	0.646
Volume rate (Hzt)	28 (26,30)	47 (44,48)	21 (21,22)	<0.0001
End-diastolic volume (ml)	144 (133,165)	143 (132,159)	150 (131,169)	0.276
End systolic volume (ml)	57 (50,71)	54 (46,65)	65 (58,78)	0.593
Ejection fraction (%)	60 (57,64)	61 (58,64)	57 (52,59)	0.001

Conclusions: We showed a good agreement between 3DE and CMR using the three tested echo systems, whereas LV EF was underestimated by SC 2000. Our results may help in the interpretation of 3DE volumes obtained using different 3DE systems.

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Prediction of treatment response for cardiac resynchronization therapy by left ventricular twist using three-dimensional speckle tracking imaging in a heart failure canine model

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Objective: To assess left ventricular (LV) twist by three-dimensional speckle tracking imaging (3D-STI) in a pacing induced heart failure canine model with left bundle-branch block (LBBB) undergoing cardiac resynchronization therapy (CRT).

Methods: After induction of left bundle branch block by radiofrequency ablation, rapid right ventricular pacing (RVP) at 200 beats/min was utilized in 22 adult beagle dogs for 6 weeks to induce heart failure. Then 15 dogs received CRT for 4 weeks and others were treated as control. Apical full-volume acquisition of the LV was obtained in conscious animals at baseline, the end of 6-week RVP and the end of 4-week CRT. Peak LV systolic twist (Ptw) and torsion (Ptor) along with peak apical and basal rotation were automatically calculated by Tom-Tec 4D LV Analysis 3.0 software to identify the ideal parameter in predicting treatment response of CRT.

Results: After 4 weeks of CRT, LVEF increased [(31.97 $\pm$ 1.47) vs. (37.47 $\pm$ 3.60)%, $p=0.002$] and LVESV decreased [(24.13 $\pm$ 3.72) vs. (21.87 $\pm$ 3.15) ml, $p=0.007$] significantly in dogs with heart failure. By shortening the delay of basal rotation [(23.73 $\pm$ 9.98) vs. (17.87 $\pm$ 5.94) ms, $p=0.009$], CRT improved peak LV systolic twist [(6.88 $\pm$ 0.99) vs. (8.03 $\pm$ 0.63)°, $p=0.008$] and torsion [(1.21 $\pm$ 0.36) vs. (1.98 $\pm$ 0.39)°/cm, $p=0.010$] instead of peak apical [(5.97 $\pm$ 0.57) vs. (6.13 $\pm$ 0.61)°, $p=0.103$] and basal rotation [(2.08 $\pm$ 0.45) vs. (2.13 $\pm$ 0.46)°, $p=0.469$]. CRT treatment response, defined as improvement of LVEF $\geq 15\%$, was observed in 9 dogs. Significant difference was found in Ptw [(7.43 $\pm$ 0.61) vs. (6.06 $\pm$ 0.89)°, $p=0.016$] and Ptor [(1.43 $\pm$ 0.45) vs. (0.67 $\pm$ 0.36)°/cm, $p=0.042$] between responders and nonresponders. The cut-off values derived from receiver-operating characteristic curve analysis were 6.73° for Ptw and 1.00°/cm for Ptor with satisfying sensitivity as 89% and 85%, specificity as 83% and 84%, respectively.

Conclusions: CRT improved LV systolic twist and reversed LV remodeling by reconciling basal with apical rotation. Peak twist and torsion evaluated by 3D-STI demonstrated potential prediction value for treatment response of CRT.

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Left ventricular propagation patterns of myocardial activation with 3D-speckle tracking echocardiography and cardiac resynchronization therapy responses

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Background: We sought to study the relation between intra-ventricular propagation pattern of myocardial activation and cardiac resynchronization therapy (CRT) responses with 3D-speckle tracking echocardiography (3D-STe), compared to the quantification of intra-ventricular dyssynchrony.

Methods: Seventy-five patients (61 ± 12 yrs, 45 males) with EF $< 35\%$ and QRS duration > 120 ms were enrolled. Left bundle branch block (LBBB) was observed

in 45 patients and non-specific conduction delay (NSCD) was in 30 patients. Activation imaging studies were performed with a 3D-STE system (Toshiba Medical Systems) in addition comprehensive echocardiographic examinations. The images were obtained with more than 30 volume/sec. The regional myocardial deformation was assessed by the area tracking method. Regional myocardial activation was defined as onset of regional contraction, which was corresponding to the timing at 20% of the maximum regional strain value.

The activation imaging allowed visualizing propagation of myocardial activation, which were analyzed before and 7 days after CRT. In addition, the regional time from QRS onset to activation was measured, and the intra-ventricular propagation time (IVPT) was calculated as the time difference between the first and latest activated segments.

Results: We found 5 propagation patterns as follows: 1) U-shaped activation pattern in which initial activation site was observed at mid septum and propagated around apex and to the basal lateral region in 36 LBBB and 3 NSCD patients, 2) direct propagation pattern from septum or anterior to lateral wall in 7 LBBB and 3 NSCD patients, 3) regional conduction delay pattern in 2 LBBB and 8 NSCD patients, 4) multi-directional delay pattern in 10 NSCD patients, and 5) no apparent propagation delay in 6 NSCD patients. IVPT in the pattern 1 to 4 did not differ, which were longer than the pattern 5. CRT responders defined as >15% reduction of left ventricular end-systolic volume at 6 months after CRT were observed in 34 patients (90%) with the U-shaped activation pattern, however, only 9 (25%) patients in the other patterns 2 to 5. In 5 CRT non-responders with U-shaped activation pattern, 4 patients showed LV pacing site estimated by activation imaging was located at the 2 or more remote segments from the latest segment before CRT.

Conclusion: Intra-ventricular propagation pattern analysis by 3D-STE derived activation imaging was useful to identify CRT responders, rather than quantification of intra-ventricular dyssynchrony. In addition, activation pattern analysis after CRT also may provide additional information about CRT responses.

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Assessment of 3D left ventricular function and 3D speckle tracking echocardiography: comparison to 2D planimetry and 2D speckle tracking

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Purpose: Three dimensional speckle tracking (3DS), measuring longitudinal, radial, and circumferential myocardial deformation, might constitute a more accurate method compared to two dimensional speckle tracking (2DS). We sought to compare the results of 3DS to those measured by 2DS analysis in patients with preserved left ventricular ejection fraction (LVEF) and chronic heart failure (CHF).

Methods: In an ongoing study, transthoracic echocardiography was performed in 52 consecutive patients, comprising standard apical 4-, 2-chamber- and long axis views; 3DS was measured after obtaining an apical 3D full volume created by the combination of four ECG-gated subvolumes. Differences of left ventricular (LV) diameter, LV mass, cardiac index, average global longitudinal peak systolic strain (GLPS), and TAPSE were calculated by using the Wilcoxon or Mann-Whitney-U test; differences of $p < 0.05$ were considered significant. After creation of a scatter plot for 2D / 3D GLPS, correlations between the 2DS and 3DS method were tested by the Spearman-Rho correlation coefficient.

Results: Out of the 52 patients, 27 had a preserved and 25 a reduced LVEF due to ischemic or dilated cardiomyopathy. LVEF was 62.5% in healthy controls vs. 38.7% in patients with CHF ($p < 0.001$). In the CHF group, TAPSE and cardiac index provided markedly lower results, but higher values in LV diameter and LV mass compared to patients with preserved LVEF. GLPS showed a significant correlation between the two methods of 2DS and 3DS (0.93, $p < 0.001$). Overall GLPS was significantly higher in the 2DS than in 3DS analysis (15.3% vs. 12.7%, $p < 0.001$); this difference persisted in patients with preserved and reduced LVEF (-21.2% vs. -17.1% and 9.5% vs. 8.3%, respectively). Also, LVEF was significantly reduced in the 3DS method compared to 2D biplane planimetry. Inter- and intra-observer variability was low (<10%).

Conclusions: 3DS and 3D assessment of left ventricular function provided significantly lower strain values in all subgroups. 2DS and planimetry might overestimate the actual spatial myocardial movement due to its inability to track the twisting, 3-dimensional myocardial displacement, resulting in a "pseudo-shortening" of the heart. On the other hand, temporal and spatial resolution of 3DS is limited compared to the high-frame rate 2DS. Despite the numerical differences, however, 3DS correlated significantly with the more established 2DS analysis and seems to constitute a promising new method to investigate myocardial systolic function.

ALL YOU NEED IS... SPECKLE

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Noninvasive activation imaging using three-dimensional speckle tracking echocardiography in wolff-parkinson-white syndrome

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Background: We have developed activation imaging with 3-dimensional speckle tracking echocardiography (3D-STE), which allows visualizing the wave front image of mechanical activation propagation.

Methods: Sixteen patients with manifest Wolff-Parkinson-White (WPW) syndrome were imaged with 3D-STE activation imaging mode, which aims to quantify a time from the onset of electrical activation to the onset of regional deformation. To visualize the timing of regional mechanical activation, if a regional endocardial area change ratio (ACR) value exceeded 25% of maximum ACR value in each 16 segment of the left ventricle, the area was colored by a colour corresponding to the time from QRS on the polar map image. 3D-STE for left ventricle, which was constructed by 6-beats, results in time resolution of 33 msec. An analyzer who was unaware of the clinical information assessed the accessory pathway location by both Arruda electrocardiogram (ECG) criteria and by 3D-STE.

Results: ECG and 3D-STE determined that the preexcitation sites were perfectly consistent with sites of successful ablation in 7 and 7 patients, within near site in 2 and 6 patients, and inconsistent in 7 and 3 patients, respectively. Among 3 patients of inconsistent with the preexcitation site evaluated by 3D-STE, ECG correctly assess the ablation site in 2 patients.

Conclusions: The activation imaging with 3D-STE may be the promising noninvasive imaging tool to localize preexcitation sites in patients with WPW syndrome, especially in conjunction with the standard ECG assessments.

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Variability in global longitudinal strain measurements between different vendors: Where do we stand? The EACVI-ASE-Inter-Vendor Comparison Study

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Background: Two-dimensional speckle-tracking-based global longitudinal strain (GLS) is a new echocardiographic parameter for the assessment of left ventricular (LV) function. Different methodological approaches, however, prevent the comparability of measurements obtained with ultrasound systems of different vendors. The European Association of Cardiovascular Imaging and the American Society of Echocardiography together with all major ultrasound system vendors have therefore initiated a task force to standardize GLS measurements. This study was initiated to test the inter-vendor variability of GLS measurements in a clinical setting.

Methods: In a unique setting with 7 different ultrasound systems in one room, 434 echocardiographic examinations were performed in 62 volunteers with normal and abnormal cardiac function. Apical 4-, 2-chamber and long-axis views were obtained, with image settings optimized for speckle tracking GLS according to recommendations of the respective vendor. In order to determine inter-observer variability, a set of apical images was taken by a second sonographer. Then, another set of apical images was taken by the first sonographer in order to determine test - re-test variability of GLS measurements. All vendors provided dedicated software to measure GLS on data sets obtained with their machines. Additionally, two independent software vendors were tested. Variability in GLS measurements were compared between vendors and with measurements of LV ejection fraction (EF, biplane Simpson's method), transmitral E velocity and E/A ratio, LV end-diastolic diameter and LV interventricular septum (IVS) and posterior wall (PW) thickness. The results from 8 vendors are presented here.

Results: Significant differences between vendors were found in GLS measurements ($P < 0.001$, ANOVA). The mean GLS from all vendors was 19.4%. The mean of each vendor differed from the mean of all vendors by a range of -2.1 to 1.5%. The interobserver mean error was 5.7-9.1% (relative percentage), while the respective value was for EF 9.5%, for E 12.7%, for E/A 20.7%, for LVED 7.9%, for IVS thickness 11.6% and for PW thickness 17.6% ($P < 0.001$, ANOVA). The intraobserver mean error was 5.4-7.6% for GLS, while for EF it was 7.6% ($P = NS$).

Conclusion: Significant differences between vendors were found in LV GLS. Interobserver variability was low and better compared to EF and standard echocardiographic parameters, while intraobserver variability was comparable to EF.

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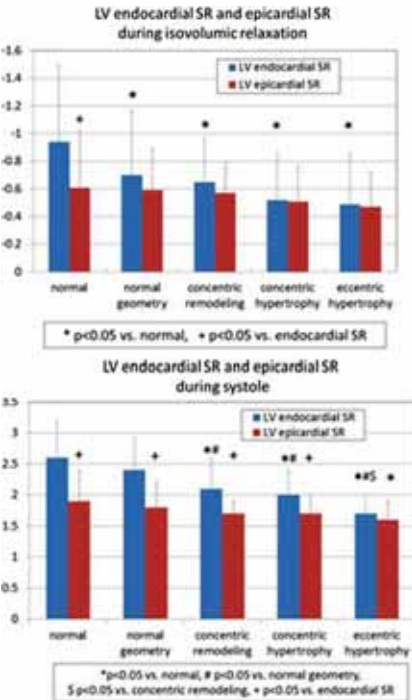
Evaluation of left ventricular endocardial and epicardial performance in hypertension assessed by the novel one-beat real-time three-dimensional speckle tracking echocardiography

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Purpose: Left ventricular (LV) pressure over load causes LV hypertrophy (LVH) that may result in endocardial ischemia and impairment of systolic and diastolic properties at endocardium more than epicardium in patients with hypertension (HTN). However, it has been difficult to examine global performance of each myocardial layer without appropriate noninvasive technology. Thus we developed the novel one-beat real-time 3-dimensional speckle tracking echocardiography with high volume rate and software to evaluate both endocardial and epicardial global strain rates (SR) of LV myocardium.

Methods: LV SR during isovolumic relaxation as LV relaxation and SR during systole as contractility at both endocardium and epicardium were measured by the 3D-STE in 85 patients with HTN (age: 69±7) and 60 normal controls (age: 69±9, LV mass: 88±14g/m²). Patients with HTN were divided into 4 groups according to LV geometry (A: normal geometry, LV mass: 92±13g/m², B: concentric remodeling, 97±12g/m², C: concentric LVH, 133±26g/m², D: eccentric LVH, 132±15g/m²).

Results: There was no difference in LV ejection fraction among 5 groups. LV SR at both myocardial layers could be measured within 3 minutes by the novel 3D-STE with volume rate of 65±5vps. LV radial SR during isovolumic relaxation at endocardium in HTN was significantly decreased compared to normal despite no reduction of SR at epicardium. (Figure)



Conclusions: LV relaxation assessed by SR during isovolumic relaxation and contractility by SR during systole at endocardium in HTN deteriorated even in early stage in proportion to the degree of LVH rather than those at epicardium, suggesting that LV endocardial ischemia and dysfunction may be caused by LV hypertrophy. The novel 3D-STE will be useful tool to examine the myocardial layer function in HTN.

P1569 | BEDSIDE

Can we detect significant coronary arterial stenosis using the left ventricular torsion?

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Background: The left ventricular (LV) rotation and torsion have been known as important speckle tracking echocardiographic (STE) parameters of LV systolic function. Their values can be impaired in patients with significant coronary artery disease (CAD). We investigated the feasibility of LV rotation and torsion in the detection of significant coronary arterial stenosis in patients with preserved LV ejection fraction and normal wall motion score.

Methods: From March 2012 to January 2013, we consecutively enrolled patients with significant CAD. Significant CAD was defined as more than 70% of diameter stenosis on coronary angiography. Patients were divided into CAD group and control group. Patients with depressed LV systolic function and abnormal regional wall motion abnormality were excluded

Results: We analyzed total 182 patients. 70 patients were female, mean age was 65±9 years old. Total 110 patients were included in CAD group, and 72 patients of CAD group were diagnosed as acute coronary syndrome. LV ejection fraction (LVEF) on echocardiography was no significant difference between control group and CAD group. (60.3±3.9 vs. 61.5±2.9, p=0.485, respectively) However, there were statically significant differences of LV torsion, apical rotation between control group and CAD group (Table 1).

Table 1

	Control group (n=72)	CAD group (n=110)	P value
Left ventricular torsion (degree)	22.8±4.9	19.5±6.8	0.038
Apical rotation (degree)	14.4±4.2	11.9±5.8	0.035
Basal rotation (degree)	-8.8±4.5	-8.3±4.9	0.651
4 chamber longitudinal strain (%)	-20.9±2.8	-19.1±2.3	0.019
2 chamber longitudinal strain (%)	-20.9±2.1	-19.3±2.4	0.042
3 chamber longitudinal strain (%)	-20.5±2.1	-19.4±2.3	0.024
Global longitudinal strain (%)	-20.2±1.8	-19.3±2.1	0.009

Conclusion: Patients with significant CAD and normal LV systolic function have lower LV torsion and apical rotation. These findings could be helpful to understand subclinical myocardial dysfunction in patients with significant CAD. LV torsion and apical rotation is feasible to investigate subclinical myocardial function.

P1570 | BEDSIDE

Differences in Tissue Doppler Imaging parameters of left ventricular systolic function according to gender and age in healthy subjects

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Purpose: Systolic Tissue Doppler Imaging (TDI) parameters are complementary tools in the evaluation of left ventricular (LV) systolic function, especially in patients with subtle systolic dysfunction despite preserved LV ejection fraction. Whether these parameters are influenced by gender and age has not been previously addressed in a large cohort of patients. We aim to report the differences in these parameters according to gender and age and provide normal reference ranges in healthy subjects.

Methods: The NORRE study is a multi-centre study involving accredited laboratories of the EACVI studying echocardiographic parameters in a large cohort of healthy population (n=734; 45.8±13.3 years; 43.6% of male). We evaluated s' wave and isovolumic contraction (IVC) peak velocities and durations at the level of the mitral annulus in the walls. Isovolumic acceleration (IVA) was calculated as the ratio of IVC peak velocity and time to peak velocity of IVC. TEI index was calculated according to current knowledge. All the parameters were analyzed according to gender and age (20-40; 40-60; >60 years).

Results: S' peak velocity was significantly higher in younger patients in all the walls except in the inferior wall (Table). A significant correlation was found between age and s' peak wave. According to gender, septal s' wave peak velocity was higher in male (9.0 vs. 8.4; p=0.045), without significant differences in the rest of the walls. Regarding IVA, no differences were found according to age and genders. No differences were found in the TEI index according to age, except in the posterior wall, where TEI index was higher in older patients (0.44 vs. 0.48 vs. 0.56; p=0.009). TEI index in the inferior wall was higher in men compared with women in the inferior wall (0.45 vs. 0.40; p=0.039).

S' wave velocities according to age

Parameters	20-40 yrs	40-60 yrs	>60 yrs	All	p-value	Correlation with age
						r p-value
S' septal (cm/s)	9.0±1.4	8.5±1.4	7.9±1.2	8.6±1.4	0.033	-0.244 0.013
S' lateral (cm/s)	11.5±2.6	9.9±2.1	8.9±3.0	10.5±2.7	0.001	-0.429 <0.001
S' inferior (cm/s)	9.9±1.5	9.3±1.6	8.9±1.7	9.5±1.6	0.141	-0.205 0.082
S' anterior (cm/s)	10.5±1.9	9.1±2.2	8.9±2.2	9.8±2.1	0.016	-0.343 0.003
S' posterior (cm/s)	11.1±1.6	9.6±1.5	9.4±2.7	10.3±1.9	0.003	-0.401 0.001

Conclusions: Normal references values for s'peak velocity should be used according to age categories given the influence of age in this parameter.

P1571 | BEDSIDE

Increased carotid artery stiffness in coronary artery disease assessed by speckle-tracking and its good association with aortic stiffness and endothelial dysfunction

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Aim: (i) evaluate carotid artery strain derived from speckle tracking ultrasound imaging (CAS) in subjects with coronary artery disease (CAD) and without coronary artery disease (N-CAD), (ii) compare CAS, to global aortic stiffness using carotid-femoral pulse wave velocity (c-f PWV) and to endothelial function using brachial flow-mediated dilatation (FMD) in subjects with CAD.

Methods: 100 subjects were prospectively included, and classified into 2 groups: subjects with CAD (CAD, n=49), subjects N-CAD (N-CAD, n=51). The CAS on the common carotid artery using speckle-tracking ultrasound imaging was measured. In the CAD, c-f PWV and FMD were evaluated and compared to CS.

Results: Age of the population was 65 ± 1.7 years. The proportion of males, diabetes and obesity in CAD was higher than N-CAD group ($p=0.0005$, $p=0.0002$, 0.0004 respectively). There was no significant difference in age and hypertension. In a multivariate analysis, age and CAD were the sole independent predictors of CAS ($r=-0.6$, $p<0.0001$; $r=-0.5$, $p<0.0001$ respectively). The CAS was significantly lower in CAD as compared to N-CAD (2.41% vs 4.48% , $p<0.0001$). In CAD group, 41% presented stable angina and 59% acute coronary syndrome (ACS). The CAS was lower in stable angina vs ACS (1.85% vs 2.92% , $p=0.02$). In the CAD group, CAS was inversely correlated to c-f PWV ($r=-0.7$, $p=0.0001$), and correlated with endothelial dysfunction ($r=0.45$, $p=0.003$).

Conclusion: Speckle-tracking ultrasound imaging is a non-invasive technique useful for the evaluation of local carotid artery stiffness. Carotid artery stiffness was higher in coronary artery disease. In CAD, carotid artery stiffness measured by speckle-tracking is associated with global aortic stiffness and endothelial dysfunction.

P1572 | BEDSIDE

Diagnosing paroxysmal atrial fibrillation in cerebrovascular ischemia using tissue Doppler imaging and speckle tracking echocardiography

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Background: Ischemic strokes (IS) and transient ischemic attacks (TIA) confer a high mortality and morbidity rate. Often the underlying cause of IS/TIAs cannot be found in a routine diagnostic investigation, but paroxysmal atrial fibrillation (PAF) may still be the cause. Tests able to detect PAF are therefore warranted.

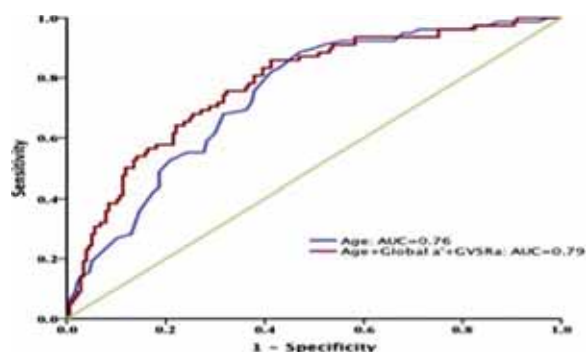
Aim: To investigate whether Tissue Doppler Imaging (TDI) and 2-Dimensional Speckle Tracking Echocardiography (2DSE) have value for diagnosing PAF in IS/TIA-patients.

Method and results: 286 patients with IS/TIA and an echocardiographic examination in sinus rhythm were identified and divided into PAF- vs. non-PAF-patients (86 vs. 200). Patients were designated as PAF-patients if they had one or more reported incidents of AF.

Using TDI in three apical projections, longitudinal myocardial velocities and annular displacements were measured in a total of 6 ventricular walls. 2DSE was investigated in three apical projections, providing deformation properties of 18 ventricular and 18 atrial wall segments.

The PAF-group showed significantly impaired Global a' , Global Ventricular Strain Rate (GVSR) a , and Global Atrial Strain Rate (GASR) a , even after multivariable adjustments. Age was also a significant discriminant of PAF. AUC for age+Global a' +GVSRa was significantly higher than AUC for age alone (0.79 vs. 0.76 , $p=0.032$).

Combining cut-off values with highest sensitivity and specificity for these three parameters improved the diagnostic accuracy, resulting in a sensitivity of 97% and a negative predictive value of 95%.



Conclusion: TDI-determined Global a' and 2DSE-determined GVSRa are significant determinants for the presence of PAF in IS/TIA-patients. Applying these may yield better risk stratification for PAF-presence.

P1573 | BEDSIDE

Global right and left atrial performance explored by speckle-tracking echocardiography

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Purpose: Atrial function is an important modulator of ventricular filling and has a prognostic role in various cardiovascular diseases. We assessed the hypothesis that global right and left atrial (RA & LA) functions might not be equal despite their accommodating identical cardiac output.

Methods: Two-dimensional speckle-tracking echocardiography was acquired from the apical 4-chamber view in 100 normal subjects. The atrial subendocardium was traced to obtain RA & LA volumes. The following volume indices were used to compute atrial function: maximum volume (Vmax), minimal volume (Vmin) & volume before atrial contraction (Vpre-a). Reservoir, conduit and booster pump functions were evaluated to explore the differences between both atria in global performance.

Results: Mean age was 38.77 ± 14.73 years with 50 females (50%). Atrial filling during ventricular systole (reservoir function), passive left ventricular filling in early diastole (conduit function) and ejection fraction were significantly higher in the LA as compared to the RA. However, atrial contraction (booster pump function) was similar (TABLE).

	Left atrium	Right atrium	P-Value
Atrial ejection fraction (%)	66.8±9.2	58.35±11.14	<0.0001
Atrial reservoir function			
1. Filling Volume (ml) (Vmax - Vmin)	35.1±10.4	27.47±11.93	<0.0001
2. Expansion index (%) ((Vmax - Vmin)/Vmin) × 100.	52.18±16.89	45.03±16.49	<0.001
3. Diastolic emptying index ((Vmax - Vmin)/Vmax) × 100.	52.85±16.85	45.62±16.5	<0.001
Atrial conduit function			
1. Passive emptying (%) of total emptying ((Vmax - Vpre-a)/(Vmax - Vmin)) × 100	34.49±10.4	26.82±11.98	<0.0001
2. Passive emptying index ((Vmax - Vpre-a)/Vmax) × 100.	52.63±16.86	45.39±16.5	<0.001
Atrial booster pump function			
1. Active emptying (%) of total emptying ((Vpre-a - Vmin)/(Vmax - Vmin)) × 100.	11.13±5.6	10.49±5.96	0.12
2. Active emptying index ((Vpre-a - Vmin)/Vpre-a) × 100.	28.99±12.79	28.82±11.35	0.44

Conclusions: The differences in global atrial function may be attributed to higher systemic pressure and resistance in the left ventricle and aorta compared to the right side circulation (right ventricle and pulmonary circulation). This would make the left ventricle and aorta less blood-accommodating with pooling of the blood inside the LA more than the RA.

P1574 | BEDSIDE

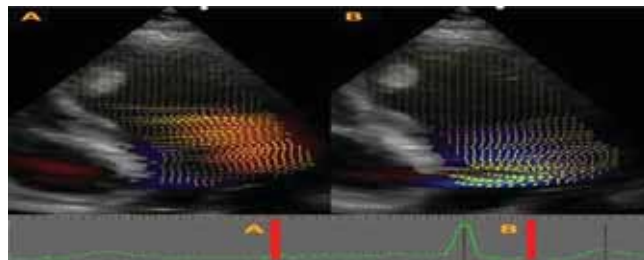
Flow mapping in ventricular aneurysms: a tool to predict the probability of thrombus development

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Introduction: Adverse remodeling after myocardial infarction includes the potential development of ventricular aneurysms. These segments with no contractility are occasionally associated to the development of thrombi. However, indications on the need for antithrombotic treatment in these patients is not well established given the absence of data to assess the risk of thrombus development. The goal of this study is to analyze the factors associated with the presence of intra-aneurysmatic thrombi as a first approach to the possibility to predict its development.

Methods: Patients with intraventricular aneurysm underwent echocardiographic examination with Vector Flow Mapping (VFM), an advanced echo-modality capable of depicting and quantifying complex intracardiac flow patterns. Flow characteristics and wall shear stress in the aneurysmatic area were analyzed using a series of mathematical calculations derived from VFM imaging mode.

Results: 11 patients (10 males, aged 70.4 ± 8.4 , LVEF 43.8 ± 10.5) were studied. Three of them (27%) presented a thrombus in the aneurysmatic region. Patients with intra-aneurysmatic thrombus presented significant differences with those with no thrombus: peak velocity of flow entering the aneurysm was decreased (5.9 ± 0.8 cm²/s vs. 9.3 ± 2.7 cm²/s, $p<0.05$), they had no reverse flow towards the apex during systole (0% vs. 75%, $p<0.05$) and maximum wall shear stress in the aneurysmatic wall, graded on a 0-to-5 scale, was reduced (1.67 vs. 4.50 , $p<0.001$).



Significantly reduced flow velocity

Conclusions: The study of ventricular aneurysms with flow mapping tools provides information on flow behavior that may be relevant to discriminate patients at risk of developing intra-aneurysmatic thrombus and who may, therefore, benefit from antithrombotic therapy.

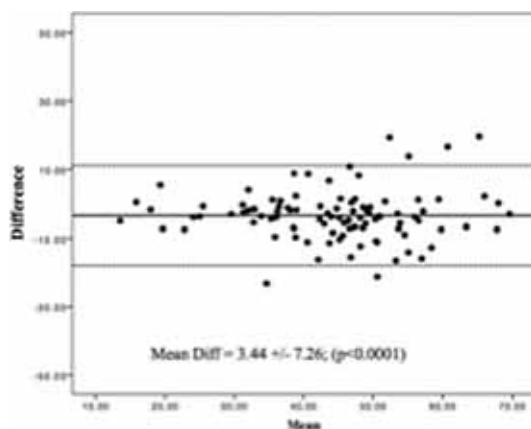
P1575 | BEDSIDE**A novel method for the non-invasive estimation of mean pulmonary artery pressure by echocardiography in comparison with right heart catheter measurements**

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Purpose: Pulmonary hypertension (PHTN) is defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest measured at right heart catheterization (RHC). Tracing the spectral Doppler signal in aortic stenosis is a recognised, reliable, and reproducible method of estimating the mean gradient across the valve. We aimed to determine if the same principle of tracing the tricuspid regurgitant (TR) continuous wave spectral Doppler signal would provide a more physiologic and representative estimation of the mPAP.

Methods: The study cohort comprised PHTN patients undergoing RHC and transthoracic echocardiograms (TTE) on the same day. Only cases with TTE studies containing "complete" TR spectral Doppler signals were included. Tracing the TR signal provided the TR mean gradient (TRMG). Right atrial pressure (RAP) was estimated based on the size and collapsibility of the inferior vena cava. The mPAP by TR (mPAP-TR) was then derived as TRMG + RAP.

Results: 100 patients (65 $\pm$ 14 years; 86% female) were included. The mPAP on RHC was 42.5 $\pm$ 12.4 mmHg and mPAP-TR was 45.9 $\pm$ 12.2 mmHg. mPAP-TR demonstrated good agreement (Intraclass correlation 0.885) and consistency (Cronbach's alpha 0.904) with invasive RHC measurements (See attached Bland-Altman plot demonstrating a relative mean difference of 3.44 $\pm$ 7.26 mmHg). The measurement of mPAP by this technique showed excellent test-retest reproducibility (Intra-observer variability 2 $\pm$ 4% and inter-observer variability 2 $\pm$ 6%). The presence of a "complete" TR spectral Doppler signal to allow accurate tracing is the only technical limitation.



Bland-Altman plot.

Conclusion: This novel non-invasive method for estimation of mPAP is useful in the assessment of PHTN severity. mPAP-TR is simple, reproducible, and correlates well with invasive RHC measurements.

HEART AND STROKE

P1577 | BEDSIDE**Relation between cryptogenic ischemic stroke and patent foramen ovale in young and middle-aged adults in northwestern China**

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Purpose: To compare the prevalence of PFO in young and middle-aged patients with cryptogenic ischemic stroke (CS) and in normal population in northwestern China.

Methods: Our case-control study included consecutive 318 young and middle-aged patients with CS (36 $\pm$ 8 years old, ranged from 18 to 50, 135 women) and 336 normal control subjects with matched age and sex (36 $\pm$ 7 years old, ranged from 19 to 50, 139 women) for group comparisons. Stroke risk factors including hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, atrial fibrillation, carotid atherosclerosis plaques and smoking, etc. were studied. Transesophageal echocardiography (TEE) tests were performed to detect the presence of PFO. The prevalence of PFO and difference of risk factor levels between the groups was compared. Then the odds ratios (OR) of a PFO was estimated in CS patients versus control subjects.

Results: The prevalence of PFO was significant higher in patients with CS than in normal control subjects (145/318, 45.6% versus 46/336, 13.7%, $P < 0.001$). The OR for PFO in CS for patients versus control subjects was 6.8 (confidence interval, 4.1 to 11.5). There were no significant differences in other stroke risk factors between two groups. The size of PFO was larger in stroke group than that in control group ($P < 0.05$).

Conclusion: PFO may play an important role in etiology of CS in young and middle-aged adults. Larger and longer PFOs may be more concomitant with ischemic attacks. More efforts should be employed in patients with CS to detect PFO for further treatment.

P1578 | BEDSIDE**Anatomical characteristics of the left atrial appendage in cardiogenic stroke with low CHADS-VASc scores**

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Purpose: In patients with atrial fibrillation (AF), left atrial appendage (LAA) morphology has been suggested to modify risk for embolic events. In this case-control study we tested the hypothesis that embolic risk in patients with low CHADS-VASc score (≤ 1) is associated with LAA characteristics.

Methods: Of 2,069 patients who underwent AF ablation, 25 (1.2%) had a prior thromboembolic event and a previously low CHADS-VASc score. Those patients were matched (1:3) for the CHADS-VASc criteria with 75 thromboembolic event-free patients and CT data were compared. LAA measurements (volume, ostium diameters, surface and circumference), morphology (cactus, chicken wing, windsock, cauliflower) and takeoff of the superior or inferior edge in relation (higher or lower) to the respective takeoff of the adjacent pulmonary vein (PV) were determined. LAA flow and heart rate from a resting ECG prior to ablation were also compared.

Results: Univariate analysis showed that patients with thromboembolic events had a higher incidence of superior LAA takeoff (i.e. higher than the left superior PV; 28% vs. 4%, $p=0.002$) and a higher incidence of hyperlipidemia (40% vs. 17%, $p=0.028$), while LAA morphologies (20% cactus, 24% chicken wing, 8% windsock, 48% cauliflower vs. 16%, 36%, 9%, 39% respectively, $p=0.69$), inferior takeoff (64% vs. 55%, $p=0.48$), and other LAA characteristics (volume: 8.8 $\pm$ 4.9 vs. 7.8 $\pm$ 3.3 ml, $p=0.24$, flow: 53 $\pm$ 21 vs. 56 $\pm$ 21 cm/s, $p=0.51$) were similar between groups. Logistic regression revealed that a superior LAA takeoff (OR: 9.1, 95% CI: 2.1 to 38.6, $p=0.003$) was the only independent predictor of thromboembolic events. There was a negative correlation between heart rate and LAA flow ($r=-0.2$ cm/s pro ml, $p=0.048$), that was that was even more pronounced for the superior LAA takeoff ($r=-0.67$ cm/s pro ml, $p=0.035$).

Conclusion: A higher LAA takeoff is associated with higher thromboembolic risk while LAA morphology is not. These findings may have implications for anticoagulation management of AF patients with low CHADS-VASc scores and higher LAA takeoff.

P1579 | BEDSIDE**Diastolic dysfunction in ischaemic stroke patients predict future cardiovascular events**

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Background and objectives: Left ventricular (LV) diastolic dysfunction is associated with major cardiovascular events including congestive heart failure (CHF), stroke, acute myocardial infarction (MI) and death. Tissue Doppler E/E', a non-invasive estimate of left atrial filling pressure and marker of diastolic function, has also been reported to predict primary cardiac events. In recent years, a transthoracic echocardiogram (TTE) has become standard of care in the assessment of patients who present with ischaemic strokes or transient ischaemic attacks (TIA). This study aims to evaluate the utility of tissue Doppler E/E' as a predictor for future cardiovascular events in stroke patients.

Methods: This was a retrospective study of 229 consecutive patients who presented to our acute stroke unit with ischaemic strokes or TIA. All patients had a TTE with the ratio of mitral velocity to early diastolic velocity of the mitral annulus (E/E') measured. Follow up data was obtained from hospital records. Outcomes of interest at 3 years included MI, CHF and all-cause death. Data analysis was carried out using SPSS 16.0.

Results: Majority of the patients were male ($n=151$). 22.3% and 8.3% had prior histories of ischaemic heart disease and CHF respectively. Logistic regression analysis showed that an E/E' of >15 independently predicted cumulative MI (17.8% vs 4.2%, $p=0.004$), CHF (15.1% vs 3.5%, $p=0.029$), and all-cause death (26.0% vs 9.1%, $p=0.004$) at 3 years.

Conclusions: In patients who present with an ischaemic stroke or TIA, the presence of LV diastolic dysfunction, as evidenced by an elevated E/E', was a predictor of future cardiovascular events. This is despite the routine use of antiplatelet and statin therapies in them. Further study is needed to determine whether more intensive efforts such as functional stress tests or coronary assessment/revascularization can benefit this group of patients.

P1580 | BEDSIDE**The relationship between left atrial enlargement and incidence of stroke in patients with atrial fibrillation: from the Fushimi AF registry**

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Purpose: Atrial fibrillation (AF) is a common arrhythmic disorder and increasing significantly. Stroke is a devastating complication of AF. Controversy exists regarding whether left atrial enlargement is a risk factor of stroke.

Methods: The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all of the AF patients in Fushimi-ku, Kyoto, Japan. Fushimi-ku is assumed to represent a typical urban community in Japan. At present, we have enrolled 3,821 patients (1.4% of total population) from March 2011 to December 2013. One-year follow-up was completed in 2,966 patients as of December 2013. Left atrial enlargement (LAE) was diagnosed if the left atrial diameter measured by transthoracic echocardiography was >45 mm. We compared the baseline clinical backgrounds and incidences of clinical events during one-year follow-up period between those with LAE and those without it (non-LAE).

Results: Patients with LAE accounted for 41.4% of all the patients. The proportion of female was comparable between LAE group and non-LAE group (39.6% vs 40.9%; $p=0.52$). LAE group was older (LAE 74.8 ± 10.1 vs. non-LAE 73.2 ± 11.0 years; $p<0.01$), and had higher CHADS2 score (2.26 ± 1.30 vs. 1.98 ± 1.36 ; $p<0.01$). Heart failure was more in LAE group, but other major co-morbidities, such as hypertension, diabetes mellitus, and the history of stroke, were comparable. LAE group showed slightly higher, but not statistically significant, incidence of stroke during one-year follow-up, compared with non-LAE group (3.0% vs 2.0%; $p=0.11$). After adjustment for CHADS2 risk factors and oral anticoagulant prescription, LAE was associated with slightly higher risk for stroke (adjusted odds ratio: 1.51, 95% confidence interval: 0.86 to 2.65, $p=0.15$). In female patients, LAE group showed significantly higher incidence of stroke during one-year follow-up (4.0% vs 1.5%; $p=0.01$), but this was not the case in male patients (2.3% vs 2.3%; $p=1.00$). In patients with CHADS2 score ≤ 1 , incidence of stroke during one-year follow-up was significantly higher in LAE group (3.1% vs 0.4%; $p<0.01$), whereas that was comparable in those with CHADS2 score ≥ 2 (2.9% vs 3.1%; $p=0.85$).

Conclusion: The Fushimi AF registry represents the clinical profile of real-world Japanese AF patients. AF patients with LAE showed higher risk profiles for stroke, and also showed higher incidence of stroke during one-year follow-up. The impact of LAE as an independent risk factor for stroke might vary depending on gender or other pre-existing risk factors.

P1581 | BEDSIDE**Prevalence of cardiac tumors in patients with cardioembolic stroke**

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Purpose: To evaluate the prevalence of intracardiac tumors in a population of patients with a cardioembolic ischemic stroke and to define their echographic characteristics.

Methods: This monocentric, retrospective study was conducted between May 2004 and November 2012. All consecutive patients with an ischemic stroke of potential cardioembolic etiology and who underwent transthoracic (TTE) and/or transesophageal echocardiography (TEE) were selected for the analysis. Intracardiac masses suspected of being cardiac tumors potentially responsible of stroke were analyzed.

Results: 2,948 patients with ischemic stroke potentially caused by cardioembolism had a TTE and a TEE. A total of 16 patients, aged from 27 to 81 years, were diagnosed as having a potential cardiac tumor and no other stroke etiology. The majority of these patients were female (62.5%). 81% of strokes were localized in the carotid territory. Echographic diagnosis include 9 fibroelastomas (small mobile mass implanted to aortic and mitral valve), 2 left atrium myxomas (heterogeneous and large ovale mass highly mobile). In addition, 3 cases of tumor on the mitral valve and 2 masses in the right atrium were associated with a PFO. After confirmation by computed tomography, magnetic resonance imaging or cardiac surgery, the final diagnosis for 7 suspected tumors was: myxoma ($n=1$) and fibroelastomas ($n=6$). The others cases did not correspond to tumor: thrombus, eustachian valve and myxoid degeneration ($n=5$).

Conclusion: In patients with stroke of potential cardioembolic mechanism, the prevalence of cardiac tumors on TTE/TEE is low (0.5%). When the diagnosis requires confirmation by a second imaging test or by surgery, the rate is lower (7/2948; 0.24%). Therefore, cardiac tumors represent a very unusual cause of ischemic stroke.

P1582 | BEDSIDE**The usefulness of combination of plasma D-dimer level, CHADS2 and CHA2DS2-VASc scores to predict effectively thromboembolic events in patients with atrial fibrillation**

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Background and purpose: Atrial fibrillation (AF) is associated with hemostatic abnormality and increases risk of thromboembolic events. Some reports show that plasma D-dimer level is increased in patients with AF. But the relation of plasma D-dimer level to thromboembolic events in patients with AF remains unknown. We report an association between the plasma D-dimer level in the first medical examination and the risk of thromboembolic events in patients with AF.

Methods: We assessed 303 nonvalvular AF patients with measured plasma D-dimer level in the first medical examination in our hospital between 1st January 2008 and 31st July 2013. We defined that elevated D-dimer level was $\geq 0.5 \mu\text{g/ml}$. Patients were excluded if they had diseases with elevated D-dimer level, such as pulmonary embolism, aortic dissection, deep vein thrombosis, malignant tumor and bleeding diseases etc. Patients with oral anticoagulant therapy were also excluded. An univariate and a multivariate analysis were performed using the logistic regression analysis.

Results: 95 patients incurred thromboembolic events and 208 patients were event free (31% versus 69%). An univariate analysis showed that D-dimer level $\geq 0.5 \mu\text{g/ml}$ (odds ratio, OR, 7.13, $p<0.01$) and age ≥ 75 years old (OR, 2.9, $p<0.01$), the presence of history of stroke (OR, 1.95, $p=0.04$), CHADS2 scores ≥ 2 (OR, 2.7, $p<0.01$), CHA2DS2-VASc scores ≥ 2 (OR, 3.53, $p<0.01$) were significantly associated with thromboembolic events. A multivariate analysis showed that D-dimer level $\geq 0.5 \mu\text{g/ml}$ was independent risk factor of thromboembolic events in each factors of CHADS2 and CHA2DS2-VASc scores (OR, 5.56, $p<0.01$). In low CHADS2 scores (0-1), patients with D-dimer level $\geq 0.5 \mu\text{g/ml}$ were significantly incurred thromboembolic events compared with D-dimer level $<0.5 \mu\text{g/ml}$ (80% versus 53%, $p=0.02$). In low CHA2DS2-VASc scores (0-1), the risk of thromboembolic events tended to be higher in patients with D-dimer level $\geq 0.5 \mu\text{g/ml}$ compared with D-dimer level $<0.5 \mu\text{g/ml}$ (75% versus 39%, $p=0.06$).

Conclusion: AF patients with D-dimer level $\geq 0.5 \mu\text{g/ml}$ in the first medical examination should be treated with oral anticoagulant therapy as well as AF patients with CHADS2 and CHA2DS2-VASc scores ≥ 2 . Especially, in patients with low CHADS2 and CHA2DS2-VASc scores (0-1), AF patients with D-dimer level $\geq 0.5 \mu\text{g/ml}$ should be stricter treated with oral anticoagulant therapy.

P1583 | BEDSIDE**The CHADS2 and CHA2DS2-VASc scores as predictors of thromboembolism in patients with non-valvular atrial fibrillation undergoing direct-current cardioversion**

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Background: The predictive value of the CHADS2 and CHA2DS2-VASc scores for thromboembolism related to direct current cardioversion (DC-CV) of non valvular atrial fibrillation (NVAF) has not been well studied. We analyze the role of individual stroke risk factors and both CHADS2 and CHA2DS2-VASc scores to predict thromboembolism in a real-world cohort of patients with NVAF undergoing DC-CV.

Methods: We studied 571 consecutive DC-CV procedures performed between January 2008 and June 2012 in 406 patients with NVAF (70.1% male, 66.4 ± 11.2 years). We calculated the association between thromboembolic risk factors and CHADS2 and CHA2DS2-VASc scores for the development of embolism. The prognostic value of both scores was compared.

Results: During a median follow-up of 668 (IQR 293-1186) days, there were 23 embolic events (4.0%), ie. an annual rate of 2.18%. Nineteen (82.6%) were strokes whilst 4 (17.4%) were peripheral thromboembolism. On multivariate analysis, factors significantly associated with thromboembolism were age (HR: 1.06, $p=0.002$) and vascular disease (HR: 3.77, $p=0.01$). Both CHADS2 and CHA2DS2-VASc scores were significantly associated with the incidence of thromboembolism after DC-CV (CHADS2: HR=1.70; 95%CI: 1.22-2.37; $p=0.002$); (CHA2DS2-VASc: HR=1.69; 95%CI: 1.31-2.18; $p<0.001$).

Abstract P1581 – Table 1

Patient number	Diagnosis	Characteristics TEE/TEO	Stroke	Clinical presentation
1	Fibroelastoma	2 mm, mitral valve, heterogeneous	Right middle cerebral artery	Aphasia
3	Fibroelastoma	<2 mm, aortic valve, homogeneous mass	Right middle cerebral artery	Dysarthria, facial paralysis
9	Fibroelastoma	3 mm, aortic valve,	Middle cerebral artery	Dysarthria, facial paralysis
11	Fibroelastoma	2.5 cm heterogeneous, mitral valve.	Left middle cerebral artery	Right hemiplegia
13	Fibroelastoma	7 mm, heterogeneous, Aortic valve.	Left middle cerebral artery	Right hemiparesia
14	Myxoma	15 mm, mobile, interauricular septum	Biencephalic stroke	Right hemiparesia
15	Fibroelastoma	8 mm, homogeneous, mobile, aortic valve	Posterior cerebral artery	Left hemiparesia

Both scores were good predictors of embolism (CHADS₂: c-statistic= 0.67; 95%CI: 0.56-0.78; p=0.005); (CHA₂DS₂-VASc: c-statistic= 0.75; 95%CI: 0.66-0.83; p<0.001), with CHA₂DS₂-VASc being superior to CHADS₂ (DeLong test, p<0.01).

Annual rate of embolic events depending on thromboembolic risk

	Annual rate of thromboembolism (%)
Embolism risk (CHADS ₂ score)	
Low (0)	0
Moderate (1)	1.65
High (>1)	3.15
Embolism risk (CHA ₂ DS ₂ -VASc score)	
Low (0 in males, 1 in females)	0
Moderate (1 in males)	0
High (>1)	2.90

Conclusions: Both CHADS₂ and CHA₂DS₂-VASc thromboembolic risk scores are good predictors of embolic risk in real-world NVAf patients undergoing DC cardioversion, with CHA₂DS₂-VASc having significantly better predictive value.

P1584 | BEDSIDE

Incidence of atrial fibrillation and subsequent medication changes in cryptogenic stroke patients with an implantable loop recorder

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Purpose: Stroke patients are at high risk of stroke recurrence. This study evaluates the risk profile, incidence of atrial fibrillation (AF), and medication changes in patients with unexplained (cryptogenic) stroke or transient ischemic attack (TIA) who underwent continuous monitoring with an implantable loop recorder (ILR).

Methods: The observational INSIGHT XT study prospectively enrolled patients who received an ILR with dedicated diagnostics for atrial fibrillation, irrespective of the clinical indication. The study was submitted to local MECs and informed consent to participate in the study and/or for using personal data was obtained. Of 1003 patients enrolled in the study between Aug 2008 and Jan 2012, 121 received the ILR to evaluate cryptogenic stroke or TIA at 20 study centers. The definition of cryptogenic stroke/TIA was at the investigators' appraisal and no standard approach to patient work-up was required.

Results: The median follow-up duration was 12.5 months (IQR 11.7, 13.4). The mean age of patients was 62±13 years and 47% were female. A stroke was the index event in 71%, whereas 29% had a TIA. At baseline 62% of patients had hypertension, 12% had diabetes, none had a history of heart failure, and 12% had a history of palpitations. The mean CHADS₂ score was 2.9±0.8 and the mean CHA₂DS₂-VASc score 4.0±1.3. At enrollment, 93% of patients were taking antiplatelet medication and 5% were on oral anti-coagulation (OAC). AF was observed in 24 patients (20%) and the mean time to diagnosis of AF was 5.7±5.1 months. Twelve of the AF-patients were started on OAC. During the study, six patients experienced a stroke or TIA (median time to event 3.6±4.6 months), of which 1 patient died.

Conclusions: We found a high proportion of patients with AF in this multicenter cohort of patients with cryptogenic stroke representing clinical practice. These patients have high CHADS₂/CHA₂DS₂-VASc scores and physicians initiated OAC based on the available diagnostic data from continuous monitoring with the ILR.

P1585 | BEDSIDE

Impact of combination of left atrial volume index and markers of thrombogenesis on risk assessment of thrombus formation in the left atrial appendage

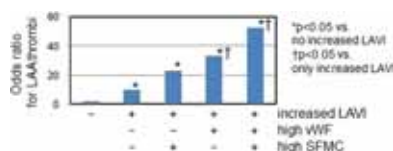
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Purpose: Left atrial appendage (LAA) is a major thromboembolic source in cardioembolic stroke. As shown in the Virchow's triad, circulatory stasis, hypercoagulability, and endothelial dysfunction, are important factors for thrombus formation. The aim of this study was to investigate whether the clustering multiple noninvasive markers of thrombogenesis based on Virchow's triad is associated with LAA thrombus formation.

Methods: We measured plasma soluble fibrin monomer complex (SFMC) as a marker of hypercoagulability and plasma von Willebrand factor (vWF) as a marker of endothelial dysfunction in 307 consecutive acute ischemic stroke patients and 168 proximal atrial fibrillation patients who underwent transthoracic and transesophageal echocardiography. We measured left atrial volume index (LAVI) which reflects LAA dysfunction as a marker of circulatory stasis.

Results: LAA thrombus was detected in 60 patients. LAVI, plasma vWF and SFMC levels were significantly higher in patients with LAA thrombus than in those

without. Multivariate regression analysis revealed that LAVI and vWF are independent risk factors after adjusting confounding factors. LAVI was a much greater risk factor than vWF and SFMC. Further, the patients with increased LAVI combined with high vWF and/or high SFMC had a greater risk for LAA thrombogenesis compared to those solely with increased LAVI (odds ratio vs. no increased LAVI; increased LAVI and high vWF and high SFMC, 52.2, p<0.0001, increased LAVI and high vWF, 33.0, p<0.0001, increased LAVI and high SFMC, 22.9, p<0.05, only increased LAVI, 9.6, p<0.05, respectively).



Odds ratio for LAA thrombi.

Conclusion: Combined assessment of LAA dysfunction with hypercoagulability and endothelial dysfunction may be a reliable evaluation for LAA thrombogenesis.

P1586 | BEDSIDE

The impact of antidotes on the outcomes of warfarin-related intracranial haemorrhage

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Introduction: Unlike all novel oral anticoagulants, there are specific antidotes for warfarin such as fresh frozen plasma (FFP) and vitamin K. However, given the slow anticoagulation reversal of these agents, the actual impact on the clinical outcomes in these situations particularly in the setting of intracranial haemorrhage (ICH) remains uncertain.

Method: This was a single-centre registry study for the period from year 1997 to 2013.

Results: A total of 968 patients with warfarin overdose and/or warfarin-related bleeding was identified. Amongst these, 86 patients had warfarin-related ICH (median age 72 years; 48.8% males). 37 patients (43.0%) had pre-existing hypertension and 28 (32.6%) had diabetes mellitus. 32 patients (37.2%) with warfarin-related ICH were admitted with therapeutic INR (INR 2 - 3); 14 (16.3%) had INR <2 and 40 (46.5%) had INR >3. 26 patients (30.2%) were given FFP, 10 (11.6%) were given vitamin K, 27 (31.4%) were given both, and 23 (26.7%) did not receive any antidote. Only 59 patients (68.6%) successfully attained INR ≤1.4 after admission. Among these cases the median time to achieve INR ≤1.4 was 16.8 hours (IQR: 34.8 hours). The overall 7-day and 30-day mortality were 31.4% and 37.2% respectively. However, there was no statistically significant difference in mortality between groups of patients that received different treatment (i.e. FFP/vitamin K/both). Nonetheless, Kaplan-Meier analysis showed a lower 30-day mortality (p=0.006) in patients that attained INR ≤1.4 within 24 hours of admission compared to those who did not (Figure 1).

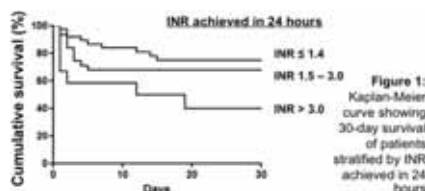


Figure 1: Kaplan-Meier survival curve showing 30-day survival of patients stratified by INR achieved in 24 hours

Conclusion: Patients with warfarin-related ICH had a very high mortality despite the availability of antidotes. Early attainment (in 24 hours) of lower INR was associated with lower short- and intermediate-term mortality.

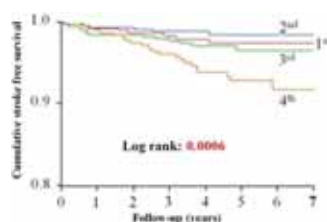
P1587 | BEDSIDE

Impact of red blood cell distribution width on incidence of stroke after elective percutaneous coronary intervention

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Background: High level of red blood cell distribution width (RDW) has been identified as a novel prognostic marker in patients with heart failure, coronary artery disease and stroke. However little is known about the relationship between RDW and incidence of stroke after percutaneous coronary intervention. Therefore, we investigated that the prevalence of stroke and RDW would be a predictive value of incidence of stroke after elective PCI treated with antiplatelet drugs.

Method and results: 1351 patients (mean age 66.9±9.7 years, male 84.1%) with stable CAD who underwent elective PCI were enrolled and followed up for a mean of 3.8 years. Primary endpoint was an incidence of stroke. Patients were divided into four groups according to quartiles of RDW. Patients with 4th quartile of RDW were significantly associated with higher incidence of stroke than those



Kaplan-Meier for incidence of stroke.

with 1st quartile of RDW after adjustment for baseline characteristics using multivariate Cox regression analysis (HR of 2.38, 95%CI 1.01-6.28, $p=0.047$).

Conclusion: Elevated RDW was strongly associated with increased risk of stroke among the patients who underwent elective coronary intervention receiving antiplatelet therapy.

P1588 | BEDSIDE

Risks for stroke and bleeding with warfarin and aspirin in patients with atrial fibrillation at different CHA2DS2VASC-scores: Experience from the Stockholm region

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Background: This study evaluated the risks for stroke and bleeding in patients with warfarin, aspirin or no treatment in patients with atrial fibrillation (AF) in the year prior to the introduction of new oral anticoagulants; using health registry data from inpatient care and specialist ambulatory care, as well as primary care.

Methods and results: Cohort study including all patients in the Stockholm region (2.1 million inhabitants) with a diagnosis of non-valvular AF ($n=41\,810$) recorded during 2005-2009. The risks for ischemic stroke, bleeding, or death were investigated at different CHA2DS2VASC scores with warfarin, aspirin, or no treatment during 2010. The three treatment groups were not comparable and confounding by indication precluded a comparative effectiveness analysis. One-year risks for ischemic stroke were higher (1.0-1.8%) with aspirin than with warfarin (0-0.7%) or no treatment (0.1-1.0%) at CHA2DS2VASC scores 0-2. Intracranial bleeds were few and similar in the treatment groups. Serious bleeds were more common in patients with aspirin. Serious co-morbidities and contraindications for warfarin treatment were common among high risk patients, but half of the aspirin treated patients with CHA2DS2VASC scores ≥ 2 seemed to be clear candidates for anticoagulant treatment with high risk for ischemic stroke, low bleeding risk and moderate mortality rate.

Conclusions: Atrial fibrillation patients with aspirin had a clinically relevant risk of ischemic stroke regardless of CHA2DS2VASC scores, but also a higher rate of complicating co-morbidities, more serious bleeds and substantially higher mortality rates which should be taken into account when considering more aggressive use of anticoagulant treatment.

PERCUTANEOUS CORONARY INTERVENTION IN HIGH-RISK SUBJECTS

P1590 | BEDSIDE

What does the new clinical syntax score have to offer? comparison of the predictive ability of syntax score I and II in patients who underwent unprotected left main angioplasty

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Aim: The SYNTAX score II, which includes prognostically important clinical variables, emerged to overcome the limitations of the purely anatomical SYNTAX score in the choice of the best revascularization strategy for patients with complex coronary artery disease.

We aimed to validate and compare the performances of the SYNTAX I (SI) and SYNTAX II (SII) as predictors of major cardiovascular events (MACE) in patients who underwent unprotected left main angioplasty (ULMA) as well as to evaluate the clinical impact of the SII guided revascularization strategy reclassification.

Abstract P1588 – Table 1. Outcomes among 26 937 AF patients with CHADS2VASC scores 2–9; with and without complicating baseline characteristics (dementia, alcohol abuse, renal disease, anemia, earlier severe bleeding, or frequent falls)

Outcomes 2010	Warfarin			Aspirin		
	Uncomplicated (n=10024)	Complicated (n=4189)	Risk ratio	Uncomplicated (n=6551)	Complicated (n=6173)	Risk ratio
Ischemic stroke	2.0 (1.7–2.3)%	2.1 (1.6–2.5)%	1.0 (0.8–1.3)	4.0 (3.5–4.4)%	5.2 (4.6–5.8)%	1.3 (1.1–1.5)
Hemorrhagic stroke	0.5 (0.4–0.6)%	0.9 (0.6–1.2)%	1.8 (1.2–2.8)	0.4 (0.2–0.5)%	1.0 (0.8–1.3)%	2.7 (1.7–4.2)
Traumatic intracranial bleeding	0.3 (0.2–0.4)%	0.6 (0.3–0.8)%	1.8 (1.1–3.0)	0.2 (0.1–0.3)%	0.7 (0.5–0.9)%	3.4 (1.8–6.4)
Any severe bleeding	1.9 (1.6–2.2)%	3.8 (3.2–4.4)%	2.0 (1.6–2.4)	1.8 (1.5–2.2)%	5.0 (4.5–5.6)%	2.7 (2.2–3.4)
Deceased (all cause)	2.9 (2.6–3.3)%	6.2 (5.5–6.9)%	2.1 (1.8–2.5)	8.4 (7.8–9.1)%	19.3 (18.3–20.3)%	2.3 (2.0–2.5)

Methods and results: Single Centre retrospective analysis of 132 patients (79.5% men, mean age 65.8 ± 12 years) who underwent ULMA between March 1999 and December 2010. Both scores were calculated using the online calculator and the published SII nomogram (presupposes independent calculation for each revascularization strategy). We estimated the discriminative ability for MACE at 4 years of both scores by ROC curve analysis. The areas under de curve (AUC) were compared by the De Long et al.

Method: To assess the predictive validity, the scores were dichotomized at their best discriminative values and individually inserted into Cox regression models with other significant variables. We analyzed the outcome of patients whose SII score favored surgical revascularization (CABG).

The median SI was 22 IQ [3.5-17.65], the median SII predictor of risk associated with CABG (CABG SII) was 8.49 IQ [4.6-18.77], the median SII predictor of risk associated with angioplasty (PCI SII) was 7.2 IQ [3.5-17.65]. There were 35 MACE (26.5%) at 4 years of follow-up. The AUC were 0.613 with the best discriminative value >23 for SI; 0.606 with the best discriminative value >6.86 for SII CABG and 0.674 with the best discriminative value >6.77 for SII PCI. There were no significant differences between the AUC for the three scores ($p>0.08$). All scores were shown to be independent predictors of MACE with HR 2.89 95% CI (1.27-6.58) for SI, HR 2.97 95% CI (1.31-6.75) for CABG SII and HR 3.3 95% [1.33-8.11] for SII PCI. Patients whose SII favoured CABG had a MACE rate of 29% and those not reclassified had a MACE rate of 24.7% ($p=0.54$).

Conclusions: Both versions of the SYNTAX score showed a poor discriminative ability for MACE occurrence at 4 years in the studied population.

The patients in whom SYNTAX II favoured surgical revascularization did not have more MACE rate.

P1591 | BEDSIDE

Risk assessment and rates of false positive cath laboratory emergent activation among patients with left bundle branch block

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Purpose: GRACE risk score is widely employed for estimating short and medium-time outcome of acute coronary syndromes (ACS). Recent trials report rates up to 15% for false positive cathlab activations (FPCLA), meaning that negative cardiac injury markers or no lesions in coronary arteries. Our aim was to evaluate Grace's utility among left bundle branch block (LBBB) derived for emergent coronary angiography (ECA) and its rate of FPCLA.

Methods: All patients ($n=1231$) derived for ECA in a high volume tertiary hospital between January 2006 and June 2013 were prospectively collected. Data concerning clinical characteristics, angiography and outcome was recorded. Last follow-up was updated in July 2013, with a mean of 20 ± 25.7 months.

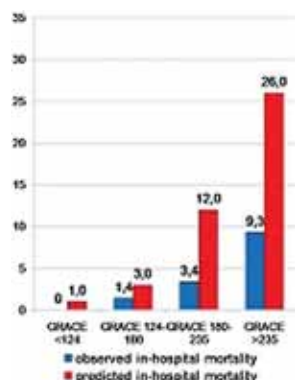
Results: Among all, 3.73% ($n=46$) showed LBBB (23.9% old, 39.13% new and 34.8% unknown). Of them, 65.5% had ST-segment elevation (54.3%, Sgarbossa criteria). Mean age was 70.9 ± 10.7 years and 63% were male. Most (91.3%) had cardiovascular risk factors such as hypertension (65%), dyslipidaemia (47.8%), diabetes (34.8%) or smoking habit (39.1%) and 21.7% had previous history of myocardial infarction. Angiographically, up to 21.7% ($n=10$) did not have coronary artery disease and among who did, 66.6% had not an acute artery occlusion. Almost one third (34.8%) of patients did not have any main artery affected and when so, single right coronary artery was the most frequent finding. Finally, angioplasty (ACTP) was performed in only 50% of cases. Clinical presentation was frequently critical, as cardiogenic shock (43.5%) or out-of-hospital cardiac arrest (19.6%), showing mean ejection fraction of $34.4 \pm 16.3\%$ on echocardiogram. Consequently, the degree of support therapy (intraaortic balloon pump in 21.7% cases) and inhospital cardiac complications was high (28.3%), reaching rates of 21.7% inhospital death. Regarding follow-up, 78.2% were discharged, after a mean hospital stay of 12 days, 25% needing readmission for heart failure (2.7%), ACS (2.7%), angina pectoris (2.7%), arrhythmia (5.5%) or not cardiac cause (13.8%). 59% were alive one year later (mean survival: 40.36 ± 6.27 months). Survival was analysed using Receiver Operating Characteristic curves, according to estimated GRACE score at admission, showing a weak predicting value in this subset of patients.

Conclusion: LBBB derived for ECA have a considerable rate of clear coronary artery tree, despite high prevalence of cardiovascular risk factors and frequent critical clinical presentation, suggesting these patients could contribute to increase FPCLA. GRACE score has shown weak predicting value in this group.

P1592 | BEDSIDE**GRACE score predicts short- and long-term mortality but overestimates the mortality risk in ACS patients treated with PCI of LM stenosis**K. Shreyder¹, E. Merkulov², V. Mironov², D. Pevzner², A. Samko², M. Ruda².¹National Research Center for Preventive Medicine, Moscow, Russian Federation;²Federal State Enterprise Rosmedtechnologies. Russian Cardiology Scientific & Industrial Complex, Moscow, Russian Federation

Aim: The purpose of the study was to assess mortality in ACS patients with significant left main coronary artery (LMCA) stenosis treated with PCI and to evaluate GRACE score as a predictor of immediate and long-term results.

Results: 269 ACS patients treated with PCI LMCA were included into the study. There were 105 STEMI and 146 NST-ACS patients with infarct/symptom-related left anterior descending artery or left circumflex artery respectively and accompanying significant LMCA stenosis, and 18 patients with symptom-related LMCA. Mean age was 65.6 years. Low LV EF (<35%) was in 41% patients. The mean GRACE score was 179.9. The mean SYNTAX score was 31. In-hospital mortality for the whole group was 3.0%. The mean follow up period was 51 months. Long-term mortality appeared to be 6.7%. NST ACS group had the lowest mortality (2.1%). Long term mortality in STEMI patients and LMCA-symptom related group 16.2% and 33.4% respectively. GRACE score higher than 179.9 was considered to be an independent risk factor of in-hospital (OR = 2.1, p=0.004) and long-term mortality (OR=2.8, p=0.002). However, the observed mortality was much lower than predicted with GRACE (3.0% vs 8.0% respectively, p=0.01). The differences between observed and predicted mortality were significant in groups of patients, divided in respect to the GRACE score percentile (fig. 1). Predicted 6-months mortality with the use of GRACE score at discharge (mean 113.4) was 12%, but the observed mortality during the follow up period appeared to be much lower (6.7%).



Conclusions: GRACE score is an important tool in assessing short- and long-term prognosis in patients with ACS treated with PCI of LMCA, but it overestimates the mortality rate.

P1593 | BEDSIDE**Increasing incidence, atypical risk factor profile and excellent long-term outcomes of young patients treated with primary PCI for ST-elevation myocardial infarction**K.S. Rathod, D.A. Jones, S.M. Gallagher, V.S. Rathod, R. Weerackody, A. Mathur, S. Mohiddin, A. Archbold, A. Wragg, C. Knight. *The London Chest Hospital, London, United Kingdom*

Introduction: There have been a number of studies focusing on the relationship between age and outcome following Primary Percutaneous Coronary Intervention (PPCI) for ST-elevation myocardial infarction (STEMI). However, the majority of these studies have focused on outcomes in elderly patients. Our aim in this study was to compare the characteristics and outcomes of young patients undergoing PPCI with those of older patients.

Methods: This study was an observational study of 3618 patients with STEMI treated by PPCI between January 2004 and September 2012 at a large PPCI centre. We compared the outcome in young patients (<45 age) with older patients (>45 age). The primary endpoint was long-term mortality with long-term major adverse cardiac events (MACE) as a secondary endpoint. Median follow-up was 3.0 years (IQR range: 1.2-4.6 years).

Results: Of the 3618 STEMI patients, 367 (10.14%) were young patients and 3251 (89.9%) were older patients. Over the follow-up period, rates of mortality (2.7 vs. 7.6; p<0.0001, Figure 1) and MACE (7.0% vs. 13.5%; p<0.0001) were significantly lower in the young group compared to the older group. After adjustment for confounding variables using multivariate analysis, young patients had lower all cause mortality when compared with older patients (HR 0.12 [95% CI: 0.04-0.38]), including after incorporation of a propensity score (HR: 0.14[95% CI: 0.04-0.36]).

Conclusions: Our data suggests that younger patients are accounting for an increasing proportion of patients treated by PPCI for STEMI. These patients are

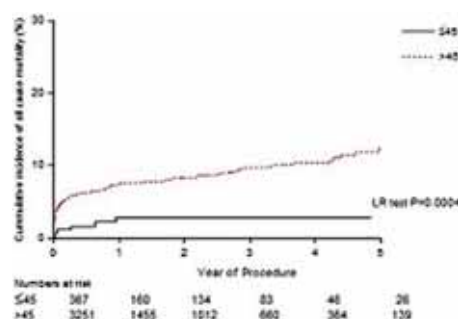


Figure 1

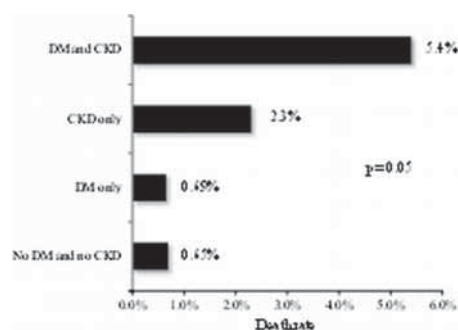
more likely to be male smokers of South Asian origin with LAD disease than older patients, but to have fewer other conventional risk factors. Furthermore, these patients have favourable in-hospital, intermediate and long-term outcomes after PPCI.

P1594 | BEDSIDE**Combined and independent impact of diabetes and chronic kidney disease among patients undergoing percutaneous coronary intervention for chronic total occlusion: results from a single center study**O.A. Meelu, M. Aquino, N. Kherada, K. Theodoropoulos, S. Roy, S. Sayeneni, R. Mehran, G. Dangas, S. Sharma, A. Kini. *Mount Sinai Medical Center, New York, United States of America*

Purpose: Diabetes mellitus (DM) and chronic kidney disease (CKD) are independent predictors of poor outcomes following percutaneous coronary intervention (PCI) and are associated with complex coronary disease, including chronic total occlusions (CTO). While CTO recanalization may improve outcomes, the impact of CTO PCI in patients with and without DM and CKD remains unclear.

Methods: We performed a retrospective analysis of 887 consecutive patients undergoing CTO PCI between 2009 and 2012. We compared clinical and angiographic characteristics in patients stratified by the presence or absence of DM and CKD (DM and CKD = 105, DM only= 289, CKD only=124 and neither=369). We accessed 1-year clinical outcomes and mortality in each subgroup.

Results: Patients with DM and CKD were older with more multi-vessel disease and severely calcified lesions. PCI success rates were lower among those with DM and CKD (61.4%) or CKD alone (62.1%), compared with DM alone (70.4%) and patients with neither condition (74.1%) (p<0.01). While 1-year overall MACE outcomes were not significantly different between groups, all-cause mortality was higher among those with DM and CKD (Figure).



Crude death rates (%) in CTO registry.

Conclusion: Successful recanalization of CTO lesions is less common among patients with both DM and CKD compared to those with neither or one condition. Excess mortality risk even after successful PCI suggests that CTO PCI should be approached with extreme caution in this unique, high risk cohort.

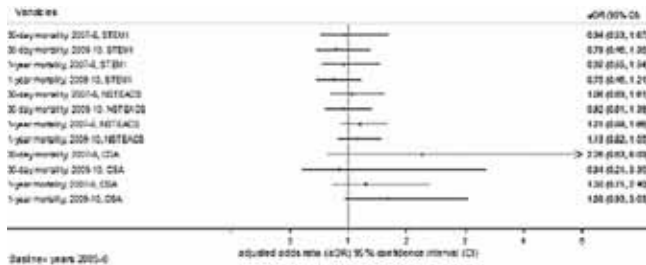
P1595 | BEDSIDE**Mortality trends after unprotected left main stem percutaneous coronary intervention in England, 2005-2010: Analysis of 5,065 cases from the British Cardiovascular Intervention Society (BCIS) registry**S. Almdarra¹, N. Curzen², P. Baxter¹, S. Fleming¹, I. Pearson¹, P. Ludman³, M. De Belder⁴, C. Gale¹ on behalf of National Institute for Cardiovascular Outcomes Research (NICOR), University College London, UK. ¹University of Leeds, Division of Epidemiology and Biostatistics, Leeds, United Kingdom; ²University of Southampton, Faculty of Medicine, Southampton, United Kingdom; ³Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom; ⁴South Tees Acute Hospitals NHS Foundation Trust, Middlesbrough, United Kingdom

Purpose: To report temporal trends in the treatment and outcomes after UPLMS PCI according to presentation by ST-elevation myocardial infarction (STEMI), non

ST-elevation acute coronary syndrome (NSTEMI/ACS) and chronic stable angina (CSA).

Methods: Prospective population-based linked cohort study of 5,065 patients from the BCIS database, 1st Jan 2005 through 31st Dec 2010.

Results: From 2005-6 to 2009-10, STEMI UPLMS PCI cases increased from 10.5 to 18.7%, on the other hand NSTEMI/ACS and CSA cases decreased: 48.9 to 45.9% and 40.6 to 35.4 respectively. Mean (SD) age was 69.6 (11.8) years for STEMI, 69.9 (12.1) years for NSTEMI/ACS and 70.6 (12.5) years for CSA. There was a preponderance of males in all years. Overall baseline risk increased; cardiogenic shock: 7.7 to 12.2%, $P=0.001$; severe left ventricular systolic dysfunction, 14.9 to 17.3%, $P=0.009$; age >80 years, 20.9 to 26.0%, $P=0.035$. Radial PCI increased from 17.6% in 2005-6 to 40.5% of cases. Compared with 2005-6, 30-day mortality in 2009-10 was stable (STEMI: adjusted odds ratio (aOR), 95% confidence interval (CI) 0.8, 0.5 to 1.4; NSTEMI/ACS 0.9, 0.6 to 1.4; CSA 0.8, 0.2 to 3.4). Likewise, 1-year mortality remained stable (STEMI aOR 0.8, 95% CI 0.5 to 1.4; NSTEMI/ACS 1.1, 0.8 to 1.5; CSA 1.7, 0.9 to 3.0). For STEMI with cardiogenic shock, 30-day and 1-year mortality rates decreased by 17.4% (95% CI, 13.4 to 21.9%) and 16.6% (12.4 to 21.3%) reaching 44.0% and 43.9% in 2009/10, respectively.



Adjusted 30-day & 1-year mortality risks.

Conclusions: In England, the number of cases of UPLMS PCI increased by over 2-fold between 2005 and 2010. Baseline risk increased and across all groups early and late mortality was stable. Although mortality rates for STEMI with cardiogenic shock declined, they remained high.

P1596 | BEDSIDE

Does the incidence and impact of dual antiplatelet therapy cessation after PCI vary among patients with and without ACS? Insights from the PARIS registry

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Background: In contemporary PCI, the risk of adverse events after DAPT cessation depends on the clinical context in which antiplatelet therapy is withdrawn. The effects of different modes of DAPT cessation have not been investigated in ACS vs. non-ACS patients.

Methods: The PARIS (patterns of non-adherence to anti-platelet regimens in stented patients) registry was an observational multicenter study of 5018 patients undergoing PCI. Cessation was categorized as physician-recommended discontinuation, brief interruption (<14 days) for surgery or disruption (due to non-compliance or bleeding). Associations between DAPT cessation and adverse events were examined using Cox regression with DAPT cessation entered as a time-updated covariate.

Results: ACS patients (n=2056, 41%) were younger and more often smokers with less DM and prior ischemic history compared to their non-ACS counterparts (n=2962, 59%). Although rates of discontinuation (40.6% vs. 39.9%, $p=0.30$) did not vary across groups, interruption (9.1% vs. 11.3%, $p=0.01$) was less frequent while disruption (17.2% vs. 12.3%, $p<0.001$) was more common after ACS. The

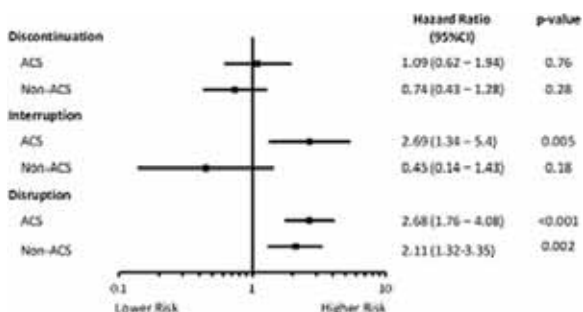


Figure 1

number of adverse events after DAPT cessation was highest following disruption, intermediate with discontinuation and lowest with interruption in both groups (Fig. 1). Risk associated with disruption and discontinuation was similar in magnitude and direction across ACS strata (Fig. 1). While risk with interruption was numerically higher among ACS patients, interaction testing was non-significant ($p=0.17$).

Conclusion: Although the incidence of DAPT cessation mode differs by presence or absence of ACS, associations between DAPT cessation and adverse events are non-differential by ACS presentation.

P1597 | BEDSIDE

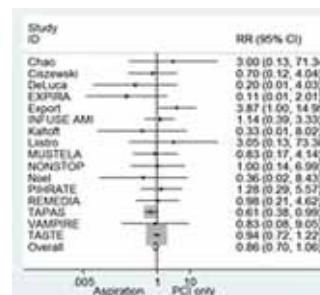
Effect of aspiration thrombectomy on outcomes in patients with acute myocardial infarction: an updated meta-analysis of randomized control trials

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Background: A recent meta-analysis suggested that aspiration thrombectomy during acute myocardial infarction (AMI) maybe associated with lower risk of all-cause mortality and major adverse cardiac events (MACE) during a 30-day follow-up (PMID: 23665372). However, findings from the TASTE randomized controlled trial (RCT) did not confirm those findings. We conducted a new meta-analysis including TASTE data to examine the effect of aspiration thrombectomy (AT) before primary percutaneous coronary intervention (PCI) vs primary PCI alone on these outcomes.

Methods: Pre-TASTE RCT (18 trials, n=3,936) and TASTE RCT (n=7,244) randomized AMI patients to PCI with or without AT. Primary outcome was 30-day mortality. Secondary outcomes including MACE, stroke, target vessel revascularization and reinfarction were also studied.

Results: All-cause mortality occurred in 2.9% and 3.4% of patients undergoing vs not undergoing AT (risk ratio {RR}: 0.86; 95% CI: 0.072-1.1; $p=0.26-0.93$; $p=0.002$; Fig. 1). RR for mortality for pre-TASTE meta-analysis and TASTE RCTs were 0.71 (95% CI: 0.51-0.99-0.92; $p=0.049$) and 0.94 (95% CI: 0.72-1.22; $p=0.629$) respectively (Fig. 1). AT was associated with significantly lower MACE events overall (RR: 0.81; 95% CI: 0.71-0.93; $p=0.002$) despite no effect in the TASTE RCT (RR: 0.85; 95% CI: 0.70-1.03; $p=0.101$).



Summary plot comparing mortality

Conclusions: Compared with conventional primary PCI alone, PCI with manual catheter aspiration thrombectomy for treatment of AMI was not associated with lower risk for all-cause mortality. The effect of AT on MACE, though significant, is inconsistent with that from the largest and most recent TASTE RCT (52% weight) and need to be interpreted with caution.

P1598 | BEDSIDE

Predictors of coronary artery aneurysm after stent implantation in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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Background: The clinical and angiographic predictors of coronary artery aneurysm (CAA) formation in patients with ST-segment elevation acute myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) is not clear. This study aims to assess the predictors of CAA formation after primary PCI.

Methods: 3428 patients who underwent PCI for STEMI were enrolled. The average period of follow-up was mean 48 months (range, 35 to 56 months) after PCI. During this time, 1304 (38%) patients were underwent follow-up coronary angiography (CAG). CAA was detected in 21 patients (1.6%). CAA occurred at the segment of stent implantation in all patients. The clinical and angiographic data were compared between patients with CAA group (n=21) and without CAA group (n=1283) (figure).

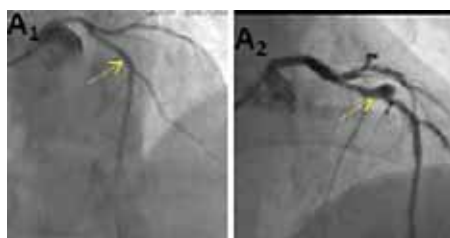


Figure 1

Results: Patients who developed CAA had longer reperfusion time, higher high-sensitivity C-reactive protein (hs-CRP) levels and neutrophil to lymphocyte ratio (NLR) than those who had without CAA. Angiographically, CAA developed proximally located lesions and lesion length was significantly greater in patients with CAA than without CAA. Statin and betablocker discontinuation were found to be an important predictor of the diagnosis of stent associated CAA. Every 1 mg/L increase in hs-CRP and implantation of drug eluting stent (DES) were independent predictors of CAA formation after STEMI.

Conclusions: Baseline elevated inflammation status and DES implantation in the setting of STEMI may predict the CAA formation.

P1599 | BEDSIDE

Transradial access for coronary artery catheterization in the elderly: are there differences between left or right approach?

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Purpose: Transradial access for coronary interventions is being routinely used despite of limitations related with technical and anatomical issues. Elderly patients have a higher risk of access-site complications related to invasive coronary catheterization. Our purpose was to evaluate feasibility of radial access and to compare left versus right radial access in very old patients.

Methods: Retrospective study of all patients ≥ 80 years who underwent coronary artery catheterization through radial access at our institution. Success rate (defined as complete procedure performed through the radial access), crossover rate, fluoroscopy time, volume of contrast and diagnostic and interventional procedures were collected. Statistical analysis was performed with the SPSS software.

Results: A total of 886 patients were included (43.7% female), mean age 82.8 ± 2.6 years (range 80-92), who underwent a radial access coronary angiography. Right radial artery (RRA) was used in 770 (86.9%) and left radial artery (LRA) in 116 (13.1%). No statistically significant differences were observed in sex or type of procedure (diagnostic or intervention) between both groups. Primary success rate was 94.8%, and access crossover was required only in 47 patients (5.2%), all in the RRA group (36 patients were changed to femoral access, 10 to LRA and 1 to right cubital access). Percutaneous coronary intervention (PCI) was performed in 352 patients (39.7%). Mean fluoroscopy time showed a trend to be shorter in RRA group (11.22 ± 9.8 min vs 12.89 ± 10.04 min, $p=0.09$), while the volume of contrast was significantly lower in the RRA group (132.9 ± 78.1 ml vs 153.2 ± 68.36 ml, $p=0.008$). When coronary angiography and PCI were evaluated independently, fluoroscopy time was similar in diagnostic procedures (RRA 7.7 ± 6.7 min, LRA 8.8 ± 4.5 min, $p=0.23$) but the volume of contrast was significantly lower in the RRA group (99.2 ± 53.9 ml vs 122.1 ± 51.4 ml, $p=0.01$). PCI patients showed no significant differences either in fluoroscopy times (RRA 17.1 ± 11.4 min, LRA 17.8 ± 12.4 min, $p=0.72$) or in volume of contrast (RRA 189.9 ± 79.8 ml, LRA 190.2 ± 67.7 ml, $p=0.98$).

Conclusions: In this series of elderly patients, transradial access success rate was high, suggesting that radial access is safe and feasible in daily practice in patients ≥ 80 years. LRA approach was not associated with a significant reduction in fluoroscopy time compared to the RRA approach (even showed a trend to longer times). LRA also showed a statistically significant higher use of contrast volume.

P1600 | BEDSIDE

Revascularisation did not improve short and medium term mortality in the elderly suffering from cardiogenic shock complicating an acute myocardial infarction: a meta-analysis

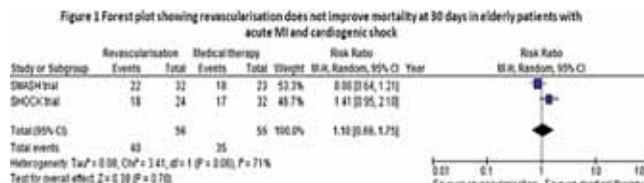
M. Waleed¹, A. Raza², K.Y.-K. Wong¹. ¹Castle Hill Hospital, Department of Cardiology, Hull, United Kingdom; ²Diana Princess of Wales Hospital, Grimsby, North East Lincolnshire, DN332B, Department of Cardiology, Grimsby, United Kingdom

Purpose: To test the hypothesis that revascularisation improves mortality in elderly patients with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS).

Methods: A systematic review was performed identifying all randomised controlled trials about revascularisation improves mortality after AMI complicated by CS, when compared with medical therapy. The eligible trials were entered into the RevMan 5 software package. For dichotomous data, the risk ratio and 95% confidence intervals were calculated. We tested for heterogeneity with the chi-squared statistic, which was considered to be significant at $p < 0.10$. Thus the results from

the trials were pooled using the random effects model to allow generalisation of the results. Z tests were used to assess the overall effect.

Results: Two eligible studies were found including a total of 111 patients (SHOCK and SMASH). 40 of 56 patients (71.4%) died within 30 days following revascularisation, compared with 35 of 55 (63.6%) who received medical therapy only [Risk ratio=1.10, 95% CI 0.69-1.75]. [Figure 1]. In the medium term, 42 of 56 (75%) died following revascularisation. This compares with 37 of 55 (67.2%) in the medically treated group. [Risk ratio=1.09, 95% CI 0.68-1.76]. In SHOCK trial, there was published data in patients aged ≥ 75 , whereas in SMASH trial, we were only able to obtain data on patients aged 65 ± 9 . But even taking into account the slightly younger cohort in SMASH trial, revascularisation did not appear to improve mortality. Definition of medium term differs slightly between the trials as we were only able to obtain 6-month mortality data in the SHOCK trial, and mortality up to 1 year in the SMASH trial.



Conclusions: Revascularisation did not improve mortality in the elderly suffering from CS complicating an AMI.

P1601 | BEDSIDE

Statin dosage and major adverse cardiovascular events after coronary angioplasty

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Aim: Evaluation of MACE incidence, inflammation and endothelium injury markers under the postprocedural statin administration in different doses.

Material and methods: 88 patients exposed to PCI have been randomized in 2 groups due to statin postprocedural administrating dose: I - simvastatin 80 mg/day 1 month period following by 20 mg/day during 11 months; II - simvastatin 20 mg/day during 12 months. Incidence of MACE (myocardial infarction, stroke, unstable angina, in-stent restenosis and in-stent thrombosis) has been evaluated upon of 1 year surveillance. The circulating markers of inflammation and endothelium injury (hs-CRP, TNF-alpha, IL-6, NO and PLA2 (phospholipase A2)) were determined using ELISA and PLAC-Test preprocedurally and after PCI: 72 hours, 1, 3, 6 and 12 months.

Results: In I-st group the MACE incidence per one year was significantly lower compared to II-nd: 27.27% (12 pts) vs 38.64% (17 pts). Notable, that in I-st group no cases of in-stent restenosis were established. In the period of 72 hours after PCI has been established a significant rise of hs-CRP, TNF-alpha, IL-6, and PLA2 in both groups while the NO plasma concentration decreased. However, even in this short period the markers of I-st group shown an attenuated inflammatory response: hs-CRP (6.86 ± 0.24 vs 7.73 ± 0.29 g/L), TNF-alpha (6.52 ± 0.28 vs 7.22 ± 0.27 pg/ml), IL-6 (5.46 ± 0.12 vs 6.53 ± 0.18 pg/ml; $p < 0.05$), PLA2 (341 ± 21 vs 429 ± 29 nm/ml; $p < 0.05$), NO (58.85 ± 2.8 vs 49.25 ± 2.8 microM/L). At the period of 1 month after PCI the markers improved in both groups, but more evident in I-st, and due to this reason they all significantly differed from II-nd group, especially PLA2 level (238 ± 16 vs 349 ± 22 nm/ml; $p < 0.01$). At distance of 3 months the markers have achieved preprocedural level only in I-st group, and after 6 months in II-nd group too. Remarkably, that during period 6-12 months the marker re-dressing dynamics was more rigid in II-nd group leading after 1 year to a conspicuous discrepancy (I vs II) of hs-CRP (3.17 ± 0.12 vs 4.85 ± 0.16 g/L; $p < 0.01$) and TNF-alpha (4.11 ± 0.23 vs 5.32 ± 0.25 pg/ml; $p < 0.01$).

Conclusions: (1) Postprocedural statin administration in high (aggressive) dose, 80 mg/day during 1 month, had a beneficial action on MACE evolution after PCI, reducing their incidence upon 1 year surveillance compared to statin dosage 20 mg/day from 38.64 to 27.27%. (2) High dose statin administration led to a more attenuated inflammatory response and endothelial injury after PCI confirmed by dynamics of postprocedural circulating levels of hs-CRP, TNF-alpha, IL-6, NO and PLA2.

CARDIOGENIC SHOCK, MECHANICAL SUPPORT AND CARDIAC SURGERY

P1603 | BEDSIDE

Extracorporeal life support in patients with refractory in-hospital cardiac arrest improves short-term and long-term survival

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Background: Cardiopulmonary resuscitation (CPR) is associated with low suc-

cess rates and variable survival outcome. Extracorporeal life support as an adjunct to CPR (ECPR) has shown encouraging survival rates in patients with refractory in-hospital cardiac arrest (IHCA). However, there is little information about the benefit of the procedure compared with conventional CPR (CCPR). The aim of this study was to compare the survival of patients receiving CCPR to that of patients with ECPR.

Methods: A total of 272 patients with witnessed IHCA of cardiac origin who had undergone CCPR and 52 patients with ECPR were included in this retrospective, propensity score-adjusted (1:1 matched), single-centre cohort study. All data were taken from hospital records. Routine laboratory parameters were measured at the time of admission and immediately after CPR and during post-IHCA care using standardised methods. The main endpoints were survival at 30 days, long-term survival, and neurological outcome defined by the Cerebral Performance Categories (CPC) score.

Results: The median follow-up duration after hospital discharge was 1136 days (IQR 823-1416). Unmatched patients with CCPR showed a tendency for better long-term survival over ECPR (37.5% vs. 23.1%; $p=0.15$). In the unmatched groups patients with ECPR had significantly higher initial APACHE II scores (20 (IQR 17.8-22.0) vs. 16 (IQR 12.5-19.0); $p=0.003$), increased dosage of norepinephrine (0.17 mcg/kg/min (IQR 0.06-0.65) vs. 0.09 mcg/kg/min (IQR 0.04-0.17); $p=0.003$), and significantly elevated levels of creatine kinase (CK) (431 U/l (IQR 246-1271) vs. 143 U/l (IQR 96-426); $p<0.0001$), CK-MB (67 U/l (IQR 32-149) vs. 41 U/l (IQR 25-84); $p<0.0001$), creatinine (1.7 mg/dl (IQR 1.03-3.0) vs. 1.16 mg/dl (IQR 0.88-1.67); $p=0.041$), and lactate (3.6 mmol/l (IQR 1.59-8.4) vs. 2.02 mmol/l (IQR 1.24-4.02); $p=0.02$) before CPR compared to CCPR. After equalizing these parameters significant differences were observed in short-term and long-term survival favouring ECPR over CCPR (27% vs. 17%; $p=0.01$ (short-term) and 23.1% vs. 11.5%; $p=0.008$ (long-term); hazard ratio [HR] 0.59 95% CI 0.39-0.91; $p=0.02$). There was no significant difference in CPC score between the groups (CCPR 1 (IQR 1-2) vs. ECPR 1.5 (IQR 1-3); $p=0.77$). The rate of refractory cardiogenic shock as a cause of in-hospital mortality was significantly higher in the CCPR group compared with the ECPR group (67.3% vs. 40.4%; $p=0.01$).

Conclusion: In our cohort study ECPR had short-term and long-term survival benefits over CCPR in patients with witnessed in-hospital cardiac arrest of cardiac origin.

P1604 | BENCH

Mechanically unloading the left ventricle and delaying coronary reperfusion limits myocardial infarct size

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Contemporary management of an acute myocardial infarction (AMI) focuses on restoring oxygen supply to limit myocardial damage. Recent data shows that more rapid coronary reperfusion fails to improve survival after AMI. The Impella CP axial-flow pump (Abiomed Inc) is designed to reduce left ventricular stroke work (LVSW). We tested the hypothesis that first reducing myocardial work and delaying coronary reperfusion improves myocardial salvage.

Methods: Left anterior descending artery (LAD) occlusion was induced by angioplasty for 90 minutes in 50kg male Yorkshire swine ($n=5$ /group). LV pressure-volume loop analysis was performed in all animals. In Group 1, the LAD was reperfused for 120 minutes. In Group 2, after 90 minutes of ischemia the Impella CP device was activated and the LAD left occluded for an additional 60 minutes (150 minutes of LAD occlusion total), followed by 120 minutes of reperfusion. The Impella CP was active throughout reperfusion.

Results: Compared to Group 1, Group 2 had reduced LVSW (1223+337 vs 504+389, $p=0.03$), LV end-diastolic volume (202+15 vs 125+38, $p<0.01$), and LV end-diastolic pressure (17+4 vs 8+4, $p=0.01$) after reperfusion (Fig. 1A). After protocol completion, hearts were perfused with Evans blue dye to calculate the area at risk (AAR), then counterstained with triphenyltetrazolium chloride to quantify infarct size. Compared to Group 1, the percent myocardial infarct size compared to the AAR was reduced in Group 2 (73+13% vs 42+15% $p=0.02$; Fig. 1B).

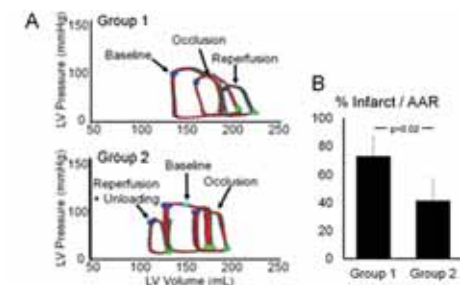


Figure 1

Conclusion: In contrast to the paradigm of primary PCI, we report the potential benefit of primarily unloading the heart with an axial-flow catheter and delaying coronary reperfusion to salvage myocardium in AMI. This is the first report to examine the potential utility of the Impella CP in myocardial salvage.

P1605 | BEDSIDE

Patients supported with left ventricular assist device as bridge-to-transplantation indication show an excellent outcome at 2 years compared with heart transplanted patients - single centre experience

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Background: Donor shortage and their ageing limit the availability and the probability of success of heart transplantation (HTx). One-year probability of survival in HTx candidates receiving a left ventricular assist device (LVAD) as a bridge to transplantation (BTT) is currently 85%, with a transplant rate of 25-40%. The aim of this study is to compare the mid-term outcome of HTx and LVAD in HTx candidates.

Methods: We considered 272 consecutive adult patients (pts) treated from 1/2006 to 2/2014. One- and 2-year survivals were evaluated according to first operation. Survival after LVAD implant was evaluated in the entire cohort ($n=72$), then excluding patients with a destination therapy (DT) indication ($n=19$, 26%), and finally in those classified as BTT at the time of operation ($n=31$; 43%), and compared with patients undergoing directly HTx ($n=200$). Patients were censored at 2-years, at the last visit, at the time of death, or at the time of HTx.

Results: Early death (30 days) rate was 11% vs. 10% in pts undergoing LVAD or HTx ($p=0.82$). One- and 2-year survival estimated by Kaplan Meier curves was also not significantly different (79.2% vs. 83.5% - hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.73-2.46, $p=0.35$ at 1 year; 75.0% vs. 81.5% - HR 1.57, 95%CI 0.88-2.78, $p=0.13$ at 2 years, in pts undergoing LVAD or HTx respectively). In LVAD pts with BTT indication, 30-days mortality was 0 ($p=0.08$ vs. HTx), and also 1- and 2- year survivals (96.8% and 83.5% vs. 83.5% and 81.5% respectively) were non significantly superior with respect to HTx (HR 0.19, 95%CI 0.03-1.36, $p=0.10$; HR 0.35, 95%CI 0.08-1.45, $p=0.15$ at 1 and 2 years respectively). Of note, only 4/31 (12.9%) and 9/31 (29%) received HTx within one and two years respectively. When excluding DT patients, intermediate results were observed in the remaining LVAD pts ($n=53$, with a 5.6% of peri-operative deaths) vs. HTx cohort: 1- and 2- year survivals (88.7% and 84.9% vs. 83.5% and 81.5% respectively) were non significantly superior compared with HTx (HR 0.70, 95%CI 0.29-1.66, $p=0.42$; HR 0.89, 95%CI 0.41-1.90, $p=0.75$ at 1 and 2 years respectively).

Conclusions: LVAD provides excellent medium term (2 years) outcome in patients deemed suitable for HTx; considerations regarding quality of life and long-term survival should guide our policies regarding timing of LVAD implantation and priorities for donor allocation.

P1606 | BEDSIDE

Hospital volume has significant impact on mortality with cardiogenic shock patients who are in need of mechanical circulatory support

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Purpose: Despite the technical advances in cardiology, cardiogenic shock as a complication of acute myocardial infarction (AMI) remains an unresolved medical challenge. Therapeutic guideline of mechanical circulatory support has not yet been established; initiating and terminating mechanical support is solely based on experiences of each individual hospital. However, data are lacking on the association between hospital experience and outcomes of mechanical support. We therefore investigated the relationship between hospital volume and mortality of mechanical support using a national inpatient database.

Methods: Using the Japanese Diagnosis Procedure Combination database between 2007 and 2013, we extracted AMI patients who underwent mechanical circulatory support (ventricular assist device, extracorporeal membrane oxygenation, and intra-aortic balloon counterpulsation). We performed multilevel logistic regression analyses fitted with generalized estimating equations because the data were clustered within hospital. Hospital volumes were categorized into tertiles (low-, 1-11 per year; medium-, 12-21; and high-volume, ≥ 22). The outcome was 30-day all-cause mortality. Predictor variables were age, gender, smoking habit, Killip class at admission, ventilator support, type of mechanical circulatory support, prior history of stroke, location of infarction (anterior or non-anterior), pre-hospital dialysis status, academic hospital or not, and hospital volumes.

Results: Of the 159337 AMI patients, 23679 underwent mechanical support. 4831 patients (20.4%) died within 30 days after admission. Compared to the low-volume group, the odds ratios of 30-day mortality for medium- and high-volume groups were 0.68 [95% confidence interval, 0.60-0.78], 0.80 [0.71-0.91], respectively. Higher age, female gender, higher Killip class, Patients with ventilator support, those with extracorporeal membrane oxygenation, those on dialysis and those hospitalized at non-academic hospitals were likely to die.

Conclusions: Hospital volume had a significant impact on 30 day all-cause mortality of AMI patients who were in need of mechanical supports. Policymakers need to consider hospital experiences when developing strategies to improve access to primary angioplasty of AMI patients.

P1607 | BEDSIDE**Impact of a mechanical circulatory support program in the survival of patients with cardiogenic shock due to an acute myocardial infarction that underwent primary angioplasty**

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Purpose: Primary angioplasty is the best reperfusion therapy for ST elevation myocardial infarction. Patients in cardiogenic shock benefit from mechanical reperfusion, but their mortality remains high even after the placement of an intra-aortic balloon. There is no clear information regarding whether an ongoing Mechanical Circulatory Support Program (MCSP) might improve the long term outcome of these patients. We have analyzed the clinical impact of a MCSP in this setting.

Methods: We have compared the in-hospital and 1 year survival of patients in cardiogenic shock in the setting of a primary angioplasty with inserted intra-aortic balloon in two different periods of time. The first period before and the second after the implantation in our hospital of a MCSP. This program included the incorporation of a specially trained staff and the availability of the extracorporeal membrane oxygenation device (ECMO) and the left ventricular or biventricular assist devices (LVAD, biVAD). Following inclusion criteria required: STEMI, cardiogenic shock by clinical and hemodynamic data, primary angioplasty and intra-aortic balloon inserted. Patients with cardiogenic shock due to mechanical complications were excluded.

Results: We included 42 consecutive patients in the first period "pre-MCSP" and 56 in the second period "post-MCSP". Clinical baseline characteristics were very similar in both groups except for a wider use of drug eluting stents in the second period (19% vs 40%; $p=0.03$). In the "post-MCSP" group 9 (16%) patients needed an ECMO and 8 (14.3%) a ventricular assist device. Six patients were included in the cardiac transplant list in the "pre-MCSP" group and four in the "post-MCSP" group. Three patients in each group finally underwent a cardiac transplant. In-hospital survival was 49.9% in the "pre-MCSP" group compared to 67.2% in the "post-MCSP" group ($p=0.03$). The 12 months survival was 39.8% in the "pre-MCSP" group vs. 59.5% in the "post-MCSP" group ($p=0.03$). The multivariate logistic regression revealed a higher risk of death in the "pre-MCSP" period (HR 2.5; CI 95% 1.04-7.5; $p=0.03$).

Conclusions: The implementation of a mechanical circulatory support program improves significantly the prognosis of patients in cardiogenic shock in the setting of a primary angioplasty.

P1608 | BEDSIDE**Extracorporeal membrane oxygenation (ECMO) therapy for acute respiratory failure increases platelet-monocyte and platelet-neutrophil complex formation within 24 hours after initiation of therapy**

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Background: Anticoagulation management in ECMO therapy is challenging since bleeding complications are known to be associated with this therapy. However, the underlying disease and the ECMO system have an impact on coagulation. We hypothesized that platelet reactivity assessed by platelet-monocyte (PMC) and platelet-neutrophil complex (PNC) formation is a read-out and could serve as a potential therapeutic target to decrease bleeding events.

Methods: Patients with acute respiratory failure requiring extracorporeal membrane oxygenation were subsequently included in a single center prospective study. Patients on treatment with antiplatelet drugs were excluded. Blood samples collected immediately before initiation of extracorporeal circulation and at 24 and 48 hours were used to assess PMC- and PNC-formation by flow cytometry via a CD41/CD45/CD14 or CD15 gating strategy. Platelet activation was assessed by P-selectin expression and binding of the GPIIb/IIIa activation-specific antibody PAC-1.

Results: We included 12 patients (17% female, 83% male) with a mean age of 59 ± 12 years and a mean time with extracorporeal circulation of 4.3 days. On-therapy mortality was 33%, bleeding events occurred in 38% of the cases. A significant increase in ADP-induced PMC-formation was observed after 24 hours on extracorporeal circulation from a mean of 6.1% to 43.6% ($p=0.046$). ADP-induced PNC formation was also significantly increased at 24 hours from a mean of 4.9% to 26.8% ($p=0.048$). Leukocyte count was unaffected, platelet count decreased over time. PAC-1 binding to the platelets increased from 0–72 hours.

Conclusion: Platelet reactivity is significantly increased upon initiation of extracorporeal circulation leading to increased platelet reactivity and platelet-leukocyte complex formation. Therapeutic approaches to reduce platelet reactivity could therefore offer a novel concept to prevent bleeding complications associated with ECMO therapy.

P1609 | BEDSIDE**Impact of models for end-stage liver disease score on outcome in patients with percutaneous extracorporeal membrane oxygenation who are scheduled to receive ventricular assist device implantation as "bridge to bridge" therapy**

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Purpose: Models for end-stage liver disease (MELD) score, an objective index for assessing end organ function such as liver and kidney, has been recently found to be useful in predicting the prognosis of patients with heart failure. In this study, we tried to elucidate the prognostic values of MELD score in patients with severe hemodynamic instability supported by percutaneous extracorporeal membrane oxygenation (p-ECMO) who were scheduled to receive ventricular assist device (VAD) implantation as "bridge to bridge" therapy.

Methods: We retrospectively reviewed consecutive 131 patients who underwent VAD implantation at the National Cerebral and Cardiovascular Center from April 2001 to December 2013. Patients who received p-ECMO insertion prior to VAD implantation were analyzed in more detail from their clinical characteristics and they were stratified according to their MELD score that were calculated just before their VAD implantation.

Results: During the study period, 30 patients (mean age 32.2 ± 11.1 years, 20 males) received p-ECMO insertion prior to VAD implantation. These 30 patients underwent paracorporeal VAD implantation and demonstrated significantly lower survival rates during their VAD support period compared to those without p-ECMO insertion prior to VAD implantation (2-year survival rate, 66.2% vs 82.7% respectively, $p=0.0015$, log-rank test). Of these 30 patients, 8 patients were successfully bridged to heart transplantation, whereas 13 patients died. Five patients were successfully weaned from VAD and 4 patients have been still supported by VAD at the end of study period. Univariate cox proportional hazard model demonstrated that MELD score significantly predict poor prognosis during their VAD support period (hazard ratio, 1.08; 95% confidence interval, 1.02-1.15; $p=0.0093$). Kaplan-Meier analysis revealed that a MELD score 18 or higher (high MELD group) was a strong predictor of mortality during their VAD support period ($p=0.0015$, log-rank test). Clinical characteristics prior to VAD implantation were compared between patients with MELD score less than 18 and those in high MELD group and diastolic dimension of left ventricle was significantly small in patients with high MELD group (68.0 ± 13.6 mm vs 73.1 ± 8.4 mm, $p=0.0456$).

Conclusions: Preoperative p-ECMO support itself was the risk factor for following VAD implantation. However, end organ function calculated by MELD score have potential to predict the prognosis in patients with p-ECMO who are scheduled to receive VAD implantation.

P1610 | BEDSIDE**Effect of intra-aortic balloon counterpulsation on short-term survival in cardiogenic shock**

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Purpose: Although current guidelines recommend intraaortic balloon counterpulsation (IABP) treatment in cardiogenic shock complicating acute myocardial infarction a recent controlled randomized trial (IABP-SHOCK II) detected no survival benefit among patients treated with IABP. However, subgroup analysis revealed a near-significant interaction between IABP and age.

Methods: We extracted data for all consecutive patients with cardiogenic shock undergoing percutaneous coronary intervention (PCI) between 2004 and 2013 from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) for five hospitals in western Sweden. Logistic regression adjusted for propensity score were used to compare the groups in regard to 30-days mortality. Analyses were performed with complete data and using multiple imputation method. Background characteristics and procedural data were used to calculate propensity score.

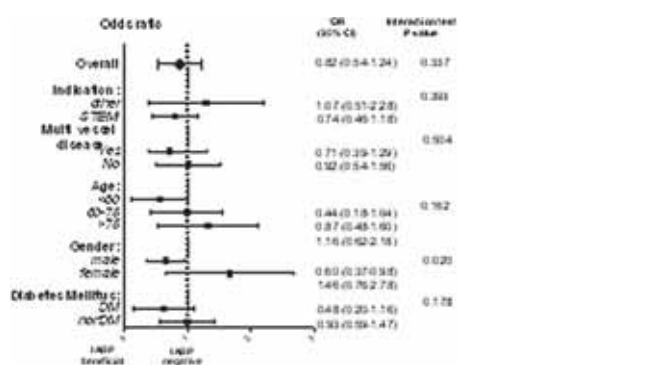


Figure 1

Results: 554 consecutive patients presented with ST-elevation and CS between 2004 and 2013.

297 patients were treated with IABP whereas 243 patients were not. Data on IABP treatment was missing for 14 patients. After adjustment with propensity score, the baseline characteristics of the two groups were well balanced. Treatment with IABP was not associated with significantly lower 30-days mortality in adjusted complete case analyses or imputed models. However, subgroup analyses revealed significant interactions between the effect of IABP treatment and patient age as well as gender ($p < 0.05$).

Conclusions: IABP during primary PCI in patients with CS was not associated with a more favorable outcome as compared with primary PCI without IABP. However, the effect of IABP treatment appear to be dependent on patient age and gender. Males and younger patients had better effect of IABP treatment.

P1611 | BEDSIDE

Application of the heartmate II risk score in patients with heartware left ventricular assist device

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Purpose: The ability to assess risk of mortality in patients undergoing insertion of Left Ventricular Assist Device (LVAD) is important in ensuring appropriate patient selection. This study sought to assess the validity of utilising the Heartmate II Risk Score (HMRS) in the Heartware LVAD population.

Methods: We retrospectively reviewed all patients ($n=75$) undergoing insertion of a Heartware LVAD at our centre from 2007 onwards. Pre-operative measurement (age, albumin, creatinine and INR) were collected, and risk scores were calculated using the HMRS calculation. The endpoints for the study were 90-day mortality, 1-year mortality, and 1-year transplant free survival.

Results: Of the 75 patients, 37 (49.3%) were classified as low risk, 28 (37.3%) medium risk and 10 (13.3%) high risk. Of the four measures collected, only pre-implant Albumin was a predictor of mortality (3.46 ± 0.07 mg/dL vs 2.95 ± 0.17 g/dL, $p=0.02$). Overall 90-day mortality was 9.3%, and similar across all three groups (Low Risk = 8.1%, Medium Risk = 10.7%, High Risk = 10%). 1-Year Mortality was 21.3%, and was also similar between the three groups (Low Risk = 18.9%, Medium Risk = 25%, High Risk = 20%). Overall 1-year transplant free survival was 50.6%, with a non-significant difference between the Low Risk and High Risk Groups (48% vs 60%, $p=0.39$).

Conclusions: In this small cohort, the Heartmate II Risk score is not predictive of 90-day or 1-year mortality in this Heartware population, although overall the mortality rates are significantly lower in this study population than in the initial HMRS derivation cohort.

P1612 | BEDSIDE

Risk of bleeding after coronary artery bypass grafting according to body mass index. A nationwide cohort study

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Purpose: The obesity paradox has been proposed to influence outcome after Coronary Artery Bypass Grafting (CABG). Previous studies have found a J-shaped relationship between risk of both bleedings and adverse cardiovascular outcomes and Body Mass Index (BMI). We conducted a study to investigate bleeding risk among CABG patients according to BMI in a nationwide cohort.

Methods: We included CABG patients >30 years admitted 2006-2011. Patients were followed for 1 year. Information on comorbidity and concomitant medication was identified by individual-level linkage of administrative registers. Patients were divided into weight classes according to WHO criteria. Hazard ratios (HRs) on 1) Fatal or non-fatal bleedings, requiring hospitalization and 2) Recurrent myocardial infarction, ischemic stroke or cardiovascular was assessed by Cox proportional Hazard Model, adjusted for age, gender, inclusion year, comorbidity, medication, previous bleeding, alcoholism & Euroscore, with normal weight ($18.5 < \text{BMI} < 25$) as reference.

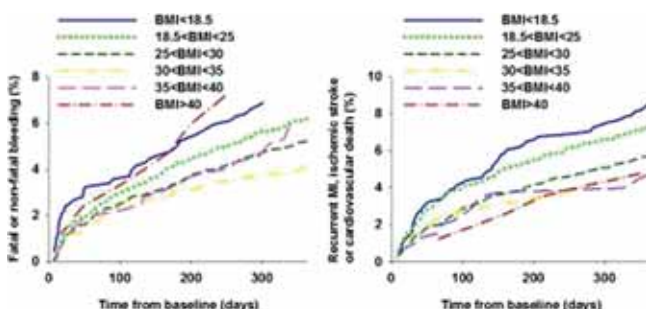


Figure 1. Kaplan Meier analyses.

Results: A total of 9542 patients (mean age 68 SD 12, 79% male) were included. Underweight patients ($\text{BMI} < 18.5$) and Obese Class III patients ($\text{BMI} > 40$) had the most bleedings within weight class (6.74% and 7.14%, respectively). Patients in Obese Class I ($30 < \text{BMI} < 35$) had significantly less risk of bleeding (HR: 0.7, 95%CI: 0.6-0.9, $P=0.027$). Overweight ($25 < \text{BMI} < 30$) and Obese Class I patients had significantly less risk of cardiovascular events (HR: 0.8, 95%CI: 0.6-0.9, $P=0.016$ and HR: 0.7, 95%CI: 0.5-0.9, $P=0.004$, respectively).

Conclusion: Obese Class I patients were less prone to bleed and Obese Class I and overweight patients had lesser risk of cardiovascular events after CABG. Our results concur with previous findings on the obesity paradox.

P1613 | BEDSIDE

Arterial closure devices in minimally invasive heart surgery

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Background: Arterial closure devices (ACDs) were introduced to replace standard compression at the puncture site following percutaneous intervention. They also allow percutaneous placement of larger cannulas. To date there is no published evidence on the use of such devices during minimally invasive cardiac surgery (MICS), where cannulation through the femoral vessels is necessary. We report our results comparing the use of ACDs with conventional surgical closure of vascular access on patients undergoing MICS.

Methods: We analyzed retrospectively 167 consecutive patients, who underwent minimally invasive cardiac surgery with groin cannulation between 9/2010 and 4/2013. Operative procedures included mitral valve repair/replacement, tricuspid valve repair/replacement, ASD closures and myxoma excisions. Of these, 89 (53%) had closure of vascular access through the use of ACD.

Results: Except for a higher incidence of endocarditis in the ACD group (10 vs 2, $p=ns$) there were no significant differences between preoperative characteristics of both groups. There was also no significant difference between groups with regard to procedure characteristics including cardiopulmonary bypass duration (133 ± 41 min) or cannula size used (19 ± 1 fr). Overall 30 day mortality was 2.39% and not different between groups. Complications at the cannulation site consisted of fistulae ($n=2$), wound infections ($n=2$) and hemotoma ($n=1$). All of them occurred in the conventional group. There was no difference in length of hospital stay or days-to-mobilization.

Conclusions: Our results indicate a benefit for ACDs in MICS, although the number of events was low in both groups. The results justify the conduct of a prospective randomized trial.

P1614 | BEDSIDE

Incidence and outcome of surgical procedures after coronary artery bypass grafting compared with those after percutaneous coronary intervention

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Background: Non-cardiac surgery after percutaneous coronary intervention (PCI) has been reported to be carrying high risk for both ischemic and bleeding complications. However, there has been no report comparing the incidence and outcomes of surgical procedures after coronary artery bypass grafting (CABG) with those after PCI.

Methods and results: Among 14383 patients undergoing first coronary revascularization (PCI: $N=12207$, and CABG: $N=2176$) enrolled in the CREDO-Kyoto registry cohort-2, surgical procedures were performed more frequently after CABG ($N=560$) than after PCI ($N=2398$) (cumulative incidence at 3-year: 27% versus 22%, $P < 0.0001$), particularly within 6-month of coronary revascularization. The risk for the primary ischemic outcome measure (death/myocardial infarction) at 30-day post-surgical procedures was not significantly different between the CABG and PCI groups (cumulative incidence: 3.1% versus 3.2%, $P=0.9$, and adjusted hazard ratio [HR]: 0.97, 95% confidence interval [CI]: 0.47-1.89, $P=0.9$). The risk for the primary bleeding outcome measure (moderate or severe bleeding by GUSTO classification) was lower in the CABG groups than in the PCI group (cumulative incidence: 1.3% versus 2.6%, $P=0.07$, and HR: 0.36, 95%CI: 0.12-0.87, $P=0.02$). There were no interactions between the timing of surgery and the types of coronary revascularization modalities (CABG/PCI) for both the ischemic and bleeding outcomes.

Conclusions: Surgical procedures were performed significantly more frequently after CABG than after PCI, particularly within 6 months after coronary revascularization. Surgical procedures after CABG as compared with those after PCI were associated with similar risk for ischemic events and lower risk for bleeding events, regardless of the timing after coronary revascularization.

DISEASE OF THE AORTA AND MEDICAL THERAPY

P1616 | BEDSIDE

The incidence and risk factors of acute kidney injury in type A acute aortic dissection

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Purpose: Acute kidney injury (AKI) after cardiothoracic surgery for acute aortic dissection (AAD) is relatively common and increases mortality. However, there are few data on the incidence and risk factors of AKI in AAD patients, as well as the impact of AKI on in-hospital mortality. In the present study, we investigated the incidence and risk factors of AKI in AAD patients.

Methods: 416 consecutive patients diagnosed as AAD (Stanford classification type A) at our institute (a 320-bed, tertiary-level heart center) between October 2006 and March 2013 were analyzed retrospectively. AKI was defined by RIFLE criteria, which is based on serum creatinine or glomerular filtration rate. Multivariate logistic regression analysis was performed to evaluate the attributable risk of AKI on in-hospital mortality. Stepwise cox proportional hazards analysis was also performed to identify independent predictors of AKI.

Results: Among the 416 patients, 392 patients (94.2%) received emergent surgical procedures, involved the ascending aorta (59.4%), aortic arch (38.0%), aortic valve (12.5%). The overall in-hospital mortality was 6.3%, and the incidence of AKI was 44.4%. The independent risk factors of AKI were coronary ostial involvement, congestive heart failure, syncope episode before admission, radiographic finding of renal malperfusion and longer cardiopulmonary bypass duration. In multivariate analysis, AKI was significantly associated with in-hospital mortality (HR 2.40 [95%CI 1.26~4.56], $p=0.007$) after adjustment of other clinical factors including age, gender, obesity, hemodynamic instability, neurological deficit before operation, coronary ostial involvement and longer cardiopulmonary bypass duration. Kaplan-Meier analysis also showed that the in-hospital mortality was strongly correlated with the severity of AKI by RIFLE criteria.

Conclusions: Acute kidney injury was common in the patients with type A acute aortic dissection. Since it was a strong predictor of in-hospital mortality, AKI should be taken into consideration in the perioperative period.

P1617 | BEDSIDE

The impact of acute kidney injury on long-term prognosis of type A acute aortic dissection

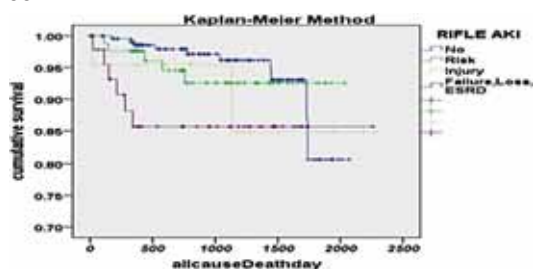
A. Sato¹, M. Higashitani¹, T. Ko¹, T. Tobaru¹, H. Aramoto², T. Fukui², M. Takayama¹, S. Takanashi², T. Sumiyoshi¹, H. Tomoike¹. ¹Sakakibara Heart Institute, Cardiology, Tokyo, ²Sakakibara Heart Institute, Cardiovascular Surgery, Tokyo, Japan

Purpose: Acute aortic dissection (AAD) is the most common catastrophic event affecting the aorta, and surgical treatment is an option for type A and complicated type B. It has been reported that acute kidney injury (AKI) is an independent outcome predictor in patients with cardiothoracic surgery. However, few data were reported about the impact of AKI on long-term prognosis in patients undergoing surgical treatment for AAD.

Methods: We examined 375 consecutive patients who underwent open surgery for Type A AAD between October 2007 and March 2013 at our hospital retrospectively. Cox regression analysis was performed to reveal the relationship between the risk of major adverse cardiac and cerebrovascular event after discharge (MACCE: death, non fatal MI, stroke) and perioperative AKI. AKI was defined by RIFLE criteria, which is based on serum creatinine or glomerular filtration rate.

Results: AKI is significantly associated with MACCE ($P=0.007$) and overall mortality ($P=0.021$).

Kaplan-Meier analysis of patients in each grade of AKI during hospitalization (risk, injury, failure&Loss&ESRD) revealed well correlation with the long-term prognosis.



Conclusions: We suggest an association between the grade of acute kidney injury and MACCE and long-term mortality in patients undergoing open surgical therapy for Type A acute aortic dissection. Acute kidney injury in hospital can be predictive indicator for prognosis of Type A acute aortic dissection from date of hospital discharge.

P1618 | BEDSIDE

Impact of development of localized dissection on clinical outcomes in acute phase of type B aortic syndromes

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Background: Aortic guidelines recommend a similar treatment in Type B aortic dissection (AD) and intramural haematoma (IMH) in patients with the same clinical risk. However, the differences in prognosis in a short-term follow-up depending on the morphological changes in the acute phase of each entity remain unknown.

Objectives: To compare morbidity and mortality of type B AD vs IMH with and without development of Localized Dissection (LD) in acute phase in short-term follow-up.

Methods: 171 patients, 86 (50%) IMH without LD (Fig. 1A), 5 (3%) IMH with LD (Fig. 1B) and 80 (47%) AD (Fig. 1C), were included prospectively in a clinical and imaging protocol. Aortic and overall mortality, surgical interventions and visceral ischaemia were collected to evaluate the clinical prognosis. LD was defined as a localized blood-filled pouch in the damaged aortic wall with a communicating orifice >3mm with periaortic haematoma associated.

Results: Patients with IMH and LD were older ($p<0.001$) and presented a higher basal maximum aortic diameter (MAD) at diagnosis (IMH with LD: 55.6 ± 12.7 , IMH without LD: 41.5 ± 8.3 , AD: 41.1 ± 8.8 mm; $p=0.02$). During the hospitalization, IMH with LD cases showed a higher overall mortality ($p<0.001$), due to the higher aortic mortality ($p<0.001$), and a higher number of cases treated invasively ($p<0.001$). A multivariate logistic regression analysis, including age and MAD, indicated the development of LD as the only independent predictive factor of aortic mortality in type B acute aortic syndromes (AAS) (OR=17.5; CI 95%=3.4-90.4).

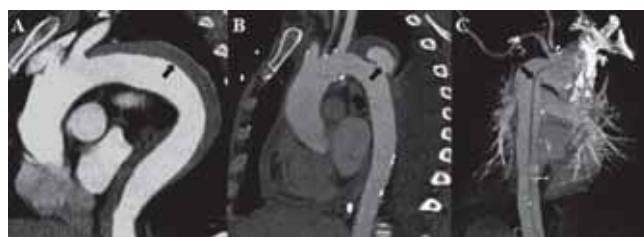


Figure 1

Conclusions: Development of LD in Type B IMH implied a higher risk of aortic complications in short-term follow-up than other AAS, independently of MAD and age. More aggressive management in this subgroup of patients is advisable if they share the same clinical conditions.

P1619 | BENCH

Prediction of cardiac and vascular events in systemic sclerosis: input from Endothelin-1 type A receptor antibodies

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Background: Cardiac and peripheral microvascular alterations are key features of systemic sclerosis (SSc). We have previously reported that angiogenic markers can predict the cardiovascular outcomes in SSc. In parallel, a cross-sectional study reported an association between severe cardiovascular complications and functional antibodies against angiotensin II type 1 receptor (AT1R) and Endothelin-1 type A receptor (ETAR).

Objective: Our aim was to investigate the respective merit of all these markers in a prospective cohort.

Methods: Serum levels of anti-AT1R and anti-ETAR autoantibodies, placenta growth factor (PIGF) and soluble vascular adhesion molecule (sVCAM) were measured with sandwich ELISA in a prospective cohort of 75 SSc patients. Circulating endothelial progenitor cells (EPCs) were quantified in peripheral blood by flow cytometry after cell sorting. The occurrence of at least one cardiac/vascular event was assessed during a planned 3-year follow-up by a composite index defined by the occurrence of at least one of the following event: a) one or more new ischemic digital ulcer (DU), b) pre-capillary pulmonary hypertension (PH) confirmed by right heart catheterization, c) left ventricular (LV) dysfunction, defined by a LV ejection fraction (EF) <50%, d) scleroderma renal crisis (SRC).

Results: The mean age of SSc patients (64 women) was 55 ± 12 year old and the mean disease duration was 9 ± 8 years at baseline. Twenty-eight patients developed at least one cardiac/vascular event (DU in 18, PH in 5, LV dysfunction in 4 and SRC in a single patient). By univariate analysis, high baseline serum levels of anti-ETAR were predictive of the occurrence of cardiac/vascular events ($p=0.002$), together with low EPC counts ($p=0.003$) and increased levels of PIGF ($p=0.0005$) and sVCAM ($p=0.009$). No predictive value of anti-AT1R antibodies was identified. Multivariate analysis confirmed high serum levels of anti-ETAR antibodies (hazard ratio, HR: 3.71, 95%CI 1.44-9.52, $p=0.03$) and PIGF (HR: 5.22, 95%CI

1.96-15.87) as independent predictors of further development of cardiac/vascular events. The combination of high serum levels of anti-ETAR antibodies and PIGF was highly predictive of cardiac and vascular events occurrence during follow-up (HR 7.27 95%CI 2.49-23.51, $P=0.0002$).

Conclusion: This study identifies for the first time anti-ETAR antibodies as an independent predictor of cardiac and vascular events in SSC. This functional antibody, together with other angiogenic markers and in particular PIGF, may serve as biomarkers to improve cardiovascular risk stratification and therefore allow earlier therapeutic intervention.

P1620 | BEDSIDE

Association of matrix metalloproteinase 2 and 9 genes single nucleotide polymorphisms with matrix metalloproteinase activity and thoracic aortic aneurysm development

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Objectives: Thoracic aortic aneurysm (TAA) is genetically heterogeneous disorder, characterized by extracellular matrix abnormalities. Matrix metalloproteinase (MMP) 2 and 9 play important role in aortic root dilatation. Purpose of this study was to identify genetic variants of single nucleotide polymorphisms (SNP) of MMP-2 and -9 genes associated with TAA.

Methods: Genomic DNA was isolated from blood of 251 pts with TAA (mean age 55.5 ± 10.3 , m:f ratio 2.8:1) and 227 controls (mean age 56.8 ± 9.4 , m:f ratio 1.8:1). Polymorphism -8202 A/G (rs11697325) of MMP9 and -735 C/T (rs2285053) analyzed using real time polymerase chain reaction. The activity and relative abundances of MMP-2,9 were assessed in aorta tissue samples from 27 TAA pts and 7 controls by quantitative immunoblotting techniques and substrate-specific zymographic analysis.

Results: Maximal aortic diameter was 54.5 ± 10.3 mm in pts with TAA. There weren't differences in genotypes between pts with bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV). Only 4 pts had family history of TAA. But 10% of pts had family history of sudden death (SD). The -735 C/T polymorphism (rs2285053) of MMP-2 gene was significantly associated with SD ($p=0.016$). We revealed a borderline statistical significance in the distribution of alleles, being C allele more frequent in patients with TAA. Aortic diameter was associated only with -8202 A/G (rs11697325) of MMP-9 gene ($p=0.02$). There was tendency to increase of latent and active tissue MMP-9 in patients with genotype AA of MMP-9 gene polymorphism -8202 A/G.

Clinical characteristic of the group

	TAA (M $\pm$ SD)	Control (M $\pm$ SD)
Age, years	55.5 ± 10.3	56.8 ± 9.4
Maximum aorta diameter, mm	54.5 ± 10.3	34.5 ± 3.7
M:F ratio	2.8:1	1.8:1

Conclusion: Specific genotypes of MMP-2 and -9 genes polymorphisms could be in part responsible for TAA development. Some genotypes of MMP-9 SNP are associated with greater dilatation of aorta. Genotyping of MMP-2 and -9 could be useful for estimating of non-modifiable risk factors in patients with TAA and also for relatives screening. Higher incidence of sudden death at a low frequency of family aneurysm can be explained by low detection of TAA.

P1621 | BENCH

Diagnostic and prognostic biomarker potential of miR-24 in abdominal aortic aneurysm disease and rupture

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MicroRNAs (miRNAs) have been identified as crucial posttranscriptional inhibitors of gene expression in response to stress and injury in cardiovascular disease (CVD) by regulating the expression levels of their target mRNAs. Lately, they have received much attention regarding their suitability and feasibility as biomarkers for CVD.

Aim was to explore the diagnostic and prognostic value of detecting circulating levels of miRNAs in abdominal aortic aneurysms (AAAs), a disease for which currently no established (protein) biomarker exists.

Using a PCR-based array platform, we profiled the 168 most abundant blood miRNAs in 20 plasma samples from AAA patients undergoing elective surgical repair vs. 20 samples from an age, risk factor, and medication matched screening cohort without aneurysm. We identified 12 miRNAs significantly altered in diseased patient samples as compared to controls. Next we investigated these 12 miRNAs in plasma (as well as in aortic tissue) from ApoE^{-/-} mice with angiotensinII (AngII)-infusion induced AAAs, to determine the potential prognostic value of miRNAs released into circulation. Indeed we were able to detect that the expression of 4 out of the 12 miRNAs (miR-126 and -668 both increased; miR-24 and -210 both decreased), was substantially altered in plasma samples from AAA mice immediately before rupture compared to mice with AAA that did not rupture for the remainder of study (28 days), as well as saline-infused controls. Using the AngII model, as well as a second mouse model of AAA disease, the porcine-pancreatic-elastase infusion model, we found that over-expression of miR-24 protects from

aneurysm progression (in the PPE model), as well as aortic rupture (in the AngII model) by repressing the expression of the gene chitinase3-like1 (Ch3l1), which regulates macrophage survival and cytokine release (from invading peritoneal macrophages) in expanding murine AAAs. Finally, the expression of miR-24 was significantly and substantially different in plasma samples from human patients with acutely ruptured AAAs ($n=7$) compared to patients with non-ruptured AAAs (abdominal aortic diameter between 55-78 mm; $n=7$) undergoing surgical repair, as well as un-diseased controls ($n=7$).

We explored the diagnostic and prognostic biomarker potential of miRNAs released into circulation during initiation, propagation, and ultimately rupture of AAA disease in mice and humans. The identification of miR-24 potentially offers great prognostic value to determine which patients present with increased risk of rapid AAA expansion and subsequent rupture.

P1622 | BEDSIDE

Neutrophil-lymphocyte ratio in acute aortic dissection

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Purpose: Acute aortic dissection (AAD) is a life-threatening disease. Neutrophil-lymphocyte ratio (NLR) is an index of systemic inflammation associated with increased cardiovascular mortality. We investigated NLR in a group of patients with AAD compared with patients with chronic aneurysms and a control group of healthy volunteers.

Methods: We evaluated pre-operative NLR, white cell blood count (WBC), platelets count (PLTs) C-reactive protein (CRP), D-dimer and cardiac enzymes in 120 consecutive patients with AAD admitted for emergency surgery (63 ± 14 years old, 89 men), 121 consecutive patients with chronic aneurysms of the ascending aorta admitted for elective repair (63 ± 11 years old, 90 men) and 121 healthy controls (63 ± 14 years old, 90 men).

Results: Levels of NLR, PLTs, WBC, CRP, D-dimer, creatine kinase (CPK), creatine kinase-MB (CK-MB) and troponin I (Tn-I) are expressed in median (interquartile range 25th-75th percentile) and are presented in Table. Patients with AAD had significantly higher elevated NLR, compared to chronic aneurysms and normal controls ($p < 0.001$). Significant associations were observed between NLR and D-dimer ($r=0.31$, $p=0.003$), CPK ($r=0.23$, $p=0.013$) and CK-MB ($r=0.26$, $p=0.005$) in patients with AAD.

Table 1. Levels of neutrophil-lymphocyte ratio, WBC, PLTs, CRP, D-dimer and cardiac enzymes in acute aortic dissection, uncomplicated chronic aortic aneurysms and normal controls

	Acute aortic dissection	Chronic aneurysms	Controls	P value
Neutrophil-lymphocyte ratio	10.1 (5.9, 14.3)	2.2 (1.7, 2.9)	2 (1.4, 3.1)	<0.001
White cell blood count, K/ μ l	12200 (10000, 16000)	7400 (6400, 8600)	7300 (6100, 8700)	<0.001
Platelets count, K/ μ l	187500 (148500, 219000)	222000 (187000, 251000)	222000 (190000, 259000)	<0.001
C-reactive protein, mg/l	8.6 (3, 19.8)	2.3 (1.2, 5.8)	2.1 (1.1, 5.6)	<0.001
D-dimer, ng/ml	5433.5 (2586, 8709.5)	456 (251, 972)	234.4 (173, 563)	<0.001
Creatine kinase, mIU/ml	114 (65, 277)	161 (44, 232)	73 (53, 107)	0.001
Creatine kinase-MB, ng/ml	1.3 (0.8, 3.3)	0.7 (0.3, 4.6)	0.7 (0.3, 1.1)	<0.001
Troponin I, ng/ml	0.1 (0, 0.2)	0 (0, 0.1)	0 (0, 0)	<0.001

Conclusion: In addition to leucocytosis, pre-operative NLR ratio is higher in patients with AAD compared to chronic uncomplicated aneurysms and normal subjects.

P1623 | BENCH

Development and implantation of tissue engineered self-expandable aortic stent grafts (bio stent grafts) using in-body tissue architecture technology in beagles

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Purpose: Stent grafts which can assimilate to native aorta are desirable for avoiding endoleaks and migration. We have developed autologous prosthetic materials with excellent mechanical and biocompatibility using "in-body tissue architecture" technology, which is a novel and practical approach of regenerative medicine based on the tissue encapsulation phenomenon. Using the technology, we firstly developed novel stent grafts covered with only autologous tissue (bio stent grafts: BSG). Their in vivo preparation method and early adaptation to aorta in a beagle model will be presented.

Methods: Preparation molds for BSG were assembled by insertion of acryl rods (diameter: 8.6 mm, length: 40 mm) into self-expanding nitinol stents (diameter: 9.0 mm, length: 35 mm). The molds ($n=6$) were embedded into subcutaneous pouches of 3 beagles for 4 weeks. Upon trimming excessive tissues around the molds after harvesting and removing each rod, the stents completely covered with autologous tissue membranes were obtained as BSGs (Photo A). Of 6 stent grafts, 3 were implanted into abdominal aorta of beagles via the femoral

artery. Follow-up aortogram and examination of aortic specimens were performed 4 weeks after implantation.

Results: Struts in BSGs were completely impregnated in thin connective tissue membrane (thickness: 250 μ m). Luminal surface of BSGs was extremely flat and smooth. BSGs were easily delivered to abdominal aorta without migration. Only after 4 weeks, luminal surface of the BSGs completely covered by thin neointimal layer with endothelial lining and smooth muscle cells content (Photo B).

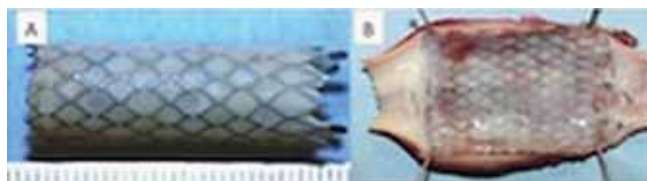


Figure 1. Biostent

Conclusions: The BSGs prepared by short-term embedding of the molds into subcutaneous layer were completely fused with native aorta in short-term implantation, which may avoid endoleaks and migration.

P1624 | BEDSIDE

Association of total atherosclerotic burden with aortic stiffness and progression of penile vascular disease

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Purpose: We investigated whether total atherosclerotic burden is related to aortic stiffness and penile vascular disease severity by using a classification that incorporates intima media thickness (IMT) and plaques from both the carotid and femoral arteries.

Methods: Sixty-five patients (58 $\pm$ 12 y/o) underwent a dynamic penile Doppler ultrasound. Penile peak systolic velocity (PSV) shows the greatest flow velocity detectable in an artery throughout the systole. Ultrasonographic measurements of IMT and plaques in the carotid and femoral arteries were evaluated and a previously described ultrasound-based morphological classification was used. Aortic stiffness was evaluated with carotid-femoral pulse wave velocity (PWV).

Results: Patients were classified into two groups: One group (high score) had increased IMT (>1.0 mm) and/or plaque in either of the four arteries and the other group (low score) had normal IMT and absence of plaques at all four arteries. Patients with high score (n=31) compared with subjects with low score had increased age-adjusted PWV ($P<0.001$) and decreased PSV ($P=0.006$), whereas these two groups did not differ regarding blood pressure, metabolic profile and smoking status. Receiver operating curve analysis showed that PWV>8.6 m/s and PSV <30 cm/s were the optimal cutoff values to predict a high score. In the entire population, femoral IMT was more strongly related to PSV than was carotid IMT (Fig. 1A, B). On the contrary carotid IMT was more strongly related to aortic PWV than was femoral IMT (Fig. 1C, D).

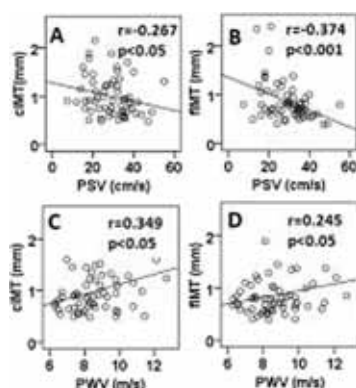


Figure 1. Carotid/Femoral IMT, PWV and penile PSV.

Conclusions: Our study shows that aortic PWV and penile PSV correlate significantly with carotid and femoral atherosclerotic burden. These data suggest a close interrelationship between ED progression, increased aortic stiffness and total atherosclerotic burden.

P1625 | BEDSIDE

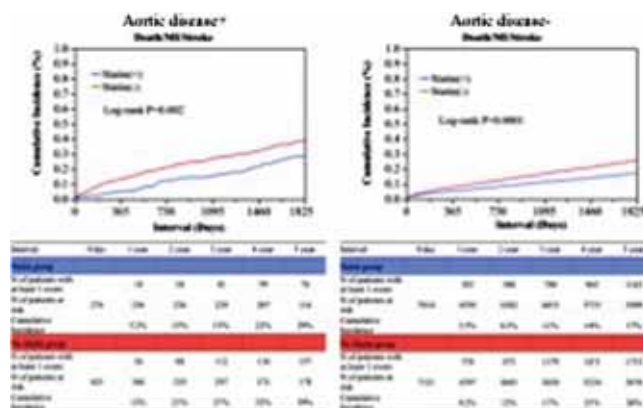
Impact of statins therapy on cardiovascular outcome in patients with aortic disease undergoing coronary revascularization

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Objective: Patients with aortic disease have poor prognosis. However, optimal medical therapy, particularly role of statins, in patients with aortic disease is still unclear.

Methods: Among 14834 consecutive patients undergoing first coronary revascularization in the CREDO-Kyoto PCI/CABG registry, we identified 699 patients (4.7%) with aortic disease.

Results: The 5-year cumulative incidence of and the risk for the primary outcome measure (composite of death, myocardial infarction and stroke) were significantly higher in patients with aortic disease than those without aortic disease (35% versus 22%, log rank $P<0.0001$, adjusted HR 1.43 [95% CI 1.23-1.66] $P<0.0001$). In patients with aortic disease, only 274 patients (39%) were treated with statins at hospital discharge, and the cumulative incidence of the primary outcome measure was significantly lower in patients treated with statins than in patients without statins (29% versus 39%, log rank $P=0.002$). After adjusting confounders, statin-use was associated with lower risk for the primary outcome measure in patients with aortic disease (adjusted HR 0.71 [95% CI 0.51-0.99], $P=0.045$) as well as in patients without aortic disease (adjusted HR 0.79 [95% CI 0.73-0.85], $P<0.0001$). There was no interaction between the effect of statins and the presence of aortic disease (P interaction=0.69).



Statins versus no statins.

Conclusion: Patients with aortic disease compared to those without aortic disease had significantly higher long-term risk for cardiovascular events. Statins therapy in patients with aortic disease was associated with lower risk for cardiovascular events with an effect size similar to that observed in patients without aortic disease.

P1626 | BEDSIDE

Comparable reduction of mortality in patients with abdominal aortic aneurysms treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers

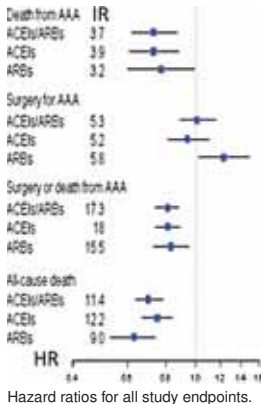
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Purpose: The renin-angiotensin-aldosterone system is thought to play a pivotal role in the pathogenesis of abdominal aortic aneurysms (AAAs). However, effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) on human AAAs remain unclear. We therefore examined whether treatment with ACEIs or ARBs influenced hard clinical endpoints in a nation-wide cohort of patients with AAA.

Methods: All patients diagnosed with an AAA during the period 1995-2011 were identified by cross-linkage of Danish nationwide registries. Patients were divided according to their ACEI and ARB treatment status and followed for up to 10 years. The risk of death from AAA and of secondary endpoints (see Figure) was evaluated by time-dependent Cox proportional hazard models.

Results: We included 11246 patients with AAA and without heart failure, of whom

1216 (10.8%) were treated with ACEIs and 430 (3.8%) received ARBs at baseline. Crude incidence rates of death from AAA per 100 patient-years were 3.7, 3.9 and 3.2 for treatment with ACEIs/ARBs (ACEIs or ARBs as a group), ACEIs, and ARBs, respectively. Hazard ratios (HRs) for death from AAA were 0.73 (95% CI 0.62-0.87, $P < 0.001$) for patients treated with ACEIs/ARBs, 0.73 (95% CI 0.61-0.88, $P = 0.001$) for those receiving ACEIs, and 0.77 (95% CI 0.60-0.99, $P = 0.043$) for those receiving ARBs, respectively. The difference in HRs between ACEIs and ARBs was not significant ($P = 0.706$). Results for all outcomes are shown in the figure.



Conclusions: Treatment with ACEIs or ARBs is associated with a comparable reduction of mortality in patients with AAA.

P1627 | BEDSIDE

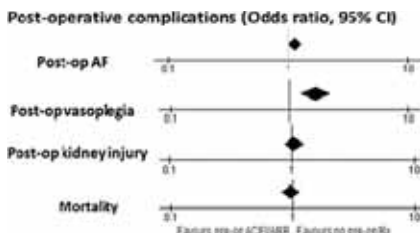
Safety of preoperative use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients undergoing cardiac surgery: A systematic review and meta-analysis of the literature

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Background: Although the long-term benefits of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in myocardial infarction and heart failure have been repeatedly proven, reports concerning their continuation in patients scheduled for cardiac surgery have produced conflicting results. The purpose of this meta-analysis was to assess the impact of preoperative ACEI/ARB on short term outcomes following cardiac surgery.

Methods: We performed a meta-analysis of articles comparing preoperative ACEI/ARB with no ACEI/ARB in patients undergoing cardiac surgery. The EMBASE, MEDLINE and CENTRAL databases were searched until the first week of October 2013. Two reviewers performed independent article review and study quality assessment. Data on atrial fibrillation, vasopressor requirements, acute kidney injury and mortality all occurring in the first month following surgery were collected. Since most included studies were retrospective, the generic inverse variance method was used to analyse adjusted odds ratios, calculating pooled odds ratios (ORs) and associated 95% confidence intervals (CIs) using a random effects model.

Results: We retrieved 24 studies (2 randomized trial, 20 cohort studies and 2 case-control studies) enrolling a total of 52378 patients. Preoperative administration of ACEI/ARB significantly increased postoperative atrial fibrillation (OR: 1.15; 95% CI: 1.01 – 1.31) and vasopressor requirements (OR: 1.65; 95% CI: 1.25 – 2.22). However no difference was observed in acute kidney injury (OR: 1.05; 95% CI: 0.86 – 1.26) or in mortality (OR: 0.96; 95% CI: 0.8 – 1.16).



Conclusion: Preoperative use of ACEI or ARB is potentially associated with an increased risk of atrial fibrillation and vasopressor requirements following heart surgery.

PERCUTANEOUS CORONARY INTERVENTION IN STEMI AND MORE

P1629 | BEDSIDE

Pre-procedural risk factors for contrast-induced nephropathy in patients undergoing primary percutaneous coronary intervention

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Purpose: Few Risk Scores for contrast induced nephropathy (CIN) in patients undergoing primary percutaneous coronary intervention (pPCI) for ST elevation myocardial infarction (STEMI) have been suggested, but they cannot be used for pre-procedural risk evaluation since the scores include variables which are not yet known, such as amount of contrast medium and use of IABP. The aim of this study was to define pre-procedural risk factors of CIN in a single centre homogeneous population.

Methods: We prospectively enrolled consecutive STEMI patients undergoing pPCI in our centre in 2005-2012 (n=1538 after exclusion of 15 patients without creatinine values after pPCI). CIN was defined as an increase in creatinine $> 0.5 \text{ mg/dl}$ in the first 72 hours; chronic kidney disease (CKD) was defined as an estimated GFR $< 60 \text{ ml/min}$. Independent predictors of CIN were evaluated with a multivariable logistic regression model.

Results: CIN occurred on 85 patients (5.5%). Patients with CIN were older, had more frequently anterior MI, a higher Killip class, a higher baseline creatinine, a TIMI flow < 3 after PCI, a higher CK peak and a lower in-hospital left ventricular ejection fraction (all $p < 0.01$). Short-, mid- and long-term mortality were higher in patients with CIN ($p < 0.001$). Independent predictors of CIN were CKD (Odds Ratio 3.41 95% Confidence Interval 1.81-6.41 $p < 0.001$), anterior acute MI (OR 2.72 95%CI 1.55-4.77 $p < 0.001$), diabetes (OR 2.47 95%CI 1.39-4.439 $p = 0.002$), prior MI (OR 2.34 95%CI 1.29-4.27 $p = 0.005$), age (OR 1.04 95%CI 1.01-1.07 $p = 0.007$), Killip class (OR 1.36 95%CI 1.06-1.73 $p = 0.015$) and haemoglobin values (OR 0.85 95%CI 0.74-0.98 $p = 0.028$).

Conclusions: CKD, anterior acute MI, diabetes, prior MI, age, Killip class and haemoglobin at admittance were independent predictors of CIN in STEMI patients undergoing primary PCI. These predictors allow appropriate risk stratification before the procedure allowing the implementation of possible preventive approaches. Also, they could be used to refine the inclusion criteria for trials assessing the effects of interventions aiming to reduce the risk of CIN among patients with STEMI.

P1630 | BEDSIDE

Impact of coronary collaterals on long term outcome in patients undergoing primary angioplasty for ST elevation myocardial infarction

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Purpose: Coronary collaterals (CC) provide an alternative source of blood supply to myocardium jeopardized by occlusive coronary artery disease and they preserve myocardial function in the setting of a chronic total coronary occlusion. The effect of CC to occluded coronary arteries during ST-elevation myocardial infarction (STEMI) is still unclear. We examined the effect of collateral flow on clinical outcomes in patients undergoing primary angioplasty for acute myocardial infarction (AMI).

Methods: We studied 790 consecutive patients (483 m, 307 f, age 64.35 ± 13.70 years). Primary PCI was performed according to standard clinical Practice. Collateral flow to the infarct-related artery was graded according to the Rentrop classification: 38% with grade 0 (no visible filling of any collateral channel), 36% grade 1 (filling of the side branches of the infarct-related artery), 16% grade 2 (partial filling of the epicardial vessel of the infarct-related artery), and 10% grade 3 (complete collateral filling of the epicardial vessel). Patients were divided into two groups: group A (patients with Rentrop grade 0 and 1) and group B (patients with Rentrop grade 2 and 3). Patients were subject to a 2-years clinical follow-up. Our endpoints were cardiac death, nonfatal reinfarction, and repeat myocardial revascularization. A combined endpoint (composite), defined as the occurrence of any endpoint (cardiac death or reinfarction or repeat revascularization) was also analyzed.

Results: Our study revealed that: 1) there are no statistically significant differences concerning the prevalence of risk factors in both groups 2) in group B, there was a increased time of reperfusion, but not enough to reach statistical significance 3) CC have a better development in patients with a history of ischemic heart disease. In particular, there was no correlation between Rentrop grade and diabetes mellitus ($p = 0.77$) and peak cardiac enzyme elevation ($p = 0.48$). The study showed an inverse correlation between the presence of anterograde flow measured before the procedure according to the TIMI flow scale and the development of CC. We could not find a significant impact of Rentrop grade on improvement of left ventricular ejection fraction after PCI ($p = 0.78$), mortality ($p = 0.86$) and major adverse cardiovascular events ($p = 0.88$).

Conclusions: Our study showed no relationship between the degree of CC and long-term prognosis in patients after AMI. Coronary collateral circulation does not

seem to play a protective role in the AMI and cannot serve as a predictor of better long-term clinical outcome in patients after STEMI treated with primary PCI.

P1631 | BENCH

The ratio of contrast volume to glomerular filtration rate predicts in-hospital and six months mortality in patients undergoing primary angioplasty for ST-elevation myocardial infarction

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The aim of this study is to determine the impact of ratio of contrast volume to glomerular filtration rate (V/GFR) on in-hospital and 6 months mortality in patients with ST-segment elevation acute myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). A total of 645 patients is prospectively enrolled. The study population was divided into tertiles based on V/GFR. A high V/GFR was defined as a value in the third tertile (>3.7). Patients in Tertile 3 had older age, higher rate of smoking, diabetes mellitus and contrast induced nephropathy, lower LVEF, hemoglobin, systolic and diastolic blood pressure. 19 patients died in hospital and 34 patients died during 6 month follow up. V/GFR was found as an independent predictor of in hospital (HR 1.07, 95% CI 1.04-1.12, p=0.001) and 6 month mortality (HR 1.08, 95% CI 1.02-1.15, p=0.003) (Table 1). We found two separate values of V/GFR for two different end points. While the ratio of 3.6 predicted in hospital mortality with 78% sensitivity and 82% specificity, the ratio of 3.3 predicted 6 months mortality with 71% sensitivity and 76% specificity.

Predictors of 6 months mortality

Variables	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.05 (1.02-1.07)	<0.001	1.03 (0.95-1.13)	0.245
Male/female	1.02 (0.80-1.19)	0.189	—	—
Diabetes Mellitus	2.92 (1.97-5.89)	<0.001	2.01 (1.39-2.64)	<0.001
Smoking	1.18 (1.11-1.25)	0.001	0.88 (0.75-1.00)	0.122
Killip class > 1	15.2 (6.65-21.7)	<0.001	7.71 (3.78-23.9)	<0.001
EF	1.51 (0.40-4.66)	<0.001	2.91 (1.26-6.72)	0.012
CIN	4.05 (2.02-6.27)	<0.001	2.99 (1.96-4.02)	<0.001
V/GFR	1.08 (1.03-1.13)	<0.001	1.07 (1.04-1.12)	0.001
LDL	1.14 (0.88-1.41)	0.622	—	—
Multi vessel disease	2.51 (1.53-3.04)	<0.001	2.55 (1.74-3.34)	<0.001
Hemoglobin	1.22 (1.10-1.35)	0.003	1.17 (1.08-1.26)	0.007

HR, hazard ratio; CI, confidence interval; EF, ejection fraction; CIN, contrast induced nephropathy; V/GFR, contrast volume-glomerular filtration rate ratio; LDL, low density lipoprotein.

In conclusion, high V/GFR level is associated with increased in hospital and long-term mortality in patients with STEMI undergoing primary PCI.

P1632 | BEDSIDE

Correlation of health related quality of life with biomarkers and mortality in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention

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Purpose: Numerous studies have analyzed the impact of quality of life on primary percutaneous coronary intervention (pPCI) in patients with acute ST-elevation myocardial infarction (STEMI), yet little is known about the effect of the measured health related quality of life (HRQoL) on hard clinical endpoints.

Methods: This was a prospective observational trial focused on assessment of HRQoL in STEMI patients treated with pPCI. Three well-recognized HRQoL tools were used including: a generic (EQ-5D) and cardiac-specific (QLI, MacNew). HRQoL was measured at three time points: before pPCI, 2 hours after and on Day 4. The biochemical markers were measured at Day 1 and in-hospital mortality was recorded. Pearson's correlation co-efficient was calculated.

Results: 103 STEMI patients were included in the study with mean age of 62 years (SD: 11.9), 27.2% of women, BMI 1.89 kg/m² (SD: 4.27), 49% treated from femoral access and 51% from radial access. The baseline HRQoL by EQ-5D VAS was 50 (SD: 22) that improved by 18.7 (+37%, p<0.001) after PCI. The mean EQ-5D health utility score two hours and 4 days after PCI were 0.46 (SD = 0.291) and 0.79 (SD: 0.248), respectively (p<0.01). The serum levels of NT-proBNP were inversely correlated with EQ-5D VAS (r = -0.348, p<0.05) and EQ-5D health utility score on Day 4 (r = -0.322, p<0.05). There was a correlation between in-hospital mortality and two MacNew domains: physical (r = -0.329, p<0.05) and emotional (r = -0.374, p<0.01).

Conclusions: The HRQoL is decreased in the acute phase of STEMI. The level of impairment seems to be correlated with the hard clinical outcomes including level of NT-proBNP and in-hospital mortality, which may suggest usefulness of HRQoL measurement in risk prediction models in STEMI population.

P1633 | BEDSIDE

Prognostic implications of baseline thrombocytopenia in patients undergoing primary percutaneous coronary intervention

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Purpose: Thrombocytopenia (TP) is a common disorder in pts presenting with acute coronary syndrome and is considered one of the risk factors for adverse cardiac events. We assessed the impact of baseline TP on mortality of pts with ST-elevation myocardial infarction (STEMI) underwent primary percutaneous coronary intervention (PCI).

Methods: Consecutive STEMI pts who underwent primary PCI between 8/2009 and 1/2011 were enrolled in a prospective registry of high volume tertiary centre. Baseline TP was defined as platelet count <150 000 platelets/mm³ at blood specimen obtained in the hospital before the time of primary PCI performed. The primary outcome was 1-year mortality.

Results: Of the 1808 pts who underwent emergency coronary angiography, 1628 (90.0%) were treated with primary PCI. Of these, 1302 pts (80%) had baseline platelet count available and included into analysis. The rate of baseline TP was 7.1% (n=93). Pts in the TP group had lower creatinine clearance and more frequent cardiovascular shock. Unadjusted 1-year all cause and cardiac mortality was significantly higher in the TP group than in the control group (Table). After multivariable adjustment for demographic and clinical characteristics, TP was an independent predictor of 1-year all-cause mortality (HR 2.35, 95% CI 1.36-4.01; p=0.02) and cardiac mortality (HR 2.24, 95% CI 1.25-4.03; p=0.007). Other independent predictors of 1-year mortality were advanced age, previous myocardial infarction, previous stroke, heart failure and elevated white blood cell count on admission.

Thrombocytopenia and mortality

1-year mortality	Thrombocytopenia (n=93)	No thrombocytopenia (n=1209)	p
All-cause, %	18.3	10.7	0.025
Cardiac, %	16.1	9.5	0.040
Noncardiac, %	2.2	1.2	0.402

Conclusion: STEMI pts with baseline TP undergoing primary PCI are at more than 2-fold higher risk of 1-year all-cause mortality and cardiac mortality than those without TP.

P1634 | BEDSIDE

Predictors of contrast media induced acute kidney injury after primary percutaneous coronary interventions; role of contrast media volume and estimated glomerular filtration rate ratio

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Purpose: Contrast media induced acute kidney injury (CI-AKI) is a relatively common complication of primary percutaneous coronary interventions (PPCI). The incidence of CI-AKI is increased up to 20% after PPCI. CI-AKI is also related with increased in-hospital morbidity and mortality rates. Therefore, early risk estimation of CI-AKI and identification of patients undergoing PPCI who are likely to develop CI-AKI may allow to the administration of therapeutic interventions capable of preventing CI-AKI. In the present study, we hypothesized that contrast media volume/estimated glomerular filtration rate (CV/e-GFR) ratio may be a predictor of CI-AKI and aimed to investigate the associations between CV/e-GFR ratio and other related factors and CI-AKI in patients undergoing PPCI.

Methods: We enrolled 597 STEMI patients undergoing PPCI. All PPCI procedures were performed in a high-volume tertiary center (>3,000 PCI/year) by expert operators. An absolute 0.3 mg/dL or more increase in serum creatinine levels compared to baseline levels within 48 hours after administration of contrast medium was considered as CI-AKI. Patients developing CI-AKI (group-1) were compared to patients without CI-AKI (Group-2).

Results: 78 of 597 (13%) patients experienced CI-AKI. The amount of contrast given during the procedure was higher in the CI-AKI group than group without CI-AKI (153ml vs. 135ml, p=0.003). Accordingly, when compared with the non-AKI group, the CV/e-GFR ratio was significantly higher in the group with CI-AKI than without (2.3 vs. 1.5, p<0.001). Significant univariate predictors of AKI were age, diabetes mellitus, hypertension, LVEF, post-procedure TIMI flow, multivessel disease, the amount of contrast volume, e-GFR<60 ml/min and CV/e-GFR>2. In the multivariate analysis, independent predictors of the AKI in the patients undergoing PPCI were found to be LVEF, GFR<60 ml/min and CV/e-GFR>2 (p<0.018, OR: 0.966, CI: 0.940-0.994; p<0.012, OR: 2.558, CI: 1.226-5.535 and p<0.001, OR: 5.917, CI: 2.825-12.395, respectively). In the ROC analysis, it was found that CV/e-GFR ratio had 70% sensitivity and 78% specificity in prediction of CI-AKI.

Conclusion: According to the present study, CV/e-GFR ratio, low GFR, LVEF are significantly associated with CI-AKI after PPCI. CV/e-GFR ratio might be a

predictor of CI-AKI. Keeping CV/e-GFR ratio below two might help reducing the risk of CI-AKI in patients undergoing PPCI.

P1635 | BEDSIDE

Predictive value of elevated D-dimer in patients undergoing primary angioplasty for ST elevation myocardial infarction

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The aim of this study was to evaluate the prognostic value of D-dimer in patients with STEMI undergoing primary percutaneous coronary intervention (PCI). The prognostic value of D-dimer has been documented in patients with acute coronary syndrome without ST-segment elevation. However, its value in acute ST-segment elevation myocardial infarction (STEMI) remains unclear. We prospectively enrolled 453 consecutive STEMI patients (mean age 55.6W12.4 years, 364 male, 89 female) undergoing primary PCI. The study population was divided into tertiles based on admission D-dimer values. The high D-dimer group (nU151) was defined as a value in the third tertile [>0.72 ug/ml fibrinogen equivalent units (FEU)], and the low D-dimer group (nU302) included those patients with a value in the lower two tertiles (<0.72 ug/ml FEU). Clinical characteristics, in-hospital and 6-month outcomes of primary PCI were analyzed. The patients of the high D-dimer group were older (mean age 60.1W13.5 versus 52.4W10.6, $P<0.001$). Higher in-hospital cardiovascular mortality and 6-month all-cause mortality rates were observed in the high D-dimer group (7.2 versus 0.6%, $P<0.001$ and 13.9 versus 2%, $P<0.001$, respectively). In Cox multivariate analysis; a high admission D-dimer value (>0.72 ug/ml FEU) was found to be a powerful independent predictor of 6-month all-cause mortality (odds ratio: 10.1, 95% confidence interval: 1.24–42.73, PU0.03). These results suggest that a high admission D-dimer, level was associated with increased in-hospital cardiovascular mortality and 6-month all-cause mortality in patients with STEMI undergoing primary PCI.

P1636 | BEDSIDE

PCI in patients with and without prior CABG in a large monitor-controlled registry: changes over the past decade

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Background: Percutaneous coronary intervention (PCI) after prior coronary artery bypass surgery (CABG) is considered more complex, less successful, and characterized by more complications.

Methods: Since 1996 invasive and interventional procedures of 130 institutions with annually over 20,000 PCI procedures are documented in a monitor-controlled registry. We analyzed the results of PCI in 2002 (n=18,822) compared to 2012 (n=21,512).

Results: While the number of PCI patients with prior CABG was 7.6% in 2002 it continuously decreased to 2.2% in 2012 ($p<0.001$). The procedural differences of patients with no prior CABG and those with prior CABG are depicted in the table.

PCI in cases with and without prior CABG

Years:	2002		2012	
	yes	no	yes	no
Prior CABG:				
N	1,421	17,401	465	21,047
MVD (%)	95.7	64.4	97.6	70.1
LM (%)	9.4	1.7	14.8	2.9
Radiation time (min)	9.8	8.3	13.0	7.8
Dye consumption (ml)	131	119	123	75
stent length (mm)	17.6	16.0	18.1	18.3
Angiographic success (%)	89.5	92.4	92.5	93.4
MACCE (%)	0.6	0.5	0.4	0.9

MVD, multi-vessel-coronary artery disease; LM, left main artery stenosis; MACCE, major adverse and cardiac and cerebrovascular events.

Conclusion: While we see more severe cases in PCI, compared to past years, in 2012 only a small number of them were really pre-operated with bypass-surgery. But, these cases appear with severe conditions, most of them with multi-vessel-diseases including left main stenoses.

P1637 | BEDSIDE

Prospective estimation of chronic total occlusion complexity and failure: New clinical and anatomic (angiography and tomography) predictors

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Aims: The final frontier of coronary percutaneous coronary intervention (PCI) remains the recanalization of chronic total occlusions (CTOs). One of the reasons for the low application rates of CTO-PCI by most physicians may be uncertainty concerning the success rate of the procedure. Improved guidelines for case selection, may favourably impact these patients.

Methods and results: Between 2012 and 2013, 105 eligible patients who were scheduled for percutaneous recanalization of a true CTO were included prospectively in the study. 98 patients underwent computed tomography (CT). By protocol we pre-defined the same 10 CTO key characteristics by conventional angiography (CA) and CT based on previously published independent predictors of failure and our team experience. Two-experienced interventional cardiologist and two imaging specialists, respectively, analysed CTO characteristics. Prospectively the Japanese-CTO score of complexity was calculated. The mean age was 62 ± 10 years old. According to the CA-Japanese-CTO score of complexity 51% of lesions were classified as difficult or very difficult. By CA 52% were severe calcified lesions. In most cases (88%) the strategy was antegrade. 58% performed with a 7F catheter. By CA, the total stent length implanted per lesion was of 51.6 ± 20.3 mm (2.2 ± 0.55 scaffolds per lesion). In all case last generation DES was implanted. Successful guidewire crossing was 86.4% and the overall success rate was 84.5%. Severe calcification by CA (37.5% vs. 11.5%, $p=0.001$) and by CT-scan ($>50\%$ cross sectional area) (26.6% vs. 60.0%, $p=0.016$) was more prevalent in failed cases. It is important to note a new anatomic characteristic "bad landing zone" (defined as distal vessel just after the CTO exit point, with reference diameter ≤ 2 mm) by CA (30.5% vs. 63.3%, $p=0.01$) was more prevalent in failed cases. By multivariable logistic regression, the only independent predictor of procedural failure was the CA-J-CTO score (odds ratio (OR) 2.5, 95% confidence interval (CI) 1.37-4.59, $p=0.003$, for each unit increase in J-CTO score) and silent ischemia as baseline clinic status before PCI-CTO (OR 4.71, CI 1.23-17.95, $p=0.02$).

Conclusions: According with the results of this prospective study, in our current era, the information provided by CA- J-CTO score; provide a significant impact in procedural results. Moreover silent ischemia as baseline clinical status was found as an independent predictor of failure of PCI for CTO. Further studies with higher sample size are required to determine whether new CA anatomic characteristic as "bad landing zone" may improve case selection.

P1638 | BEDSIDE

Interaction between access site and antithrombotic therapy and impact on bleeding outcomes in STEMI

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Purpose: In the emergent setting of ST-elevation myocardial infarction (STEMI), aggressive antithrombotic therapy is routinely employed and major or minor bleeding is primary concern as percutaneous coronary intervention (PCI). We therefore sought to compare differences in bleeding outcomes among patients undergoing TRI and TFI for STEMI at a high-volume tertiary centre.

Methods: We conducted an observational study of 1052 patients with STEMI undergoing primary PCI at a high-volume tertiary medical centre from January 2008 to April 2010. The definition of major bleeding include the cumulative occurrence within 30-day after PCI of intracranial or intraocular bleeding, haemorrhage at the access site requiring intervention, haematoma with a diameter of at least 5 cm, a reduction in haemoglobin levels of at least 4 g per decilitre without an overt bleeding source or at least 3 g per decilitre with such a source, re-operation for bleeding, or transfusion of a blood product. Minor bleeding was defined as any bleeding which did not meet the above major bleeding criteria.

Results: GP IIb/IIIa inhibitor was used in 498 (47.3%) STEMI patients. Proportion of use of GP IIb/IIIa inhibitor was significantly higher in the transradial coronary intervention (TRI) group compared with the transfemoral coronary intervention (TFI) group (68.5% vs 36.4%, $p<0.001$). Major bleeding was seen more in the TRI group than TFI group (5.6% vs 3.3%, $p=0.08$), which was not statistically significant. There was no difference of minor bleeding (1.7% vs 1.7%, $p=0.09$) between TRI and TFI groups. In GP IIb/IIIa inhibitor used group (N=498), major bleeding was seen in 3.6% and minor bleeding was seen in 8.6%, however, no bleeding complications were seen in group without GP IIb/IIIa inhibitor use (N=554).

Conclusions: GP IIb/IIIa Inhibitor use was more liberal in radial access patients, resulting in a trend towards increased major bleeding in radial access patients. GP IIb/IIIa Inhibitor use was the strongest predictor of bleeding, independent of access site in patients with STEMI.

EXPERIMENTAL STUDIES ON ISCHAEMIA

P1640 | BENCH

Interferon gamma derived from neutrophils and inflammatory monocytes is required for post-infarction survival and cardiac remodeling

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Background: Inflammatory myelomonocytic cells are involved in both the initial injury phase and the healing process of myocardial infarction (MI).

Objective: Scheduled depletion of lysozyme M positive (LysM+) immune cells in a murine model of MI would enable us to investigate their negative or protective effects in cardiac injury and healing.

Methods and results: MI was induced in 8 to 12 week old male mice (C57BL/6 background) by ligation of the left anterior descending (LAD) coronary artery. Flow cytometry analysis revealed the prototypic triphasic immune response of neutrophils, proinflammatory and reparative monocytes in infarcted cardiac tissue within 14 days after MI. Compared to sham operated LysMCre controls, LysMIDTR transgenic mice that had been depleted of LysM+ cells for 3d prior MI, revealed a decreased influx of CD45.2+/CD3-/CD11b+/Gr-1-high neutrophils into infarcted myocardium 1d post MI. Despite discontinuation of the depletion regimen, we observed a prolonged reduction of cardiac interferon gamma (INFg) and tumor necrosis factor alpha mRNA expression as well as worsening of left ventricular function as assessed by echocardiography until d28 post MI. Continuation of the depletion regimen aggravated the influx of inflammatory cells and led to premature death within 7d post MI. To more specifically assess the role of neutrophils, we depleted mice with a monoclonal anti-Gr1 antibody and found increased mortality early after MI as well as a decrease in INFg mRNA. Kaplan-Meier-curve of LAD ligated INFg-/- mice revealed a drastically decreased survival as well as attenuated inflammatory response in infarcted cardiac tissue compared to controls.

Conclusion: Our results suggest an essential role of neutrophil derived INFg for survival and cardiac remodeling following MI. We conclude that strategies to combat the inflammatory injury in MI must consider a potentially beneficial effect of early neutrophil influx into infarcted myocardium.

P1641 | BENCH

The effect of beta adrenergic and muscarinic receptors blockade on preconditioning in anesthetized rabbits

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Introduction: Remote ischemic preconditioning (PerC) protects myocardium against ischemia (isc)/reperfusion (rep) injury. Investigation of its potential clinical applicability demands elucidation of fundamental PerC-mediated mechanisms. Several studies suggest that humoral factors, systemic response or neuro-hormonal pathways link the remote conditioning organ to the heart.

Purpose: In the present study we sought to determine: i. whether beta-adrenergic and muscarinic receptors are involved in mediating PerC protection against isc/rep injury in anesthetized rabbits and ii. whether pro-survival signaling pathway with reperfusion injury salvage kinases (RISK) is involved.

Methods: New Zealand White male rabbits, weighing between 2.5-3.1 kgs, were subjected to 30-min myocardial isc followed by a 3-hour rep. PerC, with 4 repetitive cycles of 1 min isc/rep of the carotid artery, was applied, starting at the 23rd min and completed at the end of the index myocardial isc. Peripheral adrenergic beta-blockade was attained by intravenous propranolol infusion at two doses, of 0.5 mg/kg (low) and 5 mg/kg (high) and blockade of the muscarinic receptors was attained by intravenous atropine at two doses of 0.2 mg/kg (low) and 3 mg/kg (high). Propranolol and atropine were given 1 min before PerC. Animals were divided into 6 groups: Group-A: Control, no further intervention, Group-B: PerC applied in addition to the index isc-rep, Group-C: as in Group-B plus low propranolol dose, Group-D as in Group-B plus high propranolol dose, Group-E: as in Group-B plus low atropine dose and Group-F: as in Group-B with high atropine dose. Hemodynamic parameters were continuously monitored and periodically recorded. After the end of rep period the infarcted (I) and the area at risk (R) were calculated and expressed as %/R ratio. In a second series of experiments, anesthetized rabbits were subjected to the previous interventions up to the 10th min of rep, when tissue samples were excised from the ischemic region of the heart for Akt, ERK 1/2 and GSK3β assessment by immunoblotting.

Results: Infarct size was significantly reduced in all PerC groups (23.6±1.5%, 25.5±2.0%, 25.8±2.5%, 27.9±3.5% and 17.9±1.7% in groups B, C, D, E and F respectively, vs 49.5±3.9% in Group-A control, p<0.05). Phosphorylation of Akt, ERK1/2 and GSK3β was higher in all PerC groups compared to the control Group-A.

Conclusion: PerC is effective in limiting the infarct size independently of the pharmacological inhibition of beta adrenergic and muscarinic receptors. RISK pathway is steadily involved, despite sympathetic and parasympathetic blockade.

P1642 | BEDSIDE

Effect of intracoronary injection of autologous bone marrow derived progenitor cells on the global longitudinal strain in patients with ST-elevation myocardial infarction

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Introduction: The global longitudinal strain (GLS) is an important prognostic marker after myocardial infarction (MI). We studied the effect of intracoronary injection of autologous bone marrow derived progenitor cells (APC) on the GLS in ST-elevation myocardial infarction (STEMI). There is only few data on this subject.

Methods: Prospective randomized study with recruitment of STEMI patients without previous MI or major comorbidities, with a CPK peak >1000U/L, that underwent primary percutaneous coronary intervention (PCI) in the first 12 hours of MI (January 2011-May 2013). Patients were randomized 1:1 to intracoronary injection (in the first 7 days of MI) or not (controls) of APC. All received optimal medical therapy. A transthoracic echocardiogram was performed in the first 3 days of MI and repeated at 6 to 12 months, with calculations of the left ventricle ejection fraction (LVEF) using the biplane Simpson's method, and the GLS using the 2D semiautomatic method (average of all segments regional strain). Exclusion: poor echocardiographic window (3) and lost of follow-up (5). The baseline characteristics and the changes in LVEF and GLS were compared between groups (χ² and Mann-Whitney tests).

Results: In our sample of 34 patients (91% male, 50.9±9.5 years, 53% hypertension, 50% dyslipidemia, 14% diabetes), 19 received APC and 15 were controls. No differences were found in baseline characteristics, including LVEF and GLS (Table). The LVEF and the GLS improved in both groups; the GLS (but not LVEF) improvement was significantly greater in the APC group.

	Controls (15)	APC (19)	p
Anterior MI (%)	71	80	0.232
CPK peak (U/L)	2714±1270	3542±2877	0.381
Time to PCI (min)	258±136	312±216	0.380
Baseline LVEF (%)	50.5±7.6	51.3±7.6	0.763
Baseline GLS (%)	-14.7±2.3	-13.9±4.8	0.531
LVEF variation (%)	4.7±8.6	4.2±7.9	0.489
GLS variation (%)	-1.8±2.5	-3.7±2.8	0.043

Conclusion: The intracoronary APC injection in STEMI patients was associated with a greater improvement in GLS. In this context, the GLS might be more sensitive than LVEF for left ventricle systolic function assessment.

P1643 | BENCH

Novel bioactive oxidized phospholipids are produced in myocardium during ischemia reperfusion and act as mediators of cell death within cardiac myocytes

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A major therapeutic aim for myocardial infarction is early "reperfusion" of ischemic tissue. The process of ischemia followed by reperfusion (IR) causes an intense oxidative burst that results in cellular dysfunction and oxidizes intracellular molecules. Little is known about the impact oxidative stress on lipids within cardiomyocytes and their role in cardiac cell death. Using both in vivo and in vitro models of IR, our goal was to identify oxidized phospholipids generated and to determine their impact on cell viability.

The rat coronary ligation model was used for 1 hr of ischemia then 1 to 24 hrs of reperfusion. 2D echocardiography and troponin-I assay were performed to assess myocardial damage. Myocardial lipid extracts underwent lipidomic analysis with high performance liquid chromatography linked to mass spectrometry to quantify 82 distinct OxPC species, as either fragmented or non-fragmented species. Lipid extracts of post-natal rat cardiac myocytes exposed to hypoxia and reoxygenation were analyzed to determine OxPC levels. Cell viability was determined in absence and presence of known OxPC molecules (POVPC and PONPC) and non-oxidized PSPC.

In rat model of IR injury lipidomics analysis revealed a significant increase in total OxPCs after 1 hr of IR (2.06±0.34 fold vs sham, p<0.05). This increase was also seen in fragmented OxPCs (1.85±0.18 fold, p<0.05) and non-fragmented OxPCs (1.96±0.26 fold, p<0.05). After 24 hrs of IR there was a significant sustained increase of fragmented OxPCs (1.80±0.22 fold, p<0.05). Cardiomyocytes under IR conditions also demonstrated significant increase in total OxPCs (5.23±0.99 fold vs control, p<0.05) and in fragmented aldehyde species (1.52±0.11 fold, p=0.05) correlating with decreased cell viability. Exogenously added fragmented OxPC such as POVPC and PONPC resulted in a significant loss of cardiomyocyte viability after 4 hrs of exposure when compared to control non-oxidized PC, PSPC (46±5%; 40±5%, respectively, vs 9±3% PSPC, p<0.05). Exposure of cardiomyocytes to POVPC and PONPC resulted in increased mitochondrial permeability and DNA fragmentation.

We have shown for the first time that OxPCs are generated within myocardial tissue during IR and they have detrimental effects on cardiomyocyte viability. Since there are no current therapies for IR in clinical practice, fragmented OxPCs represent a novel therapeutic target to attenuate myocardial injury during IR.

P1644 | BENCH

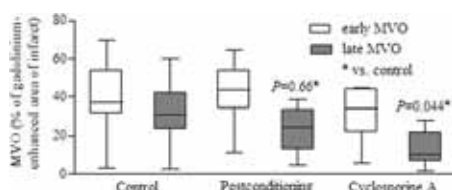
Cyclosporine A but not postconditioning reduces microvascular damage after coronary ischemia and reperfusion

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Purpose: Postconditioning and cyclosporine A prevent mitochondrial permeability transition pore opening. The effect of postconditioning versus cyclosporine on microvascular damage following coronary ischemia/reperfusion is unknown.

Methods: Pigs subjected to coronary occlusion for 1h followed by 3h of reperfusion were assigned to control (n=8), postconditioning (n=9) or cyclosporine A intravenous infusion 10-15 min before the end of ischemia (n=8). Postconditioning was induced by 8 cycles of repeated 30-s balloon inflation and deflation. After 3h of reperfusion magnetic resonance imaging, triphenyltetrazolium chloride/Evans blue staining and histopathology were performed. Microvascular obstruction (MVO, % of gadolinium-enhanced area) was measured early (3 min) and late (12 min) after contrast.

Results: Infarct size with double staining was smaller in cyclosporine ($44 \pm 7\%$, $P=0.017$) but not postconditioning pigs ($50 \pm 7\%$, $P=0.28$) versus controls ($54 \pm 4\%$). Late-MVO was significantly reduced by cyclosporine ($14 \pm 2\%$) but not postconditioning ($24 \pm 5\%$) when compared with controls ($32 \pm 5\%$) (Figure). The late-to-early MVO ratio was lower in cyclosporine (0.42 ± 0.19 , $P<0.0001$) and postconditioning pigs (0.55 ± 0.20 , $P=0.011$) than in controls (0.81 ± 0.07). Deterioration of left ventricular (LV) ejection fraction between baseline and 3h of reperfusion was smaller with cyclosporine ($-7.9 \pm 2.2\%$, $P=0.015$) but not postconditioning ($-13.2 \pm 6.3\%$, $P=0.62$) when compared with controls ($-15.6 \pm 3.7\%$). Erythrocyte stasis was higher in MVO ($4.4 \pm 4.5\%$) versus gadolinium-hyperenhanced region ($0.3 \pm 1.1\%$, $P<0.001$).



Conclusions: Cyclosporine A infusion but not postconditioning had a beneficial effect on microvascular damage and was associated with smaller infarct size and better preserved LV function when compared with controls.

P1645 | BENCH

Electron transport chain properties of mitochondria from left ventricle hypertrophy hearts as a substrate for increased vulnerability to ischemia-reperfusion

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Purpose: Left ventricular hypertrophy (LVH) is associated with a resistance to some forms of cardioprotection (1,2). Mitochondrial defects arising during ischemia set the stage for a subsequent reperfusion injury (3). There appear to be no studies comparing the effects on mitochondria of ischemia itself, as opposed to ischemia-reperfusion, in normal and LVH hearts. We have studied the effect of ischemia on mitochondria from rats with LVH to shed light on possible mechanisms of this resistance.

Methods: Hearts isolated from WKY (control) and SHR-SP (LVH) rats were subjected to 35 min normoxic perfusion or global ischemia and mitochondria were prepared immediately thereafter. Cytochrome c and b content and complex III (CIII) activity were measured spectrophotometrically. H₂O₂ production was determined by Amplex assay. Protein carbonylation was measured by western blotting as a product of 2,4-dinitrophenylhydrazine reaction. $p<0.05$ was considered significant.

Results: LVH was manifest in SHR-SP rat hearts (heart weight/body weight ratio (x 1000) 3.43 ± 0.05 vs 2.35 ± 0.03 in WKY, $n=40$). Cytochrome c/b ratios in WKY hearts were 0.938 ± 0.057 and 0.989 ± 0.043 , $n=7$, and in SHR-SP hearts 0.867 ± 0.100 and 1.006 ± 0.091 , $n=9$ following normoxia and ischemia, respectively. Normoxic SHR-SP hearts showed a markedly higher CIII activity than WKY hearts (368.1 ± 37 vs 144.02 ± 14.1 nmoles/mg*min, $n=8$; 422.6 ± 52.1 vs 203.0 ± 11.2 nmoles/nmole cyt b*min, $n=8$). Ischemia decreased CIII activity in SHR-SP hearts (to $47.8 \pm 5.9\%$, $n=9$). A non-significant decrease (to $69.5 \pm 7.8\%$, $n=7$) was also found in WKY hearts. H₂O₂ production, when measured with a mixture of CI (malate, glutamate) and CII (succinate) substrates, was decreased in postischemic mitochondria in WKY as well as SHR-SP hearts in the absence of rotenone, but not in the presence of antimycin A. There appeared to be a trend ($p<0.08$) to a lower H₂O₂ production in SHR-SP vs WKY hearts after normoxia. There was no difference in the level of protein carbonylation between any of the conditions.

Conclusions: The present data suggest that the ETC activity in LVH differs from normal hearts under normoxia (higher complex III activity and lower H₂O₂ production) and may be more vulnerable to ischemia (greater apparent damage to complex III activity). Further work is needed to determine whether these differences go some way to explain greater vulnerability of LVH hearts to ischemia-reperfusion.

P1646 | BENCH

C-type natriuretic peptide reduces ischemia-reperfusion-induced activation of mast cells and microcirculatory leakage

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Purpose: During postischemic reperfusion, the activation of mast cells (MC) is detrimental. Due to pleiotropic effects, cytokines released from MC cause tissue damage. It is unclear whether and how atrial (ANP) and C-type natriuretic peptides (CNP) regulate the activity of MC and, thereby, influence ischemia-reperfusion-induced disruption of the microvascular barrier.

Methods: Intravital microscopy was used to visualize the microcirculation within the cremaster muscle of anesthetized mice. Blood flow was temporally blocked with an arterial clamp to provoke 30 min of tissue ischemia. FITC-Dextran was injected intravenously to quantify macromolecule leakage from postcapillary venules during 60 min of reperfusion. Ruthenium Red solution was superfused to stain and count perivascular degranulated MC. These in vivo experiments were complemented with studies in cultured human MC.

Results: Compared to sham operated cremaster muscles, the ischemic cremasters displayed augmented number of perivascular degranulated MC (8 ± 2 vs. 56 ± 12 cells per mm² tissue, respectively; means $\pm$ SEM, $n=9-10$; $P<0.05$). This was consistently accompanied by robust vascular leakage of FITC-Dextran, as indicated by the ratio of the fluorescent intensity (RFI) of the adjacent interstitial space vs. the intravascular lumen (0.08 ± 0.02 in sham tissue vs. 0.27 ± 0.05 at 40 min of postischemic reperfusion; $P<0.05$). Local superfusion of CNP (100 nM, $n=9$) during reperfusion, significantly reduced the number of degranulated MC (to 15 ± 4 cells/mm²; $P<0.05$) and concomitantly reduced vascular leakage (RFI: 0.10 ± 0.02 ; $P<0.05$). Notably, superfusion with ANP (100 nM, $n=8$) only slightly decreased the number of degranulated MC (to 36 ± 8 /mm²; $P=0.77$), but effectively reduced FITC-Dextran leakage (RFI: 0.18 ± 0.07 ; $P=0.09$). In addition in cultured HMC CNP, but not ANP, induced a marked phosphorylation of the cytoskeleton-associated vasoactive stimulated phosphoprotein (VASP) at Ser237.

Conclusion: Our study shows distinct effects of NPs in the microcirculation after ischemia-reperfusion. CNP inhibited the ischemic activation of perivascular MC and the associated microvascular leakage. At difference, ANP had no effect on MC but still attenuated the disruption of the vascular barrier, possibly by direct effects on endothelial cells. Our future studies aim to dissect the cell-specific effects and signalling pathways of both NPs and possible clinical implications.

P1647 | BENCH

Cigarette smoking negates the beneficial effect of ischemic postconditioning in limiting the infarct size through insufficient activation of AKT and eNOS

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Introduction: Cigarette smoking is one of the risk factors for cardiovascular disease. Conditioning (either PreC- or PostC-) ameliorates injury that occurs upon reperfusion (rep) following myocardial ischemia (isc). The endogenous protective pathways are silenced by a number of co-morbidities, ageing and possibly by detrimental habits such as cigarette smoking.

Purpose: To investigate the effects of exposure to cigarette smoke on isc/rep injury and its potential interference with ischemic conditioning.

Materials and methods: C57BL/6 male mice were divided in 2 groups. The Cigarette Smoking group (CS), was exposed to cigarette smoke from reference cigarettes (3R4F University of Kentucky, USA) 4 times a day for 4 weeks. The Control group was exposed to room air (RA). Animals from both groups were subjected to 30 min regional myocardial isc followed by 2 hours of rep with the following interventions: RA and CS groups: Control, no further intervention, 2) PreC, 1 cycle of 5 min isc / 5 min rep before index isc and 3) PostC, 3 cycles of 10 sec isc/ 10 sec rep applied immediately after index isc. The infarct size (I) and the area at risk (R) were estimated as %/R. In a second series of experiments additional animals were subjected to the above interventions up to the 10th min of rep when the ischemic part of the myocardium was excised for biochemical measurements.

Results: Exposure to cigarette smoke did not increase the infarct size compared to the air exposed group ($38.3 \pm 3.6\%$ vs $40.9 \pm 2.2\%$ respectively, $p=NS$). Application of PreC was beneficial for both CS ($12.1 \pm 1.6\%$) and RA ($17.9 \pm 1.8\%$), $p<0.05$ vs no PreC controls. PostC failed to limit infarct size in CS animals, while the beneficial effect of PostC was preserved in RA mice ($43.3 \pm 2.2\%$ vs $17.0 \pm 2.7\%$, $p<0.05$). PreC in both groups and PostC in the RA group lead to in-

creased phosphorylation of AKT activation, whereas PostC failed to do enhance p-AKT in the CS group. Total AKT levels remained unchanged among groups. eNOS phosphorylation was evident in the CS group to a significantly higher extent in preconditioned RA and CS groups, as well as in PostC RA group.

Conclusion: Short term exposure to cigarette smoke does not per se increase infarct size. In addition, ischemic preconditioning functions in mice exposed to cigarette smoke, possibly through activation of AKT and eNOS, whilst the post-conditioning benefit is lost in mice that have been exposed to cigarette smoke for 4 weeks.

P1648 | BENCH

Changes of gene expression profiling of porcine myocardium after repetitive ischemia/reperfusion

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Background: We have analysed the gene expression profile of the myocardium after repetitive ischemia/reperfusion aiming to simulate human pre-infarction angina pectoris in an animal model ready to translate.

Methods: Under general anaesthesia domestic pigs underwent closed chest repetitive (3x10 cycle) ischemia/reperfusion by percutaneous balloon occlusion/deflation of the mid left anterior descending coronary artery. Sham balloon occlusion/deflation was performed in control pigs (n=3). After 5h (n=3) and 24h (n=3) follow-up, five myocardial samples were harvested from the heart basis (LAD1) to apex (LAD5) including the border zone of the ischemia (LAD3) localized by using anatomical landmarks (below the origin of the 2nd diagonal branch). The hypoxia inducible factor-1 (HIF1alpha), caspase-3, GATA4 and myocyte enhancer factor 2C (MEF2C) gene expression patterns of the corresponding regions were analysed by using quantitative real-time PCR (rtPCR).

Results: Repetitive ischemia/reperfusion resulted in a rapid increase in HIF1alpha and caspase-3 expression in the ischemic area and border zone, while increase in MEF2c expression was moderate. GATA4 expression was more pronounced 24h after the ischemic attack (Fig. 1).

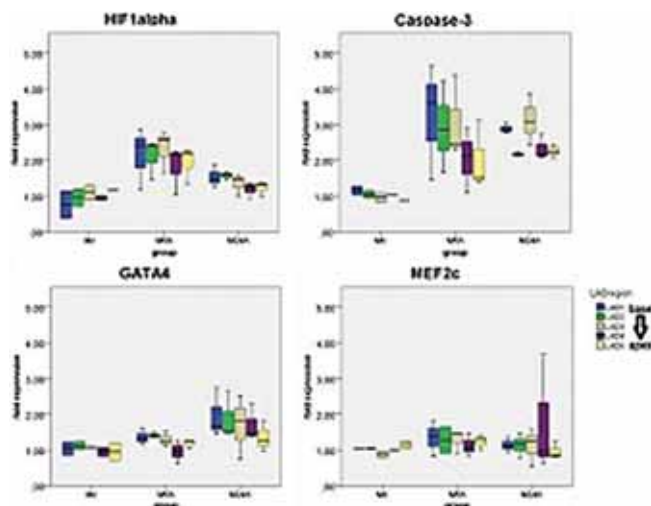


Figure 1

Conclusions: Short periods of repetitive ischemia/reperfusion without infarction cause alteration in gene expression profile of the myocardium, which might be responsible for the protective effect against subsequent infarction and necrosis.

P1649 | BENCH

Chronic treatment with NAD-containing drug induces anti-inflammatory and antioxidant changes and protects against ischemia-reperfusion injury

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Purpose: The goal of this study was to examine whether administration of first NAD⁺-containing drug, Nadcin, offers protection against I/R and whether it induces any change in the myocardial inflammation and endogenous antioxidant enzyme activities.

Methods: Rabbits were subjected to 1 h ischemia by occluding (60 or 75% reduction in left ascending coronary flow) and after ischaemia, a reperfusion phase was started, which lasted for 3 hours. The rabbits were divided into 4 groups (n=18): the sham group, the I/R group, the I/R + propranolol, and the I/R + Nadcin group. Nadcin and propranolol were administered from 15 minutes after ischaemia in-

duction. Superoxide dismutase (SOD), and glutathione peroxidase (GP) activity; malondialdehyde level (MDA); NF-kBp65, and sirtuin 1 (SIRT1) expression; and nitric oxide (NO) and proinflammatory cytokine production were examined.

Results: Nadcin (15-30 mg/kg) caused a significant reduction in infarct size, when compared with DL-Propranolol (10 mg/kg) treated hearts (45.6±1.5% vs 23.8±1.0%, p<0.001). Nadcin decreases the release of purine nucleosides by 39% (P<0.005) and oxypurines and decreased ATP breakdown in I/R. This reduction did not seem to be due to a negative inotropic action of the drug. Reperfusion under administration of Nadcin fully restored pH, developed pressure (to 93%), and NAD/NADH ratio and creatine phosphokinase activity. In the Nadcin-treated group, intestinal tissue injury, TNF-alpha level, and tissue MDA levels were significantly lower than in the I/R group (p<0.05). GP and SOD levels were significantly higher in the Nadcin-treated group than in the I/R (p<0.05) and propranolol groups. Nadcin normalized NO production and obviously upregulated the expression of SIRT1 and inhibited the activity of NF-kB. Furthermore, the protective effect of Nadcin was directly correlated with SIRT1.

Conclusions: Nadcin, as a first NAD⁺-containing drug, protects intestinal sub-acute I/R injury via the SIRT1-NF-kB pathway and occurs positive action on the antioxidant defense system. Nadcin, has a potential clinical prospect for further development of anti-injury therapy and pharmacology strategy of conserves energy in the ischemic heart.

P1650 | BENCH

Characteristics of vascular responses to drug eluting stents in rabbits: evaluated by optical coherence tomography and gene expression analyses

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Background: Recent several clinical studies suggest that second-generation cobalt-chromium everolimus-eluting stents (CoCr-EES) lead to more favorable vascular responses than first-generation sirolimus-eluting stents (SES). However, it remains unclear the difference of vascular responses between CoCr-EES and SES.

Methods: A total of 42 stents (14 bare-metal stents [BMS], 13 CoCr-EES, and 15 SES) were deployed in the iliac arteries of 31 Japanese White rabbits. Optical coherence tomography (OCT) and quantitative real-time reverse-transcription polymerase chain reaction (QRT-PCR) analyses of the neointima were performed on days 30 and 90 after the stent implantation.

Results: OCT showed that CoCr-EES and BMS had a more favorable stent-strut coverage than the SES at both 30 and 90 days after the implantation. The SES showed significantly less neointimal thickening than the CoCr-EES and BMS on day 90 (SES, 0.077±0.037; EES, 0.108±0.046; BMS, 0.119±0.076 mm, P<0.001). In the QRT-PCR analyses, on day 30, the gene expression of the angiogenic growth factors (hepatocyte and basic fibroblast growth factors) and proteoglycans (decorin, biglycan and lumican) were more upregulated in the BMS than in the SES. However, at 90 days after stenting, the gene expression of proteoglycans and collagen was more upregulated in the SES than in the CoCr-EES and BMS.

Conclusions: CoCr-EES as well as BMS demonstrated a greater strut coverage than the SES. Compared to the CoCr-EES, the vascular healing-related gene expression was rather upregulated in SES in the late phase, representing an ongoing active vascular healing process. These differences may lead to different clinical outcomes in humans.

P1651 | BENCH

Oxidative DNA damage and repair measurement by comet assay in STEMI patients

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Purpose: Acute myocardial infarction causes ischemia and generation of free oxygen radicals. Half-life of these molecules is short, measurement and accurate detection is difficult. We use DNA damage in peripheral leucocytes measured by comet assay test, using measurement of single-strand breaks (SSB), and oxidative damage of DNA by Endonuclease III (ENDO) and formamidopyridin-DNA glycosylase (FAD).

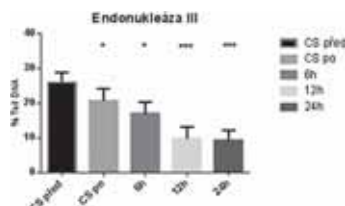


Figure 1. Oxidative damage by Endonuclease III.

Methods: In group of patients with ST-acute myocardial infarction we took samples from coronary sinus before primary PCI and after reperfusion, and peripheral venous samples after 6, 12 and 24 hours after PCI.

Results: The largest DNA damage detected by all methods (SSB, ENDO and FAD) was found before and immediately after PCI ($31.2 \pm 18.1\%$ Tail DNA). After 6 hours we detected significant decrease of DNA breaks ($16.1 \pm 4.5\%$ Tail DNA; $p < 0.05$) and with more decrease DNA repair after 12 ($12.1 \pm 6.9\%$ Tail DNA; $p < 0.0001$) and 24 hours ($13.8 \pm 6.9\%$ Tail DNA; $p < 0.0001$).

Conclusions: Acute myocardial infarction is connected with DNA oxidative damage; we can measure oxidative damage using DNA endonuclease and formamidopyridin DNA glycosylase, with significant repair after 6, 12 and 24 hours.

STEMI

P1653 | BEDSIDE

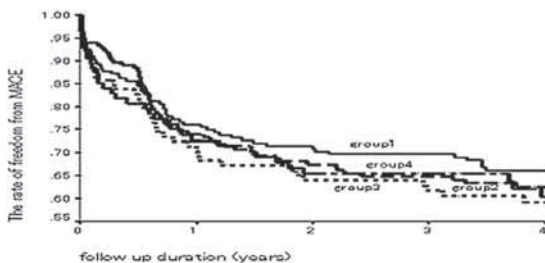
Door-to-balloon time and long-term outcome in patients with ST-T segment elevation myocardial infarction

R. Ishihara¹, A. Tosaka¹, T. Katagiri¹, T. Mizumura¹, Y. Sugimura¹, N. Abe², N. Hashizume², T. Miura², T. Tsuzimura³, T. Ishihara³. ¹Kawakita General Hospital, Tokyo, Japan; ²Shinshu University Hospital, Matsumoto, Japan; ³Kansai Rosai Hospital, Amagasaki, Japan

Purpose: In some studies, delay the door-to-balloon (DTB) time is associated with higher mortality. However, in other studies, there is no reduction in mortality despite a decrease in DTB time. In this study, we assessed whether DTB time relate long term outcome in patients with ST-T segment elevation myocardial infarction (STEMI).

Methods: This study was multicenter, retrospective observational study. We investigated a total of 724 acute myocardial infarction (AMI) patients underwent primary PCI between January 2006 and December 2010. Out of these patients, we reviewed 563 STEMI patients except not revealed accurate DTB time case. We classified that into four categories depending on DTB time; within 60 minutes (group 1), 61-90 minutes (group 2), 91-120 minutes (group 3), and longer than 120 minutes (group 4), and compared the outcome in each groups. Outcome measures were in-hospital complications (all-cause death, recurrent myocardial infarction, stroke, major bleeding or access site complications needing procedure) and major adverse cardiovascular events (MACE: all-cause death, target vessel revascularization, recurrent myocardial infarction, admission of heart failure).

Results: Mean DTB time is 115 ± 163 minutes, and mean follow up period is 3.7 years. There are 190 patients in group 1, 166 patients in group 2, 111 patients in group 3, and 96 patients in group 4. During initial hospitalization, the complications rate are 10% in group 1, 10.2% in group 2, 14.4% in group 3, and 12.5% in group 4 ($P=0.635$). Kaplan-Meier survival curves show that the rate of freedom from MACE are 66.1% in group 1, 63.4% in group 2, 60.5% in group 3, and 65.5% in group 4 at 3.7 years ($P=0.95$).



Conclusion: Reduction in door-to-balloon time doesn't relate in-hospital complications rate and it doesn't also improve long-term outcome in STEMI patients.

P1654 | BEDSIDE

Onset-to-balloon time and long-term outcome in patients with ST-T segment elevation myocardial infarction

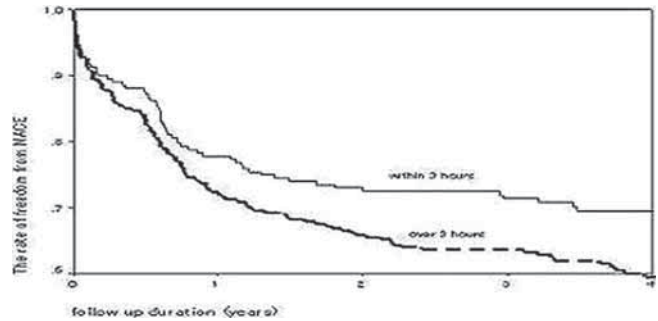
R. Ishihara¹, A. Tosaka¹, T. Katagiri¹, T. Mizumura¹, Y. Sugimura¹, N. Abe², N. Hashizume², T. Miura², T. Tsuzimura³, T. Ishihara³. ¹Kawakita General Hospital, Tokyo, Japan; ²Shinshu University Hospital, Matsumoto, Japan; ³Kansai Rosai Hospital, Amagasaki, Japan

Purpose: In some studies, delay the onset-to-balloon (OTB) time is associated with higher mortality rather than delay the door-to-balloon time. In this study, we assessed whether OTB time relate long term outcome in patients with ST-T segment elevation myocardial infarction (STEMI).

Methods: This study was multicenter, retrospective observational study. We investigated a total of 724 acute myocardial infarction (AMI) patients underwent primary PCI between January 2006 and December 2010. Out of these patients, we reviewed continuous 575 STEMI patients except not revealed accurate OTB time case. We classified that into two categories depending on OTB time; within 3 hours and over 3 hours. Outcome measures were in-hospital complications (all-cause death, recurrent myocardial infarction, stroke, major bleeding or access site complications needing procedure) and major adverse cardiovascular events (MACE:

all-cause death, target vessel revascularization, recurrent myocardial infarction, admission of heart failure).

Results: Mean OTB time is 10.6 ± 20.2 hours, and mean follow up period is 3.6 years. There are 232 patients in within 3 hours group (group 1) and 343 patients in over 3 hours group (group 2). In patients characteristics, there is statistical significant differences about mean max CPK (3340 vs 2611 , $P=0.004$), number of lesion (1.51 vs 1.69 , $P=0.008$), and left ventricular ejection fraction after PCI (55.7 vs 51.8 , $P=0.001$) between two groups. During initial hospitalization, the complications rate are 4.5% in group 1 and 5.9% in group 2 ($P=0.618$). Kaplan-Meier survival curves showed that the rate of freedom from MACE are 69.5% in group 1 and 62.0% in group 2 at 3.6 years ($P=0.039$).



Conclusion: Onset-to-balloon time within 3 hours reduces the risk of MACE in long term outcome.

P1655 | BEDSIDE

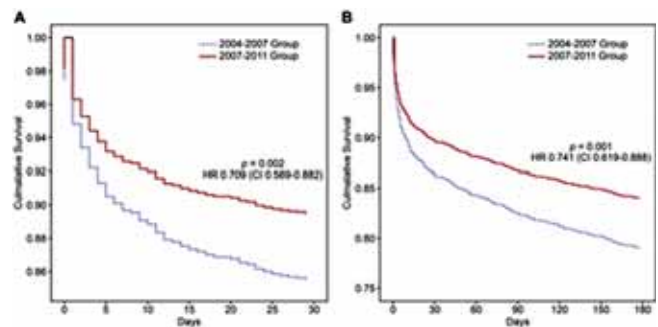
Implementation of an acute myocardial infarction clinical pathway is associated with improvement in clinical outcomes

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Purpose: Acute myocardial infarction (AMI) is associated with high mortality. However, compliance with evidence-based treatments is suboptimal. The implementation of a clinical pathway has been shown to improve adherence to AMI treatment, but whether this effect results in improved clinical outcomes is unclear. Therefore, this study was designed to explore the potential association between clinical pathway implementation and AMI clinical outcomes.

Methods: This retrospective cohort study was conducted in a department of cardiology of a university hospital. Consecutive patients admitted with a principal diagnosis of AMI between 2004 and 2011 were categorised into two cohorts: before (2004-2007) and after (2007-2011) the implementation of a clinical pathway. The case fatality rate (CFR) was assessed by multivariate logistic regression, and survival was assessed by Cox proportional hazards regression analyses.

Results: A total of 2029 consecutive AMI patients, 859 before and 1170 after the clinical pathway implementation, were identified. The in-hospital CFRs for the two cohorts were 14.6% and 10.9%, respectively (odds ratio (OR) 0.649 [CI 0.492-0.856], $p=0.002$). The 30-day CFRs were 18.4% and 14.9%, respectively (OR 0.672 [CI 0.521-0.868], $p=0.002$), and the 6-month CFRs were 26.0% and 22.9%, respectively (OR 0.700 [CI 0.555-0.881], $p=0.002$), according to the multivariate analysis. Cox regression models showed significant improvement in survival at both 30 days ($p=0.002$) and 6 months ($p=0.001$) in the post-pathway cohort.



A. 30-day and B. 6-month survival curve

Conclusions: Implementation of the AMI clinical pathway was associated with a significant reduction in the AMI CFR and improvement in survival.

P1656 | BEDSIDE**Lower in-hospital mortality in STEMI patients with postponed angioplasty after successful pre-transfer medication compared with primary angioplasty. RO-STEMI registry data**

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Background: 1. A national program for interventional therapy in STEMI pts was opened in August 2010 in Romania. 2. In real life it is difficult to perform primary angioplasty (PPCI) within the first 2 hours after the first medical contact (FMC) as guidelines recommend. In these circumstances a pharmacoinvasive approach consisting in pre-transfer medication with 150 mg. aspirin, 600 mg. clopidogrel, 5000 i.u unfractionated heparin and with/without thrombolysis is recommended.

Objective: To compare the in-hospital mortality in STEMI pts treated in Romania between January 1st 2012–December 31st, 2013 according to the therapy as follows: 1.PPCI; 2.rescue PCI; 3.postponed PCI if ECG criteria of reperfusion at admission in the PCI center; 4. thrombolysis only; 5. not undergoing reperfusion therapy.

Methods: A STEMI network consisting in 14 PCI centers and a large scale pharmaco-invasive approach is the strategy of the Romanian national program. According to our protocol, pts with FMC-to-PCI time estimated within 2 hours are directly transported to the one of the 14 PPCI centers. 2. In pts with a FMC-to-PCI longer than 2 hours pre-transfer thrombolysis is strongly recommended. Aspirin, clopidogrel and unfractionated heparin are also recommended for all pts. PPCI or rescue PCI are performed in all pts with persistence of the chest pain and of the ST-segment elevation at admission in the PCI center. For pts with cessation of the chest and more than 50% ST-segment resolution the PCI center personnel have the liberty to perform PCI immediately after admission or to postpone PCI for the next 3 to 48 hours. Pts data are recorded in the Romanian registry of STEMI (RO-STEMI registry).

Results: A total of 15955 pts were recorded in the RO-STEMI registry in 2012 and 2013. The lowest in-hospital mortality (1.98%) was seen in pts with postponed PCI (N=808) followed by PPCI (4.35%, N=7253), rescue PCI (4.43%, N=856), thrombolysis only (9.93%, N=1321, and pts not undergoing reperfusion (14.86%, N=5717). The differences between postponed PCI versus PPCI and postponed PCI or PPCI or rescue PCI versus thrombolysis alone or not undergoing reperfusion were significant ($p < 0.0001$ for all comparisons).

Conclusions: The RO-STEMI registry data suggest that a postponed PCI strategy in pts showing non-invasive criteria of reperfusion after a pre-transfer medication consisting in aspirin, clopidogrel and heparin with/without thrombolysis is followed by a lower in-hospital mortality compared with PPCI.

P1657 | BEDSIDE**A large-scale prospective cohort study on the current status of therapeutic modalities for acute myocardial infarction in China: initial results of the China Acute Myocardial Infarction Registry**

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Objective: Little is known about the management of acute myocardial infarction (AMI) in the real world in China. The purpose of this study was to build a comprehensive database on Chinese patients with AMI to elucidate their characteristics.

Methods: Among 30 provinces, municipalities or autonomous districts in China, at least one tertiary and secondary hospital was selected. Between January 2013 and November 2013, we consecutively registered all patients with AMI within 7 days after the onset of AMI in 93 participating medical institutions. A standardized case report form was used to register all the patients.

Results: A total of 10474 consecutive patients was registered (7784 men, 74.3%; 2690 women, 25.7%) with a age of 61 ± 18 years. Only 1153 (11.0%) patients used an ambulance as transportation to the hospital. Among 7442 patients (71.1%) with ST elevation myocardial infarction (STEMI), 24.7% were admitted within the first 3 h, 51.6% within 6 h, 68.2% within 12 h, 79.1% within 24 h of onset of symptoms. Primary percutaneous coronary intervention (PCI) and thrombolysis were conducted for 3312 (43.8%) and 842 patients (11.1%), respectively. Among 3032 patients (28.9%) with non ST elevation myocardial infarction (NSTEMI), primary PCI were performed in 255 patients (8.8%). During initial hospitalization, the overall in-hospital mortality rate was 4.6% and 3.8% for STEMI and NSTEMI, respectively.

Conclusion: Findings from the China Acute Myocardial Infarction Registry provide an overview of the treatment that patients actually receive and the outcome, providing the opportunity to assess daily practice in a large population of patients with AMI in China.

P1658 | BEDSIDE**In-hospital myocardial infarction: incidence, patient characteristics and clinical outcome: results from a 10 year single-centre myocardial infarction registry**

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Background: Acute ST elevation myocardial infarction (STEMI) occurring in patients while being already in a hospital (in-hospital myocardial infarction), is rarely given sufficient consideration and is also poorly characterised.

Methods: We retrospectively analysed all patients with an acute STEMI who were treated at our hospital between 2000 and 2009 (MIRLU-Registry).

Results: Between 6/2000 and 12/2009 3143 patients with an acute STEMI were included in our database. An IH-MI was present in 90 (2.9%) of these patients. The proportion of ICH-MI did not change from 2000-2009 and varied between 0.3 and 4.4% per year.

	IH-MI (n=90)	no IH-MI (n=3053)	p-value
Age	69.4±11.8	63.4±13.4	<0.001
Women	34%	29%	ns
Anterior wall MI	54.7%	48.1%	ns
Left bundle branch block (LBB)	5.6%	3.4%	ns
Cardiogenic shock	22%	11%	<0.01
Pre-hospital delay (min)	—	179	
Door-to-angio time (min)	112	47	<0.001
Symptom-to-angio time (min)	142	300	<0.001
Coronary angiography	94.4%	98.2%	<0.05
Reperfusion therapy (PCI/CABG)	73.3%	87.1%	<0.001
Hospital death	24.4%	6.3%	<0.001

Conclusions: IH-MI are present in about 3% of all STEMI in current clinical practice. We did not observe a change in IH-MI occurrence during our observational period. Patients with an IH-MI were older and presented more often in cardiogenic shock. Their in-hospital time to treatment was longer, however, total ischemic time (symptom onset to angio time) was shorter compared to non IH-MIs. Invasive diagnosis and interventional therapy was performed less frequently and in-hospital mortality was more than three times higher compared to patients without IH-MI. Therefore hospitals should be more aware of patients suffering an IH-MI.

P1659 | BEDSIDE**Management of multivessel coronary disease in STEMI patients; a systematic review and meta-analysis**

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Introduction: Appropriate management for patients with multi vessel coronary disease presenting with ST Segment Elevation Myocardial Infarction (STEMI) remains to be defined.

Methods: Medline and Cochrane Library were searched for randomized controlled trials (RCTs) or observational studies adjusted with multivariate analysis reporting about STEMI patients with multivessel coronary disease treated with culprit only or with complete revascularization, excluding those in cardiogenic shock. Prespecified analysis were performed according to strategy of complete revascularization, either during the same procedure of primary Percutaneous Coronary Intervention (PCI) or during index hospitalization. MACE (death or myocardial infarction or revascularization) at follow up was the primary end point, its single components and 90 days MACE the secondary ones.

Results: 9 studies (4 RCTS) with 4486 patients compared culprit only and complete PCI performed during the primary PCI. Rates MACE did not differ at 90 days (OR 1.39 [0.79-2.46] I2 0%) and after a follow up of 1 year (OR 0.70 [0.38, 1.27] I2 0%) as those of its single components, apart from a reduction for repeated revascularization for complete PCI (OR 0.62 [0.39, 0.98] I2 0%).

6 studies (1 RCT) with 5855 patients compared culprit only lesions and complete PCI during index hospitalization. In hospital and after 1 year MACE rates did not differ (OR 0.90 [0.67, 1.21] I2 0%), with a similar benefit regarding repeated revascularization (0.60 [0.40, 0.90] I2 0%, all Confidence Interval 95%).

Conclusions: Complete revascularization performed during primary PCI or index hospitalizations for patients presenting with STEMI appears safe at short term follow up and offers a reduction for repeated revascularization at one year.

P1660 | BEDSIDE

Similar 3-year-mortality in patients with STEMI and NSTEMI for known as well as for newly diagnosed diabetes - Results of the SWEETHEART Registry

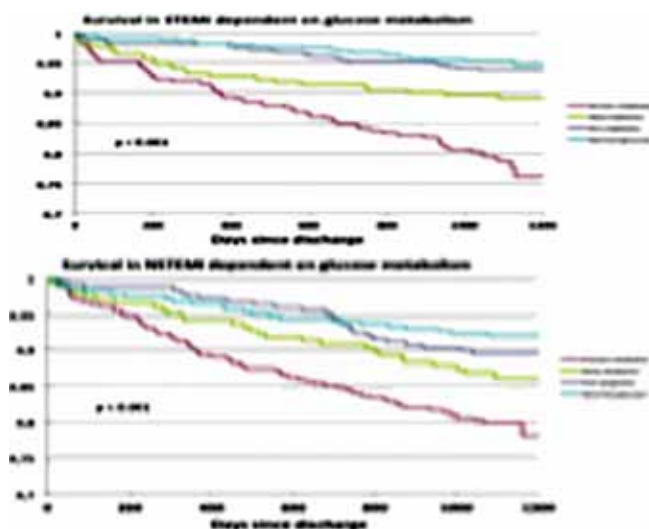
A.K. Gitt¹, J. Karcher², S.T. Schneider³, R. Zahn², P. Bramlage⁴, D. Tschoepe⁵ on behalf of SWEETHEART Study Group. ¹Heart Attack Research Center at the University of Heidelberg, Ludwigshafen am Rhein, Germany; ²Herzzentrum Ludwigshafen, Med. Klinik B, Kardiologie, Ludwigshafen am Rhein, Germany; ³Institut f. Herzinfarktforschung Ludwigshafen, Ludwigshafen am Rhein, Germany; ⁴Institute for Cardiovascular Pharmacology & Epidemiology, Mahlow, Germany; ⁵Heart and Diabetes Center NRW, Bad Oeynhausen, Germany

Background: Joint ESC/EASD guidelines recommend testing for diabetes (DM) using oral glucose tolerance test (OGTT) in patients with CAD.

Methods: The SWEETHEART-registry enrolled 2,767 consecutive patients (pts) with STEMI or NSTEMI to identify abnormal glucose metabolism and to document outcome. In pts without DM, OGTT was performed at day 4 after the MI. We examined the impact of known and newly diagnosed DM (new DM) on 3-year-outcome.

Results: OGTT detected 16.0% new DM in STEMI and 17.8% in NSTEMI. Pts with new DM were younger and suffered from less concomitant diseases. 3-year-mortality rates were high, both for known and for new DM, without differences between STEMI and NSTEMI.

	STEMI			NSTEMI		
	Known DM n=312 (20.1%)	New DM n=248 (16.0%)	p	Known DM n=377 (31.4%)	New DM n=213 (17.8%)	p
Age (y)	70	66	<0.001	72	70	<0.05
Females	33.7%	29.0%	<0.001	28.6%	32.4%	<0.001
Prior MI	18.7%	11.7%	<0.001	34.5%	14.1%	<0.001
Prior PCI	19.4%	9.3%	<0.001	30.9%	14.5%	<0.001
Prior CABG	9.0%	4.9%	<0.001	14.8%	8.0%	<0.001
Renal failure	19.3%	6.9%	<0.001	33.5%	12.3%	<0.001
PAD	12.8%	5.7%	<0.001	15.6%	9.0%	<0.001
Coro-Angio	95.5%	99.2%	<0.001	87.3%	96.7%	<0.001
PCI	84.6%	93.5%	<0.001	66.8%	79.3%	<0.001
Hosp. mortality	3.2%	4.0%	ns	2.7%	1.9%	<0.05
3-y-mortality	22.6%	11.1%	<0.001	21.0%	13.9%	<0.001



Conclusion: OGTT after acute MI identified new DM in 16.0% of STEMI and 17.8% of NSTEMI-pts. For known and new DM, 3-year-mortality was similar for STEMI and NSTEMI.

P1661

P1662 | BEDSIDE

Impact of preinfarction angina on one-year mortality in STEMI patients undergoing primary PCI

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Purpose: It has been postulated that patients with ST-segment elevation myocardial infarction (STEMI) who experience preinfarction angina might have smaller infarct size and better prognosis. Our goal was to evaluate impact of preinfarction angina on one-year mortality in STEMI patients undergoing primary percutaneous coronary intervention (primary PCI).

Methods: The study included 2266 patients with STEMI who underwent primary PCI in a high-volume center during the years 2010-2012. Patients with preinfarction angina (PA) had at least one episode of typical chest pain within 72h of presentation with STEMI. Kaplan-Meier cumulative survival curves for patients with and without preinfarction angina were compared with the log-rank test.

Results: Occurrence of preinfarction angina was reported in 69.5% of the studied population. Median time to reperfusion was significantly longer in patients with PA, as compared to patients without PA (285 minutes vs 249 minutes, $p=0.001$). The observed difference in the time to reperfusion was mainly due to the longer patient-related delay in patients with PA (165 vs 132 minutes, $p<0.001$). Health care system delay was similar in both groups ($p=0.49$). There was a trend towards lower levels of peak creatine kinase (CK) in patients with PA (1526 U/L vs 1715 U/L, $p=0.09$). Comparison of the Kaplan-Meier cumulative mortality curves with the log-rank test showed no significant difference between the two groups of patients ($p=0.385$).

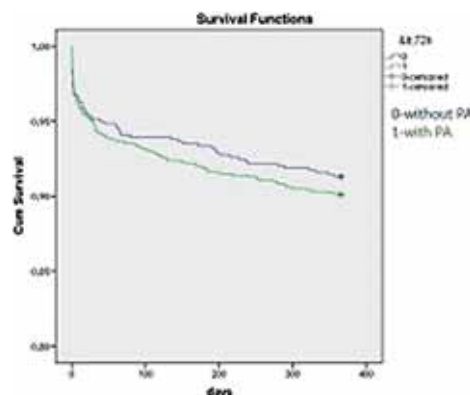


Figure 1

Conclusion: Preinfarction angina in patients undergoing primary PCI is associated with longer time to reperfusion, mainly due to longer delays in presentation. There is a trend towards lower peak CK values in these patients, but one-year mortality is similar as in patients without preinfarction angina.

P1663 | BEDSIDE

Comparison of the prevalence of cardiovascular risk factors and clinical presentation at admission in patients with takotsubo cardiomyopathy and STEMI

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Background: The clinical presentation of Takotsubo cardiomyopathy (TTC) mimics acute myocardial infarction and is most often characterized by chest pain, ST segment elevation, cardiac enzymes increase and left ventricular dysfunction.

Purpose: The aim of the analysis was to compare the prevalence of cardiovas-

cular (CV) risk factors in a population of patients (pts) with TTC and acute myocardial infarction with ST segment elevation (STEMI)

Methods: The analysis included 79 consecutive female pts diagnosed with TTC and 103 consecutive female pts with STEMI. In both groups compared the incidence of CV risk factors such as age, hypertension, diabetes mellitus, hypercholesterolemia, smoking cigarettes.

Results: The mean age of patients was 69.2 years in pts with TTC and 68.2 in the group of STEMI ($p>0.05$). Pts with TT had higher systolic blood pressure on admission (132.72 vs 124.14mmHg, $p<0.05$), lower ejection fraction (41.78 vs 45.59, $p<0.05$), a lower concentration of TnI (3.78 vs 63.17, $p<0.05$) and CKMBmass (14.76 vs 181.51, $p<0.05$). There was no differences in heart rate at admission (80.2 vs 80.8 bpm).

There was no difference in the incidence of CV risk factors such as age, hypertension, hypercholesterolemia, smoking cigarettes, diabetes mellitus ($p>0.05$) in the group of pts with the TT and STEMI. In addition, in follow-up consisting of a maximum of 7 years any pt remaining in follow-up had acute coronary syndrome diagnosed and had not performed coronary revascularization.

Conclusion: In pts with TTC the incidence of CV risk factors was the same as in the group of STEMI pts. Pts with TTC had higher systolic blood pressure, lower ejection fraction, lower TnI and CKMBmass on admission.

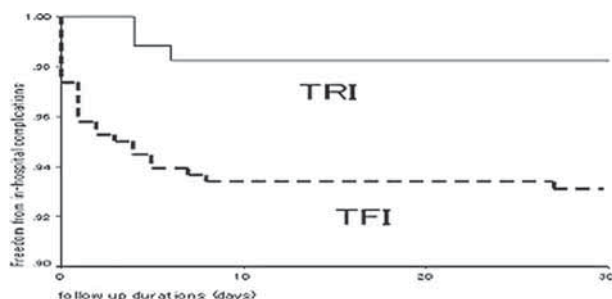
P1664 | BEDSIDE

Comparison of complications between transradial approach and transfemoral approach for patients with ST-T segment elevation myocardial infarction

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Purpose: Some trials have suggested that transradial intervention (TRI) reduces vascular complications and bleeding compared with transfemoral intervention (TFI). In this study, we aimed to assess the feasibility of TRI in patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI).

Methods and results: This study is multicenter, retrospective observational study. Between January 2006 and December 2010, we investigated a total of 783 acute myocardial infarction (AMI) patients underwent primary PCI. Out of these patients, we reviewed 553 STEMI patients except using intra aortic balloon pumping (IABP) and percutaneous cardiopulmonary support device (PCPS) patients. TRI was performed in 174 patients and TFI was performed in 379 patients. Mean follow-up period was 46 ± 25 months. Outcome measures were in-hospital complications (all-cause death, recurrent myocardial infarction, stroke, major bleeding) and major adverse cardiovascular events (MACE: cardiac death, target vessel revascularisation, recurrent myocardial infarction, admission of heart failure) at 3.8 years. During the initial hospitalisation, the complications rate was 1.1% in TRI group and 6.0% in TFI group ($P=0.025$). Kaplan-Meier survival curves showed that the freedom from MACE was 67.5% in TRI vs 68.0% in TFI at 3.8 years ($P=0.74$).



Conclusion: The in-hospital complications rate s were statistically lower in TRI group compared with TFI group, and TRI performed STEMI was feasible compared to TFI.

PREDICTORS OF OUTCOMES POST MYOCARDIAL INFARCTION

P1666 | BEDSIDE

Risk stratification for the development of heart failure after acute coronary syndrome at the time of hospital discharge: predictive ability of GRACE risk score

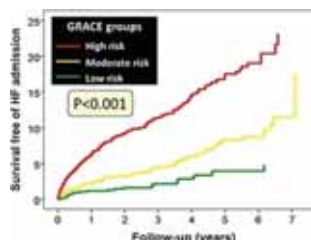
V. Gonzalez Salvado, A. Lopez Lopez, D. Iglesias Alvarez, R.A. Abellas Sequeiros, R. Gonzalez Ferreira, R. R Y Abumuaileq, S. Raposeiras Roubin, E. Abu-Assi, J.M. Garcia Acuna, J.R. Gonzalez Juanatey. University Hospital of Santiago de Compostela, Cardiology, Santiago de Compostela, Spain

Objectives: Despite encouraging declines in the incidence of heart failure (HF)

complicating acute coronary syndrome (ACS), it remains a common problem with high mortality. Being able to identify patients at high risk of HF after ACS would be of great clinical and economic impact. With this study, we assessed the usefulness of the GRACE score to predict HF after ACS.

Methods: We studied 4,137 consecutive patients discharged from a single center with diagnosis of ACS. We analyzed HF incidence, timing, and association with the follow-up mortality. Cox proportional hazards modeling was performed to assess the accuracy of the GRACE risk score to predict HF admissions in follow-up (median 3.1 years).

Results: 433 patients (10.5%) developed HF. GRACE score was an independent predictor of HF after ACS (HR 1.02, CI 95% 1.01-1.03, $p<0.001$). A risk gradient for the development of HF with GRACE risk score was shown (figure): high and moderate GRACE risk groups have been linked to a six- and two fold increased risk of HF. This risk gradient was maintained in patients with and without prior history of HF, in STEMI and NSTEMI groups, and in patients with depressed and preserved LVEF. The development of HF was associated with high mortality (54.5% vs 13.4%; HR=4.48; 95% CI, 3.84-5.24; $P<0.001$). After adjusting for GRACE risk score, HF development resulted an independent predictor of mortality.



Conclusions: GRACE risk score has shown to provide clinically relevant stratification of follow-up HF admission risk at the time of hospital discharge in patients with ACS.

P1667 | BENCH

Incidence and predictors of stroke after an acute myocardial infarction: specific aspects during the early phase and after discharge from hospital

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Purpose: Stroke is a severe complication after an acute myocardial infarction (AMI), and is closely associated with a poor prognosis. The aim of the study was to evaluate the frequency, characteristics and factors associated with in-hospital and post-discharge stroke after AMI. Prognosis at one year was also assessed for in-hospital stroke.

Methods: Observational study, including 8485 consecutive patients admitted for AMI between January 2001 and June 2010. Among others major adverse cardiac events (MACE), both ischemic and hemorrhagic stroke events were recorded during one year follow up.

Results: 168 (2%) stroke were recorded during the first year of follow-up after AMI. Most patients (123/168 (73.2%)) had a stroke during the hospital stay, and 87% within the 5 days after admission. The mortality at 30 days was higher in patients with in-hospital stroke than in patients without stroke (34.1% vs. 7.6%, $p<0.001$). After multivariate logistic regression, in-hospital stroke were independently associated with female sex (OR: 1.73, 95% CI: 1.19-2.51, $p=0.004$), previous stroke (OR: 2.21, 95% CI: 1.28-3.83, $p=0.004$), LVEF (OR: 0.96, 95% CI: 0.95-0.98, $p<0.001$), new onset AF (OR: 1.99, 95% CI: 1.25-3.16, $p=0.004$) and CRP (OR 1.006, 95% CI: 1.003-1.009, $p<0.001$). Among surviving patients ($n=7808$), 45 strokes (0.64%) were recorded during one year follow-up. After multivariate logistic regression analysis, post discharge stroke were independently associated with age (OR: 1.04, 95% CI: 1.01-1.07, $p=0.003$), previous stroke (OR: 3.69, 95% CI: 1.83-7.43, $p<0.001$) and hypertension (OR: 2.77, 95% CI: 1.26-6.08, $p=0.011$). During the ten years of inclusion, the annual rate of stroke after AMI remained stable.

Conclusions: The present study describes specific predictive factors for in-hospital stroke after AMI, with a high mortality rate. After discharge from AMI, stroke occurrence remains rare and mostly associated with a high cardiovascular risk.

P1668 | BEDSIDE

Outcome after MI in different socio-economic environments

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Purpose: To compare outcome and quality of secondary prevention in patients

after myocardial infarction (MI) of different socio-economic environments including patients from 3 teaching hospitals.

Methods: In this registry study, all patients hospitalized for MI (STEMI and NSTEMI with elevated troponin or CK-MB isoenzymes) in the year 2010 were included (exclusion criteria: Age over 75 years, survival less than 30 days after acute event, previous MI). Outcome data was extracted from treatment reports. Participation in a cardiac rehabilitation programme was quantified from questionnaires sent out in 2013. 3.5-year mortality was determined from mortality statistics and registration offices in 2013 and early 2014.

Patient characteristics of the different hospitals

	Hospital		
	Switzerland	Poland	Ukraine
Patients admitted with first ACS	547	375	164
Age, mean $\pm$ SD	59.0 $\pm$ 10.4	59.0 $\pm$ 9.9	60.4 $\pm$ 10.1
Females	26.5%	27.0%	27.4%
Smokers	49.3%	55.9%	73.5%
Diabetes	12.5%	22.3%	14.6%
Obesity BMI > 30.0	20.3%	33.3%	29.3%
Thrombolysis	0.0%	0.0%	20.1%
PTCA	100%	92.3%	0.0%
3.5-year mortality	2.9%	8.5%	14.6%
Returned Questionnaires (percent of totally admitted patients)	343 (62.7%)	204 (54.4%)	92 (56.8%)
Participation in Cardiac Rehabilitation (percent of returned questionnaires)	238 (69.4%)	105 (51.4%)	24 (26%)

Conclusions: There were substantial differences in treatment and secondary prevention measures according to low-, middle- and high income socio-economic situation. These differences lead to a 4-fold difference in mortality. Countries with low socio-economic environment should be better supported to improve care in particular for MI patients.

P1669 | BEDSIDE

The association between the magnitude of hs-troponin decline and 12 month mortality outcome

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Purpose: An observed rapid fall in hs-troponin (hs-Tn) within the first 24 hours after the peak effect is commonly observed. However, the clinical significance is unknown. We explored the relationship between magnitude of hs-Tn drop and late mortality.

Method: A dataset of all patients with hs-TnT drawn across several hospitals between 2011-2012 was used. This allowed a minimum 12-month evaluated follow up. All hs-TnT measurements were performed on the Roche Elecsys assay. Patients with no rise, continual rise and only with a single sample of hs-TnT were excluded. Mortality was assessed using the state mortality register. Patients were arbitrary divided into 0-20% (Group 1), 21-50% (Group 2) and > 50% drop (Group 3) in hs-TnT. Outcomes were compared in univariate and multivariate logistic regression.

Results: A total of 3,585 patients were available for analysis of which there were 2,270 in Group 1, 1,288 in Group 2 and 300 in Group 3. The mortality observed in Group 1 was 18.9% (430 patients), Group 2 14.7% (189 patients) and Group 3 8.7% (26 patients) ($p < 0.001$). The median age of Group 1 was 80 years, Group 2 76 years and Group 3 65 years ($p = 0.001$). Patients in Group 1 were more likely to have a lower baseline renal function (median eGFR = 52 ml/min/1.73m²), Group 2 (median eGFR = 63ml/min/1.73m²) and Group 3 (median eGFR = 73ml/min/1.73m²) ($p = 0.001$). After adjusting for the maximum troponin elevation and baseline renal function, the greater magnitude of hs-TnT decline was associated with a decrease in mortality at 12 months. (Group 2, OR=0.82 (CI=0.67-0.98, $p = 0.03$)) and Group 3, OR=0.51 (CI=0.33-0.77, $p = 0.001$)). However after adjusting for age and renal function, this was no longer statistically significant (Group 2, OR=0.93 (CI=0.76-1.13, $p = 0.45$)), Group 3, OR=0.79 (CI=0.51-1.22, $p = 0.29$)).

Conclusion: A rapid decline in hs-Tn has a better prognosis although this benefit might be explained by a younger age group.

P1670 | BEDSIDE

The evolution of high-sensitivity troponin-T in asymptomatic post-ACS patients who remained event free during 400 days follow-up

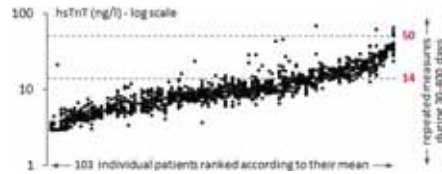
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Background: Limited data are available on high sensitivity (hs) Troponin T (TnT) and its evolution during one year follow-up in asymptomatic patients stabilised after acute coronary syndrome (ACS) admission.

Purpose: Describe 1-year hsTnT patterns in asymptomatic patients after ACS.

Methods: BIOMArCS is an observational study of ACS patients in 18 hospitals in our country. Treatment is left to the discretion of the physician. During 1 year follow-up, 20 repeat blood samples are taken at preset time intervals. Serum and plasma are separated and stored on site at -80°C within 2h, until batch analysis in the central laboratory of the Erasmus MC. This abstract describes 103 patients who remained free of death, readmission for ACS, coronary revascularisation and anginal symptoms until 400 days. We determined hsTnT with the Roche STAT on Cobas e system in their repeated samples.

Results: Mean age was 65 (SD 5) years, 79% were men, 64% had STE-ACS. Patient profile was typical for an ACS population. Discharge medication included antiplatelet therapy (99%) and statins (97%). Median peak hsTnT value within 7 days was 632 (IQR 192 to 1640) ng/l. During 30 to 400 days 1574 repeated blood samples were collected, with a median of 16 (IQR 15 to 17) for each patient. HsTnT above 14 ng/l (upper limit of normal) was observed in 26% of samples (in 49% of patients). The level of 50 ng/l was exceeded in 10 (0.6%) samples only. The within-patient variability explained 21% of total variation, and was thus much smaller than the between-patient variability (figure). The mean change in hsTnT between 30 and 400 days was -1.4 ng/l.



Conclusions: Asymptomatic post-ACS patients have fairly stable hsTnT during 400 days. Half of the patients have values above normal. Interpatient variability is substantial.

P1671 | BEDSIDE

High sensitivity troponin T predicts adverse cardiac magnetic resonance imaging changes in revascularised ST elevation myocardial infarction

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Purpose: High sensitivity troponin T (hs-TnT) is a sensitive biomarker used to diagnose acute myocardial infarction (AMI), with recent evidence suggesting it outperforms conventional TnT as a prognostic marker. Peak and time point conventional TnT levels (48 and 72 hours), are known prognostic markers. We sought to evaluate the relationship between hs-TnT levels with known adverse prognostic markers on cardiac magnetic resonance imaging (CMRI).

Methods: 90 consecutive patients with first presentation STEMI, undergoing PCI, were prospectively enrolled. Serial hs-TnT measurements were performed to determine peak, 48 hour and 72 hour levels. CMRI was performed at 5 $\pm$ 3 days (early) and 61 $\pm$ 14 days (follow-up) post STEMI. Left ventricular ejection fraction (LVEF) and mass were determined on cine MRI images by standard techniques. LV infarct size was determined by planimetry (mean $\pm$ 5SD ROI) for core scar and 3-5SD for border zone (BZ) scar on delayed gadolinium enhancement images.

Results: The study cohort (90% males, mean age 56 $\pm$ 10 years), comprised of 13 (14%) who were diabetic and 49 (54%) who presented with an anterior STEMI. Peak, 48 hour and 72 hour hs-TnT levels negatively correlated with early and follow-up LVEF. All hs-TnT level parameters positively correlated with early and LV infarct size. Hs-TnT levels additionally correlated positively with both early and follow-up LV scar border zones. Utilizing a ROC curve analysis, 72 hr hs TnT > 3,500 ng/L had a sensitivity 77% and specificity 84% in identifying patients with a follow-up LVEF < 40%.

Table 1

Parameter	Mean $\pm$ SD	Peak hs-TnT level	48hr hs-TnT level	72hr hs-TnT level
LVEF – early (%)	46 $\pm$ 8	r=-0.52	r=-0.56	r=-0.60
LVEF – follow-up (%)	50 $\pm$ 10	r=-0.54	r=-0.52	r=-0.58
LV scar – early (%)	9.8 $\pm$ 5.6	r=0.58	r=0.63	r=0.65
LV scar – follow-up (%)	8.3 $\pm$ 5.5	r=0.63	r=0.67	r=0.68
LV scar BZ – early (%)	10.7 $\pm$ 5.2	r=0.52	r=0.57	r=0.58
LV scar BZ – follow-up (%)	14.5 $\pm$ 8.2	r=0.54	r=0.59	r=0.60

All $p < 0.001$.

Conclusion: Peak, 48 hour and 72 hour hs-TnT levels are associated with adverse LV scar size and functional parameters during early LV remodeling post STEMI. 72 hour hs-TnT levels correlated best with LV scar size and reduced LVEF. With long term follow up, these may be useful surrogate markers of adverse outcomes in STEMI.

P1672 | BEDSIDE**Validation of two North-american risk scores for percutaneous coronary intervention in an European population of patients with acute coronary syndromes - comparison with GRACE risk score**

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Introduction: GRACE risk score is an established tool for risk stratification in patients with Acute Coronary Syndromes (ACS). Recently, two new tools developed in the US for hospital mortality risk stratification in patients submitted to coronary angioplasty have been published: the National Cardiovascular Data Registry (NCDR) and the Mayo Clinic Risk Score (MCRS). Both were validated in US populations. We sought to validate these score in an European population and compare its' predictive accuracy with the classical GRACE risk score.

Methods: Patients included in a single-centre ACS registry. Only patients submitted to coronary angioplasty were included in the analysis. For each score, a hospital mortality probability was given to each patient, who allowed building Receiver Operating Characteristics (ROC) curves and the Area Under Curve (AUC) was used to evaluate discriminative capacity of the model. Model accuracy was evaluated with a graphical representation of observed vs. expected mortality. We also analysed Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI) for comparison of GRACE risk score with NCDR and MCRS scores.

Results: We included in the analysis 2.148 consecutive patients admitted with an ACS and submitted to coronary angioplasty. Mean age was 63 ± 13 years, 74% males and 71% presented with ST-segment elevation acute myocardial infarction. Hospital mortality was 4.5%. In ROC curve analysis, GRACE score showed the best AUC (0.94, 95% CI 0.91 – 0.96) compared with NCDR (0.87, 95% CI 0.83 – 0.91) and MCRS (0.85, 95% CI 0.81 – 0.90). GRACE score AUC was significantly higher compared with NCDR ($p=0.0003$) and MCRS ($p=0.0003$). In model calibration analysis, GRACE score showed the best predictive power, followed by NCDR and lower with MCRS, although we might consider it adequate. With GRACE score, patients were more correctly classified compared with MCRS (NRI 0.787, 95% CI 0.596 – 0.977, $p<0.001$; IDI 0.136, 95% CI 0.073 – 0.199, $p<0.001$) and NCDR (NRI 0.792, 95% CI 0.602 – 0.982, $p<0.001$; IDI 0.148, 95% CI 0.087 – 0.209, $p<0.001$).

Conclusion: NCDR and MCRS risk scores are useful for risk stratification of hospital mortality in an European population of patients with ACS submitted to coronary angioplasty. However, GRACE score has a better predictive power, and as such it should be the preferred score to be used.

P1673 | BEDSIDE**Acute coronary syndrome in elderly patients - prognostic impact of revascularization**

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Introduction: The proportion of patients with acute coronary syndrome (ACS) who are very old is increasing. These patients are a therapeutic challenge because they are rarely included in randomized clinical trials.

Aim: Determine clinical presentation, therapeutic approach and prognosis in a population of octogenarians (Oct) with ACS.

Methods: Retrospective study of 2064 patients admitted for ACS in a coronary unit over a period of 4 years. 2 groups were defined according to age: younger (age <80 years, mean age = 60.9 ± 11.4 , $n=1795$) and Oct (age ≥ 80 years, mean age = 83.9 ± 3.4 , $n=269$).

Analysis of Oct according to therapeutic approach: percutaneous/surgical ($n=177$) vs medical ($n=92$). We determined the predictors of mortality in this group.

Results: In elderly patients there was a higher proportion of women ($p<0.001$) and comorbidities, such as chronic kidney disease ($p<0.001$), prior ACS ($p=0.001$) and previous stroke ($p<0.001$). Non ST Elevation Myocardial Infarction (NSTEMI) was the most common form of presentation in Oct ($p=0.045$). These patients had more multivessel disease ($p=0.005$), although they were less likely to receive evidence-based medical therapies or receive coronary angiography ($p<0.001$) and revascularization ($p<0.001$). Moderate to severe left ventricular dysfunction (LVD) was more common in Oct ($p<0.001$). Mortality was significantly higher in Oct than in young: 14.1% vs 2.6% in-hospital ($p<0.001$) and 29.3% vs 6.2% after 6 months ($p<0.001$), respectively.

In a sub-analysis of Oct there were no significant differences in the demographic characteristics. The Oct non revascularized had the highest prevalence of Killip class ≥ 2 on admission ($p=0.049$) and moderate to severe LVD ($p=0.034$).

The in-hospital mortality (22% vs 10.2%, $p=0.009$) and at 6 months (37.1% vs 25.1%, $p=0.046$) were higher in the non revascularized Oct.

After multivariate analysis, Killip class ≥ 2 on admission (OR 3.6, 95% CI 1.3-9.8), presence of LVD (OR 6.0, 95% CI 1.1-31.1) and GFR ≤ 60 ml/min (OR 5.9, 95% CI 1.9-18.0) were independent predictors of in-hospital death in the Oct. The presence of LVD (OR 2.5, 95% CI 1.1-6.0), in-hospital heart failure (OR 3.6, 95% CI 1.6-7.9) and absence of beta-blocker therapy (OR 3.6 95% CI 1.6-7.9) were predictors of mortality at 6 months.

Conclusion: In this review, the elderly had worse prognosis and were less likely to receive evidence-based therapy. Although mortality was higher in oct patients under medical treatment, the absence of revascularization was not an independent predictor of mortality in this population.

P1674 | BEDSIDE**Incidence and implications of changes in left ventricular systolic function in a large regional ST-elevation myocardial infarction transfer system**

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Purpose: ST-elevation myocardial infarction (STEMI) is a common clinical event, often associated with detrimental effects on left ventricular systolic function (LVSF). However, limited real world data are available regarding which patients have further detriment or improvement in LVSF post-STEMI.

Methods: The "Level I MI" STEMI regional transfer system was initiated in 2003. Consecutive STEMI patients were followed prospectively for 5 years. The Level I database and electronic medical records were analyzed to see which patients had future improvement or detriment to LVSF post-STEMI.

Results: Over ten years (March 2003-March 2013), 3,720 STEMI patients were treated in the regional transfer system. Of the 3,573 patients that survived through discharge, 3,486 (97.6%) had a documented LVEF prior to discharge. Those 1,103 (30.9%) patients that had a follow-up echocardiogram or LVFSF assessment beyond 40 days post-discharge were assessed to determine change in LVFSF. One hundred twelve (18.7%) of the 599 patients with normal LVFSF ($>50\%$) at hospital discharge had decreased LVFSF after 40 days post STEMI, including 6 patients (1%) who had decreased to $<35\%$. Thirty-five (23.3%) of the 150 patients with severely reduced LVFSF ($<35\%$) had normalization of LVFSF after 40 days, with 96 (62.7%) improving to $>35\%$.

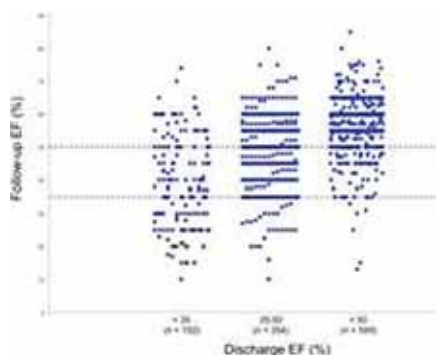


Figure 1

Conclusions: Left ventricular systolic function after STEMI changes in many patients regardless of discharge LVFSF. Close follow-up of LVFSF post-STEMI is warranted in all patients regardless of discharge LVFSF.

P1675 | BEDSIDE**The rs17228212 polymorphism in the intron of the SMAD3 gene is associated with 5-year mortality of patients with ST-elevation myocardial infarction**

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Purpose: The rs17228212 (C/T) is a single nucleotide polymorphism located within the intron of the SMAD3 gene. It was shown to be associated with coronary artery disease and myocardial infarction in a genome-wide association study with cysteine (C) as a risk allele (1). The mechanism, however, remains unknown. The aim of our study was to investigate the association of the polymorphism with 5-year overall mortality in patients with ST-elevation myocardial infarction (STEMI) treated invasively.

Methods: We included in our registry consecutive patients with STEMI treated with primary PCI who survived 48 hours from hospital admission. Genotyping was performed with a TaqMan SNP Genotyping Assay using the ABI 7500 Real Time PCR System (Applied Biosystems). The analyzed end-point was total 5-year mortality.

Results: The study group comprised 641 patients (mean age 62.0 ± 11.9 years; 25% of females, $n=160$; TIMI 3 obtained in 92.2%, $n=591$). The percentages of CC, CT and TT genotypes were: 6.1% ($n=39$), 35.4% ($n=227$) and 58.5% ($n=375$), consecutively. No significant differences were found between the genotypes in clinical characteristics. The 5-year total mortality was 16.4% ($n=105$). There died 23.1% ($n=9$) of CC homozygotes, 14.5% of heterozygotes ($n=33$) and 17.1% ($n=63$) of TT homozygotes ($p=0.047$, log-rank test).

Conclusions: The CC genotype of the rs17228212 polymorphism of the intron of the SMAD3 gene is associated with increased 5-year mortality in patients with STEMI.

P1676 | BEDSIDE**Effect of interleukin-6 genetic variability on the pathophysiology of atherosclerosis and the risk for coronary artery disease and myocardial infarction**

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Purpose: Interleukin-6 (IL-6) is an early marker of inflammatory activation, strongly related to the pathophysiology of coronary artery disease (CAD). The exact role of IL-6 gene on mechanisms of atherosclerosis remains unclear. In the present study we examined the impact of the G174C (rs1800795) genetic polymorphism of IL-6 gene promoter on inflammatory and thrombotic process, as well as on the extent of CAD in patients with stable angina pectoris.

Methods: We enrolled 405 patients with angiographically documented CAD and 295 healthy controls. Rs1800795 was estimated by PCR and digestion with SFA NI restriction enzyme. The endothelial function was determined with flow mediated dilation (FMD). High sensitivity C-reactive protein (hsCRP) (mg/l) and D-dimers (pg/l) were determined with immunonephelometry, while fibrinogen (fib) (mg/dl) with the Clauss method. IL-6 (pg/ml), TNF- α (pg/ml) and sCD40L (pg/ml) were assessed by ELISA.

Results: We have found that the C carriers compared to GG homozygotes had significantly higher levels of inflammatory markers not only in CAD (IL-6: 3.26 ± 1.13 vs 2.01 ± 0.87 , TNF- α : 6.37 ± 0.32 vs 4.80 ± 0.53 , hsCRP: 1.93 ± 0.64 vs 1.17 ± 0.49 , $p < 0.001$ for all), but also in controls (IL-6: 1.69 ± 0.4 vs 0.94 ± 0.31 , TNF- α : 2.17 ± 0.26 vs 1.32 ± 0.27 , hsCRP: 1.17 ± 0.49 vs 0.79 ± 0.39 , $p < 0.001$ for all). On the contrary, no significant effect was observed on coagulation markers in CAD patients (fibrinogen: 440.7 ± 129.2 vs 452.9 ± 141.4 , sCD40L: 1.61 ± 1.90 vs 2.29 ± 1.71 , D-dimers: 412.6 ± 215.1 vs 319.4 ± 328.3 , $p = \text{NS}$ for all). In controls, although there was a marginally positive effect on fibrinogen levels (fibrinogen: 394.4 ± 106.1 vs 365.3 ± 93.5 , $p = 0.047$) there was no effect in the rest of coagulation markers (sCD40L: 1.04 ± 2.23 vs 1.09 ± 2.31 , D-dimers: 284.9 ± 195.3 vs 288.1 ± 214.6 , $p = \text{NS}$ for all). Moreover, the C allele demonstrated a detrimental effect on endothelial function compared to GG homozygotes in CAD patients ($3.56 \pm 2.68\%$ vs $4.11 \pm 2.38\%$, $p = 0.003$) and in controls ($5.8 \pm 2.94\%$ vs $6.91 \pm 2.37\%$, $p = 0.02$). Although rs1800795 did not affect either the risk for CAD [OR=1.09, 95%CI (0.79-1.50), $p = \text{NS}$] or the risk for MI [OR=1.07, 95%CI (0.71-1.64), $p = \text{NS}$], the C allele carriers were associated with significantly more extensive CAD, as assessed by the presence of 2 or 3 vessels diseased versus one compared to GG homozygotes [OR=2.03, 95%CI (1.3-3.34), $p = 0.03$].

Conclusions: Our data suggest that the C allele of rs1800795 on IL-6 gene promoter significantly induces inflammatory processes and endothelial dysfunction, accelerating thus the atherosclerotic mechanisms in patients with already established CAD.

P1677 | BEDSIDE**Hyponatremia at discharge as a predictor of 12-month clinical outcomes in hospital survivors after acute myocardial infarction**

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Purpose: Little is known about the clinical implication of sodium levels at discharge in hospital survivors after AMI.

Methods: The study included 1,290 consecutive patients (64 $\pm$ 12 years; 877 men) who survived the index hospitalization after AMI. We determined the 12-month mortality rates of these patients.

Results: The 12-month mortality rate showed a U-shaped curve, with the lowest event rate at 137–139 mmol/L of serum sodium at discharge. Patients who died during the 12-month follow-up had lower sodium levels at discharge than those who had survived (137 ± 6 mmol/L vs 139 ± 4 mmol/L; $P < 0.014$). Hyponatremia at discharge was present in 210 patients (16.3%). In the Cox-proportional hazard model, hyponatremia at discharge (hazard ratio, 2.352; 95% confidence interval, 1.033–5.094; $P = 0.041$) was an independent predictor of 12-month mortality (Ta-

Table 1

Variables	Multivariate		
	HR	95%CI	P value
Age ≥ 70 years	1.583	0.685–3.659	0.283
Heart rate	0.997	0.978–1.016	0.754
Killip class ≥ 2	2.352	0.935–5.913	0.069
Hyperlipidemia	0.612	0.243–1.546	0.300
Previous ischemic heart disease	1.129	0.490–2.601	0.775
PCI at index hospitalization	0.405	0.182–0.902	0.027
Left ventricular ejection fraction	0.952	0.919–0.986	0.005
Creatinine at admission	1.087	0.836–1.412	0.535
Hemoglobin at admission	1.052	0.854–1.295	0.635
Log NT-ProBNP at admission	1.426	0.710–2.866	0.319
Sodium ≤ 135 (mmol/L) at discharge	2.352	1.033–5.094	0.041
Aspirin at discharge	0.382	0.116–1.249	0.111
Beta-blocker at discharge	0.675	0.303–1.505	0.337
Diuretics at discharge	1.604	0.690–3.729	0.273

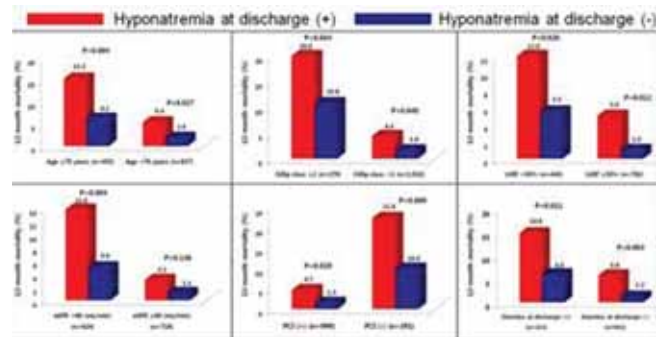


Figure 1

ble 1). In the subgroup analysis, the 12-month mortality of patients with hyponatremia at discharge was significantly higher than in those without, irrespective of age, Killip class, left ventricular ejection fraction, percutaneous coronary intervention at index hospitalization, and prescription of diuretics at discharge (Fig. 1).

Conclusion: Hyponatremia at discharge is an independent predictor of 12-month mortality in hospital survivors after AMI.

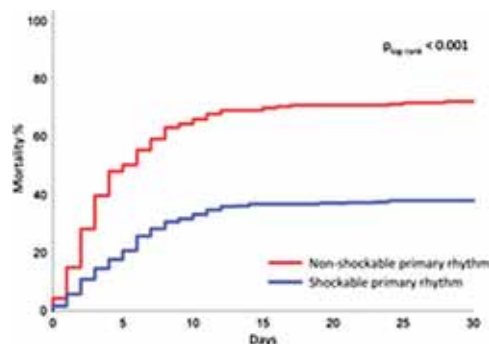
CARDIOGENIC SHOCK AND CARDIAC ARREST**P1679 | BEDSIDE****Comorbidity as a risk factor in survivors of non-shockable out-of-hospital cardiac arrest treated with hypothermia**

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Background: While the effect of hypothermia (TH) on mortality was demonstrated in out-of-hospital cardiac arrest (OHCA) patients presenting with shockable primary rhythm (SPR), the current guidelines recommend that patients from non-shockable primary rhythm (NSPR) should be cooled as well. We studied the influence of age and comorbidity on mortality in unconscious survivors of OHCA treated with TH, stratified by their primary rhythm.

Methods: Consecutive unconscious survivors of OHCA in a Capital Region treated with TH between 2002-2011 were included. Utstein-based pre- and in-hospital data collection was performed. Data on co-morbidity was coded according to the Charlson Comorbidity Index (CCI).

Results: 665 unconscious survivors of OHCA treated with TH were included, 233 (35%) presented with NSPR. Significantly fewer patients were alive 30 days after OHCA with NSPR (28% vs. 62%, $p < 0.0001$), see figure. When adjusting for potential confounders, NSPR remained a significant predictor of mortality (HR=2.26 (95% CI 1.67, 3.07)). In a stratified multivariate analysis (NSPR and SPR) adjusting for known prognostic factors including sex, time to ROSC, witnessed arrest, bystander life support and cardiac etiology, age at arrest (HR=1.28 (1.18, 1.39) per five years) was an independent predictor of mortality in SPR patients only, $p_{\text{interaction}} = 0.0018$. However having any comorbidity (CCI ≥ 1) was an independent predictor in NSPR patients (HR=1.67 (1.08-2.59)) but not in SPR patients.



Conclusion: Unconscious survivors of OHCA with a non-shockable primary rhythm treated with hypothermia, carry a significantly higher mortality rate than patients presenting with shockable rhythm. Comorbidity was an independent predictor in patients presenting with non-shockable primary rhythm but not in shockable patients.

P1680 | BEDSIDE**Mortality in patients with extracorporeal life support is predicted by early progression of pulmonary edema - a prospective study**

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Purpose: Extracorporeal life support (ECLS) serves as a powerful life-saving device in patients with cardiogenic shock refractory to conventional therapies. A potential shortcoming of veno-arterial (va) ECLS support consists in its inability to provide adequate decompression of the failing left ventricle (LV) which may further enhance backward failure with pulmonary edema.

Hypothesis: Worsening of pulmonary edema within the first 24 hours after initiation of ECLS may predict poor outcome.

Methods: Twenty-three consecutive patients with refractory cardiogenic shock ± resuscitation receiving femoro-femoral va ECLS between March and December 2013 surviving initial 24 hours were included. Pulmonary edema was evaluated by blinded analysis of chest X-rays according to Halperin (Chest 1985) with scores between 0 (normal) and 390 (fulminant bilateral edema). Continuous variables were analyzed by Mann-Whitney test, categorical variables by Fisher's exact test, survival analysis was computed by Kaplan-Meier techniques and log-rank test.

Results: Fourteen patients were diagnosed with ischemic cardiomyopathy, 6 patients with dilated cardiomyopathy, and one patient had a peripartum cardiomyopathy. Seventeen patients received cardiopulmonary resuscitation (67.5±14.1min) prior to ECLS implantation. All patients initially presented with detectable pulmonary edema (Mean score 155.7±19.5) but a differential evolution of pulmonary edema in the disease course was observed: Eleven patients exhibited an increase of pulmonary edema scores within the first 24 hours (+32.3±20.76) while twelve patients presented stable or decreasing pulmonary opacification (-10.8±4.88). Increasing pulmonary edema scores predicted poor outcome (30 day mortality: Survival 25% vs. 73%; p=0.01). Likewise, increasing pulmonary congestion was accompanied by reduced pulse pressure values (21±5.4 vs. 34±3.3; *) and a trend to larger LV diameters (66±5.9 vs. 60±2.6), potentially indicating progressive backward failure. Conversely, in patients receiving LV decompression by left ventricular assist device (LVAD) implantation (n=5) we observed resolution of pulmonary congestion (pre LVAD vs. day5 post LVAD: 183±49.2 vs. 128±45.9; p=0.01).

Conclusion: Early progression of pulmonary edema within the first 24h after ECLS implantation represents an indicator of poor prognosis. Potential therapeutic strategies may consist of early LV decompression.

P1681 | BEDSIDE**Increased mortality in women after out-of-hospital cardiac arrest is explained by an unfavorable pre-hospital risk profile**

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Purpose: Out-of-hospital cardiac arrest (OHCA) is more frequent in men than in women, and current guidelines are based on research primarily performed in men. Previous observational studies suggest an unfavorable risk profile of OHCA in females, but the impact on long-term survival is not known.

Methods: From 2002-2011 consecutive patients with OHCA treated by the physician-based EMS-system in our city were included. Pre-hospital data according to Utstein-criteria, and data on in-hospital post-resuscitation care were collected.

Results: Women represented 31% (n=571) of resuscitated OHCA. Women were significantly older (68±15 vs. 63±14 years, p<0.001), more often had OHCA in a private setting (78% vs. 57%, p<0.001), less often had bystander CPR (47%

vs. 59%, p<0.001), and primary rhythm was frequently non-shockable (63% vs. 42%, p<0.001), whereas time to ROSC was not longer (15 (IQR: 10-21) vs. 15 (9-23) minutes, p=0.4), compared with men. Cardiac etiology of the OHCA (73% vs. 84%, p<0.001) as well as acute coronary syndrome was less often seen in women (29% vs. 44%, p<0.001). Thirty-day mortality was 73% vs. 54% (p<0.001) corresponding to an unadjusted hazard ratio in women of 1.59 (95%CI: 1.38-1.83), p<0.001, Fig. 1A, but after adjusting for known prognostic factors, female gender was no longer associated with a worse prognosis (HR=1.03 (0.85-1.25), p=0.8), Fig. 1B.

Conclusions: Crude mortality after OHCA is higher in women than in men, which can be explained by differences in pre-hospital circumstances such as primary rhythm. Some of the pre-hospital risk factors in women with OHCA seem modifiable and may potentially contribute to improving survival in women.

P1682 | BEDSIDE**Association of seismic intensity after the great east japan earthquake and sudden out-of-hospital cardiac arrest**

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Background: The increased occurrence of cardiovascular diseases after the Great East Japan was reported, but the nationwide effect and quantitative cut-off of seismic intensity were not examined. Our aim is to investigate whether the association between out-of-hospital cardiac arrest (OHCA) and seismic intensity after the Great East Japan Earthquake (magnitude 9.0 on March 11, 2011) is really exist.

Method and result: From 2008 to 2011, we conducted a study on OHCA using national database of cardiac arrest registry. Incidence rate ratio (IRR) of OHCA were analyzed by Poisson regression.

A total of 2308,290 adults with OHCA were included in this study; the trend is characterized by a marked peak between March 11 and March31 in 2011 after the Great East Japan Earthquake compared to the same period in 2008-2010 all over Japan (IRR=1.72, 95%CI 1.52-1.95). Compared to the incidence of March before the earthquake, the incidence on the day of Great Earthquake was doubled. (IRR=2.42, 95%CI 1.59-3.59) The incidence rate of OHCA in 47 prefecture had a strong association with the seismic intensity in each prefecture (r=0.53, p=0.0003) (Fig. 1). Between the seismic intensity 4 and 5, the incidence of OHCA increased 27% (IRR=1.27, 95%CI 1.00-1.62). Over the seismic intensity 6, which correspond to the peak ground acceleration greater than 4 m/s², the incidence rate of OHCA doubled compared with no earthquake period (IRR=2.02, 95%CI 4.52-2.68).

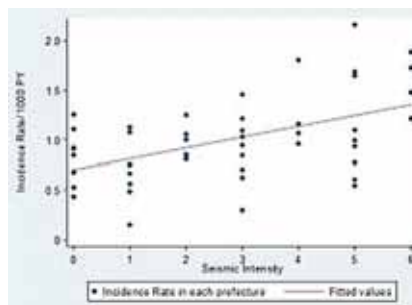


Figure 1. IR and seismic intensity.

Conclusion: Large population based registry showed significant increase of OHCA nation-widely. The risk of cardiac arrest is highest in the area of seismic intensity over 6 and tend to increase in the area of seismic intensity 4 to 5. No significant increase of OHCA was observed under the seismic intensity four.

P1683 | BEDSIDE**Long-term outcome of patients with cardiogenic shock from acute myocardial infarction with and without intra-aortic balloon pump support**

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Purpose: Previous trials in patients with cardiogenic shock from STEMI undergoing primary PCI didn't show a difference in mortality both at 30 days and 12 months between patients treated with and without IABP support. Clinical outcome at more extended follow-up has been reported less frequently. The aim of this study was to compare long-term outcome between patients with cardiogenic shock from STEMI treated with and without IABP.

Methods: A series of 544 consecutive patients admitted with cardiogenic shock from STEMI undergoing PCI were included between 2000-2012. The decision to use IABP support was made by the treating cardiologist.

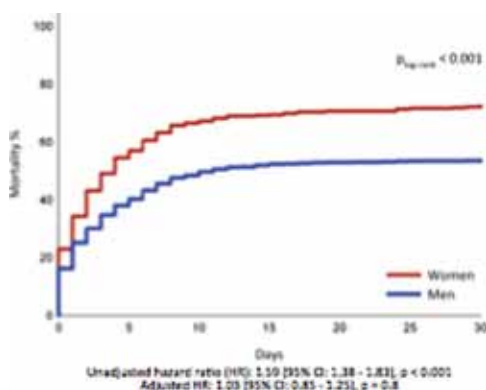
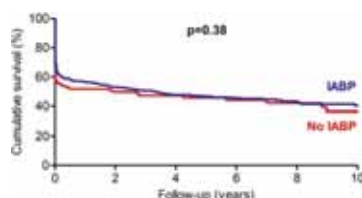


Figure 1

Results: A total of 435 patients (80%) received IABP, 109 (20%) did not. Patients with IABP had significantly higher blood pressure, heart rate and cardiac enzymes at admission, more often presented with an anterior STEMI and were more frequently treated with PCI in the left anterior descending or left main artery. Patients without IABP more often presented with out-of-hospital cardiac arrest, history of renal failure and needed more often mechanical ventilation. Other baseline characteristics were similar. Patients with IABP had a 30-day all-cause mortality of 37.0%, patients without IABP 44.4% ($p=0.10$). All-cause mortality at 10-years of follow-up was 59.9% and 63.5%, respectively (Figure, $p=0.38$). After adjustment for differences in baseline variables, mortality among the two groups remained similar (OR for 30 day mortality 0.93 (95%CI 0.54–1.62), HR for 10-year mortality 1.04 (0.74–1.47). In 30-day survivors, annual mortality rate was 2.2%.



Conclusions: Patients with cardiogenic shock from STEMI undergoing PCI who survive the first 30 days, have low annual mortality rates up to 10 years. There is no mortality difference associated with IABP support.

P1684 | BEDSIDE

Factors influencing the occurrence of cardiopulmonary arrest in the great east japan earthquake disaster

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Purpose: We have previously reported that the Great East Japan Earthquake increased the occurrence of cardiopulmonary arrest (CPA), however, the details remain to be elucidated. In this study, we assessed the association between the Earthquake and the occurrence of CPA of presumed cardiac origin in more detail.

Methods: We enrolled the patients with CPA of presumed cardiac origin by using the ambulance transport records database of Miyagi Prefecture, the center of the disaster area, from February 11 to June 30 in each year of 2008-2011 ($n=2,534$) and compared the weekly occurrences in 2011 with those in the previous 3 years.

Results: In the whole subjects, the weekly occurrence of CPA was significantly increased with the bimodal peaks noted in the first 2 weeks after the Earthquake (March 11, 2011) and in the week just after the largest aftershock (April 7, 2011) compared with the previous 3 years. Sub-group analyses for sex and age (<75 or ≥ 75 years) showed that the occurrence of CPA was significantly increased soon after the Earthquake in all groups. However, male or younger patients did not show the second peak after the largest aftershock, whereas it was still noted in female and elderly patients (Figure). Furthermore, sub-group analysis for residence (seacoast vs. inland area) showed that seacoast patients had a sustained increase in the occurrence of CPA, whereas inland patients had the bimodal peaks (Fig. 1).

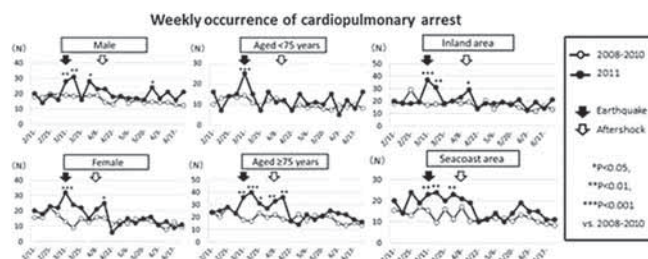


Figure 1

Conclusions: These results suggest that the increase in the occurrence of CPA after the Earthquake was influenced by sex, age and residence area.

P1685 | BEDSIDE

Long-term survival and quality of life of patients submitted to emergency coronary artery bypass grafting for post-infarction cardiogenic shock

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Objective: The long term outcome of patients submitted to emergency coronary artery bypass (eCABG) for postinfarction cardiogenic shock (post-AMI CS) is poorly known. This study was intended to evaluate the long term results of surgery in post-AMI CS patients.

Methods: We herein report the long term survival of a cohort of 67 consecutive patients submitted to eCABG for post-AMI CS at two different institutions over a eleven-year period. All data were prospectively collected.

Results: Hospital survival was 86% (58/67) with all deaths due to cardiac causes. At a mean follow-up of 78 ± 48 months (range 1-153), 43 of the 58 patients discharged from the hospital were alive (74%); 9 of the 15 late deaths (60%) were non-cardiac. Overall survival rate at the end of follow-up was 64% (43/67). The majority (41/43, 95%) of survivors were on NYHA class I-II, ischemia free, had a Karnofsky performance status >80 and an excellent quality of life basing on the Seattle Angina Questionnaire.

Conclusions: This is to date one of the largest series investigating eCABG patients; according to these data, after a high risk in-hospital phase, the long-term survival and quality of life of patients submitted to eCABG for post-AMI CS appear good. eCABG should be considered a valuable therapeutic option in this setting.

P1686 | BENCH

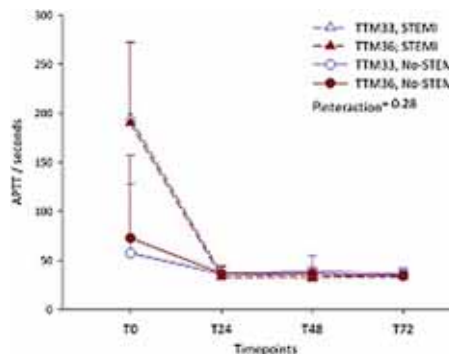
Targeted temperature management at 33°C compared to 36°C does not alter coagulations cascades and bleeding events after out-of-hospital cardiac arrest

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Purpose: Targeted temperature management after out-of-hospital cardiac arrest (OHCA) has been associated with increased bleeding events, due to temperature dependent impairment of coagulations cascades. We report the impact of a targeted temperature management at 33°C vs. 36°C on thrombocyte count, activity of the intrinsic and common pathways of coagulation and rate of clinical bleeding events.

Methods: Single centre study of 171 consecutive comatose OHCA patients assigned a targeted temperature management at 33°C (TTM33) vs. 36°C (TTM36) for 24 h as part of the TTM trial (NEJM 2013). We measured thrombocytes, Activated Partial Thromboplastin Time (APTT) and International Normalized Ratio (INR) at 0, 24, 48 and 72 h after cardiac arrest. Bleeding events were obtained from the TTM-database.

Results: Thrombocyte count decreased progressively from 228-109 L-1 at baseline to 134-109 L-1 at 72 h ($p<0.0001$). APTT was longer at admission in ST-elevation myocardial infarction patients (58%) compared to others (194 vs. 65 seconds, $p<0.0001$) due to pre-hospital treatment with heparin, but decreased to normal levels at 24-72 h. Emergency coronary angiography (<12 h) was performed in 75% and percutaneous coronary intervention (PCI) in 53% of patients, respectively. INR at baseline was 1.4 and remained unchanged throughout the observation period ($p=0.23$). Bleeding episodes were relatively rare, severe bleeding requiring blood transfusion (2%), gastrointestinal bleeding (4%) and bleeding from insertion sites (6%). All patients with severe bleeding underwent emergency PCI. There were no effects of TTM group allocation in any of the studied parameters, $p>0.2$.



APTT levels after cardiac arrest.

Conclusions: Coagulations cascades as well as clinical bleeding events are not influenced by targeted temperature management at 33°C compared to 36°C.

P1687 | BEDSIDE

Effect of coronary revascularisation on survival of patients with acute myocardial infarction and shock on ECMO

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Introduction: Management of post-myocardial infarction cardiogenic shock remains a matter of debate. Mechanical circulatory support as ECMO (extra corporeal membrane oxygenation) has shown encouraging results although evidence from randomized trials is lacking. Our goal was to evaluate whether the severity of coronary disease and myocardial revascularization may affect survival.

Methods: We performed an observational and single-center registry in a tertiary

center. All consecutive patients with post myocardial infarction refractory cardiogenic shock were included.

Results: Half of the 106 included patients (mean age 52.7 ± 10.4 years) presented a triple vessel disease. Revascularization by primary percutaneous intervention (74.5%) was attempted in most of them. The rate of 30-day survival was 36.8% (N=39). Left main critical disease (17% of all patients) and the SOFA score (Sepsis-Related Organ Failure Assessment) were independently associated with increased mortality (OR 6.1 [1.15-32.65], $p=0.0335$ and OR 1.27 [1.11-1.45], $p=0.0005$ respectively) while myocardial revascularization did not have any impact on outcome. Intra-aortic balloon counter-pulsation combined with ECMO was associated with a better survival (OR 0.24 [0.08-0.66], $p=0.0061$).

Conclusion: Survival after post-myocardial infarction refractory cardiogenic shock on ECMO is affected by the severity of the underlying coronary artery disease but not myocardial revascularization. Hemodynamic stabilization appears as a priority in combination with the use of intra-aortic balloon counter-pulsation.

P1688 | BEDSIDE

Role of intra-aortic balloon pump counterpulsation in the treatment of acute myocardial infarction complicated by cardiogenic shock: what are the real evidences from registries?

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International guidelines recommend the use of intra-aortic balloon pump (IABP) in the treatment of cardiogenic shock in the context of acute myocardial infarction as a class I treatment. However, the recent IABP-SHOCK II trial demonstrated no benefit in short- and medium-term mortality with the use of IABP. It was our objective to evaluate in a real life population of patients included in a national registry of acute coronary syndromes, the impact of IABP in hospital mortality.

Methods: We included patients admitted with acute myocardial infarction (with and without ST segment elevation) in Killip class IV or who developed it in the first 24 hours after admission. All patients underwent coronary angiography in the first 24 hours. We evaluated demographic and baseline characteristics as well as treatment. The study objective was the occurrence of in-hospital mortality. Logistic regression analysis was performed to identify independent predictors of mortality. We also performed sub-group analysis.

Results: From the 33.300 patients with myocardial infarction included in the registry, 4.2% presented with Killip class IV in the first 24 hours and 646 (43.6%) were submitted to coronary angiography and that was our study population. IABP was implanted in 19.8% of these patients. This group was younger and had higher admission heart rate. No differences were observed for other baseline characteristics or treatment except for more multivessel disease (68.5% vs. 57.2%, $p=0.013$) and more prevalence of left main disease (16.5% vs. 4.9%, $p<0.001$). There were 260 deaths, but were similar between groups (46.1% vs. 38.8%, $p=0.132$). There were also no significant differences in hospital complications. In sub-group analysis, there was no interaction with gender, age, diabetes or renal function. In patients with previous myocardial infarction and in patients without mechanical complications, the use of IABP was associated with higher mortality. In multivariate analysis, the use of IABP was associated with higher risk of hospital mortality (OR 1.77, 95% CI 1.15-2.73, $p=0.010$). The other predictors were age, smoking and previous stroke/transient ischemic attack.

Conclusions: In a real life population of patients with acute myocardial infarction, the use of IABP for the treatment of cardiogenic shock has no benefit in short-term prognosis.

ACUTE CORONARY SYNDROME – PROGNOSIS AND MANAGEMENT

P1690 | BEDSIDE

The variants rs243327, rs243330, rs33977706 and rs33932899 of the suppressor of cytokine signaling 1 (SOCS1) gene are associated with risk of developing acute coronary syndrome in patients of our country

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Background: The suppressor of cytokine signaling-1 (SOCS1) is considered an important molecule in the inflammatory process regulation, because SOCS1 interacts directly with the Janus kinases (JAK), essential intracellular mediators of immune cytokine action. In addition, inhibit IRS1 and IRS2, and block insulin signaling, degrades ASK1, inhibiting TNF signalin, and interact with Syk and CD3 subsequently blocking TCR signaling, that play a role in the development of the atherosclerotic plaque. Recently, four single nucleotide polymorphisms (rs243327, rs243330, rs33977706 and rs33932899) were associated with increased susceptibility to several inflammatory diseases. The aim of this study was to test for association between SOCS1 gene polymorphisms, and susceptibility to risk of acute coronary syndrome (ACS) development in a group of patients.

Methods: The genotyping of rs243327, rs243330, rs33977706 and rs33932899 (positions -3969 C>T, -1656 G>A, -820 G>T and +1125 G>C, respectively) sin-

gle nucleotide polymorphisms were analyzed by 5' exonuclease TaqMan genotyping assays in a group of 447 patients with ACS and 622 healthy controls.

Results: 3969 C>T, -1656 G>A, -820 G>T and +1125 G>C single nucleotide polymorphisms showed: that the "CT" genotype of the -3969 C>T SNP was significantly associated with an increased risk of ACS as compared to controls under heterozygous model (OR=1.45, 95%CI: 1.06-1.99, PHet=0.021). On the other hand, the "AG" genotype of the -1656 G/A SNP was significantly associated with increased risk of ACS when compared to controls under co-dominant and heterozygous models (OR=1.47, 95%CI: 1.06-2.03, PCo-dom=0.038 and OR=1.50, 95%CI: 1.09-2.06, PHet=0.013, respectively). Moreover, the "GT or GG" genotypes of the -820 T/G SNP was significantly associated with increased risk of ACS as compared to controls under co-dominant, dominant, and heterozygous models (OR=1.59, 95%CI: 1.11-2.28, PCo-dom=0.03, OR=1.48, 95%CI: 1.04-2.10, PDom=0.028 and OR=1.61, 95%CI: 1.12-2.31, PHet=0.01, respectively). Finally, the CG of the +1125 G/C SNP was significantly associated with increased risk of ACS when compared to controls under co-dominant and heterozygous models (OR=1.54, 95%CI: 1.08-2.21, PCo-dom=0.006, OR=1.58, 95%CI: 1.11-2.27, PHet=0.012, respectively). Models, were adjusted for gender, age, body index mass, dyslipidemia, alcohol consumption, and smoking.

Conclusion: In summary, our data suggest that the variants rs243327, rs243330, rs33977706 and rs33932899 of the SOCS1 gene play an important role as susceptibility marker for developing ACS.

P1691 | BENCH

Secreted wingless (Wnt) antagonists and risk prediction in acute coronary syndrome (ACS) a PLATO biomarker substudy

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Background: Recent studies suggest that the Wnt pathway may be implicated in vascular remodeling and atherogenesis. To gain further insight into the role of Wnt-related mediators in atherosclerotic disorders, we investigated the prognostic value of the Wnt pathway modulators serum secreted frizzled related protein (sFRP-3) and Dickkopf-1 (DKK-1) for 1-year outcome in patients with acute coronary syndromes (ACS).

Methods: sFRP-3 and DKK-1 levels were determined in serum collected at randomization to ticagrelor or clopidogrel in 4201 patients with ACS in the PLATO (PLATelet inhibition and patient Outcomes) trial. Baseline characteristics by Chi-square test (categorical variables) or Kruskal Wallis test (continuous variables), and occurrence of the primary outcome, a composite of cardiovascular death, non-fatal myocardial infarction, or stroke (n=363), by Cox proportional hazards models were compared between groups stratified by quartiles of the respective biomarker.

Results: The median (interquartile range) of DKK-1 was 0.6 (0.2 – 1.3) and of sFRP-3 13.0 (3.3 – 36.8). Higher frequencies of hypertension, diabetes mellitus, angina, previous MI and heart failure and higher levels of CRP and NT-proBNP were observed with increasing quartiles of DKK-1 ($p<0.001$ for all, except diabetes $p<0.01$), and opposite trends were seen for sFRP-3 with the lowest risk factor frequencies and CRP and NT-proBNP levels in the top quartile ($p<0.001$ for all). Similarly, while there was a decrease in proportion of ST-elevation MI with increasing DKK-1 quartile (q1: 65%, q4: 35%, $p<0.001$), this pattern was opposite for sFRP-3 (q1: 38%, q4: 72%, $p<0.001$). Both DKK-1 and sFRP-3 showed transient association with troponin I with the highest levels in the mid quartiles. Baseline levels of DKK-1 and sFRP-3 were strongly inversely correlated ($r=-0.52$, $p<0.001$). Both biomarkers were moderately but significantly associated with the primary outcome ($p<0.05$) with an inverted U shaped association with risk, in particular for sFRP-3, where the lowest HR was found in the top quartile. No significant interaction between biomarkers and effect of randomized treatment on the primary outcome was observed.

Conclusions: Higher DKK-1 was less often seen in STEMI, while this trend was opposite trend for sFRP-3. There was a significant inverted U shaped prognostic pattern of Wnt antagonists concerning outcomes in ACS. This pattern indicates a complex role for the Wnt pathways in clinical atherosclerosis involving regulation of soluble Wnt modulators.

P1692 | BEDSIDE

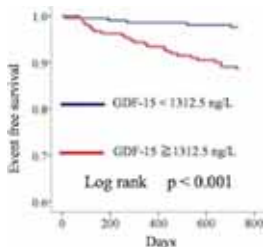
Incremental prognostic value of assessing growth differentiation factor-15 in patients with acute myocardial infarction - alps ami subanalysis-

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Purpose: The utility of inflammatory biomarkers has been proposed for risk stratification in patients with acute myocardial infarction (AMI). We sought to examine the additive value of inflammatory biomarkers over clinical features and left ventricular ejection fraction (LVEF) for prediction of cardiovascular events in patients with AMI.

Methods: We enrolled 429 patients with AMI, who were measured high-sensitivity C reactive protein (hs-CRP), growth differentiation factor-15 (GDF-15), interleukin-1 receptor family member called ST2 (ST2), and interleukin-6 (IL-6) after successful percutaneous coronary intervention (PCI). Patients were prospectively tracked for 2 years. The relation of biomarkers to cardiovascular events was assessed.

Results: In our study cohort (age 66 ± 12 years, LVEF $55 \pm 12\%$), cardiovascular events observed in 29 patients (6.8%). In Kaplan-Meier analysis, patients with high levels of GDF-15 (≥ 1312.5 ng/L) showed worse prognosis than patients with low levels of GDF-15 (< 1312.5 ng/L) ($p < 0.001$). Patients with high levels of hs-CRP, ST2, and IL-6 did not show the difference as to cardiovascular events. GDF-15 was associated with the risk of cardiovascular events after adjustment for age and LVEF (hazard ratio: 1.86, 95% confidence interval: 1.04 to 3.33; $p = 0.037$). GDF-15 provided an incremental predictive value for cardiovascular events over clinical features (incremental in global $\chi^2 = 14.89$, $p = 0.001$).



Kaplan-Meier curves according to GDF-15.

Conclusions: In patients with AMI, high levels of GDF-15 were associated with high incidence of cardiovascular events after PCI although hs-CRP, ST2, and IL-6 failed to show the difference. GDF-15 provided incremental prognostic value to clinical features.

P1693 | BEDSIDE

Pentraxin 3 (PTX3) predict adverse outcome in acute coronary syndromes - a PLATO biomarker substudy

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Purpose: PTX3 is expressed by the major cell types involved in atherosclerosis in response to inflammatory stimuli and may be regarded as a marker of local vascular inflammatory response. In the current study we investigated the association between levels of PTX3 and 1-year outcomes in patients with acute coronary syndromes (ACS).

Methods: PTX3 was determined in plasma sampled at randomization to ticagrelor or clopidogrel in 4191 patients with ACS enrolled in the PLATO (Platelet Inhibition and Patient Outcomes) trial. Patients were categorized based on quartiles of PTX3 levels and compared with respect to baseline characteristics (Chi-square or Kruskal Wallis tests for categorical and continuous variables, respectively), and to the primary composite endpoint of cardiovascular death, myocardial infarction (MI), or stroke (Cox proportional hazards models).

Results: The median (interquartile range) of PTX3 was 1.9 ng/mL (1.2 – 3.0 ng/mL). Higher PTX3 levels were associated with higher age, higher number of female gender, lower Body Mass Index, less smokers, higher frequency of chronic kidney disease ($p < 0.001$ for all), and lower occurrence of ST-elevation MI ($p = 0.0071$). Higher PTX3 levels were also associated with both TIMI and GRACE risk scores, and with higher Troponin I, NT-proBNP, and C-reactive Protein levels ($p < 0.0001$ for all). No association was found with presence of diabetes mellitus or past medical history (e.g. coronary or peripheral artery disease, congestive heart failure, or stroke). Higher rates of the primary endpoint were found in the two upper PTX3 quartiles (Q3 and Q4: 10.5 and 11.7%/year; HR [95%CI]: 1.47 [1.08-1.98] and 1.64 [1.22-2.20], respectively) in comparison to the lowest quartile (7.1%/year), $p = 0.0006$. There was no significant interaction between PTX3 levels and the effects of randomized treatment.

Conclusions: In patients with ACS, PTX3 levels are related to age and markers of myocardial damage and dysfunction, kidney dysfunction and inflammatory activity. High admission levels of PTX3 are associated with adverse clinical outcomes up to 12 months after ACS. The benefits of ticagrelor versus clopidogrel are independent of the PTX3 levels.

P1694 | BEDSIDE

Impact of fixed atherosclerotic coronary lesion in patients with coronary artery spasm on 3-year clinical outcomes

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Background: Coronary artery spasm (CAS) and fixed atherosclerotic coronary lesion (FCL) are both known to be a major cause of myocardial ischemia. However, their association and impact on long-term clinical outcomes are largely unknown.

Methods: A total of 2,797 consecutive pts without significant coronary artery disease who underwent ACh provocation test were enrolled between November 2004 and October 2010. Pts were divided into two groups according to the existence of FCL (FCL group: $n = 765$, non-FCL group: $n = 845$). We evaluated the impact of FCL in patients (pts) with CAS on 3-year clinical outcomes.

Results: At baseline, pts with FCL had a higher incidence of elderly, male, hypertension, diabetes and dyslipidemia than pts without FCL. During ACh provocation test, the FCL group showed more severe narrowing than the non-FCL group, whereas the non-FCL group had higher incidence of myocardial bridge and baseline spasm. The FCL group had a higher incidence of major adverse cardiac & cerebrovascular events (MACCE) including all-cause mortality, myocardial infarction, coronary revascularization and cerebrovascular accidents (1.3% vs. 0.2%, $p = 0.013$) at 3 years. However, there was no significant difference between the two groups after multivariate analysis before (HR; 3.85, 95%CI; 0.8-18.4, $p = 0.081$) and after propensity score matching analysis (HR; 5.13, 95%CI; 0.57-45.8, $p = 0.143$).

Table. 3-year cumulative clinical outcomes

Variable, N (%)	Entire Patients		p Value	Propensity Score-Matched Patients		p Value
	Total (n=1639)	FCL (n=764)		Total (n=1639)	FCL (n=764)	
Outcomes at 3y						
Mortality	3 (0.1)	3 (0.3)	0.407	2 (0.1)	2 (0.2)	0.500
Cardiac death	2 (0.1)	2 (0.2)	0.295	2 (0.1)	2 (0.2)	0.500
MACCE	3 (0.1)	3 (0.3)	0.407	2 (0.1)	2 (0.2)	0.500
Myocardial infarction, MI	3 (0.1)	2 (0.2)	0.407	2 (0.1)	1 (0.1)	ns
Cerebrovascular accidents, CVA	3 (0.1)	2 (0.2)	0.607			
Repeat CAD	102 (6.2)	90 (11.8)	0.121	90 (5.4)	35 (4.6)	0.202
MACCE	3 (0.1)	3 (0.3)	0.407			
Mortality, FCL vs. non-FCL						
MACCE	12 (0.7)	12 (1.5)	0.003	6 (0.4)	5 (0.6)	0.297
Mortality, FCL vs. non-FCL						
MACCE	106 (6.4)	47 (6.1)	0.603	70 (4.2)	33 (4.3)	0.401

Conclusion: In this study, the presence of FCL in vasospastic angina pts was not associated with adverse 3-year clinical outcomes as compared with vasospastic angina pts without FCL.

P1695 | BEDSIDE

Can the severity of initial presentation of coronary spasm predict the prognosis?

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Background: There are many proven risk factors to estimate the prognosis of atherosclerotic coronary disease. On the contrary to this, outcome prediction of coronary spasm is challenging. This study aimed to identify the impact of initial presentation of coronary spasm on the prognosis.

Methods: From 2001 to 2012, among ergonovine-test proven 271 consecutive coronary spasm patients, 221 patients (mean age 57.3 ± 9.7 , 178 male) were retrospectively enrolled, excluding the patients with previous percutaneous coronary intervention or angiographically more than 50% coronary stenoses. We divided the cohort with two groups depending on whether the initial presentation of the patients was angina or myocardial infarction (MI)/syncope/aborted cardiac arrest. Primary endpoint was composite of emergency room visit for anginal symptom, nonfatal MI, and cardiac arrest. Secondary endpoint was composite of non-fatal MI and cardiac arrest.

Results: Among 221 patients, angina was an initial presentation in 163 patients, MI in 45 patients, syncope in 9 patients and cardiac arrest in 4 patients. Mean follow-up duration was 3.2 years. We assigned angina patients as "group A" and non-fatal MI/syncope/aborted cardiac arrest patients as "group B". Patients in group A were older than group B (58.3 ± 9.7 vs. 54.5 ± 9.0 , $p = 0.011$). There were no intergroup differences in baseline characteristics of body mass index, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, serum monocyte count, lipid profiles, hypertension, diabetes, smoking, discharge medications and hemodynamic unstable events during ergonovine test. For primary endpoint, group B showed worse outcome than group A in Kaplan-Meier survival analysis (34.5% vs. 17.2%, log rank $p = 0.006$). For secondary endpoint, group B also showed significantly worse outcome than group A in Kaplan-Meier survival analysis (17.2% vs. 3.7%, log rank $p < 0.001$).

Conclusions: Severity of initial presentation could be a predictor for long-term outcome of patients with coronary spasm.

P1696 | BEDSIDE**Prognostic implications of the absence of chest pain in patients with high troponin levels in emergency department**

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Introduction: A positive troponin (TnI) is an independent predictor of adverse outcomes. TnI analysis is often done in the absence of chest pain. The objective of our study was to establish the prognostic value of a high TnI in the absence of chest pain, irrespective of the final diagnosis.

Methods: Retrospective analysis of adult patients admitted in our emergency department in the first semester of 2012 and who had at least a determination of TnI. Demographic, clinical data and final diagnosis were obtained from the medical records. In-hospital and 1-year survival was analyzed. Patients were categorized into four groups for analysis: chest pain and normal TnI; chest pain and raised TnI; without chest pain and normal TnI; and without chest pain and raised TnI.

Results: A total of 1035 were eligible for the study. Comparing the group of patients without chest pain and positive TnI with the other groups, these patients were older, more frequently female and with previous history of heart failure, hypertension and higher comorbidity index. Creatinine was higher and haemoglobin lower. This group of patients was less frequently diagnosed of ACS and was more frequently diagnosed of heart failure, bradyarrhythmia, respiratory and cerebrovascular disease. They were less frequently admitted to the hospital. In-hospital and 1-year mortality was higher in this group. By using a multivariable Cox proportional hazards model, and after adjustment for age, sex, heart failure, hypertension, charlson index, renal function, hemoglobin levels and presence of ACS, the absence of chest pain was an independent predictor of mortality at follow-up (Fig. 1).

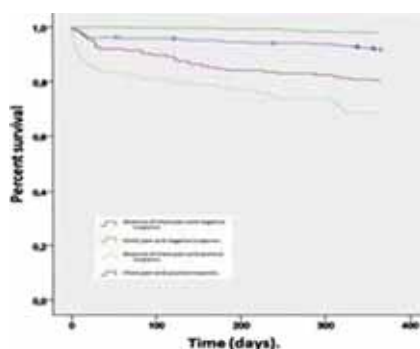


Figure 1

Conclusions: The absence of chest pain in patients with a TnI level above the reference limit is an independent predictor of mortality.

P1697 | BEDSIDE**Long term prognosis of acute coronary syndromes submitted to angioplasty in culprit vessel only-Comparison between complete treatment versus residual lesion**

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Purpose: To analyse the demographic data and outcomes of patients with acute coronary syndromes submitted to percutaneous coronary intervention in culprit vessel only comparing patients with residual nonculprit coronary lesions higher than 70% occluded (group I) versus patients without significant residual nonculprit coronary lesions (group II).

Methods: This was a prospective data bank analysis study with 580 patients (284 in the group I and 296 in the group II) with acute coronary syndromes included between May 2,010 and May 2,013. The following data were obtained: age, sex, diabetes, systemic arterial hypertension, smoke, dyslipidemia, familial history of precocious coronary artery disease, previous coronary artery disease (percutaneous coronary intervention or coronary artery bypass graft), hemoglobin, creatinine, higher troponin, left ventricle ejection fraction, medication used at hospital and coronary definitive treatment. The primary endpoint was combined events (death, non-fatal unstable angina or myocardial infarction, repeated revascularization and heart failure). Comparison between groups was made by Anova and Q-square. Long term results were studied using Kaplan-meyer curves with median follow-up of 9.86 months and was considered significant when $p < 0.05$.

Results: The median age was 63 years versus 62 years in the groups I and II, respectively. Were observed significant differences in prevalence of systemic arterial hypertension (74.4% x 81.2%, $p=0.04$), smoke (41.9% x 35.1%, $p=0.009$), familial history of precocious coronary artery disease (15.0% x 8.8%, $p=0.02$), use of B-blocker (80% x 65.6%, $p<0.001$), use of enoxaparin (87.5% x 73.2%, $p<0.001$), use of angiotensin converting enzyme inhibitor (68.1% x 56.3%, $p=0.006$), creatinine (1.15 x 1.35 mg/dL, $p=0.03$) and higher troponin (18.3 x 8.04 ng/mL, $p=0.005$), respectively between groups I and II. Long term follow

up showed similar results between groups I and II in combined events (46.1% x 53.9%, $p=0.76$).

Conclusions: In patients with acute coronary syndromes intervention in culprit vessel only showed be safe and similar prognosis were observed in long term follow-up in patients with or without significant residual coronary occlusion.

P1698 | BEDSIDE**Minimalist immediate mechanical intervention for ST-elevation acute myocardial infarction in daily practice: a single center experience**

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Background: The Minimalist immediate mechanical intervention (MIMI) strategy for STEMI aims to restore normal anterograde flow in the culprit artery and to defer potential stent implantation after a few days of optimal antithrombotic therapy. The goal of the present study was to assess the applicability of this strategy and its impact on STEMI treatment modalities in daily practice.

Methods: All consecutive patients admitted for acute STEMI in our institution between June 2010 and June 2013 were included. All patients underwent first a deocclusion of the culprit lesion (manual thrombectomy and/or balloon predilation, under double antiplatelet therapy + heparin) in order to restore antegrade flow in the culprit vessel. The MIMI strategy was considered when an optimal reperfusion (angiographic TIMI grade flow ≥ 2 + ST segment elevation regression $>50\%$ + cessation of pain) was obtained. The MIMI patients underwent a subsequent angiography control after a few days of optimal antithrombotic therapy with adjunctive angioplasty and stent implantation if required. The other patients were included in the control/standard therapy group.

Major adverse cardiovascular events (MACE: cardiac death+stent thrombosis+ recurrent myocardial infarction+ target vessel revascularization) were subsequently recorded after hospital discharge.

Results: A total of 279 patients were retained in the analysis of which 21% benefited from the MIMI strategy. The MIMI patients were significantly younger (57.9 ± 2 versus 63.1 ± 1 years, $p=0.02$), more frequently male and smoker than the others. After initial deocclusion, the TIMI grade flow was higher (2.91 ± 0.04 vs 2.42 ± 0.06 , $p<0.001$) and the culprit lesion residual stenosis less severe ($56.6 \pm 2.8\%$ versus $67.8 \pm 1.5\%$, $p=0.001$) in the MIMI group compared to the standard group. The average delay between the two procedures was 4.3 ± 3.2 days in the MIMI group, during which a significant thrombus burden reduction was observed.

The revascularization mode significantly differed between the 2 groups: the use of drug eluting stent was more frequent in the MIMI group than in the standard group (52% vs 28.5%, $p<0.001$). Moreover, 28.5% of the MIMI patients did not receive any stent on the culprit lesion (vs 9% in the standard group, $p<0.001$). Patients from the MIMI group had a favourable outcome after discharge: the 1-year actuarial survival from MACE was $96.4 \pm 2.5\%$ vs $89 \pm 2.4\%$ in the standard group.

Conclusion: The MIMI strategy seems safe and applicable in some selected STEMI patients. This option decreases the use of systematic culprit lesion stenting and was associated with a low rate of MACE.

P1699 | BEDSIDE**Efficacy of everolimus-eluting stent implantation in patients with small coronary arteries. Outcomes of 2-year clinical follow-up**

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Background: Previous studies have demonstrated that patients with small coronary artery lesions (SCAL) are at increased risk for late cardiac events after percutaneous coronary intervention (PCI). It remains uncertain whether second-generation drug-eluting stents have an advantage first-generation drug-eluting stents (DES) in patients with SCAL. This study aimed to evaluate the long-term efficacy of everolimus-eluting stent (EES) and sirolimus-eluting stents (SES) on SCAL.

Methods and results: Consecutive 360 patients with 405 SCAL, who were treated with EES (157 patients, 185 lesions) and SES (203 patients, 220 lesions) were enrolled. SCAL was defined the lesions with reference vessel diameter (RVD) <2.5 mm. Within ten months angiographic follow-up results and 3-year clinical follow-up outcomes were compared between EES and SES groups. The prevalence of diabetes was higher and the stent length was longer (23.0 ± 7.0 vs. 20.1 ± 6.8 , $p<0.05$) in EES group than in SES group. Initial success rate was similar in both groups. There was no difference in 3-year %binary restenosis, TLR (2.1vs. 4.7%), and MACE (3.8% vs 7.7%) rates between 2 groups. This similar major adverse cardiovascular events rate remained after adjustment. However, the rate of stent thrombosis was 0% in the EES group and 1.8% in the SES group ($p=0.10$).

Conclusions: EES demonstrated comparable clinical outcomes to those of SES in SCAL. The absence of stent thrombosis among patients treated with EES suggests a good safety profile for this second-generation drug-eluting stent, which should be carefully studied in a larger series of patients with SCAL.

STABLE CORONARY ARTERY DISEASE: INVASIVE AND MEDICAL STRATEGIES

P1701 | BEDSIDE

Does percutaneous coronary intervention reset disadvantage in long-term outcome in patients with functionally significant stenosis?

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Background: In patients with stable coronary artery disease, fractional flow reserve (FFR) guided percutaneous coronary intervention (PCI) for functional significant stenosis improves clinical outcome as compared with medical therapy alone. However, it is not clear whether PCI can reset disadvantage in long-term outcome to the same level of patients without significant stenosis. To evaluate the extent of therapeutic efficacy of PCI, we compared the long-term outcome between patients treated with PCI and patients without functionally significant stenosis.

Methods: Stable angina patients with visually stenotic lesions (>50% stenosis) were assessed by FFR measurements. Patients with at least one functionally significant stenosis (FFR <0.8) were treated by drug-eluting stents implantation (PCI group). Patients without functionally significant stenosis received best available medical treatment (Deferral group). Any death, myocardial infarction, stroke, and any revascularization were considered major adverse cardiac events (MACE). The incidence of MACE was compared between both groups.

Results: A total of 154 patients were enrolled in this study (114 in PCI group and 40 in Deferral group). Mean follow-up period was 577 days. The incidence of MACE was similar between the PCI and Deferral group during first 6 months (p=0.21). However, beyond 6 months follow-up, PCI group had significantly higher incidence of MACE as compared to Deferral group (33.3% vs. 3.13%; p=0.01).

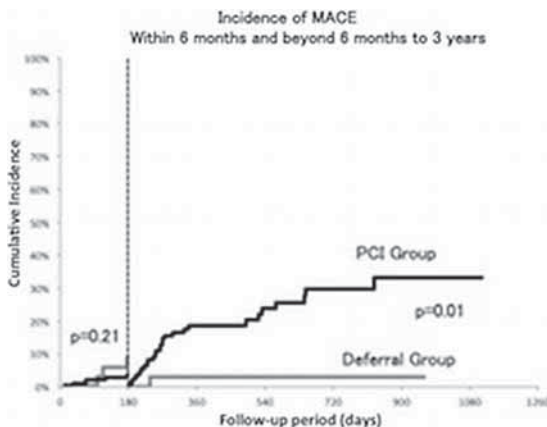


Figure 1

Conclusion: Although short-term outcome is similar, the incidence of MACE increases between 6 months and 3 years in patients with drug eluting stents treatment as compared to deferral patients.

P1702 | BEDSIDE

Reduced benefit of final kissing balloon inflation after single stenting to bifurcation lesions in patients with diabetes: Insight from the optical coherence tomography sub-study of J-REVERSE trial

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Background: Diabetes mellitus (DM) and bifurcation lesions are still leading causes of unfavorable outcomes after drug-eluting stent implantation. The impact of DM on vessel reaction to final kissing inflation (FKI) following single stenting remains uncertain.

Methods: J-REVERSE is a prospective multicenter registry of cases treated with single stenting with or without FKI to bifurcation lesions. The first 64 lesions at selected study sites were predefined for inclusion in the optical coherence tomography (OCT) sub-study and underwent 9-month follow-up OCT. In addition to standard OCT parameters, stent eccentricity index (SEI; minimum divided by maximum stent diameter) and neointimal unevenness score (NUS: maximum neointimal thickness in the cross-section (CS) divided by the average NIT of the same CS: to assess the uniformity of neointima suppression) was averaged for each

		DM			Non-DM		
		FKI (+), n=11	FKI (-), n=22	P value	FKI (+), n=19	FKI (-), n=12	P value
Proximal	Stent area (mm ²)	7.55±2.06	6.98±1.63	0.43	8.54±1.57	6.74±1.64	0.006
	Neointimal area (mm ²)	1.07±0.79	0.85±0.44	0.39	1.03±0.54	0.73±0.45	0.1
	Lumen area (mm ²)	6.52±2.21	6.17±1.51	0.59	7.53±1.74	6.06±1.68	0.027
	SEI	0.82±0.06	0.87±0.05	0.012	0.85±0.05	0.89±0.04	0.024
	NUS	1.74±0.26	1.93±0.32	0.6	2.33±0.68	2.76±0.81	0.13
Uncovered strut		1.04±2.31	1.65±3.30	0.59	1.38±3.33	3.28±6.93	0.31
Distal	Stent area (mm ²)	5.94±1.82	6.71±1.82	0.27	7.00±1.64	6.26±1.67	0.24
	Neointimal area (mm ²)	0.95±0.42	1.00±0.50	0.79	1.01±0.57	0.97±0.55	0.85
	Lumen area (mm ²)	5.00±1.87	5.73±1.86	0.29	2.72±0.45	2.55±0.43	0.33
	SEI	0.87±0.05	0.88±0.04	0.55	0.90±0.04	0.90±0.04	0.89
	NUS	1.72±0.17	1.75±0.19	0.61	1.68±0.34	1.62±0.11	0.63
Uncovered strut		0	0	NA	2.76±7.45	1.90±3.49	0.71
Bifurcation	%Jailed strut	6.16±6.60	11.89±8.52	0.06	5.73±8.18	17.84±8.37	<0.001
	Neointimal area (mm ²)	0.81±0.36	0.73±0.41	0.57	0.86±0.49	0.73±0.40	0.43
	Uncovered strut	0.27±0.69	0.65±1.43	0.31	1.51±3.99	1.58±3.33	0.96

segment (proximal, distal and bifurcation segment). We compared OCT values in FKI (+) group with those in FKI (-) both in DM patients and Non-DM patients.

Results: SEI in proximal segment and %Jailed strut in bifurcation were lower in FKI (+) group than in FKI (-) group both in DM or Non-DM patients. In proximal segment of Non-DM patients, stent area and lumen area were larger in FKI (+) group than in FKI (-) group. While in DM patients, those were not different between FKI (+) group and FKI (-) group. (table).

Conclusion: FKI for the bifurcations in DM patients could not provide an increased stent area and lumen area at proximal segment 9 months after drug-eluting stent implantation compared to that for Non-DM even though uneven stent expansion and neointimal proliferation were similar. More accelerated form of atherosclerosis may worsen a beneficial effect of FKI in DM patients.

P1703 | BEDSIDE

Two year follow-up results of everolimus and paclitaxel-eluting stents for small coronary artery diseases: final results of PLUM and SACRA registries

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Purpose: Percutaneous coronary interventions involving small coronary vessels represent a true challenge because of the increased risk of restenosis and adverse outcomes. The aim of this study is to evaluate the 2-year clinical results following small coronary stenting between everolimus- (EES) and paclitaxel-eluting stent (PES).

Methods: PLUM (PROMUS/Xience V Everolimus-ELuting Coronary Stent for sMall coronary artery disease: 264 patients with 279 lesions) and SACRA (SmAll CoronaRy Artery treated by TAXUS Liberté: 245 patients with 258 lesions) registries are prospective, multicenter registries to assess the efficacy of single EES and PES in patients with small coronary artery diseases. Inclusion criteria were 1) Lesions >75% diameter stenosis in vessels <2.5mm in diameter, 2) lesion length <28mm. The primary endpoint is clinical driven target lesion revascularization (TLR) rate at 2 year.

Results: In EES group, a non-significant trend toward rate of major adverse cardiac events, however, 2 year TLR rate was significantly lower than PES group (Table).

Two-year clinical results

	EES	PES	p
Patients, n (%)	264	245	
Lesions, n (%)	279	258	
Cardiac death at one year, n (%)	1 (0.4%)	1 (0.4%)	—
Cardiac death at two year, n (%)	1 (0.4%)	1 (0.4%)	—
Myocardial Infarction at one year, n (%)	2 (0.8%)	1 (0.4%)	—
Myocardial Infarction at two year, n (%)	2 (0.8%)	1 (0.4%)	—
TLR at one year, n (%)	11 (4.2%)	25 (10.2%)	0.009
TLR at two year, n (%)	12 (4.5%)	26 (10.6%)	0.01
TVR at one year, n (%)	20 (7.6%)	32 (13.1%)	0.06
TVR at two year, n (%)	21 (8.0%)	34 (13.9%)	0.03
Any MACE at one year, n (%)	22 (8.3%)	33 (13.5%)	0.06
Any MACE at two year, n (%)	23 (8.7%)	35 (14.3%)	0.05

Conclusion: EES showed better clinical results for treatment of small coronary artery diseases.

P1704 | BEDSIDE

Outcome after drug-eluting stents for cardiac allograft vasculopathy

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Purpose: Cardiac allograft vasculopathy (CAV) constitutes a primary cause of

death after heart transplantation. Bare metal stents (BMS) have been used for revascularization, but they are associated with a high-risk of restenosis. Limited data have shown favourable results with percutaneous coronary interventions (PCI) using drug-eluting stents (DES) in this specific population. Our study focuses on intra-stent restenosis (ISR) for DES in CAV, on new revascularisation and mortality.

Methods: 97 consecutive heart transplant recipients with successful PCI were treated with DES (n=106) and BMS (n=25). They were prospectively followed-up at one year after PCI. An angiographic lesion-based analysis at 12-month follow-up and a patient-based survival analysis were performed.

Results: The lesion-based analysis within 12 months after PCI showed an ISR rate with BMS of 12% and an ISR rate with DES of 3.8%. The target lesion revascularization (TLR) was 8% for BMS and 2.8% for DES. However, the target vessel revascularization was higher (16.5%) and the remote lesion revascularization was 8.7%, indicating the rapid occurrence of new significant lesions. Cardiac mortality at one year was 9.7% and extra-cardiac mortality was 2.9%.

Conclusions: DES are associated with a low rate of TLR and can safely be used in heart transplant recipients with coronary artery disease. However, new significant lesions occurred at one year indicating a progression of CAV.

P1705 | BEDSIDE

Efficacy of everolimus-eluting stent implantation in patients with large coronary arteries. Outcomes of 2-year clinical follow up

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Background: Previous studies have demonstrated that patients with large coronary artery lesions (LCAL) are at increased risk for late cardiac events after Percutaneous coronary intervention (PCI) with first-generation drug-eluting stents (DES), as compared with bare-metal stents. It remains uncertain whether second-generation drug-eluting stents have an advantage over bare-metal stents (BMS) in patients with LCAL. This study aimed to evaluate the long-term efficacy of everolimus-eluting stent (EES) and BMS on large coronary artery lesions.

Methods and results: Consecutive 394 patients with 441 LCAL, who were treated with EES (191 patients, 214 lesions) and BMS (203 patients, 227 lesions) were enrolled. LCAL was defined the lesions with the use of stent size of ≥ 3.5 mm. Within ten months angiographic follow-up results and 2-year clinical follow-up outcomes were compared between EES and BMS groups. The prevalence of diabetes and the case of off-label stent use were higher and the stent length was longer (24.8 $\pm$ 8.9 vs. 18.3 $\pm$ 8.5, $p<0.05$) in EES group than in BMS group. Initial success rate was similar in both groups. However, % binary restenosis (3.6 vs. 10.6%, $p<0.05$), TLR (3.6% vs. 10.1%, $p<0.05$), Stent thrombosis (1.0% vs 6.4%), and MACE (6.1% vs. 14.8%, $p<0.05$) were significantly higher in BMS group than in EES group.

Conclusions: EES implantation in patients with LCAL was safe and associated with favorable reduction of restenosis and repeat revascularization. Additionally, the fewer stent thrombosis among patients treated with EES suggests a good safety profile for this second-generation drug-eluting stent, which should be carefully studied in a larger series of patients with LCAL.

P1706 | BEDSIDE

Physiological improvement after PCI using instantaneous wave-free ratio. Diagnostic capacity of iFR to detect post-PCI residual ischemia

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Objective: To determine whether the instantaneous wave-free ratio (iFR) can be used for the evaluation of improvement of PCI, and the diagnosis of residual ischemia after PCI by comparing this acquired data with fractional flow reserve (FFR) and whole cycle Pd/Pa.

Design: A prospective observational study was undertaken in elective patients scheduled for elective PCI. Intracoronary pressures were measured at rest and during adenosine-mediated vasodilatation, before and after PCI. iFR, Pd/Pa and FFR values were calculated with on site analysis using the validated fully automated algorithms.

Subjects: 106 coronary stenoses in 100 patients who were scheduled for elective PCI were analysed.

Results: Pre-PCI, mean FFR was 0.66 $\pm$ 0.14, mean iFR was 0.76 $\pm$ 0.22 and mean Pd/Pa 0.83 $\pm$ 0.16. PCI increased all indices significantly (FFR 0.87 $\pm$ 0.09, $p<0.001$; iFR 0.94 $\pm$ 0.07, $p<0.001$; Pd/Pa 0.95 $\pm$ 0.06, $p<0.001$). The change in iFR after intervention (0.18 $\pm$ 0.17) was similar to Δ FFR 0.21 $\pm$ 0.15 ($p=0.25$)

and correlated well with each of the other indexes (Δ FFR=0.61 Δ iFR+0.10 $r^2=0.71$ $p<0.001$). Δ FFR and Δ iFR were significantly larger than resting Δ Pd/Pa (0.13 $\pm$ 0.17, both $p<0.001$). Sensitivity, specificity, positive predictive value, negative predictive value, accuracy of iFR-cutoff of 0.90 to detect the residual ischemia defined by FFR $\leq$ 0.8 after PCI was 67%, 90%, 67%, 89%, and 84% respectively.

Conclusions: The changes in coronary haemodynamics can be detected by both iFR and FFR elicited by PCI. iFR might be used to objectively document improvement in coronary haemodynamics and diagnose the presence of residual ischemia following PCI in a similar manner to FFR.

P1707 | SPOTLIGHT

Myocardial shockwave therapy improves global and regional left ventricular function in patients with stable ischemic heart disease regardless of baseline contractility

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Purpose: New myocardial revascularization method—myocardial shockwave therapy (MSWT)—stimulates angiogenesis in experimental studies. We hypothesize, that MSWT improves myocardial global and regional contraction in patients with stable ischemic heart disease, regardless of baseline contractility.

Methods: Forty patients with CCS class III-IV angina despite medical therapy were selected for MSWT, 70% of them had one or more myocardial infarctions. Myocardial ischemia was confirmed by technetium-99m SPECT evaluating transient ischemic dilatation (TID) or dobutamine stress echocardiography (DSE) evaluating wall motion score index (WMSI). MSWT was applied using commercially available MSWT generator system under echocardiographic guidance. Morphometrical and functional evaluation was performed before and 6 months after study therapy. LV ejection fraction (EF) was estimated by cardiac Magnetic resonance imaging (MRI), regional contraction was evaluated by DSE WMSI at rest and during stress. Analysis was made dividing patients into two groups according to deterioration of baseline regional contraction: by WMSI median value 1.5. The statistical software package SPSS 17.0 (version for Windows) was used for the data analysis.

Results: Baseline rest WMSI and LV EF in the Group I was 1.18 $\pm$ 0.18 and 58.6 $\pm$ 7.0%, in the Group II 1.92 $\pm$ 0.03 and 43.1 $\pm$ 10.8%, respectively. After treatment LV EF, stress WMSI and TID significantly improved in both groups (see Table). Improvement of rest WMSI was demonstrated only in Group II.

Conclusions: MSWT is a promising treatment method for patients with stable ischemic heart disease. This study demonstrates that myocardial shock wave therapy improves LV global and regional contraction at rest and during stress irrespective of baseline contractile function. MSWT may effectively enhance rest WMSI in patients with impaired LV regional contraction.

P1708 | BEDSIDE

Ivabradine and bisoprolol on doppler derived coronary flow reserve in patients with stable angina pectoris: more than heart rate

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Background: Both beta blockers and ivabradine showed to improve hyperemic coronary flow velocity and coronary flow reserve (CFR) in patients with stable coronary artery disease (CAD). There are no data on comparison of their effects. The purpose of this study was to assess the effects of ivabradine and bisoprolol on CFR in patients with stable CAD.

Methods: 59 patients (38 M, 21 F; mean age 69 $\pm$ 9 years) with stable CAD were enrolled in the study. Patients on beta blockers or ivabradine therapy, had a previous 2-week washout period from these drugs. Then baseline data were collected and all patients underwent Doppler-derived CFR. Coronary flow was assessed in the left anterior descending coronary artery (LAD), and was identified as the color signal directed from the base to the apex of the left ventricle, containing the characteristic biphasic pulsed-Doppler flow signals. CFR were determined as the ratio of hyperemic, induced by intravenous dipyridamole administration, to baseline diastolic coronary flow velocity. Patients were randomly assigned to bisoprolol and ivabradine for one month (after up-titration phase). CFR assessment was performed again at the end of treatment period.

Results: There were no significant differences in baseline characteristics between ivabradine and bisoprolol group. CFR was successfully performed in all patients. All data are reported in Table 1. Baseline CFR was not significantly differ-

Abstract P1707 – Table 1

	Group I WMSI $\leq$ 1.5 (N=15)				Group II WMSI $>$ 1.5 (N=25)			
	Baseline	After treatment	Change (%)	p value	Baseline	After treatment	Change (%)	p value
Left ventricular ejection fraction (%) (MRI)	58.6 $\pm$ 7.0	63.3 $\pm$ 7.4	7.9	0.001	43.1 $\pm$ 10.8	49.3 $\pm$ 11.9	14.2	0.001
Left ventricular stroke volume (MRI)	74.8 $\pm$ 19.8	79.0 $\pm$ 22.0	5.7	0.84	61.2 $\pm$ 26.0	72.7 $\pm$ 23.0	18.4	0.07
Wall motion score index rest (DSE)	1.18 $\pm$ 0.18	1.16 $\pm$ 0.13	-1.7	0.44	1.92 $\pm$ 0.03	1.68 $\pm$ 0.4	-12.5	<0.001
Wall motion score index stress (DSE)	1.25 $\pm$ 0.22	1.13 $\pm$ 0.17	-9.6	0.013	1.8 $\pm$ 0.41	1.57 $\pm$ 0.45	-14.65	0.004
Transient ischemic dilation (SPECT)	1.11 $\pm$ 0.1	1.07 $\pm$ 0.12	-3.6	0.005	1.18 $\pm$ 0.12	1.08 $\pm$ 0.11	-8.47	<0.001

Table 1

	Basal CFR	One month CFR	p
Ivabradine	2.67±0.55	3.52±0.64	< 0.01
Bisoprolol	2.72±0.55	3.35±0.70	< 0.01
p	ns	< 0.01	

CFR: coronary flow reserve.

ent in ivabradine and bisoprolol group. After 1 month CFR significantly increased in both groups, but it was significantly better in ivabradine group compared with bisoprolol group, despite a similar lowering of heart rate (63 ± 7 vs. 61 ± 6 – p = ns). No patient dropped out during therapy.

Conclusions: In patients with stable CAD ivabradine has a better effect on improving CFR, compared with bisoprolol, despite similar lowering of heart rate. These are probably due to a better effect of ivabradine on diastolic phase of cardiac cycle.

P1709 | BEDSIDE

Comparison of the efficacy and tolerability of ivabradine vs ranolazine vs standard medical therapy in patients of chronic stable angina pectoris despite coronary percutaneous revascularization

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Background: Despite treatment with conventional agents plus complete coronary revascularization, many patients remain symptomatic. Therefore, new drugs, as Ivabradine and Ranolazine, able to reduce ischemic episodes.

Objective was to evaluate the effects of Ivabradine and Ranolazine plus standard therapy vs only standard therapy in terms of an increased exercise tolerability and a decreased incidence of angina episodes at 30 days. Secondary end-point was to evaluate, at 6-12 months clinical follow-up, the incidence of weekly angina episodes and re-hospitalization.

Methods: One hundred thirty-five consecutive patients who underwent to percutaneous coronary intervention plus stent implantation and met inclusion criteria were randomized in three different arms to receive Ivabradine (5mg twice daily)+standard therapy, Ranolazine (375mg twice daily)+ standard therapy or conventional anti-ischemic therapy alone. After 30 days all patients were submitted to treadmill exercise test (ETT) and symptoms, ECG variations and maximal time exercise were recorded. Clinical follow-up was performed at 30 days, 6 and 12 months.

Results: Patients were randomized in three arms in a 1:1:1 ratio: Ivabradine Group 45 pts (IG), Ranolazine Group 45 pts (RG) and Control Group 45 pts (CG). No baseline clinical and therapies differences were found between groups. At 30 ± 5 days ETT was performed in all patients. During the ETT only 11.1% IG and RG did not exceed the threshold of the six minutes vs 28.8% GC (p=0.03). 5 patients in IG and in RG developed angina in the first 6 minutes of exercise (CG vs IG vs RG p=0.03). At 30 days, 24.4% developed weekly angina during daily moderate exercises in CG vs 4.5% in IG (p=0.007), and 8.8% in RG (p=0.04). At 6 months follow-up showed significant difference in angina onset between RG (5 pts) vs IG (7 pts) vs CG (19 pts) (p=0.005 CG vs IG and p=0.008 CG vs RG). At 12 months follow-up 6 weekly angina was ever greater in CG (42.2%) compared with RG (p=0.002) and (p=0.005). Re-hospitalization, for angina worsening, at 12 months was necessary in only 2 pts treated with ivabradine vs 9 pts in CG and 5 pts in RG (CG vs IG p=0.02).

Conclusions: The addition of Ivabradine/Ranolazine with standard anti-ischemic therapy in patients with complete revascularization produce an increased efficacy and safety in terms of a significant improvement of exercise tolerability, a decrease daily angina episodes and re-hospitalization angina guided.

P1710 | BEDSIDE

Effect of rosuvastatin treatment on skin microvascular function in patients with coronary artery diseases assessed by laser Doppler flowmetry

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Purpose: The involvement of microvascular bed in atherosclerosis in absence of arterial hypertension is not well established. Our aim was to investigate the impact of lipid lowering therapy by Rosuvastatin on skin microvascular function as the model of myocardial microcirculation in patients with coronary artery diseases (CAD).

Methods: 14 pts with coronary artery disease (9 male, 5 female, mean age 57.6 ± 8.1), without diabetes, hypertension, heart failure, never treated with lipid-lowering medication were examined before and after 12 weeks of Rosuvastatin treatment (10 mg/day). All pts had exertional angina CCS grade I-III and finding of severe stenoses in their coronary angiography. Antianginal therapy by β -blockers (bisoprolol 5mg/day) and nitrates (mononitrates 40 mg/day) was not discontinued. Skin microvascular function was assessed by laser Doppler flowmetry at rest, with the constrictor (respiratory and venous occlusion) and dilator (heating, electrostimulation and arterial occlusion) tests on the ulnar part of the right forearm. Amplitude–frequency wavelet analysis of blood flow oscillations was per-

formed. Time-averaged vasomotion amplitude was assessed using maximum values (Amax) in the corresponding frequency band for endothelial (Ae), neurogenic (An), myogenic (Am), venular (Av) and cardiac (Ac) sections of blood flow modulation. Values of the tissue perfusion level (M) and the amplitude modulation mechanisms evaluated in AU.

Results: Rosuvastatin treatment resulted in a decrease of total cholesterol from 6.32 ± 1.09 to 4.9 ± 1.27 mmol/l, LDL-cholesterol from 4.3 ± 0.8 to 2.94 ± 0.92 mmol/l (p<0.002). Against this background, there is an increase with a tendency to reliability level of M with 3.92 to 5.17 AU ($=0.065$), a significant increase in the amplitude vasomotion of Ae with 0.265 to 0.405 AU (<0.01), An with 0.246 to 0.403 AU (<0.003) and Am with 0.199 to 0.251 AU (<0.05), a decrease of constrictor response in the respiratory sample from 58.5 to 51.9% ($=0.074$) and the sample with venous occlusion from 65.7 to 55.1% ($=0.071$). Maximal values of skin blood flow and Ac in response to local heating increased from 17.69 to 21.4 AU (p<0.005), and from 0.318 to 0.491 AU (p=0.069) accordingly.

Conclusion: Lipid lowering improves microcirculatory blood flow in patients with CAD, this manifested by: 1) decrease in endothelial, neurogenic and myogenic tone of precapillary arterioles components (if the amplitude of the oscillations of blood flow translate to "tone language"); 2) reduction of microvascular constriction activity of skin; 3) increase vasodilator reserve of skin microcirculation.

REMOTE ISCHAEMIC PRECONDITIONING, THROMBECTOMY AND NO REFLOW

P1712 | BEDSIDE

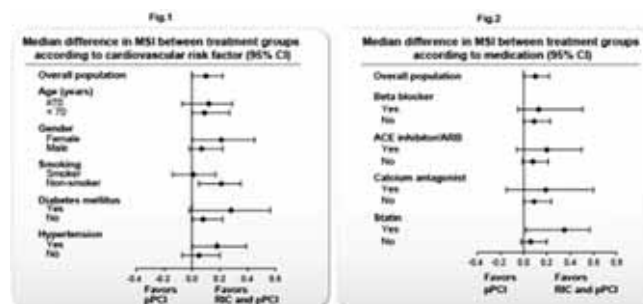
No effect modification by cardiovascular risk factors and medication on the efficacy of remote ischemic conditioning in patients with ST-elevation myocardial infarction

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Purpose: Remote ischemic conditioning (RIC) induces cardioprotection in patients undergoing primary percutaneous coronary intervention (pPCI) for ST-elevation myocardial infarction (STEMI). Experimental studies of myocardial infarction suggest that the effect of ischemic conditioning may be modulated by cardiovascular risk factors and medication. We evaluated whether cardiovascular risk factors and current medication modified the efficacy of RIC in pPCI-treated patients with STEMI.

Methods: We studied 251 patients with STEMI randomized pre-hospitally to receive pPCI with (n=126) or without (n=125) RIC (intermittent arm ischemia through four cycles of 5-minute inflation and 5-minute deflation of a blood pressure cuff). The primary endpoint was myocardial salvage index (MSI) estimated by single photon emission computed tomography. To assess effect modification, we applied stratified analyses for the difference in myocardial salvage index between the two treatment groups according to cardiovascular risk factors and medication at admission.

Results: While the effect tended to be reduced in smokers [difference in MSI in smokers of 0.01 (95% CI -0.14; 0.17) versus 0.21 (95% CI 0.05; 0.35) in non-smokers], point estimates of improvement in MSI by RIC were consistent in all other subgroups irrespective of the presence of cardiovascular risk factors (Fig. 1) and medication (Fig. 2).



Conclusion: RIC is an effective adjunctive treatment to pPCI in STEMI patients regardless of cardiovascular risk factors and current medication.

P1713 | BEDSIDE

Remote ischemic preconditioning preserves kidney function in patients with ST-elevation myocardial infarction

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Background: Several studies have shown that Remote ischemic preconditioning (RIPC) applied before percutaneous coronary intervention (PCI) in patients with evolving ST-elevation myocardial infarction (STEMI) increased myocardial

salvage. In addition, a recent study showed that RIPC before the use of contrast medium prevented contrast-induced acute kidney injury (CI-AKI) in high-risk patients. However, the role of RIPC in reducing CI-AKI in STEMI patients undergoing emergent PCI is not clear. In this study, we evaluated the impact of RIPC on CI-AKI in patients with STEMI who received emergency primary PCI, and hypothesized that RIPC applied before PCI would preserve the kidney function in patients with STEMI.

Methods: This prospective, single-blind, multicenter, randomized, sham-controlled, parallel-group study was conducted from 2012 to 2013. Consecutive patients with a suspected STEMI were randomly assigned at a 1:1 ratio to receive percutaneous coronary intervention either with or without RIPC (intermittent arm ischemia through three cycles of 5-minutes inflation and 5-minutes deflation of a blood-pressure cuff). The primary endpoint was the incidence of CI-AKI, which was defined as an increase in serum creatinine > 0.5 mg/dl or $> 25\%$ over the baseline value in the 48 hours after contrast medium administration. Secondary endpoints were the incidence of major adverse cardiac and cerebral events (MACCE) and the relative change in serum creatinine from baseline to 1 year after PCI.

Results: A total of 125 STEMI patients were enrolled during transfer to primary PCI (63 patients received RIPC before primary PCI and 62 patients received PCI alone). Thirty-one patients did not fulfill the entry criteria and were excluded. A total of 47 RIPC patients and 47 control patients met all study criteria. The incidence of CI-AKI was 10% ($n=5$) in the RIPC group and 36% ($n=17$) in the control group ($p=0.003$). The odds ratio of CI-AKI in patients who received RIPC was 0.18 (95% confidence interval: 0.05–0.64; $p=0.008$). Seventy-six of the 125 patients with STEMI were available for 1-year follow-up. The incidence of MACCE in 1 year after PCI was tended to be lower in the RIPC group (7% ($n=3$) in RIPC group versus 23% ($n=9$) in control group, $p=0.06$). The relative change in serum creatinine index from baseline at 1 year after PCI was lower in the RIPC group ($4 \pm 19\%$ increase in RIPC group versus $23 \pm 36\%$ increase in the control group, $p=0.01$).

Conclusions: In patients with STEMI, RIPC before PCI reduced the incidence of CI-AKI and was shown to preserve kidney function in 1-year follow-up.

P1714 | BEDSIDE

Ischemic postconditioning significantly reduces infarct size: systematic review and meta-analysis of randomized controlled trials

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Cardiac ischemic postconditioning (IPost), defined as rapid intermittent interruptions of blood flow in the early phase of myocardial reperfusion is feasible in patients with STEMI treated by primary percutaneous coronary intervention (PPCI). IPost significantly reduced infarct size in experimental models and produced controversial results in small clinical trials. The aim of this systematic review and meta-analysis was to provide an updated synthesis on the efficacy of IPost on accurate surrogate markers of infarct size.

Randomized controlled trials that evaluated the efficacy of IPost in STEMI patients undergoing PPCI, and provided information on surrogate markers of infarct size were considered. Main outcome was the area under the curve (AUC) of serum CK release (CK-AUC). Secondary outcomes were other surrogate biologic markers of infarct size, complete ST-segment resolution (cSTR), direct measure of infarct size by single-photon emission computed tomography (SPECT) or estimate of the infarct size by cardiac magnetic resonance (CMR). Summary measures were reported as standard mean difference (SMD) for continuous variables or risk ratio (RR) for binary variables.

Ten studies were selected including 613 STEMI patients undergoing PPCI with or without IPost. Compared to control, we observed a significant reduction of CK-AUC (SMD -2.84 95%CI -5.43 to -0.25 IU/L, $p=0.03$) and cSTR (RR 1.38 95% CI 1.08 to 1.77 $p=0.01$). Our meta-analysis suggested that IPost did not significantly reduced infarct size as estimated by CMR (-0.36 95%CI -0.88 to 0.15 $p=0.16$).

This meta-analysis dealing with accurate surrogates of infarct size such as CK-AUC and CMR-IS suggest that IPost reduces infarct size. Whether this translates into cardiac function and patient's prognosis improvement still needs to be demonstrated. Larger prospective sufficiently powered randomized controlled studies with clinical endpoints and a standardized protocol to evaluate the efficacy of IPost in STEMI patients are urgently needed.

P1715 | BEDSIDE

Prolonged effect of remote ischemic preconditioning on endothelial function in healthy volunteers and in patients with STEMI

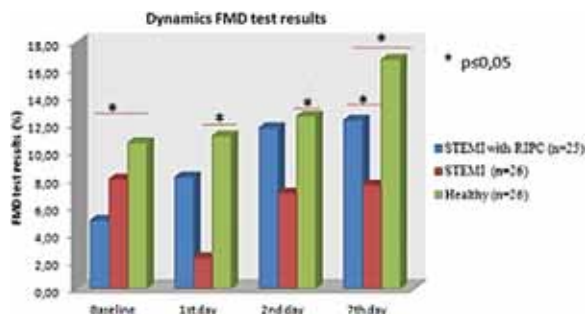
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Aim: In a previous study, we demonstrated that RIPC before PCI improves en-

dothelial function in patients with acute myocardial infarction, and that this effect persists for a week. The aim of the current study was to assess the effect of RIPC on endothelial function in healthy volunteers compared with patients with STEMI.

Methods: Twenty-six healthy volunteers underwent RIPC - by intermittent arm ischemia-reperfusion through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff to 200 mm Hg. We assessed endothelial function using the flow-mediated dilation (FMD) test on baseline, after RIPC, and again on days 2 and 7 after PCI. Patients with STEMI were randomly divided into two groups: with or without RIPC prior to primary PCI.

Results: In the group of healthy volunteers at baseline level FMD results was higher than in the STEMI group (10.6% vs. 5.0%, respectively; $p=0.005$). RIPC improved endothelial function in both the STEMI-RIPC and the healthy volunteer groups (16.7% vs. 12.3%, respectively; $p=0.05$), compared with patients with STEMI without RIPC (16.7% vs. 7.6%, respectively; $p=0.0004$). FMD test results on day 7 in healthy volunteers were considerably higher than in the groups with myocardial infarction with or without RIPC.



Conclusions: RIPC improves endothelial function in healthy volunteers as well as in patients with STEMI, and this effect also remains constant for at least a week. We surmise that the improvement of endothelial function may be one of the explanations of the effect of RIPC.

P1716 | BEDSIDE

Impact of different subtypes of microvascular dysfunction on myocardial strain in ST-segment elevation myocardial infarction patients after reperfusion therapy

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Background: Microvascular dysfunction (MD) has been regarded as a key prognostic factor for ST-segment Elevation Myocardial Infarction (STEMI) patients receiving reperfusion therapy. Cardiac Magnetic Resonance Imaging (CMR) can differentiate subtypes of MD, i.e. solo microvascular obstruction (MVO) or MVO with intramyocardial hemorrhage (IMH), which theoretically have different impacts on myocardial motions.

Methods: Sixty-three STEMI patients (5 females, 58 males,) who received primary percutaneous coronary intervention within 12 hours after symptom onset form the basis of the study. Myocardial necrosis and subtypes of MD were defined by CMR using T2-weighted and late-gadolinium-enhancement imaging technologies within 1 week. Infarction transmural for each segment were calculated. Myocardial strain was measured by 2D-speckle-tracking echocardiography (2DSTE) on the same day of the CMR examination, where peak systolic segmental circumferential (CS), radial (RS), and longitudinal (LS) strain was calculated, respectively.

Results: A total of 1134 segments were measured by 2DSTE. Segments with infarction transmural more than 50% as defined by CMR could cause significant decrease of myocardial strain compared to normal myocardium in all three dimensions (CS: 10.16 ± 20.15 v.s. 20.15 ± 7.50 ; RS: 18.52 ± 13.88 v.s. 39.07 ± 2.54 ; LS: 7.67 ± 7.27 v.s. 17.10 ± 6.57 , $p < 0.001$ in all comparisons). The existence of solo MVO had a trend further jeopardizing myocardial strain at circumferential and longitudinal direction compared to segments without MVO (CS: 7.99 ± 7.21 v.s. 10.16 ± 20.15 ; LS: 5.81 ± 7.67 v.s. 7.67 ± 7.27 , both $p > 0.05$). However, when MVO was accompanied with IMH, the deterioration of myocardial strain became significantly worse in this two dimensions (CS 4.29 ± 8.96 v.s. 10.16 ± 20.15 ; LS 4.12 ± 6.66 v.s. 7.67 ± 7.27 , both $p < 0.001$).

Change of myocardial strain

Strain	CS	RS	LS
Normal Myocardium	20.15 ± 7.50	39.07 ± 20.00	17.10 ± 6.57
Transmural Necrosis (> 50%) without MD	10.16 ± 7.81	18.52 ± 13.87	7.67 ± 7.27
Transmural Necrosis (> 50%) with solo MVO	7.99 ± 7.21	19.47 ± 18.33	5.81 ± 6.71
Transmural Necrosis (> 50%) with MVO and IMH	4.29 ± 8.96	18.61 ± 13.98	4.12 ± 6.66

Conclusion: The existence of MD, especially IMH can cause remarkably exacerbation of the myocardial motion in infarction zone, which can explain the worse prognosis in this subgroup of patients.

P1717 | BEDSIDE**Local intracoronary eptifibatide versus mechanical aspiration in patients with acute ST-elevation myocardial infarction**

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Objectives: We compared local delivery of intracoronary eptifibatide via perfusion catheter versus thrombus aspiration in primary PCI.

Background: Perfusion catheter increases local concentration of the drugs at the culprit site and prolongs their residency time.

Methods: 75 patients with acute STEMI were randomized to three groups; 25 received local intracoronary eptifibatide and verapamil via the Clearway®RX perfusion catheter, 25 patients managed by Diver Ce thrombectomy device and 25 patients managed by conventional primary PCI without thrombus aspiration. The primary end point was assessment of post procedural TIMI flow, myocardial blush grade (MPG) and corrected TIMI frame count (cTFC) in the culprit vessel territory.

Results: Perfusion catheter was superior to thrombus aspiration and to conventional PCI as regards MBG (68% vs 36% in Diver Ce arm, and 20% of in the control arm. (P-value=0.002). Also, less cTFC rates than thrombectomy and control groups (20.76±4.44 vs 26.68±8.40 and 28.16±5.96, respectively, p=0.001). Thrombus aspiration was superior to conventional PCI as regards myocardial reperfusion measured by MBG, while TIMI flow wasn't different between the 3 groups. The study showed also that intracoronary eptifibatide led to better outcomes as shown by less time to reach peak CK (mean time 13.12 hours) compared to thrombus aspiration and control groups (mean time 16.5 and 19.5 hours respectively, p-value= 0.001).

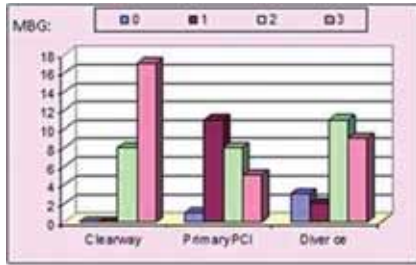


Figure 1

Conclusions: Local intracoronary eptifibatide by perfusion catheter reduces thrombus burden with better results in microvascular perfusion as assessed by cTFC and MBG compared to aspiration device or using conventional PCI.

P1718 | BEDSIDE**The effect of thrombectomy on 30-day outcomes in STEMI patients treated with bivalirudin or heparin, insights from the EUROMAX trial**

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Purpose: Thrombectomy is commonly used in primary percutaneous coronary intervention (PPCI). We studied whether 30-day clinical outcomes were affected by the use of thrombectomy in EUROMAX and whether thrombectomy affected the results of the randomized comparison between bivalirudin and heparins with optional glycoprotein IIb/IIIa inhibition.

Methods: The EUROMAX trial randomised 2218 STEMI patients to early pre-hospital administration of bivalirudin versus standard care in the context of contemporary management in 9 European countries. This analysis was performed on the subgroup that underwent PPCI in EUROMAX (n=1889), divided into those who underwent thrombectomy and those who did not. The 30-day primary end-point was death or non-CABG major bleeding.

Results: Of 1889 patients, 602 (31.9%) underwent thrombectomy. This group of patients was significantly younger, they had higher risk features of TIMI 0-1 flow in the infarct-related artery, were more likely to receive a glycoprotein IIb/IIIa inhibitor, have the procedure by radial artery access, and to be loaded with a P2Y12 inhibitor prior to coronary angiography, or be treated in France. In terms of outcomes, minor bleeding was slightly higher in the thrombectomy group (8.1% vs. 5.7%, Relative Risk (RR) 1.44, 95% confidence interval (CI) 1.01-2.03, p=0.04), otherwise there was no significant difference in the primary or secondary end-points between groups.

In the thrombectomy group, patients who received bivalirudin had a significant reduction in the primary outcome, which occurred in 3.6% of vs. 8.7% in the standard care group, RR 0.41, 95% CI 0.21-0.82, p=0.009. The secondary outcome

occurred at a rate of 4.9% in the bivalirudin group vs. 8.7% in the controls, RR 0.57, 95% CI 0.31-1.05, p=0.06. The reduction in both primary and secondary outcomes was mainly driven by reduced major bleeding (2.0% vs. 7.0%, RR 0.28, 95% CI 0.11-0.68, p=0.003). For those who did not undergo thrombectomy, results were consistent and Breslow-day testing showed that there was no interaction between randomized treatment and the use of thrombectomy, for the primary and secondary outcomes or for major bleeding.

Conclusion: In EUROMAX, despite the higher risk profile and greater use of GPI inhibitors in patients who underwent thrombectomy, the benefit of bivalirudin over heparins with optional GPI during PPCI was consistent, regardless of the use of thrombectomy, and driven by a reduction in major bleeding.

P1719 | BEDSIDE**Prognostic value of manual thrombus aspiration in patients undergoing Primary Percutaneous Coronary Intervention**

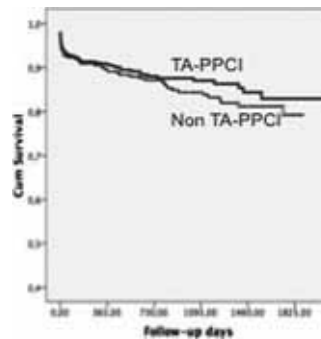
A.B. Cid Alvarez, B. Alvarez Alvarez, R. Trillo Nouché, D. Lopez Otero, R. Ocaranza Sanchez, P. Souto Castro, S. Gestal Romani, A.B. Fernandez Cislal, E. Pereira Lopez, J.R. Gonzalez-Juanatey. *University Clinical Hospital of Santiago de Compostela, Department of Cardiology, Santiago de Compostela, Spain*

Purpose: Recent studies question the value of manual thrombus aspiration (TA) before PCI in patients with ST-segment elevation infarction (STEMI). The aim of this study was to evaluate the impact of TA in a contemporary cohort of patients admitted to our hospital with STEMI who were undergoing primary percutaneous coronary intervention (PPCI).

Methods: We analyzed the data and clinical outcomes of 1044 consecutive patients undergoing PPCI between January 2009 and December 2013. We classified patients into TA-PPCI (n=666) and non TA-PPCI (n=378). Mean follow-up was 23 months. Primary end point was all cause mortality and secondary end point was major adverse cardiovascular events (MACE; death, recurrent MI, target vessel revascularization, heart failure).

Results: The median patient age was 65 years, 76.6% were men, 50.1% had hypertension, and 24% had diabetes. Percutaneous access was via the radial approach in 88% of the patients. The culprit artery was the left anterior descending in 44% of the patients, 17.3% had three-vessel disease. The variables independently associated with TA use are: sex, culprit artery, number of vessel disease and TIMI 0 before PPCI.

At the end of the follow-up 12.5% of the patients died: 11.1% in TA-PPCI group, and 15.1% in non TA-PPCI (p=0.040) (See Image 1). The incidence of major adverse cardiovascular events (MACE) at the end of the follow-up was 23.1%: 21% in TA-PPCI group and 23.7% in non TA-PPCI (p=0.022). However, after cox regression analysis, we don't find independent association between TA and mortality or MACE.



Conclusions: The use of TA in a "real-world" cohort of patients with STEMI who were undergoing PPCI was not associated with a reduction in mortality or MACE risk.

P1720 | BEDSIDE**Use and outcome of thrombectomy in patients with primary PCI for acute ST elevation myocardial infarction: results from the Euro Heart Survey PCI registry**

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Background: The clinical benefit of thrombus aspiration in patients presenting with acute ST elevation myocardial infarction (STEMI) and treated with primary percutaneous coronary intervention (PCI) is not well defined. Furthermore, little is known about the use and the clinical outcome of thrombectomy in a real world registry.

Methods: Between 2005 and 2008 a total of 7,146 consecutive patients with acute STEMI undergoing primary PCI were prospectively enrolled into the PCI-Registry of the Euro Heart Survey Programme. For the present analysis patients additionally treated with thrombus aspiration (n=897, 12.6%) were compared to those without thrombus aspiration (n=6,249, 87.4%)

Results: Patients additionally treated with thrombectomy more frequently presented with shock or had been resuscitated (table). TIMI 0-1 before PCI was much more often found among those with thrombus aspiration. After adjustment for age, female gender, anterior STEMI, prior resuscitation/shock, 3-vessel disease and TIMI 0/1 flow before PCI thrombectomy was not linked to improved hospital survival rates (odds ratio 0.76, 95% confidence interval 0.52-1.11).

	Thrombectomy	No thrombectomy	P-value
Age	62.4±12.8	62.4±12.7	ns
Female	24.3%	27.0%	ns
Anterior STEMI	41.7%	48.5%	<0.001
Prior resuscitation	10.4%	7.4%	<0.01
Shock	9.5%	7.7%	0.07
3-vessel disease	23.2%	23.3%	ns
TIMI 0-1 before PCI	73.5%	58.6%	<0.001
TIMI 3 after PCI	86.2%	90.2%	<0.001
Hospital death	5.5%	5.7%	ns
Non-fatal stroke (in-hospital)	0.2%	0.6%	ns

Conclusions: In this real-world registry the use of thrombectomy was quite low. Haemodynamically instable patients were more likely to be treated with thrombus aspiration. In the logistic regression analysis thrombectomy was not associated with an improved prognosis.

P1721 | BEDSIDE

Myocardial wash grade: a novel method to evaluate the quality of reperfusion therapy

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Background: After an acute myocardial infarction, it is important to evaluate the infarct size because it is related to mortality and morbidity. It has previously been shown that there is a good agreement between the QRS scoring system and myocardial infarct size. However, there are few methods to evaluate the quality of reperfusion therapy just on the catheter laboratory. The aim of this study was to evaluate the correlation between the QRS scoring system and Myocardial wash grade.

Methods: Consecutive 61 ST-segment elevation myocardial infarction patients meeting criteria of culprit lesion was proximal or mid portion of left anterior descending artery (LAD), onset-to-door time within 12 hours, and initial Thrombolysis in Myocardial infarction grade 0 or 1 flow were enrolled in this study. After primary percutaneous coronary intervention, we injected 15ml saline selectively into LAD using an aspiration catheter and electrocardiogram was recorded. The electrocardiographic changes as "Myocardial wash grade" were defined as following 3 types; "Persistent ST elevation", "Terminal T wave inversion", and "Coronary T wave inversion".

Results: The QRS score was significantly lower in a type of "Coronary T wave inversion" compared to a type of "Persistent ST elevation" (P<.0001). There was a good correlation between QRS scoring system and Myocardial wash grade.

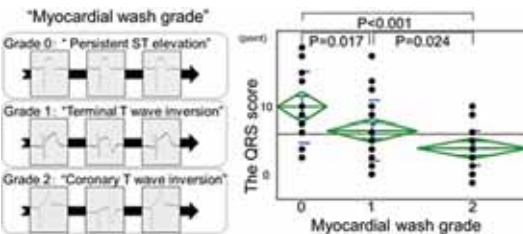


Figure 1

Conclusions: Myocardial wash grade is a simple and useful indicator of acute reperfusion quality just on-site.

P1722 | BEDSIDE

Intramyocardial hemorrhage and non-reflow phenomenon

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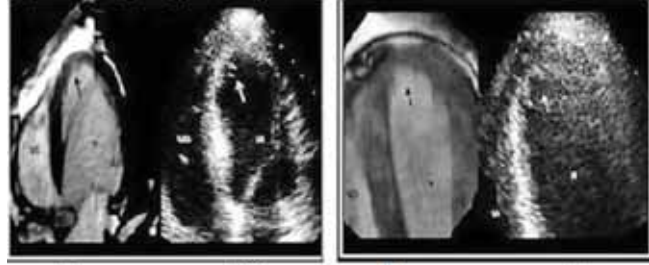
Introduction: Myocardial reperfusion can cause undesirable effects described as "reperfusion damage". Intramyocardial hemorrhage (IMH) is one of its components, caused by leakage of blood from the infarct related vessel. The cardiovascular MRI has proven to be highly sensitive for its detection. Unfavorable mechanic consequences of IMH include microvascular compression which may contribute to the non-reflow phenomenon (NRF). The aim of the study is to estab-

lish if IMH is found more frequently in patients with NRF and if it is accompanied by a greater inflammatory response.

Methods: During a 9 months period, patients with acute myocardial infarct with ST elevation (STEMI) treated by primary angioplasty were enrolled. Blood samples were taken before and after primary angioplasty. MRI studies were performed between the third and seventh day after intervention. Presence or not of NRF, IMH, microvascular obstruction (MVO), myocardial edema, proinflammatory and tissue damage markers were evaluated.

Results: 30 patients were included. The age range was 39 to 84 years (mean 61 years ±11.14), 24 were male and 6 female. 87% (n=26) had a successful revascularization. The edema and myocardial motion abnormalities were found in all patients, MVO was found in 90% (n=27) of them, 13% (n=4) presented NRF and 58% (n=15) developed IMH. IMH was found in the 25% (n=8) of patients with NRF. 65% (n=20) had suggestive images of myocardial fibers dissection by echocardiographic images and 14% (n=4) by MRI. Cardiovascular risk factors, cardiac enzymes, proinflammatory and tissue damage markers, showed no statistically significant differences.

Comparison of images suggestive of myocardial fibers dissection between ECG and MRI studies



Myocardial fibers dissection.

Conclusions: Prevalence of IMH is not greater in patients with NRF. This indicates that NRF depends on other factors of reperfusion damage rather than IMH.

HEART FAILURE PATHOPHYSIOLOGY

P1724 | BENCH

MPO-deficiency attenuates dilated cardiomyopathy in mice

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Background: The neutrophil-derived enzyme myeloperoxidase (MPO) has been shown to exert potent pro-inflammatory and pro-fibrotic effects on the vascular and myocardial level. Using muscle Lim protein (MLP)-deficient mice as a model for dilative cardiomyopathy (DCM), we herein sought to evaluate the role of MPO in this disease.

Methods and results: The deposition of MPO within the myocardium was significantly elevated in MLP-deficient (MLP-/-) mice as compared to wildtype littermates (WT) pointing towards a sustained activation of neutrophils in MLP-/- mice. Echocardiography revealed, that MLP-/- mice exhibited a reduction of the fractional shortening (FS, WT vs. MLP-/-: 24.2±1.5 vs. 11.3±1.1, p<0.001) and ejection fraction (EF, WT vs. MLP-/-: 48.4±2.5 vs. 24.7±2.2, p<0.001) compared to WT, as expected. Remarkably, MPO deficiency led to a significant improvement of left ventricular function in MLPxMpo-/- mice as assessed by echocardiography (MLP-/- vs. MLPxMpo-/-, FS: 11.3±1.0 vs. 14.7±0.8, p<0.05; EF: 24.7±2.2 vs. 31.1±1.55, p<0.05) and significantly improved contractility represented by preload recruitable stroke work (MLP-/- vs. MLPxMpo-/-, 40.9±2.2 vs. 59.8±4.6 mmHg, p<0.05) determined by left ventricular pressure-volume loops.

Reflecting the occurrence of inflammatory processes in failing myocardium, dihydroethidine staining in ventricular sections showed an enhanced ROS production in MLP-/- as compared to WT mice (3.58±0.7 vs. 1.44±0.35 AU, p<0.05), which was attenuated in MLPxMpo-/- mice (1.55±0.36 AU, p<0.01).

Given the potent nitric oxide (NO) consuming properties of MPO, ex-vivo vasoreactivity studies were performed which revealed, that impaired aortic vasodilation in MLP-deficient mice was significantly improved in MLPxMpo-/- mice (% of relaxation to 100 nM ACh treatment, WT vs. MLP-/- vs. MLPxMpo-/-, -67.22±1.92 vs. -37.51±3.83 vs. -53.98±3.11, p<0.001). This was accompanied by an increased systemic vascular resistance in MLP-/- mice, which was blunted by MPO-deficiency (WT vs. MLP-/-, 0.35±0.04 vs. 0.56±0.04 mmHg*min*ml⁻¹, p<0.01; MLPxMpo-/- 0.36±0.04 mmHg*min*ml⁻¹; MLP-/- vs. MLPxMpo-/- p<0.01).

Conclusions: The current results reveal an improvement of endothelial and left ventricular function by MPO-deficiency in a mouse model of DCM. These data underline the importance of endothelial NO-bioavailability and vascular function in the pathophysiology of cardiomyopathy and emphasize the role of MPO as a potential therapeutic target in this disease.

P1725 | BENCH**Insufficient ATP supply due to excessive degradation of adenine nucleotides by AMP deaminase underlies afterload-induced diastolic dysfunction in the type 2 diabetic heart**

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Purpose: Heart failure with preserved ejection fraction, mostly based on hypertension and/or type 2 diabetes mellitus (T2DM), often decompensates under increased afterload. Here we examined mechanisms by which T2DM augments ventricular diastolic stiffness in response to pressure overloading, focusing on cytoskeletons and cardiac metabolism.

Methods: Pressure-volume relationships (PVRs) were determined by a conductance catheter in a model of T2DM, OLETF, and its non-diabetic control, LETO (29-35 weeks old). Pressure overloading was performed by phenylephrine infusion with target systolic pressure of 200 mmHg, and changes in PVRs were assessed by ventricular volume at pre-defined pressures (end-systolic volume at 125 mmHg: ESV125 and end-diastolic volume at 20 mmHg: EDV20). Myocardial tissue was sampled with or without phenylephrine challenge and changes in energy metabolites caused by diabetes and pressure overloading were examined by metabolome analysis using CE-TOFMS/QqQ.

Results: Heart weight, interstitial collagen volumes and mRNA levels of types 1 and 3 collagens were comparable in OLETF and LETO. During pressure overloading, systolic reserves assessed by changes in ESV125 and stroke work were preserved, but diastolic stiffness was augmented as indicated by decrease in EDV20 in OLETF (from 0.24 ± 0.02 to 0.20 ± 0.02 ml, $p < 0.05$) and higher LVEDP in OLETF than in LETO (14.1 ± 1.8 vs. 5.9 ± 0.9 mmHg, $p < 0.05$). In buffer-perfused isolated heart preparations, PVRs under cardioplegic arrest did not differ between OLETF and LETO, suggesting that remodeling of extra- and intra-cellular cytoskeletons does not contribute to the increased stiffness in the beating OLETF ventricle. Metabolome analyses revealed that glycolysis was impaired and the pentose phosphate pathway was facilitated in OLETF. Under pressure overloading, malic and asparaginic acids were increased, probably reflecting activation of the TCA cycle, without a difference in lactic acid or NADH/NAD⁺ ratio between OLETF and LETO. However, ATP level was decreased by 34% with pressure overloading only in OLETF. The decline in ATP in OLETF was associated with increased IMP and decreased adenosine levels, being consistent with the 2.5-times higher activity of cardiac AMP deaminase in OLETF. ATP level was negatively correlated with relaxation time tau ($r = -0.49$, $p < 0.05$) and LVEDP ($r = -0.53$, $p < 0.05$).

Conclusions: ATP depletion due to excessive degradation of adenine nucleotides by AMP deaminase underlies residual cross-bridges in diastole, leading to acute ventricular stiffening during pressure overloading in T2DM hearts.

P1726 | BENCH**Time course transcriptome analysis after transverse aortic constriction in mice revealed Wnt-signaling as a relevant factor of Heart Failure progression**

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Purpose: Heart Failure (HF) progression is characterized by a transition from normal heart function to compensatory hypertrophy finally leading to decompensation and cardiac dilation. There is increasing evidence that the Wnt-Signaling plays an important role in cardiac hypertrophy and remodeling.

Methods: 8 weeks old male mice underwent either TAC (transverse aortic constriction) or sham surgery. Heart function was evaluated by cardiac MRI on either day 4, 14, 21, 28, 42 and 56 after surgery (n=6 per group/time point). The whole transcriptome of the pooled left ventricle (LV) of sham- and TAC-mice at each time point was analyzed by microarray (MA). The regulation of common HF genes as well as of genes of interest was validated on single sample level using Taq Man Low Density Array. In vitro studies in a hypertrophy model of HL-1 cells were used to examine the influence of the proteins encoded by the Wnt-Signaling candidate genes.

Results: In TAC-mice, systolic LV heart function declined from day 4 to day 14 (LV ejection fraction (LVEF) 38 ± 4 vs. $28 \pm 3\%$), remained on a stable level from day 14 to day 42 ($28 \pm 3\%$) (compensated stage) and showed a further pronounced decline at day 56 ($16 \pm 2\%$) (decompensated stage). This decrease in LVEF was paralleled by an increase in left ventricular mass and end-diastolic volume (LVEDV). LVEF of sham-mice remained unchanged ($55 \pm 2\%$) over time. MA analysis identified 13 genes associated with Wnt-Signaling as differentially expressed (TAC vs. sham, $fc \geq \pm 1.5$) over time. In particular, Wisp2 (WNT1 inducible signaling pathway protein 2) and the Sfrps 1, 2 and 3 (Secreted Frizzled-related protein) showed the strongest alterations in gene expression and were highly upregulated at day 14 up to day 56, whereas genes of other Wnt-factors like Dkk3 (Dickkopf 3) showed expression only at the later time points (day 42, 56). Further, Taq Man analysis of Wisp2 and Sfrp2 on single samples level revealed a significant correlation ($p < 0.0001$) between their expression and the LVEF ($rs = -0.68$; -0.64) and LVEDV ($rs = 0.61$; 0.76) in TAC-mice. First results of in vitro studies using the proteins encoded by the detected Wnt-genes in a model of hypertrophy in HL-1 cells revealed the induction of cell enlargement through Wnt3a protein.

Conclusion: Global transcriptomic analysis suggest an early participation of Wnt-Signaling in HF progression. Thereby, the expression of different Wnt-Signaling-factors seems to be dependent of the disease stage. The finding that the expression of Sfrp2 and Wisp2 correlates with heart function of TAC-mice points to an important role of Wnt-signaling in HF progression.

P1727 | BENCH**Diabetes blunted the compensatory enhancement of SUMOylation intensity of SERCA2a after myocardial Infarction**

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Background: Diabetes is an independent risk factor for heart failure and mortality after myocardial infarction (MI). In the condition of diabetes, the activity and expression of Sarcoplasmic Reticulum Calcium-transporting ATPase (SERCA2a) is decreased, leading to diastolic and systolic dysfunction of myocardium. It was recently reported that SUMOylation could elevate the activity and stability of SERCA2a. We assume that diabetes might affect the intensity of SUMOylation of SERCA2a after MI.

Methods: Diet-induced type 2 diabetic rats and controls were divided into suture ligation induced MI groups or sham groups. Primary cardiomyocytes were culture in different concentrations of glucose and insulin, and underwent oxygen deprivation (OD) for 6 or 12 hours. Echocardiograph and left ventricular pressure were measured to determine cardiac function. The intensity of SUMOylation of SERCA2a, expressions of SERCA2a, SUMO1 and enzymes of SUMOylation were evaluated.

Results: Diabetes exacerbated diastolic and systolic dysfunction of myocardium after infarction. SUMOylation intensity of SERCA2a was enhanced in 1-week-post-MI non-diabetic rats and 6-hour-OD cardiomyocytes but not in 4-week-post-MI rats and 12-hour-OD cardiomyocytes. The expression of enzyme 2 of SUMOylation, namely Ubc9, was in accordance with the SUMOylation intensity, while SUMO1 and enzyme 1 were not changed. This compensatory enhancement was almost completely blunted in 1 or 4 weeks post-MI diabetic rats. Interestingly, glucose alone increased Ubc9 expression and the SUMOylation intensity of SERCA2a of cardiomyocytes in vitro in a concentration-dependent manner; however, with addition of insulin, glucose decreased Ubc9 and SUMOylation intensity in a concentration-dependent manner on the contrary, while SUMO1 and enzyme 1 were also not changed. Additionally, overexpression of Ubc9 with lentivirus neutralized the decreasing of SUMOylation intensity caused by glucose and insulin in vitro.

Conclusions: SUMOylation intensity of SERCA2a was compensatorily enhanced in post-MI non-diabetic rats, but not in diabetic rats. SUMOylation intensity of SERCA2a decreased in cardiomyocytes with addition of high glucose and insulin in vitro, which could be neutralized by overexpression of Ubc9. These observations provide evidence that Ubc9 and SUMOylation of SERCA2a is involved in diabetes-mediated exacerbation of left ventricular dysfunction after MI.

P1728 | BENCH**The development of LV function upon LVAD-support in human heart failure is linked to the diastolic SR Ca2+ leak**

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In patients with heart failure (HF) the implantation of a left-ventricular assist device (LVAD) is used to reduce cardiac load and ensure sufficient cardiac output. Whereas some patients can subsequently be weaned from LVAD-support, other patients still need heart transplantation. To elucidate underlying mechanisms we assessed the diastolic SR Ca2+ leak at the time of LVAD implantation (HF-Im), successful LVAD explantation (HF-Ex) and heart transplantation (HF-Tx). Second, we evaluated the effects of CaMKII-inhibition on the SR Ca2+ leak in the respective groups.

We obtained left ventricular (LV) myocardial tissue and freshly isolated human cardiomyocytes (CMs). The CMs were paced at 1 Hz for 10 beats to ensure SR Ca2+ loading and scanned for diastolic Ca2+ sparks (confocal microscopy, Fluo3-AM). In HF-Im we detected a high diastolic spark frequency (CaSpF) of $0.82 \pm 0.13/10\text{-}4\text{m/s}$ that could be reduced to $0.57 \pm 0.12/10\text{-}4\text{m/s}$ by CaMKII inhibition with AIP ($1\mu\text{M}$). The amplitude of Ca2+-sparks was decreased by $5 \pm 1\%$ ($n=204$ vs. 94 , $p < 0.05$). Width and length of Ca2+-sparks were not significantly altered. In sum, CaMKII inhibition reduced the resulting calculated SR Ca2+ leak (CaSpF x duration x width x amplitude) by $60 \pm 10\%$ in HF-Im ($n=110$ vs. 76 , $P < 0.05$).

In HF-Tx, we detected an even higher CaSpF of $1.18 \pm 0.13/10\text{-}4\text{m/s}$ ($P=0.05$) and a tendency towards a higher SR Ca2+ leak compared to HF-Im (increase by $53 \pm 27\%$, $n=151$ vs. 110 , $p=0.16$), which fits to the further decreased LV-function. CaMKII inhibition reduced CaSpF (by $63 \pm 12\%$) and the calculated SR Ca2+ leak (by $88 \pm 6\%$) in HF-Tx ($P < 0.05$ each). In HF-Ex, CaSpF was $0.59 \pm 0.15/10\text{-}4\text{m/s}$ and hence lower than in HF-Tx ($n=33$ vs. 150 , $P < 0.05$), which translated into a tendency towards a decreased calculated SR Ca2+ leak ($n=33$ vs. 150 , $p=0.08$). Importantly, the CaSpF of HF-Tx CMs treated with AIP was only $0.32 \pm 0.14/10\text{-}$

4m/s and did not significantly alter from untreated HF-Ex CMs (n=25 vs 33). The SR Ca²⁺-leak of HF-Tx CMs treated with AIP was even lower than in untreated HF-Ex CMs (P<0.05) due to a smaller spark size.

The present data show that the diastolic SR Ca²⁺ leak correlates with the development of LV-function after LVAD-implantation and thus may represent an important pathomechanism. The fact that AIP reduces the diastolic SR Ca²⁺ leak in heart from patients undergoing heart transplantation despite LVAD support to levels lower than in patients who could successfully be weaned from LVAD support suggests that CaMKII inhibition may be a promising therapeutic option to increase the likelihood of a favourable clinical course after LVAD-implantation.

P1729 | BENCH

CaMKII equally triggers SR Ca²⁺ leak in human ischemic and non-ischemic heart failure

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The sarcoplasmic reticulum (SR) Ca²⁺ leak was shown to be an important pathomechanism in the development of human heart failure (HF). It has been attributed to an increased activity of Ca/calmodulin kinase II (CaMKII) leading to a hyperphosphorylation of ryanodine receptor 2 (RyR2). Interestingly, it has recently been suggested in a mouse model that the CaMKII-dependent SR Ca²⁺ leak induction is only relevant in non-ischemic HF (DCM) but not in ischemic HF (ICM) which would restrict the treatment with CaMKII inhibitors that are under development to the minority of patients with HF.

We therefore conducted Western blots experiments from 13 ICM- and 21 DCM-patients. However, neither CaMKII itself nor its respective target proteins showed a significant variation of protein expression or -phosphorylation depending on the etiology of HF. The expression of CaMKII (normalized to GAPDH; 1.016±0.078 vs. 1.016±0.075, n=28/28, P=0.99) and its autophosphorylation at Thr278 (0.343±0.063 vs. 0.442±0.050, N=20/21, P=0.22) was not significantly different in ICM vs. DCM. Conclusively, the phosphorylation of RyR2 at the CaMKII phosphorylation-site S2815 was similar in both groups (ratio of pS2815/RyR2, 0.947±0.214 vs. 0.914±0.189, P=0.91). To functionally validate these data we freshly isolated human cardiomyocytes (CMs) from end-stage failing hearts of 5 patients with ICM and 6 patients with DCM and analyzed the SR Ca²⁺ leak by confocal microscopy (1 Hz, Fluor3). We could neither detect a significant difference in SR Ca²⁺ spark frequency (CaSpF, 1.85±0.48 vs. 1.35±0.20 100µm⁻¹ s⁻¹, n=22/81, P=0.34) nor in Ca spark size, which is in line with the similar protein phosphorylation pattern (see above). Consequently, the calculated SR Ca²⁺ leak (CaSpF x amplitude x width x duration) was not different between CMs isolated from patients suffering from ICM vs. DCM (824±297 vs. 515±120, n=22/81, P=0.27). Furthermore and most importantly, CaMKII-inhibition by AIP (1 µmol/L) yielded a significant reduction of the SR Ca²⁺ leak in both etiologies (DCM: n=55 vs 87, reduction by 85±6%; ICM: n=68 vs 61, reduction by 79±8%, P<0.05 each).

In summary, our study shows comparable functional and molecular measures of the SR Ca²⁺ leak in human ICM and DCM myocardium indicating that CaMKII is equally responsible for the disruption of Ca²⁺ homeostasis in both pathologies. This is important as the inhibition of CaMKII as therapeutic measure to reduce the proarrhythmic and negative inotropic SR Ca²⁺ leak may thus not be restricted to patients suffering from DCM but beneficial for majority of HF patients.

P1730 | BENCH

Cardiac-specific microRNAs as early modulators in diabetic cardiomyopathy

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Purpose: Diabetic cardiomyopathy (DCM) accounts for more than 50% of deaths in diabetic patients. Despite all the efforts made to address this global burden, the high incidence of DCM remains a challenge to the clinicians. Importantly, heart disease in diabetics develop at a much early stage, but is often unrecognized in the subclinical stage due to the absence of pathognomonic signs, thereby restricting its early detection and active therapeutic management. Identifying the early modulators in DCM will not only help in early detection of the disease, but also allow sufficient time for optimization of the treatment. Recently microRNAs (miRs) are gaining interest as key players in the pathophysiology of several diseases including cardiovascular diseases. However, the pathophysiological role of miRs in the development of DCM is unknown. Therefore, the aim of this study was to (i) investigate the modulation of cardiac-specific miRs with the evolution of DCM and (ii) demonstrate the association between the changes in miRs and development of cardiac dysfunction.

Methods: BKS.Cg-m/+Leprdb/J mice were used as a model of type-2 diabetes which develop cardiac dysfunction as a result of high glucose and best represent the human form of type-2 diabetes. Animals were serially monitored for the change in cardiac function (left ventricular (LV) wall thickness, LV volume, ejection fraction and fractional shortening) using echocardiography every 4 weeks from 8 to 32 weeks of age (n=10) and cardiac tissues were collected at each time point

for miRs and protein expression analysis. Total RNA were extracted from the heart tissue and subjected to RT-PCR to measure the expression level of miR-1, -133, -208 and -499 that play an important role in the modulation of cardiac function.

Results: Quantitative RT-PCR analysis showed significant modulation of all the four cardiac-specific miRs: miR-1, miR-133, miR-208 and miR-499 (P<0.05 vs. non-diabetic for all comparisons) in the diabetic mice starting from 8 week of age which continued with the progression of the disease. Importantly, echocardiographic assessment of cardiac function at this time point failed to reveal any changes, with first clinically detectable diastolic dysfunction (alteration in E/A ratio) observed only at 20 weeks of age (P<0.05 vs. non-diabetic).

Conclusion: Our initial findings provide a strong evidence for modulation of cardiac specific miRs at an early stage of diabetes and opens up an intriguing possibility to develop miR-based therapies for timely management of the disease. A larger study is underway to confirm these findings.

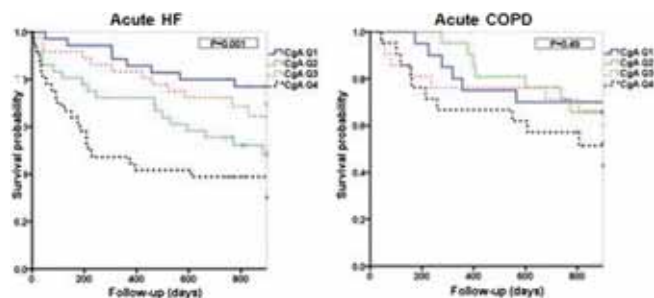
P1731 | BENCH

Chromogranin A is a potent risk marker in acute heart failure and directly associated with cardiomyocyte Ca²⁺ handling

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Background: Chromogranin A is considered as an unspecific prognostic biomarker, but given the established role of granin proteins on Ca²⁺ handling in non-cardiac cells, we hypothesized that CgA may (1) directly influence cardiomyocyte Ca²⁺ handling and (2) specifically be associated with mortality in patients with acute heart failure (HF).

Methods and results: We measured circulating CgA levels in patients with acute dyspnea due to HF (n=143) and chronic obstructive pulmonary disease (COPD, n=83) and explored the effect of the CgA fragment catestatin (Cts, CgA352-372) on cardiomyocyte Ca²⁺ handling. HF and COPD patients were matched on NYHA functional class (p=0.13) and mortality rates (median 813 days follow-up: 66 HF deaths [46%] vs. 35 COPD deaths [42%], p=0.56), but CgA levels were only associated with HF mortality (Fig). The association between CgA levels and HF mortality was also found after adjusting for other risk factors in multivariate Cox regression model: HR logCgA 1.43 (95% CI 1.11-1.83), p=0.005. By experimental methods, Cts reduced Ca²⁺ sparks in all dimensions and Ca²⁺ spark and wave frequency. Cts also increased the magnitude of cardiomyocyte Ca²⁺ transients and induced larger and faster contractions of cardiomyocytes. Previously studies have found Cts to be internalized into cells by endocytosis and we observed a direct binding of Cts to the catalytic region of the Ca²⁺/calmodulin (CaM)-dependent protein kinase II d (CaMKII_d), which is a nodal kinase regulating cardiomyocyte Ca²⁺ handling. Cts also attenuated CaMKII_d autophosphorylation in cells and perfused hearts and reduced CaMKII_d activity in vitro.



Conclusions: CgA is a potent risk marker in patients with acute HF and directly associated with cardiomyocyte Ca²⁺ handling.

P1732 | BENCH

Critical involvement of renin-angiotensin system for developing arrhythmogenic remodeling in mice with chronic heart failure and lethal arrhythmias

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Purpose: Progression of left ventricular remodeling results in cardiac dysfunction, malignant arrhythmias and sudden cardiac death (SCD). We investigated the contribution of renin-angiotensin system (RAS) activation to the arrhythmogenic remodeling and the underlying mechanisms.

Methods: We administered direct renin inhibitor (DRI) aliskiren subcutaneously to a cardiac-specific dominant-negative form of neuron-restrictive silencer factor transgenic mice (dnNRSF-Tg), which exhibiting progressive cardiac dysfunction leading to lethal arrhythmias and evaluated its effects against arrhythmogenic remodeling.

Results: DRI significantly prevented the progression of pathological remodeling

including fibrosis and improved the survival in dnNRSF-Tg. Arrhythmogenicity was substantially reduced in dnNRSF-Tg with DRI. Genetic deletion of angiotensin type 1a receptor (AT1aR) in dnNRSF-Tg prevented cardiac remodeling and SCD. In optical mapping analyses, spontaneous ventricular tachycardia (VT) and fibrillation (VF), which are initiated by a breakthrough-type focal activation and maintained by functional reentry, were observed in hearts of dnNRSF-Tg (Figure). Under constant pacing, dnNRSF-Tg hearts exhibited remarkably slowed conduction velocity contributing to generating arrhythmogenic substrates. DRI restored the conduction velocity and reduced the incidence of sustained VT. Furthermore, dnNRSF-Tg ventricles showed markedly reduced protein expression of connexin 43, which was restored with DRI.

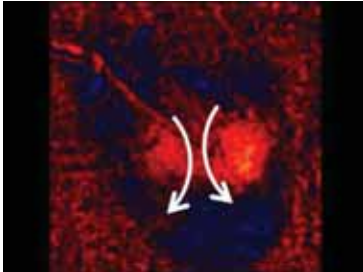


Figure 1

Conclusions: Renin inhibition or genetic deletion of AT1aR prevented pathological cardiac remodeling that leads to the generation of substrates to VT/VF and reduced the occurrence of SCD in dnNRSF-Tg. Our findings demonstrate the significant contribution of RAS activation to promoting arrhythmogenic remodeling.

P1733 | BENCH Changes in microRNAs could explain the dysfunction of the cardiac conduction system (CCS) in heart failure

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Heart failure (HF) gives rise to remodelling of ion channel, Ca²⁺-handling, gap junction, fibrosis, inflammation and apoptosis genes in the CCS and this impairs pacemaker reserve and causes heart and bundle branch block. MicroRNAs (miRs) are small non-coding RNAs which regulate gene expression. We have tested the hypothesis that they are responsible for the remodelling by using mice in which HF was produced by transverse aortic constriction. After 6–7 weeks, heart/body weight ratio increased by 139% and fractional shortening fell by 50%. Left ventricular mass and internal systolic and diastolic dimensions increased by 85%, 58% and 22%, respectively. These are indications of heart failure. Recordings from conscious mice showed 6% decrease in heart rate and 20% prolongation of QRS duration in the HF group. In anaesthetised mice (2% isoflurane), PR interval was increased by 9% and QRS duration by 17% in the HF group. In isolated sinoatrial node (SAN) preparations, cycle length was prolonged by 22% in the HF group. Superfusion of this preparation with 2 mM Cs (to block funny current, If) increased cycle length by 25% in HF and 34% in control group ($P < 0.05$). These data demonstrate dysfunction of the CCS consistent with changes in mRNA as measured by qPCR, which showed significant downregulation of HCN4 (responsible for If) and Tbx18 and Mef2c (transcription factors), and upregulation of Col1 α 1 (collagen, type 1 α 1). Expression of 384 miRs in the SAN was measured by microarray and compared to that in the left (LA) and right (RA) atrium. In the control group, 100 miRs showed significant differences in expression between the SAN and LA (47 were more abundant in SAN and 53 in LA), and 15 miRs showed significant differences in expression between the SAN and RA (11 were more abundant in SAN and 4 in RA). In HF there were 43 significant changes in miRs in the SAN. For example, miR-139-3p (using Ingenuity IPA software, predicted to affect HCN1, HCN4, SERCA2, RYR2, Tbx3, Tbx18, REST, AP1 and Mef2c) was upregulated by 1000% in the SAN. miR-501-3p (predicted to affect Cx43) was upregulated by 308% in the SAN. miR-21 (predicted to affect Col1 α 1, Nkx2-5 and Mef2c) was upregulated by 149% in the SAN. miR-202-3p (predicted to affect HCN1, HCN4, SERCA2, Cx40, Cx43, collagen 3 α 1, Tbx3, Tbx18 and Mef2c) was downregulated by 97% in the SAN. These altered miRs are predicted to target ion channel, Ca²⁺-handling, gap junction, fibrosis, inflammation and apoptosis genes. In conclusion, we have found both up- and downregulation of miRs in HF, and we suggest that this could be responsible for the adverse remodelling of the CCS.

P1734 | BENCH RNA-sequencing analysis reveals new significant alterations in transcriptional regulators of patients with ischemic cardiomyopathy

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Purpose: We hypothesized that new changes found in transcriptional regulators

could explain the novel map of gene alterations described in ischemic cardiomyopathy (ICM). The aim of this study was to identify new transcription regulators (TFs) to provide insights into the molecular mechanisms involved in the responses to ischemia, using RNA-sequencing analysis (RNA-Seq).

Methods: We analyzed by RNA-seq and qRT-PCR left ventricular tissue from 24 individuals, 17 from patients with ICM and 7 normal control subjects. Functional analysis of differentially expressed genes was performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID, version 6.7). We selected the gene ontology (GO) terms that had a p-value of ≤ 0.05 .

Results: Significance analysis of the RNA-Seq results revealed a total of 1249 genes that were differentially expressed in ICM patients; 602 genes were up-regulated (≥ 1.5 fold, $p < 0.05$) and 647 genes were down-regulated (≤ 1.5 fold, $p < 0.05$).

ChEA database contained up to 94% of our genes. ChEA enrichment analysis identified several TFs potentially implicated in ICM. We found TFs such as GATA-4 (1.74 fold), MEF2A or EP300 (2 fold). Other TF such as ESR1 (2.2 fold) or the stem-cell maintenance genes SOX2 (2.9 fold) or NANOG (2 fold) were not previously studied. HIF1A (3.02 fold) was significantly over-represented. Based on their fold difference and p value data we also highlight the identification of TFs such as BCL3 (1.7 fold) or CEBPD (3 fold).

QRT-PCR analysis revealed that patients with ICM had decreased expression of BCL3 (-3.3-fold, $p < 0.001$), CEBPD (-6.7-fold, $p < 0.001$) and CITED2 (-3.8-fold, $p < 0.001$). Expression levels of the nuclear body component gene SP100 was also lower in ICM patients (-1.5-fold, $p < 0.05$). CITED2 mRNA levels were significantly related with LV ejection fraction ($p < 0.01$).

Conclusions: The alterations found in SP100, BCL3, CITED2, and CEBPD, contribute to explain biological processes such as apoptosis, stress or hypoxia responses occurring in ICM. Our results provide a new regulatory network in ICM. Changes in CITED2 mRNA levels were related with LV function ($p < 0.01$).

P1735 | BEDSIDE Endomyocardial infiltration of macrophages, but not T lymphocytes, is associated with poor long-term prognosis in patients with dilated cardiomyopathy without severe cardiac fibrosis

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Background: The prognosis of idiopathic dilated cardiomyopathy (DCM) remains unfavorable, even after marked improvement of medical and device therapy for heart failure. We have previously demonstrated a negative impact of macrophage/monocytes cell lines on LV remodeling in ischemic heart failure. However, the role of these cells in LV remodeling in DCM was not fully elucidated. In this study, we sought to demonstrate the significance of infiltration of macrophages by investigating endomyocardial biopsy samples in patients with DCM.

Method: Of the patients admitted to our hospital with heart failure in 2005, subjects who were finally diagnosed as having DCM by excluding hypertrophic cardiomyopathy, ischemic cardiomyopathy, valvular heart disease, myocarditis, and secondary cardiomyopathy, were included in the study. Thirty-eight patients with LVEF $\leq 40\%$ were analyzed. Paraffin-embedded right ventricular endomyocardial biopsy specimens were restained with Masson's Trichrome and specific antibody to CD68 (macrophages) and CD3 (T lymphocytes). The collagen volume fraction (CVF) was calculated as the area occupied by collagens divided by the total area, and the numbers of macrophages and T lymphocytes infiltrated to the myocardium were counted in each sample. Also, patients' clinical data were obtained by reviewing the medical records. Those patients were observed for up to 8 years. Adverse events were defined as death or readmission for heart failure.

Results: The mean age was 50 ± 15 years and 79% were men. Left ventricular EF was $28 \pm 10\%$ with 42% of patients having NYHA class III or IV. Mean CVF in endomyocardial sections was $22 \pm 11\%$. We divided patients into two groups; 1) severe fibrosis: CVF $\geq 20\%$, $n = 19$, and 2) less severe fibrosis: CVF $< 20\%$, $n = 19$. During the follow-up period, 8 patients with severe fibrosis and 6 patients with less severe fibrosis experienced adverse events (42 vs. 32%, $p = \text{NS}$). In less severe fibrosis group, patients with adverse events showed greater number of CD68-positive macrophages infiltration than those without (60 ± 27 vs. 33 ± 1 /mm², $p = 0.011$) but comparable number of CD3-positive T lymphocytes (25 ± 27 vs. 22 ± 23 /mm², $p = \text{NS}$). On the other hand, the difference of infiltrated macrophages (42 ± 24 vs. 44 ± 25 /mm², $p = \text{NS}$) or T lymphocytes (33 ± 34 vs. 29 ± 30 /mm², $p = \text{NS}$) was not observed in severe fibrosis group.

Conclusions: In patients with DCM without severe cardiac fibrosis, infiltrated macrophages, but not T lymphocytes, were associated with long-term adverse outcome, indicating a role of macrophages in LV remodeling in patients with DCM.

UNDERSTANDING REMODELING

P1737 | BENCH**Disruption of oxidative PKA activation contributes to ventricular remodeling upon increased afterload**

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Recently, a novel cAMP-dependent protein kinase (PKA) activating pathway by oxidation of Rlu was identified. We hypothesized that redox-activated PKA is involved in cardiac remodeling upon pathological afterload. Homozygous knock-in mice with Rlu cysteine 17 to serine mutation (KI), which are devoid of oxidation-dependent activation, were subjected to transverse aortic constriction (TAC) and compared with wild-type (WT). At baseline, echocardiographic analysis revealed identical myocardial function and morphology (Fig. 1). Six weeks after TAC, however, KI mice showed significantly more compromised ejection fraction and accelerated left ventricular dilation (Fig. 1). Moreover, Kaplan-Meier analysis showed exaggerated mortality after TAC in KI vs. WT mice (Fig. 1). For in vivo analysis of arrhythmia inducibility, catheters were introduced into the right ventricle. Compared to WT, burst stimulation at the apex induced more ventricular arrhythmias in KI mice (Fig. 1). Confocal microscopy of isolated ventricular myocytes showed no difference in Ca spark frequency (not shown). However, L-type Ca currents (ICa) were significantly larger in KI mice (for KI vs. WT, -7.80 ± 0.46 vs. -6.46 ± 0.29 A/F, $n=14$ vs. 11). Interestingly, Caffeine-transients were significantly lower in KI myocytes (for KI vs. WT, 653.6 ± 109.9 vs. 1158 ± 163.6 nmol/L, $n=21$ vs. 12). Ca transient decay (τ) was significantly prolonged in KI vs. WT indicating a reduced SERCA function (at 0.5 Hz, 0.55 ± 0.08 vs. 0.37 ± 0.02 s, $n=14$ vs 23).

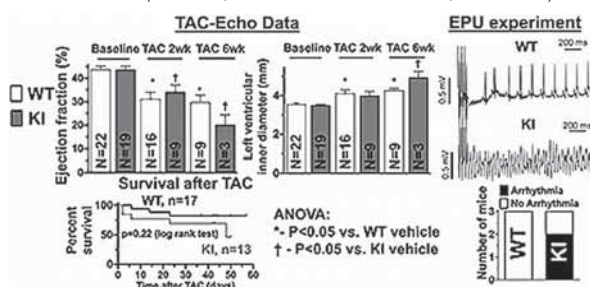


Figure 1

In conclusion: Mice lacking oxidative activation of PKA show a profound dysregulation of excitation-contraction coupling and an increased propensity for arrhythmias. Moreover, they display an enhanced ventricular remodeling upon TAC. This may be of relevance for the treatment of arrhythmias and HF.

P1738 | BENCH**Deficiency of MAP-kinase-activated protein kinase 2 (MK2) targeting mitochondrial oxidative stress protects against aging-induced cardiac remodeling and dysfunction**

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Purpose: Among diseases and disorders associated with advancing age, one of the most debilitating is the loss of normal cardiac function leading to heart failure. Inhibition of MAP-kinase activated protein kinase 2 (MK2), a major downstream target of p38 MAPK, has been proposed to revert cell aging phenotypes. Therefore, we hypothesized that MK2 could play a key role in aging-dependent cardiac pump failure.

Methods and results: Cardiac remodeling and molecular alterations were investigated in young (3 month of age) and old (24 months) wildtype (WT) mice and corresponding MK2-deficient (MK2KO) animals. The increase in left ventricular (LV) end-systolic area, LV end-systolic volume as well as the decline in fractional area shortening and ejection fraction detected by echocardiography in senescent WT mice ($n=14-16$, $p<0.01$) were substantially attenuated in old MK2KO animals ($n=12-15$, $p<0.05$). Correspondingly, the rightward shift of the pressure-volume curve, determined in vivo with conductance catheter, was prevented in old MK2KO. LV filling pressure, end-diastolic volume, and end-systolic volume were significantly decreased in old MK2KO compared with old WT mice. Amelioration of LV dilatation in old MK2KO mice was associated with significantly reduced LV pressure isovolumic decay and improved LV ejection fraction as well as dP/dt ($n=6-10$, $p<0.05$). Furthermore, old MK2KO mice displayed significantly reduced pulmonary fluid accumulation, myocardial hypertrophy and myocyte cross-sectional area ($n=6-9$, $p<0.01$). Mitochondria isolated from LV myocardium of old WT mice displayed significantly increased superoxide anion formation mea-

sured by HPLC-EC analysis of Mito-2-hydroxy-E+ compared to young WT mice ($n=6$, $p<0.01$). This was linked to marked down-regulation of uncoupling protein 3 (UCP3), manganese superoxide dismutase (MnSOD) and peroxisome-proliferator-activated receptor gamma coactivator-1 α (PGC1 α) in old WT mice. Remarkably, superoxide production as well as expression of UCP3, MnSOD and PGC1 α were nearly normalized in mitochondria isolated from LV myocardium of old MK2KO mice ($n=6$, $p<0.05$).

Conclusion: Deficiency of MK2 protects against aging-induced downregulation of mitochondrial proteins involved in maintaining the cellular redox balance, leading to amelioration of cardiac remodeling and functional deterioration. Our results highlight the potential importance of MK2 in aging-related heart failure.

P1739 | BENCH**The novel extracellular CyPA-inhibitor MM284 reduces myocardial inflammation and remodelling in a mouse model of Troponin I-induced myocarditis**

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Background: Cyclophilins (CyPs) are a group of highly conserved cytosolic enzymes that have a peptidylprolyl isomerase activity. This study analyzed the effect of the Cyclosporin A derivative MM284 in a mouse model of autoimmune myocarditis. Due to the modification of Cyclosporin A with a cell-impermeable moiety, MM284 strictly blocks extracellular activities of Cyclophilins such as CyPA. **Methods and results:** A/J mice were immunized with murine cardiac troponin I (mcTnI) at day 0, 7, and 14. Mice were treated with MM284 or diluent every second day starting at day 0. After 28 days the hearts were stained with Hematoxylin&Eosin (H&E), anti-CD3, anti-Mac-3, and Masson's Trichromestaining procedures. The evaluation of the sections was based on a scoring system. The results showed a considerable reduction of the infiltration of cells in H&E ($p<0.05$), and a reduced expression of CD3 ($p<0.05$) and Mac-3 ($p<0.01$) when treated with MM284. In parallel, the evaluation of Masson's Trichrome staining also showed a reduction of the cardiac fibrosis ($p<0.05$), when treated. In addition expression of MMP-9 was reduced significantly. In vitro migration of human monocytes was assessed using a modified Boyden chamber. In the presence of MM284, migration towards extracellular CyPA was almost completely abolished ($p<0.01$). Finally analysis of bioptic samples of patients with non ischemic cardiomyopathy revealed that severe cardiac fibrosis was associated with the expression of CyPA. **Conclusion:** Extracellular CyPs, especially CyPA play an important role in inflammatory and profibrotic processes. In the current study we found that the extracellular inhibition of CyPs via MM284 is a successful and potent pharmacological approach for the treatment of myocardial inflammation and reduction of cardiac fibrosis.

P1740 | BENCH**Alteration of atrial myocyte environment is a minor determinant of the action potential remodeling of dilated atria during heart failure in rat**

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Background: Heart failure (HF) is a major risk factor of atrial fibrillation (AF) by favoring structural remodeling of the myocardium and changes in ion currents which together compose AF substrate. Here we studied the role played by tissue factors and ion current modifications in the alterations of atrial electrical properties during HF.

Methods: HF was induced in rats by coronary ligation. Atrial remodeling was studied by echography and ECG. The substrate was evaluated by the duration of episode of AF triggered by burst pacing delivered by a transesophageal probe. To study the electrical activity of myocytes in situ, the propagated action potential (AP) was recorded by using standard microelectrode in trabeculae. Ion currents were recorded in whole cell patch clamp. The various parameters were quantified by their coefficient of variation (Cvar: ratio of standard deviation/mean expressed in %). Computer model to simulate an atrial AP was derived from Courtemanche et al. model.

Results: Two months after surgery all rats were in HF and left atria became dilated ($34 \pm 9 \text{ mm}^2$ vs. $21 \pm 4 \text{ mm}^2$ $P<0.0001$). The duration of AF triggered by transesophageal atrial stimulation is increased in HF compared to sham (7.0 ± 0.2 vs. 11.2 ± 0.3 ; $P<0.001$ sham vs HF). The duration of AF correlate with the severity of LV and LA dilatation. The resting membrane potential of AP was slightly depolarized in HF (1.4 mV ; $P<0.05$). The upstroke was slower [dV/dt] $_{\text{max}}$ ($138 \pm 39 \text{ V/s}$ vs. $110 \pm 48 \text{ V/s}$; $P<0.0001$) and were smaller in HF compared to sham. In addition, AP duration measured at 5%, 25% and 50% of the repolarization was reduced in HF. There was a marked dispersion of AP properties in HF atria (sham vs HF; Cvar of amplitude: 8.5% vs 12.5% ; $P<0.001$, dV/dt : 23.2% vs 31% and APD_{25} : 34 vs 32 $P<0.002$). The density of the sodium current did not differ between sham and HF whereas the inward-rectifier and of the voltage-dependent outward currents (IK) were increased in HF atria. The L-type calcium current (ICa) has

been previously shown to be drastically reduced in this model. HF atria showed a higher expression of fibronectin (fibrosis) and vimentin (fibroblast). Computer simulation indicated that AP shortening was caused by the unbalance between ICa and IK during the plateau phase whereas the depressed and dispersed excitability is predominantly due to electronic interactions between myocyte and coupled fibroblast, cell hypertrophy and gap junction reduction.

Conclusion: Alterations in the normal environment of atrial myocyte is a major determinant of the atrial electrical remodeling and AF substrate during HF.

P1741 | BENCH

Neuregulin-1 has opposite effects on LV compliance in eccentric and concentric remodeling

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Introduction: There is emerging evidence that left ventricular (LV) diastolic stiffening may be caused by risk factor-induced cardiac endothelial dysfunction. To date, most studies have focused on impaired nitric oxide (NO) and cyclic GMP signaling, and on the effects by pharmacologic rescue of these pathways. In this study, we examined the effect of neuregulin-1 (NRG-1), an endothelial secreted ligand of ErbB4 receptors, on LV diastolic compliance in mice. Effects of ErbB4 activation by NRG-1 on LV compliance were studied in (a) normal hearts, (b) stiff hearts (with concentric LV hypertrophy) and (c) hypercompliant hearts (with eccentric LV remodeling).

Methods: RhNRG-1 β or vehicle was administered (20 μ g.kg⁻¹.day⁻¹, i.p., 5 days/week) in 3 groups. (a) Healthy C57Bl/6 mice (n=56), (b) C57Bl/6 mice with concentric LV remodeling (n=59), induced by angiotensin II (osmotic mini-pumps, 1000 ng.kg⁻¹.day⁻¹, for 4 weeks) and (c) C57Bl/6 mice with eccentric LV remodeling (n=66) (streptozotocin-induced type 1 diabetes, 14 weeks follow-up). In vivo, LV diameters and LV diastolic compliance (slope EDPVR) were quantified by echocardiography and LV pressure-volume recordings. Ex vivo, LV collagen volume fraction (CVFR) and cardiomyocyte diameters (MyoDia) were quantified by immuno-histochemistry. Stiffness of isolated skinned cardiomyocytes was quantified. Activation of cardiac ErbB4 receptors by rhNRG-1 β was verified in each model.

Results: In the normal heart, rhNRG-1 β failed to change LV diameters, LV diastolic compliance and cardiomyocyte stiffness, both in acute (30 min) and in chronic (14 weeks) experiments. In Ang II-treated mice, rhNRG-1 β prevented the development of concentric LV hypertrophy, cardiomyocyte hypertrophy (MyoDia 13.17 vs 17.25 μ m, p<0.01), cardiomyocyte stiffening, LV fibrosis (CVFR 0.056 vs 0.152 FR%, p<0.05) and LV stiffening (slope EDPVR 0.396 vs 0.586 mmHg/ μ L, p<0.05). In type 1 diabetic mice, rhNRG-1 β prevented LV dilation (LV end diastolic diameter 11.30 vs 13.57 μ m, p<0.001), LV contractile dysfunction (slope ESPVR 23.68 vs 4.31 mmHg/ μ L, p<0.001) and LV hypercompliance (slope EDPVR 0.473 vs 0.176 mmHg/ μ L, p<0.05), but it had no effect on LV fibrosis.

Conclusion: rhNRG-1 does not change LV structure or LV compliance of the healthy heart. By contrast, rhNRG-1 prevents LV stiffening during concentric remodeling and prevents LV de-stiffening during eccentric remodeling. These circumstance-dependent protective effects by rhNRG-1 β on LV compliance attribute unique therapeutic opportunities of ErbB4 stimulation during LV remodeling.

P1742 | BEDSIDE

QRS fragmentation as predictor for reverse remodelling in cardiac resynchronization therapy patients

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Background: About 1/3 of patients do not respond clinically to cardiac resynchronization therapy (CRT), and >40% do not show LV reverse remodelling response. QRS fragmentation (QRSf) on ECG has been related with disturbances in myocardial activation due to myocardial scar and/or fibrosis. Role of QRSf as predictor of CRT response is controversial and has not been widely studied.

Methods: We reviewed clinical records of patients who underwent CRT implantation in our Institution. QRSf was defined as the presence of RSR' pattern, notching

of the R-wave or notching of the down- or upstroke of the S-wave in two contiguous leads.

Results: 40 patients (71 $\pm$ 10 years, male 80%). At inclusion, QRSf was present in 25 patients (62.5%). There were no differences in baseline characteristics. Table. After a mean follow-up of 24 $\pm$ 13 months patients with QRSf showed a significant reduction in left ventricular end-diastolic diameter (LVEDD) after biventricular pacing (60 $\pm$ 7 mm vs 51 $\pm$ 9; p<0.05) vs patients without QRSf (62 $\pm$ 8 mm vs 58 $\pm$ 7; p>0.05). No difference in improvement of EF or clinical events. Univariate analysis showed that QRSf was independent predictor of LVEDD reduction (OR 0.15 [0.02-0.99; p<0.05]).

Conclusions: The presence of QRSf was a predictor of reverse remodelling expressed as LVEDD reduction. Biventricular pacing can improve hemodynamics in patients with severe intraventricular conduction disturbances expressed as QRSf.

P1743 | BEDSIDE

Diffuse myocardial fibrosis assessed by cardiac magnetic resonance contrast-enhanced T1 mapping in heart failure with preserved ejection fraction

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Purpose: The underlying pathophysiology of heart failure with preserved ejection fraction (HFpEF) remains to be clarified. We sought to assess myocardial fibrosis, measured as extracellular volume (ECV) of the myocardium by using cardiac magnetic resonance (CMR) T1 mapping, in acutely decompensated heart failure (ADHF) with preserved ejection fraction.

Methods: Twenty-nine ADHF subjects (20men, 61 $\pm$ 20years) and 15 control subjects with normal CMR findings were prospectively enrolled. Triple-slice T1 mapping was performed by using a modified Look-Locker inversion recovery (MOLLI) sequence. ECV was quantified using hematocrit-adjusted myocardial and blood T1 values measured before and after administration of gadolinium contrast medium.

Results: Thirteen (45%) patients had HFpEF. Patients with HFpEF had significantly greater mean ECV, pre-contrast T1 than control group (31.6 $\pm$ 7.4 vs. 26.9 $\pm$ 3.0%, 1372 $\pm$ 86 vs. 1305 $\pm$ 34ms, respectively, p<0.05). However, there were no significant differences in mean ECV and pre-contrast T1 value between HFpEF and HF with reduced ejection fraction (HFrEF; 34.8 $\pm$ 7.1%, 1374 $\pm$ 79ms). Univariate analysis demonstrated that ECV was associated with the presence of late gadolinium enhancement, the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/Ea), and B-type natriuretic peptide level (r=-0.39, 0.53, 0.78, respectively, all p<0.05). High E/Ea was a significant predictor of ECV expansion (β coefficient=0.53, p<0.05).

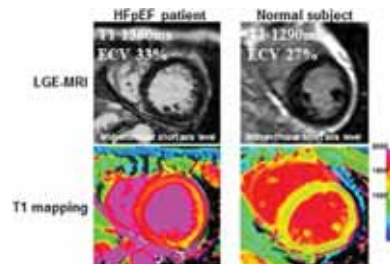


Figure 1. Representative cases.

Conclusion: The results with CMR quantification of ECV demonstrated that diffuse myocardial fibrosis was independently associated with LV filling pressures in patients with HFpEF.

P1744 | BEDSIDE

Plasma biomarkers as surrogates of myocardial fibrosis

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Purpose: Plasma biomarkers have been proposed to reflect fibrosis of several human tissues, but their specific role in detection of myocardial fibrosis has not been well established. We studied the association between galectin-3, PIINP, PINP and myocardial fibrosis measured by late gadolinium enhanced cardiac magnetic resonance imaging (MRI) and their relation to left ventricular (LV) diastolic filling measured by tissue Doppler echocardiography in patients with stable coronary artery disease (CAD).

Methods and results: We determined the galectin-3, PIINP, and PINP plasma levels and performed cardiac MRI and tissue Doppler echocardiography in 64 pa-

Table 1. Patients characteristics according to QRS fragmentation

	No QRSf (15)	QRSf (25)	p
Baseline characteristics			
Age (y)	69 $\pm$ 10	72 $\pm$ 10	0.52
Sex (male)	13 (86%)	19 (76%)	0.68
Ischemic Cardiomyopathy	9 (60%)	13 (52%)	0.74
NYHA (III-IV)	10 (71%)	14 (58%)	0.10
Sinus Rhythm	9 (60%)	12 (48%)	0.76
EF (%)	23 $\pm$ 7	21 $\pm$ 7	0.40
Clinical follow-up			
HF admissions	5 (33%)	5 (20%)	0.26
NYHA (III-IV)	4 (26%)	2 (8%)	0.12
EF	29 $\pm$ 12	33 $\pm$ 13	0.39

tients with stable CAD without a history of prior myocardial infarction. Extracellular volume assessed from myocardial late gadolinium enhancement T1 relaxation time was defined as a specific marker of myocardial fibrosis. P1NP and PIIINP did not have a significant correlation with the T1 relaxation time (NS for both), but there was a significant correlation between T1 relaxation time and galectin-3 ($r^2 = -0.33$, $p = 0.012$). The early mitral to early tissue velocity assessed by tissue Doppler echocardiography (E/E') was related to both galectin-3 ($r^2 = 0.39$, $p < 0.001$) and PIIINP ($r^2 = 0.33$, $p < 0.001$). The lowest T1 relaxation time tertile had significantly higher galectin levels ($p = 0.009$) and higher E/E' values ($p = 0.046$) compared to the highest T1 relaxation time tertile.

Conclusions: Elevated plasma levels of galectin-3 reflect the degree of myocardial fibrosis assessed by MRI and LV diastolic dysfunction, suggesting that this biomarker is a useful surrogate of structural and functional abnormality of the myocardium.

P1745 | BEDSIDE

Cardiac function in very long-term survivors of childhood lymphoma

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Purpose: Childhood lymphoma survivors (CLSs) have markedly increased risk for cardiac disease, but data on left ventricular (LV) diastolic function in CLSs are conflicting. In this cross-sectional study of 125 adult CLSs, cardiac function was assessed by echocardiography and compared to healthy controls, matched for age, gender, body weight and systolic blood pressure.

Methods: LV systolic dysfunction was defined as ejection fraction <50% (Simpson's method), or by fractional shortening <27% for women and <25% for men (M-mode measurement). LV diastolic dysfunction was defined as pulsed tissue Doppler peak early diastolic velocity (e') <8 cm/s in the septal, or <10 cm/s in the lateral mitral annulus. Increased LV filling pressure was defined as average E/e' ratio >13. Left heart valve dysfunction was defined as any stenosis, or any regurgitation graded as more than minimal, on the aortic or mitral valve.

Results: Previous diagnosis was Hodgkin's lymphoma in 81, and non-Hodgkin lymphoma in 44. Treatment included mediastinal radiotherapy (RT) in 66 (53%), and anthracyclines in 92 (74%). Mean time since diagnosis was 20.4±8.6 years, and median age at exam was 33.0 years (range 19.0-54.5). CLSs did not have more LV systolic dysfunction than controls, but LV diastolic dysfunction was 7 times more frequent ($p < 0.001$). After mediastinal RT, diastolic dysfunction was even more frequent, and 20% had signs of elevated LV filling pressure in this groups, vs. 0 among the other CLSs ($p < 0.001$). More than half of the CLSs treated with mediastinal RT had valvular dysfunction.

Prevalence of cardiac abnormalities

	Survivors (n=125)	Controls (n=125)	p-value	Mediastinal RT (n=66)	No mediastinal RT (n=59)	p-value
LV systolic dysfunction	12 (10%)	16 (13%)	0.422	8 (12%)	4 (7%)	0.312
LV diastolic dysfunction	36 (29%)	5 (4%)	<0.001	24 (36%)	12 (20%)	0.048
Increased LV filling pressure	13 (10%)	0	<0.001	13 (20%)	0	<0.001
Valvular dysfunction	39 (31%)	NA		36 (55%)	3 (5%)	<0.001
Abnormal LV dimension	15 (12%)	10 (8%)	0.312	13 (20%)	2 (3%)	0.005

LV, left ventricular; RT, radiotherapy; NA, not available.

Conclusions: LV diastolic dysfunction occurs frequently in CLSs, particularly after mediastinal RT, whereas systolic dysfunction occurs infrequently, and equally frequent in CLSs and controls in this study.

P1746 | BEDSIDE

Difference in the impact of left atrium size by presence/absence of LV systolic dysfunction among acute heart failure patients from WET-HF Registry

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Background: Left atrium (LA) size is simple and readily available parameter obtained by echocardiogram. However, its prognostic value in acute heart failure (AHF) patients has not been thoroughly investigated; particularly in patients with preserved EF (HFpEF).

Methods: We analyzed a total of 591 consecutively registered patients (49±15 years old, M/F=386/205) that were hospitalized with AHF in 3 institutions in our metropolitan area between 2008-2012; patients with ACS, no record of LVEF and atrial fibrillation were excluded. LA size was measured by 2-dimensional echocardiography on admission.

Results: The averaged LA size in heart failure patients with reduced EF (HFrEF) ($\leq 40\%$, n=274) was larger than that in HFpEF ($> 40\%$, n=237) (43.5 ± 9.7 vs 40.1 ± 8.8 mm, $p < 0.001$). During follow up period of 627±509 days, in-hospital deaths were identified in 34 patients, and 155 long-term composite events occurred. Multivariate Cox proportional hazard analysis showed that larger LA size in HFrEF group was an independent predictor for long-term adverse composite

events (HR 1.036; 95% CI 1.005-1.068; $P = 0.021$), but not in HFpEF group (HR 1.006; 95% CI 0.960-1.053; $P = 0.815$).

Conclusions: LA size on admission can predict future events in patients with HFrEF but not in HFpEF. Patients with larger LA size in HFrEF need to be paid more attention.

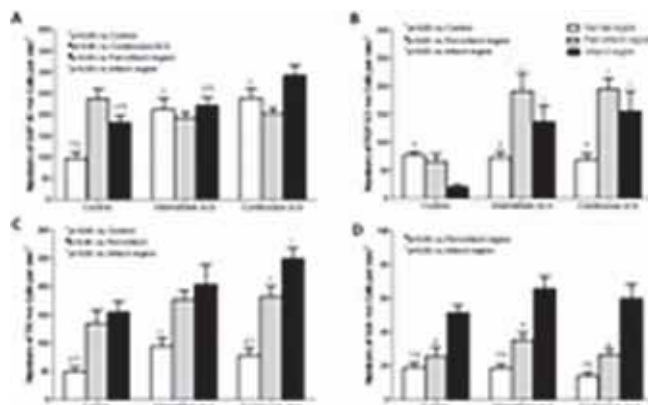
P1747 | BENCH

Remodeling of cardiac sympathetic innervation with thoracic spinal cord stimulation improves left ventricular function in a porcine model of ischemic cardiomyopathy

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Background: Prior studies demonstrate that thoracic spinal cord stimulation (SCS) improves left ventricular (LV) function in heart failure (HF), nevertheless, the mechanism of action remains unknown.

Methods and results: We performed chronic thoracic SCS (50Hz, pulse width 0.2ms) using two octrode leads implanted targeting along the midline and the left side at T1-3 levels in 30 adult pigs with ischemic HF induced by myocardial infarction and rapid ventricular pacing for 4 wks. All animals were treated with daily oral metoprolol succinate (25mg) plus ramipril (2.5mg), and randomized into control group (n=10), intermittent SCS (4 hrs x 3, n=10) or continuous SCS (24 hrs, n=10) for 10 weeks. Detail immunohistological studies on myocardial sympathetic (tyrosine hydroxylase [TH]) and parasympathetic (acetylcholinase [ACh]) nerve spouting (growth-associated protein43 [GAP-43]) and nerve innervation (protein gene product 9.5 [PGP9.5]) were performed at infarct, peri-infarct and normal regions. Both continuous and intermittent SCS significantly improved LV ejection fraction at 10 wks compared with controls ($P < 0.05$). There was no significant difference in pattern of the ACh staining over different regions between 3 groups. However, SCS-treated groups showed diffuse sympathetic nerve spouting over the infarct, peri-infarct and normal regions rather than only in the peri-infarct and infarct regions in controls (Figure). Moreover, sympathetic innervation was decreased at the peri-infarct and infarct regions in controls, but was increased at peri-infarct and infarct regions after SCS (Figure).



Conclusions: In porcine model of ischemic HF, SCS induce significant remodeling of cardiac sympathetic nerve innervation over peri-infarct and infarct regions which is associated with improvement of LV function.

P1748 | BENCH

Progressive LV dilatation in swine chronic heart failure is ameliorated by SERCA2a gene transfer

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Purpose: Heart failure is characterized by adverse left ventricular (LV) remodeling but few pharmacological agents used to treat heart failure reverse LV remodeling. Our aim in this study to determine whether sarcoplasmic reticulum Ca2+-ATPase (SERCA2a) gene transfer, a novel therapeutic approach to treat heart failure, can prevent progressive remodeling in chronic heart failure.

Methods: An extensive anterior myocardial infarction (MI) was induced in Yorkshire pigs. One month after the MI induction, pigs developed chronic heart failure as characterized by impaired LV ejection fraction, dilated LV, and increased end-diastolic pressure. The animals were randomly assigned to receive intracoronary injection of either saline or adeno-associated virus-1 SERCA2a (3.0x10¹² v.p.). LV volumes were assessed by 3-dimensional echocardiography by a blinded investigator. LV volumes were indexed to body surface area and changes before and 2 months after the gene transfer were evaluated.

Results: A total of 31 pigs were included in the study (SERCA2a n=16, Saline n=15). LV ejection fraction (EF) improved in SERCA2a gene transfer group with-

out statistical significance ($9.1\pm 15.2\%$ vs $-0.3\pm 14.8\%$, SERCA2a vs saline, $P=0.09$). Changes in EDVI and ESVI were significantly smaller in SERCA2a gene transfer group (EDVI; $2.0\pm 11.5\%$ vs $13.9\pm 14.0\%$, $P=0.01$, ESVI; $-2.5\pm 14.8\%$ vs $15.2\pm 20.7\%$, $P=0.04$, SERCA2a vs saline respectively). Stepwise multiple linear regression analysis with various baseline parameters (LVEF, ESVI, end-diastolic pressure, dP/dt maximum, dP/dt minimum, tau, heart rate, end-systolic and -diastolic pressure-volume relationship, SERCA2a gene transfer) demonstrated baseline ESVI (standardized $\beta=-0.332$, $P=0.04$) and SERCA2a gene transfer (standardized $\beta=0.411$, $P=0.01$) as independent predictors of ESVI change.

Conclusion: In chronic heart failure after MI, dilated heart itself is an independent predictor of further LV dilation and SERCA2a gene transfer attenuates or possibly reverse this remodeling.

DIABETES AND HEART FAILURE

P1750 | BEDSIDE

Insulin resistance is associated with impaired cardiac sympathetic innervation in patients with heart failure

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Purpose: Insulin resistance (IR) represents cause and consequence of heart failure (HF) and affects prognosis in HF patients, but pathophysiological mechanisms remain unclear. Hyperinsulinemia, that characterizes IR, enhances sympathetic drive and it can be hypothesized that IR is associated with impaired cardiac sympathetic innervation in HF. Yet, this hypothesis has never been investigated. Aim of the present study was to assess the relationship between insulin resistance and cardiac sympathetic innervation in non diabetic HF patients.

Methods: Ninety-five patients (88% males; 64.8 ± 11.1 years) with severe-to-moderate HF (ejection fraction $32.4\pm 9.6\%$), underwent iodine-123 meta-iodobenzylguanidine (123I-MIBG) myocardial scintigraphy to assess sympathetic innervation and Homeostasis Model Assessment Insulin Resistance (HOMA-IR) evaluation to determine the presence of IR. From 123I-MIBG imaging early and late heart to mediastinum (H/M) ratios were calculated.

Results: Fifty-eight (61%) patients showed IR and 37 (39%) were non-IR. No significant differences between IR and non-IR patients were found for age, ejection fraction, NYHA class, HF etiology and NT-proBNP levels. As expected, IR patients showed significantly higher fasting insulinemia compared to non-IR patients (16.0 ± 9.6 vs 5.2 ± 5.6 mU/L; $p<0.001$). Both early (1.68 ± 0.25 vs 1.82 ± 0.20 ; $p=0.007$) and late H/M ratio (1.50 ± 0.28 vs 1.65 ± 0.60 ; $p=0.029$) were significantly reduced in IR compared to non-IR patients, whereas washout rate did not differ between the two groups (10.7 ± 8.2 vs 9.6 ± 10.0 , respectively; $p=0.560$). In addition, early and late H/M ratio showed significant inverse correlation with fasting insulinemia ($r=-0.30$, $p=0.003$; $r=-0.21$, $p=0.04$, respectively) and HOMA-IR ($r=-0.34$, $p=0.001$; $r=-0.21$, $p=0.03$, respectively).

Conclusion: Cardiac sympathetic innervation is more impaired in patients with IR and HF compared to matched non-IR patients. These findings contribute to explain the unfavorable prognostic impact of IR in patients with HF.

P1751 | BENCH

Sitagliptin improves diastolic function and increases glucose uptake in the diabetic myocardium

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Purpose: Glucose is the main energy source in the normal heart. However, fatty-acids are used as the only substrate available in the diabetic myocardium. Sitagliptin improves hyperglycemia and insulin resistance, but it is unknown whether it could influence the cellular transporters for both glucose and fatty-acids. We have studied the effect of sitagliptin on glucose and fatty-acid uptake in the myocardium of type-II diabetic rats.

Methods: Non-obese, non-hypertensive type-II diabetic rats (Goto-Kakizaki; GK) were treated with sitagliptin (10 mg/kg/day) or vehicle. A group of Wistar rats were used as control ($N=10$ rats, each). After 20 weeks, cardiac structure and function were measured by Echo-Doppler, and glucose uptake was examined by positron emission tomography (PET). Then, hearts were isolated and processed for protein and RNA extracts. Plasma was used to evaluate metabolic parameters.

Results: As compared to Wistar rats, GK rats showed hyperglycemia (452.1 ± 63.9 vs. 208.6 ± 37.1 mg/dl; $p<0.01$), increased left ventricular posterior wall thickness (0.22 ± 0.02 vs. 0.19 ± 0.02 mm; $p<0.05$), a worsened diastolic function (deceleration time: 36.16 ± 0.96 vs. 33.72 ± 0.66 ms, and E/A ratio: 1.05 ± 0.18 vs. 1.39 ± 0.12 ; $p<0.05$ for all), and a reduction in both left ventricular diastolic (LVDD: 0.61 ± 0.03 vs. 0.80 ± 0.06 mm; $p<0.05$), and systolic (LVSD: 0.28 ± 0.06 vs. 0.53 ± 0.06 mm; $p<0.05$) diameters, without significant changes

in the ejection fraction. In addition, GK rats showed a reduced myocardial glucose uptake (30%) mainly in basal and middle regions of the heart, and a decreased expression and translocation of the glucose transporter Glut4, in favor of the fatty-acid transporter FAT/CD36. Interestingly, sitagliptin treatment attenuated hyperglycemia (322.3 ± 45.9 mg/dl; $p<0.05$), reduced the deceleration time (31.1 ± 0.51 ms; $p<0.05$), elevated E/A ratio (1.20 ± 0.18 ; $p<0.05$), and enhanced glucose uptake and Glut4 translocation to the sarcolemma ($p<0.05$).

Conclusions: Sitagliptin improves glucose uptake and diastolic function in the diabetic myocardium.

P1752 | BEDSIDE

Natriuretic peptides or glycosylated haemoglobin as markers of micro- and macro-vascular complications amongst older patients with type-2 diabetes mellitus. a report from sica-diabetes study

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Purpose: Type-2 diabetes mellitus (T2DM) is associated with a greatly increased risk of vascular disease, including cardiac dysfunction and heart failure. The plasma concentration of amino-terminal pro-brain natriuretic peptide (NT-proBNP) could be a simple tool for screening for cardiovascular disease and cardiac dysfunction amongst older patients with T2DM.

Method: Patients receiving treatment for T2DM for at least 12 months, aged >40 years and not already known to have heart or renal failure were invited to complete a symptom questionnaire and to have NT-proBNP measured as part of their annual check-up in primary care. Patients also had a physical examination, routine laboratory tests and were tested for neuropathy and retinopathy. All patients with increased NT-proBNP values and a sample of others were invited to attend for further cardiac investigations.

Results: Of 1224 patients screened, the median age was 65 (IQR: 58-72) years and 520 (42%) were women. NT-proBNP was >500 ng/L in 54 (4%), 250-500ng/L in 83 (7%), 125-250ng/L in 212 (17%), 50-125ng/L in 424 (34%) and <50 ng/L in 451 (37%). Patients with higher NT-proBNP had lower body mass index, smaller waist circumference and higher serum creatinine but had similar heart rate and blood pressure. Of patients with NT-proBNP <500 ng/L, 37% had HbA1c $>7.9\%$. 2% had serum creatinine >150 umol/L (median: 77 (65-91) umol/L), 7% had maculopathy or Grade 2+ retinopathy and 16% had micro-albuminuria. Of patients with values >500 ng/L, 29% had HbA1c $>7.9\%$, 43% had symptoms suggesting heart failure, 20% had serum creatinine >150 umol/L (median: 100 (IQR: 81-140) umol/L), 19% had maculopathy or Grade 2+ retinopathy and 40% had micro-albuminuria. On echocardiography, all but two patients had major cardiac dysfunction; 24% had left ventricular ejection fraction $<50\%$, 78% a dilated left atrium >38 mm, 30% had elevated systolic pulmonary artery pressures (>40 mmHg) and 42% patients were in atrial fibrillation. During a median follow-up of 436 (IQR: 334-503) days, the percentage of patients with a cardiovascular admission rose progressively to 8%, 13%, 19%, 28% and 26%. All-cause mortality from 0.6%, 0.6%, 1.2%, 3.9% to 9.8% for each of the NT-proBNP strata.

Conclusions: NT-proBNP is a simple method of screening for cardiac dysfunction in T2DM. A high proportion of those with elevated values have a dilated left atrium and pulmonary hypertension possibly reflecting left ventricular diastolic dysfunction. Clinical event rates increase progressively as NT-proBNP exceeds 125ng/L. NT-proBNP seems a better disease marker in T2DM than does HbA1c.

P1753 | BEDSIDE

Favorable impact of pancreas transplant alone on left ventricular diastolic function and left ventricle mass in type 1 diabetes patients

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Purpose: Type 1 diabetes mellitus (DM1) produces changes in myocardial structure and function, of which left ventricular (LV) diastolic dysfunction (DD) is an early sign. Pancreas transplant has been demonstrated to revert microvascular complications, but little is known about its effects on diastolic function. Current evidence is mostly obtained from series of combined kidney-pancreas transplant. We present a retrospective evaluation of 66 patients (pts) affected by DM1 in waiting list for pancreas transplant alone (PTA).

Methods: 66 pts with DM1 (mean age 38.7 ± 8.5 ; M/F: 25/41; mean DM1 duration 24.8 ± 8.3 years) were recruited. At the end of a mean follow up (fu) of 5 years, 43 (mean age 38.4 ± 9.2) had undergone PTA, whereas 23 (39.7 ± 6.5) were still on waiting list. Laboratory and Echo parameters were collected at the waiting list suitability evaluation (T0) and at the end of fu (T1). Data were compared between pts who received PTA and those who had not yet undergone intervention (NPTA).

Results: At T0, age, DM1 duration, and anthropometric, laboratory and Echo data were comparable between the two groups. When comparing the changes of Echo parameters during fu, an opposite trend emerged, showing an improvement in diastole and left ventricle (LV) mass indexes in PTA pts and a worsening in NPTA pts (Table 1).

Abstract P1753 – Table 1. Echo parameters

	PTA T0	NPTA T0	PTA T1	NPTA T1	ANOVA P value
IVSTd: interventricular septum diastolic thickness (mm)	9,25±1,50	8,94±1,52	8,51±1,37	9,41±1,06	0,001222*
LVPWTd: left ventricle posterior wall diastolic thickness (mm)	8,08±1,12	7,41±1,18	7,21±0,91	7,94±0,90	0,000097*
LVMI: left ventricle mass index (g/m ²)	79,25±19,37	76,58±19,64	71,00±14,45	84,66±15,44	0,002564*
E: early diastolic mitral inflow velocity (m/s)	76,35±15,80	76,35±9,77	81,00±16,17	70,06±9,66	0,009267*
E/A ratio	1,20±0,34	1,24±0,23	1,30±0,40	1,10±0,25	0,031769*
IVRT: isovolumetric relaxation time (ms)	93,39±11,64	87,81±9,20	88,45±10,96	93,64±9,24	0,010927*
EDT: E wave deceleration time (ms)	197,95±31,67	193,53±24,67	194,77±28,70	217,81±21,98	0,013251*
e': lateral mitral annulus early diastolic tissue doppler velocity (cm/s)	14,23±3,06	14,41±3,69	13,84±3,02	11,29±2,34	0,011166*
PVA duration: atrial reverse pulmonary vein flow velocity duration (ms)	102,90±13,04	97,92±12,12	91,06±14,62	94,71±7,34	0,014934*

Values are means ± standard deviation.

Conclusions: In a population of DM1 pts PTA (has) significantly improved LV diastolic Echo parameters and reduced LV mass indexes. Conversely, pts who did not receive PTA showed an increase in LV mass and wall thickness and a worsening trend in LV diastolic function.

P1754 | BEDSIDE

Impaired glucose metabolism as an independent risk for adverse cardiac events and progression of left ventricular diastolic dysfunction in dilated cardiomyopathy

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Purpose: Although diabetes mellitus (DM) has been identified as a poor prognostic risk in heart failure (HF) patients, the association between DM and therapeutic response in patients with idiopathic dilated cardiomyopathy (IDCM) has not been clarified.

Methods: Among the 109 consecutive IDCM patients in 2007 - 2011, we reviewed the institutional records of 88 patients (81%) whose clinical data were available. Laboratory data analysis and serial echocardiography were performed at baseline and at 1 year follow-up. The patients were stratified into two groups on the basis of the presence (DM+ group, n=56) or absence (DM- group, n=32) of DM at baseline. Patients were followed up until death, cardiac events (CEs) such as readmission for HF or detection of major ventricular arrhythmia.

Results: During the study period, CEs were observed in 17 patients (19%). DM was recognized as an independent predictor for CEs by multivariate analysis (adjusted hazard ratio, = 5.41; 95% confidence interval, 1.78 - 20.1; p<0.01), independent of plasma B-type natriuretic peptide level. Among the subjects with DM, the patients with increased hemoglobin A1c ($\Delta\text{HbA1c} \geq 0\%$) during 1 year had worse outcomes than those with decreased HbA1c ($\Delta\text{HbA1c} < 0\%$) (Figure, p<0.01). Moreover, there was no significant difference in left ventricular (LV) ejection fraction at 1 year (48±10 in DM+ group vs. 49±11% in DM- group, p=0.57), whereas mitral annular velocity at the early diastolic phase on tissue Doppler was significantly lower in DM+ group than those in DM- group (3.9±1.3 vs. 5.1±1.8%, p<0.01).

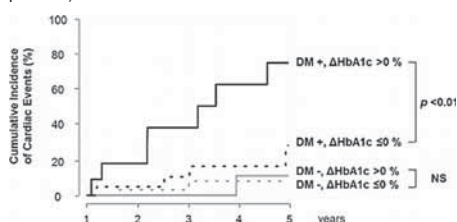


Figure 1. Kaplan-Meier analysis.

Conclusions: Impaired glucose metabolism during the clinical course has a prognostic impact for poor outcome and progression of LV diastolic dysfunction in patients with IDCM.

P1755 | BENCH

IgG-glycosylation in DCM: sugar detection may be useful to predict the efficiency of the immunoadsorption therapy

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Purpose: We have previously demonstrated that purified IgG obtained from patients with dilated cardiomyopathy (DCM) induce in the majority of the cases negative inotropic effects on isolated rat cardiomyocytes (rCM). The strength of the negative inotropic activity (NIA) correlated positively with improvement after immunoadsorption therapy (IA). From different autoimmune diseases it is known that changes in IgG-glycosylation of autoantibodies play an important role in the pathogenesis of the disease. In order to investigate its potential pathological relevance, we analyzed the glycan structures of IgG from plasma of control subjects and from plasma of DCM patients before IA (t0) and six month post IA (t6m).

Methods: Detection of sialic acid (SA) and galactose (Gal) was carried out by use of a lectin-based ELISA. NIA was defined as the ability of purified IgG to induce a reduction in cell shortening of rCM > 10%.

Results: Compared to controls, showing a median fluorescence intensity (mFI)

for SA of 1.62 (1.52;1.72) a significant decrease by 17.4% in SA of DCM-IgG was measured at t0. Here, only IgG with NIA contained significantly less SA (-28% vs. control). Interestingly, the inotropic activity of IgG correlated significantly with the amount of SA (r=0.8174). The amount of Gal in DCM-IgG was also significantly reduced by 26.9% vs. controls (mFI: 1.786 (1.6; 2.091) but with a less pronounced correlation between the sugar content and the NIA of IgG (r=0.453). Six month post IA, we found a significant increase in the amount of SA in DCM-IgG to a level similar to that of controls (p=0.001). Here, DCM-IgG with the lowest levels of SA at t0 exhibited the highest percent increase of SA at t6m (r=-0.8017). In consideration of the median increase, 87% of the DCM-IgG displaying a percent increase > than the median were NIA positive at t0. Moreover, the increase of SA in DCM-IgG with NIA came along with a significant improvement in contractility (+12%) leading to the loss of NIA. Likewise, for Gal we found a significant increase by 9% at t6m (p=0.019). And as shown for SA, the amount of Gal at t0 correlated with the increase in galactosylation at t6m (r=-8526). But in contrast to SA, 59.3% of the DCM-IgG showing a percent increase in Gal > than the median were NIA negative.

Conclusion: Our data reveal a link between the NIA of DCM-IgG on rCM and the degree of sialylation of these IgG. Moreover, since the strength of the NIA has been previously shown to be correlated with the improvement after IA, IgG-sialylation could be a predictor of the response to IA whereas IgG-galactosylation might be a marker for non-response.

P1756 | BENCH

Diabetic hyperglycemia attenuates sympathetic dysfunction and oxidative stress after myocardial infarction in rats

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Previous research has demonstrated that hyperglycemia may protect the heart against ischemic injury. The aim of the study was to evaluate the participation of autonomic modulation and oxidative stress in diabetic rats that had undergone 15 days of myocardial infarction. Male Wistar rats were divided into (n=8/group): control-sham (C), diabetes-sham (D), myocardial infarction (MI) and diabetes + myocardial infarction (DMI). Myocardial infarction was induced 15 days after diabetes induction by coronary occlusion. Cardiovascular autonomic modulation was evaluated by spectral analysis and oxidative stress profile was determined by: antioxidant enzymes activities, superoxide anion, protein carbonylation and redox balance of glutathione (GSH/GSSG) 15 days after MI and/or 30 days after diabetes onset (STZ, 50mg/kg). The diabetic and infarcted groups showed decrease in heart rate variability (p<0.05) and vagal modulation (p<0.05); however, the sympathetic modulation decreased only in diabetic groups (p<0.05). The sympatho/vagal balance and the vascular sympathetic modulation were increased only MI group (p<0.05). The diabetes induced increase in catalase concentration in D group (p<0.05). The glutathione peroxidase activity increased only in DMI group (p<0.05). The superoxide anion and protein carbonylation were increased only in MI group (p<0.05). The cardiac redox status evaluated by GSH/GSSG ratio was lower in MI group (p<0.05). In conclusion, these data suggest that hyperglycemia initiates compensatory mechanisms that could be protective to ischemia, as demonstrated by decreased sympathetic modulation, increased antioxidants enzyme and redox balance and reduction in protein carbonylation. These adaptations may be related with improvement in ventricular function and reduced infarcted area that was previously published in diabetic rats exposed to ischemic injury.

P1757 | BEDSIDE

Impact of diabetes mellitus on long-term prognosis in patients with preserved heart failure - a report from the Swedish Heart Failure Registry (S-HFR)

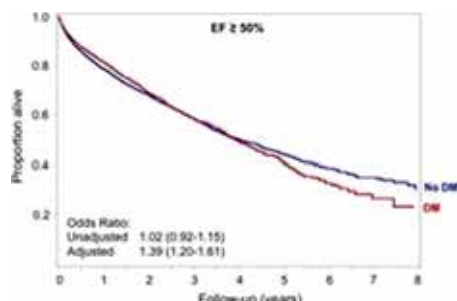
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Purpose: Patients with diabetes are at increased risk for developing heart failure.

We investigated the impact of diabetes on long-term prognosis in patients with heart failure and preserved left ventricular function from an everyday life perspective.

Methods: Patients with EF $\geq 50\%$, with (n=1658) and without (n=5047) type 2 diabetes included in the Swedish Heart Failure Registry (S-HFR) 2003-2011 were followed for mortality until 30 September 2011 (median 22.5 months). Differences in background characteristics were adjusted for in a logistic regression model.

Results: Patients with diabetes were younger (76 vs. 78 years), more often had known ischemic heart disease (47 vs. 36%), hypertension (68 vs. 52%), and more often had preserved renal function (eGFR >60 ml/min, 45 vs. 38%). NYHA classes III and IV were somewhat more common in those with diabetes (44 vs. 39%). Kaplan-Meier curves for mortality are presented in Figure 1. The unadjusted and adjusted* ORs (95% CI) for mortality were 1.02 (0.92-1.15) and 1.39 (1.20-1.61).



KM-survival curve in EF $\geq 50\%$, DM vs. noDM.

Conclusion: Our data support that diabetes is an independent predictor of mortality in patients with preserved left ventricular function. As much as 50% of patients with preserved left ventricular function had reported ischemic heart disease, which questions the concept of a pure diabetic cardiomyopathy.

* Adjusted for gender, age, duration of heart failure, weight, blood pressure (systolic and diastolic), ischemic heart disease, hypertension, atrial fibrillation, pulmonary disease, revascularisation, eGFR class, Hb class, ACE inhibitors, ARBs, beta-blockers, mineralocorticoid receptor antagonists, diuretics, digitalis, nitrates, statins and antithrombotic agents.

P1758 | BEDSIDE

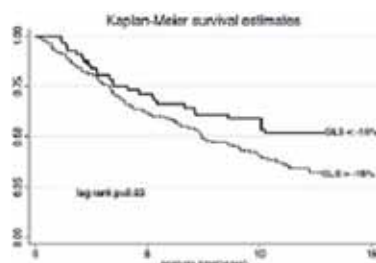
Global longitudinal strain as an important predictor of cardiovascular and all-cause mortality in advanced chronic kidney disease

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Purpose: Left ventricular (LV) systolic dysfunction is an important predictor of cardiovascular death. Global longitudinal strain (GLS) is proven to be more sensitive than conventional ejection fraction (EF) in detecting subtle changes in LV function. We sought to evaluate the prognostic value of GLS in patients with Advanced Chronic Kidney Disease (AdvCKD) Stages 4 and 5.

Methods: We followed 183 patients (57% male, 61.2% on dialysis) with AdvCKD for a mean of 7.8 ± 4.4 yrs. 112 (61%) of patients died within this time and 46 (25%) deaths were due to cardiovascular (CV) disease. GLS was calculated using 2 dimensional speckle tracking and EF was measured using Simpson's bi-plane. Normal GLS was defined at -16% . Cox proportional hazard models were used to explore the association of measures of LV function and all-cause and CV mortality.

Results: The mean GLS at baseline was $-13.6 \pm 4.3\%$ and EF was $45 \pm 11\%$. 51% of patients with EF $\geq 50\%$ had detectable abnormal GLS ($> -16\%$). GLS was a significant predictor of all-cause (Hazard Ratio (HR) 1.09 95%; Confidence Interval (CI) 1.01-1.17; $p=0.02$) and CV mortality (HR 1.12 95%; CI 1.12-1.25; $p=0.03$) following adjustment for age, diabetes mellitus, hypertension, previous cardiac events, parathyroid hormone, and allowing for transplant as a competing risk. GLS was a superior predictor of both all-cause [figure] and CV mortality outcome compared to EF. GLS $> -16\%$ was associated with a 5.6 fold increased risk of CV mortality in patients with preserved EF.



GLS & all-cause mortality.

Conclusions: GLS is an independent predictor of both CV and all-cause mortality in the AdvCKD and is more sensitive discriminator than EF for determining for LV dysfunction in this cohort.

P1759 | BEDSIDE

Comparison of the prognostic impact of diabetes mellitus between ischemic and non-ischemic heart failure - a report from the chart-2 study-

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Purpose: Diabetes mellitus (DM) is an important risk factor for mortality in patients with chronic heart failure (CHF). However, it is unclear whether the prognostic impact of DM differs between ischemic and non-ischemic heart failure (HF).

Methods: From our Chronic Heart Failure Analysis and Registry in our District-2 (CHART-2) Study (n=10,219), we enrolled 3,695 consecutive patients with symptomatic Stage C/D CHF patients (mean age 68.6 years, 68.8% male). We defined DM patients as those who had a history of DM treatment or had HbA1c $\geq 6.5\%$ (NGSP) at the time of enrollment. Impacts of DM for the composite of death, myocardial infarction, stroke, and HF admission were examined in terms of ischemic and non-ischemic etiology of HF.

Results: During the median follow-up of 3.0 years, there were 952 composite events (25.8%). The prevalence of DM was significantly higher in ischemic HF (863/1,767, 48.8%) than in non-ischemic HF (627/1,928, 32.5%) ($P<0.001$). Ischemic HF patients were characterized by older age and more male gender, and lower brain natriuretic peptide level as compared with non-ischemic HF patients. DM patients were characterized by younger age, higher body mass index, and higher prevalence of renal dysfunction in both groups. Kaplan-Meier curves showed that DM had a significant prognostic impact in ischemic HF but not in non-ischemic HF (Figure). Multivariate adjusted Cox analysis further demonstrated that DM was significantly associated with composite endpoints in ischemic HF (adjusted hazard ratio (HR) 1.33, $P=0.004$), but not in non-ischemic HF (adjusted HR 1.07, $P=0.49$) (P for interaction=0.81).

Figure. Kaplan-Meier curve for composite endpoints.

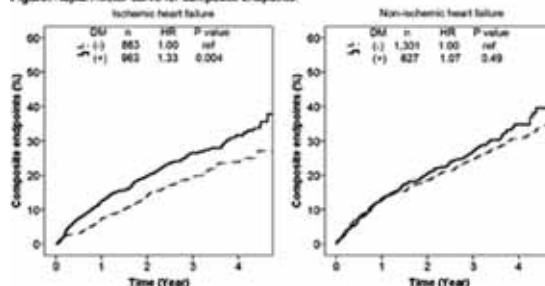


Figure 1

Conclusions: These results indicate that the prognostic impact of DM was more evident in ischemic HF than in non-ischemic HF.

HEART FAILURE MANAGEMENT II

P1761 | BENCH

Effect of cardiac resynchronization therapy on clinical course of ventricular tachycardias in patients with dilated cardiomyopathy and severe heart failure

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Purpose: To evaluate the effect of cardiac resynchronization therapy (CRT) on clinical course of ventricular tachycardias in patients with dilated cardiomyopathy (DCM).

Materials and methods: The study included a total of 70 patients with DCM aged 32 to 75 years (55 ± 12 years). All patients had NYHA functional class (FC) III heart failure (HF) with left ventricular (LV) ejection fraction (EF) of $30.1 \pm 3.8\%$, 6-minute walk test distance of 290.5 ± 64.3 m, and LV end diastolic volume (EDV) of 220.7 ± 50.9 mL. Before CRT device implantation and 1 year after it, all patients received 24-hour ECG monitoring. Patients were assigned to groups according to the registration of ventricular tachycardia (VT) paroxysms. Group 1 included 35 patients (50%) with diagnosed VT paroxysms occurring in the presence of adequate doses of antiarrhythmics. Group 2 included 35 patients (50%) without registered VT episodes. Before CRT, all patients received equilibrium radionuclide ventriculography (ERVG) with evaluation of LV EF increase. All patients received implantation of CRT devices with defibrillator function.

Results: One year after beginning of CRT, all patients showed clinical improvement: LV EF increased from $30.1 \pm 3.8\%$ to $42.8 \pm 4.8\%$ ($p \leq 0.001$); NYHA HF FC changed from III to II; 6-minute walk test distance increased from 290.5 ± 64.3 m to 377.2 ± 45.3 m ($p \leq 0.001$); and LV EDV decreased from 220.7 ± 50.9 mL to

197.9±47.8 mL ($p \leq 0.005$). During 1 year, 28 patients (80%) were completely free of VT episodes; 7 patients (20%) had unstable episodes of VT. Patients were assigned to subgroups according to the presence or absence of the registered VT episodes during CRT. No VT episodes were registered in patients whose LV EF increased by 14% and LV EDV decreased by 35 mL during 1 year of CRT ($p \leq 0.001$). Patients in whom VT paroxysms persisted during the entire period of the study showed an increase in LV EF by 9% and a decrease in LV EDV by 13 mL. The second part of the study evaluated the effects of ERVG-assessed myocardial metabolism defect (MMD) on potential development of VT episodes during CRT. No VT episodes were registered in patients whose MMD became less than 15% during CRT; if MMD exceeded 15% during CRT, patients had VT paroxysms.

Conclusions: (1) Efficacious CRT in patients with DCM statistically significantly reduces the number of VT episodes. (2) Improvement of myocardial fatty acid metabolism (LV MMD less than 15%) in patients with DCM contributes to reduction of the number of VT episodes during CRT.

P1762 | BEDSIDE

Elevated high-sensitive cardiac troponin T can predict incident heart failure admission in patients with left ventricular hypertrophy

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Background: Recently, very low circulating levels of troponin T are detectable with the new generation of highly sensitive assays (high-sensitive troponin T), and usefulness of high-sensitive troponin T as a predictor of adverse outcome not only in patients with chronic heart failure but also in general population has been reported. Left ventricular hypertrophy (LVH) is one of the most important predictor for cardiovascular events. Some previous reports have demonstrated the association between high-sensitive troponin T and LVH; however clinical significance of elevation in high-sensitive troponin T in patients with LVH has not been clarified.

Methods: 218 patients with LVH assessed with echocardiography were enrolled in our study. High-sensitive troponin T, NT-proBNP, classical coronary risk factors, estimated glomerular filtration rate (eGFR) were examined at baseline. Cardiac structure and function were also evaluated by echocardiography. Subjects were divided into two groups according to high-sensitive troponin T; high Hs-TNT group (≥ 0.014 ng/mL, $n=70$) and low Hs-TNT group (<0.014 ng/mL, $n=148$). Clinical characteristics were compared between the two groups. Associations between increasing high-sensitive troponin T and incidence of cardiac event were evaluated with Cox proportional hazards model with adjustment for cardiovascular risk factors.

Result: Compared with low Hs-TNT group, high Hs-TNT group had higher age ($p < 0.001$), lower eGFR ($p < 0.001$) and higher NT-proBNP ($p < 0.001$). In echocardiographic data, E/e' was higher ($p < 0.001$) and left ventricular mass index was higher in high Hs-TNT group compared with low Hs-TNT group. During the follow up period (mean 292 days), incidence of heart failure was significantly higher in high Hs-TNT group compared with low Hs-TNT group (7.1% vs 1.3%, $p=0.0229$), whereas there was no difference in incidence of coronary artery disease (7.1% vs 12.6%, $p=0.2266$). In multivariable Cox proportional hazards model, high Hs-TNT group had significantly increased risk for incidence of heart failure admission adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, eGFR and atrial fibrillation (Hazard ratio=7.368; 95% confidence interval=1.14 to 47.7, $p=0.036$).

Conclusion: Our results indicated that in patients with LVH, elevated high-sensitive troponin T is an independent predictor of heart failure. Cardiac troponin T is the useful biomarker for diagnosis of acute coronary syndrome.

P1763 | BENCH

Lung impedance-guided therapy of patients with chronic heart failure in outpatient clinic

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Background: Decompensation of patients with chronic heart failure (CHF) leading to re-hospitalizations for pulmonary congestion or edema (PCE) is an unresolved problem. At the initial stages of decompensation, patients have neither complaints nor overt signs of PCE. Current methods for PCE monitoring such as implantable devices, are invasive and of low sensitivity (35-76%) and monitoring by chest x-rays is both impractical and detrimental due to radiation exposure. Decreasing lung impedance (LI) is the result of an increase in pulmonary congestion. PCE monitoring was done by device which is 25-fold more sensitive than current ones due to measurement LI instead widely used transthoracic impedance.

Aim: To evaluate the effectiveness of treatment guided by the new LI device of patients with CHF.

Methods and results: We have shown previously that an LI decrease of more than 24% from dry (baseline) LI reflects the clinical threshold of lung fluid accumulation that signifies the evolution to PCE and hospitalization by >90% probability. We recruited 222 patients during the first month after hospitalization for PCE (age 67 ± 11 years, male 85%, LVEF $26 \pm 7\%$) at NYHA II/III/IV (97/86/39, respectively) and followed them in an outpatient clinic for 32 ± 21 months on a monthly

basis. Initial NT-proBNP level was 3771 ± 5185 pg/mL. Patients were randomized (1:1) into 2 well-matched groups according to treatment policy. Group 1 included patients treated according to measured LI while group 2 patients were treated by clinical assessment alone. There were 16 cardiovascular deaths and 5 non-cardiovascular deaths in group 1 and 30 and 6 in group 2, respectively ($p=0.006$). The annual number hospitalizations for PCE in groups 1 and 2 were 70 and 139, respectively ($p < 0.001$). In patients whose treatment was LI-guided (group 1) preemptive therapy was intensified 3 times more frequently than in group 2 ($p < 0.001$). The annual non PCE hospitalizations were 74 and 85 in group 1 and 2 respectively (NS).

Conclusion: Guided treatment in CHF patients reduced recurrent hospitalizations due to PCE and improved survival.

P1764 | BEDSIDE

Could the presence of depressive symptoms affect the results of exercise testing in men with systolic heart failure?

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Background: Exercise intolerance is one of the most important symptoms in heart failure (HF). It can be assessed using the cardiopulmonary exercise testing (CPX) with the assessment of peak oxygen consumption (peak VO₂) and ventilatory response to exercise (VE-VCO₂ slope) as well as a distance of 6-minute walk test (6-MWT). There are premises that the presence of depressive symptoms may affect the results of exercise testing, however, this issue has never been tested in patients with systolic HF.

Methods: We examined 197 men with systolic HF (mean age: 60 ± 11 years, NYHA class III-IV: 28%, ischaemic aetiology: 66%, mean LVEF: $31 \pm 9\%$). Depressive symptoms were assessed using the Beck Depression Inventory (BDI) where all 21 items were divided into cognitive/affective ones and somatic/vegetative. Exercise capacity was assessed based on peak VO₂ and VE-VCO₂ slope and 6-MWT distance.

Results: In men with systolic HF, mean peak VO₂ was 15.9 ± 4.8 mL/min/kg (peak VO₂ ≤ 14 mL/min/kg was present in 33.5% of pts), median VE-VCO₂ slope was 33.6 (28.8-42.3) (VE-VCO₂ slope ≥ 34 was present in approx. 50% of pts), and mean 6-MWT distance was 473 ± 118 m (6-MWT distance ≤ 450 m was present in 36% of pts). Patients with reduced peak VO₂ had more intense somatic and cognitive depressive symptoms (10 ± 5 and 8.5 ± 7) than patients with peak VO₂ > 14 mL/min/kg (6 ± 3.8 and 4 ± 3.8) (all $p < 0.0001$). Patients with VE-VCO₂ slope ≥ 34 had more intense somatic and cognitive depressive symptoms (9 ± 5 and 6.6 ± 6) than patients with VE-VCO₂ slope < 34 (6 ± 4 and 4.6 ± 4.7) ($p < 0.0001$ and $p = 0.01$, respectively). Patients with 6-MWT distance ≤ 450 m had more intense somatic and cognitive depressive symptoms (12 ± 5 and 8 ± 7) than patients with 6-MWT distance > 450 m (8 ± 5 and 4 ± 4) (all $p < 0.0001$).

In multivariable models reduced peak VO₂ was strongly associated with more pronounced overall depressive symptoms, particularly with somatic one ($b = -0.33$, $p < 0.0001$). Poor performance of 6-MWT was strongly associated with more pronounced all depressive symptoms particularly with somatic one ($b = -0.26$, $p < 0.001$). Increased VE-VCO₂ slope was strongly associated only with more severe somatic depressive symptoms ($b = 0.24$, $p < 0.001$).

Conclusions: Patients with exercise intolerance assessed during CPX and 6-MWT had more pronounced depressive symptoms. Combined depressive symptoms (both somatic and cognitive) were most associated with reduced peak VO₂ and poor 6-MWT performance. Somatic depressive symptoms were strongly related to all measures of exercise capacity. Coexistence of depressive symptoms in men with systolic HF should be considered during performance of exercise tests.

P1765 | BEDSIDE

Non-adherence to recommended therapy as a cause of heart failure decompensation

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Purpose: The cause of acute heart failure decompensation is frequently unknown. The non-adherence to the prescribed medication may be present in some individuals. The goal of the study is to assess the frequency of non-adherence to the recommended therapy in patients with acutely decompensated chronic heart failure.

Methods: Serum levels of prescribed medications were used as an indicator of drug adherence. Serum drug levels (SDLs) were evaluated by liquid chromatography and mass spectrometry. The chromatographic separation was performed on a reversed-phase column with a gradient flow of the mobile phase. The detection of analyzed substances was accomplished on a linear ion-trap mass spectrometer. The subjects were labeled as non-adherent when the serum level of at least one of the evaluated drugs was below the limit of quantification. The results of

SDLs had no influence on the clinical evaluation and acute management of the enrolled patients.

Results: The study assessed the data of 50 patients with acutely decompensated chronic heart failure. The main underlying causes of chronic heart failure were: coronary artery disease (14, 28%), combination of coronary artery disease and significant valvular heart disease (14, 28%), cardiomyopathy (8, 16%) and severe valvular heart disease (6, 12%). The acute decompensation of heart failure was caused by acute coronary syndrome (5, 10%), infection (5, 10%), arrhythmia (2, 4%), anemia (1, 2%), uncontrolled arterial hypertension (1, 2%), and progression of valvular heart disease (1, 2%). Three (6%) patients conceded omission of recommended medication, and in one individual (2%) the medication was inappropriately changed by the attending physician. In 31 patients (62%) the cause of acute cardiac decompensation remained unclear based on routine clinical exams performed. All of the evaluated drugs were detected in the sera of 28 (56%) study patients. The non-adherence was diagnosed in the remaining 22 (44%) patients. None of prescribed drugs was found in the sera of 5 (10%) patients. In patients with unknown precipitating cause of heart failure decompensation (31), the non-adherence was diagnosed in 13 (42%), none of prescribed drugs was detected in 2 (7%).

Conclusion: Our data suggest that the non-adherence to the recommended therapy may be a significant cause of acute decompensation of chronic heart failure. The assessment of serum drug levels may be used for this purpose.

P1766 | BEDSIDE

Carbon monoxide intoxication induced left ventricular dysfunction

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Purpose: Carbon monoxide (CO) intoxication could cause significant cardiac injury. Cardiac dysfunction after CO intoxication can be presented as various clinical patterns. The echocardiographic findings after CO intoxication are poorly defined. The purpose of this study was to evaluate the clinical patterns of left ventricular (LV) dysfunction using echocardiography.

Methods: One-hundred thirty two CO intoxicated patients (81 males, 46±20 year-old) with CO intoxication were enrolled. Clinical, demographic and laboratory data and transthoracic echocardiographic findings were analyzed.

Results: Left ventricular dysfunction developed in 29 patients (15 males, 47±20 year-old). The LV dysfunction group showed higher lactate level (5.8 ± 3.3 vs. 4.1 ± 3.5 mmol/L, $p=0.024$) and lower base excess (-8.2 ± 6.0 vs. -4.8 ± 4.7 mEq/L, $p=0.001$) compared with normal LV function group. Among the LV dysfunction group, 3 different echocardiographic patterns were presented (Table). Regional wall motion abnormality (RWMA) was presented in 14 patients. Akinesia of the mid and apical segments of LV with sparing of the basal segments, typical finding of Takotsubo cardiomyopathy, was presented in 8 patients. Global hypokinesia of LV was presented in 7 patients.

Table 1. Pattern of LV dysfunction

	RWMA group (n=14)	Takotsubo type CMP group (n=8)	Global HK group (n=7)	p
Age (years)	51±21	44±23	44±16	0.652
Men, n (%)	7 (50%)	1 (13%)	7 (100%)	0.001
BE (mEq/L)	-7.6±3.6	-5.0±4.1	-13.1±8.7	0.02
AST (U/L)	67.3±54.7	54.9±62.2	809.4±1000.5	0.006
Lactate (mmol/L)	5.3±2.8	4.3±2.4	8.4±2.4	0.033
CK-MB (U/L)	46.5±63.1	30.8±49.3	177.9±227.3	0.046
COHb (%)	14.1±9.6	20.3±16.7	12.3±11.9	0.415
EF (%)	43.4±15.6	37±10.3	36.4±10.5	0.409
WMSI	1.5±0.5	1.9±0.4	2	0.021

Conclusions: Our results demonstrate that CO intoxication could induce various patterns of LV dysfunction.

P1767 | BEDSIDE

Obstructive sleep apnea determines subclinical systolic biventricular dysfunction and increased arterial stiffness

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Background: Untreated obstructive sleep apnea (OSA) is associated with a high cardiovascular mortality and morbidity, probably related to the action of intermittent hypoxia on cardiac and vascular function; however, detailed mechanisms and hypotheses for early detection are still debatable.

Methods: 84 subjects (53±11 years, 20 women) were studied: 42 patients with moderate-to-severe OSA (mean apnea-hypopnea index 44 ± 21), before starting CPAP treatment, without known cardiovascular disease or risk factors, and 42 age- and sex- matched normal subjects. LV systolic function was assessed by ejection fraction (EF), mean basal systolic velocity (S'), and global longitudinal strain (GLS); RV systolic function by tricuspid annular systolic velocity (RV-S'), global strain (RVGS), and systolic pulmonary artery pressure (SPAP). Arterial function was assessed by intima-media thickness (IMT) and "e-tracking" for measuring the elastic modulus (Ep) and the augmentation index (AIx). NTproBNP was determined.

Results: Although in normal range, parameters of LV and RV systolic function were significantly lower in patients with OSA, associated with an increased NT-proBNP and arterial stiffness. Similarly, SPAP was normal in both groups, but significantly higher in the OSA patients (table).

Parameter	OSA	Control	P value
EF	57±6	67±8	≤0.01
S' (cm/s)	5.1±1.1	6.8±1.2	≤0.01
GLS (%)	-14.2±6.8	-19.3±2.6	≤0.01
NTproBNP (pg/ml)	63±6	35±2	0.03
RV-S' (cm/s)	9.4±2.8	11.7±1.8	0.03
RVGS (%)	-16.4±7.0	-20.7±8.6	0.03
SPAP (mm Hg)	22.9±10.8	18.2±8.1	0.04
IMT (mm)	0.9±0.2	0.7±0.1	≤0.01
Ep	134±47	95±50	≤0.01
AIx (%)	17.1±22.0	3.8±13.4	≤0.01

Conclusion: Patients with moderate-to-severe OSA have subclinical systolic biventricular dysfunction associated with increased arterial stiffness. Early diagnosis of these changes by new echo methods should be implemented for preventive actions.

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P1768 | BEDSIDE

Urinary uric acid level in spot sample on admission is useful as a predictive marker for in-hospital renal function disorder

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Purpose: We examined whether a spot urinalysis on admission can be useful as a new predictive marker for in-hospital renal dysfunction in patients with ADHF.

Method: A total of 280 consecutive ADHF patients who admitted to our institution between January 2013 and December 2013 from prospective registry was studied. Of them, 258 patients, who underwent urinalysis within 48 hours of admission, were included. In-hospital renal function disorder was defined as the increase in more than 25% or 0.3 mg/dL of serum creatinine.

Result: In-hospital renal function disorder was seen in 50 patients (19%), 15 of them experienced by 48 hours of admission. Patients with in-hospital renal dysfunction, compared with those without, were older, had higher serum creatinine (sCr), HbA1c, and eGFR levels, severer mitral regurgitation by echocardiography, and was more frequently treated with dobutamine, PDEIII inhibitor and nitroglycerin. On the other hand, urine creatinine (uCr), urine uric acid (uUA), urine urea nitrogen (uUN), serum uric acid (sUA)/uUA ratio, sCr/uCr ratio, serum UN (sUN)/uUN ratio, urine potassium/serum potassium ratio, uUA/uCr ratio, urinary osmolality, and plasma osmolality were significantly lower in patients with in-hospital renal dysfunction than those without. According to univariate analysis, uUA/sUA was the strongest predictor ($p<0.01$, OR=1.25) in all parameters.

Conclusion: Urinary uric acid level in spot sample divided by serum uric acid level can strongly predict in-hospital renal dysfunction in patients admitted with ADHF.

P1769 | BENCH

Non-invasive monitoring of lung impedance in chronic heart failure patients

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Background: Prevention of hospitalizations for decompensation in Chronic Heart Failure (CHF) patients is an unresolved issue. The accuracy of existing devices in predicting deterioration is only 38-76%.

Aim: We evaluated the ability of the new a non-invasive method for lung impedance monitoring to predict decompensation in CHF patients.

Methods: Monitoring CHF patients was accomplished by a device which measures "net" lung impedance (LI) instead of traditionally used transthoracic impedance. A decreasing LI reflects accumulation of lung fluid. Changes in the clinical status and LI were recorded at each monthly outpatient visit. Normal baseline LI was calculated according special algorithm for each patient. LI changes are represented as percent from baseline.

Results: 222 CHF patients (67±11 years-old, male - 85%, LVEF - $26\pm7\%$) at NYHA II/III/IV (97/86/39) were recruited after index hospitalization for acute heart failure (AHF) and followed in an outpatient clinic for 32 ± 21 months. Initial NT-proBNP level was 3771 ± 5185 pg/ml. During the follow-up period 48 patients (23.4%) died due to cardiovascular deaths. 99 patients were not hospitalized while the other 123 required 386 re-hospitalizations for AHF. 279 hospitalizations for other causes were recorded. LI decreased progressively before hospitalization. Values of LI at 1 m, 3 w, 2 w, 1 w, 3 days prior to and at the day of hospitalization decreased by 23.7 ± 11 ; 24.7 ± 11 ; 27.8 ± 13.2 ; 33.1 ± 12.2 ; 34.1 ± 10.5 and $36.8\pm10.5\%$ ($p<0.001$) from baseline value. At the time of hospitalization for a non AHF cause, LI diminished only by $12.9\pm5.9\%$ ($p<0.001$). Importantly, in all cases of AHF hospitalizations LI decreased by more than 24% from baseline while in 90% of non-AHF hospitalizations, LI decreased by less than 20%. In

CHF patients who had no hospitalizations for AHF during the monitoring period, LI decreased only by $10.2 \pm 5.2\%$.

Conclusions: Noninvasive "net" LI monitoring is a very sensitive to predict hospitalization for exacerbation of CHF. LI decrease by $>$ than 24% from baseline represents a high risk zone for re-hospitalization for AHF with 100% sensitivity and 90% specificity. Changes and intensification of therapy is mandatory when LI decreases by more than 24%.

P1770 | BENCH

Persistent long-term apparent healing in a large cohort of patients with idiopathic dilated cardiomyopathy: prevalence and characterization

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Background: Data regarding the characterization and prognostic role of persistent long-term apparent healing in large populations of patients with idiopathic dilated cardiomyopathy (IDCM) are lacking.

Methods and results: We analyzed 431 IDCM patients (potential follow-up: at least 8 years; mean follow-up: 180 ± 56 months) receiving tailored medical treatment. Apparent healing was defined as: left ventricular ejection fraction (LVEF) $\geq 50\%$ and indexed left ventricular end-diastolic diameter (LVEDDI) ≤ 33 mm/m² at mid-term follow-up (19 ± 4 months). Apparent healing was considered persistent when the above-mentioned parameters were maintained at long-term (103 ± 9 months). At mid-term 86/431 (20%) patients were apparently healed; 60% of them showed a persistent apparent healing. No baseline and mid-term predictors of persistent apparent healing were found. In persistently apparently healed patients all main clinical/laboratory parameters reached the normalization at mid-term and thereafter maintained it; conversely, in non-persistently apparently healed patients the parameters progressively worsened after the 5th year of follow-up despite their mid-term normalization. During the very-long-term follow-up, persistently apparently healed patients showed a better heart transplant-free survival (95 vs 71%; $p=0.014$) and fewer devices implantations (5 vs 24%) with respect to non-persistently apparently healed patients.

Conclusions: Persistent long-term apparent healing was evident in a remarkable proportion of IDCM patients receiving optimal medical treatment and was associated with stable normalization of main clinical/laboratory features and with excellent very-long-term survival. However no early predictors of this condition were found, highlighting the relevance of a continuous and individualized follow-up in these patients.

P1771 | BENCH

Chronic levosimendan treatment improves functional capacity of the hypertrophic and failing right rat heart

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Purpose: To investigate if chronic treatment with levosimendan can prevent and revert pressure overload induced right ventricular hypertrophy and failure in rats.

Methods: Right ventricular hypertrophy and failure was induced in male Wistar rat weanlings (77 ± 6 g) by pulmonary trunk banding (PTB) with a titanium clip compressed to an inner diameter of 0.6 mm. A control group was sham operated. Rats were randomized to treatment with vehicle ($n=10$, VEH), levosimendan (3 mg/kg/day) three weeks after surgery ($n=10$, REV), or three days prior to surgery ($n=10$, PREV). Sham operated rats received vehicle treatment ($n=16$, SHAM). Right ventricular function was evaluated at the end of study, seven weeks after surgery, by high frequency echocardiography, magnetic resonance imaging, pressure volume relations, and gross anatomy

Results: Pulmonary trunk banding induced right ventricular hypertrophy with compensated heart failure evident by a decrease in cardiac output and the absence of extra-cardiac manifestations of heart failure. Levosimendan treatment prevented and reverted deterioration of right ventricular function measured by cardiac index (Fig. 1). Deterioration of right ventricular function was prevented by levosimendan treatment measured by ejection fraction (EF) and by the load independent measure of systolic function: end systolic elastance (Ees) (EF: VEH vs. PREV $57\% \pm 2\%$ vs. $68\% \pm 3\%$, $p<0.01$; Ees: VEH vs. PREV 367 ± 57 vs. 667 ± 118 mm vs. mm Hg/mL, $p<0.05$), but only a trend towards normalization was observed using the reversal strategy.

Conclusion: Chronic treatment with levosimendan completely prevents the de-

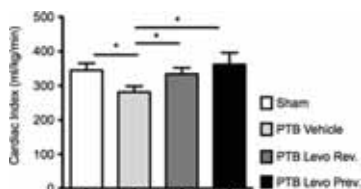


Figure 1. Cardiac index by echocardiography.

velopment of right ventricular failure and partially reverts established right ventricular failure induced by chronic pressure overload.

UNDERSTANDING HEART FAILURE WITH PRESERVED EJECTION FRACTION

P1773 | BEDSIDE

Noninvasive estimation of left ventricular filling pressures during exercise in patients with preserved left ventricular ejection fraction: comparative study, catheterization versus echocardiography

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Background: Latent heart failure at rest could be revealed in a number of patients upon exercise. The noninvasive diagnosis of this condition remain challenging. The aim of our study was to assess the value of exercise echocardiography to estimate exercise left ventricular end diastolic pressure (LVEDP). Considering left atrial (LA) remodeling as the reflect of the cumulative effects of LVEDP over time the secondary end point was to investigate LA size to predict abnormal exercise LVEDP.

Methods: Sixty patients (63 ± 10 years, 46 men) with LVEF $> 50\%$ underwent exercise cardiac catheterization and echocardiography as well. The ratio between early peak diastolic velocities of mitral inflow and annular mitral plane (E/e') was measured at rest and during exercise. LA maximal volume was measured at rest and indexed to body surface area (LAI). In order to investigate the relative expansion of the LA over the LV, the LA volume was also indexed to LV end diastolic volume (LA/LV). LVEDP > 16 mmHg was used as a threshold to define abnormal LV filling pressures.

Results: LVEDP increased significantly from 13.7 ± 5.7 to 24.1 ± 7.9 mmHg at exercise; 34 (57%) patients had elevation of LVEDP only during exercise. There was a mild correlation between LVEDP and E/e' at rest ($r=0.28$, $p=0.03$) and during exercise ($r=0.34$, $p=0.01$). With Receiver-operator characteristics curve, exercise E/e' > 8 identified patients with an abnormal exercise LVEDP with a 71% sensitivity and a 83% specificity; area under curve=0.79.

Interestingly, LA size indexes were not correlated to LVEDP at rest. However, they were correlated to exercise LVEDP ($r=0.3$ and $r=0.4$ respectively for LAi and LA/LV; $p<0.05$). LA/LV ≥ 0.5 identified patients with an abnormal exercise LVEDP with a 88% sensitivity and a specificity of 58%; area under curve=0.71. LA/LV had a better diagnostic value than LAi.

Conclusion: Exercise E/e' and LA size at rest are valuable to estimate exercise LVEDP. Taking into account the relatively high sensibility of LA/LV, this simple parameter might be useful to define the patients to whom exercise echocardiography will be the most appropriately prescribed. This new noninvasive approach of exercise LVEDP should be validated in further studies.

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Pulmonary vascular response to exercise in heart failure with reduced ejection fraction and pulmonary hypertension

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Purpose: Pulmonary vascular response patterns to exercise have not been studied extensively in symptomatic heart failure with reduced ejection fraction (HFrEF) and pulmonary hypertension (PH).

Methods: Consecutive, symptomatic HFrEF patients ($n=40$), with mean pulmonary arterial pressure (MPAP) ≥ 25 mmHg, pulmonary capillary wedge pressure (PCWP) > 15 mmHg, and cardiac index < 2.5 L/min/m², received protocol-driven, titrated sodium nitroprusside (SNP) and diuretics until mean arterial pres-

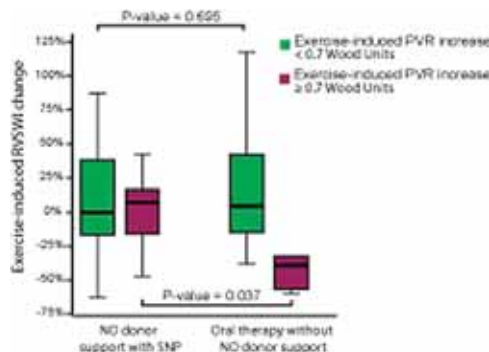


Figure 1. RVSWI change during exercise.

sure 65–75 mmHg and PCWP $\leq$ 15 mmHg, after which they performed a supine bicycle test. Afterwards, SNP was gradually withdrawn, renin-angiotensin system blockers uptitrated, and hydralazine added to maintain hemodynamic targets. Consequently, bicycle testing was repeated.

Results: Thirteen (33%) versus 27 patients (67%) presented with pulmonary vascular resistance (PVR) $\leq$ 3.5 versus $>$ 3.5 Wood Units, respectively (i.e., post-capillary versus mixed PH). After decongestion, 44% versus 20% of patients with post-capillary versus mixed PH, respectively, had MPAP $<$ 25 mmHg at rest. Significant exercise-induced PVR increase was observed twice as frequent in mixed (30%) versus post-capillary PH (15%), and associated with higher plasma NT-proBNP levels (P-value=0.001). Overall, this exercise-induced PVR increase was blunted under SNP (0.7 ± 1.0 versus 1.1 ± 2.5 Wood Units; P-value=0.661). Patients with significant exercise-induced PVR increase had a concomitant 39% decrease in right ventricular stroke work index (RVSWI), which was not observed under SNP (7% increase) or in the rest of the population.

Conclusions: A subpopulation of symptomatic HFrEF patients with PH demonstrates an exercise-induced PVR increase associated with impaired RVSWI at maximal exercise. SNP administration prevented this phenomenon.

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Characteristics of cardiac dysfunction associated with acute brain hemorrhage

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Purpose: Cardiac dysfunction associated with brain hemorrhage was not well studied. We evaluated the incidence and characteristics of acute cardiac dysfunction related with acute brain hemorrhage.

Methods: Between January and September in 2013, consecutive patients who were diagnosed with acute spontaneous or traumatic brain hemorrhage and admitted to surgical ICU were prospectively enrolled. ECG, cardiac enzyme, and echocardiography were performed in all patients. Left ventricular (LV) systolic dysfunction observed on echocardiography was considered as acute cardiac dysfunction related with brain hemorrhage when all the following criteria were satisfied: (1) accompanied ECG change and abnormal cardiac enzyme level, (2) no previous history of cardiac disease, and (3) regional wall motion abnormality (RWMA) extending beyond a single coronary arterial distribution. Otherwise, LV dysfunction was considered as cardiac dysfunction not related with brain hemorrhage. Clinical characteristics, laboratory findings, and in-hospital outcome were retrospectively reviewed.

Results: Total of 107 patients (age: 59 ± 16 years, 64 men) were collected. LV systolic dysfunction on echocardiography was observed in 18 (17%) patients. Among them 11 (10%) patients were classified as having acute cardiac dysfunction related with brain hemorrhage. While 5 patients in 11 patients with acute cardiac dysfunction showed typical apical ballooning, 6 patients showed inverted takotsubo pattern. Other abnormalities were observed in ECG, cardiac enzyme level and echocardiography were shown in the table. In-hospital mortality was observed in 19 (18%) patients. Six patients in 11 patients with acute cardiac dysfunction had in-hospital mortality (p=0.004).

Table 1. Observed cardiac abnormalities

Abnormal findings	(N=107)
ST segment elevation on ECG	15 (14%)
ST segment depression or T wave inversion on ECG	10 (9%)
Cardiac enzyme elevation	30 (28%)
Acute LV systolic dysfunction	11 (10%)
LV hypertrophy on echocardiography	48 (45%)

Conclusions: Acute cardiac dysfunction associated with acute brain hemorrhage was observed in 10% of patients and half of them showed inverted takotsubo pattern.

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Predictive value of systolic and diastolic strain rate for survival in cardiac amyloidosis patients with preserved ejection fraction

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Purpose: Recent studies showed that reduced longitudinal systolic strain assessed by speckle tracking imaging (STI) is related to increased mortality in patients with cardiac amyloidosis (CA). Since diastolic abnormalities are typical findings of CA, we hypothesized that longitudinal early diastolic strain rate (LSRdias) could be used as an early predictor for mortality in CA patients with preserved left ventricular ejection fraction (EF $>$ 50%).

Methods: Conventional echocardiography and 2D-speckle tracking imaging were performed in 41 CA patients with preserved EF (25 male; mean age 65 ± 9 years). Global and segmental longitudinal systolic strain (LSSys) and diastolic strain rate (LSRdias) were obtained in six segments of the left ventricle from apical 4-chamber views. CA patients were followed up for a median of 16 months (quartiles 5–35 months). The primary endpoint was all-cause mortality.

Results: Nineteen (46%) out of 41 CA patients died during follow-up. In respect to clinical and conventional systolic and diastolic echocardiographic data, lateral mitral annular plane systolic excursion (MAPSE) was significantly lower in non-survivors compared to survivors (7 ± 2 mm vs. 9 ± 3 mm, P=0.029). Among systolic strain parameters, mid-septal LSSys tended to be lower in non-survivors than in survivors ($-9 \pm 4\%$ vs. $-12 \pm 5\%$, P=0.052). Diastolic strain rate analysis showed that global LSRdias and basal-septal LSRdias were significantly lower in non-survivors than in survivors (all P $<$ 0.05). Basal-septal LSRdias cut-off value of 0.40 1/S was the best diastolic strain rate parameter for predicting death in this cohort (sensitivity=74% and specificity=71%). Univariate Cox analysis revealed that NYHA class III/IV (HR=3.21, P=0.017), reduced mid-septal LSSys ($<$ 11%; HR=4.05, P=0.009), reduced global LSRdias ($<$ 0.85 1/S; HR=3.97, P=0.007) and basal-septal LSRdias ($<$ 0.40 1/S; HR=4.46, P=0.005) were predictors for mortality in CA patients with preserved EF. Reduced basal-septal LSRdias (HR=4.00, 95% CI: 1.03–15.54, P=0.045) remained independently related to increased mortality in these patients after adjusting for age, gender, NYHA class, number of organ involvements and left ventricular mass index.

Conclusions: Speckle-tracking-imaging derived diastolic strain rate is a powerful predictor for survival of CA patients with preserved EF.

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Influence of Systolic Blood Pressure on Clinical Outcome in Elderly Heart Failure Patients with Preserved and Reduced Ejection Fraction Treated with Nebivolol: data from SENIORS trial

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Purpose: There is limited information about the effects of beta-blockers in HF stratified by blood pressure especially in the elderly and those with preserved ejection fraction (EF). We evaluate the effects of nebivolol on the composite outcome of all-cause mortality or cardiovascular hospitalization in elderly patients with HF stratified by SBP and EF.

Methods and results: The SENIORS trial evaluated the effects of nebivolol and enrolled 2128 patients $\geq$ 70 years with HF. Patients were divided into 2 SBP categories ($\leq$ 120 and $>$ 120 mmHg) on patients with EF $<$ 40% vs $\geq$ 40%. Mean age was 76 years, 37% were female, mean ejection fraction 36%. Low baseline SBP was associated with worse clinical outcomes irrespective of treatment group, both in patients with reduced and preserved EF. When stratified by SBP and EF nebivolol was numerically more beneficial than placebo in all groups, although this was not statistically significant. There was a similar effect in patients with reduced and preserved EF (Table 1).

Table 1. Effect of treatment according to blood pressure and ejection fraction

Primary endpoint*	Events per 1,000 years		Hazard ratio	95% CI	p value	Interaction p value
	Placebo	Nebivolol				
LVEF $<$ 40% (N=1468)						
$\leq$ 120 mmHg (N=378)	338.9	270.0	0.81	0.59; 1.12	0.20	0.65
$>$ 120 mmHg (N=1090)	223.4	195.8	0.88	0.71; 1.08	0.21	
LVEF $\geq$ 40% (N=643)						
$\leq$ 120 mmHg (N=72)	377.4	198.7	0.52	0.25; 1.09	0.08	0.20
$>$ 120 mmHg (N=571)	201.5	174.2	0.87	0.64; 1.17	0.34	

*All-cause mortality or cardiovascular hospitalization. LVEF: left ventricular ejection fraction. BP: blood pressure. CI: confidence interval.

Conclusions: Elderly HF patients with lower SBP have a worse outcome than those with higher SBP, but nebivolol appears to be safe and well tolerated with similar effect on the composite outcome of death or CV hospital admission, irrespective of baseline SBP and LVEF.

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Prognostic significance and determinants of the 6-minute walk test in patients with pulmonary hypertension associated with heart failure and preserved ejection fraction

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Background: Symptoms of exertional fatigue and dyspnea, as well as a reduced

exercise tolerance are cardinal features of pulmonary hypertension (PH) associated with heart failure with preserved ejection fraction (HFpEF). The underlying mechanisms limiting exercise capacity in this complex clinical syndrome remain incompletely understood. The aim of the present study was to define the prognostic significance and clinical determinants of the six-minute walking distance (6-MWD) in affected patients.

Methods: Consecutive patients with a definite diagnosis of PH-HFpEF, as confirmed by right heart catheter, were enrolled in our prospective, observational registry. Hospitalization for HF and/or death for cardiac reason were defined as the primary study endpoint. To establish determinants of the 6-MWD, four separate multiple regression models were constructed for TTE, hemodynamic, laboratory and pulmonary parameters. For quantification of left ventricular (LV) extracellular matrix (ECM) using the TissueFAXS and HistoQuest® software, myocardial biopsies were taken from 18 patients.

Results: Between December 2010 and July 2013, 142 PH-HFpEF patients (99 women and 43 men, mean age 71 ± 9 years) were included to the study. After a mean follow-up of 14.0 ± 10.0 months (range 0.5 – 34.0 months), 43 patients (30.3%) reached the combined endpoint. Patients in the adverse outcome group had a significantly shorter 6-MWD (246.8 ± 115.6 m versus 345 ± 110.2 m, $P < 0.001$) and a higher Borg dyspnea score (BDS; 5 ± 2 versus 3 ± 2 , $P < 0.001$). The 6-MWD (hazard ratio [HR]: 0.992; 95% confidence interval [CI]: 0.990; 0.995; $P = 0.013$) was found to be an independent predictor of outcome. Other clinical parameters associated with a worse prognosis were presence of atrial fibrillation (HR: 2.482; 95%CI: 1.198; 5.139; $P = 0.014$) and COPD (HR: 2.048; 95%CI: 1.084; 3.869; $P = 0.039$). The following parameters were found to be independent determinants of the 6-MWD: systolic and mean pulmonary artery pressures, transpulmonary gradient, pulmonary arterial compliance, hemoglobin, urea, partial pressure of carbon dioxide in arterial blood and vital capacity. There was a significant inverse correlation between the 6-MWD and the amount of ECM ($R = -0.501$, $P = 0.034$) in the heart tissue samples.

Discussion: The limited exercise capacity in PH-HFpEF patients can be explained by a variety of cardiac and non-cardiac factors that contribute to increased ECM deposition in the LV and consecutive hemodynamic alterations. We hypothesize that PH-HFpEF is a multifactorial systemic disease with end-organ damage of the heart.

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A biomarker for diastolic heart failure

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Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence and incidence, but there are no approved treatments or specific diagnostic biomarkers. Accumulated evidence indicates that increased oxidative stress and reduced nitric oxide (NO) bioavailability contribute to impaired relaxation and elevated diastolic myofilament tension leading diastolic relaxation impairment. Recently, we reported that that impaired relaxation is associated with nitric oxide synthase (NOS) uncoupling that results in oxidative modification of cardiac myosin binding protein C (cMyBP-C), induces slowed myofilament cross-bridge kinetics, and leads to diastolic dysfunction. We investigated whether plasma modified cMyBP-C could be a biomarker for diastolic dysfunction. Isolated cardiomyocytes showed increased release of cMyBP-C under oxidative stress. In a well-established mouse model of isolated diastolic dysfunction as a result of mild hypertension with deoxycorticosterone acetate (DOCA)-salt mice, circulating cMyBP-C was increased when compared to control C57/BL6 sham mice. Diastolic dysfunction increased in the intact protein, proteolytic fragments (8.77-fold, 75kD, $P = 0.045$), and S-glutathionylated form (3.72-fold). Furthermore, we compared cMyBP-C forms in serum of HFpEF patients with or without diastolic heart failure. Sixteen HFpEF patients showed elevation of total cMyBP-C (4.02 ± 1.4 -fold, $P = 0.048$), cMyBP-C fragments (2.88 ± 0.64 -fold, $P = 0.019$), and S-glutathionylated cMyBP-C (2.31 ± 0.47 -fold, $P = 0.015$), compared to healthy control group ($N = 12$). In conclusion, animals with diastolic dysfunction and humans with HFpEF show elevated plasma levels of cMyBP-C, cMyBP-C fragments, and modified cMyBP-C as compared to controls, suggesting that modified cMyBP-C may be a novel biomarker of HFpEF.

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ABSTRACT WITHDRAWN

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MiR-21 and miR-133 levels in peripheral blood mononuclear cells in patients with heart failure with preserved ejection fraction

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Purpose: MicroRNAs (miRs) are essential regulators of gene expression implicated in cardiovascular function and disease. MiR-21 and miR-133 have been shown to play a role in heart hypertrophy and fibrosis. They have also been shown to regulate proliferation and phenotypic switch of vascular smooth muscle cells. However, there are limited data regarding their role in left ventricular (LV) diastolic dysfunction. The aim of this study is to investigate miR-21 and miR-133 levels in peripheral blood mononuclear cells in patients with heart failure with preserved ejection fraction (HFPEF).

Methods: We included 33 patients with symptoms and signs of heart failure who had an LVEF $> 50\%$ and evidence of LV diastolic dysfunction (19 males, aged 58 ± 10 years). Blood samples were also obtained from 29 healthy volunteers for comparison (17 males, aged 52 ± 8 years). All subjects underwent a complete echocardiographic study.

Peripheral blood mononuclear cells (PBMCs) were isolated and microRNA levels were determined by quantitative real time reverse transcription PCR.

Results: MiR-21 levels were found to be higher (3.6 ± 0.41 versus 2.05 ± 0.31 , $p < 0.05$), while miR-133 levels were found to be lower (11.26 ± 4.9 versus 37.03 ± 8.18 , $p < 0.05$) in patients with LV diastolic dysfunction compared to healthy controls. MiR-21 levels showed strong negative correlations with E/e' ($r = -0.42$, $p < 0.001$) while miR-133 levels showed strong positive correlations with E/e' ($r = 0.40$, $p < 0.001$).

Conclusions: Patients with LV diastolic dysfunction were shown to have a strong relationship with miR-21 and miR-133 levels in peripheral blood mononuclear cells. Our findings contribute to the understanding of pathogenesis of HFPEF and might offer a future therapeutic target.

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Soluble ST2 is associated with markers of diastolic dysfunction in patients with heart failure with preserved ejection fraction in the PARAMOUNT trial

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Background: The cardiac fibrosis marker ST2 is associated with severity of heart failure and adverse prognosis in heart failure with reduced ejection fraction. The association between ST2 and clinical characteristics or measures of cardiac structure and function in patients with heart failure with preserved ejection fraction (HFpEF) is unclear.

Methods: We studied 296 patients from the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) trial with a measurement of ST2. We related ST2 levels to base-

ABSTRACT WITHDRAWN

line characteristics and echocardiographic measures and assessed the effect of randomized therapy at 36 weeks.

Results: The median ST2 level was 33.1 ng/ml (IQR 24.6-48.1). Higher ST2 was associated with older age, male sex, atrial fibrillation, higher NYHA class, higher NT-proBNP and lower eGFR (Table). Increasing ST2 levels were associated with higher E/E' and larger left atrial size (Table). Associations were similar after excluding patients with atrial fibrillation. In a multivariable model male sex, increasing NYHA class and left atrial volume were independently associated with higher ST2. Treatment with LCZ696 did not reduce ST2 levels at 12 (p=0.97) or 36 weeks (p=0.76).

Characteristics by ST2 quartiles

	Q1 8.4–24.5 (n=74)	Q2 24.6–33 (n=74)	Q3 33.1–47.1 (n=74)	Q4 48.5–260.1 (n=74)	P for trend
Age, years	69±10	70±10	71±8	74±8	0.02
Women (%)	47 (64%)	45 (61%)	38 (51%)	36 (49%)	0.04
AF (%)	17 (23%)	32 (43%)	33 (45%)	39 (53%)	<0.001
NT-proBNP (pg/mL)	774 [355, 1248]	716 [393, 1341]	957 [601, 1322]	1014 [603, 1800]	0.002
eGFR (mL/min per 1.73 m ²)	69±21	68±20	62±21	61±18	0.005
E/E'	10.9±3.9	12.6±6.0	13.3±6.9	13.7±6.6	0.02
LA volume index (mL/m ²)	32±12	35±13	36±14	40±15	<0.001

AF, atrial fibrillation; LA, left atrial; eGFR, estimated glomerular filtration rate.

Conclusion: Our findings suggest that ST2 is associated with markers of wall stress and diastolic dysfunction in HFpEF. Whether ST2 represents simply a biomarker associated with disease severity in HFpEF or contributes to the pathogenesis remains unclear.

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Evolution of left ventricular function by speckle tracking echocardiography in heart transplanted patients

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Introduction: Although ejection fraction (EF) is usually normal after heart transplantation (HT), regional systolic function can be impaired. Strain is an accurate tool for assessment of myocardial function in this patients.

Objective: To compare left ventricular function in HT patients with healthy controls in the first two years after HT.

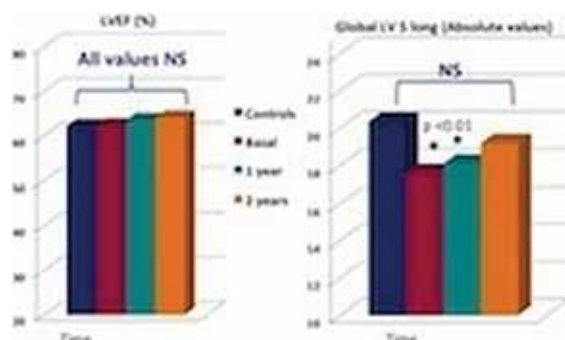
Methods: We included 29 HT patients followed over one year, 20 of them completed two years, and 13 healthy controls. Studies with endomyocardial biopsy rejection $\geq 2R$ were excluded. EF by biplane Simpsons method and interventricular septum thickness were determined. LV global longitudinal strain (GLS) by Speckle Tracking technique was measured in 12 LV segments in 4 and 2 chambers view.

Results: Our results are shown in the table below.

Evolution of LV function

	IVST	EF	Global LVS
Controls	9.4±1.8	62.2±5.2	-20.35±3.0
Basal	12.5±2.4*	62.3±8.2	-17.6±3.4*
1 year	10.64±1*	63.5±8.0	-18.1±2.3*
2 years	11.2±1.1*	64.1±7.1	-19.2±3.8

*p<0.01 compared to controls. Global LVS: global LV longitudinal strain.



Evolution of LVEF and global LVS.

Conclusions: Despite normal EF in HT patients, LV GLS values were significantly reduced compared to healthy controls in the first month after transplantation, so these reduced parameters may be interpreted as "normal" strain values in "healthy" transplant patients. They improved progressively until complete normalization after two years follow up. This is the first study to show a full recovery in LV function by Speckle-tracking technique.

YOUNG INVESTIGATORS AWARDS SESSION: CLINICAL SCIENCE

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Intracoronary autologous cardiac progenitor cell transfer in children with hypoplastic left heart syndrome: 2-year results of the TICAP trial

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Background: Hypoplastic left heart syndrome (HLHS) is one of the most high-risk lesions in children with congenital heart disease. Objective- The aim of this study is to determine whether intracoronary delivery of autologous cardiosphere-derived cells (CDCs) was feasible and safe to treat the children with HLHS.

Methods and design: This phase 1 trial (TICAP: NCT01273857) is a prospective controlled exploratory study. Four-teen patients with HLHS who are undergoing staged-2 or -3 surgical palliations were enrolled between January, 2011, and January, 2012. Seven patients constitutively assigned to receive intracoronary single-dose injection of CDCs 1 month after the surgical palliations followed by 7 patients allocated to a control group with standard care alone. The primary endpoint was to assess the safety and the secondary endpoint was the preliminary efficacy to verify the improvements of the right ventricular function as well as the clinical symptoms of heart failure status and Z scores for weight-for-age from baseline (1 month after surgical palliations) to 3, 12, and 24 months of follow-up.

Results: No complications, including cardiac death, myocardial ischemia, proarrhythmia, hospitalization for heart failure, and tumor formation, were reported within 24 months of CDC infusion. Echocardiography showed that improvement of right ventricular ejection fraction (RVEF) was greater in the CDC-treated group (+5.3±3.2%) than in controls (+0.1±3.4%, P=0.01) at 3 months after CDC infusion. This cardiac function enhancement was manifested even 1 year and 2 years after CDC infusion (+7.8±4.9% vs. +2.2±3.1% at 1 year, P=0.03; +8.8±3.7% vs. +3.4±6.4% at 2 years, P=0.04). In addition, RVEF measured by cMRI was also markedly improved in CDC-treated patients from 36.1±7.5% at baseline to 42.7±8.7% at 1 year (P=0.04) and to 42.4±7.7% at 2 years (P=0.047). Notably, heart failure status was reduced in CDC-treated group as shown by significant decrease in both Ross Heart Failure Class (2.6±0.8 at baseline vs. 1.4±0.5 at 2 years, P=0.01) and NYU PHFI (10.3±4.4 at baseline vs. 6.1±0.9 at 2 years, P=0.04), and Z scores for weight-for-age was significantly increased from -4.0±2.7 at baseline to -2.2±1.4 at 2 year (P=0.02), whereas all of these parameters did not change in control subjects.

Conclusion: These encouraging results of 2-year follow-up of TICAP trial suggest that intracoronary infusion of autologous CDCs is feasible and safe to treat the children with HLHS. This novel therapeutic strategy may impact on cardiac function as well as clinical symptom of heart failure status and somatic growth in long-term outcome.

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Performance of novel adenosine-free and established indices of coronary lesion severity using invasive and non-invasive techniques, as well as absolute quantification of myocardial blood flow

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Purpose: Ischaemia guided therapy of coronary artery disease with the use of Fractional Flow Reserve (FFR) has been shown to improve patient outcomes. Recent work has proposed the instantaneous wave-free ratio (iFR) and Basal Stenosis Resistance (BSR) as novel adenosine-free techniques to assess stenosis severity equivalent in accuracy to FFR. The diagnostic performance of these new compared to more established tests is not clear, limited by the lack of a true gold-standard test for coronary ischaemia. We aimed to investigate these processes by developing a model of coronary ischaemia with invasive, non-invasive and ex-vivo applications.

Methods: A model of coronary stenosis was developed in anaesthetised Landrace Pigs for invasive assessment of coronary haemodynamics, adenosine stress perfusion MRI (CMR), and microsphere quantification of absolute myocardial blood flow (MBF). Lesions were created using an adjustable external balloon constrictor, via a mini-thoracotomy. An intracoronary wire distal to the stenosis measured pressure and flow velocity at rest and adenosine-induced hyperemia. Perfusion CMR was performed as per clinical standards. Accurate 3-dimensional location of injected microspheres was performed using an imaging cryomicrotome.

Results: 64 lesions of varying severity were created. FFR provided the best test of coronary stenosis severity, versus HSR as the reference standard, with an area under the receiver operator characteristic curve (AUC) of 0.98, which was significantly better than iFR (AUC 0.89, P=0.026), and resting gradient (Pd/Pa) (0.86,

$P=0.005$), with a trend towards significance against BSR (AUC 0.90, $P=0.052$). FFR also provided the highest diagnostic accuracy (0.92 vs 0.86, 0.81 and 0.88 respectively). Half of these lesions were also assessed with perfusion CMR as the reference standard showing that the techniques using adenosine performed numerically better (HSR AUC 0.92, FFR 0.88) compared to those at rest (BSR 0.86, Pd/Pa 0.85, iFR 0.84). On microsphere assessment hyperemic techniques correlated best to MBF with coefficients of determination (r^2) of 0.92 (HSR), 0.89 (CMR), and 0.87 (FFR) compared to those measured at rest (iFR 0.72, BSR 0.65, Pd/Pa 0.64).

Conclusions: This novel model of coronary ischaemia has for the first time allowed a complete appraisal of the performance of novel as well as established indices of coronary lesion severity invasively, non-invasively with perfusion CMR, as well as quantification of MBF. Based on these results, the continued use of adenosine in the assessment of lesion severity is recommended.

1786 | BEDSIDE

Relationship between NLRP3 inflammasome activation in adipose tissue and atherosclerosis

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Background: Obesity causes chronic inflammation in the absence of overt infection or well-defined autoimmune processes. NLRP3 (Nucleotide binding oligomerization domain-like receptor family, pyrin domain containing 3) inflammasome senses obesity-associated danger signals, including ceramides and reactive oxygen species, and contributes to obesity-related inflammation and insulin resistance through the activation of caspase-1 and subsequent secretion of IL-1 β and IL-18. Atherosclerosis associates well with obesity, however, the role of NLRP3 activation in adipose tissue in the development of atherosclerosis remains obscure. In this study, we examined the relationship between the severity of atherosclerosis and NLRP3 inflammasome activation in adipose tissue.

Methods: We obtained subcutaneous fat tissue from 89 patients with pacemaker implantation who underwent coronary angiography, carotid ultrasonography and brachial artery flow-mediated vasodilation (FMD) measurement. In addition, we collected blood sample in periphery and coronary sinus. Then we examined the expression of inflammasome-related genes in adipose tissue, and compared them with patients' background, serum adiponectin levels, and results of coronary angiography and carotid.

Results: The mRNA levels of NLRP3, IL-1 β , and IL-18 in adipose tissue positively correlated with the number of coronary risk factors. Also, the mRNA levels of NLRP3, IL-1 β and IL-18 in adipose tissue significantly correlated with Plaque score as an index of severity of carotid atherosclerosis (Nlrp3, $r=0.538$, $P<0.01$; IL-1 β , $r=0.53$, $P<0.01$; IL-18, $r=0.47$, $P<0.05$) and Gensini score as an index of severity of coronary atherosclerosis (Nlrp3, $r=0.63$, $P<0.01$; IL-1 β , $r=0.66$, $P<0.01$; IL-18, $r=0.47$, $P<0.01$). In addition, NLRP3 mRNA levels were higher in patients with significant coronary artery stenosis compared with those in patients without significant stenosis ($P<0.05$). Furthermore, NLRP3 mRNA levels in adipose tissue were positively correlated with body mass index ($P<0.01$) and negatively correlated with serum adiponectin levels ($P<0.05$) and FMD ($P<0.05$). Immunostaining of subcutaneous adipose tissue sections revealed strong colocalization of NLRP3 with the macrophage marker CD68.

Conclusion: Activation of NLRP3 inflammasome in adipose tissue correlated well with the severity of systemic atherosclerosis. The activation of NLRP3 inflammasome in adipose tissue might associates obesity-induced chronic inflammation and atherosclerosis.

1787 | BEDSIDE

Major hypoglycemia is associated with cardiovascular death and hospitalization for heart failure: findings from SAVOR-TIMI 53

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Purpose: Hypoglycemia is associated with an increased risk of cardiovascular (CV) events, though it is unknown whether incretin based therapies modifies this association. SAVOR-TIMI 53 examined the efficacy and CV safety of saxagliptin, a DPP-4 inhibitor, compared to placebo in patients with T2DM and either established CV disease or multiple CV risk factors.

Methods: 16,492 patients were randomized to saxagliptin or placebo and followed for a median of 2.1 years. Hypoglycemia was defined as major if it required 3rd party assistance or minor if the glucose was <3.0 mmol/L and/or patients had an awareness of hypoglycemia that resolved within 30 minutes. An extended Cox model that controlled for measured confounders and had hypoglycemia as a time varying covariate was developed to examine the association between hypoglycemia and CV events. CV events were adjudicated by an independent CEC.

Results: Overall, 2368 patients (14%) had at least one hypoglycemic event: 317 had ≥ 1 major events and 2051 had only minor events. Major hypoglycemic events were associated with CV death (HRadj 1.81, 95% CI 1.06, 2.87, $p=0.02$) and hospitalization for heart failure (HRadj 1.80, 95% CI 1.04, 2.89, $p=0.02$), but not MI

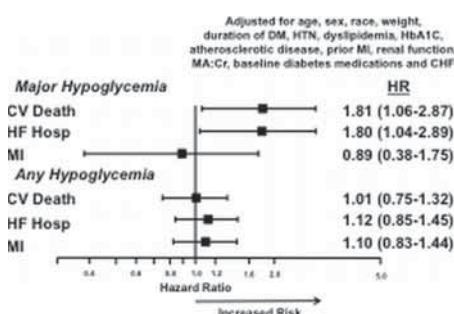


Figure 1

(Fig. 1). The risk associated with hypoglycemia was similar regardless of treatment with saxagliptin or placebo. There was no overall association between minor hypoglycemia and CV events.

Conclusions: Hypoglycemic events are common in patients with diabetes. Major hypoglycemic events, while infrequent, were associated with increased risk of CV death and hospitalization for heart failure. Further studies are needed to better understand the mechanism responsible for this association and to develop strategies that prevent these events.

YOUNG INVESTIGATORS AWARDS SESSION: CORONARY PATHOPHYSIOLOGY AND MICROCIRCULATION

1788 | SPOTLIGHT

Enhanced adventitial vasa vasorum formation in patients with vasospastic angina -Assessment with optical frequency domain imaging-

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Purpose: We have recently demonstrated that adventitial inflammatory changes including vasa vasorum (VV) formation are involved in the pathogenesis of coronary vasospasm in porcine models. However, it remains to be elucidated whether those adventitial structural changes, particularly VV formation, are also involved in the coronary hyperconstricting responses in patients with vasospastic angina (VSA). In this study, we thus examined the extent of adventitial VV formation in VSA patients and control subjects using optical frequency domain imaging (OFDI).

Methods: OFDI images of the left anterior descending coronary artery (LAD) were obtained after intracoronary injection of isosorbide dinitrate in 12 patients with acetylcholine-induced diffuse spasm in LAD and in 7 control subjects without the spasm along the LAD at every 10 mm length. OFDI clearly visualized adventitial structure of the coronary artery including VV and also enabled us to reconstruct 3D-OFDI images.

Results: Patient characteristics were comparable between VSA patients and control subjects, including sex, age, cardiovascular risks and medications. OFDI and 3D-OFDI images showed enhanced adventitial VV formation in VSA patients as compared with control subjects (Fig. 1). Quantitative analysis showed that VV area was significantly larger in VSA patients than in control subjects (VSA, 0.096 ± 0.007 vs. control, 0.035 ± 0.004 mm², $P<0.001$), whereas other morphometric parameters, including vessel diameter and wall thickness, were comparable between the 2 groups.

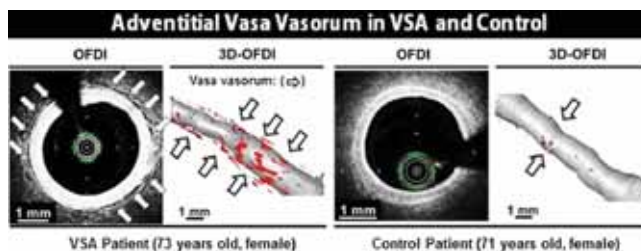


Figure 1

Conclusions: These results demonstrate for the first time that adventitial VV formation is enhanced at the spastic coronary segment in VSA patients, suggesting the important role of adventitial VV in the pathogenesis of coronary spasm.

1789 | BEDSIDE

Low endothelial shear stress is associated with high-risk coronary plaque characteristics in humans: a combined frequency-domain optical coherence tomography and computational flow dynamics study

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Purpose: Endothelial shear stress (ESS) plays a major role in the development and progression of atherosclerotic plaques. The aim of this study was to explore in vivo the relationship between local ESS and coronary plaque features, using a systematic vascular profiling which combines computational flow dynamics and frequency-domain (FD)-OCT analysis in humans.

Methods: Three-dimensional coronary artery reconstruction was performed in 21 patients (24 arteries) presenting with acute coronary syndrome using FD-OCT and coronary angiography. Each reconstructed artery was divided into consecutive 3-mm segments, and each segment was characterized by local predominant ESS pattern (defined as the minimum averaged ESS value over a 90° arc in each segment), and analyzed for the assessment of plaque characteristics by FD-OCT. Coronary segments were categorized as segments with low ESS (<1 Pascal [Pa]) and those with higher ESS (≥1 Pa). A total of 146 non-culprit segments were evaluated.

Results: Compared with segments with high ESS, those with low ESS showed higher prevalence of lipid-rich plaques (37.5% vs. 20.0%, $p=0.019$) and thin-cap fibroatheroma (TCFA) (12.5% vs. 2.0%, $p=0.037$). Overall, lipid plaques in segments with low ESS had a thinner fibrous cap (115 μm [63–166] vs. 170 μm [107–219], $p=0.004$), a greater number of cross-sections with lipid plaque (4.8±6.1 vs. 2.8±4.5, $p=0.021$), a greater lipid arc (101° [85–123] vs. 85° [71–95], $p=0.025$), and higher OCT-derived macrophage density (normalized standard deviation, NSD: 8.4% [4.8–12.6] vs. 6.2% [4.2–8.8], $p=0.017$). Segments with low ESS had more superficial calcifications (minimum calcification depth: 93 μm [50–140] vs. 152 μm [105–258], $p=0.049$), and tended to have higher prevalence of spotty calcifications (26.0% vs. 12.0%, $p=0.076$).

Conclusions: The present study shows that coronary regions exposed to low ESS are characterized by larger lipid burden, thinner fibrous cap, and higher prevalence of TCFA, suggesting a critical role of low ESS in the development of high-risk plaques in humans. In vivo combined assessment of coronary local ESS and plaque features may enable the early identification of high-risk lesions and provide opportunities for selective, pre-emptive local interventions.

1790 | BENCH

CD4+CD28null T cells are enriched at the culprit lesion site in STE-ACS and promote NET production

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Background: ST-elevation acute coronary syndrome (STE-ACS) is among the leading causes of death. Acute coronary atherothrombosis as the underlying event is still poorly understood. We hypothesized that circulating leukocytes adhere to atherosclerotic plaques and mediate thrombotic occlusion. It has been shown that circulating CD4+CD28null T cells, which release high levels of granzyme B and perforin, are increased in STE-ACS, especially in patients suffering from diabetes and/or recurrent cardiovascular events. Neutrophil extracellular traps (NETs) released by activated polymorphonuclear neutrophils (PMNs) have been shown to be a crucial component in thrombogenesis. We characterized CD4+CD28null T cells at the culprit lesion site in STE-ACS patients and tested their impact on NET formation.

Methods: We included 150 STE-ACS patients who underwent primary percutaneous coronary intervention at the Vienna General Hospital. Culprit site blood and solid thrombus material were collected during thrombectomy. In parallel, a blood sample from the femoral arterial sheath was collected. Flow cytometry was employed to measure CD4+CD28null T cells in whole blood and solid thrombus specimens. Granzyme B and perforin levels were determined in plasma by ELISA technique. Isolated PMNs were stimulated with granzyme B and/or PMA, and NET formation was assessed by immunohistochemistry.

Results: CD4+CD28null T cells were increased at the culprit lesion site both in coronary whole blood and the solid thrombus, compared with peripheral blood ($n=106$, $p<0.0001$, 7.79±9.68 vs. 9.92±11.44% of CD4+ cells; $n=20$, $p<0.01$, 8.14±10.08 vs. 13.6±14.12% of CD4+ cells). Perforin and granzyme B were decreased in coronary CD4+CD28null T cells and correlated inversely with granzyme B levels in culprit site plasma. Granzyme B induced netosis of PMNs in vitro.

Conclusion: Granzyme B/Perforin-releasing CD4+CD28null T cells accumulate at the culprit lesion site in STE-ACS, and may directly induce NETosis. Further experiments will evaluate the significance of this finding in the pathogenesis of acute coronary syndromes.

1791 | BENCH

Shedding of syndecan-4 from vascular endothelial cells induces endothelial dysfunction and impaired angiogenesis in diabetes mellitus

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Purpose: Syndecan4 (synd4), a ubiquitous cell surface heparin sulfate proteoglycan, functions as an independent receptor for numerous cellular processes. In the study, we investigated whether synd4 shed from vascular endothelial cells in diabetes mellitus (DM) and the role in the pathogenesis of impaired angiogenesis.

Methods: We detected the concentration of synd4 in the plasma of fifty type 2 DM patients by enzyme-linked immunosorbent assay (ELISA). Then we analyzed the change of soluble synd4 once a week in DM rats by ELISA and synd4 staining in endothelial cells of aorta after the sacrifice. Human umbilical vein endothelial cells (HUVECs) were used to assess the mechanism of synd4 shedding. Advanced glycation end products (AGEs) were added to stimulate synd4 shedding. Matrigel plug premixed with bFGF was injected subcutaneously in DM, synd4-/-, and wild type mice. After one week of the procedure, the level of angiogenesis was viewed by staining using Masson's Trichrome. We also use aortic ring assays to evaluate the angiogenesis of these mice and transfected the aortic rings using Ad-synd4 to rescue the impaired angiogenesis in DM mice. Finally, we observed the migration of AGEs-elicited and synd4 knockdown HUVECs using a 2D-chemotaxis slide in a live cell system.

Results: Plasma concentration of soluble synd4 of the diabetic was extremely low when comparing to the health. Soluble synd4 concentration of the type 2 DM rats was higher than that of the normal ones in the 1 week and declined to lower in the 13 weeks after onset of DM. We also confirmed that synd4 on endothelial cells of the aorta in diabetic rats was diminished at the same time by immunohistochemistry. We found that synd4 shed from HUVECs in the presence of 200 $\mu\text{g/ml}$ AGEs and when pretreatment with anti-RAGE antibody and NAC (a ROS inhibitor), the shedding was limited. When synd4 was exhausted from endothelial cells, the angiogenesis was impaired. In both the matrigel plug assay and aortic ring assay, the neovascularization was impaired in db/db and synd4-/- mice. And re-expressed synd4 could partly rescue the angiogenesis dysfunction in db/db mice. Finally, in the 2D chemotaxis slide, the mobility of AGEs-elicited HUVECs and synd4 knockdown HUVECs was diminishing, which could partly restored by re-expression of synd4.

Conclusion: We have demonstrated that the shedding of synd4 from vascular endothelial cells plays a key role in the diabetes related impairment of angiogenesis and identified synd4 as a potential therapeutic target for the vascular complications of diabetes mellitus.

YOUNG INVESTIGATORS AWARDS SESSION:
THROMBOSIS

1792 | BEDSIDE

Bleeding events and anticoagulation management of atrial fibrillation: follow-up data from the PREFER in AF registry

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Purpose: The last focused update of the ESC guidelines for the management of atrial fibrillation (AF) recommended the use of anticoagulants for the prevention of thromboembolic events for all patients with AF except in those at low risk. In spite of the global benefit of this recommendation, major bleeding remains as one of the most severe and devastating complications associated.

Methods: The PREvention of Thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF) prospectively enrolled unselected patients with AF in Austria, France, Germany, Italy, Spain, Switzerland and the United Kingdom from Jan 2012 to Jan 2013. Here, we report the risk profile in this population and the incidence of bleeding events within 1 year after inclusion.

Results: 7243 patients were enrolled (age 71.5±11 years, 60.1% male) in 461 centres. Baseline stroke risk was high (mean CHA2DS2-VASc score 3.4±1.8) as well as bleeding risk (mean HAS-BLED score 2.0±1.2; 30% of patients ≥3). A high proportion of patients with CHA2DS2-VASc score ≥2 received oral anticoagulants (4793 of 5600, 85.6%), and 70.1% of those with CHA2DS2-VASc score of 1 (468 of 668). About one year after baseline, patients receiving a novel oral anticoagulant treatment (NOAC) compared to patients on vitamin K antagonist (VKA) had a slightly higher incidence of gastrointestinal (GI) bleeding (2.1% vs. 1.2%), intracerebral (IC) bleeding (0.5% vs. 0.2%), other life-threatening major bleeding (1.6% vs. 1.1%) and hospitalizations due to bleeding (4.0% vs. 2.1%). Patients treated with NOACs tended to have a higher bleeding risk than those with VKA (mean HAS-BLED score 1.9 vs. 1.7) and more often presented an active cancer (3.4% vs. 3.2%), previous bleeding events (3.7% vs. 2.2%) or bleeding

predisposition (2.9 vs. 2.2%) as contraindication for oral anticoagulation. Surprisingly, among 766 patients that were under no anticoagulant nor antiplatelet (AP) therapy there was a tendency of a higher incidence of GI, IC and life-threatening bleeding (1.5%, 0.5% and 1.5% respectively) as compared with the VKA group, with 2.7% of hospitalizations secondary to major bleedings despite of an initially low haemorrhagic risk (mean HAS-BLED score of 1.3).

Conclusions: A relative increase in bleeding events was noted in patients treated with NOACs and those with no preventive treatment for AF, as compared with VKAs. Although a previously higher bleeding risk could explain this incidence in the NOAC group, an unexpectedly high number of bleedings remains unsolved for those with neither anticoagulants nor APs.

1793 | BEDSIDE

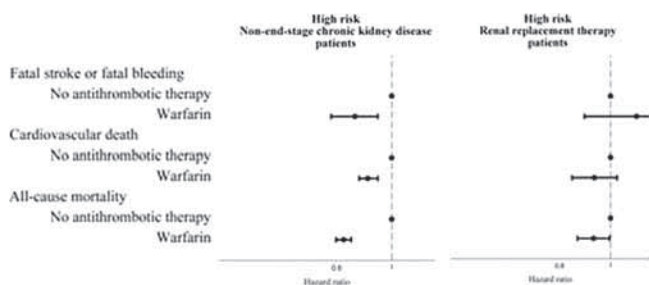
Warfarin is associated with a net clinical benefit in patients with atrial fibrillation and chronic kidney disease

A. Nissen Bonde¹, G.Y.H. Lip², P.R. Hansen¹, M. Lamberts¹, K. Hommel³, A.L. Kamper³, M. Lock Hansen¹, G.H. Gislason¹, C. Torp-Pedersen⁴, J.B. Olesen¹. ¹Gentofte University Hospital, Department of Cardiology, Gentofte, Denmark; ²University of Birmingham, Centre for Cardiovascular Sciences, Birmingham, United Kingdom; ³Rigshospitalet - Copenhagen University Hospital, Department of Nephrology, Copenhagen, Denmark; ⁴Aalborg University, Department of Health, Science and Technology, Aalborg, Denmark

Purpose: The balance between stroke reduction and increased bleeding amongst patients with atrial fibrillation (AF) and chronic kidney disease (CKD) is controversial. The purpose of this study was to assess the net clinical benefit of warfarin in patients with AF and CKD in a nationwide cohort.

Methods: By individual-level linkage of nationwide Danish registers, we identified all patients discharged with non-valvular AF from 1997 to 2011. The risk of stroke associated with non-end-stage CKD and end-stage CKD (patients on renal replacement therapy [RRT]), was estimated using Cox regression analyses. The net clinical benefit of warfarin was assessed using four endpoints including a composite endpoint of death or hospitalization from stroke or bleeding; a composite endpoint of fatal stroke or fatal bleeding; cardiovascular death; and death from all causes, respectively.

Results: From a total of 154,259 patients with non-valvular AF, we identified 11,128 patients (7.2%) with non-end-stage CKD and 1728 (1.2%) on RRT. In all CHADS-VASc risk groups, RRT was independently associated with an increased risk of stroke compared to patients without CKD. In RRT patients with CHA2DS2-VASc score ≥ 2 ("High risk", see figure), warfarin was associated with a reduction of death of all causes (hazard ratio 0.85, 95%CI 0.72-0.99). In non-end-stage CKD patients with CHA2DS2-VASc score ≥ 2 , warfarin was associated with a reduction in the composite endpoint of fatal stroke and fatal bleeding (0.71, 0.57-0.88), a reduction in cardiovascular death (0.80, 0.74-0.88), and a reduction in death of all causes (0.64, 0.60-0.69).



Conclusions: CKD increases the risk of stroke across all stroke risk strata in AF patients, and AF patients with CKD and CHA2DS2-VASc score ≥ 2 achieve a net clinical benefit from warfarin treatment.

1794 | BEDSIDE

The impact of thrombus aspiration on mortality in patients treated with primary percutaneous coronary intervention (10,929 patients)

D.A. Jones, K.S. Rathod, D.I. Bromage, A. Mathur, A. Wragg on behalf of London Heart Attack Group. *Barts Health NHS Trust, London, United Kingdom*

Background: The clinical effect of routine thrombus aspiration before primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) is uncertain. We aimed to assess the impact of thrombus aspiration on mortality in patients with STEMI treated with PPCI.

Methods: We undertook an observational cohort study of 10,929 STEMI patients treated with PPCI between 2004-2011 at 8 tertiary cardiac centres. Patient's details were recorded at the time of the procedure into local databases using the British Cardiac Intervention Society (BCIS) PCI dataset. Anonymous datasets from the 8 centres were merged for analysis. The primary end-point was all-cause mortality at a median follow-up of 3.0 years (IQR range: 1.2-4.6 years).

Results: 3572 (32.7%) patients underwent thrombus aspiration. Patients who had thrombus aspiration were significantly younger (60.8 vs. 63.0 years; $P < 0.0001$), had lower rates of prior MI (11.9% vs. 17.9%; $P < 0.0001$) but higher rates of poor

LV function (8.1% vs. 5.6%); $P < 0.0001$. Procedural success (defined as TIMI 3 flow at the end of procedure) was found to be significantly more likely in patients undergoing thrombus aspiration (89.5% vs. 86.7%; $P = 0.005$). Kaplan-Meier analysis demonstrated no difference in mortality rates between patients with and without thrombus aspiration (14.8% aspiration vs 15.3% PCI only, $P = 0.737$) (Fig. 1) during the follow-up period. After both multivariate cox analysis (HR: 0.89, 95% CI 0.65-1.23) and propensity matching (HR 0.85 95% CI 0.60-1.20) thrombus aspiration was not associated with decreased mortality.

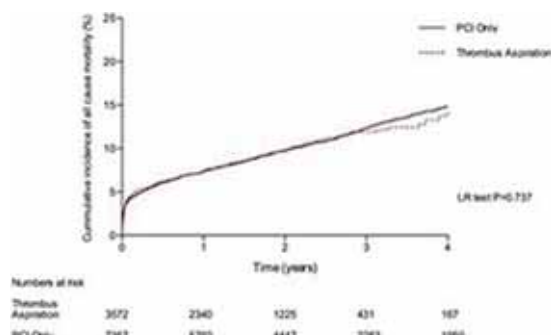


Figure 1

Conclusions: Routine thrombus aspiration does not appear to be associated with reduced long-term mortality in patients undergoing PPCI.

1795 | BEDSIDE

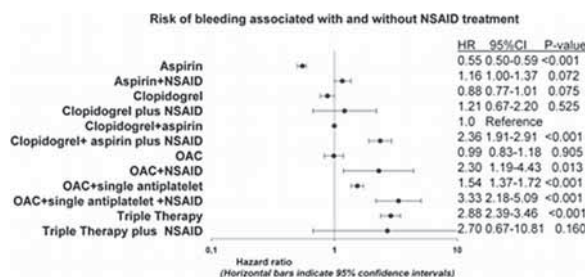
Impact of NSAID treatment on bleeding risk after myocardial infarction in patients treated with different combinations of aspirin, clopidogrel, or vitamin k antagonist - a Nationwide study

A.M. Olsen¹, M. Lamberts¹, E.L. Fosbol², R. Sorensen¹, M.L. Hansen¹, L. Kober², C. Torp-Pedersen³, G. Gislason¹. ¹Copenhagen University Hospital Gentofte, Department of Cardiology, Hellerup, Denmark; ²Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; ³Aalborg University, Department of Health, Science and Technology, Aalborg, Denmark

Purpose: Antithrombotic treatment is indicated in patients after myocardial infarction (MI) and concomitant NSAID use could pose safety concerns. We examined the risk of bleeding with ongoing antithrombotic and NSAID therapy in patients with prior MI.

Methods: Using nationwide administrative registries we studied patients aged ≥ 30 years admitted with first-time MI 2002-2010. Subsequent treatment with aspirin, clopidogrel, or vitamin K antagonist and their combinations, as well as ongoing concomitant NSAID use, was determined. Risk of fatal and non-fatal bleeding with and without NSAIDs was calculated in adjusted time-dependent Cox regression models.

Results: Of 56,668 patients (mean age 68 [SD] years; 65% men), 38% filled at least one NSAID prescription after hospitalization from MI. Bleeding requiring hospitalization occurred in 5,300 (9.3%). With aspirin plus clopidogrel as reference, the combination of aspirin plus clopidogrel with concomitant NSAID increased bleeding risk, adjusted hazard ratios HR 2.36 (95% CI 1.91-2.91). Similarly, bleeding risk was substantial with NSAID added to single antiplatelet therapy with either aspirin or clopidogrel (see Figure).



Conclusion: The use of any NSAID is associated with increased risk of fatal and non-fatal bleedings in patients following MI regardless of antithrombotic regimen. Physicians should use NSAID treatment with caution in MI patients.

YOUNG INVESTIGATORS AWARDS SESSION: POPULATION SCIENCES

1796 | BEDSIDE

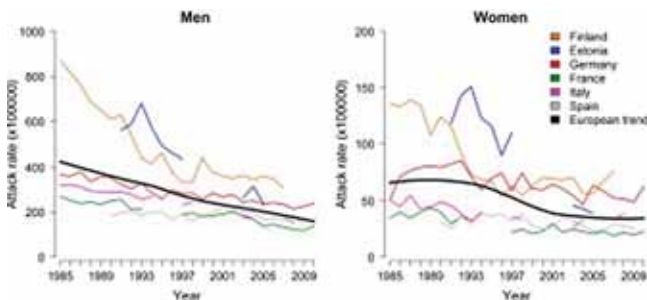
Trends in acute myocardial infarction attack rate, mortality and 28-day case-fatality in 6 European regions in the last 3 decades, the AMITIE Study

I. Roman Degano¹, V. Salomaa², G. Veronesi³, C. Meisinger⁴, J. Ferrieres⁵, T. Laks⁶, R. Elosua¹, J. Marrugat¹ on behalf of the AMITIE Study. ¹Hospital del Mar, Municipal Institute for Medical Research (IMIM), Barcelona, Spain; ²National Institute for Health and Welfare (THL), Department of Chronic Disease Prevention, Helsinki, Finland; ³University of Insubria, Centro Ricerche EPIMED, Epidemiologia e Medicina Preventiva, Varese, Italy; ⁴Hospital Augsburg, MONICA/KORA Myocardial Infarction Registry, Augsburg, Germany; ⁵University Hospital of Toulouse - Rangueil Hospital, Department of Cardiology, Toulouse, France; ⁶Regional Hospital of North Estonia, Department of Internal Medicine, Tallinn, Estonia

Purpose: To analyze trends in acute myocardial infarction (AMI) attack and mortality rates and 28-day case-fatality (CF), in 6 European regions during 1985-2010, and to compare trend estimates by region, age and sex.

Methods: Aggregated data from 8 population AMI registries (6 European countries), including population aged 35-74 years. AMI events, classified according to the WHO-MONICA and AHA/ESC algorithms, included first and recurrent events. Rates were age-standardized for the European population and trends analyzed using negative binomial and joinpoint regression. Annual percentage change (APCs) were obtained for the overall trends and for the trend segments, per country and globally. Differences by sex were examined by the parallelism test.

Results: AMI attack (Figure) and mortality rates and total and in-hospital 28-day CF, decreased consistently in almost all groups over the last 25 years (European APCs for the mentioned indicators in the population of 35-64 years: Men= -3.82%; -5.77%; -2.15%; -3.18%, and women= -3.59%; -5.51%; -2.66%; -4.01%, respectively). The decrease in CF was mainly due to the decrease in in-hospital CF. In most countries, the decrease in attack rates was the major contributor to the mortality decrease in men; while in women, the major contributor was the decrease in CF. The joint European trends showed decreases in AMI attack rate, mortality and 28-day CF, with different APCs for the population aged 35-64 and 65-74 years.



AMI attack rate trends (35-74 years).

Conclusions: Our results showed favorable trends in all analyzed AMI indicators, except for pre-hospital CF, suggesting a positive effect of the in-hospital AMI management, primary and secondary prevention strategies. However, the observed differences in regions, sex, and age groups call for improvement in specific groups and in pre-hospital CF.

1797 | BEDSIDE

Impact of change of body mass index on long-term cardiovascular events and all-cause mortality in patients with Type 2 Diabetes Mellitus

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Background: The relationship between weight change, cardiovascular events and survival in patients with type II diabetes mellitus (T2DM) is equivocal, with reports limited by confounders, size and study duration.

Methods: We investigated the relationship between Body Mass Index (BMI) change and prognosis in 4306 consecutive patients with T2DM without known cardiovascular disease. BMI was measured at baseline and again between 12 and 36 months [Median 20, Interquartile Range (IQR) 10-30 months]. The change in BMI was calculated as percentage of variation from the baseline measurement. Patients were grouped according to six categories of change in BMI: 1-10% or >10% reduction; stable BMI ($\pm 1\%$); 1-10%, 10-20% or >20% increase. Patients were followed for a median of 11.8 (IQR 9.4-14.2) years. Dates of cardiovascular events [acute coronary syndrome (ACS), cerebrovascular accident (CVA), heart failure hospitalisation (HF)] and death were recorded.

A multivariate Cox-Regression analysis including confounders and baseline comorbidity (cancer, lung diseases and chronic renal failure) was performed.

Patients with a very low BMI ($<20 \text{ kg/m}^2$) or who died in the first 5 years were excluded to reduce the influence of occult malignant diseases on weight loss.

Results: Median age was 63 years (IQR 54-72 years), 55% were men and the median BMI at baseline was $28.7 \text{ (IQR } 25.3\text{-}32.1) \text{ kg/m}^2$. In those with a baseline BMI $>35 \text{ kg/m}^2$, a reduction of $>10\%$ was associated with a lower rate of ACS events [Hazard Ratio (HR) 0.24; 95% Confidence Interval (CI) 0.07-0.88; $p<0.05$] but not with a lower mortality rate (HR 1.15 95% CI 0.61 2.16; $p=\text{NS}$). In each other baseline BMI category, a fall in BMI of $>10\%$ was not associated with a lower rate of cardiovascular events but was associated with higher mortality (HR 1.63; 95% CI 1.25-2.13; $p<0.001$).

Finally a BMI increase $>20\%$ was associated with an increased risk of CVA in those with BMI 25-30 kg/m^2 (HR 2.15; 95% 1.0-4.6; $p<0.05$), however, BMI variation was not associated with increased risk of HF.

Conclusions: In markedly obese patients with T2DM, weight loss is associated with a reduced risk of ACS but this does not translate into reduced mortality. In patients who are not markedly obese, weight loss is associated with an increase in mortality. These findings support the hypothesis of an obesity paradox in T2DM, which underlying mechanisms are still unknown.

1798 | BEDSIDE

Syncope is associated with increased risk of motor vehicle accidents- a nationwide study

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Objective: Syncope while driving a motor vehicle may cause serious consequences affecting both the driver and public safety. Therefore our aim is to determine the risk of motor vehicle accidents among a nationwide syncope population compared to the Danish background population.

Methods: In nationwide administrative registers, all Danish residents 18 years and older were followed from 2004 to 2011. Patients who had a diagnosis of syncope were identified and the outcomes were defined as first event of a motor vehicle accident requiring hospitalization or death in traffic accident. Risk models were created using Poisson regression analyses with the total Danish population as the reference.

Results: We identified 64,725 syncope patients who experienced at least 2,077 motor vehicle accidents during a mean follow-up time of 6.7 years. Crude incidence rates (IR) for traffic accident per 1000 person years according to age groups (18-43; 44-69; ≥ 70) were; IR: 16.6, CI: 15.6-17.7, IR: 6.9, CI: 6.3-7.4, IR: 4.5, CI: 4.0-5.0 and IR: 8.6, CI: 8.6-8.7, IR: 4.3, CI: 4.2-4.3, IR: 3.4, CI: 3.4-3.5 for the syncope- and background population respectively. In adjusted Poisson regression models the risk of traffic accidents according to age groups (18-43; 44-69; ≥ 70) were; RR: 1.8, CI: 1.7-1.9 $p<0.001$, RR: 1.5, CI: 1.4-1.7 $p<0.001$ and RR: 1.2, CI: 1.1-1.3 $p<0.001$ compared to the Danish background population.

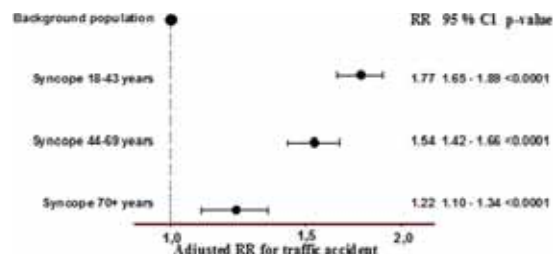


Figure 1

Conclusions: Syncope is associated with an increased risk of motor vehicle accidents and death in traffic accidents compared to the Danish background population with highest relative risk in the younger patients. Increased awareness in risk stratification and fitness to drive after syncope is warranted.

1799 | BEDSIDE

Cardiovascular risk in patients with sleep apnea with or without continuous positive airway pressure therapy among 4.5 million Danes

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Background: The prognostic significance of continuous positive airway pressure (CPAP) therapy and age on cardiovascular risk in patients with sleep apnea (SA) has never been assessed.

Methods: In nationwide databases, the entire Danish population was followed from 2000 until 2011. First-time SA diagnosis and CPAP therapy were determined. The risk of ischemic stroke and myocardial infarction (MI) was analyzed using Poisson regression models adjusted for coexistent cardiovascular medication, CPAP therapy and risk factors.

Results: Among 4.5 million individuals included, 33,727 developed SA (mean age 53 years, 80% males) and hereof 57% were treated with CPAP therapy. Median time to CPAP therapy was 115 days (IQR 35–468). Regardless of CPAP therapy, patients with SA had more comorbidity and were more often prescribed cardiovascular medication. For validation, in 153 randomly selected charts of patients registered with SA, 125 fulfilled the criteria for a SA diagnosis (positive predictive value 82%).

Cardiovascular risk

	General population		Patients with sleep apnea		Effect of CPAP therapy* Estimate (95% CI)
	Incidence rate	Incidence rate ratio	Incidence rate	Incidence rate ratio (95% CI)	
Risk of ischemic stroke (429 events in sleep apnea patients)					
18–49 years	0.4	Reference	1.2	2.41 (1.74–3.35)	0.57 (0.27–1.18)
50–65 years	2.3	Reference	3.2	1.08 (0.89–1.30)	1.08 (0.79–1.46)
65+ years	10.3	Reference	8.3	1.04 (0.88–1.24)	1.15 (0.87–1.51)
Overall	3.1	Reference	3.7	1.30 (1.16–1.47)	1.06 (0.87–1.28)
Risk of myocardial infarction (642 events in sleep apnea patients)					
18–49 years	0.4	Reference	1.8	1.86 (1.38–2.51)	1.10 (0.66–1.84)
50–64 years	2.7	Reference	5.2	1.29 (1.11–1.49)	1.01 (0.79–1.29)
65+ years	13.6	Reference	11.7	1.24 (1.08–1.43)	0.96 (0.75–1.21)
Overall	4.0	Reference	5.5	1.46 (1.32–1.60)	0.99 (0.84–1.16)

All models fully adjusted. Incidence rate per 1000 person-years. (95% CI) denotes 95% confidence interval. *Estimated effect <1 denotes a protective effect of CPAP therapy.

Conclusions: SA is associated with increased risk of ischemic stroke and MI, in particular, in patients younger than 50 years of age. In unselected real-life SA patients, data does not support a significant beneficial effect of CPAP therapy on stroke or MI.

YOUNG INVESTIGATORS AWARDS SESSION: BASIC SCIENCE

1800 | BENCH

MicroRNA-126-containing endothelial microparticles reduce neointimaformation and vascular smooth muscle cell proliferation

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Objective: Vascular smooth muscle cell (VSMC) proliferation is of importance in the pathogenesis of vascular diseases. Endothelial microparticles (EMP) have been shown to promote vascular regeneration by transferring functional microRNAs, but whether they influence VSMC biology is largely unknown. We explored the effect of EMP on neointima formation in a model of acute vascular injury in vivo and on VSMC proliferation and migration in vitro.

Methods and results: After wire injury of the carotid artery, mice were treated systemically with EMP generated from human endothelial cells. Mice treated with EMP showed a significantly reduced neointima formation (0.63 ± 0.03 vs. 0.47 ± 0.04 , $p < 0.05$, $n = 8$). Furthermore, VSMCs treated with EMP displayed significantly reduced proliferation and migration capacities in vitro, both critical steps in neointima formation. Following experiments revealed a time-dependent uptake of EMP into VSMCs in vitro and into the media of perfused vessels in vivo. In order to dissect the underlying mechanisms of EMP-promoted inhibition of VSMC proliferation and neointima formation, Taqman microRNA-array was performed and microRNA (miR)-126 was identified as the predominantly expressed miR in EMP. Furthermore, miR-126 was transported into recipient VSMC by EMP (1 ± 0.05 vs. 1.34 ± 0.05 , $p < 0.05$). Interestingly, expression of miR-126 target protein LRP6, regulating VSMC proliferation, was reduced in VSMCs after EMP treatment. Genetic knockdown of miR-126 in EMP abrogated EMP-mediated inhibition of LRP6 expression and subsequently VSMC migration and proliferation in vitro and neointimaformation in vivo, suggesting a crucial role of miR-126 in EMP-mediated neointima formation reduction. Finally, expression analysis of miR-126 in circulating MPs in 176 patients with coronary artery disease revealed that patients with high level of miR-126 within circulating MPs have a significantly reduced revascularization rate in a 6-year follow up period, supporting a central role for miR-126 in MPs in the regulation of vascular health.

Conclusions: EMP reduce neointima formation in a model of acute arterial injury in vivo and decrease proliferation and migration of vascular smooth muscle cells in vitro. The transfer of miR-126 by EMP and subsequent inhibition of LRP6 expression in VSMCs might be a possible pathway.

1801 | BENCH

Beta3adrenoreceptors protect from hypertrophic remodelling through AMP-activated protein kinase and nitric oxide synthase dependent signaling pathways

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Background: Moderate overexpression of β 3AR in cardiomyocytes attenuates

hypertrophic remodeling in hearts after neurohormonal stress, without impairment of cardiac function.

Methods: Functional analyses were carried out in wild type (WT) and heterozygote transgenic mice with cardiac myocyte-specific over-expression of human β 3AR ($\text{h}\beta$ 3TG) treated for 10 days with isoproterenol (Iso:30mg/kg/d), angiotensin II (AngII: 2mg/kg/d), with/without L-NAME (2mg/mL). In vitro hypertrophic responses to phenylephrine (PE) were analyzed in neonatal rat ventricular myocytes (NRVM) infected with a recombinant adenovirus expressing the human β 3AR (AdVh β 3).

Results: We further dissected the underlying signaling in isolated cardiomyocytes and tissues from $\text{h}\beta$ 3TG mice. Cell fractionation and Proximity Ligation Assay experiments revealed co-localization of β 3AR with constitutive NOS isoforms, eNOS and nNOS and with caveolin-3 in lipid rafts/caveolae, which was unperturbed in hypertrophic myocytes. Adult cardiomyocytes from $\text{h}\beta$ 3TG mice co-expressing β 3AR with the cGMP-sensitive FRET sensor, redcGES-DE5 exhibited higher constitutive, ODQ-sensitive cGMP production compared with WT. Non-specific NOS inhibition (L-NAME) abrogated the β 3AR-mediated protection from hypertrophic remodeling under low dose Iso in vivo and in NRVM. (L-NAME: $728 \pm 30 \mu\text{V}$ vs. L-NAME+Iso: $963 \pm 60 \mu\text{V}$; $p < 0.001$). Interestingly, we observed a L-NAME independent increase in protein synthesis in control cells (152 ± 16 (veh) vs 230 ± 27 (PE); $p < 0.01$), but not in the AdVh β 3 infected NRVM (130 ± 11 (veh) vs 103 ± 12 (PE)). As AMP-activated protein kinase (AMPK) is a known inhibitor of cardiac hypertrophy and protein synthesis, we examined its activation by β 3AR. First, we observed a colocalization of AMPK with β 3AR, eNOS and cav-3. P-Thr162-AMPK was decreased by the PE (0.5 ± 0.1), but restored in β 3AR expressing cells (0.9 ± 0.3 ; $p < 0.05$). siRNA targeting of AMPK also partly abrogated the anti-hypertrophic effect of β 3AR in response to PE. Moreover, AMPK is also an inducer of autophagy. In NRVM, β 3AR overexpression restored autophagy that was decreased by PE in ctrl cells in vitro, as measured by LC3-II/LC3-I and p62 abundance (LC3II/I ratio under PE: 0.4 ± 0.04 (GFP), 1.12 ± 0.1 ($\text{h}\beta$ 3TG), $p < 0.05$); likewise autophagy was restored in $\text{h}\beta$ 3TG mice after TAC compared with WT (LC3II/I ratio: 0.5 ± 0.1 (WT), 1.3 ± 0.3 ($\text{h}\beta$ 3TG), $p < 0.05$).

Conclusions: We conclude that β 3AR is part of a caveolar signalosome involving nNOS, eNOS and AMPK in cardiomyocytes, from which it activates both cGMP/PKG and AMPK-dependent pathways to prevent hypertrophic remodeling and maintain autophagy in the face of neurohormonal stress.

1802 | BENCH

Unique epigenetic and transcriptional regulation of induced pluripotent stem cells in patients with hypoplastic left heart syndrome

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Background: Although a number of studies have uncovered heterozygous mutations in cardiac regulatory genes caused hypoplastic left heart syndrome (HLHS), the genetic basis of HLHS remains unknown. The aim of this study is to determine the epigenetic and transcriptional network responsible for myocardial patterning and morphogenesis during cardiac development by using patient-derived induced pluripotent stem (iPS) cells.

Methods: Cardiac progenitor cells (CPCs) were isolated and two-independent iPS cell lines were generated from both HLHS and BV heart-derived CPCs, respectively. Global gene expression of HLHS- and biventricle (BV) heart-derived iPS cells was analyzed to dissect the complex genetic circuits by using human embryonic stem and iPS cells (201B7) as controls. Real-Time RT-PCR, mutation analysis, ChIP assay, and cardiac-specific gene promoter activity were examined and compared.

Results: We found one synonymous single nucleotide polymorphism in NKX2-5 and five in NOTCH1, respectively. Cardiac transcriptional factors such as NKX2-5 and HAND1, known to drive cardiac growth and morphogenesis through primary heart field development, were significantly downregulated in HLHS-derived iPS cells after differentiation compared with their levels in control 201B7 iPS- and BV-iPS-derived cardiomyocytes. ChIP assay showed that a marked decrease in dimethylated histone H3-lysine 4 and acetylated histone H3 was found within the NKX2-5 promoter regions in differentiated HLHS-derived iPS cells compared with those from BV patient. We also identified a significantly increased trimethylated H3-lysine 27 in the differentiated HLHS-derived iPS cells. In addition, NOTCH/HEY expressions were markedly reduced, those may be responsible for the obstruction in the regions of atrioventricular and outflow tract myocardium. To specify the target transcripts responsible for cardiac development of HLHS, cardiac troponin-T (TNNT2) promoter analysis was performed. Obviously, TNNT2 promoter activity was suppressed in HLHS-derived CPCs and iPS cells compared with those from BV hearts. These repressed promoter activities could be fully restored by transient transfection of NKX2-5, HAND1, and NOTCH1 genes into these stem/progenitor cells by synergistic fashion.

Conclusions: These findings suggest that patient-specific iPS cells may provide potential molecular insights to dissect the complex cardiac malformations in human. The epigenetic and transcriptional regulation of NKX2-5, HAND1, and NOTCH1 may play a crucial role in the development of myocardial growth, patterning, and morphogenesis in HLHS.

1803 | BENCH**Prolyl-isomerase-1 (Pin1) causes endothelial dysfunction and vascular inflammation in diabetes: a study in mice and humans**

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Purpose: Prolyl-isomerase-1 (Pin1) regulates function of protein substrates through isomerization of peptide bonds that link phosphoserine or phosphothreonine to proline. Pin1 triggers reactive oxygen species (ROS) production and inflammation in human cancer. Whether Pin1 is involved in cardiovascular disease remains largely unknown. This study investigates the role of Pin1 in diabetes-related vascular dysfunction.

Methods: Four to six months old male C57BL/6 WT and Pin1 knockout (Pin1^{-/-}) mice were used. Diabetes was induced by streptozocin and animals were followed for 30 days. Endothelial function was studied by dose-response curve with acetylcholine (10⁻⁹ to 10⁻⁶ mol/L). Mitochondrial ROS were measured by ESR spectroscopy. Immunoprecipitation was performed to show the interaction of Pin1 with phosphorylated p66Shc and NFκB p65 subunit. In parallel, Pin1 gene expression was assessed in peripheral blood monocytes (PBM) of 30 patients with type 2 diabetes (T2DM) and 18 healthy age-matched controls. Flow-mediated vasodilation (FMD) of the brachial artery, urinary levels of 8-isoprostaglandinF2α (8-isoPGF2α) and plasma adhesion molecules VCAM-1, ICAM-1 and MCP-1 were correlated with Pin1 gene expression. Between-variable correlations were measured by Spearman's analysis. Probability values less than 0.05 were considered statistically significant.

Results: Pin1 expression markedly increased in aortas of diabetic as compared with control mice (216±32% vs. controls, p<0.05). Immunoprecipitation showed that Pin1 recognizes phosphoserine motifs of pro-oxidant mitochondrial adaptor p66Shc and NFκB subunit p65 in the vasculature of diabetic mice. Indeed, genetic deletion of Pin1 prevented p66Shc-induced ROS production, endothelial dysfunction and NF-κB-driven upregulation of adhesion molecules VCAM-1, ICAM-1 and MCP-1. Of note, Pin1 mRNA was significantly upregulated in PBM of T2DM patients as compared with healthy controls (AU, 370±97 vs. 25±28, p<0.01). Pin1 upregulation correlated with glycated haemoglobin (r=0.44, p<0.05), FMD (r=-0.36, p<0.01), urinary 8-isoPGF2α (r=0.39, p<0.05), VCAM-1 (r=0.56, p<0.05) and ICAM-1 (r=0.53, p<0.05).

Conclusions: Pin1 drives diabetic vascular disease via mitochondrial oxidative stress and NF-κB-induced inflammation. These findings provide molecular insights for novel mechanism-based therapeutic strategies in patients with diabetes.

NURSING AND ALLIED HEALTH PROFESSIONALS INVESTIGATOR AWARD

1804 | SPOTLIGHT**Proof of concept study in nurse-led integrated chronic atrial fibrillation management**

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Purpose: Atrial Fibrillation (AF) is considered the epidemic of the new millennium. The current care is fragmented and given the aging of the population unsustainable. Therefore we developed an Integrated Chronic Care program in AF and a specialised AF-Clinic accordingly. In this study, we evaluated the efficacy and feasibility of this approach by means of a proof of concept study.

Methods: The program consists of 4 interconnected pillars: task substitution, evidence based guidelines, dedicated software, and peer-based supervision. In this program, care management is led by a nurse in close collaboration with a cardiologist, provided according to guidelines and supported by an electronic decision support system. In a RCT, 712 AF patients were randomly assigned to the AF-Clinic or Usual Care (regular care by a cardiologist). Follow-up was at least 12 months. We evaluated efficacy of the program in terms of cardiovascular (CV) hospitalization or death; cost-effectiveness (costs per QALY and per life year); guideline adherent management; quality of life, including anxiety and depression (SF-36 and HADS questionnaires). Further, we assessed patient knowledge by using the AF Knowledge Scale that was developed and validated as part of this study.

Results: The occurrence of CV hospitalization or death was significantly lower in the AF-Clinic (51 pts -14.3%) compared to Usual Care (74 pts -20.8%) demonstrating a 35% relative risk reduction, guideline adherence was significantly improved respectively. Patient knowledge improved over time and was significantly higher at follow-up in the AF-Clinic compared to Usual Care. Quality of life scores improved over time, without significant differences between groups. Finally, cost-effectiveness analysis demonstrated a 0.009 QALY gain with a reduced cost of € 1109 per patient and 0.02 life years gain with a reduced cost of € 735 per patient, in favour of the AF-Clinic.

Conclusions: We demonstrated efficacy of the Integrated Chronic Care program

in AF. Moreover, working according to this program revealed important challenges for comprehensive redesigning AF care, including: 1) prevention of inadequate diagnostic and therapeutic CV management, 2) prevention of AF-related complications and reduction of CV hospitalization and death accordingly, 3) addressing the importance of patient knowledge in activating patient self-management roles, 4) patient satisfaction issues and, 5) overcoming of exceptional high healthcare costs. These challenges can significantly contribute in controlling the AF epidemic and should become part of international guidelines for AF management.

1805 | BEDSIDE**Effects of a decision aid and additional decisional counselling on cardiac risk reduction behaviour and health outcomes: randomised controlled trial**

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Purpose: To evaluate the effects of a Decision Aid for cardiac patients with and without an additional individual decisional counselling on health outcomes and health-related quality of life mediated by adherence to cardiac risk reduction behaviour.

Methods: Design: Prospective, 3-group RCT with 4 repeated measures over 6 months.

Participants and setting: 363 patients referred to Cardiac Outpatient Clinic in Norway, being examined for coronary artery disease by an angiogram. Interventions: The intervention group I (N=121) received, for taking home, the Decision Aid prior to their scheduled angiogram; the intervention group II (N=121) in addition to the Decision Aid received an individual decisional counselling from a trained nurse counsellor in their homes prior to their angiogram; and the control group (N=121) who received "the usual care". Main outcome measures: Body Mass Index, cholesterol, blood pressure, amount of tobacco, and health-related quality of life (primary outcomes), the adherence to cardiac risk reduction behaviour (intermediate outcome), and knowledge, benefits and barriers of cardiac risk reduction behaviour, and health beliefs (mediating variables).

Results: There were no significant differences between intervention group I and the control group on any variables. Intervention group II however, had a significant decrease in Body Mass Index (p=.016), and significantly improved health-related quality of life on several dimensions: role functioning physical (p=.021), general health (p=.049), vitality (p=.025), role function limitation (p=.022) and disease perception (p=.006) compared to the control group six months after the intervention. There were no significant differences in adherence to cardiac risk reduction behaviour between any of the groups. There was a significant decrease in scores of barriers to cardiac risk reduction behavior in intervention group II compared to the control group (p=.020) at two months following the angiogram.

Conclusions: In this study the Decision Aid alone did not improve health behaviours and outcomes. Combining a Decision Aid with additional decisional counselling supported patients to individually tailor their cardiac risk reduction behaviour to their health beliefs and preferences, resulting in better health outcomes and health-related quality of life. We do not know however, if these effects would have occurred by the counselling alone, without combining it with the Decision Aid.

1806 | BEDSIDE**Heart failure medication adherence interventions: meta-analysis of adherence outcomes**

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Purpose: Adherence to medications is an essential part of heart failure (HF) self-care. Unfortunately, about half of patients taking long-term medications are non-adherent. For HF patients, medication non-adherence can lead to increased rates of exacerbation causing hospitalizations and increased morbidity and mortality. This meta-analysis aimed to synthesize the medication adherence (MA) outcomes of interventions to improve adherence to HF medications. In addition to identifying the mean improvement in MA, exploratory moderator analyses permit evaluation of demographic, methodological, and intervention components related to larger MA effect sizes.

Methods: Comprehensive search methods (electronic databases, journal hand searches, grey literature searching, etc.) were used to identify studies testing interventions designed to improve MA among patients with HF. Data from eligible studies were independently coded by two coders and analyzed using random-effects meta-analysis methods. Moderator analyses to explain heterogeneity among the studies were conducted using meta-analytic analogues of regression and ANOVA for moderators with sufficient numbers of comparisons.

Results: Searching yielded 6665 potential study reports. From these studies, we identified 29 eligible treatment versus control comparisons of MA interventions in samples of HF patients with sufficient data for coding MA outcomes (total n=4285). The mean effect size (d-index) for two-group comparisons was 0.28 (S.E.=0.096, p=.004). Heterogeneity among studies (Q=150.58, p<.001) warranted moderator analyses which found significant differences due to mean age (β=0.018, p=.003), percentage of women (β=0.008, p=.006), and the number of days from the end of the intervention until the outcome measurement (β=0.001,

$p=.045$). MA effect sizes were larger for studies conducted in Europe or Asia vs. North America (0.79 vs. -0.04, $p<.001$). Smaller effect sizes were seen for interventions with components directed at health care providers (-0.12 vs. 0.24, $p<.001$), and those including social support as an intervention component (-0.02 vs. 0.42, $p=.010$).

Conclusion: While the mean adherence effect size across all studies was significant, the effect was modest, indicating that further work is needed to develop and implement more efficacious adherence interventions among HF patients. While this synthesis is limited due to the under-reporting of MA outcomes in studies designed to improve MA, the included studies shed light on the continuing need to develop more effective interventions to improve MA interventions as part of approaches to HF self-care.

HIGH PLATELET REACTIVITY: MECHANISMS AND CLINICAL IMPLICATIONS

1910 | BEDSIDE

Efficacy of prasugrel in resuscitated patients during therapeutic hypothermia after percutaneous coronary intervention for acute myocardial infarction

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Background: Acute myocardial infarction (AMI) is the leading cause for out-of-hospital cardiac arrest. Therapeutic hypothermia substantially improves neurological outcome. However, cardiogenic shock, post resuscitation syndrome as well as hypothermia markedly reduce platelet inhibition by the thienopyridine clopidogrel. Prasugrel, a more potent thienopyridine, achieves better platelet inhibition than clopidogrel, particularly in haemodynamic stable AMI patients. Efficacy of prasugrel during therapeutic hypothermia after resuscitation has not yet been evaluated.

Methods: We investigated 21 consecutive patients (mean age 62 ± 2 years) admitted to our department following out-of-hospital cardiopulmonary resuscitation during AMI, who underwent urgent revascularization and immediate therapeutic hypothermia for 24 hours. Prasugrel efficacy was assessed by the platelet-reactivity-index (PRI; VASP assay) before and 2, 4, 6, 12, 24, 48, and 72 hours following a loading dose of 60mg via a gastric tube.

Results: During the observed period, prasugrel highly significantly reduced platelet reactivity determined by PRI despite intensive hypothermia ($p=0.0002$). In detail, mean PRI ($\pm$ SEM) was $70\pm 3\%$ before (control) and $62\pm 3\%$ at 2h (n.s. vs. control), $54\pm 5\%$ at 4h ($p<0.05$ vs. control), $44\pm 6\%$ at 6h ($p<0.01$ vs. control), $39\pm 5\%$ at 12h ($p<0.01$ vs. control), $29\pm 5\%$ at 24h ($p<0.01$ vs. control), $18\pm 4\%$ at 48h ($p<0.01$ vs. control), and $13\pm 3\%$ at 72h ($p<0.01$ vs. control) after loading.

Conclusion: In contrast to previous reports describing lack of effect of clopidogrel on platelet reactivity in resuscitated patients during therapeutic hypothermia after percutaneous coronary intervention for acute myocardial infarction, prasugrel rapidly and significantly reduced platelet reactivity even despite disturbed haemodynamic conditions, vasopressor use and therapeutic hypothermia. Prasugrel given via a gastric tube might therefore be a useful therapeutic strategy in this patient cohort at high risk, to provide strong and effective P2Y₁₂ inhibition.

1911 | BEDSIDE

Effectiveness of switching prasugrel's low responders to ticagrelor after acute coronary syndrome

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Purpose: This study aimed to assess the effectiveness and safety of switching from Prasugrel to Ticagrelor patients identified as Prasugrel low-responders one month after ACS.

Methods: 540 patients admitted for ACS with coronary stent implantation and discharged on Prasugrel 10mg were screened. Prasugrel response was assessed one month after discharge using Platelet Reactivity Index Vasodilator Stimulated Phosphoprotein (PRI VASP). High on-Treatment Platelet Reactivity (HTPR) was defined as PRI VASP $> 50\%$. Patients with HTPR were enrolled and switched to Ticagrelor 90 mg twice a day. They were re-tested a month later. The primary endpoint was defined as: comparison of degree of platelet inhibition and incidence of HTPR one month after switching to Ticagrelor 180 mg daily in patients with HTPR on Prasugrel therapy. The safety endpoint was the incidence of non access-site bleeding complications under Ticagrelor as compared with Prasugrel therapy, using the Bleeding Academic Research Consensus definition.

Results: Between March 2010 and November 2013, 22 patients were defined as HTPR on Prasugrel 10 mg one month after ACS, with a mean PRI VASP of 55.3%. Among these patients, 16 were switched to Ticagrelor 180 mg daily and, at one month, we observed a significant decrease in PRI VASP, with a mean value at 21.7% ($p<0.001$). No patients remained HTPR and 4 patients (25%) were identified as Very Low on-Treatment Platelet Reactivity (VLTPR) (PRI VASP $< 10\%$). No ischemic events were reported after switching, while 3 patients (18.7%) suffered from bleeding complications (2 BARC1 and 1 BARC2 bleedings) during Ticagrelor therapy.

Conclusion: Switch to Ticagrelor in Prasugrel's "low responders" patients is an effective strategy, leading to an adequate platelet inhibition in a large majority of patients. This biological tailored approach could be useful in preventing ischemic complications, in this specific high risk population, potentially increasing bleeding risk. This hypothesis needs to be confirmed in large clinical studies.

1912 | BEDSIDE

Antiplatelet efficacy of P2Y₁₂ inhibitors (prasugrel, ticagrelor, clopidogrel) in patients treated by therapeutic hypothermia after cardiac arrest for acute myocardial infarction

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Background: The survivors after out-of-hospital cardiac arrest (OHCA) who have electrocardiographic criteria for acute myocardial infarction (AMI) should undergo immediate coronary angiography with subsequent PCI, if indicated and then receive dual antiplatelet therapy (DAPT). Therapeutic hypothermia (TH) 32-34°C is recommended for unconscious patients after OHCA for improvement of neurological outcome and survival. TH can attenuate the effectiveness of P2Y₁₂ inhibitors due to reduction of gastrointestinal absorption, reduction of metabolic activation of prodrugs and due to increased platelet aggregation. The combined effect of these conditions on platelet inhibition efficacy of P2Y₁₂ inhibitors is unknown but there is growing evidence that insufficient response to antiplatelet therapy is associated with increased risk of thrombotic complications after PCI. The aim of this study was to compare antiplatelet efficacy of prasugrel, ticagrelor and clopidogrel in patients after OHCA for AMI treated with TH.

Methods: In single center, prospective study were enrolled 65 patients after OHCA for AMI. The subgroup of 32 pts. who underwent PCI, receive DAPT, underwent TH (32-34°C for 24 h) and survived more than 3 days was analyzed. Group A (n=20 pts.) receive prasugrel or ticagrelor and group B (n=12 pts.) receive clopidogrel via nasogastric tube. Platelet reactivity index (PRI-VASP) was measured on day 1, 2 and 3 after drug administration. A PRI-VASP under 50% is defined as effective platelet inhibition.

Results: In the group A was median values PRI-VASP significant lower compared to the group B in all monitored days (26% vs. 79% on day 1; 18% vs. 81% on day 2; 19% vs. 76% on day 3; $p<0.001$). The number of patients with high on-treatment platelet reactivity (PRI-VASP $> 50\%$) was in group A vs. B 22% vs. 82% on day 1, 16% vs. 82% on day 2, 5% vs. 83% on day 3; $p<0.001$.

Conclusion: Prasugrel and ticagrelor, but not clopidogrel, is very effective also in terms of therapeutic hypothermia in patients after OHCA for AMI. Further studies are needed to confirm the association with early- and late- term risk of thrombotic complications.

1913 | BEDSIDE

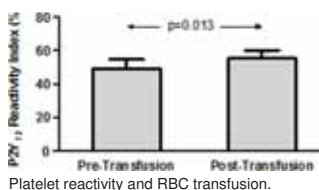
Platelet reactivity is increased after red blood cell transfusion, with greater effect in subjects on dual antiplatelet therapy

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Background: Red blood cell (RBC) transfusion is a predictor of recurrent ischemic events and mortality in patients with an acute coronary syndrome. A possible mechanism is an enhancement of platelet activation and aggregation after RBC transfusion in these subjects. The objective of the present investigation was to assess if RBC transfusion enhances platelet reactivity in patients with and without antiplatelet therapy.

Methods: Pharmacodynamic study that included patients undergoing RBC transfusion as per clinical indication. Subjects could be receiving or not antiplatelet therapy. Platelet reactivity was evaluated at two time points: a) pre: immediately before transfusion; and 2) post: 15-30 minutes after transfusion of the first RBC pack was finished. Platelet function assays included: a) Vasodilator-Stimulated Phosphoprotein analysis (primary end point) expressed as P2Y₁₂ reactivity index (PRI); b) Multiple electrode aggregometry; and c) Light transmission aggregometry.

Results: Preliminary results of the first 18 patients included are presented. Greater platelet reactivity measured by VASP was observed after transfusion of one RBC pack (pre: 48.9 ± 5.6 vs. post: 55.1 ± 5.0 ; $p=0.013$) (Figure). This effect was observed to a greater extent in patients with dual antiplatelet therapy (DAPT) with aspirin and clopidogrel (n=9; 32.4 ± 6.8 vs. 40.9 ± 5.8 ; $p=0.042$) than in those without antiplatelet treatment or aspirin monotherapy (6 and 3 subjects, respec-



tively; 65.4 ± 4.4 vs. 69.3 ± 4.8 ; $p=0.20$). Similar results were obtained with the other platelet function assays (ADP stimulus).

Conclusion: Platelet reactivity is increased after red blood cell transfusion irrespective of antiplatelet therapy, although this effect may be of greater magnitude in patients on DAPT.

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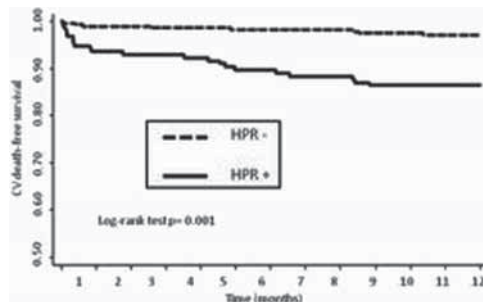
High residual platelet reactivity after clopidogrel 600 mg loading dose and 1 year mortality after drug-eluting stenting for unprotected left main coronary disease

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Background: Identifying predictors related to poor outcome in patients with unprotected left main coronary artery (ULMCA) stenosis treated with percutaneous coronary intervention (PCI) might help to improve therapeutic strategies. Objectives: The aim of this study was to investigate the impact of high on-treatment residual platelet reactivity (HPR) in patients with ULMCA stenosis treated with drug eluting stent (DES) implantation.

Methods: In this observational study, we analyzed data from patients who underwent ULMCA PCI and had prospective platelet reactivity assessment by light transmission aggregometry after a loading dose of 600 mg of clopidogrel. The primary end point of the study was cardiac mortality and the secondary endpoints were stent thrombosis (ST) and major adverse cardiac events (MACE).

Results: From July 2005 to December 2012, 434 patients were included (mean age 75.8 ± 11). The incidence of HPR after clopidogrel loading was 35.9% (HPR+ group). The estimated 1-year cardiovascular mortality was 6.7% in the overall population, 13.5% in the HPR+ group and 2.9% in patients without HPR (HPR- group) ($p<0.001$). The 1-year ST rate was 5% in the overall population, 9% in the HPR+ group and 2.9% in the HPR- group ($p<0.001$). A multivariate analysis showed that independent predictors of 1 year cardiac mortality were HPR (hazard ratio=5.05; confidence interval, 2.13-11.97; $p=0.001$), renal failure (HR=3.4; CI, 1.10-10.55; $p=0.034$), NYHA III/IV (HR=4.34; CI, 1.99-9.47; $p=0.001$) and atrial fibrillation (HR=2.59; CI, 1.14-5.88; $p=0.023$). HPR was also related to ST occurrence (HR=2.77; CI, 1.20-6.40; $p=0.017$).



Survival free from cardiovascular death.

Conclusions: HPR after 600 mg loading dose of clopidogrel is a strong marker of 1 year mortality and stent thrombosis in patients receiving DES for ULMCA.

1915 | BEDSIDE

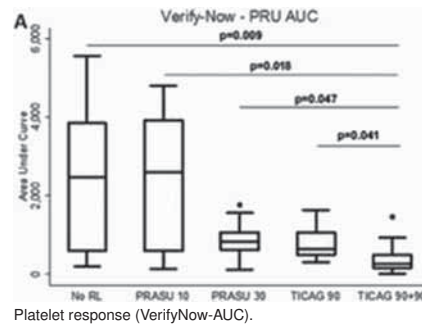
Switching patients from clopidogrel to novel P2Y12 receptor inhibitors in acute coronary syndrome: comparative effects of prasugrel and ticagrelor

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Background: Patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) commonly receive clopidogrel prior to angiography. Switching these patients to prasugrel or ticagrelor therapy may be desirable because higher platelet inhibition is expected. Objective: The present study aimed to assess the pharmacodynamic response to different reloading (RL) doses of prasugrel or ticagrelor in ACS patients previously treated with clopidogrel.

Methods: In this prospective single-centre study, we compared platelet reactivity in 50 patients treated with clopidogrel 600 mg within 5 hours and allocated to one of 5 following strategies: no switching, switching to prasugrel 10 mg, switching to ticagrelor 90 mg, RL with prasugrel 30 mg, or RL with ticagrelor 180 mg. Platelet function was assessed using VerifyNow P2Y12 Reaction Units (PRU) and Platelet Reactivity Index vasodilator-stimulated phosphoprotein phosphorylation (PRI-VASP) at 3 different times: at inclusion (before switching) and then $4h \pm 1$ (T2) and $24h \pm 4$ (T3) after inclusion. Areas under the platelet reactivity-time curves (AUC) were calculated.

Results: According to VerifyNow assay, RL with ticagrelor 180 mg lead to very low platelet reactivity at T2 (median PRU = 4 [2-6]) and T3 (PRU = [4 3-5]). PRU-AUC in this group were lower compared with clopidogrel alone ($p=0.009$), but



also compared with prasugrel 30 mg RL ($p=0.046$). Comparable findings were obtained with VASP assay.

Conclusions: In addition to clopidogrel 600 mg, RL with ticagrelor 180 mg led to greater platelet inhibition compared with the other strategies in ACS patients undergoing PCI.

1916 | BEDSIDE

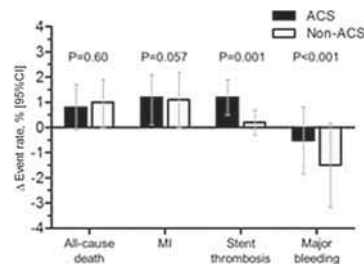
Patients receiving drug-eluting stents for stable coronary disease in the ADAPT-DES study: Impact of clopidogrel platelet reactivity on clinical outcomes

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ADAPT-DES was a large scale prospective multicentre registry study which demonstrated that high platelet reactivity (HPR) on clopidogrel was strongly related to the 1-year incidence of stent thrombosis (ST) and of myocardial infarction (MI) after successful implantation of DES, was inversely related to major bleeding, and was unrelated to mortality. Whether the impact of clopidogrel hyporesponsiveness may differ between patients presenting with acute coronary syndromes (ACS) and stable patients (non-ACS) is unknown.

A pre-specified secondary analysis of ADAPT-DES was performed in patients with ACS vs. non-ACS. Platelet reactivity was tested the day following DES-PCI using the VerifyNow P2Y12 assay.

Of 8449 pts. enrolled, 4101 (49%) presented with non-ACS. In pts. with non-ACS vs. ACS the 1-year rates of ST were 0.5% vs. 1.1% respectively ($P<0.001$); 7.5% vs. 4.6% for bleeding ($P<0.001$); 2.7% vs. 3.5% for MI ($P=0.057$) and 1.8% vs. 1.9% for all-cause death ($P=0.60$). The relation of HPR to ST (adjusted HR 1.44 [0.53, 3.88]; $P=0.47$), MI (1.54 [1.02, 2.32], $P=0.038$), bleeding (0.69 [0.54, 0.90]; $P=0.005$) and death (1.40 [0.83, 2.34]; $P=0.21$) in non-ACS pts. was consistent with that in the entire study. Due to the difference in event rates, the absolute difference in the incidence of ST according to clopidogrel responder status was substantially smaller in non-ACS compared with ACS, while in contrast that in bleeding was substantially larger as shown in the figure.



In patients with non-ACS, HPR on clopidogrel has a relatively greater absolute impact on bleeding than ischemic complications. These data suggest that intensified antiplatelet therapies aiming at the correction of clopidogrel hyporesponsiveness for prevention of ST in non-ACS patients may lead to a disproportionate increase in bleeding.

1917 | BEDSIDE

The effect of acenocoumarol on the antiplatelet effect of clopidogrel

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Introduction: Aspirin and P2Y12 inhibitors, such as clopidogrel, reduce the inci-

dence of atherothrombotic events in patients undergoing percutaneous coronary interventions (PCI) with stent implantation. However, the anticipated antiplatelet effect of clopidogrel, as assessed with platelet function assays, is not achieved in approximately a quarter of patients. These patients exhibit high on-clopidogrel platelet reactivity (HPR), which is associated with atherothrombotic events following PCI. Platelet reactivity on clopidogrel is influenced by concomitant medication that is also metabolized by the hepatic cytochrome P450 system. For example, use of the coumarin derivative phenprocoumon is associated with HPR on clopidogrel. We aimed to evaluate if concomitant use of acenocoumarol, a different coumarin derivative that is used by a substantial subset of PCI patients, is also associated with increased platelet reactivity during treatment with clopidogrel.

Methods: In a prospective, single center registry we identified all patients planned for (semi-)elective PCI who used clopidogrel and in whom the VerifyNow P2Y12 assay was performed. HPR was defined as ≥ 236 P2Y12 reaction units (PRU). Baseline characteristics were registered and patients were divided into two groups according to concomitant acenocoumarol treatment. Multiple linear regression and binary logistic regression were used to correct for significant differences in baseline characteristics.

Results: A total of 1,822 patients were identified: 113 received concomitant acenocoumarol treatment (31.9% on aspirin) and 1,709 did not (97.8% on aspirin). Platelet reactivity was significantly higher in patients using acenocoumarol compared to patients not using acenocoumarol (mean PRU 231 ± 88 vs. 188 ± 95 PRU, $p < 0.001$), as was the proportion of patients with HPR (49.6% vs. 31.6%, $p < 0.001$). Multivariable analysis revealed that age, gender, body mass index, diabetes mellitus, platelet count, non ST-segment elevation myocardial infarction < 14 days of PCI, smoking, use of proton pump inhibitors and aspirin use were also significantly associated with PRU levels. After correcting for these variables, acenocoumarol use was independently associated with a higher PRU ($+36.4$ PRU, 95% CI 14.0–58.8, $p = 0.002$) and the occurrence of HPR (OR 2.17, 95% CI 1.21–3.93, $p = 0.01$).

Conclusion: Concomitant acenocoumarol treatment in patients treated with clopidogrel is independently associated with a significantly higher PRU level and a higher HPR rate. The impact of this finding on the risk of atherothrombotic events in patients undergoing PCI requires further investigation.

1918 | BEDSIDE

New determinant of clopidogrel hypo-responsiveness in patients with dual antiplatelet maintenance therapy

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Purpose: To investigate whether there is unknown determinant of clopidogrel hyporesponsiveness in patients with dual antiplatelet maintenance therapy.

Methods: Patients with dual antiplatelet maintenance therapy using aspirin and clopidogrel more than for 1 month after percutaneous coronary intervention were enrolled prospectively. Complete medical history reviews and platelet function using VerifyNow system were evaluated. The presence of genetic variation in CYP2C19, CYP3A4, CYP3A5, MDR1 and PON-1 genes were also evaluated.

Results: Totally 458 patients were enrolled. The PRU was significantly higher in patients with female gender, hypertension, diabetes mellitus, CYP2C19 loss-of-function (LOF) allele and non-smokers. However, patients taking calcium channel blockers including amlodipine and diltiazem, statins, beta-blockers, and diuretics did not show any significant difference in PRU. In addition, patients with sustained release formulation of nitrate agents and ranitidine showed significantly higher PRU value. Patients with CYP2C19 LOF allele also showed significantly higher PRU whereas the genetic variability of CYP3A4, CYP3A5, MDR1, and PON-1 gene did not show significant difference in PRU nor influence the drug-drug intervention with diltiazem, amlodipine, and statins. Multivariate logistic regression analysis revealed older age, diabetes mellitus, current smoking, CYP2C19 LOF allele and administration of sustained release formulation nitrate agent as the independent risk factors for high PRU defined as PRU 242 or more.

Logistic regression analysis

Variate	Multivariate logistic regression		
	OR	95% CI	p
Age (decade)	1.39	1.09–1.77	0.01
DM	1.57	1.00–2.47	0.05
Current smoking	0.47	0.26–0.82	0.01
LOF allele	3.08	1.99–4.76	< 0.01
Nitrate	1.74	1.14–2.65	0.01

Multivariate logistic regression analysis for high PRU defined as 242 unit or more shows sustained release nitrate agent as the independent risk factor for high PRU.

Conclusion: Sustained release nitrate agent is a new determinant of clopidogrel hypo-responsiveness in patients with dual antiplatelet maintenance therapy.

1919 | BENCH

Changes in miR-B expression after aspirin use are correlated to the extent of reduction in platelet aggregation and might identify aspirin insensitivity

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Background: Worldwide, aspirin is the most commonly prescribed platelet inhibitor after a cardiovascular event. Despite this type of secondary prevention, many patients suffer from re events, that are thought to be due to insensitivity of the platelets to the aspirin treatment. Since we are now unable to predict which patients are prone to re events due to aspirin insensitivity, we aimed to investigate whether miRNAs could be used as a suitable marker for this purpose.

Methodology and principal findings: To investigate whether miRNA profiles are influenced by aspirin, we included 15 healthy men between the age of 45 and 65 years and determined miRNA expression profiles before and after 2 weeks of aspirin use by microRNA micro-array. These data showed, that among healthy individuals, some subjects showed marked changes in miRNA profiles after medication use, whereas others did not. To further explore this finding, we correlated the miRNA microarray results to whole blood platelet aggregation data of the same healthy individuals. The delta of miRNA expression of 5 miRNA significantly correlated with an increase in the percentage reduction in platelet aggregation after aspirin use.

We used real-time qPCR (RT-qPCR) to confirm the correlation between changes in miRNAs expression and the reduction in platelet aggregation in 25 healthy individuals. These data showed a significant positive correlation ($\rho = 0.68$; $p < 0.01$) of the delta of miRNA expression of miR-B with the percentage reduction of platelet aggregation, meaning that for these miRNAs the delta increased with an increasing percentage reduction of platelet aggregation. There were no correlations between the deltas of the other miRNAs and platelet aggregation.

Conclusion: We showed that platelet miRNA expression profiles and in particular the expression of miR-B of healthy individuals react differently to aspirin use and that these differences correlate to the extent of reduction in platelet aggregation after aspirin use. In future, these miRNA profiles might be an useful tool to identify patients at risk for re events.

SHOCK: AN UPDATE

1929 | BEDSIDE

Evolution of incidence and one-year mortality of cardiogenic shock in acute myocardial infarction from 1995 to 2010. The FAST-MI programme

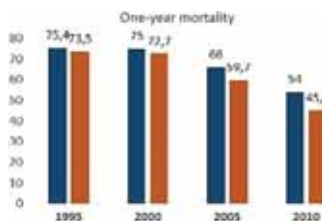
N. Aissaoui¹, E. Puymirat¹, P. Ohlmann², N. Bonnet¹, A. Lafont¹, H. Benamer³, J. Ferrieres⁴, F. Schiele⁵, T. Simon⁶, N. Danchin¹ on behalf of FAST-MI investigators. ¹AP-HP - European Hospital Georges Pompidou, Paris, France; ²University hospital, Strasbourg, France; ³Cardiovascular Institute Paris-Sud (ICPS), Massy, France; ⁴University Hospital of Toulouse, Toulouse, France; ⁵Regional University Hospital Jean Minjoz, Besancon, France; ⁶AP-HP - Hospital Saint Antoine, Paris, France

Rationale: Cardiogenic shock (CS) during AMI remains a major concern. Information on its incidence over the past 20 years is discrepant, and little is known of the evolution of mortality over time.

Methods: We analysed the incidence and one-year mortality of CS in 4 nationwide surveys carried out 5 years apart from 1995 to 2010. Consecutive STEMI and NSTEMI patients (≤ 48 hours from onset) were recruited over one-month periods.

Results: Among the 10,610 patients included in the surveys, 614 (5.8%) had CS. Incidence of CS decreased (6.9% in 1995; 4.0% in 2010, P for trend < 0.001), with consistent trends for STEMI and NSTEMI, and across age groups. Patients with CS were older than those without (74 ± 12 vs 66 ± 14 years, $p < 0.001$) and their mean age remained constant over time. In CS patients, use of PCI increased from 20% in 1995 to 73% in 2010 ($P < 0.001$), and reperfusion therapy for STEMI increased from 40% to 72%.

One-year mortality was considerably higher in CS patients (66.6% vs 10.3%). From 1995 to 2010, mortality of CS patients markedly decreased (75% to 51%,



Evolution of 1-year death in CS patients.

$P < 0.001$) (Figure), with similar patterns for STEMI and NSTEMI, and across age groups. By Cox multivariate analysis, in CS patients, age, diabetes, higher BMI and STEMI, were independent correlates of increased one-year death, while time period was associated with reduced mortality (HR 2010 vs 1995= 0.57; 95% CI: 0.40-0.83, $P=0.003$, along with early use of PCI and medications at the acute stage.

Conclusion: In these 4 nationwide surveys conducted 15 years apart, the incidence of CS decreased and one-year mortality was reduced by 43% in CS patients. Beyond a broader use of PCI and appropriate medications at the acute stage, improvement of the whole process of care is likely to have contributed to these improved results.

1930 | BEDSIDE

Clinical picture and mortality in cardiogenic shock in the contemporary era

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Aim: To investigate the contemporary clinical picture, management, and outcomes of cardiogenic shock (CS).

Methods: The European prospective CardShock study enrolled 220 patients with CS, defined as persistent hypotension (systolic blood pressure [SBP] <90 mmHg) and clinical signs of hypoperfusion. Data on clinical presentation and management were compared between different etiologies of CS. In-hospital and 90-day all-cause mortality was registered.

Results: Patients with CS were on average 67 years, 74% men. Mean SBP was 78 mmHg, heart rate (HR) 93 bpm. In-hospital mortality was 37%. The most common cause of CS were acute coronary syndromes (ACS 81%), while non-ACS etiology, including severe low-output heart failure and valvular causes, accounted for the remainder. Patients with ACS were older than those without ACS, but HR, SBP, signs of hypoperfusion, lactate levels, and LVEF were similar in both groups. NT-proBNP levels were lower in patients with ACS (median 1948 vs 6431 pg/ml, $p < 0.01$). Ninety-two percent of ACS patients underwent coronary angiogram; of which 96% were revascularized. In contrast, vasoactives and inotropes were administered to nearly every patient regardless of etiology. Compared to those with ACS, patients without ACS had lower in-hospital (24% vs 40%) and 90-day (31% vs 44%) mortality. Independent predictors of short-term prognosis are shown in Table 1.

Table 1. Independent predictors of in-hospital and 90-day mortality in CS

Variable	In-hospital mortality		90-day mortality	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (per year)	1.04 (0.99–1.08)	0.09	1.03 (0.99–1.07)	0.16
Previous myocardial infarction	3.2 (1.3–8.4)	0.02	1.9 (0.8–4.7)	0.17
Previous CABG	12.5 (2.0–77.4)	0.007	14.5 (2.1–101)	0.007
ACS	7.8 (1.9–32.6)	0.005	4.0 (1.2–13.5)	0.02
Confusion on admission	3.3 (1.2–9.0)	0.02	2.8 (1.2–7.0)	0.02
Blood lactate (per mmol/L increase)	1.4 (1.2–1.6)	<0.001	1.4 (1.2–1.6)	<0.001
LVEF (per % decrease)	1.06 (1.02–1.09)	0.001	1.06 (1.03–1.10)	<0.001

Conclusion: Cardiogenic shock is still associated with high in-hospital mortality. While most commonly due to ACS, other causes account for one-fifth of cases of CS. Despite early invasive treatment, ACS is strongly and independently associated with short-term mortality. Independent predictors of risk include common clinical variables.

1931 | BENCH

Strategies to reduce in-hospital mortality in acute coronary syndrome complicated with cardiogenic shock: a nationwide cohort study

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Background: Cardiogenic shock complicating acute coronary syndrome (ACS) is associated with a high risk of in-hospital mortality (IHM). However, limited studies investigated treatment strategies to reduce IHM among these patients.

Method: We evaluated patients with ACS and cardiogenic shock from the National Health Insurance Research Database (NHIRD) from 1997 to 2009. Cox regression analysis was used to find factors associated with IHM.

Results: Overall 1176 patients had developed cardiogenic shock during the index ACS hospitalization. Age was 71.41 ± 12.83 years old and IHM rate was 65.6%. Average admission days were 10.37 ± 36.13 . There is no significant re-

duction in IHM rate between 1997 and 2009. Patients suffered from IHM are older, have more female, higher percentage of myocardial infarction, hypertension and use of angiotensin-II receptor blocker (ARB) and calcium channel blocker, less in-hospital use of clopidogrel, statin, heparin and glycoprotein IIb/IIIa, lower percentage of diagnostic angiography and coronary revascularization but higher percentage of intra-aortic counterpulsation balloon (IABP) use. Cox regression analysis showed age (hazard ratio [HR] 1.01, $p < 0.01$), myocardial infarction (HR 1.65, $p < 0.01$), heparin (HR 0.76, $p < 0.01$), clopidogrel (HR 0.76, $p < 0.01$), statin (HR 0.79, $p = 0.05$), coronary revascularization including percutaneous coronary intervention or coronary artery bypass graft (HR 0.60, $p = 0.03$), and intra-aortic counterpulsation balloon (IABP) (HR 3.26, $p < 0.01$) to be independent predictors for IHM. Compared with those receiving all 4 treatments including heparin, statin, clopidogrel and revascularization, patients with above-mentioned 3, 2, 1 and no treatment had 1.99, 2.14, 2.54 and 2.86 folds of IHM risk, respectively (all $p < 0.02$).

Conclusion: Cardiogenic shock complicating ACS is still associated with high IHM rate under the contemporary care. Our results highlight the importance of evidence-based strategies including the antiplatelet, anticoagulation, statin and coronary revascularization among the highest risk population.

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Gender-related differences in outcome of patients with cardiogenic shock from acute myocardial infarction

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Purpose: Women have been reported to have a higher incidence of cardiogenic shock after STEMI when compared to men. However, studies on gender-related differences in short-term and long-term outcome after cardiogenic shock have been reported less frequently. We investigated gender-related differences in outcome of patients with cardiogenic shock from STEMI undergoing primary PCI.

Methods: A series of 544 consecutive patients admitted with cardiogenic shock from STEMI undergoing primary PCI were included between 2000-2012.

Results: A total of 138 (25.4%) patients were women and 406 (74.6%) were men. Women were significantly older (68.1 vs 62.3 , $p < 0.001$), had a higher incidence of hypertension, a lower incidence of prior MI, and had lower serum creatinine and CK levels at admission. Women more often presented with inferior (vs. anterior) STEMI, but less often with out-of-hospital cardiac arrest. Women more frequently underwent PCI of the left main, but less frequently of the left anterior descending artery. Other baseline characteristics were similar. Thirty-day all-cause mortality was 50% in women and 35% in men ($p = 0.001$). All-cause mortality at 10-years of follow-up was 72% and 57%, respectively (Fig. 1, $p = 0.002$). After multivariate adjustment for differences in baseline variables, mortality in women remained significantly higher (OR for 30-day mortality 2.40 (95%CI 1.46-3.94) and HR for 10-year mortality 1.53 (95%CI 1.14-2.06).

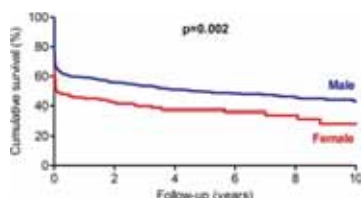


Figure 1

Conclusion: Women admitted with cardiogenic shock from STEMI undergoing primary PCI had a substantially higher mortality that persisted after adjustment in multivariable analysis. This difference developed in the first 30 days and persisted during 10 years of follow-up.

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Serum lactate in cardiogenic shock: clearance vs. single values – a biomarker substudy of the IABP-SHOCK II-trial

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Background: Serum lactate is widely used and an important biomarker for disease severity assessment in critically ill patients including those with cardiogenic shock (CS) complicating acute myocardial infarction. In sepsis and septic shock percentage of lactate reduction over time – the lactate clearance (LC) – has been extensively investigated. In CS only limited data are available.

Methods: In the randomized Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial 600 patients with CS complicating acute myocardial infarction undergoing early revascularization were assigned to therapy with IABP or no IABP. Lactate levels at baseline (L1) and after 8 hours (L2) were collected prospectively. LC was calculated for every patient (Figure 1). The areas under the

curves (AUC) of receiver operating characteristics for L1 vs. L2 vs. LC were compared with c-statistics for prediction of 30-day mortality. Youden index was used to gain best cut-off values. A multivariable Cox regression analysis for prediction of 30-day mortality was applied to assess possible independent impact for time to death prediction.

Results: For 529 of 600 patients (88.2%) L1 and L2 and consequently LC values were available. The 30-day mortality in this cohort was 39.5% (209/529). The AUCs (L1: 0.67; L2: 0.76; LC: 0.62) showed no statistical difference between L1 and LC ($p=0.20$). In contrast, L2 AUC was significantly higher than for both other parameters ($p<0.001$, respectively). Youden index calculated 3.7 mmol/L as best cut-off value for L2. In multivariable stepwise Cox regression analysis L2 ≥ 3.7 mmol/L and LC $< 3.25\%/h$ remained independent predictive of time to death ($p<0.001$ for both) with L2 showing highest χ^2 -score (103) and hazard ratio (3.03; 95% confidence interval 2.25-4.08).

Conclusion: L2 seems to be superior in prediction of death in comparison to L1 and LC. A cut-off value of 3.7 mmol/L for L2 after 8 hours showed the best discrimination for assessing early prognosis in CS.

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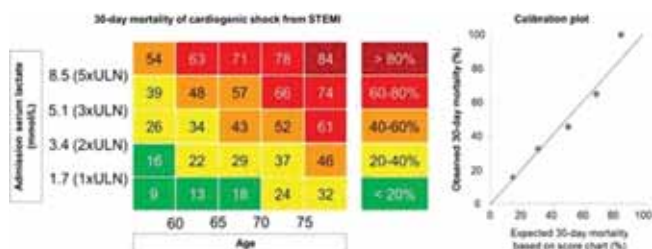
A simple score chart to assess risk of mortality at time of hospital admission for patients with cardiogenic shock from acute myocardial infarction

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Purpose: Early risk stratification is important in patients with cardiogenic shock from STEMI. We aimed to develop a simple risk score that can be used at time of hospital admission to assess risk of 30-day mortality.

Methods: A series of 544 consecutive patients admitted with cardiogenic shock from STEMI who were intended to undergo primary PCI were included between 2000 and 2012.

Results: Overall 30-day mortality was 38.4% and did not change over the years (p -trend=0.64). Baseline variables known at time of hospital admission (including cardiac history, conventional risk factors, out-of-hospital cardiac arrest, physical examination, infarct location and serum lactate level) were entered into a logistic regression model in a forward stepwise manner. Only age (OR per category 1.45, 95%CI 1.25-1.69, $p<0.001$) and serum lactate level (OR per category 1.82, 95%CI 1.53-2.18, $p<0.001$) remained independent predictors of 30-day mortality, and were subsequently used to develop a score chart (left figure) that stratifies risk of 30-day mortality into categories ranging from 0-20% to 80-100%. The calibration plot (right figure) showed a close relation between the actual mortality rates in each risk category and the expected mortality rates obtained from the score chart. C-index of the model was 0.74. Adding information on the clinical course during intensive cardiac care unit stay, intra-aortic balloon pump support, cardiac markers, and variables obtained from coronary angiography and PCI did not significantly improve predictive accuracy of the model (c-index 0.77, $p=0.32$).



Conclusions: The outcome of patients with cardiogenic shock from STEMI can be largely predicted at time of hospital admission by a simple score chart that uses two variables, namely age and serum lactate level.

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Invasive vs. non-invasive ventilation and ventilatory parameters: do they predict outcome in cardiogenic shock

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Purpose: Despite scarce data, invasive mechanical ventilation (MV) is widely recommended over non-invasive ventilation (NIV) for ventilatory support in cardiogenic shock (CS). We analysed the role of ventilation strategies (VS) for in-hospital (I-H) outcome in CS.

Methods: 220 patients from the European CardShock study were categorized by

maximal ventilatory support needed during the first 24 hours into MV and NIV groups. Clinical characteristics, treatment and outcome were analysed.

Results: Mean age was 66.6 years (SD 11.8), 73% were men. MV 134 (61%) and NIV 28 (13%) groups did not differ significantly in age, gender, medical history, etiology of CS, PaO₂/FiO₂-ratio, baseline hemodynamics or LVEF. ACS was the main cause of CS (81% in MV and 79% in NIV group). 3 (2%) of MV group was initially treated with NIV. After the first 24 hours 5 (18%) from NIV group got intubated.

Differences in laboratory and ventilatory parameters, length of hospital stay (LOS) and I-H mortality are shown in the table. MV group had significantly higher lactate level and greater need for vasoactive drugs referring to severe tissue hypoperfusion whereas NIV group seemed to be more congestive.

After adjusting for other predictors of outcome (age, history of CABG, systolic blood pressure, LVEF, lactate, ACS and need for adrenalin), mean 0-24 h FiO₂ (OR 1.04; 95% CI 1.01-1.07; $P=0.013$) was independently associated with I-H mortality. However, VS had no influence on prognosis (OR 0.41; 95% CI 0.08-2.10; $P=0.28$).

	MV	NIV	p-value
Troponin T 0h, ng/l*	5081 (9981)	7892 (10414)	0.023
NT-proBNP 0h, pg/ml*	7727 (12571)	11115 (14735)	0.041
Lactate 0h, mmol/l*	4.9 (3.9)	2.9 (3.3)	<0.001
Mean FiO ₂ 0-24h, %*	63 (19)	54 (19)	0.025
Mean PaO ₂ 0-24h, kPa*	14.6 (4.1)	12 (1.8)	0.001
Los, day*	21 (16)	17 (12)	0.29
in-hospital mortality, n (%)	61 (46)	6 (21)	0.02

*Mean (SD).

Conclusions: Though MV is generally recommended, a fair number of patients were treated with NIV. Moreover, initial VS did not affect outcome. Thus NIV seems a safe option for properly chosen CS patients. Interestingly, of the ventilatory parameters, only mean 24-hour FiO₂ independently predicted I-H mortality.

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Prasugrel vs. clopidogrel in cardiogenic shock patients undergoing primary PCI for acute myocardial infarction: results of the ISAR-SHOCK registry

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Purpose: Primary PCI is the recommended reperfusion therapy for patients with acute myocardial infarction (AMI) complicated by cardiogenic shock (CS). However, randomized data is lacking comparing different P2Y₁₂ receptor inhibitors in this setting and current guidelines still favour the use of clopidogrel. The aim of the ISAR-SHOCK registry was to compare the clinical outcome of patients treated with clopidogrel vs. prasugrel in CS patients.

Methods: Patients (n=145) with AMI complicated by CS and undergoing primary PCI in two centers between January 2009 and May 2012 were included in this registry. The use of prasugrel for patients in this registry was triggered by an individual decision-making that also reflected platelet function testing results during the acute AMI phase. The primary endpoint was 30-day all-cause mortality. Secondary endpoints were stent thrombosis (ST) and TIMI bleedings at 30-days.

Results: With regard to antiplatelet treatment in the 145 CS patients, 50 patients were initially treated or immediately switched to prasugrel while 95 patients were treated with clopidogrel. All-cause mortality was lower in prasugrel vs. clopidogrel treated patients (30% vs. 50.5%, HR: 0.51, 95% CI 0.29-0.92, $p=0.02$, see Fig. 1). There was no difference for the occurrence of ST (HR: 2.95, 95% CI 0.27-32.68, $p=0.38$) or bleeding complications (combined TIMI major and minor bleedings, HR: 1.3, 95% CI 0.75-2.26, $p=0.35$).

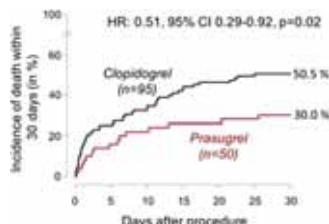


Figure 1

Conclusion: Results of the ISAR-SHOCK registry suggest that the use of prasugrel in AMI patients complicated by CS might be associated with a lower mortality risk and a comparable safety profile as compared to clopidogrel therapy. Further studies are needed to determine the optimal antiplatelet treatment regimen in this high-risk cohort of patients.

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Levosimendan to wean inotropic drugs in end stage heart failure patients

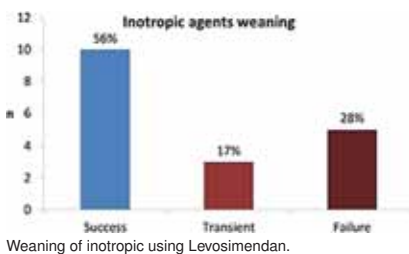
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Background: Despite mixed results in acute heart failure (SURVIVE, REVIVE), Levosimendan, a "calcium sensitizers" with a long half life, may have an interest in other clinical situation.

Purpose: To assess success rate of inotropic drugs withdrawal with Levosimendan in patient with end stage heart failure (HF) who previously failed weaning from inotropic agents.

Methods: Levosimendan was proposed to 18 end stage heart failure patients dependent of inotropic drugs between 2004 and 2013. Weaning success was defined as complete withdrawal of inotropic agents within 24 hours of intravenous infusion of levosimendan (0,1 µg/kg/min), transient success as the need to re-introduce inotropic agents within 24 hours after weaning and failure as the inability to stop inotropic agents. We also report 6-month survival rates, survival time, rates of exit from intensive care unit and home return.

Results: Mean age was 60 years old. Dilated cardiomyopathy was the leading cause of HF (50%). Mean heart rate was 90/min and blood pressure 100/62 under inotropic agents (dobutamine 94%). Mean LVEF was 24%. Mean NT-proBNP was 8658 ng/l, 17% had a creatinin Clearance <30 ml/min, 18% a factor V <50%. Figure shows weaning success rate. Mean duration of weaning was 145±191 days. At 6 months, 50% of weaned vs. 13% of not weaned patients survived. In case of successful weaning (n=10), mean survival time was 216±224 days. Ninety percent of the patients could leave the intensive care unit and 30% get back home.



Conclusion: 24 hours intravenous infusion of Levosimendan allows weaning of more than half of end stage HF patients dependent on inotropic drugs. Despite a dramatic prognosis, weaning lasted 5 months and allowed 90% of patients to leave the intensive care unit and 30% to go back home.

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Mono-center experience in safety and efficacy of the Impella device in cardiogenic shock

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Purpose: Cardiogenic shock has a high mortality, and catecholamines traditionally used to stabilize blood pressure are increasingly recognized to have unfavourable side effects. Therefore attention is directed on mechanical hemodynamic support. We want to report on safety, efficacy and handling of the percutaneous implantable microaxial Impella-pump in our institution.

Methods: First 36 patients were evaluated (28 male, 8 female, mean age 66,4 years (42-84)). Indication for hemodynamic support was: high-risk coronary intervention (n=5, "elective"), during or shortly after cardiac resuscitation (n=17, "CPR") and acute myocardial infarction with cardiogenic shock (n=14, "shock"). All patients had PCI. Hemodynamic data and medical reports were retrospectively analysed.

Results: Hemodynamic support with the Impella system was provided for an average of 54,8 hours (1,5-128 h). At implantation patients were highly catecholamine dependent, but within 2h vasopressor doses dropped significantly (e.g. in a preliminary analysis of n=16 pat. from norepinephrine mean 128,2 µg/pat. to 18,9), accompanied by lactate decrease indicating better organ perfusion. Enzyme course reflects shock in general as well as cardiac damage. Several patients had acute renal failure, renal replacement therapy was needed by 13. Difficulties related to the device mainly consisted of hemolysis and bleeding, both because of compromised plasmatic coagulation and problems at puncture site. Therefore transfusion was necessary on average of 7,4 erythrocyte concentrates (CPR) resp. 4,8 (shock group), in contrast only 0,5 in elective patients. CPR patients also needed 3,9 units of fresh frozen plasma, in shock 1,6, n=6 resp. 3 were given thrombocytes and n=6 additionally PPSB.

In several patients reposition of the device was necessary. 1 woman with peripheral artery disease and prior implantation of a dacron prosthesis had surgical vessel closure. In the elective group one patient died within 30 days after an consecutively planned CABG operation. In the shock group n=11 had survival to discharge with at least 5 were still alive 30 days later. In the CPR group however 12 patients died of progressive multiorgan failure, 1 because of ventricular rupture.

Conclusion: Use of the Impella-device can help to stabilize patients in cardio-

genic shock and to reduce vasopressor need. Even in patients after cardiac arrest is might be reasonable because it re-constitutes circulation faster and more effectively than under pure inotropic stimulation. Device-associated complications are rare and mainly required improved bleeding management.

CARDIOVASCULAR MAGNETIC RESONANCE MAKES THE DIFFERENCE

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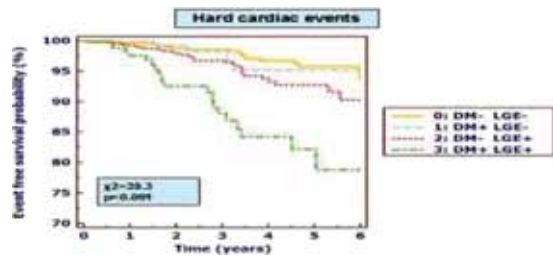
The presence of myocardial scar carries additional prognostic information in patients with diabetes who undergo late gadolinium enhancement magnetic resonance imaging

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Aims: To evaluate the prognostic significance of myocardial scar in patients with and without diabetes mellitus who undergo cardiac magnetic resonance (CMR) and late gadolinium enhancement (LGE) imaging for known and suspected coronary artery disease (CAD).

Methods: 1969 consecutive patients (age 63±12 years, 29% female, LV-ejection fraction=59±12%) underwent CMR. Patients were grouped according to the presence of LGE and diabetes mellitus as follows: group 1: absence of diabetes and LGE, group 2: presence of diabetes and absence of LGE, group 3: absence of diabetes and presence of LGE and group 4: presence of LGE and diabetes. Cardiac death and nonfatal myocardial infarction (MI) were registered as hard cardiac events. Patients with a revascularization procedure within the first three months after CMR were censored at the time of "early" revascularization.

Results: The median follow up time was 2.9 years (interquartile range 2-4.2 years). 90 Pts. (4.6%) experienced a hard cardiac event. 852 pts (43.3%) showed LGE and 328 Pts. (16.6%) had diabetes. The proportion of LGE was higher in patients with compared to those without diabetes (53.6% versus 41.2%, p<0.001 for proportions). Both diabetes and LGE were predictors of hard cardiac events (HR=2.4, CI=1.3-4.4, χ²=14.9, p=0.001 and HR=2.7, CI=1.8-4.2, χ²=19.9, p<0.001, respectively). Analyzing by Groups (1-4), patients with both LGE and diabetes exhibited markedly higher likelihood for future hard cardiac events compared to all other groups (HR=5.6, CI=2.5-12.6 group 4 vs group 1, HR=4.3, CI=1.4-13 group 4 vs group 2, HR=2.5, CI=1.1-5.8, group 4 vs. group 3, χ²=39.3, p<0.001).



Conclusion: The presence of LGE in patients with diabetes mellitus is a strong predictor of poor clinical outcome.

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Diabetes mellitus prevents ischemic preconditioning in patients with reperfused acute myocardial infarction: insight from cardiovascular magnetic resonance

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Background: Several studies suggest that preinfarction angina occurring shortly before the onset of acute ST-segment elevation myocardial infarction (STEMI) is associated with favorable outcomes by the mechanism of ischemic preconditioning. And more, recent studies demonstrated that such beneficial effects of preinfarction angina were not observed in diabetic patients. Non-invasive quantitative assessment of microvascular obstruction (MVO) by cardiovascular magnetic resonance (CMR) provides a specific biomarker of severe microvascular dysfunction. The aim of this study was to determine whether preinfarction angina was related to the presence of severe microvascular dysfunction determined by CMR in patients with acute STEMI.

Methods: The study population consisted of 202 consecutive patients with a first STEMI successfully treated with primary percutaneous coronary intervention (PCI): 161 patients without diabetes and 41 patients with non-insulin treated diabetes. Preinfarction angina was defined as angina occurred 24 to 72 hours before the onset of infarction. Late gadolinium-enhanced (LGE) CMR performed within 4 days after primary PCI was used to measure MVO.

Results: Patients with MVO were more frequently observed in patients without

angina occurred 24 to 72 hours before infarction compared to those with the preinfarction angina (65% vs 38%, $p=0.033$). In non-diabetic patients, preinfarction angina was associated with smaller sizes of LGE and MVO (13.4 ± 9.6 vs $21.9\pm 12.6\%$ of left ventricle, $p=0.0005$; 0.8 ± 1.4 vs $2.6\pm 3.3\%$ of left ventricle, $p=0.0037$, respectively). On the contrary, in diabetic patients, there was no significant difference in the total sizes of LGE and MVO (11.7 ± 14.1 vs $21.6\pm 14.0\%$ of left ventricle, $p=0.1149$; 1.7 ± 2.7 vs $3.4\pm 5.1\%$ of left ventricle, $p=0.4236$, respectively) between patients with and those without preinfarction angina.

Conclusion: Preinfarction angina limited infarct and MVO size in non-diabetic patients with STEMI. However, such beneficial effects of preinfarction angina were not observed in diabetic patients, suggesting that diabetes might prevent ischemic preconditioning.

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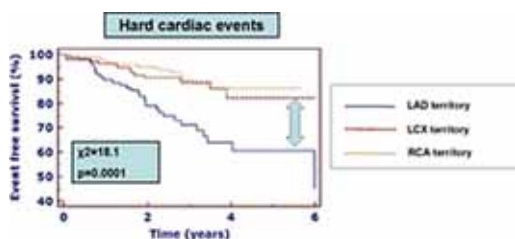
Does the localization of ischemia in patients who undergo dobutamine stress cardiac magnetic resonance imaging influence outcome?

S. Giusca¹, S. Kelle², E. Nagel³, S.J. Buss¹, V. Puntmann³, E. Wellnhofer², E. Fleck², H.A. Katus¹, G. Korosoglou¹. ¹University Hospital of Heidelberg, Cardiology Department, Heidelberg, Germany; ²German Heart Institute of Berlin, Berlin, Germany; ³King's College London, London, United Kingdom

Aims: To evaluate the impact of ischemia localization for the prediction of hard cardiac events in patients with known or suspected CAD who undergo dobutamine stress cardiac magnetic resonance imaging (DCMR)

Methods: 3166 patients (pts.), 63 ± 12 years, 27% female underwent DCMR. Pts. were grouped based on the coronary artery territory of stress induced wall motion abnormalities (WMA) using the AHA/ACC/ESC standard. Patients who showed WMA in only one territory were further analyzed. Cardiac death and nonfatal myocardial infarction were registered as hard cardiac events. Patients with an "early" revascularization procedure (in the first three months) were not included in the final survival analysis.

Results: Pts. were followed for a median of 3.1 years (interquartile range 2-4.5 years). 187 (5.9%) pts. experienced hard cardiac events. 613 pts (19.4%) had inducible ischemia in only one coronary territory (32.1% LAD, 37.4% LCX, 30.5% RCA) and were further analyzed. Pts with inducible ischemia in the LAD territory had a higher rate of hard cardiac events compared to other territories (HR=2.5, 95%CI=1.4-4.4, $\chi^2=18.1$ $p<0.001$, HR LAD vs. LCX=2.7, 95%CI=1.4-5.3, HR LAD vs. RCA=3.3, 95%CI=1.6-7.4). No difference in the likelihood of hard cardiac events was noted between RCA and LCX territories (HR=0.8, 95%CI=0.4-1.5) (see figure). In the first three years, inducible ischemia in the LAD territory was associated with a yearly event rate of ~10%, in comparison to ~4% seen in those with inducible ischemia in non_LAD territories ($p<0.001$).



Conclusions: The presence of inducible ischemia in the LAD territory is associated with a higher rate of cardiac events compared to other territories in patients with known or suspected coronary artery disease.

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Cardiac magnetic resonance based management of coronary artery disease at 3.0 Tesla: insights from a large single center experience

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Background: Cardiac magnetic resonance (CMR) has become a robust diagnostic tool for the assessment of coronary artery disease (CAD). However, little is known about the role of CMR at 3.0 Tesla for guiding management of CAD. This study was therefore aimed to describe the role of stress-perfusion/viability CMR at 3.0 Tesla for guiding the clinical management of a large and heterogeneous collective of patients with known or suspected CAD.

Methods: This was an observational single center study. Consecutive patients ($n=847$) undergoing stress / viability CMR on a 3.0 Tesla system at our institution were stratified according to CMR findings of myocardial ischemia and scar, and followed for clinical events. Multiple aspects such as appropriateness of CMR-driven coronary angiography (cath) in ischemia positive patients, diagnostic accuracy of stress-perfusion CMR into a coronary territory analysis and its prognostic value were described.

Results: Myocardial scar was detected in 298 patients (35%) and ischemia in 214 patients (25%). Among patients with evidence of myocardial ischemia, 126 (59%) underwent CMR-driven cath. The ischemic score was significantly higher

in patients undergoing cath as compared with patients followed conservatively in spite of myocardial ischemia (median [IQR] 4 [2-5] vs. 2 [1-3]; $p<0.001$). Events rates of cardiac death or non-fatal myocardial infarction were significantly lower in patients without myocardial ischemia or scar as compared to others (rate per 100 person/year [95%-CI] = 0.23 [0.03-1.62] vs. 2.30 [1.20-4.42]; $p=0.036$). The same was true for the combined end-point of cardiac death, non-fatal myocardial infarction and need of coronary revascularization (rate per 100 person/year [95%-CI] = 1.85 [0.93-3.70] vs. 38.39 [31.87-46.25]; $p<0.001$). For the latter end-point, CMR findings added incremental prognostic value as compared with clinical data only (Likelihood ratio test, $p<0.001$). Sensitivity and specificity of CMR at detecting a significant coronary lesion (>50% stenosis) were of 74% and 87%, respectively, resulting in a 94%-rate of CMR-driven cath in ischemia positive patients being clinically appropriate (i.e. evidence of >50% stenosis and/or revascularization performed).

Conclusion: CMR guided management of CAD at 3.0 Tesla is associated with a very good diagnostic accuracy at detecting significant CAD, an efficient downstream utilization of cath and a very good cardiac prognosis.

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Comprehensive prognosis assessment by cardiovascular magnetic resonance imaging following ST-elevation myocardial infarction

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Background: Although the prognostic value of cardiac magnetic resonance (CMR) imaging findings has been established in small to modest-sized single-center studies in patients with ST-elevation myocardial infarction (STEMI), a large multicenter investigation to evaluate the prognostic significance of myocardial damage and reperfusion injury is lacking. Aim of this study was to assess the prognostic impact of CMR in an adequately powered multicenter study and to evaluate the most potent CMR predictor of hard clinical events in a STEMI population treated by primary percutaneous coronary intervention (PCI).

Methods: We enrolled 738 STEMI patients reperfused by primary PCI (<12 h after symptom onset) in this CMR study at 8 centers. CMR was completed within one week after infarction using a standardized protocol. Central core laboratory-masked analyses for quantified left ventricular (LV) function, volumes, infarct size (IS), microvascular obstruction (MO), and myocardial salvage were performed. The primary clinical endpoint of the study was the occurrence of major adverse cardiac events.

Results: Patients with cardiovascular events had significantly larger infarcts ($p<0.001$), less myocardial salvage ($p=0.01$), a larger extent of MO ($p=0.009$) and more pronounced LV dysfunction ($p<0.001$). In a multivariate model including clinical and other established prognostic parameters, MO remained the only significant predictor in addition to the TIMI risk score. IS and MO provided an incremental prognostic value above clinical risk assessment and LV ejection fraction (increase of the c-index from 0.761 to 0.801, $p=0.0364$).

Conclusion: CMR markers of myocardial damage (IS and especially MO) can provide independent and incremental prognostic information in addition to clinical risk scores and LV ejection fraction in a large, multicenter STEMI population reperfused by primary PCI.

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Parallel improvement of inducible myocardial ischemia assessed by adenosine stress CMR and functional status after successful percutaneous revascularization in patients with CTO

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Purpose: Selection of patients that might benefit from a percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) of a coronary artery is a fundamental aspect in the evaluation of this population. An adenosine stress cardiac magnetic resonance (CMR) study may be useful to assess potential benefits of PCI CTO. This study aimed to assess myocardial ischemia by CMR and its relation with functional status before and after PCI for CTO.

Methods: Between November 2011 and December 2013 CMR studies were performed in 50 consecutive patients with successful PCI of CTO, and repeated after 6 months. Follow-up data have been prospectively collected in 31 patients to date. In all patients an adenosine stress CMR study was performed. Cine sequences for the analysis of regional contractile function were also obtained before and during the adenosine infusion were performed as a final part of the study protocol. The assessment of the severity of ischemia was performed by means of an ischemic score index (ISI) based on the 16-segment model of analysis of the left ventricle and calculated from the following items (relative weight is given in brackets): 1) extension of the defect (20%); 2) persistence along the duration of the perfusion sequence (20%); 3) transmural (20%); and 4) inducibility of contractile regional dysfunction under adenosine (40%). Functional status was also assessed before and after PCI by the six-minute walk test.

Results: A significant reduction in the number of segments with perfusion defect was observed at follow-up (4.9 ± 2.31 pre- vs. 1.1 ± 1.80 post-PCI, $p<0.001$). Total

ISI also improved significantly, after PCI (basal ISI $21 \pm 10.2\%$ vs. post-PCI ISI 4 ± 7.0 , $p < 0.001$).

The distance walked in the six-minute test improved at follow-up (431 ± 111.5 meters pre-PCI vs. 458 ± 110.4 meters post-PCI, $p = 0.050$). Moreover, chest pain after the six-minute walk test significantly decreased post-PCI ($p < 0.001$).

Patients with ISI $> 20\%$ before PCI ($n = 19$) showed a significant improvement in the six-minute walk test at follow-up (basal distance walked 440 ± 97.1 vs. follow-up distance walked 487 ± 83.6 meters, $p = 0.041$) that was not observed in those patients with ISI $< 20\%$ (444 ± 102.1 vs. 437 ± 115.0 meters, $p = 0.718$).

Conclusion: A successful CTO PCI leads to a reduction in inducible myocardial ischemia assessed by CMR. The improvement in the functional status, measured by the six-minute walk test, is only statistically significant in those patients with the highest ischemic burden at stress CMR, this suggesting that improvement of clinical status parallels the degree of relief of ischemia.

IMPROVING OUTCOME WITH CARDIAC RESYNCHRONISATION THERAPY: STILL A CHALLENGE

2045 | BEDSIDE

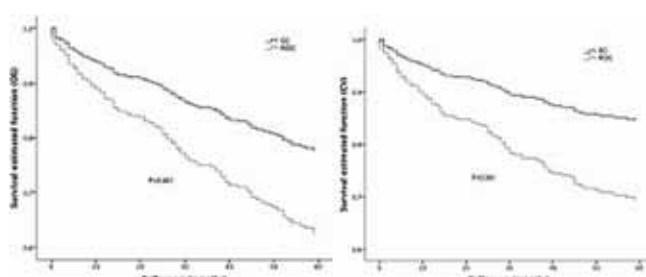
A resynchronization optimization clinic improves survival and response of heart failure patients treated with resynchronization therapy

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Background: Cardiac resynchronization therapy (CRT) improves symptoms and survival in patients with heart failure (HF). However, a large number of patients do not respond to CRT. We aim to evaluate the effect of a resynchronization optimization clinic (ROC) on the outcome and response of patients receiving CRT.

Methods: We compared outcomes of consecutive patients receiving CRT with standard care (SC) and patients followed by a resynchronization optimization clinic (ROC). Patients were followed prospectively in an integrated team consisting in a heart failure specialist and an electrophysiologist. Clinical assessment, echocardiography, functional test and quality of life were routinely performed at baseline, 6 and 12 months follow-up. A proportional hazard Cox regression model adjusted by propensity scores (based on age, ejection fraction, ischemic cardiomyopathy, atrial fibrillation, creatinine and functional class) was applied to estimate the hazard ratio and 95% confidence interval.

Results: A total of 582 patients were included in the study with a mean follow-up of 3.7 ± 2.5 yrs, 258 pt in the SC group and 324 in the ROC group. Patients in the SC group were older (68.2 ± 8 vs 66.2 ± 10 y, $p = 0.001$) and had worse creatinine (1.4 ± 0.5 vs 1.2 ± 0.5 , $p = 0.04$). After adjustment for these differences, ROC was associated with a lower hazard for overall mortality (HR 0.55, 95% CI: 0.4-0.8, $p < 0.001$) and cardiovascular mortality (HR 0.45, 95% CI: 0.3-0.7, $p < 0.001$). Clinical responder rate at twelve months follow-up was significantly higher in the ROC group (74% vs. 67%, $p = 0.04$).



Overall and CV survival curves

Conclusions: Follow-up by a CRT optimization clinic may improve overall and cardiovascular survival and increase responder rate in HF patients treated with cardiac resynchronization therapy.

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Age-specific mortality and hospital readmission risks following CRT implantation - a nationwide study

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Purpose: Cardiac resynchronization therapy (CRT) is recommended in patients with appropriate indications and survival expected to exceed one year. We aimed to evaluate mortality and hospital readmission rates in CRT-recipients according to age-categories in an unselected nationwide population.

Methods: From nationwide Danish health registers we identified all patients ≥ 40 years receiving first-time implantations of a CRT-device during 2000–2010 with multi-site pacing alone (CRT-P) or with implantable cardiac defibrillator (CRT-D). According to age-categories < 50 years, 50–59 years, 60–69 years, 70–79 years and ≥ 80 years, rates of all cause mortality and incidence rates of hospital readmission for any cardiovascular cause within 30 days and one year were assessed.

Results: From 2000–2010, first-time implantations comprised 1,398 CRT-D and 1,419 CRT-P. Median age was 68.8 years (IQR 61.4–74.8), and 22.7% were women. Over a median follow up of 2.7 years (IQR 1.7–5.1), 984 (34.9%) patients died. Although mortality rates increased with advancing age, the mortality risks were comparable across age-categories (Table). In patients receiving a CRT-P, age-adjusted cardiovascular readmission rates per person-year were 0.9 for < 50 , 0.8 for 50–59, 0.9 for 60–69, 0.8 for 70–79 and 0.8 for patients ≥ 80 years old. Corresponding age-adjusted rates per person-year for patients receiving a CRT-D were 1.6 for < 50 , 1.3 for 50–59, 1.2 for 60–69, 0.9 for 70–79, and 1.2 for patients ≥ 80 years old.

Table 1. All-cause mortality risk within 30 days and one year following first-time implantation of CRT-P and CRT-D according to age-categories

Age categories	CRT-P			CRT-D		
	N	30-day	One-year	N	30-day	One-year
< 50 years	76	0% (0)	4% (3)	77	0% (0)	6.5% (5)
50–59 years	224	0% (0)	3.6% (8)	225	1.8% (4)	6.7% (15)
60–69 years	436	2.3% (10)	11.7% (51)	510	0.8% (4)	9% (46)
70–79 years	473	3% (14)	12.3% (58)	534	0.9% (5)	10.7% (57)
≥ 80 years	210	3.8% (8)	19.5% (41)	52	1.9% (1)	9.6% (5)

Conclusions: In an unselected nationwide population over a time period encompassing the first decade of CRT implantation, 30-day and one-year mortality risks were low across all age-groups, but increased with age, in particular in CRT-P patients. Cardiovascular hospital readmissions were comparable across all age groups.

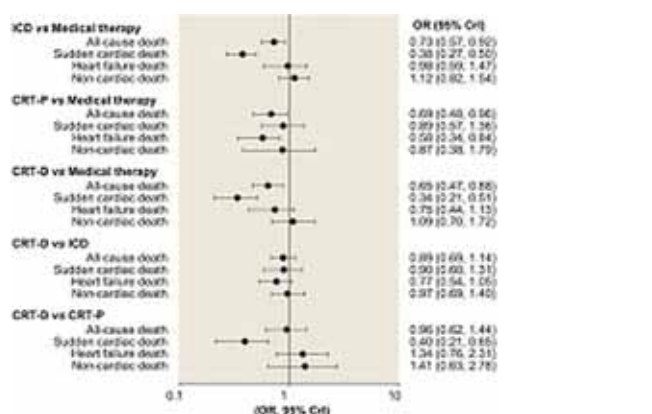
2047 | SPOTLIGHT

Combination of cardiac resynchronization and cardioverter defibrillator for heart failure with reduced ejection fraction: a network meta-analysis

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Purpose: We intended to conduct this network meta-analysis to compare the efficacy of cardiac resynchronization therapy (CRT)-defibrillator (CRT-D) with CRT-pacemaker (CRT-P) or implantable cardioverter defibrillator (ICD) in reducing mortality among patients with heart failure with reduced ejection fraction (HFrEF). **Methods:** Randomized controlled trials comparing interventions among medical therapy, ICD, CRT-P, and CRT-D in patients with HFrEF were identified through relevant databases. We performed Bayesian network meta-analyses to compare the efficacy of these therapies in the reduction of all-cause death, sudden cardiac death (SCD), heart failure death, and non-cardiac death.

Results: Thirty eligible trials with 16553 participants were identified. Compared with medical therapy, CRT-D significantly reduced all-cause death (OR 0.65, 95% CrI 0.46-0.88) and SCD (OR 0.34, 95% CrI 0.21-0.51). CRT-D trended to reduce all modes of death over ICD. When compared with CRT-P, CRT-D trended to reduce all-cause death and significantly reduced SCD (OR 0.40, 95% CrI 0.21-0.65) however trended to increase heart failure death and non-cardiac death. Sensitivity analysis revealed that CRT-D significantly reduced all-cause death (OR 0.77, 95% CrI 0.61-0.97) and heart failure death (OR 0.72, 95% CrI 0.50-0.96) over ICD after exclusion of trials studying patients with narrow QRS complex.



Conclusions: Among patients with HFrEF, CRT-D exhibited superiority over ICD only in patients with prolonged QRS duration. Current evidence is insufficient to support significant superiority of CRT-D over CRT-P. The clinical indications of

this expensive device might deserve more deliberation to target proper patient population.

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Prevalence of "TRUE LBBB" in current practice of CRT implantation

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Aim: New stricter criteria for complete LBBB definition were recently proposed. The aim of this study was to describe the current clinical practice associated with CRT implantation and how the adoption of stricter criteria for patient selection could modify recommendation classes.

Methods: We collected data from 514 consecutive patients who underwent CRT implantation from 2011 to 2013 in 35 centers. All baseline ECG were centrally reviewed in order to assess the presence of mid-QRS notching or slurring and measure the QRS duration in any leads. Indications to CRT were categorized into recommendation classes, according to current guidelines for patients in sinus rhythm: Class I in presence of LBBB (Level A with QRS duration >150ms and Level B with QRS duration 120-150ms), Class IIa Level B with no-LBBB and QRS duration >150ms and Class IIb Level B with no-LBBB and QRS duration 120-150ms. All recommendations require chronic heart failure patients with LVEF ≤35%, and NYHA functional class II, III or ambulatory IV despite adequate medical treatment.

Results: Baseline characteristics were: mean age 70±10 years, male gender 72%, ischemic etiology 44% and history of atrial fibrillation 30%. Almost all patients were in NYHA class II or III (32% and 64%, respectively). An LBBB was present in 84% of patients, while 7% had an RBBB, 8% an incomplete bundle branch block and 1% a non-specified IVCD. 41% of patients met Class I Level A recommendation, 33% Class I Level B, 7% Class IIa Level A and 5% Class IIb Level B. The remaining 14% of patients were in atrial fibrillation or had a pacemaker indication. Among patients with LBBB, 73% had mid-QRS notching or slurring in at least one lead and a QRS ≥120ms. Notching or slurring was also present in 30% of patients with a QRS <120ms. According to the novel definition, "true LBBB" was confirmed in only 39% of LBBB patients (36% male, 46% female). Therefore, 19% of Class I Level A recommendations could be reclassified as Class IIa Level B, and 32% of Class I Level B as Class IIb Level B.

Conclusion: Patients with complete LBBB may benefit the most from CRT, thus distinguish true LBBB from other conduction disorders may be clinically relevant. Novel and more specific criteria for LBBB detection, if applied in current clinical practice, may significantly impact the level of recommendation for CRT. The analysis of long-term results will clarify whether more specific selection criteria could be associated with better outcome.

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Post-CRT implant electrocardiographic score as a predictor of clinical outcome

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Background: Optimal left ventricular lead position and device programming are determinants of cardiac resynchronization therapy (CRT) response. Our study examined the ability of a simple scoring system using the post-CRT implant 12-lead ECG to predict clinical outcome.

Methods: We retrospectively analyzed ECGs of consecutive patients undergoing CRT implantation and followed up in our multidisciplinary clinic. ECG parameters: i) QRS duration, ii) time to intrinsic deflection onset (ID) and iii) voltage change in V1 lead was measured on the post-implant ECG and compared to pre-implantation parameters. Clinical outcome was assessed as a composite of all-cause death, LVAD implantation, cardiac transplantation and HF hospitalization.

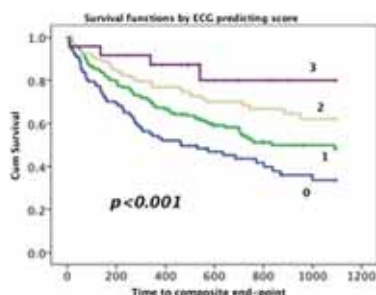


Figure 1

Results: EKG's of 487 patients were evaluated. Better survival was predicted by i) shortening of QRS duration ≥20 msec (HR 0.65 [95% CI 0.48-0.87] p=0.008), ii) 50% decreased summed voltage in V1 lead (0.67 [0.49-0.90] p=0.008) and iii) ≥40 msec ID time in V1 after pacing (0.63 [0.46-0.87] p=0.005 in univariate analysis). Each positive ECG variable was given a numerical value of 1 to create the score (ranging 1-3). The scoring system had a significant graded trend towards predicting the clinical outcome (Fig. 1, p<0.001).

Conclusion: The post-CRT 12-lead ECG score can predict long-term clinical outcomes. Prospective intra-procedural use of this scoring system to facilitate individualized LV lead placement needs evaluation.

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Long-term clinical outcomes of upgrading from chronic right ventricular pacing to cardiac resynchronization therapy in patients with heart failure

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Background: Patients with chronic right ventricular (RV) pacing upgraded to cardiac resynchronization therapy (CRT) have been excluded from majority of clinical trials of CRT. There remains to be seen whether upgrade to CRT is effective in patients with heart failure (HF) with chronic RV pacing.

Purpose: To determine long-term clinical outcomes of upgrading from chronic RV pacing to CRT.

Methods and results: CUBIC study is a multi-center registry of patients undergoing CRT during 2004-2010 at 11 institutions in Japan. A total of 945 consecutive patients were analyzed over a mean follow-up of 3.1 years after upgrade from chronic RV pacing to CRT (RVP: n=221) or primary CRT implantation (Non-RVP: n=724). Compared with Non-RVP, RVP patients were older (71 years vs. 69 years, p=0.002) and more likely to be female (38% vs. 28%, p=0.006) and to have wider QRS width (180 msec. vs. 147 msec., p<0.0001), chronic atrial fibrillation or flutter (32% vs. 19%, p<0.0001) and non-ischemic etiology (83% vs. 66%, p<0.0001). The prevalence of diabetes, chronic kidney disease (CKD) and severe mitral regurgitation were similar between the 2 groups. CRT plus ICD were more frequently indicated in Non-RVP group than in RVP (74% vs. 47%, p<0.0001). The rate of freedom from death, hospitalization for HF and composite events (CE) of death and hospitalization for HF were comparable between RVP and Non-RVP groups (at 3 years, death: 79.0% vs. 78.3%, log rank p=0.71; hospitalization for HF: 68.4% vs. 65.1%, p=0.19; CE: 60.5% vs. 56.5%, p=0.34, respectively). There was also no significant difference in the rate of reverse left ventricular remodeling defined as left ventricular end-systolic volume reduction ≥15% after 6 months (RVP: 63% vs. Non-RVP: 59%, p=0.37) and in the clinical responder rate defined as an improvement (≥1 score) of NYHA class after 6 months (RVP: 62% vs. Non-RVP: 66%, p=0.31). By Cox hazard models, the RVP was not significantly associated with an increased risk of CE relative to the Non-RVP: hazard ratio (HR) 1.09, 95% CI 0.84-1.41. Among RVP patients, independent predictors of CE were CKD (HR 1.78 95% CI 1.09-2.85), shorter duration (<5 years) of RV pacing before upgrade (HR 1.63, 95% CI 1.03-2.62) and use of ACE inhibitors or ARBs (HR 0.46 95% CI 0.29-0.73) and diuretics (HR 2.53, 95% CI 1.20-6.05). Three-year survival rate was comparable between those undergoing upgrade to CRT plus ICD and those to CRT alone (75.7% vs. 81.7%, respectively, p=0.32).

Conclusions: Long-term clinical outcomes were similar in patients undergoing upgrade to CRT from chronic RV pacing to those undergoing primary CRT.

PREDICTION AND PREVENTION OF ATRIAL FIBRILLATION

P2053 | SPOTLIGHT

Association between left atrial size and future atrial fibrillation: a 16 year follow up of 2369 women and men. Tromsø study 1994-2010

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Purpose: Atrial fibrillation (AF) increases the lifetime risk of stroke and heart failure. Several risk factors of AF have been identified. The purpose of this study was to investigate the association between echocardiographic measurements with emphasis on left atrial (LA) size and future risk of incident AF in a large population-based cohort.

Methods: A random sample of 2369 participants in the Tromsø study in Northern Norway who were 50 years and older and without AF at baseline were followed from 1994 through 2010. LA size was indexed by body surface area (BSA) and was categorized into three groups as normal (<2.2 cm/m²), moderately (2.2-2.79 cm/m²) and severely (>2.8 cm/m²) enlarged. To estimate sex-specific hazard ratios (HRs) for AF we used both age-adjusted and multivariable Cox proportional

hazards regression models adjusted for age, systolic blood pressure, heart rate, body mass index, BSA, total and HDL cholesterol, and self-reported use of alcohol, smoking, coffee, physical activity, hypertension, prevalent coronary heart disease (CHD) and diabetes.

Results: Mean age at baseline was 62.6 years and 51.4% were women. During follow-up we identified 462 cases of incident AF (193 women). LA size was associated with AF in both sexes. A moderately enlarged LA was in both women and men associated with 64% increased risk for AF compared to subjects with normal LA size. In subjects with severely enlarged LA, we found HRs for AF of 4.4 (95% CI, 2.6-7.4) in women and 3.9 (95% CI, 2-7.6) in men compared with subjects with normal LA size (p-value for linear trend <0.001). Hypertension increased risk of AF (HR 1.6; 95% CI, 1.3-1.9) in age and sex adjusted analysis. This relationship was somewhat weaker (HR 1.5; 95% CI, 1.2-1.9) with additional adjustment for LA. Similarly, prevalent CHD was in age and sex adjusted analysis associated with AF (HR 2.4; 95% CI, 1.9-3.0). When also adjusted for LA size, the HR was slightly attenuated (HR 2.2; 95% CI, 1.7-2.9).

Conclusion: Enlarged LA size was independently associated with an increased risk of future AF in both sexes.

P2054 | BEDSIDE

A new biomarker based risk score for predicting major bleeding in atrial fibrillation - the ABC (age, biomarkers, current disease) risk score

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Purpose: The benefit of oral anticoagulation in atrial fibrillation (AF) is based on a balance between reduction in ischemic stroke and increase in major bleeding. To improve the prediction of bleeding we developed a new bleeding risk score based on novel biomarkers and clinical variables.

Methods: The study included 14,537 patients with AF randomized to either warfarin (target INR 2.0-3.0) or apixaban 5 mg b.d. in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Blood biomarkers reflecting cardiovascular and renal function – high sensitivity cardiac troponin (cTn-hs), natriuretic peptide (NT-proBNP), growth differentiation factor 15 (GDF-15), cystatin-C, and hematocrit – were determined at randomization. The biomarker levels and available clinical variables were assessed in Cox-regression models predicting major bleeding where each variable with a relevant contribution to the c-statistic obtained a weight proportional to the Cox-model coefficients.

Results: The Cox-models were based on 25,150 person years of follow-up and 662 major bleeding events. The most important predictors were: GDF-15, cTnT-hs, age, hematocrit, and prior bleeding. The score obtained the acronym ABC (Age, Biomarkers (GDF-15, cTnT-hs, and hematocrit), Current disease (history of bleeding)). The ABC score yielded c-index 0.68, considerably higher than the conventional HAS-BLED score with c-index 0.59 in the same cohort. The net reclassification improvement was positive for the ABC risk score and yielded a significant improvement of 25% (p<0.001) as compared with HAS-BLED. The ABC score also achieved higher c-index compared with HAS-BLED in subgroups e.g. with no prior major bleeding, (0.68 vs. 0.58, respectively), or only on warfarin (0.68 vs. 0.59, respectively). There were consistent lower rates of bleeding with apixaban compared with warfarin across the range of the ABC score.

Conclusions: A novel and simplified risk score for predicting major bleeding using biomarker and clinical data was developed from a large cohort of patients with atrial fibrillation on anticoagulation. The ABC bleeding risk score performed better than the currently guidelines recommended risk score and may lead to improved treatment decisions in patients with AF.

P2055 | BEDSIDE

Aerobic interval training reduces the burden of atrial fibrillation

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Background: Exercise training is an effective treatment of important atrial fibrillation (AF) comorbidities. However, high levels of endurance exercise have been associated with increased prevalence of symptomatic AF. This study examines the effect of aerobic interval training in patients with AF.

Methods: 51 patients with paroxysmal or persistent AF were randomized to aerobic interval training (n=26) consisting of 4 times 4 min of treadmill exercise at 85-95% of peak heart rate, 3d/week/12 weeks or a control group (n=25). An implantable loop recorder measured time in AF continuously from 4 weeks before to 4 weeks after the intervention period. Cardiac function, lipid status and quality of life were evaluated before and after the 12-week intervention-period.

Results: There was an increase in burden of AF in the control group, and a reduction in the exercise group (P=0.001 between groups). 16 patients in the control group and 3 patients in the exercise group experienced an increase in the burden

of AF, whereas 5 patients in the control group and 10 patients in the exercise group experienced a decrease in AF burden. The rest had no change from pre to post. There was a trend towards fewer cardioversions (1 vs. 6, P=0.14) and hospital admissions (1 vs. 9, p=0.07) in the exercise group. There were no significant differences in use or changes of antiarrhythmic drugs between the groups. In the exercise group there was a significant increase in VO2Max (9.5% vs. -1.1%, p=0.002), left atrial ejection fraction during atrial systole (+1.3 percentage points (pp) vs. -2.5 pp, p=0.047) and left ventricular ejection fraction (+3.2 pp vs. -1.6 pp, p=0.03) by MRI. SF-36 measures of general health and vitality, and a significant decrease in cholesterol (-0.38 mmol/L vs. +0.13mmol/L, p=0.009) and triglyceride levels (-0.23 mmol/L vs. +0.18 mmol/L, p=0.008) compared to controls.

Conclusion: Aerobic interval training for 12 weeks clearly reduces the burden of AF in symptomatic patients. It is followed by a significant improvement in VO2Max, left atrial and ventricular function, cholesterol levels, and quality of life. Further studies are needed to evaluate the underlying mechanisms and the effect of exercise training for a longer period of time.

P2056 | BEDSIDE

Small amounts of daily walking or bicycling reduce the risk of atrial fibrillation in middle-aged and elderly women

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Purpose: This study examines the influence of physical activity at different ages and of different type on the risk of developing AF in a large cohort of Swedish women.

Methods: Information about physical activity (PA) was obtained from 36 513 AF-free women, aged 49-83 years (median age 60 years), who had completed a self-administered questionnaire at baseline in 1997. Participants reported their time spent on leisure-time exercise (moderate- to high-intensity PA) and on walking or bicycling (low- to moderate-intensity PA) throughout their lifetime (at 15, 30, and 50 years of age, and at baseline). Participants were followed up in the Swedish National Inpatient Register for ascertainment of AF. Cox proportional hazards regression models were used to estimate relative risks (RR) with 95% confidence intervals (CI), adjusted for potential confounders.

Results: During a mean follow-up of 11.0 years (SD=2.4), 2915 cases of AF were diagnosed. Walking/bicycling at baseline was inversely associated with risk of AF (RR 0.81, 95% CI, 0.72-0.92, for ≥40 min/day vs. almost never). As little as 20-39 min per day of walking or bicycling showed a reduction in the risk of AF (RR 0.86, 95% CI, 0.76-0.97). Results were similar for walking/bicycling at age 50 years. Leisure-time exercise at baseline was also inversely associated with risk of AF (RR 0.85, 95% CI, 0.75-0.95 for ≥4 h/week vs. <1 h/week). There was no association between risk of AF and leisure-time exercise or walking/bicycling at the age of 15 and 30.

Conclusion: In middle-aged and elderly women, fairly small amounts of daily walking or bicycling were associated with a reduced risk of AF. Leisure-time exercise of more than four hours a week also showed a reduction in the risk of AF.

P2057 | BEDSIDE

Mineralocorticoid receptor blockade added-on standard antiarrhythmic pharma therapy decreases the atrial fibrillation recurrences in a 24 months study

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Purpose: The alterations of atrial structure induced by the iterative atrial fibrillation (AFib) includes RAAS overexpression which could have a decisive role, aldosterone being involved in inflammation, fibrosis, remodelling. The objective of our study is to compare directly two therapeutic regimens (each with 3 sub-regimens) in order to assess the benefit of mineralocorticoid receptor blockade (MCRB) in repetitive AFib patients (pts).

Method: The study considered 1152 pts with AFib, starting from 1st Nov 2007, structured into two comparative groups, slight male and 6th decade pts predominance. The pts within the first group were treated with antiarrhythmics [amiodarone (A) 69.69%, or propafenone (P) 22.65%, or sotalol (S) 7.66%] + MCRB, while the pts in the second group were treated with antiarrhythmics (A, P, S, same

Table 1

Therapeutic Arm	AF episodes 24 mo. before	AF episodes 24 mo. after	p value
A + MCRB	9,1±2,1	3,7±2,0	<0.01
P + MCRB	9,0±2,5	3,9±2,3	<0.01
S + MCRB	8,7±2,4	4,1±2,1	<0.05
Antiarrhythmic + MCRB	9,0±2,3	3,8±1,9	<0.005
A + K	8,8±1,7	10,5±2,5	<0.01
P + K	9,1±2,4	10,3±1,7	<0.01
S + K	8,9±0,9	10,3±1,1	<0.05
Antiarrhythmic + K	8,9±2,6	10,4±2,8	<0.005

See text.

proportions) + exogenous K supplement. We compared the occurrence of AFib episodes 24 months before and after the initiation of MCRB treatment, respectively. Among exclusion criteria we mention treatment with betablockers (indirect antirenin effect), and ACE-inhibitors/ARBs (K suppliers).

Results: Table 1 displays the main outcomes of the study.

Conclusions: MCRB seems to be a valuable additional therapeutic tool in prevention AFib recurrences. This seems to be a class effect, no difference being found between spironolactone and eplerenone subgroups. MCRB brings an endogenous potassium, more metabolic friendly than exogenic uptake. Beyond, MCRB reduces RAAS activity and could also reduce the fibrosis involved in structural remodelling. These beneficial effects were independent of blood pressure lowering.

P2058 | BEDSIDE

The effects of reactive atrial antitachycardia pacing on the progression of atrial tachyarrhythmias: secondary analysis results of the randomized MINERVA trial

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Purpose: Atrial fibrillation (AF) is a frequent comorbidity in pacemaker patients. The MINERVA trial demonstrated that combining advanced pacemaker features that minimize unnecessary right ventricular pacing (MVP), atrial overdrive pace, and deliver antitachycardia pacing at arrhythmia onset and during rhythm change (Reactive ATP) reduces permanent AF risk by relative 61% compared to standard dual-chamber pacing (DDDR). We investigated Reactive ATP's role on delaying atrial tachyarrhythmia (AT/AF) disease progression in the MINERVA trial patients. **Methods:** Dual-chamber pacemaker patients with AT/AF history were randomly assigned to receive DDDR (n=385), MVP alone (n=398), or the advanced features (DDDRP+MVP; n=383). Permanent AF or complete heart block were exclusion criteria. The primary outcome of this analysis was risk of persistent AT/AF, defined as ≥ 7 consecutive days with AT/AF. Secondary endpoints comprised AT/AF rate and Reactive ATP efficacy, adjusted via the generalized estimating equations (GEE) method. Persistent AT/AF incidence was estimated through Kaplan-Meier method. Associations with persistent AT/AF risk were evaluated via multivariable Cox regression.

Results: At baseline, 982 (86%) patients had history of AF, 228 (20%) history of atrial flutter, and 197 (17%) history of atrial tachycardia. Within 2 years of follow-up, 804 (69%) patients suffered AT/AF episodes and were characterized by a median AT/AF rate of 244 beats per minute (bpm), 25th-75th percentile range=216 bpm-280 bpm. GEE adjusted Reactive ATP efficacy was 44.4% (95% confidence interval=41.3%-47.6%). Reactive ATP efficacy was significantly and inversely associated with AT/AF rate, with a success rate of 35% for AT/AF rates > 340 bpm, 47% for AT/AF rates between 240 bpm and 340 bpm and 50% for AT/AF rates < 240 bpm. At 2 years persistent AT/AF incidence (95% confidence interval) was 26% (22%-31%) in DDDR, 25% (21%-30%) in MVP and 15% (12%-20%) in DDDR+MVP ($p<0.001$ vs DDDR, $p=0.002$ vs MVP). Multivariate modeling identified high Reactive ATP efficacy ($>44.4\%$) as a significant predictor of reduced persistent AT/AF (hazard ratio (95% confidence interval)=0.42 (0.21-0.83), $p=0.013$).

Conclusions: In bradycardia patients, DDDR+MVP pacing delays AT/AF disease progression, with Reactive ATP efficacy being an independent predictor of persistent AT/AF reduction. While at baseline most of patients had history of AF, pacemaker diagnostics showed that most atrial arrhythmias started as atrial tachycardia and atrial flutter or, over time, transitioned to longer cycle lengths becoming subject to pace termination.

P2059 | BEDSIDE

Left atrial appendage closure/amputation did not affect the incidences of early post-operative atrial fibrillation occurrence or stroke: analysis based on prospective observational study

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Purpose: Atrial fibrillation (AF) is the most common cardiac arrhythmia which is highly associated with morbidity and mortality, and its incidence after cardiac surgery has been reported to be 20-30%. The most relevant complication of AF is a major increase in the risk of stroke. Since the left atrial appendage (LAA) is the main source of emboli, LAA closure or amputation in patients with chronic AF has been performed. However, the effect of LAA closure in patients without AF history on post-operative new-onset AF has not yet been elucidated. In the present

study, we investigated how surgical LAA closure or amputation affect early post-operative course including new-onset AF and stroke.

Methods: We analyzed 1856 consecutive patients (69.2% of male, mean age 66.8 ± 12.2 year-old) undergoing open-heart surgery between January 2009 and October 2013 at our institution. Among those, 805 cases (43.4%) underwent coronary bypass surgery (CABG), 803 cases (43.3%) received valvular surgery (V) and 246 cases (13.3%) undergoing combination of CABG and valvular surgery (CABG+V). The early post-operative clinical courses including paroxysmal AF occurrence between patients with and without concomitant LAA closure/amputation were compared.

Results: A total of 375 patients (20.2%) received LAA procedure. The incidence of post-operative AF was higher in patients undergoing LAA procedure as compared with those without the procedure (48.5% vs. 39.0%, $p=0.0008$); however in a subset of patients underwent CABG+V, the AF occurred less frequently in patients underwent LAA procedure (40.0 vs. 54.7%, $p=0.0416$). The incidence of stroke was not significantly different between those with and without LAA procedure (3.7 vs. 3.0%, $p=0.4933$). Multivariate analysis including pre-operative clinical characteristics, echocardiographic parameter, LAA procedure (yes=1, no=0) and surgery type (valvular=1, others=0) revealed that older age (years) [odds ratio (OR) 1.04, 95% confidential interval (CI) 1.03-1.05] and larger LA diameter (cm) [OR 1.05, 95%CI 1.03-1.06] were associated with AF development; however, neither LAA procedure or surgery type did not predict AF. The bleeding amounts, length of ICU stay and total hospital stay were not significantly different between patients with and without LAA closure/amputation.

Conclusions: LAA closure/amputation at the time of open heart surgery can be safely performed; however, it did not affect early post-operative incidences of AF development or stroke. Further investigation would be required to evaluate its long-term efficacy on preventing stroke.

NON-PHARMACOLOGICAL ISSUES IN ADVANCED HEART FAILURE

P2060 | BEDSIDE

Predictors and late incidence of persistent or recurrent heart failure after aortic valve replacement for aortic stenosis compared with aortic regurgitation

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Aim: 1. To evaluate the effect of aortic valve replacement (AVR) on long term evolution of the left ventricular (LV) systolic and diastolic performance, comparing patients (pts) with aortic stenosis (AS) to pts with aortic regurgitation (AR). 2. To identify the independent predictors for persistence or recurrence of the congestive heart failure (HF) late after isolated AVR.

Methods: 10 years prospective study on 802 pts undergoing AVR for AS (456pts) or AR (346pts). Pts were evaluated clinically and echocardiographically (including TDI) preoperatively and yearly till 10 years postoperatively. The effect of demographic, comorbid, and valve-related variables on the composite outcome of NYHA class III/IV symptoms or congestive heart failure death after surgery was evaluated with stratified log-rank tests, Cox proportional hazard models and logistic regression. Multivariable analyses were adjusted for age and gender and included left ventricular ejection fraction (LVEF) $\leq 35\%$, restrictive left ventricular diastolic filling pattern (LVDFP), renal insufficiency and logistic EuroSCORE $\geq 20\%$.

Results: 1. At 5 years postoperatively, restrictive LVDFP persisted at 37.19% of the pts from AS group and at 65.79% pts from AR group. Also, LVEF $\leq 35\%$ was found at 21.95% pts from AS group and at 56.52% pts from AR group.

2. Freedom from congestive HF or cardiovascular death at 5 and 10 years, was significantly higher in AS group (86.84% and 76.32%) compared with AR group (77.46% and 60.4%) ($p<0.05$).

3. Regression analysis identified as independent predictors for persistence or recurrence of HF late after AVR: preoperative AR (RR=21.2), E/E' ratio > 12 (RR=25.1), LA dimension index $> 30\text{mm/m}^2$ (RR=8.2), LV enddiastolic volume (LVEDV) $> 200\text{cm}^3$ (RR=8.6), preoperative NYHA class IV (RR=9.2), atrial fibrillation (AF) (RR=6.2), obstructive pulmonary disease (COPD) (RR=28.6), smoking (RR=18.7), prosthesis mismatch (RR=12.5) and 2 degree mitral regurgitation (MR) (RR=12.6) ($p<0.05$).

Conclusions: 1. LV systolic and diastolic dysfunction is reversible mostly after AVR for AS than for AR, both in the early and late postoperative term.

2. On long term, freedom from congestive HF or cardiovascular death was significantly higher in AS group. The presence of restrictive LVDFP had a significant impact on outcomes, decreasing long-term survival and increasing hospitalizations rates, mostly in preoperative AR.

3. The main predictors for persistence or recurrence of HF late after AVR were: preoperative AR, restrictive LVDFP, LA dimension index $> 30\text{mm/m}^2$, LVEDV $> 200\text{cm}^3$, preoperative NYHA class, AF, COPD, smoking, prosthesis mismatch and MR.

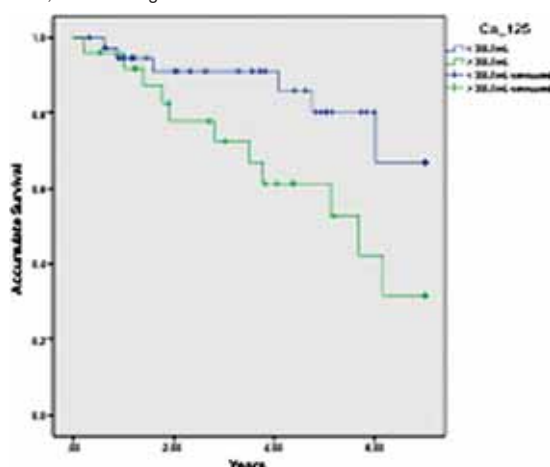
P2061 | BEDSIDE**Long-term prognostic role of Ca-125 in non-congestive patients undergoing cardiac transplantation**

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Introduction: Carbohydrate antigen 125 (Ca125) is a well-established biomarker for monitoring ovarian cancer growth. Recent studies have suggested that Ca125 serum levels are remarkably elevated in patients with heart failure (HF), being an independent predictor of mortality and heart transplantation (HT). However, its long-term prognostic role in patients undergoing a HT has not been investigated yet.

Methods: We retrospectively studied all patients who underwent a HT in our Advanced HF Unit, and had a previous determination of Ca125, since 2003 until 2012. Decompensated patients at the moment of the blood extraction and those whose survival was less than 1 month after HT were excluded. Pre-HT clinical, haemodynamical and follow-up data was analyzed.

Results: Of 173 patients who underwent a HT, 64 could be included in our study. When divided this population into normal or elevated Ca125 levels (>35 U/mL, $n=25$), no significant differences were found according to their Baseline Characteristics. Survival was significantly inferior in the "Elevated Ca125" group (94 vs. 94%, 91 vs. 72%, 80 vs. 61 and 67 vs. 31% at 1, 3, 5 and 7 years, respectively, $p=0.03$) (Figure1). Furthermore, "Elevated Ca125" group presented a clearly negative tendency to graft rejection. There were no differences according to infections, tumours or graft vascular disease.



Conclusions: In our population, non-congestive patients with high levels of Ca125 had an inferior long-term survival after Heart Transplant than those with normal levels. A tendency to less rejection existed in this group, too.

P2062 | BEDSIDE**Increased pump speed improves the exercise capacity of heart failure patients receiving left ventricular assist device support**

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Introduction: Left Ventricular Assist Devices (LVADs) are an established treatment for advanced heart failure. Continuous flow LVADs improve survival, functional status and quality of life in selected patients. However exercise capacity remains below normal despite LVAD support.

At present, patients treated with a continuous flow LVAD are maintained at fixed pump speed. We have previously shown that a reduction of pump speed adversely affects exercise capacity. Here, we investigate the effect of temporarily increasing the pump speed on exercise capacity.

Methods: We studied 20 ambulatory heart failure patients (18 males, age 52 ± 14 years) receiving support with a HeartWare HVAD ($n=14$) or Thoratec HeartMate II ($n=6$). Indication for LVAD implantation was advanced heart failure (9 non-ischaemic DCM, 7 ischaemic DCM, 4 familial DCM, 18 male, age 52 ± 14) with a bridge to transplantation strategy.

Each patient underwent two treadmill exercise test, the first at their clinical pump speed (speed-fixed) and the other at increased pump speed (speed-inc). Clinical pump speed for HeartWare HVAD was 2844 ± 200 rpm and for Thoratec HeartMate II was 9233 ± 233 rpm. To minimise the risk of left ventricular suction events, the pump speed was increased prior to exercise under echocardiographic control and we aimed to temporarily increase pump speed between 10 to 15%.

Results: Overall, the second test was done at a 13% faster LVAD speed than the first. All cardiopulmonary exercise tests ($n=40$) were adequate and the peak

respiratory exchange ratio (RER) was similar in both test (speed-fixed RER= 1.17 ± 0.12 versus speed-inc RER= 1.16 ± 0.11 , $p=0.59$). Peak oxygen uptake (pkVO_2) at speed-fixed was 15.5 ± 3.4 mL/kg/min and increased to 16.6 ± 3.6 mL/kg/min at speed-inc ($p=0.0001$). This was associated with an increase in the estimated LVAD flow at peak exercise from 7.0 ± 1.3 l/min during speed-fixed test to 8.1 ± 1.0 l/min at speed-inc test ($p=0.0014$). The ventilatory efficiency during exercise remained unchanged (speed-fixed VE/VCO₂ slope= 35.9 ± 8.2 versus speed-inc VE/VCO₂ slope= 35.2 ± 7.3 , $p=0.30$).

Conclusion: It was feasible to temporarily increase LVAD speed to increase aerobic exercise capacity and this resulted in a significant increase in peak oxygen consumption. Further studies are warranted to determine whether this phenomenon can be used to improve the exercise capacity of LVAD recipient.

P2063 | BEDSIDE**Effects of increasing donor age on the risk of permanent pacing after orthotopic heart transplantation**

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Purpose: Due to extreme scarcity of donor hearts, increasingly older and marginal donor hearts are accepted for orthotopic heart transplantation (HTx). We evaluated the relationship between the donor age and the need for pace-maker (PM) implantation early or late after HTx.

Methods: Data of all consecutive patients transplanted between 1984 until 2014 at our centre were analysed ($n=612$, 74% male; median follow up of 97 months [IQR 38-161]). Three groups were created based on donor age: Group I (0-35 y, $n=345$), Group II (35-50 y, $n=190$) and Group III (>50 y, $n=77$). The primary outcome was permanent PM implantation after HTx for either sinus node dysfunction (SND) or AV block (AVB). The need for early (<90 days after HTx) or late PM (>90 days) was evaluated. The following secondary parameters were analysed: recipient age, ischemic time and death.

Results: The mean recipient age at HTx was 46.4 ± 14.3 years [range 2-72 y] and donor age 32.8 ± 13.7 y. Significant older donor hearts were transplanted during the last ten years compared to the first ten years (40.1 ± 15.9 y vs. 25.7 ± 8.3 y, $p<0.001$) and more early PMs were implanted (10.2% vs. 1.7%, $p<0.001$). Ischemic time (176 ± 45 min vs. 181 ± 48 min vs. 186 ± 48 min, $p=ns$, respectively) was comparable for group I, II and III. Overall 11.3% (SND, $n=31$; AVB, $n=38$) received a PM after a median period of 10.6 months [IQR 1.3-94 months]. In group III a higher amount of early PM were implanted (11.7%, $n=9$) compared to group I (2.0%, $n=7$; $p=0.001$). For late PM implant equal rates were observed (6.5% vs. 6.4%, $p=ns$, respectively). In total 55% ($n=342$) died during follow up. The 10-year survival rate was 61%.



PM free survival after HTx.

Conclusions: Increasing donor age, particularly >50 years, is a major risk factor for the need of permanent pacing post-HTx.

P2064 | BEDSIDE**Outcome of heart transplantation in the urgent receptor: whom should we choose?**

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Objectives: The improvement in the medical treatment of heart failure has allowed extending the survival of patients and delaying their entry in transplant's list. Therefore, we receive receptors in worse clinical status with the need for urgent transplantation. We propose to compare the immediate and long-term results of heart transplant in patients with different levels of urgency.

Methods: From November 2003 to December 2012, 228 patients were submitted to cardiac transplantation. Pediatric patients and those in cardiogenic shock (with circulatory and/or ventilatory support) were excluded. From these, 58 (27%) were hospitalized and inotrope dependent [Group A] vs 154 (73%) who were waiting for transplant at home [Group B]. Patients in group A were younger (52.0 ± 11.3 vs 55.2 ± 10.4 ; $P=0.050$) and waited less for transplant (29.4 ± 43.8 vs 48.8 ± 45.2 days; $P=0.006$). No difference was found in gender (male sex: 77.6% vs 77.9%) or other comorbidities. Hemoglobin was lower in group A (12.2 ± 2.2 vs 13.2 ± 1.9 ; $P=0.001$) and bilirubin (1.5 ± 1.0 vs 1.1 ± 0.7 ; $P=0.014$) and creatinine (1.6 ± 1.2 vs 1.4 ± 0.4 ; $P=0.010$) were higher. Donor characteristics, such as age, sex, sex mismatch, inotropic and ventilatory support and cause of death were similar between groups. Mean follow-up time was 4.5 ± 2.7 years.

Results: No difference was found in ischemic (89.1 ± 37.0 vs 91.5 ± 34.5 ;

P=0.660) and CPB (98.5±39.5 vs 99.7±32.0; P=0.813) times, as well as in use of inotropic support for more than 48 hours postoperatively (13.8% vs 11.0%; P=0.579). No significant difference was found in the incidence of cellular or humoral rejection and cardiac allograft vasculopathy during follow-up. New onset diabetes mellitus after transplantation during the first year was slightly higher in group A (15.5% vs 11.7%; P=0.456) and these patients showed increased risk for serious infection during the same period (22.4% vs 12.3%; P=0.068). At time of transplantation higher levels of creatinine were found in group A, but that difference dissipated over time. Hospital mortality was similar between groups A and B (3.4% vs 4.5%; P=0.724). Comparable overall long-term survival (7.8±0.5 vs 7.4±0.3 years) was documented.

Conclusions: The data obtained in patients in priority list suggests that similar results are expected when comparing to those who are waiting for transplant at home. The allocation of donors to the former group of patients does not appear to reduce the efficiency of transplantation. These results may not extend to patients in more critical condition.

P2065 | BEDSIDE

Has donor heart selection become more stringent in the era of improved survival with continuous-flow left ventricular assist devices as bridge to transplant?

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Purpose: In the era of improved survival and outcomes with continuous-flow left ventricular assist devices (CF-LVADs) as bridge to transplant (BTT), we sought to evaluate if our criteria for an acceptable donor heart have become more stringent.

Materials and methods: We retrospectively reviewed all the donor offers at our institution from October 2011 to September 2012.

Results: A total of 426 donor offers were reviewed: 81% (n=344) were declined and 19% (n=82) accepted for heart transplantation. Of the declined offers, the most common causes of donor death included stroke (42%, n=144), anoxia (29%, n=102) and head trauma (23%, n=79). Ejection fraction (EF) was the strongest predictor of declining the offer, with every 1% decrease in EF increasing the odds of declining the donor heart by 6%. Older age, valvular abnormalities and IV drug use were also predictors of declining the donor offer. Death due to stroke almost doubled the odds of declining the donor heart compared to anoxia, head trauma or other causes. Elevated creatinine had a marginally significant association with probability of declining the donor offer (Table 1).

Table 1

Donor Heart Information	Odds ratio	95% Confidence Interval	p-value
Age, years	1.02	(1.00,1.04)	0.02
Cause of death			0.09
Anoxia	0.48	(0.22,1.02)	
CVA/stroke	ref		
Head trauma	0.41	(0.20,0.84)	
Other	0.51	(0.15,1.97)	
IV drug user	5.17	(1.42,33.58)	0.01
Ejection fraction, %	0.94	(0.91,0.97)	0.0002
Valve abnormalities	1.93	(1.07,3.58)	0.03
Creatinine, mg/dl	1.20	(0.96,1.60)	0.12

Odds of donor offer decline. Multivariable logistic regression analysis.

Conclusion: Donor death by stroke, decreased EF, older age, valvular abnormalities and IV drug use were identified as predictors of declining the heart for transplantation. The high percentage of declined offers reflects the quality of donor offers as opposed to change in our acceptance criteria. These data may have important implications in the current era of improved survival with CF-LVADs as BTT.

P2066 | BEDSIDE

Surveillance endomyocardial biopsy after cardiac transplantation is not worth the risk

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Purpose: Endomyocardial biopsy (EMB) is routinely performed to monitor acute cellular rejection after cardiac transplantation. However, EMB is an invasive procedure that carries a risk of adverse effects and complications. The aim of this study was to evaluate the incidence of acute rejection episodes within the first year after transplantation in surveillance EMBs, and to evaluate a risk/benefit ratio of surveillance EMBs according to rejection rate requiring treatment to complication rate.

Methods: A total of 333 adult patients after cardiac transplantation undergoing 12 surveillance endomyocardial biopsies at predefined timepoints within the first year after transplantation were studied. During this time a total of 3401 endomy-

ocardial biopsies were performed. 3328 (97.8%) were surveillance EMBs. EMBs due to clinical suspicion for acute rejection or control after biopsy proven acute rejection (n=73, 2.2%) were excluded from the study. Complications were defined as: presence of hemopericardium requiring drainage, hematoma from puncture site, pneumothorax, vascular injury and non representative endomyocardial biopsy. The benefit ratio was calculated comparing the incidence of acute rejection with the complication rate.

Results: During the first 2 weeks after HTX 643 EMBs revealed 6 rejection episodes (0.9%), 19 complications (2.9%) occurred resulting in a benefit ratio of 0.31. Three weeks after HTX 309 biopsies revealed 17 rejections (5.5%), 13 complications (4.2%) resulted in a benefit ratio of 1.3. After four weeks 303 biopsies detected 8 rejections (2.6%), 15 complications (4.9%), benefit ratio: 0.53. During week five to twelve the 5th to 7th EMBs were performed with a total of 733 biopsies revealing 22 rejections (3.0%), 30 complications (4.1%) resulted in a benefit ratio of 0.73. After that 1340 biopsies (8th to 12th EMB) detected 22 rejections (1.6%), 24 complications (1.8%) resulted in a benefit ratio of 0.88.

Conclusions: Three weeks after cardiac transplantation there is a peak of rejection. It is the only timepoint, when the risk of rejection is higher than the procedural risk of EMB resulting in a positive benefit ratio. Our data show that surveillance biopsy in the 3rd week makes sense whereas other EMBs should be performed on clinical suspicion rather than scheduled surveillance biopsies. In a modern era of immunosuppression rigid biopsy regimens should be reconsidered and further development of rejection surveillance is warranted.

NEW INSIGHTS IN ACUTE PULMONARY EMBOLISM

P2067 | BEDSIDE

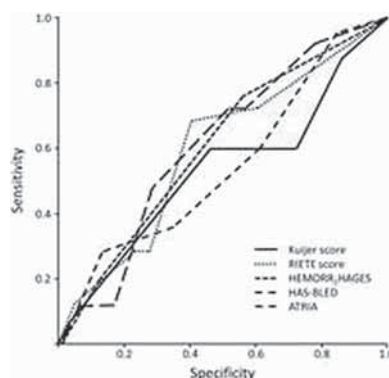
Performance of five different bleeding-prediction scores in patients with acute pulmonary embolism

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Purpose: Bleeding-prediction scores may help guiding therapeutic management of patients with acute pulmonary embolism (PE), although no such score has been validated for this patient category. We aimed to externally validate and compare two risk bleeding-scores for venous thromboembolism (VTE) with three risk scores developed for patients with atrial fibrillation in a "real-world" cohort of consecutive PE patients.

Methods: We performed a prospective observational cohort study in 425 patients with acute PE who were treated with heparins followed by vitamin-K-antagonists. The Kujier score, RIETE score, HEMORR2HAGES, HASBLED, and ATRIA were assessed at baseline. All patients were followed for the occurrence of major bleeding over a 30-day period, and over a 6-month period in a consecutive subsample of 129 patients. The accuracies of the original 3-level and newly defined 2-level outcome of the scores were compared.

Results: Overall, 25 of 425 (cumulative incidence 5.9% [95%CI 3.7-8.1%]) patients suffered a major bleeding within 30 days, with a case fatality rate of 8.0% (95%CI 1.1-26). The 6-month cumulative bleeding-incidence was 8.6% (95%CI 2.5-17%) with a case fatality rate of 0%. The predictive power of all five bleeding-scores was poor, with c-statistics ranging between 0.45 and 0.63 (Figure). Results were comparable for the 3-level and 2-level score outcomes, and for both follow-up periods. No individual score was found to be superior.



Receiver operating characteristic curves.

Conclusions: Current available bleeding-scores have insufficient accuracy to predict anticoagulation-associated bleeding in patients with acute PE. The development of a high quality bleeding-prediction score in patients with acute PE is needed to assist therapeutic decision making such as duration of anticoagulation and choice of anticoagulant agent.

P2068 | BEDSIDE**Optimized high sensitive troponin T cut-off values for risk stratification of normotensive patients with pulmonary embolism**

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Purpose: High sensitive troponin T (hsTnT) values <14 pg/ml help identify normotensive pulmonary embolism (PE) patients at low-risk. Whether optimized cut-off values for hsTnT and adjustment for age provides superior information for identification of intermediate-risk patients is unknown.

Methods: We prospectively studied 682 normotensive patients with acute PE from 13 participating European centres (median age, 70 [54-78] years). HsTnT was measured on admission using a highly sensitive quantitative electrochemiluminescence immunoassay.

Results: Overall, 29 patients (4.3%) had an adverse 30-day outcome (PE-related death, need for CPR, catecholamines, or intubation). The calculated optimal hsTnT cut-off value of 33 pg/ml (AUC, 0.74 [0.67-0.82], $p < 0.001$) was associated with a 6.32-fold increased risk of an adverse outcome ([2.55-15.87], $p < 0.001$) which was inferior compared to the prognostic information provided by the established cut-off value of 14 pg/ml (OR, 9.43 [2.22-40.00], $p = 0.002$). Although hsTnT concentrations correlated with age ($r = 0.317$; $p < 0.001$) and GFR ($r = -0.314$, $p < 0.001$), in multivariable analysis the prognostic value of hsTnT ≥ 14 pg/ml was independent from age and renal insufficiency (OR, 7.79 [1.80-33.80], $p = 0.006$). Moreover, hsTnT plasma levels on admission or its prognostic value were not affected by the duration of symptoms prior to admission. While age-adjusted hsTnT cut-off values (<65 years, 25 pg/ml; 65-79.9 years, 35 pg/ml; ≥ 80 years, 45 pg/ml) did not provide additive information in patients <80 years, hsTnT was of prognostic value in patients ≥ 80 only if the age-adjusted cut-off value was used (OR, 6.23 [2.62-14.81], $p < 0.001$). A two-step approach based on the sPESI in the first step, and either hsTnT ≥ 14 pg/ml in patients with sPESI <1 points or RV dysfunction on echocardiography in patients with sPESI ≥ 1 point(s) as a second step was developed. This simple strategy identified an "intermediate risk" population with a 11.5% rate of an adverse outcome ($n = 156$ [22.9%], sPESI ≥ 1 point(s) and RV dysfunction), and a "very low risk" population with a 0% rate of adverse events ($n = 169$ [24.8%]; sPESI <1 points and hsTnT <14 pg/ml).

Conclusion: Although troponin levels were assumed to be affected by renal function, age, and symptom duration, in the present study optimized cut-off values for hsTnT did not improve risk assessment of normotensive patients with PE. However, in elderly patients (≥ 80 years) only hsTnT ≥ 45 pg/ml predicted an adverse 30-day outcome. The use of a two-step approach might help fine-tuning risk stratification of normotensive PE patients.

P2069 | BEDSIDE**Combination with clinical parameters optimises the prognostic value of heart-type fatty acid-binding protein (H-FABP) in normotensive patients with pulmonary embolism**

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Purpose: Recent evidence derived from single-centre cohort studies suggests that heart-type fatty acid-binding protein (H-FABP) may reliably predict an adverse clinical outcome in patients with acute pulmonary embolism (PE).

Methods: We validated the prognostic performance of H-FABP in a large prospective, multicentre cohort of normotensive patients with acute PE. An adverse outcome was defined as death from any cause or haemodynamic collapse (systolic blood pressure <90 mmHg for at least 15 minutes, need for catecholamine administration, endotracheal intubation, or cardiopulmonary resuscitation) within the first 30-days. H-FABP was determined using an immunoturbidimetric assay.

Results: The study included 716 haemodynamically stable patients with acute symptomatic PE. During the 30-day study period, 41 patients (5.7%) had an adverse outcome. These patients had significantly higher baseline H-FABP values (median, 5.3 [interquartile range, 3.1 to 14.4] ng/ml) compared to patients with a favourable outcome (4.1 [2.5 to 6.5] ng/ml; $p = 0.006$). Overall, 209 patients (29.2%) had H-FABP levels above the predefined cut-off value of 6 ng/ml; of those, 19 patients (9.1%) had an adverse 30-day outcome compared to 22 (4.3%) of 507 patients with low H-FABP levels (sensitivity, 46%; specificity, 72%; positive predictive value [PPV], 9%; negative predictive value [NPV], 96%; $p = 0.01$). Using logistic regression, H-FABP ≥ 6 ng/ml was associated with a 2.2-fold increase in risk of an adverse outcome (95% CI, 1.17 to 4.17; $p = 0.015$).

In contrast to the moderate prognostic value of H-FABP alone, risk stratification could be optimized if H-FABP was combined with the simplified Pulmonary Embolism Severity Index (sPESI): Patients with elevated H-FABP levels and/or a sPESI ≥ 1 point(s) had a 19.9-fold increased risk for an adverse 30-day outcome (95% CI, 2.71 to 145.45; $p = 0.003$). Of 445 patients (62%) with both, H-FABP ≥ 6 ng/ml and sPESI ≥ 1 point(s), 38 (9%) had an adverse 30-day outcome as opposed to 3 of 271 patients (1%) with H-FABP <6 ng/ml or sPESI of 0 points (sensitivity, 93%; specificity, 40%; PPV, 9%; NPV, 99%; $p < 0.001$).

Conclusions: In this large external validation cohort, we could show that the prognostic value of H-FABP in haemodynamically stable patients with acute PE can be optimized if H-FABP is combined with clinical information based on the simplified PESI.

P2070 | BEDSIDE**Thrombolysis in hemodynamically stable patients with acute pulmonary embolism: a meta-analysis**

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Purpose: The role of thrombolysis in hemodynamically stable patients with acute pulmonary embolism (PE) remains a matter of debate. We performed a meta-analysis of randomized trials to assess the efficacy and safety of thrombolysis in these patients.

Methods: We searched in MEDLINE and EMBASE for randomized studies comparing thrombolysis and heparin for the initial treatment of PE in hemodynamically stable patients. The primary outcome of the study was overall death occurring during hospital stay or up to 30 days from acute PE. Secondary outcomes were major bleeding (MB), intracranial hemorrhage (ICH), recurrent PE and fatal bleeding. For each of these outcomes, pooled ORs and 95% confidence intervals (CI) with I-squared (I^2) for heterogeneity, were calculated. Number needed to treat (NNT) to avoid one death and number needed to harm (NNH) to cause a MB or an ICH, were also calculated.

Results: Ten studies were included in the meta-analysis (1761 patients), six with rt-PA, three with tenecteplase and one with urokinase. A not significant reduction for overall death in favor of thrombolysis compared with heparin was found (1.8% vs 2.0%; OR 0.86, 95% CI 0.45 to 1.65, $I^2 = 0.0\%$). Patients randomized to receive thrombolytic agents had an increased risk for MB (5.9% vs 1.9%; OR 2.87, 95% CI 1.68 to 4.90, $I^2 = 26.3\%$) and for ICH (1.76% versus 0.57%; OR 2.47, 95% CI 1.00 to 6.14, $I^2 = 0.0\%$), and a not significant increased risk for fatal bleeding (0.8% versus 0.4%; OR 1.49, 95% CI 0.53 to 4.19, $I^2 = 0.0\%$). A not significant reduction in recurrent PE was found in favor of thrombolysis (9 studies, 1748 patients; 1.14% vs 2.28%; OR 0.5, 95% CI 0.23 to 1.07, $I^2 = 0.0\%$). NNT to avoid one death was 334 patients. NNH to cause a MB or an ICH were 26 and 91 patients, respectively. Tenecteplase was associated with a significant six-fold higher risk of major bleeding and six-fold higher risk of ICH compared with heparin.

Conclusions: The risk for major bleeding and ICH in hemodynamically stable patients with PE is substantial with thrombolysis without evidence of a mortality benefit. This imbalance was higher in patients receiving tenecteplase.

P2071 | BEDSIDE**Fibrin clot phenotype in patients with pulmonary embolism: association with recurrent venous thromboembolism following discontinuation of anticoagulant therapy**

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Purpose: Low plasma fibrin clot permeability and lysisability have been reported in venous thromboembolism (VTE). The aim of the current study was to investigate clot properties and their determinants in patients who experienced pulmonary embolism (PE) with and without deep-vein thrombosis (DVT). Moreover, we sought to assess the effect of clot properties on recurrent VTE during follow-up.

Methods: We enrolled 99 consecutive PE patients aged 18 to 65 years (56 with PE alone and 43 with DVT combined with PE). Patients treated with thrombolysis or those with pulmonary hypertension, high-risk thrombophilia or malignancy were ineligible. We measured ex vivo fibrin clot permeability, turbidimetry and efficiency of fibrinolysis in plasma obtained after discontinuation of anticoagulation. The patients were followed for recurrent VTE.

Results: The two groups were similar with regard to demographics, comorbidities, routine laboratory parameters and the type of the VTE episode (provoked/unprovoked). Isolated PE was associated with higher fibrinogen, D-dimer, tissue plasminogen activator, and thrombin-activatable fibrinolysis inhibitor. Thrombin generation markers were similar in both groups. Patients with isolated PE compared with those following PE and DVT had lower plasma fibrin clot permeability (Ks), higher rate of D-dimer release from fibrin clots (D-Drate), higher maximum D-dimer concentration released from clots (D-Dmax), shorter lag phase, indicating faster fibrin formation, and greater maximum absorbancy (ΔAb_{max}), indicating thicker fibrin fibers (all $p < 0.05$). During a median follow-up of 30 months since the index PE, there were 6 (10.7%) VTE recurrences in patients with PE after 6.7 $\pm$ 4.0 months without anticoagulation and 19 (44.2%) patients with a

history of PE and DVT ($p < 0.001$) after 8.2 ± 4.3 months without anticoagulation ($p < 0.05$ for the time), including 3 (5.4%) and 9 (20.9%) PE episodes, respectively ($p < 0.05$). The patients with PE who experienced recurrent VTE from both groups had more frequently unprovoked VTE, higher BMI, worse fibrin clot profile and higher plasma D-dimer compared with those free of recurrences during follow-up.

Conclusions: Altered fibrin clot features differ between patients with isolated PE and those with concomitant DVT. More prothrombotic profile of plasma fibrin variables, including denser fibrin networks and more efficient clot lysis, can help identify patients at increased risk of recurrent VTE. The study provides the first evidence for prognostic value of clot phenotype after cessation of anticoagulation in predicting recurrence of VTE in patients with previous PE.

P2072 | BEDSIDE

Meta-analysis of impending paradoxical embolism

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Purpose: Impending paradoxical embolism (IPDE) occurs when thrombus is entrapped within a patent foramen ovale (PFO), most frequently occurring in the setting of acute pulmonary embolism. We aimed to review all reported cases of IPDE, compare survival with each treatment method and identify patient characteristics within each group.

Methods: Systematic electronic literature searches using a pre-defined search strategy identified 239 patients for inclusion in the review. Disease, demographic, treatment and mortality data was collected for analysis. Authors of manuscripts were contacted if information was incomplete. Non-english language studies were translated for inclusion.

Results: 239 case reports were included for review. There were 110 males and 129 females and the average age was 58 years. Common presenting symptoms were dyspnoea (74%), chest pain (28%), stroke/TIA (26%) and syncope/presyncope (23%). Most patients (82%) had pulmonary embolism confirmed by imaging. 73 patients (30%) experienced systemic embolism prior to diagnosis of IPDE. IPDE was diagnosed most frequently using transthoracic and transoesophageal echocardiography. Reported treatments included emergency surgery, thrombolysis and anticoagulation. Mortality at discharge was 15% in the surgery group, 18% in the anticoagulation group and 28% in the thrombolysis group ($p = 0.016$). There was some evidence that male sex and patients presenting with cardiac arrest, hypotension and haemoptysis were more likely to be deceased at hospital discharge. In adjusted multivariate analysis, treatment modality was not significantly associated with mortality at discharge.

Conclusions: This is the largest review of IPDE to date and attempts to provide clinicians with information regarding the diagnosis and management of this infrequently reported condition. The absence of prospective studies limits the conclusions that can be drawn from this review. Reported mortality at discharge was lower in the surgery and anticoagulation groups, however this difference was not significant in multivariate modelling.

P2073 | BEDSIDE

Use of a diagnostic computerized clinical decision support and outcomes of suspected pulmonary embolism

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Background: The diagnostic approach to patients with suspected acute pulmonary embolism (PE) evaluated in an Emergency Department (ED) may affect test utilization, test yield, and patient outcomes.

Methods: This single center cohort study aimed to determine the effects of evidence-based clinical decision support (CDS) on the use of computed tomographic pulmonary angiography (CTPA) (number of patients undergoing CTPA per 1000 ED visits), the yield (percentage of patients with CTPA positive for acute PE), and outcomes of patients with negative diagnostic work-up for PE. The study included consecutive patients with suspected PE before (preintervention period) (from January 1, 2011 to December 31, 2011) and prospectively after (postintervention period) (from January 1, 2012 to December 31, 2012) the introduction of CDS. Investigators assessed patients with negative diagnostic work-up for symptomatic venous thromboembolic events that occurred during 3-months of follow-up.

Findings: The study analyzed 652 patients preintervention and 711 patients postintervention (total 1,363). A greater proportion of patients received CTPA testing in the preintervention period than in the postintervention period (55% vs. 49%; absolute difference [AD], 6.3%; 95% CI, 1.0% to 11.6%; $P = 0.02$). CTPA use increased preintervention (21.5% increase, from 2.60 to 3.16 examinations per 1000 patients; $P = 0.17$) and decreased postintervention (25.4% decrease, from 3.19 to 2.38 examinations per 1000 patients; $P = 0.09$). Of the 362 CTPA examinations performed during the preintervention period, 112 (31%) were positive for PE. Of the 350 CTPA examinations performed during the postintervention period, 116 (33%) were positive for PE. Yield increased from 26.0% to 46.5% ($P < 0.01$)

postintervention. Of the patients with a negative diagnostic work-up for PE, the frequency of possible and definite venous thromboembolic events was low (20 of 1,065 patients; 1.9%; 95% confidence interval [CI], 1.1% to 2.7%) during follow-up. Sixteen events (16 of 492 patients; 3.2%; 95% CI, 1.7% to 4.8%) occurred in the preintervention group, whereas 4 events (4 of 573 patients; 0.7%; 95% CI, 0.0% to 1.4%) occurred in the postintervention group (AD, 2.5%; 95% CI, 0.9% to 4.6%; $P < 0.01$).

Interpretation: Implementation of evidence-based CDS in the ED for patients with suspected PE was associated with a decrease in CTPA use, an increase in CTPA yield, and a small but significant decrease in symptomatic venous thromboembolic events in patients that had a negative initial diagnostic work-up for PE.

OUTCOMES POST-MYOCARDIAL INFARCTION: NOVEL INSIGHTS

P2074 | BEDSIDE

Exploring the benefit of ACS guideline therapies in type II MI

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Purpose: Guideline-recommended pharmacotherapies have shown to reduce cardiovascular mortality post type I MI. However their use in type II MI is uncertain. This study assesses the association of pharmacotherapies individually and in combination in people with type II MI.

Method: All hospitalised patients in South Australia with a troponin level of > 15 pg/mL using high-sensitive troponin T assay over 12 months were included. Dispensing records were then matched to patients to identify medications at discharge. All patients were classified into three groups according to their principle diagnosis at index admission according to the following grouping, Group 1: Chest pain or ACS; Group 2a: other cardiac conditions; Group 2b: non-cardiac conditions. Pearson's χ^2 is used to determine the association between pharmacotherapy use (ACEI/ARB, aspirin, beta blockers, clopidogrel and statins) and death and recurrent MI at 12 months. Propensity score adjusted cox regression modeling including for age, gender, renal function, haemoglobin and various comorbidities was used to explore the benefit of using individual or combination pharmacotherapies in and reduced death and recurrent MI at 12 months.

Results: In total, 10,339 patients were included. Total number of patients in each group were, Group 1=4,385 (42.41%), Group 2a=1,698 (16.42%) and Group 2b=4,256 (41.16%). The incidence of death and recurrent MI at 12 months was highest in Group 2b (Group 1: 785/4,385 (17.9%); Group 2a: 396/1,698 (23.32%); Group 2b: 1,202/4,256 (28.24%); $p = 0.000$).

In Group 1, each individual therapies were associated with a reduction in death or MI after propensity matching. There was a stepwise reduction in events with cumulative use, which correspond with guideline recommendations.

Benefit using individual therapies was not observed in Group 2a, despite their higher risk though smaller numbers (HR of using ACEI/ARB: 0.868[0.704-1.069] $p = 0.183$; aspirin: 0.871[0.706-1.07] $p = 0.197$; statin: 0.898[0.724-1.114] $p = 0.329$). In propensity matched analysis, aspirin, ACEI/ARB and statins appear to be associated with a reduction in events in Group 2b (HR: 0.866[0.759-0.988] $p = 0.033$; 0.770[0.679-0.872] $p = 0.000$; 0.814 [0.720-0.921] $p = 0.001$ respectively).

Conclusion: Aspirin, statins and ACEI/ARB appear to be of potential benefit among patients with a troponin elevation not thought to be due to an ACS event. These agents should be formally evaluated in randomised clinical trials for type II MI.

P2075 | BEDSIDE

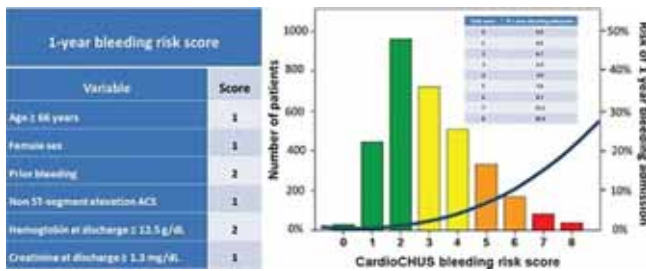
Prediction of bleeding admission in the first year after acute coronary syndrome and prognostic impact: the CardioCHUS bleeding risk score

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Purpose: Hemorrhagic complications in the first year after an acute coronary syndrome (ACS) have been strongly linked with dual antiplatelet therapy cessation and subsequently with higher cardiovascular risk and mortality.

Methods: 4,115 consecutive patients with ACS were studied. We developed ($n = 3,281$) and validated ($n = 834$) a model that identified 6 independent baseline predictors of 1-year bleeding. The performance was tested by c statistics in the derivation and validation cohorts and according to postdischarge treatment. The CardioCHUS bleeding score (range 1 to 8 points) was created by assignment of weighted integers that corresponded to the coefficient of each variable.

Results: 129 (3.1%) required hospitalization due to bleeding episodes or transfusion within the first year after ACS discharge. The rate of major bleeding increased by bleeding risk score groups: 0.6% for very low risk (score 0-2); 2.5% for low risk (score 3-4); 7.8% for moderate risk (score 5-6); and 21.7% for high risk (score 7-8). The c statistics for the CardioCHUS bleeding score was 0.79 and 0.71 in



the derivation and validation cohorts. The c statistics among treatment subgroups were 0.72, 0.79 and 0.80 for oral anticoagulation, dual and single antiplatelet therapy, respectively. In a time-updated covariate-adjusted Cox proportional hazards regression model, 1-year bleeding was an independent predictor of mortality.

Conclusion: The CardioCHUS bleeding score quantifies risk for 1-year major bleeding across all postdischarge antithrombotic treatments, which enhances bleeding risk assessment for post-discharge selection of antithrombotic treatments and the development of strategies to mitigate that risk.

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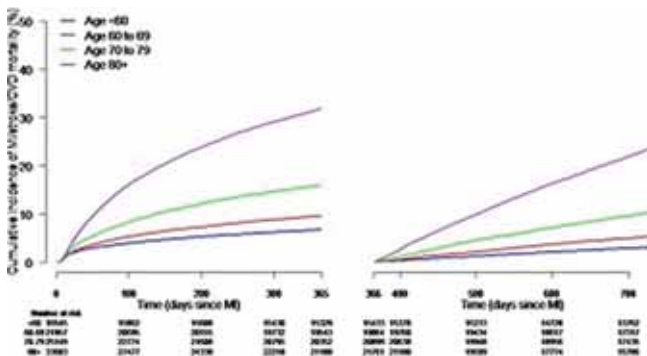
Continued high CVD risk in myocardial infarction survivors: comparison of risk first and second year after MI - results from a Swedish nationwide study

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Background: Although short-term survival after myocardial infarction (MI) is improving, the long term risks of cardiovascular disease (CVD) in a clinical practice setting are not known. The aim of this study was to investigate the CVD risk during the first and second year post discharge after non-fatal MI using nationwide registry data.

Method: All patients surviving an MI in Sweden between July 1 2006 and June 30 2011 were identified and followed in the compulsory nationwide patient registry which includes all discharge diagnoses. These data were also linked to the cause of death register. The primary endpoint consisted of MI, stroke and CVD mortality. Hazard ratios (HR) adjusted for gender, age, stroke, MI, diabetes and heart failure (HF) are reported.

Results: A total of 97 254 patients (median age 74 years) with 2.7 years median follow up covering 277 118 patient-years were included. Age (60-69 vs <60: HR [95% CI]: 1.37 [1.30-1.44], 70-79 vs <60: 2.18 [2.08-2.29], 80+ vs <60: 4.59 [4.38-4.81]), prior MI (1.46 [1.42-1.50]), stroke (1.59 [1.55-1.63]), diabetes (1.36 [1.33-1.39]) and HF (1.67 [1.63-1.71]) were all independently associated with higher risk of the primary endpoint in the first year. For patients without a non-fatal MI the first year, the overall risk remained high in the second year (11.3% compared with 18.3% in the first year), and the relative importance of each risk factor was similar to the first year (Figure).



MI, stroke or cardiovascular mortality.

Conclusions: Nationwide data for all non-fatal MI patients in Sweden show that the CVD risk remains high also in the second year post MI and that the relative importance of risk factors appears similar over time.

P2077 | BEDSIDE

Health outcomes in patients with stable coronary artery disease following myocardial infarction; construction of a PEGASUS-TIMI-54 like population in UK linked electronic health records

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Purpose: This study estimates event rates of MI, stroke and death, bleeding and medication use in a routinely treated UK population similar to the ongoing PEGASUS-TIMI-54 trial (NCT01225562) using the CALIBER linked electronic health records.

Methods: The trial-equivalent population was constructed by applying the selection criteria to patients in CALIBER hospitalized with acute coronary syndrome (ACS) in 2005-2010 who remained stable in the first year following their index ACS. Criteria for inclusion were MI as the index ACS, aged ≥ 50 and at least one of the following risk factors: ≥ 65 at stable CAD date, use of diabetes medication, >1 prior MI or eGFR <60 ml/min; and for exclusion: history of stroke, on dialysis pre/post index MI or use of oral anticoagulants within 30 days. The primary composite endpoint was MI, stroke or cardiovascular death.

Results: 15,070 patients were identified with ACS (10,084 MI) and at least one high risk factor was present in 76% (5512/7238) of those remaining event-free 12 months following index MI. A further 1059 patients were excluded from the trial-like cohort due to prior stroke (684), dialysis (46) or use of oral anticoagulant (442). The trial-like population consisted of 4,453 stable post-MI patients (39% women, median age 74 [IQR 67-82] years, 49% NSTEMI, 31% STEMI and 20% unclassified). Major comorbidities were diabetes requiring medication (22%), kidney disease (27%), MI prior to the index MI (24%), heart failure (26%), respiratory disease (29%) and peripheral arterial disease (13%). Over a median follow-up of 1.5 (IQR 0.7-2.5) years 481 events were observed (208 non-fatal MI, 97 non-fatal stroke, and 176 CVD deaths). Cumulative composite event rates in the 1st, 2nd and 3rd year post-stable MI were 7.3% (6.4-8.1), 12.3% (11.1-13.5), and 17.7% (16.1-19.4). Incidence of bleeding requiring hospitalization in the first 3 years was 1.7 per 100 person-years, (4.8% per 100 person-years for any bleeding leading to healthcare contact). Following index MI use of statins and aspirin doubled ($\sim 94\%$ in the first year post-MI), with $>90\%$ continuing these medications throughout the post-stable period. Use of clopidogrel was 77% in the year following the index MI, but dropped to 42%, 20% and 16% in the 1st, 2nd and 3rd year post stable CAD. **Conclusions:** In this real-world stable post-MI PEGASUS-TIMI-54-like UK population with high use of secondary prevention medications subsequent CVD event rates were high and bleeding rates were substantial. This highlights the need for clinicians to monitor and balance the benefit vs. risk of antiplatelet therapy in these patients.

P2078 | BEDSIDE

Long-term mortality among young patients with acute myocardial infarction referenced against a background population

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Background: Young patients with acute myocardial infarction (AMI) have a more favorable prognosis than older patients with AMI. However, there are limited data comparing the prognosis of young AMI patients with young population controls. Because of their increased resilience, the prognosis of young AMI patients may approximate that of age-matched community counterparts over time.

Methods: We studied 15,151 patients diagnosed with AMI from 2000-2005, of which 601 patients were ≤ 40 years of age (young). The relative mortality ratio was calculated as the ratio of the observed mortality of patients with AMI over the expected mortality estimated from the background Singapore population ($n=3,771,700$) with similar sex, age and period characteristics. A relative mortality ratio of <1.0 or >1.0 indicates lower or greater mortality, respectively, than the background population.

Results: The 12-year all-cause and cardiovascular mortality of young vs. older patients was 12.8% vs 50.7% ($P<0.001$) and 9.2% vs. 34.5% ($P<0.001$) respectively. The adjusted hazard ratio (95% confidence interval, C.I.) for all-cause and cardiovascular mortality comparing young with older patients was 0.20 (0.16-0.27) and 0.27 (0.20-0.36) respectively. The relative mortality ratio (95% C.I.) of young vs. older patients at 1 year, 3 year, 5 year and 9 year was 1.03 (1.02-1.05) vs. 1.24 (1.23-1.25), 1.04 (1.03-1.07) vs. 1.33 (1.31-1.34), 1.06 (1.04-1.09) vs. 1.40 (1.38-1.41), and 1.10 (1.07-1.14) vs. 1.57 (1.53-1.61), respectively.

Conclusions: Despite a five-fold lower long-term mortality than older patients, young AMI patients remain at a significantly greater cumulative risk of long-term mortality than an age-matched background population. Better measures are needed to mitigate the long-term residual risk associated with young onset AMI.

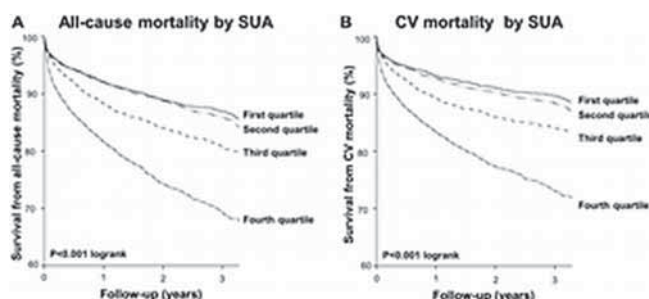
P2079 | BEDSIDE**Serum uric acid is associated with mortality and heart failure hospitalizations in patients with complicated myocardial infarction: analysis from High Risk Myocardial Infarction Database Initiative**

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Background: Serum uric acid (SUA) levels predict poor outcome in patients with stable coronary heart disease. Whether SUA predicts outcome in acute myocardial infarction (MI) complicated by reduced left ventricular (LV) function, heart failure (HF) or both is unknown.

Methods: We studied the association between baseline SUA and outcomes using univariable and multivariable Cox models in an individual-patient data meta-analysis of 4 large randomized trials of high-risk MI (CAPRICORN, EPHEUS, OPTIMAAL and VALIANT; N=28,771).

Results: SUA was available in 12,677 patients (median follow-up 1.9 years). Patients were separated into quartiles (Q) according to baseline SUA (Q1, 45-280; Q2, 281-344; Q3, 345-420; Q4, 420-1640 micromol/l). Patients in higher SUA quartiles were older, more symptomatic, and had more comorbidity. Renal failure prevalence was 10-fold higher in Q4 vs Q1. All-cause survival at 3-years was 86.8% in Q1 vs 69.4% in Q4 (fig. A). Most deaths were due to CV disease (fig. B). In univariable analysis, all-cause mortality rose across SUA quartiles (Hazard ratio (HR)=1.06, confidence interval (CI)=0.92-1.22 for Q; HR=1.57, CI=1.31-1.71 for Q3; HR=2.70, CI=2.23-2.89 for Q4; Q1 as reference). A similar trend was observed for CV mortality (HR=2.70, CI=2.35-3.10 for Q4 vs Q1) and HF hospitalization (HR=1.72, CI=1.61-1.84 for Q4 vs Q1). Multivariable analysis models adjusted for baseline characteristics consistently showed that SUA independently predicted all-cause mortality (HR=1.78, CI=1.51-2.09 for Q4 vs Q1), CV mortality and HF hospitalization. Analysis in patients without diuretics yielded similar results.



SUA and mortality in complicated MI.

Conclusions: Elevated SUA was a strong and independent predictor of poor clinical outcomes in patients after acute high-risk MI complicated by reduced LV function, HF or both.

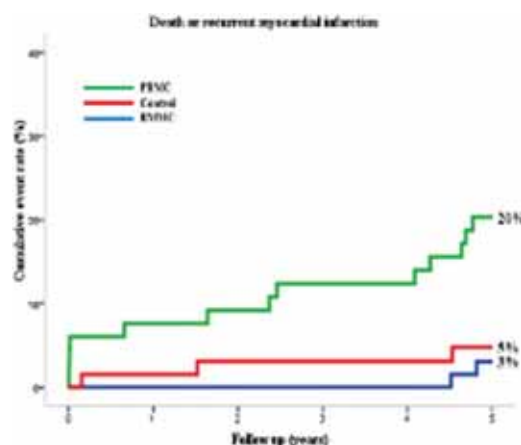
P2080 | BEDSIDE**Long-term follow-up after intracoronary infusion of mononuclear cells from bone marrow or peripheral blood after acute myocardial infarction: 5 year results of the randomized controlled HEBE trial**

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Objectives: There is limited data on the long-term outcomes of intracoronary bone marrow cell therapy. This study reports the long term follow-up of intracoronary infusion of bone marrow mononuclear cells (BMMC) and peripheral blood mononuclear cells (PBMC) compared to controls in acute myocardial infarction patients; the results of the randomized controlled HEBE study.

Methods: The HEBE study is a multicenter trial that randomized 200 patients with large first AMI treated with primary percutaneous coronary intervention (PCI) to either intracoronary infusion of BMMC (n=69), PBMC (n=66), or standard therapy (n=65). Patients were followed for 5 years after AMI to assess clinical adverse events, including death, myocardial reinfarction and hospitalisation for heart failure.

Results: During five years of follow-up, six patients assigned to the PBMC group died, compared to two patients in the control group (p=0.27). Ten patients treated with PBMC therapy had a recurrent myocardial infarction, compared to one in the control group (p=0.009). The composite endpoint of death, recurrent myocardial infarction was significantly higher in the PBMC group compared to controls (14 patients versus 3 patients, p=0.008). Improvement of left ventricular ejection fraction (LVEF) during follow-up was $4.2 \pm 8.6\%$ in the BMMC group and $3.0 \pm 8.3\%$ in



the PBMC group, compared to $4.0 \pm 8.6\%$ in the control group (p=0.37 and p=0.17, respectively).

Conclusion: Term follow-up of the HEBE trial showed no beneficial effect of intracoronary delivery of mononuclear cells from bone marrow or peripheral blood on regional and global systolic myocardial function at follow-up. However, major clinical cardiovascular adverse events were significantly higher in the PBMC group.

VALVE SURGERY: FROM PREDICTION TO OUTCOME**P2081 | BEDSIDE****Graft sizing in David reimplantation technique using echocardiographic based formulas**

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Purpose: It remains unclear whether a transthoracic echocardiography (TTE)-based formula may help in selecting the graft size during David reimplantation technique for aortic root dilation.

Methods: Forty-nine patients (47 ± 11 years old, 84% men) who underwent David reimplantation technique were evaluated. Leaflet height and leaflet area TTE-based formulas were developed to select the graft size (Figure 1). The implanted graft size was based on the David's formula ($\text{diameter} = 2 \times \frac{2}{3} \times \text{leaflet height} + 2$), measuring the leaflet height with surgical callipers. The agreement between these formulas and the eventually implanted graft size was evaluated in 26 patients who underwent isolated David reimplantation without additional leaflet repair. In addition, the incidence of mild residual aortic regurgitation (AR) for each formula was evaluated.

Results: The incidence of mild residual AR was 24% in all patients. The implanted grafts were divided into quartiles and were compared to the TTE-based formulas. The Kappa measure of agreement between the implanted graft size and calculated size using the leaflet height and leaflet area TTE-based formulas was 0.335 (p=0.002) and 0.366 (p<0.001), respectively. In patients who received the same or smaller graft than calculated using the leaflet height and leaflet area TTE-based formulas, the incidence of mild AR was 10% and 8%, respectively, whereas in patients who received a larger graft than calculated, the incidence of mild AR was 38% and 46%, respectively (p=0.124 and p=0.027, respectively).

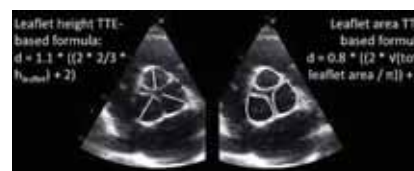


Figure 1. TTE-based formulas.

Conclusion: In patients undergoing David reimplantation technique, graft sizing can be performed with TTE. The incidence of mild residual AR was lower when the implanted graft was similar or smaller than calculated compared to a larger implanted graft than calculated.

P2082 | BEDSIDE**Sutureless aortic valve replacement: Single center comparison of the 3F Enable and the Perceval S valves**

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Objective: The 3F Enable and Perceval S aortic valves are new generation devices of Nitinol-stented bio-prostheses, designed for sutureless aortic valve re-

placement (AVR). Primary objective of this clinical trial was to assess clinical performance of both devices and to compare hemodynamic variables.

Methods: Up to November 2013, 106 patients with severe aortic stenosis underwent sutureless AVR either with the 3F Enable (n=55) or the Perceval S valve (n=51). Concomitant procedures (CABG, PFO-closure, or carotid endarterectomy) were performed in 13 (24%) and 18 (35%) patients, respectively (p=.135). Clinical and echocardiographic follow-up was performed annually.

Results: Mean aortic cross-clamp time was longer in the 3F Enable group [40±14 min vs 30±8 min in the Perceval S group (p=0.001) in patients undergoing AVR without concomitant procedures and 50±21 min vs 41±10 min respectively in patients undergoing AVR and concomitant procedures (p=.131). A high rate of mild intra-prosthetic regurgitation in the Perceval S group was noticeable, significantly different to the 3F Enable group (p=.001). All leaks of 3F Enable devices were mild, however, 4 patients in the Perceval S group revealed moderate and 1 moderate to severe leaks.

During follow-up period of 837±815 days in the 3F Enable group and 758±424 days in the Perceval S group 5 patients (9%) and 3 patients (6%) died, respectively. All deaths were not device related.

Conclusion: Our results confirmed the clinical efficacy of sutureless AVR with the 3F Enable and Perceval S valves. The risk of reoperation was higher in the 3F Enable cohort. Implantation time seems to be shorter with the Perceval S prosthesis, however, hemodynamic parameters of the 3F Enable prosthesis during follow-up are more favourable.

P2083 | BEDSIDE

Do mitral valve surgery for functional mitral regurgitation is still an option in surgical treatment of idiopathic dilated cardiomyopathy?

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Aim: To assess the outcome of surgery of functional mitral regurgitation in patients with idiopathic dilated cardiomyopathy.

Methods: We retrospectively rewired 152 patients (135 men, 17 women; mean age 45,4±7,25 years) with severe functional mitral valve regurgitation due to dilated cardiomyopathy who were operated on between 2004 till 2013. 38 pts were in New York Heart Association class IV and 114 were in class III with significant elevation of heart failure markers (BNP level preoperatively was 806; QL 245-QH 1482). Most of pts had severe enlarged LV (mean end-diastolic size 73,7±7,1 mm, end-systolic size 63,7±7,2 mm and end-diastolic volume 293±79ml) with depressed systolic function (mean LV ejection fraction -26,1±6,6%). Concomitant procedures were tricuspid repair (139 pts) and atrial fibrillation ablation (32 pts). In 37 pts (24%) epicardial LV lead was fixed with subsequent CRT implantation during the same hospitalization. Mitral valve annuloplasty with different types of undersized ring were performed in 106 patients, and 46 had mitral valve replacement (in 6 pts mechanical and in 40 pts biological).

Results: There were no perioperative deaths, in 2 pts BiVAD were started due to inability to wean from CPB. 4 patients (2,6%) died within 30 days postoperatively. Overall freedom from MR ≥2+ was 96,1%. Both LV end-diastolic and end-systolic volumes indexed significantly decreased (both p=0.0001). After MV repair ejection fraction increased from 25,2±7,5% to 29,2±9,4% (p=0,04). Follow-up was 100% complete. The mean follow-up was 47,6±4,1 months. 1-years survival was 82,5±0,04%, 5-years - 51,7±0,08%. The fact of mitral valve replacement versus repair did not influence survival (hazard ratio (HR) 1,35; 95%CI 0,82-2,29; p=0,26). The type of ring used for annuloplasty not affected survival (long-rank p=0,37). The preoperative NYHA class was only found as independent risk factors for an increased mortality within the five years of surgery in multivariate Cox regression (hazard ratio (HR) 4,53; 95% CI 2,7-13,5, p=0.004). In 8 patients heart transplantation were performed after mean 486 (30-1501) days; in 5 patients LVAD or BiVAD were implanted after mean 476 (48-2084) days.

Conclusion: Mitral valve surgery can be performed successfully in these high risk patients with IDCM with low hospital mortality, clinical improvement and a moderate recovery of LV function. The mitral valve replacement versus repair did not negatively affect survival in these patients with severe dilated LV and it mostly depends on factors related to the patient's condition at the time of surgery.

P2084 | BEDSIDE

Euroscore II is inappropriate for predicting risk in octogenarian patients after cardiac surgery

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Purpose: Octogenarian patients have higher morbimortality after cardiac surgery and surgical risk prediction in these patients is limited. Our aim was to evaluate predictive value of EuroSCORE II (ES II) for in-hospital mortality in octogenarians undergoing cardiac surgery.

Methods: All octogenarians operated on (jan 2006 - jan 2014), excluding aortic surgery. Demographic, clinical, laboratory, surgical, ES II, and mortality variables were analyzed. Predictive ability of ES II was compared for performance (observed / expected mortality, O / E), calibration (Hosmer-Lemeshow), discrimination (ROC curve) and Net Reclassification Improvement.

Results: 200 patients [83±3years, 53% men, EuroSCORE I and II, 10.1 (7.9-17.2) and 3.6 (2.6 to 5.5)], respectively. The surgeries were: CABG (35.9%), Isolated Valve surgery (41.1%) and CABG + Valve (22.9%). Selected outcomes were: reoperation (5.2%), major complications (12.5%), hospital mortality (12.0%). EuroSCORE II was higher in the CABG group than in the CABG + Valve and Valve isolates (6,1±4.8% vs 4.2% ± 3.6 and 4.5±3.4%, p=0.028). On multivariate analysis, independent predictors of mortality were only LVEF (OR = 1.1, 95 CI 1.01-1.11) and COPD (OR= 5.1, 95 CI 1.21-21.2). For clinical performance of the ES II in different surgical groups, the O/E ratio was: Global (2.55), CRM (2.76), valve (1.69), CABG + valve (3.36), p<0.05 for all values. The calibration for groups of low, moderate, high and very high risk was respectively 0, 2.88, 2.50, and 2.6 (Hosmer - Lemeshow test p<0.01). The accuracy of the EuroSCORE II was slightly superior to the EuroSCORE I, although both have shown poor discrimination (ROC AUC 0.686 and 0.647, respectively, p<0.05). ES II appropriately reclassified the risk in relation to ES I, in only 7.3% of patients (NRI for events: 65.2%; NRI for non events: -57.9%).

Conclusions: In octogenarians, the ES II was not an independent predictor of death, underestimated the surgical risk, had low discrimination (although higher than the ES I) and poor calibration in the different risk categories. It appropriately reclassified only 7% of patients, compared to the ES I. New specific risk scores to this age group should be developed and validated to enable adequate stratification of cardiac surgical risk.

P2085 | BEDSIDE

Obstructive sleep apnea in patients after surgery for type A Acute Aortic Syndrome: highly prevalent and related to on aneurysmal aorta evolution by imaging

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Aims: There are some theoretical reasons why the thoracic aorta may be affected in obstructive sleep apnea (OSA). The purpose of this study was to determine prevalence and the influence of OSA on aneurysmal aorta evolution (AAE) in patients who have had surgery for a type A acute aortic syndrome (AAS).

Methods and results: In this cross-sectional study, 62 patients operated in emergency for AAS had a measurement of the maximum speed of aortic diameter progression (VmaxAo), during a median follow up of three years. Each patient had undergone the following investigations: 24-hour blood pressure (BP) monitoring, biological assays, carotid-to-femoral pulse wave velocity and polysomnography. The prevalence of OSA and uncontrolled hypertension were high (89%, and 77% respectively). Forty two patients (67%) presented no AAE. Mean nocturnal oxygen saturation (SpO2) was significantly lower in patients with AAE than in those without AAE (92.5% ± 1.9 vs. 93.6% ± 1.7, p<0.04). In patients who recorded progression in aortic diameter, the VmaxAo was significantly correlated to the 24-hour SBP (r=0.374, p=0.013) and mean nocturnal SpO2 (r=-0.381, p=0.02). In multivariate analysis, VmaxAo was independently and positively correlated to mean nocturnal SpO2 (p=0.02). Logistic regression modeling showed that mean nocturnal SpO2 was independently associated with AAE (OR=4.36, 95% CI 1.34 to 17.34; p=0.01).

Conclusions: This study shows a high prevalence of OSA in patients after surgery for AAS. Moreover, severe nocturnal hypoxemia was significantly related to a more rapid AAE. These findings prompt a systematic search and treatment of OSA during patient follow-up.

P2086 | BEDSIDE

Incidence and clinical impact of homograft stenosis in long term follow up after ross intervention

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Purpose: Ross intervention is an alternative to mechanical prosthesis implantation in children and young adults who need aortic valvular replacement. Homograft stenosis and the need of homograft reintervention are possible complications in these patients. Our aim was to describe the incidence and the clinical impact of this complication in a prospective series of a reference cardiovascular surgery hospital.

Methods: Since November 1997 to July 2009, a total of 107 patients requiring aortic valve surgical treatment underwent Ross surgery (mean age 30±11 years, 69% male, 21 patients <18 years). In all of them, a comprehensive clinical and echocardiographic evaluation was performed before the intervention and at discharge, at 6, 12 months and annually after surgery.

Results: Only one patient died before discharge. After up to 15 years of follow up (median 11 years, interquartile rank 8-13 years), echocardiographic data were

available in 91 patients (85%) and clinical data in 104 patients (98%). 26/91 patients (29%) developed at least moderate homograft stenosis (peak echocardiographic gradient ≥ 36 mmHg) and 10/104 patients (9.6%) underwent 13 procedures over the homograft: in 3 patients, the homograft was substituted surgically, 3 patients underwent a percutaneous pulmonary valve implantation and one patient needed a stent implantation. The other 3 patients underwent 2 procedures: a stent implantation and, years later, a percutaneous pulmonary valve implantation; a percutaneous pulmonary valve implantation and a surgical intervention years later; and finally, a pulmonary valvuloplasty and years later, a percutaneous pulmonary valve implantation. This patient died because of an acute myocardial infarction as a complication of the last procedure. Survival free from homograft stenosis and homograft intervention was 96%, 82% and 75%, and 99%, 94% and 91% at 1, 5 and 10 years, respectively. Pediatric patients (<18 years) had a worse survival free from homograft stenosis (HR 3.50, 95%CI 1.56-7.90, $p=0.002$), although there was not significant differences regarding homograft reintervention (HR 2.01, 95%CI 0.52-7.78, $p=0.31$). Younger age of the homograft donor was also a predictor of stenosis (HR 0.97, 95%CI 0.94-0.99, $p=0.046$).

Conclusion: In this study, probabilities of homograft stenosis and reintervention at ten year after Ross operation were 25% and 9% respectively, and only one patient had a reintervention related death. A younger donor and recipient age was associated with a higher rate of stenosis.

P2087 | BENCH

Key factors to develop histogenesis in a novel autologous heart valve implantation

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Purpose: There are some attempts to use tissue engineered materials for heart valvular substitutes, but it is not clear how the substitutes changes in histogenesis after implantation. We are developing a novel autologous aortic valve (Biovalve), using simple, safe and economical in-body tissue engineering which is based on a tissue encapsulation phenomenon in the living body. In this study, we investigated key factors in histogenesis when the Biovalve was implanted in a large animal model.

Methods: Biovalves were prepared by 2-month embedding of the molds, assembled using plastic rods in the subcutaneous spaces of goats. After extracting the molds and removing the plastic rods only, Biovalve with tri-leaflets similar to those of the native aortic valves were constituted from completely autologous connective tissues. We combined the Biovalve with a metric stent for transcatheter aortic valve implantation. Fourteen Biovalve Stents were implanted in the aorta in situ with transcatheter apical approach technique.

Results: The Biovalve Stents were successfully implanted in aortic position. Angiography showed smooth movement of the leaflets with a little regurgitation under the systemic circulation. The Biovalve Stents were extracted 1, 2 or 5 months after implantation to observe their histogenic process. The leaflets of the Biovalve kept their shape and elasticity even after 5 months and neither calcification nor thrombi were observed. Histological examination showed the cell migration inside the Biovalve body and laminar endothelialization on the surface of the valve leaflets even in 1 month after implantation. Their histogenesis have gradually advanced in 5 months, but were interrupted when the Biovalve tissues were not attached enough on the native vascular wall tissue.

Conclusion: The Biovalve satisfied the higher requirements of systemic circulation in goats for 5 months with the histogenic potential that was mainly induced by cell migration from the native vascular tissues contacting with the Biovalve.

CARDIO-RENAL INTERACTION

P2088 | SPOTLIGHT

The association between kidney function within the normal or mildly impaired range and incident cardiovascular disease- a population based study with over 10 million patient-years of follow-up

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Background: Worse renal function is associated with incident cardiovascular disease (CVD) in patients with significant chronic kidney disease, but there are sparse data regarding this association in the normal or mildly impaired range of renal function.

Aim: To examine this association in a large adult cohort with no prior CVD.

Methods: We analyzed all patients in a national database >22 years with no prior CVD and with a glomerular filtration rate (GFR) >60 but <130 ml/min/1.73m². GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) formulas. Incident CVD was defined as either myocardial infarction, unstable angina

pectoris, coronary revascularization (percutaneous and coronary artery bypass graft), or cerebrovascular accident.

Results: Our cohort, 43% males, with a mean age of 49.6±17.0 years (approximately 33% <40 years) had a GFR of 93.0±17.1 ml/min/1.73m². During a median follow up of 96.0 months and >10 million patient-years of follow-up, a total of 103,506 and 104,315 events were recorded (incident CVD rate 4.4% and 4.6% using CKD-EPI and MDRD formulas, respectively). Adjusting for age, gender and CVD risk factors, an increase of 10 units in GFR was independently associated with a decrease of 2.3% and 0.9% in incident CVD, using CKD-EPI and MDRD, respectively ($p<0.001$ for both). Using net reclassification analysis, stratifying patients to GFR deciles, CKD-EPI was more accurate in predicting incident CVD than MDRD (Net Reclassification Index = 0.10, $p<0.001$).

Conclusion: Our findings, derived from a large, population-based cohort, demonstrate that an increase in GFR in the normal or mildly impaired range is independently associated with reduced incident CVD in adults with no prior CVD. Thus, worse renal function across the spectrum, especially as assessed by the CKD-EPI formula, may be used as an independent risk marker for incident CVD.

P2089 | BEDSIDE

Study of associations between chronic kidney disease and cardiovascular and metabolic risk factors in the working population

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Objective: To investigate the influence of chronic kidney disease (CKD) and its association with vascular risk factors, in a working population and the relevance of occult CKD.

Methods: Between 2010-2011, ICARIA project included 128,588 workers (77.2% males, mean age 39.3 years, range 16 to 75), who underwent two consecutive yearly medical check-ups and had information for eGFR according to CKD-EPI equation (serum creatinine was measured by a IDMS traceable method). CKD was defined by two eGFR <60 ml/min 1.73m². Creatinine level within the normal range with an abnormal eGFR was considered occult CKD.

Results: Multivariate analyses show that blood pressure and total cholesterol (positively) and HDL, LDL (negatively) were associated with CKD. Metabolic factors were associated (positively). 22% of female workers meet the criteria for occult CKD (data not shown).

Logistic regression-associated factors

Variables (units)	Chronic kidney disease eGFR < 60 ml/min 1.73m ² (CKD-EPI)*			
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
BMI (kg/m ²)	1.10 (1.07-1.14)	<0.0001	0.91 (0.84-0.98)	0.0132
Waist circumference (cm)	1.05 (1.04-1.06)	<0.0001	1.05 (1.03-1.08)	0.0001
SBP (mmHg)	1.04 (1.04-1.05)	<0.0001	1.03 (1.01-1.04)	0.0003
DBP (mmHg)	1.06 (1.05-1.08)	<0.0001	1.02 (1.00-1.04)	0.0872
Smoking ^a	0.83 (0.60-1.15)	0.2536	0.76 (0.51-1.12)	0.1626
HDL-cholesterol (mg/dl)	0.97 (0.96-0.99)	<0.0001	0.95 (0.92-0.98)	0.0033
LDL-cholesterol (mg/dl)	1.00 (1.00-1.01)	0.4659	0.96 (0.93-0.98)	0.0017
Triglycerides (mg/dl)	1.00 (1.00-1.00)	<0.0001	1.00 (0.99-1.00)	0.1264
Serum glucose (mg/dl)	1.01 (1.01-1.02)	<0.0001	1.01 (1.00-1.01)	0.0285
White collar occupation	0.71 (0.51-0.98)	0.0372	1.04 (0.71-1.53)	0.8456
SD (Alcohol standard drink) ^b	0.92 (0.77-1.11)	0.3866	0.90 (0.74-1.10)	0.3055
Total serum cholesterol (mg/dl)	1.00 (1.00-1.01)	0.2247	1.04 (1.01-1.07)	0.0080

Odds ratios (OR), 95% confidence intervals (CI), expressed per unit of each variable. ^aCurrent consumption of at least one cigarette or pipe per day. ^bDrinkers (moderate/severe) vs non drinkers/occasional. ^cChronic Kidney Disease - EPIdemiology.

Conclusions: CKD is associated with an increased risk for cardiovascular and metabolic diseases that could be delayed by early detection and treatment, particularly by lowering blood pressure and other associated risk factors, included also at the occult stage.

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P2090 | BEDSIDE

Impact of chronic kidney disease and coronary heart disease on cardiovascular risks in high-risk hypertensive patients: a subanalysis of the CASE-J Ex

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Objective: Chronic kidney disease (CKD) has been shown to be an independent risk factor not only for end stage renal failure but also for cardiovascular morbidity and mortality. Recent studies suggested that CKD has the same impact on the incidence of cardiovascular (CV) events as a history of coronary heart disease (CHD). The present study was aimed at examining the impact of CKD and a

history of CHD on CV risk in high-risk hypertensive patients, as a subanalysis of CASE-J Ex.

Methods: The CASE-J trial compared the effects of the angiotensin II receptor blocker candesartan and the calcium channel blocker amlodipine on the incidence of CV events in 4,703 high-risk Japanese hypertensive patients. The CASE-J Extension (CASE-J Ex) was an observational study designed to evaluate their long-term effects, incorporating an additional 3-year follow-up of the CASE-J trial. CKD was defined as estimated glomerular filtration rate <60 ml/min/1.73m² or proteinuria at baseline. We divided them into four groups according to baseline characteristics as follows, non-CKD without a history of CHD (n=2,222), non-CKD with a history of CHD (n=337), CKD without a history of CHD (n=1,885), and CKD with a history of CHD (n=259). The primary endpoint was CV events including sudden death, cerebrovascular, cardiac, renal, and vascular events. We used the multiple Cox regression analysis to estimate the hazard ratio (HR) and 95% confidential interval (CI) with adjustment for baseline characteristics (prior antihypertensive treatment, allocated drug, age, sex, body mass index, diabetes mellitus, a history of cerebrovascular events, left ventricular hypertrophy, peripheral vascular disease, hyperlipidemia, smoking, systolic and diastolic blood pressure).

Results: Of 4,703 patients, 339 (7.2%) patients experienced CV events for a rate of 15.9 per 1000 person-years during 4.5 $\pm$ 1.9 years of follow-up. CKD with a history of CHD most frequently experienced CV events among four groups (adjusted HR: 4.87; 95%CI: 3.22-7.36; P<0.001). Both non-CKD with a history of CHD and CKD without a history of CHD more frequently experienced CV events compared to non-CKD without a history of CHD (adjusted HR: 3.23; 95%CI: 2.12-4.92; P<0.001, adjusted HR: 2.81; 95%CI: 2.12-3.73; P<0.001, respectively). However, there was no significant difference in the risk of CV events between non-CKD with a history of CHD and CKD without a history of CHD (P=0.480).

Conclusion: The present study suggested that patients with CKD have CV risk equivalent to patients with a history of CHD in high-risk hypertensive patients.

P2091 | BEDSIDE

Statins and Cardiovascular Primary Prevention in Individuals with Normal Renal Function: A Meta-analysis

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Purpose: Multiple meta-analyses have been performed of lipid lowering therapies for cardiovascular primary prevention in the general population without consideration of renal function. We therefore aimed to perform a systematic review and meta-analysis of lipid lowering therapies for cardiovascular primary prevention in individuals with normal renal function (estimated glomerular filtration rate >60 ml/min).

Methods: We performed a systematic review of Medline using a pre-defined search criteria and without language restrictions. We also reviewed other sources including the Cochrane Central Register of Controlled Trials and recent meta-analyses in both the general population and chronic kidney disease. We then performed a meta-analysis of the eligible trials using a random effects model. Our pre-defined primary outcome was cardiovascular events and our pre-defined secondary outcomes were total mortality, coronary heart disease events and stroke.

Results: Five trials were identified, all trials providing analysis by renal function were post-hoc subgroup analyses of statins in the general population. All trials presented analysis using the Modification of Diet in Renal Disease formula for estimated glomerular filtration rate.

The pooled risk ratio for cardiovascular disease events was 0.72 (95% confidence interval (CI) 0.63 to 0.83, p<0.00001). For the secondary outcomes the risk ratios were 0.82 (95% CI 0.71 to 0.95, p=0.008) for total mortality, 0.71 (95% CI 0.62 to 0.81, p<0.00001) for coronary heart disease events and 0.67 (95% CI 0.40 to 1.14, p=0.14) for stroke.

When compared to a meta analysis using the whole trial data, there were trends in all groups towards overestimation of the benefit of statins when renal function was not considered. For cardiovascular events this overestimation was by 5% (p=0.18) and for mortality 10% (p=0.09).

Conclusions: Statins for primary prevention of cardiovascular disease in individuals with normal renal function are effective. However compared to general population studies, they may have less efficacy. Renal function should be considered as a potential cause of heterogeneity in future meta-analyses of statins in cardiovascular disease.

P2092 | BEDSIDE

Predictors and outcome of worsening renal function in patients admitted with acute decompensated heart failure

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Background: Worsening renal function (WRF) is a common complication during the treatment of acute decompensated heart failure (ADHF) and is termed cardiorenal syndrome (CRS) type I, and is associated with worse outcomes.

Aim: The goal of this study was to determine the prevalence and the clinical predictors of WRF among patients hospitalized for acute decompensated heart failure and the association with adverse in-hospital outcomes.

Methods: We prospectively enrolled 150 consecutive patients admitted with ADHF. ADHF was defined using the European Society of Cardiology criteria. WRF was defined as the occurrence, at any time during the hospitalization, of both a $\geq 25\%$ and a ≥ 0.3 mg/dL increase in serum creatinine from admission.

Results: Overall, 45.3% of patients developed WRF. Patients with CRS type I were relatively older (65.26 $\pm$ 8.0 vs 55.78 $\pm$ 13.94 years, p<0.0001). The independent predictors of CRS type I analyzed with a multivariable logistic regression were history of diabetes mellitus, p=0.007, elevated HbA1c, p=0.004, chronic kidney disease, p=0.049, Anemia, p=0.003, and in-hospital intravenous furosemide dose >240 mg/day p=0.001. Although the in-hospital mortality of CRS type I patients was not increased significantly, the length of stay was 9 days longer [mean 18.46 $\pm$ 10.26 days (range 8–45) vs. mean 9.05 $\pm$ 2.51 days (range 6–15), p<0.0001. Development of the CRS type I was significantly associated with diuretic resistance (26.5% vs 12.2% p=0.02) and complications defined as circulatory shock, cardiac arrest, myocardial infarction, stroke, major infection/sepsis, and clinically significant hypotension (35.3% vs 15.9% p=0.006).

Conclusion: CRS type I is common in patients admitted with acute decompensated HF. Such patients have longer hospital stay, more complicated course and are more diuretic resistant but have similar mortality as those without CRS type I. Diabetes mellitus, history of CKD and daily furosemide dose are the most important predictors of the occurrence of CRS type I.

P2093 | BEDSIDE

Association between five-year clinical outcome and chronic kidney disease stage in patients undergoing percutaneous coronary intervention

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Background: It is well known that percutaneous coronary intervention (PCI) is associated with higher rates of in-stent restenosis (ISR) and major adverse cardiovascular events (MACE) in hemodialysis (HD) patients than in non-HD patients. However, the association between the chronic kidney disease (CKD) stage and the long-term outcome of PCI is unclear.

Methods: To identify the factors that are associated with MACE in PCI patients, we divided 1,192 patients from among 1,564 patients who underwent PCI in our database of the FU-Registry (UMIN000005679) into 5 stages of CKD, and evaluated the association with MACE for 5 years.

Results: The frequency of MACE in stage 1 (eGFR ≥ 90 ml/min/1.73m², n=229), stage 2+3 (30 $\leq$ eGFR <90 , n=820), stage 4 (eGFR <30 , n=49), and stage 5D (hemodialysis, n=94) increased as the CKD stage increased. While there was a significant difference in the clinical outcome between stage 1 and other stages, no difference in MACE was observed between stages 2+3 and stage 4. In addition, body mass index, prior CABG and insulin use, but not LDL-C, were independent predictors of MACE in stage 5D in a multivariate analysis, while opposite trends were seen in CKD stages 1 to 4.

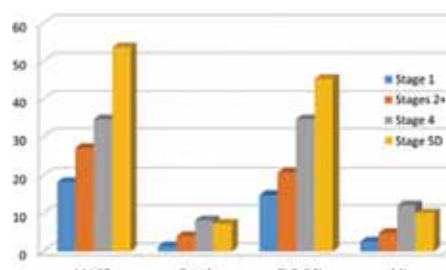


Figure 1. % MACE according to the stage of CKD

Conclusion: These data indicate that stage 1 (CKD) may help protect against, while stage 5D promotes, MACE, and the risk of MACE is the same between 30 $\leq$ eGFR <90 . While the application of lipid management at PCI may not necessarily be beneficial in HD patients, the same can not be said for non-HD patients.

P2094 | BEDSIDE

Clinical impact of serum uric acid on the incidence of atrial fibrillation in a population-based cohort study

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Purpose: Current evidence suggests that serum uric acid (UA) could be a marker of oxidative damage, a factor reported as a part of the mechanism of atrial fibrillation (AF). Previous report indicated that the association of UA with AF risk differed by race and gender. However, no prospective study has examined the association between higher UA and incident AF in Asians. We assessed the hypothesis that higher UA is associated with increased incident AF in a Japanese urban cohort.

Methods: A total of 6,906 participants (aged 30–84 years; 47% men) without prior AF were followed for 12.8 years, who underwent standard 12-lead electrocardiograms and biochemical examinations at baseline in a population-based prospective cohort. AF was diagnosed when AF or atrial flutter was present on electrocardiograms during a biannual health examination or when AF was indicated as annual questionnaires responses or medical records. UA levels were categorized into quartiles. Cox proportional hazards ratios (HRs) and 95% confidence intervals (CIs) for incident AF were analyzed after adjustment of cardiovascular risk factors such as age, body mass index, hypertension, hypercholesterolemia, diabetes, smoking, alcohol, and estimated glomerular filtration rate.

Results: During the follow-up, we identified 244 cases of incident AF (166 in men and 78 in women) including 31 cases of paroxysmal AF. In men, compared with the lowest UA quartile (<5.2 mg/dl) group, the multivariable-adjusted HRs (95% CIs) for incident AF were 1.12 (0.71 to 1.75; $p=0.64$) in the UA 5.2 to 5.9 mg/dl group, 1.03 (0.64 to 1.65; $p=0.92$) in the UA 6.0 to 6.7 mg/dl group, and 1.68 (1.09 to 2.61; $p=0.02$) in the highest UA quartile (>6.7 mg/dl) group. In women, compared with the lowest UA quartile (<3.9 mg/dl) group, the multivariable-adjusted HRs (95% CIs) for incident AF were 0.67 (0.31 to 1.43; $p=0.29$) in the UA 3.9 to 4.4 mg/dl group, 0.70 (0.35 to 1.40; $p=0.31$) in the UA 4.5 to 5.1 mg/dl group, and 1.25 (0.65 to 2.37; $p=0.50$) in the highest UA quartile (>5.1 mg/dl) group. Even after adjustment of cerebral and cardiovascular diseases, higher UA is associated with increased incident AF in men. Probabilities for trend were 0.03 and 0.37 in men and women, respectively.

Conclusion: The higher levels of UA were associated with an increased risk for incident AF in Japanese general population of men independent of confounding factors.

REGIONAL AND ETHNIC PROFILES

P2095 | BENCH

Clinic and ambulatory hypertension among high altitude dwellers. HIGHCARE-ANDES Highlanders Study

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Background: Arterial hypertension is highly prevalent among lowlanders, being a major risk factor for mortality and disability worldwide. However, little is known about its prevalence and determinants in high altitude dwellers. Moreover, available information relies on casual office blood pressure (BP) measurements, while data obtained with ambulatory BP monitoring are lacking.

Aim of ANDES Highlanders study was to explore hypertension prevalence and determinants in a sample of high altitude inhabitants.

Methods: We performed ambulatory BP monitoring and collected basic clinical information in randomly selected adults (18–65 years) permanently living in Cerro de Pasco, Peru (4300 m). Rates of BP control according to different BP variables and the relation between presence of hypertension and several clinical variables were assessed.

Results: Complete data were obtained in 286 subjects (age 38.2±13.1y, 143M/143F, BMI 25.3±3.4 kg/m², SpO₂ 86.4±4.4%, hemoglobin 17.8±2.8 g/L). Office hypertension (systolic (S)BP≥140 and/or diastolic (D)BP≥90 mmHg) was found in 19 (6.6%) subjects. Rates of ambulatory hypertension were: 11.2% for 24h BP (≥130/80mmHg), 10.8% for daytime (≥135/85 mmHg), 13.4% for night-time (≥120/70 mmHg). Diastolic hypertension was more frequent than systolic hypertension (10.1 vs. 6.3% for 24h BP), the difference depending mainly on nocturnal hypertension (12.9 vs. 6.3%). Individuals with elevated 24h BP significantly differed from normotensives in terms of age (48.3±12.7 vs. 37.0±12.6y), BMI (27.2±2.9 vs. 25.1±3.5 kg/m²), SpO₂ (84.8±4.8 vs. 86.6±4.3%) and hemoglobin (20.1±3.3 vs. 17.5±2.6 g/L). In logistic regression analysis including age, sex, BMI, 24h heart rate, hemoglobin and SpO₂ the factors independently associated with hypertension were: age, SpO₂ and hemoglobin for daytime hypertension; age, 24h HR and sex for night-time hypertension. Independent association with hemoglobin was found for diastolic but not for systolic hypertension.

Conclusions: Our study suggests that hypertension prevalence is low but not negligible among Andean high altitude dwellers, being higher when considering ambulatory rather than office BP values. There are relevant differences in factors associated with daytime vs. night-time and diastolic vs. systolic hypertension and increased blood viscosity due to polycythemia appears to play a relevant role in hypertension among highlanders.

P2096 | BEDSIDE

Gene-gene interactions between Paraoxonase 1 and Interleukin 1 receptor-like 1 on the risk of essential hypertension: the large-scale association study of the Japanese population

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Purpose: In polygenetic disorders, such as essential hypertension (HT), the investigation of gene-gene interactions rather than determination of single gene effects is crucial to better understand the contribution of genetic factors. We wished to evaluate SNP-SNP interactions between Paraoxonase1 (PON1) and Interleukin 1 receptor-like 1 (IL1RL1) genes by comparing the effects of each SNP alone with the combined effects of the two SNPs on HT risk.

Methods: We analyzed 19362 Japanese subjects, including 8733 HT cases and 10629 non-hypertensive controls enrolled in the All Japan Community Genome Bank Project by Jichi Medical University. All DNA samples and clinical data were obtained from this project. SNP (rs662, GG/GA/AA) on PON1 and SNP (rs1041973, CC/CA/AA) on IL1RL1 were genotyped by TaqMan probe method. HT was defined as SBP≥140 and/or DBP≥90mmHg or current antihypertensive medications. We stratified all subjects into four groups according to gender and age (≤49 or ≥50) and performed statistical analyses in each group. The effects of each SNP alone and combinations of two SNPs on HT risk were analyzed by using multivariate logistic regression models to estimate the strength of the associations by odds ratios (ORs) adjusted for age and body mass index (BMI). The OR of SNP alone was calculated by using homozygous non-risk genotype as reference. To assess the joint ORs of the two genotypes combined for PON1 and IL1RL1 interaction, we subdivided the subjects into 9 strata according to cross-classified genotypes. We then obtained the ORs for each strata relative to the first stratum defined by non-risk genotype for both genes.

Results: Prevalence of HT showed that the risk genotypes for PON1 were minor homozygote (AA) in subjects aged ≤49 and major homozygote (GG) in subjects aged ≥50, while for IL1RL1 were minor homozygote (AA) in subjects aged ≤49 and ≥50. The ORs (95%CI) of homozygous risk genotypes were 1.31 (M≤49, 0.94–1.83), 0.96 (F≤49, 0.64–1.45), 1.17 (M≥50, 0.98–1.40) and 1.14 (F≥50, 0.96–1.36) for PON1 alone, and 1.46 (M≤49, 0.86–2.47), 1.38 (F≤49, 0.73–2.60), 1.16 (M≥50, 0.87–1.54) and 1.06 (F≥50, 0.81–1.39) for IL1RL1 alone. The joint ORs (95%CI) of combined homozygous risk genotypes were 5.49 (M≤49, 1.40–21.6), 1.37 (F≤49, 0.16–11.8), 1.62 (M≥50, 1.02–2.57) and 1.00 (F≥50, 0.65–1.54).

Conclusions: SNP-SNP interactions between PON1 and IL1RL1 had significant effects as risk factors for HT development in men aged ≤49 and ≥50. However, the effect was prominent in men aged ≤49. SNP-SNP interactions between PON1 and IL1RL1 may contribute to young-onset hypertension in Japanese men.

P2097 | BEDSIDE

Synergistic effect of gestational hypertension and postpartum incident hypertension on cardiovascular health: a nationwide population study

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Aims: Gestational hypertension (GH) is a common complication of pregnancy and is associated with increased risk of incident hypertension in later life (IH) and cardiovascular events. However, the interactive effect of GH and IH on postpartum cardiovascular health remains unclear.

Methods and results: A nationwide population-based study was conducted using one million individuals from the Taiwan National Health Insurance database. Records from 1997 to 2009 were used to identify 1303 pregnant women with GH and without previous cardiovascular disease. The control group comprised 5212 pregnant women without GH, matched for age and date of delivery. During the follow-up period (median duration, 5.8 years), 170 cardiovascular events developed. Women with GH had significantly higher risk of cardiovascular events (hazard ratio [95% confidence interval], 3.37 [2.48–4.58]) and IH (6.93 [5.38–8.92]) than controls. Compared with women without GH or IH, there was a significantly higher risk of cardiovascular events for women without GH but with IH (relative risk [95% confidence interval], 2.24 [1.54–3.25]), women with GH but without IH (3.94 [1.87–8.32]), and women with GH and IH (14.75 [9.57–22.74]). The synergy index was 3.29 (95% confidence interval, 1.47–7.40), suggesting a positive interaction between GH and IH.

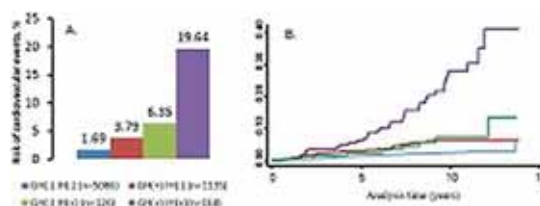


Figure 3

Conclusions: GH increased the risk of subsequent IH. Women with both GH and IH were more at risk of cardiovascular events than women with either GH or IH. The synergistic adverse effect of GH and IH on postpartum cardiovascular health indicates that more attention should be paid to this population.

P2098 | BEDSIDE**The “half marathon” of hypertension and diabetes: “the winner” of the 25 years’ long race in the Serbian cohorts of the seven countries study**

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Purpose: In the presented analysis we focused on whether hypertension (HTA) arrives prior diabetes (DM) or vice versa, hoping to learn something new regarding cardiometabolic risk profile of the SCS-Serbia cohorts and its impact on specific vascular mortality (cardio-v. and cerebro-v.).

Methods: The 3 Serbian cohorts were all men aged 40-59yrs at entry, subsequently followed every 5 years. Presence of DM and HTA and their progression over 25 year FU where studied aiming to assess their relationship and impact on cardiovascular and cerebrovascular mortality.

Results: 1552 men were divided in 4 groups based on HTA and DM presence (Table 1), while mortality data (Figure 1) showed the strongest positive correlation for HTA (irrelevant DM), in particular with cardiovascular mortality, while cerebrovascular mortality was steady over time. DM-influence was mild due to low percentage of DM.

Table 1

	Baseline	5y FU	10y FU	25y FU
HTA total	534	632	774	643
DM total	11	62	90	80
HTA+ DM-	530	594	720	572
HTA- DM+	7	24	36	9
HTA+ DM+	4	38	54	71
HTA- DM-	25	43	194	39

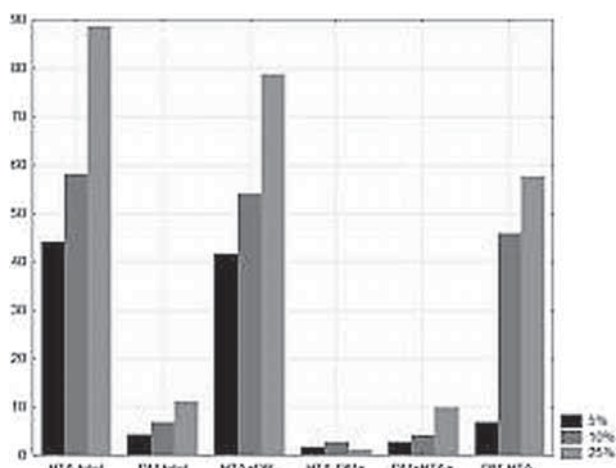


Figure 1

Conclusion: In the Serbian cohorts of the SCS, as a result of the 25y FU, we have shown HTA appearing much earlier than DM and influencing cardiovascular mortality, in particular.

P2099 | BEDSIDE**The estimation of the vascular status parameters, depending on the gene polymorphism carrier of the angiotensin II receptor type 1 considering the ethnicity of patients with AH**

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Angiotensin II receptor type 1 (AT2R1) is one of the candidate genes associated with the pathology of the cardiovascular system. According to the data of the association between AT2R1 gene polymorphism and endothelial dysfunction as well as remodelling processes and vascular wall stiffness that men and women of different ethnic groups have, it is of great interest to study the disturbances in arterial stiffness based on ethnic, gender and genetic factors in its evolution, particularly among indigenous population of the Republic of Mordovia.

Therefore, the aim of the study is to examine the indices of the vascular status depending on AT2R1 gene polymorphism and ethnicity of the patients with arterial hypertension (AH) in the Republic of Mordovia.

156 patients with primary AH II-III, II stage (WHO classification / GCF (2004/2010)) were tested on the elastic properties of vessels. Three groups: Moksha (n=50), Erzya (n=58) and Russian (n=48) patients with AH were formed. The groups were of the same age, sex and level of blood pressure (SBP and DBP)

(p>0.05). For the pulse wave analysis the suprasystolic method of sphygmogram registration with the use of Arteriograph “TensioClinic” was applied.

Studying the Mordovian-Erzya male patients with AH, the carriers of “adverse” genotype CC of gene AT2R1 the significantly higher indices of pulse wave velocity (PW) (RCC / AA = 0,045) have been obtained. In Erzya females with AG, the carriers of genotype CC the augmentation index (AIX) (RCC / AA = 0,032) of central blood pressure (CAP) (RCC / AC = 0,049) prevails, the correlation AIX: r=0,250; p=0,043 with polymorphism AT2R1 has been found.

In Russian males with AH, the carriers of genotype CC gene AT2R1 the significantly higher indices of PW (RCC / AA = 0,040) and AIX (RCC / AA = 0,032) have been found. In Russian females with AH, the carriers of genotype CC the significantly higher indices of PW (RCC / AA = 0,005 and RCC / AC = 0,001), AIX (RCC / AA = 0,047) have been shown. As a result of the correlation analysis the interdependence of AIX and AH polymorphism AT2R1 (AIX: r=0,316; p=0,02) has been found in Russian females.

The Assessment of the key parameters of vascular status in patients with AH, the carriers of “adverse” genotype CC of AT2R1 gene showed a significant increase in PW and AIX in Erzya and Russian females, compared to the carriers of favorable genotypes. The results of two-factor analysis of variance allowed us to draw the conclusion about the certain influence of two factors on CAP (p=0.036) in female patients with AH – AT2R1 gene polymorphism and ethnicity.

P2100 | BEDSIDE**The role of cardiotonic steroids in salt-sensitive hypertensive patients of georgian ethnicity**

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Purpose: Since Georgians traditionally consume salty food, the study was aimed to investigate the prevalence of salt sensitive hypertension in this population. Moreover, among factors that determine salt-sensitivity endogenous cardiotonic steroids (endogenous ouabain and marinobufagenin) have been considered. The second objective of our study was to determine the relationship between endogenous cardiotonic steroids and salt sensitivity in Georgian hypertensive patients and their family members.

Methods: A total of 323 ethnically Georgians (127 males and 196 females, aged from 19 to 78 years) from 123 families were tested for salt-sensitivity using a high salt/low salt protocol. Anthropometry, blood pressure monitoring, and 24 hr urinary sodium excretion were performed. Initially salt-sensitivity had to be assessed by the difference of mean arterial pressure (≥ 3 mm Hg) on high (200 mmol/day) vs. low (40 mmol/day) salt diet, however since all subjects consumed very high salt, later we skipped high salt diet and placed subjects only on one-week low salt diet. In parallel with determination of salt-sensitivity, plasma and urine levels of marinobufagenin and ouabain were measured.

Results: Our results show that virtually all hypertensives and their family members consumed high amount of salt with a mean of 348 ± 104 mmol/24h (> 20 g daily). Salt sensitivity was detected in 84 (68%) of hypertensive subjects and in 43 family members. A high prevalence of salt-sensitive was found in women and positive correlation of salt-sensitivity with age was found. Plasma levels of marinobufagenin in salt-sensitive hypertensives almost twice exceeded those of salt-resistant subjects (0.92 ± 0.08 nmol/l in salt sensitive and 0.33 ± 0.02 nmol/l in salt resistant, $p < 0.05$).

Conclusions: Our data confirm a very high sodium consumption by Georgian subjects which is closely linked with a high incidence of salt-sensitive hypertension. The very high salt consumption in the Georgian population may be the rational basis for intervention in order to reduce the prevalence of hypertension. Significantly increased levels of marinobufagenin might indicate its contribution to the development of salt-sensitivity.

P2101 | BEDSIDE**New tools for a better prediction of total cardiovascular risk of Romanian adult hypertensive population**

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Purpose: To analyze the predictive value of new cardiovascular (CV) risk factors for CV risk assessment in the adult Romanian hypertensive (HT) population.

Methods: A total number of 978 hypertensive adults identified in national representative SEPHAR II survey were evaluated by anthropometric, BP and arterial stiffness measurements: aortic pulse wave velocity (PWVao), aortic augmentation index (AIXao), revers time (RT) and central SBP (SBPao), 12 lead ECGs and laboratory workup. Values above the 4th quartile of mean SBP standard deviation (s.d.) defined increased BP variability. Log(TG/HDL-cholesterol) defined athero-

genic index of plasma (AIP). Serum uric acid levels above 5.70mg/dl for women and 7.0mg/dl for males defined hyperuricaemia (HUA). CV risk was appreciated based on the 2013 ESH/ESC risk stratification chart. Binary logistic regression using a stepwise likelihood ratio method (adjustments for major confounders and collinearity analysis) was used in order to validate predictors of high and very high total CV risk class.

Results: The mean BP value of the study group was 149.96/ 89.18mmHg. Forty percent of hypertensives had a very high CV risk. Predictors of high and very high CV risk class validated by regression analysis were: increased visit-to-visit BP variability (OR: 2.49; 95%CI: 1.61–3.88), PWVao (OR: 0.83; 95%CI: 0.70–0.98), AIXao (OR: 0.98; 95%CI: 0.96–0.98), RT (OR: 0.98; 95%CI: 0.96–0.99), SBPao (OR: 1.04; 95%CI: 1.03–1.05), AIP (OR: 3.29; 95%CI: 1.87–5.8) and HUA (OR: 2.09; 95%CI: 1.20–3.64) (Fig. 1).

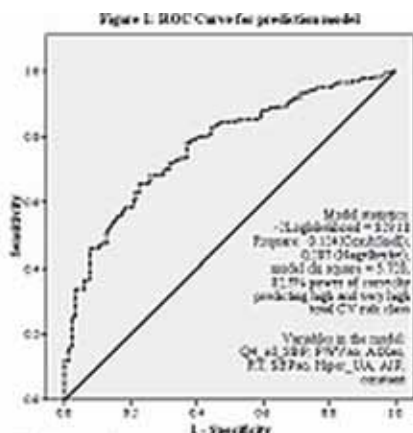


Figure legend: Model adjusted for age, sex, mean arterial pressure, treatment and treatment control. CH, CHD; SBP, 1st quartile of SBP; standard deviation; SBP, systolic blood pressure; PWVao, aortic pulse wave velocity; AIXao, aortic augmentation index; RT, heart rate; HUA, hyperuricaemia; AIP, atherogenic plasma index.

Conclusions: The results of our study suggests that the new CV risk factors such as increased BP variability, arterial stiffness indices, hyperuricaemia and AIP are useful tools for identifying hypertensives at high and very high CV risk.

LIPID LOWERING TREATMENT: NEW FINDINGS

P2102 | BEDSIDE

The effect of apolipoprotein E polymorphism on the response to lipid-lowering treatment with atorvastatin

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Background: Statins are one of the most commonly prescribed classes of drug worldwide and therapy is highly effective in reducing low-density lipoprotein cholesterol (LDLc) levels and cardiovascular events. In spite of these well recognized benefits, there is large variability in clinical response to statin treatment. These differences may be due to the interaction of environmental and genetic factors that affect drug bioavailability, receptor function or ligand structure.

Purpose: Our objective was to assess the effect of apolipoprotein E (ApoE) gene polymorphism on response to atorvastatin.

Methods: Our study included 60 consecutive patients, hospitalized for ACS (55.6±9.8 years, 86.2% men, 60.3% STEMI). DNA was extracted from leucocytes and analyzed by the PCR-RFLP protocol. Lipid profiles with a calculation of LDLc were performed before and 6 to 8 weeks after initiation of atorvastatin 40mg/day. We proposed a definition of resistance to atorvastatin (reduction in LDLc <20%) and then looked for correlations between clinical factors, the polymorphism of Apo E gene and the lipid response to atorvastatin 40mg/day.

Results: The average baseline LDLc was 1.13 g/l ± 0.4; baseline LDL cholesterol was lower in E4 allele (ApoE) carriers (p=0.06). At the end of the follow up period, the absolute reduction of LDLc was -0.35g/l ± 0.43 and the relative reduction of -23.90% ± 31.68. Resistance to atorvastatin was noted in 37.9% of patients. In univariate analysis, this resistance was inversely correlated with baseline LDLc (p<0.01). The E4 allele (ApoE) was associated with a higher risk of resistance (p=0.01). In multivariate analysis the studied polymorphism was not independently associated with response to atorvastatin and only the baseline LDLc was predictive of the response and of the resistance to atorvastatin.

Conclusion: This study objectified, in univariate analysis, a correlation between low baseline LDLc, poor response to atorvastatin and E4 (ApoE) allele. Multivariate analysis, however, calls into question the interest of genetic markers compared to the only baseline rate of LDLc to predict the resistance to atorvastatin.

P2103 | BENCH

Pharmacogenetic GWAS meta-analysis of LDL cholesterol response to statins

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Purpose: Statins are widely prescribed for the prevention and treatment of cardiovascular disease with great proven effectiveness of 20-30%. However, there is inter-individual variability in LDLc response to statins, which may be partly due to pharmacogenetic variation. The only genetic variants consistently reported from previous studies are located within the APOE and LPA gene regions. To determine whether additional loci may influence LDLc response to statins, we formed the Genomic Investigation of Statin Therapy (GIST) consortium and conducted a pharmacogenetic meta-analysis of genome-wide association studies (GWAS) of LDLc response to statins, the largest, most comprehensive study of its kind conducted to date.

Methods: The meta-analysis comprises GWAS datasets from both randomized controlled trials and observational studies, including approximately 40,000 statin-treated subjects. Response to statin treatment was defined as the difference between the natural log transformed LDLc levels on- and off-treatment and was assessed using a linear regression model adjusted for baseline LDLc, age, sex, study specific covariates, and statin dose. Additional functional analyses were performed to elaborate our findings.

Results: Overall, at genome-wide significant level ($P < 5 \times 10^{-8}$), we have identified two new loci: SORT1/CELSR2/PSRC1 (rs646776, $\beta = -0.013$, SE=0.002, $P = 1.05 \times 10^{-9}$) and SLCO1B1 (rs2900478, $\beta = 0.016$, SE=0.003, $P = 1.22 \times 10^{-9}$), which have not been previously identified in GWAS. Furthermore we have successfully confirmed the known associations with APOE (rs445925, $\beta = -0.043$, SE=0.005, $P = 1.58 \times 10^{-18}$) and LPA (rs10455872, $\beta = -0.059$, SE=0.006, $P = 1.95 \times 10^{-11}$).

Our results were further investigated and validated with additional functional analyses, that collectively confirmed a strong biological and functional role in statin response for several strongly associated gene loci, including APOE, and SORT1/CELSR2/PSRC1. Furthermore, a weaker LDLc lowering response, assessed by a genetic risk score including our four lead SNPs, was significantly associated with an increased risk of coronary artery disease in the CARDIoGRAM and C4D consortium ($P = 2.9 \times 10^{-19}$).

Conclusions: Our results demonstrate that apart from the previously identified APOE and LPA loci, two new loci, SORT1/CELSR2/PSRC1 and SLCO1B1, also have modest but genome-wide significant effect on LDLc response. Our findings advance the understanding of the pharmacogenetic architecture of statin response, and illustrate that SNPs with modest effect on LDL response to these widely used drugs can influence coronary artery disease risk.

P2104 | BEDSIDE

Circulating PCSK9 predicts future risk of cardiovascular events independently of established risk factors

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Purpose: The secreted protein proprotein convertase subtilisin/kexin type 9 (PCSK9) is a promising new target for lowering of plasma LDL cholesterol and prevention of cardiovascular disease events (CVD) but the relationship between circulating PCSK9 and incident CVD is so far unknown. We analysed serum PCSK9 concentrations as predictor for first-time CVD in a prospective cohort study of 4,232 men and women from Stockholm, aged 60 at the time of recruitment.

Methods: Incident CVD was recorded yearly by matching to national registries. After 15 years of follow-up, a total number of 491 incident events (fatal and non-fatal myocardial infarctions, unstable angina, deaths from coronary heart disease, fatal and non-fatal ischemic strokes) were recorded. Cox Proportional Hazards model was used to calculate Hazard ratios (HR) with 95% confidence intervals (CI).

Results: Baseline serum PCSK9 concentrations predicted incident CVD; concentrations in the upper quartile, as compared to lower concentrations, were associated with a HR of 1.46 (95% CI 1.18-1.79). Adjustment for sex, LDL, HDL, Lp(a) and triglycerides resulted in a decrease of the HR (HR 1.38 95% CI 1.12-1.71). The HR was further reduced to 1.31 (95% CI 1.05-1.63) after additional adjustment for hypertension, diabetes, smoking, obesity and physical inactivity. Conversely, PCSK9 concentrations in the lowest quartile of the distribution were,

as compared to higher values, significantly associated with a reduced risk of suffering a CVD event: HR 0.79 (95% CI 0.63-0.99) after full adjustment.

Conclusion: We demonstrate for the first time that serum PCSK9 concentrations are associated with future risk of CVD, independently from other cardiovascular risk factors.

P2105 | BEDSIDE

Effects of RG7652, a monoclonal antibody against proprotein convertase Subtilisin/Kexin type 9, on LDL cholesterol in patients with coronary heart disease or high risk: Results from the EQUATOR study

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Purpose: Proprotein convertase subtilisin/kexin type 9 (PCSK9) down-regulates hepatic low-density lipoprotein (LDL) receptors and plays a key role in cholesterol metabolism and coronary heart disease risk. RG7652 (MPSK3169A) is a fully human IgG1 monoclonal antibody (mAb) directed against PCSK9. This study evaluated the safety and LDL-cholesterol (LDL-c) lowering effects of RG7652 when added to standard of care therapy in patients with established coronary heart disease (CHD) or a high risk of CHD.

Methods: This international, double-blind Phase II study randomized patients to one of five dose regimens of RG7652, or placebo, given subcutaneously every 4, 8 or 12 weeks, for 24 weeks. The primary objectives were to evaluate the safety and LDL-c lowering effects of RG7652 in patients with CHD or high risk of CHD, with baseline LDL-c between 90-250 mg/dL on standard of care therapy, including statin medications if tolerated. The modified intent-to-treat (mITT) population was used for efficacy analysis, and all patients who received at least one study treatment were included in safety analyses.

Results: 248 patients with median age 64 years (range 37-80), 43% women, were randomized in nine countries. At baseline, 52% of patients had established CHD, 46% were type-2 diabetic, 82% were on statins and the mean LDL-c was 126 mg/dL (3.3 mmol/L). On average, treatment with RG7652 reduced LDL-c by as much as 56-74 mg/dL (48-60%, $p < 0.0001$) from baseline to nadir for each of the dose regimens, as compared to placebo, with a dose-dependent magnitude and duration of effect. There were no unexpected safety findings, and the overall incidence of adverse events (86% and 88%) and serious adverse events (10% and 13%) were similar in the RG7652 arms (combined) and the placebo arm, respectively. The pharmacokinetics of RG7652 suggested target-mediated clearance.

Conclusions: RG7652 safely decreased LDL-c in patients with CHD or high CHD risk on standard of care therapy. The results of the EQUATOR study support further development of anti-PCSK9 monoclonal antibodies in Phase III lipid and cardiovascular outcomes studies.

P2106 | SPOTLIGHT

The ABCA1 agonist CS-6253 generates functional nascent HDL particles resulting in efficient cholesterol SR-BI delivery to hepatic cells and shows macrophage specific cholesterol mobilization and ather

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Background: CS-6253 is a selective 26 amino acid ABCA1 agonist peptide derived from the C-terminal of apoE with molar equi-potency to that of apoA-I, high stability and solubility. We investigated CS-6253's ability to promote lipid transfer between nascent (n)HDL particles and plasma lipoproteins and examined cholesterol influx from remodelled HDL-like particles to hepatic cells through the SR-BI receptor. In addition CS-6253 properties were assessed in several animal models.

In vitro methods and results: nHDL-like lipoproteins from CS-6253 was generated by incubating CS-6253 in the presence of BHK cells expressing ABCA1 labelled with 3[H]cholesterol and 3[H] choline; native apoA-I was used as control. These nHDL particles were incubated with plasma at 37°C. CS-6253 increased LCAT activity significantly, although about 50% less efficiently than nHDL-apoA-I (fractional esterification rate (FER) 11.40±0.045%/h vs. 22.32±0.86%/h, $p < 0.05$). The majority of 3[H] cholesterol from nHDL-CS-6253 was esterified by LCAT, resulting in an increase in α 1-migrating HDL-like particles in plasma. The phospholipid transfer protein (PLTP) promoted significant phosphatidyl choline transfer to apoB lipoproteins in-vitro illustrating physiological remodeling in the presence of plasma lipoproteins. We then investigated cholesterol delivery from HDLs to hepatic tissue via SR-B1 using Fu5AH cells. The SR-BI-mediated cholesterol influx into Fu5AH cells was more efficient for HDL-CS-6253 (Km=0.30±0.05 ug/ml) than for HDL apoA-I (Km = 0.37±0.13 ug/ml).

In vivo methods and results: In apoE KO mice significant increases in macrophage specific cholesterol mobilization to feces was found by a single

30mg/kg single free CS-6253 peptide ip injection compared to PBS control (+49%, $p < 0.01$). In apoE KO mice made atherosclerotic by 14 week high-fat-diet CS-6253 ip treatment 25mg/kg/48h for 6 weeks days reduced whole aorta atherosclerosis by (-34%, $p < 0.01$). In rats CS-6253 showed an 8 hour half-life.

Conclusion: The ABCA1 agonist CS-6253 shows reverse cholesterol transport properties in vitro and potent anti-atherosclerosis actions in vivo. Given the high potency, high solubility and long half-life it is projected that CS-6253 can be administered sc once weekly for the stabilization/regression of atherosclerosis and to obviate the need for certain invasive procedures.

P2107 | BEDSIDE

Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on mechanisms regulating LDL-C levels in patients with dyslipidemia

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Purpose: The CETP inhibitor evacetrapib (EVA) has been shown to significantly reduce LDL-C levels as monotherapy and in combination with statins. However, the mechanisms responsible for this reduction are not completely understood. We evaluated the effect of EVA on mechanisms regulating LDL-C levels in patients with dyslipidemia.

Methods: Patients (n=398) with elevated LDL-C or low HDL-C in the multicenter, randomized, double-blind, parallel, placebo-controlled trial were studied. Percent changes from baseline in serum lathosterol, campesterol, PCSK9 levels, and LDL particle distribution were evaluated after 12 weeks of placebo (PBO), EVA monotherapy, statins alone, or EVA with statins (see Table). The effect of EVA on PCSK9 gene expression and secretion was also evaluated in vitro in a HepG2 cell model (+/- mevastatin).

Results: Statins alone increased PCSK9 (+29.4%, $p < 0.001$), decreased lathosterol (-43.6%, $p < 0.001$) and had no effect on campesterol levels. Results for EVA monotherapy and in combination with statins are shown in the Table. Lathosterol and campesterol levels were not affected by EVA monotherapy or in combination with statins. Although EVA monotherapy increased PCSK9 levels, this increase was not dose-dependent and was partly due to a 6.8% decrease in the PBO group. Conversely, PCSK9 levels decreased when EVA was given with statins. EVA monotherapy was associated with an increase in large LDL particles, whereas a decrease in small and very small LDL particles was observed with EVA in combination with statins. In vitro, EVA (at concentrations of $\geq 3.7 \mu\text{M}$) dose-dependently decreased relative PCSK9 gene expression in HepG2 cells treated for 24hrs, and PCSK9 secretion from HepG2 cells at 24 and 48hrs in the presence or absence of mevastatin.

	EVA monotherapy ^a % Change	p-value	EVA in combination with statins ^b % Change	p-value
Lathosterol ^c	-8.5 (-17.9, 0.9)	0.137	-0.4 (-6.9, 6.2)	0.921
Campesterol ^c	4.3 (-4.2, 12.8)	0.408	-1.0 (-7.0, 5.0)	0.789
PCSK9	14.8 (6.3, 23.2)	0.004	-8.0 (-14.0, -2.1)	0.026
Total LDL particles	-38.6 (4.5)	<0.001	-14.6 (3.1)	<0.001
Large LDL particles	84.7 (28.3)	0.003	22.1 (19.8)	0.264
Small LDL particles	-28.3 (54.7)	0.605	-99.3 (38.2)	0.010
Very small LDL particles	-29.8 (40.5)	0.463	-71.7 (28.1)	0.011

Results are LS Mean (SE), or difference in LS Mean (90% CI) compared to placebo (for EVA monotherapy) or compared to statin monotherapy (for EVA in combination with statins). ^aPooled EVA monotherapy (30 mg, 100 mg, 500 mg), ^bPooled EVA (100mg) in combination with simvastatin (40 mg), atorvastatin (20 mg) or rosuvastatin (10 mg), ^cNormalized by total cholesterol.

Conclusions: In patients with dyslipidemia, EVA monotherapy or in combination with statins did not significantly affect markers of cholesterol synthesis and absorption. EVA monotherapy increased PCSK9 by 14.8% (6.3, 23.2; $p = .004$), while EVA with statins reduced PCSK9 by 8.0% (-14.0, -2.1; $p = .026$).

P2108 | BENCH

High-density lipoprotein subfractions are associated with circulating monocyte subsets in patients with stable coronary artery disease

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Background: High-density lipoprotein (HDL) particles are highly heterogeneous in structure and the role of HDL subfractions in atherogenesis are not well understood. Recently, it has been suggested that small HDL (HDL-s) may be dysfunctional in patients with metabolic syndrome or coronary artery disease (CAD). Monocytes and monocyte-derived macrophages are considered to play a key role in atherosclerotic diseases. Circulating monocytes can be divided into three subtypes according to their surface expression of CD14 and CD16 in pro- and anti-inflammatory subtypes. Our aim was to examine whether monocyte subsets are associated with HDL subfractions in patients with atherosclerosis.

Methods: We included 90 patients with angiographically stable CAD. Monocyte

subsets were defined as classical monocytes (CD14+CD16-; CM), intermediate monocytes (CD14+CD16+; IM) and non-classical monocytes (CD14-CD16++; NCM). HDL subfractions were measured by an electrophoresis method on polyacrylamide gel.

Results: Patients with HDL-s levels in the highest tertile (HDL-s $\geq$ 13mg/dL; n=37; T3) showed the highest levels of pro-inflammatory NCM (14.7 $\pm$ 7% vs. 10.7 $\pm$ 5% and 10.8 $\pm$ 5%; p<0.01) when compared with patients in the middle (HDL-s=9-12mg/dL; n=27; T2) and the lowest tertile (HDL-s=0-8mg/dL; n=26; T1). Additionally, patients in the highest HDL-s tertile showed lower CM levels than patients in the middle and lowest tertile (79.3 $\pm$ 7% vs. 83.7 $\pm$ 6% and 83.9 $\pm$ 6%; p<0.01 for T3 vs. T2+T1). Levels of IM were not associated with HDL-s levels (5.9 $\pm$ 3% vs. 5.6 $\pm$ 3% vs. 5.3 $\pm$ 3% for T3, T2 and T1, respectively). In contrast, intermediate and large HDL particles as well as total HDL were not associated with monocyte subset distribution.

Conclusion: High HDL-s levels are associated with an increase of pro-inflammatory NCM and a decrease of the more anti-inflammatory CM. This suggests that HDL-s could have dysfunctional anti-inflammatory properties in patients with established CAD.

IMAGING THE AORTIC VALVE AT THE TAVI ERA

P2109 | BEDSIDE

The progression of ascending aorta dilatation with both congenital bicuspid and non-bicuspid aortic stenosis

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Purpose: To describe the progression of ascending aortic (AscAo) dilatation in congenital bicuspid aortic valve (CBAV) and compare that with non-bicuspid aortic valve (NBAV).

Methods: There were 19,786 patients with at least one ECHO. Of these 234 had a CBAV, (prevalence, 1.2%). Group 1 (n=258) comprised the CBAV. Group 2 was the NBAV, (N=5,843). Patients in the NBAV with a mean aortic gradient $\leq$ 5mmHg were excluded. The Group 1. numbers are higher as a patient could progress from mild to moderate or moderate to severe AVS over the 14 years of data collection. The two groups were sub-divided into, mild, moderate or severe based on mean aortic valve gradient (AVG) according to the ASE guidelines. The AscAo measurement was taken from the 2D images. ANOVA and Tukey-Kramer testing or a t-test was performed when appropriate.

Results: The CBAV there show a statistically significant difference with ANOVA in the AscAo as the AVG Progressed. Tukey-Kramer testing indicated this was only between mild and moderate AVS. In the NBAV there was a progressive increase in the diameter of the ascending aorta which was also statistically significant. Similarly, Tukey-Kramer testing showed this was only significant between mild and moderate AVS. There were significant differences in the AscAo measurements between the CBAV and the NBAV for all severity grades. Those with NBAV are significantly older, see Table 1.

Table 1

AS	Group 1. Bicuspid AS				Group 2. Non-bicuspid AS			
	N	Age	AVG	AscAo	N	Age	AVG	AscAo
Mild (6-19mmHg)	196	47.0 $\pm$ 15.1	8.6 $\pm$ 4.3	35.6 $\pm$ 6.3	5051	65.6 $\pm$ 16.2	8.4 $\pm$ 3.2	32.6 $\pm$ 4.7
Moderate (20-40mmHg)	46	56.8 $\pm$ 11.5	27.1 $\pm$ 6.7	38.1 $\pm$ 7.2	610	74.3 $\pm$ 10.4	26.3 $\pm$ 5.6	34.1 $\pm$ 4.6
Severe ($>$ 40mmHg)	16	58.8 $\pm$ 8.7	52.8 $\pm$ 10.2	39.1 $\pm$ 3.8	182	75.9 $\pm$ 10.0	52.8 $\pm$ 10.7	34.4 $\pm$ 5.3
ANOVA	258	<0.0001	<0.0001	<0.01	5843	<0.0001	<0.0001	<0.0001

AVG, mean aortic valve gradient (mmHg); AscAo, ascending aorta (mm); AS = aortic stenosis.

Conclusions: For both CBAV and NBAV dilatation of the AscAo occurs when the AVG is mild to moderate, further increase in severity of AVG has no influence on the AscAo measurement. The pathology of the aortopathy is cystic medial necrosis in the younger CBAV and atherosclerosis in the older NBAV group. The rates of progression of AscAo dilatation are similar for both groups, however patients with CBAV start off with a significantly larger AscAo diameter.

P2110 | BEDSIDE

Aortic root geometry and its impact on measurements

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Background and aim: Aortic root (AoR) diameter measurements are usually performed in long-axis views by transthoracic echocardiography (TTE) and in coronal and sagittal slices by multidetector-gated computed tomography (MDCT). The usual TTE diameter obtained from one sinus of Valsalva (SV) to another yields slightly higher values than those obtained from one SV to the opposite aortic commissure viewed by MDCT. We sought to assess the accuracy of TTE in the evaluation of AoR dimensions compared with MDCT, and the potential influence of AoR geometry on these measurements.

Methods: Sixty patients (mean age: 65 $\pm$ 11; 54% men) with a severe aortic valve disease (stenosis or regurgitation) were evaluated with TTE and MDCT for AoR measurement. Three different echocardiographic methods were used: leading

Table 1. TTE methods on aortic assessment

	Leading-leading	Inner-inner	Outer-outer
Interobserver variability (ICC)	0.99	0.98	0.99
Intraobserver variability (ICC)	0.98	0.92	0.96
Mean difference MDCT vs TTE (mean $\pm$ SD)	(-)-0.81 $\pm$ 1.91 p=0.50	2.19 $\pm$ 1.83 p=0.0001	(-)-3.55 $\pm$ 2.29 p=0.0001

TTE: transthoracic echocardiography; ICC: intraclass correlation coefficient; MDCT: multidetector-gated computed tomography; SD: standard deviation.

edge-to-leading edge, inner-to-inner and outer-to-outer and results were compared with those obtained by MDCT. MDCT measurements from one SV to another were also compared with measurements from each SV to the opposite commissure. Asymmetry was considered if one diameter was $\geq$ 10% larger than the others.

Results: The three methods showed excellent interobserver and intraobserver variability and reproducibility. The leading-to-leading method showed the best agreement with MDCT (Table 1). AoR was asymmetric in 5 patients (8.3%), 4 of whom had bicuspid aortic valve. No relationship was found between mean diameters (40mm) and asymmetry.

Conclusions: TTE is an accurate technique for the assessment and follow-up of AoR diameters in valve patients. The leading-to-leading approach is that which shows the best agreement with MDCT measurements of AoR dimensions. Asymmetry of the AoR may lead to overestimation of AoR diameters. The presence of asymmetry is independent of aortic diameters, but closely related to valve morphology.

P2111 | BEDSIDE

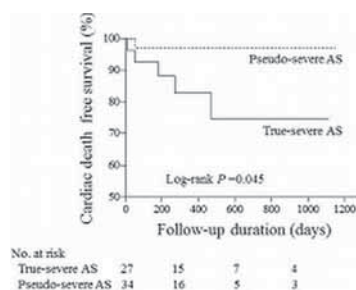
Prognostic value of projected aortic valve area in patients with paradoxical low-flow low-gradient severe aortic stenosis: Japanese Multicenter Aortic Stenosis (JUST) Study

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Purpose: We hypothesized a subset of patients with paradoxical low-flow, low-gradient severe aortic stenosis (PLFLG-SAS) despite preserved ejection fraction might be pseudo-severe AS due to low-flow status, and the measurement of projected aortic valve area (AVAproj) could discriminate from true-severe to pseudo-severe AS.

Methods: 3D stress echocardiography was performed in 61 patients with PLFLG-SAS (AVA $\leq$ 1.0cm²; stroke volume index $\leq$ 35ml/m²; mean pressure gradient (PG) $\leq$ 40mmHg). Stroke volume was determined by 3D volumetric method. AVA was plotted against transvalvular flow (Q) at each stage; valve compliance (VC) was derived as a slope of the regression line fitted to AVA versus Q plot. AVAproj was calculated as AVArest+VC $\times$ (250-Qrest). The primary endpoints were cardiac death (CD) and major adverse cardio-cerebrovascular events (MACE).

Results: Of these, 27 (44%) patients had AVAproj $<$ 1.0cm² (true-severe AS) and 34 (56%) had AVAproj $\geq$ 1.0cm² (pseudo-severe AS). During a mean of 420-day follow up, MACE developed 23 patients (37.7%) including 6 CD (9.8%). Kaplan-Meier analysis showed that the pseudo-severe AS had a significantly higher survival rate than the true-severe AS (p=0.045, Figure). Cox proportional-hazard analysis revealed that AVAproj was an independent predictor for MACE (hazard ratio: 0.27, p=0.013).



Conclusions: More than half of Japanese PLFLG-SAS patients revealed pseudo-severe AS using AVAproj. This is one possible reason why Japanese PLFLG-SAS has a better prognosis compared to Western countries.

P2112 | BEDSIDE

Echocardiographic predictors of pulmonary hypertension in patients with severe aortic stenosis

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Purpose: Pulmonary hypertension (PH) is associated with adverse outcomes in

different cardiac diseases. Thus, in severe aortic stenosis (SAS), the development of PH may have impact in prognosis, but its prevalence is largely unknown as well as the underlying mechanisms. The aim of this study is to determine the prevalence of PH in patients with SAS and to find echocardiographic predictors of pulmonary artery systolic pressure (PASP).

Methods: We retrospectively studied consecutive patients, included between February 2008 and December 2012, with isolated SAS diagnosed by conventional echocardiography-Doppler, using the EAE criteria for severity. Patients with non-sinus rhythm, ejection fraction <50% and inconclusive assessment of PASP were excluded. In all patients we assessed: left ventricle (LV) end-diastolic and end-systolic dimensions and wall thickness, fractional shortening, left and right atrium dimensions, biplane ejection fraction and PASP. LV diastolic function was classified in normal pattern, impaired relaxation, pseudonormal and restrictive, according to the EAE guidelines and using the transmitral flow (E and A velocities and E deceleration time), pulmonary venous flow (S/D) and mitral annulus tissue Doppler velocities (E', A'). E/E' was determined in a subgroup of patients.

Results: We included 243 patients (110 male, 73±12 year-old). Moderate to severe PH (PASP>45 mmHg) was found in 29% of the population. In 74% of patients, diastolic dysfunction patterns were found. PASP was correlated with left atrial dimension (R=0.29, P=0.04), mitral inflow velocities E (R=0.41, P<0.01), A (R=0.33, P=0.02), E/A ratio (R=0.44, P=0.001) and E deceleration time (R=0.29, P=0.037). Moreover, more severe degrees of diastolic dysfunction had higher values of PASP. In a subgroup of 92 patients, we found a significant correlation between PASP and E/E' ratio (R=0.67, p=0.001).

Conclusions: Our findings suggest that echocardiographic markers of diastolic dysfunction are predictors of PH, thus emphasizing its role in the genesis of PH in SAS. Its prognostic value will be evaluated in a future prospective trial.

P2113 | BEDSIDE

Impact of energy loss index on left ventricular mass regression after successful transcatheter aortic valve implantation

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Background: The energy loss index (ELI) currently has been utilized as new functional index to assess the severity of aortic stenosis (AS). The aim of this study was to investigate the effect of the ELI on left ventricular mass indexed (LVM) regression in patients after successful transcatheter aortic valve implantation (TAVI).

Methods: A total of 33 patients with severe AS who successful underwent TAVI with Edward Sapien XT bioprosthesis was studied. Transthoracic echocardiography was performed to measure the LVM before TAVI (pre-LVM) (n=33) and repeated 6 months later (post-LVM) (n=33). The ELI was calculated as [effective orifice area (EOA) × aortic cross sectional area] / (aortic cross sectional area - EOA) divided by the body surface area (BSA). The LVM regression rate (%) was calculated as 100 × (post-LVM minus pre-LVM) / (pre-LVM). A cardiac event was defined as composite of heart failure requiring hospitalization or cardiac death.

Results: LVM indexed regressed significantly (146.7±43.8g/m² to 131.2±36.8g/m², P=0.008) at 6 months after TAVI. The ELI increased from 0.46±0.12 cm²/m² to 1.96±1.14 cm²/m², P<0.005. The dimensionless index (DI) also increased significantly (0.21±0.04 to 0.49±0.1, P<0.005). The LVM index regression rate negatively correlated with the ELI (R=-0.7, P<0.001). By receiver operating characteristic (ROC) curve analysis, ELI <1.14cm²/m² predicted smaller (<35%) LVM regression rates. Patients with ELI <1.14cm²/m² had significantly lower cardiac event-free survival.

	Before TAVI	6 months after TAVI	p-value
Aortic valve resistance (dynes.cm.s-5)	280±117	61±31	<0.005
Dimensionless index	0.21±0.04	0.49±0.1	<0.005
Energy loss index (cm ² /m ²)	0.46±0.12	1.96±1.14	<0.005
LVEF (%)	51.6±16.8	56.5±16.4	0.008
LV mass indexed (g/m ²)	146±44	131±37	0.008

Conclusions: The ELI could predict LVM regression after successful TAVI with Edward Sapien XT bioprosthesis. It is still uncertain whether the ELI is a stronger predictor of clinical events than other indices, and further larger scale study is needed to elucidate the clinical impact of ELI in patients with TAVI.

P2114 | BEDSIDE

Transcatheter aortic valve implantation in patients with left ventricular dysfunction: does basal two-dimensional strain have predictive value?

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Introduction: Severe aortic stenosis associated with left ventricular systolic dysfunction (LVSD) poses a risk for conventional aortic valve replacement. Transcatheter aortic valve implantation (TAVI) is an alternative treatment for these patients. The aim of the study was to analyse changes in left ventricular ejection fraction (LVEF) and global left ventricular longitudinal systolic strain (GLS) and ascertain which parameters predict LVEF improvement after TAVI.

Methods and results: 130 patients were selected for TAVI because of inoperable severe aortic stenosis. LVSD was present in 33 (25.4%). Mean age was

77.7±10.5 years. Technical approach was transfemoral, transapical and transaortic in 51.5%, 36.4% and 12.1% of cases, respectively. LVEF was measured using the biplane Simpson's method and GLS was obtained by speckle-tracking analysis. Before implantation, LVEF was 39.1±9.2% and GLS -9.9±2.8%. Immediately after the TAVI procedure, LVEF improved significantly (43.9±9.7%; p=0.001) but GLS did not (-10.3±2.9%; p=0.538). After a mean follow-up period of 1.81±1.4 years, LVEF also showed a significant improvement compared to the basal situation (46.7±11; p=0.008), but was not significant compared to the immediate post-implantation (-10.3±2.9; p=0.538). GLS improved significantly compared to basal situation (-12.9±4.3%; p=0.006), and also to the immediate postoperative exam (-13.5±4.5%; p=0.044). Comparison of basal GLS >9% (N=19) versus GLS ≤9% (N=14) is shown in the attached table.

Comparison of basal GLS (>9% vs ≤9%)

	GLS ≤9% (n: 14)	GLS >9% (n: 19)	p
LVEF (%) pre-TAVI	33.3±8.3	42.8±6.7	0.0001
GLS (%) pre-TAVI	-7.3±1.6	-11.5±1.8	0.0001
LVEF (%) immediate post-TAVI	36.9±9.1	47.6±6.3	0.0001
GLS (%) immediate post-TAVI	-8.8±1.7	-11.7±3.05	0.003
LVEF (%) long-term follow-up	40.27±12.71	50.4±6.7	0.006
GLS (%) long-term follow-up	-11.05±5.2	-14.5±2.6	0.019

Conclusions: Patients with aortic stenosis with LVSD presented a significant improvement in GLS one year after TAVI. Pre-TAVI GLS >9% was associated with a greater increase in left ventricular ejection fraction after the procedure. Thus, GLS may provide additional information for TAVI candidate selection.

P2115 | BEDSIDE

Measurement of energy loss index is recommended in assessment of tricuspid aortic stenosis without significant left ventricular hypertrophy

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Background: Continuous wave Doppler echocardiographic transaortic pressure gradient may be sometimes overestimated in patients with aortic stenosis (AS). Pressure recovery phenomenon is caused if kinetic energy is converted to potential energy at the downstream of the stenotic aortic valve, and this phenomenon occurs in some patients with AS, causing the overestimation. Thus, it is recommended to use the energy loss index (ELI) for the assessment of AS in such a circumstance. AS is frequently associated with left ventricular hypertrophy (LVH) which is a major compensatory mechanism in response to pressure overload. However, it is unclear whether there is a relation between pressure recovery and LV hypertrophy (LVH) in patients with AS.

Purpose: We aimed to compare the differences in Doppler measurement of pressure recovery between patients with tricuspid and bicuspid AS, and to explore the relationship between pressure recovery phenomenon and the presence of LV hypertrophy (LVH).

Methods: We retrospectively studied 105 patients with ages of 60 years or older who underwent aortic valve replacement for AS. Aortic valve was tricuspid in 86 patients and bicuspid in 19 patients. Echo measurements were conducted before surgery. We used the continuity equation to measure the aortic valve area index (AVAI). ELI was calculated according to the following validated equation: AVA × Aa/(Aa - AVA)/m², where Aa is the aortic area at the ST junction level and m² is the body surface area. Significant LVH was defined as left ventricular mass index of ≥132 g/m² for men and of ≥109 g/m² for women. We compared pressure recovery between patients with LVH and without LVH.

Results: An index of relative discrepancy between ELI and AVAI, (ELI - AVAI)/AVAI was significantly greater in patients with tricuspid aortic valve than in those with bicuspid aortic valve (0.18±0.10 vs. 0.13±0.04, p<0.05). (ELI - AVAI)/AVAI was greater in patients without significant LVH than in those with LVH among those with tricuspid severe AS (0.18±0.11 vs. 0.14±0.05, p<0.05). (ELI - AVAI)/AVAI was greater in patients without significant LVH than in those with LVH among those with bicuspid severe AS (0.15±0.04 vs. 0.11±0.03, p<0.05).

Conclusions: Pressure recovery was greater in patients with tricuspid aortic valve than in those with bicuspid aortic valve and was greater in tricuspid aortic valve patients without LVH than in those with significant LVH. Thus, it is recommended to measure both AVAI and ELI if the patients have tricuspid aortic stenosis without significant LVH.

NIGHTMARES IN LEAD EXTRACTION

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Predictors of effectiveness and complications of cardiac implantable electronic devices lead extraction in patients with systems older than 10 years

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Background: Many studies have clearly identified the risk factors of CIED leads extraction (LE). The outcome of patients with multiple old leads is not yet clearly known.

Methods: Patients with IA or B indication for LE of PM or ICD leads more than 10 years after first implant, were randomized to use either mechanical extraction only or a combination of mechanical extraction and excimer laser technique. The primary endpoint was the efficiency and safety of the extraction procedure.

Results: 227 pts (141 M, 86 W, mean age 64±21 years) with sepsis and evidence of bacterial endocarditis (139) or defect in the PM/ICD pocket (88). The average time from the first implant of the electrodes (EL) was 147±29 months. The group included 121 ICD EL (97 dual coil), 89 atrial and 181 ventricular pacing EL, 17 LV EL. Average procedure time was 148±41 min. In 114 patients we used the combination of an excimer laser (SLS II Spectranetics Corporation, USA) and mechanical extraction (Evolution®, Cook Medical, USA) in 113 patients we performed only mechanical extraction (in 21 cases transfemoral approach). Complete extraction was achieved in 212 patients (93%), no patient died immediately, 30-days mortality rate was 4.85%. Complications occurred in 7.48% of patients. Predictors of complications are summarized in Table 1.

Table 1. Predictors of lead extraction complications

Characteristics	Odds ratio	95% CI	P
Multiple electrodes (>4)	14,11	12,6–17,7	<0,01
Mechanical extraction only	13,77	11,4–15,5	<0,01
Dual-coil ICD leads	12,59	9,9–14,7	<0,01
Repeated generator exchanges (> 3)	6,07	4,5–7,6	<0,01
Limited operator experience (<50 cases)	5,97	4,8–7,6	<0,01
Sepsis	5,03	4,4–6,5	<0,01
Congestive heart failure	4,82	3,7–5,4	<0,01
Diabetes with complications	4,76	3,9–5,5	<0,01
Renal failure	2,79	1,9–4,3	<0,01
BMI > 30	1,77	1,3–2,9	<0,01

Conclusions: The presence of multiple electrodes, use of mechanical LE only, dual coil ICD leads, sepsis, renal failure and short-term operator experience were strongly associated with procedure complications.

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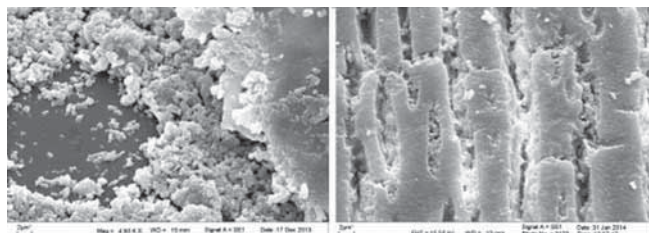
Optim insulation failure in transvenously extracted implantable cardioverter-defibrillator leads

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Purpose: Optim insulation is believed to present increased durability, improved lubricity and flexibility comparing to both silicone and polyurethane insulations. The aim of the study was to analyze the outer Optim insulation morphology.

Methods: 11 consecutive patients (pts.) (9 male) underwent transvenous lead extraction because of chronic pocket infection (CPI) (2/11), infective endocarditis (IE) (1/11), both CPI and IE (3/11) and non-infective indications (5/11 pts.). The mean patients age was 62,6 years (ranged 46-73). 11 Optim leads were analysed with optical microscope and scanning electron microscope.

Results: The mean number of implanted leads was 1,6 (ranged 1-2), the mean number of procedures until removal was 1,2, the mean time from the last procedure was 22,5 (ranged 3-46 months), the mean dwell time was 28,2 (ranged 3-58) months. 6 leads with time less than 24 months since implantation presented outer insulation failure- the youngest 3 months old. The type insulation failure was similar to silicone biodegradation (B), environmental stress cracking of polyurethane (P) and abrasion (A). 9/11 presented BPA in the intracardiac part, 8/11 BPA intravenously, 2/11 BPA, 2/11 A, 2/11 B were noticed in the pocket.



Optim lead insulation damage-BAP changes

Conclusions: The outer Optim insulation may undergo biodegradation aggra-

vated by wear leading to abrasions. Lead insulation failure was observed in infective and non-infective conditions, and may appear even 3 months since implantation.

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Dry late heart wall perforation with icd lead - in most of patients the cardiac surgery can be avoided

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The goal: Analysis of perforating ICD leads extraction safety.

Methods: TEE & TTE and other preoperative findings were analyzed.

Results: We have extracted 2574 ingrown leads from 1536 patients; in 390 due to infection (39,4%) or different form of lead dysfunction (63,6%). In 86 pts (22%) different forms of perforation of RVA with ICD lead. ECHO: dry perforation (tip in epicardial space, no fluid) 64 (74%), small "lens" of dense fluid round the lead tip 6 (7%), wet perforation (thin layer of fluid 5 (6%), deep subepicardial tip penetration 4 (5%) but in 3 (%) of pts diagnosis was based on other symptoms (P/S/I abnormalities). Indications for TLE: "lead dysfunction" (P/S/I abnormalities) 54 (62%), diagnosed perforation 13 (15%) and infection 13 (15%). In most pts has late perforation or late diagnosed asymptomatic perforation; Time implantation – diagnosis: aver.51,0 (1-146) mth; <3 mth: 4, 3m-2year: 17, 2-5y: 35, >5 y: 35, in 59/86 (69%) over 3 y. All perforating leads were extracted and it made possible to avoid of open-chest surgery in all of pts. with perforation. But surgery was necessary in two pts. with cardiac tamponade caused by RAA wall damage. Impression: during repetitive ICD lead implantation we have to avoid previous tip location region because renewed perforation is possible (lead may to wander into old channel).

Patients/procedures	Proper endocardial tip location	Perforating lead (epicardial, subepicardial)	P
Number pts/procedures	304	86	–
Number of leads extracted/perforating leads	487 / 0	144 / 86	–
Non-infective Indications %	177 (58,2%)	71 (82,6%)	<0,001
Major complications %	2 (0,66%)*	1 (1,2%)	0,003
Minor complications %	4 (1,3%)	1 (1,2%)*	NS
Full radiological success %	294 (97,0%)	85 (98,8%)	NS
Clinical success	302 (99,3%)	85 (98,8%)	NS
Average implant duration – in months (mean) (SD)	50,1 (39,7)	50,2 (32,9)	NS

*Two cardiac tamponade/surgery but due to extraction of atrial lead, **1 hemopericardium asymptomatic hemodynamically, treated conservatively.

Conclusion: 1. Permanently implanted ICD leads, recognized as perforating heart wall may be extracted transvenously, providing all individually well-chosen safety precautions. 2. Dry heart wall perforation with ICD leads consist late complication and utility of TLE designed tools are necessary in all pts.

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Transvenous removal of pacing and ICD leads: single italian referral center experience

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Introduction: Device related complications are rising the need of Transvenous Lead Removal (TLR). Transvenous extraction of Pacing (PL) and Defibrillating Leads (DL) is a highly effective technique. Aim of this report is to analyse the longstanding experience performed in a single Italian Referral Center.

Methods: Since January 1997 to December 2013, we managed 2113 consecutive patients (1611 men, mean age 65.4 years) with 3843 leads (mean pacing period 71.1 months, range 1-420). PL were 3144 (1522 ventricular, 1303 atrial, 319 coronary sinus leads), DL were 699 (678 ventricular, 6 atrial, 15 superior vena cava leads). Indications to TLR were infection in 83% (systemic 28%, local 55%) of leads. We performed mechanical dilatation using a single polypropylene sheath technique (Cook Vascular - Leechburg PA, USA) and if necessary, other intravascular tools (Catchers and Lassos, Osypka, Greentig-Whylen, G); an Approach through the Internal Jugular Vein (JA) was performed in case of free-floating leads or failure of the standard approach.

Results: Removal was attempted in 3834 leads because the technique was not applicable in 9 PL. Among these, 3757 leads were completely removed (98.0%), 38 (1.0%) partially removed, 39 (1.0%) not removed. Among 3748 exposed leads, 587 were removed by manual traction (15.6%), 2799 by mechanical dilatation using the venous entry site (74.7%), 25 by femoral approach (FA) (0.7%) and 262 by JA (7.0%). All the free-floating leads were completely removed, 26.5% by FA and 72.5% by JA. Major complications occurred in 12 cases (0.56%): cardiac tamponade (11 cases, 2 deaths), hemothorax (1 death).

Conclusions: Our experience shows that in centers with wide experience, TLR using single sheath mechanical dilatation has a high success rate and a very low incidence of serious complications. TLR through the Internal Jugular Vein increases the effectiveness and safety of the procedure also in case of free-floating or challenging leads.

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Dry heart wall perforation - the new epidemy or better diagnosed old phenomenon ?

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Theoretically increased risk of dysfunctional perforating lead extraction inclined us for attempt to localise tip of lead in relation to epicardium and the commonness of the observed phenomenon was surprising.

Goal: Retrospective analysis computer data-base referential centre of transvenous lead extraction (TLE) in our country. TEE & TTE and other preoperative findings were analyzed. We have extracted 2574 ingrown leads from 1536 patients; 211 leads presented signs of perforation (8% of leads & 14% of procedures).

Results: ECHO: dry perforation (tip in epicardial space, no fluid) – 168 (79.6%), small lens" of dense fluid round the lead tip – 17 (8%), wet perforation (thin layer of fluid – 26 (12.3%), deep subepicardial tip penetration – 15 (7%) but in 23 (11%) of pts diagnosis was based on other symptoms. Indications for TLE: "lead dysfunction" (pacing/sensing impedance abnormalities) – 108 (51.2%), diagnosed perforation 47 (22%), infection – 28 (13%), other – 26 (12%). In 11 pts all parameters of pacing/sensing/impedance were normal (5%) but in other drop of sensing (71) or sizzles (13) were noted (40%) rise of Pth in 107 or loss of pacing (23) were observed (62%) and rise in 77 or drop in 15 of impedance (44%) were noted in different combinations. In 24 of PM pts Pth was lower in BP than UP configuration. Subjective symptoms (in 41/21121% only): 28 atypical chest pain, "pacing intolerance" 6, extracardiac pacing 5. Perforating lead location: RVA 166, "RVOT" 32 and RAA -13. Perforating lead's model: PM BP-112, ICD HV-85, PM UP-13. Active fixation 98, passive –113. Time implantation – diagnosis: aver.68,5 (1-316) mth, <3 mth –13, 3m-2-year -32, 2-3y –19. 147/211 (70%) perforations were diagnosed >3 y after implantation. Dry perforation was rarely visible in standard chest X-ray (10/211), standard ECHO showed very low sensitivity; the tip of lead must to be search using additional projections. Pacing / sensing / impedance parameters abnormalities may to guide for proper diagnose. It gradual deterioration seems to be most frequent but non-specific symptoms.

Conclusion: 1. "Dry" perforation (without cardiac tamponade or marked volume of fluid in pericardial space) consists relatively frequent finding in pts referred for TLE (14%). It demonstrates usually as "lead dysfunction" mask but in remaining pts may be asymptomatic.

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Utility of the mechanical systems for transvenous lead extraction. The analysis of experience with extraction of 2574 permanently implanted leads in 1536 pts

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Necessity for transvenous lead extraction (TLE) rises using two basal techniques: mechanical and energy delivering systems. The first, is counted as safer but less effective. The aim: analysis of the effectiveness & safety of mechanical systems for TLE.

Methods: We have extracted 2574 ingrown (PM >12, ICD >6 mths) leads in 1536 pts. (61,1% M) mean age 64,6y, with PM and ICD systems. 72,7% leads were PM-BP, 10,1% - PM-UP, 15,3% ICD and 1,9% consisted VDD PM leads. 65,4% - passive and 34,6 - active fixation. 35,3% were RA (RAA, BB), 5,9% LA (CS, CSO), 54,9% RV (RVA, RVOT), 3,6% LV vein and 0,2% LA or LV (erroneous placement). Mean dwelling time was 82,9 mths. In 40,5% of pts. 2 leads were explanted, in 47,2% - single and in the remaining 12,0%-3 (max.6) leads. The most common (58,8%) indications for TLE were non-infective; local pocket infection and endocarditis the were less frequent (14,0% & 28,2%).

Results: Aver. procedure time was 109,0 min. (30-430). Lead venous entry approach was used for most (84,1%) of leads; femoral approach were used for free floating leads and combined (including jugular approach) for extraction of broken leads - in 1,6% and 2,2% respect. Simple extorsion and traction was utilized in 11,7% for active fixation leads. Full radiol. success: 94,8%; remained tip only 2,3%, led fragment (<4 cm) 2,4% and only 9 leads were left due to high risk of tricuspid valve damage or urgent surgery. Clinical success: 98,6%. Major complications appeared in 21 cases (1,4%): 11 hemopericardium (surgery), 5 hemopericardium (drainage) and 1 hemothorax (drainage), 1 hemothorax (surgery), 1 pulmonary embolism 1 severe hypotonia and 1 cerebral stroke. Minor complications were more frequent (25; 1,63%): pulmonary embolism (CT only) (4), hemothorax (3), hemopericardium (7) tricuspid regurgitation (6), subclavian vein thrombosis (2), blood transusion 3. Problems were solved without invasive intervention. 5 procedure related deaths and 5 in postoperative period were noted. Technical complications (prolonging procedure, forced to change venous approach and utilize additional technique and tools) appeared in 233 (15,2%) cases.

Conclusions: 1. TLE in experienced centre is very effective (nearly 95%) even in cases very old (>20 y) and dual-coil ICD leads 2. In experienced centre it is safe procedure (0,32% of death); major complications are infrequent (1,4%) 3. TLE may to need numerous complementary techniques; disposal of alternative techniques are necessary to completion procedure of 4% procedures 4. Cardio-surgery stand-by is necessary (was utilized in 12/1536; 0.8% of procedures).

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Impact of coils and fixation mechanism on implantable cardioverter defibrillator lead extraction

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Background: Percutaneous removal of implantable defibrillator (ICD) leads remains a difficult procedure, despite the fact that extraction techniques have been improved and advances in lead technology have been made in order to reduce fibrous tissue growth along the lead, thereby easing extraction. We evaluated the effectiveness and safety of a mechanical single-sheath extraction technique, described the occurrence and location of fibrous adhesions detected during the procedure, and investigated the relationship between the presence of adhesions and patient and lead characteristics.

Methods and results: We studied 545 consecutive patients who underwent transvenous extraction of 582 ICD leads from 1997 to 2012. Our technique achieved a success rate of 99%, causing no major complications. Fibrotic adhesions were found during removal of 547 leads requiring mechanical dilatation. Areas of adherence were in the subclavian vein (78%), the innominate vein (64%), the superior vena cava (65%) and the heart (73%). Dwell-time, passive fixation and dual-coil lead design were independently associated with adhesions. Dual-coil lead design was associated with adhesions in the innominate vein and in the superior vena cava, coil treatment (expandable polytetrafluoroethylene-coated or medical adhesive back-filled coils) prevented adhesions in the superior vena cava, and the passive fixation mechanism was associated with adhesions in the heart.

Conclusions: Mechanical single-sheath extraction of ICD leads proved safe and effective. The presence of fibrotic adhesions was frequently associated with longer lead dwell-time, passive fixation and dual-coil lead design. By contrast, the use of treated coils prevented intravenous adhesions.

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Efficacy and feasibility of cardiovascular implantable electronic devices lead extraction in elderly patients

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Background: In contemporary practice, the proportion of elderly individuals in the population is growing and the need for percutaneous transvenous lead extraction in elderly patients has been increasingly required. The elderly have more risk factors than younger patients needing lead extraction. However, the safety of lead extraction for elderly patients remains unclear.

Methods: Between 2005 and 2013, we collected data of 250 consecutive patients who underwent percutaneous transvenous lead extraction and compared incidence of major adverse events (MAE; death, myocardial infarction, stroke, cardiac tamponade, Pulmonary Embolism, blood transfusion or pneumothorax) between patients <80 years and patients ≥80 years old.

The primary endpoint of this study was incidence of MAEs after procedure. The secondary endpoint was hospitalization period.

Results: There were 68 patients (27.2%) with age ≥80 years and 182 patients (72.8%) with age <80 years. The most common indication for lead extraction in elderly patients was infection (97.1%). All patients underwent successful transvenous removal of endocardial leads. Two of 68 patients (2.9%) had evidence of MAE in elderly patients. No significant difference of MAE was found in the elderly group (2.9 vs. 2.2%, P=0.921). There was no difference in hospitalization periods between those age ≥80 years and age <80 years (37.9±31.3 days vs 31.4±27.4 days, P=0.105).

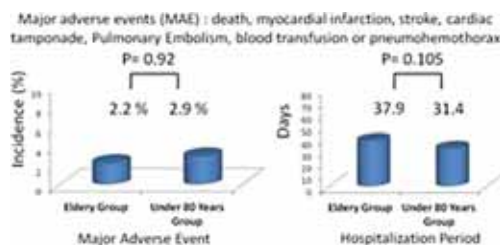


Figure 1. Incidence of MAE and hospitalization period.

Conclusions: In elderly patients, percutaneous transvenous lead extraction could be performed safely without prolonged hospital stay.

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Riata lead extraction: technical approach and procedural implications of transvenous removal

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Introduction: Riata (R) and Sprint Fidelis (S) leads were recalled by the Food

and Drug Administration because of an increased rate of failure due to conductor fracture or insulation abrasion. Treatment options include intensifying monitoring and possible recalled lead replacement, with or without extraction. According to lead design and type of failure, procedural extraction complexity may be different.

Aim of this study was to assess the extraction profile of R leads with and without cable exteriorization in comparison to S Leads.

Methods: From January 1997 to December 2012, we included in the analysis all the consecutive R and S extracted transvenously.

Results: Among 545 consecutive patients with 582 ventricular ICD leads extracted, we identified 51 S (S Group) and 102 R (R Group). Indications to removal were ineffective in the majority of cases (70%) and with a prevalence of dual coil leads (90%). Baseline patients and lead characteristics resulted comparable between groups.

Results: Success rate was very high in both groups (100% S leads vs 99% R leads, $p=NS$) without major complications. R leads required more often MD (98% vs 92%, $p=0.05$) and larger sheaths, a more frequent crossover to the transjugular approach (ITA) (8% vs 2%, $p=0.10$), and a final longer extraction time (11 ± 18 vs 18 ± 23 min). Overall, the rate of complex extraction procedures (CEP) resulted higher in the R Group (32% vs 14%, $p=0.02$). Presence of cable externalization was a major independent predictor of difficult extraction and necessity of ITA.

Conclusions: Extraction of R leads is feasible and effective. However, extraction of R leads is more complex than S leads. Lack of coil backfilling and cable externalization in R group may account for these differences. The decision to extract or not to extract R leads should be carefully individualized.

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Transvenous lead extraction - more risky in cases with non-infective indications?

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There is considerable controversy regarding different safety of transvenous lead extraction (TLE) in relation to procedure indications and non-infective are sometime recognized as more risky. Objective: Analysis of safety and feasibility of TLE in our material.

Methods: We have extracted 2167 ingrown endocardial leads from 1283 patients within the last 7 years. We analyzed complications and technical problems related to percutaneous lead removal procedures referring these problems to three (different indications) groups.

Results:

Patients/procedures	Local pocket infection	Lead dependent endocarditis	Non-infective indications	P
Number	330	224	729	—
Age of pts	68,7 (13,7)	65,3 (14,8)	62,2 (17,8)	<0.001
Sex-females %	89 (27,0%)	73 (32,6%)	327 (44,9%)	<0.001
Number of leads extracted (mean) (SD)	1,95 (0,76)	2,21 (0,85)	1,46 (0,74)	0.032
Average implant duration - in months (mean) (SD)	72,3 (54,5)	65,4 (62,8)	87,3 (64,7)	0.002
Number of procedures before extraction (mean) (SD)	2,19 (1,18)	2,28 (1,46)	1,74 (1,09)	<0.001
Full radiological success (%)	317 (96,1%)	206 (92,0%)	687 (94,2%)	0.1232
Technical problems during TLE* (%)	46 (13,9%)	40 (17,8%)	123 (16,9%)	0.3825
Major complications (%)	1 (0,3%)	5 (2,2%)	13 (1,8%)	0.1075
Minor complications (%)	3 (0,9%)	3 (1,3%)	16 (2,2%)	0.2930
Procedure related death	0 (0,0%)	1 (0,4%)	3 (0,4%)	0.4975

*Lead break, lead fragmentation, strong lead to lead adhesions, dislodgement of functional lead, change of approach necessity.

Impression: TLE in pts with local pocket infection seems to be very slightly more effective and safe; it may be explained by lower percentage of female pts. Higher percentage of complications in both another groups can be explained with longer implant duration, higher percentage of female pts. and toxemia.

Conclusions: There is no simple relation between TLE effectiveness/safety and main indication to the procedure.

VASCULAR CELLS AND NEW VESSELS

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Acetyltransferase Gcn5 triggers Nox2 upregulation and oxidative stress in diabetes

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Purpose: The mammalian acetyltransferase gene non-derepressible 5 (Gcn5) modulates gene expression via acetylation of histones. In neutrophils, pharmacological inhibition of Gcn5 suppresses NADPH oxidase activity and ROS generation. Whether Gcn5 modulates oxidative stress in the cardiovascular system

remains largely unknown. The present study investigates Gcn5 role in diabetes-related vascular dysfunction.

Methods: Human aortic endothelial cells (HAECs) were exposed to normal (NG, 5mmol/L) or high glucose concentrations (HG, 25 mmol/L) in the presence or in the absence of Gcn5 pharmacological inhibitor CPTH2 or siRNA-mediated knock-down. Superoxide anion (O₂⁻) was measured by ESR spectroscopy. Gene expression of Nox2 was assessed by Real-Time PCR. In parallel, 30 patients with type 2 diabetes (T2DM) and 18 age-matched healthy controls were enrolled. All patients underwent flow-mediated vasodilation (FMD) of the brachial artery to assess endothelial function. Urinary levels of 8-isoprostaglandinF_{2α} (8-isoPGF_{2α}) were measured as a marker of oxidative stress. Chromatin immunoprecipitation (ChIP) experiments were performed to investigate the interaction of Gcn5 with Nox2 promoter. Gene expression of Gcn5 and Nox2 were assessed in peripheral blood monocytes (PBM) by Real-Time PCR. Data are presented as percentage of control. Between-variable correlations were measured by Spearman's analysis.

Results: HG significantly increased Gcn5 gene expression in HAECs ($155\pm 20\%$ vs. NG, $p<0.05$). NADPH subunit Nox2 was also upregulated upon high glucose exposure ($155\pm 20\%$ vs. NG, $p<0.05$). Interestingly, either Gcn5 inhibition or gene silencing prevented hyperglycemia-induced Nox2 upregulation and O₂⁻ increase, suggesting its modulatory role on endothelial NADPH oxidase expression. ChIP assay revealed that Gcn5 is responsible for acetylation of lysine 14 residue of histone 3 (H3K14) on Nox 2 promoter. Gcn5 expression was also increased in PBM of diabetic patients ($455\pm 155\%$ vs controls $p<0.05$) and significantly correlated with Nox2 ($r=0.32$, $p<0.05$). Consistently, Gcn5 significantly correlated with endothelial dysfunction ($r=-0.33$, $p<0.05$) and oxidative stress ($r=0.46$, $p<0.05$), assessed by FMD and 8-isoPGF_{2α}, respectively.

Conclusions: Acetyltransferase Gcn5 is a critical regulator of hyperglycemia-induced Nox2 upregulation in the human endothelium. We show that Gcn5-dependent acetylation of H3K14 leads to an open chromatin and active Nox2 transcription. Targeting Gcn5 may represent a future therapeutic approach to prevent vascular complications in patients with diabetes.

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Sonic hedgehog signaling promotes the fibroproliferative response in neointima formation following vascular injury

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Purpose: There is emerging evidence that adventitial cells significantly contribute to neointima formation after vascular injury. Sonic hedgehog (Shh) is a regulator of vasculogenesis and is reactivated in the context of proliferating cells and differentiation of vascular progenitors in the adult. Aim of the study was to determine the role of Shh in orchestrating the response of the adventitia to vascular injury.

Methods and results: Wire-mediated endovascular injury of the femoral artery was performed in C57BL/6 mice to induce neointimal lesion formation. Staining for Ki-67 showed that the majority of proliferating cells were located in the adventitial layer. Shh was significantly up-regulated in perivascular cells as well as in the intimal lesion at 4 and 7 days after injury compared to sham-operated arteries, as determined by qPCR and immunohistochemistry (IHC). Moreover, we detected a prominent expression of Shh in the adventitia of human atherosclerotic plaques as compared to healthy mammalian arteries using IHC. In vitro, stimulation of human aortic adventitial fibroblasts (AoAF) with Platelet-derived growth factor-BB resulted in a significantly increased expression of Shh and its receptor Patched-1. Incubation of AoAF and human coronary artery smooth muscle cells (HCASMC) with recombinant Shh dose-dependently induced cell proliferation and migration. The specific Shh inhibitor GDC-0449 (Vismodegib) was not only effective in attenuating Shh signaling but also prevented the Shh induced functional effects in AoAF in a dose-dependent manner. Following wire-induced injury, local application of GDC-0449 via a self-degrading Pluronic® F-127 Gel significantly reduced neointimal lesion formation (neointima/media ratio: 2.19 ± 0.17 vs. 0.88 ± 0.19 , $n=5$, $P<0.05$). This was associated with a reduced proliferation of total cells and in particular adventitial cells. Interestingly, Shh-expressing and proliferating cells in the adventitia were identified as Sca-1+ cells suggesting Shh as a critical regulator of perivascular stem cell function during neointimal lesion formation. The effects of Shh inhibition on the downstream signaling pathways are currently investigated.

Conclusions: Shh signaling is critically involved in neointimal lesion formation by augmenting vascular cell proliferation and as a potential regulator of perivascular stem cell function. Therefore, these data add significantly to our understanding of vascular proliferative diseases.

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Effect of autophagy deficiency in smooth muscle cells on vascular function

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Purpose: Autophagy is a subcellular housekeeping mechanism which is essential for optimal cellular function by ridding the cell of damaged proteins and organelles. Although autophagy deficiency in cardiomyocytes leads to heart failure, very little is known about the importance of this process in smooth muscle

cells (SMCs), in particular its role in SMC contractility and calcium homeostasis. The goal of this study was to investigate whether defective autophagy in SMCs had an impact on SMC-dependent vascular reactivity, SMC-calcium mobilizing pathways and arterial stiffness. **METHODS** SMC contractility (organ chambers), calcium homeostasis (FURA-2) and arterial stiffness (myograph) were investigated in aortic segments of mice containing a SMC-specific deletion of the essential autophagy gene *Atg7* (*Atg7^{F/F} SM22 α -Cre⁺*) and in corresponding controls (*Atg7^{+/+} SM22 α -Cre⁺*) at 3.5 months of age. **RESULTS** SMCs of *Atg7^{F/F} SM22 α -Cre⁺* mice developed contraction at lower KCl concentrations (EC50: 17.9 ± 0.4 vs 20.7 ± 0.4 mM KCl, $p < 0.001$, $n = 5$). However, there was no difference in sensitivity for the L-type calcium channel blocker diltiazem (logEC50 *Atg7^{F/F}* vs. *Atg7^{+/+}*: -6.08 ± 0.08 vs. -6.22 ± 0.09 logM, $p = 0.245$, $n = 5$). Furthermore, segments of *Atg7^{F/F} SM22 α -Cre⁺* mice showed significantly higher inositol triphosphate-mediated transient contractions (AUC 146 ± 19 vs 84 ± 9 mN*s; $p < 0.01$, $n = 5$). In line with this finding, expression of the sarco/endoplasmic reticulum calcium ATPase-2 (SERCA2) as well as the calcium influx that refills the sarcoplasmic reticulum (SR) after emptying by inositol triphosphate, were higher. Interestingly, SMCs of *Atg7^{F/F} SM22 α -Cre⁺* mice also showed elevated cytosolic baseline calcium concentrations, which could be abolished by the non-selective cation channel blocker 2-aminoethoxydiphenyl borate. Stress-strain experiments showed that arterial stiffness was slightly increased in segments of *Atg7^{F/F} SM22 α -Cre⁺* mice. **CONCLUSION** Our study indicates that autophagy plays an important role in the cardiovascular system and that defective autophagy in SMCs leads to changes in vascular function.

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Sphingosine-1-phosphate receptor 1 (S1PR1) promotes vascular remodeling via interleukin-6 (IL-6) after vascular injury in mice

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Purpose: Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid mediator that mediates diverse cellular responses including cell proliferation, survival, and migration. In clinical setting, serum S1P concentration was known to a predictive marker for the presence and severity of obstructive coronary artery disease in human. S1P acts through 5 members of S1P-specific G-protein coupled receptors (S1PR1-S1PR5). According to recent study, expression of S1PR1 is elevated in tumor cells and this elevation contributes to interleukin-6 (IL-6) gene upregulation, thereby accelerating tumor growth and metastasis. Vascular inflammation and smooth muscle cell proliferation contribute to vascular remodeling and obstructive vasculopathies such as atherosclerosis and restenosis following angioplasty. However, pathophysiological roles of S1P and S1PR1 in atherosclerosis are not known. Here we examined whether S1P could be involved in the development of neointima formation.

Methods and results: We performed unilateral carotid artery ligation in male C57BL/6 mice. 4 weeks after carotid artery ligation, neointima formation was confirmed. S1PR1 mRNA expression was 1.4 folds higher in injured arteries than in control. Next, we generated mice that overexpressed S1PR1 (Tg-S1PR1) under the control of α -smooth muscle actin promoter. Tg-S1PR1 and nTg mice were subjected to carotid artery ligation. After 4 weeks following this intervention, Intima/Media ratio was significantly increased in Tg-S1PR1 mice compared with nTg mice (0.76 ± 0.16 vs. 0.35 ± 0.05 , $P < 0.01$), and neointima area was significantly higher in Tg-S1PR1 mice than in nTg mice (2.3 ± 0.6 vs. 0.9 ± 0.1 $103 \mu\text{m}^2$, $P < 0.01$). Proliferative cells in the neointima were determined by immunohistochemical staining with Ki-67 monoclonal antibody. The number of Ki-67-positive proliferating cells in the neointima were also increased in Tg-S1PR1 mice compared with nTg mice (Ki-67 positive cells 4.02 ± 0.87 vs. $2.20 \pm 0.32\%$, $P < 0.05$). To examine the exact role of S1PR1 during vascular remodeling, we obtained vascular smooth muscle cells (VSMCs) from Tg-S1PR1 and nTg mice. The expression levels of IL-6 mRNA in VSMCs were significantly increased in Tg-S1PR1 compared to nTg. Concentrations of IL-6 in conditional media from VSMCs were significantly greater in Tg-S1PR1 than in nTg mice. To reveal the role of S1PR1-IL-6 axis during vascular remodeling, administration of neutralization antibody of IL-6 was significantly reduced neointima formation in Tg-S1PR1 mice.

Conclusions: Overexpression of S1PR1 promotes neointimal formation via IL-6 after vascular injury.

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Exercise promotes post-ischemic collateral artery growth mediated by inducible nitric oxide expression of monocytes

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Background: Collateral artery growth (arteriogenesis), an important adaptive response to hampered arterial perfusion, reduces cardiovascular mortality. The effects of physical exercise on arteriogenesis, particularly the role of nitric oxide derived from spleen and bone-marrow-derived mononuclear cells, are hitherto unknown.

Methods and results: After three weeks of voluntary treadmill exercise (daily running distance 5.5 ± 1.0 km), ligation of the left femoral artery was performed in

C57BL/6 mice. Hindlimb perfusion as assessed by Laser Doppler Imaging (LDI) immediately after surgery did not differ from sedentary mice. However, prior exercise improved hindlimb perfusion restoration up to seven days after femoral artery ligation, also when exercise was stopped at the time of ligation (perfusion restoration to $52.8 \pm 4.1\%$ of non-ligated control versus $34.8 \pm 2.0\%$ in sedentary animals ($p < 0.001$)). This was accompanied by an accumulation of peri-collateral macrophages and increased expression of endothelial (eNOS) and inducible nitric oxide synthase (iNOS) in hindlimb collateral tissue ($229 \pm 47\%$ of sedentary controls, $p = 0.011$) and in mononuclear cells of the blood ($2387 \pm 572\%$, $p = 0.025$) and the spleen ($226 \pm 60\%$, $p = 0.035$).

Clodronate liposome injections reduced circulating monocytes to 42.3% of control (liposomes without clodronate) 24h after injection. In the reticuloendothelial system (spleen), macrophage content fell to $4.1 \pm 0.2\%$ of control. Monocyte depletion but not splenectomy attenuated exercise-induced perfusion restoration (perfusion recovery was only $57 \pm 10\%$ after 3 ($p = 0.056$) and $59 \pm 13\%$ of placebo-treated mice after 7 days, which was comparable to the sedentary group). Also, peri-collateral macrophage accumulation and up-regulation of iNOS were inhibited. iNOS-deficient mice did not show the exercise-induced perfusion restoration. Transplantation of bone marrow-derived mononuclear cells from iNOS-deficient mice into wildtype (WT) animals inhibited exercise-induced collateral artery growth ($28.4 \pm 2.8\%$ of non-ligated hindlimb (iNOS-/- into WT) versus 57.4 ± 4.2 (WT into WT), $p < 0.001$).

Conclusion: Exercise prior to femoral artery ligation increases the speed of perfusion restoration and enhances mononuclear iNOS expression. The perfusion increase is delayed by macrophage depletion. These data reveal that, in addition to a beneficial effect on vascular endothelium, physical exercise improves post-ischemic arteriogenesis through monocyte/macrophage related mechanisms.

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PDI-TF regulates migration and microvessel formation

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Purpose: We have previously reported that tissue factor (TF) translocates to the migratory front in migrating cells together with cytoskeleton proteins and regulates stable microvessel formation. The aim of this study was to investigate whether in human vascular smooth muscle cells (HVSVC) the ER-stress protein PDIA2 (protein disulphide-isomerase family A member 2) regulates intracellular TF polarization during HVSVC migration affecting vascular remodeling and angiogenesis.

Methods: Primary cultures of HVSVC were obtained from coronary arteries of human explanted hearts. The cell surface localization of PDIA2 and the interaction with TF in HVSVC was analyzed by confocal microscopy. A nucleofector device was used for PDIA2 and TF silencing by small interfering RNA (siRNA). Implantation of cell-loaded matrigel plugs in nude mice was performed to investigate in vivo migration and angiogenesis. PDIA2/TF expression in human remodeled coronary arteries was analyzed.

Results: PDIA2 co-localizes with TF in the front edge of motile HVSVC (97% and overlap coefficient of 0.95 and Pearson's correlation of 0.84; $P < 0.05$). Immunoprecipitation of TF shows a direct interaction TF-PDIA2 in the cell surface. TF cell-surface expression is significantly reduced in PDIA2-silenced-HVSVC and cell migration is significantly inhibited (60%; $P < 0.05$). PDIA2 silenced cells show increased TF-rich microparticle shedding. In vivo implants of PDIA2 silenced HVSVC together with endothelial cells in nude mice showed a significant impairment in mature complex microvessel formation. Hemoglobin content normalized to the weight of the analyzed fragment of collagen plug was in TF or PDIA2 silenced plugs: 46.5 ± 1.3 and 42.3 ± 0.9 respectively vs. 86.3 ± 2 mg/ml in control.

Conclusions: These results indicate that TF is chaperoned by PDIA2 to the cell membrane and to the cell migratory front when migration is initiated. Absence of PDIA2 impairs the intracellular trafficking and processing of TF-protein favoring its uncontrolled release. Hence, TF regulated microvessel formation is under the control of the ER-protein PDIA2.

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The cd200-cd200 receptor axis controls arteriogenesis and local tissue t lymphocyte influx

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Purpose: During arteriogenesis pre-existing collateral anastomoses undergo enlargement in response to shear stress to restore blood flow in ischemic tissues. This process involves activation of the immune system for recruitment and activation of inflammatory cells that enables collateral artery growth. The CD200-CD200 receptor inhibitory axis is highly involved in controlling myeloid cell function, but the role in arteriogenesis is still to be elucidated. We hypothesized that disruption of the CD200-CD200 receptor axis promotes arteriogenesis in a murine hindlimb ischemia model.

Methods: Cd200-/- and wildtype mice underwent unilateral femoral artery ligation. Perfusion recovery was monitored using Laser-Doppler analysis over seven

days. Histology was performed on hindlimb muscles to assess inflammatory cell influx (T cells and macrophages in perivascular space) and collateral vessel geometry and numbers. To validate the results from Cd200^{-/-} mice, wildtype (C57Bl/6J) mice were treated with a specific CD200R agonist after surgery, followed by laser-Doppler analysis and histological analysis.

Results: Cd200^{-/-} mice had an increased perfusion recovery compared to wildtype (Cd200^{-/-} vs wildtype; 39%±3.3 vs 24%±3.0; $p=0.002$ at day 3; 59%±3.7 versus 53%±6.6; $p=0.10$ at day 7), accompanied by increased vessel geometry in the non-ischemic muscle at seven days ($P<0.05$). Histology also revealed a significant increase in T cell influx (Cd200^{-/-} vs wildtype; 4.3±0.8 vs 1.6±0.3, $P=0.01$ at day 3; 3.8±0.5 vs 1.9±0.3, $P=0.01$ at day 7), but not in macrophage influx. Angiogenic vessel numbers (CD31+ vessel per muscle fiber) in the ischemic muscle were increased following surgery compared to wildtype (Cd200^{-/-} vs wildtype; 1.0±0.06 vs 0.8±0.04 $P<0.001$ at day 3; 1.1±0.05 vs 0.7±0.06 $P=0.02$ at day 7). CD200R agonist treatment resulted in a significant inhibition of perfusion recovery at day 7 (CD200R vs IgG; 56%±5.0 vs 84%±9.7, $P<0.05$). In addition, collateral vessel geometry was lower ($P<0.05$) as well as influx of T cells (CD200R vs IgG; 6.4±0.9 vs 3.6±0.6, $P=0.03$).

Conclusions: This study confirms the causal role of CD200-CD200R inhibitory axis during arteriogenesis in a murine hindlimb ischemia model. Lack of CD200R signalling results in enhanced perfusion recovery, accompanied by increased collateral vessel growth and local T cell recruitment. These data were confirmed by triggering the CD200R in vivo, resulting in opposite effects.

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The APJ receptor: involvement in PECAM-1 induced mechanotransduction

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Aim: Application of fluid shear stress to endothelial cells (ECs) elicits not only the formation of NO via PECAM-1 induced PI3K-signaling but also PECAM-1/integrin-mediated adaptive cellular stiffening. Previously, we did show an apelin-12/APJ-dependent induction of PI3K/Akt/eNOS signaling, which resulted in an increased NO production in human ECs. Here, we present data, which suggest a flow-induced association of APJ with PECAM-1 effecting not only NO-production but also cellular adaption of the cytoskeleton.

Methods: HUVEC were transfected with specific APJ siRNA and transduced with adenoviral vectors for F-actin and APJ. Subsequently, we applied physiological shear stress (1.5 dyne/cm²) to WT and APJ-deficient (APJ^{-/-}) HUVEC using ibidi[®] μ-slides I Luer. To determine interactions of APJ and PECAM-1, HUVEC were fixed and stained for PECAM-1 after shear stress exposure, and analyzed using confocal laser scanning microscopy (CLSM). Furthermore, WT and APJ-HUVEC were subjected to Atomic Force Microscopy (AFM). Cell-stiffness was analyzed using the Hertz-Model (HM) to calculate the Young's Modulus (YM).

Results: To show an association of APJ and PECAM-1, we determined the Manders' coefficient under static and flow conditions via CLSM. We found a time-dependent association of APJ and PECAM-1 under shear stress only ($P<0.05$). In APJ- ECs we also found a loss of cell-cell contacts accompanied by a loss of flow-induced eNOS ($P<0.01$) and PECAM-1 ($P<0.01$) mRNA expression leading to a decreased NO-release. PECAM-1 is also known to play a role in adaptive stiffening of ECs subjected to mechanical forces. Therefore, we determined the influence of APJ-silencing on the elasticity of ECs. In accordance with the literature our AFM data show a stiffness-increase of 85% ($P<0.05$) in WT HUVEC after onset of flow. Interestingly, for flow-exposed/WT HUVEC we found significantly higher YM-values of about 195% ($p<0.01$) compared to flow-exposed/ APJ- cells. In correlation with stiffness measurements we also observed a flow-induced reorganization of actin-cytoskeleton structures in WT ECs using live cell imaging, which was impaired by APJ-silencing.

Conclusion: In HUVEC, shear stress elicits signals through PI3K/Akt/eNOS resulting in an increase in NO-production, which might be related to a mechanically induced association of APJ and PECAM-1. Additionally, APJ silencing results in a loss of cell-cell contacts, changes in morphology, and a loss of adaptive stiffening in response to the mechanical force. These results lead us to the assumption, that the APJ receptor is sufficient for PECAM-1-dependent responses to fluid flow.

MULTIMODALITY APPROACH TO THE HYPERTROPHIC VENTRICLE

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Angiotensin converting enzyme inhibitors improve longitudinal myocardial deformation to a greater extent than angiotensin receptor blockers in hypertensives: a 3 year follow-up study

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Background: Impaired left ventricular (LV) myocardial deformation markers in-

dicate the presence of subclinical systolic and diastolic LV dysfunction. Blood pressure, arterial stiffness, LV mass, and impaired coronary microcirculation determine LV function in hypertensives. We investigated the effects angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARB) on the above parameters during a 3- year follow up.

Methods: In 110 untreated patients (age: 54±11 years) with essential hypertension and 50 healthy controls with similar age and sex, we measured a) blood pressure parameters by 24h ambulatory blood pressure monitoring b) Carotid to femoral artery pulse wave velocity (PWV) c) Coronary flow reserve (CFR) after adenosine infusion, LV mass/m², the global longitudinal strain (GLS) and systolic (LongSR) and diastolic (LongSRE) strain rate, using conventional and speckle tracking echocardiography at baseline and after a 3-year follow up. Thirty-two patients were treated with ACE and 78 with ARB. We characterized as well-controlled patients those with 24h systolic and diastolic blood pressure <130/80 mmHg

Results: Compared to controls, hypertensives had lower CFR, (2.5±0.6 vs 2.9±0.6) GLS (-19±2 vs. -23±2), LongSR (-1.02±0.2 vs -1.2±0.2), LongSRE (-0.9±0.3 vs -1.2±0.5) and higher PWV (10.5±2 vs 9.2±1.5), LV mass/m² and blood pressure ($p<0.01$ for all comparisons). Compared to baseline, patients had increased GLS, LongSR, LongSRE, reduced LV mass and blood pressure ($p<0.01$, for all comparisons), similar PWV and CFR ($p=ns$) while 70% were well-controlled after 3-years of treatment. Among all measured markers, there was a significant effect of the type of treatment (ACE vs. ARB) on the changes on GLS, LongSR, LongSRE ($p<0.05$). Thus, patients on ACE had a greater improvement of GLS (18±2 vs. -21±2), LongSR (-1.03±0.1 vs -1.13±0.1), LongSRE (-0.8±0.4 vs -1.05±0.3), than patients on ARB (GLS: -19±3 vs. -19.5±3, LongSR: 1.05±0.2 vs. -1.0±0.3, LongSRE: 0.9±0.3 vs -1.01±0.3). No such interaction was observed between treatment and LV mass, PWV and blood pressure. At f/u, the changes of the above markers were similar between those with and those without well-controlled 24h blood pressure ($p=0.7$).

Conclusions: Treatment with ARB and ACE improve longitudinal myocardial deformation in hypertensives during 3 years of treatment. There is a greater improvement of myocardial deformation after ACE than ARB treatment despite a similar effect these drugs on PWV, LV mass and blood pressure suggesting a direct effect of ACE on myocardial function.

2161 | BEDSIDE

Noninvasive estimation of left ventricular systolic and diastolic properties in patients with hypertension assessed by a novel one-beat real-time 3-dimensional speckle echocardiography

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Purpose: Left ventricular (LV) systolic and diastolic properties in patients with hypertension (HTN) are deteriorated by pressure overload, resulting in heart failure with reduced or preserved ejection fraction (EF). We developed a novel one-beat real-time 3-dimensional speckle tracking echocardiography and software to measure LV contractility and relaxation and examined LV systolic properties such as LVEF and contractility and diastolic properties such as LV relaxation and stiffness in HTN.

Methods: We examined 41 patients with HTN without LV hypertrophy (LVH) (age: 69±8), 44 patients with HT and LVH (age: 70±5) and 60 controls (age: 69±10). LV contractility and relaxation was assessed by strain rate (SR) during systole and isovolumetric relaxation (IVRT) using the novel 3D-STE. LV stiffness was calculated as LV stress / strain. Pulmonary capillary wedge pressure (PCWP) was estimated as 12.4–10.7 × log left atrial (LA) active emptying function/minimum LAV as we reported. LV stress was calculated as LV systolic or diastolic radius x systolic blood pressure (BP) or PCWP/LV end systolic or diastolic thickness (Th). LV strain was calculated as (end systolic Th – end diastolic Th)/end systolic Th.

Results: LV radial SR at systole and IVR were reduced in HTN. LV stiffness was increased in HTN with LVH associated with increase of LV diastolic stress compared with control and HTN without LVH (Table, * $p<0.05$ vs. control, + $p<0.05$ vs. HTN without LVH).

	Control	HTN without LVH	HTN with LVH	P value
EP, min/10	125±13/70±9	133±12/75±10	138±12/74±10	<0.001
LV mass, g/m ²	88±14	94±12	133±22*	<0.001
LVEF, %	67±6	67±6	67±9	0.934
E/a'	9.5±2.1	10.8±2.6*	12.8±3.7**	<0.001
PCWP, mmHg	6.9±2.8	7.3±2.5	10.8±3.9**	<0.001
Systolic stress	128±25	138±27	144±33*	0.022
Diastolic stress	17.6±7.0	16.7±5.5	23.5±11.7**	<0.001
LV stiffness	52.2±24.8	59.3±33.7	87.9±44.6**	<0.001
SR at systole, s ⁻¹	2.6±0.6	2.3±0.54*	1.9±0.34**	<0.001
SR at IVR, s ⁻¹	-0.9±0.6	-0.7±0.4*	-0.5±0.3**	<0.001

Conclusion: LV contractility and relaxation in HTN was reduced compared with control despite no difference in LVEF among 3 groups. Although LV stiffness in HTN without hypertrophy was comparable to control, LV stiffness in HTN with hypertrophy was increased. LV properties and feature in HTN could be noninvasively assessed by the novel 3D-STE.

2162 | BEDSIDE**The cardiac time intervals measured by tissue doppler imaging m-mode echocardiography in persons with hypertension or renal impairment**

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Purpose: The cardiac time intervals are intimately related to cardiac function and disease. Color Tissue Doppler Imaging (TDI) M-mode through the mitral leaflet is an easy, fast, and precise method to estimate the cardiac time intervals. The purpose of this study was to test the hypothesis that the cardiac time intervals reveals reduced myocardial function in persons with hypertension and impaired renal function in the general population.

Methods: Within the Copenhagen City Heart Study, a large community based population study, cardiac function was evaluated in 1,687 participants by both conventional echocardiography and by TDI. The cardiac time intervals, including the isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), and the ejection time (ET) were obtained by TDI M-mode through the mitral leaflet. IVCT/ET, IVRT/ET and the myocardial performance index (MPI)=(IVRT+IVCT)/ET were calculated.

Results: The cardiac time intervals revealed impaired systolic and diastolic cardiac function in participants with hypertension (n=613; IVRT (Mean±SD): 108±24 ms, p<0.001; IVCT: 39±15 ms, p<0.001; ET: 280±29 ms, p<0.001; IVRT/ET: 0.39±0.11, p<0.001; IVCT/ET: 0.14±0.06, p<0.001; MPI: 0.53±0.15, p<0.001) and renal impairment, defined by eGFR ≤60 mL/min/1.73m² (n=85; IVRT: 108±24 ms, p<0.001; IVCT: 40±17 ms, p=0.002; ET: 289±27 ms, p=0.26; IVRT/ET: 0.38±0.09, p<0.001; IVCT/ET: 0.14±0.06, p<0.001; MPI: 0.52±0.12, p<0.001), compared to controls (n=989; IVRT: 93±20 ms; IVCT: 35±12 ms; ET: 286±23 ms; IVRT/ET: 0.33±0.08; IVCT/ET: 0.14±0.06; MPI: 0.53±0.15, p<0.001). After adjustment for age, gender, BMI, eGFR, Heart Rate, diabetes, cholesterol, smoking status, atrial fibrillation, previous ischemic heart disease, previous ischemic stroke and conventional echocardiography (LVEF, LA dimension, LVMI, E/e', LV dimension, Dec time, E/A-ratio) only the diastolic time interval (IVRT (p<0.001)) and the combined indexes, including information on both the systolic and diastolic performance (the IVRT/ET (p=0.002) and the MPI (p=0.029)), remained significantly associated with the presence of hypertension. Furthermore, after multivariable adjustment only the systolic time intervals (the IVCT (p=0.042) and the IVCT/ET (p=0.032)) and the combined index (the MPI (p=0.036)) remained significantly associated with the presence of severe renal impairment, defined by eGFR ≤40 mL/min/1.73m².

Conclusion: In the general population, persons with hypertension and reduced renal function have impaired cardiac function determined by the cardiac time intervals independently of the results of conventional echocardiography.

2163 | BEDSIDE**Increased left atrium volume but not fibrosis predicts long-term outcome in hypertrophic cardiomyopathy. A cardiac magnetic resonance study**

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Background: It has been suggested that increased left atrial (LA) dimension and LA volume determined by transthoracic echocardiogram is associated with worse outcomes in HCM. CMR can measure precisely LA volume without limitations of echocardiography. We sought to determine the prognostic impact of LA volume determined by CMR in HCM patients.

Methods: We retrospectively studied all HCM patients undergoing CMR at 5 centers during the period 2006-2012. CMR findings were analyzed in relation to the appearance of a major adverse clinical event (heart failure requiring hospitalization, appropriate ICD discharge, aborted SCD and cardiovascular death) during follow-up.

Results: 399 patients (69% male, mean age 53±6 years, NYHA I 57%, LVEF 68±11%, maximum wall thickness 19±4 mm, 29% with LVOT obstruction) were studied.

On CMR study, left atrial volume (LAV) was 99.9±37.6 cm³ and LAV indexed by body surface area (LAVind) was 54±20.7 cm³/m². After administration of gadolinium, 32% patients had fibrosis and 20% had extensive fibrosis (≥3 segments).

During a follow-up period of 38±24 months, 40 patients (10%) presented 45 clinical events (32 heart failure requiring hospital admission, 4 cardiovascular deaths, 3 aborted SCD and 6 appropriate ICD discharges).

Patients with adverse events showed higher LAV and LAVind (131.6±49.7 vs 96.5±34.4 cm³ and 74.6±30.3 vs 51.8±18.2 cm³/m²; both p<0.01). Other markers of poor prognosis on CMR were lower LVEF (59±16 vs 69±11%; p<0.01) and increased LV end-diastolic diameter (48±7 vs 45±7 mm; p=0.03).

In contrast, the presence of fibrosis/extensive fibrosis was not associated with adverse events during follow-up (10% vs 9%; p=0.78 and 13% vs 9%; p=0.27, respectively).

A LAV cut-off value of >96.5cm³ predicted events with 80% sensitivity and 63% specificity and a LAVind>62.1 cm³/m² with a 67% sensitivity and 79% specificity.

Conclusions: Increased left atrial volume is a marker of major clinical events among HCM patients. Our data suggest that enlarged LAV is a better marker than fibrosis for diastolic dysfunction and increased LV end-diastolic pressure in HCM patients.

2164 | BEDSIDE**Myocardial MR spectroscopy (MRS) as in noncompetitive athletes and patients with hypertrophic cardiomyopathy**

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Purpose: To evaluate myocardial energetic metabolism with 31P-MRS and 1H-MRS in healthy volunteer, athletes and patients affected with hypertrophic cardiomyopathy (HCM) in order to define early metabolic modifications.

Materials and methods: We prospectively performed a cardiac 1.5-T MR in 24 subjects: 15 athletes (A), 8 patients affected with HCM (H) and 7 healthy volunteers (V). With subjects in supine position, ECG-triggered cine steady-state free precession (true-FISP) and 1H-MRS point resolved spectroscopy sequence (PRESS) was performed. For the 1H-MRS a single voxel was placed into the septum. With patients in prone position a 31P-MRS multivoxel chemical shift imaging sequence was acquired. Heart function was measured segmenting cine images with Syngo-Argus software. 1H-MRS spectra were processed using jMRUI software; 31P-MRS spectra using Spectroscopy-Argus. Kruskal-Wallis and Jonckheere-Terpstra tests were used. Data were reported as median (interquartile interval).

Results: Ejection fraction (%), indexed end-diastolic volume (ml/m²), end-systolic volume (ml/m²), mass (g/cm²) and septal thickness (mm) were 68, 95, 30, 72 and 10 for group A, respectively; 68, 73, 20, 81 and 18 for group H, respectively; 63 (p=0.865), 78 (p=0.011), 29 (p=0.013), 45 (p=0.008) and 6 (p<0.001) for group V, respectively. Creatine phosphate (PCr), gammaATP and inorganic phosphate (Pi) were 25, 5.3, 0.3 for group A, respectively; 22, 5.4, 0.4 for group H, respectively; 27 (p=0.428), 6.2 (p=0.701), and 0.0 (p=0.114) for group V, respectively. PCR/gammaATP was 5.2 in group A, 3.7 in group H and 4.2 in group V (p=0.307); total creatine was 0.7, 0.6, and 0.0, respectively (p=0.037); lipids were 0.0, 1.5, and 0.2, respectively (p=0.042).

Conclusions: An alteration of energetic metabolism in HCM patients with a reduction of PCR/gammaATP ratio and an increase of Pi concentration is confirmed. Athlete's heart, independently from morphologic and functional adaptation, is not associated with energy metabolism alterations. In HCM patients there is a significantly increase of myocardial lipids and a reduction of PCR/gammaATP.

2165 | BEDSIDE**Should indexation of left ventricular mass be sex and ethnic specific? A report from the EchoNoRMAL meta-analysis**

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Purpose: It is recommended that left ventricular mass (LVM) be indexed by a measure of body size to account for the association between body and heart size. But our understanding of indexation for non-Europeans is limited. This study derives sex- and ethnic-specific powers of height (ht) and body surface area (BSA) to index LVM measured by echocardiography.

Methods: The EchoNoRMAL individual person data meta-analysis includes population-based data on 22404 adult volunteers without cardiovascular disease or risk factors. Log-log linear regression modeled sex- and ethnic-specific relationships between LVM and each measure of body size (ht, BSA by DuBois equation). The slope of ht or BSA equates to the power it is raised to for indexation. The powers were significantly different when the 95% confidence interval for their

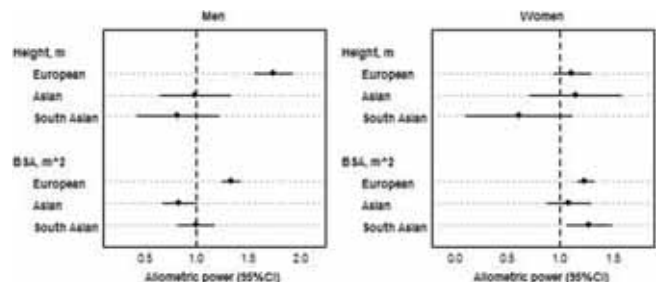


Figure 1. Powers of height & BSA, LVM indexation.

difference excluded zero. Results are reported for Europeans (E), Asians (A) & South Asians (SA) of any weight.

Results: Of 13378 healthy subjects from 32 studies, there were: 4021 E, 564 A, 572 SA men; 4668 E, 570 A, 569 SA women. The slope of ht for E men was 1.7 which was significantly different to the slopes for A (1.0) & SA (0.8). For women, the slope of ht was 1.1 for E, which was not different to A (1.1) or SA (0.6). The slope of BSA for E men was 1.3, which was significantly different to the slopes found for A (0.8) and SA (1.0). For women, the slope of BSA was 1.2 for E, which was not different to A (1.1) or SA (1.3) (Fig. 1).

Conclusions: Sex- and ethnic-specific indexation of LVM is indicated. Indexation of LVM by $ht^{1.7}$ would be appropriate for E men however this cannot be applied across other ethnicities, or to women. Similarly, indexation of LVM by $BSA^{1.3}$ would be appropriate for E men but not A or SA men. Ethnic differences in indexation are less apparent among women.

BASIC AND TRANSLATIONAL SCIENCE HOT LINE ON CARDIAC DISEASE

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Modelling Brugada syndrome using patient-specific induced pluripotent stem cells

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Brugada syndrome (BrS), a cardiac genetic disease, is one of the major causes of sudden cardiac death in healthy young people. However, the underlying electrophysiological and molecular mechanisms have not been completely understood. A major challenge in cardiac translational research is the lack of tissue culture systems replicating human pathology to study disease mechanisms and to identify druggable targets. Aim of this study was to study the pathophysiology and molecular mechanisms of BrS in vitro using patient-specific induced pluripotent stem cells (iPSCs) as a renewable and unlimited source for cardiomyocytes (CMs). In this study, iPSCs were generated from a 45-year-old healthy donor and a 50-year-old patient with BrS putatively caused by the heterozygous point mutation C5435A in the gene SCN5A coding for the α -subunit of the cardiac sodium channel (NaV1.5). The generated iPSCs showed pluripotency and were able to differentiate into spontaneously beating CMs. Voltage-gated sodium current (INa) measurements revealed a significantly reduced current with a delayed activation in BrS-CMs compared to control cells, indicating a loss of function of NaV1.5. In BrS-CMs, the intermediate inactivation of sodium channels was slightly but not significantly enhanced whereas steady-state inactivation, recovery from inactivation, and persistent INa were not affected. Action potential (AP) measurements showed a reduced Vmax and higher arrhythmic tendencies in BrS-CMs compared to control cells. A significantly higher variability of the AP durations as well as early and delayed afterdepolarizations could be observed. AP measurements in control cells under the treatment with the sodium channel blocker flecainide suggest that the increased variability of action potential duration in BrS-CMs is linked to the reduced INa. However, treatment of BrS-CMs with quinidine, a class I antiarrhythmic agent which is currently investigated for its therapeutic effect on BrS, could not reduce the beat-to-beat variability of AP durations. Furthermore, quantitative real-time PCR showed that SCN5A was slightly but not significantly upregulated in BrS-CMs compared to the control cells with an allele-specific balanced expression. However, the full-length NaV1.5 protein was detected in BrS-CMs at a level of 82% compared to the control. These data demonstrate that patient-specific iPSCs can be used to model BrS in vitro and may provide the platform for the development of personalized drug therapy.

2171

Transplantation of adipose tissue mesenchymal cells conjugated with PLGA microspheres foster c-kit+ progenitor cells and cardiac regeneration through paracrine signaling

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Rationale: Adipose tissue-derived mesenchymal stromal cells (AT-MSCs) may contribute to repairing ischemic cardiovascular tissue. The engraftment and survival of transplanted stem cells in the harmful microenvironment of host tissue may be improved by combining such cells with scaffolds to delay apoptosis and enhance their regenerative properties.

Objectives: We examined whether poly (lactide-co-glycolide) (PLGA) microspheres (PAM) functionalized with vascular endothelial growth factor (VEGF) enhance survival, growth and differentiation of AT-MSCs. We also compared the therapeutic efficacy of transplanted AT-MSCs conjugated with VEGF-microspheres with injection of conditioned medium from AT-MSCs in a murine model of acute myocardial infarction (AMI).

Methods: We used non-functionalized (empty) or VEGF-releasing microspheres coated with murine AT-MSCs. Twelve month-old male C57BL/6 mice under-

went coronary artery ligation (Lig), followed by randomization into 6 groups (n=5/group): I. Sham operation, II. AMI control (saline PBS 20 μ L), III. AMI followed by intramyocardial injection with AT-MSCs only (2.5×10^5 cells/20 μ L), or IV. concentrated medium from AT-MSCs (CM, 20 μ L), or AT-MSCs (2.5×10^5 cells/20 μ L) conjugated with empty microspheres (V) or VEGF-releasing microspheres (VI).

Results: Growth-curve and differentiation assays showed that VEGF-releasing microspheres did not impact proliferation or osteogenic and adipogenic differentiation of AT-MSCs. Conversely, AT-MSCs conjugated with VEGF-releasing microspheres inhibited H₂O₂-induced apoptosis, and this effect was dependent on the VEGF/Akt axis, since reverted by pre-incubation with the Akt inhibitor LY294002 or an anti-VEGF receptor antibody. In a Matrigel assay, AT-MSCs conjugated with VEGF-releasing microspheres were more pro-angiogenic than AT-MSCs alone. When compared with AT-MSCs alone, AT-MSCs conjugated with VEGF-releasing microspheres decreased the area of fibrosis and increased myogenic marker expression, arteriogenesis (Fig. 1A, immunofluorescence staining with anti- α -smooth muscle actin conjugated with Cy3 red fluorochrome (Cy3-ASMA), number of cardiac-resident c-Kit positive cells (Fig. 1B, $p < 0.05$ vs PBS+lig) and myocardial fractional shortening (FS) when transplanted into the infarcted hearts of C57 mice (%FS: I. 40 ± 11 , II. $15 \pm 3^{**}$, III. $29 \pm 7^{\circ}$, IV. $33 \pm 7^{\circ}$, V. 20 ± 1 , VI. $34 \pm 7^{\circ}$) ($^{**}p < 0.01$ vs sham; $^{\circ}p < 0.05$ and $^{\circ}p < 0.01$ vs Lig+PBS; anova test). All such effects, however, were fully paralleled by the injection of CM ($p < 0.01$ vs PBS+lig).

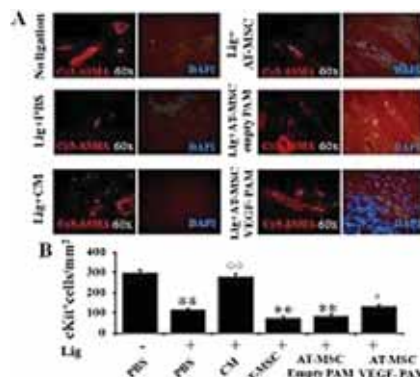


Figure 1. Arteriogenesis and number of ckit+ cells.

Conclusions: AT-MSCs conjugated with VEGF-releasing microspheres exert a paracrine effect, paralleled by the injection of CM, that may have therapeutic applications to enhance arteriogenesis, survival of AT-MSCs and the endogenous regenerative capacity of the heart. Such effects improve left ventricular function after AMI.

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Role of TRPM4 in ventricular action potential and signal conduction through the heart

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TRPM4 is a calcium-activated, but calcium-impermeable, non-selective cation channel and plays an important role in different calcium-dependent cell functions in many cells including mast cells, chromaffin cells and neurons. Trpm4 expression was also shown in atrial and ventricular cardiac tissue, but the physiological function in the heart is still largely unresolved. Recently, gain-of-function mutations in the Trpm4 gene have been associated with conduction disorders, such as Progressive Familial heart Block Type 1, Right Bundle Branch Block and Brugada Syndrome. In this study, the contribution of TRPM4 to the ventricular action potential was established and its role in cardiac conduction in the whole heart was evaluated by use of Trpm4 knockout (Trpm4KO) mice. Patch-clamp experiments and membrane potential measurements showed that TRPM4 is activated during repolarisation of the ventricular action potential and that the duration of the action potential in cardiomyocytes of Trpm4KO mice was significantly shorter compared to wild-type (WT) cardiomyocytes. Since TRPM4 influences action potential and increased expression of Trpm4 (due to gain-of-function mutations) is associated to conduction disorders, we further investigated the effect of Trpm4 loss on signal conduction through the heart. Therefore, electrocardiographic intervals were determined in WT and Trpm4KO mice. In conscious mice, 2-lead surface ECG was measured via telemetry. RR, PR, QRS and QTc intervals were calculated and no differences were found between the 2 genotypes. To investigate impulse propagation and possible conduction abnormalities more in detail, we performed intracardiac electrophysiological studies on WT and Trpm4KO mice. Atrial, His and ventricular potentials were analyzed in intracardiac electrograms and atrial-His and His-ventricular intervals were equal in WT and Trpm4KO mice. Taken together, we can conclude that loss of Trpm4 results in shorter ventricular action potentials, but that this has no influence on impulse propagation and conduction properties through the heart.

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Prediction of acute rejection in heart recipients: interest of circulating miRNAs

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Purpose of the study: Histological assessment of endomyocardial biopsies is the gold standard for diagnosis of acute rejection. However the sampling procedure is invasive, sometimes associated with severe side effects, and pathologists' appreciations are disparate due to the absence of a clear consensus, especially concerning AMR. Therefore, new biomarkers could both ease diagnosis on biopsy and contribute to early diagnosis and outcome prediction during the transplantation. MicroRNAs (miRNAs) are endogenous, single-stranded molecules that may repress target genes through degradation of the mRNA and/or inhibition of protein expression. miRNAs have been largely studied, especially in cancer, and their deregulation have been shown to be linked to many diseases, upon which diabetes, infarctus, ischemia lesions or atherosclerosis. Here, we studied 14 miRNAs expression in a cohort of 100 patients, recipients having frozen endomyocardial biopsies samples and concomitant serum. These miRNAs were chosen from an in silico analysis conjugating relevant bibliography analysis and databases screening (TargetScan, MiRBase).

Methods: Samples from 100 patients, harvested and frozen in two centres (HEGP and La Pitié Salpêtrière Hospital) were used. All biopsies were seen by trained pathologists and graded in term of rejection: 50 patients presented no rejection (0R, pAMR0: control group) 19 presented ACR (1R-3R) and 31 presented AMR/mixed rejection (pAMR1-3, 1R-2R) (rejection group, n=50). Total RNA was extracted from the tissue and/or the serum and qPCR analysis was conducted. In parallel, DSA was assessed using Luminex technique. In situ hybridization was also conducted using paraffin-embedded biopsies from patients presenting severe AMR and/or ACR.

Results: Six miRNAs showed a significantly different tissue expression during rejection ($p < 0.01$): inflammatory miR-155 and 451, endothelial miR-10a and 92a, cardiac miR-21 and 31. All of these 6 miRNAs discriminated AMR from controls ($p \leq 0.01$) while miR-155, miR-451, miR-10a, and miR-31 differentiated ACR from controls ($p = 0.03$). Three miRNAs (miR-451, miR-10a, and miR-21) were able to discriminate ACR and AMR ($p \leq 0.005$). We demonstrate significant association (spearman correlation) between the tissue and serum expressions for miR-155 ($p < 0.0001$), miR-10a ($p = 0.0002$), miR-92a ($p = 0.0317$) and miR-31 ($p = 0.0212$). In situ hybridization for miR-92a showed an endothelial distribution, whereas 10a was also present in inflammatory cells and 31 was mostly found in interstitial cells.

Conclusion: This study provides evidence that regulation in the expression of miRNA occurs during heart rejection, not only at the tissue level in the EMB but also in the concomitant serum. This suggests that miRNA may represent interesting biomarkers for better investigating heart transplant rejection.

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Notch3 is an important mediator of cardiac adaptation to pressure overload

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Objective: Notch3, a receptor expressed in vascular smooth muscle cells (VSMC), has a key role in the integrity of resistance arteries by controlling the maturation of VSMC. Data are shown that Notch3-deficient mice subjected to hypertension developed a heart failure (Boulos and al., Hypertension, 2011), however mechanisms are unknown. The goal of the study was to decipher the role of Notch3 signaling pathway in the heart in response to pressure overload.

Methods and results: To reach our objectives, mice lacking expression of the Notch3 gene (N3^{-/-}) or WT mice was perfused by continuous infusion of Angiotensin II (AngII) for 28 days (1 µg/kg/min). In response to hypertension, N3^{-/-} mice developed a severe heart failure conversely to WT+AngII mice with lower shortening fraction (-12%, $p < 0.05$), higher cardiac hypertrophy (+35%, $p < 0.05$) associated with major alterations of the coronary compartment [decreased F-actin content in the media (-20%, $p < 0.05$), lack of medial hypertrophy]. To eliminate congenital defect biases, we used mice with conditional deletion of RBPJk, the transcriptional factor mediating Notch3 canonical pathway, selectively in VSMC (SMMHC-CRE ER T2, RBPJk loxp/lox) at 4 weeks-old with tamoxifen. Using same AngII protocol, we show that in response to hypertension, mice inactivated for RBPJk in VSMC developed a severe heart failure with dramatic decrease in shortening fraction (-50%, $p = 0.0005$), LV dilatation (+34%, $p < 0.05$), and cardiac hypertrophy (+14%, $p < 0.05$).

Conclusion: Altogether, we provide lines of evidence that alterations of Notch3/RBPJk signaling pathway in the coronary arteries might play a role in the occurrence of heart failure in response to chronic increase in blood pressure.

2175

A mutation in elongator protein 2 can cause a severe form of familial hypertrophic cardiomyopathy

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Background: Elongator protein 2 (ELP2) is known as a STAT3-interacting protein and one of subunits of elongator, which can regulate RNA elongation via its histone acetyltransferase activity. It remains to be solved whether ELP2 plays an important role in cardiac hypertrophy.

Purpose: Our purpose is to identify new gene mutations that cause familial HCM, which can progress into dilated-phase HCM (d-HCM) by using next-generation DNA sequencing analysis.

Methods: We examined a patient and her elder brother who both presented with complicated severe HCM and whose parents are married cousins. The elder brother had died suddenly as a boy; his autopsy revealed that he had developed HCM. The patient was diagnosed with HCM, and during the 20-year follow-up, HCM progressed to d-HCM. The patient received a left ventricular-assist device implant, and the patient is currently on a waiting list for cardiac transplantation. The parents are healthy. We hypothesized that a causative allele was transmitted to both the patient and the elder brother as an autosomal recessive mutation that caused familial HCM.

Analysis of cDNA from cardiac samples revealed that MYH7, MYBPC3, TNNT2 and TNNI3 sequences from the patient was normal. The patient and each of her parents provided informed written consent for genetic testing. The genome analysis and whole-exome sequencing was performed with samples from each of the three participants. An exome capture kit and a next-generation DNA sequencing analyzer were used to sequence each exon library. Sarcomere organization in H9C2 cells overexpressed with ELP2 and localization of ELP2 in biopsy samples were investigated.

Results: The genome exome analysis showed 345 single nucleotide polymorphisms (SNPs) that caused amino acid change for which the patient was homozygous and both parents were heterozygous. After excluding all known common (5%) SNP gene mutations in the SNP Database (dbSNP), a gene of elongator protein 2 (ELP2), encoding one of six elongator subunits, was the only identified gene that is possibly associated with cardiac muscle. The identified missense mutation was a 2385 GA nucleotide transition in the final exon 22 of ELP2 isoform 2 encoding one of six elongator protein subunits. The resultant E795G substitution replaces a polar carboxylic glutamate with a nonpolar glycine. The H9C2 overexpressed with mutant ELP2 showed a distinct sarcomere organization compared with control cells overexpressed with normal ELP2. Based on immunohistochemistry, the localization of ELP2 in the patient's endomyocardial biopsy sample was different from in control samples.

Conclusions: These results indicate both that mutations in ELP2 can cause a familial form of HCM and that ELP2 may be a new target for treatment of cardiac hypertrophy.

ANTICOAGULATION THERAPY “THE TIMES THEY ARE A CHANGING”

2185 | BEDSIDE

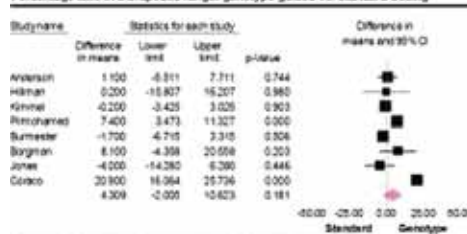
A meta-analysis of randomized trials of genotype-guided versus standard dosing of warfarin

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Purpose: The randomized controlled trials (RCTs) comparing genotype-guided dosing (GD) of warfarin with standard dosing (SD) have shown mixed outcomes. We performed a meta-analysis of all published RCTs on warfarin dosing comparing GD versus SD in adult patients (> 18 years).

Methods: With specific terms, PubMed, Cochrane Central Register of Clinical Trials and EMBASE were searched for RCTs published from 2000 to January 2014 comparing GD with SD in patients with any indications of warfarin use. Random-effects model was used to compute summary effects. Heterogeneity was tested with I² index. A p-value of < 0.05 was considered statistically significant.

Percentage time in therapeutic range: genotype-guided vs. standard dosing



Meta-analysis of percentage time in therapeutic range between genotype-guided vs. standard dosing

Results: 9 RCTs with a total of 2378 randomized patients were identified. In comparison to SD, GD resulted in significant reduction in major hemorrhage (Odds ratio: 0.38, 95% confidence interval: 0.19–0.75, p -value: 0.006) and time-to-maintenance dose in days (mean: -9.5, 95% confidence interval: -18.0 to -0.9, p -value: 0.029). GD did not result in significant difference in % time in therapeutic range (mean: 4.30, 95% confidence interval: -2.00 to 10.62, p -value: 0.18), INR > 4 (Odds ratio: 0.90, 95% confidence interval: 0.74 to 1.10, p -value: 0.32), venous thromboembolism (Odds ratio: 0.61, 95% confidence interval: 0.26 to 1.42, p -value: 0.26), and all-cause mortality (Odds ratio: 0.73, 95% confidence interval: 0.31 to 1.69, p -value: 0.46).

Conclusions: The current meta-analysis of randomized controlled trials shows that genotype-guided dosing of warfarin results in significant reduction in major hemorrhage and time-to-maintenance dose when compared to standard dosing.

2186 | BEDSIDE

Low thrombin activatable fibrinolysis inhibitor levels increase the efficiency of long-term warfarin therapy

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Thrombin activatable fibrinolysis inhibitor (TAFI) is a component of fibrinolysis, which acts by inhibiting the assembly of fibrinolytic factors on the fibrin surface. Our previous pilot study showed that low TAFI levels may increase the risk of bleedings during long-term warfarin (W) therapy in pts with venous thromboembolism (VTE). Influence of TAFI on the efficiency of W therapy in VTE pts is not yet clear.

Purpose: To determine the influence of TAFI levels on the efficiency of long-term W therapy in VTE pts.

Methods: One hundred and eleven pts (76 men) in the age 18-76 (mean 54±14) years with deep vein thrombosis (DVT) and/or pulmonary embolism (PE) were included in the study. Pts received unfractionated or low molecular weight heparin for at least 5 days followed by long-term W therapy (international normalized ratio 2.0-3.0). TAFI levels were measured during the first month of W therapy by a chromogenic assay. Compression ultrasonography was performed at baseline and after 1, 3, 6 and 12 months of therapy. The follow-up period was 12 months. Using compression ultrasonography, we estimated the frequency of total clot lysis in deep veins after 12 months of W therapy. Total clot lysis was defined if a vein was compressed completely, and a vein lumen was free from thrombotic masses. Endpoint of efficiency was the presence of total clot lysis in deep veins in combination with the absence of DVT/PE recurrences.

Results: TAFI levels were measured in 98 of 111 pts. Median of TAFI levels was 106 (interquartile range 90-133) %. Twenty four pts had low TAFI levels (<90%), and 74 pts had high TAFI levels (≥90%). Ninety pts finished the follow-up period. After 12 months, the frequency of total clot lysis was 22%. All these pts had no DVT/PE recurrences. In pts with low TAFI levels, the efficiency of W therapy was significantly higher – 42% vs 8.5% ($p=0.002$). Univariate Cox regression showed that low TAFI levels are associated with a 5-fold increase of the efficiency of W therapy (HR 5.28; 95% CI 1.73-16.15; $p=0.004$). Multivariate Cox regression showed that low TAFI levels (HR 9.52; 95% CI 1.94-46.87; $p=0.006$) and 3 clinical factors – thrombolytic therapy in PE pts (HR 36.29; 95% CI 5.44-242.08; $p<0.001$), DVT of upper extremities (HR 5.87; 95% CI 1.59-21.60; $p=0.008$) and the maintenance of occlusive thrombosis in deep veins after 1 months of treatment (HR 0.10; 95% CI 0.01-0.80; $p=0.029$) are independent predictors of the efficiency of W therapy.

Conclusion: TAFI levels <90% increase the efficiency of long-term W therapy in VTE pts.

2187 | SPOTLIGHT

The predictive value of the SAME-TT2R2 score for anticoagulation control and adverse outcomes in anticoagulated patients with atrial fibrillation

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Background: Oral anticoagulation (OAC) is highly effective preventing stroke and

mortality in non-valvular atrial fibrillation (NVAf) patients. However, the efficacy and safety of vitamin K antagonists (VKAs, the main OAC drug used) strongly depends upon the quality of anticoagulation control, as reflected by the average percentage of the time in therapeutic range (TTR) of INR 2.0-3.0. An easy, simple prediction of which AF patients are likely to do well on VKA (with good average TTR) could guide decision-making between using VKAs and novel OACs. Recently, it has been proposed and validated the SAME-TT2R2 score [Sex, Age (<60 years), Medical history (at least 2 of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs) [all 1 point], as well as current Tobacco use (2 points) and Race (non-Caucasian; 2 points)].

Methods: In a consecutive and steady cohort of NVAf patients on OAC attending our anticoagulation clinic, we tested the hypothesis that new SAME-TT2R2 score as a predictor for good average TTR, and whether this translated into adverse events in a “real world” cohort of patients with NVAf. At six months after inclusion, we calculated the percentage of INR measures within the therapeutic range during the previous 6 months, as an estimation of the TTR.

Results: We studied 972 patients (49% male, median age 76 years. The median CHA2DS2-VASc score 4 (IQR 3-5) and median HAS-BLED score was 2 (IQR 2-3). The incidence of both bleeding, adverse cardiovascular events (including stroke/thromboembolism) and mortality during the follow-up was higher with increasing SAME-TT2R2 score. The SAME-TT2R2 score was predictive for the composite of all adverse events [Hazard Ratio, HR: 1.32 (1.17-1.50); $p<0.001$], adverse cardiovascular events [HR 1.52 (1.28-1.83); $p<0.001$], and all-cause mortality [1.41 (1.16-1.67); $p=0.001$]. A trend was also observed for major bleeding events [1.23 (0.99-1.53); $p=0.059$]. Patients with increasing baseline SAME-TT2R2 score had significantly lower mean TTR at 6 months after inclusion ($p=0.043$).

Conclusion: In a “real world” cohort of consecutive patients with NVAf, a high SAME-TT2R2 score (reflecting poor anticoagulation control with poor TTR) was associated with more bleeding, adverse cardiovascular events and mortality during follow-up.

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2188 | BEDSIDE

Methods of kidney function assessment in non-valvular atrial fibrillation in the era of new oral anticoagulants

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Background and objective: There is little consensus about what should be the method to calculate new oral anticoagulant dosage adjustments. The aim of this study was to describe the methods used for the assessment of kidney function before prescribing new oral anticoagulants in patients with atrial fibrillation.

Material and method: Cross-sectional study based on a survey of 642 Spanish physicians from 17 hospitals and 8 primary care centres.

Results: The MDRD and Cockcroft-Gault equations were the most frequently used: 46.6% and 39.1% respectively, while the 24 hour urine creatinine excretion and the CKD-EPI equation are the less used for this purpose: 3.3% and 1.0% respectively. Cardiologists and nephrologists were the specialists who more frequently used the MDRD equation (52.0% and 66.7% respectively), while the emergency physicians were the ones who most frequently use CG equation (45.9%).

Conclusion: The results of this study show that there is a high variability in the methods used for renal function assessment before prescribing new oral anticoagulants in daily clinical practice. MDRD equation is the most frequently used in this setting. As previous studies report that the use of the MDRD equation overestimates creatinine clearance, this may result in higher doses of this drugs and eventually imply serious adverse safety events.

Abstract 2188 – Table 1. Methods of renal function assessment

Methods	Medical specialty							Total (n=489)
	Cardiology (n=152)	Emergency (n=98)	Internal med. (n=97)	Neurology (n=46)	Nephrology (n=9)	Hematology (n=30)	Primary care (n=57)	
Serum creatinine	11 (7.2%)	24 (24.5%)	9 (9.3%)	12 (26.1%)	0 (0%)	1 (3.3%)	7 (12.3%)	64 (13.1%)
MDRD	79 (52%)	24 (24.5%)	40 (41.2%)	19 (41.3%)	6 (66.7%)	13 (43.4%)	21 (36.8%)	202 (41.3%)
Cockcroft-Gault	46 (30.3%)	45 (45.9%)	31 (32%)	14 (30.4%)	0 (0%)	10 (33.3%)	18 (31.6%)	164 (33.5%)
24h creatinine excretion	1 (0.7%)	0 (0%)	5 (5.1%)	1 (2.2%)	0 (0%)	4 (13.3%)	5 (8.7%)	16 (3.3%)
MDRD + CG	10 (6.5%)	4 (4.1%)	6 (6.2%)	0 (0%)	3 (33.3%)	0 (0%)	3 (5.3%)	26 (5.3%)
CG + CKD-EPI	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
CKD-EPI	2 (1.3%)	0 (0%)	2 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.8%)
Others	2 (1.3%)	1 (1%)	4 (4.1%)	0 (0%)	0 (0%)	2 (6.7%)	3 (5.3%)	12 (2.5%)

MDRD, Modification of Diet in Renal Disease equation; CG, Cockcroft-Gault equation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation.

2189 | BEDSIDE**Comparison of estimated glomerular filtration rate equations for dosing new oral anticoagulants in patients with atrial fibrillation**

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Background: New oral anticoagulants (NOAC) require dosing adjustment according to renal function status. The aim of this study was to determine the discordance in hypothetical recommended dosing of NOAC using kidney function estimates based on different estimated Glomerular Filtration Rate (GFR) equations in patients with atrial fibrillation (AF).

Methods: Cross-sectional analysis of 910 consecutive patients with AF and indication for oral anticoagulation from our outpatient anticoagulation clinic. GFR was estimated by using the following equations: Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). For dabigatran, rivaroxaban and apixaban, we identified dose discordance when there was a disagreement in recommended dose based on different equations.

Results: Among the overall population, relative to CG the discordance in dabigatran dosage was 11.4% for MDRD and 10% for CKD-EPI, whereas the discordance in rivaroxaban dosage was 10% for MDRD and 8.5% for CKD-EPI. The lowest discordance was observed for apixaban, being 1.4% for MDRD and 1.5% for CKD-EPI. In patients with CG <60 mL/min or in the elderly (≥75 years), the discordance in dabigatran and rivaroxaban dosages were higher than in the whole population, ranging from 13.2% to 30.4%. The discordance in apixaban dosage remained <5% in these patients.

Conclusions: In this population, the discordance in dabigatran and rivaroxaban dosages using different estimated GFR is frequent, especially among the elderly patients with renal impairment. Further studies are needed to clarify the clinical importance of these discrepancies and the best anticoagulant dosages depending on the use of different equations estimated GFR.

2190 | BEDSIDE**Left atrial thrombi and spontaneous echo contrast in patients with atrial fibrillation who were taking warfarin or novel oral anticoagulants before cardioversion**

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Introduction: Warfarin reduces the risk of stroke and systemic embolism following cardioversion in patients with atrial fibrillation. It was reported that the novel oral anticoagulants, dabigatran and rivaroxaban had similar efficacy compared with warfarin. But the data of left atrial thrombus and spontaneous echo contrast is limited.

Methods: Total 170 patients [102 patients in warfarin group, 68 patients in novel oral anticoagulant group (40 in dabigatran, 28 in rivaroxaban)] underwent transesophageal echocardiography before cardioversion. We compared the positive rate of left atrial thrombus or spontaneous echo contrast between warfarin group and novel oral anticoagulant group. At 30 days after cardioversion, the incidence of stroke, systemic embolism and major bleeding were analyzed.

Results: Baseline characteristics were similar between groups. Among 170 patients, there was no thrombus in left atrium. Positive rate of spontaneous echo contrast in transesophageal echocardiography was 25.5% in warfarin group and 30.9% in novel oral anticoagulant group (P=0.441). Continuous treatment with anticoagulants for ≥3 weeks before cardioversion was 95.1% in warfarin group and 89.7% in novel oral anticoagulant group (P=0.225). At 30 days after cardioversion, the incidence of stroke was 2.0%, 1.5%, respectively (P=0.999). There was no major bleeding event.

Conclusion: The positive rate of thrombus and spontaneous echo contrast in patients with atrial fibrillation receiving anticoagulants was not different in warfarin and novel oral anticoagulant group. Also the incidence of stroke and systemic embolism after cardioversion was not different in two groups.

NEW AND UNIQUE: TREATMENT OF STRUCTURAL HEART DISEASE

2211 | BEDSIDE**Percutaneous transcatheter obliteration of mitral prosthetic paravalvular leaks**

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Introduction: Prosthetic paravalvular leaks (PVL) of biological or mechanical heart valves implanted surgically are sometimes responsible of heart failure or hemolysis requiring reoperations, which are often of high risk. The percutaneous

occlusion of these leaks is an alternative treatment. The aim is to assess the feasibility and efficacy of percutaneous transcatheter obliteration of paravalvular leaks. **Methods:** Fourteen patients underwent transcatheter closure of prosthetic mitral paravalvular leaks from September 2009 to December 2013 in one center. All patients had symptoms and signs of hemolysis and/or severe cardiac failure with high surgical risk. Each percutaneous transcatheter intervention was guided by three dimensions trans-esophageal echocardiography (3D TOE) and performed with different kinds of Amplatzer devices.

Results: Patients had high operative risk (average logistic EuroSCORE 1 = 19,1%) mainly because of previous cardiac surgeries (3 times in 4 patients, 2 times in 8 patients and 1 time in 2 patients) and comorbidities. Implantation of a device was impossible in 4 patients without any complication. Implantation of a device has been technically successful in 10 patients (71,5%): out of them, 7 (50%) were immediately dramatically improved and remained asymptomatic in the follow up. In the 3 other patients, 1 had an immediate migration of the prosthesis into the left atrium without consequence, 1 had few months after on 2 occasions enlarged the leak in spite of 2 new successful implantations of prosthesis and finally died of heart failure, 1 patient had a severe complication with a dramatic worsening of the hemolysis on a residual leak leading to death in spite of the full occlusion of the residual leak with a second device.

Conclusions: Transcatheter closure of paravalvular leaks is technically feasible and facilitated by the 3D TEO and the provision of new devices. Despite the difficulties, the results of this short series demonstrate that this technique represents an attractive alternative to surgery in these high risks patients.

2212 | BEDSIDE**Transcatheter closure of large patient ductus arterioles with the self-expanding mushroom-shaped duct occluder**

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Purpose: To assess the immediate, short, and intermediate-term results of catheter closure the large patent ductus arteriosus (PDA) with the self-expanding mushroom-shaped ductus occluder (DO) from a single center.

Methods: Between March 2008 and December 2012, 318 patients underwent attempted transcatheter closure of PDA in our center, of whom DO was used in 73 (23%) patients with large-sized PDA (71 female, with ages ranging from 17 to 73 years). Large PDA is defined as ductus diameter ≥6 mm. The size of device selected was generally at least 1-2 mm larger than ductus diameter. 49 (67%) patients were symptomatic. 8 (11%) patients were in severe heart failure. Six patients had successful closure PDA by using ventricular septal defect occluder. A hemodynamic study was performed and the Qp/Qs ratio was calculated in each patient. Ten minutes after detachment of device, an aortogram was performed to check the presence of residual shunt and aortic arch obstruction.

Results: The ductus diameter ranged from 6,2 to 12 mm (mean 8,9±1,4 mm). The mean Qp/Qs ration was 2,7±0,7. Pulmonary arterial hypertension (pulmonary arterial systolic pressure ≥40 mm Hg) was present in 43 (59%) patients. There were 59 patients with morphologic type A ductus, 3 with type B ductus, 9 type C ductus and 2 type E ductus. DO was successfully deployed in all patients. The size of device deployed ranged from 8 to 14 mm. 1 patient experienced severe complication: a diminished femoral pulse, which recovered on the next day. Four patients had a large groin hematoma, which was managed by local compression. No other significant complications occurred. All 73 patients were available for 1-month and 12-months echocardiographic follow-up. 36 patients had a moderate residual shunt through the occluder immediately after device deployment. However, none had residual flow across the device in 24 hours after the procedure. Complete occlusion was documented by the echocardiography in all patients for 1-year follow-up. No patient had left pulmonary artery stenosis. Severe pulmonary arterial hypertension was in 9 (21%) of 43 patients at 1 year after a device implantation.

Conclusion: Transcatheter closure of large-sized ductus with DC is effective and safe.

2213 | BEDSIDE**Intraprocedural assessment of mitral valve area with 3D-TEE during percutaneous mitral valve repair**

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Purpose: Percutaneous mitral valve repair with the Clip device can reduce mitral regurgitation by improving coaptation of the leaflet and will result in a reduction of effective mitral valve area. To prevent complications and achieve optimal clinical outcomes, intraprocedural monitoring for significant stenosis is mandatory. While transvalvular gradients measured with continuous Doppler are used routinely, the value of 3D planimetry of the valve area has not been examined conclusively despite being recommended as the standard modality for native valve stenosis.

Methods: Echocardiographic intraprocedural data from 130 consecutive patients undergoing Clip-therapy were analyzed retrospectively with 3D software tools. Mitral valve area was determined by planimetry of each individual orifice for 3D MVA and each color Doppler jet for vena contract area (3D VCA). Follow up TTE and TEE were reviewed for gradients.

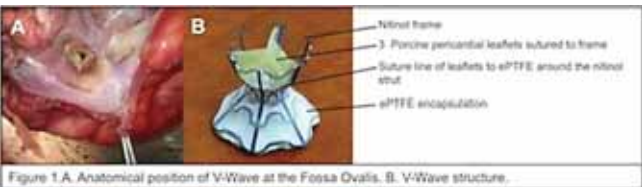
Results: Of 130 patients had 88 had 1 Clip, 34 had 2 Clips, 3 Clips were implanted in 3 patients and 1 patient had 4 Clips implanted. Four patients had no Clip implanted after showing signs of significant stenosis with temporary clip placement. All 4 had 3D MVA <1.5 cm² with 3D planimetry. Of the remaining 126 Patients, 19 had mean Gradients above 5 mmHg at discharge or in follow-up. MVA analysis yielded MVA <2 cm² in 11 of 19 patients using the pressure half time method and in 14 of 19 using 3D planimetry. 20 Patients had an intraprocedural mean gradient of 5 mmHg or greater. 35% of these patients however had gradients below 5 mmHg at discharge and in follow-up. The patients with low gradients after the procedure had higher heart rates (81 vs. 69 bpm), and mitral valve areas in both PHT-MVA (2.15 vs. 1.97 cm²) and 3D MVA (1.83 vs 1.77 cm²). After Clip-Implantation the residual mitral valve area measured during the procedure was 2.21±0.84 cm² with 3D planimetry (3D MVA) vs. 2.33±0.83 cm² for the pressure half time method (p=0.170). Intraprocedural mean gradients increased significantly from 2.86±1.63 mmHg to 3.68±1.82 mmHg at discharge (p<0.001) and then remained stable in follow up (3.48±1.87 mmHg; p=0.75).

Conclusion: As Doppler gradients are influenced by heart rate and hemodynamic situation, 3D- planimetry can be helpful during PMVR to assess the probability of significant stenosis. Gradients at discharge are generally higher than during the procedure. When borderline doppler results are obtained or patients have bradycardia, 3D planimetry of the mitral valve area should therefore be considered as an alternative and possibly more sensitive method.

2214 | BEDSIDE
Left atrial decompression through left-to-right interatrial shunt for the treatment of left cardiac heart failure: first-in-man experience with the V-Wave device

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Background: Elevated filling pressure of left atrium (LA) is associated with poorer outcomes in patients with chronic heart failure. The V-Wave is a new device (Fig. 1) intended to decrease LA pressure by shunting of blood from LA to right atrium (Table 1A).



Methods: Two patients with left ventricular dysfunction and NYHA class III despite optimal treatment, pulmonary wedge> 18mmHg and no right heart dysfunction were planned for FIM V-Wave experience.

Results: The patients were treated successfully. Left-to-right shunt was verified postprocedurally and at 3-month by TEE (Results in Table 1B).

Table 1				
A. Procedural steps:				
1. Venous femoral approach;				
2. Transeptal puncture;				
3. V-Wave implantation at the fossa ovalis (14 French sheath).				
B. Main data at baseline and follow-up of the first patient treated with V-Wave				
Parameters	Patient 1		Patient 2	
	Baseline	3-month FU	Baseline	1-month FU
Qp/Qs	1.00	1.17*	0.9	1.1*
Wedge	19	8	19	14*
NYHA functional class	III	II	III	II
Duke activity status index, %	32.2	38.2	10.7	26.95
Kansas city Cardiomyopathy Questionnaire	39.06	77.6	40.62	72.92
NTproBNP, ng/mL	502	322	8986	6750

Conclusions: Decompression of LA through left-to-right shunt with the V-Wave device is feasible in humans. Complete results of the V-Wave FIM experience (5 patients) will be presented at the meeting.

2215 | BEDSIDE
2-year clinical outcome after left atrial appendage closure with the amplatzer cardiac plug device in patients with non-valvular atrial fibrillation and contraindications for anticoagulation therapy

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Introduction: Left atrial appendage (LAA) closure can be an attractive option for patients with non-valvular atrial fibrillation (NVAf) with contraindication to anti-coagulants. The aim of this study is to observe the rate of stroke and bleeding events in a 2-year follow-up period after LAA closure with the Amplatzer Cardiac Plug device.

Methods: A multicenter retrospective registry was made of 167 consecutive patients after ACP implantation in 12 hospitals in Spain (10) and Portugal (2). Procedural was successful in 158 patients (94.6%). The incidence of stroke and major bleeding so as ecocardiographic findings was evaluated over a 2-year follow-up period after implantation.

Results: Mean age was 74.7±8.6 years. 61.1% were males. Median CHADS2 and HASBLED scores were 3 (2-4) and 3 (3-4). LAA closure indications were: gastrointestinal bleeding in 30.5%, intracranial hemorrhage in 22.8%, other hemorrhages in 16.8%, thromboembolic events under anticoagulant therapy in 7.2%, high-risk of bleeding in 4.2% and others in 19.2%. The observed 24-month rates of stroke and major bleeding events were 63% and 54% lower than expected according to CHADS2 and HASBLED scores (4.4 vs 12%; p=0.001 and 5.7 vs 12.5%; p=0.002).

2-year clinical and ecographic findings	
24-month clinical follow-up	158 patients
Death	17 (10.8%)
Major bleeding	9 (5.7%)
Significant non-major (relevant) bleeding	7 (4.4%)
Any bleeding	16 (10.1%)
Stroke	7 (4.4%)
Any event	30 (19.0%)
Ecographic findings during follow-up	
Device thrombosis	13 (8.2%)
Atrial septal defect	18 (11.4%)
Leak (<3mm)	13 (8.2%)

Conclusion: Reductions in stroke and bleeding events after LAA closure become evident from the first year onwards. This could be explained by the formation of thrombi on the device in the first months in the case of stroke, and by the bleeding events more often during the first year, with a rate that is very similar to anticoagulant treatment in elderly patients.

2216 | BENCH
Treatment of severe mitral stenosis with percutaneous balloon commissurotomy in pregnant patients in a tertiary Tunisian center of cardiology

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Pregnancy can cause life-threatening complications in women with mitral stenosis. Frequently, there is an urgent need to increase the mitral valve area mechanically.

In selected cases, percutaneous mitral balloon commissurotomy (PMBC) has emerged as a safe and effective alternative to surgical commissurotomy.

Aim: To present our experience of PMBC by the Inoue technique in sixteen pregnant patients with severe symptomatic mitral stenosis.

Methods: During 15 years, in our department, 379 PMBC were successfully performed in women, 16 of them pregnant at around 24 weeks of gestation. The patients were in New York Heart Association (NYHA) functional class III or IV who did not respond positively to drug treatment.

Results: Percutaneous mitral commissurotomy was performed in 16 pregnant females aged 33±5.03 years (range 23-38 years) with severe mitral stenosis at around 24 weeks of gestation. All patients were in New York Heart Association functional class III or IV at the time of procedure. After the procedure, all patients showed marked immediate clinical and hemodynamic improvement, NYHA functional class I- II. After dilatation, the mean left atrial pressure decreased from 28±6.53 to 13±4.85 mmHg (p=0.037), the mitral valve pressure gradient decreased from 21±5.88 to 7.5±5.34 mmHg (p=0.015) and the calculated mitral valve area increased from 1±0.18 to 2±0.37 cm². During the procedure, there were no maternal or fetal complications. All patients had uneventful term deliveries of normal babies. In follow up, one patient who had moderate mitral regurgitation after valvuloplasty developed severe mitral regurgitation, requiring surgical correction after 4 years and another patient developed restenosis requiring a second PMBC.

Conclusions: Percutaneous mitral balloon commissurotomy is a safe and effective procedure for selected pregnant patients with severe mitral stenosis who are refractory to medical treatment. Severe mitral regurgitation requiring immediate surgery may occur occasionally. The possible harmful effects to the fetus from its exposure to radiation during PMBC are unknown

NOVEL CONCEPTS IN HEART FAILURE THERAPY

2221 | BEDSIDE

Riociguat for heart failure with secondary pulmonary hypertension: post-hoc analysis of the LEPHT study

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Purpose: Selective pulmonary vasodilation in patients with pulmonary hypertension due to systolic LV dysfunction (PH-sLVD) may result in adverse increases in PCWP when PVR is elevated. This exploratory post-hoc analysis of the LEPHT study compared the effects of the novel soluble guanylate cyclase stimulator, riociguat, in PH-sLVD patients with PVR ≤ 240 vs >240 dyn-s/cm⁵ at baseline.

Methods: 201 patients with systolic HF and mPAP ≥ 25 mmHg were randomized to riociguat (0.5, 1, or 2 mg tid) or placebo for 16 wks.

Results: Ischemic etiology (57 vs 30%) and diabetes mellitus (51 vs 34%) were more frequent in patients with PVR >240 dyn-s/cm⁵ at baseline; other baseline characteristics were well balanced between subgroups. At Wk 16, riociguat 2 mg decreased SVR in patients with low PVR and high PVR at baseline (Table). Riociguat 2 mg was associated with a significant decrease in PCWP in the low PVR subgroup and no significant changes in PCWP in patients with high baseline PVR. Riociguat 2 mg also significantly increased stroke volume and pulmonary artery compliance (PAC), and improved MLHF questionnaire score in the low PVR subgroup at Wk 16. The relationship between PAC and PVR showed a favorable shift with riociguat 2 mg in the low PVR subgroup.

Conclusion: Improvements in hemodynamics and QoL with riociguat were greater in PH-sLVD patients with low baseline PVR than those with high baseline PVR.

2222 | SPOTLIGHT

Pro-atrial natriuretic peptide1-126: a novel guanylyl cyclase-A activator with selective renal enhancing and cardiac unloading properties which goes beyond carperitide and nesiritide

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Purpose: The atrial natriuretic peptide (ANP) precursor proANP1-126 is produced in the atria and processed to mature ANP1-28 (carperitide) which activates the guanylyl cyclase receptor-A (GC-A) and its second messenger cGMP. ProANP1-126 is found in the human circulation and we previously reported that proANP1-126 activates GC-A in vitro and is processed into ANP1-28 in human circulation, but its in vivo bioactivity is undefined. We sought to determine if proANP1-126 is biologically active in vivo compared to other GC-A agonists carperitide and nesiritide (BNP) currently approved for human heart failure.

Methods: We investigated the in vivo actions of proANP1-126 compared to carperitide, nesiritide or placebo in normal canines (667 pmol/kg bolus injection, n=5/group). Circulating ANP or BNP and cGMP levels, hemodynamic and renal functions were determined over 180 min. *p<0.05 vs placebo, †p<0.05 vs carperitide, ‡p<0.05 vs nesiritide.

Results: ProANP1-126 administration had a significantly longer half-life (23.9 min†) than carperitide (ANP, 10.6 min) or nesiritide (BNP, 8.2 min). At 180 min, only proANP1-126 significantly increased urine volume (176.1 ml†) and urinary sodium excretion (20.8 mEq†) with enhanced tubular actions compared to placebo (44.7 ml, 6.0 mEq) but not carperitide (57.0 ml, 8.2 mEq) or nesiritide (68.1 ml, 12.3 mEq). Nesiritide markedly decreased mean arterial pressure (-22.6 mmHg*) and increased cardiac output (+2.3 l/min*) greater than proANP1-

126 (-12.2 mmHg, +0.7 l/min) or carperitide (-12.3 mmHg, +0.4 l/min) after 5 min from administration. ProANP1-126 (-3.72 mmHg at 90 min†) and nesiritide (-3.14 mmHg at 10 min) had sustained decreases of pulmonary capillary wedge pressure, but not carperitide (-1.0 mmHg at 20 min).

Conclusions: The GC-A activator proANP1-126 represents a unique renal enhancing and cardiac unloading peptide with longer half-life than the other GC-A activators, carperitide or nesiritide. The current findings supports the novel concept of proANP1-126 as a key circulating natriuretic peptide in cardiorenal homeostasis as well as a potential innovative therapeutic beyond carperitide or nesiritide for cardiorenal diseases.

2223 | BEDSIDE

Presence of high renal arterial resistance index is independently associated with the increase of loop diuretic dose in heart failure outpatients

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The aim of this study was to evaluate whether abnormalities in Renal Resistance Index (RRI), a parameter reflecting renal perfusion, are associated to changes in diuretic therapy in a group of chronic heart failure (CHF) outpatients.

We enrolled 188 outpatients (77% males, 65±14 years, NYHA class 2.3±0.6, left ventricular ejection fraction, LVEF, 34±10%) with CHF, in stable clinical conditions (>1 month), who were taking loop diuretics. Peak systolic velocity and end diastolic velocity of segmental renal artery was obtained by pulsed Doppler flow and RRI was then calculated. Furosemide equivalent dose was evaluated at baseline and after 1 year. During the study, it was prescribed the minimum furosemide dose able to keep patients in stable clinical conditions.

The mean diuretic dose increased from 71±71 to 85±104 mg/die and 35 patients (18%) needed an increase of diuretic dose $\geq 50\%$. Baseline diuretic dose was not different when groups with and without diuretic dose increase were compared (77±72 vs. 71±73 mg/die, p:0.63). At univariate regression analysis RRI was associated with 1-year increase $\geq 50\%$ (p<0.001) and it remained significantly associated (p:0.042) in a multivariate model including the other univariate predictors, i.e. LVEF, peak of tricuspid annulus excursion, estimated central venous pressure, NT-proBNP and GFR-EPI. Figure 1 shows as a RRI ≥ 71 was associated both to a significantly higher baseline diuretic dose and to its increase at 1 year.

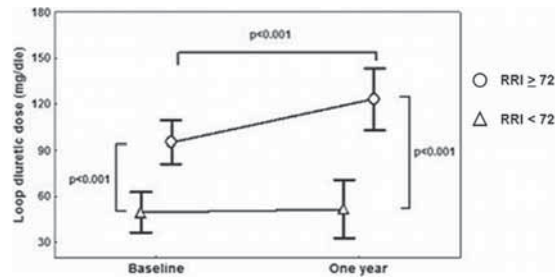


Figure 1

In conclusion, our findings demonstrate that an altered RRI, which reflects abnormal renal perfusion, is associated both to higher baseline loop diuretic dose and to its significant increase over 1 year, thus suggesting its possible clinical usefulness in order to better detect patients prone to develop diuretic resistance.

2224 | BEDSIDE

Efficacy and safety of different types of bronchodilator therapy in patients with chronic heart failure due to coronary artery disease combined with chronic obstructive pulmonary disease

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Purpose: To compare clinical efficacy and safety of indacaterol and tiotropium administration in patient with chronic heart failure due to coronary artery disease combined with chronic obstructive pulmonary disease.

Abstract 2221 – Table 1. Least-squares mean difference (95% CI) of selected parameters at Wk 16: riociguat 2 mg vs placebo

LS mean difference (95% CI) [No. of pts (riociguat 2 mg/placebo)]	Overall ^a	PVR ≤ 240 dyn-s/cm ⁵	PVR >240 dyn-s/cm ⁵
Stroke volume (SV), mL	11.3 (4.9 to 17.6)	17.5 (6.9 to 28.1) n=22/25	6.8 (-0.7 to 14.4) n=32/31
Cardiac index, L/min/m ²	0.4 (0.2 to 0.5)	0.6 (0.3 to 0.9) n=22/25	0.2 (-0.02 to 0.4) n=32/31
Systemic vascular resistance (SVR), dyn-s/cm ⁵	-239 (-363 to -115)	-282 (-466 to -98) n=21/25	-209 (-385 to -33) n=32/31
Pulmonary capillary wedge pressure (PCWP), mmHg	-2.1 (-5.0 to 0.8)	-6.5 (-10.6 to -2.4) ^b n=22/25	1.2 (-2.5 to 5.0) ^b n=31/31
Pulmonary artery compliance (PAC), mL/mmHg	0.9 (0.4 to 1.5)	1.7 (0.9 to 2.6) ^c n=22/25	0.4 (-0.2 to 1.0) ^c n=32/30
Minnesota Living with Heart Failure (MLHF) total score ^d	-8.2 (-13.3 to -3.1)	-12.0 (-21.1 to -2.8) n=27/30	-6.1 (-12.3 to 0.1) n=40/39

All data are from the per-protocol population unless stated otherwise. ^aCombined PVR subgroups; ^bp<0.05 for interaction (low PVR and high PVR vs treatment [placebo and riociguat 2 mg]); ^cp<0.005 for interaction (low PVR and high PVR vs treatment [placebo and riociguat 2 mg]); ^dintention-to-treat population.

Methods: After enrollment in this trial 124 patients (87 men and 37 women), aged 65.2 ± 6.9 years, with CHF classes II to III (New York Heart Association) combined with moderate to severe COPD (GOLD-2011) and with initial ejection fraction of the left ventricle (LVEF) less than 45%, were randomized into three groups – tiotropium (18 μ g daily, n=41), indacaterol (150 μ g daily, n=40) and tiotropium+indacaterol group (18/150 μ g daily, n=43). Patients of all groups received the complex CHF treatment comprising diuretics, nebivolol, losartan, cardiac glycosides (if necessary) and basic COPD therapy (inhalation corticosteroids). Echocardiography, exercise tolerance (6-min walk distance), 24-hour electrocardiography and blood pressure monitoring were assessed at baseline and after 6 months of treatment, respiratory function test was assessed at baseline, after 1 month and after 6 months. The quality of life was evaluated by MY-HFQ, SGRQ and mMRC.

Results: After 6 months of therapy the improvement of clinical condition and quality of life were marked in all groups. In 1st, 2nd and 3rd group LVEF was increased by 7.6%, 6.1% and 12.0%, pulmonary hypertension decreased by 8.5%, 9.3% and 17.0%, episodes of silent myocardial ischemia decreased by 15%, 16.9% and 21.9%, respectively. Towards the end of the observation period, in all groups there was a confident and authentic increase of forced expiratory volume during 1st second (FEV1) which made 5.0%, 8.8%, and 12.0% accordingly. 6-min walk distance increased by 18.7%, 23.1% and 29.8% accordingly. Patients showed statistically significant and clinically meaningful reduction of SGRQ score (16.6%, 20.4%, 25.0%) and MYHFQ score (27.9%, 24.9%, 32.0%), significant improvements in MMRC dyspnea grade (22.1%, 25.2%, 28.5% respectively). All treatments were well tolerated.

Conclusions: The tiotropium and indacaterol inclusion in the structure of complex therapy in patients with CHF combined with COPD raises efficiency of treatment, improves quality of life, basic parameters of central hemodynamics and pulmonary function. Efficacy of long-acting inhaled anticholinergic agent (tiotropium) and long-acting β -agonist (indacaterol) in patient with CHF due to CAD combined with COPD are similar. Combination of these drugs significantly enhances the positive effects of the therapy.

2225 | BEDSIDE

Carvedilol vs. metoprolol succinate and risk of mortality in patients with heart failure: national cohort study

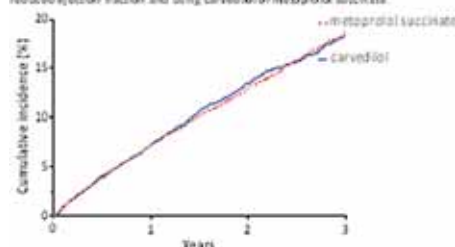
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Purpose: Carvedilol and metoprolol succinate both reduce mortality in patients with heart failure (HF), but the comparative clinical effectiveness of these drugs is unknown. We tested the hypothesis that carvedilol is superior to metoprolol succinate.

Methods: From a Danish national HF registry linked with health care and administrative databases, we identified a cohort of patients with incident HF with reduced left ventricular ejection fraction (LVEF; $\leq 40\%$) who received carvedilol (n=6026) or metoprolol succinate (n=5638). All-cause (primary outcome) and cardiovascular mortality (secondary outcome) at up to 3 years follow-up were analyzed using Cox regression with propensity score-adjustment.

Results: Patients were mean 69.3 (SD 9.1) years, 71% were men, and 51% were admitted to hospital at index HF diagnosis. During median 2.4 (IQR 1.0-3.0) years of follow-up, 875 carvedilol users and 754 metoprolol users died; the cumulative incidence of mortality was 18.3% and 18.8%, respectively. The adjusted hazard ratio (aHR) for carvedilol vs. metoprolol was 0.99 (95% CI 0.88-1.11); the corresponding absolute risk difference was -0.07 (95% CI -0.84 to 0.77) deaths per 100 person-years. Estimates were consistent across subgroup analyses by sex, age, levels of LVEF, NYHA class, and history of ischemic heart disease. A higher proportion of carvedilol users achieved the recommended daily target dose (50 mg; 3124 [52%]) than did metoprolol users (200 mg; 689 [12%]); among patients who reached the target dose, the aHR was 0.97 (95% CI 0.72-1.30). The aHR for cardiovascular mortality was 1.05 (95% CI 0.88-1.26).

Cumulative incidence of all-cause mortality among patients with heart failure with reduced ejection fraction and using carvedilol or metoprolol succinate.



Conclusions: These findings from real-world clinical practice indicate that the effectiveness of carvedilol and metoprolol succinate in patients with HF is similar.

2226 | BEDSIDE

Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial

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Purpose: Intravenous loop diuretics are a cornerstone of therapy in acutely decompensated heart failure (ADHF). We sought to determine if there are any differences in clinical outcomes between intravenous bolus and continuous infusion of loop diuretics.

Methods: Subjects with ADHF within 12 hours of hospital admission were randomly assigned to continuous infusion or twice daily bolus therapy with furosemide. There were 3 co-primary endpoints assessed from admission to discharge: the mean paired changes in serum creatinine and estimated glomerular filtration rate (eGFR), and reduction in B-type natriuretic peptide (BNP). Secondary endpoints included the rate of acute kidney injury (AKI) change in body weight and six months follow-up evaluation after discharge.

Results: A total of 43 received a continuous infusion and 39 were assigned to bolus treatment. At discharge, the mean change in serum creatinine was higher ($+0.8 \pm 0.4$ vs. -0.8 ± 0.3 mg/dl $p < 0.01$), and eGFR was lower (-9 ± 7 vs. $+5 \pm 6$ ml/min/1.73m² $p < 0.05$) in the continuous arm. There was no significant difference in the degree of weight loss (-4.1 ± 1.9 vs. -3.5 ± 2.4 kg $p = 0.23$). The continuous infusion arm had a greater reduction in BNP over the hospital course, (-576 ± 655 vs. -181 ± 527 pg/ml $p = 0.02$). The rates of AKI were comparable (22% and 15% $p = 0.3$) between the two groups. There was more frequent use of hypertonic saline solutions for hyponatremia (33% vs. 18% $p < 0.01$), intravenous dopamine infusions (35% vs. 23% $p = 0.02$), and the hospital length of stay was longer in the continuous infusion group (14. 3 ± 5 vs. 11.5 ± 4 days, $p < 0.03$). At 6 months there were higher rates of re-admission or death in the continuous infusion group, 58% versus 23%, ($p = 0.001$) and this mode of treatment independently associated with this outcome after adjusting for baseline and intermediate variables (adjusted hazard ratio=2.57, 95% confidence interval, 1.01-6.58 $p = 0.04$).

Conclusions: In the setting of ADHF, continuous infusion of loop diuretics resulted in greater reductions in BNP from admission to discharge, however, this appeared to occur at the consequence of worsened renal filtration function, use of additional treatment, and higher rates of rehospitalization or death at six months.

PROTECTING THE HEART

2235 | BENCH

Pharmacological characterization and elucidation of the molecular mechanism of action of a novel purine analogue which has superior effects to ischemic postconditioning

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Introduction: We have previously shown that purine analogues designed as potential NO donors were cardioprotective in sustained ischemia (isc) and reperfusion (rep). The novel purine analogue 6-[4-(6-Nitroxyhexanoyl)piperazin-1-yl]-9H-purine (MK118) resulted in a greater reduction of infarct size compared to ischemic postconditioning (PostC).

Purpose: Pharmacological characterization of MK118 and elucidation of the molecular mechanism which is responsible for the enhanced reduction of the infarct size.

Materials and methods: During the initial pharmacological characterization of MK118, we determined the cGMP levels in smooth muscle cells in the absence of a phosphodiesterase inhibitor, after exposure to different concentrations (ranging from 1-500 μ M) of MK118 and of Diethylenetriamine NONOate (DETA NONOate) and sodium nitroprusside (SNP) which are very potent NO donors. For the in vivo evaluation of the underlying cardioprotective mechanism, male rabbits were subjected to 30 min regional isc of the heart followed by 3 hours rep and divided into 6 groups: 1) Control, with no further intervention, 2) PostC, with 8 cycles of 30 sec isc/ 30 sec rep, 3) MK118 (iv bolus at the 20th min of isc and the 1st min of rep in a total dose of 3.8 μ mol/kg), 4) MK118 plus the NOS inhibitor L-NAME (10mg/kg iv as bolus at the 19th min of isc), 5) MK118 plus the PI3K inhibitor Wortmannin (60 μ g/kg iv as bolus at the 19th min of isc) and 6) MK118 plus the adenosine receptor inhibitor SPT (10mg/kg iv as a bolus 20 min before isc). The infarct size (I) was estimated as % of the area at risk (R). In a second series of experiments, animals were subjected to 30 min of isc followed by 10min of rep when myocardial tissue samples were excised for determination of eNOS, Akt, GSK3 β and STAT3.

Results: In vitro exposure of cultured smooth muscle cells to MK118 did not change cGMP levels, unlike the effect seen with DETA NONOate and SNP that led to enhanced cGMP levels. L-NAME and SPT did not alter the infarct limiting effect of MK118 ($15.9 \pm 1.5\%$, $13.8 \pm 1.4\%$ vs $13.4 \pm 1.9\%$, respectively, $p = \text{NS}$), whilst inhibition of PI3K by wortmannin abrogated it ($34.04 \pm 1.9\%$, $p < 0.05$). eNOS and

Akt were similarly activated in MK118 and in PostC groups but not in controls. MK118 and PostC also caused similar phosphorylation of GSK3 β and STAT3.

Conclusion: MK118 significantly reduces infarct size compared to PostC. This cardioprotective effect is related to Akt and STAT3 activation, as well as GSK3 β inhibition and is independent of NO release, endogenous NO production and adenosine receptor activation.

2236 | BENCH

Phospholamban is a final effector of ischemic postconditioning and H2S induced cardioprotection

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Background: The novel gasotransmitter hydrogen sulfide (H₂S) has been shown to inhibit phosphodiesterase activity, increase cGMP levels and activate cGMP-dependent protein kinase (PKG), leading to vasodilation and angiogenesis. Protection by postconditioning (PostC) in the heart involves the activation of the cGMP/PKG pathway that, in turn, reduces apoptosis and inhibits mitochondrial permeability transition pores (mPTP), caused by increased intracellular Ca²⁺. Preliminary data from our group showed that exogenous administration of H₂S induces pharmacological postconditioning through the activation of the PKG.

Purpose: As phospholamban (PLN) regulates cytosolic Ca²⁺ levels, we sought to determine the role of PLN in ischemic PostC and in H₂S-induced pharmacological PostC.

Methods: Twenty three wild type Sv129J and twenty one PLN(−/−) homozygous knockout mice of both sexes were subjected to 30 minutes regional ischemia (isc) of the heart followed by 2 hours of reperfusion (rep). Wild type and PLN(−/−) animals were divided in three subgroups with the following additional interventions: 1) Control, no further intervention, 2) NaHS group, administration of NaHS as a bolus dose of 100 μ g kg^{−1} at the 20th minute of sustained isc and 3) PostC group, application of 3 cycles of 10 seconds isc - 10 seconds rep immediately after prolonged isc. The infarct size (I) and the area at risk (R) were estimated in percent (%).

Results: No significant differences were detected in the (R) among the studied groups. Control wild type had similar %I/R compared to PLN(−/−) control animals (42.1 $\pm$ 2.6% vs 38.0 $\pm$ 2.9%, p=NS). In wild type animals, PostC application and NaHS administration conferred a significant benefit compared to control (14.9 $\pm$ 2.1% and 15.5 $\pm$ 1.2% respectively vs 42.1 $\pm$ 2.6%, p<0.05). However, neither PostC nor NaHS conferred cardioprotection in PLN(−/−) animals (45.2 $\pm$ 2.1% and 42.2 $\pm$ 1.5% respectively, p<0.05 vs wild type PostC and NaHS groups).

Conclusion: Our findings suggest that ischemic and pharmacological postconditioning induced by H₂S administration requires PLN activation.

2237 | BENCH

Concomitant therapy with vagal nerve stimulation (VNS) and total flow support of left ventricular assist device (LVAD) maximally suppresses the infarct size in ischemia reperfusion (IR) model

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Purpose: Even the recent advances in the management of acute myocardial infarction cause the inevitable loss of myocardium, which impairs cardiac function and leads to worsening heart failure in the long term. It has been established that LVAD reduces the infarct size in IR model as well as VNS. In this study, we investigated how the combination of VNS with LVAD impacts on reducing the infarct size in IR dogs.

Methods: We allocated 17 anesthetized dogs into 4 groups, Control (n=5), VNS (n=4), LVAD (n=4) and VNS+LVAD (n=4). After a median sternotomy, we ligated the major branches of the left anterior descending coronary artery for 90 min and reperused for the following 300 min. We titrated the amplitude of VNS to lower heart rate by 10-20%. We set the LVAD flow to create a totally LVAD-dependent circulation where LV no longer ejects. We performed each treatment from the beginning of ischemia and assessed the infarct size (normalized by the risk area) at the end of the reperfusion.

Results: Mean aortic pressure did not differ among 4 groups (Control: 91 $\pm$ 6.1, VNS: 95 $\pm$ 12, LVAD: 102 $\pm$ 7.0 and VNS+LVAD: 97 $\pm$ 4.9mmHg). Left atrial pressure was much lower in LVAD and VNS+LVAD (Control: 13 $\pm$ 1.7, VNS: 9.9 $\pm$ 1.7, LVAD: -1.6 $\pm$ 1.6, VNS+LVAD: 0.0 $\pm$ 0.85mmHg, p<0.0001). VNS and LVAD significantly reduced the infarct size (Control: 44 $\pm$ 2.4, VNS: 28 $\pm$ 2.1 and LVAD:

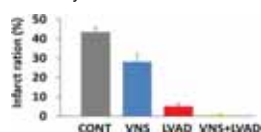


Figure 1. Infarct size/area at risk (%).

5.0 $\pm$ 1.6%, p<0.001), showing the % reduction relative to Control was 36% and 88%, respectively. However, VNS+LVAD further reduced and almost nullified the infarct size (0.55 $\pm$ 0.55%, p<0.0001).

Conclusion: The combination therapy of VNS with total flow support LVAD maximally suppresses the infarct size in IR model without compromising hemodynamics. It could serve as a powerful therapeutic strategy to preclude post MI heart failure.

2238 | BENCH

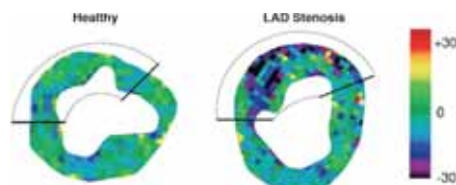
Administration of exogenous oxygen may worsen myocardial ischemia

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Purpose: It has been demonstrated that hypoxemia has a vasodilating effect on coronary arterioles. Although recent guidelines limit the use of excessive oxygen concentrations after cardiac arrest, the impact of hyperoxemia on myocardial oxygenation is not well understood. Oxygenation-sensitive (OS) cardiovascular magnetic resonance (CMR) allows for monitoring gas-dependent changes in myocardial oxygenation.

Methods: An MRI-compatible flow probe was implanted on the proximal left anterior descending (LAD) coronary artery in 16 swine. In 8 animals an acute LAD stenosis was created with a hydraulic occluder. The severity of stenosis was assessed by measuring fractional flow reserve (FFR). Blood gases were set to physiologic levels (paO₂=100mmHg, paCO₂=40mmHg) and OS cine images were acquired using a clinical MRI system (3T). Measurements were repeated after paO₂ was increased to 300mmHg. OS-CMR images were analysed in end-systolic frames.

Results: Mean FFR across the induced stenoses was 0.63 $\pm$ 0.02. During hyperoxemia, coronary blood flow was reduced by 14.8 $\pm$ 4.9% (p<0.05) in the control animals and by 15.6 $\pm$ 2.6% (p<0.01) in the animals with stenotic vessels. In OS-CMR images of animals without stenosis the +1.99 $\pm$ 0.94% change in signal intensity (SI) did not differ from the remote myocardium. In animals with induced stenosis SI decreased by 3.20 $\pm$ 2.23% in the LAD territory, as opposed to the increases in both the remote myocardium of the same animal (2.64 $\pm$ 1.45%) and the LAD territory of the healthy group (p<0.05).



Changes in signal (%) during hyperoxemia.

Conclusions: Hyperoxemia may lead to a net reduction of tissue oxygenation in myocardial segments with severe coronary artery stenosis. Therefore, in these patients, the administration of oxygen may have detrimental effects.

2239 | SPOTLIGHT

Complement factor 5 blockade reduces porcine myocardial infarction size and improves cardiac function

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Purpose: Inhibition of the complement system has proven beneficial in various animal species but not in clinical studies of myocardial infarction (MI). Coversin (Ornithodoros moubata complement inhibitor, OmCI) selectively blocks complement factor 5 (C5) activation and has been shown to dampen the inflammatory response in experimental sepsis. We hypothesized that correctly timed inhibition of C5 would reduce infarction size and improve ventricular function in a porcine model of MI.

Methods: Left anterior descending coronary artery was occluded for 40 min in 16 pigs (20 $\pm$ 1kg) and reperused for 240 min. Coversin or placebo was given intravenously 20 min after occlusion and throughout reperfusion. The extent of infarction was measured ex vivo as percentage of infarcted tissue in the area at risk using Evans blue and tetrazolium chloride staining, and magnetic resonance imaging (MRI). Tissue Doppler echocardiography was performed from apical 4-chamber view at baseline and end of reperfusion. Systolic displacement was measured as mean values from septal and lateral mitral annulus movements. Interleukin-1 β (IL-1 β) was analysed in myocardial microdialysis fluid. Values are presented as mean $\pm$ SD, and groups were compared with Student's t-test.

Results: Coversin significantly reduced MI by 39% (p<0.05, Fig. 1A) and increased systolic displacement by 31% (p<0.01, Fig. 1B). MRI correlated to histological findings (19% reduced infarction in left ventricle, R=0.92, p<0.01). IL-1 β

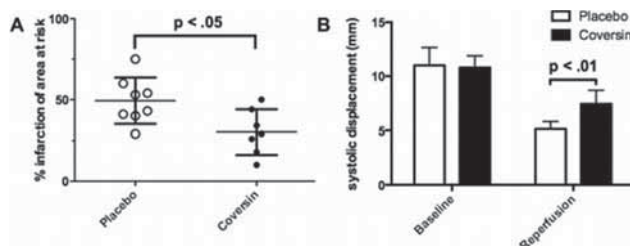


Figure 1. Effect of C5 blockade in MI.

was increased in the infarction area and was not different from baseline in coversin treated animals ($p < 0.05$).

Conclusions: Selective C5 inhibition reduced size of infarction and improved ventricular function in a MI pig model. Coversin may thus have potential as a therapeutic agent in MI.

2240 | BENCH

Preserved cardioprotective effect of ischemic preconditioning during mild hypothermia in isolated rat hearts

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Purpose: Ischemic preconditioning (IPC) and mild hypothermia (MH) reduce cardiac ischemia-reperfusion (IR) injury. Because patients with cardiac arrest due to acute myocardial infarction benefit from MH, we aimed to investigate whether the cardioprotective effect of IPC is preserved during MH.

Methods: Isolated rat hearts perfused a.m. Langendorff underwent 40 min stabilization/40 min global ischemia/120min reperfusion at 37 °C. IPC was induced by two cycles of 5 min IR. MH (34 °C) was induced during the whole ischemic period (MH-I), for the final 20 min of ischemia and through reperfusion (MH-I20), during reperfusion (MH-R) or during the total study protocol (MH-T). The cardioprotective effect was evaluated by hemodynamic recovery and infarct size (IS). To evaluate potential mechanisms we analyzed intermediary metabolism by microdialysis.

Results: MH reduced IS (Fig. 1) and improved hemodynamic recovery compared to normothermic controls when applied during ischemia, but not when applied during reperfusion alone. Addition of IPC further reduced IS significantly in all MH protocols. Although IS was consistently lower in all protocols combining IPC with MH during ischemia, MH did not significantly reduce IS over and above IPC alone (MH-I: $p = 0.34$, MH-I20: $p = 0.16$, MH-R: $p = 0.68$ MH-T: $p = 0.07$). During ischemia interstitial concentrations of lactate and purine metabolites were lowered by MH but not IPC.

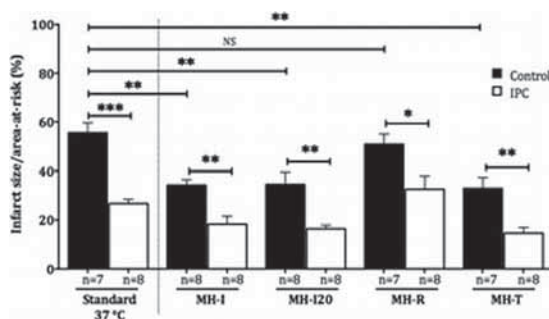


Figure 1. Infarct size.

Conclusion: The cardioprotective effect of IPC is preserved during MH and adds further protection to the cardioprotective effect of MH during ischemia. The additive cardioprotective effect and differences in metabolism during ischemia may reflect different cardioprotective targets by MH and IPC.

THE FUTURE IS NOW: CARDIOVASCULAR DISEASES IN THE ELDERLY

2249 | BEDSIDE

Centenarians and their heart: a prospective registry with comprehensive geriatric assessment, ECG, echocardiography, and follow-up

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Background: Data on the cardiac characteristics of centenarians are scarce. Our hypothesis is that the heart of a centenarian shows typical age-related anatomical and physiological changes. The aim of this study was to describe ECG, echocardiography, and blood test results in a cohort of centenarians and to correlate them

with survival and with clinical data obtained from the medical history and a comprehensive geriatric assessment.

Methods: Prospective multicenter registry of 118 centenarians (28 men and 90 women) with a mean age of 101.5 ± 1.7 years.

Results: Normal ECG recordings were more frequent in women (31.3% vs. 8.7%, $p = 0.01$). The mean duration of the PR interval was 195 ± 43 ms, 27 subjects (23%) presented atrial fibrillation or flutter, 15% had left and 9% right bundle branch block. Echocardiography was performed in 100 subjects (84.7%). Mean left ventricular (LV) dimensions were 4.0 ± 0.7 cm (end-diastolic) and 2.6 ± 0.7 cm (end-systolic). Mean LV ejection fraction was $60.0 \pm 10.5\%$. Mean LV posterior wall thickness was 1.1 ± 0.19 cm. The most frequent valve disease was aortic regurgitation, which was present in 49% (36 mild, 11 moderate, and 2 severe). Moderate or severe valve aortic stenosis was found in 16% and mitral insufficiency in 15%. Diastolic dysfunction was assessed in 79 subjects, 55 of whom (69.6%) presented it. The variables independently associated with the ability to walk 6 m were nutritional assessment and LV dilation. All subjects underwent a complete follow-up for at least 6 months. Independent predictors of mortality were age, aortic regurgitation, and the Charlson and Katz indexes.

Conclusions: Our results add to our knowledge of cardiac anatomy and function in centenarians and, thus, help us to better understand the process of aging and exceptional longevity. Most centenarians have ECG alterations, and abnormalities in echocardiography are almost universal. One-fifth present atrial fibrillation, and most have echocardiographic evidence of diastolic dysfunction and left atrial enlargement. LV dilation was present in 14% and was independently associated with the ability to walk 6 meters. Aortic regurgitation was found in 49% and was associated with mortality. Our data suggest an age-related effect on the heart that influences functional status and prognosis. This effect should be taken into account in the development of possible strategies to prevent or mitigate it.

2250 | BEDSIDE

Self-detection of atrial fibrillation in aged population - 1-year follow-up of LietoAF study

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Background: Disabling stroke is often the first manifestation of atrial fibrillation (AF) in older subjects. Our objective was to assess motivation and capability of older people to learn pulse palpation and continue regular pulse measurements, and to evaluate whether this kind of self-assessment is helpful to detect silent AF.

Methods: A total of 205 persons aged ≥ 75 years were randomly selected to participate in the programme where a trained nurse gave a maximum of ten minutes individual education on pulse palpation. The success of training and outcome events were evaluated during follow-up at 1, 4 and 12 months.

Results: A total of 139 subjects (68%) learned the pulse palpation and performed regular palpation during the 1 month follow-up period. Their motivation to regular daily pulse palpation gradually declined from 86% at 4 months to 10% at 12 months of follow-up. During the 1 year follow-up, new AF was found in 5, intermittent advanced atrioventricular block leading later to pacemaker implantation in 2, stroke/transient ischemic attack in 6, and death in 4 subjects. These outcome events were more common (15.8 vs 1.7%, $p = 0.001$) in the 57 patients who observed irregular pulse during the follow-up.

Conclusion: A simple nurse-based education is effective in training of pulse palpation to active older people. The motivation to continue regular pulse palpation and to react to self-detected pulse irregularities is challenging.

2251 | BEDSIDE

Stroke and bleeding in super-elderly patients with atrial fibrillation: From one-year follow-up of the Fushimi AF Registry

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Purpose: Atrial fibrillation (AF) is a common arrhythmic disorder among the elderly, and is increasing significantly as the population ages (reportedly 0.6% of total population in Japan). However, data regarding super-elderly AF patients (≥ 85 years of age) are quite limited. The purpose of this study is to investigate the one-year outcomes of super-elderly patients in the Fushimi AF Registry.

Methods: The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all of the AF patients in Fushimi-ku, Kyoto, Japan. Fushimi-ku is densely populated with a total population of 283,000, and is assumed to represent a typical urban community in Japan. At present, we have enrolled 3,821 patients (1.3% of total population) from March 2011 to December 2013. We previously reported the baseline clinical characteristics, and here we report the one-year outcomes of 2,966 patients. We divided the entire cohort into two groups, super-elderly group (≥ 85 years of age; $n = 443$, 14.9% of total) and others ($n = 2,523$).

Results: Elderly patients were more often female (65.7% vs. 36.0%), more lightweight (body mass index 21.0 vs 23.3), and had higher CHADS2 score (2.82 vs. 1.92; $p < 0.01$). Heart failure and previous stroke were more in super-elderly patients (41.3% vs. 24.4%; $p < 0.01$, and 29.8% vs. 17.5%; $p < 0.01$, respectively). Super-elderly patients experienced more episodes of major bleeding (4.5% vs. 1.6%; $p < 0.01$), and received lower warfarin prescription (39.1% vs.

52.2%; $p < 0.01$). During one-year follow-up, there were more stroke events in super-elderly patients (5.2% vs. 2.1%; $p < 0.01$), but there was no significant difference in bleeding (5.2% vs. 4.1%; $p = 0.31$). All-cause death and hospitalization for heart failure were more in super-elderly patients (20.8% vs. 5.9%; $p < 0.01$, and 7.2% vs. 3.5%; $p < 0.01$, respectively). Among super-elderly patients, those with oral anticoagulants paradoxically showed a trend toward increased stroke events compared with those without, although not statistically significant (7.5% vs. 3.7%; $p = 0.08$), whereas no significant difference in bleeding (5.2% vs. 5.2%; $p = 1.00$). In addition, stroke events were comparable between female and male patients (6.6% vs. 4.5%; $p = 0.37$), but bleeding was less in female patients (2.8% vs. 9.9%; $p < 0.01$).

Conclusions: Elderly patients with AF showed higher incidence of stroke, but no significant increase in bleeding, perhaps due to under-use and under-dose of oral anticoagulants in the real-world clinical practice.

2252 | BEDSIDE

Impact of statin therapy on cardiovascular outcomes after coronary revascularization in elderly patients: observations from the CREDO-kyoto registry cohort-2

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Background: Statin therapy has demonstrated the primary and secondary preventive effects in cardiovascular disease in middle-aged population. However, effects of statin therapy on cardiovascular outcomes in elderly population after coronary revascularization, especially in those aged over 80 years, have not been fully elucidated.

Methods: Among 14834 patients undergoing first coronary revascularization in 2005-2007 in the CREDO-Kyoto registry cohort-2, patients were divided into 2 strata based on the age and patients in each stratum were further divided into 2 groups based on the statin therapy at discharge; the ≥ 80 years old stratum: 2017 patients (statin group: N=765, non-statin group: N=1252) and the < 80 years old stratum: 12817 patients (statin group: N=6523, non-statin group: N=6294).

Results: Through 5-year follow-up, cumulative incidences of major adverse cardiovascular events (MACE: composite of cardiovascular death, myocardial infarction and stroke) were significantly lower in the statin group than in the non-statin group in both strata (23.4% vs 32.0%, $P = 0.0003$ in the ≥ 80 years old stratum and 11.5% vs 16.1%, $P < 0.0001$ in the < 80 years old stratum). After adjusting confounding factors, statin therapy significantly reduced the risk for MACE not only in those aged < 80 years (adjusted hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.74-0.91, $P = 0.0001$) but also in those aged ≥ 80 years (adjusted HR 0.77, 95% CI 0.63-0.93, $P = 0.009$). Statin therapy was also associated with significantly lower risks for all-cause death (adjusted HR 0.76, 95% CI 0.64-0.9, $P = 0.001$, in the ≥ 80 years old stratum and adjusted HR 0.77, 95% CI 0.69-0.86, $P < 0.001$, in the < 80 years old stratum) and cardiovascular death (adjusted HR 0.74, 95% CI 0.57-0.94, $P = 0.01$, in the ≥ 80 years old stratum and adjusted HR 0.76, 95% CI 0.65-0.89, $P = 0.0005$, in the < 80 years old stratum).

Conclusions: Statin therapy significantly reduced the risk for cardiovascular events even in the elderly individuals aged over 80 years. Statin therapy should be considered even in those elderly after coronary revascularization.

2253 | BEDSIDE

Age-gender interaction in the prediction of incident cardiovascular disease based on GFR in patients with CKD stages 1-2

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Background: We have recently demonstrated that worse renal function is associated with incident cardiovascular disease (CVD) in CVD naïve patients with CKD stages 1-2. However, whether this association exists in both genders in all age-groups is not known.

Aim: To examine the association between glomerular filtration rate (GFR) and incident CVD in men and women with CKD stages 1-2 and examine gender-age interactions, in a large, population-based cohort.

Methods: We analyzed all patients in a national database > 22 years with no prior CVD and with a glomerular filtration rate (GFR) > 60 and < 130 ml/min/1.73m². GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Incident CVD was defined as either myocardial infarction, unstable angina pectoris, coronary revascularization (percutaneous and coronary artery bypass graft), or cerebrovascular event. Incident CVD was analyzed separately in men and in women in 3 age-groups (young-22-40 years; middle-aged 41-60 years and elderly > 61 years).

Results: Our cohort included 43% males, with a mean age of 49.6 ± 17.0 years. During a median follow-up of 96.0 months and more than 10,000,000 years of follow-up, men had more incident CVD as compared to women (35,446 vs. 23,515 total incident CVD). Incident CVD was higher in men in all age groups (0.6% vs. 0.2% in young; 6.2% vs. 2.0% in middle-aged; 13.4% vs. 8.4% in elderly,

men vs. women, respectively). Adjusting for age, gender and CVD risk factors, an increment of 10 units in GFR was independently associated with a decrease of 5.7%, 4.1% and 5.7% in incident CVD in young, middle-aged and elderly men ($p < 0.001$ for all) and a decrease of 6.6%, 3.5% and 6.9% in the same age-groups in women ($p < 0.001$ for all).

Conclusion: Although incident CVD differs in men and women, as well as in different age groups, an increase in GFR even in the CKD 1-2 range is a prognosticator of reduced incident CVD in both genders and all ages.

2254 | BEDSIDE

Should we screen every patient aged 65 years and older for PAD? New results of the Hungarian ERV-registry

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Epidemiological data have shown that patients with clinical and preclinical stages of peripheral arterial disease (PAD) have high risk of cardiovascular mortality. The prevalence of PAD is increasing worldwide; therefore early diagnosis can be an important tool in cardiovascular prevention. By the measurement of the ankle-brachial index (ABI), PAD can be diagnosed in early asymptomatic stage in the primary care practice. Previous guidelines recommended ABI measurement in patients aged 70 years and older regardless of risk-factor status. The new ACC/AHA guideline for PAD recommends lowering the PAD detection age to 65 years, acknowledging that the ABI test would be used in an incrementally larger "at-risk" population. The objective of the present study was to evaluate the prevalence of low ABI in patients at age of 65 years and over in the ERV-registry. ABI measurement (calculated with the higher value at the ankle) was performed in 100 431 men and women (43 580 males; mean age: 59.2 years) in 295 primary care practice by trained nurses.

The prevalence of PAD (ABI ≤ 0.9) was 15.1%. In patients at age of 65 years and over the prevalence of low ABI (≤ 0.9) was 20%. In patients aged 70 years and older the prevalence of PAD was 22%.

The prevalence of PAD is high in patients at age of 65 years and over. ABI should be measured in patients who have exertional leg symptoms, non-healing wounds, in patients between the age of 50-64 and who have a cardiovascular risk factor and in patients aged 65 years and older, regardless of risk-factor status. ABI should become a routine measurement in the primary care practice for patients at risk.

ATRIAL FIBRILLATION: HOW TO IMPROVE THE OUTCOMES

2263 | BEDSIDE

A prospective study on safety of catheter ablation procedures: contact force guided ablation negates the risk of cardiac perforation and offers equal safety compared to magnetic navigation procedures

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Purpose: Contact force (CF) sensing catheters are becoming the standard for ablation procedures and provide advantages regarding safety and efficacy. This study aimed to evaluate if CF catheters reduce cardiac perforations and other major complications during ablation procedures and offer equal safety compared to the magnetic navigation system (MNS).

Methods: Data from 1,517 ablation procedures from our prospective registry were analyzed. Ablations were performed using either CF guided catheters (CF group, n=248), non-CF catheters (nCF group, n=813), or MNS (n=456). Four subgroups were analyzed: atrial fibrillation (AF, n=557), supraventricular tachycardia (SVT, n=715), ventricular tachycardia (VT, n=190) and pts with congenital heart defects (CHD, n=55). The primary endpoint of this study was incidence of cardiac perforation. Secondary endpoints were major complications (death, tamponade, major bleeding, thrombo-embolic event, permanent AV block) and minor complications (inguinal hematoma, temporary AV block) within 30 days of the procedure.

Results: Complications occurred in 11.3% (n=172) of the procedures. In 2.8% (n=43) a major complication occurred, 0.9% (n=13) had a perforation, 8.5% (n=129) had a minor complication and 2 pts died (0.1%). No cardiac perforation occurred in the CF group, which was significantly different from nCF procedures (0.0% vs. 1.6%; relative risk 0.76, 95% CI 0.74-0.79, $p = 0.031$) and equal to MNS (0.0%). This was also observed in the AF subgroup (0.0% vs. 3.3%; RR 0.67, 95% CI 0.63-0.72, $p = 0.021$), and the occurrence of major complications was lower for CF versus nCF procedures (2.1% vs. 7.8%, $p = 0.010$). For CF guided AF procedures the average force per RF application was 9.6 ± 4.3 g; the maximum force was 28.4 ± 14.5 g; the force-time integral was 300 ± 156 gs. For the SVT, VT and CHD subgroups perforation rates were not different between CF and nCF procedures (0.0% vs. 0.2%, $p = 0.883$; 0.0% vs. 3.0%, $p = 0.378$; 0.0% vs. 0.0%, $p = \text{NA}$, respectively).

Conclusion: CF-guided catheter ablation is superior to nCF and non-inferior to MNS procedures with regard to procedural safety and avoids cardiac perforation. This difference is due to a reduction of cardiac perforation and major complications in the AF subgroup.

2264 | BEDSIDE

Impact of hospital volume on complication rate of catheter ablation in patients with atrial fibrillation

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Purpose: Although catheter ablation of atrial fibrillation (AF) is commonly performed throughout the world, data regarding complication rates of the procedures are limited to those from high-volume centers. Moreover, previous data lacked information about the impact of hospital volume on complication rates in catheter ablation of AF. We therefore investigated the relationship between hospital volume and complication rate of AF ablation using a national inpatient database.

Methods: Using the Japanese Diagnosis Procedure Combination database between 2010 and 2013, we extracted AF patients who underwent catheter ablation. We performed multilevel logistic regression analyses fitted with generalized estimating equations because the data were clustered within hospital. Hospital volumes were categorized into quartiles (very low, 1-65 per year; low, 66-130; high, 131-246 and very high, ≥ 247). In-hospital death, stroke, esophageal perforation and pericardial effusion were defined as complications.

Results: Of 32574 AF patients, 460 patients experienced complication. Compared to the lowest-volume group, likelihood of complication for the highest-volume groups was significantly low [Odds ratio, 0.61; 95% confidence interval, 0.39-0.95].

	Odds ratio	95% confidence interval	
		Lower bound	Upper bound
Hospital volume	≥ 247	0.61	0.39
	131-246	0.85	0.50
	66-130	0.74	0.49
	1-65	1.00	0.
Age	≥ 75	2.68	1.77
	50-74	1.76	1.30
	1-49	1.00	4.06
			2.39
Female gender	1.14	0.94	1.37
Dialysis	2.30	1.50	3.52
Prior history of stroke	1.14	0.47	2.79

Conclusions: Patients who underwent AF ablation at the very-high-volume hospitals experienced significantly less complication than those at the very-low-volume hospitals. We need to consider regionalization of AF ablation to provide better quality of the procedures.

2265 | BEDSIDE

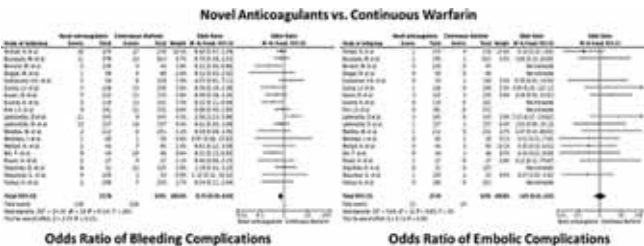
Novel oral anticoagulants vs continuous warfarin peri-ablation of atrial fibrillation: a meta-analysis of embolic and bleeding complications

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Introduction: Continuous warfarin (CW) has become a preferred peri-ablation strategy for pts with atrial fibrillation (AF). However, novel oral anticoagulants (NOAC) have overtaken W in the non-ablation setting. There are concerns that peri-AF ablation use of NOAC may be associated with worse outcome than CW, but individual studies may be too small given low procedural complication rates. More robust data analyses would be of great value.

Methods: We conducted a meta-analysis of all published papers (n=9) and abstracts (n=10) to date that compared complication rates for peri-AF ablation use of NOAC vs. CW. Bleeding complications included pericardial effusion, groin hematoma, GI bleeding and embolic complications included stroke/TIA or systemic embolism. We used the Mantel-Haenszel fixed effect model for pooling the study results, with a random effects model for heterogeneous samples/results.

Results: The 2578 pts on a NOAC (87.4% dabigatran) were similar to the 3291 pts on CW. NOAC were stopped 2.5-96 hrs pre- and restarted 1-48 hrs post-procedure. Composite bleeding rates were significantly lower in NOAC pts (5.35%) vs CW pts (6.87%), (OR 0.74, 95% CI 0.59-0.93; I² = 26%). Composite embolic rates were similar in both groups (0.50% in NOAC vs 0.43% in CW, OR 1.05, 95% CI 0.53-2.05; I² = 0%; Figure)



Conclusions: This meta-analysis demonstrates that NOAC are a legitimate alter-

native for peri-AF ablation anticoagulation. They are associated with a decrease in bleeding and no significant increase in embolic events compared to CW. However, a randomized study to evaluate the two anticoagulation strategies is needed, and to determine optimal time to discontinue and resume NOAC therapy.

2266 | BEDSIDE

Discontinuation period and periprocedural events of novel oral anticoagulation in patients undergoing catheter ablation of atrial fibrillation

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Introduction: The optimal strategy for periprocedural anticoagulant for radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF) is unknown, especially in patients receiving novel oral anticoagulant (NOAC).

Methods: The study included 596 patients with paroxysmal or persistent AF (446 males, 62 $\pm$ 11 years old) who underwent RFCA. Among them, 363 patients received warfarin (W group, 63 $\pm$ 10 years, 255 males, CHADS2 score 1.1 $\pm$ 1.0 points), and 233 patients received NOAC (Dabigatran in 198 patients and Rivaroxaban in 35 patients). All patients received NOAC or dose-adjusted warfarin for at least 1 month before RFCA. NOAC was discontinued on the evening before the procedure in 131 patients (NE group, 60 $\pm$ 11 years, 109 males, CHADS2 score 0.8 $\pm$ 0.9 points), or the morning of the procedure in 102 patients (NM group, 60 $\pm$ 10, 82 males, CHADS2 score 0.8 $\pm$ 0.8 points). Warfarin was continued at a maintenance dose (INR 2.0-3.0) during and after RFCA. We investigated patient characteristics and periprocedural complications in 3 groups.

Results: There was no periprocedural death in any group. Figure 1 shows stroke events among 3 groups. Pericardial tamponade occurred in 1 patient in NE group, 2 patients in W group, and none in NM group. No serious bleeding occurred in any group. In W group, arteriovenous fistula occurred in 1, and false aneurysm in 3 patients.

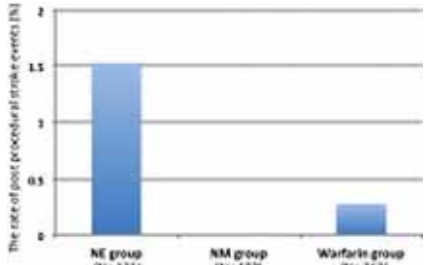


Figure 1. Post procedural stroke events among 3 groups.

Conclusions: Discontinuation period of NOAC is important factor to reduce post procedural events. Shorter discontinuation of NOAC is optimal strategy for RFCA of AF.

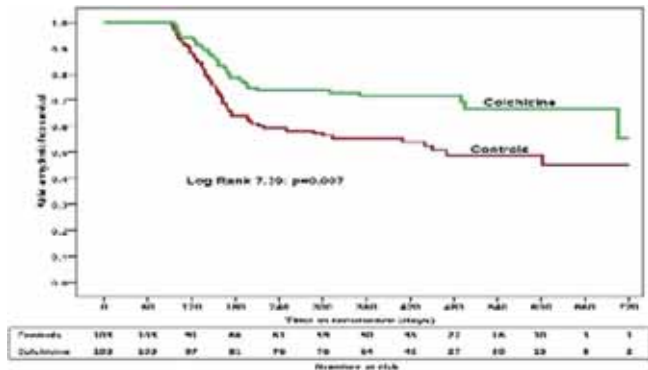
2267 | BEDSIDE

Colchicine for prevention of atrial fibrillation recurrence after pulmonary vein isolation: mid-term efficacy and effect on quality of life

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Background: We have previously shown that colchicine treatment is associated with decreased early recurrence rate after ablation for atrial fibrillation (AF).

Objective: The purpose of this study was to test the mid-term efficacy of colchicine in reducing AF recurrences after a single procedure of pulmonary



vein isolation in patients with paroxysmal AF. Assessment of quality of life (QoL) changes was a secondary objective.

Methods: Patients with paroxysmal AF, slated for ablation, were randomized to a 3-month course of colchicine, 0.5 mg twice daily, or placebo and followed for a median of 15 months (with a 3-month blanking period). QoL was assessed with a general purpose health-related QoL tool (26-item World Health Organization QoL questionnaire) at baseline, 3 and 12 months.

Results: 223 randomized patients underwent ablation and 206 patients were available for analysis (age 62.2 ± 5.8 years, 144 male). AF recurrence rate in the colchicine group was 31.1% (32 of 103) versus 49.5% (51 of 103) in the control group ($p=0.010$), translated in a relative risk reduction of 37% (odds ratio 0.46; 95% confidence interval 0.26-0.81). The number-needed-to-treat was 6 (95% confidence interval 3.2-19.8). Physical domain QoL scores at 12 months were 63.6 ± 13.8 in the colchicine group and 52.5 ± 18.1 in controls, while psychological domain scores were 56.1 ± 13.7 versus 44.7 ± 17.3 ($p<0.001$, for both).

Conclusion: Colchicine treatment after pulmonary vein isolation for paroxysmal AF is associated with lower AF recurrence rate after a single procedure. This reduction is accompanied by corresponding improvements in physical- and psychological-health-related QoL scores.

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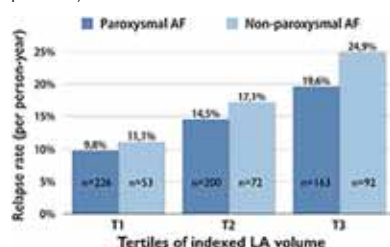
Left atrial size is more important than the type of atrial fibrillation in predicting the long-term success of catheter ablation

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Purpose: The efficacy of atrial fibrillation (AF) catheter ablation in patients with persistent AF and normal sized left atrium (LA) or with paroxysmal AF and dilated LA is not well established. The purpose of this study was to assess the predictors of outcome after AF ablation, focusing on the interplay between LA size and type of AF.

Methods: We assessed 809 consecutive patients with symptomatic drug-refractory AF undergoing 905 percutaneous pulmonary vein isolation procedures in two different centers. LA volume was assessed by cardiac CT prior to AF ablation. The study endpoint was symptomatic and/or documented AF recurrence.

Results: The majority of patients (73.2%, $n=592$) had paroxysmal AF, and the mean indexed LA volume was 55 ± 20 ml/m². During a mean follow-up of 2.4 ± 1.7 years, there were 525 recurrences (no blanking period). The relapse rate of patients with paroxysmal AF in the highest tertile of indexed LA volume was higher than the relapse rate of patients with non-paroxysmal AF in the two lower tertiles. Conversely, the relapse rate of patients with non-paroxysmal AF but small LA was lower than for paroxysmal AF and large LA (Figure). In Cox regression analysis, indexed LA volume was the strongest independent predictor of AF recurrence (HR 1.16 for each 10ml/m² $p<0.001$), followed by female gender (HR 1.58, 95%CI 1.21-2.06, $p=0.001$) and non-paroxysmal AF (HR 1.31, 95%CI 1.02-1.69, $p=0.036$).



Conclusion: When selecting patients for AF ablation, more importance should be given to LA volume than to the type of AF.

Poster Session 3

FOCUS ON DIABETES

P2272 | BEDSIDE

Combination of type 2 diabetes and overweight is linked to an increased incidence of atrial fibrillation in a general urban cohort population

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Background: Atrial fibrillation (AF) is the most common type of chronic arrhythmia and is associated with increased risks of mortality and cardiovascular disease (CVD). However, no prospective study has examined the combined effect of type 2 diabetes (DM) and body mass index (BMI) on the incidence of AF in a general population. We assessed the hypothesis that combinational DM and overweight increase the risk of incident AF using a general urban cohort population.

Methods: A total of 6,906 participants (30-84 years old) in the Suita Study were initially free of AF and prospectively followed up for incident AF. Standard 12-lead

electrocardiograms (ECGs) were obtained from all subjects in the supine position. The subjects were diagnosed with AF when AF or atrial flutter was present on ECGs obtained during a biannual routine health examination or when AF was indicated as a present illness by questionnaire result, medical records, or registration of CVD events during follow-up. The glucose categories were defined as follows: DM (fasting plasma glucose levels [FPG] ≥ 126 mg/dL, non-FPG ≥ 200 mg/dL, or receiving medication for DM); impaired fasting glucose (IFG; FPG=100–125 mg/dL or non-FPG=140–199 mg/dL); and normal glucose tolerance (NGT; FPG <100 mg/dL or non-FPG <140 mg/dL). Categories of BMI, calculated as weight (kg) divided by height (m) squared, were defined as follows: underweight (<18.5 kg/m²), normal weight (18.5 to <25 kg/m²), and overweight (≥ 25 kg/m²). Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) were analyzed after adjusting for age, sex, (DM, BMI), hyperlipidemia, hypertension, smoking, drinking, chronic kidney disease, CVD at baseline.

Results: During the 13 years of follow-up, 253 incident AF events occurred (4.2 for men and 1.7 for women per 1,000 person-years). IFG and DM were not observed increased risk of incident AF (adjusted HRs=1.08 and 1.32; 95% CIs=0.82–1.42 and 0.78–2.23, respectively). Compared with normal weight, the adjusted HR (95% CIs) of incident AF for overweight was 1.35 (1.01–1.80). Compared with NGT and normal weight, the adjusted HR (95% CIs) of incident AF was 2.92 (1.46–5.83) for DM with overweight. DM with normal weight and non-DM with overweight were not linked to an increased risk of incident AF. The interactions between sex and DM and BMI for incident AF were not significant. After omitting the non-fasting subjects (3.4%), all of the results were similar.

Conclusion: DM with overweight is an important risk factor for incident AF. Appropriate body weight is important for preventing AF in DM populations.

P2273 | BEDSIDE

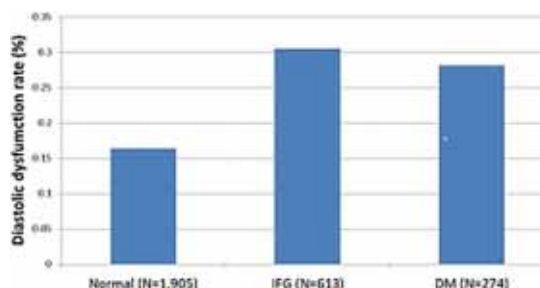
Impaired fasting glucose is independently associated with left ventricular diastolic dysfunction among middle-age adults

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Purpose: Left ventricular diastolic dysfunction (LVDD) is the initial echocardiographic derangement in diabetic cardiomyopathy. However, data are limited on the association between impaired fasting glucose (IFG) and LVDD. The aim of the current study was to investigate whether IFG is associated with LVDD among middle age adults.

Methods: We investigated 3,201 subjects who were annually screened, had their baseline fasting glucose level documented, and completed Doppler echocardiography. Subjects with left ventricular systolic dysfunction or valvular heart disease were excluded. LVDD was diagnosed according to current guidelines based on pulsed-wave Doppler examination of mitral inflow and Doppler tissue imaging of the mitral annulus. Final study population included 2,972 subjects and was divided to three groups: euglycemia ($N=1,095$), IFG ($N=613$) and diabetes mellitus (DM; $N=274$).

Results: Mean age of study population was 60 ± 12 and 75% were men. LVDD was diagnosed in 577 (21%) subjects and was more common among IFG and DM (Figure). Compared with euglycemic subjects, those with IFG and DM had larger left atrium areas (19 ± 4 mm vs. 20 ± 4 and 21 ± 5 mm respectively; $p<0.001$), longer E-wave deceleration time (215 ± 52 msec vs. 219 ± 55 and 229 ± 61 msec respectively; $p=0.02$) and higher ratios of E-wave to peak velocity of early diastolic mitral annular motion (10 ± 8 cm/s vs. 11 ± 4 and 12 ± 5 cm/s respectively; $p<0.001$). Multivariate binary logistic regression model adjusted to age, gender and hypertension, showed that subjects with IFG were 72% more likely to have LVDD compared with euglycemic subjects (95% CI [1.39-2.15], $p<0.001$).



Prevalence of diastolic dysfunction.

Conclusions: IFG is independently associated with LVDD among middle aged adults. Our findings support the early evaluation of diastolic function in this population.

P2274 | BEDSIDE**Advanced glycation end-products are associated with left ventricular structure and function primarily in individuals with normal glucose metabolism -The Hoorn Study-**

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Purpose: Type 2 Diabetes (T2D) is characterized by unfavorable structural and functional cardiac alterations. The accumulation of advanced glycation end-products (AGEs) is believed to play an important role in the pathobiology of this phenomenon. Population-based data on this topic is scarce.

Therefore, the purpose of the study was to investigate the association between the plasma AGEs, NE-carboxymethyl-lysine (CML), pentosidine and NE-carboxyethyl-lysine (CEL), and left ventricular (LV) structure and function, in participants with normal glucose metabolism (NGM), impaired glucose metabolism (IGM) and T2D.

Methods: In this population-based, cross-sectional, study (N=693; 280 NGM, 171 IGM and 242 T2D) participants underwent a standardized echocardiogram. The protein-bound plasma levels of CML, pentosidine and CEL were measured. The analyses were stratified according to glucose metabolism status and adjusted for: sex, age, prior cardiovascular disease, hypertension and (or) the use of antihypertensive medication (including ace-inhibitors), total cholesterol-high density lipoprotein cholesterol ratio, triglycerides, the use of lipid-lowering medication, smoking, estimated glomerular filtration rate and waist circumference. Linear regression analysis was used to investigate the associations between the individual AGEs and both LV structure and function.

Results: After adjustment, plasma CML was positively associated with both left atrial (LA) volume index and LA volume x LV mass index (both diastolic function parameters) in NGM only (regression coefficient (β) (95%CI)): 0.053 (0.011; 0.095) and 0.064 (0.002; 0.126), respectively. Pentosidine was positively associated with both LA volume index and LA volume x LV mass index in NGM (0.056 (0.013; 0.099) and 0.084 (0.021; 0.147), respectively), and with LA volume x LV mass in IGM (0.080 (-0.003; 0.164)). Diastolic function was not associated with any of the AGEs in T2D. Systolic LV function (i.e. ejection fraction) was negatively associated with CML in NGM (-1.221 (-2.311;-0.131) and positively associated in T2D (1.007 (0.104; 1.909)).

Conclusions: In NGM, both plasma CML and pentosidine were positively associated with diastolic dysfunction and CML was negatively associated with systolic function. In IGM a similar pattern emerged, though less consistent, whereas in T2D these associations were either non-existent or even reversed. The latter suggests that the role of plasma AGEs in the pathobiology of cardiac structure and function changes with deteriorating glucose metabolism.

P2275 | BEDSIDE**Pitavastatin reduced C-reactive protein without increasing the incidence of diabetes in Japanese individuals with impaired glucose tolerance (J-PREDICT study)**

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Purpose: Statins may increase the incidence of diabetes mellitus (DM). Statins with lower risk of developing DM are thus helpful to treat high risk patients for CHD. We assessed the effect of pitavastatin (PIT) on the incidence of diabetes.

Methods: This study was a prospective randomized, controlled trial evaluating the effect of PIT on the incidence of diabetes (n=1,269; 635 Control [lifestyle modification alone], 634 PIT [PIT 1-2 mg + lifestyle modification]) in Japanese subjects with impaired glucose tolerance. The primary outcome was incidence of

DM defined as 2-h plasma glucose of ≥ 200 mg/dL or fasting plasma glucose of ≥ 126 mg/dL measured at least once.

Results: 213 patients (39.9%) in the PIT group developed DM as compared with 254 patients (45.7%) in the control group (HR: 0.82; 95% CI: 0.68- to 0.99; P=0.041). LDL cholesterol (P<0.001), triglycerides (P<0.001) and HDL cholesterol (P=0.01) were improved in the PIT group compared with the control group. Hs-CRP was reduced by 20% in the PIT group, and this change was significantly different between groups (P=0.001).

Conclusions: Unlike the effects of statins in previous reports, PIT was not associated with an increased incidence of diabetes. In terms of the balance of benefit and risk, it is likely that PIT can be prescribed without paying attention to the risk of developing DM.

P2276 | BEDSIDE**Impact of diabetes mellitus on carotid atherosclerotic plaque inflammatory status in patients with coronary artery disease**

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Purpose: Patients with diabetes mellitus (DM) are more prone to stroke than non-DM patients. Carotid atherosclerosis is a major cause of stroke. Although inflammation that is implicated in the progression of atherosclerosis seems to be pronounced in patients with DM, similar carotid plaque ultrasound characteristics and distributions have been shown in both patient-groups. The aim of this study was to evaluate the impact of DM on morphological and functional carotid artery characteristics in patients with documented coronary artery disease (CAD).

Methods: Consecutive patients (n=333) with significant CAD documented by coronary angiography were evaluated by: 1) ultra-sound echo-color Doppler (US-ECD) study of both carotid arteries, and 2) microwave radiometry (MR), a new noninvasive method, which allows the in vivo measurement of the internal temperature of tissues reflecting local inflammation. During ultrasound, intima-media thickness of common carotid arteries (ccIMT) was evaluated. Carotid plaques were identified as focal intima-media thickening ≥ 1.2 mm and were evaluated for their thickness. ΔT by MR was defined as the maximum temperature difference of both carotid arteries. Vessel- and patient based analysis were performed to determine the impact of DM on morphological and functional carotid artery characteristics.

Results: Hundred-twenty seven patients had DM (38.1%). Carotid plaques were identified in 110 patients with DM and in 179 patients without DM (86.6 vs 86.9%, p=0.94). Patients with DM had similar ccIMT in both vessel- and patient-based analysis (0.97 ± 0.20 versus 1.00 ± 0.12 mm, p=0.06; 0.94 ± 0.02 versus 0.94 ± 0.01 mm, p=0.93, respectively). Patients with DM had similar carotid plaque thickness in both vessel- and patient-based analysis (1.97 ± 0.97 versus 2.07 ± 1.10 mm, p=0.23; 2.22 ± 0.99 versus 2.47 ± 1.23 mm, p=0.06, respectively). Interestingly, patients with DM exhibited higher ΔT in both vessel- and patient-based analysis (0.81 ± 0.66 versus 0.61 ± 0.64 °C, p<0.001; 1.05 ± 0.62 versus 0.84 ± 0.62 °C, p=0.003, respectively).

Conclusions: Functional abnormalities may be more profound to structural changes in patients with non-significant carotid artery stenosis and DM. The impact of these functional carotid artery characteristics on patient prognosis still remains to be elucidated.

P2277 | BEDSIDE**Relation between endothelial function and exercise-induced myocardial ischemia in type 2 diabetic patients**

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Purpose: A significant number of asymptomatic patients with type 2 diabetes mellitus (T2DM) develops significant ST-segment depression (STD) (>1 mm) during exercise stress test (EST), suggesting myocardial ischemia (MI) related to either macrovascular or microvascular coronary artery disease. Aim of this study was to assess whether there is any relation between endothelial dysfunction and EST-induced myocardial ischemia in this kind of patients.

Methods: We studied 100 non insulin-dependent T2DM patients (age 62.7 ± 8.8 years, 68 M) without any symptom or evidence of cardiovascular disease. All patients underwent a symptom/sign limited EST and assessment of the endothelium-dependent function through measurement of flow-mediated dilation (FMD) following 5-minute forearm ischemia of the right brachial artery. Endothelium-independent function was also assessed through nitrate-mediated dilation (NMD) of the right brachial artery in response to sublingual administration of 25 μ g of nitroglycerin.

Results: STD (horizontal or downsloping STD >1 mm) during EST was induced in 22 patients (22%, group 1), whereas 78 (78%, group 2) showed normal ECG during the test. No differences in age, gender, cardiovascular risk factors, drug therapy, blood glucose and glycated haemoglobin levels were observed between the 2 groups. However, group 1 patients, compared to group 2, showed signifi-

Table 1. Primary and secondary outcomes for the incidence of diabetes

Definition of diabetes	Incidence rate No. (/1,000 person-years)		Hazard ratio (95% CI)	P value
	Pitavastatin [n=534]	Control [n=556]		
Primary outcome				
Elevated FPG ^a or 2-h PG ^b , at least once	213 (162.8)	254 (186.0)	0.82 (0.68–0.99)	0.041
Secondary outcomes				
Elevated FPG, at least once	84 (64.2)	112 (82.0)	0.76 (0.57–1.01)	0.06
Elevated FPG, at least twice	34 (26.0)	44 (32.2)	0.73 (0.46–1.16)	0.18
Elevated 2-h PG, at least once	186 (142.1)	209 (153.1)	0.90 (0.74–1.11)	0.32
Elevated 2-h PG, at least twice	112 (85.6)	115 (84.2)	1.02 (0.78–1.34)	0.86

Abbreviations: FPG, fasting plasma glucose; PG, plasma glucose. Hazard ratio, 95% confidence interval (CI), and p value (log-rank test) were stratified according to the prespecified 5 assignment factors (sex, age, body mass index, 2-h plasma glucose, and presence of hypertension). ^aDefined as concentration of ≥ 126 mg/dL. ^bDefined as concentration of ≥ 200 mg/dL.

cantly lower values of both FMD (3.7 ± 0.7 vs. $5.2 \pm 1.6\%$, respectively, $p < 0.001$) and NMD (11.2 ± 1.3 vs. $11.8 \pm 1\%$, respectively, $p = 0.015$).

Conclusions: Our data suggest that in asymptomatic T2DM patients without any evidence of cardiovascular disease both endothelium-dependent and endothelium-independent vascular dysfunction play a significant role in the exercise-induced myocardial ischemia.

P2278 | BEDSIDE

Endothelial glycocalyx is similarly impaired in diabetic patients and first degree relatives and is linked with abnormal aortic elastic properties and myocardial deformation

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The integrity of endothelial glycocalyx plays a vital role in vascular permeability, inflammation and elasticity. The association between damage of endothelial glycocalyx, impaired arterial elastic properties, and LV function in diabetics and first degree relatives has not been explored.

Methods: In 40 untreated patients (age: 51 ± 12 years) with newly diagnosed type II diabetes, 20 first degree relatives with normal oral glucose tolerance test and 25 controls of similar age and sex and no atherosclerotic risk factors we measured: a) carotid-femoral pulse wave velocity (PWV; m/sec-Complior SP ALAM), central systolic blood pressure (cSBP-mmHg), augmentation index (AI%), reflection time (RT-ms) and diastolic reflection area (DRA) of the aortic pulse wave, an index of coronary perfusion (Arteriograph TensioMed); b) S', E' (m/sec) and E'/A' of mitral annulus by Tissue Doppler; c) LV longitudinal strain (GLS, %), systolic (LongSr, 1/sec) and diastolic (LongSrE, 1/sec) strain rate, using speckle tracking echocardiography; d) perfusion boundary region (PBR, μ m) of the sublingual arterial microvessels (ranged from 5 to 25 μ m) using Sideview, Darkfield imaging (Microscan, Glycocheck). The PBR in microvessels is the cell-poor layer which results from the phase separation between the flowing red blood cells (RBC) and plasma. The PBR includes the most luminal part of glycocalyx that does allow cell penetration. Increased PBR is considered an accurate index of reduced endothelial glycocalyx thickness because of a deeper RBC penetration in the glycocalyx.

Results: Compared to controls, diabetics and relatives had higher PBR (2.1 ± 0.25 vs. 2.05 ± 0.25 vs. 1.89 ± 0.1) AI (27 ± 16 vs. 24 ± 15 vs. 17 ± 14) and DRA (44 ± 12 vs. 49 ± 13 vs. 68 ± 27), ($p < 0.05$). Diabetics and relatives had similar PBR, AI and DRA ($p = ns$). Compared to controls, diabetics had also higher PWV (10.9 ± 2 vs. 8.9 ± 2), cSBP (137 ± 19 vs. 116 ± 17), reduced RT (118 ± 26 vs. 151 ± 14), GLS (-16 ± 4 vs. -20 ± 3), LongSr (-0.8 ± 0.2 vs. -1.1 ± 0.3), LongSrE (0.8 ± 0.2 vs. 1.3 ± 0.5), S', E' and E'/A' ($p < 0.05$). Reduced endothelial glycocalyx thickness as assessed by increased PBR was related with increased PWV ($r = 0.35$), reduced RT ($r = -0.42$) and DRA ($r = -0.36$) in diabetics ($p < 0.05$). These associations were more prominent for PBR measured in the microvessels ranged from 20 to 25 μ m. Increased PWV were related with reduced S' ($r = -0.48$), E' ($r = -0.63$), E'/A' ($r = -0.63$), GLS ($r = 0.48$), LongSr ($r = 0.35$), LongSrE ($r = -0.51$) respectively ($p < 0.05$).

Conclusion: Endothelial glycocalyx is impaired in newly diagnosed diabetics and first degree relatives and is related with abnormal aortic elastic properties leading to impaired LV longitudinal deformation in diabetics.

P2279 | BEDSIDE

Asymptomatic low fasting blood glucose is associated with enhanced thrombin generation and unfavorable fibrin clot properties in patients with type 2 diabetes and high cardiovascular risk

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Objective: To investigate the effect of low blood glucose on fibrin clot formation, properties and degradation in type 2 diabetes mellitus (T2DM).

Methods: In 165 patients with T2DM and high cardiovascular risk, we measured ex vivo plasma fibrin clot permeation [Ks], turbidity and efficiency of fibrinolysis including clot lysis time- [t50%], together with thrombin generation and platelet activation markers in relation to fasting blood glucose.

Results: Patients with asymptomatic low fasting glucose (< 4.5 mmol/l) ($n = 38$) had lower Ks (-11% , $p = 0.0001$), prolonged t50% ($+10\%$, $p < 0.0001$), higher peak thrombin generation ($+21.3\%$, $p = 0.002$) and a trend towards higher plasma CD40 ligand ($+16.2\%$, $p = 0.09$) as compared to patients with glucose ≥ 4.5 mmol/l ($n = 127$). Kinetics of fibrin formation was unaffected by low glucose. There was a U-shape type of relationship between glycemia and peak thrombin generation, Ks and t50%. In patients with HbA1c $< 6.0\%$ ($n = 26$) there were the most potent correlations between fasting glucose and both Ks ($r = 0.53$, $P = 0.006$) and t50% ($r = -0.46$, $P = 0.02$). Fasting glucose concentration influenced Ks ($F = 7.82$, $P = 0.0006$), t50% ($F = 9.24$, $P = 0.0002$) and PF4 even after adjustment for age, fibrinogen, HbA1c and T2DM duration.

Conclusions: In T2DM patients fasting glycemia < 4.5 mmol/l is associated with enhanced thrombin formation and formation of denser fibrin clots displaying lower lysisability, especially when strict glycemia control was achieved (HbA1c $< 6.0\%$).

Our findings may partly explain increased cardiovascular risk in T2DM patients on intensive glucose lowering treatment.

P2280 | BEDSIDE

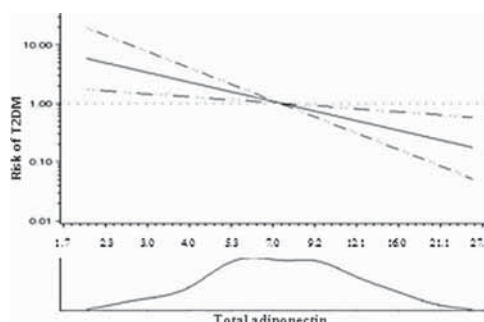
High adiponectin and reduced risk of T2DM in patients with STEMI

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Background: Adiponectin is an insulin-sensitizing hormone with anti-inflammatory effects produced in adipose tissue. Plasma adiponectin is decreased in several metabolic disorders including type 2 diabetes mellitus (T2DM), and in healthy humans, high adiponectin associates with reduced risk of T2DM. However, little is known of the relationship between adiponectin and T2DM in patients with myocardial infarction, where adiponectin is elevated and associates with a poor prognosis. Accordingly we investigated adiponectin and risk of T2DM in patients with ST-segment elevation myocardial infarction (STEMI).

Methods: We prospectively included 735 patients with STEMI treated with primary-PCI, from September 2006 to December 2008 at a tertiary cardiac centre. Blood samples were drawn immediately before PCI, and total plasma adiponectin measured in all samples. Patients were followed for 5 years. Risk of T2DM was analysed using a competing risk analysis.

Results: Higher adiponectin associated with decreased risk of T2DM ($p < 0.001$). Even after adjustment for confounding risk factors (age, gender, hypertension, hypercholesterolemia, current smoking, previous MI, BMI, blood-glucose, eGFR, CRP, peak-TnI and proANP) higher adiponectin remained an independent predictor of reduced risk of T2DM: hazard ratio for 1 SD increase in adiponectin (log2-transformed): 0.42 (95% CI 1.24-1.74; $p = 0.003$). Importantly, high adiponectin added to the predictive value of blood-glucose, with the combination of high blood-glucose and low adiponectin vastly increasing the risk of T2DM, HR 11.7 (4.5-31.0, $p < 0.001$)



Adiponectin and adjusted risk of T2DM.

Conclusions: Higher plasma adiponectin is independently associated with decreased risk of T2DM in patients with MI. Importantly, adiponectin added significantly to the predictive value of blood-glucose.

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Progression of coronary atherosclerosis: importance of adequate lipid control in diabetic patients

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Background: Intravascular ultrasound (IVUS) imaging represents the predominant approach for evaluating progression of coronary atherosclerosis (CA). IVUS provides a precise and reproducible method for determining changes in coronary atheroma burden. Previous studies have confirmed that low levels of LDL-cholesterol (LDL) are associated with a slower CA progression. However, the potential relationship between adequate control of HDL-cholesterol (HDL) and triglycerides (TG) and CA progression remains unknown.

Objective: We sought to investigate CA progression in relation to the extent of lipid control (LDL, HDL and TG) in diabetic patients.

Methods: One hundred nine diabetic patients (mean age 68 ± 9 years, 34 [31%] female) undergoing serial IVUS studies were analyzed (media time interval 474 days). A validated system for volumetric IVUS analysis (EchoScan, TOMTEC) was used for off-line, three-dimensional reconstruction and volumetric analysis. Target lipid levels were those of current guidelines. Levels of LDL, HDL and TG were carefully monitored. Lumen and external elastic membrane volumes, normalized total atheroma volume (TAV) and percent atheroma volume (PAV) were calculated in the target segment in each patient, at baseline and at follow-up. CA progression was measured and defined as the change of TAV and PAV (Δ TAV and Δ PAV). The primary objective was to determine whether inadequate lipid control in diabetic patients is associated with increased CA progression.

Results: In our population of diabetic patients with a high prevalence of statin therapy (89%), inadequate control of the levels of LDL (LDL >70 mg/dl) was not associated with a greater CA progression. However, diabetic patients with inadequate control of both HDL and TG (HDL <40 mg/dl and TG >150 mg/dl) showed significantly most CA progression as measured by the ΔTAV (7.7 ± 21.9 mm³ vs -3.8 ± 19.3 mm³, $p=0.006$) and by the ΔPAV ($1.2 \pm 4.9\%$ vs $-0.5 \pm 3.4\%$, $p=0.034$).

Conclusions: Diabetic dyslipidemia (low HDL and high triglycerides levels) is associated with increased CA progression. These findings suggest the need for intensive lipid control in diabetic patients with coronary artery disease, with especial emphasis to obtain adequate control of HDL and TG levels.

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Right ventricular and right atrial deformation in normotensive patients with prediabetes and type 2 diabetes mellitus: a two- and three-dimensional strain analysis

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Objective: To evaluate right ventricular (RV) and right atrial (RA) deformation obtained by two- (2DE) and three-dimensional echocardiography (3DE) in patients with prediabetes and type 2 diabetes mellitus.

Methods: This cross-sectional study included 51 untreated normotensive subjects with prediabetes, 60 recently diagnosed normotensive untreated diabetic patients and 56 healthy controls of similar sex and age. All the subjects underwent laboratory analyses and comprehensive 2DE and 3DE examination.

Results: 3DE RV end-diastolic volume index progressively reduced from the controls throughout the prediabetics to the diabetics (70 ± 10 vs. 64 ± 8 vs. 57 ± 8 ml/m², $p<0.01$), whereas 3DE RV end-systolic volume index was higher in the controls comparing with the prediabetics and the diabetics (26 ± 4 vs. 24 ± 4 vs. 22 ± 4 ml/m², $p<0.01$). However, there was no difference in 3DE RV ejection fraction among the three groups (63 ± 4 vs. 62 ± 5 vs. $61 \pm 6\%$, $p>0.05$). 2DE RV strain was decreased in the subjects with prediabetes and diabetes comparing with the controls (27 ± 5 vs. 26 ± 4 vs. $24 \pm 4\%$ for RV strain, $p=0.01$). The same results were obtained for RA global strain (44 ± 8 vs. 40 ± 7 vs. $37 \pm 7\%$, $p=0.01$), as well as for RV and RA systolic and early diastolic strain rates; whereas RV and RA late diastolic strain rate was increased in these patients. The fasting blood glucose level correlated with 3DE RV end-diastolic volume ($r=-0.39$, $p<0.01$) and RV global strain ($r=-0.26$, $p=0.03$); whereas the HbA1c level correlated with 3DE RV end-diastolic volume ($r=-0.35$, $p<0.01$), RV global strain ($r=-0.32$, $p=0.01$) and RA global strain ($r=-0.25$, $p=0.04$).

Conclusion: RV and RA myocardial mechanics and function evaluated by 3DE and 2DE strains are significantly impaired in the prediabetics and diabetics. The indicators of glucose control significantly correlated with the RV and RA deformation.

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Identifying prediabetes in essential hypertensive patients with the findrisc questionnaire

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Objective: The Finnish Diabetes Risk Score questionnaire (FINDRISC) is a practical validated tool to estimate the risk for future type 2 diabetes mellitus (T2DM). This study sought to evaluate the potent associations of the FINDRISC with the metabolic profile of newly-diagnosed essential hypertensives (EH).

Design and methods: 757 consecutive non-diabetic patients (52 ± 13 years, 53% males, body mass index 29 ± 5 kg/m²) were studied. Fasting plasma glucose (FPG), 2-hour post-load glucose (2hPG) and HbA1c were measured. Patients with all three measures in the normal range were considered as euglycemic, while those with more than one measure in the prediabetic range were considered as having advanced glycaemic impairment (AGI). Age, BMI, waist circumference, history of antihypertensive drug treatment and high blood glucose, physical activity and daily consumption of fruits and vegetables were determined for the calculation of FINDRISC. The score ranges from 0 to 26 points with higher score representing higher T2DM 10-year risk.

Results: The glycaemic profile of the participants was as follows: euglycemic 56.34%, impaired fasting glucose (IFG) 22.8%, impaired glucose tolerance (IGT) 0.26%, impaired HbA1c 10.6%, while 10% of the patients presented AGI. The prevalence of pre-diabetes and metabolic syndrome (MS; IDF criteria) was 48% and 53%, respectively. Regarding FINDRISC, 13.4% of patients had score <7, 37.1% 7-11, 21.6% 12-14, 24.1% 15-20 and 3.8% >20. Euglycemic patients had score 10 ± 4 while pre-diabetics 14 ± 4 ($p<0.05$). MS patients had FINDRISC 14 ± 4 while non-MS patients 9 ± 4 ($p<0.05$). The score was 14 ± 4 in AGI, 13 ± 4 in IFG and 12 ± 4 in impaired HbA1c. 54.1% of patients with score ≥ 12 had at least one glycaemic measure abnormal, while 67% of those with score <12 had all measures normal. FINDRISC was correlated to FPG ($r=0.32$, $p<0.001$), 2hPG ($r=0.23$, $p=0.027$) and HbA1c ($r=0.29$, $p<0.001$). The area under ROC curve for

FINDRISC to detect dysglycemia was 0.67 (95%CI 0.63-0.71), with the optimal cut-off level being 11 points (sensitivity 72%, specificity 61%).

Conclusions: Almost half of middle-aged, newly-diagnosed hypertensives are pre-diabetics. The FINDRISC is proved as a useful, cost-effective tool for identifying these individuals.

DIABETES RELOADED!

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Association of genetic variants of the alpha-kinase 1 gene (ALPK1) with type 2 diabetes mellitus in community-dwelling Japanese individuals

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Purpose: We previously showed that genetic variants of the alpha-kinase 1 gene (ALPK1) were significantly associated with chronic kidney disease in Japanese individuals with diabetes mellitus by a genome-wide association study. Although genetic variants in ALPK1 were related to chronic kidney disease for individuals with diabetes mellitus, whether ALPK1 is a susceptibility locus for diabetes mellitus has not been elucidated. The purpose of the present study was to examine a possible association of rs2074388 (G→A, Gly565Asp) and rs2074379 (G→A, Met732Ile) of ALPK1 with type 2 diabetes mellitus in community-dwelling Japanese individuals.

Methods: Study subjects comprised 5959 community-dwelling individuals (495 subjects with type 2 diabetes mellitus, 5464 controls) who were recruited to a population-based cohort study in Inabe City, Japan. Subjects with type 2 diabetes mellitus had a fasting plasma glucose level of ≥ 6.93 mmol/L or a blood glycosylated hemoglobin (hemoglobin A1c) content of $\geq 6.5\%$ or were taking antidiabetes medication. The control individuals had a fasting plasma glucose level of <6.05 mmol/L and a blood hemoglobin A1c content of <5.6%, and they had no history of diabetes mellitus or of taking antidiabetes medication. Genotypes of polymorphisms were determined by the multiplex bead-based Luminex assay, which combines the polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology.

Results: Comparisons of allele frequencies or genotype distributions by the chi-square test revealed that the rs2074388 (allele, $P=0.0095$; genotype, $P=0.0244$) and rs2074379 (allele, $P=0.0111$; genotype, $P=0.0304$) of ALPK1 were significantly ($P<0.05$) associated with type 2 diabetes mellitus. Multivariable logistic regression analysis with adjustment for age, sex, body mass index, and smoking status revealed that the rs2074388 ($P=0.0040$; odds ratio, 1.33; dominant model) and rs2074379 ($P=0.0058$; odds ratio, 1.32; dominant model) were significantly associated with type 2 diabetes mellitus. The rs2074388 and rs2074379 were in linkage disequilibrium. Haplotype analysis of these polymorphisms revealed that the frequency of the minor haplotype, G (rs2074388)–G (rs2074379), was significantly (permutation $P=0.010$) higher, whereas that of the major haplotype A–A was significantly (permutation $P=0.015$) lower, in subjects with type 2 diabetes mellitus than in controls.

Conclusions: ALPK1 may be a susceptibility locus for type 2 diabetes mellitus in Japanese individuals.

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Glycemic variability assessed by continuous glucose monitoring and its correlation with renal and myocardial damage after coronary stenting

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Purpose: Previous studies have demonstrated a significant impact of pre-procedural blood glycaemic levels (pre-BGLs) on post-procedural myocardial and renal damage in patients undergoing percutaneous coronary intervention (PCI). Recently, the analysis of glucose fluctuations within a predefined interval, defined as glycemic variability (GV), has been shown to estimate patients' metabolic status better than single spot glycaemic determinations; however, its influence on PCI outcomes has not been characterized yet. The aim of this study is to evaluate the correlation between peri-procedural GV, assessed by continuous glucose monitoring (GCM), and myocardial and renal damage, the latter also assessed by Neutrophil Gelatinase-Associated Lipocalin (NGAL), after coronary stenting.

Methods: GV in the peri-procedural period was continuously monitored by a small subcutaneous device, in 28 patients with diabetes mellitus type 2 undergoing PCI, and measured by multiple indexes: Standard Deviation (SD), Coefficient of Variability (CV), Mean Amplitude Glycemic Excursions (MAGE; MAGE-up, considering nadir-to-peak fluctuations and MAGE-down, peak-to-nadir excursions) and Continuous Overall Net Glycemic Action (CONGA, measuring intraday glycemic swings occurring over predetermined intervals: 1 hour, 2 hours, 4

hours). Serum creatinine, NGAL and Troponin I levels were measured before and after PCI.

Results: A significant correlation was observed between NGAL variation and CV ($r=0.404$, $p=0.045$), SD ($r=0.408$, $p=0.043$), MAGE ($r=0.407$, $p=0.043$), MAGE-up ($r=0.467$, $p=0.019$) and CONGA-4 ($r=0.461$, $p=0.021$). Moreover, at the multivariate analysis, CONGA-4 remained an independent predictor of NGAL increase ($p=0.042$). A similar association was found between GV indexes and serum creatinine variation. Post-procedural increase of Troponin I significantly correlated with CONGA-2 ($r=0.390$, $p=0.040$). Patients with peri-procedural myocardial infarction showed higher mean values of CONGA-1, CONGA-2 and MAGE-down, compared with patients without this complication, with CONGA-1 being an independent risk factor for its occurrence ($p=0.041$).

Conclusions: Our results show a significant correlation of GV with renal and myocardial damage after coronary stenting. Thus, continuous monitoring of glycemic excursions during the peri-procedural period may provide important prognostic information and guide individualized therapeutic protocols for euglycemia.

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Alcohol drinking and 10-year incidence of diabetes mellitus: the ATTICA study

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Aim: The aim of this work was to evaluate the nature of a potential dose-response relationship, between alcohol drinking and 10 year incidence of diabetes.

Methods: During 2001-2, 1514 men and 1528 women (>18 years) without any clinical evidence of cardiovascular disease (CVD) at the baseline examination, living in Athens greater area, Greece, were enrolled in the ATTICA study. In 2011-12, the 10-year follow-up was performed. Several demographic, lifestyle, clinical and biochemical characteristics of the participants, as well as dietary habits, including alcohol consumption (translated to ethanol intake in g/day and type of alcohol drink), were evaluated, in relation to the development of diabetes as defined according to WHO-ICD-10 criteria (fasting blood glucose >125 mg/dL or the use of antidiabetic medication). Participants were classified based on their daily ethanol intake in two categories: abstention or high intake versus moderate intake. The effect of the type of drink consumed was evaluated using the ratio wine-to-other spirits. In the present work, 1679 participants (47±14 yr, 49.9% men) who had no history of diabetes at baseline examination were studied.

Results: The 10-year incidence of diabetes was 11.6 per 100 men and 11.2 per 100 women. 55% of the participants reported at least low alcohol consumption on a weekly basis. Data analysis revealed that abstention or high consumption of alcohol (defined as <10 g for women and <20 g for men) was associated with 2.01-times (95%CI 1.14, 3.53) higher risk of developing type 2 diabetes, as compared to moderate consumption, after taking into consideration age, sex, abnormal waist circumference, physical activity, education, overall diet quality, family history of diabetes and the common cardiovascular risk factors; thus, a U-shaped relationship was evident. When type of alcohol consumed was taken into account, through the ratio wine-to-other other spirits, an inverse relationship was observed, i.e., the higher the ratio the lower the risk of diabetes (Relative Risk = 0.38, 95%CI 0.55, 1.00), adjusting for the aforementioned factors.

Conclusions: Our results suggest a U-shaped relationship of ethanol consumption and the development of diabetes, within a 10-yr period. Furthermore, wine drinking against other spirits ratio exerted a significant protection, underlying the pleiotropic benefits from wine of cardiometabolic risk.

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Impact of short-term exercise training on QT dispersion and double product in diabetic patients after myocardial infarction

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Purpose: The aim of this study was to establish the influence of short-term exercise training on QT dispersion and double product (DP), in diabetic patients after myocardial infarction.

Methods: The study involved 353 patients after myocardial infarction, in the sinus rhythm without AV blocks or branch blocks. Average age of patients was 56.8 years. Patients were randomly divided into the physical training group (TG: 311 patients) and non-training group (NTG: 42 patients). Patients were of similar age, site of infarction and baseline stress test duration. Diabetes was present in 102 (32.8%) patients in the TG and in 14 (33.3%) patients in the NTG. In all subjects standard ECG and exercise test on treadmill were performed and after that TG patients were included in rehabilitation treatment for three weeks. TG patients were instructed to follow a training program using the bicycle ergometer (10 min, 2 times a day) and walking. The patients continued to take the same medications in same doses. From standard ECG corrected QT dispersion (QTdc) was calculated.

Results: Before starting with the program of physical training, TG patients with diabetes had significantly higher values of QTdc (80.5 ± 26.2 vs 68.7 ± 23.1 ms;

$p<0.001$), while the values of DP did not significantly vary (12183.4 ± 1973.4 vs 11982.5 ± 1856.2 beat/min x mmHg; p -NS) in comparison to those without diabetes. After three weeks in TG, significant reduction of QTdc was found (from 80.5 ± 26.2 to 72.7 ± 23.6 ms; $p<0.025$ in patients with diabetes and from 68.7 ± 23.1 to 57.4 ± 21.2 ms; $p<0.001$ in patients without diabetes). After three weeks in TG, significant reduction of DP was found (from 12183.4 ± 1973.4 to 11578.1 ± 1696.2 beat/min x mmHg; $p<0.02$ in patients with diabetes and from 11982.5 ± 1856.2 to 11169.6 ± 1510.3 beat/min x mmHg; $p<0.001$ in patients without diabetes). In contrast, the non-training group showed no significant changes. In TG patients with diabetes, after program of physical training, significant reduction of glycemia was found (from 8.2 ± 3.1 to 7.4 ± 1.8 mmol/L; $p<0.01$).

Conclusions: The study showed that patients with diabetes have a higher value QTdc, probably due to diffuse interstitial fibrosis. Short-term exercise training has favourable effects on QT dispersion and double product in patients after myocardial infarction. In patients without diabetes physical training had more favourable effects on the followed parameters. Physical training led to the significant decrease of myocardial oxygen uptake at rest and probably decreased the possibility of arrhythmia events.

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Association of a genetic variant of the zinc finger protein 259 gene (ZNF259) with type 2 diabetes mellitus in Japanese individuals

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Purpose: Genetic variants that contribute to susceptibility to type 2 diabetes mellitus in Japanese individuals remain to be identified definitively. Various loci and genes that confer susceptibility to coronary heart disease (CHD) have been identified for Caucasian populations by genome-wide association studies (GWASs). Given that type 2 diabetes mellitus is an important risk factor for CHD, we hypothesized that some polymorphisms might contribute to the genetic susceptibility to CHD through affecting the susceptibility to type 2 diabetes mellitus. The purpose of the present study was to examine a possible association of type 2 diabetes mellitus in Japanese individuals with 15 polymorphisms identified as susceptibility loci for CHD in the previously GWASs.

Methods: Study subjects comprised 3757 individuals (1444 subjects with type 2 diabetes mellitus, 2313 controls) who visited the participating hospitals between 2002 and 2012. Subjects with type 2 diabetes mellitus had a fasting plasma glucose level of ≥ 6.93 mmol/L or were taking antidiabetes medication. The control individuals had a fasting plasma glucose level of <6.05 mmol/L and had no history of diabetes mellitus or of taking antidiabetes medication. Genotypes of polymorphisms were determined by the multiplex bead-based Luminex assay, which combines the polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology. To compensate for multiple comparisons, we adopted the criterion of a false discovery rate (FDR) of <0.05 for statistical significance of association.

Results: Comparisons of allele frequencies by the chi-square test revealed that the rs964184 (G→C polymorphism) of the zinc finger protein 259 gene (ZNF259) was significantly ($P=0.0017$, FDR = 0.0260) associated with type 2 diabetes mellitus. Multivariable logistic regression analysis with adjustment for age, sex, and body mass index revealed that rs964184 of ZNF259 was significantly ($P=0.0012$; odds ratio, 1.25; dominant model) associated with type 2 diabetes mellitus with the minor C allele representing a risk factor for this condition. Fasting plasma glucose levels ($P=0.0171$; GG, 6.86 ± 3.27 mmol/L; GC, 7.10 ± 3.44 mmol/L; CC, 7.32 ± 3.78 mmol/L; means $\pm$ SD) and blood glycosylated hemoglobin (hemoglobin A1c) content ($P=0.0123$; GG, $6.80\pm1.79\%$; GC, $6.85\pm1.07\%$; CC, $7.26\pm2.18\%$; means $\pm$ SD) significantly differed among ZNF259 genotypes.

Conclusions: ZNF259 may be a susceptibility locus for type 2 diabetes mellitus in Japanese individuals.

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Hemoglobin A1c is associated with coronary artery calcium in non-diabetic Korean adults

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Introduction: Although many studies have reported that hyperglycemia could contribute to the development and progression of atherosclerosis, limited data have addressed the relationship of hyperglycemia with coronary artery calcification, especially in non-diabetic Asian population.

Objectives: The present study was performed to evaluate the association between hemoglobin A1c (HbA1c), as a marker of chronic hyperglycemia, and coronary artery calcification in non-diabetic Korean adults.

Methods: Coronary artery calcium score (CACS) and HbA1c level were investigated in a total of 12,853 individuals (10,521 men, mean age, 42 ± 6.9 years)

who participated in our Health Study between 2010 and 2011. Individuals were divided into 4 groups according to HbA1c quartiles (≤ 5.40 , 5.41–5.60, 5.61–5.80, and $> 5.80\%$).

Results: The overall prevalence of presence of CAC among total individuals was 9.5%; according to HbA1c quartiles, the prevalence of CAC(+) group was 6.0%, 7.7%, 11.2%, and 15.2% in the lowest, 2nd, 3rd, and highest HbA1c quartiles, respectively. The CAC(+) group had unfavorable cardiometabolic and lipid profiles. In a multivariate regression analysis after adjusting for variables with a univariate relationship ($p < 0.20$), the 3rd and highest quartile group of HbA1c had higher odds ratios (ORs) for the presence of CAC compared with that of the lowest quartile group [OR(95% confidence interval (CI)), 1.113(0.910, 1.361), 1.413(1.157, 1.726), and 1.670(1.344, 2.076) in the 2nd, 3rd, and highest HbA1c quartiles, and increasing quartiles of HbA1c was also associated with the presence of CAC (p for trend < 0.001). Moreover, absolute serum HbA1c level had a significant relationship with the presence of CAC and increasing CACS, respectively [OR(95% CI) 1.366(1.131, 1.649), $p = 0.001$; standardized $\beta = 0.045$, $p < 0.001$, respectively]. According to NFG and IFG groups, HbA1c level was associated with CACS in the NFG group (standardized $\beta = 0.045$, $p < 0.001$), but the association had a trend toward increasing CACS (standardized $\beta = 0.035$, $p = 0.068$) in the IFG group.

Conclusion: This study showed an independent relationship between serum hemoglobin A1c level and coronary artery calcification in non-diabetic Korean adults. This could suggest that individuals with increased HbA1c level should be paid an attention for more accurate cardiovascular risk stratification, even though HbA1c level would not be over diabetic range.

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Predictive value of dysglycaemia biomarkers in the prognosis of patients with acute myocardial infarction with and without ST segment elevation

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Dysglycaemia is associated with a worse prognosis in patients (p) with an acute myocardial infarction (AMI). The glucometabolic alteration parameter that gives a better assessment of the future major adverse cardiovascular events (MACE) in that p is analyzed.

Aim: To investigate the predictive value of admission glucose level (GA), glycosylated hemoglobin (HbA1c) and fasting glucose (FG) in the prognosis of p with AMI (with and without ST segment elevation).

Methods: We determine the GA, HbA1c and FG in 236 consecutive patients with diagnosis of AMI. GA was categorized as ≥ 155 or < 155 mg/dl, HbA1c as ≥ 6.5 or $< 6.5\%$ and FG as ≥ 126 or < 126 mg/dl. We prospectively analyzed the relationship of admission glucose level, fasting glucose and HbA1c with one year incidence of cardiovascular death, new non-fatal myocardial infarction or readmission for acute heart failure (composite primary outcome (CPO)). Optimal threshold glycemia level on admission to predict CPO was obtained by ROC curves. Furthermore, a stratified analysis was performed for known diabetes mellitus status at admission.

Results: We include 236 p (145 p non-ST segment elevation and 91 p with ST segment elevation), average age (SD) 69 (13.4) years, 28% women. The proportion of CPO in categories by GA (≥ 155 or < 155 mg/dl) was 48.8 y 27%, respectively ($p = 0.001$), by HbA1c (≥ 6.5 o $< 6.5\%$) was 46.5 y 27.9%, respectively ($p = 0.009$) and by FG (≥ 126 or < 126 mg/dl) was 42.9 and 31.3%, respectively ($p = 0.121$). In multivariate analysis GA showed a significant association with incidence of CPO (hazard ratio (HR):2.036 (95% confidence interval (CI):1.124-3.689; $p = 0.019$) even after adjusting, according to risk CV factors, previous invasive strategy and GRACE score, but HbA1c (HR: 1.389, 95% CI: 0.752-2.566; $p = 0.294$) and FG (HR: 0.705 95% CI: 0.329-1.512; $p = 0.369$) was not. Among 143 p without diabetes GA (≥ 155 or < 155 mg/dl) showed tendency to association with CPO (HR: 3.412, 95% CI: 0.987-11.793; $p = 0.052$), but not statistically significant.

Conclusions: In our study of patients with and without ST segment elevation AMI, glucose level at admission was the only independent predictor value of 1-year MACE, ahead of markers of chronic glycometabolic disregulation such as HbA1c. In patients without diabetes, glucose level at admission was also the only which showed tendency to association with MACE.

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Insulin resistance is related with increased arterial stiffness and abnormal wave reflection during postprandial hyperglycemia

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Studies link hyperinsulinemia with arterial stiffness. Arterial stiffness is associated with increased risk for cardiovascular disease. We investigated whether insulin resistance as assessed after fasting or during oral glucose tolerance test (OGTT) is related with arterial stiffness and wave reflection.

Methods: In 60 consecutive subjects without known diabetes a standard 75-gr oral glucose tolerance test (OGTT), was performed and plasma glucose and serum insulin levels were measured at 0, 30, 60, 90 and 120min after glucose loading. At the same time intervals, we measured the carotid-femoral pulse wave velocity (PWVc) using the Complior apparatus and aortic PWV (PWVa), central systolic blood pressure (cSBP) and augmentation index (AI) using an oscillometric method (Arteriograph). We measured insulin resistance a) after fasting, using homeostatic model assessment (HOMA) and hepatic insulin sensitivity (HIS) b) during OGTT using Matsuda index and insulin sensitivity index (ISI).

Results: Patients with abnormal OGTT (n=24) had higher baseline PWVc (10.4±2 vs. 9.1±1.8 m/sec, $p < 0.05$), PWVa (9.4±1.9 vs. 6.9±1.8 m/sec, $p < 0.05$), AI (24±9 vs. 17±11%, $p < 0.05$), insulin (14±6 vs. 11±4 μ U/ml, $p < 0.05$), glucose levels (114±26 vs. 93±7 mg/dl, $p < 0.05$), HOMA, (3.7±1.3 vs. 2.7±1.7, $p < 0.05$) and lower HIS (0.34±0.24 vs. 0.46±0.18, $p < 0.05$), ISI (55.8±22 vs. 90±17, $p < 0.05$), Matsuda index (3.2±1.6 vs. 4.5±1.2, $p < 0.05$) and similar age, sex and BMI than those with normal OGTT ($p < 0.05$).

Of all indices, decreasing ISI was best related to increasing PWVc, PWVa cSBP and AI measured at baseline ($r = -0.37$, $r = -0.63$, $r = -0.30$, $r = -0.45$, $p < 0.05$), at 30 min ($r = -0.39$, $r = -0.64$, $r = -0.31$, $r = -0.46$, $p < 0.05$), 60 min ($r = -0.44$, $r = -0.65$, $r = -0.47$, $p < 0.05$), 90 min ($r = -0.52$, $r = -0.70$, $r = -0.33$, $r = -0.48$, $p < 0.05$) and 120 min ($r = -0.54$, $r = -0.69$, $r = -0.30$, $r = -0.45$, $p < 0.05$) during OGTT. Similar associations were observed between Matsuda index and vascular markers ($p < 0.05$). Although, HOMA and HIS were related with baseline values of vascular markers ($p < 0.05$), they showed only borderline association with these markers during OGTT.

Conclusions: Patients with abnormal OGTT have increased arterial stiffness and abnormal wave reflection compared to those with normal OGTT. Indices of insulin resistance calculated during OGTT predict abnormal arterial wall elastic properties and wave reflection at baseline and post glucose challenge better than indices of insulin resistance calculated during fasting. Insulin resistance appears to determine arterial stiffness after acute postprandial hyperglycemia.

P2293 | BEDSIDE

Increased arterial stiffness and retinol binding protein 4 are associated with adverse prognosis in type 2 diabetes patients

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Purpose: The progression of atherosclerosis in type 2 diabetes (T2DM) is considered multifactorial. Apart from the increased prevalence of classical risk factors, hyperglycemia, insulin resistance and inflammation may contribute to the progression and rupture of atherosclerotic plaques. The aim of this study was to investigate the association of biochemical markers of inflammation and insulin resistance with indices of subclinical atherosclerosis and assess their role in the long term prognosis in T2DM patients without known cardiovascular (CV) disease.

Methods: We enrolled and followed up (median time 9 years) 119 patients (median age 65 years, females 70%) with T2DM and not known CV disease. Arterial stiffness was assessed by measuring carotid-femoral pulse wave velocity (PWV) using arterial tonometry. Endothelial function was assessed by endothelium-dependent vasodilation of brachial artery using ultrasound. YKL-40, C-reactive protein and NGAL were used as indices of inflammation while retinol binding protein 4 (RBP4) and fatty acid binding protein 4 were used as indices of insulin resistance. The prognostic role of the vascular and biochemical indices for total mortality and CV events during follow-up was assessed using Cox regression analysis.

Results: There were 11 deaths (from all causes) and 21 CV events recorded in the follow-up. PWV was positively associated with YKL40 and NGAL ($p < 0.05$ for all). Increased PWV (HR 3.5, $p = 0.031$), YKL40 (HR 2.9, $p = 0.021$) and NGAL (HR 2.5, $p = 0.05$) were associated with the occurrence of CV events in univariate analysis, but only increased PWV (i.e. > 10 m/sec) (HR 3.2, $p = 0.049$) remained an independent predictor of CV events after adjustments for classical risk factors. Higher glucose levels and lower body mass index (BMI) were also independently associated with CV events ($p < 0.05$ for both). Total mortality was significantly associated with increasing RBP4 in univariate and multivariate analysis (HR 2.3, $P = 0.015$ for a 40% increase in RBP4).

Conclusions: In T2DM patients, increased arterial stiffness was associated with arterial inflammation (YKL40 and NGAL). Increased arterial stiffness and hyperglycemia were independent predictors of CV events while BMI showed a paradoxical inverse relation with these events. Insulin resistance as assessed by increased RBP4 was the most important predictor of total mortality in our population.

P2294 | BEDSIDE**HbA1c help prediction of severity of coronary artery disease in non-diabetic patients**

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Background: Among the known risk factors for cardiovascular disease, type 2 diabetes mellitus (T2DM) ranks as one of the most potent. It has been recognized that normal fasting blood glucose and increased HbA1c levels in patients without diabetes are risk factors for cardiovascular events and subclinical atherosclerosis. Lowering HbA1c was shown to be associated with reduction of microvascular, neuropathic and possibly macrovascular complications in patients with diabetes mellitus. However, in non-diabetic patients, very few reports have examined the relationship between HbA1c and extent of coronary artery disease.

Objectives: The aim of this study was to examine the relationship between HbA1c level and extent of coronary artery disease (CAD) in non-diabetic patients scheduled for elective coronary angiography.

Methods: We studied 408 consecutive non-diabetic patients (mean age 54.4±9.5 years) with or without previous history of myocardial infarction, who were scheduled for elective coronary angiography due to clinical reasons. All patients had no previous coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting). Extent and severity of CAD was assessed by Gensini score. Gensini score >30 was considered severe coronary atherosclerosis. Echocardiography was done to assess left ventricular ejection fraction (LVEF) and regional wall motion score index (RWMSI) in all patients. Patients were divided into a high risk group (HbA1c 5.7 - 6.4%, n=292) and a low risk group (HbA1c <5.7%, n=116).

Results: Patients in both groups had comparable prevalence of hypertension, smoking and family history of CAD. No significant difference was noted as regards age, gender, body mass index, waist circumference, waist to hip ratio or lipid profile. Presentation with myocardial infarction was more prevalent in the high risk group. Patients in the high risk group had higher Gensini score (45.1±36.7 vs. 26.8±26, p<0.000), higher RWMSI (1.2±0.3 vs. 1.1±0.3, p=0.017) and lower LVEF (54±9.8 vs. 57.2±9.7, p=0.005). HbA1c showed positive correlation with Gensini score (r=0.243, p<0.000). Patients with Gensini score >30 had higher values of HbA1c (6.0±0.48 vs. 5.75±0.54, p<0.000). HbA1c value of 5.85 showed a sensitivity of 70% and a specificity of 50% for prediction of severe coronary atherosclerosis (Gensini >30) (95% CI, 0.582 – 0.690; p<0.000).

Conclusion: HbA1c is significantly associated with CAD and may predict the extent of atherosclerosis in non-diabetic patients.

P2295 | BEDSIDE**Evolution of undiagnosed glucose metabolism disturbances one year after acute coronary syndromes in a large Swiss prospective cohort**

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Introduction: Measurement of fasting plasma glucose (FPG) is recommended in patients admitted for acute coronary syndrome (ACS), but controversies exist on initiating anti-diabetic treatment for mildly undiagnosed glucose metabolism disturbances.

Methods: 2248 patients with ACS were enrolled in a prospective study from July 2009 to December 2012 in four Swiss university hospitals and had FPG measured during hospitalization. Using the diagnostic criteria of the American Diabetes Association (ADA), we stratified patients in 4 groups: (1) normal glucose metabolism if FPG <5.6 mmol/l, (2) undiagnosed pre-diabetes mellitus (DM) if FPG 5.6-6.9 mmol/l, (3) undiagnosed DM if FPG ≥7 mmol/l and (4) known DM. After 1-year, we assessed FPG and anti-diabetic treatment.

Results: Among 2248 patients admitted for ACS, 525 (23%) had normal glucose metabolism, 814 (36%) undiagnosed pre-DM, 501 (22%) undiagnosed DM and 408 (18%) known DM. Patients with undiagnosed DM presented significantly more ST-elevation on ECG, bigger size of infarction and hemodynamic instability at admission (p<0.001). At 1-year, among patients with initially undiagnosed pre-DM, 287 (42.1%) had persistent pre-DM and 35 (5.1%) developed DM without treatment, while 9 (1.3%) had new anti-diabetic treatment. Similarly, among patients with initially undiagnosed DM, 31 (7.9%) had persistent untreated DM and 150 (38.0%) pre-DM, while 31 (7.9%) had new anti-diabetic treatment. Overall, 534 (49.6%) of patients with undiagnosed pre-DM and DM normalized FPG at 1-year without treatment.

Conclusion: Undiagnosed glucose metabolism disturbances are common in patients admitted with ACS, but reassessment of FPG is needed in stable conditions to adequately classify and initiate treatment.

METABOLIC SYNDROME – WHAT'S NEW?**P2297 | BEDSIDE****Differential predictive value of metabolic syndrome for coronary artery disease evaluated with cardiac computed tomography according to the presence of diabetes in Korean population**

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Background: Despite the controversial inclusion of established diabetes in the definition of MetS, the predictive value of MetS for coronary artery disease (CAD) according to diabetes status was not elucidated in Asian population.

Methods and results: We evaluated the association between MetS and CAD using the parameters including any plaque, obstructive plaque, and coronary artery calcium score (CACS) >100 according to diabetes status in 2,869 Korean subjects who underwent cardiac computed tomographic angiography. There were 2,308 non-diabetics (80%) and 561 diabetics (20%); 793 (34%) and 385 (69%), respectively, had MetS. Incidence of any plaque, obstructive plaque, and CACS >100 was significantly higher in non-diabetics with MetS than in those without MetS, but not in diabetics. MetS was independently associated with any plaque (OR 1.55, P<0.001), obstructive plaque (OR 1.51, P<0.005), and CACS >100 (OR 1.47, P<0.05) in only non-diabetics. The number of MetS components also independently associated with any plaque (OR 1.22, P<0.001), obstructive plaque (OR 1.25, P<0.001), and CACS >100 (OR 1.21, P<0.01) in only non-diabetics. Multiple logistic regression analysis revealed that diabetes tended to affect all these parameters more strongly than MetS.

Conclusions: MetS was an independent predictor for the presence and severity of CAD in only non-diabetic subjects. A concurrent diagnosis of MetS might be of little value for predicting CAD in diabetic subjects among Korean population.

P2298 | BEDSIDE**Target organ damage in hypertensive patients with metabolic syndrome: divergent associations with several glycaemic indices**

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Purpose: Arterial stiffness and microalbuminuria are markers of target organ damage and carry significant cardiovascular risk. Disorders of glucose metabolism such as metabolic syndrome and diabetes mellitus II have been associated with both arterial stiffness and microalbuminuria but whether it is glucose per se or other indices of glucose metabolism that have the most powerful effect on target organ damage is unknown. The aim of the present study was to investigate the independent relationship of blood glucose, glycated haemoglobin and insulin resistance with arterial stiffness and microalbuminuria in hypertensive patients with metabolic syndrome.

Methods: We studied 524 never treated hypertensive patients with metabolic syndrome defined by Adult Treatment Panel III criteria. Arterial stiffness was assessed by measuring carotid-femoral pulse wave velocity (PWV) using the Complior device. Microalbumin excretion was measured after 24h urine collection and albumin to creatinine ratio (ACR) was estimated. All patients underwent full laboratory assays, including insulin measurement and estimation of HOMA, glycated haemoglobin (HbA1c) and high sensitivity C-reactive protein (hsCRP).

Results: In the whole population the mean values of PWV and ACR were 8.8 m/s and 36.8 mg/g, respectively. Both PWV and ACR were significantly associated with all indices of glucose metabolism (p<0.001 for the association of PWV and ACR with glucose, HbA1c and HOMA). When all glycaemic indices were entered in the same model of multivariate analysis, after adjustment for age, gender, body mass index, smoking, mean arterial pressure and hsCRP, PWV was independently related to HOMA (b=0.09, p=0.03) whereas ACR was independently related to HbA1c (b=0.58, p=0.001) and glucose levels (b=0.34, p=0.03).

Conclusions: In hypertensive patients with metabolic syndrome, among indices of glucose metabolism, insulin resistance is the most powerful determinant of arterial stiffness whereas glycated haemoglobin has the strongest association with microalbuminuria. Given the prognostic value of arterial stiffness and microalbuminuria, the present findings emphasize the need for measurement, apart from glucose levels, also the insulin levels and HbA1c in all patients with hypertension and metabolic syndrome in order to improve their risk stratification.

P2299 | BEDSIDE**Components of metabolic syndrome crucially affect central aortic pressure in the general population**

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Purpose: Metabolic syndrome (MetS) promotes atherosclerotic process and increases a risk of cardiovascular disease. We investigated an impact of MetS and

its components on central aortic pressure (CAP), an excellent surrogate maker of cardiovascular disease, in the general population.

Method: CAP was measured in 7295 subjects (male=4590, age=56.8±12.0 years) who visited our hospital for a yearly physical checkup from January to December 2012 and a cross-sectional analysis was performed. Brachial blood pressure (BP) (oscillometer) and radial artery pressure waveforms (tonometer) were recorded using an automated device, and CAP was estimated using systolic pressure corresponding to the second systolic peak of radial pressure waveforms (HEM-9000AI). The MetS was defined according to the Japanese criteria (the presence of two or more of the following items in subjects with obesity; (1) elevated triglycerides and/or decreased high density-lipoprotein cholesterol [dyslipidemia], (2) elevated BP, and (3) impaired glucose tolerance [IGT]).

Results: Physical checkup revealed that 1148 subjects had MetS (male/female=21.5%/5.9%). CAP was higher in subjects with than without MetS (142.9±19.1 vs. 127.8±19.8 mmHg). The presence of MetS independently predicted an increase in CAP ($p<0.0001$). Among metabolic factors, obesity and elevated BP were correlated with CAP in multivariate regression analysis. Furthermore, CAP levels were increased with increasing the number of the component of MetS in each individual (without metabolic component, 114.8±12.1; 1 component, 132.1±19.5; 2 components, 138.4±19.0; components ≥ 3 , 142.8±19.1 mmHg). In analysis with normotensive subjects, brachial BP and CAP were higher in subjects with than without metabolic components, but they were not affected by the number of metabolic components. In contrast, in subjects with elevated BP, brachial BP, but not CAP, values were increased with increasing the number of metabolic components (1 component, 136.6±15.6; 2 components, 137.4±15.3; components ≥ 3 , 139.0±16.7 mmHg). Similar results were obtained in sub-analysis of subjects without any medications ($n=5037$).

Conclusions: The presence of MetS increases CAP. Among metabolic components, obesity and elevated BP were the independent predictors of CAP. Furthermore, the impact of obesity, dyslipidemia or IGT on CAP was affected by brachial BP levels. This suggests that an intervention to modify life style aiming at adequate body weight and normal brachial BP may contribute to the reduction of cardiovascular risk at least partially through a reduction in CAP.

P2300 | BEDSIDE

Preclinical atherosclerosis and metabolic syndrome increase cardio- and cerebrovascular events rate: a 20-year follow up

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Background: Intima-media thickness (IMT) is a validated marker of preclinical atherosclerosis and a predictor of cardiovascular events.

Patients: We studied a population of 529 asymptomatic patients (age 62±12.8 years), divided into two groups of subjects with and without Metabolic Syndrome (MetS).

Methods: All patients, at baseline, have had a carotid ultrasound evaluation and classified in two subgroups: the first one without atherosclerotic lesions and the second one with preclinical atherosclerosis (increased IMT or asymptomatic carotid plaque). Cardiovascular endpoints were investigated in a 20-years follow-up.

Results: There were 242 cardiovascular events: 144 among patients with MetS and 98 among in healthy controls (57.4% vs. 35.2%; $P<0.0001$). 63 events occurred in patients with normal carotid arteries, while 179 events occurred in patients with preclinical atherosclerosis (31.8% vs. 54.1%; $P<0.0001$). Of the 144 total events occurred in patients with MetS, 36 happened in the subgroup with normal carotid arteries and 108 in the subgroup with preclinical atherosclerosis (45% vs. 63.15%; $P=0.009$). 98 events occurred in patients without MetS, of which 27 in the subgroup with normal carotid arteries and 71 in the subgroup with preclinical atherosclerosis (22.88% vs. 44.37%; $P=0.0003$). In addition, considering the 63 total events occurred in patients without atherosclerotic lesions, 36 events were recorded in the subgroup with MetS and 27 events in the subgroup without MetS (45% vs. 22.88%; $P=0.0019$). Finally, in 179 total events recorded in patients with preclinical carotid atherosclerosis, 108 happened in the subgroup with MetS and 71 happened in the subgroup without MetS (63.15% vs. 44.37%; $P=0.0009$). The Kaplan-Meier function showed an improved survival in patients without atherosclerotic lesions compared with patients with carotid ultrasound alterations ($P=0.01$, HR: 0.7366, CI: 0.5479 to 0.9904).

Conclusions: Preclinical atherosclerosis lead to an increased risk of cardiovascular events, especially if it is associated with MetS.

P2301 | BEDSIDE

Metabolic syndrome patients are characterized by excess sympathetic overdrive and arterial stiffening in resistant hypertension

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Purpose: Resistant hypertension is related to sympathetic overdrive and arterial stiffening, while there are scarce data whether metabolic syndrome further potentiates sympathetic activity and vascular abnormalities in this setting. The aim of this study was to assess the effect of the metabolic syndrome on muscle

sympathetic nerve activity (MSNA) and arterial stiffness in resistant hypertensive patients.

Methods: We studied 24 patients with resistant hypertension [age: 58±10 years, 15 males, office blood pressure (BP): 178/94±15/12 mmHg, 24-hour BP: 149/84±15/11 mmHg, under 4.2±0.5 drugs] that underwent transthoracic echocardiographic study and blood sampling for assessment of the metabolic profile. Metabolic syndrome was defined according to the Adult Treatment Panel III criteria and arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV). In all participants sympathetic drive was assessed by MSNA estimations based on established methodology (microneurography).

Results: Resistant hypertensive patients with metabolic syndrome ($n=11$) compared to those without ($n=13$) exhibited higher waist circumference (108.1 ± 5.4 vs. 94.6 ± 9.2 cm, $p=0.001$), fasting glucose (131.8 ± 2.9 vs. 94.6 ± 2.1 mg/dl, $p<0.05$), office systolic BP (186 ± 17 vs. 171 ± 15 mmHg, $p<0.001$) and left ventricular mass index (134.2 ± 18.1 vs. 124.6 ± 17.2 g/m², $p=0.001$). Moreover, metabolic syndrome patients compared to those without were characterized by greater levels of carotid to femoral PWV (11.7 ± 0.8 vs. 9.3 ± 1.1 m/sec, $p<0.001$) and sympathetic nerve traffic as reflected by MSNA levels (84.2 ± 2.8 vs. 75.1 ± 2.2 bursts per 100 heart beats, $p<0.001$). In all participants MSNA was related to waist circumference ($r=0.38$, $p=0.002$) and office systolic BP levels ($r=0.35$, $p<0.05$) but there was no association with PWV values ($p=NS$).

Conclusions: In resistant hypertensive patients, metabolic syndrome is associated with high MSNA and PWV levels. These findings support that metabolic syndrome further deteriorates sympathetic activity and arterial stiffening characterizing resistant hypertension.

P2302 | BEDSIDE

Gradual adverse prognostic effect of metabolic syndrome and diabetes mellitus in essential hypertensive subjects

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Purpose: Metabolic syndrome (MS) is associated with increased risk for atherosclerotic cardiovascular disease, whereas its prognostic role in hypertension remains controversial. The aim of the present study was to assess the prognostic role of MS and Diabetes Mellitus (DM) for the incidence of adverse events in a cohort of essential hypertensives.

Methods: We followed up for a median period of 40 months (IQR 28-60 months) 2176 essential hypertensives free of cardiovascular disease (mean age 57.6 years, 1010 males, office blood pressure (BP) = 143.4/89.2 mmHg). All subjects had at least one annual visit and at baseline underwent complete echocardiographic study for estimation of left ventricular mass index (LVMI) and blood sampling for assessment of metabolic profile. MS was defined according to the updated NCEP III criteria. Endpoint gradual of interest was the incidence of stroke, coronary artery disease (CAD) and their composite.

Results: MS was present at baseline in 819 hypertensives (37.6%) and DM in 305 (14%). The incidence of the composite end-point was 3.1% (20 patients with stroke, 50 with CAD, 2 with both) over the whole follow-up period. Patients with MS compared to those without MS or DM exhibited greater office systolic BP (by 2.8 mmHg, $p=0.002$), waist circumference (by 9.9 cm, $p<0.001$), body mass index (by 3.1 kg/m², $p<0.001$) and LVMI (by 2.7 g/m², $p=0.029$) while did not differ regarding age and gender. Patients with DM compared to those without DM or MS were older (by 4 years, $p<0.001$) and exhibited greater office pulse pressure (by 4.2 mmHg, $p<0.001$), waist circumference (by 8.5 cm, $p<0.001$), body mass index (by 2.8 kg/m², $p<0.001$) and LVMI (by 4.4 g/m², $p=0.006$). Incidence of the composite end-point was significantly higher in patients with DM (5.9% vs. 1.9%, log rank $p<0.001$) and MS (3.7% vs. 1.9%, log rank $p=0.024$) compared to those without DM or MS, as well as in patients with DM compared to those with MS (log rank $p=0.018$).

Conclusions: Metabolic syndrome and diabetes mellitus independently predict adverse events in essential hypertensive subjects.

P2303 | BEDSIDE

Metabolic syndrome (MetS) predicts cardio- and cerebrovascular events in a twenty years follow-up. A prospective study

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Background and purpose: Metabolic Syndrome (MetS) is a cluster of cardiovascular risk factors, considered as emerging and promoting atherosclerosis. This study aimed at the evaluation of the influence of MetS on the prediction of cerebro- and cardiovascular events during a 20 years follow-up period in an asymptomatic population of middle-aged subjects.

Methods: We evaluated 529 asymptomatic persons through a prospective study. Study population was divided into two subgroups: patients with and without MetS. Echo-color-Doppler was used in order to assess the presence of subclinical atherosclerosis.

A 20 years follow-up study was carried out in order to estimate the incidence of cerebro- and cardiovascular, fatal and non fatal, events (AMI, stroke, abdominal aortic aneurysm, TIA, angina pectoris).

Results: 242 cerebro- and cardiovascular events were registered, 43 fatal (24 in MetS and 19 in controls) and 199 non fatal (120 with MetS and 79 without it, $p < 0.0001$). Free-events survival was lower in patients suffering from MetS ($p < 0.0012$; HR 0.6847; C.I.95%: 0.5274– 0.8889). Ultrasound showed a higher prevalence of subclinical atherosclerosis in patients with MetS than in the unaffected ones (68.12% vs. 57.5% $p < 0.01$; OR = 1.58 with C.I.95% = 1.10–2.28, $p < 0.01$).

Conclusions: Patients with MetS have a higher cardiovascular risk that can be explained by atherosclerotic changes: the components of MetS interact to affect vascular thickness synergistically and promote the development of subclinical atherosclerosis. So we recommend to prevent the development of MetS abnormalities and to investigate the presence of subclinical atherosclerosis by echocolor-Doppler in order to stratify more accurately the global CV risk.

P2304 | SPOTLIGHT

Metabolic syndrome is associated with and predicted by resting heart rate: cross-sectional and longitudinal findings from Kailuan study

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Background: Although higher resting heart rate (RHR) has emerged as a predictor for lifespan, the underlying mechanisms remain obscure. The present investigation was to test whether there was a positive relationship between RHR and metabolic syndrome (MetS) and whether RHR was a predictor of future metabolic syndrome.

Methods and results: A large vocational cohort (Kailuan Study) was surveyed in 2006–2007 and some were followed-up longitudinally. MetS was diagnosed when a participant presented at least 3 of the following: abdominal adiposity, low HDL cholesterol, high triglycerides, hypertension, and impaired fasting glucose. RHR was derived from ECG recording. Firstly, a clear and positive association between RHR and MetS was found in a cohort of 89 860 participants recruited in 2006–2007: the odds ratio of having MetS was 1.49 (95% confidence interval, 1.32–1.69) in subjects with RHR at 95–104 beats/minute than at 55–64 (reference) after adjusting for age, sex, education, cigarette smoking, alcohol drinking, physical activities, BMI, hypertension, diabetes and hyperlipidemia, inflammation marker and renal function. Secondly, during 4 years follow-up of 43,725 individuals who had no MetS when recruited, higher RHR predicted greater risk of MetS incidence longitudinally: the odds ratio of having MetS 4 years later was 1.41 (95% confidence interval, 1.21–1.65) in subjects with RHR at 95–104 than at 55–64 after all adjustments.

Conclusion: Kailuan Study provides evidence that higher RHR is an independent risk factor for existing MetS, and for future incidence of MetS.

P2305 | BEDSIDE

Predictive value of 1,5-anhydro-d-glucitol for prevalence of coronary artery disease in non-diabetic adults

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Purpose: Elevation of glycated hemoglobin (HbA1c) level is predictive of the prevalence of coronary artery disease (CAD) and mortality. Serum 1,5-anhydro-d-glucitol (1,5-AG) levels rapidly decrease concomitantly with the excretion of glucose in urine. Serum 1,5-AG is a useful clinical marker for short-term glycemic status. 1,5-AG reflects glycemic excursions more sensitively than HbA1c, especially in the postprandial state. Postprandial hyperglycemia is one of the important risks of CAD. The aim of this study was to evaluate 1,5-AG and HbA1c as the predictors of CAD in patients with and without diabetes mellitus.

Methods: The subjects consisted of 612 consecutive patients who underwent their first coronary angiography from July 2011 to January 2014. The association between prevalence of CAD and 1,5-AG or HbA1c levels were evaluated. Correlation between 1,5-AG or HbA1c and severity of CAD were also assessed. Severity of CAD was quantified by the SYNTAX score.

Results: The patients with CAD ($n=289$, 47.2%) presented significantly lower 1,5-AG and higher HbA1c values than the patients without CAD (1,5-AG: $12.9 \pm 8.6 \mu\text{g/ml}$ vs. $18.3 \pm 9.2 \mu\text{g/ml}$, $p < 0.0001$, HbA1c: $6.4 \pm 1.3\%$ vs. $5.8 \pm 0.8\%$, $p < 0.0001$). Multivariable logistic regression analysis presented that both 1,5-AG and HbA1c were independent predictors for prevalence of CAD. In addition, both 1,5-AG and HbA1c significantly correlated with the SYNTAX score ($\rho = -0.262$, $p < 0.0001$, $\rho = 0.282$, $p < 0.0001$, respectively). When the study patients were limited to non-diabetic patients ($n=422$), only 1,5-AG showed the independent predictive value for CAD (Odds ratio; 0.972, 95%CI 0.946–1.000, $p=0.046$) in a multivariable logistic regression model (sex, age, hypertension, dyslipidemia, smoking habit and renal function were adjusted).

Conclusions: Both 1,5-AG and HbA1c were the independent predictors for CAD and significantly correlated with the SYNTAX score. Among non-diabetic patients, 1,5-AG level independently predicted prevalence of CAD. In contrast, HbA1c could not present predictive value for CAD. 1,5-AG may be superior to HbA1c in predicting CAD in non-diabetic population.

EMERGING DIETARY CONCEPTS

P2307 | SPOTLIGHT

Industrial trans fat in popular foods is still a health issue in europe: a market basket investigation

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Purpose: To minimise the intake of industrial trans fat (I-TF) and thereby reduce the risk of coronary heart disease, nearly all European countries rely on food producers to voluntarily reduce the I-TF content in food. The objective of this study was to investigate the efficiency of this strategy in 2012–2013 in 20 European countries.

Methods: The I-TF content in pre-packaged biscuits/cakes/wafers was assessed in a market basket investigation. Three large supermarkets were visited in each capital, and in some countries, three additional ethnic shops were included.

Results: A total of 598 samples of biscuits/cakes/wafers with "partially hydrogenated vegetable fat" or a similar term high on the list of ingredients were analysed, 312 products had more than 2% of fat as I-TF, exceeding the legislatively determined I-TF limit in Austria, Switzerland, Iceland, Norway, Hungary and Denmark; the average was 19%. In seven countries, no I-TF was found, whereas nine predominantly Eastern European countries had products with very high I-TF content. The products in the remaining four countries had intermediate levels. Of the five countries that were examined using the same procedure in 2006, three had unchanged I-TF levels in 2013, and two had lower levels. The 18 small ethnic shops examined in six Western European countries sold 83 products that contained an average of 23% of the fat as I-TF, all imported from countries in South-eastern Europe. In Sweden, this type of imported food was also available in large supermarkets.

Conclusion: The findings suggest that subgroups of the population in many countries in Europe still consume I-TF in amounts that increase their risk of coronary heart disease. Under current EU legislation, the sale of products containing I-TF is legal but conflicts with the WHO recommendation to minimise the intake of I-TF. A EU-legislative limit on I-TF in foods is an effective strategy to achieve this goal.

P2308 | BEDSIDE

Early life famine and telomere length: data from Siege of Leningrad population

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Objective: During Second World War (1941–1944) inhabitants of Leningrad (now Saint-Petersburg) were exposed to long-term famine with possible impact on cardiovascular outcomes in follow-up period. The aim of our study was to assess the influence of starvation on telomere length and prevalence of cardiovascular diseases in survivors of Leningrad Siege during Second World War (1941–1944) comparing with control group.

Design and methods: 305 survivors of Leningrad Siege (81 males and 224 females) were examined (64–86 years). All participants were interviewed by special questionnaire regarding risk factors, previous medical history and antihypertensive therapy. Blood pressure (BP) and anthropometry were performed according to standard guidelines. Echocardiography (Vivid 7) and electrocardiography (ECG) were performed. The diagnosis of AF was exposed on the basis of anamnesis and ECG records. Fasting serum lipids and plasma glucose were measured on Hitachi-902. Control group of age and sex matched subjects ($n=47$, 67–84 years) was born in the other parts of USSR with no exposure to severe famine and lived in Leningrad after the Siege. Relative telomere lengths were measured by quantitative PCR and the ratio of telomere repeat copy number to single gene copy number (T/S) was calculated for each DNA sample. Informed consent was obtained from all participants.

Results: Age differences between groups are not significant ($p=0.24$ according to Fisher criteria). Survivors of Siege of Leningrad had lower anthropometric data (height 162.4 ± 8.6 vs 165.9 ± 8.4 cm ($p=0.007$) and weight 72.5 ± 14.9 vs 78.3 ± 13.9 kg ($p=0.02$)), higher HDL level (1.44 ± 0.32 vs 1.29 ± 0.27 mmol/l, $p=0.008$). There were no significant differences in the prevalence of cardiovascular disease in 2 groups: only prevalence of atrial fibrillation was slightly higher in the control group (8 (18.3%) vs 25 (8.2%), $p=0.05$).

Survivors has shorter telomere length 0.77 ± 0.54 versus controls 0.72 ± 0.56 ($p < 0.001$) both in males and females.

Conclusions: Early life famine is associated with telomere shortening in both genders but not with cardiovascular diseases. Perhaps negative outcome after famine can be compromised by long-term post-siege period.

P2309 | BEDSIDE**Malnutrition is a key prognostic factor in patients with heart failure with preserved ejection fraction**

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Background: Malnutrition is one of the unfavorable prognostic factors in patients with heart failure (HF). Prevalence of HF with preserved ejection fraction (PEF) (defined as left ventricular ejection fraction >50%) has been increased and there is an obvious association between HF-PEF and hypertension, diabetes mellitus, and insulin resistance. However, association between malnutrition and clinical outcomes in patients with HF-PEF remains to be elucidated.

Methods and results: We evaluated controlling nutritional status score (CONUT), prognostic nutritional index (PNI), and geriatric nutritional risk index (GNRI) in 190 patients with HF-PEF (mean 69.9±11.6 years) admitted to our hospital. CONUT consists of serum albumin level and total cholesterol level, and total lymphocyte count. PNI consists of serum albumin level and total lymphocyte count. GNRI consists of serum albumin level and ratio of body weight to ideal body weight. Patients were prospectively followed with the endpoints being cardiovascular death or rehospitalization. There were 56 events including 14 deaths and 42 rehospitalizations during a median follow-up of 14.0 months. Patients with cardiac events showed more severe New York Heart Association (NYHA) functional class and lower left ventricular ejection fraction (LVEF) compared with those without. Total lymphocyte count, serum albumin, and total cholesterol level were lower in patients with cardiac events. As a result, patients with cardiac events showed higher CONUT score (6, IQR 3.5-8 vs. 2, 0-3, $P<0.001$), lower PNI score (30.4, 27.3-36.1 vs. 38.9, 35.7-42.4, $P<0.001$), and lower GNRI score (84.9, 77.5-92.3 vs. 96.3, 90.8-102.7, $P<0.001$) compared with those without. The correlations between each nutritional index and clinical parameters were examined. CONUT score correlated with age, LVEF, and serum brain natriuretic peptide (BNP) level. PNI score correlated with age, LVEF, and serum BNP level. GNRI score correlated with age, LVEF, and serum BNP level. In Cox proportional hazards analysis, higher CONUT score (hazard ratio 9.0, 95% CI 3.2-25.2), lower PNI score (3.6, 1.7-7.7), and lower GNRI score (6.3, 2.7-14.9) were independently associated with cardiac events after adjustment of age, gender, NYHA functional class, and serum BNP level. Kaplan-Meier analysis revealed a significantly higher cardiac event rate was observed in patients with malnutrition than in those without.

Conclusion: Malnutrition was associated with unfavorable outcomes in patients with HF-PEF. Evaluating nutritional status may provide valuable prognostic information in patients with HF-PEF.

P2310 | SPOTLIGHT**Endothelial function in obese and overweight patients: the role of olive oil, fish and nuts**

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Aim: To assess the effect of olive oil, non fried fish and nuts on endothelial function in overweight and obese patients.

Methods: 47 overweight and obese patients (24 men, mean age 54±11 years) were studied. All patients were educated to follow a controlled diet for 3 months, under closely supervision of a physician and a dietitian, who met participants every week. At the beginning and at the end of this first phase, endothelial function by using flow-mediated dilatation (FMD) technique was assessed. Diet did not provide measurement of foods calories and weights. Furthermore, 22 patients continued the dietary treatment and were assigned to 3 groups: Group A: diet + olive oil; Group B: diet + fish; Group C: diet + nuts. 25 continued the controlled diet (control group). They were followed-up for 15 months and, before study ending, FMD was measured. Data coming from groups A, B and C were compared to control groups.

Results: Our study showed a positive effect of standard diet on endothelial function with a significant increase of FMD values recorded at 3 months follow-up as compared to the baseline ($p<0.001$). At the end of the study (18 months), we observed a significant improvement in endothelial function as compared to baseline ($p=0.03$). Olive oil, fish and nuts enriched diets showed favorable effects on endothelial function: we observed significant higher FMD values in all the 3 groups (A, B and C) as compared to controls at the end of study ($p=0.02$, $p=0.03$ and $p=0.04$ respectively).

FMD values after 3 and 18 months of diet

All the patients (N=47)	Group A (n=7)	Group B (n=8)	Group C (n=7)	Control group (n=25)	p
At 3 months	5.4±0.4	5.8±2.2	5.8±2.2	5.7±2.4	ns
At 18 months	7.1±1.0*	7.3±2.1**	7.6±2.0***	6.3±1.5	
p	0.017961	0.049951	0.027993	0.042208	

Conclusions: A controlled and supervised diet and the introduction of functional foods (olive oil, fish and nuts) seemed to be able to improve endothelial function in overweight and obese subjects after a short (3 months) and medium (18 months) period.

P2311 | BEDSIDE**Genetic variants involved in interindividual variability in vitamin E bioavailability: towards a better understanding of the role of vitamin E in the aetiology of cardiovascular diseases**

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Purpose: Vitamin E is essential for human health and may play a role in the aetiology of cardiovascular diseases. However, its absorption efficiency is widely variable (i.e. between 10% and 79%). This might partly explain the lack of agreement in the results of clinical trials aiming to prevent cardiovascular disease occurrence through vitamin E supplementation. This high interindividual variability is assumed to be due to both dietary and genetic factors. Several polymorphisms have been identified but existing studies have so far focused on single SNPs that only explained a minor fraction of the variability of such a complex phenotype. This study thus aimed to identify a combination of SNPs that could explain a significant part of the variability in vitamin E bioavailability.

Methods: Thirty-eight healthy male volunteers consumed a meal containing a vitamin E supplement (134 mg α -tocopheryl acetate). Volunteers were genotyped using whole-genome microarrays. α -tocopherol (TOL) concentration was measured in plasma chylomicrons isolated at regular time intervals over 8 h postprandially. The association of SNPs in or near candidate genes (59 genes representing 4475 SNPs) with the postprandial chylomicron TOL response (0 to 8 h area under the curve) was assessed by partial least squares regression, a multivariate statistical approach.

Results: The postprandial chylomicron TOL response to the meal was highly variable (CV of 81%). Data obtained allowed us to generate a validated significant model ($P=1.8.10^{-8}$) that included 28 SNPs in 11 genes (ABCA1, ABCG1, APOB, BET1, IRS1, LIPC, NAT2, PNLP, SLC10A2, SREBF2, ZNF664). This model explained 82% of the variance and allowed us to accurately predict a subject's vitamin E absorption (Spearman Rho=85% between the measured and predicted vitamin E response). For all these SNPs, univariate analysis showed that subjects who bore different genotypes exhibited a significantly different vitamin E absorption (q -value <0.05).

Conclusions: The ability to respond to vitamin E appears to be at least in part genetically determined. A combination of SNPs in 15 genes related to both vitamin E and chylomicron metabolism can explain a large part of the variability in vitamin E absorption in males. These results could allow a better understanding and design of future clinical trials aiming at studying the association of vitamin E supplementation with the prevention of cardiovascular diseases.

P2312 | BEDSIDE**Consumers of fresh dairy products and consumers of cheese exhibit different dietary patterns**

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Background: Recommendations for healthy food choice emphasize the consumption of two to three servings of dairy products per day. Choice of dairy product may substantially vary according to overall dietary pattern. We aimed to describe dietary patterns and adherence to dietary recommendations according to the consumption of different types of dairy products.

Methods: Data from the French nation-wide 2010 CCAFCross-sectional dietary survey were analysed. Food groups were collected with a 7-day food record. Fresh Dairy Products (FDP) included all fresh dairy except dairy desserts and Greek yogurts. Cheese included all cheese except cottage cheese. The PANdiet (Probability of Adequate Nutrient intake) score was used to assess adherence to dietary and nutritional recommendations.

Results: The sample comprised 948 French people, who were women and men recruited from the general population, with age ranging from 25 to 64 years. While 22% of the sample consumed no FDP during the record, 30% were categorized as low consumers (1 to 3 servings per week), 26% were medium (4 to 6 servings/w) and 22% high consumers (more than 6 servings/w). The distribution of cheese consumers was: 9% of non-consumers, 37% of low (1 serving/day), 31% of medium (2 servings/d), and 23% of high consumers (more than 2 servings/d). Compared to low consumers, high FDP and cheese consumers were both characterized by significantly ($p<0.05$) higher intakes of fruits and vegetables. High FDP consumers also exhibited significantly higher intakes of simple sugars (+25%) than low FDP consumers, and had significantly lower intakes of pastas (-27%), ready-to-eat meals (-16%), and alcoholic beverages (-22%). No significant difference was observed as regard to daily energy intake, and total fat, saturated fat, or sodium intake. On the other hand, high cheese consumers exhibited significantly higher daily energy intake (+23%), and significantly higher consumptions of alcohol (+96%), total fat (+31%), saturated fat (+41%) and sodium (+36%), compared to low cheese consumers, with no difference as regard to simple sugar intake. The PANdiet score was significantly better among high FDP consumers

than among low consumers, but it was significantly worse among high cheese consumers than among low consumers.

Conclusion: Consumers of fresh dairy products and consumers of cheese adopt different dietary patterns with varying intakes of simple sugars, fats, and sodium. Adherence to dietary recommendations is better among high consumers of FDP than among people with lower consumptions.

P2313 | BENCH

Chronic dietary supplementation with inorganic nitrate recovers age-related cardiac dysfunction

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Background and objectives: Ageing is the predominant risk factor for cardiovascular diseases and contributes to increased cardiovascular morbidity and mortality in the elderly. Cardiovascular functions are regulated by nitric oxide (NO). The micronutrient inorganic nitrate, abundant in our everyday diet, is a major source for nitrite and NO and has recently been shown to reverse age-related vascular dysfunction. We hypothesized that age-related cardiac functions could be improved by a chronic dietary nitrate supplementation in senescent mice.

Methods: A chronic dietary nitrate supplementation regimen was performed in young and old C57Bl6 wild-type mice for 8 weeks with age-matched mice as controls. Age related myocardial diastolic function was assessed non-invasively via echocardiographic pulsed wave and tissue doppler (early and late mitral inflow and anulus velocity pattern, E/A and E/A', respectively) and in-vivo microtip catheter measurements. To elucidate the underlying impacts of dietary nitrate on cardiac functions we determined NO-species, cGMP levels and cGMP dependent protein kinase activity and applied noninvasive cardiac manganese-enhanced MRI to study in-vivo calcium cycling.

Results: Aged mice displayed an abnormal cardiac diastolic pattern, which was reversed by dietary nitrate supplementation (mean±SD, E/A young 1.6±0.3 vs old 1.1±0.3 vs old nitrate 1.5±0.2, p<0.05 and E/A' young 1.4±0.2 vs old 0.8±0.1 vs old nitrate 1.3±0.5, p<0.05; end-diastolic pressure volume relationship young 0.07±0.02 vs old 0.15±0.03 vs old nitrate 0.10±0.02, p<0.05 and isovolumic relaxation constant tau young 5.1±1.2 vs old 9.1±2.7 vs old nitrate 5.6±1.7, p<0.05).

Mechanistically, dietary nitrate supplementation increased plasma nitrite content in old mice (young 1.3±0.6 µmol; old 0.8±0.5 µmol vs old nitrate 4.2±1.4 µmol, p<0.05), enhanced cGMP levels (young 144±66 fmol/mg protein, old 95±35 fmol/mg protein vs old nitrate 231±142 fmol/mg protein, p<0.05) and PKG activity in old mice (young 0.65±0.30 activity/mg protein, old 0.40±0.16 activity/mg protein vs old nitrate 1.1±0.5 activity/mg protein, p<0.05). This was substantiated by altered calcium cycling in nitrate supplemented old mice (young 1.57±0.17 enhancement ratio; old 1.34±0.14 enhancement ratio vs old nitrate 1.6±0.1 enhancement ratio, p<0.05).

Conclusion: We observed an altered age-related myocardial dysfunction, which was reversed by dietary nitrate supplementation. Our findings provide insights that undermine the impact of dietary micronutrients to counteract cardiac aging.

P2314 | SPOTLIGHT

Cardiac safety of so called “energy drinks”

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Over 50 million litres of more than 120 so called “energy drinks” have been consumed in 2011 in France. Because of their association with adverse events (EDAEs), these drinks have recently raised national awareness in France. They are sodas enriched with an array of substances already present in food, such as caffeine, taurine and vitamins. Each individual drink usually contains up to the caffeine content of two espressos. When taken in great quantity, they are suspected to induce a sensation of excitation and facilitate among others, serious adverse events in predisposed subjects.

Material and methods: Spontaneously reported EDAEs in France have been collected between 1/1/2009 and 30/11/2012 in the context of national nutritional vigilance scheme. Their causal relationship with the different brands of drinks have been assessed by means of a specific scale.

Results: Among the 257 adverse events that have been notified during the survey, 45 were excluded for lacking data. Most of the EDAEs were of cardio-vascular origin (n=95), followed by psychiatric (n=74) and neurological (n=57). In 54 cases (25.5%) the causality of ED was deemed possible, in 18 (8.5%) likely, and 7 cases (3.3%) very likely. Cardiovascular cases included cardiac arrests, sudden or unexplained deaths (n=9), and mainly other rhythm disorders (n=43), angina (n=13) and hypertension (n=5). “Caffeine syndrome” associating tachycardia, anxiety, and headaches was present in 60 of the cases.

In conclusion, “energy drinks” are associated with adverse events among which cardiovascular events. Due to a potentially strong underreporting bias, it seems

necessary to inform certain predisposed subjects of such risks, as unknown amounts of caffeine resulting from “serial drinks” in dance clubs or during physical exercise, two popular yet particularly risky situations, could facilitate the emergence of complex cardiac arrhythmias. Moreover, health professionals should be aware of EDAEs and the necessity to report them in a specific vigilance system, such as Nutrivigilance in France.

P2315 | SPOTLIGHT

Perioperative vitamin- D-status in high-risk patients undergoing cardiac surgery. a prospective single centre analysis

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Aims: Recent evidence suggests that preoperative vitamin D deficiency (25-hydroxyvitamin D = 25(OH)D) is independently associated with major cardiac events in cardiac surgical patients. The aim of the current study was to evaluate the perioperative vitamin 25(OH)D levels in high-risk patients undergoing cardiac surgery and to investigate their association with in-hospital mortality and morbidity.

Methods and results: Hundred high-risk patients (mean age 72±10 years, mean EuroSCORE II 6.1±4.5%) scheduled for elective cardiac surgery were enrolled in this prospective study. Blood samples were taken in five different time-points (pre-operatively (T1), day of surgery (T2), first (T3) second (T4) and 5th (T5) postoperative day). Of the study cohort 44% had preoperatively deficient (10-20 ng/ml) 45% severe deficiency (<10 ng/ml) and 11% normal 25(OH)D values. Cardiac surgery led to a reduction of 25(OH)D-concentration (T1 to T2, p: 0.004). Female patients had in all time points lower 25(OH)D-levels (p: 0.001). In-hospital mortality was 7% and the incidence of permanent neurological deficit 3%. Postoperative deficiency of 25(OH)D was associated with an increased in-hospital-mortality (p<0.041) and hospital stay (p: 0.002).

Conclusion: Cardiac surgical procedures in high-risk patients fortify preoperative 25(OH)D deficiency. Deficient postoperative 25(OH)D-levels are associated with an increase of in-hospital mortality. Thus, further studies should clarify the potential benefits of perioperative vitamin D supplements.

DIABETES AND OBESITY – A DEADLY COMBINATION

P2317 | BEDSIDE

Oral glucose tolerance test is still needed in patients with coronary artery disease

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Purpose: New 2013 European Guidelines on Diabetes and Cardiovascular Diseases recommend fasting plasma glucose (FPG) and glycated haemoglobin A1C (HbA1c) for diagnosing disorders of glucose metabolism, and performing an oral glucose tolerance test (OGTT) is now only suggested in doubtful cases. This guideline is substantially different from the previous one and lacks clear evidence in patients with coronary artery disease. Our purpose was to evaluate the diagnostic accuracy of FPG and HbA1c and the added value of OGTT.

Methods: FPG, HbA1c and OGTT (75g, 2-h) were prospectively evaluated in a consecutive group of patients with CAD submitted to PCI. ADA criteria were used to define diabetes (FPG ≥126 mg/dl and/or 2-h glucose ≥200 mg/dl and/or HbA1c ≥6.5%) and pre-diabetes (FPG 100–125 mg/dl and/or 2-h glucose 140–199 mg/dl and/or HbA1c 5.7–6.4%).

Results: 350 patients were included (mean age 61.1±11.5 years, 76% male). Taken together, OGTT and HbA1c identified 54 (15.4%) new cases of diabetes (DM) and 205 (58.6%) cases of pre-DM; only 91 (26.0%) patients had a normal glucose metabolism. Taken alone, HbA1c identified 21/54 new cases of DM (Sens 38.9%, NPV 90.0%, AUC ROC 0.78; Kappa 0.52, p<0.0001), as compared with 26/54 cases identified with FPG alone (Sens 48.1%, NPV 91.9%, AUC ROC 0.88; Kappa 0.61, p<0.0001) and 46/54 cases identified with 2-h glucose (Sens 85.2%, NPV 97.4%, AUC ROC 0.97; Kappa 0.91, p<0.0001). FPG+HbA1c (the strategy recommended in the new guidelines) only identified 37/54 patients with DM (Sens 68.5%, NPV 94.6%, Kappa 0.79, p<0.0001). Performing the OGTT in a subset of patients with high risk for diabetes (adapted Framingham Diabetes Risk Score >12; n=123, 35.1% of the total population) identified 49/54 dts cases of DM (Sens 90.7%, NPV 98.3%, Kappa 0.94, p<0.0001). Performing the OGTT in all patients with pre-DM in the initial FPG+HbA1c evaluation (n=209; 59.7% of the total population) identified 51/54 dts (Sens 94.4%, NPV 99.0%, Kappa 0.97, p<0.0001).

Conclusions: Using only FPG and HbA1c, as recommended by the 2013 guidelines, would leave undiagnosed around 1/3 of new cases of DM in CAD patients. Performing an OGTT in all patients with pre-DM in the FPG+HbA1c evaluation (almost 2/3 of the patients) identifies the majority of patient with DM. Only routine use of OGTT and HbA1c identifies all patients with undiagnosed DM.

P2318 | BEDSIDE**Effect of gestational diabetes mellitus (GDM) on arterial stiffness**

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Objective: Gestational diabetes mellitus (GDM) may be associated with cardiovascular diseases. However, the relation between aortic stiffness and GDM is not clear. The present study aims to evaluate the aortic stiffness parameters by comparing GDM with a healthy control group via transthoracic echocardiography.

Methods: This was a cross-sectional study involving the monitoring of 62 pregnant women (33 with GDM and 29 with uncomplicated pregnancy as controls) during the third trimester. The aortic strain, aortic distensibility, and aortic stiffness values were measured via transthoracic echocardiography. The average systolic and diastolic measurements were calculated following three consecutive measurements.

Results: Data on age, blood pressure levels, heart rate, and basic echocardiography were similar in both groups. BMI was significantly higher in the GDM group ($p < 0.01$). Aortic strain and distensibility were significantly lower in the GDM group ($p < 0.01$). Aortic stiffness index was significantly higher in the GDM group ($p < 0.01$) (Table 1).

Table 1. Clinical characteristics and measurement of aortic elastic parameters in the gestational diabetes group and the control group

	Gestational diabetes (n: 33)	Control group (n: 29)	p-value
Age (years)	30,18±5,7	29,66±4	0,68
Body mass index (kg/m ²)	28,72±5,02	26,10±3,8	<0,05
Aortic diastolic diameter (mm)	24,52±3,4	22,69±3,1	0,33
Aortic systolic diameter (mm)	27,30±3,4	26,34±3,1	0,26
LV diastolic diameter (mm)	46,18±4,5	46,21±4,2	0,90
LV systolic diameter (mm)	29,42±5,6	30,14±3,1	0,50
Aortic strain (%)	12,29±4,2	16,43±5,3	<0,01
Distensibility (cm ² dyne ⁻¹)	6,24±2,4	7,76±3,2	<0,01
Aortic stiffness index	4,02±1,3	3,19±1,1	<0,01

Aortic stiffness parameters did not exhibit any significant difference between the insulin-receiving GDM group and the diet-controlled GDM group. Postprandial glucose levels were positively correlated to the level of the aortic stiffness index ($p: 0.04$) and were negatively correlated with the level of aortic strain ($p < 0.01$) and distensibility ($p: 0.03$).

Conclusion: Arterial stiffness is increased in women with GDM compared to the control group. There is a correlation between postprandial glucose and arterial stiffness.

P2319 | BEDSIDE**Essential hypertension: when ingredients contains “a little more sugar”**

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Background: Sustained hyperglycemia, even in the prediabetic range, is associated with endothelial dysfunction, vascular stiffness and adverse cardiovascular outcomes. Aim of our study was to explore the additive effects of impaired glycated-hemoglobin (HbA1c) on essential hypertension sequelae.

Methods: We studied 465 never treated, newly diagnosed, essential hypertensive patients stage I-III (mean age 52±13 years, 47% female), non-diabetic and without known cardiovascular disease. Evaluation of hypertension was performed according to ESH Guidelines. Traditional glycemic indices (fasting plasma glucose-FPG, HbA1c and 2hr oral glucose tolerance-OGTT) were performed in all patients. Euglycemic group (E) included patients with all the above glycemic indices normal (FPG <100 mg/dl + HbA1c <5.7% + OGTT <140mg/dl), while impaired HbA1c group (IH) included patients with HbA1c in prediabetic range (5.7-6.4%).

Results: The mean values of HbA1c and FPG were higher in IH compared to E (92±7 vs. 90±7, $p=0.001$), while they did not differ regarding OGTT ($p=0.455$). Moreover, IH compared to E were older (54±12 vs. 49±14, $p=0.003$), had higher ultrasonographic-derived preperitoneal and visceral fat thickness (18.9±6.4 vs. 17±7 mm, $p=0.019$ and 70.1±29 vs. 60.3±24.5 mm, $p=0.003$, respectively), with higher prevalence of metabolic syndrome (80,5% vs. 26,1%, $p<0,001$), while they didn't differ regarding gender (males 48,4% vs. 50,6%, $p=0.723$), BMI (28±5 vs. 29±5 kg/m², $p=0.133$), waist and hip circumference, waist to hip ratio and prevalence of abdominal obesity ($p>0.05$ for all). With the only exception of the family history of cardiovascular disease (54% vs. 41%, $p=0.004$), the two groups didn't differ significantly regarding classical cardiovascular risk factors, including office and 24hr blood pressure and heart rate ($p>0.05$ for all). However, IH presented higher prevalence of diastolic dysfunction (76% vs. 58%, $p=0.008$), c-f PWV (8.9±2.4 vs. 8.2±1.6, $p=0.002$) and carotid plaques (55% vs. 40%, $p=0.017$), and lower TDI Em/Am (0.89±0.2 vs. 1±0.4, $p=0.007$), while they did not differ regarding LVMI, carotid IMT, ankle-brachial index, ACR and Aix ($p>0.05$ for all).

Conclusion: In essential hypertension, presence of impaired HbA1c augments arterial stiffness, carotid atherosclerosis and left ventricular diastolic dysfunction. Compared to anthropometric measurements, preperitoneal and fat thicknesses represents more sensitive indices of impaired glycated-hemoglobin.

P2320 | BEDSIDE**Exaggerated insulin secretion is a risk of hypoglycemia in patients with cardiovascular disease**

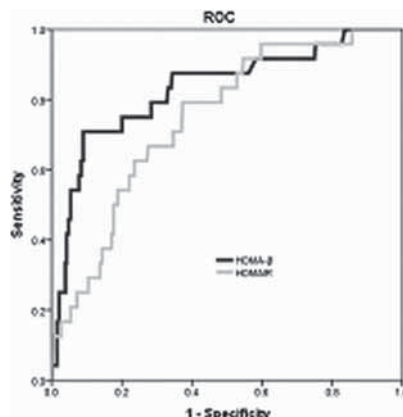
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Purpose: Recently, hypoglycemia is suggested to induce the cardiovascular disease and endothelial cell dysfunction through increasing the platelet aggregation as well as the catecholamine secretion. However, characteristics of glycemic and insulin secretion profile in patients with hypoglycemia are still unknown. Hereby, we have planned to clarify the characteristics of oral glucose tolerance test profile in heart disease patients with hypoglycemia during OGTT.

Methods: Four hundred eighteen consecutive patients without known diabetes mellitus (66±11 y.o., 284 male) who admitted in order to detect the coronary artery disease during April 2006 to June 2013 were enrolled. Cine-angiography and 75g OGTT were performed. Fasting hypoglycemia was defined as blood glucose below 80 mg/dL at fasting blood glucose. Patients were classified into two groups (Group H and Group N) due to the existence of hypoglycemia.

Results: Hypoglycemia occurred in 24 patients (6.6%). Fasting blood glucose was lower ($p<0.001$) in Group H (76±2mg/dL) than that in Group N (98±12 mg/dL), although HbA1c was similar (5.8±0.3 vs. 5.9±0.5%, n.s.). As for the insulin resistance, HOMA-IR of both groups was almost within normal value although it was lower in Group H (0.88±0.44) than in Group N (1.51±0.94, $p<0.001$). HOMA-β in Group H was greater than that in Group N (135.6±74.0 vs. 68.3±39.9, respectively, $p<0.001$).

The accuracy of HOMA-IR and HOMA-β to predict fasting blood hypoglycemia were moderate. A receiver operating characteristic analysis (ROC) found that HOMA-IR had an area under the curve (AUC) of 0.74 (95%CI: 0.65-0.83) ($p<0.001$) and HOMA-β had an AUC of 0.83 (95%CI: 0.73-0.92) ($p<0.001$).



Conclusions: Patients with exaggerated insulin secretion tend to induce fasting blood hypoglycemia.

P2321 | BEDSIDE**Effects of dipeptidyl peptidase-4 inhibitor and alpha-glucosidase inhibitor on left ventricular diastolic dysfunction in type 2 diabetes: results of 3D trial**

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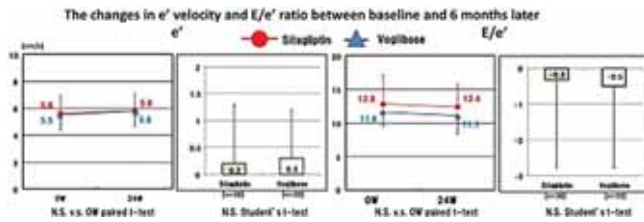
Background: Left ventricular (LV) diastolic dysfunction is frequently observed in patients with type 2 diabetes. Dipeptidyl peptidase-4 inhibitor (DPP-4i) attenuates postprandial hyperglycemia (PPH) and may have cardio-protective effects. We compared the effects of the DPP-4i, sitagliptin, and the alpha-glucosidase inhibitor, voglibose, on LV diastolic function in patients with type 2 diabetes.

Methods: We conducted a prospective, randomized, open-label, multicenter study, and recruited diabetic patients with LV diastolic dysfunction. Patients received sitagliptin (50mg/day) or voglibose (0.6mg/day). The primary endpoints were changes in e' and E/e' ratio from baseline to 6-month later.

The secondary efficacy measures included glucose, HbA1c, GLP-1, lipid profiles, oxidative stress markers and inflammatory markers.

Results: Study was completed in 40 patients in the sitagliptin group and 40 patients in voglibose group. There was a significant increase in GLP-1 level between baseline and 24 weeks after in sitagliptin group (4.8 ± 4.7 vs. 7.3 ± 5.5 , $p < 0.05$). A decrease in HbA1c and body weight were significantly greater in sitagliptin group (-0.7 ± 0.6 vs. -0.3 ± 0.4 , $p < 0.005$, -1.3 ± 3.2 vs. 0.4 ± 2.8 , $p < 0.05$). There were no significant changes in e' velocity and E/e' ratio from baseline to 6-month later in both groups.

Analysis of covariance demonstrated that pioglitazone use is an independent factor associated with changes in e' and E/e' ratio. Among those without the use of pioglitazone, e' increases and E/e' ratio decreases in both sitagliptin and voglibose groups.



Conclusions: Our trial showed that sitagliptin reduces HbA1c greater than voglibose, but that both were not associated with improvement in echocardiographic parameters of LV diastolic function in type 2 diabetic patients.

P2322 | BEDSIDE

Determinants of left ventricular hypertrophy and diastolic function: role of obesity

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The role of obesity in left ventricular (LV) hypertrophy and diastolic function is not clear and the effect of hemodynamic and hormonal environment must be considered.

Objective: To establish the influence of obesity in the presence of LV hypertrophy and in diastolic function.

Methods: 125 consecutive morbidly obese patients referred for bariatric surgery and 67 normal weight volunteers underwent transthoracic echocardiography. Adipokines, inflammation and metabolic profile were determined. Logistic and regression analysis were performed for hypertrophy and diastolic function determinants, respectively.

Results: Hypertrophy was determined by obesity and hypertension (table). Diastolic function was determined by hypertrophy, adipokines and inflammatory circulating markers. Proinflammatory and profibrotic factors had an independent direct effect on E/e' ratio whereas anti-inflammatory factors had an independent indirect influence on E/e' ratio.

Table 1

Hypertrophy*	Odds ratio	Confidence interval (95%)	p value
Obesity	12.29	2.48–60.76	0.002
Hypertension	2.86	0.91–8.95	0.07
Diastolic function**	Change in E/e' ratio	Confidence interval (95%)	p value
Hypertrophy	2.18	0.66–3.71	0.005
Leptin	0.12	0.07–0.16	<0.001
TPAI1	-0.31	-0.5–0.01	0.003
IL-6	0.08	-0.002–0.16	0.05
IL-10	-0.02	-0.04–0.003	0.02
TNF- α	0.09	0.02–0.16	0.013
GLP-1	-0.07	-0.14–0.02	0.02

Variables in the model: *Obesity, hypertension, sex, HOMA, adiponectin. **Obesity, hypertension, hypertrophy, stroke vol, left atrial vol, adiponectin, IL-6, IL-10, GLP-1, NT-ProBNP, Ghrelin, IL-6, t-PAI1, HOMA, MCP-9, MCP-1, leptin, TNF- α , CRP.

Conclusions: Obesity is a strong independent factor for left ventricular hypertrophy but it does not have an independent influence on diastolic function. Diastolic dysfunction is determined by ventricular hypertrophy, leptin and inflammation circulating markers.

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P2323 | BEDSIDE

General and regional adiposity as determinants of cardiovascular risk

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Objective: The present study sought to compare the various obesity measures as predictors of dyslipidemia, dysglycemia and essential hypertension.

Design and methods: A total of 1140 consecutive, non-diabetic subjects (51 ± 13

years, 49% males) were studied. Body mass index (BMI), body fat content (FAT), using a portable bioelectric impedance body composition analyzer, waist (WC) and hip (HC) circumference and waist-to-hip circumference ratio (WHR) were measured/calculated. Visceral (V), perirenal (R) and mesenteric (M) fat thicknesses were also measured using a linear ultrasound probe.

Results: The prevalence of dyslipidemia, dysglycemia and essential hypertension was 88.1%, 44.2% and 67.2%, respectively. The prevalence of 0, 1, 2 or all 3 dysmetabolic conditions was 3.1%, 22.3%, 43.5% and 31.1%, respectively. Compared to patients with 1 and 2, patients with all 3 dysmetabolic conditions were predominantly male (39% vs. 45% vs. 68%, $p < 0.001$), older (50 ± 14 vs. 51 ± 12 vs. 55 ± 12 years, $p < 0.001$), with higher BMI (27 ± 4 vs. 28 ± 5 vs. 29 ± 5 kg/m², $p < 0.001$), FAT ($32 \pm 8\%$ vs. $34 \pm 8\%$ vs. $35 \pm 7\%$, $p = 0.004$), WC (90 ± 13 vs. 93 ± 13 vs. 98 ± 13 cm, $p < 0.001$), HC (103 ± 10 vs. 105 ± 10 vs. 107 ± 9 cm, $p < 0.001$), WHR (0.87 ± 0.08 vs. 0.88 ± 0.08 vs. 0.91 ± 0.08 , $p < 0.001$), V (57 ± 24 vs. 62 ± 24 vs. 72 ± 26 mm, $p < 0.001$), R (10 ± 4 vs. 11 ± 4 vs. 13 ± 5 mm, $p < 0.001$) and M fat (11 ± 4 vs. 12 ± 4 vs. 13 ± 5 mm, $p < 0.001$). All the obesity markers significantly ($p < 0.001$) discriminated subjects with all 3 dysmetabolic conditions except FAT ($p = 0.082$). WHR and WC had the highest area under the curve followed by V, BMI, R, M and FAT (Table).

Table 1

	Area under the curve	95% Confidence interval	p-value
Waist-to-hip ratio	0.627	0.585–0.669	<0.001
Waist circumference	0.623	0.581–0.665	<0.001
Visceral fat	0.620	0.575–0.665	<0.001
Body mass index	0.599	0.557–0.642	<0.001
Perirenal fat	0.594	0.546–0.641	<0.001
Mesenteric fat	0.592	0.545–0.638	<0.001
Body fat content	0.573	0.492–0.654	0.082

Conclusions: Among the various obesity markers, WHR, WC and Visceral fat emerge as the most significant determinants of dysmetabolic diseases while measures of total body fat (i.e. BMI and FAT) have less predictive power.

P2324 | BEDSIDE

Average daily heart rate, smoking and overweight: is there connection?

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Background: High average heart rate (HR) may leads to progression of coronary artery disease, poor course of heart failure and it also decreases expected life duration. However, the influence of smoking and overweight on average HR remains poor investigated in healthy young people.

Aim: The aims of the study were to estimate how overweight or smoking influences on average daily heart rate in young people and to reveal possible cumulative effect of both these conditions on HR.

Methods: We included 675 medical students into study, 277 men and 398 women were among them. Each person completed short standard questionnaire concerning lifestyle, diet, smoking and underwent the measurement of the height, weight and calculation of the body mass index (BMI). The four groups were separated from the total cohort. Non-smokers with normal weight ($BMI = 22.8 \pm 2.1$ kg/m²) formed the 1st group. The second one consists of overweight non-smokers ($BMI = 27.7 \pm 1.9$ kg/m²). The third group includes smokers with normal weight ($BMI = 22.1 \pm 2.4$ kg/m²). Overweight smokers ($BMI = 27.3 \pm 2.2$ kg/m²) were enrolled into 4th group. The size of all groups was the same ($n = 31$) in order to increase the sensitivity of the statistical criteria. Daily electrocardiogram (ECG) monitoring was performed to all subjects in 4 groups.

Results: The average daily HR was higher in case of overweight (82.8 ± 4.1 vs 73.5 ± 3.9 , $p = 0.03$) and smoking (83.6 ± 5.4 vs 73.5 ± 3.9 , $p = 0.028$). The average daily HR was also higher in group of overweight smokers than in nonsmokers with normal weight (84.5 ± 4.8 vs 73.5 ± 3.9 , $p = 0.027$). However, HR in case of isolated smoking, isolated overweight or combination of both these conditions was almost the same. The possible explanations of the received data are the follow, smoking leads to increasing of the level of noradrenalin in plasma and therefore cause a high HR. Overweight is connected with higher average HR due to poor physical form.

Conclusion: The overweight and smoking increases average HR itself. There are no cumulative effect of these two conditions on average HR. Young people that smoke, have excessive weight or both need to be closely followed in order to diminish cardiovascular risk in future.

P2325 | BEDSIDE

Combined arterial-ventricular stiffening is associated with insulin resistance in childhood obesity

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Background: Insulin resistance is known to be associated with cardiovascular dysfunction in adulthood obesity. However, few studies have examined insulin resistance and cardiovascular function in overweight/obese children. The purpose of this study is to assess the relationship between arterial-ventricular stiffness and cardiovascular risk factors in children.

Methods: Echocardiography was performed in 226 children aged 6 to 15 years (BMI 18 to 34 kg/m²). Left ventricular (LV) end-diastolic volume, LV mass, transmitral peak flow velocity (E), and mitral annular myocardial velocity (Em) were measured. LV mass/volume ratio was calculated. Stroke volume (SV) was measured using aortic diameter and pulsed Doppler velocity profile. SV was indexed for body surface area (SVI). Effective arterial elastance (Ea) was estimated by end-systolic pressure/SVI. End-systolic elastance (Ees) was calculated by a modified single-beat method using systolic and diastolic blood pressure, SV, EF, timing intervals, and an estimated normalized ventricular elastance at arterial end diastole. High sensitive C-reactive protein (hs-CRP), fasting glucose, insulin, and homeostasis model assessment for insulin resistance (HOMA-IR) were also assessed.

Results: Ea and Ees increased significantly with BMI ($r=0.29$ and 0.18 , $p<0.01$, respectively). Arterial-ventricular coupling (Ea/Ees ratio) did not change with BMI. LV mass/volume ratio was positively associated with increased BMI ($r=0.45$, $p<0.01$). There were significant relationships between BMI and fasting glucose ($r=0.14$, $p<0.05$), insulin ($r=0.51$, $p<0.01$), HOMA-IR ($r=0.52$, $p<0.01$), and hs-CRP ($r=0.24$, $p<0.01$). Ea, Ees, and LV mass/volume ratio correlated significantly with insulin ($r=0.23$, 0.18 , and 0.32 , $p<0.01$, respectively) and HOMA-IR ($r=0.22$, 0.17 , and 0.28 , $p<0.01$, respectively). No significant relationships were observed between LV mass/volume ratio and arterial-ventricular stiffness and hs-CRP.

Conclusions: Obesity-related insulin resistance associated with combined arterial-ventricular stiffening may contribute to the increased prevalence of later cardiovascular diseases.

P2326 | BENCH

Peroxisome proliferator activated receptor (PPAR) α /gamma agonist aleglitazar reduces the inflammatory-mediated expression of monocyte chemoattractant protein (MCP)-1 selectively in human adipocyte

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Excessive adiposity in obese individuals is accompanied by low-level inflammation, which is a mechanistic link between obesity and related cardiovascular and diabetic complications. Antagonizing inflammation in the metabolic syndrome and diabetes is a current therapeutic goal in such conditions. Co-ligands of PPAR α and γ , combining in a single molecule the metabolic- and inflammatory-regulatory properties of α and γ agonists, are one such therapeutic option. Adipose tissue production of MCP-1 orchestrates monocyte-macrophage recruitment into inflamed adipose tissue. We therefore investigated whether the dual agonist ALE, in comparison to selective agonists for PPAR α and γ , fenofibrate (FENO) and rosiglitazone (RSG) respectively, regulates MCP-1 expression in fully differentiated human Simpson-Golabi-Behmel syndrome adipocytes (SGBS cells) and human umbilical vein endothelial cells (HUVEC), and explored underlying mechanisms.

Methods: SGBS cells and HUVEC were treated with 0.01-1000 nmol/L ALE and RSG or 5-50 μ mol/L FENO for 24 h before stimulation with 10 ng/mL TNF α . Conditioned media were then tested for MCP-1 release by ELISA, while in parallel, MCP-1 mRNA expression was investigated by RT-PCR, the activation of NF- κ B by transactivation assay, and the activation status of p38 mitogen-activated protein (MAP) kinase, Jun N-terminal kinase (JNK) and p44/42 extracellular-signal-regulated kinase (ERK1/2) were assessed by Western analysis using antibodies recognizing the phosphorylated (activated) forms of each kinase.

Results: In SGBS cells, but not in HUVEC, ALE, RSG and FENO reduced TNF α -induced MCP-1 release in a concentration dependent manner, with a maximal inhibitory concentration, at 10 and 125 nmol/L for ALE and RSG respectively ($P<0.01$) and 50 μ mol/L ($P<0.01$) for FENO. At the same concentrations ALE also reduced MCP-1 mRNA expression by 40% ($P<0.05$ versus TNF α). At 10 nmol/L ALE minimally inhibited TNF α -induced activation of NF- κ B, but significantly reduced the activation of p38 MAP kinase and JNK.

Conclusions: ALE, at concentrations as low as 10 nmol/L, which ensure the half-maximal activation of both PPAR α and PPAR γ , selectively reduces the expression of MCP-1 in mature adipocytes but not in endothelial cells. Such effect seems to be mediated, at least in part, by the interference with the activation of p38 MAP kinase, known to be involved in the inflammatory-mediated expression of MCP-1. Overall, these data suggest that ALE may benefit diabetic and obese patients suppressing, in a highly cellular-selective fashion, the contribution of adipose tissue to systemic and perivascular inflammation.

TARGET ORGAN DAMAGE IN HYPERTENSION I

P2328 | BEDSIDE

MicroRNA-9 and microRNA-126 expression levels in patients with essential hypertension: potential markers of target organ damage

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Purpose: MicroRNAs (miRs), as essential gene expression regulators, modulate

cardiovascular development and disease and thus they are emerging as potential biomarkers and therapeutic targets in cardiovascular disease. We assessed the expression levels of the microRNAs miR-9 and miR-126 in patients with untreated essential hypertension and healthy individuals.

Methods: 60 patients with untreated essential hypertension and 29 healthy individuals participated in the study. All patients underwent two-dimensional echocardiography and 24-h ambulatory blood pressure monitoring. MicroRNA expression levels in peripheral blood mononuclear cells were quantified by real-time reverse transcription polymerase chain reaction.

Results: Hypertensive patients showed significantly lower miR-9 (9.69 ± 1.56 versus 41.08 ± 6.06 , $p<0.001$) and miR-126 (3.88 ± 0.47 versus 8.96 ± 1.69 , $p<0.001$) expression levels compared with healthy controls. In hypertensive patients, miR-9 expression levels showed a significant positive correlation ($r=0.437$, $p<0.001$) with left ventricular mass index. Furthermore, both miR-9 ($r=0.312$, $p=0.015$) and miR-126 ($r=0.441$, $p<0.001$) expression levels in hypertensive patients showed significant positive correlations with the 24-h mean pulse pressure.

Conclusions: Our data reveal that miR-9 and miR-126 are closely related to essential hypertension in humans, as they show a distinct expression profile in hypertensive patients relative to healthy individuals and they are associated with clinical prognostic indices of hypertensive target organ damage in hypertensive patients. Thus, they may possibly represent potential biomarkers and candidate therapeutic targets in essential hypertension.

P2329 | BEDSIDE

Early onset of androgenetic alopecia is related with target organ damage in never treated hypertensive young men of our country

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Purpose: The relationship between androgenetic alopecia (AGA) and essential hypertension is under investigation. The purpose of the present study is the evaluation of the relationship of subclinical damages due to hypertension with the presence and severity of androgenetic alopecia in untreated young male hypertensives with early AGA onset.

Methods: We performed a cross sectional study in 62 newly diagnosed and untreated young male hypertensives with AGA. Group A patients had an AGA onset before the age of 30 years ($n=27$, mean age 42 ± 7 years) while Group B patients had an AGA onset after the age of 30 years ($n=35$, mean age 47 ± 5 years). Blood pressure was measured by 24h ambulatory blood pressure measurement (ABPM). Carotid to femoral pulse wave velocity (PWV), office (PP) and 24h (ABPM) pulse pressure were assessed as indices of arterial stiffness. Intima-media thickness of the common carotid arteries (IMT) was measured by ultrasonography. Left ventricular hypertrophy (LVMI) and coronary microcirculation (CFR) were estimated by echocardiography. 24h urine collection was performed for microalbumin (MAU) estimation. AGA was classified according to the Hamilton-Norwood scale (severity), age of onset, duration and body hair growth.

Results: No significant differences were found within groups regarding age, BMI, smoking habit, LDL levels, systolic and diastolic office and 24h blood pressure, PP, 24h PP, PWV, IMT, LVMI, CFR and MAU. However, only in Group A patients: i. PP was related with AGA duration ($r=0.45$, $p<0.05$) and Norwood scale ($r=0.33$, $p<0.05$), ii. 24h PP was related with AGA duration ($r=0.36$, $p<0.05$) and Norwood scale ($r=0.41$, $p<0.05$) and iii. IMT was related with AGA duration ($r=0.36$, $p<0.05$).

Conclusions: The severity and duration of AGA are related with increased arterial stiffness and carotid atheromatosis in young male hypertensives with early onset of alopecia. Further studies are needed to investigate if the underline pathophysiologic mechanism is based on the long-standing substances release from the hair follicles or the over expression of either androgen receptors or 5 α -reductase in the kidney.

P2330 | BEDSIDE

Serum uric acid and left ventricular hypertrophy in nigerian patients with essential hypertension

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Background: Hypertension is a cause of left ventricular hypertrophy (LVH), an independent cardiovascular risk factor. Although serum uric acid is elevated in hypertension, its role in the occurrence of LVH remains uncertain. In resource poor settings, the identification of a relatively inexpensive risk marker like uric acid may be beneficial in directing more targeted cardiac investigations.

Objective: To assess the relationship between serum uric acid and LVH in untreated patients with essential hypertension.

Methods: A cross-sectional study was carried out in one hundred and thirty (85 females, 45 males) newly diagnosed untreated patients with essential hypertension in the out-patient clinics of our university. Sixty-five healthy age and sex matched non-hypertensive individuals served as controls for comparison. Left ventricular hypertrophy was evaluated by trans thoracic echocardiography. Blood samples were collected for assessing uric acid levels.

Results: Hyperuricaemia was present in 46.9% and 16.9% of cases and con-

trols respectively ($p < 0.001$). Mean serum uric acid was significantly higher among the patients with hypertension ($379.7 \pm 109.2 \mu\text{mol/l}$) compared to controls ($296.9 \pm 89.8 \mu\text{mol/l}$; $p < 0.001$). Left ventricular hypertrophy was present in 55.4% of the cases and 10.8% of the controls ($p < 0.001$) and the commonest geometric pattern among the cases was concentric hypertrophy while the majority of the controls had normal left ventricular geometry. Among the hypertensive patients, LVH was commoner in the hypertensive patients with hyperuricaemia compared to those with normal serum uric acid levels (70.5% versus 42.0%, $p = 0.001$). There was a significant linear relationship between mean uric acid levels and the left ventricular mass index ($r = 0.336$, $p < 0.001$). In regression analysis, uric acid was a significant independent predictor of left ventricular hypertrophy ($\beta = 0.246$, $p = 0.003$).

Conclusion: These results indicate that serum uric acid is associated with the presence of LVH in patients with hypertension even at the time of diagnosis, thus is a reliable marker of cardiovascular risk in this patient population.

P2331 | BEDSIDE

The association of central hemodynamics and serum markers with cardiovascular disease in Japanese men

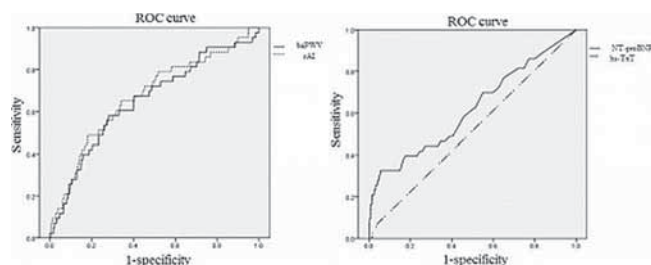
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Purpose: Recently, arterial stiffness, central hemodynamics, and serum markers of cardiovascular damages (high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal-proBNP (NT-proBNP)) have been much focused as biomarkers of predictor of cardiovascular morbidity and mortality in the general population.

Aim: The present study was conducted to examine the association of these markers with cardiovascular disease in Japanese men having annual health checkup.

Methods: Hs-cTnT, NT-proBNP, some blood data and anthropometric parameters including radial augmentation index (rAI), brachial-ankle pulse wave velocity (baPWV), were obtained in 1427 Japanese male subjects coming to health check-ups. We defined brain and cardiovascular disease as subjects having past history of cerebro-cardiac disease, and subjects treating now for cerebro-cardiovascular disease.

Results: In this study subjects, the hs-cTnT ($\geq 0.009\text{ng/ml}$) was detected in 4.1% (59 subjects). The subjects having cerebro-cardiovascular disease were 3.0% (43 subjects). The area under the receiver operator characteristic curve for hs-cTnT, NT-proBNP, baPWV, and rAI were 0.514, 0.618, 0.651, and 0.673 (95%CI: 0.425-0.604, 0.522-0.715, 0.563-0.740, and 0.585-0.761), respectively. Logistic regression analysis demonstrated that NT-proBNP (Odds ratio = 1.7, 95%CI: 1.3-2.7) ($p < 0.001$) and rAI (Odds ratio 1.7, 95%CI: 1.1-2.8) ($p = 0.03$), but not hs-cTnT ($p = 0.930$) and baPWV ($p = 0.574$), were significant variable to identify cardiovascular disease after the adjustment of confounding variables.



Conclusion: The central hemodynamics and NT-proBNP may be independent markers for the screening of cardiovascular disease in middle-aged health Japanese men. However, the hs-cTnT may not be useful for the screening of cardiovascular disease in these subjects.

P2332 | SPOTLIGHT

The prevalence of undiagnosed hypertension, diabetes and target organ damage in a rural community in western Kenya

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Purpose: To determine the prevalence of undiagnosed hypertension, diabetes and end renal or cardiac injury in Mutwot, one of the nine rural villages in Mosoriot division, Nandi County in western Kenya.

Methodology: Study conducted in two phases. Phase 1: a cross sectional study of adults aged > 18 years between June 2012 and August 2013 and included home based screening of HIV, blood pressure (BP) and random blood sugar (RBS) by trained community health workers as part of ongoing screening of these diseases in Mosoriot. Subjects with a BP $\geq 140/90$ mmHg or RBS of ≥ 8 mmol/l were referred to Mosoriot health center for confirmatory testing. Those who failed to follow up were traced to their homesteads for confirmatory testing. During phase 2, 150 newly diagnosed hypertensives and 150 age- and gender-matched non-hypertensive, non-diabetic, non-HIV controls were screened for evidence of renal and cardiac injury. Renal injury was defined as urine microalbuminuria > 3 0mg/dl and/or estimated glomerular filtration rate (eGFR) of < 60 ml/kg/1.73 m²,

using MDRD calculator. Cardiac injury was defined as electrocardiographic left ventricular hypertrophy (ECG-LVH) using standard criteria. Rates of renal and cardiac injury in cases and controls were performed using conditional logistic regression and exact McNemar tests.

Results: Phase 1: Two hundred and thirty four (234) out of the 1586 subjects screened in the community were suspected to be hypertensive and 9 were suspected to be diabetic. Five and three were known hypertensive and diabetic respectively. Upon follow up, 101 (43%) were confirmed to be hypertensive and 5 (56%) to be diabetic. Eleven (4.7%) subjects could not be traced. The prevalence of undiagnosed hypertension was 101/1586 (6.4%, 95% CI 5.2 to 7.7%) while that of diabetes was 5/1586 (0.32%, 95% CI 0.10 to 0.73%).

The phase 2 participants were 99% rural dwellers, 65% female, median age of 58 years and 79% had an education of less than 8 years. Odds of microalbuminuria were 17.0 times higher (95% CI 2.3 to 127.7, $p = 0.006$) in cases (22/150, 15%) compared to controls (2/150, 1%). Cases (18%) were more likely than controls (5%) to have ECG-LVH (OR=5.3, 95% CI 1.8 to 15.3, $p = 0.002$), and more likely (8% vs. 1%) to have impaired eGFR (OR=6.0, 95% CI 1.3 to 55.2, $p = 0.01$).

Conclusion: Undiagnosed hypertension is 6.4% and diabetes is less than 1% in this rural community in Kenya. The odds of microalbuminuria, ECG-LVH and impaired eGFR were higher among the newly-diagnosed hypertensives compared to controls.

P2333

ABSTRACT WITHDRAWN

P2334 | BEDSIDE

Cardio-vascular risk factors, comorbidities and target organ damage in hypertensive patients

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Purpose: There is clustering of cardio-vascular risk factors in hypertensive pa-

tients (Pts) and accumulation of their negative effect on target organs' damage. The purpose of this study is to evaluate the general cardio-vascular risk and comorbidities in hypertensive Pts, who seek specialized cardiology care.

Methods: 931 treated hypertensive Pts were included during the first visit: 347 (37.27%) males, 584 (62.73%) females. After a mean follow-up of 12 months (6-20 months) 263 (28.25% of the initially recruited Pts) went through a follow-up evaluation: 178 females (30.48% of all recruited females), 85 males (24.49% of all recruited males). The mean age was 65.90 ± 10.00 years. We gathered full medical history, physical examination, laboratory screening, echocardiography, intima-media thickness, office and home measured blood pressure, ambulatory blood pressure monitoring, Montreal Cognitive Assessment and Mini Mental State Examination. All the Pts were on combination treatment. SPSS 19 was used for the statistical analysis.

Results: 198 (21.26%) of the Pts had only one cardio-vascular risk factor – hypertension. The largest number 394 (42.32%) of Pts were those who had ≥ 3 cardio-vascular risk factors. 209 (22.94%) were smokers, 488 (54.28%) had dyslipidemia, 250 (26.88%) were with diabetes and 276 (29.68%) were obese. 588 (71.44%) of the Pts were with high and very high SCORE result (for high-risk countries). Among the patients with suboptimal home-measured blood pressure significantly more ($p < 0.0001$) had diabetes, left ventricular hypertrophy and mild cognitive impairment. 318 (72.44% from the given SCORE group) of the patients with very high SCORE result were with suboptimal home measured blood pressure. The corresponding percent for the low risk group was 12 (40%). The Pts with very high cardio-vascular risk had significantly higher blood pressure values ($p = 0.0002$ for the systolic and $p = 0.023$ for the diastolic) than those with low risk.

Conclusions: There is accumulation of cardio-vascular risk factors in hypertensive Pts. The majority of them are with high and very high risk cardio-vascular risk. Those at the highest risk have poor blood pressure control and the highest blood pressure values, which leads to elevated target organ damage (manifested with mild cognitive impairment, left ventricular hypertrophy, elevated intima-media).

P2335 | BEDSIDE

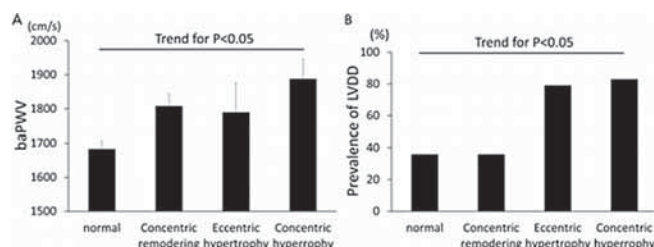
Arterial stiffness is associated with left ventricular geometry and diastolic dysfunction in the elderly

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Purpose: Increased arterial stiffness is reported to be associated with left ventricular hypertrophy (LVH) and LV diastolic dysfunction. However, the impact of arterial stiffness on LV geometry including concentric LVH, eccentric LVH and concentric remodeling and on the interplay between LV geometry and LV diastolic dysfunction (LVDD) have not been fully elucidated.

Methods: 431 subjects (mean 70 years, 57% men, 41% diabetes mellitus) were evaluated after exclusion of patients with coronary artery disease, severe valvular disease, cardiomyopathy and LV ejection fraction $< 50\%$. The brachial-ankle pulse wave velocity (baPWV), a marker of arterial stiffness, was measured using a Form BP. LV structure (LV mass index [LVMI], relative wall thickness [RWT]) and the parameters of LV diastolic function (e' and E/e') were determined using echocardiography. LV geometry was determined by RWT and LVMI, and LVDD was defined using E/e' , LVMI, and LAVI according to ESC guideline.

Results: When patients were classified based on LV geometry, baPWV and prevalence of LVDD in patients with concentric LVH was the highest than those in patients with other LV geometry (Figure). There was a significant correlation between baPWV and LVMI ($r = 0.17$, $p < 0.01$), RWT ($r = 0.20$, $p < 0.01$), e' ($r = 0.34$, $p < 0.01$), and E/e' ($r = 0.16$, $p < 0.01$). When patients were divided into tertile according to baPWV, multiple logistic analysis revealed that the highest tertile of baPWV was independently associated with concentric LVH (odds ratio: 2.53, 95%CI: 1.03 to 6.23, $p = 0.04$) and LVDD (odds ratio: 2.16, 95%CI: 1.32 to 3.57, $p < 0.01$) after adjustment of covariates.



P2336 | BEDSIDE

Home blood pressure measurement (HBPM) + telemonitoring (TLM) in patients with chronic kidney disease (CKD) in a care program: a pilot study

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Introduction: In Belgium CKD patients with an eGFR < 45 ml/min/1.73 m² can be followed in a multidisciplinary care program. Many of them have a home blood pressure monitor but in spite of this, no good blood pressure control.

Purpose: 1. Does HBPM+TLM improves blood pressure (BP) control in patients with CKD? 2. Is TLM an added value for both the patient and general practitioner (GP)?

Methods: 15 patients with CKD in a care program, having a home BP monitor during > 1 year, with treated but uncontrolled BP ($> 140/90$ mmHg). An ESH validated full automatic upper-arm-blood-pressure-monitor was used and measured values were transmitted to a database via a bluetooth-enabled mobile phone. Each TLM session lasted 5 days (2 x 3 measurements/day). After each TLM session the GP adapted the antihypertensive medication in consultation with the nephrologist. The added value of TLM for patients and GP's was evaluated with a questionnaire.

Results: Average age of the patients: 75 years. Mean eGFR (MDRD): 28 ml/min/1.73 m². Mean BP: 151/74 mmHg. HBPM + TLM revealed 4 (26%) patients with white coat hypertension. After an average of 2 TLM sessions and 4.7 months, mean BP was 133/67 mmHg (fig). This BP amelioration could be realised without increasing the amount of pills (change type of medication, combination therapy). Most of the GP's consider HBPM+TLM as an added value if additional support by the care program promotor (patient education and reporting) and feedback by the nephrologist is available. Patients experience TLM as a better follow-up (faster evaluation of results and adaptation of medication by GP).

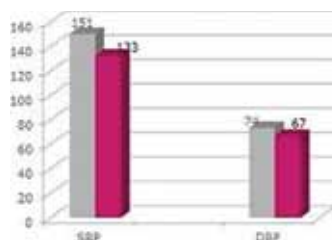


Figure 1. Change in mean SBP and DBP.

Conclusions: HBPM + TLM results in better and faster BP control. TLM is an added value but support of both patient and GP is essential.

P2337 | BEDSIDE

Arterial blood pressure monitoring and arterial stiffness values in patients with arterial hypertension with chronic obstructive pulmonary disease

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Purpose: The aim of the study was analysis of arterial blood pressure monitoring (ABPM) data and arterial rigidity (AR) values in patients with arterial hypertension (AH) with chronic obstructive pulmonary disease (COPD) in different stage of disease.

Methods: The study included 58 male patients with AH and COPD. Mean age was 63.3 ± 8.9 years. There were 1st degree of AH in 6 patients, 19 patients had 2nd degree of AH and 3d degree of AH was determined in 33 patients. Duration of disease was 5.6 ± 5.2 years for AH and 7.7 ± 5.9 years for COPD. All patients were divided into three groups. There were 18 patients with moderate COPD, 21 patients with severe COPD and 19 patients with very severe obstruction. All three groups were comparable with the general parameters of the examined patients. Comparison group included 50 male patients with essential AH without chronic respiratory diseases. Control group included 22 healthy male individuals. Comparison group subjects were comparable with examined patients on age sex distribution, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure and duration AH. Control group subjects were also comparable on gender and age with examined ones. Twenty-four-hour ABPM and arterial stiffness measurement were performed using BPLab[®] MnSDP-2 apparatus. For assessment of arterial stiffness we used pulse transit time (PTT2), (dP/dt)/max and augmentation index (Alx) indexes. Values of Alx less than -10% a normal, and values greater than or equal to -10% are pathological.

Results: As severity of COPD progresses, AR tends to increase. In patients with severe and very severe COPD significant decrease of PTT2 index, increase of Alx indexes versus patients of comparison group and control subjects have been observed ($p < 0.001$). Patients with COPD and AH had considerably lower PTT2 index as compared with other groups. We observed significant lowering of PTT2 at nighttime in main group in comparison with other clinical series ($p < 0.01$). Mean Alx value during nighttime in all patients with COPD was significantly higher than

LV geometry, arterial stiffness and LVDD.

Conclusions: Increased arterial stiffness influence LV geometry as well as the interplay between LV geometry and LV diastolic dysfunction in the elderly.

during daytime value. There is prevalence of abnormal Alx during 24-hour monitoring.

Conclusion: Pronounced increasing of AR is most common in patients with severe and very severe COPD. There is trend of rising APBM readings in patients with COPD combined with AH as with normal and increased rigidity. We observed circadian variation of AR parameters with prevalence of nocturnal abnormality. Thus it is reasonable perform 24-hour ABPM on patients with AH and COPD.

TARGET ORGAN DAMAGE IN HYPERTENSION II

P2339 | BEDSIDE

The role of metabolic syndrome and the ventricular geometry The evaluation of TOD in hypertension study

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Background: The cardiac effects of hypertension include a variety of structural changes such as increases in left ventricular mass (LVM). But little information is available on the importance of the metabolic syndrome which induce different left ventricular geometry patterns.

Objective: We sought to assess the prevalence of left ventricular geometry patterns in a large selected hypertensive population with verified Metabolic Syndrome.

Methods: A total of 2404 untreated and treated essential hypertensives consecutively attending, for the first time, our hospital out-patient hypertension clinic and included in METHOD Study (Metabolic syndrome Target of Hypertension Organ Damage Study), an observational ongoing registry of hypertension-related target organ damage (TOD), were considered for this analysis.

All patients underwent extensive clinical, laboratory and ultrasonographic investigations searching for cardiac (and extracardiac) TOD. Geometry Patterns were defined according to LVMI (Left Ventricular Mass Index) and RWT (Relative Wall Thickness) criteria.

Results: Eccentric Hypertrophy pattern was present in 672 (27.95%) patients, Concentric Hypertrophy pattern in 965 patients (40.14%) and Concentric remodelling pattern in 405 (16.85%) patients. Compared with 362 (15.06%) patients with normal left ventricle geometry, those with eccentric or concentric hypertrophy as well as those with concentric remodelling were older, more frequently overweight, had higher systolic blood pressure as well as uric acid levels and included a greater proportion of subjects with diabetes hyperlipidemia and renal impairment (Creatinine levels >1.4 in males or >1.2 in females). The prevalence of hypertriglyceridemia was similar in patients with normal geometry and those with concentric remodelling.

According to a logistic regression analysis, fasting blood glucose >7.0 mmol/l, renal impairment, systolic and diastolic blood pressure, age and female sex were the main independent predictors of eccentric hypertrophy pattern.

Finally independent predictors of concentric remodelling were fasting blood glucose >7.0 mmol/l, Female Sex and Systolic Blood Pressure

Conclusions: Hyperglycemia, age and female sex component of metabolic syndrome seems to be the majors denominators of the different geometry patterns of the left ventricle. Systolic blood pressure is common participant of factor of hypertrophy or remodeling whereas Diastolic Blood Pressure contributes mainly to eccentric hypertrophy. Hyperlipidemia and hyperuricemia play an important role in development concentric hypertrophy.

P2340 | BEDSIDE

The influence of arterial hypertension on the initiation and progression of atrial fibrillation

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Purpose: To determine the influence of arterial hypertension (AH) on the course of various forms of atrial fibrillation (AF).

Methods: 87 patients were examined (42 men and 45 women, mean age 49.7±8.2 years). Patients were divided into 4 groups according to the type of AF and the presence of AH: 1 - with paroxysmal AF (AFpr) + AH (22 patients); 2 - with persistent AF (AFps) + AH (23 patients); 3 - with AFpr without hypertension (20 patients); 4 - AFps without hypertension (22 patients). The data of daily electrocardiogram monitoring (DECGM) and daily blood pressure monitoring (DBPM) were evaluated.

Results: It was found, that patients with AFpr + AH and AFps + AH had significantly higher systolic blood pressure variability (SBPV) and diastolic blood pressure variability (DBPV) than patients with AF without hypertension (SBPV, mm Hg: 16.5±1.7; 11.8±1.3 respectively (p<0.05); DBPV, mm Hg: 13.6±1.3; 9.2±1.1 respectively (p<0.05)). The blood pressure load (a "pressure-time" index for systolic and diastolic blood pressure) was raised from 43% to 68% in patients of groups 1 and 2 respectively, compared to 9% and 15% of patients in groups 3 and 4 respectively.

A significant increase of the number of patients with AFps compared with AFpr was detected along with the increase of the duration of hypertension by 21.3±3.5 months (1,325; 95%; confidence interval 1,128 – 1,557; p<0.01).

Conclusions: The presence of arterial hypertension contributes to the more severe course of atrial fibrillation. The increased indexes of daily blood pressure monitoring raise the frequency and duration of atrial fibrillation paroxysms and promote the development of persistent atrial fibrillation.

P2341 | BEDSIDE

Assessment of arterial stiffness with an easy method in preeclamptic patients

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Background: Arterial stiffness is the term used to define the rigidity of arterial walls. Arterial stiffness and its hemodynamic results have been shown to be associated with increased cardiovascular morbidity and mortality in previous studies. Women with a history of pre-eclampsia in past pregnancies have a higher risk of developing cardiovascular disease later in life. In this study, we aimed to assess the arterial stiffness with a noninvasive and easily applicable oscillometric method in pregnant with and without preeclampsia.

Methods: Ninety pregnant patients with a mean age of 30.7±6.5 years were included in the study. Patients were divided into two groups based on the presence of pre-eclampsia. Vascular measurements were performed with a Mobil-O-Graph 24-h PWA Monitor, an automatic oscillometric device.

Results: All of vascular function parameters were significantly higher in the patients with pre-eclampsia. In the pre-eclampsia group the PWV value was positively correlated with gestational age, maternal age, glucose, creatinine, augmentation index and central blood pressure. In linear regression analysis, the PWV value was found to be positively correlated with gestational age, maternal age and central systolic blood pressure. In women with severe pre-eclampsia had significantly higher blood pressures, PWV, Alx and cardiac output in comparison to mild pre-eclampsia.

Table 1

Variables	Pearson's correlation analysis		Linear regression analysis	
	r value	P value	β value	P value
Maternal age (years)	0.357	0.016	0.186	0.030
Gestational age (weeks)	0.631	<0.001	0.225	0.023
Glucose (mg/dL)	0.342	0.022	0.123	0.109
Creatinine (mg/dL)	0.437	0.003	0.080	0.372
Augmentation index (%)	0.349	0.019	-0.037	0.705
Central systolic blood pressure (mmHg)	0.828	<0.001	0.602	<0.001
Central diastolic blood pressure (mmHg)	0.649	<0.001	0.068	0.543

Conclusion: Oscillometric PWV measurement is generally accepted as the most reproducible, rapid, easily applicable and low-cost non-invasive method for the assessment of large artery stiffness and it may contribute to estimation of future cardiovascular risk profiles of patients admitted with pre-eclampsia.

P2342 | BEDSIDE

Diurnal systolic blood pressure load relates with aortic stiffness in patients with newly diagnosed arterial hypertension with dipping status

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Background: Blood pressure (BP) load, defined as the percentage of abnormally elevated BP readings, is usually provided on the report of ambulatory BP monitoring. The relationship between blood pressure load, independently from blood pressure level, and target organ damage in hypertension disease is under discussion. Aortic stiffness is considered valuable index of subclinical damage in hypertensive patients offering to cardiovascular risk estimation. We aimed to explore the relationship between diurnal systolic blood pressure load and aortic stiffness in patients with newly diagnosed essential hypertension regarding their dipping status.

Methods: We studied 218 patients with newly diagnosed and never treated essential hypertension (mean age 51±11 years, 189 males). We performed: a. 24h ambulatory blood pressure measurement (ABPM) in order to measure blood pressure load and estimate dipping status and b. carotid-femoral artery pulse wave velocity (PWV) in order to evaluate aortic stiffness. We divided total population in Group A (n=156, dippers) and Group B (n=82, non-dippers).

Results: No significant differences were found within groups regarding PWV, BMI, systolic and diastolic BP in office and ABPM, mean BP, office pulse pressure, diurnal BP systolic load. However, Group A patients were younger with decreased 24h pulse pressure had increased systolic and diastolic blood pressure and pulse pressure in office and 24h ABPM measurements. In Group A, diurnal BP systolic load was related with indices of aortic stiffness: PWV (r=0.21, p<0.01), pulse pressure (r=0.24, p<0.01) and 24h pulse pressure (r=0.51, p<0.001). No such relationship was found in Group B patients. In a multivariate regression analysis, where systolic BP (office or ABPM), pulse pressure (office or ABPM) and mean

BP were inserted as independent variables, PWV was dependent only from mean BP and 24h pulse pressure in dipper hypertensives.

Conclusions: Diurnal systolic blood pressure load BP load relates with aortic stiffness indices in dipper untreated hypertensive patients, but not independently of BP level. The significance of this index regarding arterial stiffness is lost in hypertensive patients with non-dipping status, where different pathophysiologic mechanisms are present leading to a more augmented 24h blood pressure load.

P2343 | BEDSIDE

Extreme dipping as an independent predictor of left ventricular hypertrophy

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Purpose: Development of left ventricular hypertrophy (LVH) is a multifactorial and incompletely understood process. Aim of our study was to determine the effect of blood pressure's (BP) circadian abnormalities on LVH.

Methods: We studied 780 consecutive newly diagnosed, never treated, non-diabetic, hypertensive patients stage I-III (51±13 years old, 45.3% females). Echocardiographic left ventricular mass calculation was performed from parasternal long axis and normalized for height in meters to the power of 2.7 (LVMI). Using established cutoffs (>49 for males and >45 g/m^{2.7} for females), the study population was split in group with normal (n=649) and increased LVMI (n=131). Dipping status was defined according to day-night SAP circadian variation from 24 hour ambulatory blood pressure monitoring.

Results: Patients with LVH were older (54±13 vs 51±13, p=0.018), while there was no difference regarding gender (females 43.7 vs 45.6, p=0.693). Prevalence of dippers was higher in patients with no LVH (50% vs. 35.6%), while there was no difference in the prevalence of non-dippers between the two groups (34.2 vs. 35.6). Moreover, prevalence of extreme dippers and reverse dippers was higher in patients with LVH (18.6% vs. 9.3% and 10.2% vs. 6.5%). Logistic regression analysis revealed that, compared to dippers, extreme dippers had 2.9 higher odds (95% CI: 1.5-5.5, p=0.001) of LVH, independent of age, gender and body mass index, while reverse and non-dippers had no significant difference (OR: 1.8, 95% CI: 0.8-4, p=0.132 and OR: 1.3, 95% CI: 0.8-2.3, p=0.315, respectively).

Conclusion: Extreme dipping status is an independent predictor of left ventricular hypertrophy.

P2344 | BEDSIDE

Early morning blood pressure, pulse wave velocity, central aortic pressure and predictive risk factors of Ischemic Stroke in masked hypertensive patients

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Objectives: The clinical significance of early morning hypertension (EMHT) is not still somewhat clear. We evaluated the prevalence of masked early morning or nocturnal hypertension (NHT) and effects of arterial stiffness, pulse wave velocity (PWV) and wave reflections on central aortic pressure (CAP) in hypertensive patients with ischemic stroke (IS).

Methods: We analyzed a total 450 hypertensive patients with IS, investigate masked hypertension (MHT) using 24hr ambulatory blood pressure monitoring (ABPM). Among the MHT, classified as masked EMHT (early morning BP ≥135/85 mmHg and night-time BP ≤120/70 mmHg), Masked NHT (Daytime BP ≤135/85 mmHg and night-time BP ≥120/70 mmHg). And using radial artery applanation tonometry, aortic pulse analysis was performed in MHT.

Results: 128 patients was observed MHT with ischemic stroke. EMHT was found in 55.6% of MHT patients (n=71). Compared with patients with both EMHT and NHT, EMHT had higher aortic pulse wave velocity (PWV) and augmentation index (AI) and AI75 (AI to HR 75 beat/min), ASP (Central aortic systolic pressure) and pulse pressure were also higher in the EMHT.

Conclusion: Our results suggest that higher prevalence of masked EMHT. A significant increase of early morning BP, especial systolic BP, might be predictive risk factor of ischemic stroke events rather than nocturnal BP. Hence ASP measurements might be particularly important for the early detection of ischemic stroke event.

TAVI: THE ANNULUS AND THE VENTRICLE

P2346 | BEDSIDE

Influence of gender on mortality and perioperative outcomes in patients undergoing transcatheter aortic valve implantation: insights from the FRANCE 2 Registry

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Aim: Transcatheter aortic valve implantation (TAVI) is an alternative to surgical aortic valve replacement in high risk patients, avoiding the risks of thoracic surgery and extracorporeal circulation. The relative event rates following TAVI are not well described and seem to differ between genders. We sought to determinate gender imbalances in TAVI patients in regard of baseline presentation, management, and prognosis.

Methods and results: A total of 3972 patients underwent TAVI and were prospectively included in the FRANCE 2 registry.

Women (n=1967) presented older age, lower rates of coronary artery disease, chronic obstructive pulmonary disease, renal failure and arrhythmia, but higher prevalence of hypertension and congestive heart failure (43.7% vs 39.7%; p=0.010). EuroSCORE was similar between genders. Women presented smaller aortic annulus sizes and were implanted with smaller bioprostheses.

Women presented higher rates of major bleedings and vascular events at one month. Men presented higher mortality rates than female (23.7% vs 19.3%; p=0.021). Female gender, NYHA class III or IV, transapical approach and moderate to severe postprocedural aortic regurgitation were independent predictors for one-month all-cause mortality. We found a specific interaction between gender and EuroSCORE that settle EuroSCORE to be not discriminant in women to establish one-month mortality. Female gender was an independent predictor of one-year survival (HR 0.71 95%CI [0.57-0.88]).

Conclusion: Men and women presented many differences in baseline characteristics, procedural and clinical outcomes. Notably women presented an 18.5% decrease in one-year all-cause mortality compared to men but higher rates of major bleedings and vascular events. Not only actual predictive scores seem to be inconvenient to female TAVI patients, but specificities in procedural management of female patients should be studied further.

P2347 | BEDSIDE

Gender-specific differences and hospital outcomes in patients undergoing transcatheter aortic valve implantation and conventional surgery: results from the German aortic valve registry

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Background: Transcatheter aortic valve implantation (TAVI) appears to be an effective alternative to conventional aortic valve replacement (AVR) for the treatment of aortic stenosis in surgical high-risk patients. However, gender differences in patients treated with TAVI or conventional aortic valve replacement (AVR) have been poorly investigated.

Methods: From 2011 to 2012, 30,292 consecutive patients undergoing repair for aortic valve disease were prospectively enrolled into German Aortic Valve Registry (GARY). For the present analysis patients were divided into four categories: females treated with TAVI or AVR and males treated with TAVI or AVR.

Results: Female patients had a comparable general health status, but were older and more likely to be treated with TAVI than male patients (table). Among those with AVR, concomitant coronary bypass surgery was more often performed in male patients (38.8 versus 28.2%). In the TAVI group the transfemoral access route was more frequently used among females (72.2 versus 63.3%). The rate of TIA/stroke was similar in all groups, but significant aortic regurgitation (≥ II°) and vascular complications were more often observed in the TAVI cohort. The incidence of in-hospital death was lowest in male patients with AVR, followed by female patients with AVR and both TAVI groups.

	Female AVR N=7,395	Male AVR N=13,626	Female TAVI N=5,118	Male TAVI N=4,153
Age (mean)	71.9 yrs.	68.4 yrs.	82.0 yrs.	79.7 yrs.
ASA ≥ 3	85.3%	84.7%	90.8%	90.1%
Residual insufficiency ≥2°	0.4%	0.4%	5.0%	7.2%
TIA/stroke	2.9%	2.5%	3.3%	2.5%
Vascular complications	1.3%	1.1%	10.4%	6.7%
Hospital mortality	3.8%	2.6%	5.3%	5.3%

Conclusions: Female patients undergoing repair for aortic valve disease were older and more likely to be treated with TAVI in comparison to their male counterparts. In-hospital mortality was higher in female patients treated with AVR, whereas mortality rates were similar in both groups treated with TAVI.

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Influence of gender on outcome following Transcatheter Aortic Valve Implantation (TAVI): Meta-Analysis of the Literature

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Objectives: This study sought to undertake a comprehensive meta-analysis of studies investigating differences in outcome after Transcatheter Aortic Valve Implantation (TAVI) in women compared to men.

Background: Sex differences exist in pathogenesis, clinical presentation and outcome in aortic stenosis (AS). Still limited information is available concerning sex differences in periprocedural complications and outcome after TAVI.

Methods: PUBMED, MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were screened. Inclusion criteria were: AS treated with all forms of TAVI; studies targeting specifically on sex/gender differences; and at least two of the following outcome data: 30-day all-cause mortality, all-cause mortality during follow-up (> 3 months), major vascular complications, and major bleeding. Exclusion criteria were studies in which gender was merely considered in subgroup analysis.

Results: 11 observational studies with a total of 5867 patients (3087 women, 2780 men) were included. At 30 days (10 studies, 2716 women, 2438 men), female sex was associated with a significant, 25% lower mortality rate [odds ratio (95% confidence interval) = 0.75 (0.60-0.94)]. Nine studies with 4985 patients (2578 women, 2407 men) providing data on mortality during follow-up reported a significant survival advantage for women [0.67 (0.53-0.83)]. Whereas major vascular complication rate was greater in women (9 studies, 2757 women, 2536 men) [1.72 (1.39 to 2.14)], major bleedings (7 studies, 1977 women, 1899 men) were not significantly different between genders [1.12 (0.91, 1.37)].

Conclusions: There is evidence for a significant overall survival benefit in women over men treated with TAVI.

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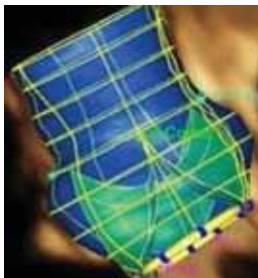
Evaluation of the aortic valve and root with new automated quantitative 3-dimensional model in candidates for transcatheter aortic valve replacement

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Background: Progress in the technique of transcatheter aortic valve replacement (TAVR) requires good knowledge of the aortic root. With this aim new specialized software appears with the ability of automated quantitative modeling of the aortic valve (AV) and root from 3D transesophageal echocardiography (3D TEE). The purpose of this study was to validate this model with the measurements made manually.

Methods: 21 patients (84.48±6.22 years, 66.7% females) undergoing TAVR in our center where included. The diameters and areas of the aortic annulus (AA), sinus of valsalva (SV) and sinotubular union (STU) were manually measured by 3D TEE. Afterwards, the images were analyzed using the new software (Figure 1).

Results: We found a moderate correlation and interobserver variability between the automated and manual measurements at the level of the AA: Intraclass correlation coefficient was 0.618 (0.227-0.838), (r: 0.635, p: 0.000), good correlation and interobserver variability for the SV area: ICC was 0.775 (0.495-0.910), (r: 0.778, p: 0.000) and moderate correlation for the STU area: ICC was 0.621 (0.231-0.839) (r: 0.630, p: 0.000).



Conclusions: Automated 3D quantification of the AV and aortic root is possible. There is a proper correlation between manual and automated measurements analyzed by the new model. The assistance in percutaneous techniques such as TAVR is one of the possibilities of this new software. Prospective studies are necessary to define its applicability.

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30-day interim analysis of transfemoral aortic valve implantation using a 29mm balloon expandable transcatheter heart valve: results from the SOURCE XT sub-registry

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Purpose: TAVI is an alternative treatment for high-risk patients with severe, symptomatic, calcific aortic stenosis. Screening examinations in first generation TAVI feasibility and post market studies confirmed the need for a valve size for patients with larger aortic annuli. A sub-registry of SOURCE XT was initiated for the 29mm SAPIEN XT transcatheter valve (THV) and next generation transfemoral delivery system (TF-DS) to collect post market data.

Methods: The multicenter, observational SOURCE XT sub-registry prospectively enrolled a total of 105 patients receiving the size 29mm THV with the TF-DS through a 20Fr expandable introducer sheath. 30-day follow-up was 99% complete.

Results: The mean patient age was 80.6±7.7 years. The size 29mm THV was primarily implanted in male patients (93.3%), whose cardiac anatomy and body size supported a larger THV device. The mean Logistic EuroSCORE was 18.6±12.4% with the majority of patients in NYHA class III/IV (65.7%) at baseline. High burden comorbidities included congestive heart failure (49.5%), diabetes mellitus (37.1%), renal insufficiency/failure (26.7%), cancer (25.7%), pulmonary hypertension (24.8%), prior CABG (20.0%), and history of stroke (13.3%). Device success was 95.8%. The incidence of VARC outcomes at 30-days was very low with major bleeding at 9.6%, life-threatening bleeding at 4.8%, major vascular complications at 5.8%, re-hospitalization at 4.9%, and stroke 1.9%. No myocardial infarction was observed and 9.6% required a new pacemaker implantation. Substantial functional improvement was seen at 30-days compared to baseline, with the majority of patients in NYHA class I/II (95.7%) and significantly better overall quality of life (ED-5Q, p<0.0001). Hemodynamic parameters, including mean gradient (8.7±3.2mmHg) and effective orifice area (2.1±0.4cm²) showed significant improvement to baseline (p<0.0001), with a remarkably low incidence of moderate and severe paravalvular leak (1.4%). Based on the current analysis, the overall survival at 30-days was 97.1%.

Conclusion: The 30-day interim analysis of the SOURCE XT transfemoral sub-registry demonstrates early safety and effectiveness of the size 29mm THV with high device success and is associated with a low incidence of mortality (2.9%), stroke, bleeding complications and re-hospitalizations, while demonstrating significantly improved patient functional capacity and hemodynamic performance with a very low incidence of moderate/severe PVL.

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Outcomes of TAVI in patients with severe aortic stenosis and large aortic annulus

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Purpose: To assess device safety, procedural success and early 30-days outcomes of the 31mm self-expanding transcatheter heart valve, in comparison with the other device sizes.

Methods: The study includes 76 consecutive patients who underwent transcatheter aortic valve implantation (TAVI) with 26mm self-expanding valve (n=21, 28%), 29mm (n=20, 26%) and 31mm (n=35, 46%).

Results: Patients with 31mm prosthesis were significantly younger (26mm: 83±6 y.o.; 29mm: 85±5; 31mm: 79±8; p=0.001), prevalently males (26mm: 19%; 29mm: 40%; 31mm: 91%; p=0.00001) with higher STS scores (26mm: 21±15%; 29mm: 20±16%; 31mm: 32±15%; p=0.01) and lower left ventricular ejection fraction (26mm: 53±17%; 29mm: 55±7%; 31mm: 45±12%; p=0.04). A device success was obtained in 71 (93%) cases in the overall population, without significant differences between groups. 5 patients required acute valve-in-valve therapy. Procedural, fluoroscopy and revalving times and procedural outcomes did not differ. At discharge we observed similarly a significant reduction in transaortic mean gradient and increase in aortic valve area; the incidence of paraprosthesis regurgitation was significantly minor in 31mm valve when compared with 29mm. Pace-maker implantation, bleeding, vascular and renal complications were similar. Time of hospitalization in CRS 31mm patients did not differ from the other groups and 30-days outcomes were similar.

Conclusions: The 31mm self-expanding transcatheter heart valve can be safely implanted in patients with complex aortic valve disease, large annuli, dilated left ventricles, severe aortic regurgitation and low annular calcifications.

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Evaluation of aortic annulus geometric change after transcatheter aortic valve replacement by three-dimensional transesophageal echocardiography

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Background: Aortic annulus diameter is critical information for transcatheter aortic valve replacement (TAVR). Because aortic annulus is of an oval shape, three-dimensional measurements are indispensable. However, the geometric change of aortic annulus after TAVR is unclear. Thus, we tried to evaluate the shape and size of aortic annulus before and after TAVR by three-dimensional transesophageal echocardiography (3D-TEE).

Methods: In 27 patients (82.7±8.1 y/o) patients with severe aortic stenosis undergoing TAVR with SAPIEN XT prosthesis (23mm or 26mm), 3D-TEE was performed before and after replacement. Some patients were enrolled in PREVAIL JAPAN study. We performed the off-line analysis of aortic annulus geometry by the dedicated software (Q-LAB, Philips). We defined the aortic annulus as the plane formed by the 3 lowest points of aortic valve cusp and measured manually aortic annulus long diameter (DL), short diameter (DS) and Planimetry of the area (AAA) by multi-planar reconstruction images before replacement. Geometric mean diameter (DGM) was calculated as $[2 \times \sqrt{AAA/\pi}]$. Noncircularity of aortic annulus was calculated as eccentricity index (INECC) $[1-(DS/DL) \%]$. After replacement, we also measured the external geometry of stent frame at the inflow level in the same way.

Results: Aortic valve area (0.56 ± 0.12 vs. $1.36 \pm 0.20 \text{ cm}^2$, $p < 0.01$) and mean pressure gradients (54 ± 19 vs. $12 \pm 3 \text{ mmHg}$, $p < 0.01$) were improved after replacement. AAA (3.38 ± 0.69 vs. $3.66 \pm 0.63 \text{ cm}^2$, $p < 0.01$) and DGM (20.7 ± 2.1 vs. $21.5 \pm 1.8 \text{ mm}$, $p < 0.01$) were significantly increased ($0.86 \pm 0.76 \text{ mm}$) and INECC was decreased (16.9 ± 6.1 vs. $2.8 \pm 2.9\%$, $p < 0.01$) after replacement.

Conclusions: The replaced prosthetic valve was larger than aortic annulus before TAVR and changed the shape into a circle. Aortic annulus should be three-dimensionally measured in view of the geometric change after TAVR.

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Influence of body-mass-index on survival of aortic stenosis patients treated by transcatheter vs. surgical valve replacement or medical therapy only: insights on obesity-paradox from the PARTNER trial

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Purpose: To evaluate for possible influence of body mass index (BMI) on survival of patients with severe aortic stenosis (AS) in different treatment strategies.

Methods: Patients who underwent transcatheter aortic valve replacement (TAVR) in the PARTNER trial were evaluated according to their BMI ($n=2,519$): underweight ($<18.5 \text{ kg/m}^2$, $n=109$), normal weight ($18.5-25 \text{ kg/m}^2$, $n=1,029$), overweight ($25-30 \text{ kg/m}^2$, $n=800$), obese ($30-40 \text{ kg/m}^2$, $n=484$), morbidly obese ($\geq 40 \text{ kg/m}^2$, $n=97$). In addition, outcomes of patients treated by surgical valve replacement (SAVR, $n=287$) or medical management only (MM, $n=177$) were evaluated according to their BMI.

Results: In the total group of patients that underwent TAVR: obese patients were younger, had lower STS score and worse 6-minute walk performance at baseline (table). Patients that were underweight and those with morbid obesity had the highest 30-day mortality. After propensity matching, adjusting for dissimilarity between the normal weight, overweight and obese groups, obese patients had lower 1-year mortality than patients with normal body weight (18.7% vs. 29.4%, $p=0.002$). Multivariate analysis revealed that obesity was a strong independent predictor for 1-year survival after TAVR: obesity vs. normal weight, odds ratio 1.37 (CI, 1.05-1.78, $p=0.02$); obesity vs. underweight, odds ratio 2.13 (CI 1.4-3.22, $p<0.001$). In patients that underwent SAVR or MM, a trend towards lower 1-year mortality appeared in obese patients, compared to those with overweight and normal weight: SAVR, 19.2% vs. 26% vs. 25.7%; MM, 42.5% vs. 48.1% vs. 54.4%, respectively.

Table 1. Baseline characteristics and clinical outcomes of patients that underwent TAVR

	Underweight (n=109)	Normal weight (n=1,029)	Overweight (n=800)	Obese (n=484)	Morbidly obese (n=97)	p-value
Age (yrs)	85.9±6.3	86.5±6	84.9±6.4	80.7±8	76.8±7.8	<0.001
STS score (%)	12.9±3.9	11.9±4.5	11.1±3.6	10.8±3.7	10.8±3.9	<0.001
6MWT (m)	96±103	116±117	110±117	86±103	58±89	<0.001
30-day mortality	9.2%	7.7%	4.6%	4.1%	9.3%	0.007
1-year mortality	33.2%	25.6%	21%	17.1%	17.6%	<0.001

6MWT: 6-minute walk test.

Conclusions: In patients with severe AS undergoing TAVR, those having obesity had better survival than those with normal body weight, after adjustment for differences in baseline characteristics. The "obesity-paradox" was evident in high-risk AS patients across different treatment modalities.

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Left ventricular mass regression in high-risk aortic stenosis patients undergoing transcatheter aortic valve replacement

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Background: Left ventricular mass index (LVMI) regression is associated with improved outcome following surgical aortic stenosis treatment. However, it is presently unknown whether the LVMI regression occurs in elderly higher-risk individuals undergoing transcatheter aortic valve replacement (TAVR).

Methods: From a prospective cohort of patients undergoing TVAR we systematically collected echocardiographic data. Both left ventricular mass and the left atrium diameter index (LADi) were calculated during screening and post procedure, and at 30 days, six months and one year follow-up. Increased LVMI was defined as $>115 \text{ g/m}^2$ in men, and $>95 \text{ g/m}^2$ in women. Longitudinal LVMI and LADi changes over time were assessed through mixed models in patients with and without increased LVMI.

Results: The study included 311 patients (mean age: 83 ± 8 years old). At baseline, 50% of patients had increased LVMI (mean= $135 \pm 28 \text{ g/m}^2$). These patients were more often females (57% vs. 39%; $p<0.01$), had more balloon valvuloplasty (41% vs. 23%; $p<0.01$), a lower left ventricular ejection fraction ($53\% \pm 14$ vs. $58\% \pm 10$; $p<0.01$), and had an increased LADi (2.6 ± 0.4 vs. 2.3 ± 0.4 ; $p<0.01$) compared to patients with normal LVMI. A significant decrease in the LVMI occurred over time among patients with increased LVMI at baseline ($p<0.0001$) (Fig. 1).

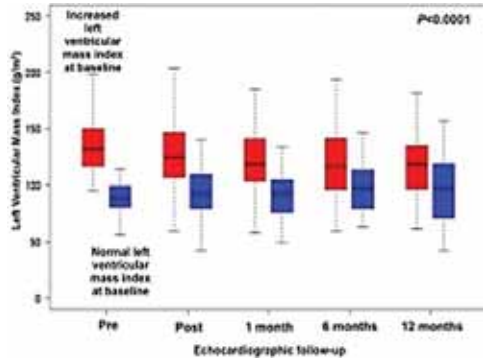


Figure 1

Conclusions: TVAR is associated with a continuous and sustained LVMI regression at one year. This finding suggests that TAVR is able to reverse the ventricular pathological changes induced by chronic pressure overload in high-risk elderly patients.

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Impact of left ventricular hypertrophy on the outcome of transcatheter aortic valve implantation

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Purpose: This study sought to evaluate the impact of left ventricle hypertrophy (LVH) on outcomes after transcatheter aortic valve implantation (TAVI).

Methods: In a retrospective analysis of the prospectively maintained registry, we divided 353 consecutive patients into 2 groups according to the degree of LVH which we used left ventricular mass index (LVMI) as a parameter. We compared patients with $\text{LVMI} \leq 140$ ($n=179$) to those with $\text{LVMI} > 140$ ($n=174$). Baseline characteristics, procedural and outcome variables were compared.

Results: Patients with higher LVMI had a smaller body surface area (BSA) ($1.67 \pm 0.17 \text{ m}^2$ vs. $1.73 \pm 0.21 \text{ m}^2$, $p=0.02$). Patients with higher LVMI had lower ejection fractions ($48.9 \pm 11.8\%$ vs. $54.7 \pm 9.6\%$, $p<0.001$) and larger LV chamber size (left ventricle end diastolic volume (LVEDV) $112.6 \pm 44.5 \text{ ml}$ vs. $90.2 \pm 31.6 \text{ ml}$, left ventricle end systolic volume (LVESV) $59.7 \pm 35.0 \text{ ml}$ vs. $41.8 \pm 22.1 \text{ ml}$, $p<0.001$ respectively). Otherwise baseline characteristics were similar. The device success rate according to the Valve Academic Research Consortium (VARC)-2 criteria was comparable between the two groups (94.4% vs. 93.1%, $p=0.626$). The 30-day all-cause and cardiovascular mortality were comparable between the two groups, however, 1-year rehospitalization rate for heart failure, all-cause and cardiovascular mortality were significantly higher for patients with higher LVMI group (rehospitalization 18.2% vs. 7.1%, $p=0.015$, all-cause 21.2% vs. 10.0%, $p=0.008$, cardiovascular mortality 12.3% vs. 5.3%, $p=0.034$). Kaplan-Meier survival curves at 1-year follow-up demonstrated the 1-year survival rate significantly lower in higher LVMI group (log-rank: 0.017). Multivariate logistic regression analysis showed $\text{LVMI} > 140$ to be an independent predictor of death at 1-year (OR 2.5, 95% CI 1.1-6.4, $p=0.046$).

Conclusions: Compared with patients undergoing TAVI with lower LVMI, those

with higher LVMI >140 had worse 1-year outcome and rehospitalization rate. Advanced LV hypertrophic patients undergoing TAVI should be carefully managed.

P2356 | BEDSIDE

Effect of pressure unloading on myocardial remodelling in patients undergoing TAVI

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Objective: The regression of left ventricular hypertrophy (LVH) after aortic valve replacement is a favorable effect of LV pressure unloading. However, no biological markers are currently established to reliably monitor LV mass regression after transcatheter aortic valve implantation (TAVI). Therefore, the objective of the present study was to investigate the time course and prognostic impact of serum biomarkers of extracellular matrix (ECM) remodelling over a 6 month period after TAVI.

Methods and results: In this study, thirty-two high-risk patients (81.1±5.8 years, female 59%, EuroSCORE 28.3±13.1%) underwent TAVI (transfemoral: n=24, 75%; transapical: n=8, 25%) for symptomatic, high-gradient AS (MPG 41.1±13.8 mmHg). In these patients, plasma levels of matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinases-1 (TIMP-1) and -4 (TIMP-4), growth differentiation factor-15 (GDF-15), as well as two fetal molecular variants of Tenascin-C (B+ Tn-C and C+ Tn-C) were measured at baseline, at 1 week and at 1, 3 and 6 month after valve replacement.

During a 6-month follow-up period, LV mass index decreased in trend from 171.7±62.1 g/m² to 140.9±57.6 g/m² (p=0.06), LV ejection fraction increased from 50.1±19.9 to 59.0±14.2 (p=0.013). This was accompanied by an extensive ECM reorganization represented by significant increases of TIMP-1 (121.1±43.3 vs. 140.1±40.0; p=0.008), TIMP-4 (3120.4±1335.9 vs. 3805.2±1525.1; p=0.001) and GDF-15 (2295.6±1209.9 vs 2967.8±1379.2, p=0.005) serum levels. In contrast, plasma levels of MMP-9 (92.3±150.9 vs. 57.1±36.4; p=0.51) and C+ Tn-C (35.9±22.2 vs. 32.5±13.4; p=0.001) decreased.

During 6 month follow-up, the structural changes of the myocardium were accompanied by a functional improvement with a significant increase in 6 min-walk distance from 148±113m to 192±129m (p=.036). The number of patients in NYHA class ≤ II increased from 6.3% (n=2) before to 78.1% (n=25; p<.0001) after TAVI.

Conclusion: Pressure unloading after TAVI results in mid-term LV mass index reduction and functional improvement, which are accompanied by a complex structural and functional re-organisation of the cardiac ECM. The changes in the serum biomarker levels observed in this study likely reflect reverse remodelling with a switchover from a high matrix turnover in disease-associated active tissue remodeling, to physiological cardiac tissue homeostasis after TAVI.

COMPLICATIONS AFTER TAVI

P2358 | SPOTLIGHT

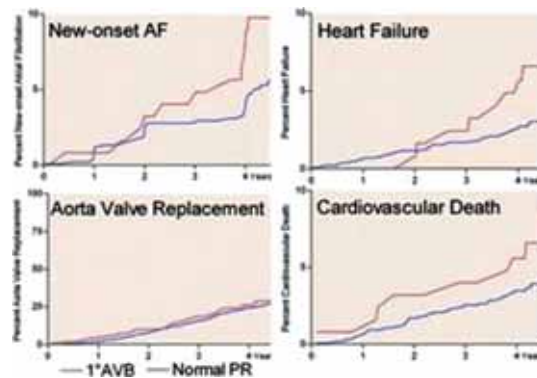
First degree atrioventricular block is associated with increased risk of atrial fibrillation and heart failure in patients with aortic stenosis: the SEAS study

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Purpose: First-degree atrioventricular block (1°AVB) has been considered a benign finding. However, there is limited evidence of the prognostic impact of 1°AVB in patients with asymptomatic mild to moderate aortic stenosis (AS).

Methods: All patients in sinus rhythm on baseline ECGs in the SEAS study of mild-to-moderate AS. The relationship of baseline 1°AVB (PR >220 ms) to new-onset atrial fibrillation (AF), heart failure (HF), aortic valve replacement (AVR) and cardiovascular death was evaluated in 1,421 patients with no history of AF. Cox multivariable models added age, sex, randomized treatment allocation, systolic and diastolic blood pressure, thyroid stimulating hormone, C-reactive protein, pulse, left atrial volume, time-varying peak aortic jet velocity, left ventricular (LV) ejection fraction and LV mass and medical treatment.

Results: At baseline, 76 (5.3%) patients had 1°AVB. During 6,142 patient-years of follow-up; new-onset AF occurred in 85 (6%), HF in 50 (3.5%), AVR in 399 (28%) and cardiovascular death in 62 patients (4.4%). In univariate analyses, 1°AVB was associated with new-onset AF (HR: 3.1 [95%CI: 1.7-5.6], p<0.001), HF (HR: 2.5 [95%CI: 1.1-5.8], p=0.038) and AVR (HR: 1.5 [95%CI: 1.0-2.2], p=0.041), but not cardiovascular death (p=0.323). In multivariate Cox models, 1°AVB remained associated with new-onset AF (HR: 2.4 [95%CI: 1.3-4.5], p=0.009) and HF (HR: 2.1 [95%CI: 1.0-4.4], p=0.05), but not AVR or cardiovascular death (both p≥0.60, Figure). Finally, prolonged PR interval, treated as a con-



1°AVB and risk of outcome.

tinuous variable, was in itself associated with more severe AS ($\beta=0.09$, $p<0.001$ for linear trend).

Conclusions: In asymptomatic AS, 1°AVB is independently associated with risk of new-onset AF and HF. Furthermore, longer PR interval is associated with more severe AS in itself.

P2359 | BEDSIDE

Incidence of prosthetic valve endocarditis at patients after TAVI

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Transcatheter percutaneous aortic valve implantation is a new technique for aortic valve stenosis and regurgitation. Because of short time of usage we are still have not all information about follow-up of this group of patients. Some studies suggests then up to 20% of patients after TAVI dies because of infection complications, however the information about incidence of prosthetic valve endocarditis (PVE) is limited.

The aim of the study was analysis of series of 129 patients after TAVI between 03/2010 and 03/2014. At 63% of patients Medtronic Corevalve was implanted, at 35% Edwards Sapien XT and at 2% Medtronic Engager. In 73% cases transfemoral access was used, in 15% direct aorta, in 8% subclavian and 4% apical. 44% of patients have implanted 29 mm bioprosthesis, 42% - 26 mm, 23 mm 8% and only 6% 31 mm.

In one year follow up we found 3 patients who met the diagnostic criteria valve endocarditis. The first patient had endocarditis on native mitral valve as a complication of severe pneumonia but TAVI prosthesis was not infected (26 mm Corevalve). The second patient had endocarditis on right atrium catheters during sepsis due to transplantation complications, however the Edwards Sapien XT 29 mm had no signs on PVE. At third patient we observed typical PVE on Medtronic Corevalve 29 mm due to urosepsis. Only the first patient survived (33%), the second died because of non-cardiological complication of transplantation, the third dies due to PVE complications.

Infective endocarditis after TAVI is rather rare complication (2%), and not always the bioprosthesis implanted by TAVI procedure is affected by PVE. However in cases of PVE of TAVI implanted valve we found 100% of mortality.

P2360 | BEDSIDE

Impact of permanent pacemaker implantation on left ventricular function and outcome of patients with aortic valve stenosis

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Background: Aortic stenosis (AS) is the most common valve disease nowadays with an increasing prevalence, especially in elderly population. In these patients, coexisting degeneration of the electrical conduction system, leading to sick sinus syndrome or advanced atrioventricular block, requiring implantation of permanent pacemaker (PM), is commonly encountered. Very little information, however, is available in literature on the impact of PM implantation on the natural history of patients with asymptomatic AS.

Methods: From our Valve Disease Registry (1989-2013), we identified 59 patients (52% males, age 75±9 years), with asymptomatic moderate or severe AS (mean jet aortic velocity 3.4±0.8 m/s, mean ejection fraction 56±9%), that required permanent right ventricular PM implantation. All patients were evaluated by transthoracic echocardiography immediately before and at least 6 months after PM implantation and clinically followed-up. As control group we considered 205 asymptomatic patients with AS with similar baseline findings (54% males, mean age 74±6 years, mean jet aortic velocity 3.3±0.6 m/s, mean ejection fraction 56±7%, p=ns for all).

Results: The mean follow-up period was 4.1±3.3 years for the PM group and 4.2±2 years for the control group (p=ns). There was not significant difference in the mean progression of the severity of AS (last jet aortic velocity 4.0±0.8 m/s in PM group and 4.1±0.8 m/s in controls; p=ns). On the contrary, mean ejection frac-

tion was significantly lower at the last follow-up in PM group ($48 \pm 10\%$ vs $53 \pm 9\%$, $p < 0.001$). Furthermore, patients in PM group had major clinical events (death or aortic valve replacement) in 74.6% of cases vs 57.6% of controls ($p = 0.027$).

Conclusions: Permanent right ventricular pacing plays an unfavourable role on left ventricular function and outcome of patients with AS. Our findings suggest that these patients should be followed-up more closely or biventricular pacing should be considered in selected cases.

P2361 | BEDSIDE

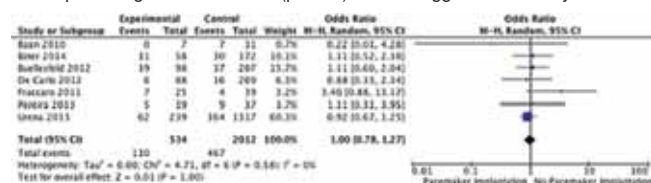
Mortality in patients requiring pacemaker implantation following transcatheter aortic valve replacement: Insights from a systematic review and meta-analysis

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Purpose: While the incidence of permanent pacemaker (PPM) implantation following transcatheter aortic valve replacement (TAVR) has been established, the effect of PPM implantation on mortality is less well described. Thus, we performed a meta-analysis to determine the impact of PPM following TAVR on all-cause mortality.

Methods: PubMed and Cochrane CENTRAL were searched for studies reporting data on patients that underwent PPM implantation following TAVR. Primary end-point was all-cause mortality. Summary effect estimates were generated with random-effects modeling to compare all-cause mortality between patients requiring PPM and patients not requiring PPM.

Results: We identified 39 studies pertinent to PPM implantation after TAVR were assessed at the full-text level. We abstracted data from 7 published studies. Among the 7 included studies, all-cause mortality data during follow-up was available on 534 patients that received PPM implantation following TAVR compared with 2012 patients that did not receive PPM implantation. As seen in the figure, requirement of PPM implantation following TAVR did not increase all-cause mortality during follow-up compared with patients that did not require PPM implantation following TAVR (pooled odds-ratio: 1.00 [95% CI 0.78-1.27], $p = 1.00$). Heterogeneity was extremely low with an I^2 of 0% and visual inspection of the funnel plot along with Peters' test ($p = 0.43$) did not suggest small study bias.



Conclusions: Our current meta-analysis suggests that the need for PPM following TAVR does not increase the risk of all-cause mortality. Further studies directed towards changes in left ventricular function, cost, length of stay, valve type and post-pacemaker complications should shed light on the overall effect of PPM implantation in patients following TAVR.

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Left bundle branch block after transcatheter aortic valve implantation: 1-year prognostic significance

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Purpose: Conflicting results are reported about the prognostic impact of left bundle-branch block (LBBB) after transcatheter aortic valve implantation (TAVI). We sought to evaluate the 1-year prognostic significance of new and persistent LBBB post-TAVI using the CoreValve Revalving System.

Methods: In our center 98 patients underwent TAVI implantation for severe symptomatic aortic stenosis (valve area $< 1 \text{ cm}^2$; all transfemoral approach, but 3 subclavian approach). Three patients who died within 24 h for major procedural complications (1 cardiac tamponade, 1 life-threatening arrhythmias, 1 failure of TAVI), and 3 patients who died within 7 days precluding the evaluation of persistent LBBB on ECG (1 stroke; 1 lung failure; 1 irreversible shock) were excluded from the analysis. All complications were evaluated according to Valve Academic Research Consortium definition.

Results: Among 92 patients, 34 (37%) (group A) developed a new and persistent LBBB and the remaining 58 (group B) did not. At baseline logistic EuroSCORE (17.8 ± 11.6 vs. 20.9 ± 15.8 , $P = 0.270$) and septal wall thickness ($14.3 \pm 1.7 \text{ mm}$ vs. $14.8 \pm 1.9 \text{ mm}$, $P = 0.778$) were not different between group A and B. After TAVI with similar markers of myocardial damage (peak troponin I: $3.8 \pm 4.9 \mu\text{g/l}$ vs. $4.5 \pm 8.2 \mu\text{g/l}$, $P = 0.939$) and of inflammation (peak white blood cells: $11.6 \pm 4.6 \times 10^9/\text{l}$ vs. $12.7 \pm 6.2 \times 10^9/\text{l}$, $P = 0.342$), a higher rate of advanced atrio-ventricular block (AVB) was found in group A vs. group B (50% vs. 22.4%, $P < 0.001$). The LBBB plus AVB was strongly correlated with permanent pacemaker implantation (PPI) ($P < 0.0001$), and at 30-days a higher rate of PPI was found in group A (59% vs. 19%, $P < 0.0001$). At 1-year the recovery of left ventricular (LV) ejection fraction (EF) was similar between group A and B (baseline to 1-year: EF $2.6 \pm 8\%$ vs. $4.2 \pm 8.3\%$, $P = 0.379$); 10 patients died (8 for non-cardiac cause) and 9 were hos-

pitalized for heart failure (HF); 5 (14.7%) events occurred in group A ($P = 0.281$). By adjusted Cox analysis the development of acute kidney injury (AKI) and the EuroSCORE were associated with a poor outcome (all cause mortality and HF) (HR 5.96, 95% CI 2.08 to 17.11, $P < 0.0001$; HR 1.05, 95% CI 1.006 to 1.096, $P = 0.025$, respectively), but not the development of LBBB ($P = 0.279$).

Conclusions: After TAVI, 34% of patients developed a new and persistent LBBB without marker of more advanced myocardial damage or inflammation. LBBB was associated with a higher rate of 30-days PPI, without impairment of recovery of LV systolic function. The development of AKI, rather than LBBB, increases the risk of mortality and HF hospitalization at 1-year.

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Predictors of permanent pacemaker implantation after transcatheter aortic valve implantation with the Medtronic CoreValve system

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Background: High-grade conduction disturbances (CD) requiring permanent pacemaker (PPM) implantation (impl) occur in up to 34% of patients (pts) following transcatheter aortic valve implantation (TAVI) with the Medtronic CoreValve (MCV). Knowledge about possible predictors might help to decrease the rate of PPM impl.

Aim of the study: The aim of this study was to assess the anatomical and ECG predictors of postinterventional PPM impl in pts undergoing TAVI with MCV.

Methods: From July 2010 until June 2012 in total 198 pts with high surgical risk underwent transfemoral TAVI with the MCV system (26/29/31 mm).

Pts (23) with pre-existing PPM or bifascicular block were excluded from the study leaving 175 pts for retrospectively evaluation for ECG, anatomical, and procedural predictors for PPM impl after TAVI. To evaluate procedural data, device position was measured on fluoroscopy as distance between the proximal aspect of the MCV stent frame below the native aortic annulus.

Results: We analyzed 175 pts (mean age 79.8 ± 0.65 years, log Euroscore $24.2 \pm 0.81\%$, mean pressure gradient $44.2 \pm 1.04 \text{ mmHg}$, AVA $0.65 \pm 0.01 \text{ cm}^2$, LVEF $50.6 \pm 0.8\%$). A total of 42 (24%) pts underwent PPM-impl post TAVI. 19 (10.9%) pts showed pre-operative CD, including first degree AV block, right (RBBB) and left bundle branch block (LBBB).

Pts with PPM impl showed a significant longer pre-procedural PQ interval versus pts without PPM-impl ($201.3 \pm 8.9 \text{ ms}$ versus $175.7 \pm 4.3 \text{ ms}$, $p = 0.04$).

Pre-existing LBBB was not associated with PPM impl. There was no pt with a pre-existing LBBB in the PMM group (PMM versus no-PMM: 0 versus 9.8%). Pre existing RBBB showed a slightly enhanced trend in the PPM group but was not statistical significant (16.7% versus 5.2%; $p = 0.05$).

The depth of the device impl showed also no significant difference (PPM versus no-PPM = $12.2 \pm 0.38 \text{ mm}$ versus $11.6 \pm 0.21 \text{ mm}$; $p = 0.177$), but was only associated with a new onset LBBB. LBBB group versus non-LBBB group: $12.05 \pm 0.307 \text{ mm}$ versus $11.15 \pm 0.316 \text{ mm}$; $p = 0.05$. The overall rate of new post procedural LBBB was 38.9%.

In a multivariate logistic regression analysis for predictors of post-interventional PPM impl including pre-PQ time, pre-existing LBBB, pre-existing RBBB, pre existing atrial fibrillation and depth of implantation, only pre-PQ time interval turned out as independent predictor for PMM impl.

Conclusions: Only a prolonged pre-PQ time interval turned out as independent predictor for PMM impl after TAVI. The implantation depth of the CoreValve was not associated with PPM Implantation but with a new-onset LBBB after TAVI.

P2364 | BEDSIDE

Impact of left ventricular conduction defect with or without need for permanent right ventricular pacing on functional and clinical recovery after TAVR

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Background: Left ventricular conduction disturbances (VCD) are relatively common after transcatheter aortic valve replacement (TAVR). Previous publications show different impact of left bundle-branch block (LBBB) with or without need for permanent pacemaker implantation (PM) on survival. Effects on patients' functional outcome is still unclear.

Methods and results: 212 patients (Age 80.8 ± 6.4 years, logEuroscore $28.95 \pm 17.37\%$) underwent TAVR with use of the CoreValve prosthesis. Follow-up (FU) included clinical examination and standardized echocardiography. After TAVR 125 (59%) patients showed VCD, whereof 41 (19%) patients were implanted with new PM, 33 (16%) had preexisting PM, and 48 (23%) showed new LBBB with intrinsic AV conduction.

After 9 months FU the presence of VCD was associated with less improvement of left ventricular ejection fraction (LVEF) (LVEFbaseline $54.5 \pm 15.9\%$, LVEFFU $51.7 \pm 18.2\%$, $p = 0.8$) if compared to patients without VCD (LVEFbaseline $53.8 \pm 12.9\%$, LVEFFU $63.4 \pm 10.1\%$; $p < 0.01$). Only the presence of PM was associated with higher functional NYHA classes ($p < 0.05$), and higher levels of NT-proBNP ($p < 0.05$), when compared to patients without VCD or patients with LBBB alone. 20.4% of PM patients remained in NYHA class ≥ 3 after TAVR,

as compared to 5.3% without VCD and 4.7% with LBBB ($p<0.001$). Independent predictors for all-cause mortality were aortic regurgitation index ($p=0.001$), a higher EuroSCORE ($p=0.01$), and impaired LVEF ($p=0.04$).

Conclusion: The occurrence of VCD is common after TAVR and is associated with unfavorable left ventricular functional recovery. The combination of both VCD and permanent RV pacing has adverse impact on heart failure related symptoms after TAVR.

P2365 | BEDSIDE

Impact of TAVI on primary hemostasis disorders

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Purpose: Aortic valve stenosis (AVS) can be complicated by bleeding associated with primary hemostasis disorders. These latter include acquired type 2A von Willebrand syndrome which is a deficiency of high molecular weight multimers of von Willebrand factor (vWF), due to increased proteolysis of vWF through the stenotic valve. The association of AVS and gastrointestinal bleeding (GIB) from angiodysplasia is defined as Heyde's syndrome. It is unclear yet if the beneficial effect of surgical valve replacement on these disorders is applicable to patients undergoing transcatheter aortic valve implantation (TAVI).

Methods: From November 2012 to December 2013, we prospectively enrolled 49 consecutive patients with severe AVS addressed for TAVI in our institution. Bleeding complications and transfusion needs were evaluated. Biological primary hemostasis parameters (with analysis of vWF) were assessed at baseline and one week after the procedure.

Results: The mean age was 84 years and 55% were male. Mean logistic euroSCORE was 31.9%. 9 patients (18.4%) had history of GIB or noninvestigated anemia, with 1 (2%) Heyde's syndrome. Both commercially available prosthetic valves were used. Thirty-day mortality was 8.3%. 20 patients (41.7%) had bleeding complications (9 life-threatening bleedings (18.8%), 9 major bleedings (18.8%), 2 minor bleedings (4.2%)). There was no fatal bleeding, and no GIB was observed. 24 patients (50%) were transfused with red blood cells (RBC) during hospitalization, 89 units of RBC were transfused in total (1.85 units per patient). Hemoglobin level was lower one week after TAVI compared to before the procedure (10.18 vs 11.59 g/dl, $p<0.05$). There was a significant increase at one week of vWF antigen, vWF activity (Ristocetin Cofactor), and vWF collagen-binding activity, consistent with the improvement of primary hemostatic abnormalities involving vWF.

Conclusions: Bleeding complications are frequent in patients with AVS undergoing TAVI, and possibly linked to primary hemostasis abnormalities involving vWF. These abnormalities are significantly improved after TAVI. Moreover, our observations, although limited to a small single-center study, suggest the fact that Heyde's syndrome can be cured by TAVI.

P2366 | BEDSIDE

Importance of complete coverage of all major aortic arch cerebral arteries with a novel neuro-deflection device in patients undergoing TAVR: Results from the DEFLECT I study

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Background: Up to 60% of the new DW MRI lesions occur in the distribution of the cerebellum/brainstem and posterior region of the brain. The DEFLECT I trial demonstrated a 53% reduction in total ischemic burden to the brain with neuro-deflection compared to historic controls.

Objectives: We report the results of the TriGuard™ EDD used during TAVR in 28 consecutive patients in the DEFLECT I trial comparing full versus incomplete coverage of the cerebral aortic branches.

Methods: DEFLECT I is a registry designed to demonstrate the safety and performance of the EDD in pts undergoing TAVR. The EDD is a nitinol mesh filter of 250 microns aimed to cover all major cerebral arteries in the aortic arch. This sub-analysis was performed to assess the importance of covering all cerebral take-offs. The primary end-points were the mean total number of new lesions and mean single and total lesion volume of new DW MRI lesions from pre- to post-procedure with full arch coverage (FC, 3 cerebral branches covered) compared to incomplete coverage (IC) during TAVR and after the TAVR delivery system was removed.

Results: A total of 28 TAVR pts with paired DW-MRI were enrolled; 80% (21/28) of the pts had FC during TAVR, 5/28 IC, and 2/28 were unknown due to loss of analyzable imaging data. Of these, a total of 17/28 patients had FC, 10/28 IC, and 1/28 case was unknown after removal of the TAVR delivery system. The

mean number of lesions per pt was numerically lower ($p=NS$) with FC compared to IC (FC 4.5 ± 6.5 and IC 7.8 ± 5.3 during TAVR and FC 4 ± 6.7 and IC 7.2 ± 4.9 after TAVR removal). Compared to pts with IC, the mean single volume of new ischemic brain lesions was lower after TAVR removal (0.09 ± 0.12 vs. 0.22 ± 0.12 cm³, $p<0.01$) and at TAVR completion (0.11 ± 0.12 vs. 0.19 ± 0.12 cm³, $p=0.07$). The mean total lesion volume was less with FC after TAVR removal than with IC (0.5 ± 0.91 vs. 1.3 ± 0.85 cm³, $p<0.05$). The mean total lesion volume was numerically lower with FC after TAVR completion than with IC (0.6 ± 0.94 vs. 1.14 ± 0.69 , $p=0.2$).

Conclusions: This sub-analysis of the DEFLECT I study demonstrates that full coverage of all three cerebral aortic branches can reduce significantly the mean and total volume of new ischemic brain lesions. The most significant reduction was seen when the positioning of the deflector was maintained until the TAVR delivery system was removed. This is the first report to prove the concept that embolic protection during TAVI reduces larger volume embolic brain lesions.

P2367 | BEDSIDE

Feasibility and exploratory efficacy evaluation of the embrella embolic deflector system for the prevention of cerebral emboli in patients undergoing transcatheter aortic valve implantation

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Purpose: Very few data exist on the value of using embolic protection devices during TAVI procedures. The objectives of this study were to determine the procedural safety, technical feasibility and exploratory efficacy of the Embrella Embolic Deflector (EED) system in patients undergoing TAVI.

Methods: This pilot study included 52 patients who underwent transfemoral TAVI with the SAPIEN XT valve. The EED system was used in 41 patients; while 11 patients underwent TAVI without embolic protection (control group). The occurrence of cerebral microembolization was monitored during the entire TAVI procedure by transcranial Doppler (TCD), and cerebral DW-MRI examinations were performed at baseline, within 7 days and at 30 days following TAVI.

Results: The EED system was successfully deployed at the level of the aortic arch in all patients with no complications. The deployment of the EED system was associated with a high number of high-intensity transient signals (HITS) as evaluated by TCD (48 [17-198] HITS), and the total number of HITS during the TAVI procedure was higher in the EED group than in the control group ($P<0.001$). The DW-MRI performed within 7 days after TAVI showed the presence of new ischemic lesions in all patients in both EED and control groups, with a mean number of 7 (3-13) lesions per patient. The use of the EED system was associated with a lower lesion volume compared to the control group (30 [20-50] mm³ vs. 50 [30-70] mm³, $P=0.003$). All new cerebral lesions had disappeared at the DW-MRI performed at 30 days following TAVI. Two strokes unrelated to the EED device occurred at days 2 and 29 after TAVI.

Conclusions: This study showed the feasibility and safety of using the EED system in TAVI procedures. The EED system did not prevent the occurrence of cerebral microemboli during TAVI or new transient ischemic lesions as evaluated by DW-MRI, but it was associated with a reduction in lesion volume. Further studies are warranted to determine the efficacy of using the EED system during TAVI procedures.

P2368 | BEDSIDE

High-on-treatment-platelet-reactivity in interventional valve procedures

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Purpose: Since introduction of transcatheter aortic valve implantation (TAVI) and interventional clipping of the mitral valve, many patients with high surgical risk underwent those procedures. Major complications are ischemic events as well as vascular and bleeding complications. Therefore, optimal antiplatelet medication is challenging, especially as most patients are octogenarians. In this study, we investigated the incidence of clopidogrel and aspirin high on treatment platelet reactivity HTPR in patients undergoing interventional valve repair procedures.

Methods: We analyzed data of a monocentric real world cohort of 386 interventional valve procedures between 2009 and 2013. In 210 patients of this cohort, platelet function tests during hospital stay were performed. Vasodilator-stimulated protein phosphorylation (VASP) assay was used for evaluation of clopidogrel antiplatelet effects and light-transmission aggregometry for aspirin. Patients (age 80 ± 9 ; 57% male) were on optimal medical therapy according to clinical guidelines. Complications were defined using the valve academic research consortium (VARC) provided standardized definitions of clinical complications.

Results: 62% of patients undergoing interventional valve procedure had clopidogrel HTPR. Aspirin antiplatelet effects were insufficient in 12% of patients. 22% of investigated patients had a VARC complication. The incidence of HTPR to clopidogrel as well as aspirin therapy did not differ between patients with- and without VARC- complications. Ischemic complications were observed in 3% of patients undergoing interventional valve procedures, bleeding complications in 22%. Clopidogrel and aspirin HTPR was not-significantly higher in patients with ischemic complications in comparison to patients without ischemic complications (clopidogrel: 83% vs. 61%; $p=0.26$; aspirin: 33% vs. 19%; $p=0.36$). Furthermore, no significant differences existed between clopidogrel, respectively aspirin HTPR in patients with bleeding complications in comparison to patients without bleeding complications (clopidogrel: 58% vs. 71%; $p=0.065$; aspirin: 18% vs. 19%; $p=0.83$).

Conclusion: In conclusion, clopidogrel HTPR occurs in almost two-third of patients undergoing interventional valve repair. Future studies investigating optimal antiplatelet regimen after TAVI should consider the high incidence of clopidogrel HTPR and monitor clopidogrel antiplatelet effects carefully.

P2369 | BENCH

TAVI failure: systematic appraisal of published data

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Purpose: Bioprosthetic surgical valve failure is well described, however no study has described transcatheter heart valve (THV) failure in a large series. We performed a systematic review of published literature to investigate the causes, diagnosis, management and outcomes of THV failure.

Methods: Between January 2002 and October 2013, all published studies reporting patient level data on THV failure were identified by systematic electronic search. Outcomes were defined according to the VARC criteria.

Results: Among 56 publications and 69 individual cases of THV failure, prosthetic valve endocarditis (PVE) (n=29), structural valve failure (n=8), and THV thrombosis (n=12) were identified. The microbiological profile of THV PVE was similar to that of surgical PVE, though up to 1/3 of patients underwent surgical intervention. THV thrombosis occurred at a mean 8 ± 7 months post implantation and was successfully treated with anticoagulation in 2/3 of patients.

Two novel causes of THV failure were identified: 13 cases of late THV embolization and 7 cases of THV compression following cardiopulmonary resuscitation. These failure modes have not been reported in surgical aortic valve replacement, and all involved balloon expandable THV systems. Potential risk factors for late THV embolization include THV undersizing/underexpansion; bicuspid and non-calcified aortic valve; and asymmetric root calcification.

Conclusions: THVs are susceptible to failure modes typical of surgical bioprostheses and unique to the design of THVs. THV compression and late embolization represent complications previously unreported in the surgical literature. Management of THV PVE, valve thrombosis, and structural valve failure differed considerably from surgical bioprosthetic failure.

IMAGING IN AORTIC STENOSIS

P2371 | BEDSIDE

Harmonizing cut-off values for stenosis severity between aortic valve area and aortic valve area index

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Background: Adjustment of aortic valve area (AVA) by body surface area (BSA) is intuitively convincing and current guidelines recommend calculation of AVAindex (AVA/BSA) to improve comparability between patients with diverging body size. We have recently shown that the current AVAindex cut-off value for severe

stenosis of $0.6\text{cm}^2/\text{m}^2$ dramatically increases the prevalence of severe stenosis compared to the AVA cut-off 1.0cm^2 . Consequently, we set out to harmonize cut-off values for severe stenosis between AVA and AVAindex.

Methods: We compared aortic valve related event rates according to quintiles of AVA and AVAindex in 1525 asymptomatic patients followed for a mean of 46 months from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study.

Results: The relationship between the cut-off values of AVA 1.0cm^2 and AVAindex $0.6\text{cm}^2/\text{m}^2$ is based on a BSA of 1.67m^2 . The BSA in SEAS was 1.89m^2 . In the quintile with the most severe stenosis patients had an AVA $0.70\pm0.1\text{cm}^2$ corresponding to an AVAindex of $0.4\text{cm}^2/\text{m}^2$ and the event rate was 0.5. Patients in the second quintile demonstrated an AVA of $1.0\pm0.1\text{cm}^2$ and an AVAindex of $0.5\pm0.1\text{cm}^2/\text{m}^2$ and had an event rate of 0.4 (Fig. 1).

Conclusions: Patients with a mean AVA of 1.0cm^2 have near identical event rates compared to patients with AVAindex $0.5\text{cm}^2/\text{m}^2$ suggesting that cut-off values for AVAindex should be lowered.

P2372 | BEDSIDE

Can aortic stenosis severity assessment be improved by direct measurement of left ventricular outflow tract area by computed tomography?

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Background: Estimation of aortic valve area (AVA) using the continuity equation is vulnerable to measurement error. Left ventricular outflow tract dimension (LVOTd) is often underestimated by transthoracic echocardiography (TTE) and when squared in the continuity equation, may lead to an underestimation of AVA and overestimation of aortic stenosis (AS) severity. Multi-slice computed tomography (MSCT) is often used for the delineation of aortic anatomy prior to therapeutic intervention and thus offers the opportunity for direct measurement of LVOT area (LVOTa), potentially providing a more accurate assessment of AVA.

Method: We assessed patients with symptomatic severe aortic stenosis referred for therapeutic intervention. All patients underwent resting TTE and MSCT as part of a clinical assessment. All TTE studies were performed according to established guidelines. CT LVOTa was determined by direct planimetry of a short axis image at the level of the LVOT (double-oblique method). AVA was calculated using the continuity equation using either TTE LVOTd or CT LVOTa in addition to TTE Doppler data.

Results: 64 patients (mean age 83 ± 5 years, 41% (n=26) female) were included in the analysis. The majority of patients had preserved LV ejection fraction (77%, LVEF >50%) and the mean aortic valve gradient was $46\pm17\text{mmHg}$. Mean AVA using CT LVOTa was larger than the TTE derived AVA ($0.85\pm0.26\text{ cm}^2$ vs. $0.65\pm0.23\text{ cm}^2$, $p<0.005$). AVA by CT LVOTa demonstrated a stronger correlation with mean AVG ($r=-0.44$, $p<0.05$) than TTE derived AVA ($r=-0.39$, $p<0.05$).

Conclusion: AVA is larger when calculated using CT derived LVOT area and correlates better with mean AV gradient than TTE derived AVA. A combined multi-modality approach using CT and TTE may provide a more accurate assessment of AS severity. Further studies with comparison to invasive data are required.

P2373 | BENCH

Aortic annulus sizing strategy in TAVI; comparison of echocardiography and CT, impact on aortic regurgitation incidence and patient prognosis

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Background: Trans aortic valve implantation (TAVI) is an alternative to surgery in high-risk patients. The aim of this study was to evaluate the predictors of mortality in the TAVI registry of our institution.

Methods: 136 consecutive patients undergoing TAVI were included between February 2010 and August 2013. The aortic annulus sizing for prosthesis choice was done by TEE in 29 patients and by CT in 107 patients. Aortic calcium volume was measured in 67% of patients who have got CT. Follow-up was performed at 1, 6, 12 and 24 months.

Results: Aortic annulus sizing by TTE and TEE echocardiography (TEE) were well correlated ($r=0.73$, $p=0.0001$, $n=51$) but were significantly lower than CT sizing ($p<0.0001$). The incidence of AR $\geq 2/4$ was 13% and was not significantly different according to the strategy (echo vs. CT) of aortic annulus sizing for prosthesis choice. No predictor of AR $\geq 2/4$ was identified (including cover index by TTE, TEE or CT, prosthesis/annulus ratio). Calcium volume was not associated either with AR with or mortality. Aortic regurgitation $\geq 2/4$ was a significant predictor of mortality.

Conclusion: This study showed that aortic annulus sizing by echocardiography is significantly lower than sizing by CT. AR have an independent prognostic on survival. Prevention of aortic regurgitation is an important issue for the future of this technique.

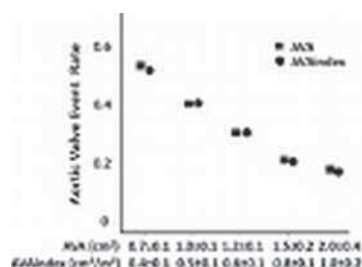


Figure 1

P2374 | BEDSIDE**Dynamics of aortic annulus morphology during cardiac cycle: implication for TAVI procedure**

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Purpose: The transcatheter aortic valve implantation (TAVI) is a technique in rapid expansion, the accurate measurement of the annulus size is the key point for the appropriate implantation of the valve prosthesis and for limit complications such as dislodgment, peri-valvular leakage, complete atrio-ventricular block, or annular rupture.

Aim of this study was the assessment of dynamics of aortic annulus morphology during cardiac cycle.

Methods: 14 patients (age 83, male/female 10/4) with severe aortic valve stenosis (TAVI group) and 10 patients (age 64, male/female 6/4) with suspected CAD (Control) underwent coronary CT angiography (spiral ECG gated acquisition, LightSpeed VCT 128, GE Healthcare, during iv administration of iodinated contrast medium). The image dataset (slice thickness 0.6 mm) was reconstructed at 10% increments over the cardiac cycle (phase 0 to 9 starting from tele-diastole), generating a 4-dimensional CT dataset. The following measurements of annulus were done for each ECG gated phase: maximum (MxD, mm), minimum (MnD, mm), mean diameter (MD, mm), ellipticity index (EI, (MxD/MnD)), cross-sectional area (CSA, mmq), and perimeter (Perim, mm).

Results: According with the ECG-gated phase, the maximum, minimum and the percentage change of each parameter resulted the following in TAVI and Control group respectively: MxD: 27.95±3.2 (phase 0), 25.46±3 (phase 5), 8.9% and 28.22±3.5 (phase 0), 26.74±2.5 (phase 5), 5.2%; MnD: 20.83±2.4 (phase 1), 17.51±2.4 (phase 6), 15.9% and 21.27±2.6 (phase 2), 18.77±2.6 (phase 6), 11.7%; MD: 23.7±2.5 (phase 0), 21.7±2.2 (phase 6), 8.4% and 24.4±3.2 (phase 0), 22.73±2 (phase 6), 6.8%; EI: 1.52±0.2 (phase 6), 1.28±0.1 (phase 2), 15.8% and 1.47±0.2 (phase 6), 1.24±0.1 (phase 2), 15.6%; CSA: 452.88±102.7 (phase 0), 388.97±84.1 (phase 6), 14.1% and 476.75±131.6 (phase 0), 403.62±73.3 (phase 6), 15.3%; Perim: 79.81±9.0 (phase 0), 75.86±11.1 (phase 5), 4.9% and 84.52±13.8 (phase 0), 76.82±9.1 (phase 7), 9.1%. We found no significant difference between TAVI and Controls.

Conclusion: The morphology of aortic annulus is modified throughout the cardiac cycle; the annulus resulted bigger in telediastole and smaller in systole and protodiastole, the annulus shape resulted more elliptic in diastole than in systole. Perim showed the lesser percentage variation during cardiac cycle in TAVI patient.

P2375 | BEDSIDE**Morphology of the left ventricle tract assessed by tridimensional echocardiography and its impact in aortic stenosis severity evaluation**

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The continuity equation quantification method of the aortic valve area (AVA) is dependent on left ventricular outflow tract (LVOT) diameter. It is assumed to be circular for the purpose of LVOT area calculation. This is one of the main sources of error of the method.

Purpose: Assess the LVOT morphology in patients with aortic stenosis (AS), compare the anatomic dimensions of the LVOT with the calculated area of the LVOT when it is assumed circular and its influence in AS severity quantification.

Population and methods: 47 patients (pts), 33 males, age 74±6.9 years with moderate or severe AS by transthoracic echocardiography (TTE) underwent transesophageal echocardiography (TOE). Tridimensional TOE acquisition of the LVOT and aortic valve in 3D zoom was performed. Planimetry of the aortic valve orifice and LVOT were performed after correct alignment of the cross sectional area in mesosystole with multiplanar reconstruction software.

The AVA for each patient was recalculated employing the LVOT area by 3D in the continuity equation (3DcontEq). The morphology of the LVOT was classified according to the closest geometric shape.

Results: The LVOT was ellipse shaped in 40 pts, circular in 3 pts, other shapes 4 pts.

The area of the LVOT by 3D planimetry was significantly higher than when it was derived by the diameter in parasternal long axis LVOT = 3,12±0,63 cm², LVOT 3D = 3,79±0,80 cm², Mean difference = 0,67±0,63 cm² p<0,001. As a consequence the recalculated AVA by 3DcontEq was bigger: AVA cont=0,89±0,25 cm²; AVA cont 3D= 1,10±0,30 cm², mean difference =0,20±0,18 cm², p<0,001.

After correction of the LVOT area 12 pts considered severe by ETT were reclassified as moderate and 4 pts with moderate AS were reclassified as mild AS. 19 patients were classified as low gradient severe AS by ETT, of these 9 were considered moderate after correction of the LVOT area by 3D.

The correlation between the AVA by 3D planimetry was slightly better when the functional AVA was calculated with the continuity equation corrected for the LVOT 3D (r=0,74, p<0,001) than with the classic continuity equation (r=0,73, p<0,001).

Conclusions: The majority of these pts had ellipse shaped LVOTs. The assumption of a circular LVOT in the continuity equation method overestimated the severity of stenosis. Calculating the AVA by the continuity equation with 3D planimetry of the LVOT increases the concordance with the anatomic area (3D planimetry)

of the aortic valve and identifies pseudo-severe AS. The authors propose that the AVA calculation should be corrected with the LVOT 3D area if the AS seems significant by ETT.

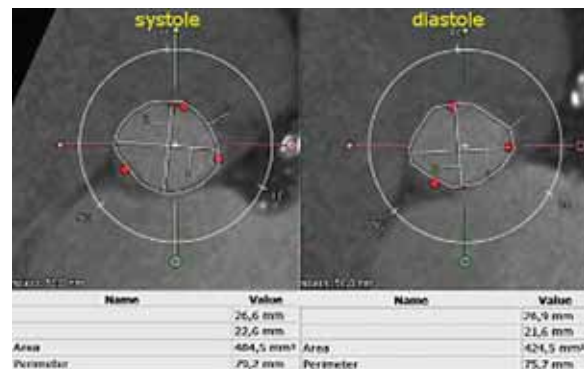
P2376 | BEDSIDE**Area and perimeter derived effective annulus diameter: comparison with direct intraoperative sizing**

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Objectives: A precise annulus sizing is of paramount importance for successful Transcatheter aortic valve implantation (TAVI). Currently, multislice computed tomography (MSCT) is the method of choice for determination of annulus dimensions. However, it remains unresolved whether 1) measurements should be performed in systole or diastole and 2) if calculation of the effective annulus diameter should be based on area or perimeter. Aim of our study was to compare MSCT results with direct intraoperative sizing of the annulus.

Methods: Conventional aortic valve replacement was performed in 52 patients, and the annulus was measured intraoperatively after decalcification using metric sizers. All patients had primarily been evaluated for TAVI including MSCT, but were deemed inappropriate for various reasons. The effective annulus diameter was determined derived by area (AsysA, AdiaA) and perimeter (AsysP, AdiaP) in systole and diastole, respectively. Furthermore, the potential change of prosthesis size was simulated for the various measurement approaches compared to IntraOp when TAVI would have been performed using the Edwards Sapien XT device.

Results: Best agreement with IntraOp was shown for AsysA by Bland-Altman analysis (mean difference [limits of agreement]): IntraOp vs. AsysA -0.36 mm [-2.22 to 1.51]; intraOp vs. AdiaA 0.42 mm [-1.77 to 2.61]; IntraOp vs. AsysP -1.08 mm [-3.01 to 0.86] and IntraOp vs. AdiaP -0.45 mm [-2.81 to 1.91]. Simulation of TAVI showed least change of strategy with AsysA (26.9%), followed by AdiaA (30.8%), AdiaP (34.6%) and AsysP (38.5%).



MSCT: annulus in systole and diastole.

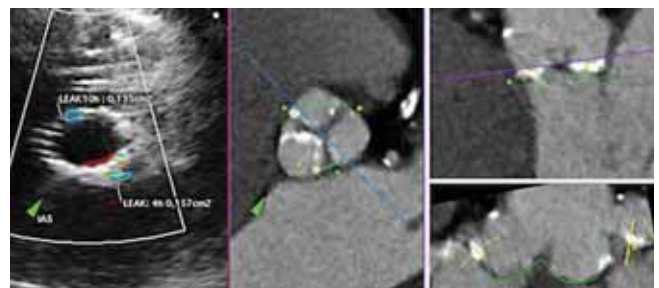
Conclusion: Compared to surgical sizing area derived measurement in systole represents the best approach for annulus determination. Perimeter derived measurement in systole may lead to overestimation of the annulus size.

P2377 | BEDSIDE**Impact of 3D aortic annulus shape and calcification on paravalvular regurgitation post TAVI**

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Background: Aortic annulus is a 3D structure and has a major impact on paravalvular regurgitation.

Method: Cardiac Computed Tomography was performed in 71 patients before TAVI. 3D Annulus shape was obtained point-by-point following the aortic cusp



3D aortic annulus calcifications and PAR.

insertion to aortic wall. In average 25 points covered the entire annulus circumference including the nadir and also the commissures of cusp insertion. Calcic 3D annular apposition was noted and compared with the echocardiography for detection of PAR after TAVI. We use a 12-quadrant clockwise segmentation. Annulus calcium surface (mm²) was measured and PAR was quantified using the planimetry of vena contracta.

Results: 71 patients were included in the study. 40 patients have mild or moderate PAR and 27 with moderate PAR. Annulus calcium was highly predictive of PAR (AUC 0.88) beyond valve calcium volume (AUC 0.7). In addition, annulus calcium (AC) location and site of PAR are closely related (Pearson's coef correlation 0.84).

Conclusion: Annulus calcium 3D location strongly correlate with sites and number of paravalvular regurgitations. Annulus calcium protrusion accurately predicts PAR after TAVI.

P2378 | BEDSIDE

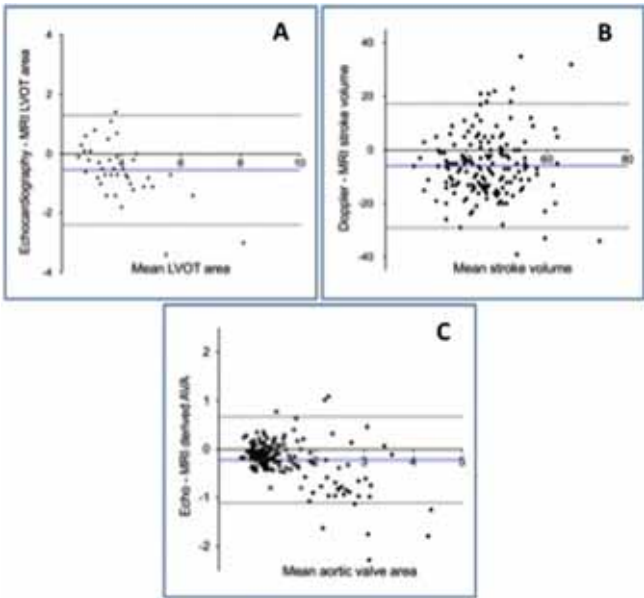
Echocardiography underestimates stroke volume and aortic valve area: implications for the classification of patients with small-area low-gradient aortic stenosis

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Purpose: Discordance between small aortic valve area (AVA, <1.0 cm²) and low mean pressure gradient (MPG, <40 mmHg) affects a third of patients with moderate or severe aortic stenosis. We hypothesized that this is largely due to inaccurate echocardiographic measurements of the left ventricular outflow tract area (LVOTarea) and stroke volume alongside inconsistencies in recommended thresholds.

Methods: 133 patients with mild to severe aortic stenosis (AS) and 33 controls underwent comprehensive echocardiography and magnetic resonance imaging (MRI). Stroke volume and LVOTarea were calculated using both echocardiography and MRI, and the effects on AVA measurements assessed. The relationship between AVA and MPG measurements was then modeled with non-linear regression and consistent thresholds for these parameters calculated. Finally the impact of these modified AVA measurements and novel thresholds on the number of patients with small-area low-gradient AS was investigated.

Results: Compared to MRI, echocardiography underestimated LVOTarea (-0.5 [95%CI -2.4 to 1.3] cm²; Fig. A), stroke volume (-5.9 [95%CI -29.1 to 17.3] mL/m²; Fig. B) and thereby AVA (-0.22 [95%CI -1.11 to 0.67] cm²; Fig. C). An AVA of 1.0 cm² corresponded to MPG of 24mmHg based on echocardiographic measurements and 37mmHg after correction with MRI-calculated stroke volumes. Based on conventional measures, 50 patients had discordant small-area low-gradient AS. Using MRI stroke volume and the revised thresholds, a 42% reduction in discordance was observed (n=29).



Bland Altman plots.

Conclusions: Echocardiography underestimates LVOTarea, stroke volume and therefore AVA. The thresholds based on current guidelines are inconsistent. In combination, these factors explain >40% of patients with discordant small-area low-gradient aortic stenosis.

P2379 | BEDSIDE

Prognostic value of stroke volume assessed using transthoracic 3d echocardiography in patients with aortic stenosis: a comparison with 2d echocardiography

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Purpose: Accurate assessment of disease severity is critical for the subsequent appropriate treatment in patients with aortic stenosis (AS). This study aimed to elucidate the prognostic value of stroke volume (SV) using 3D transthoracic echocardiography (TTE) in patients with AS.

Methods: This prospective study included 105 AS patients with aortic valve area (AVA) <1.0cm² who underwent 2D and 3D TTE. SV was calculated according to the conventional Doppler and 3D methods. AVA was calculated using the continuity equation (CE). The definition of AS severity was based on indexed AVA≤0.6cm²/m². Major adverse cardiovascular events (MACE) were recorded in all patients.

Results: SV (64±15 vs. 55±21ml) and AVA (0.70±0.21 vs. 0.60±0.22cm²) were greater in the Doppler method than 3D method (all p<0.001). The prevalence of severe AS was lower in the Doppler method (72 patients, 69%) than 3D method (88 patients, 84%, p=0.003). During the mean of 184-day follow up, MACE were identified in 63 patients (60%), including 9 patients (8.6%) with cardiac death. In reclassification analysis, indexed AVA derived by 3D TTE improved the prediction of MACE by 10% (Fig. 1).

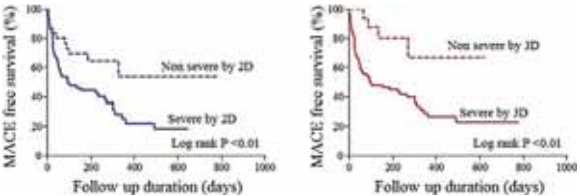


Figure 1

Conclusions: CE obtained from the conventional Doppler method has a potential risk for overestimation of SV and AVA in Japanese population. 3D SV have a stronger and additive prognostic value than the conventional Doppler method.

P2380 | BEDSIDE

Feasibility of assessing for preoperative left ventricular contractile function using two-dimensional speckle tracking echocardiography in patient with aortic stenosis

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Background: The development of postoperative left ventricular dysfunction is a frequent complication in patients with severe aortic stenosis (AS) and implies a poor prognosis. The purpose of this study was to elucidate the predictive value of post-operative left ventricular dysfunction by using both tissue Doppler imaging and two-dimensional speckle tracking echocardiography (2D-STE) in patients with severe AS.

Methods: Forty patients with severe AS scheduled for aortic valve surgery were enrolled. The study population was divided into two groups, according to post-operative decrease in left ventricular ejection fraction (LVEF): Group 1 (G1), with postoperative LVEF decreases <10%, and Group 2 (G2), with postoperative LVEF decreases >10%. There were no significant difference in age between two groups (G1: 70±10 N=29, G2: 76±9 N=11). There were no significant differences in LVEF between two groups. Preoperative 2D-STE was carried out four chamber of longitudinal strain.

Results: Peak systolic velocity of mitral annulus (S) and global longitudinal strain (GLS) was significantly lower in G2 compared with G1 (S: p=0.03, GLS: p=0.003, Table). Especially, preoperative speckle tracking-derived longitudinal strain values at the level of the interventricular septum indicated a postoperative LVEF decreases of >10% (p=0.007, Table). Their indicative values were greater than other regional myocardium, but the most strong effective predictor was GLS.

Longitudinal strain			
	Group 1	Group 2	p value
LVEF	64.3±7.2	69.5±8.4	p=NS
S septal	5.8±1.0	5.0±1.0	p=0.03
S lateral	7.3±1.5	6.2±0.9	p=0.03
Global	16.0±2.4	12.7±2.1	p=0.003
Basal septal	16.0±3.1	12.3±5.0	p=0.007
Mid septal	17.8±2.4	15.0±4.2	p=0.04
Mid lateral	15.5±5.0	10.6±2.7	p=0.004
Basal lateral	14.6±2.8	10.9±4.5	p=0.04

Conclusion: GLS allows the accurate detection of early abnormalities in left ventricular contractile function. This tool might assist clinicians in the optimal timing of surgery in patients with severe AS.

P2381 | BEDSIDE**The association between aortic valve weight and echocardiographic indices of aortic stenosis severity in 465 patients with isolated aortic stenosis and preserved left ventricular ejection fraction**

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Purpose: To determine the of association between aortic valve weight (AVW), as a measure of total AV calcium burden, and echocardiographic (echo) indices reflecting aortic stenosis (AS) severity in patients (pts) with normal ejection fraction (EF) undergoing aortic valve replacement (AVR) for severe isolated AS.

Methods: Between 2010-13, 465 patients (pts) undergoing AV replacement (AVR) for severe isolated AS, (mean age 76.8 (9.3) yrs, 56% men, AVA index 0.36 (0.10 cm²/m², EF=61.3±4.6%, 11% bicuspid valves), had AVs weighed (AVW=2.4±0.9 g), and preoperative echo studies. Pearson correlation was used to measure the linear association between AVW and the echo variables and a number of covariates were included through the calculation of partial correlation.

Results: Women have a lower AVW than men (2.1 (0.7)g vs. 2.6 (0.9) g, respectively, $p < .0001$) even when normalized for BSA ($p=0.01$). Compared with pts with tricuspid valves or with low gradients, those pts with bicuspid valves or mean gradients ≥ 40 mm Hg had higher AVW ($p=0.0002$ and $p=0.001$, respectively). Other associations were similar between genders and pts with normal vs. low stroke volumes. The unadjusted and adjusted correlations of AVW with echo variables are shown in the table.

The correlations between AVW with AS

Variable	Corr coeff	p-value	Corr coeff	p-value*	Corr coeff	p-value**
Dimensionless index	-0.27	<0.0001	-0.25	<0.0001	-0.25	<0.0001
Mean gradient	0.21	<0.0001	0.21	<0.0001	0.18	0.0003
Peak gradient	0.21	<0.0001	0.20	<0.0001	0.18	0.0004
Peak velocity	0.20	<0.0001	0.20	<0.0001	0.18	<0.0001
AV resistance	0.16	0.001	0.16	0.001	0.17	0.002
AV area	-0.14	0.005	-0.15	0.002	-0.16	0.003
Energy loss index	-0.11	0.04	-0.12	0.04	-0.15	0.02
LV stroke work loss	0.04	0.67	0.01	0.88	-0.02	0.81

*Adjusted for BSA; **adjusted for age, gender, BSA, diabetes, renal insufficiency, hypertension, CAD, heart failure, cardioactive meds.

Conclusions: 1. In severe isolated AS with normal EF, AVW is most closely associated with dimensionless index. 2. Women have lower AVW than men even when adjusted for BSA, while bicuspid aortic valves have higher AVW than tricuspid valves. 3. These findings may help in the interpretation of non-invasive evaluation of AV calcium load and AS severity in challenging cases.

P2382 | BEDSIDE**Relationship between segmental longitudinal strain and symptomatic status in severe aortic stenosis: Real-time three-dimensional speckle-tracking echocardiography**

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Purpose: The aim of this study was to evaluate the relationship between strain by 3-dimensional (3D) speckle tracking echocardiography (STE) and symptomatic status in patients with severe aortic stenosis (AS) and normal left ventricular ejection fraction (LVEF $\geq 50\%$).

Methods: Conventional and 3D STE were performed in 69 patients (mean age 69.3±8.4 yrs) with severe AS (aortic valve area <1 cm², AV Vmax >4 m/sec or mean PG >40 mmHg) and normal LVEF but without overt coronary artery disease. Severe AS patients were divided into two groups: asymptomatic (n=55) and symptomatic group (n=14).

Results: Global longitudinal strain (GLS) measured by 2D and 3D was not different in asymptomatic and symptomatic AS group. In 3D segmental LS analysis, basal LS was reduced in both. Interestingly, mid anteroseptal and apical anterolateral 3D LS were significantly decreased in symptomatic AS group compared to asymptomatic (Fig. 1). 2D STE also showed the same results.

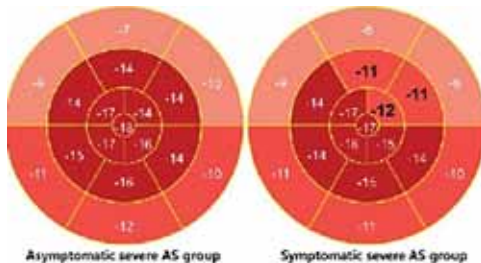


Figure 1. RT 3D LS in severe AS patients.

Conclusions: Three-dimensional segmental strain was related to symptomatic status in severe AS. Three-dimensional STE may give additional information in the decision-making process for patients with severe asymptomatic AS.

RISK PREDICTION IN AORTIC STENOSIS**P2384 | BEDSIDE****Echocardiographic predictors of a long term outcome of a large cohort of patients with bicuspid aortic valve**

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Purpose: Bicuspid aortic valve (BAV) is the most common congenital cardiac malformation. There is still uncertainty about the management of patients (pts) with BAV. The aim of this retrospective study was to assess echocardiographic prognostic factors of a large population with BAV.

Methods: Inclusion criteria was the presence of a BAV at ultrasound examination. We collected echocardiographic data at enrollment, mid-term and last follow-up. We considered aortic valve replacement (AVR), aortic surgery and death as a clinical combined end-point and focused on prevalence, determinants and evolution of complications. Predictors of outcome were determined by logistic regression.

Results: Our study included 337 BAV out of 81147 pts (0.42%) consecutively referred for echocardiographic examination to our Cardiology Department from 1/1/93 to 28/1/14. Mean duration of follow-up was 9.6±6.6 years (yrs). At baseline 185 pts (54.9%) were ≤ 30 yrs of age and 256 pts (76%) were males. Mean age at first examination was 29.4±19.9 yrs. 137 pts (40.7%) were hypertensive. Prevalence of complications at baseline was: 25 pts (7.4%) with at least moderate aortic stenosis (AS) 72 pts (21.4%) with at least moderate aortic regurgitation (AR), 102 pts (30.7%) with aortic dilatation (defined as an aortic ratio (art) 1.2 to 1.5 calculated on the basis of the expected aortic diameter using Roman's formula) and 24 pts (7.1%) with aortic aneurysm (art >1.5). 68 pts (20.2%) underwent AVR and/or aortic surgery during follow-up. 12 pts died (7 due to cardiovascular (CV) causes: 2 of them for endocarditis 2 for aortic dissection (AD) 2 for heart failure and 1 for Eisenmenger disease); mean age at death was 66.2±21 yrs for these 12 patients. At univariate analysis, baseline echocardiographic predictors of the combined endpoint were: thickened aortic cusps (AC) ($p < 0.001$), calcified AC ($p < 0.001$), AD ($p = 0.01$), aortic dilatation or aneurysm (Adiau) ($p = 0.001$), the degree of AR ($p < 0.001$) and the degree of AS ($p < 0.001$). At multivariate analysis, baseline echocardiographic predictors of the combined endpoint were: the degree of AR (OR 1.69, 95% CI 1.331 – 2.144, $p < 0.001$), the degree of AS (OR 1.634, 95% CI 1.296 – 2.061, $p < 0.001$) and Adiau (OR 2.266, 95% CI 1.372 – 3.745, $p = 0.001$).

Conclusions: Different from other reports, our series was composed mostly by young pts. A higher baseline degree of AR or AS and the presence of Adiau were independently correlated to the combined endpoint during follow-up. Long term follow-up showed low CV mortality (2.1%) and a high prevalence of cardiac surgery (20.2%).

P2385 | BEDSIDE**Value of cardiopulmonary exercise and non-invasive haemodynamic assessment in patients with asymptomatic severe aortic stenosis**

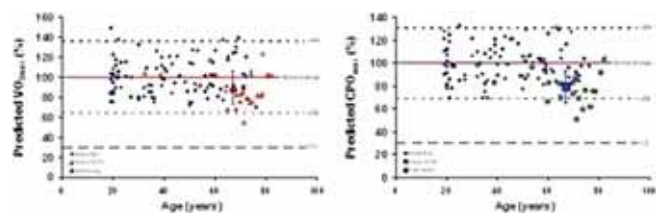
P.S. Lynas, D. Schlosshan, L.B. Tan. *Leeds Teaching Hospitals NHS Trust, Molecular Cardiovascular Medicine, Leeds, United Kingdom*

Purpose: Timing of aortic valve replacement in patients with asymptomatic aortic stenosis (VD) is controversial. Exercise testing may uncover symptoms and early cardiac dysfunction. We investigated the functional correlates why patients remain asymptomatic despite having severe VD identified echocardiographically by conducting cardiopulmonary exercise (CPX) testing combined with haemodynamic assessment.

Methods: Twenty one consecutive patients with severe VD (ERO 0.80±0.21 cm² MPG 42.64±13.78 mmHg) underwent maximal CPX tests. Central haemodynamics including cardiac output were measured non-invasively at rest and during peak exercise. The results were compared to normal values from a cohort of healthy controls and depicted as % of predicted for normal healthy controls.

Results: The following preliminary observations were made and are depicted on the graphs: (1) All patients except one (5%) had peak oxygen consumption (VO₂max) within the ranges for healthy controls, but (2) Five patients (24%) had cardiac power output (CPOmax) below the range for healthy controls. (3) When plotted together, relative to healthy controls the CPOmax of patients with severe AS were lagging below the VO₂max, suggesting that the measurement of VO₂max alone may not pick out the ones with early cardiac dysfunction.

Conclusion: Haemodynamic assessment during exercise using direct indicators



CPO and CPX data; % age-adjusted value.

of cardiac function may be more sensitive than conventional cardiopulmonary exercise parameters in detecting early cardiac decompensation in patients with severe asymptomatic aortic stenosis.

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Cardiopulmonary exercise testing in asymptomatic or equivocal symptomatic aortic stenosis

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Objective: To evaluate the feasibility, reproducibility and normal values of cardiopulmonary exercise testing (CPX), to assess the cardiac function from the measurements obtained, and to describe the information beyond that obtained from echocardiography and functional classification in patients judged asymptomatic or equivocal symptomatic from moderate to severe aortic stenosis (AS/ES-AS).

Methods: Prospectively, 131 patients (mean age 72.1 ± 9.3 years and V_{max} 3.92 ± 0.77 m/s) with AS/ES-AS were evaluated by NYHA classification, echocardiography and CPX with inert gas rebreathing (IGR). The predicted normal values were set according to authoritative recommendations.

Results: CPX was feasible for >99% of the patients. On average, the patients reached $97 \pm 22\%$ of the predicted peak oxygen consumption (pVO_2) (reflects cardiac output) and $109 \pm 24\%$ of the predicted pVO_2 /heart-rate (pO_2 pulse) (reflects stroke volume (SV)). A significant subnormal pVO_2 (<83% of predicted) was noted in 26.1% of the patients. Abnormal trajectories for O_2 pulse and for O_2 pulse and VO_2 were found in 25.2% and 13.2% of the patients, respectively. The coefficient of variability by test-retest was 5.4% for pVO_2 and 4.6% for pO_2 pulse. By IGR, the mean increase in SV from rest to exercise was $29 \pm 22\%$. A $V_{max} > 4$ m/s was not associated with subnormal pVO_2 or pO_2 pulse, lack of increase in SV, or higher frequency of abnormal trajectories. Kappa for NYHA class vs. absolute and percentage reached of predicted pVO_2 was low: 0.16 and 0.21, respectively. Increase in systolic blood pressure <20 mm Hg was not associated with abnormal pVO_2 , pO_2 pulse or trajectories.

Conclusions: CPX appears to be a promising tool for the diagnosis of functional limitation and hemodynamic compromise, serial assessments, and categorization of patients with AS/ES-AS.

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Clinical significance of serial BNP changes in asymptomatic patients with aortic stenosis

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Background: The ESC guidelines emphasized the usefulness of B-type natriuretic peptide (BNP) measurements for the management of asymptomatic patients with aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF). The aim of this study was to determine the impact on outcome of serial BNP changes during follow-up.

Methods and results: We studied 63 asymptomatic patients with AS (1.0 ± 0.2 cm²) and preserved LVEF (69±6%) that underwent BNP level measurement at baseline and then after each 6- or 12- months. BNP significantly increased between baseline and the last measurement (101 ± 140 vs. 180 ± 229 pg/mL; $p < 0.001$). Annualized BNP changes were calculated as the difference between the last and baseline BNP measurements divided by the time between them (24 ± 16 months). Mean annualized BNP change was $+47 \pm 82$ pg/mL/year. After the last BNP measurement, patients were followed-up (28 ± 19 months) for the occurrence of adverse cardiac events (symptoms, aortic valve replacement). Thirty-five patients presented an adverse cardiac event. Those patients had a more severe AS (peak velocity: 3.9 ± 0.7 vs. 3.5 ± 0.6 m/s; $p = 0.023$), a larger indexed left atrial area (10.6 ± 2.4 vs. 8.6 ± 2.1 cm²/m²; $p = 0.001$) and a higher increase in annualized BNP ($+69 \pm 93$ vs. $+21 \pm 55$ pg/mL/year; $p = 0.014$). There was a significant graded relationship between higher annualized BNP changes (according to

tertiles) and decreased cardiac event-free survival (log rank test, $p = 0.017$). Using Cox proportional hazards model, annualized BNP changes were significantly associated with increased risk of adverse cardiac events (HR: 3.03, 95% CI: 1.3–6.9; $p = 0.009$).

Conclusion: In asymptomatic patients with AS and preserved LVEF, serial BNP changes may unmask patients at higher risk of developing Class I indications for aortic valve replacement.

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Valvulo-arterial impedance is the best mortality predictor during long term follow-up in asymptomatic patients with moderate or severe aortic stenosis and normal ejection fraction

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Introduction and aim: Risk stratification is particularly complex in asymptomatic patients with hemodynamically significant aortic stenosis (AS). The aim of this study was to assess which hemodynamic/Doppler-echocardiographic parameter best predicts mortality, as a hardest clinical endpoint, in asymptomatic patients with moderate or severe AS and normal LV EF.

Method: This prospective study included 128 consecutive asymptomatic patients who met the criteria for a diagnosis of moderate or severe AS [aortic valve area (AVA) ≤ 1.5 cm², mean gradient (Pmean) >30mmHg]. The mean follow-up was 8 (27.5) months. Transthoracic echocardiography exam was performed using standard echocardiographic views. The mathematically derived parameters that represent LV workload and hemodynamic severity of AS, such as valvulo-arterial impedance (Zva), energy loss index (ELI) and stroke work loss (SWL) were calculated as previously described. Clinical data at follow-up was obtained in all patients by direct patient examination or telephone interview. The ethics committee of the hospital approved the study, and all patients gave written informed consent.

Results: The mean age was 66.47 ± 10.53 ; 59% males. The average AVA was 0.81 ± 0.19 cm², mean pressure (Pmean) was 43.26 ± 9.34 mmHg and V_{max} was 4.27 ± 0.44 m/s, while mean LV EF was $72.24 \pm 6.37\%$. Average values of NT-proBNP were high; 858.11 ± 1710.62 pg/ml and mean E/E' was 12.73 ± 5.16 . Mean Zva was 5.15 ± 1.77 Hg ml⁻¹·m², mean ELI was 0.59 ± 0.20 cm²/m² and mean SWL was $39.24 \pm 11.67\%$. During follow-up 61 patient (47.59%) underwent aortic valve replacement surgery. Out of 11 patients who died (8.59%), 10 died before being operated (one patient refused operation), while one patient died after surgery due to the postoperative infection. Based on Cox univariate analysis, the following were shown to be predictors of mortality: indexed stroke volume (SVi), AVA, S, Zva, ELI and aortic valve resistance (AVR). These parameters were further analyzed with Cox multivariate analysis and the Zva was found to be the best single predictors for mortality (HR = 1.734; CI = 1.397 - 2.152; $p < 0.001$). The Zva value of 5.5 mmHg·ml/m² was identified as the best (cut-off) predictive value for the occurrence of death with sensitivity 67% and specificity 72%.

Conclusion: The Zva is the best mortality predictor in asymptomatic patients with moderate or severe AS and normal LV EF. However, future studies are needed to further focus on predictors of outcome in order to expand our knowledge on how to optimally select asymptomatic patients at risk who may benefit from early aortic valve replacement.

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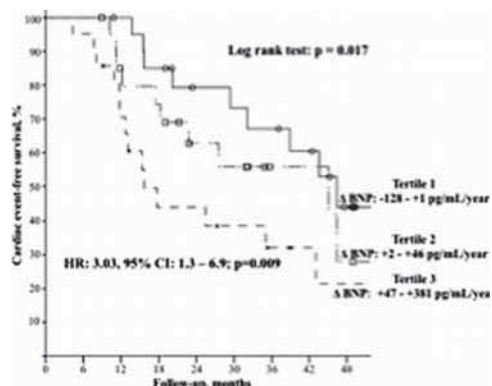
Advancing age and differences in outcomes in patients with asymptomatic mild to moderate aortic stenosis

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Background: Aortic stenosis (AS) is a progressive disease but there is incomplete understanding of the characteristics and outcomes associated with advancing age.

Methods: The Simvastatin and Ezetimibe in Aortic Stenosis population of 1,873 patients with mild/moderate AS was divided in two groups (younger/older) by the median age 67. Primary outcome was a composite endpoint of aortic valve replacement (AVR), congestive heart failure due to progression of AS (CHFAS) or death from cardiovascular causes (CVD).

Results: Mean age was 59.9 and 75.6 years in the younger and older group, respectively, followed for 4.3 years. The older group included more women (44.8 vs 32.7%), had more hypertension (58.9 vs 44.5%), prior atrial fibrillation (12.2 vs 6.9% all $p \leq .001$), higher total cholesterol (5.8 vs 5.7 mmol/L $p = .031$), smaller aortic valve area index (0.60 vs 0.65 cm²/m²), less bicuspid valves (2.5 vs 8.7%, both $p \leq .001$) but similar left ventricular mass index (98 vs. 97 g/m² $p = 0.81$) compared to the younger group. The younger group had been diagnosed with AS longer than the older group (3.0 vs. 2.5 years, $p = .002$) and were more frequently



current or former smoker (58.9 vs. 51.6%, $p=.002$). 314 (32.7%) younger and 320 (35.1%) older patients reached the composite primary outcome ($p=0.16$), without a difference in AVR ($p=0.20$). CVD was more common among the older (HR 4.14, adjusted HR 3.02 CI 1.69-5.37, both $p\leq.001$). CHFAS was more common among older in unadjusted analyses (HR 3.40, $p<.001$), but not in adjusted analyses ($p=0.07$). CVD post-AVR was more common in the older group (HR 3.35 CI 1.40-8.02 $p=.007$) but there was no difference in 30-day all-cause mortality post-AVR ($p=0.11$). CHFAS is an indication of surgical intervention, however only 11 (30.6%) of the older vs. 12 (100%) younger received AVR (HR 10.08 CI 4.01-25.34 $p\leq.001$). All younger patients with CHFAS receiving AVR survived post-operative follow-up (1.5 ± 1.3 year). The risk of CVD among older patients with CHFAS not receiving AVR was significantly higher compared to older patients receiving AVR (HR 8.61 CI 1.82-40.84 $p=.022$).

Conclusion: Older patients with AS have similar incidence of AVR and CHFAS but higher incidence of CVD. However, older patients with indication of AVR due to CHFAS do not receive AVR to the same extent as younger patients although older patients have similar 30-day post-operative mortality.

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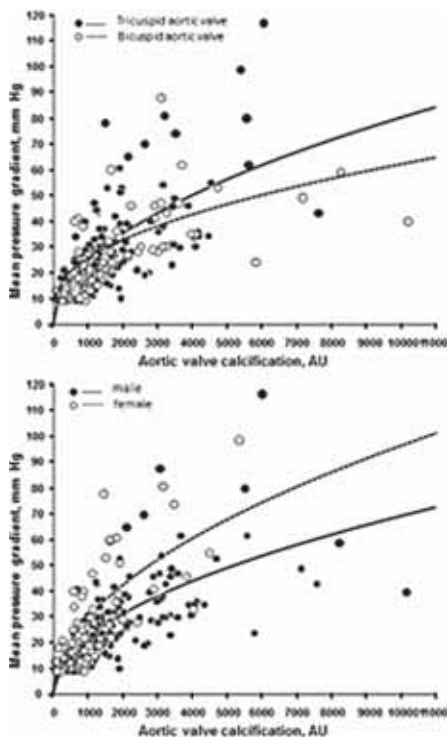
Progression of aortic valve calcification in aortic stenosis - Impact of anatomy and severity. The COFRASA - GENERAC Study

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Background: Degree of aortic valve calcifications (AVC) is closely related to aortic stenosis (AS) hemodynamic severity but the influence of gender and valve anatomy has been seldom evaluated. In addition, the impact of baseline AS severity on AVC progression remained unclear.

Methods: In 295 patients with at least mild AS, we prospectively evaluated AS hemodynamic (mean pressure gradient, MPG) and anatomic severity (AVC score measured using tomography) at baseline and yearly thereafter.

Results: A good correlation was observed between AVC and MPG overall ($r=0.70$, $p<0.0001$) but for the same hemodynamic severity, AVC load was higher in patients with bicuspid than tricuspid aortic valve and in male than in female ($p=0.008$ and $p=0.017$ respectively). In multivariate analysis after adjustment for hemodynamic severity both gender ($p<0.0001$) and valve anatomy ($p=0.001$) were independent determinants of AVC load. Hemodynamic and anatomic changes were well correlated ($r=0.55$, $p<0.0001$) but AVC progression was strongly related to baseline severity ($r=0.46$; $p<0.0001$ for MPG and $r=0.57$, $p<0.0001$ for AVC). Baseline MPG and AVC were predictors of AVC progression in univariate and multivariate analysis (both $p<0.0001$) whereas gender ($p=0.33$) and valve anatomy ($p=0.20$) were not.



Conclusion: Degree of AVC is closely related to hemodynamic severity but both gender and valve anatomy were independent determinants of AVC load. More importantly, AVC progressed faster with increasing hemodynamic and anatomic

severity but not differently according to valve anatomy or gender. Our results suggest that a medical strategy aiming at preventing AVC progression may be useful in all subsets of AS patients including those with severe AS.

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Carotid intima-media thickness is a strong predictor of incident aortic stenosis: a prospective cohort study

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Purpose: Stenosis of the aortic valve is the most common valve disease requiring surgical valve replacement in western countries. Previous studies have suggested that aortic stenosis (AS) shares the same risk factor profile as coronary artery disease. To our knowledge no study has examined the relation of vascular ultrasound measurements with AS in a population-based study.

Methods: A random subset of middle-aged participants in the population-based Malmö Diet and Cancer study underwent ultrasound analysis of the right carotid artery, including measurement of intima-media thickness (IMT) in the common carotid artery (CCA) and the carotid bifurcation (BF). Subjects with prevalent AS were excluded, leaving 3522 participants for statistical analyses, of whom 50 had incident AS during up to 20 years of follow-up. Potential risk factors were tested for association with AS in age- and sex-adjusted and multivariable-adjusted Cox regression analyses. IMT-CCA and IMT-BF were analysed in separate models.

Results: Significant risk factors in age- and sex-adjusted analyses were ($p<0.05$): high BMI, high LDL cholesterol, hypertension, diabetes, IMT-BF and IMT-CCA. In contrast, smoking, HDL, triglycerides, C-reactive protein, height, and leukocyte count were not associated with AS ($p>0.05$). In the multivariable-adjusted analysis, IMT-CCA and IMT-BF, LDL, and diabetes remained strongly and significantly associated with incident aortic stenosis (Table 1).

Predictors of incident aortic stenosis

	IMT-CCA	HR	95% CI	p	IMT-BF	HR	95% CI	p
BMI (kg/m ²)	1.07	1.07	0.99–1.15	0.08	BMI (kg/m ²)	1.07	1.00–1.15	0.07
LDL (mmol/L)	1.33	1.33	1.01–1.76	0.04*	LDL (mmol/L)	1.34	1.02–1.77	0.04*
Hypertension	1.79	1.79	0.84–3.82	0.13	Hypertension	1.81	0.85–3.85	0.12
IMT (SD)	4.88	4.88	1.08–21.97	0.04*	IMT (SD)	2.12	1.01–4.45	0.04*
Diabetes	3.45	3.45	1.43–8.29	0.006*	Diabetes	3.34	1.38–8.07	0.007*

Hazard ratios (HR) with 95% confidence intervals (CI) from multivariable-adjusted analyses, incl. sex and age, and incorporating significant covariates from age- and sex-adjusted analyses. SD, standard deviation of log IMT.

Conclusions: Traditional cardiovascular risk factors were individually associated with incident AS, but only IMT-CCA, IMT-BF, LDL, and diabetes remained independently associated in multivariable models. AS represents a vascular disorder strongly related to IMT, with implications for the pathophysiology and prevention of this disease.

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The low-density lipoprotein-density-pressure theory identifies asymptomatic aortic stenosis patients benefiting from cholesterol lowering therapy: the seas study

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Purpose: Examine if the low-density lipoprotein (LDL)-density-pressure theory identifies aortic stenosis (AS) patients that benefit from cholesterol-lowering therapy.

Methods: Asymptomatic patients with mild-to-moderate AS randomized (1:1) to 40 mg Simvastatin + 10 mg Ezetimibe combination vs. placebo and ≥ 2 in-study echocardiograms. Primary endpoint in this substudy was impact of randomization on the association between LDL changes and progression in AS severity, as determined by peak aortic jet velocity. Treatment effect was analyzed by separating patients in 4 groups according to LDL levels (≥ 160 mg/dl) and AS severity (<3.0 m/sec).

Results: 1,682 patients followed for a mean of 4.4 years (7,373 patient-years of follow-up). Among those with elevated LDL and mild AS at baseline, LDL lowering was associated with less AS progression in the active-arm ($\beta=0.18$ [95% CI: 0.08 to 0.27, $p<0.001$]), but not among those receiving placebo ($\beta=-0.08$ [95% CI: -0.19 to 0.03, $p=0.14$], Table 1). In contrast, there was no detectable treatment effect on the association between changes in LDL and AS severity in the 3 other groups (all $p\geq 0.42$ for interaction). Similarly, the treatment effect was also

Table 1. Achieved cholesterol-lowering impeded aortic stenosis progression in patients with mild aortic stenosis and elevated low-density-lipoprotein levels (p=0.0003)

LDL levels (<160 mg/dl)	p*	LDL levels (≥160 mg/dl)	p*
Velocity (≥3.0 m/sec)			
Active (n=57): β=0.07, p=0.31	0.56	Active (n=400): β=0.01, p=0.76	0.44
Placebo (n=51): β=0.02, p=0.71		Placebo (n=386): β=0.06, p=0.17	
Velocity (<3.0 m/sec)			
Active (n=49): β=0.13, p=0.20	0.42	Active (n=346): β=0.18, p=0.0003	0.0004
Placebo (n=45): β=0.01, p=0.96		Placebo (n=348): β=0.08, p=0.14	

Abbreviations: LDL: low-density lipoprotein; Active treatment: 40 mg Simvastatin + 10 mg Ezetimibe. *P-value for interaction (difference in slope) by randomization status.

missed when combining information from all four groups, active vs. placebo-arm was not associated with a detectable difference in AS progression (cumulative mean difference 0.01 m/sec [95% CI: -0.1 to 0.1, p=0.80]).

Conclusion: Stratifying asymptomatic AS patients by the LDL-density-pressure theory identifies a subgroup of patients with elevated LDL and mild AS, which may benefit from cholesterol-lowering therapy, whereas other processes may play larger roles in AS development in patients with low LDL and more advanced AS (SEAS study: NCT00092677).

FLOW IN AORTIC STENOSIS

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Impact of low flow state on cumulative mortality of high-risk patients undergoing transcatheter aortic valve intervention

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Purpose: Although low ejection fraction (LVEF) has been reported to be an independent risk factor of increased mortality following surgical aortic valve replacement, its impact on post-procedural transcatheter aortic valve intervention (TAVI) outcome has yielded conflicting results. Moreover a low-flow state, i.e. reduced left ventricular stroke volume index (SVi), can occur with both reduced and preserved LVEF. The objective of this study was to evaluate the impact of pre-procedural SVi, LVEF, and transvalvular gradient on 2-year all cause mortality following TAVI.

Methods: Patients with severe and symptomatic aortic stenosis (AS) (effective orifice area [EOA] ≤1cm²) who underwent TAVI at our institution were prospectively enrolled. Primary end-point was 2-year all cause mortality was defined according to the criteria proposed by the Valve Academic Research Consortium.

Results: We included 116 patients (mean age: 80.1±7.3 years). Sixty-nine (59%) patients had normal flow (SVi>35ml/m²) and 47 (40.5%) low flow (SVi<35ml/m²). Overall, the primary end point occurred in 20 (17%) patients during a median follow-up period of 24 months. Patients with low flow had higher 2-year all cause mortality compared with those in the normal flow group (31.8% versus 16.0%, p<0.01). Mortality was also increased in patients with low LVEF compared with those with normal LVEF (31.8% versus 16.0%, p<0.01). Patients with low mean gradient (<40 mm Hg) had higher 2-year all cause mortality compared with those in the normal flow group (26.0% versus 15.0%, p<0.01). By multivariate analysis SVi was the only ultrasound independent predictor of 2-year mortality (OR: 0.95, 95%CI: 0.917-0.998, p=0.039). Low LVEF and low mean gradient were not found to be independent predictors of 2-year mortality.

Conclusions: Low SVi but not low LVEF or low gradient is an independent predictor of 2-year cumulative mortality following TAVI in high risk patients with severe AS. SVi should be integrated in the risk stratification process of these patients.

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Transcatheter aortic valve implantation in patients with low gradient aortic stenosis and preserved left ventricular ejection fraction

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Background: Transcatheter Aortic Valve Implantation (TAVI) is an established alternative to surgery for selected patients with severe symptomatic aortic stenosis. Low gradient AS (LGAS) with preserved LV ejection fraction (AVA <1.0cm², MAVG <40mmHg and LVEF >50%) is thought to be due to low stroke volume and patients are said to have a poorer prognosis. The impact of TAVI in these patients has not been previously explored.

Method: All patients undergoing TAVI with CoreValve at our institution were eligible for study inclusion. Detailed quantitative echocardiography was performed according to ASE guidelines. Only patients with LVEF >50% at baseline were included and further stratified according to baseline mean aortic valve gradient (>40mmHg or <40mmHg). Echocardiographic and clinical outcomes were compared at 12 months.

Results: 38 patients (mean age 83±8 years, 46% female, mean EuroScore 17±9%) were analysed. 12 month echo and clinical data was available for 34 patients; 11 (29%) with LGAS and 23 (61%) with MAVG>40mmHg (4 patients were lost to follow up (1 LGAS)). There were no deaths in either group. At 12 months, echo parameters were similar for both groups, including LVEF, global longitudinal strain and markers of diastolic function. Quality of life score (Minnesota Living

with Heart Failure Questionnaire) and functional status (NYHA class) post TAVI were similar in both groups.

Conclusion: TAVI is an effective therapy for patients with low gradient severe aortic stenosis with similar improvements in post procedural aortic valve haemodynamics, quality of life and functional status as those patients with high gradient severe aortic stenosis.

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Patients with low-flow, low-gradient aortic stenosis are in substantial risk after Transcatheter Aortic Valve Implantation, but survivors demonstrate a substantial clinical improvement

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Purpose: Previous studies showed that patients with impaired left ventricular (LV) function and low-flow, low-gradient (LFLG) aortic stenosis (AS) are associated with high operative risk and poor long-term outcome after surgical aortic valve replacement. The aim of this study was to investigate the clinical outcome of LFLG AS after transcatheter aortic valve implantation (TAVI).

Methods: 580 consecutive patients in high operative risk underwent TAVI with the Medtronic Corevalve Edwards Sapien prostheses at our institution between June 2008 and October 2012. Full data of 469 patients was collected. Of these, 258 patients presented with normal-flow, high gradient (NFHG) AS (aortic surface area (ASA) <1.0 cm², mean gradient (ΔPmean) >30 mmHg, LV ejection fraction (LVEF) >50%) and 36 patients with LFLG AS (ASA <1.0 cm², ΔPmean <30 mmHg, LVEF <30%). Clinical follow-up, echocardiography and measurements of NT-pro-BNP levels were analyzed at 10 days, 4 weeks, 6 month and 1 year after TAVI.

Results: Patients with LFLG AS had a much lower survival rate at 12 month after TAVI compared to patients with NFHG AS (41% vs. 86%, p<0.0001). Nevertheless, surviving patients with LFLG AS showed a significant and steady rise in LVEF after 4 weeks (before 24.2±4.7% vs. 30 days 37.0±13.2%, p<0.05), after 6 month (39.5±12.1%) and 1 year (52.0±4.3%) and a reduction of NT-proBNP (before 11653±8085 ng/L vs. 12 month 1844±1273 ng/L, p=n.s.). Furthermore, these patients showed reduced symptoms of heart failure resulting in an improved NYHA functional class (LFLG vs. NFHG: Δ4 weeks: -1.2±0.7 vs. -1.3±0.6; p=n.s.; Δ6 month: -1.3±0.4 vs. -1.2±0.7; p=n.s.; Δ12 month: -1.6±0.4 vs. -1.2±0.8; p=n.s.).

Conclusions: This study shows that the all-cause mortality, 12 month after TAVI in patients with LFLG AS is notably high. However, surviving patients presented an enormous improvement in myocardial function and a high clinical benefit.

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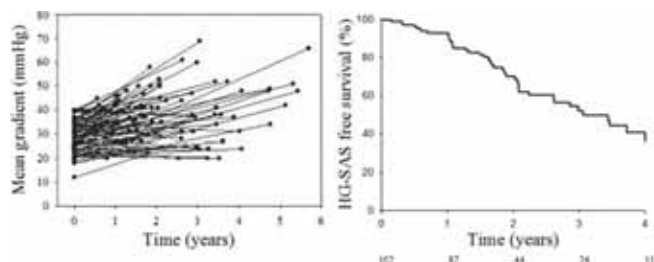
Paradoxical low gradient aortic stenosis is not an end-stage of disease as it progresses to high gradient aortic stenosis: an echocardiographic follow-up study

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Background: Paradoxical low gradient severe aortic stenosis (PLG-SAS) is a recently described subset of aortic stenosis which is, since its description, highly challenging. Some authors consider this new pattern as a more advanced stage of disease than high gradient severe aortic stenosis (HG-SAS) whereas others think just the opposite. The aim of the present work was to test this theory by studying the progression of their mean gradient over time.

Methods: Between 2000 and 2010, 105 consecutive patients (51 men, 77±9 years) with PLG-SAS (mean transvalvular gradient ≤40 mmHg, indexed aortic valve area <0.6cm²/m² and left ventricular ejection fraction ≥50%) at the time of inclusion had an echocardiographic follow-up ≥6 months. Mean gradient progression was assessed in a first time by using a paired t-test and in a second time, using a Kaplan-Meier analysis where the recording of a high gradient (>40 mmHg) was considered as an event.

Results: During a median follow-up of 21 months (range 6 – 68 months), the severity of aortic stenosis had progressed significantly: the mean gradient increased from 29±6 mmHg to 38±11 mmHg (p<0.001). At the end of follow-up, 46 (45%) had reached the stage of HG-SAS, 38 (37%) remained at the stage of



Mean gradient progression.

PLG-SAS but significantly increased their mean transvalvular gradient (from 26 ± 5 mmHg to 32 ± 5 mmHg, $p < 0.001$) and 18 either had maintained or decreased their mean transvalvular gradient over time. Interestingly, in 11 out of these 18 patients, the reduction in mean transvalvular gradients was contemporary to the development of left ventricular dysfunction.

Conclusion: PLG-SAS progresses almost systematically to the classical HG-SAS. This suggests that PLG-SAS represents a less advanced stage of disease than HG-SAS.

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Outcomes of patients with moderate-severe and severe aortic stenosis and preserved left ventricular ejection fraction: impact of stroke volume index

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Background: We sought to determine predictors of outcomes in a contemporary group of moderate-severe & severe aortic stenosis (AS) patients & preserved ejection fraction, based on stroke volume index (SVI) & AS subtypes.

Methods: We studied 1637 AS patients with aortic valve area (AVA) ≤ 1.3 cm² evaluated between 1/07-12/08 (excluding severe other valve disease). Clinical & echo data was recorded. Patients were classified into following AS subtypes: moderate-severe (n=368, AVA 1.1-1.3 cm², 68 ± 15 years, 62% men), standard severe (n=670, AVA ≤ 1 cm² & mean gradient ≥ 40 mm Hg, 70 ± 12 years, 60% men) & paradoxical severe (n=591, AVA ≤ 1 cm² & mean gradient < 40 mm Hg, 71 ± 12 years, 56% men). SVI was calculated as: [left ventricular outflow tract (LVOT) velocity time integral x LVOT area]/body surface area. SVI ≥ 35 ml/m² was normal. All-cause mortality was recorded.

Results: At 4.7 ± 2 years, 1024 (63%) had AV replacement (AVR) & 359 (22%) patients died. 64% had normal SVI. Mortality was different in moderate-severe (19%), standard severe (20%) paradoxical AS (26%) (log-rank 9, $p = .01$). Mortality was different in normal vs. abnormal SVI (20% vs. 26%, log-rank 7, $p = 0.01$). On multivariable time-dependent survival analysis, age (Hazard ratio or HR 1.04 [1.03-1.05]), Functional Class or FC (HR 1.44 [1.28-1.62]), lower glomerular filtration rate or GFR (HR 1.25 [1.17-1.32]), AS subtype (HR 1.01 [1.002-1.014]), SVI (HR 0.79 [0.64-0.97]) & AVR (HR 0.32 [0.25-0.41]) impacted survival (all $p < 0.05$). Kaplan-Meier curves of the patients, based AS subtypes, SVI and AVR are shown in Fig. 1A, B.

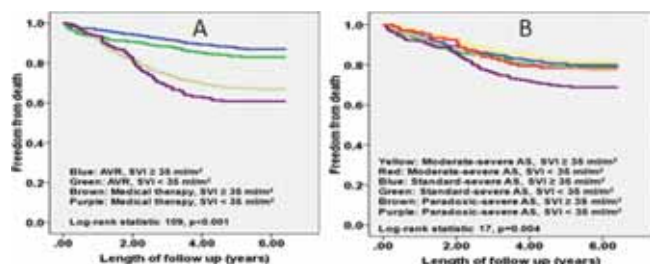


Figure 1

Conclusion: Patients with paradoxical severe AS & abnormal SVI have higher mortality compared to other subtypes. Greater mortality is predicted by increasing age, low GFR and higher FC, while AVR predicted improved survival.

P2399 | BEDSIDE

Impact of low flow on long-term survival in patients with severe aortic stenosis and preserved left ventricular ejection fraction: a cardiac catheterization study

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Background: Previous studies suggested that a low flow defined as an indexed stroke volume (SVI) ≤ 35 ml/m² may be an important determinant of outcome in patients with severe aortic stenosis (AS). However, its quantification using echocardiography may be subject to error measurement. The aim of this study is to determine the impact of low SVI determined during cardiac catheterization on long-term survival among patients with severe aortic stenosis and preserved LV ejection fraction.

Methods and results: Between 2000 and 2010, 768 patients with preserved LVEF ($> 50\%$) and severe AS (valve area ≤ 1 cm²) without other valvular heart disease underwent cardiac catheterization. SVI was derived from catheterization data.

Mean age was 74 ± 8 years, 42% were female, 46% had coronary artery disease and mean LVEF was $72 \pm 10\%$. Overall, low SVI was found in 27% of AS patients. As compared to patients with normal SVI, those with decreased SVI were significantly older ($p < 0.0001$) and had more frequently atrial fibrillation ($p < 0.0001$); in addition, they had lower LVEF ($p = 0.04$), aortic valve area ($p < 0.0001$), mean

pressure gradient ($p = 0.001$), systemic arterial compliance ($p < 0.0001$) and higher systemic vascular and pulmonary resistances ($p < 0.0001$).

Ten-year survival was significantly reduced in patients with lower SVI as compared to those with normal SVI ($41 \pm 5\%$ vs. $63 \pm 3\%$; $p = 0.0007$). After adjustment for all other risk factors, SVI was independently associated with long-term survival (hazard ratio = 0.97, 95%CI: 0.95-0.99; $p = 0.01$).

Conclusion: Low SVI measured invasively is frequent in patients with severe AS and preserved LVEF and is a powerful and independent predictor of survival. SVI should be systematically measured and used as an additional parameter for risk stratification of patients with severe AS.

P2400 | BEDSIDE

Natural history of paradoxical low-flow low-gradient aortic stenosis

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Background: Among patients (pts) with severe aortic stenosis (sAS) and preserved ejection fraction (EF), those with low flow (LF) and low gradient (LG) have an adverse prognosis. It has been proposed that this condition represents a late-stage point of sAS. We investigated if LFLG sAS is the evolution of a normal-flow (NF) high-gradient (HG) stage or a different entity directly progressed from moderate aortic stenosis.

Methods: From the transthoracic echocardiography (TTE) database, we identified pts with sAS (aortic valve area < 1 cm²) and preserved EF ($\geq 50\%$), and from these pts with LFLG sAS, defined as stroke volume index < 35 ml/m² and mean aortic valve gradient < 40 mm Hg, who had at least one additional TTE within 5 years prior to the index qualifying TTE. These pts were age/sex/date matched 2:1 with additional two groups who also had ≥ 1 TTE during the 5 years prior to the index TTE: NFHG sAS and NFLG sAS.

Results: There were 78 pts with LFLG sAS; a HG stage preceded the index TTE in 4 (5%). Compared to 156 pts with NFLG and 149 with NFHG sAS, pts with LFLG sAS experienced a different remodeling process with increasing relative wall thickness, reduction in LV end diastolic diameters (-0.2 vs. 0.3 vs. 0.7 mm/year, $p = 0.001$) and no changes in left ventricular (LV) mass index (Fig. 1). Changes in LV structure were paralleled by a reduction in deceleration time (11 vs. 1 vs. -1 msec/year, in the LFLG, NFLG and NFHG groups, respectively, $p < 0.01$) suggesting increased chamber stiffness, and a significant reduction in EF in LFLG sAS compared to pts with NF sAS (1 vs. 0% /year, $p = 0.01$)

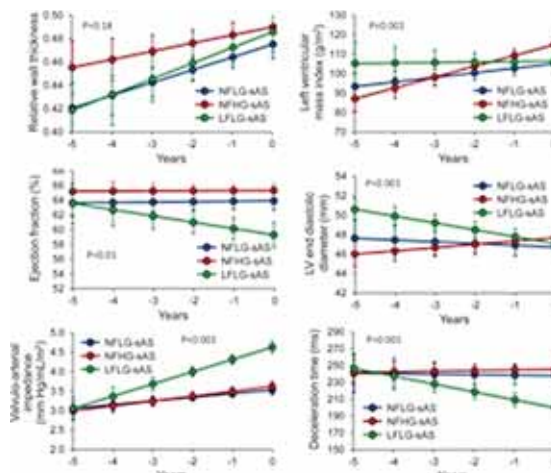


Figure 1

Conclusion: In most pts, LFLG sAS should not be considered the natural progression of HG sAS but rather as a distinct presentation of sAS due to a unique remodeling pathway.

P2401 | BEDSIDE

Low- and high-gradient aortic stenosis - differences in progression from non-severe to severe stage disease

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Objectives: The aim of the present study was to evaluate disease progression in patients with aortic stenosis (AS) from an earlier stage to severe stage in relation to the transvalvular gradient. We hypothesized that differences in hemodynamics and myocardial function can be detected already at a non-severe AS stage.

Methods: Clinical and conventional echocardiographic including 2D-strain-speckle-tracking data of 77 AS patients, each with a minimum of two documented echocardiograms, one at a non-severe (baseline) and one at a severe stage (follow-up) were analyzed, based on transvalvular pressure gradient (low-gradient

[LG] vs. high-gradient [HG], with 40 mm Hg as cutoff). The LG/AS group was subdivided into normal-flow [NF] and low-flow [LF], with 35 ml/m² indexed stroke volume (SV) as cutoff.

Results: Already at baseline (valve area 1.3±0.3 cm²) LG groups had significantly reduced left ventricular (LV) longitudinal function and more comorbidities than HG patients. This was reflected by a significantly higher baseline valvulo-arterial-impedance in LF/LG group resulting in a more pronounced SV reduction over the course of 3.3±1.7 years (mean follow-up). HGAS showed a faster progression of stenosis (increase in peak transvalvular flow velocity per year (Vmax/y): HGAS Vmax/y=0.4±0.3 m/s, NF/LG Vmax/y=0.3±0.3 m/s, LF/LG Vmax/y=0.1±0.3 m/s; p<0.001) and less clinical symptoms than patients with LG/AS (NYHA III and IV: HGAS 36%, NF/LG 72%, LF/LG 83%; p<0.001).

On univariable analysis, the combination of vascular comorbidities, impaired systolic function, increased afterload and reduced transvalvular flow was identified to be predictive for the development of a LG/AS (Global Strain≤17%, OR: 5.778, 95%CI: 1.976-16.891, p<0.001; mean transvalvular velocity ≤2.1 m/s, OR: 5.271, 95%CI: 1.745-15.921, p=0.003; Systemic arterial compliance ≤0.8 ml·mm Hg⁻¹·m⁻², OR: 5.107, 95%CI: 1.501-17.375, p=0.009).

Conclusion: In AS patients with a high gradient physiology the valve is the primary problem, leading to a fast reduction in aortic valve area. In contrast, low gradient AS is a systemic disease with valvular and vascular afterload stress, resulting in a slower AS progression. Therefore, myocardial, valvular and vascular parameters help to predict development of LG/AS and subsequently clinical outcome already in an early stage of disease.

P2402 | BEDSIDE

Prognostic impact of global left ventricular hemodynamic afterload in severe aortic stenosis with preserved ejection fraction: a cardiac catheterization-based study

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Background: Previous studies suggested that global left ventricular (LV) hemodynamic afterload as assessed by valvulo arterial impedance (Zva), may be an independent predictor of mortality in patients with severe aortic stenosis (AS) and preserved LV ejection fraction (LVEF). However, its quantification using echocardiography may be subject to error measurement. The aim of this study is to determine the prevalence and impact on long-term survival of high Zva, purposely measured by cardiac catheterization.

Methods and results: Between 2000 and 2010, 768 patients with preserved LVEF (>50%) and severe AS (valve area ≤1cm²) without other valvular heart disease underwent cardiac catheterization. Zva was derived from catheterization data and calculated using following formula: mean aortic gradient + systolic blood pressure / indexed LV stroke volume. Zva was considered high when >5 mmHg/mL/m² based on previous studies. Mean age was 74±8 years, 42% were females, 46% had coronary artery disease and mean LVEF was 72±10%. Overall, high Zva was found in 42% of all AS patients.

Patients with high Zva were significantly older (p<0.0001), and more often female (p<0.0001), they had significantly smaller aortic valve area (p<0.0001), higher mean gradient (p=0.001), lower indexed stroke volume (p<0.0001) and cardiac output (p<0.0001), significantly higher LVED filling pressures (p=0.03), systolic pulmonary artery pressure (p=0.0005), higher capillary wedge pressure (p=0.006), reduced systemic arterial compliance (p<0.0001), but higher systemic vascular resistances (p<0.0001).

Ten-year survival was significantly reduced in patients with higher Zva (50±5%) as compared to those with lower Zva (67±3%; p=0.01). After adjustment for all other risk factors, Zva was independently associated with reduced long-term survival (hazard ratio [HR]=1.12 95% CI: 1.009-1.22; p=0.03). Of interest, high Zva remains associated with reduced survival as compared to low Zva, in patients with normal LV stroke volume, but was no longer significant in low flow patients (LV stroke volume>60mL: 49±8vs. 69±4%, p=0.012; LV stroke volume≤60mL: 49±7 vs. 53±13%, p=0.96).

Conclusion: In this large cardiac catheterization-based study, high Zva, estimated invasively, is frequent in patients with severe AS, and appears as a powerful and independent predictor of survival. Zva should be used as an additional parameter for risk stratification of severe AS, more particularly in patients with normal flow.

P2403 | BEDSIDE

Right ventricular dysfunction and prognosis in patients with low-flow, low-gradient severe aortic stenosis

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Background: Patients with low LVEF, low-flow low-gradient severe aortic stenosis (LFLG AS) represent a challenging cohort with high morbidity and mortality. Although right ventricular dysfunction (RVD) is an important predictor of outcomes after CABG, its impact on the risk-stratification of patients with LFLG AS is unknown.

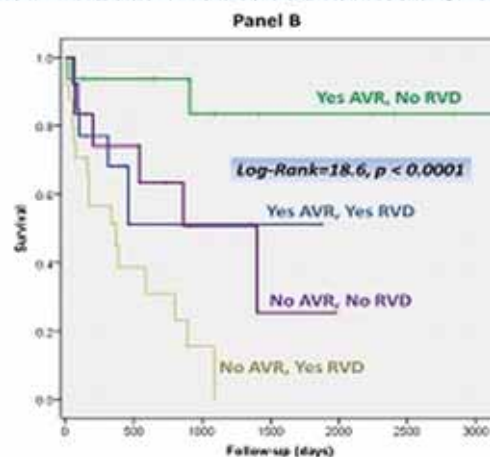
Methods: 65 consecutive LFLG severe AS patients (80% men) who underwent low-dose dobutamine stress echocardiogram between May/04 and June/13 were

studied. The mean age was 74±9 yrs; LVEF 29±10%; AV area index 0.49±0.1 cm²/m²; mean AV gradient 22±7 mmHg. Contractile reserve defined as >20% increase in stroke volume was present in 40% of patients. RVD defined as tricuspid annular plane systolic excursion <16 mm, measured in the apical 4-chamber view, was present in 37 patients (57%).

Results: After a median follow-up of 13 months, there were 29 aortic valve replacements (AVR) and 30 deaths. In a multivariate Cox proportional hazards model, presence of RVD (HR=3.36, p=0.006) was an independent predictor of all-cause mortality, despite adjustment for AVR (p=0.007) and presence of contractile reserve (p=0.36) (Panel A). Patients with RVD who underwent AVR had worse survival and similar to those patients who did not undergo AVR (Panel B). Baseline RVD added incremental value in the risk stratification of these patients (X2 increased from 10.7 to 18.6, p=0.005).

Panel A Independent Predictors of All-Cause Mortality (*)			
Variables (Model X ² =18.8, P<0.0001)	Chi-Square	Hazard Ratio (95% CI)	P Value
Aortic Valve Replacement	7.2	0.10 (0.12 – 0.72)	0.007
Right Ventricular Dysfunction	7.6	3.36 (1.42 – 7.93)	0.006
LV Contractile Reserve	0.83	0.71 (0.34 – 1.50)	0.36

(*) Number of variables chosen on the basis of events rate and selected upon clinical relevance



Conclusions: In this cohort of low LVEF and LFLG severe AS patients, preoperative RVD was an independent predictor of adverse outcomes. Survival benefit derived from AVR was attenuated by the presence of preoperative RVD. Larger multicenter studies are needed to understand whether transcatheter AVR might be a better option than conventional surgical AVR for LFLG severe AS patients with RVD.

MORE ON TAVI

P2405 | BEDSIDE

Pre-existent aortic regurgitation protects against the adverse effects of paravalvular leakage after transcatheter aortic valve implantation

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Purpose: Paravalvular leakage (PVL) after transcatheter aortic valve implantation (TAVI) is associated with mortality. Hypothetically, a hypertrophied and stiff left ventricle does not well tolerate acute aortic PVL versus one preconditioned by pre-existent aortic regurgitation (AR). Accordingly, we evaluated the effect of pre-existent AR.

Methods: We included all consecutive patients who underwent a TAVI in our centre from June 2009 to July 2013. We prospectively evaluated the severity of pre-existent AR and PVL by echocardiography. Mortality was registered at 12 and 24 months.

Results: In total, 399 patients (mean age 80.9±6.9 years, 44.9% male) underwent a TAVI. Moderate/severe pre-existent AR existed in 56 patients (14.0%) and moderate/severe PVL occurred in 50 patients (12.5%). The 1-year survival rate was lower in patients with a PVL versus no PVL (71.0% vs. 81.1%; p=0.019). In those who developed a PVL, pre-existent AR independently predicted 1- and 2-year survival (HR: 2.8, 95%CI: 1.6 to 5.2; p=0.001, resp. HR: 2.3, 95%CI: 1.3 to 3.9; p=0.002). Pre-existent AR did not influence survival in patients who developed no PVL.

Conclusions: Pre-existent AR independently predicts long-term survival, especially in patients with residual PVL. Thus, pre-existent AR is a protective factor to tolerate acute PVL after TAVI.

P2406 | BEDSIDE**Predictors and long-term prognosis of perivalvular regurgitation after transcatheter aortic valve implantation**

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Introduction: Paravalvular regurgitation (PVR) after transcatheter aortic valve implantation (TAVI) has been associated with increased morbidity and mortality. Our aim was to study TAVI PVR occurrence and to determine its long-term impact on outcomes.

Methods: Single centre prospective registry of 145 consecutive TAVI procedures in 144 patients (pts) with aortic valve stenosis. Mean age was 80 ± 7.7 years, 69 (41%) male, 85 (58.6%) treated with self-expandable and 69 (41.4%) with balloon expandable valve. Mean aortic annular diameters were 22.2 ± 2.7 mm (coronal) and 20.8 ± 2.1 mm (sagittal), by angioCT. The protocol first transthoracic echocardiography (TTE) was performed in-hospital and assessed PVR according to color Doppler fraction of prosthetic ring circumference. The second TTE evaluation was realized at a median of 11 IQ [4-25] months.

Logistic regression was applied to determine the independent predictors of PVR at first TTE among clinical, imaging and procedural variables. The event rate of death, rehospitalization, NYHA III/IV and VARC2-eficacy endpoint was estimated by binary logistic regression for the presence and severity of PVR. Survival curves for the presence and severity of leak were constructed (log rank test).

Results: PVR was identified in 96 pts (66%) in the first TTE, it was mild, moderate and severe in 56%, 8.6% and 1.4% respectively, 2 pts lost their mild leaks and eight developed PVR during the follow up. Univariate predictors for PVR were: chronic renal failure, peripheral arterial disease, previous thoracic radiotherapy, thoracic malformations, porcelain aorta, transfemoral vascular access, previous aortic valvulotomy, type of implanted prosthetic valve and the absence of balloon dilatation after implantation ($p < 0.01$). At multivariate analysis, only auto-expandable prosthesis implantation remained a predictor of PVR (OR 3.94, 95% CI [1.88 to 8.33], $p = 0.0001$).

During the follow-up (15.6 months [5.9-26.9]) 25 deaths (17.2%) and 35 efficacy events (24%) including 21 (15%) rehospitalizations for cardiovascular causes, occurred. Fourteen pts (9.6%) remained in NYHA III/IV functional class. The presence of PVR was not associated with any of these events ($p > 0.1$ for all variables). Survival analysis evidenced a non-significant split of the curves according to the presence and severity of PVR (mild vs. moderate/severe; $p = 0.142$).

Conclusion: The prevalence of paravalvular regurgitation after TAVI is considerable and it appears to be associated with the type of implanted prosthetic valve. It remains stable during the follow-up and does not have an impact in clinical outcomes.

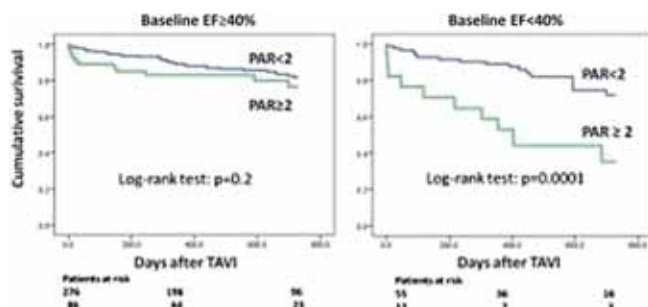
P2407 | BEDSIDE**Influence of baseline ejection fraction on prognostic value of paravalvular aortic regurgitation in patients after transcatheter aortic valve implantation**

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Background: Moderate/severe paravalvular aortic regurgitation ($PAR \geq 2$) after transcatheter aortic valve implantation (TAVI) has been associated with increased mortality. Whether baseline ejection fraction (EF) has influence on prognostic value of PAR is unclear.

Methods: Between January 2007 and December 2012, 434 patients with native severe aortic stenosis underwent TAVI in our hospital. Patients were divided in two groups as preserved EF group ($EF \geq 40\%$, $n = 362$) and low EF group ($EF < 40\%$, $n = 72$). PAR before discharge was assessed by transthoracic echocardiography and impact of PAR on mortality were compared in the two groups.

Results: At baseline, low EF group had lower age and aortic gradients and worse renal function as compared to preserved EF group. In addition, low EF group had higher prevalence of diabetes, coronary artery disease and significant baseline mitral and aortic regurgitation. In-hospital mortality was significantly higher in low EF group as compared to preserved EF group (11.0% vs 2.5%, $p < 0.01$). After TAVI, $PAR \geq 2$ occurred 23% of the patients and was significantly associated with reduced 2-year survival rate only in the low EF group (82% vs 35%, log-rank $p < 0.001$ and 89% vs 89%, log-rank $p = 0.2$ in preserved EF group). In multivariate



Kaplan-Meier curves.

analysis, $PAR \geq 2$ had 2.9-fold increase in mortality risk in low EF group, whereas in preserved EF group, $PAR \geq 2$ was not associated with a significant mortality risk.

Conclusions: In our study, $PAR \geq 2$ after TAVI was associated with increased 2-years mortality only in patients with low baseline EF. Our data suggest that baseline EF is a potential modifier on prognostic value of PAR. Careful attention to PAR is needed especially for low baseline EF patients.

P2408 | BEDSIDE**Paravalvular regurgitation after TAVI, a comparison**

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Background: Significant paravalvular aortic regurgitation (PVAR) after transcatheter aortic valve implantation (TAVI) impacts long-term mortality. The Direct Flow Medical (DFM) aortic valve has a repositionable non-metallic pressurized support structure designed to minimize aortic regurgitation.

Objectives: Prospective non-randomized comparison of PVAR after DFM versus SAPIEN XT valve implantation in high risk patients with severe aortic stenosis.

Methods: One hundred thirty nine consecutive high surgical risk patients (mean age 82.5 ± 6.4 y, 47% male, mean log EuroScore 18.6%) with severe aortic stenosis were evaluated immediately post implant for PVAR by transesophageal echo (TEE). PVAR was graded as "none or trace", "mild", "moderate", "severe" according to the VARC criteria. One hundred eight patients received a SAPIEN XT and 31 patients a DFM valve. Both groups did not differ in patients demographics, log EuroScore, severity of baseline aortic stenosis, degree of valve calcification based on CT, and valve sizing, which was performed by TEE and CT.

Results: Thirty day mortality was 2.8% for SAPIEN XT and 0% for DFM. For PVAR see Table.

	Non or trace	Mild	Moderate	Severe	p
DFM %	74	23	3	0	0.001
Edwards %	36	54	9	0	

Conclusions: Compared to SAPIEN XT the DFM valve significantly reduces PVAR which may have an impact on long-term prognosis.

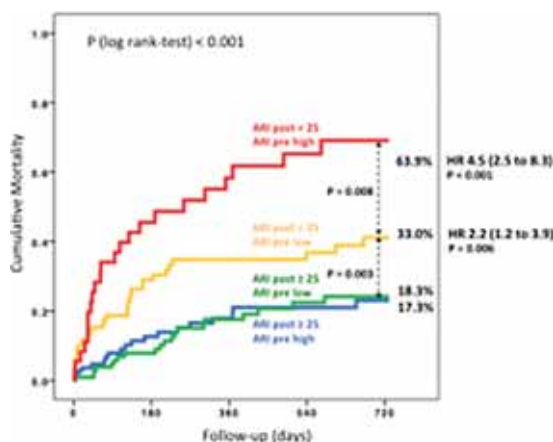
P2409 | BEDSIDE**Identification of parameters contributing to the variability of the aortic regurgitation index in a two-center TAVI cohort**

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Background: For precise quantification of paravalvular aortic regurgitation (AR) in patients undergoing transcatheter aortic valve implantation (TAVI), the assessment of hemodynamics with the AR Index is helpful. In this study, we assess parameters, which impact the AR Index.

Methods: Pre- and post-procedural Indices was calculated as ratio of the transvalvular gradient between diastolic blood pressure (DBP) in the aorta and left-ventricular end-diastolic pressure (LVEDP) to the systolic blood pressure (SBP): $[(DBP - LVEDP) / SBP] \times 100$. Multivariate regression analysis was used to identify parameters, which contribute to the variability of the AR Index.

Results: 523 patients (age 81.2 ± 6.5 years) underwent TAVI in two independent institutions. The post-procedural AR Index was significantly associated with 2-year mortality ($P < 0.001$). In multivariate regression analysis, the AR Index was independently associated with STS score ($P = 0.020$), EF ($P = 0.049$), cover index ($P < 0.001$), heart rate ($P = 0.027$), and the pre-procedural AR Index ($P < 0.001$) but not with the prosthesis type ($P = 0.77$).



In patients with an AR index ≥ 25 after TAVI, outcome was independent from the pre-procedural AR Index. However, patients with an AR Index < 25 could be further stratified by the pre-procedural AR Index (Figure): while patients with low pre-procedural AR Index had an only 2.2-fold higher risk ($P=0.006$), a pre-procedural high AR Index ≥ 34 was associated with a 4.5-fold higher 2-year mortality risk ($P<0.001$).

Conclusions: Patients with an AR Index below 25 have a significantly impaired prognosis after TAVI. In these patients, a low pre-procedural AR Index before the procedure is associated with a more favorable outcome and might indicate resilience against the impact of paravalvular aortic regurgitation.

P2410 | BEDSIDE

Assessment of paravalvular aortic regurgitation after transcatheter aortic valve implantation using cardiac magnetic resonance imaging: a comparative study with echocardiography and angiography

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Aims: Assessment of paravalvular aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) using Edwards SAPIEN XT valve remains challenging using transthoracic echocardiography (TTE) or angiography. Cardiac magnetic resonance imaging (c-MRI) has a low intraobserver and interobserver variability in the assessment of regurgitant volumes and might be more reliable to assess AR post-TAVI. We therefore aimed to evaluate the value of c-MRI to assess paravalvular AR after TAVI.

Methods and results: Between February 2012 and March 2013, 132 consecutive patients underwent successful TAVI using exclusively Edwards SAPIEN XT prosthesis. AR was evaluated by c-MRI, TTE and angiography in 45 patients (27 women, mean age 84.1 ± 7.1 years). Angiography was performed immediately after TAVI whereas TTE and c-MRI were performed one month after implantation. At baseline c-MRI, the mean aortic regurgitant fraction (ARF) was $21.3 \pm 12.5\%$. A significant AR ($>$ grade II) was present in 24 (56%) patients using c-MRI ($30 < \text{ARF} < 50\%$) whereas it was only observed in 18 (40%) and 12 (27%) patients using TTE and angiography, respectively. Interestingly, there was a poor correlation between c-MRI and TTE ($r=0.16$, $p=0.28$) and between c-MRI and angiography ($r=0.30$, $p=0.06$). In contrast, there was a good correlation between TTE and angiography ($r=0.6$, $p<0.001$). TTE underestimated AR by one degree in 9 patients, and by two degrees in 6 patients as compared to c-MRI.

Conclusions: The results of our study suggest that TTE and angiography may underestimate the severity of AR after TAVI as compared to c-MRI. Furthermore, there is a poor correlation between c-MRI and TTE or angiography. Further studies are mandatory to confirm our results in a larger population.

P2411 | BEDSIDE

Hemodynamic evaluation of aortic regurgitation after transcatheter aortic valve implantation using the dimensionless aortic regurgitation index compared to cardiac magnetic resonance imaging

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Background: More-than-mild periprosthetic aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) has been associated with increased mortality and morbidity. The AR index (ARI) has been recently proposed as an objective indicator for the severity of AR immediately after TAVI, but has only been validated against echocardiography, which has limitations in accurate assessment of periprosthetic leaks. Cardiac magnetic resonance imaging (MRI) is an alternative, non-invasive and observer-independent method for the quantification of AR. We therefore sought to evaluate the performance of the ARI compared to cardiac MRI.

Methods: 118 patients (pts.) treated with transfemoral TAVI between 10/08 and 10/13 and examined with cardiac MRI 1-2 weeks after TAVI were included in this analysis. The dimensionless ARI was calculated from post-TAVI pressure tracings according to the formula: $(\text{diastolic blood pressure} - \text{left ventricular enddiastolic pressure})/\text{systolic blood pressure} \times 100$. Phase-contrast MRI was conducted to quantify the degree of AR. A regurgitant fraction (RF) $\leq 15\%$ was graded as mild, 16–30% as moderate, 31–50% as moderate-severe and $> 50\%$ as severe AR. A RF $< 1\%$ was classified as no AR.

Results: The median age of the cohort was 81 years (range 52–92 y); 70 pts. (59%) were women. 68 pts. (58%) were treated with the CoreValve prosthesis and 50 pts. (42%) received a Sapien XT valve. The mean ARI calculated at the end of the TAVI procedure was 26.7 ± 6.3 .

Cardiac MRI revealed a median RF of 4.8% (range 0.03–47.6%). 16pts. (14%) had a RF $< 1\%$ and were classified as no AR, 80 pts. (68%) had mild AR, and 22 pts. (18%) had significant AR (15 pts. with moderate and 7 with moderate-severe AR). No significant correlation was observed between the calculated ARI and RF calculated by MRI ($r=-0.03$; $p=0.71$). The ARI was similar in pts. with no/mild AR compared to those with significant AR based on MRI (26.9 ± 6.3 vs. 26.2 ± 6.6 ; $p=0.69$). Of the 22 pts. with significant AR only 8 (36%) had an ARI < 25 . Mortality rates at 6 months follow-up were 9% (2/22) in pts. with a RF $> 15\%$

and 3.1% (3/96) in pts. with a RF $\leq 15\%$. Regarding the ARI, mortality at 6 months was 2.5% (1/40) in pts. with an ARI < 25 and with 5.1% (4/78) even higher in pts. with an ARI ≥ 25 .

Conclusion: The proposed dimensionless ARI showed no correlation with the aortic RF calculated by cardiac MRI and thus its validity could not be confirmed using MRI-based flow measurements. In our study cohort, MR derived aortic RF shows a trend to predict mortality at six months more reliably than the AR index.

P2412 | BEDSIDE

Hemodynamic assessment of aortic regurgitation after transcatheter aortic valve implantation: diastolic pressure time index

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A relevant peri-prosthetic aortic regurgitation (periAR) after transcatheter aortic valve implantation (TAVI) is present in up to 20% of cases and might be associated with an adverse outcome. Therefore, correct assessment of periAR directly after TAVI is essential to guide further intervention in cases of a relevant regurgitation. Given the shortcomings of angiographic quantification of aortic regurgitation, it was aim of our study to identify a simple and reproducible hemodynamic parameter for the assessment of periAR.

Methods: Data from 362 consecutive patients who were treated with the Medtronic CoreValve (Medtronic Inc., Minneapolis, MN, USA) or Edwards SAPIEN (Edwards Lifesciences Inc., Irvine, CA, USA) bioprosthesis for symptomatic aortic valve stenosis were analysed. PeriAR was assessed by aortic-root angiography according to Sellers. For hemodynamic evaluation of periAR, the diastolic pressure time index (DPT-Index) was calculated: left ventricular and aortic pressures were simultaneously determined after TAVI and the area between the aortic and left ventricular pressure-time curves (DP-Area) was measured during diastole. The DP-Area was divided by the duration of diastole and adjusted for the scaling of the pressure-time curve to calculate the DPT-Index. The DPT-Index was finally adjusted for the respective systolic blood pressure (SBP) of the patient: $\text{DPT-Index-adj} = (\text{DPT-Index}/\text{SBP}) \times 100$.

Results: Patients with angiographically non-relevant periAR (grade < 2) had a higher DPT-Index-adj (30.9 ± 6.8) as compared to those with relevant periAR (grade ≥ 2 ; 26.2 ± 5.8 ; $p<0.05$). In patients who survived until one year after TAVI, DPT-Index-adj was significantly higher (31.3 ± 6.5) in comparison to patients who died within the first year after TAVI (27.3 ± 6.8 ; $p<0.05$). The optimal cutoff value of the DPT-Index-adj for the prediction of all-cause mortality at 1 year was 27.9. Patients with DPT-Index-adj < 27.9 had a significant higher 1-year mortality risk in comparison to patients with DPT-Index-adj > 27.9 : 41.4% versus 13.5% [HR: 3.8, 95% CI: 2.4 to 5.9; p (log rank-test) < 0.001]. In multivariate regression analysis, a DPT-Index-adj < 27.9 independently predicted 1-year mortality (HR: 2.5, 95% CI: 1.8 to 3.7; $p<0.001$).

Conclusion: The diastolic pressure time index is significantly lower in patients with relevant periAR and predicts 1-year mortality after TAVI. The DPT-Index is a simple, investigator-independent parameter that should be considered to differentiate between relevant and non-relevant periAR in order to guide intraprocedural decision making.

P2413 | BEDSIDE

Diagnostic and prognostic value of NT-proBNP in patients with paravalvular leakage after transcatheter aortic valve implantation

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Background: N-terminal segment of B-type natriuretic peptide pro-hormone (NT-proBNP) provides prognostic information in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI). Furthermore, NT-proBNP is associated with higher mortality risk in patients with aortic regurgitation. The aim of the present study was to examine the prognostic and diagnostic potential of NT-proBNP as a biomarker in patients with paravalvular aortic regurgitation (AR) after TAVI within a 12-month follow-up period.

Methods: A total of 395 consecutive patients with severe aortic stenosis undergoing elective TAVI were included in the study. AR was measured on the second day after TAVI using echocardiography. Blood samples were collected before TAVI and 4 h and 1, 2, 3, and 6 days afterwards. Serum was processed immediately and frozen at -80°C until assay. NT-proBNP was measured in serum with an electrochemoluminescence immunoassay using monoclonal antibodies. Patient follow up was for 1 year.

Results: Paravalvular AR $\geq 1^\circ$ was observed in 196 (49.7%) patients, and in 46 (11.7%) patients the AR was $\geq 2^\circ$. Sixty-six (16.9%) patients died during the one-year follow-up. Patients with AR post-TAVI had a higher mortality rate [41 [20.9%] vs. 25 [12.6%]; $P=0.005$] compared with those without AR. There were no differences in baseline characteristics between deceased and surviving patients. NT-proBNP levels were similar at baseline between survivors and non-survivors ($\text{AI} < 1^\circ$: $2,540.0 \text{ ng/L}$ [996.7–5,511.8] vs. $\text{AI} \geq 1^\circ$: $2,127.0 \text{ ng/L}$ [1,045.0–4,972.5],

respectively; $P=0.6$), whereas NT-proBNP levels on the second day after TAVI were higher in non-survivors with $AR \geq 1^\circ$ compared with survivors, where $AR < 1^\circ$ (6,881.0 ng/L [3,103.0-10,279.0] vs. 2,758.0 ng/L [1,346.0-4,419.0]; $P<0.001$). The risk of mortality was higher if NT-proBNP was increased by at least 10% between the first and second day after TAVI (multivariate Cox regression analysis adjusted for age, estimated glomerular filtration rate, left ventricular ejection fraction, and atrial fibrillation: hazard ratio 2.6; $P=0.03$). The second day after TAVI was the best time point for predicting one-year mortality (AUC 0.807 [95% CI 0.63-0.99; $P=0.004$]).

Conclusion: NT-proBNP provides prognostic information predicting mortality within 1 year in patients with AR after TAVI. These findings demonstrate that serial NT-proBNP measurements can be used for risk stratification and determination of further therapeutic measures in patients with AR after TAVI.

P2414 | SPOTLIGHT

Transcatheter valve in valve is an elegant solution to a surgical problem

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Background: Reoperation for degenerated bioprosthesis is a surgical challenge with increased perioperative morbidity and mortality compared to the primary operation. The introduction of transcatheter heart valve (THV) therapy has opened a new treatment option for these patients. Valve-in-valve offers a big advantage: You see the valve frame on x-ray and therefore easily can adjust your x-ray to the optimal angle of implantation, and secondarily to that avoid using contrast. However, it is very important to have exact knowledge of the type and size of the inoperated bioprosthesis, to be able to choose the right THV size and also at which height in the bioprosthesis the optimal implantation for the THV is.

Material and methods: Since the start of our THV programme with the Edwards Sapien valve system September 2008 we have treated 19 patients with degenerated bioprosthesis. All patients were discussed for conventional surgery and recommended for THV therapy. We have rejected one patient because the inoperated valve (Mitroflow 21mm) was too small for available transcatheter valves.

Results: We have treated 13 patients with degenerated aortic bioprosthesis, 5 with degenerated mitral bioprosthesis and 1 with degenerated tricuspid bioprosthesis, see tables for baseline data, procedural data and follow-up data. Periprocedurally one patient died of circulatory failure and one suffered a stroke (fortunately good recovery). One valve embolized to the left ventricle because of operator failure (missed to retract the so-called pusher), the patient was operated immediately with good result. All surviving patients have good valve function and almost no paravalvular leakage. We have seen no late complications.

Conclusion: Valve-in-valve implantation offers a new treatment option for patients with degenerated bioprostheses. On one hand the procedure is straight forward because you clearly see the inoperated bioprosthesis, on the other hand it is mandatory to know the exact type and size of the bioprosthesis to avoid missizing and misplacement.

ATRIAL FIBRILLATION: MISCELLANEOUS

P2416 | BEDSIDE

The French screening campaign of atrial fibrillation in general practice: qualitative evaluation of the campaign (awareness, interest, and impact on daily practice)

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Context: Atrial fibrillation (AF) affects nearly 750 000 patients in France and this number is expected to double by 2050. AF is a severe disease with important consequences in terms of morbidity and mortality but still under-diagnosed. An AF screening campaign (Profil FA) was deployed in 2013 among family physicians (GP) in 16 French sites with a simple questionnaire based on heartbeat measurement, AF linked symptoms and thromboembolic patient risk (CHADS-VASC items).

The project was evaluated quantitatively in terms of detection capacity as well as qualitatively in terms of interest and satisfaction for the GP.

The main objective of this campaign qualitative assessment was to collect physician opinion on PROFIL FA, patient's acceptance and to estimate impact of the campaign on the daily practice.

Method: After campaign completion and quantitative results disclosure (see Profil FA results) a survey was proposed to the 603 participating physicians (on line questionnaire or face to face with medical rep.).

Several dimensions were explored (level of awareness, collaboration with cardiologist, practice impact, patient acceptance, program satisfaction, operational assessment).

Results: 365 questionnaires were collected (response rate of 60%) and analyzed. Overall, 76% GP estimated the campaign has positively raised their awareness (min 48.5% in Bourgogne and max 100% in Côte d'Azur/Nice). The campaign helped to point out the relative high frequency of AF in elderly patients

(65% GP) and to systematically measure heartbeat in this population (61% GP). Cardiologist orientation was higher in GP with higher AF awareness. Overall the campaign helped better collaboration with cardiologist for 58% participating GP. Cardiologist orientation was well accepted by 85% patients but with better level of acceptance in rural environment ($P=0.047$).

Triggers for cardiologist orientation are irregular heartbeats (93%GP), symptoms evoking AF (81% GP), secondary prevention of thromboembolic event (60.5%GP), CV risk factors (54.8%) and age (41.7%). Overall campaign satisfaction was 7.2/10 (min 5.6 in Normandie and max 8.4 in Côte d'Azur/Nice). Satisfaction was 7.6 in GP in GP improving awareness and 5.9 in others ($p<0.0001$).

Conclusion: The simple Profil FA campaign aiming to detect unknown AF in patients >65y helped to raised GP's awareness of the disease in GP, improved collaboration with cardiologist. The satisfaction index shows the positive impact of the campaign for the GPs. Nevertheless attention should be paid to interregional differences to optimize outcomes of campaign.

P2417 | BEDSIDE

Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH Score

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Background: Presence of left atrial low-voltage areas (LVAs) is frequently observed in patients with atrial fibrillation (AF) and may predict recurrences.

Methods: In a cohort of 238 patients, voltage maps were created after circumferential pulmonary vein isolation. LVAs were defined as electrograms amplitudes <0.5mV. Based on regression analysis, univariate clinical predictors for LA substrate were identified. These parameters were used to establish a dedicated risk score (DR-FLASH score: Diabetes, Renal function, persistent Form of AF, LA>45mm, Age>65Y, female Sex, Hypertension). Consecutively, this risk score was prospectively validated in a multicenter cohort of 187 patients. Moreover, the association of the score with recurrences of atrial tachycardias in 1 year follow-up was tested in a historic cohort of 484 patients.

Results: DR-FLASH score effectively identified LVA substrate in 238 patients (C-statistic, 0.810, $p<0.001$, OR 2.5, 95%CI 1.9-2.3, $p<0.001$).

In the prospective multicenter validation cohort, the predictive value of DR-FLASH score was confirmed (C-statistic, 0.760, $p<0.001$). The probability for the presence of LA substrate increased by a factor 2.1 (95%CI, 1.5-2.8, $p<0.001$) with each point.

Furthermore, the risk of recurrence after AF ablation increased by a factor of 1.3 (95%CI, 1.1-1.5, $p<0.001$) with every additional point and was almost 2 times higher in patients with Dr-FLASH>3 (OR 1.7, 95%CI, 1.1-2.8, $p=0.026$).

Conclusions: DR-FLASH score represents a reliable clinical tool to identify LVA substrate, representing arrhythmogenic substrate indicative of recurrences. The score may hence be of great clinical utility in order to identify patients, who may require further substrate modification instead of pulmonary vein isolation alone.

P2418 | BEDSIDE

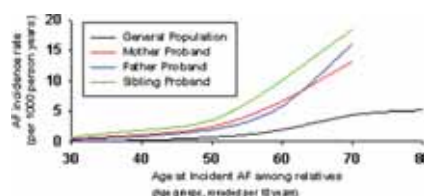
Familial clustering and subsequent incidence of atrial fibrillation among first-degree relatives in Denmark

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Purpose: Atrial fibrillation (AF) is a common cardiac arrhythmia and associated with increased morbidity and mortality. Data regarding familial clustering of this arrhythmia are sparse and could help identify high-risk patients and guide screening.

Methods: Using nationwide Danish registry data (1978-2010) we identified all first-time AF patients (probands) in Denmark born after 1895 who were alive at 1978. Relatives to these probands were grouped according to proband-relation: offspring from mother proband, offspring from father proband, or sibling to proband. The age-specific incidence rate of AF was estimated and with the general population as reference we calculated rate ratios (RR) for incidence of AF. This was done using multivariable Poisson regression analysis.

Results: We included 59,394; 91,194; and 9,016 AF-probands who were mothers (median age 73 years, IQR 65-79), fathers (69 years, IQR 61-76), and siblings (44 years, IQR 36-50), respectively. A total of 116,056 and 192,887 offspring from mother- and father-probands and 16,376 proband-siblings were screened for incident AF, and this was recorded in 2072 (1.8%), 2394 (1.2%), and 196 (1.2%) relatives, respectively. The incidence of AF was higher among those with a parent or a sibling with AF (Figure). Adjusted RRs for incident AF were 2.17 (95% CI 2.06-2.30) for offspring from maternal probands, 1.74 (95% CI 1.67-1.82) for



AF incidence by familial association.

paternal offspring, and 4.41 (95% CI 4.32-4.50) for siblings. Subgroup analyses showed increased RRs with younger aged probands.

Conclusions: Familial AF was associated with an increased incidence of AF in first-degree relatives compared with the general Danish population. Our results suggest that familial AF is a major risk factor for developing this prevalent and morbidity-prone cardiac arrhythmia.

P2419 | BEDSIDE

High physical fitness; associated with increased or reduced atrial fibrillation risk in middle-aged men?

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Purpose: Smaller studies have demonstrated increased atrial fibrillation (AF) risk among long-endurance trained athletes. However, limited and inconsistent data are available concerning level of fitness and AF risk in the general population. We aimed to investigate associations between measured physical fitness and incident AF in men.

Methods: In 1972-1975, as part of a prospective cardiovascular survey, 1997 healthy middle-aged Norwegian men were tested with a symptom-limited bicycle exercise ECG test. Physical fitness was calculated as total exercise work capacity divided by body weight. Incident AF was documented by scrutiny of medical records in all Norwegian hospitals. Risk estimations were analysed in quartiles of age-adjusted PF using adjusted Cox proportional hazards models.

Results: During 35 years of follow-up, 253 men developed AF (13%). Men with age-adjusted physical fitness in the upper quartile had significantly reduced long-term AF risk in multivariate analyses compared with the rest of the cohort. Further analyses in deciles and subgroups with baseline elevated blood pressure, showed that the men with the very highest fitness had slightly increased risk compared to men with high (but not extreme) fitness.

Table 1. Risk of AF in hazard ratios according to quartiles of age-adjusted physical fitness

Age-adjusted physical fitness	AF events	Hazard ratio*	p-value
Highest quartile (n=510) vs. the remaining quartiles (n=1487)	65 (12.7%) 188 (12.6%)	0.74 (0.55-1.00)	0.047

*Multivariable adjusted for age, systolic blood pressure, left ventricular hypertrophy, resting heart rate, height, relative heart volume (by x-ray), body mass index (BMI) and including the significant interaction term BMI × relative heart volume.

Conclusions: High physical fitness in healthy middle-aged men was associated with approximately 25% lower long-term risk of incident AF. Men with very high fitness, however, seemed to have a slightly increased risk compared to those with more moderate high fitness, especially if their resting blood pressure was elevated.

P2420 | BEDSIDE

Galectin-3 is associated with worse clinical outcome in patients with atrial fibrillation: A substudy from the ARISTOTLE trial

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Purpose: Galectin-3 is a novel biomarker of cardiac fibrosis and myocardium remodeling. Our aim was to investigate the distribution levels of Galectin-3 and its association with clinical outcomes in patients with atrial fibrillation (AF).

Methods: The ARISTOTLE trial included patients with AF and increased risk of stroke that were randomized to apixaban 5 mg b.i.d. or warfarin (INR 2-3). Levels of Galectin-3 were measured, by the Abbott assay, in plasma samples obtained at randomization from 1996 patients. The association between baseline levels of Galectin-3 and the composite outcome of stroke, systemic embolism (SE) or death, and major bleedings was evaluated in Cox proportional hazard models.

Results: Quartiles of Galectin-3 were Q1≤13.7, Q2=13.8-16.4, Q3=16.5-20.2, and Q4≥20.2, with a mean level of 17.7 ng/mL. Increasing CHA2DS2-VASc and HAS-BLED scores were associated with higher level of Galectin-3. During follow-up (median 3.0 years), 261 stroke/SE/deaths and 125 major bleedings occurred. Annual rates of stroke/SE/deaths ranged from 2.62% in Q1 to 7.63% in Q4 and

the hazard ratio (95% CI) for Q4 vs Q1 was 2.94 (2.02-4.27) (effect of biomarker p<0.0001). Annual rates of major bleedings ranged from 1.69% in Q1 to 3.66% in Q4 and the hazard ratio for Q4 vs Q1 was 2.19 (1.30-3.69) (p=0.0236).

Conclusions: In patients with AF, Galectin-3 was associated with increased risk of stroke, SE or death, and major bleeding. Our findings suggest that this novel biomarker might help refine risk stratification in AF patients.

P2421 | BEDSIDE

Formation and resolution of left atrial thrombus during dabigatran therapy: a JHRS survey report

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Since dabigatran (Dabi) was launched on March 14, 2011 in Japan, electrical cardioversion (EC) of atrial fibrillation (AF) has been planned and attempted during Dabi therapy, providing an opportunity to examine both formation and resolution of atrial thrombus (AT) in this clinical setting. Accordingly, the Japanese Heart Rhythm Society made a retrospective survey of the incidence and the fate of AT among 299 institutions from December 2012 to January 2013.

There were a total of 199 patients (pts) with planned EC who also underwent either transesophageal echocardiography (TEE) or computed tomography to rule out AT before EC. Of these 199, AT was found in 9 pts (4.5%). These 9 pts with AT were older (68.7 vs 61.3 years, p=0.075) and had higher CHADS2 scores (2.1 vs 0.9, p=0.037) than those without AT. Of the 9 pts with AT, 1 developed AT within 3 weeks of Dabi 150mg bid, whereas the remaining 8 pts received a lower dosage, 110mg bid, for 4 weeks or longer. Notably, in 3 of these 8, the dosage of 110 mg bid was inappropriately low since the conditions recommended for dosage reduction in Japan such as high age, low creatinine clearance, p-glycoprotein inhibitor co-administration, and prior GI bleeding were absent. In 6 of the 9 pts with AT, the second TEE was done >6wks later, disclosing a complete resolution of AT in 5, i.e., on the same dosage in 2, after an increased dosage of Dabi in 2, and after switching to warfarin in 1. EC was carried out in both 190 pts without AT and 5 with AT after its resolution. There were 2 cases of stroke developing 3 and 21 days, respectively, after EC while on Dabi. Importantly, no AT was found before EC in these cases. The former had CHADS2 score 0, but received inappropriately low dosage of 110mg bid. There was 1 case of major bleeding in the large intestine during Dabi therapy.

In conclusion, AT developed in 4.5% of AF pts receiving Dabi. Older pts with higher CHADS2 score receiving inappropriately lower dosage or shorter duration of Dabi administration are likely to have AT, which can resolve with a prolonged or increased dosage. Nevertheless, AT can also develop even under a recommended dosage and duration of Dabi. Therefore, it is important not only to pay attention to Dabi dosage and duration before and after EC, but to perform TEE before EC in all Dabi pts.

P2422 | BEDSIDE

Rhythm control strategies in atrial fibrillation: inter-country differences in Europe. Follow-up data from the PREFER in AF registry

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Purpose: Rhythm control can be a valid strategy for patients with paroxysmal or persistent atrial fibrillation (AF) based on factors such as the degree of symptoms, age or activity levels. This strategy needs to be frequently supplemented by the use of antiarrhythmic drugs or interventions. There is a lack of comparative data concerning the use of these resources in different parts of Europe.

Methods: The PRevention of thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF) prospectively enrolled unselected patients with AF in 7 European countries including France (FR), Germany (GE), Italy (IT), Spain (SP) and the United Kingdom (UK) from Jan 2012 to Jan 2013 in 461 centres. Here we report the patterns of rhythm control strategies used at baseline and within 1 year of follow-up (FU).

Results: At baseline, in 7243 patients enrolled, 30.0% had paroxysmal, 24.0% had persistent, 7.2% had long-standing persistent, and 38.8% had permanent AF. Half of them received rhythm control therapy. During the 1 year of FU 5% of patients underwent pharmacological cardioversion (from 2.4% in GE to 7.8% in IT). Electrical cardioversion was performed in 7.6% of patients. Electrical cardioversion was one of the preferred methods in the UK for a rhythm control strategy (14.9%) and it was performed mainly in an outpatient setting (82.6%). On the opposite, in the rest of countries electrical cardioversion varied from 2.9% in SP and 7.7% in IT, and it required hospitalization in >60% of cases. Catheter ablation procedures remained low (3.8%), but with important regional variations (from 2.6% in FR and SP to 6.1% in UK). Rate of electrical cardioversion and catheter abla-

tion procedures during FU was reduced (from 18.1 to 7.6% and from 5.0 to 3.8%, respectively), possibly reflecting unsuccessful attempts to restore sinus rhythm. Among antiarrhythmic drugs amiodarone remained as the most frequently used in 16.8% of patients (from 8.8% in UK to 25.2% in FR). Flecainide or propafenone was used in 9.6% (from 3.7% in UK to 14.3 in FR), and sotalol in 4.0% (from 1.1% in SP to 6.6% in FR). The use of dronedarone was significantly lower during FU (2.1%; from 0.2% in FR to 4.9% in GE) as compared with baseline (4%).

Conclusions: Despite a relative homogeneity in the percentage of patients receiving rhythm control therapies for AF in these different European countries, there are big regional variations regarding the preferred method between interventional (ablation/electrical cardioversion) or pharmacological strategies.

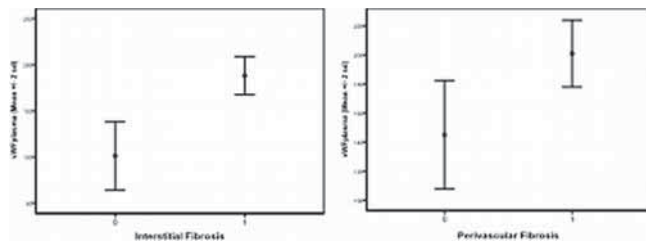
P2423 | BEDSIDE

Plasma vWF levels are involved in AF development in ischaemic patients undergoing cardiac surgery

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Atrial fibrillation (AF) occurs in ~30% of patients undergoing coronary artery bypass grafting (CABG) and in 40% of patients after valve surgery. von Willebrand factor (vWF) is a biomarker of endothelial dysfunction and prothrombotic state. vWF is an independent risk factor for adverse events in AF patients. We included consecutive haemodynamically stable patients undergoing programmed cardiac surgery with cardiopulmonary bypass pump. We determined vWF before cardiac surgery and recorded AF development by prolonged ECG monitoring. We evaluated fibrosis in tissue sample from the right atrial appendage.

We studied 100 patients for CABG (n=58) or aortic valve replacement. 29 patients developed post-surgical AF. We found higher levels of plasma vWF in CABG patients versus valvular patients (200 ± 66 vs 157 ± 84 IU/dl; $p=0.015$). We found an association between vWF levels and interstitial fibrosis [OR 1.01 95%CI (1.00-1.03), $p=0.042$] and perivascular fibrosis [OR 1.01 95%CI (1.00-1.02), $p=0.017$] in the tissue (Fig 1). An association of the patient type with AF development was shown ($p=0.034$). Thus, we decided to investigate the prognosis in the two cohorts separately. We observed that vWF values above the 4th quartile were predictive of AF at a borderline significance [OR 4.5 95%CI (0.98-20.6), $p=0.053$]. In a multivariate model adjusted by clinical and demographical data ($p<0.15$ in univariate analysis) vWF levels remained as independent prognostic predictor for AF in ischaemic patients [OR 6.3 95%CI (1.14-34.71), $p=0.035$]. Valvular patient showed no association between vWF and AF development.



vWF levels are associated with fibrosis.

vWF levels are higher in ischaemic versus valvular patients undergoing cardiac surgery. Plasma vWF levels are associated with tissue fibrosis and seems to be involved in AF development after CABG.

P2424 | BEDSIDE

Predictors for new-onset post-operative atrial fibrillation in patients undergoing aortic valve replacement

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Aim: 1. Defining the independent predictors for new-onset post-operative atrial fibrillation (POAF) in patients (pts) undergoing aortic valve replacement (AVR) and their adjusted value for calculation of a preoperative risk score.

2. Assessment of the independent prognostic value of the LV diastolic dysfunction and left atrium (LA) dilatation for POAF development in these pts.

3. Identifying the predictors for recurrent atrial fibrillation (AF) and their implications for postoperative course in AVR pts.

Material and method: Prospective study on 802 pts who underwent AVR for aortic stenosis (456pts) or aortic regurgitation (AR) (346pts). Patients were evaluated clinically and by echocardiography (including TDI) preoperatively and postoperatively at 10, 20 and 30 days. All were in sinus rhythm without history of AF.

Statistical analysis used SYSTAT and SPSS programs for regression analysis and for relative risks and correlation coefficient calculations. Multivariable analyses were adjusted for age and gender including left ventricular ejection fraction (LVEF) $\leq 35\%$, restrictive LV diastolic filling pattern (LVDFFP), renal insufficiency and logistic EuroSCORE $\geq 20\%$.

Results: POAF occurred in 320 of 862 patients (39.9%).

1. Regression analysis identified as independent predictors for POAF: restrictive LVDFFP (RR=23.42), preoperative AR (RR=10.31), LA dimension in-

dex $> 30\text{mm/m}^2$ (RR=13.92), advanced age (RR for 10-year increase=2.09), LVEF $\leq 35\%$, LV endsystolic diameter (LVESD) $> 55\text{mm}$, higher body mass index, NYHA class III/IV, comorbidities

2. The presence of a restrictive LVDFFP increased the POAF risk by 23.42 fold and the rate of POAF increased exponentially with diastolic dysfunction severity ($p<0.001$)

3. Predictors of recurrent POAF (occurred at 44.69% of POAF pts) included restrictive LVDFFP, age > 75 years, LA dimension index $> 30\text{mm/m}^2$, LV end-systolic volume (LVESV) $> 85\text{cm}^3$, bicaval venous cannulation, moderate mitral regurgitation (MR), severe pulmonary hypertension (PHT).

Conclusions: 1. The independent predictors for POAF initiation after AVR were: restrictive LVDFFP, preoperative AR, advanced age, LVESD $> 55\text{mm}$, LVEF $\leq 35\%$, obesity, NYHA class III/IV and comorbidities

2. Restrictive LVDFFP and LA dilatation has a powerful independent and incremental predisposing value for the initiation of POAF after AVR and their evaluation may be very useful during risk stratification of patients undergoing cardiac surgery

3. The only independent predictors for recurrent POAF after AVR were: restrictive LVDFFP, older age, LA dimension index $> 30\text{mm/m}^2$, LVESV $> 85\text{cm}^3$, bicaval venous cannulation, moderate MR, severe PHT.

P2425 | BEDSIDE

Efficacy of omega-3 fatty acids alone or in combination with antioxidant vitamins on postoperative atrial fibrillation prevention: a meta-analysis

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Purpose: The effect of omega-3 polyunsaturated fatty acids (PUFA) on the prevention of postoperative atrial fibrillation (POAF) remains controversial based on individual studies. The aim of this meta-analysis was to ascertain the protective role of PUFA on POAF when it was used alone or in combination with antioxidant vitamins.

Methods: Studies were identified through PubMed, CENTRAL, EMBASE, reviews and reference lists of relevant papers. The odds ratio (OR) was calculated for POAF. Statistical analyses were performed with Review Manager 5.0.

Results: 11 randomized controlled trials with 3137 patients were included in the analysis. 8 studies reported isolated administration of PUFA as the sole intervention, 3 administered concomitant vitamins C and E therapy. Combined result showed that the use of PUFA alone did not reduce the incidence of POAF compared with the control (OR: 0.76; 95% confidence interval [CI]: 0.57-1.03; $P=0.08$; $I^2=52\%$). However, combination therapy with PUFA and vitamins C and E reduced the incidence of POAF by 68% (OR: 0.32; 95%CI: 0.17-0.60; $P=0.0005$; $I^2=38\%$).

Conclusions: Combination therapy with PUFA and vitamins C and E is effective in the prevention of POAF while PUFA alone not.

P2426 | BEDSIDE

Cardioversion of atrial fibrillation or atrial flutter decisively improves severity and type of sleep disordered breathing

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Purpose: Sleep disordered breathing (SDB) with obstructive sleep apnea (OSA) is associated with an increased risk of onset or recurrence of atrial fibrillation and atrial flutter. We sought to prospectively document SDB frequencies, type and severity in patients with atrial arrhythmias and we aspired to determine whether cardioversion into sinus rhythm has an immediate influence on type and severity of SDB.

Methods: A consecutive group of 138 patients (67.8 ± 10.3 years, 67.4% male) was prospectively enrolled in our study and underwent multichannel cardiorespiratory polygraphy (PG) screening before and immediately (within 24 hours) after electrical cardioversion (CV) into sinus rhythm. In addition PG studies were repeated after four weeks of CV.

Results: 95.2% of the study population patients with atrial fibrillation ($n=119$; 86.2%) or atrial flutter ($n=19$; 13.8%) had SDB with an Apnea-Hypopnea-Index (AHI) of $\geq 5/\text{h}$. Immediately after CV AHI decreased significantly ($23.4 \pm 16.3/\text{h}$ to $16.3 \pm 11.5/\text{h}$, $p<0.001$). In contrast, after four weeks of follow up overall SDB severity was comparable to prior CV, even if atrial dysrhythmia did not recur at four weeks follow up. However, central respiratory events markedly improved with a significant reduction of patient's presenting with central sleep apnea directly after CV: $n=53$ (42.7%) to $n=23$ (26.7%), $p<0.001$. In addition, there was a trend towards a further reduction in central events after 4 weeks of follow-up ($n=8$, 20%, $p=\text{n.s.}$).

Conclusions: SDB is highly prevalent co-morbidity in patients with atrial dysrhythmia. While CV seems to have no long lasting effect on total AHI, this study reveals a significant reduction in central respiratory events. This may be explained by unmasking preexisting obstructive respiratory events. These findings may implicate that diagnostic PG leading to distinguished therapy of SDB should be performed after restoration of cardiac rhythm. Thus, the optimal time span between CV and diagnostic PG leading to therapeutic indications need to be determined by further studies.

P2427 | BEDSIDE**Pharmacokinetics and pharmacodynamics of dabigatran etexilate 75 mg BID in patients with severe chronic kidney disease: prospective validation of a post hoc determined dose**

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Purpose: Dabigatran etexilate (dabigatran) is a direct oral thrombin inhibitor approved for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation. Dabigatran is predominantly renally excreted (~80%), so patients with creatinine clearance (CrCl) <30ml/min were excluded from phase-3 studies. Based on post-hoc pharmacokinetic modeling, the FDA approved dabigatran in a lower dose of 75mg twice daily (BID), for patients with severe chronic kidney disease (CKD) (CrCl 15-30ml/min[1]). We investigated the pharmacokinetics (PK) and pharmacodynamics (PD) of this dose in patients with severe CKD.

Methods: In this open-label study, 15 patients received dabigatran 75mg BID for 7 days (steady state) followed by 4 days of wash-out. PK and PD blood samples were collected every 24 hours and full profiles over the dosing interval were obtained on the first and last day of dabigatran intake.

Results: Based on interim data from 10 patients (CrCl 15-29ml/min), the geometric mean (geometric coefficient of variation) C_{max,ss} and AUC_{tau,ss} of total dabigatran were 230ng/mL(61.8%) and 2380ng*h/mL (59.8%), respectively. No drug accumulation occurred at the end of the treatment period. The observed mean concentration of dabigatran correlated well with values predicted by the PK model (Fig. 1).

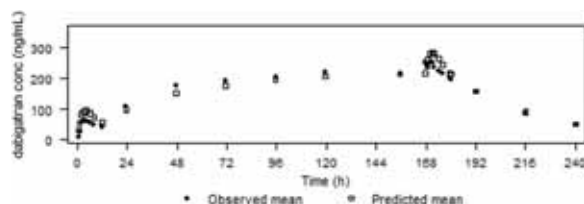


Figure 1. Observed and predicted mean concentration-time profiles of total dabigatran after administration of dabigatran etexilate 75mg BID.

No patient developed an adverse cardiovascular event or major bleed. Final data in 15 patients will be presented at the congress.

Conclusion: The results confirm that, on average, the dabigatran etexilate 75mg BID regimen achieves the targeted drug exposure in patients with severe CKD without accumulation.

CATHETER ABLATION OF ATRIAL FIBRILLATION

P2429 | BEDSIDE**First application of a novel, multi-site, high-resolution epicardial, mapping approach**

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Purpose: Ablative therapy of atrial fibrillation (AF) is aimed at targeting either the trigger or substrate perpetuating AF. At present, there are no diagnostic tools for identification of the arrhythmogenic substrate. The goal of the present study was to assess feasibility and the safety of a novel, multi-site high resolution epicardial mapping approach.

Methods: 150 consecutive patients underwent intra-operative, high-resolution epicardial mapping of the entire atria (using 60-128 unipolar electrodes/1-4 cm²) during sinus rhythm (SR) and acutely induced or persistent AF. Activation, voltage and conduction maps were created automatically at every location. Hemodynamic parameters, mean arterial pressure (MAP), right atrial pressure (RA), ST-segment alterations (ST) and level of anaesthesia (bispectral index (B.I.S)) before and during SR/AF mapping were compared.

Results: SR and AF was present in respectively 120 and 30 patients; AF was non-inducible in 10. Average AF duration was 5.3±6.7 minutes per patient needing 3±3 AF inductions in order to complete AF mapping. The total mapping time was significantly reduced by introduction of a larger mapping electrode (4 cm²), respectively 25±7 versus 15±5 minutes (p<0.0001). Hemodynamic parameters before and during SR mapping were respectively MAP 70±11/69±11 mmHg (p<0.22), RA 10±4/10±4 mmHg (p<0.15), ST 0.09±0.54/-0.08±0.49 mm (p<0.31) and BIS 37±9/39±8 (p<0.06). During AF, these values were MAP 71±11 vs 67±10 mmHg (p<0.004) and RA 10±4 vs 11±4 mmHg (p<0.0001). B.I.S did not differ between AF and SR (P<0.91). In the entire study population, a total of 11,675 seconds were obtained from 2235 atrial sites. Stability of the mapping electrode was demonstrated by a beat-to-beat variation of SR cycle length and peak-to-peak amplitude of the unipolar electrogram recorded from the cen-

tral area of the right atrial appendage, respectively less than 0.04±14.42 ms and -0.01±0.53 mV. Complications were not observed

Conclusion: Intra-operative multi-site, high resolution epicardial mapping of the atria is feasible and safe.

P2430 | BEDSIDE**Validation of the coronary vessels near the ablation line on the mitral isthmus in the chronic phase after the catheter ablation**

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Purpose: The linear catheter ablation on the lateral mitral isthmus (LMI) often requires radiofrequency (RF) energy delivery inside the coronary sinus (CS) or the great cardiac vein (GCV) which runs close to the left circumflex coronary artery (LCX). The acute occlusion of the LCX close to the ablation site in the cardiac vein has been reported during catheter ablation. This study evaluated the influence of linear ablation at the LMI on the anatomy of LCX, CS and GCV by cardiac multi-detector computed tomography (MDCT) in the chronic phase, i.e., 1 year after ablation.

Methods and results: We performed MDCT on 28 patients (22 males, age 59.4±10.7 years) both before and after linear ablation on the LMI. The LMI ablation was performed under the guidance of the CARTO system with 3D geometric reconstruction of the left atrium (LA) from MDCT images. RF energy was delivered with 20-35 W with a saline irrigation speed of 17 or 30 mL/min. The bidirectional LMI conduction block was 78.6% (22/28), ablation from CS or GCV was needed in 50% (14/28) patients. The observational period from LMI ablation to follow-up MDCT was 12.4±5.4 months on average. The distance from endocardial ablation site to LCX was longer than to CS (6.4±3.4 and 3.9±4.7 mm, p<0.01, respectively). The distance between from CS ablation site to LCX was 4.5±3.5 mm. At the about 1-year follow-up observation, there was no significant change in diameter of LCX or CS comparing before and after the ablation, from 2.61±0.67 to 2.61±0.56 mm (P=1.00) or from 4.30±0.64 to 4.37±0.93 mm (P=0.50), respectively. There was no stenosis or occlusion in LCX or CS.

Conclusions: In the half of LMI ablations, ablation from CS or GCV was needed to achieve complete bidirectional LMI block. At the 1-year follow-up, there was no remarkable change in the diameter of LCX, CS or GCV. Although LCX and CS or GCV are located close each other, RF application from the cardiac venous system did not always accompany the narrowing of the adjacent LCX.

P2431 | BEDSIDE**MRI characterization of cryoballoon and radiofrequency ablation lesions after pulmonary vein isolation**

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Introduction: Cryoballoon (CA) and radiofrequency (RF) ablation are effective techniques to treat patients with paroxysmal atrial fibrillation (AF). Delayed-enhanced cardiac magnetic resonance (DE-CMR) allows the identification of ablation lesions (scar) and gaps. We aimed to compare the DE-CMR characteristics of the ablation lesions and gaps between both CA and RF ablation in patients with paroxysmal AF, and evaluate the clinical implications (recurrence rate).

Methods: We prospectively included 23 patients with paroxysmal AF undergoing a first ablation procedure (9 RF, 14 CA). A DE-CMR was performed 6±3 months postablation. The endocardium and epicardium of the left atrium (LA) were manually segmented on axial plane slices. A 3D volume-rendered LA reconstruction was created using the segmented DE-CMR data. A pixel signal intensity map was projected on the 3D reconstruction and color-coded to display healthy areas and scar. The gap size was defined as the proportion (%) between the gap length and the total perimeter of the PV antrum. To evaluate the gap location, each group of ipsilateral PVs was divided into 4 quadrants (anterior, posterior, carina and superior or inferior).

Results: We analyzed a total of 92 PVs (36 RF, 56 CA). There were gaps in 80.6% and 91.1% of PVs in RF and CA group, respectively. The gap size was 31% and 41% in the RF and CA group, respectively (p=0.217). The most common location of the gaps differed between groups: the inferior quadrant of the right inferior PV in the RF group (78% vs. 86% in CA group, p=0.624) and the superior quadrant of the left superior PV in the CA group (93% vs. 44% in the RF group, p=0.01). After 8 (6-12) months follow-up, 33% and 64% in the RF and CA group had recurrences, respectively (p=0.214).

Conclusion: Anatomic gaps on DE-CMR were common after RF and CA ablation. There was a trend toward a higher recurrence rate in the CA group compared to RF group; this finding might be related to a bigger gap size in the CA group or the differences in the location of the gaps between techniques.

P2432 | BEDSIDE

Cryoballoon to esophagus distance predicts low esophageal temperatures during pulmonary vein isolation using the second generation cryoballoon

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Purpose: Catheter ablation of atrial fibrillation (AF) using the second generation cryoballoon (CB2) has been associated with low luminal esophagus temperatures (LET) and <20% esophageal lesions if no LET cut off value has been applied. We sought to determine predictors of low LET analyzing anatomical and procedural data.

Methods: Patients (pts) undergoing a 28mm CB2-pulmonary vein isolation (PVI) procedure were included. An esophageal temperature probe (TP) was introduced and served as LET monitor. CB freeze duration was set to 240s and premature CB freeze termination was lead by LET <15°C to avoid LET 12°C. A video recording system recorded simultaneously 28mm CB and esophagus temperatures. The shortest fluoroscopic distance between the CB and the LET probe was always measured (LAO 40°, RAO 30°) and correlated with LET. Low esophageal temperature was arbitrarily defined as LET <25°C. All patients underwent an esophageal endoscopy 24 hours after the procedure.

Results: 161 CB applications in 23 pts (16 male, 20 paroxysmal AF, 65±12 years) were recorded and analyzed. The left inferior PV was characterized by the lowest LET but warmest CB temperature. 19/161 (12%) applications were characterized by a LET <25°C. A significantly shorter CB-TP distance (4.2±0.8mm vs 16.3±0.8; p<0.001) but not minimal CB temperature (-50.4±1.0 vs -50.4±0.5; p=0.98) were predictors of LET <25°C. A significant linear correlation between CB-Probe distance and LET could be demonstrated (Pearson r=0.49, p<0.0001). Post PVI esophageal endoscopy revealed just one lesion in a single patient (1/23 - 4%).

Conclusion: A short anatomical distance between the esophagus and the 28mm CB is the key determinant for low LET whereas CB temperature does not predict low LET. Importantly, LET guided freeze interruption is associated with a decreased incidence of esophageal lesions.

P2433 | BEDSIDE

The discordant changes of left atrial structure and function after radio-frequency catheter ablation of atrial fibrillation

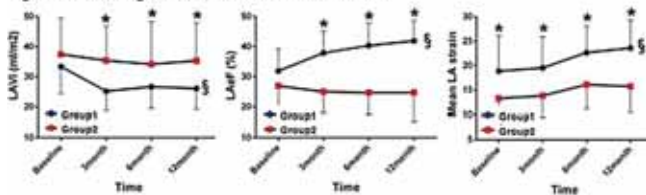
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Background: The decrement of left atrial (LA) volume and increment of LA function after successful radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF) were reported. However, serial changes of LA volume and function after RFCA have scarcely been studied. The purpose of this study was to evaluate changing patterns of LA volume and function and compare the patterns in patients with and without recurrence after RFCA.

Methods: 46 consecutive patients with AF (F/M = 13/23, mean age = 57.1±8.4 years) referred for RFCA were enrolled. Echocardiography with LA deformation images by speckle-tracking was performed before, 3 month, 6 month and 1 year after RFCA. Patients were divided into 2 groups (Group 1: maintenance of sinus rhythm; Group 2: recurrent AF during 1 year follow-up) for analysis.

Results: Group 1 was 31 patients (68.9%) and 15 patients (31.1%) were Group 2. At baseline, LA longitudinal strain (LAS) were lower in Group 2 than Group 1. But other parameters were not different between both groups. After RFCA, diminution of LAVI was seen during initial 3 months FU and then it was maintained for 1 year, in Group 1. But, LA functional parameter of LAeF and LAS were gradually increased during 1 year FU, in Group 1. However, in Group 2, LA size and LA function were not changed during FU (Fig. 1). And the change of LAVI during 3month after RFCA was independently related with AF recurrence at 1 year by multivariate analysis (Odd ratio: 0.603, P=0.017).

Figure1. The changes of left atrial volume and function



Conclusion: Reverse structural and functional remodeling of LA occurs after successful RFCA, but time sequence was different. And the magnitude of LA structural remodeling at 3 month after RFCA was related with the maintenance of SR. Therefore, the assessment of LA size at 3 months after RFCA appears to have a good prognostic importance.

P2434 | BEDSIDE

Cryoballoon vs. radiofrequency ablation of paroxysmal atrial fibrillation: no impact of pulmonary vein anatomy in midterm procedural success

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Background: Pulmonary vein (PV) electrical disconnection is the mainstay of treatment in catheter ablation of paroxysmal atrial fibrillation (PAF). Cryoballoon (CRYO) ablation has been introduced in more recently than radiofrequency (RF) ablation, the standard technique in most centers, and head-to-head studies assessing sinus rhythm maintenance beyond 12 months are currently very scarce. PV frequently display anatomic variants (left common trunk at and right supernumerary veins), which are thought, according to some authors, to compromise the results of CRYO.

Methods: Single-centre study, comprising 614 consecutive pts undergoing a first procedure of PAF ablation (CRYO = 287 and RF = 327 pts). Comparisons between CRYO and RF ablation were performed concerning safety and efficacy endpoints during a 12 median follow-up (IQR = 7-19).

Results: Baseline characteristics (age, gender prevalence, body mass index, AF duration, left atrial volume, left ventricle ejection fraction, CHADS2 and HAS-BLED) did not differ between groups. No differences were found regarding the number of PV at left (1.8±0.4 RF vs 1.8±0.4 CRYO; p=0.17) and right (2.2±0.5 RF vs 2.2±0.4 CRYO; p=0.10). CRYO pts presented more relapses during hospitalization (4.9% vs 9.1%; P=0.04), but use of class I or III anti-arrhythmic agents was similar (15.0% vs 16.4%; p=0.37). However, no differences were found during the 3 months blanking period (14.4% RF vs 16.7%; p=0.10) and at mid-term (18.3% RF vs 17.8% CRYO; log rank p=0.25). Complication rate was similar, except for phrenic palsy that was more frequent in CRYO (2.4% vs 0.3%; p=0.02). We observed no interaction of PV anatomy on mid-term procedural success: presence of a left common pulmonary trunk (log rank p=0.30); presence of right supernumerary veins (log rank p=0.33).

Conclusions: The cryoballoon performed similarly, at mid-term, to radiofrequency ablation of PAF in all different PV anatomic subsets. The presence of PV anatomic variants should not discourage the referral of patients for cryoablation of PAF.

P2435 | BEDSIDE

Radiation exposure in pulmonary vein isolation for paroxysmal atrial fibrillation: a comparison between cryoballoon ablation and 3D-mapping guided radiofrequency ablation

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Background: The new development of radiology-based ablation techniques renders radiation exposure an important issue in cardiac electrophysiology. Aim of the study was to evaluate the radiation exposure of cryoballoon ablation compared to the 3D-mapping guided irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation (AF) undergoing first pulmonary vein isolation (PVI).

Methods: A total of 36 consecutive patients with paroxysmal AF who underwent first PVI at our clinic between December 2012 and November 2013 were analyzed. 17 patients underwent cryoballoon ablation and 19 patients irrigated radiofrequency ablation. Radiofrequency ablation was guided by the three-dimensional navigation system NavX. Patients who needed additional lines or substrate modification were excluded.

Results: Baseline characteristics were not different between both groups (Table 1). Complete PVI could be achieved in all patients. No severe adverse event occurred in both groups.

Table 1. Clinical characteristics and ablation details of patients undergoing first PVI due to paroxysmal AF

	Cryoballoon (n=17)	Irrigated RF + 3D mapping (n=19)	p-value
Age (years)	63 (50-67)	64 (52-73)	n.s.
Female	53%	53%	n.s.
BMI (kg/m ²)	26 (23-33)	26 (24-30)	n.s.
Radiation dose (cGy·cm ²) for:			
- catheter placement	10 (10-30)	10 (0-30)	n.s.
- transeptal puncture	90 (30-135)	60 (30-150)	n.s.
- geometry	n.a.	10 (7-25)	
- ablation	280 (150-425)	5 (2.5-17)	0.01
Ablation time (sec)	2100 (1920-2490)	1950 (1785-2535)	n.s.
Total fluoroscopy time (min)	18 (14-22)	8 (7-14)	0.001
Total radiation dose (cGy·cm ²)	380 (190-590)	85 (50-220)	0.01

Conclusions: In PVI using cryoballoon ablation the total fluoroscopy time is twofold and the total radiation dose 4 times increased compared to the 3D-mapping guided irrigated radiofrequency ablation. The higher fluoroscopy time and dose in cryoballoon ablation derives from the ablation procedure when fluoroscopy is needed to verify the occlusion of the pulmonary veins before ablation.

P2436 | BENCH**Reduction of radiation exposure in cryoballoon ablation procedures: a single center study applying intracardiac echocardiography and other radio-protective measures**

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Purpose: Cryoballoon (CB) ablation has been widely adopted as a valuable alternative technique in pulmonary vein isolation (PVI) for paroxysmal atrial fibrillation (PAF). The population treated is relatively young and radiation protection is of major importance. We aimed to demonstrate that radiation exposure can be markedly reduced by intracardiac echocardiography (ICE) and optimized settings of the X-ray system.

Methods: A total of 140 patients were studied. In 57 consecutive patients (31 male, 58±14 years, BMI 26.7±4.2 kg/m², LA 38±6 mm, LVEF 54.9±0.7) (group 1) undergoing CB PVI for treatment of PAF ICE was applied for transseptal puncture, confirmation of PV occlusion, guidance of wires, mapping catheters and CB and monitoring of complications. PV angiography prior to CB inflation was skipped. Thereby, fluoroscopy was avoided whenever possible. During fluoroscopy a reduced frame rate (3/s instead of 7.5/s) was chosen, distance of patient and detector was kept minimal and collimation was consequently applied. The "Care Position" functionality (Siemens, Forchheim, Germany) was used to avoid fluoroscopy during table movements. Patients from group 1 were compared to 73 similar preceding consecutive patients (45 male, 61±12 years, BMI 26.5±3.8 kg/m², LA 40±6 mm, LVEF 55±3%) (group 2).

Results: No complications occurred. Total fluoroscopy time could be reduced from 18.7±6.2 to 12.1±5.5 s ($p<0.0001$). Radiation exposure was 1652±1265 $\mu\text{Gy}\cdot\text{m}^2$ in group 1 compared to 5134±2451 $\mu\text{Gy}\cdot\text{m}^2$ in group 2 ($p<0.0001$). Total procedure times were 108.7±23.1 min in group 1 compared to 107.0±25.6 min in group 2 ($p=\text{n.s.}$). While total freezing time could be reduced from 2126±706 to 1874±414 s ($p=0.01$). At 6 month follow-up 74.5% vs. 84.1% ($p=0.26$) were free from recurrences, more patients in group 1 were followed using implantable devices (23 vs. 7%; $p=0.01$).

Conclusion: Radiation exposure in CB PVI could be markedly reduced without prolonging procedure times or affecting the outcome. Moreover, ICE seems to reduce total freezing times.

P2437 | BEDSIDE**Relationship between left atrial appendage morphology and recurrences of atrial fibrillation after radiofrequency catheter ablation**

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Background: The previous studies have shown that left atrial appendage (LAA) remodeling (dilatation, stretching, and reduction in pectinate muscle volume, as well as endocardial fibroelastosis) occurs frequently in long-standing AF. The anatomical characteristics of the LAA and its relationship with recurrences of AF after radiofrequency catheter ablation (CA) have not been established.

Objective: The aim of this study was to investigate whether the morphological features of the LAA predict AF recurrences after CA.

Methods: We studied 230 AF patients who underwent a successful CA and CT (mean age, 60.4±0.5 years; 99 women; paroxysmal/persistent=134/96). Extensive encircling pulmonary vein isolation and cavo-tricuspid isthmus bidirectional block procedures were performed initially and, if needed, additional ablation lines were created in the LA, such as a roof line, perimitral isthmus line or anterior line, or ablation of complex fractionated atrial electrograms. The AF recurrences were examined during a mean follow-up period of 657.6±319.9 days. According to the previous reports, the LAA morphology was classified into 4 types: Cactus, Cauliflower, Chicken Wing, and Windsock.

Results: The prevalence of Cactus, Chicken Wing, Windsock, and Cauliflower types was 25 (10.9%), 145 (63%), 15 (6.5%), and 45 (19.6%), respectively. Among the 72 patients who had AF recurrences, the prevalence of each type of LAA morphology was a Cactus in 9 (36%), Chicken Wing in 37 (25.5%), Windsock in 7 (46.7%), and Cauliflower in 19 (42%), respectively. The AF recurrences were found more frequently in patients with non-Chicken Wing morphologies (Group A; 41.1%) compared to those with the Chicken-Wing category (Group B; 25.5%; $p=0.03$). A multivariate Cox proportional hazards regression analysis revealed that the chicken LAA morphology (Hazard ratio (HR)=0.621, 95% confidence interval (CI): 0.391-0.987, $p=0.044$), the LA diameter (HR=1.04, 95% CI: 1.008-1.081, $P=0.017$), and paroxysmal AF (HR=0.449, 95% CI: 0.279-0.721, $P<0.001$) were associated with AF recurrences after CA. In group A, the prevalence of a previous TIA/stroke ($p=0.002$) and a smoke like echo ($p=0.027$) were greater than that in group B.

Conclusions: Determination of the LAA morphologies might be useful for predicting AF recurrences.

P2438 | BEDSIDE**Watchman LAA occlusion combined with catheter ablation is feasible in AF patients with high stroke risk and a contraindication for anticoagulation**

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Purpose: Catheter ablation (CA) often relieves symptoms in drug-refractory atrial fibrillation (AF), but freedom of AF is never certain. Oral anticoagulation therapy (OAC) remains warranted in high stroke risk patients even after CA. Left atrial appendage (LAA) occlusion (LAAO) is a viable alternative for prevention of thromboembolic complications in patients with 1 or more stroke risk factors. We describe a series of 64 patients where LAAO was combined with CA in one single procedure.

Methods: Symptomatic patients with drug-refractory AF (CHA2DS2-VASc ≥ 1) and contraindication(s) for OAC were included. A pre-procedure TEE was performed to assess LAA size and anatomy, and exclude thrombus or structural cardiac abnormality. All procedures were accomplished under general anaesthesia and TEE guidance. Phased RF multi-electrode CA was carried out; PVAC PVI in PAF, and additional MASC&MAAC CFAE ablation in PersAF. After CA, LAAO was performed using the Watchman device. CA was performed under therapeutic INR and OAC was maintained the first 3 months, unless there was an absolute contraindication for OAC in which case LMWH was used for 2 weeks, followed by Aspirin and Clopidogrel. At 3 months, OAC was switched to Aspirin if LAAO criteria were met on TEE. Rhythm follow-up was performed with serial ECG in all, and Holter recording at the physician's discretion.

Results: From Sept 2009-Oct 2013, a total of 64 patients (23 female, mean age 64±8 years) underwent CA (PVI only in 45, PVI+CFAE in 19 patients) combined with LAAO. The median CHA2DS2-VASc score was 3 (range 1-7). OAC contraindications were history of stroke under OAC (52%), major bleeding under OAC (14%), combination of stroke and major bleeding under OAC (9%), preference to stop OAC (20%), or other (5%). Watchman LAAO was performed with complete acute occlusion in all, with a median number of 1 device (range 1-3). The mean total procedure time was 97±24 min, with additional 38±20 min for LAAO. Adverse events during 60 day follow-up included 1 procedural major groin bleeding, and 1 device embolisation with successful groin extraction. TEE at 60 days showed that 86% of patients met all criteria for successful sealing (residual flow <5 mm), allowing them to discontinue OAC. In the remaining patients, OAC was maintained if possible until LAAO was accomplished later. Complete 1 year follow-up in 41 patients showed a stroke rate of 0%.

Conclusion: LAAO combined with CA for AF can be performed successfully and safely in one single procedure, with favourable effect on stroke occurrence during 1 year follow-up.

P2439 | BEDSIDE**Effect of obstructive sleep apnea on sinus rhythm maintenance in patients after ablation for paroxysmal atrial fibrillation**

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Purpose: Obstructive sleep apnea (OSA) is a sleep disorder affecting many patients with atrial fibrillation (AF). OSA contributes negatively to natural history of AF, patients' risk profile and prognosis. The aim of this study was to assess the relationship between OSA and sinus rhythm maintenance in patients after ablation for paroxysmal AF.

Methods: We enrolled 186 consecutive patients admitted to our department for paroxysmal AF ablation. Prior to the ablation procedure all patients, in addition to standard work-up, underwent a whole-night polygraphy sleep study for the diagnosis of OSA. After the procedure all patients were followed up for mean time of 36 months for the reoccurrence of AF, which was diagnosed when AF was detected in 24-hour ECG Holter monitoring, and/or when a patient reported symptoms of AF. OSA positive patients were those with apnea-hypopnea index of ≥ 5 per hour. Patients were subsequently divided into groups according to the OSA severity: mild OSA was defined as AHI between 5 and 15, moderate OSA was AHI of >15 and ≤ 30 per hour, and AHI >30 per hour was the criterion for severe OSA.

Results: After excluding patients disqualified from procedure, and those with central sleep apnea, the study population consisted of 176 patients (113 (64.2%) males, mean age 58.0 years). OSA was present in 73 (41.4%) patients, while in 90 (51.1%) cases we observed reoccurrence of AF. It was more often in patients with, than without OSA (61.1% vs. 44.2%; $p=0.03$). We also observed that the number of patients in whom AF was detected during the follow up period depended on severity of OSA (44.2% vs. 60.9% vs. 60.0% vs. 71.4%; p for trend 0.005; for non-OSA, mild, moderate and severe OSA respectively).

Conclusions: OSA is highly prevalent in patients with AF. Occurrence of OSA lowers chances on successful AF ablation. Early screening, and treatment for OSA in AF patients, may improve low success rates of AF ablation procedure.

P2440 | BEDSIDE**Drastically decrease of left atrial pressure in patients with hypertrophic cardiomyopathy by catheter ablation for atrial fibrillation**

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Purpose: Atrial fibrillation (AF) refractory to medical therapy in hypertrophic cardiomyopathy (HCM) patients deteriorates the clinical status. Outcomes of radiofrequency catheter ablation (RFCA) for AF in HCM patients are controversial. We investigated the efficacy and acute hemodynamic effects of RFCA for AF in HCM patients.

Methods: We consecutively enrolled drug-refractory AF patients with HCM (HCM group, n=15) and without HCM (NHCM group, n=106). Extensive encircling pulmonary vein isolation (EEPVI) and bidirectional cavotricuspid isthmus block were performed in all patients. Left atrial (LA) pressures were measured using hemodynamic catheterization just after the trans-septal puncture and after completion of EEPVI (Pre- and post-LA pressures). We compared clinical parameters, echocardiographic parameters, electrophysiological parameters, LA pressures and recurrence rate in the both groups.

Results: The pre-LA pressures were significantly higher in the HCM group than in the NHCM group (the mean pre-LA pressure: 15.8 ± 4.8 mmHg vs. 11.5 ± 3.3 mmHg, $p < 0.01$). Post-LA pressures in the HCM group significantly decreased, and became similar to those in the NHCM group (Figure). No significant difference in the rate of early recurrences (within 30 days after ablation) was observed between the HCM and NHCM groups (20% vs. 5.7%, $p = 0.08$). The rate of late recurrences (>30 days after ablation; LRs) was also similar in the both groups during a mean 436 ± 282 days follow-up periods (LRs: 6.7% vs. 7.6%, $p = 0.83$).

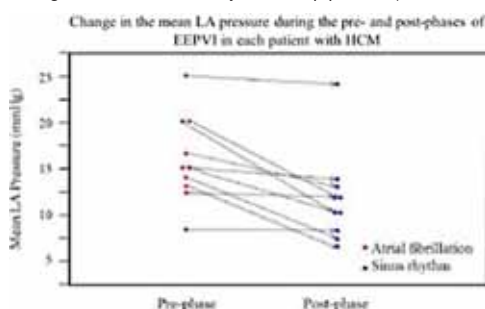


Figure 1

Conclusions: The LA pressure in the HCM group drastically decreased immediately after the EEPVI. The RFCA of AF was effective and safe for restoring long-term sinus rhythm and should be considered a therapeutic option in HCM patients.

BASIC AND ELECTROPHYSIOLOGIC MECHANISMS IN ATRIAL FIBRILLATION

P2442 | BEDSIDE**Circulating serum levels of growth differentiation factor-15 and neuregulin-1 in patients with paroxysmal non-valvular atrial fibrillation**

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Purpose: Growth differentiation factor-15 (GDF-15) and neuregulin-1 (NRG-1) are novel diagnostic and prognostic biomarker for several cardiovascular diseases. However, the potential role of these biomarkers in patients with non-valvular atrial fibrillation AF is not known. We aim to evaluate if patients with paroxysmal non-valvular AF have a higher circulating serum GDF-15 and NRG-1 compared to control subjects.

Methods: We enrolled 67 consecutive patients with paroxysmal AF and 67 subjects without AF as controls matched for sex, age and atherosclerotic risk factors that presented to our hospital between August 2012 and June 2013. All subjects underwent electrocardiogram and echocardiographic exam. Serum levels of GDF-15 and NRG-1, superoxide dismutase (SOD), catalase (CAT), high-sensitivity C-reactive protein (hs-CRP) were measured in every patient.

Results: No significant difference in the serum levels of SOD, CAT and hs-CRP were found between two groups. GDF-15 was significantly higher in patients with paroxysmal AF than controls (1473.14 ± 628.52 vs 1233.592 ± 262.76 pg/ml, $P < 0.05$). Likewise, patients with paroxysmal AF had higher levels of NRG-1 compared to controls (14.15 (8.55-21.00) vs. 10.29 (5.36-16.73) ng/ml, $P < 0.05$). Multivariable analyses demonstrated that baseline values of serum GDF-15 was independently associated with paroxysmal AF (OR: 1.002, 95%CI: 1.000-1.003, $P < 0.05$). NRG-1 was not independently associated with paroxysmal AF.

Conclusions: We demonstrated an association between increased serum GDF-15 and NRG-1 levels and AF, however, only GDF-15 was an independent biomarker for paroxysmal AF in the multivariable analyses. Undoubtedly, larger

studies are needed to further examine this potential association as well as the underlying mechanisms.

P2443 | BEDSIDE**Hemodynamic, haemostatic and genetic aspects of ischemic stroke in patients with atrial fibrillation**

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Purpose: To evaluate hemodynamic, haemostatic indicators and genetic polymorphisms associated with the risk of ischemic stroke in patients with atrial fibrillation.

Methods: Studied were 100 patients with ischemic heart disease and permanent atrial fibrillation, mean age - 62 ± 7.6 years. All the patients were divided into three groups: 1 group comprised 30 patients with a CHA2DS2-VASc score of 1; 2 group - 40 patients with a CHA2DS2-VASc score of 2; 3 group - 30 patients with a CHA2DS2-VASc score more than 2. Patients of all groups were age and sex matched. All the patients underwent transthoracic and transesophageal echocardiography. We evaluated haemostatic indicators such as thrombin activatable fibrinolysis inhibitor (TAFI), fibrinogen, antithrombin, soluble fibrin-monomer complexes (SfMC), ADP-platelets aggregation and genetic polymorphisms of cytochrome P450 2C9 (CYP2C9), vitamin K epoxide reductase complex subunit 1 C1173T, G3730A and plasminogen activator inhibitor - 1 4G(-675)5G

Results: The increasing of CHA2DS2-VASc score was associated with an increase of TAFI ($R = 0.42$; $p = 0.0001$), antithrombin ($R = 0.27$; $p = 0.01$) levels, ADP-platelets aggregation activity ($R = 0.37$; $p = 0.0002$) and left atrial dimension ($R = 0.5$; $p = 0.0001$); with a decrease of left atrial appendage peak emptying flow velocity ($R = 0.32$; $p = 0.002$) and also with the presence of CYP2C9*1 genotype ($R = 0.42$; $p = 0.00002$). Discriminant analysis showed that TAFI and CYP2C9*1 genotype had the largest contribution in risk stratification of ischemic stroke development with F-criteria of 12.9 and 6.1 respectively.

Conclusion: In patients with permanent atrial fibrillation the increasing of CHA2DS2-VASc score is accompanied by an increasing of anticoagulant and platelets aggregation activities, hypofibrinolysis, left atrial appendage hemodynamic impairment and the presence of genotype CYP2C9*1.

P2444 | BEDSIDE**Epicardial adipose tissue volume predicts atrial fibrillation recurrence after pulmonary vein isolation**

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Purpose: Obesity is an established risk factor for atrial fibrillation (AF). It has been proposed that epicardial adipose tissue (EAT) might play a key role in promoting arrhythmogenesis due to its pro-inflammatory properties and anatomical proximity to myocardium. The aim of this study was to investigate the relationship between EAT volume and clinical characteristics and recurrence of AF.

Methods: Epicardial fat volume was measured using computed tomography prior pulmonary vein isolation (PVI). Patients were divided into two groups according to their AF severity: 74 patients (age 56 ± 11 yr, 60 male) had paroxysmal AF and 28 patients (age 57 ± 10 yr, 25 male) had persistent AF. Echocardiographic parameters and C-reactive protein (CRP) levels were also assessed. Patients were followed for 3 months for AF recurrence.

Results: In comparison to patients with paroxysmal AF, patients with persistent AF had significantly higher EAT volume (109.9 ± 47.7 vs 88.1 ± 37.9 cm³, $p = 0.02$). Epicardial fat volume correlated with BMI ($\rho = 0.54$, $p < 0.001$), left atrium long axis diameter ($\rho = 0.31$, $p = 0.002$) and CRP levels ($\rho = 0.29$, $p = 0.003$). After 3 months follow-up AF recurrence was observed in 26% of patients. Total EAT was significantly greater in patients relapsing into AF than in those who maintained sinus rhythm (115.8 ± 38.2 vs 86.6 ± 38.2 cm³, $p = 0.002$). Importantly, total EAT volume was predictive of 3 months AF recurrence after PVI (RR = 1.01, 95% CI: 1.001 to 1.018, $p = 0.018$).

Conclusion: Epicardial fat is associated with AF severity, LA diameter and AF recurrence after ablation. This suggests a local effect of epicardial fat tissue on the arrhythmogenic substrate promoting AF. Interventions targeting epicardial adipose tissue may be beneficial.

P2445 | SPOTLIGHT**Flow-mediated dilation is associated with cardiovascular events in non-valvular atrial fibrillation patients**

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Purpose: Atrial fibrillation (AF) is associated with multiple atherosclerotic risk factors and predisposes to cardiovascular events (CVE). Endothelial dysfunction is associated with atherosclerosis and independently predicts CVE. Aim of the study was to evaluate the association between endothelial dysfunction as assessed by flow-mediated dilation (FMD) and CVE in AF patients.

Methods: We prospectively measured FMD in 514 non-valvular AF patients on anticoagulant treatment with vitamin K antagonists. Patients were followed-up for a mean time of 23.5 months. The main composite outcome of the study was the occurrence of ischemic events in the coronary and cerebral circulation.

Results: Mean value of FMD was $5.08 \pm 4.33\%$. A CVE occurred in 44 patients (8.56%): non-fatal myocardial infarction (MI) in 7, fatal MI in 2, stent/coronary artery by-pass graft (CABG) in 10, ischemic non-fatal stroke in 9, fatal stroke in 3, transient ischemic attack (TIA) in 1, and cardiovascular deaths in 12. Patients who experienced a CVE showed a significantly reduced FMD compared to those who did not (3.88 ± 3.62 vs 5.21 ± 4.38 , $p=0.019$). After dividing population in two groups, above and below the median value of FMD, an increased rate of CVE was observed in patients with impaired FMD ($p=0.006$). At multivariable analysis, impaired FMD (HR 2.19 CI 95% 1.18-4.08, $p=0.013$), age (HR 1.07 CI 95% 1.02-1.11, $p=0.001$), history of MI/CABG (HR 2.14 CI 95% 1.14-3.99, $p=0.017$) and history of stroke/TIA (HR 2.21 CI 95% 1.08-4.52, $p=0.030$) predicted CVE.

Discussion: AF patients suffer from impaired artery dilatation. Reduced FMD is associated with increased risk of CVE suggesting that impaired artery dilation predisposes to atherosclerotic complications.

P2446 | BEDSIDE

Atrial late potentials and atrial substrate remodeling in patients with atrial fibrillation

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Background: Patients with atrial fibrillation (AF) often have a low-amplitude potential in the terminal part of filtered P-wave (atrial late potential: aLP). However, it remains unknown what aLP reflects in AF patients. On the other hand, electrical remodeling of the atria can be precisely evaluated by the quantitative voltage map analysis using 3D mapping system. In this study, we hypothesized that we could substitute "non-invasive" aLP for "invasive" 3D mapping system to evaluate the atrial electrical remodeling and investigated the relationship between aLP and atrial substrate remodeling in AF patients.

Methods: The P-wave single-averaged electrocardiogram (P-SAECG) was recorded in 45 patients with paroxysmal AF who underwent PV isolation. Filtered P-wave duration (fPWD) and root-mean-squared voltage of the terminal 20ms of $\leq 2.0 \mu V$ (RMS20) were assessed by P-SAECG. The left atrial (LA) global contact mapping during sinus rhythm was performed and LA voltage zone index (LAVZI) was defined as an area with voltage $<0.5mV$ divided by total LA surface area.

Results: LAVZI showed a strong positive correlation with fPWD and a strong negative correlation with RMS20 ($r=-0.82$, $p<0.01$; $r=0.68$, $p<0.01$, respectively). LV volume by echocardiography was also positively correlated with fPWD and negatively correlated with RMS20 ($r=0.57$, $p<0.05$; $r=-0.69$, $p<0.01$, respectively). In addition, LA appendage flow was negatively correlated with fPWD ($r=-0.49$, $p<0.05$). fPWD was significantly longer and RMS20 was lower in patients with AF for more than 1 year than those for less than 1 year. However, there were no significant correlations between aLP parameters and other echocardiographic findings such as left ventricular ejection fraction or plasma BNP concentration.

Conclusions: aLP reflects precisely atrial substrate remodeling in AF patients. aLP might serve as non-invasive tool for monitoring the atrial substrate remodeling in patients with AF.

P2447 | BENCH

Atrial fibrillation impairs ventricular mitochondrial function

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Purpose: While it has been shown that induction of AF depresses left ventricular function, the characterisation of the responsible underlying cellular and molecular mechanisms remain uncertain. In particular, we hypothesized that irregular ventricular activation (ie R-R interval variation) plays a central role, possibly via effects on mitochondrial function given the role of mitochondrial dysfunction in heart failure. The aim of this study was to evaluate the effects of irregular R-R interval on ventricular gene expression, mitochondrial function and physiology.

Methods: Irregular or regular pacing with the same average rate (7Hz x 30 min) was performed in Langendorff perfused mouse hearts followed by mitochondrial isolation and functional analysis (Seahorse XF analyser) and quantitative immunoblotting. In addition, irregular or regular atrial pacing was conducted for 30 min in an ovine model.

Results: Acute irregular pacing in isolated mouse hearts caused a significant reduction in systolic (dP/dtmax: mmHg/s 4495 ± 242 vs. 3635 ± 228 ; regular vs. irregular pacing; $p<0.05$) and diastolic function (dP/dtmin: mmHg/s -2468 ± 214 vs. -2244 ± 229 ; regular vs. irregular pacing; $p<0.05$). Mitochondria from irregularly paced hearts demonstrated a significant reduction in oxygen consumption rate (OCR) at maximal respiration (451.5 ± 51.5 vs. 272.2 ± 22.4 pmol/min; control vs. irregular paced; $p<0.05$). The mitochondrial spare respiratory capacity was also reduced in irregular paced heart (141.3 ± 53.3 vs. -0.25 ± 27.5 pmol/min; control vs. irregular; $p<0.05$). Consistent with the mouse studies, short term irregular pacing in sheep also reduced left ventricular contractility (+dP/dtmax, pre 2295 ± 830 vs post 1030 ± 114 mmHg/s, $p<0.05$) and reduced relative phosphorylation of phospholamban (cont 1.12, paced 0.9 ADU, $p<0.05$).

Conclusions: Irregular ventricular rhythm in the context of AF induces fundamental changes in mitochondrial function and significant gene expression changes of key proteins involved in calcium handling. As such, AF induced depression of mitochondrial function would be expected to accentuate the progression of HF. The precise mechanism of AF induced mitochondrial dysfunction requires further investigation.

P2448 | BEDSIDE

Fibrillatory pattern of dissociated pulmonary venous activity is the novel characteristics of the triggering ectopy for atrial fibrillation

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Background: Pulmonary veins (PVs) play an important role in the arrhythmogenesis of atrial fibrillation (AF). Rapidly firing ectopic foci in PVs have been shown to be the triggers for AF. Radiofrequency (RF) energy ablation can be delivered at the PV ostium with the endpoint of distal PV disconnection. After PV isolation, isolated intrinsic ectopic beats are sometimes recorded on circular mapping catheter. This dissociated PV activity (DPVA) could be the remaining foci of atrial ectopies, which has not been demonstrated.

Objective: We hypothesized that DPVA was the trigger ectopy and examined the concordant ratio of the localization and pattern of DPVA with those of trigger ectopy. The localization was determined among 4PVs. The pattern was determined as (1) isolated ectopic beats, (2) regular ectopic rhythm, or (3) fibrillation.

Method and results: This is a single center prospective study. We defined trigger ectopy as the documented ectopic foci that spontaneously initiated AF during ablation. Consecutive 110 patients (82 paroxysmal and 28 persistent AF) undergoing AF ablation were enrolled. DPVA was recorded using a multielectrode mapping catheter. All PVs were successfully isolated in all patients. Among 440 isolated PVs, we recognized trigger ectopies in 73 (17%) PVs (culprit PVs) and isolated activities in 184 (42%) PVs. Culprit PVs had DPVA more frequently than non-culprit PVs (59% vs. 38%, $p<0.001$). The pattern of DPVA was isolated ectopic beats (31%), regular ectopic rhythm (62%), or PV fibrillation (7%); and 29% of isolated ectopic beats, 16% of regular ectopic rhythm, and 71% of PV fibrillation were determined as trigger ectopy. Therefore, the concordant ratio between DPVA and trigger ectopy was the highest in PV fibrillations ($p<0.001$). In other words, fibrillatory DPVA was frequently observed in culprit PV but non-fibrillatory DPVA was not.

Conclusions: Fibrillatory DPVA was strongly associated with trigger ectopy. PV with fibrillatory DPVA after isolation would have high probability of being culprit PV of AF.

P2449 | BENCH

Identification of microRNA-mRNA dysregulations that drive the development of atrial fibrillation

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Purpose: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, yet there are no effective pharmacologic treatments, underscoring a lack in the current understanding of the molecular mechanisms of AF. Using atrial samples from patients with paroxysmal AF (pAF) or in normal sinus rhythm (SR), we performed state-of-the-art transcriptomic studies in order to test the hypothesis that early molecular changes in pAF lead to microRNA (miRNA)-mRNA dysregulations which further drives AF progression.

Methods: High quality total RNA including miRNA was isolated from atrial biopsies of age-matched and sex-matched pAF and SR patients (n=4-5 per group). The average time before last episode of AF in the pAF group was 2 days. A portion of the RNA was used for miRNA microarray while another portion from the same or similar samples was used for RNA-sequencing. Putative targets of miRNAs were searched using TargetScanHuman6.2 while functional annotation clustering was performed using DAVID.

Results: RNA-sequencing identified 177 genes that are differentially expressed in pAF patients ($P<0.05$), including some involved in immune response. Meanwhile, miRNA microarray identified 49 miRNAs that are both differentially expressed ($P<0.1$) and highly abundant (signal>500) in pAF patients, including a number of newly discovered miRNAs. The predicted targets of these miRNAs were searched against the list of 177 differentially expressed genes from RNA-sequencing. The intersecting genes were further filtered for those that changed in the expected direction (opposite from the miRNA changes), yielding 27 pairs of miRNA-mRNA regulations (consisting of 17 miRNAs and 21 mRNAs) that are altered in pAF versus SR patients. Functional annotation clustering revealed an enrichment of genes involved in transcriptional regulations (Enrichment Score = 0.31), consistently with the notion that miRNA-mRNA dysregulations drive further transcriptional changes. Since most of these differentially regulated miRNA-mRNA pairs have not been previously studied, a few of them were selected for validation using quantitative real-time (qRT)-PCR and 3'UTR luciferase reporter assay.

Conclusions: To the best of our knowledge, this is both the first transcriptomic analysis and miRNA microarray study using samples from pAF patients. By intersecting results from these two parallel studies, we provide novel insights into

the miRNA-mRNA regulations that may drive the progression of AF to more persistent forms, via transcriptional dysregulations. This may open new avenues of investigation into AF pathogenesis and the development of novel therapeutics.

P2450 | BEDSIDE

The role of preoperative administration of L-carnitine in the prophylaxis of post CABG atrial fibrillation

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Purpose: Atrial Fibrillation (AF) is one of the most common complications in patients who undergo coronary artery bypass grafting (CABG) surgery. The reported incidence of postoperative AF ranges from 25% to 40% post-CABG. AF can cause atrial pump dysfunction resulting in ventricular filling impairment with an increase in the incidence of heart failure and development of stroke, thus contributing to the rise of post-CABG disability and mortality. The aim of this study was to evaluate the effect of L-carnitine administration on postoperative AF following CABG surgery.

Methods: Two hundred and fifty patients undergoing elective CABG surgery, without history of AF or previous L-carnitine treatment, were enrolled and randomly assigned to a L-carnitine group (L-carnitine 3000 mg/d, n=125) or a control group (Placebo, n=125) starting 2 days preoperatively and continuing for 2 days after surgery. The primary endpoint was the occurrence of postoperative AF. C-reactive protein (CRP) levels were assessed in all patients by means of high sensitive CRP kits before surgery as baseline levels and 48 hours postoperatively.

Results: The incidence of AF was 13.4% in our population. L-carnitine significantly reduced the incidence of postoperative AF (7.5% in L-carnitine group versus 19.4% in placebo; $P=0.043$) and postoperative CRP level versus placebo (8.79 ± 6.9 versus 10.83 ± 5.7 ; $P=0.021$)

Comparison of patients' demographic data

Variable	Case	Control	P value
Sex	54	45	0.077
Male	13	22	
Age (y)	60.01 ± 9.23	59.88 ± 7.98	0.185
Ejection fraction%	45.37 ± 8.80	42.83 ± 10.19	0.126
Family history Yes	31.3%	53.7%	0.009
Diabetes mellitus Yes	34.3%	41.8%	0.374
Hypertension Yes	62.7%	59.7%	0.723
Hyperlipidemia Yes	52.2%	47.8%	0.604
Previous MI Yes	18.2%	22.4%	0.547

Conclusion: Our study revealed that L-carnitine administration before CABG surgery may inhibit and reduce the incidence of post-CABG AF and so its complications.

P2451 | BENCH

Exploring the role of Pitx2 and candidate genes in human and murine atrial tissue

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Genome-wide association studies (GWAS) have found polymorphic loci on Chromosome 4q25 that associate with atrial fibrillation (AF). The closest gene to these loci is the Paired-like homeodomain transcription factor 2 (Pitx2). Pitx2c is the predominant isoform in the heart. We have shown that heterozygous Pitx2c+/- mice are more susceptible to AF and that Pitx2c is more highly expressed in the left atrium (LA) than the right atrium (RA) in mice and patients. We measured mRNA and protein expression levels of candidate genes generated by gene arrays in Pitx2+/- mouse atria, in human and murine atrial tissue.

We studied LA and RA from 36 mice (18 Pitx2c+/-, 18 littermate WT, 14-20 weeks) and from patients in sinus rhythm (n=7), chronic (n=13) and paroxysmal AF (n=13), all undergoing open heart surgery (CABG or valve surgery, mean age 70). Transcript levels of candidate genes were quantified by RT-PCR and protein levels were quantified by western blot relative to calnexin protein expression. LA mRNA levels of Ccl21, Ddit4l, Phlda1, Ppp1r1b, Scara5, Tnni2, and Cxcl14 were higher than RA in WT and Pitx2c+/- mice. Ccl21 and Ddit4l mRNA was lower in Pitx2c+/- LA compared to WT LA ($p=0.0098$, $p=0.0385$, respectively). In patients, Ccl21 and Pitx2c mRNA was higher in LA than RA of SR, chronic AF and paroxysmal AF groups (Ccl21 $p=0.000$, $p=0.001$, $p=0.014$; Pitx2c $p=0.017$, $p=0.000$, $p=0.000$; respectively). Further, Ddit4l and Ppp1r1b were expressed at lower levels in the LA of patients with chronic AF compared to those in SR (Ddit4l $p=0.044$, Ppp1r1b $p=0.008$); Ccl21 was expressed at lower levels in the LA of patients with AF compared to the LA of patients in SR ($p<0.05$).

PITX2 protein levels in mice were higher in LA than RA ($p=0.005$; 8 WT and 8 Pitx2c+/-). Genotype affected Pitx2 mRNA, but not protein expression in mice. Human PITX2 protein expression in LA and RA was heterogeneous and was neither related to SNP status of rs2200733 and rs6838973, nor different in LA and RA.

RT-PCR confirms differential expression of several genes downstream of Pitx2, including a left-right difference of gene expression. PITX2 protein is higher in LA than RA in mice, but in human atria PITX2 protein levels are unrelated to mRNA levels. Pitx2 mRNA could therefore exert its regulatory effects in the heart by direct (e.g. miRNA) regulation of RNA expression. Ccl21 emerges as a potentially important protein regulated by Pitx2 in mouse and human atria. These findings need further investigation, including the assessment of protein levels of candidate genes.

ELECTROPHYSIOLOGIC INSIGHT IN CLINICAL ELECTROPHYSIOLOGY

P2453 | BEDSIDE

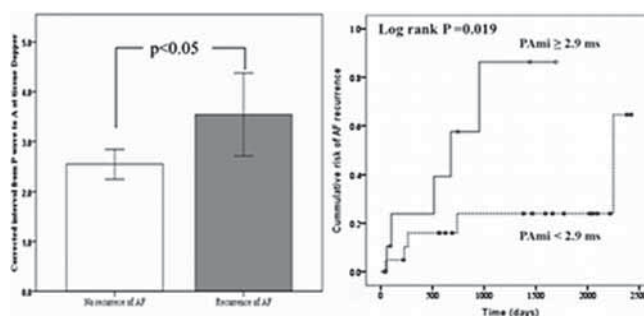
Atrial electro-mechanical conduction time could predict the recurrence of atrial fibrillation

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Back ground: A prolonged total atrial conduction time may reflect the electro-anatomical substrate for atrial fibrillation (AF). The aim of this study is that a total atrial conduction time can predict the recurrence of AF after attack of paroxysmal AF.

Methods: Thirty five patients (mean age 48.9 yrs, 21 women) who were diagnosed as paroxysmal AF enrolled. Those patients with more than 65 years, thyroid disease, low EF (<50%) and prior anti-arrhythmic agent medication were excluded. A total atrial conduction time was assessed by transthoracic echocardiography following sinus conversion. The total atrial conduction time was determined as the time interval from beginning of P-wave to initiation and peak of the late diastolic wave in the mitral inflow via pulse wave velocity (PAi and PAp) and septal annulus wave via tissue Doppler velocity (PAmi and Pamp). All intervals were corrected by PR interval.

Results: During follow up (mean 34 months), 12 patients (34.3%, women 7) experienced recurrent AF. Age, sex, history of hypertension and diabetes, EF, left atrial dimension, PAi, PAp, Pamp and anti-arrhythmic agent medication were not different between both groups. Only corrected PAmi in the recurrent AF significantly was prolonged compared to it in the no-recurrent AF (3.54 ± 1.31 vs. 2.54 ± 0.68 ms, respectively). In the multivariate analysis, after adjusting with age, EF, history of hypertension, PAmi was associated with the recurrence of AF. Cut off value of corrected PAmi of 2.90 ms could predict the AF recurrence with sensitivity of 67% and specificity of 78%.



Conclusion: The atrial electro-mechanical conduction time assessed by time interval between P-wave and A wave in tissue Doppler image could predict the recurrence of AF in the patients with paroxysmal AF.

P2454 | BEDSIDE

Correlation between atrial fibrillation cycle length and fractionation as a predictor of long-term atrial fibrillation free survival

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Purpose: Fractionation of electrograms is associated with local fibrosis but can also occur during functional conduction block. We hypothesized a differentiation between structural and functional fractionation can be a predictor of atrial fibrillation (AF) free survival. The aim of the present study was to assess the potential value of a mean atrial fibrillation cycle length (AFCL) to fractionation correlation coefficient as a predictor of AF free survival after pulmonary vein isolation (PVI).

Methods: 28 patients with "lone" AF planned for PVI were included. A steerable twentypolar catheter with 5 splines (PentaRay, Biosense Webster) was inserted in the left atrial appendage. During AF, 10 bipolar electrograms (EGMs) were recorded during 15 seconds. AFCL was determined manually, a fractionation score was calculated automatically using criteria based on complex fractionated atrial EGMs criteria. Receiver operating characteristic curve analysis was

performed to define the optimal cut-off value for mean AFCL to fractionation correlation coefficient (AFCC). Median follow-up was 73 months.

Results: Mean age was 53 years and 86% had paroxysmal AF. Mean AFCL was 171 ms, mean fractionation score was 10 activations per second. Mean AFCC was -0.324. Eighteen patients were free of AF at the end of the study period. The AFCC was significantly higher in patients who were free of AF compared to patients who were not ($z = -0.478$ vs $z = -0.049$, $p < 0.001$). The AFCC predicted long-term AF free survival with an accuracy of 96% ($p < 0.001$). With a cut-off of -0.170, the sensitivity was 90% and the specificity was 100%.

Conclusion: In the present study, the mean AF cycle length to fractionation correlation coefficient was significantly associated with long-term AF free survival and can potentially be used as a predictor of long-term AF free survival after ablation.

P2455 | BEDSIDE

Characterization of signal-averaged vector-projected high resolution ECG and genetic polymorphisms of *scn5a* in brugada syndrome

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Purpose: Brugada syndrome is associated with a high risk of lethal arrhythmia, partly caused by genetic polymorphisms in the SCN5A that encode an a subunit of cardiac sodium ion channel. In this study, we verified the characterization of morphology of precordial V1-2 in 12-Leads ECG, late potentials (LPs), interlead difference of activation recovery time by 187ch high-resolution ECG and genetic polymorphisms of SCN5A.

Method: We used originally developing 187-ch signal-averaged vector-projected high resolution ECG (DREAM-ECG) that can evaluate 12-leads ECG and abnormalities of ventricular depolarization and repolarization. This DREAM-ECG consisted of an input box with high resolving power amplification, vector-projected matrix lead synthesizer, and data handling section. We recorded 10 minute of body surface ECG by using Mason-Likar lead system at resting supine position. Synthesized 187-ch ECG based on vector-projection theory was generated. The existence of LPs was defined by the LAS40 ≥ 44 msec and fQRS ≥ 127 msec on signal averaged XYZ leads ECG. The values for the mean activation recovery time (RT) dispersion were automatically calculated by the mean difference between the greatest RT interval (RTmax) and the smallest RT interval (RTmin). Corrected RT intervals were calculated by Bazett's formula. Genetic screening for 11 mutation sites of SCN5A was performed in 40 patients with Brugada like ECG.

Results: The 12L-ECG revealed 10 coved type, 30 saddle-back type ECG. The value of RTc dispersion was higher in BrS with coved type than those in saddle-back type (40 ± 5.2 vs. 29.3 ± 2.3 , $p < 0.05$). The existence of LP was not significantly different between saddle back type and coved type (16/30 vs. 7/10, ns). Missense mutations were detected 8 samples of H558R, 5 samples of R1193Q and 2 samples of P1090L. In the context of genetic polymorphisms of SCN5A and DREAM-ECG, H558R hetero mutation was identified in 6 out of 10 Brugada syndrome with coved type. The 12L-ECG morphology of 4 patients with R1193Q and 2 patients with P1090L were saddle-back type. The 21 patients out of 27 patients with no mutation demonstrated saddle-back type on 12L-ECG.

Conclusion: Signal-averaged vector-projected high resolution 187-ch ECG and the SCN5A mutation may provide a new insight for risk stratification in patients with Brugada syndrome.

P2456 | BEDSIDE

Periodic repolarization dynamics predicts mortality in diabetic post-infarction patients

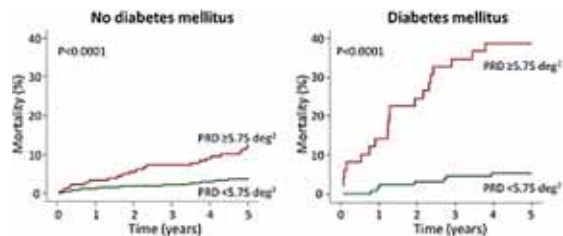
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Purpose: Periodic repolarization dynamics (PRD) refers to low frequency cyclic changes of repolarization instability related to sympathetic nerve activity. Diabetic post-infarction patients can suffer from regional inhomogeneities of autonomic innervation which may contribute to increased vulnerability to malignant tachyarrhythmias and which may be captured by PRD.

Methods: The study included 908 survivors of acute myocardial infarction (MI). Within the 2nd week after MI, a 30 minute high resolution ECG was performed in Frank leads configuration under standardized conditions. PRD probes the spectral power of spatiotemporal variations of repolarization in the low frequency range (< 0.1 Hz). In line with previous studies, PRD ≥ 5.75 deg2 was considered abnormal. Primary endpoint was 5-year total mortality. Multivariate analysis included reduced left ventricular ejection fraction (LVEF) $\leq 35\%$, GRACE-score ≥ 120 , heart rate > 75 bpm, SDNN ≤ 70 ms and QT variability index > 0.47 .

Results: During follow-up of 5 years, 69 patients died. 179 patients (19.7%) suffered from diabetes mellitus. PRD was significantly higher in diabetic than non-diabetic patients (3.4 (median, IQR 4.7) deg2 vs. 2.7 (4.1) deg2, $p < 0.05$). PRD was a very strong predictor of mortality in diabetic patients with 5-year mortality

rates of 38.8% and 5.4% in patients with abnormal and normal PRD, respectively ($p < 0.001$). Multivariately, abnormal PRD was the strongest predictor of mortality in diabetic patients (hazard ratio 5.7 (95% CI 2.3-14.0), $p < 0.0001$) outperforming reduced LVEF $\leq 35\%$ (1.3 (0.5-3.2), $p = 0.606$).



Risk stratification by PRD.

Conclusions: Increased PRD identifies diabetic post-infarction patients at very high risk of subsequent death. Future studies are needed to test whether these patients benefit from prophylactic therapies.

P2457 | BENCH

Renal denervation reduces atrial fibrillation complexity in goats independently from changes in blood pressure

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Introduction: Atrial fibrillation (AF) leads to structural and neural remodeling in the atrium, which enhances AF complexity and perpetuation. Renal denervation (RDN) reduces renal and whole-body sympathetic activity. The effect of RDN on AF complexity and atrial structural and neural remodeling is unexplored.

Methods and results: Sixteen goats were instrumented with an atrial endocardial pacemaker lead and a burst pacemaker. Percutaneous catheter-based RDN was performed in 8 goats (RDN-AF). 8 goats with RDN sham procedure served as a control (SHAM-AF). AF was induced and maintained electrically for 6 weeks. High-resolution mapping was used to record epicardial conduction patterns in the free wall of the right and left atrium. Shortening of atrial effective refractory period was more pronounced in SHAM-AF compared to RDN-AF (99 ± 5 ms vs. 118 ± 8 ms, $p < 0.05$). Median conduction velocity was increased in RDN-AF compared to sham (75 ± 9 cm/s vs. 65 ± 10 cm/s, $p < 0.01$). Median AF cycle length was not significantly different between the groups (137 ± 31 ms vs. 131 ± 25 ms, $p = 0.74$). Left atrial AF complexity (5.7 ± 2.1 fibrillation waves/AFCL vs. 8.5 ± 2.0 waves/AFCL, $p < 0.01$) and incidence of breakthroughs (2.3 ± 1.2 waves/AFCL vs. 4.0 ± 1.4 waves/AFCL, $p < 0.01$), was lower in RDN-AF compared to SHAM-AF. Furthermore, the degree of endomyocardial fibrosis, tyrosine hydroxylase expression, and growth-associated protein positive nerve staining were all lower in RDN compared to sham. Importantly, blood pressure and ventricular contractility were not significantly different between both groups.

Conclusions: RDN reduces AF complexity and attenuates atrial structural and neural remodeling in goats with persistent AF independently from changes in blood pressure.

P2458 | BEDSIDE

Renal denervation for improving outcomes of catheter ablation in patients with atrial fibrillation and hypertension: early experience

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Objectives: The aim of this study was to assess the potential role of renal denervation as an adjunct to pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF) and moderate resistant or truly resistant hypertension.

Background: Renal artery denervation has provided incremental AF suppression after PVI in patients with AF in the setting of drug-resistant hypertension, but the potential role of renal denervation in patients with less severe hypertension is unknown.

Methods: Patients with a history of symptomatic, paroxysmal (P) AF or persistent (Pers) AF and moderate resistant hypertension (office BP $\geq 140/90$ mm Hg and $< 160/100$ mm Hg; $n = 48$) or truly resistant hypertension ($\geq 160/100$ mm Hg; $n = 38$) were eligible for the study. Patients were randomized to PVI only or PVI with renal artery denervation and were followed-up for one year to assess maintenance of sinus rhythm, and monitor changes in blood pressure.

Results: At the 12-month follow-up, 26 of the 41 (63%) PVI with renal artery ablation patients were AF-free on no antiarrhythmic drugs vs 16 of the 39 (41%) patients in the PVI-only group ($p = 0.014$). The results in patients with resistant hypertension revealed that 11 of the 18 (61%) PVI with renal artery ablation patients

vs 5 of the 18 (28%) PV only patients were AF-free on no antiarrhythmic drugs ($p=0.03$). In patients with moderate resistant hypertension, the differences in AF recurrence rates were less dramatic after PVI with renal ablation vs PVI only: 11 of 21 (52%) vs 15 of 23 (65%) respectively ($p=0.19$). The superior efficacy of adding renal ablation was apparent in persistent AF patients (HR 0.39; 95% CI, 0.18 to 0.85; $p=0.02$), in patients with resistant hypertension (HR 0.37; 95% CI, 0.14 to 0.93; $p=0.03$), and especially in patients with persistent AF and resistant hypertension (HR 0.25; 95% CI, 0.09 to 0.72; $p=0.01$).

Conclusions: Renal artery denervation can improve the results of PVI, especially in patients with persistent AF and/or truly resistant hypertension.

P2459 | BENCH

A CNS cell group that controls electrical stability of the heart

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Introduction: Electrical stimulation of the vagus nerve has been shown to protect against ventricular tachyarrhythmia (VT). The exact mechanism of this effect is unknown. It also remains unclear whether acute or chronic withdrawal of tonic vagal efferent activity to the heart predisposes the heart to VT. We used triple-synuclein-null mice on a c57/bl6 background as a model of autonomic dysfunction associated with sustained reduction in vagal tone, while in a rat model we genetically targeted vagal preganglionic neurones in the dorsal motor nucleus of the vagus nerve (DVMN) for their selective acute silencing using a pharmacogenetic approach.

Methods: In 12 male Sprague-Dawley rats (380-420g), lentiviral vectors were used to transduce DVMN neurones to express an inhibitory Gi-protein-coupled *Drosophila* allatostatin receptor (AlstR) or GFP control. Applying allatostatin peptide rapidly silenced transduced neurones. To investigate the role of age-dependant autonomic dysfunction, young (2-3 months) and old (12-16 months) TKO and wild type (WT) mice were used. Anaesthetised with urethane (1.3g/kg, i.p.), an octapolar electrode catheter was inserted into the jugular vein and advanced into the right atrium and ventricle. The animals underwent programmed electrical stimulation of the right ventricle to obtain ventricular effective refractory period (VERP). Ventricular tachycardia (VT) inducibility by burst pacing was also assessed.

Results: Acute inhibition of the DVMN vagal preganglionic neurones in rats resulted in reduced VERP (34.0 ± 1.2 ms vs 44.5 ± 3.8 ms, $p=0.018$) and longer cycle length when burst pacing cycle was required to induce ventricular tachyarrhythmia (46.3 ± 6.5 ms vs 21.4 ± 3.3 ms, $p=0.0039$). Young TKO mice showed no difference in VERP (37.0 ± 5.2 ms vs 37.0 ± 3.1 ms, $p=0.9$). However, in older TKO mice there was a reduction in VERP (30.6 ± 0.8 ms vs 43.38 ± 3.1 ms, $p=0.001$). Systemic administration of methyl atropine (1mg/kg, i.p) to WT mice mimicked the pro-arrhythmic phenotype of synuclein deficiency.

Conclusion: This study demonstrates that decreased activity of a distinct population of vagal preganglionic neurones predisposes the heart to ventricular arrhythmia by reducing the effective refractory period. We hypothesise that CNS disorders associated with autonomic dysfunction (modelled here by global synuclein deficiency) and decreased DVMN activity may lead to a pro-arrhythmic phenotype.

P2460 | BENCH

Telemetry study on spontaneous ventricular arrhythmias in a transgenic model

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Purpose: Cardiac arrhythmia constitutes a major disease burden and forms a research target. Establishing animal models that possess known arrhythmic substrates, e.g. cardiac fibrosis, is critical for mechanistic and therapeutic studies. We employed telemetry to study the arrhythmia profile in transgenic (TG) mice with cardiac fibrosis.

Methods: Male wild-type (WT) mice at 5-6 months of age, and TG mice with cardiac overexpression of β_2 -adrenoceptor (β_2 -AR) were studied at 5 (TG5) and 9 (TG9) months of age ($n=5$ each). Mice were maintained on a 12:12 h light-dark cycle. ECG telemetry probes were implanted and mice were allowed to recover for 2 weeks. Telemetry ECG was recorded from conscious mice in their home cage for a period of 48 h. Hearts were harvested and left ventricular (LV) fibrosis was determined by hydroxyproline assay.

Results: Heart rates (HR) were higher in TG mice at both ages versus WT during 12 h light (WT: 544 ± 9 , TG5: 601 ± 7 , TG9: 617 ± 2 bpm) and 12 h dark cycles (WT: 616 ± 5 , TG5: 654 ± 7 , TG9: 679 ± 9 bpm, both $P < 0.05$). Activity across 48 h was similar among the groups. LV collagen content increased by 2-fold in TG5 and 3-fold in TG9 over WT level (both $P < 0.01$). TG mice exhibited spontaneous onset of ventricular ectopic beats (VEB) and episodes of ventricular tachycardia (VT). Frequency of VEBs was ~6-fold greater in TG9 than TG5 group ($P < 0.05$) with

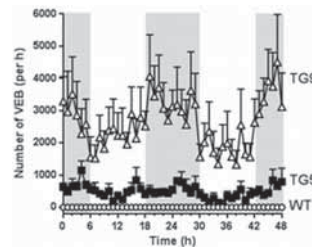


Figure 1

evident circadian variation (Figure). VT was also more prevalent in older than younger TG mice ($P < 0.05$).

Conclusions: We characterized the β_2 -AR TG as a model of ventricular tachyarrhythmias by demonstrating age-dependency and circadian variation in the severity of arrhythmia. This phenotype, together with presence of cardiac fibrosis and enhanced β -adrenergic signalling make this model useful to investigate novel therapies.

P2461 | BENCH

Effects of the site of origin and coupling interval of premature ventricular depolarizations on the hemodynamic and mechanical response in pigs with and without pacing-induced cardiomyopathy

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Purpose: Frequent ventricular premature depolarizations (VPD) can cause or worsen a previously acquired cardiomyopathy. This effect has been associated with the burden of VPD. However, its mechanism remains unknown. The aim of this study was to analyze the acute hemodynamic and mechanical effects of VPD arising from different ventricular sites at different coupling intervals (CI) in normal and cardiomyopathic pig hearts.

Methods: Four control pigs with normal hearts and four with pacing-induced cardiomyopathy (CM) were studied. Echocardiographic measurements were used to validate the animal model. VPDs were performed at decreasing CI from 16 left (8 epicardial and 8 endocardial) and 3 right ventricular sites. Left ventricular (LV) and right ventricular (RV) pressure, arterial pressure, aortic blood flow (ABF) and the ECG were continuously recorded.

Results: A total of 608 VPD were evaluated. No hemodynamic or mechanical differences between epicardial and endocardial locations were noticed. A deleterious effect on ABF and maximum LV dP/dt associated with shorter coupling intervals was found ($p < 0.001$), and this was more prominent in the CM group ($p < 0.001$). All VPDs at 500 ms CI in the control group generated ABF, but 22% in the CM group did not ($p < 0.001$). VPD that did not generate ABF (non-flow VPD) were significantly increased at decreasing CI in both groups ($p < 0.01$) with a more manifest effect on the CM animals (23.9% vs. 44.3% at 450 ms CI, $p < 0.05$). At very short CI, differences between the groups tended to disappear. The regional analysis (8 LV regions [epicardial + endocardial] and 3 RV regions) showed that at 450 ms CI, only the anterolateral basal and medial regions of the LV generated more than 25% non-flow VPD in the control group, whereas, in the CM group, all regions generated more than 25% non-flow VPD.

Conclusions: The coupling interval of ventricular premature depolarizations plays a major role in their deleterious effect on the heart. In addition, based on the rate of non-effective beats, the site of origin may also be critical. Remarkably, extrasystolic beats have a more detrimental effect on cardiomyopathic rather than in normal hearts.

P2462 | BENCH

Defibrillation threshold of ventricular fibrillation in a porcine model of mild therapeutic hypothermia

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Purpose: Mild therapeutic hypothermia (MTH) is being used in post-resuscitation care for its anticipated neuroprotective effect. The relation between MTH and malignant ventricular arrhythmias has not been exactly clarified. The aim of the study is to compare defibrillation threshold of ventricular fibrillation before and after initiation of MTH in whole body porcine model.

Methods: Veno-arterial extracorporeal membrane oxygenation (ECMO) with cooling circuit was introduced in fully anesthetized pigs ($n=10$) for temperature management and myocardium protection. Ventricular fibrillation (VF) was provoked by ventricular rapid pacing each three times during normothermia and after reaching the target temperature (32 degrees Celsius in the pulmonary artery). The transcutaneous defibrillation threshold was estimated as the lowest energy of biphasic shock (70-100-150-200-270 J gradually) which terminated VF.

Results: Defibrillation threshold of VF in normothermia was 270 (IQR 188; 270) J as compared during maintaining of MTH 150 (150; 270) J, $p=0.001$. Also the number of shocks necessary to terminate VF was during MTH lower than in normothermia - 3 (3; 5) vs. 5 (4; 5), $p=0.0001$.

Conclusions: Defibrillation threshold of VF in a whole body porcine model is during MTH lower than in normothermia condition.

CLINICAL OUTCOMES IN ATRIAL FIBRILLATION I

P2464 | BEDSIDE

Daily physical activity and risk of atrial fibrillation

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Vigorous exercise and endurance training increase the risk of atrial fibrillation (AF). The association between daily physical activity (PA) during leisure time and working hours with the risk of AF is largely unknown.

The aim of the present study was to investigate the association between the level of daily PA and the risk of AF in a large cardiovascular longitudinal study, the 60 years old men and women from our city.

A cohort consisting of every third man and woman reaching the age of 60 in our large city area during the years 1997-1998 ($n=4232$) was studied. Anamnestic records, an ECG, and blood samples were collected at baseline. PA was classified in four different categories: during leisure time as sedentary (I) <2h/week; mild (II) low intensity PA >2h/week; moderate (III) regular motion >30 min 2-3 times/week and sustained (IV) as regular training >3 times/week. Correspondingly, PA during working hours was graded according to the intensity of the work as very mild (I), mild (II), intense (III), very intense (IV) and to the time spent sitting at work as always sitting (I), sitting more than half day (II), sitting less than half day (III) and never sitting (IV).

Incident cases of AF were ascertained via the Swedish national hospital discharge register. Risk of AF was calculated by Cox regression and expressed as hazard ratio (HR) with 95% confidence intervals (CI) at the univariate analysis and after adjustment for sex, hypertension, diabetes, smoking, obesity, left ventricular hypertrophy, previous myocardial infarction.

During 12 years of follow up AF incidence rate was 4.4/1000 person-years. Leisure-time PA showed a U-shaped relationship with the risk of AF, with a trend toward an increased risk in group I [HR 1.22, 95% CI (0.81-1.83)], and IV [HR 1.54, 95% CI (0.97-2.45)] as compared to group II and III, in the fully adjusted model. We observed a 37% reduction in AF risk (HR 0.63, 0.42-0.94 (95%CI)) in the fully adjusted model, in individuals physically active during working hours as compared to those sitting most of the time at work. The intensity of work was not associated with AF risk neither at the univariate (HR 0.82 and 95%CI (0.45-1.48)) nor at the multivariate analysis [HR 0.68 95%CI (0.37-1.25)].

The results suggest a possible U-shape relationship between leisure time PA with trends toward higher risks both in those with low PA as well as in those with regular training. PA during working hours may also decrease risk for AF. These data need to be confirmed in larger cohorts before recommendations on preventive measures can be taken.

P2465 | BEDSIDE

Impaired mobility in community-dwelling older adults with atrial fibrillation

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Purpose: Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with increased stroke and mortality. Although AF is associated with self-reported walking deficits, research comparing objective physical performance in AF versus non-AF patients is lacking. This study examined the independent associations between AF and objectively measured gait and mobility using data from a large, nationally representative study of community-dwelling adults.

Methods: 4526 participants who took part in wave 1 of The Irish Longitudinal Study on Ageing (TILDA) were included in this analysis. Inclusion criteria was age ≥ 50 years, Mini-Mental State Examination (MMSE) score ≥ 24 , and completion of either the Timed Up-and-Go (TUG) test or a usual walking speed test using the GAITrite walkway. AF was diagnosed objectively according to ESC guidelines using a 5 minute surface electrocardiogram recording. Covariate information was gathered through computer aided personal interviews. Linear regression analyses were performed to study differences in mobility performance between participants with and without AF, adjusting for socio-demographics, physical, cognitive, mental and behavioural health and frailty.

Results: In this community-dwelling sample (mean age 62.3 years; range 51-89), the prevalence of AF was 3.1% ($n=112$) increasing to 6.6% in participants aged ≥ 70 years (11.7% in males; 2.7% in females). The AF group were older, frailer, more likely to be male, less educated and on more cardiovascular drugs and have poorer behavioural health patterns compared to the non-AF group. They were also 1.5 s slower in TUG and had a 13 cm/s slower usual gait speed compared to the non-AF group. In multivariable analysis, AF was independently as-

sociated with slower TUG ($\beta=1.04$; 95% CI=1.01, 1.08; $p<0.05$) and slower usual gait speed ($\beta=-3.66$; 95% CI=-7.11, -0.22; $p<0.05$). There was also a significant age*AF interaction effect in the model for usual gait speed ($\beta=-.453$, 95% CI=-0.885, -0.020, $p=0.040$). After adjusting for all confounders, adults with AF walked 3.90 cm/s more slowly than adults without AF at age 70, declining by a further 4.5 cm/s for every additional decade.

Conclusion: AF is independently associated with slower usual gait speed in community-dwelling adults aged 70 years and older, placing them at increased risk of falls and injuries with implications for anti-coagulant therapy. This warrants the early recognition and treatment of AF in older adults to improve physical function and reduce the risk of adverse outcomes.

P2466 | BEDSIDE

Utility of non-invasive assessment of left atrial function and diastolic filling parameters in predicting recurrence of atrial fibrillation following catheter ablation

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Purpose: Unfavorable left atrial (LA) remodeling increases the risk of recurrent atrial fibrillation (AF) after catheter ablation (CA). However, specific measures of LA function that could predict recurrence are not well defined. We sought to determine whether LA contractile dysfunction defined by LA strain imaging predicts early (<3 months after CA) or late (>3 months after CA) recurrence of AF.

Methods: Patients (pts) who underwent CA for AF between September 2008 and September 2010 were included. A transthoracic echocardiogram was performed at baseline, at 24 hours after CA and at 3 months. Peak longitudinal strain of the inferior LA wall was measured during atrial contraction (LAa strain) and Δ LAa strain was defined as change in strain from baseline to 24 hours. AF recurrence was confirmed by electrocardiogram or ambulatory rhythm monitoring. The Cox proportional hazards model was used to investigate the relationship between clinical and LA variables and AF recurrence.

Results: A total of 175 pts (135 male, 62 ± 11 years) were included. Baseline LA strain was -17 ± 5 . LA strain decreased 24 hours after ablation (mean Δ LAa strain 4 ± 6). Early recurrence of AF (<3 months) was documented in 54 pts (31%). Persistent AF was the strongest predictor of early AF recurrence (hazard ratio (HR)=2.85, $P=2.9\text{e-}4$), followed by lower baseline total LA emptying fraction (HR=0.96, $P=1.8\text{e-}4$), higher diastolic pulmonary vein inflow (HR=30.61, $P=2.1\text{e-}4$) and higher early diastolic (E) mitral inflow (HR=10.37, $P=3.4\text{e-}4$) velocities. Baseline LA strain and Δ LAa strain were not associated with early AF recurrence. Of the 108 patients with long-term follow-up (26 ± 13 months), late AF recurrence was documented in 44 pts (41%). In contrast to early AF recurrence, a larger Δ LAa strain was associated with risk of late AF recurrence (mean 5.9 vs 1.9, HR 1.11, $P=0.018$). Other measures of LA function, including baseline LA strain and total LA emptying fraction, were not associated with late AF recurrence. Early AF recurrence was a strong predictor of late AF recurrence (HR=2.6, $P=0.0019$).

Conclusions: Non-invasive assessment of LA function and hemodynamic parameters before and following CA for AF may be useful in predicting early and late recurrences of AF. These data are easily obtained and may be helpful in guiding management following CA.

P2467 | BEDSIDE

Sex- and age-stratified 20-year changes in the prevalence of atrial fibrillation in general population

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Purpose: Atrial fibrillation (AF) has increased globally and is believed to increase in the future; therefore, we analysed its prevalence in the recent 20 years.

Methods: We analysed the large annual health check-up database with annual 12-lead electrocardiogram (ECG) results of the residents in our prefecture. AF was diagnosed using ECGs of 3,127,123 participants aged 50-79 years (64.6 ± 7.6 years; men, 36.8%) during 1993-2012.

The prevalence of AF was sex- and age-stratified (50-59, 60-69 and 70-79 years).

Logistic regression analysis was performed to the model including age, height, body mass index (BMI; kg/m^2), smoking, daily alcohol, hypertension (HTN) and diabetes mellitus as risk factors for incident AF in 2012 in those without AF in 2007.

Results: AF prevalence peaked in 2007 (3.41%, 2.06% and 0.76% for men aged 70-79, 60-69 and 50-59 years, respectively) before levelling in 70-79-year-old men and decreasing in those aged <70 years. In 70-79-year-old women, AF prevalence peaked in 2008 (1.28%), but its prevalence decreased in women aged <70 years (0.46% and 0.14% in 1993 and 0.30% and 0.08% in 2012 in women aged 60-69 years and 50-59 years; $p<0.0001$, $p<0.05$, respectively).

Significant risk factors for incident AF in women were ageing, height, large BMI (odds ratio per unit: 1.09, confidence interval: 1.04-1.14, $p<0.001$), daily alcohol and HTN. Among these risk factors, continuous decrease in BMI of women aged <70 years (from 23.80 in 1993 to 22.72 in 2012, $p<0.001$) was concordant with the decrease in AF. Average age and height were maximal in 2012, with little change in daily alcohol and HTN.

Conclusion: We report a low and decreasing prevalence of AF with a decrease

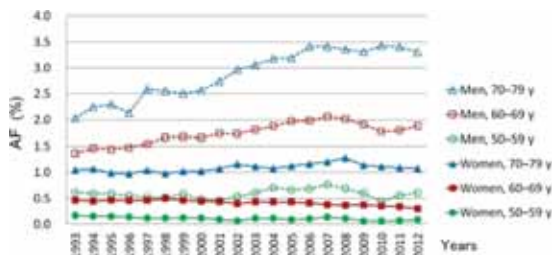


Figure 1. Sex- and age-stratified AF prevalence.

in BMI in women aged <70 years. However, the mechanism of this decrease remains unclear.

P2468 | BEDSIDE

Incidence of hospitalization for heart failure in patients with paroxysmal and sustained type of atrial fibrillation: one-year follow-up of the Fushimi AF Registry

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Purpose: There is well-documented relationship and complex interaction between AF and heart failure. However a relationship between heart failure and the types of AF (paroxysmal, persistent or permanent) AF is unknown.

Methods: The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all of the AF patients in Fushimi-ku. Fushimi-ku is densely populated with a total population of 283,000, and is assumed to represent a typical urban community in Japan. At present, we have enrolled 3,821 patients (1.4% of total population) from March 2011 to December 2013. One-year follow-up was completed in 2,966 patients as of December 2013. We compared the baseline clinical characteristics and one-year outcomes in patients with paroxysmal AF (PAF; n=1,398, 47.1%) and those with sustained (persistent or permanent) AF (SAF; n=1,568, 52.9%).

Results: Patients with PAF were younger (PAF vs. SAF: 72.6±11.5 vs. 75.0±10.0 years of age; p<0.01), and were more symptomatic (the proportion of patients with any AF-related symptoms: 66.7% vs. 35.5%; p<0.01). They were less likely to have a history of stroke (17.3% vs. 25.5%; p<0.01), heart failure (17.7% vs. 35.1%; p<0.01), chronic kidney disease (CKD; 32.6% vs. 37.4%; p<0.01). The CHADS₂ score was smaller in patients with PAF (1.86±1.30 vs. 2.23±1.35; p<0.01). Patients receiving the prescription of oral anticoagulants at enrollment were much less in PAF (38.2% vs. 66.0%; p<0.01). During the one-year follow-up period, there was no significant difference in stroke (n=31 vs. 50) (2.2% vs. 3.2%; p=0.10), all-cause death (n=109 vs. 131) (7.8% vs. 8.4%; p=0.58) or major bleeding (n=20 vs. 26) (1.4% vs. 1.7%; p=0.62) between PAF and SAF. In patients with PAF, the incidence of hospitalization for heart failure was less (n=40 vs. 81) (2.9% vs. 5.2%; p<0.01). After the adjustment by age and gender in multiple logistic regression models, PAF was independently associated with the incidence of hospitalization for heart failure (adjusted odds ratio, 0.59; 95% confidence interval, 0.39 to 0.86; p<0.01).

Conclusion: Patients with PAF were younger, had less co-morbidities and thus had lower CHADS₂ score, compared with those with SAF. During the one-year follow-up period, there was no difference in stroke between PAF and SAF, but AF patients with PAF had lower risk of hospitalization for heart failure.

P2469 | BEDSIDE

Is cardiovascular death a primary driver of mortality in higher age groups of patients with non-valvular atrial fibrillation? Results from the GARFIELD Registry

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Purpose: To investigate the influence of age on baseline characteristics and clinical outcomes in patients with non-valvular atrial fibrillation (AF).

Methods: In the ongoing, international registry, GARFIELD, a total of 12,458 prospective patients were enrolled at 739 sites in 30 countries between March 2010 and January 2013. Results are reported at 1-year follow-up.

Results: A total of 29.2%, 31.9% and 38.9% of patients were aged <65, 65–74 and ≥75 years, respectively. Increasing age was associated with a higher rate of comorbid conditions. Oral anticoagulant (OAC) use increased proportionately with age, and antiplatelet (AP) therapy was used more often in patients <65 years.

Variable	<65 years (N=3639)	65–74 years (N=3972)	≥75 years (N=4847)	P-value
Age, years, mean (SD)	55.6 (7.7)	69.9 (2.8)	80.8 (4.5)	<0.001
Congestive heart failure, %	19.2	18.9	22.0	<0.001
Coronary artery disease, %	15.9	20.8	21.9	<0.001
Diabetes, %	19.6	25.1	21.4	<0.001
Hypertension, %	72.2	80.8	79.6	<0.001
CHADS ₂ , mean (SD)	1.3 (0.9)	1.6 (1.0)	2.6 (1.0)	<0.001
CHA ₂ DS ₂ VASc, mean (SD)	1.8 (1.2)	3.2 (1.2)	4.4 (1.3)	<0.001
HAS-BLED, mean (SD)	0.6 (0.7)	1.6 (0.8)	1.8 (0.8)	<0.001
OAC/OAC+AP/AP/None, %	38.3/13.6/ 32.3/14.9	45.6/17.8/ 25.7/10.2	47.8/15.5/ 25.8/10.3	
1-year outcomes (unadjusted), %				
Stroke/SE	0.8	1.6	2.0	<0.001
Major bleeding	0.5	0.9	1.6	<0.001
Mortality	2.2	3.8	9.0	<0.001
CV/non-CV death	1.1/1.1	1.6/2.2	3.9/5.1	0.329
Myocardial infarction	<0.1	0.1	0.2	
Non-haemorrhagic stroke	<0.1	<0.1	0.2	

The unadjusted event rates of stroke/systemic embolism (SE), major bleeding and mortality increased by 2.5-, 3- and 4-fold, respectively, in patients aged ≥75 years compared with those <65 years. In patients aged ≥65 years, cardiovascular (CV) death accounted for less than half the rate of all-cause death.

Conclusion: Increasing age was associated with higher risks of stroke/SE, death and major bleeding events in patients with non-valvular AF. CV-related death was not the main cause of death in patients ≥65 years.

P2470 | BEDSIDE

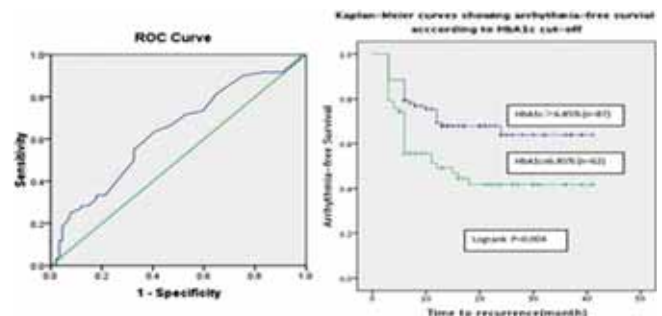
High level of HbA1c predicts ablation outcome in patients with paroxysmal atrial fibrillation and type 2 diabetes mellitus

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Purpose: Type 2 DM was associated with higher risk of AF. Whether the level of HbA1c affects the radiofrequency catheter ablation outcome is unknown. The aim of this study is to evaluate whether the baseline level of HbA1c could predict procedural outcome in patients with paroxysmal AF and type 2 DM who undergoing ablation.

Method: One hundred forty nine patients were selected for the study and their baseline level of HbA1c was evaluated before ablation. All the patients underwent pulmonary vein antrum isolation and extensive follow-up by ECG, Holter and office visit.

Result: Out of 149 patients, 60 (40.3%) patients developed recurrence after average follow-up of 14±10 months. Baseline level of HbA1c was higher in recurrent patients than that of patients remained arrhythmia free (HbA1c =7.18% ±1.04% vs. 6.79% ±1.12%, p<0.05). After adjusting for age, gender and duration of DM, left atrium size (HR =1.10, p=0.001) and HbA1c (HR =1.28, p=0.016) was found to be a significant predictor of recurrence. The receiver operating characteristic (ROC) analysis of multivariable prediction model showed that an HbA1c cut-off value >6.85% predicted recurrence with 55.0% sensitivity and 67.4% specificity (AUC=0.634, figure left). The success rate was in 69.0% in >6.85% and 46.8% in ≤6.85% group (log-rank p=0.004, figure right).



ROC curve and Kaplan-Meier curves.

Conclusion: The high level of HbA1c is associated with an increased risk of recurrence of atrial tachyarrhythmia in patients with PAF and DM who undergoing catheter ablation.

P2471 | BEDSIDE

Incident atrial fibrillation in treated arterial hypertension: the Campania-Salute Network (CSN)

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Purpose: Atrial Fibrillation (AF) is the most common arrhythmia worldwide. Although management strategies have been developed, AF negatively impacts on

cardiovascular (CV) mortality and morbidity. Despite the association with arterial hypertension is well established, to date the knowledge of factors influencing AF development is incomplete, especially in sub-populations at high risk. Accordingly, we analyzed characteristics and risk profile in patients participating to Campania-Salute Network (CSN) registry, to investigate frequency and determinants of AF development.

Methods: From the CSN, we selected 6905 hypertensive patients (52±12 years, 57% men, 5% diabetic, 41% obese), without history of AF, prevalent CV disease and with left ventricular (LV) ejection fraction ≥50%, and no more than stage III CKD (by simplified MDRD).

Results: During follow-up (median 47 months, inter-quartile range 10-71 months) a first AF episode occurred in 107 patients (rate of 4/1000 patients/year). In exploratory statistics, patients who developed AF (AF group) were older, and exhibited higher body mass index (BMI), heart rate and systolic blood pressure (BP) both at baseline and at the time of the last available visit (all $p < 0.01$), than patients who did not developed AF (no-AF group). They also had lower ejection fraction, higher LV mass and mitral peak-E velocity, and larger left atrial (LA) diameter (all $p < 0.001$). At baseline, AF group was taking more medications ($p < 0.001$) due to more frequent prescription of diuretics ($p = 0.005$), ACE inhibitors ($p = 0.002$), β -blockers ($p = 0.02$) and Ca^{++} channel blockers ($p < 0.001$). Cox regression by a backward building procedure including all covariates that were significantly different between the two groups demonstrated significant hazard ratios for older age (HR=1.08/yr; CI: 1.06-1.11; $p < 0.0001$), higher BMI (HR=1.08/kg×m⁻²; CI: 1.03-1.13; $p = 0.001$), higher number of antihypertensive meds (HR=1.48; CI: 1.17-1.86; $p = 0.001$), enlarged LA diameter (HR=1.03/cm×m⁻¹; CI: 1.01-1.05; $p = 0.003$), and less use of diuretics (HR=0.52; CI: 0.28-0.96; $p < 0.04$).

Conclusion: Older age, higher BMI, larger LA diameter, and increased need for more medications are characteristics of an hypertensive phenotype at high risk for incident AF. Identification of the risk of incident AF in arterial hypertension may allow to better modulate antihypertensive therapy for prevention. Our analysis suggests that diuretics, helping both control of BP and atrial wall stretching, might have a role in prevention of AF in high risk individuals.

P2472 | SPOTLIGHT

Brady-tachy sinus node disease after atrial fibrillation ablation

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Purpose: Brady-tachy sinus node dysfunction (SND) is commonly associated with persistent atrial fibrillation (AF), but it is often unidentifiable during arrhythmia. We prospectively studied patients with persistent and long standing persistent atrial fibrillation referred to our centre for transcatheter AF ablation to detect clinical characteristics predictive of underlying SND.

Methods: From January 2007 to November 2013 we enrolled patients with persistent AF with indication to transcatheter ablation. They underwent AF ablation with pulmonary vein (PV) isolation and linear lesions with nonfluoroscopic navigation systems (Carto3, NavX Velocity), and they were all implanted with subcutaneous ECG monitoring device (loop recorder Reveal XT) at the moment of procedure. All patients received a CareLink monitor for remote control. Maintenance of sinus rhythm and pathologic pauses were assessed by monthly loop recorder checks with CareLink transmissions and in case of symptoms patients performed an unscheduled transmission. Moreover all patients were clinically re-evaluated every six months.

Results: We enrolled 144 patients with persistent AF (101 males, aged 68.52±10.13 years), and we followed them up for a mean of 123.76±376.20 months. Twelve patients (8.3%) underwent definitive pacemaker (PM) implantation, in one case due to advanced atrioventricular block, and in 11 cases because of pathologic pauses due to sinoatrial block during sinus rhythm (6 patients) or to slow rate AF (5 patients). Only 4 out of the 11 patients implanted with PM for SND were symptomatic. Elderly patients were found to be at significantly higher risk of SND (71±9 yrs vs 64.46±9.67 yrs, $p = 0.032$), as well as patients with hypertension (9/11 vs 54/132, $p = 0.02$). Moreover, patients diagnosed with SND had a higher probability of earlier AF recurrences and to have a higher AF burden during follow-up, even without reaching statistical significance.

Conclusions: Continuous remote ECG monitoring with loop recorder is useful to detect a high number of patients with persistent and long standing persistent AF and underlying asymptomatic sick sinus syndrome, otherwise undiagnosed. Older age and hypertension are significantly associated with latent SND, and patients with SND appear to be more prone to develop early AF recurrences with higher AF burden after ablation because of advanced atrial disease.

P2473 | BEDSIDE

Atrial fibrillation in first acute myocardial infarction

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Purpose: To compare the risk factors and in-hospital outcome in patients who developed Atrial Fibrillation during first acute myocardial infarction (AMI) compared to those in Sinus rhythm (SR).

Methods: 12871 patients with first AMI admitted (January 1991 to December 2012) were divided into 2 groups, (AF) Group: 227 (1.8%) and Sinus Rhythm (SR) Group, 12644 (98.2%).

Results: The overall age was 59±12 years, but AF Patients were older (65±12 years vs. sinus rhythm 53±12 years $p < 0.001$). Female gender, diabetes and hypertension were more common in AF group respectively as compared to SR Group $p < 0.001$ for all. On the other hand, Smoking and Dyslipidemia were more frequent in SR Group, $p < 0.001$ and $p < 0.002$ respectively. Arabs were 156 (68.7%) in AF Group and 5028 (39.7%) in SR Group $p < 0.001$. Asians were 5985 (47.3%) in SR Group and 48 (21.1%) in AF Group $p < 0.001$. Mean cholesterol, LDL and TG were higher in AF Group as compared to SR Group $p < 0.001$. In-hospital mortality was higher in AF Group as compared to SR Group. In-hospital mortality was 46 (20.3%) in AF Group and 894 (7.1%) in SR Group $p < 0.001$. VF occurred more frequently in AF Group 65 (28.6%) vs. 131 (1%) in SR Group $p < 0.001$. CVA occurred in 5 (2.2%) patients in AF Group and 54 (0.4%) patients in SR Group $p < 0.04$. Congestive heart failure occurred 659 (5.1%) patients 31 (13.7%) in AF Group and 628 (5%) in SR Group $p < 0.001$. Ejection Fraction $\leq 35\%$ was seen in 35 (15.4%) in AF Group and 874 (6.8%) in SR Group $p < 0.004$. Mean hospital stay was 7±5 days for AF Group and 5±3.5 days for SR Group $p < 0.001$.

Conclusion: Patients having AF are more likely to be diabetic and hypertensive as compared to patients in sinus rhythm. AF in First AMI was associated with more in-hospital mortality, mechanical and electrical complications as compared to patients in sinus rhythm.

CLINICAL OUTCOMES IN ATRIAL FIBRILLATION II

P2475 | BEDSIDE

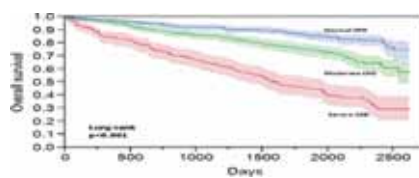
Predictors of mortality in patients with persistent atrial fibrillation: role of chronic kidney disease

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Background: Chronic Kidney Disease (CKD) is associated with increased cardiovascular mortality. Its association with survival in subjects with Atrial Fibrillation (AF) has not been described.

Methods: Subjects with persistent AF undergoing elective electrical cardioversion from 1/2000 to 12/2005 at our clinic were followed for mortality through 12/2008. Renal function was assessed at time of cardioversion and defined based on estimated glomerular filtration rate (GFR). A GFR >60 ml/min/1.73m² was considered normal, GFR 40-60 ml/min/1.73m² as moderate CKD, and GFR <40 ml/min/1.73m² as severe CKD. Kaplan-Meier method assessed mortality. Groups were compared using the log-rank test. Cox proportional hazard model was used to assess independent association of CKD with long-term survival after adjusting for potential confounders.

Results: A total of 1206 patients were included. Of these 544 had normal renal function, 454 moderate CKD, and 208 severe CKD. Patients with CKD as compared to normal renal function, were more likely to be female and had greater prevalence of comorbidities including hypertension, coronary artery disease, and heart failure. Over a median follow up of 4.2 years (IQR 2.6-5.6), patients with CKD had lower survival rates ($p < 0.001$) (Figure). After adjusting for baseline comorbidities, moderate CKD (HR 1.6, 95% CI 1.2-2.1) and severe CKD (HR 4.4; 95% CI 3.2-5.9) were independent predictors of mortality.



Survival in relation to renal function.

Conclusion: CKD is a powerful and independent predictor of long-term mortality in patients with persistent AF undergoing elective electrical cardioversion. Further studies evaluating mediators of this association are needed.

P2476 | BEDSIDE

Mortality in valvular and non-valvular atrial fibrillation: insights from a nationwide cohort analysis - TRAF (Turkish AF database)

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Background: Atrial fibrillation (AF), the most common clinical arrhythmia, has a valvular or nonvalvular etiology and causes significant morbidity and mortality. However, there is no robust data about the occurrence and the predictors of mortality in patients with valvular AF. Our objective was to compare the predictors and rates of all-cause mortality in valvular and nonvalvular AF patients in a large cohort.

Methods: We analyzed the records of 542,130 patients over the age 18 who had the diagnosis of valvular and non-valvular AF according to ICD-10 code I48 from

a nation-wide claims and utilization management system. The main descriptive statistics of the entire study population contained in the database include the age, gender, prescribed drugs, comorbidities and mortality.

Results: Among all cohort, 402,674 (74.3%) patients had non-valvular and 139,456 (25.7%) patients had valvular AF. All-cause mortality rates in the whole cohort were 21.2% for non-valvular AF versus 16.2% for valvular AF ($p<0.001$) in 5 years. In patients with non-valvular AF older age, CHADS₂, CHA₂DS₂-Vasc, hospitalization for heart failure and diagnosis of heart failure and also in patients with valvular AF older age, hospitalization for heart failure, warfarin use, heart failure and hospitalization for AF were found to be the significant predictors of all-cause mortality.

Conclusion: Although the exact mechanism has not been highlighted, patients with non-valvular AF had worse long-term prognosis compared to valvular AF patients. Age and heart failure found as the most important common prognostic factors in prediction of all-cause mortality in these group of patients.

P2477 | BEDSIDE

Electrophysiological implications on the thinning of left atrial wall; complex fractionated electrogram, voltage and cycle length

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Purpose: Atrial scars are strongly related to slow anisotropic conduction. Their relationship to atrial thickness has not yet been investigated. This study sought to evaluate the relationship between left atrial wall thickness (LAWT) imaged by multidetector computer tomography (MDCT) and arrhythmia substrate in atrial fibrillation (AF).

Methods: Atrial MDCT of 20 patients with AF (12 persistent AF) was registered with mapping geometry (NavX electro-anatomical system, version 8.0, St. Jude Medical, St. Paul, Minnesota). Left atrium (LA) was divided as 28 sites in every patients, total available 539 sites were analyzed. The fractionation, local mean cycle length (MCL) and voltage of LA were analyzed with regard to LAWT.

Results: There were large variations in LAWT (median: 1.77 mm, range 0.77-4.17 mm), LA voltage (median: 0.15 mV, range 0.02-6.01 mV) and local MCL (median: 180.87 ms, range 51.53-825.67 ms). LAA base had the thickest LAWT (2.27 ± 0.51 mm), the highest voltage (1.26 ± 1.37 mV) and the shortest MCL (169.35 ± 176.93 ms). In contrast, posterior wall showed the thinnest LAWT (1.66 ± 0.43 mm) and the lowest voltage (0.43 ± 0.82 mV), and the floor of LA showed the longest MCL (384.41 ± 177.80 ms). LAWT was thinner in areas without than in those with complex fractionated electrogram (1.71 ± 0.42 vs. 2.38 ± 0.65 mm, $p<0.001$). There was negative correlation between LAWT and local MCL ($r=-0.116$, $p=0.019$). Finally, LAWT was significantly thinner in areas ($n=206$) with low voltage (<0.1 mV) than those ($n=333$) with high voltage (≥ 0.1 mV) (1.82 ± 0.55 vs. 1.93 ± 0.58 mm, $p=0.04$).

Conclusions: Thin LAWT was associated with low LA voltage, long local MCL and less complex fractionated electrogram. These findings suggest that the structural remodeling is related with functional change of atrial substrate in patients with AF.

P2478 | SPOTLIGHT

Feasibility and effectiveness of structured hospital based nurse-led atrial fibrillation service

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Purpose: A randomized trial has documented that structured nurse-led Atrial Fibrillation (AF) service is superior to conventional AF service. Nurse-led AF service was established at 2 regional hospitals, January 2012. We report early results related to feasibility of this service, here defined as achieved adherence to guidelines recommendation on use of oral anticoagulant (OAC), and outcomes such as major bleeds (ISTH definition), TIA, stroke and mortality.

Methods: We report on all patients referred by cardiologists to nurse-led AF clinics at 2 regional hospitals from January 2012 to December 2013. Patients were recruited from a population base of 260,000 people. The AF-service consisted of 1-4 scheduled visits plus unscheduled visits including telephone service during one year, depending on patients need. The AF nurse specialist provided patient

education, risk factor control, and stimulated empowerment, compliance and adherence in these patients. During follow-up treatment was adjusted according to clinical guidelines. Patient education was repeated and adherence and compliance was controlled. Follow-up data were obtained from AF clinics files and from electronic patient files, which secure complete follow-up. Follow-up ended 31.12.2013.

Results: During the study period 598 AF patients were seen. Mean (range) age 68 (30; 90) years, 64% men, 62% paroxysmal AF. Mean CHA₂DS₂-VASC score 2.4 (0; 7), mean HASBLED score 0.8 (0; 3). Mean number of visits were 1.9 (1; 7). At first visit 98% of patients with a CHA₂DS₂-VASC ≥ 1 were on OAC (62% warfarin, 38% NOAC). Of patients with a CHA₂DS₂-VASC ≥ 2 were 99% on OAC (61% warfarin, 39% NOAC). During 449 (0; 1,9) years of follow-up we observed 1 TIA, 0 stroke, 4 major bleeds and 6 deaths of which 1 was cardiovascular, 4 cancer-related, and 1 unclassified.

Conclusions: Compared to published data on use of OAC and prognosis in AF, our early results of structured nurse-led AF service suggest great promise for the future. Further evidence and long time follow-up data are warranted.

P2479 | BEDSIDE

A prospective study of supraventricular activity and incidence of atrial fibrillation

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Purpose: Atrial fibrillation (AF) is thought to be caused by an electrical trigger reaching a susceptible atria. Such a trigger could be present long before the occurrence of arrhythmia. We sought to determine if supraventricular extrasystoles (SVES) and supraventricular tachycardias (SVT) measured at 24 h Holter ECG were associated with increased incidence of AF.

Methods: In 1998-2000, 389 individuals (44% men, mean age 65 years) were examined using 24 h Holter ECG. Six individuals with prevalent AF were excluded. After a mean follow-up of 10.3 years there were 45 cases of incident AF. Hazard ratios (HR) were computed using multivariable Cox regression modelling adjusting for age, gender, systolic blood pressure and HOMA-IR.

Results: Frequency of SVES as well as SVT episodes per 24 h were independent predictors of incident AF, HR 1.26, 95% confidence interval (CI) 1.07-1.49, $p=0.0006$; and HR 1.35, 95% CI 1.10-1.65, $p=0.004$ respectively. Further adjustment for smoking, education grade, alcohol use, use of medication and physical activity did not substantially alter results, nor did analysis using competing risks regression accounting for a competing risk of death. Incidence of AF was substantially increased especially in individuals with SVES in the top quintile of the distribution.

Conclusion: SVES and SVT independently predict AF.

P2480 | BEDSIDE

Incidence and predictors of post-operative new onset atrial fibrillation in rheumatic heart disease patients undergoing valve surgery

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Purpose: The relative risk of stroke in rheumatic heart disease (RHD) patients with Atrial Fibrillation (AF) is 17-fold. There is paucity of studies focusing on the occurrence of de-novo AF after valve surgery for RHD. The current study was designed to look for the incidence and predictors of new onset AF in RHD patients undergoing valve surgery.

Methods: Postoperative patients who had undergone valve surgery for RHD during the previous 5 years and who were in NSR preoperatively were recruited from the outdoor patient department. Their rhythm status at follow up was assessed by electrocardiogram (ECG) recordings. Pre-operative demographic profile and valve hemodynamics on echocardiography were analyzed.

Results: Of the 405 patients (male=250, female=155) studied, 39 patients (9.63%) developed AF at a follow-up of 5 years (mean 2.65 ± 1.3 years). At surgery, the mean age of patients in normal sinus rhythm (NSR) was 29.41 ± 12.83 years compared with 33.18 ± 12.86 years in patients with AF, which suggested trend towards significance ($P=0.068$). Pre-surgery left atrial (LA) size was significantly larger in patients with AF compared to NSR (58.64 ± 15.43 mm vs. 45.51 ± 7.88 mm, $P<0.0001$). Pre-surgery severe mitral valve disease was significantly associated with de-novo AF ($P=0.004$) compared to severe aortic valve disease. There was no difference with regards to the etiology of mitral valve disease (severe mitral stenosis vs. mitral regurgitation, $p=0.86$).

Abstract P2479 – Table 1

	Model 1			Model 2			Model 3		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Number of SVES/24 h	1.27	1.09–1.50	0.002	1.26	1.07–1.49	0.006	1.32	1.11–1.57	0.002
Number of SVT/24 h	1.36	1.21–1.66	0.002	1.35	1.10–1.65	0.004	1.46	1.18–1.80	0.001
Maximum heart rate at SVT	1.08	0.95–1.24	0.24	1.04	0.90–1.19	0.62	1.07	0.93–1.23	0.36
Maximum duration of SVT	1.18	0.98–1.43	0.09	1.14	0.93–1.140	0.22	1.22	0.98–1.51	0.07
Presence of ESVEA	3.21	1.72–5.99	<0.0001	2.89	1.54–5.45	<0.0001	3.75	1.88–7.45	<0.0001

Model 1: Adjusted for age, sex. 383 cases, 45 events. Model 2: Adjusted for Model 1 + height, weight, systolic blood pressure and HOMA-IR. 375 cases, 45 events. Model 3: Adjusted for Model 2 + smoking status, alcohol use, education grade, medication (beta-blockers, calcium channel blockers, diuretics and lipid lowering agents) and physical activity at baseline. 373 cases, 44 events. SVES, supraventricular extrasystoles; SVT, supraventricular tachycardias; ESVEA, excessive supraventricular ectopic activity.

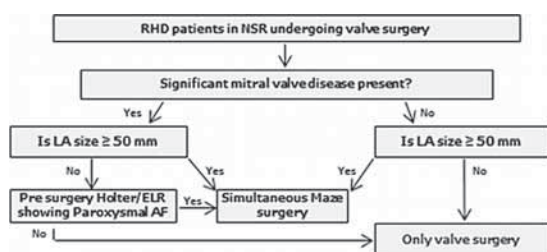


Figure 1. Algorithm for RHD patients in NSR.

Conclusion: RHD patients with significant mitral valve disease and a large LA are at high risk of developing late onset de-novo AF. Pre-operative LA size ≥ 50 mm predicted AF with a sensitivity of 77% and a specificity of 70%. These might constitute a subset for a simultaneous maze procedure during the valve surgery (Fig. 1).

P2481 | BEDSIDE

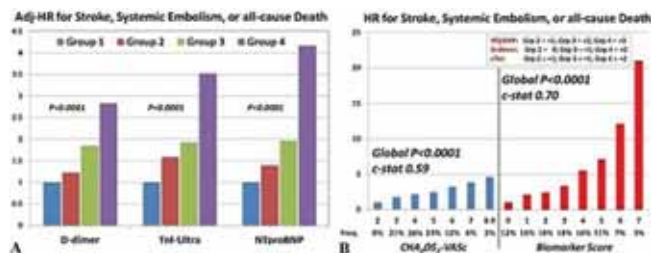
Cardiovascular biomarker score and clinical outcomes in patients with atrial fibrillation enrolled in the ENGAGE AF-TIMI 48 trial

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Background: Treatment decisions in atrial fibrillation (AF) are based on clinical assessment of the risk of stroke, systemic embolism (SEE), or death. The CHA2DS2-VASc risk score is pragmatic and widely used but has moderate discrimination. We investigated the performance of multiple cardiovascular biomarkers alone and in combination as a biomarker score for risk prediction in patients with AF.

Methods: We measured cardiac troponin (cTnI), NTproBNP, and D-dimer at baseline in 4880 subjects enrolled in the biomarker substudy of the ENGAGE-AF trial of the FXa inhibitor edoxaban vs. warfarin. All endpoints were adjudicated by a central events committee. Median follow-up was 2.8 years.

Results: Each of the biomarkers examined was associated with a graded risk of stroke/SEE/death after adjustment for the CHA2DS2-VASc score (global $p < 0.0001$, Panel A). NTproBNP, cTnI, and D-dimer each identified a >2.5 -fold gradient of risk across groups of increasing concentration. A multimarker risk score was developed, assigning tiered points for higher concentrations (Panel B). The biomarker score provided greater discrimination than CHA2DS2-VASc (Panel B) and when combined with CHA2DS2-VASc improved the c-statistic to 0.71 ($p = 0.004$ vs. markers alone; $p < 0.0001$ vs. CHA2DS2-VASc alone).



Conclusion: A multimarker risk score appears to significantly enhance the assessment of risk compared with traditional clinical risk stratification alone for stroke/SEE/death in patients with AF. Incorporation of biomarkers into clinical decision-making for anticoagulation in AF warrants consideration.

P2482 | BEDSIDE

Clinical characteristics and one-year outcomes of atrial fibrillation patients under rate- or rhythm-control strategy: From the Fushimi AF Registry

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Purpose: Atrial fibrillation (AF) increases the risks of stroke, congestive heart failure (CHF) and mortality, and the prevalence of AF is increasing significantly (reportedly, 0.6% of total population in Japan). There are two major treatment strategies for AF: rate-control and rhythm-control. Recent clinical trials in patients with AF have shown that a rate-control strategy was non-inferior in preventing clinical events, compared with a rhythm-control strategy.

Methods: The Fushimi AF Registry, a community-based prospective survey, was designed to enroll all of the AF patients in Fushimi-ku, Kyoto, Japan. Fushimi-ku is densely populated with a total population of 283,000, and is assumed to represent a typical urban community in Japan. At present, we have enrolled 3,821

patients (1.4% of total population) from March 2011 to December 2013. One-year follow-up was completed in 2,965 patients as of December 2013. We aimed to investigate differences in baseline clinical characteristics and one-year outcomes between AF patients under rate-control strategy ($n = 1,089$, 37%), rhythm-control strategy ($n = 570$, 19%), and neither of them ($n = 1,306$, 44%).

Results: The mean age was lower in rhythm-control group than rate-control or neither group (rate, rhythm, neither: 74.0 ± 10.4 , 71.7 ± 10.8 , 74.7 ± 10.1 y; $p < 0.01$). Rate-control group was lower in systolic blood pressure (121.9 ± 18.2 , 125.5 ± 18.4 , 126.3 ± 19.6 mmHg; $p < 0.01$), had higher prevalence of CHF (39.1%, 13.9%, 22.5%; $p < 0.01$), higher prevalence of coronary artery disease (19.2%, 11.0%, 13.6%; $p < 0.01$), received more oral anticoagulants (66.1%, 50.5%, 42.8%; $p < 0.01$) and more antiplatelet agents (33.5%, 28.2%, 28.7%; $p = 0.02$). Rhythm-control group was lower in resting heart rate (78.3 ± 15.5 , 74.3 ± 14.3 , 78.7 ± 16.1 bpm; $p < 0.01$), had lower CHADS2 score (2.17 ± 1.29 , 1.71 ± 1.25 , 2.11 ± 1.39 ; $p < 0.01$), fewer previous stroke (18.2%, 14.4%, 22.4%; $p < 0.01$), and were more symptomatic (47.1%, 73.7%, 40.3%; $p < 0.01$). One-year mortality was significantly lower in rhythm-control group (8.5%, 3.9%, 9.6%; $p < 0.01$), and the incidence of CHF hospitalization was significantly higher in the rate-control group (6.2%, 1.8%, 3.3%; $p < 0.01$). The incidence of stroke was not significantly different between the three groups (2.6%, 1.9%, 2.8%; $p = 0.5$).

Conclusion: The Fushimi AF registry represents the clinical profile of real-world Japanese AF patients. Rate-control and rhythm-control are two different treatment strategies of AF patients. The two strategies were selected depending on the clinical background such as age, symptom, and various comorbidities, and this affected the one-year clinical outcomes.

P2483 | BENCH

Cognitive and psychosomatic impairments in patients with different forms of atrial fibrillation

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Aims: To determine the features of cognitive and psychosomatic impairments in patients with different forms of atrial fibrillation (AF) using sensitive diagnostic techniques.

Materials and methods: We examined 81 patients (33 women and 48 men) aged 62.8 ± 9.6 years: 33 people with persistent form of AF, 34 – with paroxysmal AF, in 14 cases – permanent AF. AF cases were such disease as: hypertension in 45 patients (55.5%), ischemic heart disease in 23 people (28.4%), myocardial in 5 patients (6.2%), mitral valve defect 1 person (1.2%), idiopathic AF in 7 patients (8.6%). Comparison group of persons without AF matched by sex and age and the underlying pathology was examined. We evaluated the cognitive function of participants using the program "Status PF". Visual memory, attention span, vision field, cognitive abilities (simple analogy, linguistic thinking), neurodynamics (simple visual-motor response, complex visual-motor reaction, the reaction to a moving object). A daily monitoring of ECG was used for registration subclinical forms of atrial fibrillation.

Results: We found that decline visual memory occurred in all patients with AF. They reproduced 3.8 ± 1.5 numbers and 4.5 ± 1.5 words, whereas in the comparison group 5.5 ± 1.5 numbers and 6.0 ± 1.4 words ($p < 0.01$). Attention was declined almost twice. For example, founding of numbers in the test "vision field" by patients with AF took 32.9 ± 14.6 seconds and in the comparison group 18.4 ± 2.6 seconds ($p < 0.01$). Mild impairment mind abilities were identified. Patients earned 8.0 ± 2.7 points in the test "Linguistic Mind (induction)", versus 10.0 ± 2.0 points ($p < 0.01$) and the test "Linguistic Thinking (abstract)" - 3.88 ± 2.94 points, versus 10.0 ± 2.0 points ($p < 0.001$). Results in test "Simple analogy" and results in of the comparison group were comparable: 16.8 ± 8.1 points and 15.5 ± 3.5 points. Most significantly different parameters were registered in neurodynamic. Speed of response of the patient 666.9 ± 180.8 msec in the test "Simple visual-motor reaction", whereas in the comparison group response takes about 250-300 msec ($p < 0.001$). Test results "Reaction to a moving object" prevailed delay response by more than 5 msec compared with those without AF, which indicates the development of inhibitory processes of nervous activity.

Conclusion: All patients with AF have a mild impaired cognitive function (memory, attention, thinking, of neural processes). MRT signs of transient microcirculatory impairment may be indicate microembolic AF complications, including subclinical forms. These forms may cause cognitive impairment.

P2484 | BEDSIDE

Baseline characteristics and clinical outcomes of patients with atrial fibrillation undergoing catheter ablation: from the Fushimi AF registry

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Background: Catheter ablation (CA) has become an effective treatment for atrial fibrillation (AF), yet it is not well established as a first-line intervention for the AF management, with limited cohort investigations including clinical outcome data.

Methods: The Fushimi AF Registry, a community-based prospective survey, was

designed to enroll all of the AF patients in Fushimi-ku, Kyoto, starting from March 2011. Baseline characteristics and clinical outcome during the 1-year follow-up of AF patients who underwent CA (AF-CA: n=148) were compared with those who did not undergo CA (AF-nCA: n=2,557).

Results: AF-CA patients showed distinct baseline characteristics compared with AF-nCA patients; they were younger (67.7 year of age vs. 74.7), had less comorbidities and lower CHADS2 score (1.44 vs. 2.1). Furthermore, they were more symptomatic (85% vs. 48%), more often paroxysmal type (66% vs. 46%), and received more class I antiarrhythmic drugs (50% vs. 19%). Despite lower CHADS2 score, the use of oral anticoagulants was similar (51% vs. 54%; NS) at baseline. During the 1-year follow-up, AF-CA patients had less adverse events compared with AF-nCA; stroke or systemic embolism (0% vs. 3.2%), all cause death (1.3% vs. 7.1%), and major/minor bleeding (2.0% vs. 4.6%).

Conclusion: The Fushimi AF registry represents the clinical profile of real-world Japanese AF patients, and also could provide prospective data on indications and outcomes of CA through long-term follow-up.

CLINICAL OUTCOMES IN ATRIAL FIBRILLATION III

P2486 | BEDSIDE

Risk of acute myocardial infarction in patients with atrial fibrillation having a CHA2DS2-VASc score of 0 or 1

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Background: The risk of acute myocardial infarction (AMI) in patients with atrial fibrillation (AF) having a CHA2DS2-VASc score of 0 (for males) or 1 (for females) has not been investigated before. The goal of the present study was to compare the risk of AMI among AF and non-AF subjects with a low CHA2DS2-VASc score.

Methods: This study used the "National Health Insurance Research Database" in Taiwan. A total of 7,254 AF males (CHA2DS2-VASc score = 0) and 4,860 AF females (CHA2DS2-VASc score = 1) without receiving antithrombotic therapies were selected as the study group. For each study patient, one age-, sex-, and CHA2DS2-VASc score matched subject without AF were randomly selected to constitute the control group (n=12,114). The clinical endpoint was the occurrence of AMI.

Results: During the follow up of 5.7±3.6 years, 258 patients (1.1%) suffered from AMI with an annual incidence of 0.29% and 0.10% for AF and non-AF patients, respectively. AF was a significant risk factor of AMI with a hazard ratio (HR) of 2.927 (95% confidence interval [CI] = 2.214-3.869, p<0.001) after the adjustment for potential confounders. The Kaplan-Meier curve of freedom from AMI is shown in Figure 1. Although the AF increased the risk of AMI in AF females (HR = 4.215) more substantially than in males (HR = 2.720) compared to non-AF patients, the risk of AMI was higher in AF males than that of females with an adjusted HR of 2.235 (95% CI = 1.608-3.106, p<0.001).

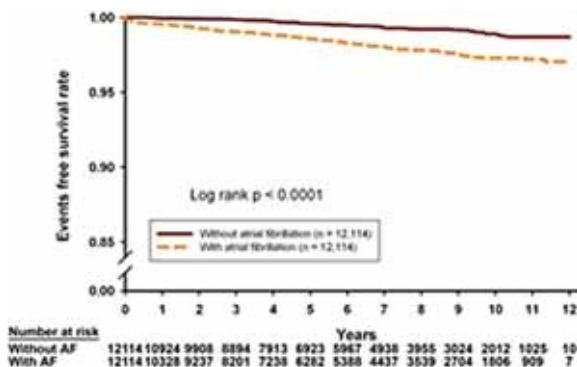


Figure 1 KM curve in AF and nonAF

Conclusions: In patients with a CHA2DS2-VASc score of 0 or 1, AF was an important risk factor of AMI.

P2487 | BEDSIDE

Predictors of left ventricular function improvement after radiofrequency ablation in a large cohort of patients referred for atrial fibrillation ablation

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Introduction: Radiofrequency Ablation (RFA) for Atrial Fibrillation (AF) is a well-established treatment modality when medical therapy fails. Patients with diminished Left Ventricular Ejection Fraction (LVEF) at baseline that recover after proper management of AF are retrospectively labeled as having Tachycardia Induced Myopathy (TIM). However, predictors of recovery at the time of the ablation have not been well defined in the literature.

Purpose: We aim to fill this gap by providing a predictor model for LVEF improvement after AF RFA.

Methods: Prospectively collected data on 37 relevant clinical variables of 153 consecutive patients with AF and decreased LVEF (<50%) that underwent RFA at a tertiary care center were analyzed. Two groups were identified: a group that fully recovered LVEF to an absolute value of ≥50% and those that did not recover to that extent. Relevant clinical variables of the two groups were compared by univariable analysis. Variables that were statistically significant at a 0.1 significance level were entered in a stepwise logistic regression analysis and kept in the final model if they were significant at the 0.05 significance level. The final multivariable logistic prediction model of LVEF recovery was assessed for goodness of fit and discriminatory power.

Results: Univariable analysis showed that being female (p: 0.015), presenting with higher pre-RFA ejection fraction (p: 0.003), absence of Internal Cardioverter Defibrillator (ICD) (p: 0.046), previous AF RFA (p: 0.019), shorter duration of the QRS (p: 0.031) and paroxysmal as compared to persistent AF (p: 0.05) were positive predictors of LVEF recovery above 50%. Age, left atrium diameter, history of coronary artery disease, rhythm and heart rate among others were not found to be associated with LVEF recovery in this cohort. The final model included baseline ejection fraction, gender, ICD and number of previous ablations (Homes Lemeshow p: 0.9093 and area under ROC: 0.7114).

Conclusions: The 4 variables that were kept in the final model may be used to identify those patients that are more likely to recover LVEF after AF RFA, provide personalized advice to patients, and serve as a guide for future research. In the future, we will validate this model in another cohort of patients.

P2488 | BEDSIDE

Left atrial mechanics predict the success of pulmonary vein isolation in patients with atrial fibrillation

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Background: Atrial fibrillation (AF) is a common arrhythmia with relevant impact on mortality and morbidity. Pulmonary vein isolation (PVI) is an established therapy in patients who remain symptomatic under optimal medical therapy. However, up to 70% of patients present with recurrence of AF after PVI. Therefore, identifying ideal candidates is an unmet clinical need. LA fibrosis is associated with reduced LA function. Analysis of left atrial mechanics using 2D speckle tracking echocardiography (STE) might give more insight into LA substrates and be therefore of predictive value.

Methods: This prospective single-center pilot study included 31 patients (mean age 62.3±9.1 years, 19 males) with AF who underwent PVI and 20 matched healthy controls (mean age 60.6±6.6 years, 10 males). 2D STE strain indices of LA reservoir (RLA), conduit, and, if feasible, contractile function were analyzed before and six months after PVI. Assessment of the LV diastolic function was based on standard indices. Responders to PVI were defined as being asymptomatic and free of AF in a 7-days Holter-ECG after 6 months.

Results: At baseline, all patients with AF had significantly lower reservoir and contractile function compared to controls. After 6 months, 17 patients (54.8%) were identified as responders. At baseline, the reservoir function was significantly higher in responders compared to non-responders (32.7±11.1% vs. 22.9±10.9%, P=0.019). Only in responders, RLA and contractile LA function improved and reached normal values whereas LA function remained unchanged in non-responders. In a ROC analysis, a RLA value of ≥19.5% discriminated responders and non-responders in patients with persistent AF with a sensitivity of 86% and a specificity of 100% (P=0.012; AUC 0.943, KI 0.81-1.0).

Conclusion: Left atrial reservoir function helps to predict efficacy of PVI after 6 months. Only in responders, reservoir and contractile function normalized within 6 months after PVI indicating a lower level of atrial remodeling at baseline. No deleterious effects of ablation were detected in non-responders.

P2489 | SPOTLIGHT

The APPLE score - a novel score for the prediction of rhythm outcomes after repeated catheter ablation of atrial fibrillation

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Background: Recurrence of atrial fibrillation (AF) occurs in up to 50% within one year after catheter ablation but prediction remains challenging. Recently, we developed a novel score for the prediction of rhythm outcomes after single AF ablation which demonstrated significant superiority to CHADS2 and CHA2DS2-VASc scores and was validated in an external data set. The current study was performed to 1) prove the predictive value of the APPLE score (one point for Age > 65 years, Persistent AF, imPaired eGFR (<60 ml/min/1.73m²), Left atrial diameter ≥43 mm, left ventricular Ejection fraction <50%) in patients undergoing repeat AF ablation and 2) compare it with the CHADS2 and CHA2DS2-VASc scores.

Methods and results: 321 consecutive patients from The Leipzig Heart Center AF Ablation Registry (60±10 years, 65% male, 70% paroxysmal AF) undergoing repeat AF catheter ablation were included. Using serial ECG and 7-day Holter

ECG monitoring between 3 and 12 months after ablation, AF recurrences >30 sec were observed in 113 patients (35%). While the CHADS2 (AUC 0.577, 95% CI 0.505-0.650, $p=0.037$) and CHA2DS2-VASc scores (AUC 0.590, 95% CI 0.518-0.663, $p=0.015$) demonstrated low predictive value, the APPLE score ranging from 0 to 5 points, showed better prediction of AF recurrences (AUC 0.617, 95% CI 0.548-0.687, $p=0.002$). Patients with APPLE score of 0 (20% of cohort), 1 (32%), 2 (23%), and ≥ 3 (8%) had AF recurrence rates of 18%, 38%, 39%, and 56%, respectively ($p=0.001$). Compared to patients with an APPLE score of 0, the risk (OR) for AF recurrences was 2.9 (95% CI 1.4-6.3, $p=0.006$), 3.0 (95% CI 1.3-6.6, $p=0.007$) and 6.0 (95% CI 2.2-16.8, $p=0.001$) for APPLE scores 1, 2, or ≥ 3 , respectively.

Conclusion: The novel APPLE score is superior to the CHADS2 and CHA2DS2-VASc scores for prediction of rhythm outcomes after repeat AF catheter ablation and may be a suitable prognosticator to identify patients with low, intermediate or high risk for AF recurrences.

P2490 | BEDSIDE

Predictors of long term outcome of single catheter ablation of atrial fibrillation in patients with ischemic and non-ischemic cardiomyopathies

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Background: Atrial fibrillation (AF) frequently coexists with cardiomyopathies and is associated with worsened cardiovascular outcome, aggravated heart failure symptoms and more frequent ventricular arrhythmia. In that context, catheter ablation which has been proved to reduce AF burden and improve left ventricular function can ameliorate those adverse effects but the identification of suitable patients is crucial. Therefore, this study aimed to evaluate predictors of long term success after AF ablation.

Methods: In 73 consecutive patients (mean age 59 ± 10 years, 85% male, mean EF $37 \pm 12\%$) with ischemic ($n=30$) or dilated cardiomyopathy ($n=43$) undergoing AF catheter ablation, the predictors of long term outcome were analysed by Cox proportional hazards model. AF recurrence was monitored with 7-day Holter ECG after 6 and 12 months after ablation.

Results: During mean follow-up of 14 ± 10 months, AF recurrence was observed in 32 patients (44%). The median freedom from AF was 11 ± 3 months and was comparable with regard to aetiology of cardiomyopathy and AF type. Multivariate model revealed diabetes mellitus (HR 2.395, 95%CI 1.063-5.398, $p=0.035$) left atrial dimension (HR 1.067 per mm increase, 95%CI 1.006-1.132, $p=0.032$) and left ventricular enddiastolic dimension (HR 0.941 per mm increase, 95%CI 0.894-0.989, $p=0.017$) as independent predictors for AF recurrence.

Conclusions: Diabetes mellitus, left atrial dimension, and left ventricular dimension are associated with late AF recurrence after catheter ablation.

P2491 | BEDSIDE

Randomized comparison of continuous and intermittent heparin infusion during catheter ablation of atrial fibrillation; COHERE (Continuous Heparin infusion REferring to ablation of atrial fibrillation)

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Background: We hypothesized that continuous heparin infusion would be favorable for maintenance of heparin concentration during catheter ablation of atrial fibrillation (AF).

Methods: One hundred forty two patients undergoing AF ablation were consecutively enrolled and randomized to intermittent or continuous heparin infusion. A 100 u/kg bolus of heparin was injected just after femoral artery puncture. The dose of heparin was determined to maintain optimal activated clotting time (ACT) (300-400 sec), which were checked every 30 minute during procedure. The primary endpoint was the frequency of the maintenance of optimal ACT.

Results: There was no significant difference of age (years, 61 ± 10 vs. 60 ± 12 , $P=0.89$), sex (male, 45/71 vs. 52/71, $P=0.5$), body surface area (m^2 , 1.73 ± 0.20 vs. 1.78 ± 0.20 , $P=0.14$) and baseline INR (1.86 ± 0.58 vs. 1.84 ± 0.48 , $P=0.82$) between intermittent and continuous group. In intermittent group, the frequency of optimal ACT was only about 55%. After learning curve, the frequency of optimal

	Intermittent infusion (n=71)	Continuous infusion (n=71)	P
Before learning curve (n=60)			
Total dose of heparin (u)	12873 $\pm$ 3924	12896 $\pm$ 3755	0.98
Heparin infusion time (hr)	2.4 $\pm$ 0.5	2.4 $\pm$ 0.6	0.91
Average of ACT (sec)	383 $\pm$ 39	330 $\pm$ 37	<0.01
Standard deviation of ACT (sec)	64 $\pm$ 34	43 $\pm$ 18	<0.01
The frequency within optimal ACT (300-400 sec)	77/143 (53.8%)	79/144 (54.9%)	0.95
After learning curve (n=82)			
Total dose of heparin (u)	13565 $\pm$ 4140	11118 $\pm$ 3106	<0.01
Heparin infusion time (hr)	2.1 $\pm$ 0.7	2.2 $\pm$ 0.6	0.57
Average of ACT (sec)	365 $\pm$ 50	345 $\pm$ 41	0.04
Standard deviation of ACT (sec)	50 $\pm$ 32	30 $\pm$ 18	<0.01
The frequency within optimal ACT (300-400 sec)	96/172 (55.8%)	128/179 (71.5%)	<0.01

ACT was raised up to about 70% with lower dose of total heparin in continuous group (Table).

Conclusions: During catheter ablation of AF, continuous heparin infusion was useful to maintain optimal ACT range with lower dose of heparin and small ACT fluctuations.

P2492 | BEDSIDE

N-acetyl cysteine for the prevention of early recurrence after radiofrequency catheter ablation in patients with persistent atrial fibrillation: a randomized, double-blind, placebo-controlled study

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Introduction: Early recurrence (ER) after radiofrequency catheter ablation (RFCA) in patients with atrial fibrillation (AF) is associated with endothelial dysfunction caused by iatrogenic myocardial injury. Although N-acetylcysteine (NAC) may effectively reduce the incidence of post-operative AF, there was no data regarding effect of NAC on prevention of ER after AF ablation.

Methods: We randomly assigned 100 consecutive patients with persistent AF to NAC ($n=50$) or placebo ($n=50$) group. NAC was intravenously infused for 1 h before RFCA at a dose of 50 mg/kg, followed by continuous infusion for 48 h after RFCA at a dose of 50 mg/kg/day. Immediately before and after RFCA, index of microvascular resistance (IMR) was assessed at left anterior descending coronary artery and blood samples were obtained from coronary sinus for analysis of nitric oxide (NO) and activated leukocyte cell adhesion molecule (ALCAM).

Results: There were no significant differences between 2 groups in baseline demographics, CHADS2 score, and left atrial volume (LAV). IMR and ALCAM was increased, and NO was decreased after RFCA. Compared with placebo group, changes in IMR and NO were significantly diminished in NAC group. During follow-up period of 3 months, AF recurred 19 patients in placebo group and 7 patients in NAC group ($P=0.007$). In multivariate logistic analysis, NAC administration, LAV, and change in IMR were independently related to ER.

Conclusions: NAC administration was significantly reduced ER after RFCA in patients with persistent AF. These might attribute to prevent the deterioration of endothelial function caused by iatrogenic myocardial damage.

P2493 | BEDSIDE

Incidence and clinical characteristics of transient ST-T elevation during transseptal catheterization for atrial fibrillation Ablation

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Background: Transient ST-T elevation is a rare complication during transseptal catheterization. This study aimed to delineate the incidence, characteristics of transient ST-T elevation during transseptal catheterization for atrial fibrillation (AF) ablation.

Methods: From January 2006 to January 2013, consecutive patients underwent transseptal catheterization for circumferential pulmonary vein radiofrequency ablation in our hospital were enrolled prospectively. Breakthrough transseptal catheterization was performed guided by fluoroscopy.4

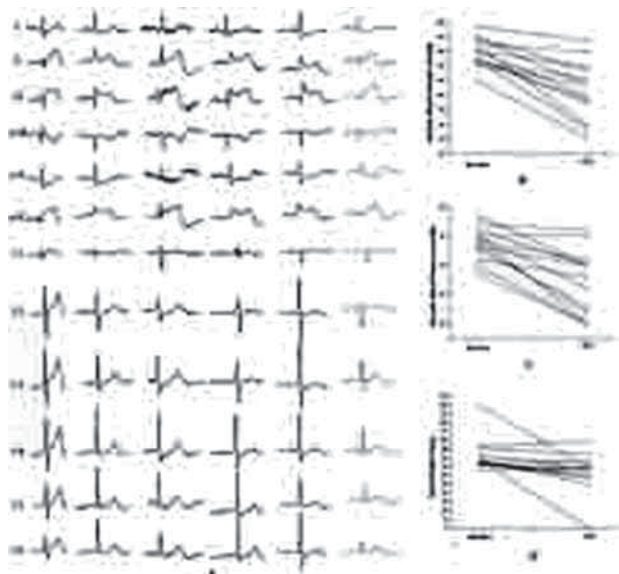


Figure 1

Results: Out of the 3452 patients, 13 patients (0.38%) (mean age 57 ± 8 , 6 female, 12 paroxysmal AF, mean left atrial diameter 35.4 ± 3.8 mm) had ST-T elevation during transseptal catheterization (Fig. 1A). ST-T elevation was found after transseptal puncture in 10 patients and after pulmonary vein venography in 3 patients. The systolic blood pressure (129 ± 10 mmHg VS. 104 ± 20 mmHg, $P < 0.001$) (Fig. 1B), diastolic blood pressure (78 ± 6 mmHg VS. 64 ± 11 mmHg, $P < 0.001$) (Fig. 1C) and heart rate (83 ± 19 bpm VS. 64 ± 23 bpm, $P = 0.022$) (Fig. 1D) significantly decreased when ST-T elevation was found. Eleven patients complained of chest pain, one patient complained of dizziness and one patient had no symptoms. Coronary artery angiography was performed in one patient with negative finding. All the patients recovered in 4.2 mins (2–10 mins) with dopamine or fast saline iv drip. Catheter ablation of AF was completed in all the patients without sequelae and other complications. Four of the 13 patients (30.8%) had recurrence after a mean 21.7-month follow-up.

Conclusion: ST-T elevation was a rare complication of transseptal catheterization without sequelae. Catheter ablation of AF could be safely completed in these patients.

P2494 | SPOTLIGHT

Presence and extent of coronary artery disease as predictor for AF recurrences after catheter ablation? The Leipzig Heart Center AF Ablation Registry

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Background: Previous studies have suggested that occlusion of the right coronary artery (RCA) promotes atrial fibrillation (AF) by creating a right atrial substrate. However, the presence and extent of coronary artery disease (CAD) is usually not considered to tailor AF ablation strategies. In particular, right atrial ablation is not routinely being performed in patients with RCA disease. Therefore we analyzed the possible association between the presence and extent of CAD and rhythm outcomes of left-atrial AF catheter ablation.

Methods and results: 1310 patients (60 ± 10 years, 67% males, 63% paroxysmal AF) from The Leipzig Heart Center AF Ablation Registry undergoing de novo AF catheter ablation were included. Of those, 152 patients (11.6%) had significant CAD (stenosis $> 50\%$); 89 (59%) had one, 35 (23%) two and 28 (18%) three vessel disease; 72 (47%) patients had RCA involvement. AF recurrences were defined as any atrial arrhythmia occurring within first week (early recurrences, ERAF) or between 3 and 12 months (late recurrences, LRAF) after ablation and were assessed with serial 7-day Holter ECG. In CAD patients, 38% suffered ERAF and 34% LRAF which was comparable to 37% and 33% in non-CAD patients ($p = 0.848$ and 0.787 respectively). Among patients with CAD, neither the location (RCA versus non-RCA, 38% and 37%, $p = 0.879$ for ERAF and 39% versus 32%, $p = 0.420$ for LRAF) nor the extent of CAD (single versus multiple vessel disease, 37% and 43%, $p = 0.516$ for ERAF and 32% versus 46%, $p = 0.131$ for LRAF) were associated with rhythm outcomes after AF catheter ablation.

Conclusions: The presence and extent of CAD seems not to impact on rhythm outcome of AF catheter ablation in the entire cohort. However, individualized AF ablation strategies need to be assessed to improve overall outcomes.

P2495 | BEDSIDE

NT-proBNP as a marker for silent AF

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Background: Atrial fibrillation (AF) is a common cause of ischaemic stroke. This risk can be ameliorated using oral anticoagulant (OAC) therapy. Screening for atrial fibrillation (AF) using pulse palpation is recommended above the age of 65 according to the European Society of Cardiology. AF detection remains difficult however, as it can be intermittent, and asymptomatic.

NT-proBNP is an established cardiac biomarker, indicating congestive heart failure. It can also be used as a predictor for stroke risk in patients with AF, especially if used in addition to the CHA2DS2-VASc risk stratification score. An increased NT-proBNP is associated with development of AF.

Methods: The STROKESTOP study is a mass-screening study using intermittent ECG recordings for detection of undiagnosed atrial fibrillation (AF) comprising 6 888 screened individuals. Preliminary results show that 3% of the screened population have previously unknown AF, and furthermore that 2% of the participants had known AF, that was not treated with OAC. In a substudy to the STROKESTOP study 89 patients with undiagnosed AF and 500 patients without detected AF had blood samples drawn for NT-proBNP analysis.

Results: Individuals with newly diagnosed AF ($n = 89$) had a NT-proBNP mean of 555 ± 583 , vs those in sinus rhythm ($n = 500$) mean 268 ± 408 ($p = 0.011$). Clinical characteristics did not differ between the groups.

Conclusion: A significantly increased NT-proBNP was found in individuals with silent AF as compared to individuals without AF. NT-proBNP can be used as a marker for undiagnosed/silent AF.

ISCHAEMIA AND CARDIOPROTECTION

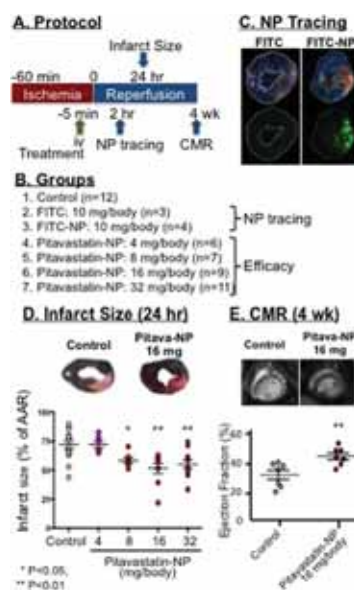
P2497 | BENCH

Nanoparticle-mediated targeting of pitavastatin into reperfused myocardium reduces ischemia-reperfusion injury in a preclinical pig model

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Background: There is an unmet need to develop an innovative cardioprotective modality for acute myocardial infarction, for which current interventional reperfusion therapy is hampered by ischemia-reperfusion (IR) injury. We recently reported that nanoparticle (NP)-mediated treatment with pitavastatin exerts cardioprotection from IR injury through activation of PI3K-Akt pathway and inhibition of inflammation in rat IR model. To obtain a preclinical proof of concept, this study examined effects of pitavastatin-NP on IR injury in a conscious pig model.

Methods and results: Forty-eight mini-pigs were surgically instrumented with a cuff occluder at the left circumflex coronary artery (LCX) and telemetry transmitters to continuously measure an electrocardiogram, arterial blood pressure, heart rate. LCX was occluded for 60 minutes and intravenously treated with FITC, FITC-NP or pitavastatin-NP 5 min before reperfusion under conscious conditions (Fig. A, B). Tracing study showed that FITC-NP but not FITC solution accumulated in the ischemic myocardium (Fig. C). Pitavastatin-NP dose-dependently reduced infarct size (Fig. D). Cardiac magnetic resonance (CMR) revealed that pitavastatin-NP (16 mg/body) improved ejection fraction 4 weeks after IR injury (Fig. E). Treatment with pitavastatin-NP increased the phosphorylation of Akt, reduced apoptosis and oxidative stress in the myocardium, but exerted no effects on blood pressure, heart rate or serum biochemistry.



Conclusion: NP-mediated targeting of pitavastatin protects the heart from IR injury without apparent adverse side effects in a preclinical conscious pig model. We are planning to submit this result to the Investigational New Drug and carry out a phase I/II clinical trial.

P2498 | BENCH

Inhibition of DPP-4 restores myocardial autophagic flux and reduces mortality after myocardial infarction in diabetic rats

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Purpose: The mechanism by which diabetes increases mortality after myocardial infarction (MI) remains unclear. In this study, we examined the hypothesis that disturbed autophagic processes are involved in aggravation of heart failure after myocardial infarction (MI) by type 2 diabetes mellitus (T2DM), which is treatable by a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Methods and results: Body weight (625 ± 8 vs. 523 ± 5 g), fasting plasma glucose (FPG: 288 ± 41 vs. 135 ± 6 mg/dl) and glycoalbumin (15.3 ± 2.0 vs. $10.1 \pm 0.7\%$) were significantly higher in OLETF, a rat model of obese T2DM, than in LETO, a non-diabetic control (both 25–30 weeks of age). Treatment with vildagliptin (10 mg/kg/day), a DPP-4 inhibitor, for 2 weeks did not significantly affect body weight, FPG or glycoalbumin level in OLETF. Under baseline conditions after a 12-hr fast, levels of phospho-Akt, -mTOR and -p70S6 kinase in the myocardium

were lower and phospho-AMP kinase and -ULK-1 were higher in OLETF than in LETO, indicating pro-autophagic signaling in OLETF. LC3-II level was higher in OLETF than in LETO, though p62 protein levels were comparable. The mRNA levels of LAMP2, Rab7, and cathepsins were similar in LETO and OLETF. At 12 hrs after MI by ligation of the left coronary artery, LC3-II protein in the non-infarcted remote myocardium increased in LETO. In OLETF, however, LC3-II protein was decreased and p62 protein accumulated in the non-infarcted remote myocardium after MI, indicating disruption of autophagic clearance. Treatment with vildagliptin increased LC3-II level and reduced p62 protein after MI in OLETF, indicating restoration of autophagic flux. The effects of vildagliptin on autophagic flux were mimicked by exenatide (10 mg/kg/day), a GLP-1 receptor agonist. Mortality at 48 hrs after MI in OLETF (70%) was significantly higher than that in LETO (19%). Vildagliptin did not affect post-MI mortality in LETO (17%) but significantly reduced mortality in OLETF (20%). The mitigation of mortality in OLETF by vildagliptin was mimicked by exenatide (37%) and was abrogated by chloroquine (10 mg/kg/day), an inhibitor of autophagy (67%), administered for 7 days before MI.

Conclusion: The findings suggest that disturbed autophagic clearance in the non-infarcted myocardium contributes to increased severity of heart failure by T2DM. Inhibition of DPP-4 reduces post-MI mortality presumably by restoration of autophagic processes in the non-infarcted region of the diabetic myocardium.

P2499 | BENCH

Carbon monoxide releasing molecule alters microRNA expression and improves structural and functional cardiac recovery after myocardial injury

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Purpose: Carbon monoxide (CO), produced by heme oxygenase-1 (HO-1) from heme, is an endogenous paracrine factor involved in the regulation of blood pressure, cardiac structure and function. The mechanisms behind the cardioprotective properties of CO are still poorly understood. We studied the effects of a synthetic CO releasing molecule (CORM-3) on cardiac remodelling and repair after myocardial injury as well as on expression of microRNAs (miRNAs), novel molecules regulating gene function.

Methods: Male Wistar rats with myocardial infarction (MI), induced by coronary ligation (n=75), or sham-operated controls (n=75) were treated from day 4 to day 14 after MI either with synthetic CORM-3 (20 mg/kg i.p.) or with inactive iCORM and sacrificed at 2, 4 or 8 weeks after MI. Infarct size, amount of cardiomyocytes, and vascular and capillary densities in the infarct and border areas were determined. Ki67 staining was used to quantify proliferative cells and c-kit staining to determine stem/progenitor cells. Cardiovascular disease miScript miRNA PCR Array was used for miRNA profiling and real time RT-PCR for quantification of individual miRNAs. Western blotting was utilized to evaluate protein expression and echocardiography to assess cardiac structure and function.

Results: Treatment with CORM-3 enhanced recovery of MI compared with iCORM. CORM-3 increased the proportion of cardiomyocytes ($p < 0.05$ vs. iCORM) and capillary and vascular densities ($p < 0.05$ vs. iCORM) in the infarct area. Ejection fraction improved ($p < 0.05$) and left ventricular volumes decreased ($p < 0.05$) in CORM-3 treated MI groups compared to iCORM treated rats with MI. The amount of Ki67+ cardiomyocytes or c-kit+ progenitor cells did not differ between CORM-3 and iCORM MI groups. Compared to iCORM treated rats, CORM-3 treatment increased protein expression of angiogenic factors VEGF-B, Hif-1 α , HGF and PGF, and up-regulated the expression of several miRNAs (including miR-133a and miR-208a) which were down-regulated at weeks 2 and 4 after MI.

Conclusions: The synthetic CO releasing molecule CORM-3 improved both structural and functional cardiac recovery after myocardial injury. These effects were associated with increased expression of angiogenic factors and altered expression of several miRNAs involved in myocardial homeostasis, remodelling, and repair. Modulation of HO-1-CO axis and selected miRNAs may prove novel drug targets to facilitate cardiac recovery after myocardial injury.

P2500 | BENCH

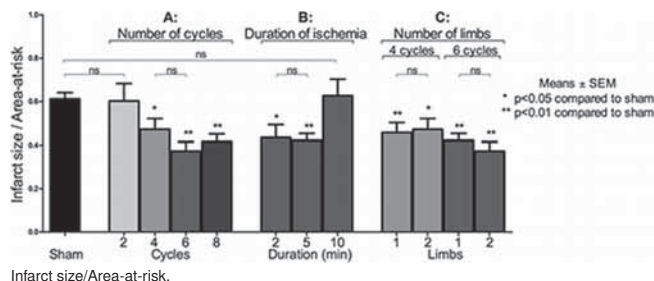
Optimizing the cardioprotective effects of remote ischemic preconditioning

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Purpose: Remote ischemic preconditioning (rIPC) induced by brief periods of ischemia and reperfusion (IR) to a limb induces protection against cardiac IR injury. The extent to which the number of cycles, duration of each cycle and quantity of muscle mass determines the efficacy of rIPC for cardioprotection remains unknown. To optimize the efficacy of rIPC-induced cardioprotection, we investigated the impact of each of these potential determinants.

Methods: Using male C57BL/6 mice, we compared sham with rIPC treated animals (n=10 in each group). The rIPC-protocol consisted of; (A) 2, 4, 6 or 8 cycles, (B) 2, 5 or 10 min duration of ischemia in each cycle and (C) single or two hind-limb occlusions. Each period of ischemia was followed by 5 min of reperfusion. Limb ischemia was induced by using a compressing tourniquet. Following rIPC, hearts were subjected to 25 min of global ischemia and 60 min of reperfusion in an ex-vivo perfusion model. Cardioprotection was evaluated by infarct size and post-ischemic hemodynamic function.

Results: The number of rIPC-cycles increased the efficacy of cardioprotection up to 4 cycles, whereas no further protection was seen with 6 and 8 cycles. The amount of muscle mass (number of limbs) had no influence on the efficacy of protection. Cycles of 2 min ischemia offer the same protection as cycles of 5 min, whereas elongated cycles of 10 min ischemia abrogated protection. Post-ischemic hemodynamic function improved in parallel with infarct size.



Conclusions: The number and duration of rIPC cycles, rather than the mass of the effector organ, determine the efficacy of rIPC. rIPC protocols using prolonged periods of ischemia (10 min) do not protect against IR.

P2501 | BENCH

Bnip3 is associated with Bax activation during myocardial ischemia/reperfusion-injury in vivo

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Purpose: An acute myocardial infarction (AMI) is associated with cell death of cardiac myocytes via apoptosis and necrosis. The mitochondrial outer membrane permeabilization (MOMP) at the onset of myocardial reperfusion is a major determinant of cardiomyocyte death via apoptosis. MOMP is regulated by pro- and anti-apoptotic Bcl-2 family members. BH3-only proteins, functions as a sensor of stress and transduce these signals to the downstream effectors Bax and Bak, which activation results in the formation of the MOMP, release of apoptogens and finally to caspase activation and cell death. One interesting BH3-only proteins is "Bcl-2 family members BCL2/adenovirus E1B 19kDa protein-interacting protein 3" (Bnip3). Bnip3 is expressed in adult murine and human hearts. The canonical function of Bnip3 during myocardial Ischemia/Reperfusion (I/R) injury is considered to be the trigger of the Bax/Bak pore formation. In an ex vivo I/R model the inhibition of Bnip3 led to a reduction of the infarct size and release of the apoptogens cytochrome C and apoptosis inducing factor (AIF). But the underlying mechanisms are still unidentified.

Methods and results: In vivo I/R showed no influence on the transcription and the expression of Bnip3 in mice hearts. To localize Bnip3 we isolated cytosol and mitochondria and separated mitochondria outer and inner membrane fraction. We found, that Bnip3 monomer and dimer are localized in cytosol and mitochondria outer membrane. We could show that Bnip3 interact in vivo with Bax by immunoprecipitation and EPR-spectroscopy. Using the TAT-fusion protein TAT-Bnip3 Δ TM (encoding the carboxyl terminal transmembrane deletion mutant of Bnip3 which act as a dominant negative blocker of Bnip3-induced cell death) we performed an inhibition of Bnip3 and analysed the impact on the infarct size in a murine in vivo I/R-Model with 30min of ischemia and 24h of reperfusion. The inhibition of Bnip3 led to a significant reduction of the infarct size (37 ± 7 vs. $18 \pm 3\%$ INF/AAR, $n=5$, $p=0.0007$) whereas the overexpression using TAT-Bnip3 led to an increase ($49 \pm 9\%$ INF/AAR, $n=9$, $p=0.048$). To show, that Bnip3 is involved in Bax activation we analyzed the concentration of active monomer Bax in vivo after 30min ischemia and 5min and 4h reperfusion with and without overexpression of Bnip3 using Western Blot. The overexpression led to an earlier activation of Bax. There was an increase of active Bax after 5min whereas under basal condition we found these increase after 4h.

Conclusion: Bnip3 is involved in cell death during myocardial I/R injury by activation of the pore forming factor Bax.

P2502 | BENCH**Postconditioning increases Nrf2 transcriptional activation via PKC pathway and protect hearts against reperfusion injury**

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Purpose: Our goal is to provide further information on the endogenous protective mechanisms activated by postconditioning (PostC) in the myocardium, evaluating the activation of the transcription factor Nrf2 by the cardioprotective kinases PKC and PI3K.

Methods and results: Myocardial post-ischemic damage in vivo was produced in male rats by occluding the left anterior descending coronary artery followed by 10 and 60 min of reperfusion (IR group). PostC was applied after artery occlusion (IR+PostC), followed by 10 and 60 min of reperfusion. Haemodynamic parameters i.e., left ventricular pressure, heart rate, +dP/dt and -dP/dt were maintained in IR+PostC group in compare to IR group. Accordingly, both infarct size and ROS levels were significantly lower in IR+PostC than in the IR group. At such levels, ROS played a role as signaling molecules triggering the intrinsic myocardial protective mechanisms, as we observed an important increase in Nrf2 phosphorylation at Ser40 and Thr/ Tyr residues, which concurred with PKC and PI3K activation. We also observed a higher binding capacity of Nrf2 to the ARE sequence after 60 min of reperfusion and an augmented antioxidant response. Significant increase in both the protein levels and in the enzymatic activity of antioxidant proteins regulated by Nrf2: glutathione S-transferase (GST), copper/zinc-superoxide dismutase (Cu/Zn-SOD) and γ -glutamyl cysteine synthetase (γ -GCS) was observed. To determine the role of cardioprotective kinases in the activation of the Nrf2 pathway, we inhibited PKC or PI3K and evaluated Nrf2 activation, along with the expression and activity of downstream antioxidant enzymes. Our results indicate that PKC is crucial for Nrf2 activation, since its inhibition with chelerythrine was associated with decreased Nrf2 phosphorylation, lower ARE-binding capacity and diminution in protein levels and enzymatic activities of GST, Cu/Zn-SOD and γ -GCS. Therefore, we propose that the PKC/Nrf2 signaling pathway is part of the endogenous protective mechanisms activated by PostC. On the other hand, we found that PI3K inhibition diminished cardiac performance, although Nrf2 is not target of PI3K, at least not directly.

Conclusions: We propose that the PKC/Nrf2 pathway activation is critical for long-term maintenance of PostC-conferred cardioprotection against reperfusion injury by increasing the antioxidant defense system.

P2503 | BENCH**Cardioprotective and angiogenic effects of miRNAs in human cardiac progenitor cell exosomes**

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Background: Exosomes (Exo), actively secreted nanosized membrane vesicles, are being recognized as crucial carriers of proteins, mRNA and miRNA between cells, representing a key component of intercellular communication. We have shown that Exo from human cardiac progenitor cells (Exo-CPC) significantly reduced cardiomyocyte (CM) apoptosis and stimulated angiogenesis both in vitro and in vivo. We analyzed the miRNA transcriptional profile of Exo-CPC compared to exosomes from normal human dermal fibroblasts (Exo-NHDF).

Methods: CPC were derived from atrial explants of patients who underwent heart valve surgery. Exo, precipitated with ExoQuick, were characterized by electron microscopy and FACS analysis. miRNA profiling was analyzed with RT-PCR based assays. Transfection-based miRNA gain- and loss-of-function studies were performed in CM and HUVEC.

Results: Exo-CPC were 46.2±16.9 nm in size. They expressed the Exo markers CD9, CD63, and CD81. miRNA transcriptional profiling identified miRNA132, miRNA133a, miRNA146a-3p, miRNA181a, miRNA210-3p and miRNA323-5p among the most highly upregulated miRNA in Exo-CPC vs. Exo-NHDF. miRNA323-5p in Exo-CPC was further upregulated after CPC exposure to hypoxia in vitro. Transfection of pre-miRNA323-5p, pre-miRNA181a, and pre-miRNA132 into HL-1 CM significantly enhanced tolerance to hy-

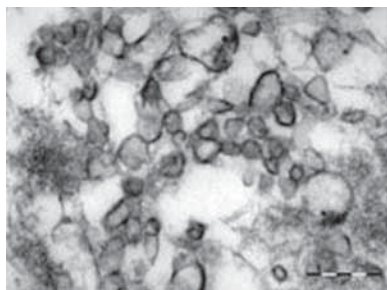


Figure 1. Exosomes.

poxia/reoxygenation injury ($p < 0.05$ vs. CTRL). Forced miRNA132 overexpression in HUVEC exerted angiogenic effects.

Conclusions: Exo-CPC are cardioprotective both in vitro and in vivo. They are markedly enriched in anti-apoptotic and pro-angiogenic miRNA compared to Exo-NHDF. Hypoxia further increases cytoprotective miRNA in Exo-CPC. Finally, in gain-of-function experiments we identified cardioprotective miRNA against hypoxia/reoxygenation injury.

P2504

ABSTRACT WITHDRAWN

P2505 | BENCH**Infarct size variations induced by left coronary artery ligation in experimental myocardial infarction model: angiographic analysis of coronary anatomy**

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Purpose: Experimental groups with comparable myocardial infarction (MI) are difficult to establish. We determined whether infarct size variations induced by left coronary artery (LCA) ligation might be caused by coronary artery branching pattern.

Methods: We examined coronary anatomy in normal Lewis rats (n=50) and an

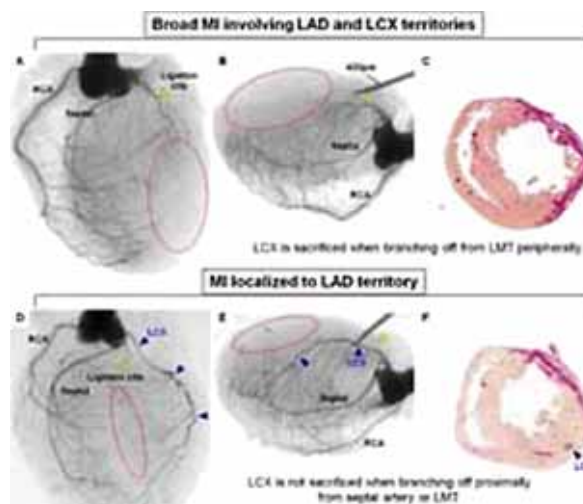


Figure 1. Coronary angiography in MI rats.

MI model induced by LCA ligation immediately below (high ligation, $n=50$) or 2 mm distal to left atrial appendage (LAA) (low ligation, $n=25$). Barium sulfate in 7% gelatin was injected into a coronary artery via a catheter inserted from the right carotid artery, and histological analyses were performed.

Results: The rats had a large septal artery arising invariably from proximal part of the LCA ($n=30$) or right coronary artery ($n=20$). Thirty-three (66%) showed left circumflex artery (LCX) branching peripherally from a relative long left main trunk (LMT), and the others (34%) had an LCX from the proximal part of the septal artery or a short LMT. In the low ligation group, MI localized to an LAD territory was universally created. In the high ligation group, 64% ($n=32$) had broad MI involving the LAD and LCX territories, and the others (36%) had MI localized to an LAD territory, with intact LCX branching from the septal artery or a short LMT proximally to the LAA (figure). Territory of the septal artery was not sacrificed in any MI model, because of its anatomical feature.

Conclusions: Infarct size variations were caused not only by ligation site but also by varying LCX branching patterns. There are potential risks to create different extents of MI, particularly when targeting a broad range of MI, while creation of an MI model involving a septal territory is impossible.

P2506 | BENCH

Metabolic and molecular approaches to treatment of de novo acute heart failure (AHF)

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Purpose: Acute heart failure (AHF) is a clinical emergency, with high mortality and re-hospitalizations. Our model of de novo AHF examines the molecular survival activating factor enhancement (SAFE) pathway activated by sphingosine-1-phosphate (S1P), a component of HDL. S1P activates SAFE pathway by binding to its receptors which via the phosphorylation of signal transducer and activator of transcription 3 (STAT3) translocate to the nucleus and promote cell survival and improve recovery. We tested the involvement of the S1P-activated SAFE pathway in rat hearts subjected to de novo AHF. We also examined the combined effect of metabolic therapy by glucose-insulin (GI) and S1P.

Methods: AHF was induced by a reducing the perfusion pressure of the Langendorff perfused rat heart from 100cm H₂O to 20cm H₂O. Acute stress was imposed in the AHF phase by low glucose (2.5mmol/L) and elevating free fatty acids (FFA) (1.3mmol/L), thus creating combined hypotensive and metabolic stress. GI 11.1mmol/L and 0.3mU respectively was added in the recovery phase following AHF, S1P (10nM) was also added in separate experiments. The involvement of the (SAFE) pathway was examined, by AG490, an inhibitor of SAFE, and by Western blots for activation of signal transducer and activator of transcription 3 (STAT3).

Results: S1P improved the heart rate (HR) versus controls (148.8 ± 26.4 vs. 37.9 ± 9.7 ; $n=6$; $p<0.01$) BPM. Treatment by AG490 reduced heart rate vs. S1P (42.3 ± 17.1 vs. 148.8 ± 26.4 ; $p<0.05$ vs. S1P+AG490; $n=6$). STAT3 was increased ($p<0.05$) in the nuclear fraction in hearts treated with S1P vs. those treated with S1P+AG490. There was no change in the LV developed pressure. Combined GI and S1P in the recovery phase improved HR vs. controls (214.4 ± 19.2 vs. 66.5 ± 22.6 BPM; $p<0.001$ vs. controls; $n=8$) and improved LV developed pressure, indicating better contractility (177.2 ± 38.6 vs. 20.5 ± 8.3 mmHg, $p<0.001$ vs. controls; $n=8$).

Conclusions: S1P activates the SAFE pathway by up-regulating STAT3 in the nuclear fraction in model de novo AHF and improves cardiac function by increasing HR, thus indicating enhanced sinus node activity. The combination of metabolic GI and molecular S1P therapies improve HR and contractility, thus suggesting principles of future therapy against AHF.

GROWTH FACTORS AND CARDIAC SIGNALING PATHWAYS

P2508 | BENCH

Cardiomyocyte apoptosis in patients with severe aortic stenosis. Potential involvement of microRNA-10b

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Purpose: Cardiomyocyte apoptosis may have a detrimental impact on cardiac structure and function in patients with severe aortic stenosis (AS), as shown for other cardiopathies. On the other hand, microRNAs may regulate this process.

Methods: Endomyocardial biopsies were obtained from 28 patients with AS during valve replacement. Left ventricular (LV) morphology and function were assessed by echocardiography. Cardiomyocyte apoptotic index (CMAI) was quantified by TUNEL. Bax, Bcl-2 and BNIP3 were determined by western blot. MicroRNA profile was studied in 10 patients (5 from each subgroup) by TLDA, validating those of interest by real time RT-PCR in the whole population. microRNAs potential target genes were identified with the Microcosm, miRanda and PicTar databases.

Results: Cardiomyocyte apoptosis was increased ($P<0.01$) in AS patients compared with control subjects. By cluster analysis of CMAI, 2 subgroups of patients were identified: subgroup 1 (CMAI $\leq 0.08\%$; $n=16$) and subgroup 2 (CMAI $> 0.08\%$; $n=12$). The higher activation of the apoptotic process in subgroup 2 patients was verified by a higher expression ($P<0.05$) of the Bax/Bcl-2 and BNIP3/Bcl-2 ratios. Subgroup 2 patients showed a lower cardiomyocyte density ($P<0.001$) and LV ejection fraction ($P<0.05$), and a higher prevalence of clinical heart failure ($P<0.05$) and NT-proBNP levels ($P<0.05$) than patients from subgroup 1. Additionally, CMAI was inversely associated ($P<0.05$) with cardiomyocyte density and LV ejection fraction and directly associated ($P<0.05$) with NT-proBNP in all patients.

The TLDA analysis showed 70 microRNAs altered ($P<0.05$) more than 4-fold in patients from subgroup 2 compared with subgroup 1, with 64 down-regulated and 6 up-regulated. Focusing on those with the highest fold-change, the repression in patients from subgroup 2 of miR-10b and miR-338-3p ($P<0.05$), which present pro-apoptotic predicted target genes (e.g. caspase 9 and Fas ligand), was validated in the whole AS population. These microRNAs were inversely associated ($P<0.05$) with the CMAI. Additionally, miR-10b inhibition in HL-1 adult cardiomyocytes increased ($P<0.05$) the susceptibility of these cells to suffer apoptosis both in baseline conditions and in the presence of staurosporine.

Conclusion: Cardiomyocyte apoptosis is increased in AS patients, mainly in a subgroup of patients, and is associated with diminished cardiomyocyte density and the development of heart failure. MiR-10b down-regulation may be involved in this process, emerging as a potential therapeutic target.

P2509 | BEDSIDE

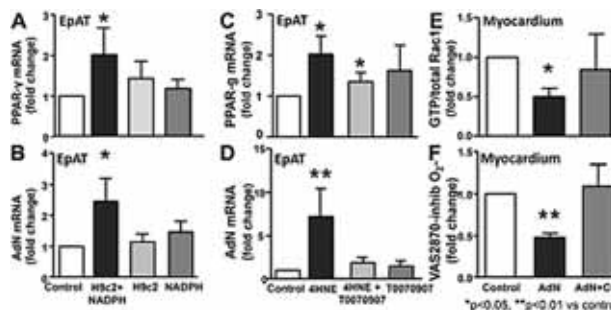
Myocardial redox state as a regulator of PPAR-gamma signalling in epicardial adipose tissue of patients with ischemic heart disease: insights from the Oxford CABG Bioresource

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Background: Epicardial adipose tissue (EpAT) may have a role in heart disease development via the release of active adipokines. We've studied the impact of myocardial redox state on EpAT biology in patients undergoing coronary artery bypass grafting (CABG) as well as the effects of AdN on myocardial redox state.

Methods: In 250 patients from the Oxford CABG Bioresource (OCB) undergoing elective CABG we collected EpAT and right atrial appendage (RAA) samples. In additional 55 patients, EpAT was incubated a) +/- H9c2 cardiomyocytes +/- NADPH 100uM, b) +/- the oxidation malonyldialdehyde (MDA, 1mM), c) +/- 4-hydroxynonenal (4HNE, 30uM) +/- the PPAR-gamma inhibitor T0070907 (20uM) for 16h. RAA was incubated ex-vivo +/- AdN (10ug/mL) +/- Compound C (CC, 10uM) for 2h. EpAT was used for gene expression studies, while RAA samples for western blots and lucigenin-enhanced chemiluminescence experiments to assess O₂-generation and NADPH oxidase activity (+/-NADPH 100uM, +/-VAS2870 40uM).

Results: In OCB, higher levels of myocardial NADPH oxidase activity were associated with higher AdN gene expression in EpAT (not shown). As shown in Figure, PPAR- γ (A) and AdN (B) gene expression were increased in EpAT that was co-incubated with NADPH-stimulated H9c2 cells. 4-HNE increased PPAR- γ (C) and AdN expression in EpAT (D) in a T0070907-inhibitable manner, while MDA had no effect. AdN inhibited Rac1 activation (E) and reduced NADPH oxidase activity in RAA (F) in an AMPK dependent manner (reversed by CC).



Conclusions: We propose for the first time a novel "inside to outside" signal from the myocardium to EpAT: under conditions of increased myocardial oxidative stress 4-HNE induces a PPAR- γ -mediated upregulation of AdN gene in EpAT, which then exerts a paracrine inhibition of myocardial NADPH oxidase.

P2510 | BENCH**Effects of adipokines in cardiac structure**

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Heart failure (HF) represents a major and growing problem in the developed countries and several risk factors, such as obesity, are associated with its development. Obesity is defined as a pro-inflammatory state associated with an increased secretion of factors, named adipokines, which regulate the function of several organs and tissues. Epicardial adipose tissue segregates adipokines that can act in a paracrine and vasocrine manner on the myocardium, exerting direct effects in fibroblasts and cardiomyocytes. This project aimed at investigating the potential role of adipokines in cell proliferation and collagen production by cardiac fibroblasts and evaluating the crosstalk between epicardial adipose tissue and the myocardium.

Experimentally, atria tissue from 25th week old ZSF1 lean (ZSF1 Ln, n=11) and ZSF1 obese (ZSF1 Ob, n=11) rats was used for the isolation of cardiac fibroblasts, as well as for obtaining conditioned medium from pericardial adipose tissue. Fibroblasts were cultured separately with apelin (100 nM) and adiponectin (10 µg/ml). After 48h, BrdU assays and Sirius Red staining were performed in order to evaluate the effect of those adipokines in cell proliferation and collagen production, respectively. Moreover, organotypic cultures were obtained from cardiac explants from 7 day-old Wistar rats and incubated with conditioned medium from pericardial adipose tissue of obese and lean groups. After 24h of incubation, fibrosis and cross-section area of hematoxylin-eosin stained cardiomyocytes were assessed.

Incubation with apelin and adiponectin led to a significant increase in fibroblasts' proliferation in both groups (p=0.0496). In ZSF1 Ln, apelin induced a significant decrease in collagen secretion, while in ZSF1 Ob it increased collagen secretion and production (p=0.0054). Adiponectin significantly reduced collagen synthesis in both groups and decreased collagen secretion in ZSF1 Ln (p<0.001). Regarding the organotypic cultures, pericardial adipose tissue secretome from obese rats triggered a significant increase in fibrosis deposition (3.48±1.51% vs 4.79±1.53%, p<0.05) and in the cross-section area of cardiomyocytes (100.7±18.98 µm² vs 111.25±24.02 µm², p<0.05), compared with the secretome from lean animals.

Adipokines produced by adipose tissue depots from obese animals seem to modulate the cardiac structure, through changes in extracellular matrix components and cardiomyocytes, features typically related to the appearance of diastolic dysfunction.

P2511 | BEDSIDE**Modulation of the transforming growth factor-beta effects in mitral valve prolapse**

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Purpose: The impact of angiotensin II receptor blockers (ARB) on extracellular matrix production by inhibition of the transforming growth factor-β (TGF-β) has been shown recently in vitro in cultured valvular interstitial cells obtained from patients with mitral valve prolapse (MVP) undergoing mitral valve repair.

Our aim was to evaluate the effect of ARB therapy on TGF-β serum level and possible impact on valve myxomatous degeneration in vivo.

Methods: A total of 233 asymptomatic patients (mean age: 53.8±12.9) with severe mitral regurgitation (MR) due to mitral valve prolapse were enrolled in our retrospective, non-randomized, single-center study between 2009 and 2011. Concentrations of TGF-β1 and β2 in serum were determined by enzyme-linked immunosorbent assay. Standard echocardiography extended with assessment of MR volume and length and thickness of the mitral valve leaflets was performed in all patients (EchoPAC[®]08, GE).

Results: According to the case reports only 43 patients (18.5%) received losartan or telmisartan (study group). Majority of the patients (190; 81.5%) did not receive any ARBs (control group). There were no significant differences between groups in age (54.8±11.3 vs. 52.6±12.9; p=0.26), other medical treatment (β-blockers: 39% vs. 36%; χ²=0.16, p=0.69 and diuretics: 27% vs. 33%; χ²=0.36, p=0.55), heart rate (82.6±14.4 vs. 74.2±15.7 b.p.m.; p=0.0007) and blood pressure (135.5±17.8 vs. 142.4±15.1 mm Hg; p=0.009).

TGF-β1 levels despite large dispersion were significantly higher in subjects without ARB therapy (55.9±70.7 ng/ml) than in ARB group (16.1±32.9 ng/ml; p=0.0003), as well TGF-β2 (7.6±0.5 vs. 2.2±1.5 ng/ml; p<0.0001).

Subjects in control group had significantly longer (anterior leaflet: 28.6±3.5 vs. 23.4±3.1 mm, p<0.0001; posterior leaflet: 15.2±2.6 vs. 13.8±2.9 mm, p=0.002) and thicker (anterior leaflet: 4.2±1.1 vs. 3.5±1.4 mm, p=0.0004; posterior leaflet: 5.0±1.3 vs. 3.7±0.82 mm, p<0.0001) mitral valve leaflets (echocardiographic signs of myxomatous degeneration) than in ARB group. Mitral regurgitation had the similar effective regurgitant orifice area (0.38±0.12 vs. 0.40±0.14 cm²; p=0.38) and volume (69.5±9.8 vs. 72.3±8.6 ml; p=0.08) by PISA in both groups.

Conclusions: Patients with MVP and significant MR may benefit in valve myxomatous degeneration, but not in MR volume from ARB therapy, probably due to its ability to inhibit TGF-β signaling.

P2512 | BENCH**Antagonism of protease-activated receptors salvages vascular endothelial dysfunction in KK-Ay diabetic mice: a novel mechanism of rivaroxaban, an oral factor Xa inhibitor**

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Purpose: Protease activated receptors (PARs) are G protein-coupled receptors that are known to regulate endothelial nitric oxide synthase (eNOS) activity. Ser1177 and Thr495 are regulatory sites of eNOS, which control production of nitric oxide (NO), a vasodilator of arteries. In endothelial cells, coagulation factor Xa and thrombin are known to synergistically activate PAR-1 and PAR-2, but the roles of PARs in diabetic endothelial dysfunction are largely unknown.

Methods: Diabetic male KK-Ay mice were treated with normal chow containing 0.005% rivaroxaban, a factor Xa inhibitor, or vehicle for 3 weeks. Age-matched male mice served as controls. Vascular responses to phenylephrine, acetylcholine and sodium nitroprusside were evaluated in ex vivo aortic rings. Phosphorylation of eNOS-Thr495, a negative regulatory site of eNOS, and -Ser1177, a positive regulatory site of eNOS, was determined using Western blot analysis with phosphospecific antibodies and was normalized to total levels of eNOS. Levels of transcriptional factors and cytokine mRNA were determined by semi-quantitative RT-PCR.

Results: Treatment of KK-Ay mice with rivaroxaban did not affect food intake, body weight, blood pressure and metabolic parameters evaluated in oral glucose tolerance test and insulin tolerance test. However, treatment of KK-Ay mice with rivaroxaban recovered vascular dilatation response to acetylcholine (two-way ANOVA p<0.05), while responses to phenylephrine and sodium nitroprusside were comparable between vehicle- and rivaroxaban-treated KK-Ay mice. Phosphorylation of eNOS-Thr495 and -Ser1177 in KK-Ay was improved by rivaroxaban toward to wild type. In vitro experiments using Human Umbilical Vein Endothelial Cells (HUVEC) demonstrated that autoclaved glucose and Nε-(carboxymethyl)lysine (CML), an important advanced glycation endproducts (AGE) found in vivo, increased levels of phospho-eNOS at Thr495, but decreased phospho-eNOS at Ser1177. Rivaroxaban inhibited these AGE-induced alterations of eNOS phosphorylation.

Conclusions: These results suggest that antagonism of protease-activated receptors salvages vascular endothelial dysfunction in KK-Ay diabetic mice via attenuation of eNOS phosphorylation by AGE contents. The pleiotropic effects of rivaroxaban other than anti-coagulation activity may be beneficial for vascular endothelial function.

P2513 | BENCH**PPAR-gamma and Lipocalin mediates stress induced insulin resistance**

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Introduction: Several studies clearly show that chronic stress increases the risk of metabolic syndrome and cardiovascular diseases. The mechanisms through which this association occurs are yet largely unknown. At this level the role of white adipose tissue (WAT) and inflammation is gaining increasing attention due to its involvement in obesity and diabetes. The main objective of this study was to explore the role of WAT and its regulators in the pathophysiology of metabolic syndrome and stress-related insulin resistance.

Methods: Weight matched adult rats were equally divided in two groups. The experimental group was submitted to a chronic unpredictable stress protocol during four weeks while the control group was gently handled throughout. After stress half of the animals were sacrificed and an extensive analysis was performed comprehending morphologic, metabolic and molecular parameters. The other half was allowed to "recover" during five additional weeks and a similar analysis was performed afterwards.

Results: Stress triggered an insulin resistance phenotype that persisted after recovery. Animals submitted to chronic stress displayed a glucose intolerance phenotype with higher levels of glucose during the glucose tolerance test after stress (AUC: 11890±1282 vs. 15495±1893, p<0.01) and after recovery (AUC: 12210±1815 vs. 15150±1136; p<0.05). In accordance, insulin levels were elevated after stress (0.79±0.58 µg/mL vs. 2.21±0.81 µg/mL, p<0.05) and after recover (0.94±0.45 µg/mL vs. 1.88±0.44 µg/mL, p<0.05). The molecular analysis showed that chronic stress significantly decreased the expression of PPAR-gamma in the WAT both after stress (fold-change to controls of 0.47±0.10, p<0.05) and after recovery (fold-change to controls of 0.68±0.04, p<0.05). Chronic stress significantly increased the levels of Lipocalin-2 (Lcn2; a recently described adipokine implied in inflammatory response) in WAT after stress (fold-change to controls of 5.45±2.32, p<0.01). Given the multiple sources of Lcn2 in mammals an immunohistochemistry was performed to ascertain the origin of this inflammatory molecule; its analysis revealed Lcn2-positive infiltrating cells in the WAT after stress.

Conclusion: These data suggest that the deregulation of PPAR-gamma expres-

sion and the generation of a pro-inflammatory environment driven by Lcn2 in the WAT might underlie stress-related insulin resistance.

P2514 | BENCH

Investigation of action potential properties of native atrial and ventricular cardiomyocytes from the early embryonic to the adult stage allows the determination of the developmental stage of iPSCM

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Purpose: Cardiomyocytes (CM) derived from induced pluripotent stem cells (iPSCM) are promising candidates for cell therapy, drug screening and developmental studies. They possess immature electrophysiological properties, but an exact characterization of their developmental stage and subtype differentiation is hampered by a lack of knowledge of action potential (AP) properties of native CM from different developmental stages. Thus, we have investigated AP properties of murine CM and established a database that allows classification of iPSCM.

Methods: Hearts from 129S2PasCrl were harvested at days 9-10, 12-14 and 16-18 post coitum as well as 1 day, 3-4 days, 1-2 weeks, 3-4 weeks and 6 weeks post partum. Until day 12 p.c. AP recordings in left and right atria and at apical, medial and basal left and right ventricles were performed with glass microelectrodes in preparations of the whole chambers. Older ventricles were not sufficiently supplied by diffusion and dissected into 150 µm thick viable tissue slices; recordings were performed in apical, medial and basal slices. AP recordings of iPSCM were performed in early- (day 11-16 of differentiation, EDS) and late (day 21-26, LDS) stage embryoid bodies.

Results: During pre- and postnatal development, APs of atria and ventricles underwent significant changes. In both, atria and ventricles, the maximal diastolic potential (MDP) became more negative from days 9-10 p.c. to 1-2 weeks p.p. AP duration at 50% of repolarization (APD50) decreased considerably in atria and ventricles from days 9-10 p.c. to 3-4 weeks p.p. and increased slightly until 6 weeks. APD90 in atria and even more in ventricles decreased from days 9-10 p.c. to 1-2 weeks p.p. and then increased until 6 weeks, resulting in a consistent decrease of APD50/90 ratio in atria and ventricles from days 9-10 p.c. to 6 weeks p.p. No significant differences were found between left and right atria as well as apical, medial and basal left and right ventricles. AP measurements in EDS and LDS iPSCM showed an increase of MDP and a decrease of APD50, APD90 and APD50/90 with time. The developmental stage and subtype of differentiation could be classified according to the data gathered from native CM: EDS iPSCM matched ventricular CM at days 9-10 p.c., LDS iPSCM matched ventricular CM at days 3-4 p.p.

Conclusions: Significant changes in AP morphology occur during pre- and postnatal murine heart development. This systematic analysis enables a classification of developmental stage and subtype differentiation of stem cell-derived cardiomyocytes and supports that iPSCM undergo a physiological developmental process.

P2515 | BENCH

TMEM16A mediated calcium-activated chloride current synchronizes repolarization within mammalian ventricular myocardium

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Background: Recently identified TMEM16A is responsible for calcium-activated chloride current (ICl(Ca)) in the heart. Opening of this channel contributes to transient outward current; however, it can potentiate formation of delayed afterdepolarizations, especially in calcium-overloaded cells. The aim of this work was to study the role of ICl(Ca) in various regions of ventricular myocardium.

Methods: Electrophysiological studies were performed using conventional sharp microelectrode, whole-cell patch-clamp and action potential (AP)-clamp techniques in enzymatically dissociated canine cardiomyocytes. ICl(Ca) was dissected by perfusion of anthracene-9-carboxylic acid (9-AC, 0.5 mM). Western blot analysis and immunofluorescence of TMEM16A were carried out to visualize its distribution pattern in different regions of canine ventricular myocardium.

Results: Blocking of ICl(Ca) increased AP duration (APD) in midmyocardial and subendocardial cells (from 233.00±9.12 ms and 211.35±16.00 ms to 257.34±10.82 and 227.20±17.41 ms, n=15 and n=7, respectively), while decreased that in myocytes derived from the subepicardial layer (from 195.18±6.05 ms to 181.99±11.08 ms, n=7). APD was increased with a greater extent by 9-AC in cells isolated from basal position and having longer initial APD compared to apical ones (from 251.72±11.99 ms and 234.52±8.72 ms to 282.01±11.03 ms and 252.15±10.44 ms, n=13 and n=16, respectively). Application of 9-AC increased the beat-to-beat variability of repolarization (from 2.33±0.09 ms to 3.19±0.22 ms, n=30). In spite of different effect on APD, similar current amplitudes were recorded in every ventricular region, which is supported by the identical expression pattern of TMEM16A in the canine ventricle. The amplitude of the current was about twice as much compared to control during sympathetic activation mimicked by the beta-adrenoceptor agonist isoprenaline (10 nM) (1.15±0.11 pA/pF

in control, n=13 and 2.43±0.11 pA/pF in isoprenaline, n=4). Blockade of this current prevented AP shortening during beta-adrenergic activation. Occurrence of early afterdepolarizations (EAD) was increased after ICl(Ca) blockade, especially at low heart rates and sympathetic activation.

Conclusion: ICl(Ca) equilibrates the apparent transmural and apico-basal temporal difference in repolarization, diminishes the extent of beat-to-beat variability of APD in the ventricles and has a protective role against generation of EAD.

P2516 | BENCH

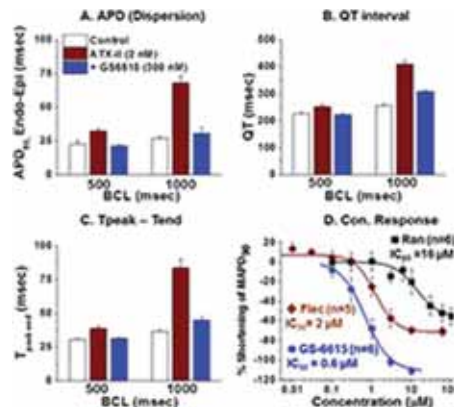
A novel, potent, and selective inhibitor of cardiac late sodium current reduces transmural dispersion of repolarization and suppresses experimental arrhythmias

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Purpose: Enhanced, pathological late Na⁺ current (late I_{Na}) in the mammalian heart is pro-arrhythmic. Inhibition of this current is a novel strategy to suppress afterpotentials and sodium-dependent calcium overload associated with cardiac arrhythmias. This study introduces GS-6615 (dihydrobenzoxazepinone), a potent and selective inhibitor of late I_{Na} that is currently in clinical development for the treatment of ventricular tachyarrhythmias.

Methods: The effects of GS-6615 to inhibit cardiac late I_{Na} versus other ion currents were determined using rabbit isolated ventricular myocytes, isolated left ventricular wedge preparation and perfused hearts. Anti-arrhythmic actions of GS-6615 were characterized in ex vivo models of reduced repolarization reserve in comparison to ranolazine (Ran) and flecainide (Flec).

Results: GS-6615 inhibited late I_{Na} in ventricular myocytes with an IC₅₀ of 0.13 µM and did not prolong action potential duration (APD) and QT or QRS intervals (surrogates for inhibitions of I_{Kr} and peak I_{Na}) in rabbit isolated heart. GS-6615 reduced the ATX-II induced increase in transmural dispersion of repolarization (TDR; APD90, endocardium – APD90, epicardium), QT interval and Tpeak-Tend (Panels A-C) in rabbit isolated wedge preparation. Compared to Ran (IC₅₀ = 16 µM) and Flec (IC₅₀ = 2 µM), GS-6615 was potent (IC₅₀ = 0.6 µM) in preventing and reversing the pro-arrhythmic effects (afterpotentials, torsades de pointes) of the late I_{Na} enhancer ATX-II in rabbit isolated heart (Panel D).



Conclusions: Our results show that selective inhibition of late I_{Na} is effective in suppressing arrhythmogenic markers (afterpotentials and TDR) associated with ventricular tachyarrhythmias.

P2517 | BENCH

Plasma concentrations of afamin are associated with the prevalence and development of metabolic syndrome

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Aims: Afamin is a human plasma vitamin E-binding glycoprotein primarily expressed in the liver and secreted into the bloodstream. Since little is known about (patho)-physiological functions of afamin, we decided to identify phenotypes associated with afamin by investigating transgenic mice overexpressing the human afamin gene and performing large-scale human epidemiological studies.

Methods and results: Transgenic mice overexpressing afamin revealed increased body weight and serum concentrations of lipids and glucose. We applied a fixed-effects meta-analysis using age- and sex-adjusted baseline and follow-

up investigations in the population-based Bruneck (n=826), SAPHIR (n=1499), and KORA F4 Studies (n=3060). Mean afamin concentrations were 62.5 ± 15.3 , 66.2 ± 14.3 , and 70.6 ± 17.2 mg/L in Bruneck, SAPHIR and KORA F4, respectively. Per 10 mg/L increment in afamin measured at baseline, the number of metabolic syndrome components increased by 19% (incidence rate ratio (IRR)=1.19 (95%CI 1.16-1.21), $p < 0.0001$). With the same afamin increment as used at baseline we observed an 8% gain in components between baseline and follow-up (IRR=1.08 (95%CI 1.06-1.10), $p < 0.0001$). Afamin concentrations at baseline were highly significantly related to all individual metabolic syndrome components at baseline and follow-up. This observation was most pronounced for elevated waist circumference (OR=1.79 (95%CI 1.54-2.09), $p < 0.0001$) at baseline and OR=1.46 (95%CI 1.31-1.63), $p < 0.0001$ for change during follow-up and for elevated fasting glucose concentrations (OR=1.46 (95%CI 1.40-1.52), $p < 0.0001$, and OR=1.46 (95%CI 1.24-1.71, $p < 0.0001$, respectively).

Conclusion: This study in transgenic mice and more than 5,000 participants in epidemiological studies in humans shows afamin being strongly associated with the prevalence and development of metabolic syndrome and all its components.

INTEGRATIVE PHYSIOLOGY

P2519 | BEDSIDE

Evaluation of cardiac axis changes related to obesity and aging by surface electrocardiogram and cardiac computed tomography

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Background: Changes in the cardiac electrical axis measured with surface electrocardiogram (EKG) are postulated to be related to changes in cardiac orientation. We sought to determine the correlation between in vivo cardiac orientation using cardiac computed tomography (CT) and the electrical cardiac axis in the frontal plane determined by surface EKG in young to middle aged individuals without structural heart disease. We then compared this with age matched obese individuals and older individuals without structural heart disease.

Methods: 124 patients who underwent CT coronary angiography were studied retrospectively. Group 1 included those between 30 and 60 years old with a normal body mass index (BMI). Group 2 included those between 30 and 60 years old who were obese. Group 3 included those greater than 60 years old with a normal BMI. Those with structural heart disease or thoracic deformities were excluded. In vivo cardiac orientation was determined along the long axis on CT and correlated with the electrical cardiac axis on surface EKG.

Results: In Group 1 (n=59), the mean CT axis was $38.1 \pm 7.8^\circ$ (20.9° – 56.2°) whilst the mean EKG axis was $51.8 \pm 26.6^\circ$ (-37.6° – 125.8°), Pearson r value 0.12 ($p=0.365$). In Group 2 (n=36), the mean CT axis was $25.1 \pm 6.2^\circ$ (11.65° – 38.21°) whilst the mean EKG axis was $20.1 \pm 23.9^\circ$ (-28.1° – 56.3°), Pearson r value 0.05 ($p=0.808$). In Group 3 (n=29), the mean CT axis was $34.4 \pm 9.1^\circ$ (15.48° – 52.1°) whilst the mean EKG axis was $34.4 \pm 30.3^\circ$ (-30° – 82.4°), Pearson r value 0.26 ($p=0.209$). The CT and EKG axis had a more leftward rotation in Group 2 compared with Group 1 ($p < 0.0001$). The CT axis however did not appear to be markedly different in Group 3 compared with Group 1 ($p=0.05$), whilst there was a leftward swing of the EKG axis ($p=0.01$).

Conclusion: There is no simple relationship between an individual's anatomical and electrical cardiac axis. Obese individuals have a more leftward rotation of both their axes when compared with age-matched normals, which may be secondary to elevation of the diaphragm. Older individuals had a more leftward rotation of their electrical cardiac axis only, which may reflect underlying conduction disturbances in this age group.

P2520 | BENCH

Calcification of the coronary arteries identifies the least vulnerable vessel or lesion: a pathology study

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Aim: The aim of the current study is to assess if calcification of the coronary artery is able to predict the disease burden and vulnerability of a lesion.

Methods: Sudden coronary deaths were selected from the institute's coronary artery pathology database based on the availability of a post-mortem X-ray performed following removal of the epicardial coronary arteries from the heart. On X-ray the total artery and the calcification area of the left main and three coronary arteries were measured. All coronary arteries were serially sectioned at 3-4 mm intervals, embedded in paraffin, and stained with H&E and Movat pentachrome. All histologic sections were evaluated for the type of lesion according to modified AHA criteria, quadrants of calcification, type of calcification (micro, focal, sheet, or nodular), and percentage stenosis.

Results: A total of 54 sudden cardiac deaths (207 vessels, 3195 lesions) were divided into three groups based on total area percentage of calcification on X-ray (17 low-Ca <5%, 19 medium-Ca $\geq 5\%$ – $\leq 20\%$, 18 high-Ca >20%). Percentage calcification increased with age (low 45, medium 56, high 61 years; $p=0.001$) and was higher in diabetics (diabetes 42% vs. non-diabetes 14%; $p < 0.001$). Fibrocal-

cific plaque was more frequently observed in the high-Ca compared to the low-Ca (low 7%, medium 24%, high 50%; $p < 0.001$) and calcified sheets often involved 3 to 4 quadrants of the plaque. In contrast, prevalence of pathological intimal thickening (PIT) and fibroatheroma was less in high-Ca compared with medium-Ca and low-Ca (low-Ca 60%, medium-Ca 39%, high-Ca 21%; $p < 0.001$). Increasing stages of plaque progression were associated with greater percent area stenosis, higher calcification burden and more severe types of calcification. The amount of calcification was a determinant of plaque vulnerability with 50% of plaque ruptures seen in low-Ca of the vessel, as compared to only 13% of cases with high-Ca of the vessel.

Conclusion: In a cohort of sudden coronary death cases, progression of coronary plaque is associated with higher percentage stenosis and coronary calcification. Moreover, calcification burden of the coronary vessel is associated with a decrease in prevalence of PIT and fibroatheroma, and increase in fibrocalcific plaques. Plaque rupture occurs most frequently in those with less calcification. In conclusion, coronary calcification burden of the coronary system is not associated with an increased risk of acute coronary events.

P2521 | BEDSIDE

Prevalence and clinical features of microfistulas between coronary artery and left ventricle: Single center experience

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Objectives: Coronary artery fistulae are an infrequent malformation and the prevalence was reported approximately 0.1-0.4% according to previous studies. However, there is not enough study about microfistulas from coronary arteries to the left ventricle especially Turkish People. The purpose of this study was to evaluate the prevalence and clinical features of microfistulas in subjects undergoing coronary angiography for the assessment of coronary artery disease.

Study design: In this retrospective study, we have researched the cardiac catheterization laboratory database between January 2008 and July 2013. The presence of microfistulas was established according to the following criteria: 1) direct filling of the heart cavity during selective coronary injection without interposing "capillary" phase or venous filling; and 2) visualization of small vessels interposed between the epicardial coronary vessels and the heart cavity and emptying into the heart.

Results: Microfistulas were found in 12 (0.11%) of the 11403 coronary angiographies. There were seven (58.3%) female patients; mean age was 70.2 ± 10.8 years and contemporary severe coronary artery stenosis was noted in two (16.7%) patients. Chest pain was the most frequently encountered complaint and second one was dyspnea. Microfistulas were originated from the left anterior descending artery (100%), circumflex artery (66.7%), and right coronary artery (58.3%). In addition, multiple microfistulas were seen in six (50%) patients, bilateral microfistulas in three (25%) patients and unilateral microfistula in three (25%) patients, and all of them were terminated in the left ventricle.

Conclusion: Our study found an overall 0.11% percent incidence of microfistulas. Furthermore, microfistulas are rare cardiac anomaly which sometimes cause cardiac symptoms and otherwise is detected during routine coronary angiography.

P2522 | BENCH

Human heart failure is associated with sodium channel mRNA degradation mediated by reduced HU proteins

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Human heart failure has been associated with reduced cardiac sodium channel current, in part because of a reduction in SCN5A mRNA abundance. Reduced SCN5A is thought to contribute to the arrhythmic risk in heart failure. The reduction in cardiac SCN5A mRNA abundance is reflected in circulating white cells that also express SCN5A. We hypothesized that reduced mRNA stability would contribute to reduced SCN5A mRNA abundance in heart failure. The SCN5A mRNA 3'-untranslated region (UTR) contains two sets of AU-rich elements (ARE), which mediate ARE-mediated mRNA decay. Hu proteins, members of the ARE-binding protein family, were overexpressed in human cardiomyocytes and were found to increase wild-type SCN5A mRNA level significantly. Wild-type SCN5A mRNA increased 46.3% ($P=0.004$) and 60.7% ($P=0.008$) with HuR and HuB overexpression, respectively. This suggested Hu family proteins might play an important role in regulation SCN5A expression by stabilizing SCN5A mRNA. HuR is one of the members of Hu protein family, and its mRNA was decreased 38.9% ($P=0.034$) in peripheral white blood cells of heart failure patients with implanted cardioverter-defibrillator (ICD) and evidence of appropriate event-driven therapy. The decrease of HuR mRNA correlated with a reduction of wild-type SCN5A mRNA expression in these patients. Our results demonstrate an additional layer of SCN5A post-transcriptional regulation in addition to alternative splicing that can contribute to sodium channel downregulation in heart failure. In addition, our results suggest

that circulating HU protein assessment may be useful in arrhythmic risk stratification, and HU protein elevation may help reduce arrhythmic risk in heart failure.

P2523 | BENCH

Metformin protects against cardiac mitochondrial dysfunction and improves insulin response in rats fed high fat diet

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A diet rich in fatty acids is known to induce insulin resistance and the metabolic syndrome. Furthermore, such diet may impair mitochondrial function and cardiac dysfunction may develop. Metformin (MET) is an antidiabetic drug and the first-line drug of choice for the treatment of type 2 diabetes. MET decreases hyperglycemia primarily by suppressing glucose production by the liver. The molecular mechanism of MET is incompletely understood; one suggested mode is activation of AMPK. However, another mechanism is inhibition of complex I and therefore increasing the AMP/ATP ratio. This mechanism contrasts with the positive effects of MET in type II diabetes.

Therefore, we assessed the influence of MET treatment on cardiac and mitochondrial function during chronic high fat feeding.

Male Sprague-Dawley rats received either standard diet (SD - 9% cal. from fat) or high fat diet (HFD - 60% cal. from fat). Additionally, animals received an oral dose of MET (300mg/kg/d) or placebo. At the age of 23 weeks, cardiac function (echocardiography), glucose tolerance (i.p. GTT 2g/kg), cardiac mitochondrial function (respiratory capacity) and cardiac insulin response (Western blot analysis) were assessed.

HFD induced body weight gain was significantly attenuated with MET (NC 556±17 vs. HFD 629±8 vs. NC-MET 452±16 vs. HFD-MET 561±18g). This reduction in weight gain through MET was also confirmed by a decrease in epididymal fat. Echocardiography revealed no long term influence of either HFD or MET on cardiac morphology, systolic and diastolic function (E/E': 16.7±1.6 vs. 17.2±0.5 vs. 14.1±0.9 vs. 17.0±0.6).

Whole body glucose tolerance was attenuated with HFD and treatment with MET did not improve this loss in sensitivity (AUC: 775±41 vs. 1051±85 vs. 914±89 vs. 1184±56). Furthermore, cardiac insulin response was significantly reduced with HFD suggesting cardiac insulin resistance. This decrease in insulin sensitivity was abolished with MET (Akt/P-Akt: 2.13±0.07 vs. 1.45±0.14 vs. 1.98±0.15 vs. 1.82±0.10).

Concomitantly, with cardiac insulin resistance, cardiac mitochondrial function was also deteriorated. Maximal respiratory capacity of isolated mitochondria was significantly reduced with HFD. Treatment with MET was able to compensate for this reduction (glutamate: 316±36 vs. 216±19 vs. 437±147 vs. 319±23; succinate: 550±5 vs. 440±38 vs. 661±163 vs. 635±47 nmoles O/min/mg). Coupling between ATP production and oxygen consumption was unaffected by HFD and MET.

Oral treatment with metformin improves cardiac insulin sensitivity and prevents mitochondrial dysfunction triggered by high fat diet.

P2524 | BENCH

Long-term serotonin reuptake inhibitor administration enhances diet-induced obesity and impairs leukocyte recruitment into adipose tissue in mice

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Purpose: Metabolic syndrome leads to aseptic inflammation of visceral adipose tissue and insulin resistance and strongly associates with atherosclerosis. Increased food intake promotes adipocyte growth and recruitment of pro-inflammatory immune cells to the adipose niche. We recently observed that platelet-derived serotonin promotes neutrophil recruitment to sites of acute inflammation and therefore hypothesized that serotonin affects traits of the metabolic syndrome.

Methods: Wild-type (WT) in the presence and absence of a selective serotonin reuptake inhibitor (SSRI, fluoxetine) or tryptophan hydroxylase (Tph-) ¹–/– mice lacking non-neuronal serotonin consumed high fat diet for 16 weeks. Leukocytes were analyzed by flow cytometry.

Results: SSRI administration reduced platelet serotonin levels by 80%. During HFD body weight increased by 100.3±5% in WT, 112.8±4% in SSRI-treated

mice - but only by 72.2±10% in Tph1–/– mice (n≥8, p<0.01). Food intake assessed by metabolic caging did not differ between the groups. Tph1–/– mice showed improved insulin tolerance and glucose tolerance was significantly impaired. These data suggest an insulin secretion deficiency. While macrophage content in visceral adipose tissue was similar, that of CD8+ T-cells was reduced from 20.1±2.1% in WT to 7.6±0.8% (p<0.01) in Tph1–/– mice and 14.6±2.3% (p=0.1) in mice treated with SSRI.

Conclusion: Lack of platelet-derived serotonin in Tph1–/– mice protects from diet-induced obesity and pro-inflammatory leukocyte recruitment into adipose tissue. SSRI-treated mice are protected from leukocyte infiltration but gain more weight in response to HFD. This identifies serotonin as an important mediator at the interface of metabolic disease and inflammation.

P2525 | BENCH

Inducible, heterozygous Ryr2 knockout mice reveal a key role for SR Ca2+ release in cardiac metabolism

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Background: Heart failure is a multi-faceted condition characterized by numerous functional lesions including contractile dysfunction and metabolic inflexibility. The cardiac ryanodine receptor (RyR2) Ca²⁺-release channel plays an essential role in excitation contraction and is functionally reduced by up to 50% in multiple models of heart disease including both hypertensive and diabetic cardiomyopathies. Given that Ca²⁺ release is known to stimulate oxidative energy metabolism, RyR2 is poised to have an additional role in pacing cardiomyocyte metabolism. To test which aspects of heart failure may be downstream of RyR2 dysfunction, we have developed a model whereby RyR2 protein is reduced to a stable 50% level in adult cardiomyocytes. The overall objective of our research is to test whether a 50% reduction in RyR2 signalling can be an upstream driver of cardiac pathology and metabolic dysfunction.

Methods and results: We generated a conditional, haploinsufficiency model for RyR2 function by crossing mice with only one floxed RyR2 allele with a cardiac specific, tamoxifen-inducible Cre deleter mouse line. This deletion led to a stable 50% decrease in RyR2 mRNA and RyR2 protein levels a month after tamoxifen injection. Despite decreased RyR2 levels, no significant changes were observed in cardiac output measured by echocardiography or in the contractility of isolated cardiomyocytes. Only minor decreases in cardiac output were observed during ex vivo perfusion of isolated working hearts. However, we did observe a significant decrease in glucose oxidation during working heart perfusion despite no significant reductions in ATP levels or in the oxidation of other metabolic substrates. Unbiased proteomic and metabolomic analyses identified significant decreases in key TCA cycle intermediates and a compensatory up-regulation of Ca²⁺ sensitive metabolic proteins. Targeted biochemical analysis revealed further mechanistic details linking partial RyR2 ablation to metabolic changes. Collectively these results indicate that a chronic, stable 50% decrease in RyR2, even without alterations in heart function, is sufficient to alter cardiac cellular metabolism and impede the use of glucose as a substrate for oxidative ATP metabolism.

Conclusions: These results provide evidence that RyR2 is critically involved in stimulating oxidative metabolism in cardiomyocytes. Furthermore, these findings show that RyR2 dysfunction is able to disrupt cardiac metabolism regardless of its effects on excitation-contraction, which suggests a role for RyR2 dysfunction in mediating cardiac dysfunction in heart disease.

P2526 | BENCH

Direct load- and heart rate-independent control of ventricular contractility by a distinct population of vagal preganglionic neurones

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Purpose: To identify vagal preganglionic neurones which directly control left ventricular contractility using an experimental model to fix loading and heart rate conditions, applying this model to pharmacological activation and pharmacogenetic inhibition of neurones from the dorsal motor nucleus of the vagus nerve (DMVN). **Methods:** Male Sprague-Dawley rats (380-420g) were anaesthetised with pentobarbitone sodium (induction 60 mg/kg i.p.; maintenance 15–20 mg/kg/hr i.v.) and artificially ventilated. Femoral artery and vein were cannulated to monitor arterial blood pressure (ABP) and for the infusion of fluid and drugs.

Following C1 spinal transection and atenolol (2mg/kg/h i.v.) treatment to remove sympathetic tone, vasopressin (30pg/kg/h i.v.) was infused to restore ABP. Transoesophageal atrial pacing (confirmed with lead II ECG) and fixed loading conditions allow the maximum first differential of left ventricular pressure (LVdP/dt max) to be used as a load independent index of contractility. With the prone head stereotactically fixed, the dorsal surface of the brainstem was exposed. Bilaterally, three discrete regions (0.5 mm apart) of vagal preganglionic neurones were activated by microinjection of the excitatory neurotransmitter glutamate (10mM, 40 nl, pH 7.4) verified by concurrent injection of fluorescent microspheres. In a second group, DMVN neurones were transduced with a lentiviral vector (LV)

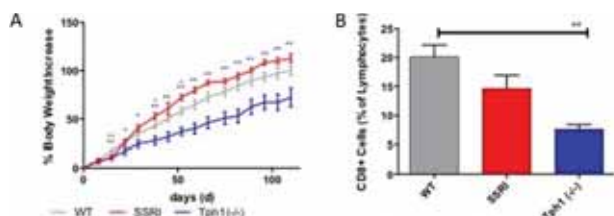


Figure 1: WT, SSRI-treated and Tph1^{-/-} mice consumed a high fat diet (HFD) for 16 weeks. Relative bodyweight increase during 16 weeks of diet is displayed as percentage of bodyweight before feeding. (B) CD8+ cytotoxic T-cells in visceral adipose tissue (VAT) were determined by flow cytometry.

to express an inhibitory Gi-protein-coupled *Drosophila* allatostatin receptor (AlstR). Application of the AlstR ligand – the insect peptide allatostatin (5 μ M) produced rapid and reversible silencing of targeted vagal preganglionic neurones. These were targeted with two stereotaxic microinjections of a viral suspension containing either PRSx8-AlstR-eGFP-LV or PRSx8-eGFP-LV control.

Results: Activation of neurones in the left caudal DVMN resulted in a significant load-independent decrease in LVdP/dt max by -692 ± 193 mmHg/s ($n=11$, $p<0.0025$). This effect was abolished following intravenous administration of atropine methyl nitrate (2mg/kg, $n=7$). Acute inhibition of the DVMN neurones expressing AlstR following application of allatostatin resulted in a significant increase in LVdP/dt max by 922.3 ± 193 mmHg/s ($n=6$, $p<0.001$).

Conclusion: The data obtained challenges the prevailing view which persists in both the scientific and educational literature that the vagal innervation of the ventricle is sparse and insignificant. We demonstrate direct load- and heart rate-independent tonic control of ventricular contractility by a distinct population of vagal preganglionic neurones.

P2527 | BENCH

miR-208a/b decreases cardiac L-type Ca²⁺ current by targeting CACNA1C and CACNB2 mRNA

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Purpose: Recent evidence have demonstrated that microRNAs, small non-coding RNA that regulate expression of target mRNA by binding to their 3'-untranslated regions (3'-UTR), can be partially responsible of the atrial fibrillation (AF)-induced electrical remodelling. Among them, microRNA-208a (miR-208a) and miR-208b are cardiac-specific microRNAs. It was demonstrated that miR-208b expression increases in right atrial appendages of AF patients. Since reduction of L-type Ca²⁺ current (I_{Ca,L}) density is a hallmark of the electrical remodelling, the aim of the present study was to determine whether miR-208a and miR-208b modulate I_{Ca,L}.

Methods: I_{Ca,L} was recorded at room temperature using Ba²⁺ as charge carrier (I_{Ba}) in HL-1 cells transfected or not with miR-208a and miR-208b mimics (at a final concentration of 30 nM) by whole-cell patch-clamp.

Results: Neither miR-208a nor miR-208b modified cell size as assessed by cell capacitance measurement (48.6 ± 8.7 and 39.8 ± 9.9 vs 34.7 ± 2.0 pF; $P>0.05$). Under control conditions, maximum I_{Ba} density was reached at +20 mV (-5.9 ± 1.0 pA/pF). miR208a and miR208b decreased peak I_{Ba} density at potentials positive to +10 (-2.2 ± 0.4 pA/pF for miR208a and -1.8 ± 0.3 pA/pF for miR208b at +20 mV; $P<0.01$ vs control). None of these microRNAs modified the voltage dependence of activation and inactivation. Importantly, a negative control miRNA failed to modify I_{Ba}, demonstrating the specificity of the observed effects. Bioinformatic algorithms such as miRanda and TargetMiner predicted that 3'UTR of both $\alpha 1C$ (CACNA1C) and $\beta 2$ (CACNB2), but not $\alpha 2\delta$ (CACNA2D) subunits can be targeted by miR-208a and miR-208b. These predictions were confirmed by luciferase reporter assays demonstrating that miR-208a and miR-208b produced a concentration-dependent decrease in the luciferase activity in CHO cells transfected with CACNA1C and CACNB2 3'UTR regions.

Conclusions: These results suggest that miR-208a and miR-208b may contribute to the development of AF-induced electrical remodelling, by means of a reduction of I_{Ca,L}.

P2528 | BEDSIDE

Association of genetic variants of the phosphatase and actin regulator 1 gene (PHACTR1) and the CDKN2B antisense RNA 1 (CDKN2BAS1) with coronary heart disease in Japanese individuals

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Purpose: Although various loci and genes that confer susceptibility to coronary heart disease (CHD) or myocardial infarction (MI) have been identified for Caucasian populations in genome-wide association studies (GWASs), genetic variants related to these conditions in Japanese individuals have not been identified definitively. The purpose of the present study was to examine a possible association of CHD or MI in Japanese with 15 polymorphisms identified as susceptibility loci for these conditions in the previously GWASs.

Methods: Study subjects comprised 4746 Japanese individuals (2462 subjects with CHD including 1822 with MI, 2284 controls) who visited the participating hospitals between 2002 and 2012. We selected 15 polymorphisms (each with a minor allele frequency of ≥ 0.05 in Japanese) reported by the previous GWASs for CHD or MI. Genotypes of polymorphisms were determined by the multiplex bead-based Luminex assay. To compensate for multiple comparisons, we adopted the criterion of a false discovery rate (FDR) of <0.05 for statistical significance of association.

Results: Comparisons of allele frequencies for 2462 subjects with CHD and 2284 controls by the chi-square test revealed that the rs9369640 of the phosphatase and actin regulator 1 gene (PHACTR1) ($P=0.00001$, FDR = 0.0002) and rs4977574 of the CDKN2B antisense RNA 1 (CDKN2BAS1) ($P=0.0042$, FDR = 0.0315) were significantly associated with CHD. Multivariable logistic regression analysis with adjustment for age, sex, body mass index, smoking status, and the prevalence of hypertension, diabetes mellitus, and dyslipidemia revealed that the rs9369640 ($P=0.0006$; odds ratio, 0.73; dominant model) and rs4977574 ($P=0.0043$; odds ratio, 1.26; recessive model) were significantly associated with CHD. The minor C allele of rs9369640 was protective against CHD, whereas the minor G allele of rs4977574 was a risk factor for this condition. Next, a relation of 15 polymorphisms to MI was examined among 1822 subjects with MI and 2284 controls. Comparisons of allele frequencies by the chi-square test revealed that the rs9369640 of PHACTR1 ($P=0.00002$, FDR = 0.0003) and rs4977574 of CDKN2BAS1 ($P=0.0003$, FDR = 0.0019) were significantly associated with MI. Multivariable logistic regression analysis with adjustment for covariates revealed that the rs9369640 ($P=0.0005$; odds ratio, 0.70; dominant model) and rs4977574 ($P=0.0004$; odds ratio, 1.37; recessive model) were significantly associated with MI.

Conclusions: The rs9369640 of PHACTR1 and rs4977574 of CDKN2BAS1 may be susceptibility loci for CHD and MI in Japanese individuals.

COMPUTED TOMOGRAPHY IN ASYMPTOMATIC HIGH RISK SUBJECTS

P2530 | BEDSIDE

Is metabolic syndrome predictive of coronary artery disease burden, and prognosis beyond its individual components? Results from the CONFIRM Registry

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Background: Metabolic Syndrome (MetS) is shown to increase the risk of cardiovascular disease and mortality. However, it is not yet known if MetS has any additive prognostic value beyond its individual risk factors (RF). The purpose of this study is to compare the prevalence, severity of coronary artery disease (CAD) and prognosis of patients with and without MetS.

Methods: The study cohort consisted of 27,125 consecutive individuals who underwent 64 detector row CCTA at 12 centers from 2003 to 2009. Patient with known CAD, unknown statin use or unavailable lipid profile were excluded. MetS was defined as per NCEP/ATP III criteria. We focused on 3900 patients who had measured RF for MetS and were not on statin therapy. Of these, 690 patients met the diagnostic criteria for MetS. Propensity matching was performed for age, sex, smoking status and family history of premature CAD with patients without MetS (no-MetS) with 0, 1, or 2 MetS RF. CAD was defined as none, non-obstructive (1–49% stenosis), or obstructive ($\geq 50\%$ stenosis). Major adverse cardiac events (MACE) was defined as MI, acute coronary syndrome, all cause mortality and late revascularization. MACE was assessed by risk-adjusted Cox proportional hazards models.

Results: MetS group had higher rates of obstructive 1, 2 and 3-vessel/left main disease compared to no-MetS group with 0 or 1 RF (13.8 vs. 8.8%, 4.5% vs. 2.4% and 2.3% vs. 0.9%, respectively; $p<0.01$). However, presence of obstructive 1, 2 and 3-vessel/ left main disease was not significantly different between MetS and no-MetS group with 2 RF (13.8 vs 10.5%, 4.5% vs 2.8% and 2.3% vs 1.3%, respectively; $p=$ non significant (NS)). At 2.2 year follow up, MetS group had higher MACE compared to no-MetS subgroups with 0 or 1 RF (4.4% vs 1.6%; $P<0.01$). There was no statistically significant difference in MACE between MetS group and no-MetS subgroup with 2 RF (4.4% vs 3.2% $P=NS$).

Conclusion: The prevalence and severity of CAD as well as MACE rate are significantly higher in MetS group compared to no-MetS group. However, these differences are not significant when comparing MetS group with no-MetS subgroup with 2 RF. These findings challenge the prognostic value of MetS as a syndrome beyond the sum of its components.

P2531 | BEDSIDE

Assessing the pretest probability of obstructive coronary disease - can we afford to ignore the cardiovascular risk factors?

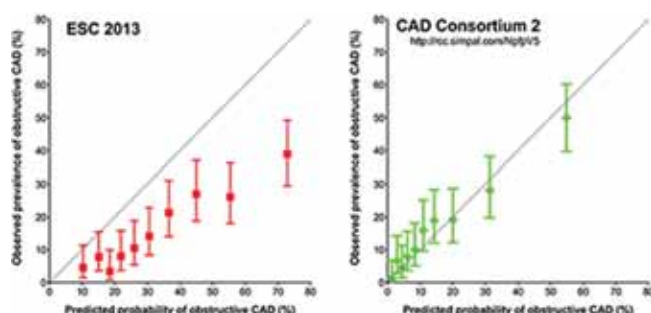
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Background: The European Society of Cardiology (ESC) 2013 Guidelines on

stable coronary artery disease (CAD) establish the assessment of pretest probability (PTP) as the first diagnostic step. However, the endorsed method for calculating PTP accounts only for age, sex and typicality of symptoms. Recently, a new score was proposed (CAD Consortium 2), which adds cardiovascular risk factors to the calculation of PTP. The aim of this study was to compare the accuracy and discriminative power of the two methods in patients undergoing coronary CT angiography (CCTA) for suspected CAD.

Methods: We evaluated 889 patients (370 men, age 58 ± 12 years) without known CAD undergoing CCTA for stable chest pain. Data on diabetes, hypertension, smoking and dyslipidaemia were collected prospectively. Chest pain was classified as typical, atypical or non-specific according to standard criteria. Each patient's PTP was calculated as recommended by the ESC 2013 guidelines, and with the CAD consortium 2 score. Obstructive CAD was defined as coronary stenosis $\geq 50\%$ on 64-slice dual-source CCTA.

Results: Obstructive CAD on CCTA was present in 144 patients (16.2%). The observed prevalence was significantly inferior to the predicted by the ESC2013 method, but very similar to the CAD consortium estimate (Figure). The C-statistic for CAD consortium 2 was significantly better than for the ESC2013 method (0.760 vs. 0.725, $p=0.006$). Using the CAD consortium 2 score would result in a net reclassification improvement of 17.6% ($p=0.005$).



P2535 | BEDSIDE**Diagnostic accuracy of coronary computed tomography angiography and single-photon emission computed tomography in renal transplantation candidates**

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Purpose: Before patients with end stage renal disease are listed for renal transplantation, screening for coronary artery stenosis is frequently needed. Despite low sensitivity and specificity non-invasive modalities are preferred. The aim of this study was to compare the diagnostic accuracy of coronary artery stenosis with single-photon emission computed tomography (SPECT), coronary computed tomography angiography (CCTA), and their combination (hybrid scan) using invasive coronary angiography as reference.

Methods: We prospectively evaluated patients with chronic kidney disease stage 5 referred for renal transplantation by CCTA, SPECT and invasive coronary angiography. According to our pre-defined protocol, interpretation of CCTA and SPECT were merged to an integrated hybrid imaging result. Significant stenosis was defined as more than 50% diameter stenosis by invasive coronary angiography. Data were analyzed by two experienced cardiologists and nuclear medicine experts blinded to patient data and results.

Results: We enrolled 138 patients with mean age 54 (SD: ±11) years, 68% males and 45% treated with dialysis. Median time from study inclusion to invasive coronary angiography was 34 days (10th and 90th percentiles: 24 and 48 days). The overall prevalence of significant CAD by invasive angiography was 21.7%. Sensitivity, specificity and area under the receiver-operating curves (ROC) are listed in table 1. Diagnostic accuracy evaluated by ROC was significantly higher for the hybrid scan than for SPECT ($p < 0.05$) whereas the accuracy by hybrid scan and CCTA was similar.

Table 1

	Sensitivity	Specificity	ROC area
SPECT	60% (CI: 41–77%)	81% (CI: 72–88%)	0.70 (CI: 0.61–0.80)
CCTA	93% (CI: 78–99%)	63% (CI: 53–72%)	0.78 (CI: 0.72–0.85)
Hybrid scan	73% (CI: 54–88%)	86% (CI: 78–92%)	0.80 (CI: 0.71–0.88)

Conclusions: With coronary angiography as gold standard, a hybrid scan of CCTA and SPECT had higher diagnostic accuracy than SPECT. Combination of CCTA and SPECT may be recommended as preferred diagnostic standard for preoperative evaluation before renal transplantation.

P2536 | BEDSIDE**Coronary computed tomography angiography in asymptomatic high-risk patients: non-calcifying and total coronary plaque burden predict outcome**

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Purpose: To prospectively assess the value of coronary computed tomography angiography (CTA) in asymptomatic patients with high-risk of coronary artery disease (CAD), and to identify risk factors for adverse outcome.

Methods: 711 consecutive asymptomatic patients (61.8y, 40.1% females) with high lifetime risk of CAD were prospectively examined with coronary calcium score (CCS) and CTA. Coronary arteries were evaluated for atherosclerotic plaque (non-calcified vs. calcified) and stenosis (mild <50%; intermediate 50–70% or high-grade >70%) per coronary segment. Segment involvement score (SIS, total number of segments with coronary plaque) and noncalcified-(nc) SIS were calculated. Primary endpoints were major adverse cardiac events (MACE) (STEMI, NSTEMI, cardiac death); secondary endpoints were A) coronary revascularization procedures (PCI or CABG) and B) >50% stenosis by invasive angiography. Cox-Hazard Model was applied.

Results: Of 711 patients, 28.3% were negative for CAD and 17.7% positive (CAD+) by CTA: 15.6% had plaques without stenosis, 23.9% mild, 10.7% intermediate and 21.5% high-grade stenosis. CCS-zero was found in 43% and non-calcified plaques in 100 (32.7%) of all CCS 0 patients.

The mean follow-up period was 2.65 years (up to 8 years). MACE rate was 0% in CAD-negative patients and higher (1.2%) in CAD+ by CTA. Coronary revascularization rate was 5.5%.

Patient with SIS ≥ 5 had a hazard ratio (HR) of 6.49 (95%CI: 1.63–25.76, $p < 0.013$) for MACE, patients with ncSIS ≥ 1 an HR of 2.36 (95%CI: 1.20–4.63, $p < 0.01$) for secondary endpoint.

The sensitivity of CTA for stenosis >50% compared to invasive angiography was 92.9% (95%CI: 83.0–98.1) and for conjunct primary/secondary endpoints, NPV was 99.4% (95%CI: 98.3–99.8)

Conclusions: CAD-prevalence in CTA in asymptomatic high-risk patients is high. CCS zero does not exclude CAD. CTA safely rules out risk of MACE and CAD. Total coronary plaque burden and non-calcified plaques (even if only one segment is involved) increase the risk for adverse outcome.

P2537 | BEDSIDE**Prevalence and severity of coronary artery disease among asymptomatic diabetic patients evaluated by coronary computed tomography angiography**

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Background: In the asymptomatic but high-risk patients of coronary artery disease (CAD), the appropriate use of coronary CT angiography (CCTA) remains uncertain. We examined the characteristics of CAD by CCTA among the asymptomatic type 2 diabetic patients without known or suspected CAD and major cardiovascular events of those patients.

Methods: Consecutive patients ($n=168$) with asymptomatic type 2 diabetes without known or suspected CAD who underwent CCTA were enrolled. The CAD was classified by CCTA as normal-mild, moderate, or severe. The patients were followed-up for MACE for 1062±372 days. Medical treatment and other cardiovascular measurements such as carotid artery atherosclerosis, perivascular stiffness and LV diastolic dysfunction, were also evaluated.

Results: Severe stenosis was detected in 90 (54%) patients. 16 (9.5%) patients underwent PCI or CABG following this CCTA result. Other patients underwent optimal medical therapy. Among all patients, 3 major cardiovascular events occurred. In patients with moderate stenosis, one patient developed sudden death due to unknown origin. In patients with severe stenosis, 1 patient with OMT alone developed brain infarction, and 1 patient with PCI underwent reintervention for stent restenosis. Other cardiovascular measurements appeared associated with moderate to severe coronary stenosis.

Conclusion: More than half of asymptomatic type 2 diabetic patients had moderate to severe coronary stenosis. Treatment with OMT with/ without coronary intervention in those patients may lead to good outcome.

P2538 | BENCH**New algorithm for calculation of the continuum of coronary artery calcification progression**

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Purpose: Coronary artery calcification (CAC), a marker of atherosclerosis, can be determined by computed tomography (CT) and demonstrates an exponential percentile increase depending on age and gender. We analyzed the changes in age and gender dependent percentile distribution of CAC during a five year follow-up period in a general population cohort based on repeated electron beam CT (EBCT).

Methods: In 1633 men and 1848 women (age 45–75 years), repetitive EBCT was performed 5.1±0.3 years apart. Our conjecture was that a subject's CAC increases with age along the given percentile at t0. Therefore, we estimated $\log(CAC(t1) + 1)$ using only the baseline CAC quantile $Q(t0)$, sex, and increased age by time between scans (time) from $\log(CAC(t1) + 1) = I(Q(t0)) + \beta(Q(t0))(\text{age} + \text{time})$.

Results: For men, the estimated age at which a given percentile reaches a given value of CAC is plotted in Fig. 1A, corresponding prediction limits are given for CAC 400. For example, if the CAC value in a man corresponds to the 40th percentile, CAC=100 is reached with 69.4 (64.2–73.6) years and CAC=400 with 77.7 (73.5–81.7) years. If CAC corresponds to the 80th percentile, CAC=100 is reached at 48.3 (44.7–58.6) years and CAC=400 at 63.3 (61.3–69.6) years. For women, the age at a given CAC is much higher than in men (Fig. 1B) and CAC values <50th percentile mean that CAC=100 are not reached until 85 years and with a level <70th percentile CAC=100 are not reached before the age of about 70 years.

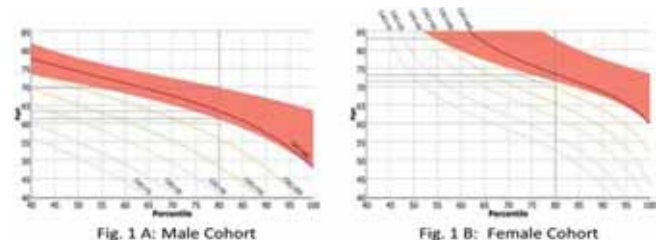


Figure 1. Percentile distribution of CAC.

Conclusion: The new algorithm for calculating the continuum of coronary artery calcification progression allows the estimate of the age at which threshold of risk are reached and enables a distinct discussion of the physician with the patient concerning his life expectancy of CAC progression.

P2539 | BEDSIDE**Epicardial fat volume. A novel risk biomarker for the subclinical coronary artery**I.V. Vassiliadis¹, E. Despotopoulos², O.C. Kaitozis³, C. Tekedis⁴, S. Koropoulis⁴.¹Euroclinic Hospital, Institute Euromedica -Encephalos, Athens, Greece;²Institute Euromedica-Encephalos, 251 Hellenic Airforce Hospital, Athens, Greece; ³Institute Euromedica-Encephalos, Athens, Greece; ⁴251 Hellenic Airforce Hospital, Athens, Greece

Background: Epicardial fat volume (EFV) measurement, using cardiac computed tomography (CT) has been shown to be a reliable marker of coronary atherosclerosis, and greater EFV is associated with coronary artery disease (CAD). However, little is known on the relation between the amount of EAT and the severity of coronary atherosclerosis in identifying high risk patients with subclinical CAD. The aim of this study was to investigate the relationship between EFV and severity of coronary artery disease measured by CT.

Methods: We retrospectively analyzed data of 600 individuals with suspected coronary artery disease who were referred for evaluation with cardiac CT from 2007 to 2012. Subjects who had history of primary coronary intervention or coronary artery by-pass graft were excluded. Thickness of epicardial adipose tissue (EAT cm³), was measured on noncontrast multiplanar reformat images with parasternal short axis view at basal, mid-ventricular and apical levels and horizontal long axis view as the sum of the EAT areas with 2mm thick from the whole heart. CAD severity was determined by the presence of significant coronary stenosis (>50% luminal narrowing of at least one major coronary artery), high coronary artery calcium score (CACS>100) and plaque characteristics (any plaque causing significant stenosis and/or vulnerable plaques), in the subsequent CT angiography

Results: In the finally studied population of 434 consecutive individuals, 155 (35, 7%) had atherosclerotic coronary artery disease and 279 (64, 3%) of them were normal. Overall, 75.2% were male; mean age was 58±18 years with a mean EAT 155, 54 cm³. Patients with coronary atherosclerosis had significantly greater mean EAT compared to normals (p=0.011). Linear regression analysis revealed that the incidence of significant stenosis, atherosclerotic plaque and high calcium score increased with EFV (P<0.01).

Conclusion: EFV measured by 64-slice CT scanning, was closely associated with significant CAD and its measurement might be used in addition to CACS CT angiography as an early indicator of increased risk of coronary atherosclerosis.

P2540 | BENCH**Glycemic status and coronary atherosclerosis in asymptomatics: evaluation by coronary CT angiography**

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Objectives: We investigated the prevalence, extent, and severity of coronary artery disease (CAD) in normal glucose regulation (NGR), prediabetes and diabetes of varying duration using dual-source coronary computed tomography angiography (CCTA) in individuals without chest pain.

Methods: We consecutively enrolled 2758 patients without CAD undergoing CCTA, and divided into NGR, prediabetes, and diabetes groups based on their diabetes history, fasting plasma glucose and glycated hemoglobin levels. 1446 diabetic patients were reclassified into three groups according to the duration of diabetes: <5 years, 5–10 years, and ≥10 years. We compared the various results of CCTA among groups.

Results: Diabetic patients showed significantly greater degrees of coronary

artery calcium score (CACS), atheroma burden obstructive score (ABOS), segment involvement score (SIS), and segment stenosis score (SSS), compared with NGR or prediabetes individuals (p<0.001 for all). Longer duration of diabetes was associated with higher rate of CAD (p<0.001), and proportionately greater degree of CACS, ABOS, SIS, and SSS on CT scans (p<0.001 for all). Diabetes, even newly diagnosed or with the duration of less than 5 years was associated with an increased risk of CAD as compared with NGR individuals [diabetes duration <5 years (odds ratio (OR) 2.15, 95% confidence interval (CI) 1.294–3.574, p<0.001); 5–10 years (OR 3.461, 95% CI 1.850–6.472, p<0.001); ≥10 years (OR 9.152, 95% CI 5.557–15.072, p<0.001)], although no differences were found between NGR and prediabetes individuals.

Conclusions: In asymptomatic individuals, the prevalence, extent and severity of CAD are significantly higher in patients with long-standing diabetes. However, prediabetes was not associated with an increased risk of CAD.

PET AND SPECT FOR VISUALISATION OF INFLAMMATION**P2542 | BENCH****18F-anti-VCAM-1 nanobody for PET/CT imaging of inflamed atherosclerotic plaque**G. Bala¹, A. Blykers², C. Xavier², K. Gillis¹, S. Tierens², B. Descamps³, C. Vanhove³, T. Lahoutte⁴, B. Cosyns¹, S. Hernot². ¹University Hospital (UZ) Brussels, Centrum voor Hart-en Vaatziekten - CHVZ, Brussels, ²Free University of Brussels (VUB), In Vivo Cellular and Molecular Imaging - ICMI, Brussels, ³Ghent University, iMinds-IBiTech-MEDISIP, Dept. of Electronics and Information Systems, Ghent, ⁴University Hospital (UZ) Brussels, Nuclear Medicine, Brussels, Belgium

Purpose: Vascular cell adhesion molecule-1 (VCAM-1) is expressed in inflammatory atherosclerotic lesions and is a potential target for the molecular imaging of vulnerable plaques. A mouse/human cross-reactive anti-VCAM-1 nanobody (Nb) radiolabeled with ^{99m}Tc has previously demonstrated to allow detection of VCAM-1 positive plaques using SPECT/CT. Because of its superior spatial resolution, higher sensitivity, and more accurate quantification, Positron Emission Tomography (PET) is more appropriate for clinical use. Therefore, we aimed to validate the 18F-labeled anti-VCAM-1 Nb as a potential PET tracer and show its ability to image VCAM-1 expression by PET/CT in a mouse model of atherosclerosis.

Methods: The anti-VCAM-1 Nb (cAbVCAM1-5) was labeled using the prosthetic group N-succinimidyl-4-18F-fluorobenzoate (18F-SFB) and purified by size exclusion chromatography. In vitro cell binding studies using TNF-α stimulated bEND5 cells were carried out to assess the functionality of the tracer. In vivo μPET/CT imaging was performed at 2h30 post-injection using 20–30 weeks-old ApoE^{−/−} mice on a Western diet (Group 1) and normally fed C57BL6 control mice (n=3 per group), which were injected with 18F-anti-VCAM-1 Nb. To demonstrate the specificity, additional ApoE^{−/−} mice were injected with 18F-labeled non-targeting control Nb or with 70-fold excess of unlabeled anti-VCAM-1 Nb. Ex-vivo evaluation (n=6 per group) of plaque uptake in different aorta segments based on lesion-extension index was assessed by using gamma well counting.

Results: After 18F-labeling (radiochemical purity >99%), 18F-labeled anti-VCAM-1 Nb showed significantly more binding to VCAM-1 positive cells compared to negative cells. Atherosclerotic lesions in the aortic arch of ApoE^{−/−} mice injected with 18F-anti-VCAM-1 Nb were successfully identified using μPET/CT imaging, while background signal was observed in the aortic arch of the control groups. These results were confirmed by ex vivo analysis where uptake of 18F-anti-VCAM-1 Nb was significantly higher compared to control groups and increased with the lesion-extension index (score 0: 0.68±0.10, score 1: 1.18±0.36, score 2: 1.49±0.37, score 3: 1.48±0.38%ID/g). In the Group 1, lesion-to-heart and lesion-to-blood ratios were high (11.2 and 3.13, respectively).

Conclusion: Mouse/human 18F-anti-VCAM-1 Nb allows non-invasive PET/CT imaging of VCAM-1 expression in atherosclerotic plaques in a mouse model and may represent an attractive tool for imaging vulnerable atherosclerotic plaques in patients.

P2543 | BEDSIDE**Quantitative 18F-Fluorodeoxyglucose positron emission Tomography/Computed Tomography for the discrimination of infective from non-infective implantable cardiac electronic device pocket complications**F.Z. Ahmed¹, J. James¹, C. Cunningham¹, C. Fullwood¹, I. Armstrong¹, B. Clarke¹, J. Sandoe², P. Arumugam¹, M. Mamas¹, A.M. Zaidi¹. ¹Manchester Royal Infirmary, Manchester Heart Centre, Manchester, United Kingdom; ²University of Leeds, Leeds, United Kingdom

Purpose: Confirmation of implantable cardiac electronic device (ICED) pocket infection can be difficult when patients present with mild or non-specific symptoms that may or may not be due to infection. The aim of this study was to investigate the utility of 18F-Fluorodeoxyglucose positron emission tomography with combined computed tomography (18F-FDG PET/CT) in the early diagnosis of ICED pocket infection.

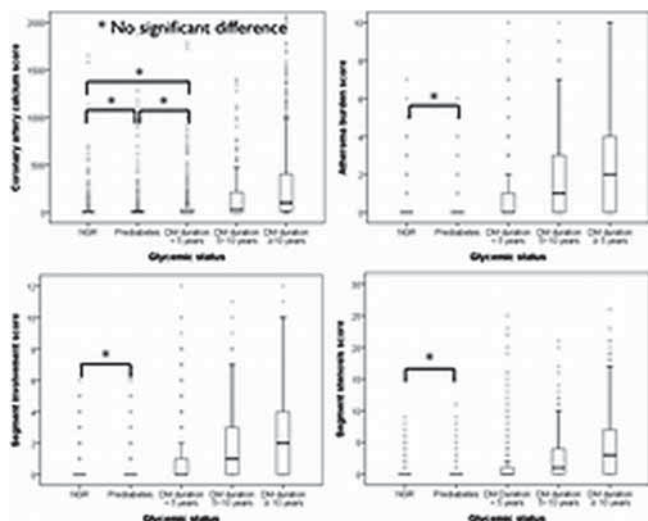


Figure 1. CCTA findings.

Methods: Eighteen patients with possible ICED pocket infection were evaluated using 18F-FDG PET/CT and blood markers of infection prior to deciding on the clinical need for ICED extraction. These patients included those with mild symptoms (localized pain in the region of the ICED generator pocket, with or without mild erythema) in the absence of definite features of infection (significant erythema, abscess formation, purulent discharge or erosion). 18F-FDG PET/CT values from these patients were correlated to the persistence or progression of clinical signs (the current clinical gold standard for diagnosing ICED infection), and to two separate cohorts of patients: patients with definite infection ($n=20$), and control subjects ($n=35$) undergoing 18F-FDG PET/CT scanning for other indications. An SUV(max) of >2 on 18F-FDG PET was considered abnormal.

Results: Nine (50%) patients with possible infection had increased 18F-FDG uptake in the region of the ICED generator pocket. Infection was confirmed on clinical grounds in 8 out of these 9 patients; these patients subsequently underwent ICED extraction. A pathogen was recovered from extracted samples in 7 out of 8 patients (88%). Patients with confirmed infection ($n=28$) had significantly higher 18F-FDG uptake around the ICED pocket compared to non-infected cases and controls (SUVmax 4.75 [2.85-5.55] vs. 1.35 [1.30-1.85] vs. 1.0 [1.25-1.70] respectively, $p<0.001$). The sensitivity and specificity of the 18F-FDG scan to detect infection using SUV max was 93% [CI 76%-99%] and 87% [CI 73%-95%] respectively.

Conclusions: ICED infection may first manifest as mild symptoms in the region of the generator pocket. 18F-FDG PET/CT is sensitive and specific for the discrimination of infective from non-infective ICED pocket complications.

P2544 | BEDSIDE

Differential aortic inflammation and calcification in abdominal aortic aneurysm and atherosclerosis

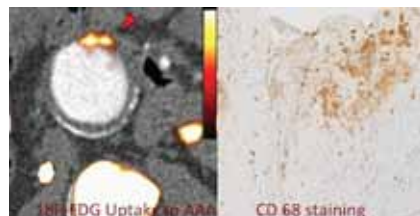
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Purpose: The vascular biology of both abdominal aortic aneurysm (AAA) and atherosclerosis remain incompletely understood. We hypothesized that inflammation and calcification may have a differential contribution to the pathogenesis of both diseases.

Methods: In 63 patients with asymptomatic AAA and 19 age- and sex-matched patients with atherosclerosis, we measured inflammation and calcification using 18F-fluorodeoxyglucose (18F-FDG) positron and computed tomography (PET-CT). Inflammation and calcification were quantified using 18F-FDG target-to-background ratios (TBR) and Agatston scores.

Results: Thrombus within AAA had low 18F-FDG uptake compared to the wall of the aneurysm ($p<0.0001$). 18F-FDG uptake was higher in the aneurysmal aorta than in non-aneurysmal aorta (mean TBR 2.23 ± 0.45 vs. 2.12 ± 0.45 , $p=0.02$). Compared to patients with atherosclerosis only, both aneurysmal and non-aneurysmal aortae showed higher 18F-FDG activity (total aorta mean TBR 2.23 ± 0.45 vs. 1.68 ± 0.21 , $p<0.0001$; abdominal aortic mean TBR 2.23 ± 0.45 vs. 1.68 ± 0.21 , $p<0.0001$) in patients with AAA. Calcification in aneurysmal aorta was greater than in non-aneurysmal segments (Agatston 4918 [2901-8008] vs. 1017 [139-2226], $p<0.0001$). There was no significant difference between total aortic calcification between patients with AAA and atherosclerosis (Agatston total aorta 5136 [3297-9360] vs. 3735 [1425-8261] $p=0.180$).



Conclusion: Aortic inflammation is more pronounced in AAA than in atherosclerosis. Moreover, even with adjacent atheroma, aortic inflammation is more marked suggesting an exaggerated systemic vascular inflammatory response in patients with AAA. This is further supported by the findings of increased aortic calcification in aneurysmal disease: a marker of end-stage necrotic inflammation.

P2545 | BEDSIDE

Impact of fluorodeoxyglucose uptake in right ventricle on adverse events in patients with cardiac sarcoidosis: observational study of combined use of FDG-PET and LGE-MRI

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Purpose: F18-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and late gadolinium enhanced cardiovascular magnetic resonance (LGE-MRI) are both frequently used to diagnose cardiac sarcoidosis. Although some studies reported that these modalities could predict the cardiac prognosis or detect the

myocardial damages, there are still some limitations for clinical application because of limited resolution of each modality. Therefore, the aim of this study was to assess the relationship between these two modalities to predict the cardiac prognosis in patients with cardiac sarcoidosis.

Methods: Consecutive 20 patients with cardiac sarcoidosis diagnosed by consensus criteria according to modified Japanese Ministry of Health guidelines were enrolled in this study. FDG-PET and/or LGE-MRI were examined in all patients before steroid treatment, and left ventricle (LV) and right ventricle (RV) involvements in FDG-PET and/or LGE-MRI were evaluated respectively. Furthermore, the relationship between the findings of these modalities and adverse events including cardiac death, sustained ventricular tachycardia/ventricular fibrillation or implantable cardiac defibrillators discharge were also analyzed.

Results: In the 20 patients, 15 patients underwent FDG-PET. Thirteen patients (87%) had FDG uptake in LV and 6 patients (40%) in RV. Four patients (27%) experienced adverse events. Interestingly, FDG uptake in RV significantly correlated with adverse events ($p=0.004$) whereas LV uptake and maximum standardized uptake value did not. Ten patients (50%) underwent both LGE-MRI and FDG-PET. Of 10 patients, 8 patients (80%) had LGE in LV whereas only 2 patients (20%) in RV. Two patients (20%) experienced adverse events. In contrast to FDG-PET, LGE in RV, LGE in LV, and number of LGE segment did not correlate with adverse events. Among 2 patients with adverse events, a patient had both FDG uptake and LGE in RV, and the other patient had FDG uptake and negative LGE in RV. Positive predictive value of FDG uptake in RV for adverse events was 67%, LGE in RV was 25%, and combined FDG and LGE in RV was 100%, respectively.

Conclusion: RV uptake of FDG-PET may be useful for a prognostic predictor of cardiac sarcoidosis. LGE-MRI alone may mispredict adverse events especially in patients with thin ventricular walls because of the limited resolution. Complementary usage of these two modalities is recommended in detecting adverse events in patients with cardiac sarcoidosis.

P2546 | BEDSIDE

Impact of liver transplantation on the progression of myocardial sympathetic denervation assessed by 123-I MIBG imaging in familial amyloid polyneuropathy

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Patients with familial amyloid polyneuropathy (FAP) V30M-TTR have documented myocardial sympathetic denervation assessed by 123-I metaiodobenzylguanidine (MIBG) imaging which correlates with the severity of neurological involvement. Liver transplantation is widely used to attenuate the progression of the disease, but it is still contradictory its impact on the evolution of cardiac involvement. We aimed to evaluate the impact of liver transplantation on the progression of myocardial denervation in V30M-TTR FAP patients.

Methods: Prospective observational study of consecutive patients with V30M-TTR mutation who underwent annual cardiac evaluation and periodic determination of the heart/mediastinum (H/M) 123-I MIBG uptake ratio.

Results: 202 patients (45 ± 14 years, 55.9% female) were evaluated and followed for a median of 52 months. Of these, 73 patients underwent liver transplantation. To assess the impact of liver transplantation on the progression of cardiac denervation, the late H/M uptake ratios of the images performed prior to liver transplantation ($n=100$) were compared with the H/M uptake ratios of the images acquired subsequently ($n=87$). It was found that the progression of disease, evaluated by the decrease in late H/M as a function of time, was significantly attenuated from the time of liver transplantation. In fact, until the time of liver transplantation the late H/M ratio declined $0.47/\text{year}$ (Pearson $R=-0.469$, $p<0.001$, Spearman's $Rho=-0.379$, $p<0.001$). After transplantation no statistically significant correlation was observed between the elapsed time and the decrease in the late H/M ratio.

Conclusion: Liver transplantation permits stabilization of cardiac denervation in V30M-TTR FAP. After transplantation, the values of the late H/M uptake ratios remain stable over time, without recovery or further deterioration. Thus, it is crucial that the treatment is carried out at an early stage of the natural history of the disease.

P2547 | BEDSIDE

Perspective evaluation and prognostic value of myocardial sympathetic denervation assessed by 123I MIBG scintigraphy in familial amyloid polyneuropathy

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Introduction: Familial amyloid polyneuropathy (FAP) V30M TTR is an autosomal dominant disease characterized by progressive impairment of sensory-motor and autonomic nerve fibers. Myocardial scintigraphy with 123I-metaiodobenzylguanidine (MIBG) is a noninvasive method for quantification of cardiac sympathetic denervation. We sought to evaluate the progression of cardiac sympathetic denervation in serial 123I MIBG imaging and to examine its impact on the prognosis.

Methods: Observational study of V30M TTR mutation carriers subject to an-

nual cardiac evaluation and periodic 123I-MIBG imaging with determination of the heart/mediastinum (H/M) uptake ratio.

Results: 202 patients (45±14 years; 56.9% female) were enrolled. During a median of 52 months, 430 MIBG scintigraphic studies were performed. With aging, there was a progressive decrease in the early H/M (Pearson's $r=-0.11$, $p=0.021$; Spearman's $Rho=-0.32$, $p<0.001$) and late H/M (Pearson's $r=-0.35$, $p<0.001$; Spearman's $Rho=-0.31$, $p<0.001$) and a trend for an increase in the washout rate (Pearson's r NS; Spearman's $Rho = 0.10$, $P=0.04$). With increasing duration of symptoms there was a progressive decrease in the early H/M (Pearson's r NS; Spearman's $Rho=-0.17$, $p=0.004$) and late H/M (Pearson's $r=-0.21$, $p<0.001$; Spearman's $Rho=-0.22$, $p<0.001$) while the washout rate remained unchanged. Multivariate Cox regression analysis, adjusted for age and considering multiple exams per patient, showed that the only independent predictors of death were age and late H/M. The risk increased with age (HR=1.058, 95% CI 1.036–1.080, $p<0.001$) and correlated inversely with the late H/M ratio (HR=0.153, 95% CI 0.071–0.329, $p<0.001$). Kaplan Meier survival analysis revealed that the risk of death differed significantly according to the tertiles distribution of the early H/M (Log-rank $p<0.001$) and late H/M (Log-rank $p<0.001$). Patients belonging to the 3rd tertile (early H/M ratio >2.01) had a risk 13 times higher than those belonging to the 1st tertile (H/M ratio <1.74 ; HR=13.72, 95% CI 4.89–38.49, $p<0.001$). Regarding the late H/M ratio, patients belonging to the 2nd or 3rd tertile had a risk of death 6 times higher than those belonging to the 1st tertile (late H/M ratio <1.70 ; HR=6.24, 95% CI 3.52–11.04, $p<0.001$).

Conclusion: In patients with V30M TTR-FAP myocardial sympathetic denervation assessed by MIBG imaging increases with age and duration of symptoms. The severity of denervation quantified by late H/M ratio is an independent prognostic marker.

P2548 | BEDSIDE

Useful parameter of myocardial fatty acid metabolism and blood flow mismatch for the diagnosis and the detection of myocardial injury in active cardiac sarcoidosis

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Purpose: F18-FDG-PET is recently reported to be useful for the diagnosis and its detection of active myocardial inflammation in patients with cardiac sarcoidosis (CS). In contrast, the assessment of myocardial injury and left ventricular function are clinically important for the future risk management. The aim is to clarify whether FDG uptake as a parameter of active inflammatory process is associated with myocardial injury detected by I-123 BMIPP (BMIPP) and TI-201 (TL) which reflect fatty acid metabolism and myocardial blood flow, respectively. BMIPP is reported to be sensitive for the detection of myocardial injury compared to TL.

Methods: Thirty patients with suspected CS who underwent FDG-PET/CT and BMIPP/TL dual SPECT were enrolled in the study (18 male, 55±12 year old). FDG-PET/CT image was obtained under 24-hrs strict carbohydrate restriction diet and heparin infusion 15 min before FDG administration. PET and SPECT images were divided into 17 segments, and SUVmax as a FDG uptake on each segment was measured. BMIPP and TL defect was scored in each segment visually 0–4 (0, normal; 4, absent), and we classified each segment as normal, mismatched, and matched defect between the both tracers. BMIPP and TL total defect score was calculated as BMDS and TLDS. CS was diagnosed based on the Japanese Ministry of Health and Welfare clinical criteria and/or cardiac MRI in case without pacemaker implantation as well as FDG-PET results. Cardiac function was assessed by quantitative gated TL-SPECT to generate LVEF (%) and end-diastolic volume (EDV).

Results: CS was finally diagnosed in 18 patients. SUVmax in whole heart was much higher in CS than that in no CS (6.08±3.19 vs. 2.48±1.22; $p=0.0006$). There was no difference in BMDS (14.7±11.7 vs. 9.1±7.7), TLDS (9.8±10.2 vs. 7.4±7.6), LVEF (42±15 vs. 37±16%) and EDV (108±40 vs. 126±53mL) between CS ($n=18$) and no CS patients ($n=12$), whereas mismatch score (BMDS-TLDS) was significantly higher in CS (4.83±3.42 vs. 1.69±1.80, $p=0.02$). Among the CS patients, SUVmax was significantly higher in mismatched (4.30±2.43) than normal (3.40±2.20) and matched segments (3.44±2.07).

Conclusion: Myocardial fatty acid metabolism and blood flow mismatch as determined by BMIPP and TL SPECT may be beneficial finding for the diagnosis and the assessment of pathophysiology of active cardiac sarcoidosis.

P2549 | BEDSIDE

Utility of epicardial adipose thickness by echocardiography as a predictor for coronary plaque vulnerability determined by coronary CT angiography

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Objective: The aim of this study is to investigate the relationship of EAT (Epicardial adipose tissue) by echocardiography and high risk plaque evaluated with coronary CT.

Methods: We enrolled 406 patients (mean age 64 years, 231 men). EAT by echocardiography was simultaneously measured on the free wall of the right ventricle from a parasternal long-axis view at end-systole. High risk coronary plaque (HRP) components were defined as the presence of non-calcified plaque (NCP) including low-density plaque (<50 HU), spotty calcium and positive remodeling (re-modeling index >1.05). In accordance with a ROC curve analysis, patients were assigned into two groups: thin (<5.6 mm) or thick (≥ 5.6 mm) EAT group.

Results: Compared to the thin EAT group, the thick EAT group had a higher prevalence of low density plaque (31% vs. 18%, $p<0.01$), positive remodeling (53% vs. 42%, $p=0.02$), spotty calcification (24% vs. 11%, $p<0.01$) and HRP (22% vs. 10%, $p<0.01$). The thickness of EAT was also correlated with the number of low-density plaque and HRP, and coronary artery calcium score as well as age, body mass index, visceral adipose tissue (VAT) area. Multiple logistic analysis revealed that thick EAT was a significant predictor of HRP (odds ratio: 2.21, 95% CI: 1.21 to 4.02, $p=0.01$) along with diabetes, and gender after adjustment of age, gender, hypertension, dyslipidemia, VAT area. The ROC curve analysis showed the AUC was 0.66 (0.59 to 0.73, $p<0.01$) and sensitivity and specificity to detect HRP were 65% and 61% with cut off value of 5.6mm.

ORs of thick EAT for coronary plaques

Plaque components	Age and sex adjusted		Multivariate (Model 1) ^a		Multivariate (Model 2) ^b	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Low-density plaques	1.73 (1.06–2.81)	0.03	1.66 (0.99–2.76)	0.05	1.65 (0.99–2.75)	0.05
Positive remodeling	1.19 (0.76–1.85)	0.46	1.10 (0.70–1.75)	0.68	1.06 (0.66–1.70)	0.82
Spotty calcium	2.21 (1.26–3.87)	<0.01	2.13 (1.20–3.81)	0.01	2.12 (1.18–3.79)	0.01
Low-density plaques with positive remodeling	1.79 (1.10–2.92)	0.02	1.72 (1.03–2.87)	0.04	1.71 (1.02–2.86)	0.04
All three characteristics	2.21 (1.26–3.87)	<0.01	2.13 (1.20–3.81)	0.01	2.10 (1.15–3.84)	0.01

^aAdjusted for age, hypertension, dyslipidemia, diabetes mellitus, current smoking, BMI, and VAT.

^bAdjusted for variables in Model 1 and CAC scores.

Conclusion: The thickness of EAT by echocardiography was significantly associated with coronary CT parameters, and can be informative to assess coronary high risk plaques.

P2550 | BENCH

Apoptosis is a potential mechanism for severe calcific coronary artery disease

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Background and aim: Severe coronary calcification, irrespective of luminal stenosis, may cause limiting symptoms, but does not respond to conventional management policies. Little is known about its exact pathophysiology. The aim of this study is to identify metabolic disturbances that distinguish calcific coronary artery disease.

Methods: We studied 34 patients with coronary artery calcification (CAC), 17 with severe CAC (score >250) and 17 with moderate CAC (score <250) and compared them with 26 controls with no calcification. The metabolic profiling analysis of patients serum was conducted using untargeted ultra-performance liquid chromatography coupled to mass spectrometry of serum organic extracts. Metabolic separation was achieved using an Acquity UPLC system and detection using a Xevo G2 Q-TOF MS. Features were then extracted using MarkerLynx package. Metabolite structural assignment was accomplished based on tandem MS spectra. Pathway analysis included, calculating correlation coefficients, and using CytoScape software for visualisation. Metabolites were mapped to metabolic pathways using the KEGG database. Multivariate Statistical Analyses were performed using the SIMCA-P+ 12 software.

Results: A total of seven different dysregulated sphingomyelins were detected, all consistently lower in severe CAC compared with controls ($p=0.000001 - 0.01$). Sphingomyelins were not different between moderate CAC and controls, but significantly lower in severe CAC compared with moderate CAC ($p=0.0000006 - 0.1$).

Conclusion: Despite similar age and conventional risk factors, patients with severe coronary calcification have clear evidence for disturbed ceramide metabolism consistent with advanced cell apoptosis.

P2551 | BEDSIDE

A study of LAA morphology in rheumatic heart disease

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Introduction: Assessment of Left atrium appendage (LAA) morphology by computed tomography (CT) has been shown to be important in prediction of stroke in patients with non valvular atrial fibrillation (AF). Of the four morphologies of LAA described (Chicken-wing [CW], Cauliflower, Cactus and Windsock), CW morphology is associated with lowest stroke incidence as compared to other three (non-

Chicken wing (non CW)). Non-CW morphologies have been shown to confer additional risk of stroke in non valvular AF.

No study has compared LAA morphology and stroke prevalence in Rheumatic valvular AF and compared with non valvular AF.

Methodology: We studied 106 consecutive patients with AF who attended the outpatient clinic. All patients underwent CT for evaluation of LAA morphology.

Observations - Mean age of patients was 56.5 years and 50.94% were males. 15 (14.15%) had history of previous stroke. Out of 106 patients, 49 (46.22%) had rheumatic valvular affection, 6 (12.24%) of them had history of stroke. 57 patients had non-valvular AF, 9 (15.78%) had history of stroke. Clot in LAA was noted in the 28 of 106 (26.41%) patients.

Amongst rheumatic valvular AF patients, 32 (65.3%) had CW morphology and 4 (12.5%) patients had history of stroke. 17 patients (34.7%) had non-CW morphology of LAA and 4 (23.5%) had history of stroke.

Amongst the 57 non valvular AF patients, 28 (49.1%) had CW morphology; 1 (3.57%) had history of stroke. 29 patients had non-CW morphology (50.9%) and 8 (27.5%) had h/o stroke.

Conclusions: Findings of our observational study indicate low prevalence of stroke in non valvular AF patients with CW morphology (3.57%) as compared to non CW morphologies (27.5%). In rheumatic valvular AF group, prevalence of stroke in CW morphology was 12.5%, which is 3.5 fold higher as compared to non valvular AF group. In non CW morphology the prevalence of stroke was comparable, in both the groups. CHADS score is not applicable to rheumatic valvular AF and LAA morphology also does not help significantly based on our study. Assessment of stroke risk in rheumatic valvular heart disease remains a challenge.

PERFUSION IMAGING FOR PROGNOSIS

P2553 | BEDSIDE

Yield of diagnosis and prediction of patients undergoing both stress echocardiography and stress myocardial perfusion imaging

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Purpose: Stress echocardiography (SE) and stress myocardial perfusion imaging (MPI) SPECT are both recommended to assess CAD and to predict cardiac outcome. We investigated the yield of referring patients for both stress modalities.

Methods: During 2010 -2013, we sorted out from the cardiology data base, 320 patients who underwent both SE and MPI within time interval of 6 months. Excluded patients who underwent intervention or cardiac event during this period. The patients were compared by, image quality, test results: normal, abnormal (ischemia – scar/wall motion abnormality) non diagnostic/equivocal test, additional findings. In patients who underwent coronary angiography within 3 months, correlation of stress MPI and SE with coronary catheterization was done. The patients were followed up for prediction of composite outcome (cardiac death, MI, ACS, CABG, PCI).

Results: Of the 309 patients, there were 35% women and 54% had CAD. Time interval between SE and stress MPI was 76 ± 52 days. The first test was performed by SE in 201 (65%) patients. Image quality: adequate/inadequate, 99% and 1% by MPI and 82% and 18% by SE. Additional findings (valve disease, PHT, LVH...) were documented by SE in 31%. Test results: normal, abnormal (ischemia/scar), equivocal; 60%, 16% and 24% for SE and 66%, 29% and 5% for MPI ($\chi^2=17$, $p<0.002$). Forty three (14%) pts underwent coronary angiography; 11 were non obstructive and 32 had $\geq 70\%$ stenosis. Significant correlation was found by stress MPI ($\chi^2=19.9$, $p<0.018$) and non significant ($\chi^2=15.9$, 0.069) by SE. During 4 yrs follow-up, there were: 36 patients with composite cardiac outcome; 11 with cardiac death and MI and 25 with ACS, PCI and CABG, which were not predicted by SE but significantly predicted by MPI ($p<0.001$).

Conclusion: The majority of patients underwent SE prior stress MPI and had substantial equivocal or non diagnostic tests. About third of the patients had additional cardiac finding diagnosed by SE only. The catheterization results as well as cardiac outcome seems to be better identified by stress MPI.

P2554 | BEDSIDE

Normal myocardial perfusion gated-SPECT with positive stress test: different prognosis in men and woman

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Purpose: Annual mortality after normal myocardial perfusion gated-SPECT found in most studies is very low (<1%). However, other variables such as sex, age, diabetes, the type of stress and the history of coronary artery disease, have shown to have influence in this good prognosis of patients with a normal perfusion. The objective of this study was to analyze the prognosis of normal myocardial perfusion SPECT in women and men according with the stress test results.

Methods: We analyze the stress test results in 2414 patients (mean age 62.8 ± 13.5 years, 1438 women) who had normal stress-rest gated-SPECT. A stress test was considered positive for ischemia when we observed a horizon-

tal or down-sloped ST depression of ≥ 1 mm. Follow-up was 5.1 ± 3.4 years. We recorded cardiac complications (CC, non fatal myocardial infarction or cardiac mortality) and coronary revascularization (R) in women and men.

Results: Stress test was positive in 407 (16.9%) patients, in 15.9% of women and 17.5% of men. CC (6.5% vs 2.3%; $p=0.005$) and CC + R (11.6% vs 4.8%, $p=0.001$) were more frequent in men with positive stress test than men with a negative stress test. These differences were not observed in women. In the multivariate analysis we observed that CC and CC + R were more frequent in men with positive stress test (sHR: 2.8 [CI 95%: 1.3 to 6.3]; sHR: 2.5 [CI 95%: 1.4 to 4.4]; respectively) than in women with positive stress test.

Conclusions: Men with normal gated-SPECT of myocardial perfusion but with positive stress test have a worse prognosis than women with the same results. Sex and abnormal stress tests are variables that may modify the good prognosis of a normal myocardial perfusion.

P2555 | BEDSIDE

Non-stenotic coronary lesions: how to manage these patients

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Coronary angiography has diagnostic limitation in identifying non-stenotic coronary lesion (NSCL) responsible for ischemia. Myocardial perfusion defects in patients (pts) with NSCL have often been unreasonably considered by invasive cardiologists as being "false positive". We evaluated a prognostic value of gated SPECT MPI in unselected group of the pts with NSCL over a 24 month period of follow-up.

170 pts (115 males, 67.6%; age 42-68 years; mean age 56.4 ± 9.2 years) with NSCL (stenosis of 50% or less of LAD and 70% or less of any other coronary artery or its major branches, $FFR \geq 0.80$) were enrolled into the study. Retrospective analysis of 86 pts with NSCL and subsequent positive MPS performed within 6 months from the time of coronary angiography (study group) and 84 pts with normal scan results (control group) was performed. Follow-up period was for 24 months from the time of MPI or up to the time of major coronary event (MCE) - first occurrence of cardiac death or myocardial infarction.

Over a two-year follow-up, approximately 11% of the pts in study group had MCE as compared to 3.2% in the control group ($P<0.01$). Abnormal MPI, EF <35% and high levels of hs-CRP were independent predictors for MCE in the study group. In multivariate analysis only an abnormal MPI remained to be an independent predictor regardless of size or severity of perfusion abnormalities ($P<0.005$).

Pts with NSCL on coronary angiography and myocardial perfusion defects have relatively high event rate (11%) of MCE over a period of 24 months from the time of MPI. So, we highly recommend gated SPECT MPI to be obligatory performed in all cases of NSCL to avoid life-threatening coronary complications in forthcoming future.

P2556 | BEDSIDE

Frequency and long-term prognostic importance of myocardial perfusion deficits in patients with non-specific chest pain admitted to a coronary care unit with a suspected acute coronary syndrome

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Purpose: To assess the frequency and long-term prognostic importance of stress-induced myocardial perfusion deficits in pts with non-specific chest pain (NSCP) admitted to the coronary care unit (CCU) with a suspected acute coronary syndrome (ACS).

Methods: During a 21-month period all pts discharged from the CCU without evidence of present or prior coronary artery disease and without other medical conditions that could cause the chest pain were prospectively screened to identify potential pts with NSCP. Eligible pts underwent careful history taking and a stress myocardial perfusion scintigraphy (MPS) within four weeks. MPS studies were interpreted without knowledge of clinical findings. MPS was defined as pos-

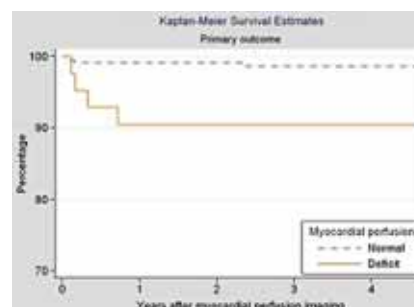


Figure 1. Survival rate during 4 years.

itive in the presence of reversible or irreversible deficits. Follow-up were 4 years with cardiac death, ACS or coronary revascularization as the primary end-point.

Results: Of 458 eligible pts 272 accepted participation and had stress MPS done. Mean age was 52.8 yrs (SD±11.1), and 115 were women (42%). A positive MPS was found in 42 pts (15%). Pts with MPS deficits were older (56.5 vs 52.1 yrs, $p=0.02$) but less frequently had a family history of coronary artery disease (38 vs 61%, $p<0.01$). During follow-up four deaths occurred but none were of cardiac origin. Another four pts (10%) with MPS deficits had a primary end-point vs three (1%) among pts with normal MPS (Fig. 1). Age-adjusted Cox model showed that pts with MPS deficits had a HR of 7.70 (95% CI=1.67;35.49) of non-fatal cardiac end-points compared to pts with normal MPS results.

Conclusions: In NSCP pts admitted to the CCU for a suspected ACS, MPS deficits are shown in 15%. During long-term follow-up pts with perfusion deficits have a nearly 8 times increased risk of non-fatal cardiac clinical events compared to pts without deficits.

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Chronic kidney disease and stress left ventricular systolic function in adenosine stress myocardial perfusion imaging predict future cardiovascular events

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Background: Adenosine stress myocardial perfusion imaging (MPI) is widely applied for detection of coronary ischemia as well as exercise MPI. Chronic kidney disease (CKD) has been considered to be a strong predictor for cardiovascular events. However, the precise predictors of future events evaluated by using combination of indices from adenosine stress MPI and clinical characteristics remain to be uncertain. The objective of this study is to determine the predictors from adenosine stress MPI that will affect the future cardiac events in patients suspected of coronary artery disease.

Methods: A total of 1,256 consecutive patients (male/female 801/455, age 71±11 years) suspected of coronary artery disease underwent adenosine MPI. The outcomes of interest were the hard events (cardiovascular death and sudden death) and the non-fatal events (heart failure worsening, acute coronary syndrome, aortic dissection and aneurysm). Stress left ventricular ejection fraction (LVEF), summed stress score (SSS), summed rest score (SRS), age and presence of clinical risk factors (diabetes mellitus, dyslipidemia, hypertension and CKD) were evaluated.

Results: A total of 25 cardiovascular deaths and 70 cardiovascular non-fatal events occurred over 778±354 days of follow-up. Univariate Cox analysis showed that predictors for total cardiac events were age (hazard ratio 1.03; $P<0.05$), stress LVEF (hazard ratio 0.96 $P<0.001$), SSS (hazard ratio 1.06; $P<0.001$), SRS (hazard ratio 1.05; $P<0.001$), presence of DM (hazard ratio 1.53; $P<0.05$), and presence of CKD (hazard ratio 2.86; $P<0.001$). Multivariate Cox analysis showed that presence of CKD (hazard ratio 2.32; $P<0.001$), stress LVEF (hazard ratio 0.96 $P<0.001$), and SSS (hazard ratio 1.03; $P<0.05$) were the independent predictors of total cardiovascular events.

Conclusion: Our study suggests that SSS and stress LVEF in adenosine stress ECG-gated myocardial perfusion SPECT imaging were the independent and strong predictors for the future cardiovascular events especially in the presence of CKD.

P2558 | BEDSIDE

Early risk stratification with myocardial perfusion imaging is not necessary in troponin negative patients with known coronary artery disease who present with possible acute coronary syndromes

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Purpose: In the absence of elevated troponins, patients with known CAD are often considered at intermediate risk when they present to the Emergency Department with possible ACS. These patients frequently undergo MPI as a basis for discharge. We hypothesize that negative serial troponin testing identifies CAD patients that are low risk for short term events and are unlikely to benefit from early revascularization.

Methods: Between October 2004 and August 2011, we identified 1,235 consecutive patients with known CAD and negative serial troponin testing who were referred from our Emergency Department for MPI. These patients were risk stratified according to TIMI scores. We assessed rates of abnormal MPI, revascularization through 30 days, and all cause mortality.

Results: Patients were elderly (65.2±12.3), mostly male (56.1%), and had intermediate TIMI risk scores (3±1). Increasing TIMI scores correlated with reversible perfusion defects and revascularization, but overall rates of severe reversible perfusion defects and revascularization were low. After a follow-up of 3.51±1.93 years, there were 138 deaths (11.2%) (Figure1). At 30 days, only one patient had died. After matching according to TIMI scores in patients with a reversible perfusion defect (n=332), we were unable to identify a risk stratum that realized a survival benefit with early revascularization (TIMI 1-2:24.2% v. 40%, $p=0.59$; TIMI 3-27.3% v. 23.5%, $p=1$; TIMI 4-5:31.2% v. 45.0%, $p=0.30$).

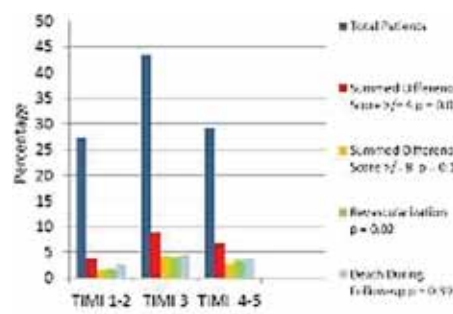


Figure 1. Myocardial, dynamic revascularization, and mortality stratified by TIMI scores.

Conclusions: Patients with known CAD who present with possible ACS and negative serial troponin testing should be considered low risk within 30 days of presentation. MPI offers low yield for early risk stratification. These patients can be discharged without further immediate testing and managed as stable CAD patients.

P2559 | BEDSIDE

Simultaneous PET/MR imaging for predicting left ventricular function after myocardial infarction

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Objectives: Myocardial PET imaging using the radiolabeled glucose analog 18F-FDG delineates regional glucose utilization as a marker of viable cardiomyocytes. MRI including late gadolinium enhancement (LGE) technique identifies increased extravascular space in areas of infarction and scar. In this study we measured simultaneously regional myocardial 18F-FDG uptake and LGE in patients early after acute myocardial infarction (AMI). Both parameters were compared with changes of left ventricular function after six months.

Methods: 28 patients with primary AMI underwent initial simultaneous PET/MRI 5 to 7 days after PCI. Follow-up imaging by MRI only was performed in 20 patients about 6 months after PCI. In a first step, myocardium was defined as "PET normal" based on the established threshold of more than 50% 18F-FDG uptake compared to remote myocardium or as "MR non-transmural" when LGE transmural was less than 50%. In a second step, variable thresholds for regional 18F-FDG uptake or LGE transmural were evaluated.

Results: In the "PET normal" group the EF was higher compared to the "PET abnormal" group both early after acute MI as well as at follow-up (EF initial: 48±10% vs. 59±8%, $p<0.05$; EF follow-up: 49±11% vs. 63±2%, $p<0.03$), while no differences for the EF were found between "MR non-transmural" and "MR transmural" patients (EF initial: 48±9% vs. 52±11%, $p=NS$; EF follow-up: 48±12% vs. 55±10%, $p=NS$). The improvement of the regional wall motion was significantly better in the "PET normal" vs. the "PET abnormal" group (-0.1±0.7 vs. -1.0±0.8, $p<0.05$), while no significant difference was found when patients were analyzed based on MRI transmural criteria (-0.1±0.8 vs. -0.5±0.8, $p=NS$). 7 patients (35%) showed discrepant findings, i.e. myocardium was "abnormal" based on PET and "non-transmural" based on MR. At follow-up, the regional myocardial function of these patients was inferior compared to the PET normal/MR non-transmural group (0.3±0.5 vs. 1.6±0.5, $p<0.003$) and showed no difference compared to the PET abnormal/MR transmural group (1.9±0.8, $p=NS$). Based on our results, thresholds which are associated with LV function recovery are a regional 18F-FDG uptake of more than 50% and a LGE transmural of less than 25%.

Conclusions: The simultaneous assessment of LGE transmural and 18F-FDG uptake in patients after AMI using a hybrid PET/MR system is feasible. The established PET "viability" parameter predicts accurately the regional LV function outcome after AMI, however, the established MRI parameter of LGE transmural might not apply for these patients.

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Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease

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Purpose: Recent studies have demonstrated the improved diagnostic accuracy for detection of coronary artery disease (CAD) when myocardial blood flow (MBF) is quantified in absolute terms. One of the challenges, however, is the lack of uniformly accepted cut-off value for detecting hemodynamically significant coronary

stenoses. The aim of the study is to determine optimal cut-off values for absolute myocardial perfusion and to evaluate the diagnostic accuracy of quantitative [15O]H₂O PET derived MBF in a clinical cohort of patients from a large collaborative study.

Methods: A total of 330 patients (mean age 61±9 years, 192 men) with a predominantly intermediate pre-test likelihood of CAD underwent both quantitative [15O]H₂O PET imaging and invasive coronary angiography in conjunction with fractional flow reserve (FFR) measurements. A stenosis >90% and/or an FFR ≤0.80 was considered obstructive, while a stenosis <30% and/or an FFR >0.80 was considered non-obstructive.

Results: Hemodynamic significant CAD was diagnosed in 116 (41%) out of 281 patients that fulfilled the study criteria for definition of CAD. Resting perfusion was 1.00±0.26 and 0.92±0.23 mL·min⁻¹·g⁻¹ in regions supplied by non-stenotic and significantly stenosed vessels, respectively (p<0.001). During stress myocardial perfusion increased to 3.26±1.05 and 1.78±0.74 mL·min⁻¹·g⁻¹, respectively (p<0.001). The optimal stress perfusion cut-off value was 2.3 mL·min⁻¹·g⁻¹. The corresponding value for myocardial flow reserve (MFR) was 2.50. With these cut-off values, sensitivity, specificity and accuracy of hyperemic MBF for the detection of functionally relevant CAD were 87, 84, and 85%, respectively at a per patient basis and 85, 83 and 84% at a per vessel based analysis. The corresponding values for the MFR were 84, 73 and 77% at a per patient level and 79, 80 and 80% at a per vessel level. In addition, there was a significant impact of gender and age on diagnostic accuracy of quantitative MBF measurements.

Conclusion: The optimal cut-off values for detecting flow limiting stenosis were 2.3 mL·min⁻¹·g⁻¹ and 2.5 for hyperemic MBF and MFR, respectively. For diagnosing hemodynamically significant CAD, absolute hyperemic MBF was superior to MFR. Quantitative MBF measurements using [15O]H₂O PET provide high diagnostic performance, but both gender and age should be taken into account.

P2561 | BEDSIDE

Beneficial effects of aortic valve replacement on myocardial energetics in aortic valve stenosis patients

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Purpose: Aortic valve stenosis (AVS) is characterized by pressure overload-induced left ventricular hypertrophy (LVH). It is unclear whether hypertrophied hearts of AVS patients are energetically compromised and reversal of cardiac hypertrophy by aortic valve replacement (AVR) is able to reverse changes in contractile efficiency. The present study was conducted to investigate myocardial external efficiency (MEE) – the ratio between external work and myocardial oxygen consumption (MVO₂) – in AVS patients and to assess the effect of AVR on MEE. AVR-induced changes in MEE were correlated with exercise parameters.

Methods: Ten AVS patients were included (normal coronary arteries, mean age 62±10 years, 7 male). Echocardiography and cardiopulmonary exercise test were performed prior to AVR and repeated after 4 months to assess peak aortic valve gradients and exercise parameters, respectively. Changes in left ventricular mass (LVM) and volumes were assessed by cardiovascular magnetic resonance (CMR) imaging and external work was calculated. Additionally, [11C]-acetate positron emission tomography (PET) was performed to obtain MVO₂. Next, MEE was calculated and compared with 14 healthy controls (mean age 48±11 years, 9 male).

Results: Four months after AVR, peak aortic valve gradient decreased from 88±20 to 24±12 mmHg, (p<0.001), as well as LVM index from 104±21 to 74±15 g·m⁻² (p<0.001). MVO₂ significantly decreased from 0.11±0.03 to 0.09±0.02 mL·min⁻¹·g⁻¹, (p=0.02), which was comparable to the MVO₂ observed in controls (0.10±0.02 mL·min⁻¹·g⁻¹). In addition, cardiac work significantly decreased from 15439±2631 to 10774±2446 mmHg·mL, (p<0.001), reaching similar values as in controls (10117±2268 mmHg·mL). Consequently, AVR resulted in a significant improvement in MEE from 32±7 to 37±5%, (p=0.02). A significant correlation was observed between absolute changes in MEE (ΔMEE) with absolute changes in exercise work (ΔWork; r=0.74; p=0.02) and absolute changes in peak VO₂ (Δpeak VO₂; r=0.67, p=0.03).

Conclusions: At 4 months follow-up, the detrimental effects of AVS are partially reversed by AVR in patients with normal coronary arteries and preserved ejection fraction, evident from regression of left ventricular hypertrophy and improvement of MEE.

P2562 | BEDSIDE

Prediction of cardiac events at non-culprit lesions in patients with acute coronary syndromes by plaque characteristics on coronary computed tomography angiography

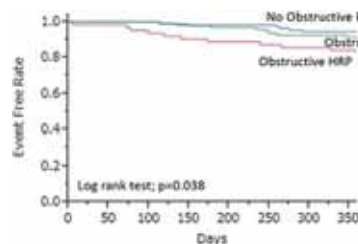
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Purpose: Several studies reported that preventive percutaneous coronary inter-

vention (PCI) to non-culprit plaques with moderate to severe stenosis improved prognosis of patients with acute coronary syndromes (ACS). These studies focused on only luminal stenosis. The aim of this study was to investigate whether non-culprit obstructive plaque characteristics detected by coronary computed tomography angiography (CTA) stratify the risk of cardiac events in patients with ACS.

Methods: We studied 265 patients who underwent CTA within one month after ACS. All patients were performed PCI to culprit lesions. After exclusion of culprit lesions of ACS and staged PCI lesions, the presence of obstructive plaque (OP; >50% stenosis) and high risk plaque (HRP; positive remodeling and/or low attenuation plaque) were evaluated on CTA. Cardiac events were defined as composite of ACS and late revascularization in de-novo lesions.

Results: OP was detected in 156 patients (58.9%). Of those, obstructive HRP was observed in 63 patients (23.8%). Cardiac events occurred in 26 patients (9.81%); 7 ACS and 22 late revascularizations. Kaplan-Meier analysis showed that patients with obstructive HRP had significantly higher incidence of cardiac events (event rate: 17.5 vs 8.60 vs 6.42%, p=0.038) (Figure). On Cox hazard analysis, adjusted hazard ratio was 3.62 (95% CI: 1.36 to 10.60; p=0.010) in patients with obstructive HRP and 1.48 (95% CI: 0.51 to 4.53; p=0.46) in those with obstructive non-HRP compared to those without OP.



Kaplan-Meier curves for cardiac events.

Conclusions: Patients with obstructive HRP had higher risk of cardiac events than those with obstructive non-HRP. The evaluation of non-culprit plaque characteristics by CTA might influence the strategy of secondary prevention of patients with ACS.

ECG AND SIGNAL PROCESSING

P2564 | BEDSIDE

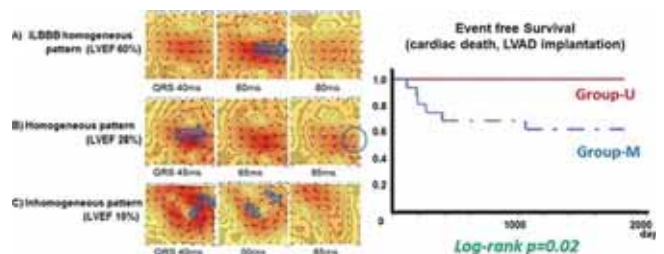
Homogeneous LV conduction sequence on MCG predicts an excellent long-term prognosis in narrow QRS patients after cardiac resynchronization therapy

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Despite the discouraging results of an echo-based study (EchoCRT), some patients with narrow QRS (<130ms) undoubtedly benefit from cardiac resynchronization therapy (CRT). Using multi-channel magnetocardiography (MCG) with high spatial resolution, we tested the hypothesis that narrow QRS patients with homogeneous left ventricular (LV) conduction, presumably identical to that caused by LBBB alone (isolated LBBB with normal LV function, iLBBB), would benefit from CRT with subsequently a favorable long-term prognosis.

Methods: 64-Ch MCG recordings (1kHz), yielding QRS current mapping, were performed in subjects with iLBBB (n=15) and narrow (<130ms) QRS patients (LVEF = 24±8%) with heart failure (HF) scheduled for CRT (n=27). We determined CRT response by 6 month echocardiography and conducted long-term follow-up for cardiac events (cardiac death and LVAD implantation).

Results: On MCG mapping, all of iLBBB subjects exhibited homogeneous LV conduction sequence constantly from right to left direction with the latest activation occurring in the lateral LV site. Similar uniform conduction was recognized in 11 HF patients (Group-A), while inhomogeneous conduction characterized by multi-directional currents was noted in other 16 patients (Group-B). LVEF, NYHA class, and the presence of CLBBB on ECG were comparable between the groups, however, responder was more frequently found in Group-A (8/11) than in Group-B (2/16, p=0.003). More importantly, Kaplan-Meier analysis revealed a marked difference in cardiac events (0/11 vs. 6/16, p=0.02).



Representative QRS arrow pattern.

Conclusion: MCG mapping is a promising tool to identify a subset of heart failure patients who have narrow QRS but would benefit from CRT with subsequently an excellent clinical outcome.

P2565 | BEDSIDE

Utility of the ST-segment deviation score in the risk prediction of patients with suspected acute myocardial infarction

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Purpose: ST-segment deviation score (STDS), a summation of all ST-segment deviations from baseline in a standard 12-lead ECG, has shown to correlate with mortality in patients with acute coronary syndrome. However, it is unknown whether these findings can be generalized to the clinical important setting of unselected patients presenting with acute chest pain, in which the early and reliable detection of patients at higher risk still presents an unmet clinical need.

Methods: In this prospective diagnostic study STDS was determined in 1404 consecutive patients presenting to the emergency department (ED) with symptoms suggestive of acute myocardial infarction. Primary endpoint was the occurrence of all-cause mortality within 30 days and 730 days. Patients with left ventricular hypertrophy or bundle branch block were excluded. The STDS was defined as the sum in millimeters (1mm = 1mV) of the absolute value of ST-segment deviations in all 12 leads of the first recorded ECG.

Results: Fourteen (1%) patients died within 30 days and 65 (5%) within 730 days. STDS at presentation in the highest tertile (≥ 4.7 mm) compared to the intermediate or lowest tertile (< 2.7 mm) was associated with an increased risk for death in the ensuing 30 days (HR 4.5, $p=0.007$) and 360 days (HR 2.4, $p<0.001$). Multivariate analysis showed that initial STDS levels remained an independent predictor of death within 30 days after adjustment for high-sensitive cardiac troponin T levels at presentation (HR 5.0, $p=0.008$) or TIMI-risk score (HR 5.5, $p<0.001$).

Conclusions: STDS, a simple and easily feasible clinical tool, helps in the risk stratification of unselected patients presenting with acute chest pain to the ED, as it independently and reliably predicts the short and long term mortality in this clinical important setting.

ClinicalTrials.gov number, NCT00470587

P2566 | BEDSIDE

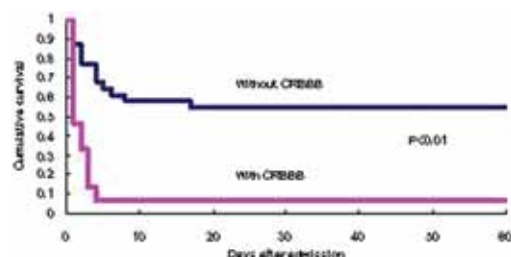
Complete right bundle-branch block is a marker of worse outcome in survivors after out of hospital cardiac arrest

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Purpose: Several studies have found increased mortality in patients with complete right bundle-branch block (CRBBB) and concomitant cardiovascular disease, and this conduction disturbance has been shown to be a strong predictor of mortality among patients with chronic coronary artery disease. However, the newly acquired CRBBB after resuscitation of cardiac arrest (CA) is unclear about an impact on mortality.

Methods: Of 395 consecutive patients with out-of-hospital CA for the last 18 months, 46 patients (31 male, 67 ± 12 years old) without evidence of terminal non-cardiac disease, trauma, airway obstruction, drowning, or intoxication were resuscitated at hospital arrival. They were divided into following two groups: 1) with CRBBB; 2) without CRBBB. Baseline demographic, clinical and electrocardiographic characteristics were analyzed and the survival was evaluated. CRBBB on electrocardiography was defined as QRS prolongation ≥ 120 ms, rSR, complex in lead V1 or V2, and a slurred S waves in lead I, aVL, and V5 or V6.

Results: CRBBB was identified in 15 patients. There was mostly no significant difference in baseline characteristics including the presence of ischemic heart disease between two groups, but QRS and QTc duration were longer in patients with CRBBB than those without CRBBB (164 ± 29 vs 120 ± 32 [ms]; $P<0.01$, 474 ± 45 vs 441 ± 43 [ms]; $P=0.03$, respectively). The time until return of spontaneous circulation was not different (31.5 ± 16.5 vs 24.3 ± 15.2 [min]; $P=0.15$), but patients with CRBBB had markedly lower in >30 days survival than those without CRBBB (6.7 vs 45.2 [%], log-rank test; $P<0.01$).



Kaplan-Meier curve for CA.

Conclusions: Presence of CRBBB after resuscitation might suggest the poor prognosis in the CA patients.

P2567 | BEDSIDE

ST-segment deviation score in the early diagnosis of acute myocardial infarction

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Purpose: The ST-segment deviation score (STDS) has been invented for the early detection of ischemic signs in a standard 12-lead-electrocardiography (ECG) in patients with symptoms suggestive of acute myocardial infarction (AMI). However, little is known about the optimal cutoff-values or the time of measurement in the repolarisation-phase.

Methods: We conducted a prospective study to examine the diagnostic accuracy of the STDS in 1404 consecutive patients who presented with symptoms suggestive of AMI to the emergency department. Patients with left ventricular hypertrophy or bundle branch block were excluded. The STDS was defined as the sum in millimeters (1 mm = 1 mV) of the absolute value of ST-segment deviations in all 12 leads of the initially recorded ECG. The STDS was determined at several timepoints during the electrocardiographic phase of repolarisation. The final diagnosis was centrally adjudicated by two independent cardiologists.

Results: AMI was the adjudicated final diagnosis in 248 (18%) patients (206 NSTEMI, 42 STEMI). The diagnostic accuracy of the STDS-measurements obtained at presentation, as quantified by the area under the receiver operating characteristic curve (AUC), was best at J-point (0.67; 95% confidence interval 0.64-0.69) with decreasing accuracies during later phases of significantly (AUCs ranging between 0.55-0.65, $p<0.05$ for comparisons). E.g. a cutoff value of 8.4 mm in the STDS resulted in a positive likelihood ratio of 3.5 for the diagnosis of an AMI. In the setting of a non-diagnostic ECG at presentation ($n=1130$, 80%), the AUC of STDS-measurements at J-point tended to be superior to later sites with an AUC of 0.54 (95%CI 0.51-0.57; $p>0.05$ for all comparisons). The optimal cutoff value for the STDS in this clinically important subgroup was 2.7 mm with a sensitivity of 70% and a specificity of 41%.

Conclusions: The STDS in acute chest pain patients for the early diagnosis of AMI is determined best at J-point and, in conjunction with clinical examination and biomarker findings, might be of particular help to select patients without a diagnostic ECG but at higher risk of having an AMI.

ClinicalTrials.gov number, NCT00470587

P2568 | BEDSIDE

Clinical usefulness of a QRS scoring system for estimating rapid progression of myocardial infarction in patients with ST-segment elevation myocardial infarction

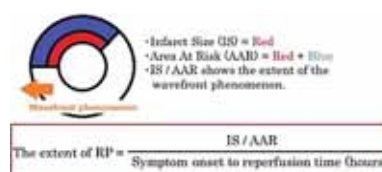
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Background: Patients with ST-segment elevation myocardial infarction (STEMI) sometimes show rapid progression of myocardial infarction (RP). Estimating RP is important in clinical settings however there is no method to evaluate RP. We hypothesize that dividing QRS scores on admission by the number of hours from symptom onset to admission (QRSscore/Time) could estimate the extent of RP.

Methods: We included 74 patients (62 ± 11 years, male=62) with a first STEMI reperfusion within 6 hours. All patients underwent an electrocardiogram on admission, and cardiac magnetic resonance imaging (CMR) at 9 days using 1.5T MAGNETOM Avanto.

We defined the extent of RP as the speed of the wavefront phenomenon using the following formula (see Fig.): infarct size (IS) divided by area at risk (AAR) and symptom onset to reperfusion time (hours). IS was defined as the infarct core using LGE-CMR, and AAR was defined as the infarct-related edema using T2-weighted CMR with off-line analysis (Q-MASS, Medis). QRS scores were calculated as a previous report described.

Results: Univariate analysis showed the predictors of the extent of RP in the sample's highest tertile were hypertension and QRSscore/Time. In particular, QRSscore/Time was strongly associated with the extent of RP ($R=0.49$, $P<0.001$). We observed the same tendency when limiting the sample group of patients to those with anterior STEMI ($n=35$, $R=0.51$, $P<0.001$). Multivariate analysis showed that QRSscore/Time was the strongest predictor of RP (OR=1.792, 95%CI 1.319-2.433, $P<0.001$).



Conclusion: We can estimate the extent of RP in patients with STEMI using QRSscore/Time.

P2569 | BEDSIDE**Prediction of atrial fibrillation recurrence in patients with pulmonary vein isolation by P-wave signal-averaged electrocardiogram**

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Background: The noninvasive methods for predicting atrial fibrillation (AF) recurrence after the first pulmonary vein isolation (PVI) has not been well described. The aim of this study was to assess the usefulness of the P-wave signal-averaged electrocardiogram (P-SAECG) in predicting the recurrence of AF after the first PVI.

Methods: P-SAECG was recorded within 1 week, before (pre) and after (post) the first PVI session in consecutive 87 idiopathic AF patients (EF $\geq 50\%$, BNP ≤ 200 pg/ml). Filtered P-wave duration (FPD) and root mean square voltages in last 20 msec of the filtered P-wave (LP20) were measured.

Results: After the PVI session, the mean follow-up periods was 12 ± 7 months. During the follow-up period, 22 of 87 patients experienced recurrence of AF (n=11: Paroxysmal-AF, n=11: Persistent-AF). Pre-FPD or Pre-LP20 was not significantly different between non-recurrence group and recurrence group. However, Post-FPD of paroxysmal-AF recurrence group was significantly shorter than non-recurrence group and Post-LP20 of paroxysmal-AF recurrence group was significantly larger than non-recurrence group. And then, Post-FPD was significantly shorter in the case of left pulmonary vein (LPV) re-conduction at the time of 2nd PVI session, than in the case of LPV non re-conduction. And, Post-LP20 was significantly larger in the case of LPV re-conduction at the time of 2nd PVI session, than in the case of LPV non re-conduction. As a result, the Post-LP20/FPD of paroxysmal-AF recurrence group was significantly higher than non-recurrence group (0.024 ± 0.009 vs. 0.015 ± 0.007 $\mu\text{V}/\text{msec}$, $p < 0.05$).

Conclusion: The post-LP20/FPD may be useful for predicting a paroxysmal-AF recurrence in idiopathic AF patients with PVI.

P2570 | BEDSIDE**Hypertension and the electrocardiogram: a study in a large primary care telecardiology database in Brazil**

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Purpose: The 12-lead electrocardiogram (ECG) is the most readily available non-invasive test for the detection of cardiac disease in primary care. The detection of preclinical cardiac abnormalities is a key clinical step in hypertension management, and several guidelines for hypertension recommend an ECG in hypertensive patients to improve risk prediction. The objective of this study is to assess the prevalence of ECG abnormalities in patients with hypertension who were attended at primary care centers in Brazil.

Methods: In this observational and retrospective study, all 12-lead standard digital ECGs analyzed by cardiologists of a public telemedicine service in Brazil, from January to December 2011, were assessed. This service attends primary care of 660 cities in our state. ECGs were sent by remote healthcare professionals through internet to be analyzed by cardiologists who are trained and experienced in the analysis and interpretation of ECG. The prevalence of ECG abnormalities in patients with hypertension was assessed.

Results: During the study period, 82,125 primary care patients with hypertension underwent ECG (mean age 60.8 ± 13.5 years, 63.7% females). The most common comorbidities besides hypertension were diabetes (14.2%), smoking (11.4%), hyperlipidemia (7.0%) and Chagas disease (5.6%). Regarding the ECG analysis, 48.3% of them had no abnormalities, and the mean number of abnormalities per patient was 0.9 ± 1.1 (range 0-9). Regarding the rhythm, 2.9% had atrial fibrillation or flutter, 3.2% ventricular premature beats, 2.4% supraventricular premature beats and 0.6% were pacemaker users. Left bundle branch block (LBBB) was observed in 2.4% of the ECGs, incomplete LBBB in 1.8%, right bundle branch block (RBBB) in 4.6% and left anterior hemiblock in 8.7%. First degree atrioventricular block was found in 2.5%, second and third degree in less than 0.1% each. There was electrocardiographic evidence of left ventricular and atrial hypertrophy in 5.2% and 3.2% of patients, respectively, and pathological Q waves in 1.5%. Non-specific repolarization abnormalities were observed in 29.4% of the patients.

Conclusion: In this large sample of primary care patients with hypertension, ECG abnormalities were observed in more than 50% of patients. The most common abnormalities were non-specific repolarization abnormalities, RBBB, LBBB, left ventricular hypertrophy, premature beats and atrial fibrillation.

P2571 | BEDSIDE**Selective beat averaging to evaluate ventricular repolarization adaptation to deconditioning after 21-days of head-down bed-rest**

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Purpose: The study of QT/RR relationship is important for the clinical evaluation

of possible risk of life-threatening ventricular tachyarrhythmias. As deconditioning is a risk factor for cardiovascular disease, our aim was to assess the effects of 21-days of reduced gravitational stimulus and immobilization by head-down (-6 degrees) bed-rest (BR) on ventricular repolarization.

Methods: 8 healthy men (mean age 30 ± 5) were studied at DLR as part of the European Space Agency BR studies. High fidelity (1000 Hz) Holter ECG (12-leads, Mortara Instrument) was acquired before (PRE), the last day of BR (HDT21), and five days after the BR conclusion (POST). The night period (23:00-06:30) was selected for the analysis. X,Y,Z leads were derived using inverse Kork matrix and vectorcardiogram computed. Selective beat averaging was used to obtain averages of P-QRS-T complexes preceded by the same stable heart rate (defined for each 10 msec bin amplitude, in the range 900-1200 msec). For each averaged waveform (i.e., one for each bin), T-wave maximum amplitude (Tmax), T wave area, RTapex and RTend, ventricular gradient amplitude (VG) and QRST spatial angle were automatically extracted.

Results: Compared to PRE, at HDT21 both RTapex and RTend resulted shortened (-3% and -4%, respectively), together with a decrease in T-wave amplitude (-13%) and area (-16%). VG was diminished by 13%, and QRST angle increased by 6% ($p < 0.11$). At POST, all parameters returned to their control values.

Changes in ventricular repolarization

	PRE	HDT21	POST
Tmax (microV)	566 $\pm$ 127	442 $\pm$ 120* [#]	601 $\pm$ 160
T wave area (mV.msec)	71 $\pm$ 11	54 $\pm$ 14* [#]	75 $\pm$ 17
RTapex (msec)	275 $\pm$ 17	264 $\pm$ 21* [#]	281 $\pm$ 17
RTend (msec)	383 $\pm$ 27	366 $\pm$ 22*	378 $\pm$ 17
VG (microV)	78 $\pm$ 28	56 $\pm$ 28*	62 $\pm$ 42
QRST (angle)	47 $\pm$ 30	54 $\pm$ 29	40 $\pm$ 26

* $p < 0.05$ vs PRE; [#] $p < 0.05$ HDT21 vs POST (one-way Anova for paired data and Tukey test).

Conclusions: Sustained reduced gravitational stimulus and immobilization affected ventricular repolarization during the night period. This should be taken into account in patients with cardiovascular diseases, when immobilized in bed, to proper adjust the pharmacological therapy in order to avoid further complications.

P2572 | BENCH**Assessment of the ST dynamics by telemetry ECG method to determine the indications for emergency angioplasty after thrombolysis**

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Aim: To investigate the value of ST-segment dynamics in telemetry ECG monitoring in patients with acute coronary syndrome with ST segment elevation (ACS STE) to determine the indications for emergency coronary angioplasty.

Methods: The study included 25 patients with ACS STE, 17 men and 8 women with signs of effective thrombolysis, performed within the first 3 hours of the disease onset. All patients in the Cardiac Intensive Care Unit conducted under telemetric ECG using complex "Astrokard® - Telemetry" with an analysis of the ST segment dynamics on the 12-lead automatically with subsequent medical verification.

Results: Mean age 56.5 ± 1.8 years. The average time from the start of angina attack before TLT was 2.56 ± 0.33 h. The patients were divided into 2 groups. Group 1 included 14 patients (56%) who did not register the new ST-segment deviation from the contour in the process of monitoring. Patients in this group have not been performed emergency coronary angiography. The delayed coronary angiography revealed the chronic coronary artery stenosis without signs of thrombosis. Hospital mortality was absent. Group 2 included 11 patients (44%), in which after 98 ± 12 minutes of the effective TLT the re-elevation of ST segment by 1 mm or more in 2 contiguous leads, lasting more than 1 minute, were fixed. Re-elevation of ST segment was preceded the angina attack recurrence by 15 ± 7.5 minutes. The emergency coronary angiography was performed in patients of group 2. In 8 patients (72.7%) the signs of thrombosis of the infarct-related coronary artery (TIMI 0-1) were revealed and emergency angioplasty with restoration of blood flow in the TIMI 2 in 25% of patients and TIMI 3 in 75% of patients were performed. Re-thrombosis of infarct-related coronary artery in group 2 was significantly more frequent than in patients of group 1 ($p < 0.0001$). In 4 of these patients with three-vessel lesion angioplasty of the infarct-related artery was not performed due to technical reasons. Mortality in the group 2 was 9% (1 patient), and significantly higher than mortality in the group 1 ($p = 0.01$).

Conclusions: Re-elevation of ST segment by 1 mm or more is a reliable diagnostic criterion of infarct-related coronary artery re-thrombosis. Telemetric ECG allows us to identify the patients for whom an emergency percutaneous coronary intervention after the effective systemic thrombolytic therapy is necessary.

P2573 | BENCH**QT dynamics and microvolt T-wave alternans in patients with ventricular arrhythmias during exercise test**

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It is important to study electrical instability markers in patients with idiopathic ven-

tricular arrhythmia (VA). A combination of non-invasive risk stratification markers for determining the presence of myocardial electrical instability is more actually. The best way is to reveal it during any modulation of the autonomic nervous system, such as physical exercise. In last years, much attention is paid to markers of changing repolarization - microvolt T-wave alternans (MTWA) and QT interval duration.

Objective: To study the dynamics of VA, MTWA, repolarization changes and the recovery heart rate (HRR) during exercise test in patients with idiopathic VA.

Materials and methods: 49 patients (26 men, mean age 43 ± 12 years) with idiopathic VA (more than 300 per hour, day-long type). Structural cardiac pathology was excluded by ECG, echo and stress-echoCG, cardiac MRI. Exercise treadmill-test (ETT) (protocol Bruse) was performed without any therapy, up to submaximal heart rate 85% or more. We studied MTWA, HR, VA, QT / QTc pre-test, peak and recovery period (RP) during ETT.

Results: The volume of the achieved load was 10.6 ± 2.4 and MET. HRR1 min was 26.5 ± 9.5 bpm (normal). VA was in 66% patients - mean 6.3 single ventricular ectopic complexes (sVE/min), at the peak ETT VA was in 44%, mean 3.4 sVE/min . At rest, QT 378.1 ± 25.2 / QTc 433.5 ± 19.9 ms, at the peak ETT QT 326.7 ± 42.2 / QTc 478.1 ± 44.9 ms ($p < 0.05$). QTc duration of more than 470 ms was in 61%, at ETT peak. MTWA was positive in 33.3% patients, and nine of them had an extending QTc, and other - normal. The probability of long QT syndrome diagnosis using diagnostic score is low in all the patients.

Conclusions: We observed the high detection of ventricular arrhythmias during ETT (44% of patients), combined with an increase in QTc and MTWA. It could suggest an increased myocardial electrical instability in patients with idiopathic VA.

COMPLEX PCI

P2575 | BEDSIDE

New-generation drug-eluting stents for unprotected left main coronary artery disease improve clinical outcomes?

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Background: About 5 years has passed since 2nd-generation drug-eluting-stent (DES) launched in Japan. Recent available data have shown the feasibility and the safety of new DES, but clinical outcomes data for left main coronary artery disease were scarce.

Objective: To evaluate the 1-year clinical outcomes in patients with unprotected left main coronary artery (ULMCA) disease treated with overall new DES options.

Methods: We analyzed retrospectively consecutive 2627 patients undergoing PCI angioplasty with sirolimus-, paclitaxel-, zotarolimus-, (...), and everolimus-eluting stents from October 2008 to December 2013 in our hospital. A total of 151 patients with symptomatic coronary artery disease underwent angioplasty and were implanted some stents for de novo ULMCA lesions.

Results: Clinical follow-up was performed in 144 patients (95.4%) over a median of 295 days. There were no significant differences between two groups in lesion or patient characteristics, however procedure time was shorter in 2nd-generation DES group (136.9 ± 77.1 min vs 103.9 ± 56.5 min, $P < 0.01$). The mean SYNTAX score was comparable with in both group (25.8 ± 11.0 vs 26.9 ± 10.9 , $P = 0.61$). TLR was extremely lower in 2nd-generation DES group compared with 1st-generation DES group (1.8% vs 22.6%, $P < 0.01$).

	1st generation DES (n=32)	2nd generation DES (n=119)	p value
SYNTAX score	25.8 ± 11.0	26.9 ± 10.9	0.611
Procedure time, min	136.9 ± 77.1	103.9 ± 56.5	0.008
Late lumen loss, mm	0.85 ± 0.54	0.34 ± 0.52	<0.001
Death, %	0.0%	1.7%	0.460
MI, %	0.0%	0.0%	
TLR, %	22.6%	1.8%	<0.001
TVR, %	29.0%	4.4%	<0.001
MACE, %	22.6%	3.5%	<0.001

Conclusions: A good safety and efficacy profile has been shown with the use of 2nd-generation DES for the treatment of ULMCA disease, with a significant decrease in the need for repeat revascularization when compared to 1st-generation DES. In this study, the use of new DESs for ULMCA disease, including complex treatment like 2-stent-technique, appears to have promising safety and efficacy, with results at 1-year clinical follow-up.

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Early vascular healing after titanium-nitride-oxide-coated stent vs. platinum chromium everolimus-eluting stent implantation in patients with acute coronary syndromes

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Purpose: Recent data suggests a paradigm shift in stent thrombosis (ST) occurrence as evidenced by lower rates of early and late ST in patients treated

with platinum chromium everolimus-eluting stents (PtCr-EES) compared to traditional bare metal stents. Nevertheless, data on early vascular healing response of novel stent devices are scarce. In this randomized prospective trial, we sought to compare early healing and neointimal coverage of vessels treated with bioactive titanium-nitride-oxide-coated stents with thin strut platform (BAS) versus PtCr-EES at 2 months follow-up in patients with ACS.

Methods: Thirty-eight patients with ACS were randomized to receive either BAS (n=19) or PtCr-EES (n=19). Neointimal strut coverage and apposition was examined by OCT and intravascular coronary flow reserve measurement (CFR) at 2 months.

Results: At 63 ± 8 days, 302 cross-sections (3412 struts) were analyzed in the BAS group, and 324 cross-sections (3460 struts) in the PtCr-EES group. Mean $\pm$ SD neointimal thickness was 240 ± 127 μm and 65.4 ± 59.5 μm for BAS and PtCr-EES, respectively ($p < 0.001$). Median [IQR] percentage of uncovered struts was 1.2 [2.8] % vs. 11.3 [17.7] % ($p < 0.001$). Median percentage of malapposed struts was 0 [1.20] % vs. 0.68 [3.59] % ($p = 0.026$). CFR values between groups were comparable.

Follow-up measurements at 2 months

Variable	BAS (n=19)	PtCr-EES (n=19)	p value
Total number of struts analysed	3412	3460	
NIH area (mm ²)	1.94 ± 1.01	0.427 ± 0.647	<0.001
Mean NIH thickness (μm)	240 ± 127	65.4 ± 59.5	<0.001
Uncovered struts	66 (1.91)	510 (14.9)	<0.001
Percentage of uncovered struts	1.2 [2.8]	11.3 [17.7]	<0.001
Percentage of cross-sections with uncovered struts	8.6	54.0	<0.001
Malapposed struts	27 (0.791)	63 (1.82)	<0.001
Percentage of malapposed struts	0 [1.20]	0.68 [3.59]	0.026
Coronary flow reserve	2.92 ± 1.26	2.58 ± 1.36	0.450
Abnormal coronary flow reserve (≤ 2)	4 (26.7)	9 (47.4)	0.296

Continuous variables are presented as mean $\pm$ SD or as median [IQR], while categorical variables are presented as frequency (percentage).

Conclusions: BAS showed rapid and comprehensive neointimal coverage at 2 months as compared to PtCr-EES, with significant neointimal hyperplasia. Furthermore, less strut malapposition was found in BAS.

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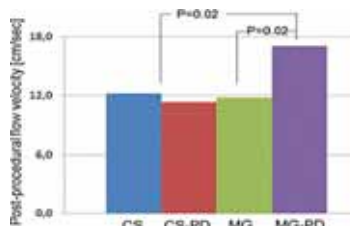
Mesh-covered stent implantation in addition to a distal embolic protection device leads to significantly higher velocity rates in highly degenerated bypass lesions

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Background: Percutaneous coronary intervention (PCI) for the treatment of aortic coronary saphenous vein graft lesions (SVG) may include distal embolic protection devices (PD) to reduce atherothrombotic embolization. The potential benefit of the combination of a mesh-covered MGuard stent (MG) with a distal embolic protection device remains unknown.

Methods: This study analyzed 78 consecutive patients with SVG-PCI between 2010 and 2012 in four groups (conventional stenting (CS) vs. MGuard stent (MG) with or without PD). Only patients with a SVG degeneration score ≥ 1 were included. Post-procedural creatine kinase was assessed (CK, U/l). Graft dimensions were measured using quantitative coronary angiography. Adjusted TIMI frame counts were determined and estimated TIMI velocity rates (VE) were calculated accordingly (cm/sec).

Results: SVG degeneration score was 1.4 ± 0.5 and significantly lower in grafts treated by CS (n=29) as compared to all other patients (1.8 ± 0.8) treated with either PD (n=8), MG stents (n=28), or both (n=9), ($p = 0.01$). CK release was lowest in MG stents including a PD (MG-PD: 142 ± 77 vs. 440 ± 1160 ; $p = 0.3$). Also, post-procedure VE was significantly higher in the MG-PD group (17.1 ± 7.2) as compared to the MG stent alone (11.8 ± 5.1 , $p = 0.02$) or the conventional stent with or without PD (11.7 ± 5.7 , $p = 0.02$).



VE depending on treatment approach.

Conclusion: The complementary application of a mesh-covered stent including a distal embolic protection device showed significantly higher TIMI velocity (VE) post PCI and a trend towards reduced CK release. This may be an appealing concept for a prospective randomized clinical trial in highly degenerated SVG lesions.

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Revascularization strategies for patients with multiple vessel disease and unprotected left main with a cobalt-chromium rapamycin eluting stent (ERACI IV Registry)

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Objectives: The primary endpoint of ERACI IV Registry was to assess the incidence of major adverse cardiovascular events (MACCE) in patients (pts) with coronary artery disease (CAD) using Firebird-2 (2nd generation rapamycin eluting stent) vs. ERACI III population (Drug eluting stent [DES] and bypass surgery [CABG] arms) at 30 days, 6 and 12 months of follow-up.

Methods: From March 2013 to February 2014, 225 pts with CAD undergoing DES implantation in 15 centers in Argentina were prospectively included. The registry was approved and monitored by an independent safety committee. Inclusion criteria were indication of myocardial revascularization and lesions $\geq 70\%$ in 2, 3 coronary arteries and/or unprotected left main disease. Exclusion were poor ejection fraction, recent STEMI (<72 hours), previous PCI with DES, lesion diameter ≤ 2.5 mm, renal failure and contraindications for dual antiplatelet therapy. MACCE was defined as any cause of death, myocardial infarction (MI), stroke or unplanned revascularization. Stent thrombosis was also analyzed. The only DES allowed was Firebird-2 (MicroPort Medical Shanghai CO, Ltd), whereas in ERACI III first DES generation was used.

Results: Baseline characteristics included age 63.8 ± 11.1 years, 84.4% of males, 29.7% of diabetics, 56% had unstable angina and 67.7% of pts 3 vessels or left main disease. 1.7 ± 0.9 lesions treated per pts and 1.82 rapamycin eluting DES implanted. Procedural success was 100%. At discharge 100% received thienopyridines (58.3% clopidogrel, 28.0% prasugrel and 13.7% ticagrelor). 30 days results are reported in Table.

30 days results from ERACI IV Registry

	ERACI III DES (225)	ERACI III CABG (225)	ERACI IV Firebird 2 (225)	P value
Any death	0.9%	5.7%	0.4%	0.004
MI (Q)	0.9%	5.7%	0.4%	0.001
Death + MI + stroke	1.8%	11.4%	1.8%	<0.001
Target vessel revascularization	1.3%	0.0%	0.4%	0.23
Target lesion revascularization	1.3%	0.0%	0.0%	0.11
MACCE	4.4%	12.3%	1.3%	<0.001

MI: myocardial infarction; MACCE: death, MI, stroke and target vessel revascularization.

Conclusions: At 30 days ERACI IV registry showed a remarkable low incidence of MACCE and any other components of the primary end point. Complete six months follow up will be available at the time of presentation.

P2579 | SPOTLIGHT

Long-term outcomes of optimal medical therapy versus percutaneous coronary intervention for patients with coronary chronic total occlusion

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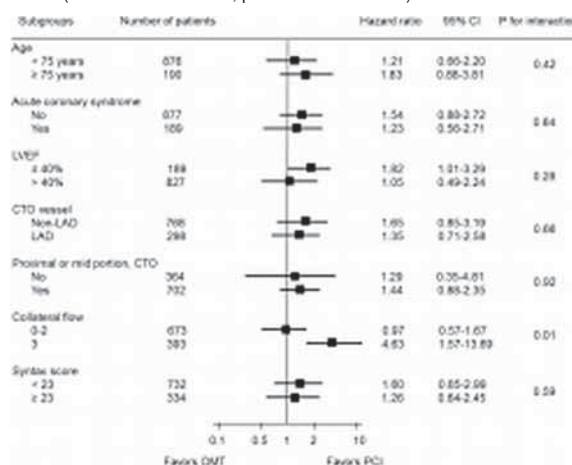
Objectives: To investigate the association of treatment strategy with clinical outcomes in patients with chronic total occlusion (CTO).

Background: Limited data are available on long-term clinical outcomes of CTO patients received optimal medical treatment (OMT) as compared with percutaneous coronary intervention (PCI).

Methods: Between March 2003 and February 2012, 2074 patients with CTO were enrolled in a retrospective, observational registry. Among these, we studied CTO patients who underwent OMT or PCI. We classified patients into the OMT group (n=664) and the PCI group (n=883) according to treatment strategy. Propensity-score matching was also performed. The primary outcome was cardiac death.

Results: The median follow-up duration was 45.8 (interquartile range: 22.8 to 71.1) months. Of PCI group, 699 patients (79.2%) underwent successful revascularization. After propensity-score matching (533 pairs), there was no significant difference in the rate of cardiac death between the OMT group and PCI group

(hazard ratio [HR], 1.57; 95% confidence interval [CI], 0.91-2.72, p=0.11). However, the successful CTO recanalization had a lower rate of cardiac death than either failed PCI or OMT in matched population (527 pairs) (HR, 2.69; 95% CI, 1.42-5.09, p=0.002). On subgroup analysis, the rate of cardiac death was significantly lower in the PCI group than in the OMT group among patients with collateral flow 3 (vs collateral flow 0-2, p for interaction 0.01).



Subgroup analysis.

Conclusions: Successful CTO recanalization appears to be associated with reduced long-term cardiac mortality, but not initial treatment strategy. In CTO with collateral flow 3, PCI should be considered as the preferred strategy.

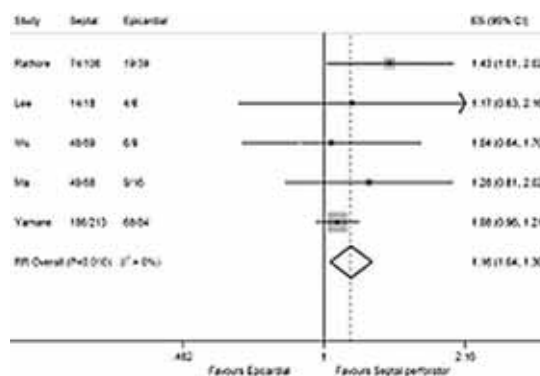
P2580 | BEDSIDE

Retrograde wiring of collateral channels of the heart in chronic total occlusions: a systematic review and meta-analysis of safety, feasibility and incremental value in achieving revascularisation

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Aims: To conduct a systematic review and meta-analysis on retrograde wiring of chronic total occlusions (CTO).

Methods and results: We searched publications from 1966 to June 2013 in medline and embase databases with inclusion of studies detailing success rates of retrograde wiring (n>10) and complications. We analysed individual data on successful retrograde wiring and collateral vessel used. 17 case series (n range 17-378) with a total of 1818 CTO revascularisation attempts fulfilled criteria for inclusion. The majority of cases were undertaken by CTO dedicated operators. Procedural CTO revascularisation success rates ranged from 67-90.6% with a large proportion having previously failed an "antegrade" approach. The septal perforator collaterals and epicardial channels were used in 75% (n=1356) and 21% (n=384) of cases respectively. Septal perforating wiring (80%) was significantly more likely to be successful compared to epicardial coronary artery wiring (68.8%) when chosen by the operator as a route of retrograde access to the CTO body. RR 1.16 (95% CI: 1.04, 1.30; p=0.010). (figure) Although collateral/coronary perforation was not infrequent (n=90, 5%) serious acute complications were uncommon; in the combined population 12 cases of cardiac tamponade (0.7%) requiring pericardiocentesis, and 2 deaths (0.1%).



Conclusions: Septal perforator channels are significantly more likely to be successfully retrogradely wired compared to epicardial vessels when either is selected, by reference to their anatomical suitability, as a route of access. Successful retrograde wiring of collateral channels in selected patients undertaken by "CTO

dedicated" operators can significantly enhance the chances of revascularisation of complex CTOs with a low risk of acute serious complications.

P2581 | BEDSIDE

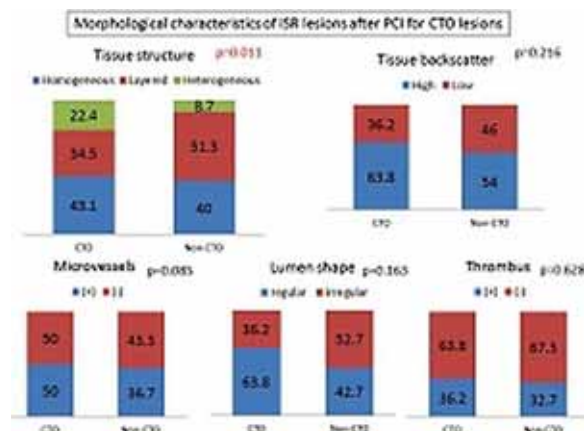
Morphological characteristics of in-stent restenosis lesions after percutaneous coronary intervention for chronic total occlusive lesions assessed with optical coherence tomography

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Background: Little is known about morphological characteristics of in-stent restenosis (ISR) lesions after percutaneous coronary intervention (PCI) for chronic total occlusive (CTO) lesions.

Methods: Between June 2008 and January 2013, we performed optical coherence tomography (OCT) for 58 ISR lesions after PCI for CTO lesions and 150 after elective non-CTO lesions. We examined the difference between tissue morphologies of ISR lesions after CTO lesions and those after non-CTO lesions. The morphological assessment of neointimal tissue as to restenotic tissue structure, tissue backscatter, microvessels, lumen shape, and thrombus at the minimum lumen area site was performed.

Results: The results are shown in the figure.



Conclusions: The pathophysiology of ISR lesions after PCI for CTO lesions might be different from those after non-CTO lesions.

P2582 | BEDSIDE

Dedicated bifurcation BIOSS stent in the treatment of distal left main stem stenosis - International Registry

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Purpose: The aim of this study was to assess the effectiveness and safety profile of the distal LMS stenosis treatment with the dedicated bifurcation stent BIOSS: in subgroup I paclitaxel-eluting BIOSS[®] Expert and in subgroup II sirolimus-eluting BIOSS[®] LIM.

Methods: The enrollment of patients with coronary artery disease and NSTEMI-ACS started in January 2010 in three centers in Bulgaria, Poland and Spain. Decision for LMS stenting was based on the Heart Team consensus. Patients with STEMI were excluded from the study. Provisional T-stenting was the obligatory strategy. Control angiography was planned at 12 months in all patients. The primary end point is the rate of death, myocardial infarction, in-stent thrombosis or target lesion revascularization (TLR) at 12 month after PCI. Here, we present 6-month clinical data from both groups and complete angiographic data from BIOSS[®] Expert group. At the time of ESC Congress 2014 angiographic data from BIOSS[®] LIM will be also completed.

Results: There were enrolled 158 patients (62 in Expert group and 96 in LIM group). The average age was 65.7±12.5 yrs and 19.7% were female. PCI in NSTEMI-ACS was performed in 17.8% of patients. Moreover, 73.4% were with hypertension, 81.4% with dyslipidemia, 32.1% with diabetes, 39.2% with prior MI, 43.3% with prior PCI and 17.4% with prior CABG. The mean SYNTAX score was 21.52±6.58 and EuroScore II – 1.73% ± 1.6%. True bifurcations were treated in 70.1% of cases.

All BIOSS[®] stents were implanted successfully. The nominal stent parameters were as followed: BIOSS[®] Expert subgroup - 4.07±0.26 mm (proximal diameter) x 3.36±0.26 mm (distal diameter) x 16.61±1.72 mm (length) and BIOSS[®] LIM subgroup - 3.90±0.4 mm x 3.17±0.39 mm x 16.81±2.06 mm. Side branch stent was implanted in 25.9% and 21.4% of patients, respectively. Almost 62% of procedures were performed from radial access, and 83% with a 6F catheter.

After 12 months in BIOSS[®] Expert group angiographically driven TLR rate was 9.6%, whereas clinically driven TLR was 3.2%. In BIOSS[®] LIM group data are

pending - at 6 months there were no death or MI. Moreover, in BIOSS[®] Expert group angiographic data disclosed that the late lumen loss was as following: in the main vessel - 0.21±0.1 mm, in the main branch - 0.26±0.12 mm and in the side branch - 0.14±0.09 mm.

Conclusions: Dedicated bifurcation BIOSS[®] stents seem feasible devices with promising effectiveness and safety profile in distal LMS stenosis. Complete BIOSS[®] LIM angiographic data will answer the question if the used drug is more important or maybe the stent design is crucial.

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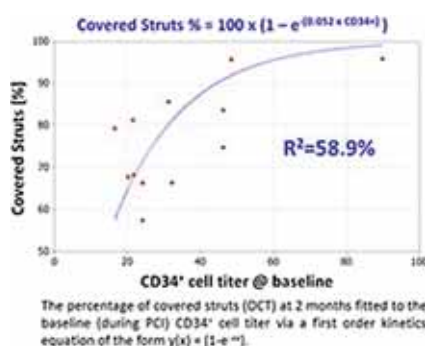
Early healing profile of the new Dual Therapy EPC-Capturing Sirolimus DES; correlation of OCT coverage at 2 months to baseline CD34+, CD34+/KDR+ cell titer: Subset analysis of the EGO-COMBO Study

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Background: The Dual Therapy DES (EPC-capturing antibody & abluminal sirolimus coatings) is the first DES utilizing CD34+ antibody coating for rapid endothelialization to enhance healing (measured by OCT % strut coverage). Using 4 sequential OCT FUs baseline to 24M, the EGO-COMBO study is the first study ever designed to determine the healing profile of a DES. Correlations of the endothelial progenitor cell (EPC) titres with early strut coverage % were studied.

Methods: 61 patients treated by Dual Therapy DES received 4 sequential OCT FUs at baseline (optimal stent apposition), at early FU (1:2:2:1 ratio in 4 monthly groups 2nd to 5th month for % strut coverage in 6 OCT Categories), 9M (late neointima), & 24M (long term outcomes), with core lab. adjudication of all clinical events, QCA & OCT analyses. Circulatory baseline (during PCI), 3M & 9M EPC cell titres were analysed, using FACS analysis of fluorescent labeled blood samples for CD34, CD133 & KDR epitopes, and combinations thereof.

Results: Using the best fit to a first order kinetics equation in the form $y(x) = (1 - e^{-ax})$, very early strut coverage (first patient group at 2nd month, n=12; 84.3% OCT coverage at 60 days) for this DES showed adequate correlation with baseline CD34+ cell titres ($R^2 = 58.9\%$) & slightly lower with CD34+/KDR+ ($R^2 = 47.8\%$). Correlations were largely absent for other epitopes and at later time points (n=49).



EPC Coverage Correlation

Conclusions: This subgroup analysis appeared to corroborate the effectiveness of CD34+ EPC capturing. Rapid early healing (84.3% stent strut coverage at 60 days) correlated positively with the baseline CD34+ & CD34+/KDR+ cell titres. Later (3-5 months) correlations were not found, likely because majority of stent struts had healed & were covered by 2 months.

P2584 | BEDSIDE

Which is best for pre-dilatation in bioresorbable vascular scaffold implantation: non-compliant or compliant balloon?

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Purpose: Bioresorbable Vascular Scaffold System (BVS) is the last generation, fully absorbable vascular treatment system which is used for critical coronary stenoses. Despite its widespread use, technical and procedural details about BVS implantation is not very clear and need to be considered. In this study; we aim to compare the effectiveness of non-compliant balloon (NCB) and compliant balloon (CB) systems which are used for pre-dilatation before BVS implantation.

Methods: Sixty-eight (68) BVS treated lesions were analysed in the present study. Non-compliant balloon was performed to thirty-three (33) lesions and compliant balloon was performed to thirty-five (35) lesions. Two groups were compared to each other in terms of lesion properties and procedural features. Lesion

analysis was performed by quantitative coronary angiography (QCA) measurements.

Results: There is no statistically significant difference between two groups in terms of lesion properties (reference vessel diameter, minimal lumen diameter, mean lesion length) before intervention.

Mean stent length and used opaque volume were similar between two groups. Procedure time and fluoroscopy time were significantly lower in NCB group. Minimal lumen diameter after stent implantation was similar between groups (2.9 ± 0.33 vs 2.8 ± 0.25 ; $p: 0.36$) but number of post dilated lesions after stent implantation was significantly higher in CB group. (5 vs 14; $p < 0.03$).

	Non-Compliant balloon (n: 33)	Compliant balloon (n:35)	p value
Minimal lumen diameter (mm)	1.09 ± 0.27	1.1 ± 0.26	0.25
Mean lesion length (mm)	20.9 ± 6.33	19.3 ± 8.48	0.39
Mean stent length (mm)	23.2 ± 6.44	21.1 ± 9	0.27
Reference vessel diameter (mm)	2.7 ± 0.62	2.7 ± 1	0.86
Minimal lumen diameter after PCI (mm)	2.9 ± 0.33	2.8 ± 0.25	0.36
Procedure time (min)	28.6 ± 5.8	37.2 ± 12.8	0.001
Fluoroscopy time (min)	10.2 ± 3.45	15.1 ± 8.03	0.002
Opaque volume (ml)	106.9 ± 21.72	122 ± 39.48	0.05
Number of post dilated lesion	5 (15.2%)	14 (40%)	0.03

Conclusions: In conclusion; pre-dilatation with NCB before BVS implantation reduces the need for post dilatation. In addition; use of NCB reduces the procedure and fluoroscopy time.

P2585 | BEDSIDE

A prospective randomized study of the paclitaxel-coated balloon catheter in bifurcated coronary lesions: 9-month angiographic and 24-month clinical results

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Introduction: Percutaneous coronary intervention (PCI) for bifurcation lesions remains a challenge even with the use of drug-eluting stents (DES). Paclitaxel drug-eluting balloons (pDEB) might provide an attractive option to minimize side branch (SB) restenosis. Our purpose was to compare, in a multicenter randomized trial, angiographic and clinical outcomes with pDEB plus bare metal stent (BMS) vs DES in de novo bifurcated lesions.

Methods: 108 patients were randomized. Sequential main branch (MB)/SB dilatation with pDEB with provisional T-stenting with BMS in MB was performed in pDEB-group and with DES in DES-group. The primary end-point was 9-month late lumen loss (LLL). Secondary end-point was incidence of major adverse cardiac events (MACE): death, myocardial infarction, AML, or target lesion revascularization, TLR.

Results: Mean age was 64.8 ± 11.2 years. Diabetes was present in 31.5%. 68.5% had acute coronary syndrome and 79.6% had SB disease. Mean stent diameter and length in MB was 2.96 ± 0.35 mm and 20.13 ± 5.69 mm. Mean balloon diameter used in SB was 2.32 ± 0.31 mm. 9-month angiographic follow-up was performed in 86 patients (80.4%). In-segment MB and in ostium of SB LLL was 0.16 ± 0.38 and -0.03 ± 0.51 mm in pDEB vs 0.31 ± 0.48 mm and -0.04 ± 0.76 mm in DES ($p=0.15$ and $p=0.983$). MACE was 17.3% in pDEB vs 7.1% in DES ($p=0.105$). TLR (15.4 vs 3.6%; $p=0.045$) and target vessel revascularization (17.3 vs 3.6%; $p=0.018$) were significantly higher in pDEB, due to higher restenosis of MB (13.5 vs 1.8%; $p=0.027$) in pDEB.

	All patients (N=108)	pDEB (N=52)	DES (N=56)	p
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1
Non-fatal AML	4 (3.7%)	2 (3.8%)	2 (3.6%)	1
TLR	10 (9.3%)	8 (15.4%)	2 (3.6%)	0.045
MACE	13 (12%)	9 (17.3%)	4 (7.1%)	0.105
MB restenosis	8 (7.4%)	7 (13.5%)	1 (1.8%)	0.027
SB restenosis	5 (4.6%)	3 (5.8%)	2 (3.6%)	0.670
MB in-segment LLL (mm)	0.23 ± 0.43	0.31 ± 0.48	0.16 ± 0.38	0.150
SB ostium LLL (mm)	-0.04 ± 0.64	-0.04 ± 0.76	-0.03 ± 0.51	0.983

Conclusions: The strategy pDEB bifurcation pretreatment with BMS implantation showed greater LLL and increased incidence of MACE than that with DES. Both strategies showed similar results on the SB.

IMAGING, PCI TECHNIQUE AND NEW DEVICES

P2587 | BEDSIDE

Stent underexpansion is not predictor of stent thrombosis after intravascular ultrasound-guided stent implantation using either bare metal stent or 1st and 2nd generation drug-eluting stent

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Background: Stent underexpansion has been considered an important risk of stent thrombosis. The present study evaluated the effect of stent underexpansion on stent thrombosis.

Method: Between January 2005 and December 2013, 5,002 lesions in 3,630 patients underwent IVUS-guided PCI using bare metal stents (BMS) (n=878), 1st generation DES (n=1,695), and 2nd generation DES (n=2,429). Stent underexpansion was defined as minimal stent area <80% of mean proximal and distal reference lumen areas.

Table 1

	BMS	1st generation DES	2nd generation DES
Stent thrombosis	10 (1.1%)	11 (0.7%)	5 (0.2%)
Early	9 (1.0%)	3 (0.2%)	4 (0.16%)
Stent underexpansion	4 (44%)	1 (33%)	2 (50%)
Late	1 (0.1%)	0 (0%)	1 (0.04%)
Stent underexpansion	0 (0%)	0 (0%)	1 (100%)
Very late	0 (0%)	8 (0.5%)	0 (0%)
Stent underexpansion	0 (0%)	0 (0%)	0 (0%)

Result: See Table. **Conclusions:** Stent underexpansion is not a predictor of very late stent thrombosis after IVUS-guided PCI using either BMS or 1st and 2nd generation DES.

P2588 | BEDSIDE

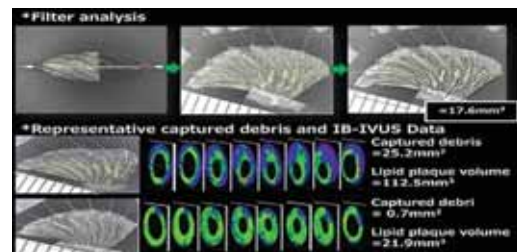
Association between the volume of lipid plaque and the amount of debris captured by a filter type distal protection device in patients after coronary stent implantation with acute coronary syndrome

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Background: Disruption of atherosclerotic plaque by balloon or stent expansion and distal embolism may be a major cause of peri-procedural myocardial injury during percutaneous coronary intervention (PCI). However, the relationship between lesion characteristics and the amount of plaque particles released during the procedure is unclear.

Method: From April 2010 to October 2013, we enrolled 81 consecutive acute coronary syndrome patients who underwent PCI with a filter-type distal protection device following integrated backscatter intravascular ultrasound (IB-IVUS) analysis. The volumes of each plaque component (lipid, fibrous and calcified plaques) within the target lesion were calculated by IB-IVUS analysis software according to IB value. The area of the debris captured by the protection filter was measured by microscopic evaluation (Figure).

Results: The lipid and fibrous volume were significantly correlated with area of captured debris ($r=0.353$ $p=0.001$, $r=0.639$ $p<0.001$). Through multiple regression analysis after adjusting for clinical and procedural parameters and other plaque components, we found that the lipid volume was independently correlated with the area of captured debris (<0.001).



Filter analysis and representative data.

Conclusion: The volume of lipid-rich plaque was associated with the amount of procedure-related debris released and captured by the filter device. These findings provide insights into the mechanisms of distal embolism during PCI.

P2589 | BEDSIDE**One-year clinical outcomes of total stent length after percutaneous coronary intervention with biolimus-eluting stent and everolimus-eluting stent**

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Purpose: Total stent length (TSL) after first-generation drug-eluting stents (DES) implantation was associated with adverse cardiac events. However, it remains unclear whether TSL after newer-generation DES implantation has impacts on clinical outcomes. Our aim was to assess the relationship between TSL and clinical outcomes after the Nobori biolimus-eluting stent (BES) and the Xience/Promus everolimus-eluting stent (EES) implantation.

Methods: A total of 2272 patients with 3146 lesions undergoing BES (1270 patients with 1751 lesions) and EES (1002 patients with 1395 lesions) implantation between February 2010 and July 2012 were analyzed. Patients and Lesions were divided into quartile groups based on TSL. In BES group, TSL per patient (PA: 8 to 18 mm [n=341], PB: 19 to 28 mm [n=296], PC: 29 to 56 mm [n=365], PD: 57 to 220mm [n=268]), and TSL per lesion (LA: 8 to 18 mm [n=661], LB: 19 to 24 mm [n=294], LC: 25 to 38 mm [n=360], LD: 39 to 130 mm [n=436]). In EES group, TSL per patient (PA: 8 to 18 mm [n=253], PB: 19 to 33 mm [n=269], PC: 34 to 56 mm [n=249], PD: 57 to 176mm [n=231]), and TSL per lesion (LA: 8 to 18 mm [n=507], LB: 19 to 23 mm [n=256], LC: 24 to 38 mm [n=285], LD: 39 to 134 mm [n=347]). In the BES and EES groups, we assessed the 1-year cumulative incidence of clinically driven target lesion revascularization (TLR) and definite stent thrombosis based on TSL per patient and lesion groupings, and cardiac death and myocardial infarction in the TSL per patient groups.

Results: In per-lesion data, longer TSL increased TLR rates ($p=0.006$) but did not increase rate of ST ($p=0.12$) in the BES group. In contrast, longer TSL did not increase TLR rate ($p=0.64$) and rate of ST ($p=0.58$) in the EES group. In per-patient data, TLR rates and rate of ST did not increase with increasing TSL in the two groups. Incidence of cardiac death and myocardial infarction also did not increase with increasing TSL in the two groups.

Conclusions: TSL per lesion has significantly impacts on TLR rates in the BES group, whereas do not in the EES group. Longer TSL per lesion and patient is not associated with increased incidence of stent thrombosis through 1 year in the two groups.

P2590 | BEDSIDE**High density lipoprotein cholesterol and definite stent thrombosis**

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Background: Despite the use of dual antiplatelet therapy (DAP), continued improvement in coronary stents and stent deployment; stent thrombosis (ST) remains a concern. Many characteristics including clinical, procedural and angiographic have been identified for ST. Low HDL-c is an independent predictor of acute platelet-dependent thrombus formation. We sought to study the role of HDL-c in the development of definite ST.

Methods: We retrospectively examined percutaneous coronary intervention (PCI) database at our large academic center between 1/1/06 and 4/30/13. Patients with definite stent thrombosis within 1 year of index stent placement (acute, subacute and late as per academic research consortium definition) were identified. Detailed manual review of electronic medical records and review angiographic images were performed to identify patients with definite ST. Incidence of definite ST per 1000 person-months (p-m), clinical/lesion characteristics and procedural findings were compared between patients with low (<40 mg/dl) or normal/high HDL (≥ 40 mg/dL) at index stent placement.

Results: A total of 8,385 patients with 10,547 cardiac catheterizations had stent placement during the study period. The study sample included 4075 patients who had a lipid profile reported within 3 months of index PCI. Of those, 49.4% had low HDL, 41.5% were male, 82.5% were Caucasian, 28.2% had diabetes, 34.4% presented with STEMI at index PCI, 86.2% had a post procedure TIMI score of 3, 97% received clopidogrel as second anti-platelet agent. Out of 63 patients with ST, 47 (74.6%) didn't have any definite identifiable cause of ST (interruption of DAP or complication of primary stent placement). The rate of ST was slightly higher in patients with low HDL-c compared to those with normal/high HDL-c but the difference was not significant (1.53/1,000 p-m versus 1.12, $p=0.22$). Among patients with diabetes, ST was significantly higher in individuals with HDL <40 (2.04/1000 p-m, versus 0.36/1000 p-m, rate ratio: 5.38, 95% CI=1.47-37.46, $p=0.0084$). Patients without diabetes did not have any predisposition to ST based on HDL-c (1.39/1000 p-m versus 1.23, rate ratio: 1.13, 95% CI 0.61-2.13).

Conclusion: Diabetic patients with HDL <40 have strong predisposition to definite ST. HDL functionality may be more important than HDL mass for its anti-thrombotic property. These initial observations would need to be confirmed in a larger patient population.

P2591 | BEDSIDE**Impact of non-compliant balloon on long-term clinical outcomes in coronary bifurcation lesions: results from the COBIS (COronary Bifurcation Stent) II registry**

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Purpose: Non-compliant balloon (NCB) allows higher pressures without over-dilatation than compliant balloon (CB) in the case of side branch dilatation or kissing inflation, and may reduce side branch dissection or restenosis. We sought to investigate the impact of NCB on long-term clinical outcomes of patients receiving coronary bifurcation intervention.

Methods: From 18 major coronary intervention centers in our country, 2,897 consecutive patients were enrolled between January 2003 and December 2009. We compared major adverse cardiac events (MACE: cardiac death, myocardial infarction, or target lesion revascularization) between the NCB group (752 patients [26%]) and the CB group (2145 patients [74%]).

Results: NCB and CB were similarly used for left main bifurcation lesions (30.9% vs. 29.0%, $p=0.33$) and true bifurcation lesions (51.5% vs. 52.0%, $p=0.81$). In the NCB group, the two-stent strategy (30.9% vs. 25.1%, $p=0.002$), side branch pre-dilatation (40.6% vs. 31.2%, $p<0.001$), and final kissing balloon inflation (52.1% vs. 44.6%, $p<0.001$) were performed more frequently. The NCB group had a lower tendency in the rate of side branch occlusion during the procedure than did the CB group (6.2% vs. 7.7%, $p=0.19$). During median follow-up of 36 months, MACE occurred in 296 (10.2%) patients. The NCB group had a significantly lower risk of MACE than the CB group (hazard ratio [HR] 0.67; 95% confidence interval [CI] 0.50-0.89; $p=0.006$). NCB was associated with a lower risk of death (HR 0.50; 95% CI 0.30-0.83; $p=0.007$), cardiac death (HR 0.17; 95% CI 0.05-0.57; $p=0.004$), the composite of cardiac death or myocardial infarction (HR 0.48; 95% CI 0.27-0.85; $p=0.01$), and target vessel revascularization (HR 0.77; 95% CI 0.59-1.00; $p=0.05$).

Clinical outcomes

	Non-compliant balloon (n=752)	Compliant balloon (n=2145)	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Death	19 (2.5)	99 (4.6)	0.54 (0.33-0.87)	0.01	0.54 (0.32-0.93)	0.03
Cardiac death	3 (0.4)	39 (1.8)	0.21 (0.07-0.69)	0.01	0.16 (0.04-0.58)	0.006
Cardiac death or MI	15 (2.0)	75 (3.5)	0.55 (0.32-0.96)	0.03	0.51 (0.28-0.92)	0.03
TLR	53 (7.0)	177 (8.3)	0.83 (0.61-1.13)	0.24	0.73 (0.52-1.02)	0.07
TVR	75 (10.0)	255 (11.9)	0.82 (0.63-1.06)	0.12	0.74 (0.56-0.98)	0.04
MACE	62 (8.2)	234 (10.9)	0.73 (0.55-0.97)	0.03	0.65 (0.48-0.89)	0.007

Conclusions: The use of NCB is associated with favorable long-term clinical outcomes than CB in patients undergoing coronary bifurcation intervention.

P2592 | BEDSIDE**Reduced radial expansion of the everolimus-eluting bioresorbable vascular scaffold compared to the metallic everolimus-eluting stent**

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Background: Everolimus-eluting bioresorbable vascular scaffolds (BVS) represent a novel treatment option for coronary artery disease. First clinical and angiographic results seem to be promising, however data on its handling and procedural performance are scarce. The aim of our study was to assess the radial strength of BVS by Optical Coherence Tomography (OCT) in clinical routine.

Methods: Post-implantation, OCT images of 40 BVS were evaluated and compared to 40 metallic everolimus-eluting stents (EES). Gross device underexpansion was defined as an in-stent minimal lumen area (MLA) $\leq 80\%$ of the average reference lumen area. The primary endpoint was the radial expansion at the site of the MLA defined by the diameter-ratio between maximal- and minimal diameter (Figure 1).

Results: Patients receiving BVS were younger than those with EES (54.0 ± 11.2 versus 61.7 ± 11.4 , $p=0.012$), the remaining baseline, vessel and lesion characteristics were comparable between groups. Lesion preparation was more frequently performed and inflation time was longer in the ABSORB™ than in the XIENCE™ group, respectively ($n=34$ versus $n=23$, $p=0.006$; 44.2 ± 12.8 versus 25.6 ± 8.4 sec-

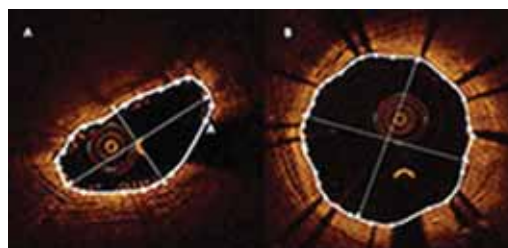


Figure 1. BVS (A) and EES (B).

onds, $p < 0.001$). There were no significant differences in maximal inflation pressures and postdilatation-frequencies with non-compliant balloons between groups. Although device underexpansion was not significantly different, diameter-ratio was significantly higher in the BVS compared to the EES group, respectively ($n=11$ versus $n=12$, $p=1.000$; 1.46 ± 0.20 versus 1.32 ± 0.19 , $p=0.004$).

Conclusion: Our data show, that local radial expansion is significantly reduced in BVS compared to EES. Although the clinical consequences of this finding are unclear, the reduced local radial expansion should be considered in the PCI strategy especially in calcified lesions.

P2593 | BEDSIDE

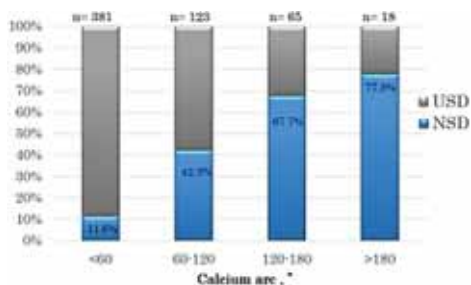
Impact of calcified plaque on stent strut distribution of bioresorbable vascular scaffolds versus metallic everolimus-eluting stents: an optical coherence tomography analysis

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Purpose: The aim of this study was to evaluate, using optical coherence tomography (OCT), the impact of underlying plaque morphology on strut distribution of bioresorbable vascular scaffolds (BVS 1.1) versus metallic everolimus eluting stents (EES).

Methods: Among 39 patients who underwent elective percutaneous coronary intervention (PCI) ($n=20$ in BVS group, $n=19$ in EES group), a total of 1200 post-PCI OCT frames (BVS: 590 frames; EES: 610 frames) were analyzed. Non-uniform strut distribution (NSD) was defined as a frame with maximum inter-strut angle $> 120^\circ$.

Results: The percentage of frames with NSD was significantly higher in the BVS group (26.1% [154/590] vs. 19.0% [116/610], $p=0.003$). In the EES group the arc of calcium in frames with NSD was not significantly different compared to that in frames with uniform strut distribution (USD) ($34.6 \pm 44.4^\circ$ vs. $35.6 \pm 47.1^\circ$, $p=0.83$). However, in the BVS group the arc of calcium was significantly greater in frames with NSD as compared to those with USD ($85.2 \pm 62.6^\circ$ vs. $21.0 \pm 41.7^\circ$, $p < 0.01$). On multivariable analysis, after adjustment for post-dilatation balloon size and maximum inflation pressure, a calcium arc $> 75^\circ$ was identified as an independent predictor of NSD after BVS implantation (odds ratio [OR]: 12.1, 95% confidence interval [CI]: 7.9-18.8, $p < 0.01$).



The percentage of NSD in BVS group

Conclusions: The presence of calcified plaque behind BVS struts appears to be an independent predictor for NSD, particularly when the calcium arc exceeds 75° . For calcified lesions, meticulous lesion preparation, including use of dedicated devices, may help prevent NSD after BVS stent implantation.

P2594 | SPOTLIGHT

Bioresorbable vascular scaffold for coronary bifurcation lesions - results from the Real Absorb Registry

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Background: The use of Absorb Bioresorbable vascular scaffold (BVS) has largely been restricted to simple lesions with a relatively small experience in complex lesions. While it has been recommended to avoid BVS across side branch (SB) > 2.25 mm diameter, such bifurcations contribute nearly 25% of patients who undergo percutaneous coronary intervention (PCI). The strategies and results in such lesions yet remain undefined. We report the intermediate results of BVS in bifurcation lesions with SB > 2.25 mm (BL) from our Real Absorb Registry.

Methods and results: The "Real Absorb Registry" is a single centre registry of all Absorb BVS implanted in real life patients since its approval for unrestricted clinical use in December 2012 onwards. A total of 480 lesions in 365 patients were treated with 542 BVS. Among them 80 patients had 81 bifurcation lesions. The main bifurcation site was LAD/D1 in 77% ($n=63$). True bifurcation was found in 71% ($n=58$) of patients. Side branch (SB) was wired in 71% ($n=58$) and recrossed in 43% ($n=35$). Pre dilatation and post dilatation of main branch (MB) was done in all patients. Provisional Stenting strategy was planned in 84% ($n=68$). Elective two BVS strategy was performed in 13 lesions (T stenting = 7, V stenting = 4 and T and micro protrusion TAP stenting = 2). Device implantation was successful in all patients. 3 patients had SB threatened closure following main branch stenting and underwent salvage with a BVS by T and protrusion (TAP) technique through the struts of MB BVS. Final simultaneous low pressure kissing

dilatation (Snuggle Dilatation) was done in 35% ($n=29$). OCT Imaging was done in 9 patients. At median follow up of 158 days (range 14-196 days) there were 1 myocardial infarction (1.2%). There were no death, scaffold thrombosis or target vessel revascularization.

Conclusion: Treatment of Bifurcation lesions with BVS is feasible, safe and has favourable immediate and short term outcomes. When using single stent strategy SB access, SB optimization and SB salvage is feasible after stenting main branch. When two stent technique is needed, T stenting may be the preferred technique of choice though micro TAP is also feasible for obtuse angled SB. The long term safety and choice of technique in BL will be determined by future studies.

P2595 | BEDSIDE

Clinical outcome of rotational atherectomy in complex calcified coronary lesions: data from the large multicenter Italian registry ROTATE

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Purpose: The ROTATE (ROTational ATHERectomy) multicenter Italian registry was developed to assess the short and long term outcome after RA in a large real world population.

Methods: From April 2002 to December 2013 a total of 801 consecutive patients, treated with rotational atherectomy in 8 different hospitals, were collected in the Italian multi-center ROTATE registry.

Results: Baseline patient characteristics were: mean age 70.6 ± 9.8 years, 79.3% male, 37.3% diabetes mellitus and 39.9% previous PCI. More than a third of patients (35.2%) were treated with RA during the hospitalization for an acute coronary syndrome. In 29.9% of cases the procedure was performed by trans-radial approach. The most frequently treated coronary artery was the left anterior descending (48.6%) followed by the right coronary (23.9%); protected and unprotected left main stem lesions were respectively faced in 1.8% and 3.3%. Chronic total occlusions were 8.9% of total and 19.8% of procedures were IVUS-guided. Use of intra-aortic balloon pump was needed in 4.9%. The most used burr sizes were the 1.5 mm (43%) and the 1.25 mm (37%). Median total stent length per patient was 41.6 ± 24.1 mm. The majority of patients were treated with first and second generation DES, only 9.9% did not received a DES. Serious procedural complications, perforation and no/slow flow, occurred respectively in 0.6% and 1.3% of cases. In hospital death occurred in 0.8%, myocardial infarction (Q and nonQ wave infarction) in 5.9% and stroke in 0.4%. The incidence of in-hospital major cardiac adverse events defined as death, MI and target vessel revascularization was 7.2%, with no differences between gender and clinical presentation, whereas it resulted lower in the trans-radial approach patients (3% in trans-radial vs 9% in trans-femoral, $p=0.002$). In a multivariate regression model analysis (covariates: age, sex, weight, diabetes mellitus, ejection fraction, AHA/ACC lesion type, vascular approach, IVUS guidance), only diabetes mellitus and IVUS guidance were independent predictors of in-hospital events. The 1- and 3-year overall survival (Kaplan-Meier estimate) was 96.1% and 87.7% while MACCE (death, MI, stroke and revascularization)-free survival was respectively 87.6% and 69.8%.

Conclusions: ROTATE registry represents the largest European data set of patients treated with rotational atherectomy in the DES era. RA appears to be feasible and effective, with a high rate of procedural success and favourable short and long term outcome even in this very complex real world population

P2596 | BEDSIDE

Impact of polymers and stent drugs on stent thrombosis: a report from the SCAAR Registry

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Purpose: To evaluate the impact of polymer type and stent drug on definite stent thrombosis (ST) in drug-eluting stents (DES).

Methods: We evaluated 80 797 stent implantations in Sweden from January 2007 to December 2013. The stent types were: Cypher and Cypher Select, $N=5221$; Taxus Express and Taxus Liberté, $N=10 019$; Endeavor, $N=3372$; Resolute and Resolute Integrity, $N=16 760$; Xience V, Xience Prime and Xience Expedition, Promus, Promus Element, Promus Premier, $N=42 750$; Biomatrix and Nobori, $N=2672$.

Definite ST was defined according to ARC definitions.

Results: A total of 730 ST (454 early/late ST and 276 very late ST) occurred, during a mean follow-up of 2.6 ± 1.8 years. The ST rates according to polymer type and stent drug are shown in Fig. 1.

Cox regression analysis showed significant collinearity between the stent drug and polymer. A lower rate of early/late ST was observed in Biomatrix/Nobori (0.5%), Resolute/Resolute Integrity (0.5%) and Xience/Promus (0.4%) stents versus Cypher (0.8%), Taxus (0.7%) and Endeavor (1.2%), $p < 0.01$. Very late ST

rate was not significantly different between Endeavor, Resolute/Resolute Integrity (0.1%) and Xience/Promus (0.1%), $p=NS$.

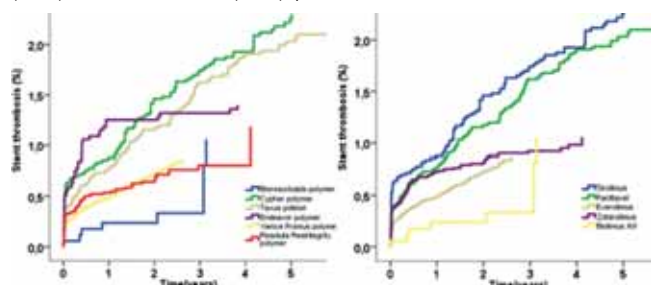


Figure 1

Conclusions: Although statistically significant differences in ST rates were observed between the different polymers and stent drugs, it was not possible to discriminate between the impact of polymer type or stent drug in the incidence of ST.

P2597 | BEDSIDE

Percutaneous treatment of coronary bifurcation: a network meta analysis of randomized controlled trial

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Purpose: The optimal percutaneous management of patients presenting with coronary bifurcation lesions remain to be defined.

Methods: Randomized controlled trial (RCT) comparing different treatments for bifurcation lesions were included. Major Adverse Cardiovascular Events (MACE, a composite end point of death, myocardial infarction, target lesion revascularization [TLR]) was the primary end point, while each single event of the MACE composite endpoint was evaluated separately as Stent Thrombosis (ST). Main analysis included studies evaluating different kind of treatment (provisional, T stenting, crush, culotte and double kissing double crush, DK crush) along with type of implanted stents (BMS, sirolimus and paclitaxel stents defined as first generation DES and Everolimus Eluting Stent [EES]) with or without final kissing balloon (FKB).

Results: Provisional strategy was evaluated in eleven studies with first generation DES and FKB (1819 patients) and without FKB in one RCT with 239, in two studies with BMS and FKB (67 patients), in one RCT with BMS and drug eluting balloon (40 patients) and in three studies with EES (408 patients). Crush stenting with first generation DES and FKB was appraised into three studies with 601 patients, T stenting with first generation DES and FKB in one RCT (101 patients), DK crush with first generation DES in 101 patients in one study and with EES in 2 studies with 395 patients and culotte into two studies (215 patients with first generation DES and 209 with EES).

Provisional with EES did not result inferior to DK crush with EES (OR 0.58:0.29-1.1), to culotte with EES (OR 1.8: 0.7-4.1) and to crush and T stenting with first generation DES (OR 1.1: 0.4-1.9 and OR 1.2: 0.03-5 respectively). DK crush presented the highest probability of performing bests. About target lesion revascularization, provisional strategy was not inferior to two stent techniques, apart from DK crush which resulted superior (OR 0.42: 0.21-0.87), with the highest probability of performing bests. About stent thrombosis, no strategies performed superior to the others, with provisional with EES with the highest probability of performing bests.

Conclusion: Provisional strategy did not perform inferior to two stent techniques, apart from DK crush which resulted more efficacious for target lesion revascularization. Provisional strategy performed best for reducing ST.

P2598 | BEDSIDE

The effect of complete percutaneous revascularization with and without IVUS guidance in the drug-eluting stent era

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Background: The impact of complete revascularization (CR) with and without intravascular ultrasound in drug-eluting stent (DES) era is presently unknown.

Methods: The study included patients with multivessel disease (≥ 2 epicardial vessels with $\geq 70\%$ stenosis) who were subjected to percutaneous coronary intervention (PCI). When all epicardial and significant branches (≥ 2.5 mm) were successfully treated it was considered CR, otherwise it was incomplete revascularization (IR). The primary outcome was the adjusted risk for the composite death /Q-wave myocardial infarction (Q-MI) at one year. Secondary outcomes were freedom from target lesion (TLR), target vessel revascularization (TVR), and stent thrombosis with and without IVUS guidance.

Results: The study included 2132 consecutive patients (n=4299 lesions) who underwent PCI with at least 1 DES between 04/2003 to 05/2012. CR was achieved

in 41% of the patients, and 61% of the lesions were IVUS guided. CR group was associated with lower rates of death/Q-MI at 1 year (adjusted HR: 0.6 95% CI: 0.4-0.9; $P=0.048$). Freedom from TVR and TLR was lower in CR vs. IR group (89% vs. 93%; Log Rank $P<0.001$) and (91% vs. 95%; Log Rank $P<0.001$). Stent thrombosis rates tended to be lower in the CR group (0.3% vs. 1.0%; $P=0.074$). IVUS increased the freedom from TLR in both CR (93% vs. 87%; Log Rank $P=0.041$) and IR (96% vs. 93%; Log Rank $P<0.010$) groups.

Conclusions: CR reduces the rates of death/Q-MI at 1 year with a cost of higher rates of repeat revascularization compared to IR. IVUS-guided PCI improves outcome irrespective of the completeness of revascularization strategy. Our study suggests that CR with IVUS guidance is viable strategy to treat multi-vessel patients in the DES era.

ACUTE MYOCARDIAL INFARCTION AND PCI

P2600 | SPOTLIGHT

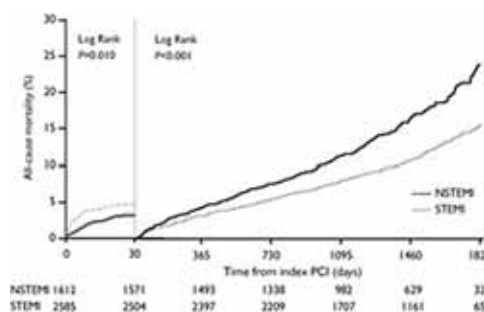
Long-term mortality of patients with ST-segment elevation versus non-ST-segment elevation myocardial infarction in the drug-eluting stent era: 5-year results of a large real-world registry

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Background: Difference in long-term mortality between ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) have been demonstrated in a few studies. It remains unclear in the drug-eluting stent (DES) era.

Methods: We consecutively enrolled acute myocardial infarction (AMI) patients who underwent percutaneous coronary intervention (PCI) in the CORE-AMI (CONvergent REgistry of cAtholic and chonnAm university for AMI) from January 2004 to December 2009. Of 4,748 AMI patients, 2,607 and 1,617 patients who treated with only DES were diagnosed with STEMI and NSTEMI, respectively. The primary endpoint is 30-day all-cause mortality and mortality from 31 days to 5 years. We performed landmark analysis at 30 days.

Results: Median follow up duration was 43.3 months (interquartile range 29.4 to 59.7 months). All-cause mortality rate at 30 days was higher in STEMI (3.6%; 94 patients) than NSTEMI (2.4%; 39 deaths; $P=0.031$). On the other hand, mortality from 31 days to 5 years was higher in NSTEMI (17.4% vs. 13.7%; 273 deaths vs. 343 deaths; $P=0.001$). After adjustment with clinical and angiographic characteristics, STEMI is associated with 30-day mortality (hazard ratio (HR) 1.54, 95% confidence interval (CI) 1.06-2.25, $P=0.025$) and NSTEMI is independent predictor for mortality from 31 days to 5 years (HR 1.26, 95% CI 1.07-1.48, $P=0.006$).



Conclusion: STEMI was associated with a higher risk of short-term mortality, but NSTEMI was associated with a higher risk of long-term mortality in the DES era.

P2601 | BEDSIDE

Early versus delayed percutaneous coronary intervention in patients with non-ST elevation acute coronary syndromes

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Introduction: International guidelines advocate early angiography and percutaneous coronary intervention (PCI) for high-risk patients presenting with non-ST elevation acute coronary syndromes (NSTEMACS). Scoring systems, particularly the GRACE and TIMI scores, have been used in clinical trials to identify high-risk patients. In real-world practice, the use of these scoring systems to guide timing of intervention appears to be limited. Thus it is unclear which patients are more likely to receive early PCI and how this impacts on short and long term clinical outcomes.

Objectives: The aim of this study is to compare the clinical characteristics and outcomes, both 30-day and 12 month, of patients with NSTEMACS depending on the timing of their PCI from initial presentation.

Methods: The Melbourne Interventional Group Registry was analysed from 1st January 2005 until December 31st 2011. Patients who underwent PCI within a calendar day of presentation were included in the early PCI group. The delayed PCI group included all patients receiving intervention after one calendar day, but within the index admission. Patients transferred from a non-PCI capable hospital were excluded. Clinical characteristics and outcomes were obtained. The primary efficacy end points were 30-day and 12-month mortality, myocardial infarction (MI), target vessel revascularization (TVR) and major adverse cardiovascular events (MACE). The primary safety endpoint was in-hospital bleeding complications.

Results: 4307 patients with NSTEMI/ACS were included in the analysis with 51% undergoing PCI within a calendar day of admission. Patients undergoing delayed PCI were more likely to be older (67yrs vs 64yrs, $p<0.01$), have troponin elevation (70% vs 66%, $p<0.01$), have diabetes (32% vs 25%, $p<0.01$), have had a previous MI (33% vs 26%, $p<0.01$) and previous CAGS (14% vs 8%, $p<0.01$). Delayed PCI was associated with higher 12-month mortality (5% vs 3%, $p=0.03$), MI (8% vs 5%, $p<0.01$) and MACE (15% vs 12%, $p<0.01$). On multivariate analysis, delayed PCI was not an independent predictor of mortality at 12-months with an odds ratio of 0.95 (95% confidence interval, 0.68-1.31).

Conclusions: In an Australian PCI cohort, patients with NSTEMI/ACS and high risk features were more likely to undergo delayed PCI. Delayed PCI was not an independent predictor of mortality at 12-month outcomes.

P2602 | BEDSIDE

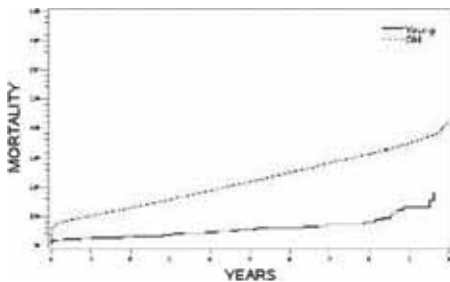
Short- and long-term outcomes after PCI for young patients with ST-elevation myocardial infarction

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It is well known that ST-elevation myocardial infarction (STEMI) is associated with an impaired acute prognosis, and early invasive management is recommended. However, the prognosis in patients 45 years or younger has not been well characterized.

Methods: We included consecutive STEMI patients from 2003-2012 (68,101 patient-years follow-up) who were treated in Eastern Denmark and Southern Sweden with percutaneous coronary intervention (PCI). We included 16,776 consecutive from the Eastern Danish Heart Registry and the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Short- and long-term mortality between young (≤ 45) and older (> 45) STEMI patients was compared.

Results: We identified 1036 (6.2%) patients up to 45 years of age (mean age 40.7 vs. 66.2 years, $p<0.001$). Patients in the young group were predominantly men (79.7% vs. 71.2%) and smokers (71.3% vs. 44.2%, $p<0.001$) but with a lower prevalence of hypertension (17.3% vs. 39.9%), hyperlipidemia (18.2% vs. 24.1%), diabetes (8.9% vs. 12.5%) and previous myocardial infarction (7.0% vs. 12.6%, all $p<0.001$) compared to older patients. Young patients had a 0.8% annual mortality (Figure). Both, 30-day-mortality (adjusted hazard ratio [HR] = 0.29, CI 0.15-0.57, $p<0.001$) and mortality after 30 days and onwards (HR=0.22, CI 0.14-0.33, $p<0.001$) was significantly lower in the young group.



Conclusions: STEMI patients, age 45 years or younger, treated with primary PCI have an excellent prognosis after treatment with primary PCI. Long term annual survival is more than 99% in these patients.

P2603 | BEDSIDE

Association between hospital characteristics, missed care opportunities and mortality in patients with STEMI. A cohort study on behalf of NICOR

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Purpose: Hospital outcomes are used to evaluate hospital care, yet data concerning the relationship between the provision of guideline recommended care,

hospital characteristics and mortality are limited. We investigated associations between hospital missed opportunities for care (HMO), hospital characteristics and mortality for patients with STEMI, 2007-2010.

Methods: For 59,811 patients with STEMI across 234 hospitals, we constructed a nine-point scale representing guideline recommended care processes. Case mix was standardised for risk of cardiovascular events using mini-GRACE variables and 30 day and 1 year all-cause mortality quantified. Hospitals were categorised by patient volume and facilities for percutaneous coronary intervention (PCI).

Results: HMO (quintile 1 vs. quintile 5) were associated with increased adjusted 30-day mortality (1.4% vs. 1.9%, OR 1.43 95% CI 1.02 – 2.01) but not adjusted 1-year mortality (7.3% vs. 10.1%, OR 1.04 95% CI 0.84-1.28). Pre-hospital ECG and timely reperfusion were key contributors to overall HMO. Opportunities for care missed early in the management of STEMI were significantly associated with later missed opportunities; a 1% increase in missed pre-hospital ECG was associated with a 0.66% increase in probability of missing timely revascularisation, 22.9% increase in missing discharge medication and a 1.5% increase in missing cardiac rehabilitation. Higher volume hospitals and those with PCI facilities had fewer missed care opportunities.



Conclusion: For STEMI, there was a significant association between hospital missed opportunity for care, hospital facilities and early but not later mortality. Hospitals with fewer missed opportunities for care more frequently had PCI facilities and were higher volume centres.

P2604 | BEDSIDE

The time of cardiovascular adverse events onset in patients with acute myocardial infarction after successful revascularization is independently predicted by proteolysis activity level

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Background: Blood flow restoration after myocardial revascularization does not eliminate further atherosclerosis progression, microcirculation changes, acute and chronic postinfarction remodeling. All these processes include matrix degradation and restructuring. The objective of this study was to determine the proteolysis indexes, such as matrix metalloproteinases (MMP) activity and tissue inhibitors of MMP (TIMP), impact on the further course of the disease in patients (pts) with acute ST – elevation myocardial infarction (STEMI) after successful revascularization.

Methods: We investigated the successive changes of intracoronary and venous serum MMP9, MMP2 activity (gelatin-zymography; referent value=100% from normal subject plasma pool) and their interrelation, TIMP1 levels in 384 samples from 64 pts with STEMI before and after successful PCI, at discharge (7th day). Follow-up was approximately 1.5 years. ROC analysis, Spearman correlation analysis were used to test the statistical significance of the differences among the calculated index values.

Results: In all patients the occurrence of early main adverse cardiovascular events was significantly associated with high TIMP1 level ≥ 116 ng/ml (AUC = 0.63 $\pm$ 0.09; $p=0.0005$) in systemic blood, MMP2 activity level $\geq 100\%$ in coronary arteries (AUC = 0.67 $\pm$ 0.07; $p=0.005$) before revascularization and MMP2 activity level $\leq 100\%$ in systemic blood (AUC = 0.93 $\pm$ 0.05; $p=0.003$), MMP9/MMP2 interrelation value ≥ 0.6 (AUC = 0.7 $\pm$ 0.08; $p=0.0007$) in systemic blood in 7 days after revascularization. For all indexes sensitivity ranged from 60% to 88%, specificity from 49% to 97%. For the first time it was revealed that a moderate increase of MMP2 activity level in systemic blood in 7 days after revascularization was associated with the later cardiovascular adverse events occurrence ($p=0.0002$).

Conclusion: In pts with STEMI additional determination of MMP2 and MMP9 systemic blood activity and MMP9/MMP2 activity interrelation on 7-th day after revascularization is recommended in order to predict the time of main adverse cardiovascular events occurrence even after successful revascularization thereby promptly identify patients subgroup for prolonged aggressive medical therapy.

P2605 | BEDSIDE

Long term prognostic value of percutaneous coronary intervention in elderly patients (more than 85 years old) with acute coronary syndrome

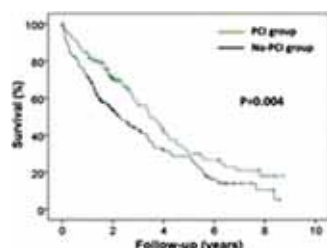
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Introduction: Elderly patients with acute coronary syndrome (ACS) constitute a

particular risk group in relation to percutaneous coronary intervention (PCI). Few data are available in relation with the long-term benefit of PCI in these patients. This study was performed to evaluate the long-term prognostic value of PCI in patients ≥ 85 years.

Methods: We performed a retrospective analysis in a contemporary registry of 5,303 consecutive ACS patients. From them, 399 (7.5%) were ≥ 85 years old (54.5% female; 36.8% STEMI, 55.8% NSTEMI and 7.5% UA). 64 died during in-hospital phase (16.0%). Using Cox proportional hazards regression analysis, we evaluate the long-term prognostic value of PCI in the remaining 335 patients, in terms of mortality and reinfarction, after adjusting by confounding variables. Survival curves over the follow-up period (2.4 ± 2.1 years) were estimated using the Kaplan-Meier estimation.

Results: 206 patients (61.5%) died during the follow-up (52.2% in PCI group vs 67.8% in no-PCI group, $p=0.004$). After adjustment by sex, cardiovascular risk factors, history of stroke, history of coronary artery disease, chronic kidney disease, left ventricular ejection fraction, and medications at discharge, the use of PCI during the hospital stay resulted as a protector factor for follow-up mortality (HR 0.73, CI 95% 0.53-0.98, $p=0.039$). Separating unstable angina (UA) from acute myocardial infarction (AMI), we found that PCI resulted only protective factor in AMI patients (HR 0.63, CI 95% 0.46-0.87, $p=0.005$), not in UA patients (HR 1.43, CI 95% 0.29-7.12, $p=0.660$).



Long term prognosis.

Conclusion: PCI is independently associated with lower follow-up mortality in elderly patients with AMI, but not in elderly patients with UA.

P2606 | BEDSIDE

Lack of association between living alone and long-term mortality in patients with acute myocardial infarction undergoing percutaneous coronary intervention

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Purpose: To evaluate the prognostic impact of living alone in patients with acute myocardial infarction (AMI) who underwent percutaneous coronary intervention (PCI).

Methods: The CREDO-Kyoto AMI registry was a cohort study of patients with AMI enrolled in 26 hospitals in Japan from 2005 through 2007. For the current analysis, we included those patients who underwent PCI within 24 hours of symptom onset and were assessed their living status to determine if living alone would be an independent prognostic risk factor.

Results: Among 4175 patients eligible for the current analysis out of 5429 patients enrolled in the CREDO-Kyoto AMI registry, 520 patients (12.5%) were living alone at the time of hospital admission. The cumulative 5-year incidence of all-cause death was 18.3% in the living alone group and 20.5% in the not living alone group (log rank $P=0.62$). After adjusting for potential confounders, risk of the living alone group relative to the not living alone group for all-cause death was not significantly different (adjusted hazard ratio: 0.81, 95% confidence interval 0.64-1.04; $P=0.11$).

Conclusions: Living alone was not associated with higher long-term mortality in patients with AMI who underwent PCI within 24 hours of symptom onset in the current primary PCI era.

Abstract P2606 – Table 1. Clinical outcomes

Outcome	Number of patients with events (cumulative incidence)		Unadjusted Living alone			Adjusted Living alone		
	Living alone	Not living alone	HR	95% CI	P value	HR	95% CI	P value
All patients	N=520	N=3655						
All-cause death	88 (18%)	719 (21%)	0.95	(0.77–1.16)	0.62	0.82	(0.65–1.03)	0.08
Cardiac death	49 (10%)	424 (12%)	0.90	(0.68–1.18)	0.46	0.78	(0.57–1.05)	0.10
Myocardial infarction	26 (5.9%)	173 (5.4%)	1.06	(0.70–1.55)	0.76	0.97	(0.62–1.45)	0.94
Stroke	29 (6.4%)	211 (6.6%)	0.97	(0.65–1.39)	0.87	0.97	(0.64–1.42)	0.90
Readmission for heart failure	60 (14%)	275 (8.7%)	1.50	(1.13–1.97)	0.01	1.16	(0.84–1.58)	0.35

Cumulative incidence was estimated by the Kaplan-Meier method. Unadjusted and adjusted HR and 95% CI were estimated by the Cox proportional hazard models.

P2607 | BEDSIDE

Risk assessment of complete left bundle branch block based on left ventricular ejection fraction for sudden cardiac death in myocardial infarction patients

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Purpose: Low ejection fraction (EF) is a risk factor of sudden cardiac death (SCD) in myocardial infarction (MI) patients; however, the impact of complete left bundle branch block (CLBBB) on SCD is unclear. Thus, we examined the relationship between CLBBB and SCD based on EF.

Methods: A total of 1346 patients underwent sirolimus-eluting stent (SES) implantation for old MI or acute MI from 2002 to 2007, 937 of whom underwent echocardiography or left ventriculography, and electrocardiography after 8 months and were categorized into three groups according to EF: normal, $>55\%$; low, 35–55%; and very low, $\leq 35\%$. The incidence of SCD was compared between CLBBB and non-CLBBB based on EF.

Results: The median follow-up time of the 937 patients was 2251 days. A total of 28 SCD occurred and the table shows the ratio of SCD between CLBBB and non-CLBBB based on EF.

The incidence of SCD

	All	EF $>55\%$	EF 35–55%	EF $\leq 35\%$
All	28/937 (3.0%)	3/410 (0.7%)	17/456 (3.7%)	8/71 (11%)
Non-CLBBB	22/896 (2.5%)	3/405 (0.7%)	16/431 (3.7%)	3/60 (5%)*
CLBBB	6/41 (14.6%)	0/5 (0%)	1/25 (4%)	5/11 (45%)*

* $P=0.0016$.

Conclusions: In MI patients after SES implantation, CLBBB patients with EF $\leq 35\%$ may be a risk factor of SCD.

P2608 | BEDSIDE

Impact of transradial approach on long-term mortality after PCI in real-life population

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Background: The rate of transradial approach (TRA) to PCI is increasing worldwide but there is still conflicting data regarding its impact on mortality.

Purpose: The purpose of this study was to compare the mortality after TRA versus transfemoral approach (TFA) PCI in large cohort of consecutive patients within the nationwide, real-life registry.

Methodology: The statistical analysis was based on first PCI procedure via TRA (N=22,245) and TFA (N=75,325) collected in the Czech National PCI Registry between January 2005 and June 2011. After adjustment for sex, age, body-mass index, PCI indication, ejection fraction, left anterior descending artery as target vessel and Killip class for STEMI only, the balanced dataset was matched 1:2 TRA (N=21,730): TFA (N=43,460) (average age 65 ± 11). The long-term mortality up to 6 years was assessed independently from the operators. Three main groups of patients were identified based on their primary diagnoses: ACS with/without ST elevations (STEMI; NSTEMI) and stable CAD.

Standard statistical methodology was applied in the analysis. Association of TRA to short term mortality was described using odds ratios, long-term mortality was described using Kaplan-Meier methodology and TRA vs. TFA was compared by means of log rank and Breslow tests.

Results: The use of TRA was associated with significant decrease of long-term

30-day mortality

	Balanced dataset			p
	Femoral	Radial	OR (95% CI)	
N	43 460	21 730		
All patients	2.9%	1.6%	0.563 (0.500; 0.635)	<0.001
Indication to PCI				
Stable CAD	0.5%	0.5%	0.985 (0.652; 1.486)	0.941
ACS – NSTEMI	2.5%	1.4%	0.567 (0.453; 0.711)	<0.001
ACS – STEMI	5.5%	3.9%	0.692 (0.583; 0.823)	<0.001

mortality in patients with ACS, both with STEMI and NSTEMI. This difference was specifically observed during the 30-day follow-up (Table 1)

Conclusion: In real-life practice, the TRA PCI was associated with significant long-term decrease of mortality in patients with ACS (both STEMI and NSTEMI). This difference was particularly observed during the 30-day follow-up. No difference was observed in patients with stable CAD.

P2609 | BEDSIDE

Efficacy and safety of dual drug-eluting Cilotax stent for primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction

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Purpose: Cilotax stent is a first dual drug-eluting stent with multilayer of two medication, paclitaxel and cilostazol, and biodegradable polymer. It is designed to attenuate the risk of stent thrombosis or restenosis as compared with paclitaxel alone by the additional antiplatelet effect of cilostazol. Thus, we investigated the efficacy and safety of dual drug-eluting Cilotax stent for primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI), compared with those of other second-generation drug-eluting stents (DES).

Methods: A total of 258 consecutive patients with STEMI and indication to primary PCI were enrolled. Among those, 86 (33%) patients were treated with an everolimus-eluting stent between June 2008 and October 2009, 77 (30%) with a zotarolimus-eluting stent between November 2009 and September 2010, and 95 (37%) with Cilotax stent between January 2012 and January 2013. We excluded the patients who had been cardiogenic shock at admission, received thrombolytic therapy or had no follow-up data at 1 year. Major adverse cardiac event (MACE), defined as the composite of cardiac death, recurrent myocardial infarction (MI), or target lesion revascularization at 1 year, were compared in patients treated with the Cilotax stent (n=95, 37%) versus the other second-generation DES (n=163, 63%).

Results: Baseline characteristics were similar between both groups. The cumulative incidence of MACE was 5.3% for the Cilotax stent group and 1.2% for the other second-generation DES group at 1-year follow-up (p=0.104). The Cilotax stent group had a trend to a higher rate of recurrent myocardial infarction, compared with the other second-generation DES group (4.6% vs. 0.6%, p=0.063). The cumulative incidence of cardiac death or target lesion revascularization was similar between the Cilotax stent group and the other second-generation DES group (1.1% vs. 0.0%, p=0.368; 0.0% vs. 0.6%, p=1.000). There was no significant difference in rate of definite stent thrombosis between the Cilotax stent group and the second-generation DES group (2.1% vs. 0.6%, p=0.559).

Conclusions: The Cilotax stent was safe and effective for primary PCI in patient with STEMI, although a statistically nonsignificant trend for more recurrence of myocardial infarction was noted. Further investigation with larger subject and long-term follow-up was warranted.

P2610 | BENCH

Drug eluting stents in female diabetic patients with acute myocardial infarction undergoing primary percutaneous coronary intervention

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Background: The aim of study was to compare different coronary stents used during primary percutaneous coronary intervention (PCI) in female patient with acute myocardial infarction (AMI) and diabetes mellitus (DM).

Methods: We selected 1799 consecutive AMI female patients (68.9±10.2) with DM undergoing primary PCI and divided them into 5 groups based on the types of drug eluting stents implanted. Sirolimus-eluting stent (SES), Paclitaxel-eluting stent (PES), Everolimus-eluting stent (EES), Biolimus-eluting stent (BES), Zotarolimus-eluting stent (ZES). Study end point was 12-month major adverse cardiac events (MACE), a composite of death, fatal and nonfatal myocardial infarction and target vessel revascularization.

Results: Mean Hemoglobin A1c level of SES, PES, EES, BES, ZES was 7.7±1.1%, 7.8±1.3%, 7.8±1.1%, 7.6±1.2%, and 7.7±1.2% respectively (p=0.195). 928 patients (51.6%) patients prescribed oral hypoglycemic agents (OHA) and 871 patients prescribed OHA and insulin both. Ejection fraction, systolic blood pressure were no significant difference in five groups. The incidence of 12-month MACE in SES, PES, EES, BES, ZES was 8.3%, 8.9%, 4.2%, 4.5%, and 5.2%, respectively (p=0.02). Kaplan Meier analysis show significant difference between SES and BES (p=0.046), SES and EES (p=0.025), PES and BES (p=0.021), PES and ZES (p=0.039), PES and EES (p=0.011). Independent predictors of one-year MACE were family history (OR 17.06, 95% CI 8.412-34.61, p<0.001), serum glucose level (OR 0.304, 95% CI 0.140-0.661, p=0.024), serum creatinine level (OR 3.933, 95% CI 1.194-12.96, p=0.024).

Conclusion: In female patient with AMI and DM, EES and BES would be better therapeutic option than SES and PES for one-year follow up and this result warranted further long-term follow-up.

P2611 | BEDSIDE

Real world comparison of MGuard stent versus bare metal stent for ST elevation myocardial infarction

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Purpose: To assess MGuard stent (MGS) safety and efficacy for STEMI in the real world and compared to bare metal stent (BMS).

Methods and results: 262 patients were included in a single center. In 35,9% MGS was implanted. After propensity score matching two equivalent groups for basal and periprocedure variables of 79 patients were established. The mean follow-up was 321±12,94 days. No differences were found in all-cause mortality (7,6% in both groups), MACE (20,3% vs. 12,7%; p=0,198) or non cardiac mortality and non fatal infarction (6,3% in both groups). TLR was significantly higher in MGS group (11,4% (9) vs. 1,3% (1) p<0,01; RR 10,02[1,23-81,16]). (Figure 1 and Table 1)

Table 1. Basal and periprocedural characteristics. Events during follow-up

	MGS (n=79)	BMS (n=79)	p
Basal and periprocedural characteristics.			
Age (years)	59 [51,69]	62 [56,76]	0,141
Gender (male%)	86,1 (68)	87,1 (74)	0,513
Hypertension (%)	46,8 (37)	40,5 (32)	0,423
Diabetes mellitus (%)	20,3 (16)	12,7 (10)	0,198
Hypercholesterolemia (%)	50,6 (40)	45,6 (36)	0,524
Smoking (%)	62,0 (49)	53,2 (42)	0,260
Infarct related artery (right coronary artery) (%)	55,7 (44)	64,6 (51)	0,213
Basal TIMI flow (0%)	88,6 (70)	86,1 (68)	0,566
Post-stent TIMI flow (3%)	97,5 (77)	94,9 (75)	0,339
Thrombectomy	83,5 (66)	82,3 (65)	0,833
Total stent length (mm)	23,13±13,65	23,65±11,16	0,794
Maximal stent diameter (mm)	3,30±0,38	3,34±0,47	0,610
Events during follow-up			
All cause mortality	7,6 (6)	7,6 (6)	1
MACE	20,3 (16)	12,7 (10)	0,198
Target lesion revascularization	11,4 (9)	1,3 (1)	0,009

Conclusion: Our study is the first to compare MGS with BMS for STEMI in the real world and seems to confirm that even though MGS is a safe device and doesn't increase mortality, is linked to high rate of long-term TLR.

SCORES, COMPLEX REVASCULARISATION

P2613 | BEDSIDE

The prognostic impact of the residual CABG SYNTAX score to predict long-term outcomes after percutaneous coronary intervention in patients with prior coronary artery bypass graft surgery

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Background: Patients with coronary artery bypass grafting surgery (CABG) require a repeat revascularization procedure. Redo CABG has a worse clinical outcome, which accounts for the increase in the number of patients referred for percutaneous coronary intervention (PCI). Since the CABG SYNTAX score has been a quantitative measure of coronary anatomical complexity after CABG, we investigated the prognostic impact of residual CABG SYNTAX score after PCI in patients with prior CABG.

Methods: A total of 400 consecutive patients with prior CABG who were hospitalized for PCI between 2004 and 2011 (male 84%, age 70±8 years) were included. The CABG SYNTAX scores before (=baseline) and after PCI (=residual) were calculated. The patients were divided into the following 3 groups according to the residual CABG SYNTAX score; low (≤17, n=138), intermediate (>17, <30, n=130) and high score groups (≥30, n=132). The primary outcome was major adverse cardiac events (MACEs) including cardiovascular death, myocardial infarction and unplanned revascularization. A multivariate Cox regression analysis was performed to identify independent predictors of MACEs.

Results: The mean baseline, residual and those differences CABG SYNTAX scores were 31±13, 24±13 and 6±6, respectively. During a median follow-up

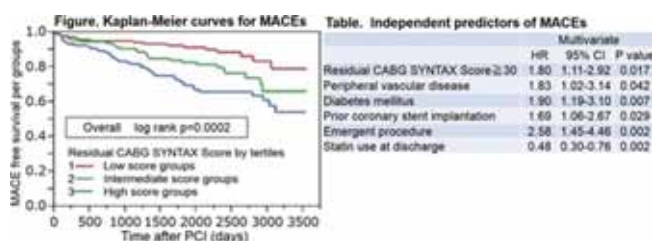


Figure 1

of 6 (4–8) years, the prevalence of MACEs was significantly different among the 3 groups (low, 11.6%, medium, 20.8%, high, 31.8%, $P=0.0002$) (Fig. 1). The multivariate analysis revealed that the residual CABG SYNTAX score (≥ 30) was associated with substantially low MACEs-free survival (hazard ratio: 1.80, 95% CI: 1.11–2.92, $P=0.017$) (table).

Conclusions: The residual CABG SYNTAX score was shown to be a powerful prognostic indicator, and is useful tool for risk stratification for CABG patients undergoing PCI.

P2614 | BEDSIDE

Prognosis and disease progression in patients under 50 years old undergoing PCI: The CRAGS (Coronary aRtery diseAse in young adults) study

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Objective: Young patients undergoing percutaneous coronary intervention (PCI) are generally considered at low procedural risk, but the potentially aggressive nature of coronary artery disease and long expectancy of life expose them at high risk of recurrent coronary events. The extent and determinants of disease progression in this patient subset remain largely unknown. The aim of the present study was to evaluate general risk factors for late outcomes after PCI among patients ≤ 50 years old.

Approach: A multicenter European retrospective registry which enrolled 1617 patients (age ≤ 50 years) undergoing PCI between years 2002 to 2012. The median follow-up was 3.0 years.

Results: The majority of patients were smokers, but on adequate secondary prevention medication including statins, aspirin, beta-blockers and ACE-inhibitors/AT-blockers. At 5 years, survival was 97.8%, freedom from major adverse cardiac and cerebrovascular events 74.1%, from repeat revascularization 77.8% and from myocardial infarction 89.9%. Altogether 13.5% of patients had a disease progression as an indication for repeat revascularization. Other indications for repeat revascularization were restenosis (7.1%) and stent thrombosis (2.1%) at 5 years follow-up. Independent predictors of disease progression after PCI were multivessel disease, diabetes and hypertension.

Conclusion: PCI is associated with excellent survival in patients ≤ 50 years old. Nevertheless, every eighth patient underwent repeat revascularizations due to disease progression in the median follow-up of three years despite guideline-adherent medication underscoring the need for more effective secondary prevention than currently available. Disease progression caused nearly two times more ischemic recurrences than restenosis.

P2615 | BEDSIDE

The efficacy of second-generation drug-eluting stent for the treatment of left main and/or three-vessel disease: propensity matched analysis

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Background: The efficacy of second-generation drug-eluting stent (DES) for the treatment of left main disease (LM) and/or three vessel disease (3VD) remains unclear.

Methods: Between April 2008 and January 2013, 326 patients with LM and/or 3VD were treated by percutaneous coronary intervention in our institution. In these patients, 154 patients were treated with first-generation DES and 137 patients were treated with second-generation DES. There were some differences in baseline characteristics between the 2 groups, so we performed propensity matching to minimize the impact of confounding factors. Target lesion revascularization (TLR) and major adverse cardiac events (MACE) were compared between the two groups at 3 years.

Results: After propensity matching, there were 101 patients in each group. In the propensity matched cohort, incidence of TLR and MACE at 3 years were higher in first-generation DES compared with second-generation DES (TLR: 23.8% vs. 7.9%; $P=0.003$, MACE: 31.7% vs. 12.9%; $P=0.002$). Regarding the analysis stratified by the SYNTAX score, incidence of TLR and MACE in low and intermediate SYNTAX scores were tend to be high in first-generation DES group but there were no statistical significance (low score, TLR: 14.6% vs. 5.9%; $P=0.258$, MACE: 18.8% vs. 11.8%; $P=0.481$, intermediate score, TLR: 27.3% vs. 6.5%; $P=0.116$, MACE: 40.9% vs. 9.7%; $P=0.052$). On the other hand, in high SYNTAX scores the rates of TLR and MACE were significantly higher in first-generation DES group (TLR: 35.5% vs. 11.1%; $P=0.020$, MACE: 45.2% vs. 16.7%; $P=0.048$).

Conclusions: In propensity matched analysis, second-generation DES significantly improved TLR and MACE in patients with LM and/or 3VD compared with first-generation DES.

P2616 | BEDSIDE

Analysis of long term mortality based on SYNTAX-Score and residual SYNTAX-Score in left main patients in acute setting

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Background: The SYNTAX-Score is a powerful indicator of long-term mortality in patients with left main coronary artery (LMCA) or multivessel disease undergoing percutaneous coronary intervention (PCI). The residual SYNTAX-Score (rSS), relating to completeness of coronary revascularization, is an additional valuable tool to predict long-term clinical outcome in PCI patients. However, the prognostic impact of these scores to predict 2 years survival after PCI for acute coronary syndrome involving the LMCA has not yet been demonstrated. We want to assess in patients with left main and multivessel disease correlation based on the Syntax score and long term mortality.

Methods: We retrospectively assessed long-term survival in 238 consecutive patients undergoing emergency PCI for acute coronary syndrome (i.e. STEMI or high-risk NSTEMI) from January 2005 to December 2011. All culprit lesions involved the LMCA, thus in all patients the LMCA was stented. We accurately reviewed the angiogram of all patients and calculated the SYNTAX-Score and the rSS, defined as the SYNTAX-score after PCI. The effect of reduction of SYNTAX-Score on all-cause mortality was assessed by dividing patients into tertiles of risk.

Results: 134 subjects underwent PCI for STEMI, and 104 for NSTEMI. Mean age was 67, mean SYNTAX and rSS score were 24. The mean follow-up was 2 years. Patients in the highest tertiles of risk score experienced a dramatically elevated mortality rate compared to the extremely low mortality rate in the lower tertiles. A Roq curve of survival and difference between SYNTAX-Score pre and residual SYNTAX score has been calculated. We used the Youden Index to identify a cut off value related to better survival and that was 13. We also analyzed the survival related to the difference between the SYNTAX Score and the residual SYNTAX score in the intermediate and high risk SYNTAX tertiles using chi square test. In patients with difference less than 13 survival was 54%. In patients with difference equal or more than 13 survival was 82.9% (p -log value: 0.002). In patients with intermediate SYNTAX score the higher difference between SYNTAX pre and post is related to survival with odds ratio growing 0.85 related to delta SYNTAX (CI 1.03–1.20 p 0.007).

Conclusions: In our high risk LMCA patients the difference between SYNTAX score and residual SYNTAX score predicted a better outcome. A difference in SYNTAX/rSS equal or higher than 13 is related to better 2 years survival in intermediate tertile patients.

P2617 | BEDSIDE

Long-term prognostic value of deep spotty calcification for prediction of future revascularization: a prospective three-vessel intravascular ultrasound study

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Purpose: It is unclear what characteristics of plaque are associated with progression of stenosis in coronary arteries.

Methods: Consecutive 45 patients with coronary artery disease who underwent 3-vessel intravascular ultrasound (IVUS) examinations were prospectively enrolled in this study. Qualitative and quantitative IVUS analyses were performed for each non-significant non-culprit lesions. The maximum arc and the location (superficial or deep) of calcium were assessed at minimum lumen area (MLA). The longitudinal length of calcium was also measured. Quantitative analysis of plaque characterization was performed by scoring for echogenicity against the adventitia: brighter (hyperechogenic) or less bright (hypoechoic), and the percentage of hyperechogenic plaque was calculated. The primary end point was the occurrence of non-culprit lesion-related revascularization (NCLR) during 6-years follow-up periods.

Results: A total of 163 non-significant non-culprit lesions with mild to moderate stenosis were identified on baseline 3-vessel IVUS. Of those 6 lesions of 6 patients required NCLR during follow-up periods. There were no significant differences in quantitative IVUS parameters including remodeling index and plaque burden between lesions with and without NCLR. Also, the percentage of hyperechogenic plaque in the lesion with NCLR was similar to that of the lesion without NCLR (35.3% vs. 34.1%, $P=0.87$). However, frequency of deep calcium with the maximum arc of $<90^\circ$ was significantly higher in lesions with NCLR than in lesions without NCLR (50.0% vs. 3.8%, $P=0.002$). Moreover, the length of calcium was shorter and the maximum arc of calcium was significantly smaller in lesions with NCLR compared to lesions without NCLR (3.0mm vs. 5.9mm, $P=0.07$ and 46.7° vs. 117.8° , $P=0.02$, respectively).

Conclusions: A deep spotty calcium deposition on IVUS predicts the occurrence of revascularization for non-significant non-culprit lesions during 6-year follow-up periods. Spotty calcium may be a surrogate marker for plaque progression and subsequent revascularization in the future.

P2618 | BEDSIDE**Periprocedural myocardial infarction predicts worse clinical outcome in patients undergoing percutaneous coronary interventions of chronic coronary total occlusion**

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Purpose: Periprocedural myocardial infarction (PMI) after percutaneous coronary intervention (PCI) has been associated with higher mortality. PMI might occur more frequently during challenging procedures such as PCI of chronic coronary total occlusion (CTO). However, the prognostic implication of PMI in CTO-PCI remains unclear.

Methods: From January 2006 to September 2012, 715 consecutive patients (pts) undergoing PCI of CTO in major native coronary arteries were screened for this registry at 3 centers. Only pts with available pre- and post-PCI troponin (cTn) were finally included (n=442). PMI was defined as an elevation of cTn >5 times URL in pts with normal baseline values or a rise of cTn >20% if baseline values were elevated. Pts were grouped into: a) successful CTO-PCI and no-PMI (Group A, n=195); b) successful CTO-PCI with PMI (Group B, n=133); failed CTO-PCI (Group C, n=114). Major adverse cardiovascular events (MACE: composite of overall death plus non-fatal myocardial infarction plus target vessel revascularization) were assessed in 431 patients (97%) at a median follow-up of 25 months (10-37).

Results: The 3 groups did not differ significantly with respect to clinical characteristics. MACE rate was significantly lower in pts treated with successful CTO-PCI without PMI, and progressively increased in case of PMI or failed CTO-PCI (Group A= 9%, Group B= 15%, Group C= 28%, HR: 1.57 (1.24-2.18), p<0.01). MACE-free survival was also significantly higher in Group A at Kaplan-Meier analysis (Log-Rank: 7.17, p<0.01).

Conclusions: Occurrence of PMI during PCI of CTO is associated with worse clinical outcome, yet superior to patients with failed CTO recanalization.

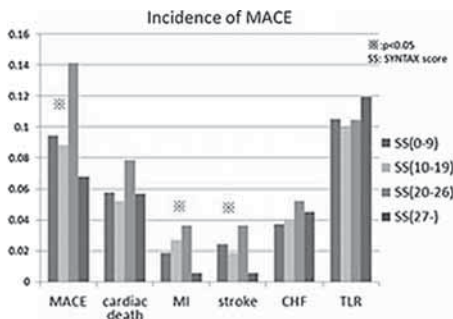
P2619 | BEDSIDE**Value of SYNTAX score to predict long-term outcomes in patients undergoing percutaneous coronary intervention**

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Purpose: The SYNTAX score (SS) is useful to quantify the extent of coronary artery disease (CAD) based on the location and complexity of each lesion. To investigate the association among clinical outcomes and value of the SS in patients undergoing percutaneous coronary intervention (PCI) with CAD. And to evaluate whether the SS is a predictor of long-term cardiovascular outcomes in patients treated with PCI.

Methods: A cohort of 1701 patients (69.7±10.7 years old, 77% male) who underwent PCI for CAD was analyzed from ICAS (Ibaraki Cardiovascular Assessment Study) multi-center registry between April 2007 to April 2010. We divided patients into 4 groups according to value of SS: Low SYNTAX (low SS; 0-9: n=743), Mid SYNTAX (mid SS; 10-19: n=590), High SYNTAX (high SS; 20-26: n=191), and Very High SYNTAX (VH SS; 27-: n=176). Clinical outcomes were defined as Target Lesion Restenosis, and Major adverse cardiovascular event (MACE) which included cardiac death, myocardial infarction, stroke, or hospitalization for worsening heart failure.

Results: Mean follow up period was 440 days. MACE was significantly higher in high SS than other three groups (Kruskal Wallis test p<0.05), and surprisingly there was remarkable difference between high SS and very high SS. Similar significant difference was recognized between four groups in stroke and myocardial infarction (MI). The incidence of heart failure or restenosis were no difference between four groups (CHF p=0.78, TLR p=0.94).



Incidence of MACE.

Conclusions: High SYNTAX score provides worse clinical outcome than very high SYNTAX score in patients with CAD in this registry. This conclusion would

suggest that sudden cardiovascular event associates to other elements such as focal inflammation or ruptured plaque closely, from complexity of the lesion.

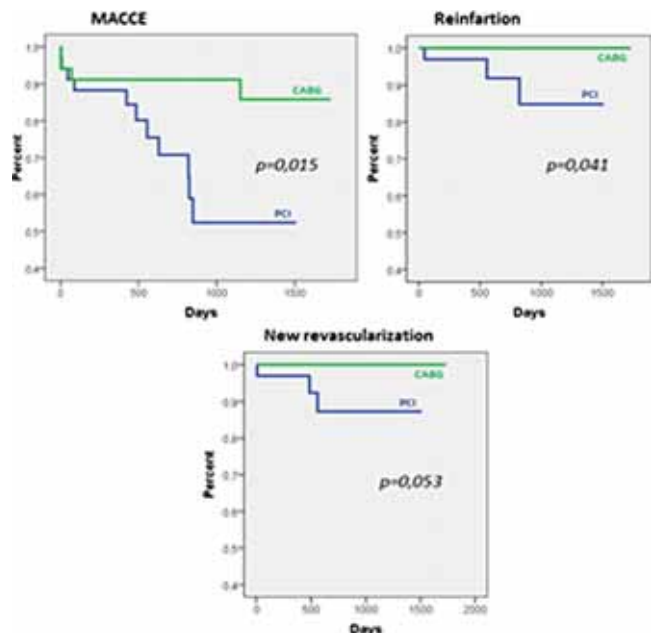
P2620 | BEDSIDE**Coronary artery bypass graft surgery versus percutaneous coronary intervention for the treatment of unprotected left main coronary artery disease: a real world study with propensity score matching**

B. Bochar Villanueva¹, A. Berenguer-Jofresa¹, R. De La Espriella-Juan¹, C. Albiach-Montanana¹, P. Garcia-Gonzalez¹, F. Paredes-Vignoli², D. San Miguel-Cervera¹, J.V. Vilar-Herrero¹, F. Pomar-Domingo¹, S. Morell-Cabedo¹. ¹University General Hospital of Valencia, Department of Cardiology, Valencia, Spain; ²University General Hospital of Valencia, Department of Cardiac Surgery, Valencia, Spain

Purpose: Current guidelines recommend coronary artery bypass graft (CABG) surgery for the treatment of unprotected left main coronary artery (ULMCA) stenosis, although percutaneous coronary intervention (PCI) has recently proven to be an alternative in selected patients. The aim of our study was to compare the long-term outcomes of CABG versus PCI in the treatment of ULMCA disease.

Methods: We retrospectively studied 352 patients (68.0±10.2 years) with ULMCA disease undergoing CABG (n=307) or PCI (n=45) between January 2009 and June 2013. After matching by propensity score (n=68), we analysed the baseline characteristics of the sample and the rate of events. We performed a multivariate Cox regression model to predict the probability of major adverse cardiovascular and cerebrovascular events (MACCE) and a survival analysis with the Kaplan-Meier method.

Results: Mean follow-up was 889±470 days. The PCI group had a higher rate of MACCE (32.4% vs 11.8%, p<0.05) and a trend to more reinfarction and new revascularization. There were no differences in mortality between the two groups. Only a EUROSCORE II over 6 (HR 3.019, 95% CI 1.050 to 8.679, p=0.04) and conducting CABG (HR 0.247, 95% CI 0.076 to 0.801, p=0.02) were independent predictors of MACCE. In survival analysis, PCI group had an inferior MACCE-free survival (Log Rank 5.922, p=0.015) and Reinfarction-free survival (Log Rank 4.182, p=0.041) compared with CABG group, with a tendency to inferior New Revascularizations-free survival (see Figure).



Kaplan-Meier survival curves.

Conclusions: Despite the advances of PCI in recent years, CABG had better long-term outcomes in the treatment of ULMCA disease, especially at the expense of lower rate of reinfarction and new revascularizations.

P2621 | BEDSIDE**Impact of the Residual SYNTAX Score on 5-year clinical outcomes after sirolimus-eluting stents implantation**

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Background: Incomplete revascularization after percutaneous coronary intervention (PCI) is common, and most studies have suggested that incomplete revascularization is associated with a worse prognosis compared with complete revascularization. However, formal quantification of the extent and complexity of residual atherosclerosis after PCI has not been performed. The Residual SYN-

TAX Score (RSS), which has been previously published, is determined as the SYNTAX score remaining after completion of PCI. We sought to assess its ability to stratify long-term outcomes in all patients who underwent PCI with sirolimus-eluting stents (SES).

Methods: Between August 2004 and March 2005, 218 patients were treated with SES at our institution. In the case of staged PCI procedure, the final planned procedure was used as the entry point for this study. Clinical follow-up was evaluated at more than 5 years. The RSS was available for 175 (80.2%) patients, except 43 patients with prior coronary artery bypass grafts surgery.

Results: Average follow up period was 5.7 ± 0.3 years. Patients were divided according to their RSS into tertiles defined as: RSS=0 ($n=116$), $0 < \text{RSS-LOW} \leq 5$ ($n=27$), RSS-HIGH > 5 ($n=27$). RSS-HIGH was significantly associated with a higher death rate (RSS=0: 18.1%, RSS-LOW: 22.3%, and RSS-HIGH: 41.6%; log-rank $p=0.030$) and major adverse cardiovascular events (37.3%, 51.9%, and 78.9%, respectively; log-rank $p=0.030$). After multivariate analyses, independent predictors for major adverse cardiovascular events were the RSS (hazard ratio [HR]: 1.58, 95% confidence interval [CI]: 1.20 to 2.07; $p=0.001$), hemodialysis (HR: 2.62, 95% CI: 1.45 to 4.74; $p=0.001$), and age (HR: 1.02, 95% CI: 1.00 to 1.05; $p=0.037$).

Conclusions: The RSS is a useful score to predict the long-term outcomes in patients treated with SES in the real world setting.

P2622 | BEDSIDE

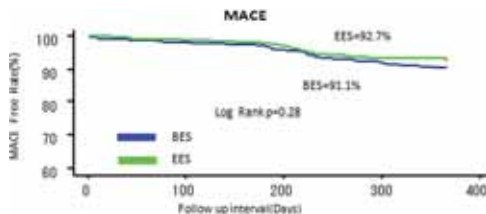
Comparison of one-year clinical outcomes in patients with diabetes mellitus after coronary intervention with biolimus- and everolimus-eluting stent

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Purpose: Recent pivotal studies have shown that biolimus-eluting stent (BES) is as safe and efficacious as everolimus-eluting stent (EES) with a durable biocompatible polymer. However, the effectiveness of BES in a real-world setting of diabetic patients is currently unclear. We compared one-year clinical outcomes after the use of BES versus EES for the treatment of diabetic patients.

Method: We enrolled 1266 consecutive patients with the NOBORI BES, 563 (44.5%) of whom had diabetes mellitus (DM). As a historical control group, a total of 1043 consecutive patients with the XIENCE/PROMUS EES between February 2010 and April 2011 were enrolled, 466 (44.7%) of whom had DM. The primary endpoint was the rate of major adverse cardiovascular events (MACE), defined as a composite of cardiac death, myocardial infarction, definite stent thrombosis, clinically driven target lesion revascularization (TLR) at 1-year.

Result: Baseline characteristics were similar between the BES and EES groups. At 1-year, the incidence of MACE was not significantly different between the BES and EES group (8.9% vs. 7.3%, $P=0.28$). Cumulative incidence of myocardial infarction, definite stent thrombosis, and clinically driven TLR were not significantly different between the 2 groups (1.0% vs. 0.9%, $P=0.71$, 0.9% vs. 0.9%, $P=0.94$; 7.3% vs. 4.7%, $P=0.08$, respectively). The incidence of TLR and Target vessel revascularization (TVR) was not significantly different between the 2 groups (11.9% vs. 11.6, $P=0.58$; 13.7% vs. 12.2%, $P=0.40$, respectively).



MACE at 1 year.

Conclusion: One-year clinical outcome after biodegradable polymer BES implantation in diabetic patients is not significantly different from that after durable polymer EES. This study suggests that both BES- and EES-use are acceptable in a real-world setting of diabetic patients.

P2623 | BEDSIDE

Syntax score-based assessment for stent failure among patients who underwent drug eluting stent implantation

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Background: Stent failure is major determinant factor of prognosis among patients who underwent drug eluting stent (DES) implantation, and frequency of stent failure was increased with syntax score. However, detail of that interaction between stent failure and syntax score is still unclear.

Methods: Among total of 1286 patients who underwent PCI with DES, we investigated 123 patients with DES failure. Stent failure was defined as angiographic restenosis or stent thrombosis. We divided them into three groups according to tertile of syntax score based on initial angiogram (low; 1-11, intermediate; 12-24, and high; > 25), and compared pattern of stent failure and long-term outcomes

among them. Stent fracture was assessed by fluoroscopy or IVUS in each case. Major adverse cardiac event was comprised from all cause death, non-fatal myocardial infarction, and re-target lesion revascularization (re-TLR).

Results: According to syntax score stratification, patients with DES failure was 29 cases in low, 39 cases in intermediate, and 55 cases in high syntax score tertile. Total stent length was increased with syntax score (mm; 30.1 ± 19 , 31.6 ± 17 , and 47.2 ± 24 , $P=0.0003$), and prevalence of overlapping stent was increased with syntax score (20.7%, 41.0%, and 67.3%, $P=0.0001$). Based on follow-up angiography, prevalence of focal restenosis was 75.0% of DES failure, and it was not different among those tertile. However, stent fracture was detected in 26.0% of DES failure, and it was frequently seen in patients with high syntax score (7.0%, 15.4%, and 43.6%, $P=0.0002$). Multivariate analysis revealed that syntax score (OR: 1.05, 95%CI: 1.02-1.09, $P=0.003$), RCA lesion (OR: 3.40, 95%CI: 1.13-10.2, $P=0.03$), and overlapping stent (OR: 6.90, 95%CI: 1.42-33.5, $P=0.02$) was independently related with occurrence of stent fracture. TLR including 2 cases of CABG was performed in all cases, but it was failed in 1 case. And survival analysis showed stent fracture was only independent predictor of occurrence of MACE among patients with DES failure (HR: 3.70, 95%CI: 1.20-11.3, $P=0.02$).

Conclusions: Among patients with DES failure, prevalence of stent fracture was increased with syntax score, and it was related to worse outcomes during subsequent follow-up periods. RCA lesion, overlapping stent, and complexity of coronary artery disease may influence on occurrence of stent fracture, and prevention of stent fracture might be key to improve outcomes among patients with high syntax score.

P2624 | BEDSIDE

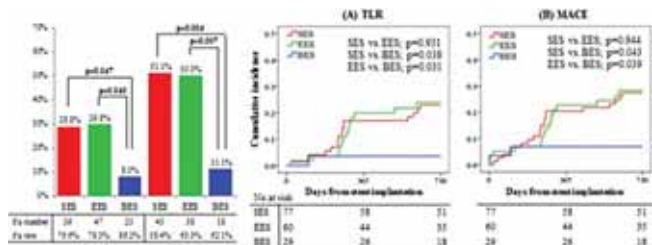
Clinical and angiographic outcomes of full metal jacket stent implantation for right coronary artery: comparison between different drug-eluting stents

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Purpose: Full metal jacket (FMJ) stent implantation has been used to treat diffuse coronary artery disease (CAD). However, the differences in outcomes after FMJ procedure between the implanted drug-eluting stent (DES) types were unknown. Thus, we evaluated clinical and angiographic outcomes after FMJ stent implantation for the right coronary artery (RCA) between sirolimus-eluting stent (SES), everolimus-eluting stent (EES), and biolimus-eluting stent (BES).

Methods: We defined FMJ as stenting without gaps from the ostium to the bifurcation of the RCA. The study population consisted of 166 consecutive patients who had been treated for de novo diffuse CAD with SES (77 patients), EES (60 patients) or BES (29 patients) from April 2004 to December 2012 in a single center. The patients who had 2 or more different DES types were excluded. Angiographic follow-up was routinely performed at 8 and 20 months after the procedure. Clinical outcomes were evaluated by major adverse cardiac events (MACE) and target lesion revascularization (TLR) at 2 years after the procedure. MACE was defined as a composite of cardiac death, non-fatal MI, and TLR. We compared the clinical and angiographic outcomes between patients based on the implanted stent types.

Results: The angiographic restenosis rate was significantly lower in the BES group than in the SES and EES groups, both at 8 months and 20 months (Fig. 1). The cumulative incidence of TLR was significantly lower in the BES group than in the SES and EES groups (Fig. 2A). The cumulative incidence of MACE was also significantly lower in the BES group than in the SES and EES groups (Fig. 2B).



Conclusions: In treating diffuse CAD requiring FMJ procedure, BES implantation was associated with more favorable outcomes compared with SES or EES implantation.

CHRONIC TOTAL OCCLUSIONS AND BIFURCATIONS – PCI

P2626 | BEDSIDE

Long-term follow up after antegrade versus retrograde recanalization of chronic total coronary occlusions

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Background: The recanalization success rate of chronic total coronary occlu-

sions (CTO-PCI) can be increased by a retrograde approach. The impact of the retrograde compared to the antegrade PCI on long-term outcome is unknown.

Aim of the study: To evaluate the long-term MACCE rate (death, myocardial infarction, coronary bypass surgery and stroke) in patients after retrograde versus antegrade CTO-PCI.

Methods and results: In a prospective study from January 2008 to June 2012 436 consecutive patients with CTO's (≥ 3 months old) were enrolled. Mean age was 63.4 ± 10.3 years, 86% were male. The retrograde PCI, which was used only after a failed antegrade intervention, was performed in 18% ($n=79$) of patients. Patients with retrograde CTO-PCI had more frequently previous bypass surgery, RCA as target vessel (79.7% vs. 56.8%, $p<0.0004$), longer lesion length (46 vs. 30 mm, $p<0.001$), longer procedure duration (108.2 vs. 63.2 min, $p<0.0001$), higher contrast volume (433.6 vs. 267.6 ml, $p<0.0001$), longer fluoroscopy time (61.2 vs 30.1 min, $p<0.0001$) and higher radiation exposure (285.3 vs. 145.0 Gy cm^2 $p<0.0001$).

Long-term overall MACCE rate (mean follow up 590 ± 461 days) was not different after retrograde vs. antegrade CTO-PCI (14.3% vs. 15.1%). Same was true for the components of MACCE (death 5.7 vs. 8.5%, myocardial infarction 2.8 vs. 2.6%, bypass surgery 8.6 vs. 5.3%, stroke 0 vs. 2.6%)

However, patients with failed antegrade PCI had a significantly higher long-term MACCE rate compared to successful antegrade PCI (29.2 vs. 12.5%, $p<0.04$), whereas the MACCE rate of failed vs. successful retrograde PCI was not different (14.3 vs. 14.3%).

Conclusions: Despite more patients with previous coronary bypass surgery and more complex target lesions and procedures the overall long-term MACCE rate after retrograde CTO-PCI is not different to antegrade CTO-PCI. Why the long-term MACCE rate is higher only after failed vs. successful antegrade but not after failed vs. successful retrograde CTO-PCI deserves further studies.

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Procedural and long-term outcomes in patients with chronic total occlusions treated by retrograde approach

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Purpose: The retrograde approach has been developed to improve the procedural success in CTO lesions. However, little is known about how the retrograde procedure affects the long-term outcomes. We investigated the impact of the retrograde approach for chronic total occlusion (CTO) recanalization on procedural and long-term outcomes.

Methods: A total of 641 consecutive patients with 711 CTO lesions underwent percutaneous coronary intervention (PCI) at our institution between October 2005 and December 2008. The procedural and 5-year clinical outcomes were compared between 235 patients treated with the retrograde approach for at least 1 CTO and 406 patients treated with the antegrade approach alone.

Results: The procedural success rates were 80.9% and 92.9% ($P<0.01$). The retrograde CTO PCI was performed in 36.7% of patients. Coronary perforation including collateral channel injury was significantly more common in the retrograde CTO PCI than in the antegrade CTO PCI (15.7% vs. 5.7%, $P<0.01$). The median follow-up time was 5.3 years (interquartile range: 4.9 to 6.1 years). The cumulative 5-year incidence of cardiac death was similar between the 2 groups (5.8% vs. 5.7%, $P=0.93$). The cumulative 5-year incidence of revascularization for a vessel excluding target CTO vessel was similar between the 2 groups (61.3% vs. 59.5%, $P=0.70$). In the successful recanalization, the cumulative 5-year incidence of target vessel revascularization was similar between the 2 groups (34.9% vs. 30.2%, $P=0.15$). By multivariate analysis, procedural failure was an independent predictor of cardiac death (hazard ratio 2.84, 95% confidence interval 1.30 to 6.21, $P<0.01$).

Conclusions: The retrograde approach to support the successful recanalization is not significantly different compared with the conventional antegrade approach at long-term outcomes of patients with CTO undergoing PCI.

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Predictors of successful chronic total occlusion (cto) revascularization- is there still a role for the old predictors?

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Background: A Chronic total occlusion (CTO) is one of the most technically challenging lesions for percutaneous coronary intervention (PCI). Only a small part of CTOs are intervened, perhaps because procedural success is limited by difficulties crossing and/or dilating the occluded segment. Improved techniques and the introduction of newer dedicated devices [wires, micro-catheters] have improved the success rate in crossing and treating CTO lesions.

Aims: We hypothesized that by using new tools and techniques, the known predictors of failure of CTO recanalization [heavy calcification, blunt/non-tapered occlusion, bridging collaterals] become less significant. We thus aimed to analyze the effects of these predictors on success of recanalization.

Methods: We analyzed a total of 323 consecutive patients in whom CTO recanalization was attempted. We compared patient and angiographic characteristics between successful recanalization group (259 patients) and failed recanalization

group (64 patients). CTO was defined as occlusion duration of >3 months or of unknown duration. Successful recanalization was defined as crossing a CTO lesion.

Results: Procedural success was observed in 80% of attempts.

Angiographic characteristics

P-value	Procedural success (n=259)	Procedural failure (n=64)	Angiographic characteristics
0.2	2.7%	11%	Heavy calcification
0.01	23%	39%	Bridging collaterals
0.04	50%	65%	Side branch
0.01	27%	44%	Blunt/Non tapered occlusion
0.3	63%	71%	Stiff wire
0.9	76%	73%	Hydrophilic wire
0.3	37.5%	23%	Left anterior descending CTO
	27%	36%	Left circumflex CTO
	32%	37.5%	Right coronary CTO
0.001	25%	57%	CTO duration >12 m
0.03	26 $\pm$ 22	56 $\pm$ 12	Total fluoroscopy time (min)
0.3	254 $\pm$ 84	223 $\pm$ 100	Total contrast volume (ml)

Conclusions: Despite the use of dedicated wires, and new techniques of revascularization, the old predictors of failure of recanalization still played a role.

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The factor of improvement of distal vessel diameter after percutaneous coronary intervention of chronic total occlusion in chronic phase

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Background: Although the vessel diameter distal to the recanalized CTO lesion is often smaller than expected immediately after recanalization, the vessel tends to increase their diameter after one year. Therefore, we assessed how the distal segment vessel diameter would increase at 1-year follow-up.

Methods: Consecutive patients ($n=104$) who received successfully recanalization of CTO lesions from July 2007 to October 2011 and had 1-year follow-up catheterization were analyzed. We classified them into two groups by the Rentrop collateral flow grade: Group A, grade 0 to 2 and Group B, grade 3. We evaluated by IVUS the plaque burden and minimum lumen diameter of the distal vessel segment immediately after recanalization. Vessel diameter distal to the recanalized CTO lesions (at 10mm from distal stent edge) was compared between follow-up and immediately after recanalization (baseline) by quantitative coronary angiography.

Results: Vessel diameter increased significantly from baseline to follow-up (1.9 ± 0.7 mm vs. 2.3 ± 0.7 mm, $P<0.05$). Vessel diameter increased more in Group B than in Group A (74.0% vs. 94.4% mm $P<0.05$). There was no significant difference in IVUS findings between the patients with and without vessel diameter increase.

Conclusion: Vessel diameter in the distal segment of CTO lesion increased at 1-year follow-up especially in the patients with good collateral flow.

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One-Year Clinical Outcomes with Biodegradable polymer Biolimus-Eluting Stent in Chronic Total Occlusion: Comparison With Durable Polymer Everolimus-Eluting Stent

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Purpose: Recent pivotal studies have shown that biolimus-eluting stent (BES) is as safe and efficacious as everolimus-eluting stent (EES). However, the effectiveness of BES in a real-world setting of chronic total occlusion (CTO) lesion is currently unclear. We compared one-year clinical outcomes after the use of BES versus EES for the treatment of CTO lesions.

Method: Between February 2011 and June 2012, we underwent percutaneous coronary intervention with the BES (1276 patients with 1752 lesions) or EES (1045 patients with 1446 lesions) were analyzed. Of these, 152 patients with 157 lesions (9.0%) and 137 patients with 142 lesions (9.9%) had CTO lesions. The primary endpoint was the cumulative rate of major adverse cardiac events, defined as a composite of cardiac death, myocardial infarction, definite stent thrombosis, clinically driven target lesion revascularization (TLR) at 1-year.

Results: Baseline characteristics were similar between the BES and EES groups. Total stent length did not differ between the 2 groups (52.8 ± 26.0 mm vs. 52.7 ± 30.1 mm, $p=0.98$). Diabetic patients and hemodialysis patients were similar

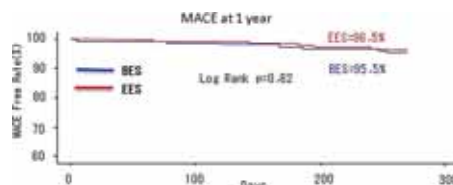


Figure 1

between the 2 groups (46.5% vs. 44.3%, $P=0.75$; 3.2% vs. 2.8%, $P=0.95$, respectively). At 1-year, cumulative incidence of MACE and clinically driven TLR were not significantly different between the 2 groups (4.5% vs. 3.5%, $p=0.62$; 3.8% vs. 2.8%, $p=0.60$, respectively). Stent thrombosis was similar between the BES and EES groups (0.6% vs. 0%, $p>0.99$).

Conclusions: One-year clinical outcome after biodegradable polymer BES implantation in CTO lesions is not significantly different from that after durable polymer EES. This study suggests that both BES- and EES-use are feasible with efficacy and safety in a real-world setting of CTO lesion.

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Impact of calcium distribution for successful revascularization of coronary artery CTO lesion: Assessed from computed tomography coronary angiography

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Purpose: The success rate of percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) is lower than overall success rate of other forms of PCI. Recent report suggested that severe calcified patterns at occluded segment by CT coronary angiography (CTCA) were prevalent in failed PCI. CTCA is potentially a useful imaging modality for characterization of CTO lesion. We aimed to investigate whether distribution of intramural calcification is related to wire penetration for occluded segment as observed CTCA.

Methods: This was a prospective observational study carried out in our institution between April 2007 and December 2013. We performed CTCA in a consecutive cohort of eligible patients who were scheduled for PCI of CTO. CTCA was performed with a 64-slice MSCT. The degree of calcification was evaluated by cross-sectional lumen views along the occluded segment. Further we analyzed the calcium spots which occupied at the occluded segment by cross-sectional lumen views. Intramural calcification (IC) was defined as the lesion which calcium spots occupied at the center of the lumen from cross-sectional lumen views, and Extramural calcification (EC) was defined as the lesion which calcium spots without the center of the lumen from cross-sectional lumen views. We compared with wire lesion cross success rate and technical success rate between two groups.

Results: In a cohort of 256 patients with 286 CTO lesions were attempted. Two hundred and fifty-two of 286 (88.7%) CTO lesions were successfully revascularized with PCI. Of the 34 CTO lesions with failed PCI, 27 failed cases were due to failure of crossing the CTO lesions with angioplasty guidewires. Seven failed cases were due to failure of crossing the CTO lesions with the angioplasty balloon. Two hundred and eighty-six calcified CTO lesions were divided into two groups: IC group (73 lesions) and EC group (213 lesions). Assessing from CTCA; either the frequency of calcification at the entry, calcification at the exit, length of occluded segment or calcium score of occluded segment were similar between two groups. Wire lesion cross success rate in EC group was significant higher than that of IC group (EC vs. IC: 94.8% vs. 49.3%, $p<0.001$). And technical success rate in EC group was significant higher than that of IC group (EC vs. IC: 90.6% vs. 43.8%, $p<0.001$).

Conclusions: Intramural severe calcification has an impact on wire lesion cross success rate during wire penetration for CTO. CTCA is the only modality to assess the occluded segment before PCI procedure and a possibility that procedural success can be predicted.

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Influence of stent length on long-term clinical outcomes after percutaneous coronary intervention for chronic total occlusions

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Purpose: Chronic coronary total occlusions (CTO) when successfully treated are often stented over very long sections. Studies have shown a correlation between stenting length and the occurrence of major adverse cardiac events (MACE) at follow up, but no data exist regarding CTO PCI.

Methods: A total of 1343 patients underwent CTO PCI at our center between January 2004 and January 2012. We investigated the relationship between stenting characteristics including the type, total number and stent length and major adverse cardiac events (MACE) and its components, cardiac death, myocardial infarction (MI) and target vessel revascularization (TVR).

Results: Procedural success was achieved in 1000 (74.4%) patients where a total of 1674 stents (BMS: 7.7% DES: 92.3%) were deployed in 1139 chronically occluded vessels with a mean stent length of 47.45 ± 24.82 mm per patient. Follow-up was obtained in 92.5% of cases at a median 4.1 years (IQR: 2.4-6.5 years). As predicted, patients treated with BMS had a higher rate of MACE than DES (34.4% vs. 18.5%, $p=0.003$) mainly driven by target lesion revascularization (TLR) (16.4% vs. 7.5%, $p=0.015$). Focusing only on the DES treated patients, stent length did not correlate with cardiac death ($p=0.848$, ns) or MI ($p=0.890$, ns), but it emerged as an independent predictor of MACE ($p=0.031$) mainly driven by a higher incidence of TVR (52.7 ± 26.9 mm vs. 46.9 ± 24.5 mm, $p=0.043$). By multivariate analysis, only stent length (OR 1.011, 95%CI 1.003-1.018; $p=0.005$) and

ostial CTO (OR 3.378, 95%CI 1.46-7.80, $p=0.004$) were independently associated with TVR.

Conclusions: In this large prospective series, stent length was associated with a higher rate of major adverse cardiac events, mainly driven by TVR. This may have implications for stent selection and consideration for other treatment options in the setting of long CTO lesions.

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Very long term clinical outcome after percutaneous coronary intervention for chronic total occlusion: does procedural success matter?

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Background: Whether successful percutaneous coronary intervention (PCI) of a coronary chronic total occlusion (CTO) is associated with better very long-term clinical outcome is the subject of debate.

Objectives: Using a large prospective database of patients treated for CTO, we sought to compare their very long-term outcome on the basis of success/failure of PCI procedure.

Methods: Between 2004 and 2012, a total of 1,320 consecutive patients underwent PCI for CTO in our centre (14 operators). We compared cardiac death, target vessel revascularisation (TVR), myocardial infarction (MI) and major adverse cardiac events (MACE) in patients with successful versus failed PCI at a median follow up of 4.2 years (IQR: 2.5-7.0 years). Procedural success was defined as achievement of residual stenosis <50% with TIMI-3 flow in the target vessel.

Results: Successful treatment of CTO by PCI was achieved in 990/1320 (75.0%) patients. These patients were younger (63 ± 11 Vs. 65 ± 11 , respectively $p<0.01$), had lower rates of hypertension (56.5% Vs. 66.9%, $p<0.01$), previous MI (19.4% Vs. 30.0% $p<0.0001$), previous PCI (34.4% Vs. 42.1%, $p=0.02$), and previous CABG (5.5% Vs. 13.4%, $p<0.0001$) than those in whom PCI success was not achieved. In addition, patients with successful PCI were more frequently treated for left anterior descending artery CTO (34.1 vs. 22.1%, $p<0.0001$) and had better baseline left ventricular ejection fraction ($57 \pm 9\%$ vs. $55 \pm 9\%$, $p=0.04$). PCI success was associated with significantly lower rates of cardiac death (5.3% vs. 11.7% for patients with failed PCI, $p<0.0001$) and MACE (19.5% vs. 26.3% respectively, $p=0.001$). Successful PCI (HR: 0.5, 95% CI: 0.32-0.81, $p=0.005$), diabetes (HR: 2.44, 95%CI: 1.52-3.83), left ventricular ejection fraction (per percent increment, HR: 0.96, 95% CI: 0.94-0.99, $p=0.004$) and age (per year increment, HR: 1.06, 95% CI: 1.03-1.08, $p<0.0001$) were independent predictors of cardiac death at follow-up. There was a strong interaction between diabetes and procedural success or failure. Indeed, cardiac mortality rate was 4.1% (30/731 patients) after successful and 6.6% (15/227 patients) after failed PCI in non-diabetics, whereas it was 6.9% (18/259) and 19.4% (20/103) in diabetic patients, respectively ($p<0.0001$).

Conclusions: In this large cohort of CTO-patients, successful PCI was associated with improved long-term survival at up to 9 years. Successful PCI of CTO is associated with superior cardiac death reduction among diabetic patients vs. non-diabetics, suggesting strong efforts to recanalize occluded coronary arteries in these patients.

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Regular drug eluting stent versus dedicated bifurcation BioSS LIM stent in coronary bifurcation treatment - randomized POLBOS II study

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Purpose: POLBOS II study is the continuation of POLBOS I study (POLish Bifurcation Optimization Strategy), in which paclitaxel-eluting stent BioSS® Expert was assessed in the treatment of coronary bifurcations.

Methods: In POLBOS II study patients with stable coronary artery disease or NSTEMI-ACS who signed informed consent were randomized to the group where dedicated bifurcation sirolimus-eluting BioSS® LIM stent was implanted or to the group where regular DES was used. The enrollment was proceeded between November 2012 and August 2013 in five centers in Poland and Spain. Patients with STEMI or Medina type 001 bifurcation lesions were excluded from the study. Provisional T-stenting was the obligatory strategy. An angiographic control was planned at 12 months in all patients. The primary end-point of the study is the rate of death, MI, ST and TLR after 12 months. Here, we present complete 6-month clinical follow-up. At the time of ESC Congress 2014 angiographic follow-up will be completed.

Results: BioSS® LIM was implanted in 85 patients (50.6%) and regular DES was deployed in 83 patients (49.4%). A fourth of participants were females. The average age of patients did not differ significantly between groups (BioSS vs DES: 66.7 vs 65.5 yrs). In BioSS group there were significantly more patients

with hypertension (97.2% vs 87.5%), diabetes (44.4% vs 37.5%) and chronic kidney disease (13.9% vs 9.5%).

The dominant vessel was LAD (BiOSS vs DES: 46% vs 57%) followed by LMS (37% vs 18%, respectively). According to Medina classification true bifurcations were present in 65%. In DES group 20% of stents eluted sirolimus, 24% - paclitaxel and 45% - everolimus. There were following nominal stent parameters: in BiOSS group 3.73±0.43 mm (proximal diameter) x 3.03±0.4 mm (distal diameter) x 17.7±2.9 mm (length) and in DES group: 3.29±0.52 mm x 20.1±6.9 mm. Except for 1 (1.2%) case in DES group and 1 (1.2%) in BiOSS group all stents were implanted successfully without any serious periprocedural complications. There was the necessity to implant the second stent in the side branch in 6.2% and 1.6% cases in BiOSS group and DES group, respectively. At six months all patients were uneventful, except for one patient in each group where TLR was observed.

Conclusions: Collected data demonstrates comparable immediate and short-term clinical results for both studied group. Full data enable to answer the question if BiOSS[®] LIM comparable to regular DES and if it is superior to BiOSS[®] Expert stent assessed in POLBOS I study.

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Short-term clinical outcomes after implantation of the everolimus-eluting bioresorbable vascular scaffold in bifurcation lesions: the ABSORB Expand Study

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Purpose: The everolimus-eluting bioresorbable vascular scaffold has shown promising angiographic results and clinical outcomes in the context of first-in-man trials including simple lesions. Safety and efficacy of the Absorb BVS in more complex lesions, however, cannot be directly extrapolated from these data. We thus sought to evaluate the clinical impact of Absorb BVS on short-term outcomes in patients with more complex lesions in real-world clinical settings.

Methods: Since September 2012, Thoraxcenter commenced the ABSORB Expand single-arm registry using the Absorb BVS for patients with de novo complex lesions. We assessed bifurcation lesions treated with the Absorb BVS, involving a side branch (SB) >2.0mm, ostial lesion >40% stenosed, or a SB requiring pre-dilatation. Two-dimensional quantitative coronary angiography was performed with a dedicated bifurcation analysis algorithm and software. The primary endpoint was a device-oriented composite endpoint (DoCE) including cardiac death, myocardial infarction, and clinically driven target lesion revascularization.

Results: Consecutive 39 patients with 40 bifurcation lesions were studied. Mean age was 61.4 and 74.4% were male. Four patients presented with unstable angina and 13 patients were diagnosed as non-ST elevation myocardial infarction. Although 14 lesions (35.0%) revealed true bifurcation, 38 (95.0%) bifurcation lesions were treated by one-scaffold approach. Pre-procedure mean reference vessel diameter and diameter stenosis were 3.08mm and 40.1% in proximal main vessel (PMV), 2.24mm and 41.0% in distal main vessel (DMV), and 2.03mm and 19.5% in SB, respectively. Post-procedural diameter stenosis were 16.9%, 11.9%, and 19.2% in PMV, DMV, and SB, respectively. Absorb BVS implantation did not alter the distal bifurcation angle (DMV-SB) pre- and post-procedurally (49.1 vs. 45.4 degrees, $p=0.11$). In 16 lesions (40.0%), jailed polymeric struts were fenestrated at the ostium of SB. Although 2 lesions (5.0%) revealed SB occlusion immediately after Absorb BVS implantation, post-procedural TIMI flow grade 3 was obtained in all main vessels and SBs. Neither DoCE nor scaffold thrombosis were reported at 30 days follow-up.

Conclusions: The Absorb BVS appeared to be safe and feasible for the treatment of bifurcation lesions in real-world clinical settings.

PROGNOSTIC FACTORS IN ACUTE CORONARY SYNDROMES

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Prognosis of non ST elevation myocardial infarction in patients with high hemoglobin levels at admission

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Background: Previous studies have found that in patients with ST elevation myocardial infarction (STEMI) the presence of higher levels of hemoglobin (Hb) at baseline were associated with greater in-hospital mortality once erythrocytosis may predispose to a prothrombotic state.

Objectives: We aim to assess whether in patients with non-ST elevation myocardial infarction (NSTEMI) higher Hb levels at admission are also associated with a worse prognosis when compared to individuals with the same diagnosis and lower Hb values.

Methods: 3799 consecutive patients with admission diagnosis of NSTEMI between 01/10/2010 and 01/10/2013 included in the database of a prospective national registry of acute coronary syndromes were analysed. 403 patients with no initial Hb levels evaluation were excluded. Patients were divided into 3 groups according to the values of Hb on admission: group 1 - Hb <12 g/dL, group 2 - Hb ≥12 and <16 g/dL, and group 3 - Hb ≥16 g/dL.

Results: 3396 patients entered the study of which 20.7% were included in group 1, 70.3% in group 2 and 9.1% in group 3. When compared with patients in group 2, the group with higher Hb levels had a higher proportion of males, patients were younger, with a higher body mass index, a higher % of smokers and lower GRACE score. Patients in group 1 were older, with higher GRACE score and higher creatinine values. The lower in-hospital mortality was observed in the group of subjects with Hb ≥16 g/dL (1.3%) whereas the mortality rate observed for patients with Hb <12 g/dL was about 4 times higher (5.4%, $p<0.001$). In multivariate analysis the value of Hb above 12 g/dL proved to be a protective factor compared with Hb ≤12 g/dL (OR 0.215, 95% CI 0.083-0.555).

Conclusion: Unlike observed in previous studies where higher Hb levels were associated with a worse prognosis in patients with STEMI, in this study it appears that in the context of NSTEMI increased values of Hb at admission are associated with a more favorable prognosis.

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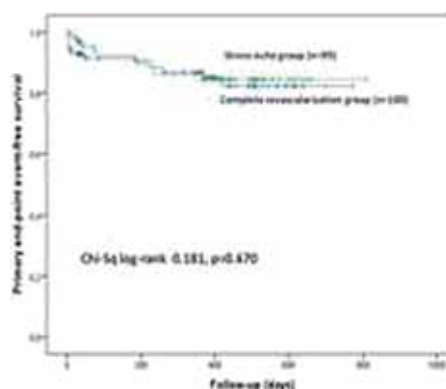
Preventive revascularization does not offer clinical advantage over a selective invasive strategy in patients with ST-segment elevation myocardial infarction and multivessel disease

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Purpose: In patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease treated by primary percutaneous coronary intervention (PPCI) the management of non-culprit stenoses remains controversial. We sought to investigate whether staged-complete revascularization offers clinical advantage over ischemia-driven revascularization in this subset of patients.

Methods: From 2010 through 2013 we enrolled 199 patients with STEMI and multivessel disease who underwent infarct-artery PPCI and randomly assigned them to either complete staged revascularization (CR, 100 patients) or ischemia-guided revascularization following the results of a stress-echocardiogram during admission (SE, 99 patients). The primary outcome was a composite of cardiovascular death, non-fatal MI, revascularization of any vessel or admission due to heart failure. An intention-to-treat analysis was used.

Results: Twenty-seven patients in the SE group underwent staged revascularization of at least one non-culprit vessel. During a median follow-up of 1 year we found no differences between groups in the occurrence of the primary end-point (13.3% in the CR group vs. 11.7% in the SE group, $p=0.743$; hazard ratio in the SE group 0.67, CI95% 0.38-1.89). There were no differences as well in the individual components of the primary end-point: cardiovascular death (0% CR vs. 1.1% SE, $p=0.490$), non-fatal MI (5.1% CR vs. 3.6% SE, $p=0.721$), any vessel revascularization (8.2% CR vs 10.6% SE, $p=0.556$) and heart failure (1% CR vs. 0% SE, $p=1.000$).



Survival curves for primary end point.

Conclusion: Complete revascularization did not offer clinical net advantage over a strategy of stress-echo guided revascularization in patients with STEMI and multivessel disease.

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Early detection of cytochrome c in acute myocardial infarction identifies patients at higher risk of adverse outcomes

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Purpose: Cardiac troponins are commonly used as diagnostic and prognostic

biomarkers in patients with acute myocardial infarction (AMI), and for risk stratification to guide triage decisions and aid in treatment selection. In addition to sensitive markers of ischemic cell death, however, remains a need for new biomarkers of apoptotic cell death associated with myocardial reperfusion injury. Indeed, at the cellular level, reperfusion has been demonstrated to be a potent inducer of apoptosis through the activation of the mitochondrial apoptotic pathway and release of apoptotic factors, including cytochrome c, into the cytosol where they activate the apoptotic cascade. Cytochrome c has been shown to transiently increase in the early phase of AMI, and its peak value to be associated with clinical, angiographic, and imaging variables of reperfusion. Despite these preliminary findings support the concept that cytochrome c is a potential biomarker of myocardial reperfusion injury, no study has investigated, so far, the potential clinical and prognostic value of its early (at hospital presentation) measurement in AMI patients.

Methods: Serum cytochrome c (ELISA method) was measured at hospital admission in 753 consecutive patients with AMI (313 STEMI and 440 NSTEMI). In-hospital and 1-year mortalities were evaluated as primary end point. Results were analyzed according to the presence of positive or negative cytochrome c values at hospital admission.

Results: At hospital presentation, cytochrome c was detectable in the blood of 280 (37%) patients (positive group; median value 0.87 [0.63-1.29] ng/ml), whereas it was not detectable in the remaining 473 (63%) patients (negative group). The two groups were similar for all the evaluated variables, except for troponin I (TnI) value at hospital admission and TnI peak value that were significantly higher in positive group. In-hospital and 1-year mortality rates were significantly higher in patients with positive cytochrome c at hospital presentation than in those with a negative cytochrome c value (5.4% vs. 0.8%; $P < 0.001$, and 9% vs. 4.8%; $P = 0.028$, respectively). Moreover, in the positive group, in-hospital mortality was higher in patients with a cytochrome c value above the median value than in those with a cytochrome c value below the median value (8.6% vs. 2.1%; $P < 0.001$).

Conclusions: Cytochrome c can be detected at hospital presentation in about 40% of AMI patients. Cytochrome c positivity, as well as the extent of its rise, is closely associated with short- and long-term mortality.

P2640 | BEDSIDE

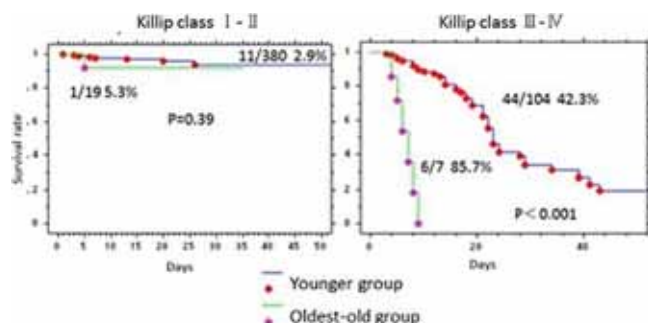
In-hospital clinical outcomes of the oldest-old patients with acute myocardial infarction treated with primary percutaneous coronary intervention

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Purpose: The aim of the present study was to assess the early clinical outcomes of the oldest-old patients (aged ≥ 90 years) with acute ST-segment elevation myocardial infarction (STEMI) following primary percutaneous coronary intervention (PCI).

Methods: A total of 510 consecutive patients with acute STEMI who underwent primary PCI within 12 hours of symptom onset between January 2009 and December 2013 were enrolled. The in-hospital mortality was compared between oldest-old (26 patients, 5.1%, 92.7 ± 3.0 years) and younger patients (71.7 ± 13.4 years).

Results: There were no differences about the rate of TIMI 0-1 flow at presentation (76.9 vs 74.0% , $P = 0.74$), use of stents (96.2 vs 95.0% , $P = 0.80$), and the final rate of TIMI 3 flow (84.6 vs 84.3% , $P = 0.96$) between the oldest-old group and the younger group. The overall in-hospital mortality was significantly higher in the oldest-old group than the younger group (26.9 vs 11.4% , $P < 0.001$). When compared by baseline Killip class, the in-hospital mortality of the oldest-old was similar in the Killip class-II (5.3 vs. 2.9% , $P = 0.39$), but was significantly higher in the Killip class III-IV (85.7 vs 42.3% , $P < 0.001$). The final rate of TIMI 3 flow and the baseline Killip class III-IV were identified as independent predictors of the in-hospital mortality of the oldest-old patients.



In-hospital mortality by the Killip class

Conclusions: In oldest-old patients with acute STEMI following primary PCI, the in-hospital mortality was not inferior to the younger patients in the low Killip class. A high Killip class and low final rate of TIMI3 flow predict an unfavorable outcome in the oldest-old patients treated with primary PCI.

P2641 | BEDSIDE

Outcomes of STEMI patients with heart failure and multivessel disease: arguments for preventive angioplasty beyond PRAMI

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Objective: To identify a subgroup of high-risk patients who might benefit from preventive revascularization according to heart failure (HF) at admission.

Background: In ST-segment elevation myocardial infarction (STEMI) patients with multivessel disease (MVD), treatment of non-infarct related coronary arteries may reduce the risk of events compared with treating only the culprit artery.

Methods: Prospective, observational registry of 1 963 STEMI patients consecutively treated with primary PCI between February 2007 and September 2013; 1788 patients with Killip class I to III and only infarct responsible artery treatment were included. The primary end-point was in-hospital cardiac mortality (IHCM). Secondary end-points included 1-year major adverse cardiac events (MACE: cardiac death, non-fatal myocardial infarction, and revascularization of the non-infarct related artery).

Results: In patients without HF (Killip I) at admission, MVD was not associated with IHCM (0.5% single-vessel disease (SVD) vs. 1.2% MVD; $p = 0.24$) or 1-year MACE (1.1% SVD vs. 2.4% MVD; $p = 0.05$). In contrast, MVD was associated with a 6-fold higher IHCM (1.6% SVD vs. 9.6% MVD; $p = 0.005$) and a 5-fold higher 1-year MACE (2.4% SVD vs. 12.8% MVD; $p = 0.001$) in STEMI patients with Killip II-III. In patients with MVD, Killip II-III at admission was the strongest predictor of IHCM (RR 5.19 CI: 95% 2.35-11.41; $p < 0.001$). Image A shows in-hospital death from cardiac causes and image B shows MACE at one year follow-up according to Killip class.

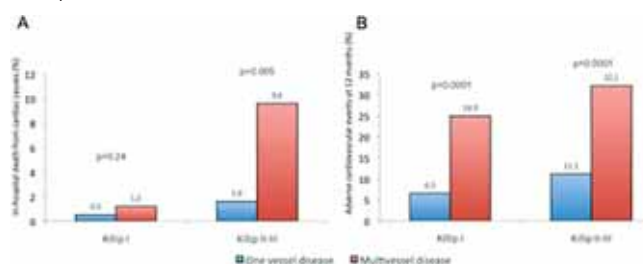


Figure 1

Conclusion: In STEMI patients with MVD, HF at admission was associated with poor outcomes while in patients without HF no differences were observed irrespective of MVD. These findings could aid in the identification of patients that might benefit from preventive primary PCI.

P2642 | BEDSIDE

Atrial fibrillation during ST-elevation acute myocardial infarction: prevalence, predictors and impact in the treatment and mortality

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Purpose: To determine the incidence of the first episode of Atrial Fibrillation during hospitalization for ST elevation acute myocardial infarction (STEMI), to identify possible predictors of its onset and to assess its impact on therapy and in-hospital mortality.

Methods: We evaluated 3254 P with STEMI enrolled in a multicentre national registry. We considered two groups: P with AF and P without AF. We recorded age, gender, cardiovascular and non-cardiovascular co-morbidities, results of coronary angiography, number of angioplasties performed, in-hospital and at discharge therapy. We evaluated left ventricular ejection fraction (EF) and the presence of the following complications: heart failure (HF), need for mechanical ventilation, stroke, major bleeding and high grade atrio-ventricular block. We compared the in-hospital mortality and performed multivariate analysis to identify predictors of the incidence of AF and to assess the impact of AF in in-hospital mortality.

Results: The incidence of AF in STEMI was found in 6.1% (197 P). Patients with AF were older (71 ± 12 vs 62 ± 14 years, $p < 0.001$), more females (34.5% vs 24.4%, $p = 0.002$), had higher prevalence of hypertension (72.4% vs 59.6%, $p < 0.001$), valvular heart disease (3.7% vs 1.1%, $p = 0.008$), previous HF (5.6% vs 1.8%, $p = 0.002$) and chronic renal failure (6.2% vs 2.8%, $p = 0.007$). There were no differences in the number and type of vessels with disease. Patients with AF received more therapy during hospitalization and at discharge with vitamin K antagonists (7.7% vs 1.5% and 12.3% vs 2.5%, $p < 0.001$), loop diuretics (59.4% vs 24.3% and 51.3% vs 19.3%, $p < 0.001$), aldosterone antagonists (27.0% vs 12.0% and 25.0% vs 11.1%, $p < 0.001$), amiodarone (67.9% vs 4.1% and 37.4% vs 1.6%, $p < 0.001$) and digoxin (10.2% vs 0.3% and 2.6% vs 0.3%, $p < 0.05$). AF was associated with worse EF ($p < 0.001$), higher prevalence of worsening HF (46.2% vs 16.2%, $p < 0.001$), need for mechanical ventilation (10.7% vs 3.4%, $p < 0.001$), stroke (4.6% vs 0.8%, $p < 0.001$), high grade atrio-ventricular block (12.7% vs 5.4%, $p < 0.001$) and major bleeding (6.1% vs 1.8%, $p < 0.001$). In-hospital mortality was higher in P with AF (13.7% vs 4.6%, $p < 0.001$), however, by multivariate analysis the presence of AF wasn't an independent predictor of in-hospital mor-

tality. There were identified as independent predictors of AF: age and previous history of HF.

Conclusions: In our population of P with STEMI, the incidence of AF was 6.1% and is associated with an increased prevalence of in-hospital complications and mortality. The age and previous history of HF were identified as independent predictors of AF.

P2643 | BEDSIDE

Gender and age effects on in-hospital mortality of ST-elevation myocardial infarction: a nationwide registry study

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Purpose: Previous studies have suggested that women may have higher mortality than men after myocardial infarction. We studied gender and age differences in in-hospital mortality of ST-elevation myocardial infarction (STEMI).

Methods: In-hospital mortality of all STEMI admissions (n=27 993) of patients aged ≥30 during 2001-2008 in 22 hospitals with a coronary angiography was studied. Data was collected from national hospital discharge registry (FHDR). Admissions with STEMI as primary (91%), secondary (7%) or tertiary (2%) discharge diagnosis were included. Hospital transfers during the same treatment period (14% of admissions) were combined. Majority (66%) of patients were men. The median age was 69 years.

Results: Total in-hospital mortality rate of STEMI was 11.9% (95%CI 11.5-12.3%). Women had higher unadjusted mortality rate than men (HR 1.59; 95%CI 1.49-1.70, p<0.0001). However, when adjusted for age and co-morbidities, there was no difference in mortality between genders (HR 1.00; 95%CI 0.93-1.07, p=0.90). Mortality was highly dependent of age, with an estimated increase of 36% (95%CI 33-38%) per 5-year increase in age (p<0.0001). STEMI was complicated by ventricular arrhythmia/resuscitation or pneumonia/septicemia more commonly in men. In contrast, women had anterior infarction more commonly. Additional independent predictors of in-hospital mortality in multivariate regression analysis were ventricular arrhythmia/resuscitation (HR 2.05; 95%CI 1.73-2.43, p<0.0001), pneumonia/septicemia (HR 1.17; 95%CI 1.02-1.33, p<0.05), peripheral artery disease (HR 2.30; 95%CI 1.81-2.93, p<0.0001), malignancy (HR 1.80; 95%CI 1.42-2.28, p<0.0001), neurological or neurovascular disease (HR 1.73; 95%CI 1.46-2.05, p<0.0001) and diabetes (HR 1.17; 95%CI 1.03-1.33, p<0.05). In-hospital mortality of STEMI was reduced during 2001-2008 by estimated 3.5% (95%CI 2.0 - 4.9%) per year (p<0.0001).

Conclusion: In-hospital mortality of STEMI does not appear to be affected by gender itself, but increases significantly with age and co-morbidities.

P2644 | BEDSIDE

Prognosis of acute myocardial infarction associated to occlusion of the circumflex artery

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Background and aim: In the context of ST elevation myocardial infarction (STEMI) the traditional 12-lead electrocardiogram is sometimes not sufficient to detect the occlusion of the circumflex artery (CX). The European guidelines recommend the realization of V7, V8 and V9 leads in patients who present with chest pain and without significant electrocardiographic changes.

In daily clinical practice of emergency department those leads are rarely made. We intend to compare whether patients with acute myocardial infarction (AMI) secondary to occlusion of the CX are more often diagnosed with non-ST elevation myocardial infarction (NSTEMI) compared with patients with AMI due to occlusion of other epicardial arteries and assess whether this group of patients not undergoing primary angioplasty, has a worse in-hospital prognosis.

Methods: We analysed 2306 patients included in a prospective national registry of Acute Coronary Syndromes with admission diagnosis of AMI between 01/10/2010 and 01/10/2013 and who had occlusion of one major epicardial coronary artery in the coronary angiography which was considered the culprit lesion. Patients were divided into 3 groups according to the occluded artery: Group 1 – left anterior descending artery (LAD); Group 2 – CX; Group 3 – right coronary artery (RCA). Each group was divided into 2 subgroups according to the classification of the AMI: Subgroup A: NSTEMI and B: STEMI.

Results: Of the 2306 patients, 1014 (44%) were included in group 1, 384 (16.7%) in group 2 and 908 (39.4%) in group 3. The % of patients with an epicardial artery occlusion (culprit lesion) and classified as NSTEMI in groups 1, 2 and 3 was 30.8, 37.7 and 31.5, respectively. In-hospital mortality in groups 1 and 3 was higher for subgroups B when compared with their homonyms of subgroup A (7 vs 0.7%, p=0.004; 4.6 vs. 0%, p=0.009, respectively) while for group 2 there was no statistically significant difference between the 2 subgroups (4.8 vs 1.7%, p=0.101).

Among the subgroups B, there was a tendency for performing primary angioplasty later in patients with occlusion of the CX when compared with occlusions of LAD and RCA (door balloon time: 165', 156' and 148', respectively, p=0.08).

Conclusion: Patients with AMI due to occlusion of the CX are most often classified as NSTEMI, with consequent delay in revascularization. It should be rein-

forced the importance of the realization of V7, V8 and V9 leads in any patient with chest pain and no significant electrocardiographic changes.

P2645 | BENCH

Prognostic importance of tricuspid annular plane systolic excursion in acute myocardial infarction with ST segment elevation

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Tricuspid annular plane systolic excursion (TAPSE) is method to a measure the distance of systolic excursion of the right ventricular (RV) annular segment along its longitudinal plane. TAPSE represents longitudinal function of the RV, in the same way as mitral annular plane systolic excursion by Doppler tissue imaging does with the left ventricle. TAPSE is applied for quantitative of the myocardial contractility of RV and depends on ejection fraction of left ventricle (LVEF) as well.

The aim of this study is to evaluate the prognostic importance of TAPSE in acute phase of left ventricular inferior wall ST elevation myocardial infarction (STEMI). Subjects were 136 patients with left ventricular inferior wall STEMI who were admitted to hospital within 6 hours of the first symptoms of STEMI and treated by intravenous thrombolytic agents and/or coronary angioplasty. The echocardiographic examination was done within 48 hours of STEMI onset to measure LVEF and TAPSE. TAPSE was measured as the total distance displacement of the tricuspid annulus from end-diastole to end-systole.

The study subjects were divided into 2 groups, according to the TAPSE values. 58 patients fall into group A with TAPSE value ≤14 mm and 78 patients fall into group B with TAPSE value ≥14 mm. All subjects were taken into the 10 days hospital follow up.

There were no significant differences in basal characteristics of patients (age, male/female gender, % of hypertension and diabetes mellitus).

In-hospital mortality rate was significantly greater in group A (5/58 pts.-8.62%) than in group B (4/78 pts. - 5.12%) (p<0.05). Several ventricular arrhythmias and atrial fibrillation were observed in 19/58 patients of group A (32.7%) and in 11/78 patients of group B (14.1%) (p<0.05).

Incidence of sinoatrial and atrioventricular II-III degree blockades were significantly higher in group A (10/58 pts. - 17.24% vs. 6/78 pts. - 7.69%) (p<0.05).

There were no significant differences in LVEF values between patients groups. The incidence of right ventricular involvement in inferior wall STEMI is significantly higher in group A (3/58 pts. - 53.44%) than in group B (14/78 pts.- 17.94%) (p<0.01).

Patients with inferior wall STEMI and right ventricular myocardial infarction (RVMI) had significantly lower TAPSE value (16.7±1.9 mm) than patients without RVMI (21.9±2.1 mm) (p<0.01).

In acute phase of inferior wall STEMI TAPSE value ≤14mm is associated with higher in-hospital mortality and severe complications. TAPSE was significantly lower in patients with RVMI than in patients without RVMI and these patients have a worse prognosis.

P2646 | BEDSIDE

One year re-infarction rates in non-culprit vessels following index ST elevation myocardial infarction in patients with multivessel coronary artery disease

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Background: Recent clinical trials have re-emphasised the potential benefit of complete revascularisation including stenting of non-culprit lesions in the setting of acute ST segment elevation myocardial infarction (STEMI). Real world data on the outcome of such patients are lacking.

Purpose: To assess the number of patients with an index STEMI and multivessel coronary artery disease (MVCAD) that subsequently re-infarct or require urgent revascularisation to a previously non-culprit vessel within 1 year.

Methods: We analysed all patients receiving primary percutaneous coronary intervention (PPCI) for STEMI at our large teaching trust covering two interventional sites between January 2008 and January 2013. Outcomes were determined by matching patients to the hospital trust clinical data archive (CDA), and through our local British Cardiovascular Intervention Society (BCIS) database to ensure capture of all re-admissions to our trust for NSTEMI, recurrent STEMI and unstable angina (UA) after the index STEMI.

Results: A total of 1121 patients (mean age 62±14, 75% male) were included in the analysis. Of them, 373 (33%) had severe multivessel disease (defined as the presence of stenoses ≥75% in at least 2 epicardial arteries or 50% in the left main stem). Within the following year 16 patients (4.3%) with severe MVCAD were re-admitted for urgent intervention, 12 (3.2%) due to another myocardial infarction (5 with STEMI and 7 with non-STEMI) and 4 due to UA requiring intervention. A non-culprit vessel was the target for revascularisation in 8 (2.1%) patients. Sixteen patients (4.5%) without subsequent re-infarction received planned revascularisation. In PRAMI the non-fatal MI rate in those not receiving preventive PCI was 8.7% (median follow up 23 months).

Conclusion: In this unselected STEMI population, the event rate in the first year after infarction is lower than in PRAMI. Specifically, re-infarction within one year

following an index STEMI involving a previously non-culprit vessel is relatively low. Planned revascularisation of non-culprit vessels in a timely manner may explain this finding.

P2647 | BEDSIDE

Survival in patients with ST-segment elevation myocardial infarction and significant versus non-significant coronary artery disease

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Purpose: There is limited knowledge on the prognosis of patients presenting with suspected ST-segment elevation myocardial infarction (STEMI) and non-significant coronary artery disease (CAD) where revascularization therapy is not indicated. We aimed to study survival in patients with suspected STEMI and significant versus non-significant CAD.

Methods: We included all patients receiving acute coronary angiography (CAG) with suspected STEMI at a high-volume PCI center during a 3.5 year period (2009-2013). Significant CAD was defined as coronary artery stenosis diameter $\geq 50\%$ with indication for revascularization or, if not technically possible, medical treatment. Non-significant CAD was defined as either a normal CAG or CAD with coronary artery stenosis diameter $<50\%$ with no indication for revascularization. Patients were followed from the time of CAG to the event of death or end of study period. The Kaplan-Meier method was used to estimate survival probabilities. Cox regression was used to assess the association between significant versus non-significant CAD and the risk of death during follow-up.

Results: We included 3,407 patients with suspected STEMI, of which 418 patients (12%) had non-significant CAD. The median follow-up time was 460 days (inter quartile range 186-733 days). Compared to patients with significant CAD, patients with non-significant CAD were younger and more frequently women with a lower body mass index and a lower prevalence of hypertension, smoking, and family history of ischemic heart disease. The risk of death within 30 days and 3 years was 3% (95% confidence interval [CI] 1-4%) and 13% (95% CI 8-17%) for patients with non-significant CAD compared to 7% (95% CI 6-8%) and 17% (95% CI 15-19%) for patients with significant CAD. Having non-significant CAD was associated with a lower risk of death (hazard ratio [HR] 0.69 [95% CI 0.49-0.96], $p=0.028$). However, after adjusting for age this was no longer statistically significant (HR 0.82 [95% CI 0.59-1.14], $p=0.237$). Additional adjustment for gender and multiple cardiovascular risk factors did not change the association further (HR 1.16 [95% CI 0.75-1.81], $p=0.501$).

Conclusion: In a large single center study of patients with suspected STEMI, we found no difference in short- or long-term survival between patients with significant versus non-significant CAD when the age difference between the two groups was taken into account. This finding suggest that acute chest discomfort in combination with ST-segment elevation but with absence of significant CAD is not trivial and may warrant further medical attention.

P2648 | BEDSIDE

Comparison of the ability of CADILLAC and TIMI risk scores to predict short- and very long-term mortality in STEMI patients undergoing primary PCI

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Purpose: Early risk stratification in STEMI patients is of prognostic and therapeutic importance. Our aim was to compare the ability of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) and the Thrombolysis In Myocardial Infarction (TIMI) risk scores to predict short- and very long-term mortality in patients undergoing primary PCI.

Methods: We examined 845 consecutive STEMI patients who underwent primary PCI in a high-volume catheterization laboratory in 2009. Separate logistic regression models were created for CADILLAC and TIMI risk scores. Predictive accuracy of both models was assessed by comparing ROC curves.

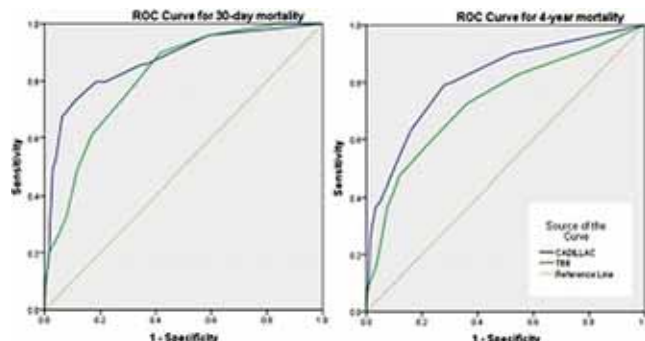


Figure 1. ROC curves

Results: Overall mortality at 30 days and four years was 5.8% and 20.1% respectively. CADILLAC risk score showed strong predictive accuracy for both 30-day and four-year mortality ($C=0.87$, 95%CI: 0.85-0.89 and $C=0.81$, 95%CI: 0.78-0.84). Albeit less accurate, TIMI risk score was also predictive of 30-day ($C=0.82$, 95%CI 0.79-0.84) and four-year mortality ($C=0.73$, 95%CI: 0.7-0.77). Comparison of ROC curves showed more accurate predictivity of the CADILLAC risk score, as compared to the TIMI, for four-year mortality ($p=0.0005$), and a trend towards better predictivity for 30-day mortality ($p=0.066$). At 30-days the Hosmer-Lemeshow test revealed good model fit for the CADILLAC ($p=0.51$), but poor agreement of predicted and observed mortality for the TIMI risk score ($p=0.063$). At four years both CADILLAC and TIMI had good model fit ($p=0.44$ and $p=0.16$, respectively).

Conclusion: Both TIMI and CADILLAC risk scores appear to be accurate predictors of short- and very long-term mortality in STEMI patients undergoing primary PCI. CADILLAC risk score appears to have more discriminatory power than TIMI risk score, at both 30 days and four years.

ACUTE CORONARY SYNDROMES – MEDICAL THERAPY AND COMORBIDITIES

P2650 | BEDSIDE

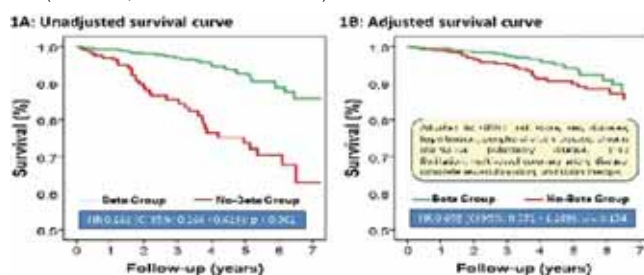
Should we recommend the use of betablockers in patients with preserved left ventricular ejection fraction after an acute myocardial infarction treated with primary angioplasty?

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Objective: The aim of this study was to analyze if betablockers after a ST-elevation myocardial infarction (STEMI) in patients with preserved left ventricular ejection fraction (LVEF) reduces mortality in the current era of primary angioplasty.

Methods: This was a retrospective analysis which included 820 consecutive STEMI patients discharged with preserved LVEF $\geq 50\%$. We assessed the incidence of death during follow-up (median 3.3 years, interquartile range 1.9 - 5.3 years) using multivariate Cox regression models, stratifying by GRACE risk groups and success of percutaneous coronary intervention (PCI).

Results: Betablockers were given in 78.5% of patients, in who the mortality rate was lower (5.6% vs 19.3) in comparison with no-betablocker group. After multivariate analyses, betablocker use was not a significant independent predictor of follow-up mortality (Hazard Ratio [HR] 0.658, 95% Confidence Interval [CI] 0.371 to 1.169). After stratifying by GRACE risk categories and by success of PCI, post-discharge betablocker therapy showed a protective effect only in high-risk patients (HR 0.262, CI 95%: 0.164 to 0.419) and in those with incomplete revascularization (HR 0.468, CI 95%: 0.227 to 0.967).



Survival BB vs NoBB.

Conclusions: The only subgroups of post-STEMI patients with preserved LVEF underwent primary PCI that have long-term benefit in reducing mortality are those at high GRACE risk and those with incomplete revascularization.

P2651 | BEDSIDE

LDL cholesterol levels in asymptomatic post-ACS patients remain above ESC targets despite statin treatment

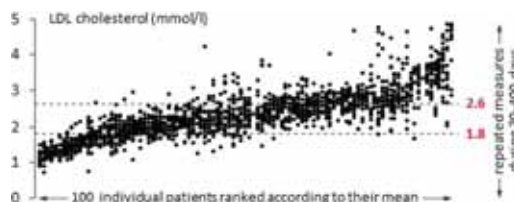
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Background: Limited data are available on LDL cholesterol levels during one year follow-up in asymptomatic patients stabilised after acute coronary syndrome (ACS) admission treated with statins.

Purpose: Describe 1-year LDL patterns in asymptomatic post-ACS patients treated with statins.

Methods: BIOMarCS is an observational study of ACS patients in 18 hospitals in our country. Treatment is left to the discretion of the physician. During 1 year follow-up, 20 repeat non-fasting blood samples are taken at preset time intervals. Serum and plasma are separated and stored on site at -80°C within 2h, until batch analysis in the central laboratory of the Erasmus MC. This abstract describes 100 patients treated with statins, who remained free of death, readmission for ACS, coronary revascularisation and anginal symptoms until 400 days. We determined LDL with the Roche Cobas c system in their repeated samples.

Results: Mean age was 65 (SD 5) years, 79% were men, 64% had STE-ACS. Patient profile was typical for an ACS population. In the 400-day period a total of 1691 blood samples were collected, with a median of 18 (IQR 15 to 19) per patient. Median LDL was 2.31 (IQR 1.93 to 2.74) mmol/l. LDL above 1.8 mmol/l was observed in 81% of samples; levels above 2.6 mmol/l were found in 33% of samples (in 64% of patients). The within-patient variability was related to their mean LDL level (figure), but, within patients, LDL varied randomly between follow-up visits. Overall, the within-patient variability explained 30% of total variation and was thus smaller than the between-patient variability. (Data on total and HDL cholesterol are available).



Conclusions: Asymptomatic post-ACS patients treated with statins do not reach LDL targets recommended by the ESC guidelines.

P2652 | BEDSIDE

Long-term outcomes in patients switching from angiotensin-converting-enzyme inhibitors to angiotensin receptor blockers after incident ST elevation myocardial infarctions

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Purpose: Angiotensin-converting enzymes inhibitors (ACEI) are recommended for patients with ischemia heart disease to reduce the risk of death and nonfatal cardiovascular events. Angiotensin receptor blockers (ARB) are the alternatives for patients intolerant to ACEI. It is not known whether the ARB users switched from ACEI is as effective as non-switchers. We conducted a nationwide cohort study to evaluate the effectiveness of ARB on survivors of acute ST-elevation myocardial infarction (STEMI) in Taiwan.

Methods: A population-based inception STEMI cohort was constructed by using the Taiwan National Health Insurance claims data between year 2002 and 2010. Only survivors of the first STEMI with ACEI treatment during and after the index hospitalization were included. We excluded patients who had ever been treated with ACEI/ARB within one year preceding the STEMI, and was treated with ARB before ACEI prescription. Outcome was defined any cause of death after index hospitalization. Cox proportional models adjusting for sex, age, years of hospitalizations, comorbidities and medication was applied to estimate the effects of ARB on all-cause mortality. Inverse probability treatment weighting was then incorporated to deal with time-varying exposure.

Results: Total 17,498 patients were received ACEI therapy after index hospitalization, including 4,575 ARB switchers. Cumulative incidence of deaths was 2.75% in ARB switchers and 3.53% in non-switchers ($P=0.012$). Considering the covariates of genders, ages, year of index hospitalization, duration of hospitalization, comorbidities and medication, ARB did not significantly reduced the risk of death (HR, 0.86; 95% CI, 0.71 to 1.05; $p=0.131$) with inverse probability treatment weighting.

Conclusion: Among the patients with ST-elevation myocardial infarction, there were no differential effects of ARB switchers on all cause of death, as compared to ACEI therapy.

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Impact of beta-blocker therapy on long-term mortality after a non-ST-elevation acute coronary syndrome in patients with preserved left ventricular ejection fraction in the PCI era

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Background: Although BB therapy is widely recommended for indefinite long-

term use in all patients who recover from Acute Coronary Syndrome (ACS) and do not have contraindications, these recommendations are based mainly on evidences obtained before the reperfusion and thrombolytic eras. Little data exist in the current era of PCI, particularly in patients with Non-ST-Elevation ACS (NSTEMI-ACS) with preserved left ventricular ejection fraction (LVEF).

Aim: To evaluate the impact of BB after a NSTEMI-ACS in patients with preserved LVEF.

Methods: To address this hypothesis, we performed a retrospective analysis in contemporary registry of 1,139 consecutive NSTEMI-ACS patients (80.2% with Non-ST-Elevation Myocardial infarction [NSTEMI] and 19.8% with unstable angina [UA]) with LVEF $\geq$ 50% underwent PCI. We performed multivariate Cox regression models to evaluate the association between BBs and mortality during follow-up (median 3.1 years, interquartile range 1.7-5.0 years), stratifying by type of NSTEMI-ACS, GRACE risk groups, and degree of revascularization.

Results: BBs were given in 71.6% of patients, in who the mortality rate was lower (5.6% vs 19.3%). After multivariate analyses, BB use showed a protective effect in follow-up mortality (Hazard Ratio [HR] 0.468, 95% Confidence interval [CI] 0.323 to 0.678). Stratifying by subgroups, post-discharge BB therapy maintained its protective role only in patients with NSTEMI (HR 0.428, CI 95%: 0.288 to 0.637) and in those with high GRACE risk (HR 0.456, CI 95%: 0.277 to 0.750). Moreover, the association of BBs with lower long-term mortality was maintained in both groups of complete and incomplete revascularization.

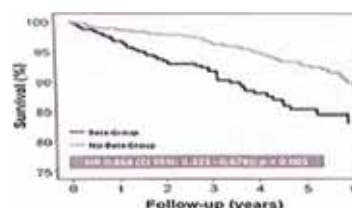


Figure 1

Conclusion: Our study provides new evidence for NSTEMI-ACS guidelines according the protective effect of post-discharge BBs in patients with preserved LVEF.

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Medical therapies in the emergency setting of patients not undergoing invasive workup

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Purpose: Patients with acute coronary syndrome (ACS) do not necessarily undergo coronary angiography and are managed acutely in a noninvasive manner. We investigate how soon evidence based secondary prevention therapies should be started after an ACS in this population.

Methods: The study populations consisted of 8214 ACS patients, of these 4156 patients (42.0% non ST-elevation (STE) ACS and 58.0% STE-ACS patients) that did not received reperfusion treatment. Patients were admitted at 57 hospitals reporting data to the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC) registry (ClinicalTrials.gov, NCT01218776), from October 2010 to February 2014. We assessed the use of beta-blockers, statins and angiotensin-converting enzyme inhibitors in the emergency setting, (within 24 hrs since hospital admission) and their effects on in-hospital incidence of death.

Results: There were 2451 patients that received all 3 drugs in the emergency setting (group 3), 982 patients with 2 medications (group 2), 384 patients with 1 medication (group 1) and 252 patients that did not receive any drugs (group 0). The mortality rate was 4.8%, 11.1%, 29.2% and 65.7% in group 3, 2, 1 and 0, respectively. Benefits were observed both in non STE-ACS (incidence of mortality: 3.0%, 9.0%, 19.7%, and 58.7%, in group 3, 2, 1 and 0, respectively) and in STE-ACS (incidence of mortality: 6.1%, 13.1%, 34.7%, and 68.8% in group 3, 2, 1 and 0, respectively). The advantage of multiple combination of prevention therapies was confirmed by multivariable analysis. The absolute risk reduction was of greater magnitude and statistical significance ($p<0.001$) in those patients with non STE-ACS (adjusted OR: 0.11, 95%CI: 0.04-0.26) than in those with STE-ACS (adjusted OR: 0.07, 95%; 0.04-0.11).

Conclusions: Concomitant use of secondary prevention therapies in the emergency setting is associated with reduced of in-hospital mortality for those ACS patients not undergoing invasive workup.

P2655 | BEDSIDE**ApoA1 is independently associated with recurrent ischemic events and death in acute coronary syndrome patients**

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Background: Apolipoprotein A1 (ApoA1), the main protein component of high density lipoprotein (HDL) cholesterol, is inversely related to coronary heart disease and stroke. Little is known about ApoA1 levels on admission in patients with acute coronary syndrome (ACS) and relation to subsequent ischaemic events.

Methods: ApoA1 levels were measured (immunoturbidimetric analysis (Architect), Apolipoprotein A1 kit, Abbott) in non-fasting plasma samples collected within 24 h after admission in 14,938 ACS patients in the PLATOlet inhibition and patient Outcomes (PLATO) trial and evaluated as a predictor of the occurrence of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI) and non-haemorrhagic stroke, and its individual components as well as all-cause mortality. A Cox proportional hazards regression model was used including established and newer risk factors for CV disease (age, gender, diabetes, heart failure, previous MI, non-haemorrhagic stroke, peripheral artery disease, previous CABG, previous PCI, hypertension, smoking, troponin I, cystatin C, NT-proBNP), ACS subtype (STEMI, NSTEMI-ACS), randomized treatment (ticagrelor, clopidogrel) and statin treatment on admission.

Results: During 12 months follow-up, the composite endpoint occurred in 951 patients. Mean ApoA1 level was 1.02 (0.26 SD) g/L. Higher ApoA1 was associated with a lower risk of the composite endpoint, and the individual occurrence of CV and all-cause death. ApoA1 was not associated with risk of MI or stroke alone.

HRs for 1 SD increase of ln ApoA1 levels in relation to outcome

	Hazard ratio	95% confidence interval	p-value
ACS (n=14,938)			
CV death/MI/stroke	0.89	0.83–0.95	<0.001
MI	0.93	0.85–1.02	0.112
CV death	0.83	0.75–0.92	<0.001
Stroke	0.83	0.69–1.01	0.059
All-cause death	0.81	0.74–0.89	<0.001

Conclusions: In a large cohort of ACS patients, higher ApoA1 levels predicted ischaemic events independently of CV disease risk factors. ApoA1 seems to add incremental information on risk for coronary events and death beyond traditional and newer risk factors in patients with ACS.

P2656 | BEDSIDE**Prognosis of new-onset atrial fibrillation in patients with acute coronary syndrome**

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Background: Few studies have previously explored the potential prognostic role of different types of atrial fibrillation (AF) in patients with acute coronary syndrome (ACS). We conducted a retrospective cohort study to determine the prevalence and the prognostic implications of new-onset AF in patients with ACS admitted to a Coronary Care Unit (CCU).

Methods: We analyzed 5,640 patients with ACS admitted to a CCU (STEMI 2,690 and NSTEMI 3,130) and identified patients with preexisting, new-onset (AF at the moment of admission or developed during CCU stay) or no AF, to determine the incidence and prognosis at the CCU in the setting of ACS.

Results: A total of 299 patients were diagnosed with AF (5.1%). Preexisting AF accounted for 2% of these cases, whereas new-onset AF constituted 3.1% of the cases (AF at admission, 1%; AF at the CCU, 2.1%). The prevalence of AF at the CCU in patients with STEMI was 2.6% and 1.7% in the NSTEMI group. All-cause mortality was significantly higher in the groups with AF at the CCU (15.1%) or preexisting AF (12.1%), in comparison to patients with AF at the moment of admission (3.1%) or without AF (5.2%, $P=0.001$). The risk of death (OR 3.23, CI 95% 1.93-5.92), stroke (OR 6.18, CI 95% 1.83-20.87), cardiogenic shock (OR 3.28, CI 95% 1.63-6.62), inotropic requirements (OR 4.07, CI 95% 2.61-6.33) and vasopressors requirements (OR 4.89, CI 95% 3.3-7.23) was higher in patients with new-onset AF that developed during the CCU stay.

Conclusions: The presence of AF among patients with ACS has different prognostic implications. The new-onset AF developing during the CCU stay is probably a marker of severity and may be used as an independent predictor of all-cause mortality.

P2657 | BEDSIDE**Relative reduction of one-year mortality over the past 15 years in AMI patients is less in patients developing atrial fibrillation at the acute stage. Results from the FAST-MI programme**

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Background and aim: Development of atrial fibrillation (AF) at the acute stage of myocardial infarction (AMI) has been shown to be associated with a poorer prognosis. However, the extent to which both incidence and prognosis of AF during AMI have changed over the past decades has not been evaluated so far.

Methods: We analysed 30-day and one-year mortalities, through 4 nationwide French surveys carried out 5 years apart from 1995 to 2010 (FAST-MI programme), in relation with the development of AF during AMI. Among the 10588 consecutive STEMI and NSTEMI patients (≤ 48 hours from onset) enrolled over one-month periods, 787 (7.4%) developed AF.

Results: From 1995 to 2010, the proportion of patients developing AF decreased markedly (1995: 12.1%, 2000: 8.4%, 2005: 5.7%, 2010: 5.1%, $P<0.001$). Mean age remained stable in non-AF patients (1995: 66 ± 14 years, 2010: 65 ± 14 years, $P=0.92$), and in AF patients (1995: 75 ± 10 years, 2010: 74 ± 13 years, $P=0.58$). Thirty-day mortality significantly decreased in both non-AF (11.9 to 3.4%, $P<0.001$) and AF groups (19.6 to 8.2%, $P<0.001$). One-year mortality also significantly decreased in non-AF patients, from 17% in 1995 to 8% in 2010 (adjusted HR=0.47, 0.39-0.55, $P<0.001$), but the decrease was not significant in AF patients, from 30% in 1995 to 21% in 2010 (adjusted HR=0.72, 0.47-1.09, $P=0.12$). Re-AMI (2.5 to 1.0% vs 2.1 to 3.8%) and stroke (0.9 to 0.4% vs 1.5 to 0.6%) decreased significantly in non-AF but not in AF patients. Consistent trends in incidence and prognosis were found when stratified by age, sex or type of AMI.

Conclusion: The incidence of AF at the acute stage of MI decreased markedly over time. The relative reduction of mortality was less pronounced in patients with AF, suggesting room for further improvement.

P2658 | BEDSIDE**Effect of socioeconomic status on mortality in patients after acute myocardial infarction**

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Objectives: The purpose of this observational study was to evaluate the prognostic effects of socioeconomic status on mortality after hospitalisation for acute myocardial infarction (AMI) in Gothenburg metropolitan area in Western Sweden.

Methods: Data were obtained from the SWEDEHEART registry (Swedish Web-system for Enhancement of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) for patients hospitalized for ST-elevation myocardial infarction (STEMI) and non-STEMI in the city of Gothenburg in Western Sweden. Between 1995-2013, 41825 patients (43% female) were hospitalized in the three city hospitals. Of these, 10895 (36% female) were treated for AMI. The AMI patients were divided in low (N=4280), middle (N=3570) and high (N=3048) group according to the tertiles of income and education based on the city area where they lived. The groups were compared using Cox proportional hazards regression with multilevel modelling to account for clustering of patients within different hospitals. Adjustments for differences in baseline characteristics were made for the following: age, gender, smoking habits, hypertension, diabetes, hyperlipidaemia, previous CABG, previous PCI, revascularisation treatment, STEMI and calendar year.

Results: There were 37.6% patients with STEMI and 62.4% with non-STEMI. The mean follow-up time was 5.4 years. The patients in the lowest income/education group were younger and were more likely to have diabetes, smoking and previous AMI (all $P<0.01$). After adjustment and compared to the high income/education group, the risk of dying was higher in both middle and low income/education group (HR 1.13, 95% CI 1.04-1.22, $P=0.03$ and 1.21, 95% CI 1.11-1.30, $P<0.001$; respectively).

Conclusions: Low socioeconomic status is associated with higher risk for long-term mortality in patients after AMI. Understanding and reducing socioeconomic disparities should be prioritised in order to improve prognosis after AMI in future.

ACUTE CORONARY SYNDROMES: COMORBIDITIES AND OUTCOMES

P2660 | BEDSIDE

The level of serum gamma-glutamyl transferase is a predictor of mortality in patients with acute myocardial infarction

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Purpose: Serum gamma-glutamyl transferase (GGT) is able to catalyse low-density lipoprotein oxidation and associated with metabolic syndrome. Therefore, an increase in serum level of GGT may be associated with adverse cardiovascular outcome in patients with ischemic heart disease. We investigated whether higher GGT levels are related with increasing mortality in AMI patients.

Method: A total of 2213 AMI patients were consecutively enrolled in the COREA-AMI (Convergent Registry of cAtholic and chonnAm university for AMI) registry after the exclusion of patients with acute liver injury. Patients were divided into 2 groups according to normal (n=1961) or elevated levels of serum GGT (n=252). The primary clinical outcome was all-cause mortality. For validation of survival data, the vital status was obtained in 100% of patients from the Office of Statistics, Korea.

Result: Both groups showed similar demographic and angiographic characteristics. Patients with elevated GGT levels revealed significantly higher all-cause mortality during 6.6 year of follow-up (20.6% vs 14.3%, $P=0.006$). The multivariate Cox proportional hazards model identified the increased serum GGT level as an independent correlate of long-term mortality (hazard ratio 1.53, 95% confidence interval 1.01-2.31, $p=0.044$). In subgroup analysis, stronger associations were observed among the subjects presenting with ST elevation myocardial infarction, low level of HDL cholesterol, pre-diabetes range of HbA1c (from 5.7% to 6.4%) and female gender.

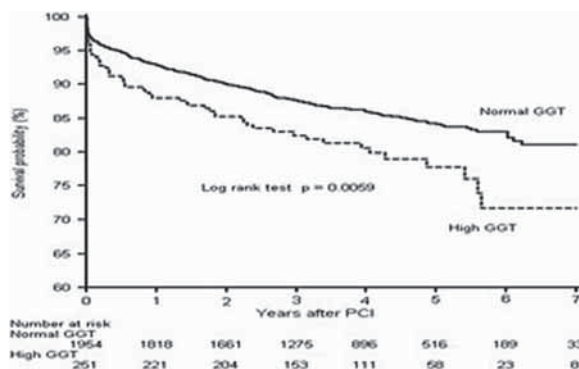


Figure 1. Survival indexed PCI

Conclusion: The elevated serum GGT level is an independent predictor of long-term mortality in patients with AMI, especially the patients with ST elevation myocardial infarction, low level of HDL cholesterol, pre-diabetes range of HbA1c and female gender.

P2661 | SPOTLIGHT

Association of peripheral-blood transcriptome with prognostic markers of myocardial damage assessed by cardiovascular magnetic resonance after reperfusion ST-elevation myocardial infarction

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Purpose: Aim of the present study was to identify associations of global gene expression in peripheral blood mononuclear cells (PBMC) with established cardiovascular magnetic resonance (CMR) markers of myocardial damage and prognosis after ST-elevation myocardial infarction (STEMI).

Methods: We enrolled 100 patients with STEMI (70.0% men, age 60.8 ± 11.9 years) after primary angioplasty within 12h after symptom-onset [median pain-to-balloon time 237 min (IQR 150–376)].

After reperfusion [median time interval 19.5 hrs (IQR 15–25)] whole blood was collected to perform high throughput transcriptome analysis in isolated PBMC using Illumina HumanHT-12 v4 Expression BeadChips. Subsequently, T2-weighted, SSFP-CINE, and contrast-enhanced CMR was performed within one week after infarction to assess the left ventricle ejection fraction (MR-EF), the myocardial

salvage index (MSI), and to visualize late microvascular obstruction in relation to the infarct size (late MO/IS).

Results: After pre-processing accounting for relevant confounders, expression levels of 9949 genes were analysed. Among these, expression of one gene involved in the regulation of protein stability correlated strongest with MR-EF [p -value = 1.7×10^{-5} ; false discovery rate (FDR) < 0.21]. Another four genes were associated with late MO/IS at a FDR < 0.25 (corresponding to $p < 9.4 \times 10^{-5}$). No relevant links were found for MSI. Considering the top-associated transcripts at a less stringent cut-off p -value, KEGG pathway and gene ontology enrichment analysis was performed. MR-EF was found to associate with genes involved in posttranslational protein modification (24-fold enrichment, $p = 3.0 \times 10^{-3}$) and nucleoside metabolism (5-fold enrichment, $p = 2.0 \times 10^{-2}$).

Genes correlating with late MO/IS were linked with several immunomodulatory pathways including the cellular response to calcium ion (104-fold enrichment, $p = 2.0 \times 10^{-4}$), and lymphocyte differentiation (10-fold enrichment, $p = 1.5 \times 10^{-2}$).

Conclusion: We identified several candidate gene transcripts in association with CMR-predictors of prognosis after STEMI, providing potential targets for translational research strategies.

P2662 | BEDSIDE

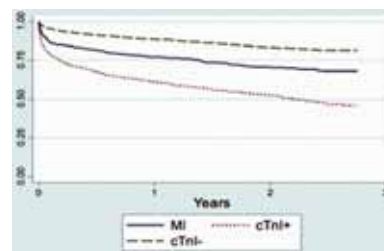
Prognostic importance of cardiac troponin in the era of the universal definition: observations from an unselected hospital cohort

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Purpose: In 2007 the universal definition of myocardial infarction (MI) was launched. We set out to study the prognostic importance of this re-definition in the setting of hospitalized pts having cardiac troponin measured for a suspected acute MI.

Methods: During a one-year period we prospectively studied unselected pts admitted to a university hospital. All pts having troponin I (cTnI) measured were included. The MI diagnosis was according to the universal definition, including typical rise/fall cTnI pattern, symptoms, ECG changes or imaging evidence of an acute MI. A cTnI value > 30 ng/L was considered the decision limit for the diagnosis of MI. Pts were followed for at least one year with all-cause mortality as the clinical endpoint. Multivariate Cox regression analysis was performed.

Results: From January 2010 to January 2011 totally 3762 qualified for inclusion. Of these 488 had MI, 1089 had cTnI > 30 ng/L but did not fulfill the MI diagnosis (TnI+), and 2185 had no cTnI elevation (TnI-). TnI+ pts were older (mean age 75 ± 14 yrs) than MI (mean age 71 ± 13 yrs) and TnI- pts (mean age 63 ± 17 yrs) ($p < 0.0001$). TnI+ pts also had significantly more co-morbidities: diabetes, renal failure, heart failure and COPD. During a median follow-up of 2.1 years 1085 pts died. Mortality differed between the groups: MI pts 31%, TnI+ pts 51%, and TnI- pts 18% ($p < 0.0001$; figure). In multivariate Cox regression analysis the hazard ratio for cTnI+ pts was 1.9 (95% CI 1.6-2.3) and for MI pts 1.5 (95% CI 1.3-1.9) when compared with cTnI- pts.



Long-term survival rate.

Conclusion: In the era of the universal definition more than two-thirds of pts with cTnI elevation do not have an acute MI. Indeed, the long-term mortality in these pts is significantly higher than in pts with a diagnosed acute MI.

P2663 | BEDSIDE

Cardiac troponin I for prediction of clinical outcomes and cardiac function through three months follow-up after primary percutaneous coronary intervention for ST-elevation myocardial infarction

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Purpose: Circulating levels of cardiac troponin I (cTnI) following ST-elevation myocardial infarction (STEMI) are associated with infarct size and chronic left ventricular dysfunction, but the relation to clinical endpoints and biochemical measures of global cardiac function remains less well-defined. The objective of this study was to investigate whether various cTnI variables were associated with clin-

ical outcomes and cardiac function through three months follow-up after primary percutaneous coronary intervention (PCI) for STEMI.

Methods: A substudy of the PROTECTION AMI trial. CTnI was measured at several time points during the index hospitalisation and patients were followed for three months before reassessment including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and left ventricular ejection fraction (LVEF) measurements. In multivariable regression models with a composite clinical endpoint (death, cardiogenic shock during the index hospitalization, congestive heart failure, or serious arrhythmia), NT-proBNP >118 pmol/L or LVEF <40% as dependent variables, different cTnI variables (admission, several post-PCI single-points, estimated peak and estimated area under curve (AUC) were tested after adjustments for age, gender, hypertension, diabetes, prior heart failure, prior MI, systolic blood pressure, heart rate, weight, Killip class category, infarct location and time from symptom onset to PCI.

Results: 1066 patients all receiving PCI within six hours were included. The median (quartile 1-3) cTnI levels were 0.4 (0.1-0.4) µg/L at admission, 33.1 (12.8-72.1) µg/L after 16-24 hours, 9.1 (3.9-17.5) µg/L after 70-80 hours and 1349 (486.1-3003) µg*hr/L for AUC. In the multivariable models for predicting clinical events, NT-proBNP >118 pmol/L or LVEF <40%, all post-PCI single-points and estimated cTnI variables were found to be independently associated to the dependent variables (p for all <0.001). The C-statistic of the clinical endpoint model improved from 0.767 (baseline model with clinical risk factors) to 0.832 when cTnI at 16-24 hours was added and 0.843 when cTnI AUC was added. Respectively, for the NT-proBNP model from 0.789 to 0.860 and 0.858, and for the LVEF model from 0.683 to 0.841 and 0.854. Quantified by the integrated discrimination improvement the addition of these cTnI variables significantly bettered prediction (p for all <0.001).

Conclusions: cTnI measurements taken after primary PCI for STEMI are associated with clinical outcomes and cardiac function through three months follow-up. These results suggest that cTnI is a useful risk stratification tool in STEMI patients.

P2664 | BEDSIDE

Maximum apnea duration is superior to apnea-hypopnea index when predicting clinical outcomes in patients with acute myocardial infarction

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Aims: We hypothesized that sleep parameters other than the apnea-hypopnea index (AHI) might have significant impacts on cardiovascular outcomes in patients with acute myocardial infarction (AMI).

This study aimed to determine the most useful sleep parameter for the prediction of unfavorable clinical outcomes.

Methods: In total, 302 first AMI patients undergoing primary percutaneous coronary intervention were included. All patients underwent polysomnography at first admission, and AHI, maximum apnea duration (MAD), lowest arterial oxygen saturation (SaO₂), time spent with SaO₂ of ≤90%, and arousal index were calculated. The primary outcome measures were cardiac death, recurrence of acute coronary syndrome (ACS), and readmission for heart failure. Major adverse cardiac events (MACE) were defined as composite end points of the individual clinical outcomes.

Results: The mean follow-up duration was 4.0±1.7 years. Patients with ACS recurrence (n=33) exhibited significantly higher AHI, MAD, and arousal index than those without. Patients with MACE (n=46) exhibited similar results. Cox regression analysis adjusted for sleep parameters, age, body mass index, hypertension, diabetes, dyslipidemia, and current smoking indicated that MAD was an independent predictor of ACS recurrence and MACE [hazard ratio = 1.018, 95% confidence interval (CI) 1.004-1.031, $p=0.009$; hazard ratio = 1.015, 95% CI 1.004-1.027, $p=0.010$, respectively]. AHI could not predictor either. The ACS-free and MACE-free survival estimates in patients with a MAD of ≥46.0 s (n=102) were significantly poorer than in those with a MAD of <46.0 s (n=200); the log-rank p values were 0.09 and 0.007, respectively.

Conclusions: The novel finding in this study is that MAD was the most useful sleep parameter for predicting long-term clinical outcomes.

P2665 | BEDSIDE

Interaction of chronic kidney disease and statin benefit could be different between 5-year mortality and re-infarction in patients who survived ST-elevation myocardial infarction

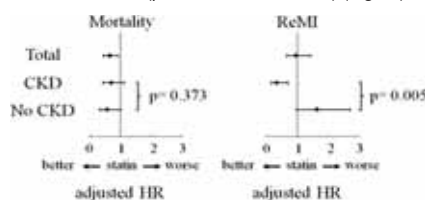
M. Hara¹, Y. Sakata², D. Nakatani¹, S. Suna¹, M. Usami¹, S. Matsumoto¹, M. Nishino³, T. Kitamura⁴, S. Hikoso¹, Y. Sakata¹ on behalf of the OACIS investigators. ¹Osaka University Graduate School of Medicine, Cardiovascular Medicine, Suita, Japan; ²Tohoku University Graduate School of Medicine, Cardiovascular Medicine, Sendai, Japan; ³Osaka Rosai Hospital, Cardiology, Sakai, Japan; ⁴Osaka University Graduate School of Medicine, Division of Environmental Medicine and Population Sciences, Department of Social and Environmental Medicine, Suita, Japan

Purpose: Statin therapy can reduce cardiovascular risk even in patients with

chronic kidney disease (CKD). However, it is unclear whether the benefit of statin therapy is different between patients with and without CKD after ST-elevation myocardial infarction (STEMI) in the contemporary percutaneous coronary intervention (PCI) era.

Methods: From the database of the Osaka Acute Coronary Insufficiency Study, the present study enrolled 2,947 consecutive STEMI patients (median 65 y.o., 78.5% male, and 92.1% underwent PCI) whose serum creatinine was measured median 19 days after the onset. CKD was defined as having estimated glomerular filtration rate <60 mL/min/1.73m². The impact of statin therapy for 5-year mortality and re-myocardial infarction (ReMI) was assessed using multivariate Cox regression analysis in patients with and without CKD. Adjusted covariates included age, gender, classical coronary risk factors, enrollment year, infarct size, KILLIP, PCI, and medications at discharge.

Results: Among study population, 1,099 patients (37.3%) had CKD. There were 190 all-cause death and 128 ReMI events during 5-year follow-up. Statin therapy was associated with lower mortality in all study population (adjusted hazard ratio (HR) 0.65, 95% confidence interval 0.45-0.93, $p=0.017$) without significant difference between patients with or without CKD (p for interaction=0.373). In contrast, statin therapy was associated with lower ReMI events only in patients with CKD, but without CKD (p for interaction=0.005) (Figure).



Clinical impact of statin therapy.

Conclusions: Our results suggested that benefit of statin therapy for ReMI was different between patients with and without CKD after STEMI in the contemporary PCI era, while it was comparable for mortality. Further study is warranted to confirm our results.

P2666 | BEDSIDE

Estimation of renal function in patients with acute coronary syndrome: different equations, different results?

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Purpose: Chronic kidney disease has an unquestionable negative impact on the prognosis of patients (P) with acute coronary syndromes (ACS). Traditionally, eGFR is estimated by MDRD equation (Eq). Three new equations recently emerged, based on serum creatinine (CKD-EPI Cr), serum cystatin-C (CKD-EPI Cc) or combination of both (CKD-EPI Cr/Cc). These equations have already been validated in renal dysfunction screening, however, studies in the area of ACS are still scarce. The aim was to evaluate the prognostic value of these Eq on prediction of long-term mortality (M) in P admitted for ACS; and to determine the best Eq and compare it with traditional MDRD as well.

Methods: Study of 801 P (67.3±13.3y, 68.5% male) admitted for ACS in a cardiac care unit along 3 years, in which the serum Cr and Cc were determined at admission. P were considered as belonging to a high risk group (HR) if GFR <60mL/min/1.73m² and low risk (LR) if GFR ≥60mL/min/1.73m². Follow-up regarding M was performed.

Results: According to the different Eq, P were considered to be high risk in 29.8% by MDRD, 30.6% by CKD-EPI Cr, 28.3% by CKD-EPI Cr/Cc and 27.3% by CKD-EPI Cc.

Mortality on follow-up (23.7±9.8 months) was 18.1%, and all Eq showed to be predictors of this endpoint ($p<0.001$). However, CKD-EPI Cc is the Eq that included a greater number of P with events in the HR group (39.7%), followed by the CKD-EPI Cr/Cc (37.0%), CKD-EPI Cr (32.7%) and MDRD (32.2%). Comparison of these 4 Eq through ROC curves confirmed that CKD-EPI Cc has the highest ability to predict M (AUC 0.782), being superior to all others Eq ($p<0.001$). When compared to MDRD, CKD-EPI Cc reclassifies 13.1% of the P in both directions.

Reclassifying P from LR to HR group (5.5%) was associated with an increased risk of events. The M rate of these reclassified P was similar to the M of their new HR group (45.5% vs 38.3%, $p=0.386$) and higher than the M of non-reclassified P of previous LR group (45.5% vs 9.4%, $p<0.001$).

Reclassification of the P from HR to LR group (7.6%) was associated with a lower risk of events. The M of these P was similar to the LR group (14.8% vs 9.4%, $p=0.187$) and lower than the non-reclassified P of HR group (14.8% vs 38.3%, $p<0.001$). The NTI index was 0.12 (CI 0.04 to 0.20, $p=0.003$).

Conclusions: The CKD-EPI Cc equation showed the highest sensitivity and specificity for the prediction of long-mortality. These results reinforce the added value of cystatin-C as a risk marker in P with ACS. Its use in clinical practice may allow a better risk stratification of these P, hence accurate management. More studies are warranted to validate these results.

P2667 | BEDSIDE**Post-Extrasystolic T-wave changes predicts late mortality after myocardial infarction**

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Background: Post-extrasystolic T-wave change (PEST) is a phenomenon described first by PD White in 1915. He observed that the T-wave of the first normal beat after a ventricular premature complex (VPC) often is altered in terms of augmentation, decrease or a change in the direction of the T-wave vector. This observation was confirmed in many experimental studies. In a contemporarily-treated cohort of acute MI patients, we tested whether PEST provides prognostic information and how this information compares to that of established risk assessment.

Methods and results: 941 consecutive patients (mean age 61 years, 19% female) presenting with acute MI were enrolled between May 2000 and March 2005. All patients underwent 30-minute recordings of high resolution ECG (1.6 kHz sampling of orthogonal XYZ leads). 224 patients showed VPCs during these 30-minutes. We quantified PEST by two variables (1) change in T-wave area and (2) change in the angle of the T-wave vector in each case compared to the average of three T-waves before and after the first post-extrasystolic beat. PEST was defined as ratio TPEST/T±3 area <1 and ratio TPEST/T±3 angle ≥5°. PEST was present in 63 of the 224 patients. Primary endpoint was total mortality during a follow-up period of five years. Uni- and multivariate analyses were performed with traditional risk stratifiers like LVEF ≤35%, GRACE score ≥120 points and VPC count ≥5 per 30 minutes.

During the follow-up, 26 of the patients died. PEST shows the strongest association with mortality in the univariable analysis followed by GRACE score, frequent VPCs and reduced LVEF. In the multivariable analysis only PEST and GRACE score were independent predictors of mortality (see table).

Uni- and multivariate Cox regression

Variable	Univariate			Multivariate		
	Hazard ratio	chi square	p-value	Hazard ratio	chi square	p-value
PEST	4.22 (2.0-9.1)	13.5	<0.0001	4.33 (2.0-9.5)	13.3	<0.0001
LVEF <35%	2.57 (1.1-5.9)	5.0	0.025	1.45 (0.6-3.5)	0.7	0.409
VPC ≥5 per 30 min	3.08 (1.3-7.3)	6.5	0.010	2.18 (0.9-5.3)	3.0	0.083
GRACE score ≥120 pts	3.94 (1.6-9.8)	8.8	0.003	3.69 (1.4-9.5)	7.4	0.006

Conclusions: PEST is significantly associated with mortality in patients with acute myocardial infarction. PEST was independent of standard risk predictors. PEST presumably indicates abnormal transmural gradient in repolarization time.

P2668 | BEDSIDE**In-hospital and long-term mortality for patients 80 years or older with acute ST-segment elevation myocardial infarction. An eastern Norway cohort study 2005-2011**

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Purpose: Patients ≥80 years with ST-elevation myocardial infarction (STEMI) are underrepresented in clinical trials, and little is known about long-term mortality of this population in the era of primary coronary intervention (PCI). Our hospital has offered primary PCI without age restrictions for several years. We aimed to study in-hospital and long-term mortality of STEMI patients ≥80 years compared to younger patients.

Methods: Single-centre observational cohort study. All consecutive STEMI-patients admitted to our hospital between 01.09.2005 and 31.12.2011 were included in a local registry. Predelineated data including in-hospital mortality were registered. Vital status was obtained from the National Cause of Death Registry with censoring date 31.12.2011.

Results: A total of 4525 patients with a confirmed diagnosis of STEMI were registered; 600 patients (13%) were ≥80 years. The percentage undergoing coronary angiography and PCI if indicated, was lower in patients ≥80 years compared with younger patients (83% vs. 98%), but there was no difference in symptom-to-balloon times. In the total cohort, in-hospital mortality was 4% for patients <80

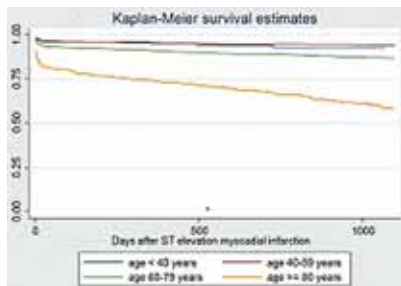


Figure 1

and 17% for patients ≥80 years. In the invasively treated patients (96% of all), in-hospital mortality was 3.4% in patients <80 years and 13% in patients ≥80 years. The median follow-up time was 2.5 years. Survival in invasively treated patients ≥80 years was 66% after 1 year and 58% after 2 years (Figure). Factors associated with long-term mortality were prehospital resuscitation, elevated serum creatinine and PCI.

Conclusion: Mortality after STEMI was high in patients ≥80 years compared to younger patients. Although in-hospital mortality was relatively low in patients treated invasively, only 58% were alive after 2 years.

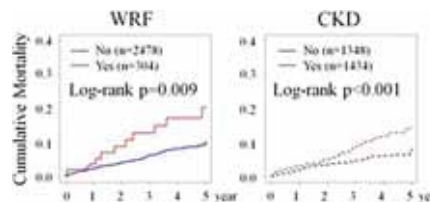
P2669 | BEDSIDE**Worsening renal function is more strongly associated with long-term mortality than chronic kidney disease after ST-elevation myocardial infarction**

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Purpose: Worsening renal function (WRF) is associated with worse outcomes in patients with left ventricular systolic dysfunction and heart failure. The purpose of the present study is to assess the prognostic impacts of WRF in patients with ST-elevation myocardial infarction (STEMI), drawing a comparison between WRF and chronic kidney disease (CKD).

Methods: From the database of the Osaka Acute Coronary Insufficiency Study, the present study enrolled a total of 2,782 consecutive STEMI patients (median 67 y.o., 77% male, and 94% underwent percutaneous coronary intervention) whose creatinine values both on admission and at discharge were available. We defined WRF as an increase in serum creatinine levels greater than 0.3 mg/dL from hospitalization to discharge for STEMI. CKD was defined as estimated glomerular filtration rate (e-GFR) less than 60 mL/min/1.73m² at discharge. The impacts of WRF and CKD were assessed using multivariate Cox regression analysis for 5-year all-cause mortality after discharge.

Results: Among the study population, 10.9% had WRF and 51.6% had CKD at discharge. There were 142 all-cause deaths during a median of 716 (quartile 214-1440) days follow-up. The adjusted hazard ratio and 95% confidence interval (CI) for 5-year mortality was 6.39 (3.15-12.94, p<0.001) for the presence of WRF, and 1.67 (1.11-2.52, p=0.0137) for CKD. Multivariate logistic regression analysis revealed that independent predictors of WRF were baseline creatinine on admission (adjusted odds ratio 1.89, 95% CI 1.14-3.06, p=0.011), body mass index (1.05, 1.01-1.09, p=0.012), and dyslipidemia (0.72, 0.53-0.98, p=0.039).



Conclusions: The impact of WRF for long-term mortality was greater than that of CKD after STEMI in the contemporary percutaneous coronary intervention era.

P2670 | BEDSIDE**In-hospital acquired anemia: prognostic predictor in acute coronary syndromes**

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Purpose: Admission anemia is a recognized predictor of poor prognosis in acute coronary syndromes (ACS). There is a growing interest in understanding the prognostic value of in-hospital acquired anemia, "nosocomial anemia" (NA). We sought to determine the prevalence, predictors and prognostic value of NA in ACS.

Methods: Retrospective study including 1345 P with ACS consecutively admitted to a coronary care unit over 3 years and during a minimal 6 months follow-up. NA was defined as an in-hospital hemoglobin (Hb) drop until WHO anemia diagnosis criteria, and was further classified as mild (Hb >11g/dL) or moderate/severe (Hb ≤11g/dL). P were excluded if they had admission anemia (n=321) or bleeding complications with hemodynamic instability/invasive treatment (n=17).

Results: During hospitalization, 329 P developed NA, these P were older (59±12 vs 66±13y; p<0.001) and more often had hypertension (65.5% vs 59.1%; p=0.04), chronic renal failure (3.0% vs 1.2%; p<0.001) and atrial fibrillation (7.6% vs 4.4%; p=0.04). At admission, they had lower mean levels of Hb (13.9±1.2 vs 15.0±1.2g/dL; p<0.001) and higher levels of creatinine (1.0±0.4 vs 0.9±0.3mg/dL; p<0.001), type B natriuretic peptide (3187±5097 vs 1489±2553pg/mL; p<0.001) and C-reactive protein levels (20.8±39.9 vs 10.5±21.9mg/L; p<0.001). The echocardiographic evaluation showed that they

had more often left ventricular systolic dysfunction (LVSD) (56.8% vs 47.1%; $p < 0.001$) and mitral regurgitation grade $\geq$ II/IV (14.9% vs 6.6%; $p < 0.001$). During hospitalization, they had a higher incidence of respiratory infections (7.9% vs 1.8%; $p < 0.001$) and heart failure (38.6% vs 18.4%; $p < 0.001$). They were more often managed with more aggressive treatments, including the use of inotropic agents ($p < 0.001$) and intra-aortic balloon ($p = 0.004$). Femoral vascular access for cardiac catheterization was performed more often in P with NA (10.0% vs 5.2%; $p = 0.002$). After multivariate analysis, admission Hg, respiratory infections and LVSD persisted as independent predictors of NA. In-hospital (4.3% vs 0.9%; $p < 0.001$) and 6 months (4.3% vs 1.1%; $p = 0.003$) mortality was higher in P with NA. In-hospital major adverse cardiovascular events were also higher in this group (45.0% vs 15.9%; $p < 0.001$), but this trend didn't persist in follow-up. Moderate/severe NA was an independent predictor of in-hospital (OR 2.5; CI95%: 1.15-5.30; $p = 0.02$) and 6 months mortality (HR 1.8; CI95%: 1.18-2.8; $p = 0.006$).

Conclusion: NA was a common complication in ACS. Moderate/severe NA was an independent predictor of in-hospital and 6 months mortality. Admission Hg, respiratory infections and LVSD were independent predictors of NA.

P2671 | BEDSIDE

Butyrylcholinesterase predicts cardiac mortality in young patients with acute coronary syndrome

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Background: The number of acute coronary syndrome (ACS) in young people (≤ 65 years) is continuously rising. While a large quantity of prognostic factors in ACS are already established less attention has been paid to their age-dependent prognostic value and their relevance in younger patients so far. The aim of our study was to assess the age-dependent prognostic impact of butyrylcholinesterase, which has been shown to be inversely associated with cardiac mortality.

Methods: We retrospectively included 624 patients with ACS into our cohort study. Patients were randomized and stratified into equal groups ($n=208$ per group) according to age "45-64 years", "65-84 years" and "over 85 years". Cox regression hazard analysis was used to assess the influence of butyrylcholinesterase on survival. The multivariate model was adjusted for clinical confounders and variables with a significant association with butyrylcholinesterase.

Results: After a mean follow-up time of 5 years, 154 (24.7%) patients died due to cardiac causes including 11 patients (5.3%) between 45-64 years, 44 patients (21.2%) between 65-84 years and 99 patients (47.6%) > 85 years. Median butyrylcholinesterase concentrations significantly differed between age groups with 7.20 kU/l (IQR=5.90-8.63) in young patients (45-64 years), 6.71 kU/l (IQR=5.70-8.00) in middle-aged patients (65-84 years) and 5.97 kU/l (IQR=5.04-6.90) in very old patients (> 85 years, $p < 0.001$). Butyrylcholinesterase showed a protective effect on survival free of cardiac mortality in the entire study cohort with an adjusted HR per one standard deviation (1-SD) of 0.70 (95% CI 0.53-0.93, $p = 0.01$). A significant interaction between butyrylcholinesterase and age groups was found ($p = 0.008$). Analysis of the age strata showed the strongest protective effect in the age group 45-64 years with an adjusted HR per 1-SD of 0.28 (95% CI 0.12-0.64, $p = 0.003$), and a decreasing association with mortality with increasing age (65-84 years: adjusted HR per 1-SD 0.66 [95% CI: 0.41-1.06], $p = 0.087$; > 85 years: adjusted HR per 1-SD 0.89 [95% CI: 0.58-1.38], $p = 0.613$).

Conclusion: Butyrylcholinesterase is a specific predictor for cardiac mortality in younger patients with ACS with an age between 45 and 64 years, while no significant association could be detected in all other age classes. The exact pathophysiological mechanisms and the age-dependent effect of butyrylcholinesterase on cardiac mortality need to be elucidated in future studies.

INFLAMMATION AND ACUTE CORONARY SYNDROMES

P2673 | BENCH

Chemokine (CXC motif) ligand 16 (CXCL16) and osteoprotegerin (OPG) as predictors of outcome in patients with acute coronary syndromes (ACS) a PLATO biomarker substudy

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Background: Early identification of patients with poor prognosis may help to optimize therapy in patients with acute coronary syndromes (ACS). Both CXCL16 and OPG may play a modulatory role in platelet-mediated vascular inflammation and, at least partly, represent different inflammatory pathways. We evaluated factors associated with OPG and CXCL16 levels, their relation to 1 year outcome and interactions with platelet inhibition in patients with ACS.

Methods: CXCL16 and OPG levels were determined in serum collected at randomization to ticagrelor or clopidogrel in 4185 patients with ACS in the PLATO (PLATElet inhibition and patient Outcomes) trial. Baseline characteristics by Chi-square test (categorical variables) or Kruskal Wallis test (continuous variables), and occurrence of the primary outcome, a composite of cardiovascular death,

non-fatal myocardial infarction, or stroke ($n=362$), by Cox proportional hazards models were compared between groups stratified by quartiles of the respective biomarker.

Results: The median (interquartile range) of CXCL16 was 5.10 (4.4 - 6.0) and of OPG 2.6 (2.0 - 3.6). Patients with higher CXCL16 and OPG serum levels were older and more frequently were female and had a medical history including hypertension, diabetes mellitus, angina pectoris, heart failure, PCI, and chronic renal disease. In addition, patients with higher CXCL16 but lower OPG had a higher frequency of smoking, prior PCI, angina pectoris and ST-elevation MI. Higher CXCL16 levels were also associated with more previous MI and peripheral artery disease. Finally, higher CXCL16 and OPG were strongly associated with increased TIMI and GRACE risk scores and higher levels of troponin I, NT-proBNP and CRP. There was a higher incidence of the primary endpoint in the highest (12.1%/year) versus the lowest (7.4%/year) CXCL16 quartile (HR 1.63 95% CI [1.22-2.18], $p = 0.004$ in comparison to the lowest quartile). For OPG there was an increased risk of the primary outcome in the two higher quartiles (11.2 and 11.4%/year) (HR 1.64 [1.21-1.22] and 1.68 [1.24-2.28], $p = 0.002$ in comparison to the lowest quartile 6.8%/year). No significant interaction between biomarkers and effect of randomized treatment on the primary outcome was observed.

Conclusions: In patients with ACS higher serum levels of CXCL16 and OPG are associated with clinical risk factors and adverse outcome but did not identify subgroups of patients with specific benefits from more intense antiplatelet therapy.

P2674 | BEDSIDE

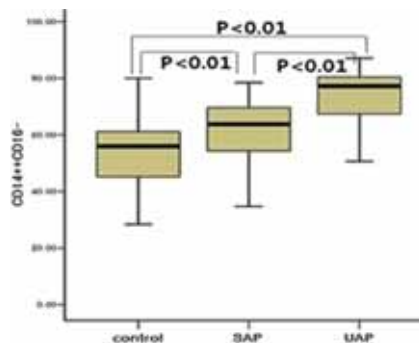
The classical CD14++ CD16- monocyte count is a risk factor for coronary artery disease

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Purposes: The white blood cell and neutrophil count has been considered as risk factors for coronary artery disease (CAD), while the data of monocytes' role in CAD is rare. Monocyte can be classified as classical and non-classical monocyte by absence or presence of CD16 surface molecule and each monocyte subset has different functional characteristics in atherosclerosis. Therefore, we hypothesized that monocyte subset rather than total monocyte count might be associated with CAD.

Methods: We enrolled 208 consecutive patients (mean age; 63 ± 11 years, $MF=121:87$) with stable (SAP) or unstable (UAP) angina and control patients whose coronary angiogram showed no significant stenosis. We measured percent of each monocyte subset using flow cytometry. After gating mononuclear cells by forward and side scatter properties, we defined monocyte subpopulation according to the surface expression pattern of CD14 and CD16.

Results: 1. The percent of CD14++CD16- monocyte was lower in unstable angina compared to control (4.8 ± 5.1 vs $9.1 \pm 6.4\%$, $p < 0.01$) or stable angina patients (4.8 ± 5.1 vs $7.5 \pm 7.4\%$, $p < 0.01$). 2. The percent of CD14++CD16- monocyte was higher in unstable angina compared to control (72.4 ± 13.8 vs $53.4 \pm 12.2\%$, $p < 0.01$) or stable angina patients (72.4 ± 13.8 vs $61.0 \pm 13.4\%$, $p < 0.01$) (Figure 1). 3. There were no significant differences in the percent of CD14++CD16- and CD14++CD16+ monocyte when it progresses from one vessel to three vessel disease among stable angina patients. 4. There was no significant difference in total monocyte count among these patients groups.



Conclusion: The monocyte subpopulation, in particular, elevated CD14++CD16- subset might be a risk factor coronary artery disease and also be involved in plaque vulnerability.

P2675 | BEDSIDE

Prognostic impact of platelet macrophage migration inhibitory factor in patients with symptomatic coronary artery disease

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Background: Macrophage migration inhibitory factor (MIF) is involved in the progress of atherosclerosis and plaque destabilization and plays a pivotal role

in the development of acute coronary syndromes and other inflammatory diseases but the prognostic impact of platelet MIF expression in symptomatic coronary artery disease (CAD) is unknown. We investigated the expression of MIF on platelets in consecutive patients with ischemic heart disease (HF).

Methods: In 338 CAD patients, platelet activation markers and MIF expression were assessed by flow cytometry. Clinical parameters including cardiovascular risk factors, cardiovascular comedication and demographic variables were recorded. Follow up regarding clinical endpoints was performed at a median of 310 days. The primary endpoint was a combination of all-cause death, recurrent myocardial infarction and urgent revascularization.

Results: Platelet-MIF expression correlated with platelet activation marker CD62P and PAC1 (spearman rank coefficients 0.34 and 0.47, $p > 0.001$ respectively). Platelet MIF expression was significantly lower in patient with a combined endpoint during follow up (mean $13.8 \text{ MFI} \pm 8.44$ versus 16.1 ± 8.42 , $p = 0.042$). In Kaplan-Meier analysis low platelet MIF expression ($\leq$ median i.e. 13.7 MFI) was significantly associated with worse cumulative survival of the primary combined endpoint (log rank $p = 0.002$). In multivariate Cox regression analysis lower platelet MIF levels remained an independent predictor of combined events after adjusting for relevant cardiovascular risk factor, demographic variables and comedication.

Conclusions: The present finding suggest that low platelet expression is an independent risk marker for recurrent major cardiovascular events and urgent revascularization in patients with symptomatic CAD. It is tempting to speculate that platelets serve as a relevant storage pool for MIF thus contributing to enhanced extracellular MIF levels previously shown to be independently associated with poor prognosis in cardiovascular disease.

P2676 | BEDSIDE

LDL cholesterol and triglycerides levels are independent predictors of cardiovascular events in HIV-HCV co-infected patients: ANRS CO13-HEPAVIH

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Purpose: HIV infection increases the risk of mortality with cirrhosis, liver failure and hepatocarcinoma in HCV co-infected patients. The risk and spectrum of cardiovascular diseases (CVD) in this population are not well assessed with contradictory previous results.

Methods: We used the French prospective multi-center HEPAVIH-ANRS CO13 cohort, to prospectively collect all CVD events, atherosclerotic [coronary death, acute coronary syndrome, coronary revascularization, ischemic stroke, peripheral arterial disease] and other [Heart failure, thromboembolic venous disease] occurring during the entire follow up. Chi 2 test was used for qualitative variables and Wilcoxon test for quantitative variables to screen potential CVD predictors. A Cox model was performed to identify CVD predictors among adjusted selected parameters with a $p < 0.10$ in univariate analysis.

Results: Among 1175 HIV-HCV co-infected patients (70% men, mean age: 45.0 years) included from January 2006 to January 2008 and followed till September 2013 (median follow-up: 57.6 months), we observed 42 CVD events overall among 28 patients. The incidence of all events was 8.3 per 1,000 person-years (95% confidence interval [CI]: 5.0-11.6) and 5.6 per 1,000 person-years (CI95: 2.3-8.9) for a first event. Atherosclerotic CVD events include 4 coronary deaths, 10 acute coronary syndromes, 1 coronary revascularization, 8 peripheral arterial disease events and 2 ischemic strokes. Three thromboembolic venous events occurred. As compared with patients without CVD, those who developed ≥ 1 CVD event were more frequently men ($p = 0.009$), had a higher median CD8 cell count ($p = 0.039$), were more frequently lipoatrophic ($p = 0.040$), and had a higher total cholesterol level ($p = 0.0165$), LDL cholesterol level ($p = 0.013$) and triglyceride level ($p = 0.0002$). HCV eradication following treatment did not influence the occurrence of CVD events ($p = 0.17$). Multivariate analysis identified serum LDL-cholesterol (relative risk [RR]=6.2 CI [1.58-24.35], $p = 0.009$) and triglyceride level (RR=2.01, CI= [1.21-3.33], $p = 0.008$) as independent predictors of CVD occurrence.

Conclusion: In HIV-HCV co-infected patients, CVD events are mainly driven by atherosclerotic CVD particularly acute coronary syndromes and peripheral arterial diseases. Serum LDL-cholesterol and triglyceride levels appear as the only independent CVD predictors.

P2677 | BEDSIDE

S100A8/A9, potentially important link between circulating neutrophils, traditional CV risk factors and CV risk in apparently healthy women

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Purpose: S100A8/A9 is an innate immune mediator with pro-inflammatory prop-

erties. Previously published data suggest that S100A8/A9 is pro-atherogenic and promotes the development of cardiovascular (CV) disease. The purpose of our study was to identify the circulating cell populations and the CV risk factors that influence plasma levels of S100A8/A9 in humans. Additionally, we aimed to assess whether S100A8/A9 is associated with the incidence of CV disease in apparently healthy middle-aged individuals, independently of traditional CV risk factors and high-sensitivity C-reactive protein (hsCRP).

Methods: We measured S100A8/A9 in 664 individuals with no previous history of CV disease, randomly selected from the Malmö Diet and Cancer study population. We examined the correlations between S100A8/A9 and circulating cell counts, BMI, smoking, diabetes, hyperlipidemia, and hypertension at baseline. The associations between S100A8/A9 and the incidence of acute CV events during a median follow-up period of 16 years were assessed in Cox regression analyses adjusted for CV risk factors and hsCRP.

Results: Plasma S100A8/A9 was strongly correlated with blood neutrophil numbers. There were no correlations with monocytes, lymphocytes or platelets, suggesting that neutrophils are the main cellular source of systemic S100A8/A9. We found positive independent associations between S100A8/A9 and smoking, BMI, glycosylated hemoglobin (HbA1c) and LDL and a negative association with HDL. S100A8/A9 was correlated with the incidence of coronary events [HR (95% CI) per 1 SD: 1.72 (1.12-2.64); $P = 0.013$] and CV death [1.81 (1.14-2.89); $P = 0.012$] in women, independently of other CV risk factors and hsCRP. In contrast, when adjusting for CV risk factors and S100A8/A9, hsCRP was associated with incident coronary events and CV death in men, but not in women. Neither biomarker predicted the incidence of stroke.

Conclusions: Our results support the value of S100A8/A9 as an important link between circulating neutrophils, traditional CV risk factors and CV disease. The important differences revealed by our study regarding the value of S100A8/A9 and hsCRP for CV risk prediction in men and women need to be further explored.

P2678 | BEDSIDE

Association of small dense LDL serum levels and circulating monocyte subsets in patients with stable coronary artery disease

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Background: Atherosclerosis is considered to be an inflammatory disease in which monocytes and monocyte-derived macrophages play a key role. Circulating monocytes can be divided into three distinct subtypes, namely in classical monocytes (CM; CD14++CD16-), intermediate monocytes (IM; CD14++CD16+) and non-classical monocytes (NCM; CD14+CD16++). Low density lipoprotein particles are heterogeneous in size and density, with small, dense LDL (sdLDL) crucially implicated in atherogenesis. The aim of this study was to examine whether monocyte subsets are associated with LDL subfractions.

Methods: We included 90 patients with angiographically stable coronary artery disease and determined monocyte subtypes by flow cytometry. sdLDL was measured by an electrophoresis method on polyacrylamide gel.

Results: Patients with sdLDL levels in the highest tertile (sdLDL $\geq 4 \text{ mg/dL}$; T3) showed the highest levels of pro-inflammatory NCM ($15.2 \pm 7\%$ vs. $11.4 \pm 6\%$ and $10.9 \pm 4\%$, respectively; $p < 0.01$) when compared with patients in the middle (sdLDL = $2-3 \text{ mg/dL}$; T2) and lowest tertile (sdLDL = $0-1 \text{ mg/dL}$; T1). Furthermore, patients in the highest sdLDL tertile showed lower CM levels than patients in the middle and lowest tertile ($79.2 \pm 8\%$ vs. $83.9 \pm 7\%$ and $82.7 \pm 5\%$; $p < 0.01$ for T3 vs. T2+T1). Levels of IM were not related to sdLDL levels ($5.6 \pm 4\%$ vs. $4.6 \pm 3\%$ vs. $6.4 \pm 3\%$ for T3, T2 and T1, respectively). Furthermore, sdLDL levels were not associated with inflammatory markers. In contrast, total LDL levels were not associated with monocyte subset distribution.

Conclusion: The atherogenic lipoprotein fraction sdLDL is associated with an increase of NCM and a decrease of CM. This could be a new link between innate immunity, lipid metabolism dysregulation and atherosclerosis.

P2679 | BEDSIDE

The level of cytokines as a risk factors of cardiovascular diseases in patients with rheumatoid arthritis

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Comorbid medical conditions are common in patients with rheumatoid arthritis (RA). First brought to light with observations of increased mortality in RA, studies noted the increased rates of cardiovascular events (Michaud K., F. Wolfe, 2007). A characteristic feature of rheumatoid arthritis (RA) is an imbalance between the overproduction of proinflammatory cytokines predominantly macrophage nature: tumor necrosis factor- α , interleukin-1, interleukin-6 (TNF- α , IL-1, IL-6). In recent years, IL-1, 6, and TNF- α is given great importance in the formation of hypertension and atherosclerosis (Mazur V., 2005).

The aim of the study was to reveal the relationship between the level of IL-1 and TNF- α in serum and indicators of cardiovascular diseases in patients with RA.

Materials and methods: 565 RA patients (diagnosis according to the criteria of ACR/EULAR 2010) from the rheumatology in-patient clinic with the mean age

43.4±10; 95.4%ACCP-positive patients; II, III activity on DAS28; 85.4% female and duration of the disease 3-15 years were reviewed. The level of cytokines (IL-1, TNF- α) were estimated with the use of ELISA. We assessed blood pressure (BP), level of LDL, triglycerides (TG) and hs-CRP.

Results: Analysis of the results revealed the statistically significant increase level of IL-1 and TNF- α in the serum of RA patients ($p<0.01$). We revealed statistically significant correlation between the level of cytokines (IL-1 TNF- α) and parameters of cardiovascular diseases: BP $r=0.742$ ($p<0.02$), $r=0.521$ ($p<0.05$); LDL $r=0.621$ ($p<0.01$) and $r=0.578$ ($p<0.05$) accordingly; TG $r=0.512$ ($p<0.01$) and $r=0.364$ ($p<0.05$); hs-CRP $r=0.821$ ($p<0.05$) and $r=0.632$ accordingly.

Conclusion: Proinflammatory cytokines (IL-1 and TNF- α) may be indirect risk factors of development and progression for hypertension and atherosclerosis in patients with rheumatoid arthritis, which should be considered when examining patients and the prescription of basis therapy.

P2680 | BEDSIDE

Ghrelin receptor deficiency aggravates instability of atherosclerotic plaque and vascular inflammation in low-density lipoprotein receptor-null mice

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Ghrelin has been found to be associated with anti-inflammation, inhibition of atherosclerotic plaque formation and plaque stability in cardiovascular system. We investigated whether ghrelin affected the atherosclerotic plaque and immune inflammation of atherosclerosis. We crossed ghrelin receptor knock out mice (GHSR-/-) into a low-density lipoprotein receptor-null (LDLR-/-) mouse line. In this model, atherosclerotic lesions were promoted by feeding a high-fat, high-cholesterol Western-type diet for 18 weeks, following a standard protocol. Serum lipid levels, atherosclerotic plaque on aortic arches, and the expression of ICAM-1 and VCAM-1, T cell, macrophage and smooth muscle cell of atherosclerotic plaque were observed. Though the serum lipid levels and atherosclerotic plaque area on aortic arches were not significantly different between in GHSR+/+/LDLR-/- mice and GHSR -/-LDLR-/- mice, the protein expression of ICAM-1 and VCAM-1 in atherosclerosis plaque were increased in GHSR -/-LDLR-/- mice than that in GHSR+/+/LDLR-/- mice. T cell and macrophage were more, while the smooth muscle cells of atherosclerosis plaque were less in GHSR -/-LDLR-/- mice than that in GHSR+/+/LDLR-/- mice. In conclusion, ghrelin receptor deficiency aggravates instability of atherosclerotic plaque and vascular inflammation but not atherosclerotic plaque area, which will provide novel avenues for the treatment of atherosclerosis patients.

P2681 | BEDSIDE

Monocyte subpopulation counts and function are associated with global longitudinal strain in patients with normal ejection fraction after ST elevation myocardial infarction

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Introduction: Monocytes, with 3 different subsets, are implicated in the initiation and progression of the atherosclerotic plaque, plaque instability and rupture. Mon1 are the "classical" monocytes with inflammatory action, whilst Mon3 are considered reparative with fibroblast deposition ability. The function of the newly described Mon2 subset is yet to be fully described. In PCI era, fewer patients have globally reduced left ventricular ejection fraction post infarction, hence the importance of studying regional wall motion abnormalities and deformation at segmental levels using global longitudinal strain (GLS) as the gold standard for studying subclinical ventricular function and remodelling. Little is known of the role for the 3 monocyte subpopulations in determining global strain in STEMI.

Methodology: STEMI patients (n=101, mean age 64±13 years; 69% male) treated with percutaneous revascularization were recruited within 24 hours post-infarction. Peripheral blood monocyte subpopulations were enumerated and characterized using flow cytometry after staining for CD14, CD16 and CCR2. Phenotypically, monocyte subpopulations are defined as: CD14++CD16-CCR2+ (Mon1), CD14++CD16+CCR2+ (Mon2) and CD14+CD16++CCR2- (Mon3). Monocytes phagocytic activity was measured using flow cytometry. Transthoracic echocardiography was performed within 7 days & 6 months post infarct to assess GLS via speckle tracking.

Results: STEMI patients with EF $\geq 50\%$ by Simpson's biplane (n=52) had GLS assessed. Using multivariate regression analysis higher counts of Mon1 and Mon2 and phagocytic activity of Mon2 were significantly associated with GLS

Multivariate regression analysis of monocytes and GLS

Monocytes mean fluorescence intensity (cells/ μ l)	Global longitudinal strain (%) seven days post infarct			Global longitudinal strain (%) six months post infarct		
	R value	R ² value	P-value	R value	R ² value	P-value
Mon 1	0.88	0.77	0.001	0.85	0.73	0.001
Mon 2	0.71	0.50	0.03	0.74	0.54	0.02
Phago Mon1	0.58	0.33	0.24	0.52	0.27	0.53
Phago Mon 2	0.32	0.12	0.03	0.50	0.25	0.69

(after adjusting for age, time to hospital presentation, and peak troponin levels). At 6 months, the convalescent GLS remained associated with higher counts of Mon1, Mon 2.

Conclusion: In patients with normal or mildly impaired EF post infarction, higher counts of Mon1 and Mon2 are correlated with GLS within 7 days and at 6 months of remodelling. Adverse clinical outcomes in patients with reduced convalescent GLS were predicted with Mon1 and Mon2 suggestive of an inflammatory role for the newly identified Mon2 subpopulation.

P2682 | BEDSIDE

Role of inflammatory and sympathetic activation in anxiety and depression interaction with myocardial infarction

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Purpose: To examine the relationships of subclinical inflammation biomarkers, autonomic imbalance and anxiety and depressive syndromes in patients with myocardial infarction (MI).

Methods: 106 patients with ST-segment elevation MI, mean age 61.4±1.6 years, were enrolled. At days 5-7 the heart rate variability was assessed, plasma inflammatory biomarker concentrations (high-sensitivity C-reactive protein – CRP, interleukins IL-1 β , IL-6, IL-8, IL-10, interferon - $\text{INF}\gamma$, tumor necrosis factor - TNF α) were measured by ELISA and psychometric testing using the Zung Self-Rating Depression scales, State-Trait Anxiety Inventory (Spielberger-Hanin) was done. The data were analyzed using the "STATISTICA 6.0" software package (StatSoft).

Results: Patients with depression and increased levels of state and trait anxiety had significantly higher CRP and $\text{INF}\gamma$ plasma concentrations as compared to those without depression or anxiety symptoms. Depression was associated with significantly higher concentrations of inflammatory cytokines IL-1 β (72.2±1.3 vs. 49.5±7.7 in patients without depression, $p=0.08$), IL-8 (104.5±4.4 and 43.8±1.2, respectively, $p=0.009$) and reduced anti-inflammatory IL-10 (1.0±0.2 and 2.1±0.4; $p=0.01$), as well as with the sympathetic nervous system activation, as assessed with the SDNN. In the group of patients with myocardial infarction, who had a marked increase in the sympathetic nervous system activity (SDNN <70 ms), the levels of IL-1 β , IL-8, TNF and $\text{INF}\gamma$ were significantly higher as compared to those in patients with the normal SDNN values. Indeed, IL-1 β levels were 164.5 (152, 174) and 108 (96, 110), respectively, IL-6 levels: 4.48 (2.2, 6.3) and 3.44 (2.4, 4.9) IL-8: 81.3 (76; 92) and 41 (28;51); TNF α levels: 37.4 (28.6, 44.4) and 2.63 (1.9, 4.3); $\text{INF}\gamma$ 94.9 (91; 101.2) and 21.6 (18.3, 23), $p<0.001$ in all cases. The resulting differences did not depend on the severity of myocardial infarction.

Conclusion: The presence of myocardial infarction in patients with sub-acute symptoms of depression and increased anxiety is associated with more severe inflammatory and sympathetic activation, which may explain a well-known adverse prognostic role of anxiety and depression syndrome in MI.

P2683 | BEDSIDE

Subclinical inflammation quantified by Interleukin-6 for detection of exercise-induced myocardial ischemia

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Background: Existing data support the assumption that subclinical inflammation and IL-6 are involved in the development of atherosclerosis, the pathophysiological hallmark of coronary artery disease (CAD). Nonetheless, clinical data evaluating the value of IL-6 measurements to detect functionally significant CAD are sparse. The aim of this study was to investigate the value of an Interleukin-6 (IL-6) measurement to detect exercise-induced myocardial ischemia (MIS).

Methods: We included 1539 patients referred to our university hospital for CAD evaluation with rest/stress myocardial perfusion single photon emission tomography (MPI-SPECT). All clinical information available to the treating cardiologist was used to quantify the clinical judgment regarding the presence of MIS using a visual analogue scale prior to bicycle exercise stress-testing. IL-6 measurements were obtained before stress-testing in a blinded manner. The presence of MIS was adjudicated based on MPI-SPECT combined with coronary angiography findings.

Results: MIS was detected in 647 (42%) participants. IL-6 levels were significantly higher in patients with MIS (1.6 ng/l [95%CI 1.0-2.7] versus 1.3 ng/l [95%CI 0.8-2.1], $p<0.001$) and remained an independent predictor of MIS in multivariable analysis ($p<0.005$). Receiver operating characteristics (ROC) analysis showed only poor diagnostic accuracy of IL-6 for detection of MIS as quantified as area under the curve (AUC) of 0.59 ($p<0.001$). Combining clinical judgment prior to exercise testing with IL-6 levels revealed no relevant increase in diagnostic accuracy 0.67 (combination) vs. 0.65 (clinical judgement alone) ($p<0.005$).

Conclusion: Although statistically significant associated with MIS, IL-6 measurements do not seem to provide clinically relevant additional information to clinical judgement of the treating cardiologist in the detection of MIS in patients with suspected CAD.

P2684 | BEDSIDE**The relationship between neutrophil/lymphocyte ratio and infarct-related artery patency before mechanical reperfusion in patients with ST-elevation myocardial infarction**

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Objectives: Reduced baseline coronary flow in infarct-related artery (IRA) before a primary percutaneous coronary intervention (PPCI) increases mortality in patients with ST-elevation myocardial infarction (STEMI). Increased neutrophil/lymphocyte (N/L) ratio has been linked to poor clinical outcomes in patients with STEMI. We investigated whether the N/L ratio, as measured at admission, was associated with IRA patency before mechanical reperfusion in patients with STEMI undergoing PPCI.

Patients and methods: A total of 404 patients who had undergone PPCI on a single culprit artery were enrolled in this study. According to thrombolysis in myocardial infarction (TIMI) flow grade in the IRA before PPCI, the study population was divided into two groups as TIMI 0 or 1 group (occluded IRA) and TIMI 2 or 3 group (patent IRA).

Results: The N/L ratios were found to be significantly higher in the TIMI flow 0/1 group when compared with the TIMI flow 2/3 group (6.08 ± 3.94 vs. 4.01 ± 2.87 , $P=0.001$). The absence of early IRA patency was associated with higher Syntax score, mean platelet volume, CK-MB, and troponin T levels ($P=0.0001$, $P=0.03$, $P<0.001$, and $P=0.004$, respectively), and lower left ventricular ejection fraction ($P=0.02$). Multivariate logistic regression analysis showed that the N/L ratio and Syntax score were independent predictors of IRA patency (odds ratio: 1.89, 95% confidence interval: 1.82–1.98; odds ratio = 2.80, 95% confidence interval: 1.75–3.86, respectively; $P=0.001$).

Conclusion: The N/L ratio has been found to be associated independently with early IRA patency before PPCI in patients who have undergone PCI for STEMI. This simple and cheap parameter can provide useful information on the related risk evaluation in these patients.

STABLE ANGINA: PROGNOSIS AND OUTCOME**P2686 | BEDSIDE****Assessment of chest pain: Results from a rapid access chest pain clinic in England**

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Background: Patients referred to our Rapid Access Chest Pain Clinic (RACPC) are seen within 2 weeks; however, the referrals must fulfill certain criteria: 1) no previous history of ischaemic heart disease 2) chest pain less than 6 weeks duration and 3) never been investigated in the past. Exclusion criteria includes severe aortic stenosis, uncontrolled hypertension, left bundle branch block and males younger than 30, and females younger than 40. We report findings from referrals to our RACPC in the year 2013.

Methods: All patients referred to our RACPC were included in this study and their details and outcome of investigations were collected prospectively.

Results: 367 patients were seen in the clinic during 2013. 12 referrals (3.3%) were deemed inappropriate as they did not meet the NICE referral criteria. Of the remaining 355 (54.1% male, 45.9% female), only 2% were younger than 40 and the modal age group was 61–69 (35%). 183 patients underwent exercise tolerance testing (ETT) to aid further investigation and management. 52% of the total number of patients were referred for an angiogram and 13% for functional imaging (46% of these had a subsequent angiogram). Of those who had an angiogram, 43% were found to have severe coronary disease, 36% of this subgroup underwent PCI, and 54% had CABG.

Of the 12 “Low risk” patients who had angiograms, only 1 patient had significant coronary disease, however, 66 out of 129 in the “High risk” group had significant disease.

Conclusion: Despite the lack of CT calcium scoring capabilities, RACPC remains an invaluable service to investigate and manage patients with a new presentation of stable chest pain. Correct risk stratification is crucial to identify the appropriate investigations and avoid unnecessary invasive intervention.

P2687 | SPOTLIGHT**Prognostic role of high sensitive troponin T in patients with chronic ischemic heart disease undergoing percutaneous coronary intervention**

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Purpose: The cardiac biomarkers levels were examined in order to predict short and long term prognosis after percutaneous coronary interventions in patients with chronic ischemic heart disease in several studies. Nevertheless, these studies results were conflicting. The aim of the this study was to investigate effects of Hs-TnT levels after successful, elective percutaneous coronary intervention in the patients with stable angina pectoris for predicting major adverse cardiovascular events within one-year.

Methods: 100 patients (76 males and 24 females) presented stable angina pectoris where Department of Cardiology in our University Hospital who underwent successful, elective percutaneous coronary intervention were included the study. The patients who are elevated troponin I levels before procedure (>0.1 ng/ml) were excluded from the study. Hs-TnT levels were measured at before procedure, at 3-4. and 12-24. hours after procedure. For the positive value of Hs-TnT level was considered >14 pg/ml. The patients followed-up for major adverse cardiovascular events (death, acute coronary syndrome and stroke) along one-year.

Results: In the study; Hs-TnT levels were reached the positive value in 36% of patients at 3-4. hours after procedure (early period); in 54% of patients at 12-24. hours after procedure (late period). Major adverse cardiovascular events (MACE) rates within one-year were found to be significantly higher in the patients who are had positive Hs-TnT levels in early period after procedure (36,1% vs. 15,6%; $p=0.026$). This significant relationship continued into the logistic regression analysis (odds ratio=3,36, % 95 C.I. 1,09-10,33; $p=0.034$). Although incidence of MACE increased in the patients who are had positive Hs-TnT levels in late period after procedure within one-year, there was no statistically significance (27,8% vs. 17,4%; $p=0.243$). Additionally, Hs-TnT levels before the procedure were similar in the patients who observed MACE within one-year (median 3,7 pg/ml vs. 4,1 pg/ml; $p=0.485$). Although Hs-TnT levels after procedure was higher in the patients who observed MACE within one-year; there was no statistically significance (median, early period 16,1 pg/ml vs. 10,7 pg/ml, $p=0.342$; late period 25,7 pg/ml vs. 15,0 pg/ml, $p=0.376$).

Conclusions: Hs-TnT which are measured at particularly 3-4. hours after successful, elective percutaneous coronary intervention in the patients who have stable angina pectoris may be effective for predicting major adverse cardiovascular events within one-year. However, results of the this study must be supported by more extensive large studies.

P2688 | BEDSIDE**Geriatric nutritional risk index predicts cardiovascular and all-cause mortality in chronic haemodialysis patients after coronary revascularization**

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Background: Although coronary revascularization, regardless of surgical or percutaneous procedures, has been commonly performed in chronic haemodialysis (HD) patients with coronary artery disease, poorer prognosis still remains major problems in such population. Recently, protein-energy wasting (PEW) or malnutrition have been considered to be strongly associated with chronic inflammation and advanced atherosclerosis. We investigated whether geriatric nutritional risk index (GNRI), developing as a simplified marker of the PEW, predicts cardiovascular (CV) and all-cause mortality after coronary revascularization in HD patients.

Methods: A total of 785 HD patients undergoing coronary revascularization (622 with percutaneous coronary intervention and 163 with coronary artery bypass graft) were examined. The GNRI was calculated from pre-procedural tests, as follows: $GNRI = (14.89 \times \text{albumin}) + [41.7 \times (\text{body weight} / \text{body weight at BMI of } 22)]$. Thereafter, patients were divided into quartiles according to GNRI levels; quartile 1 (Q1): <88.6 , Q2: 88.7–94.1, Q3: 94.2–99.3 and Q4: >99.4 . They were followed up for up to 10 years.

Results: During follow-up period (median: 43 months), there were 250 cases of deaths (31.8%) including 138 cases of CV deaths (17.6%). Kaplan-Meier survival rates for 10 years were 43.9%, 60.7%, 69.6% and 82.7% for CV mortality ($p=0.0002$), and were 20.9%, 42.4%, 56.6% and 70.3% for all-cause mortality in Q1, Q2, Q3 and Q4, respectively ($p<0.0001$). Even after adjustment for other confounders, GNRI [hazard ratio (HR) 2.55, 95% confidence interval (CI) 1.43–4.55, $p=0.0016$ for Q1 vs. Q4], age (HR 1.02, 95%CI 1.01–1.04, $p=0.012$), multi-vessel disease (HR 1.62, 95%CI 1.17–2.23, $p=0.0032$), ejection fraction (HR 0.98, 95%CI 0.97–0.99, $p=0.0081$) and C-reactive protein (HR 1.08, 95%CI 1.04–1.13, $p=0.0001$) were identified as independent predictors for CV mortality. GNRI also independently predicted all-cause mortality (HR 2.30, 95%CI 1.42–3.72, $p=0.0008$ for Q1 vs. Q4).

Conclusion: Declined GNRI which reflect PEW state was closely associated with both CV- and all-cause mortality after coronary revascularization in chronic HD patients.

P2689 | BEDSIDE**The vast majority of patients with coronary artery disease and atrial fibrillation have indications for antithrombotic therapy**

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Purpose: Atrial fibrillation (AF) has been a subject of an extensive research in

patients with acute myocardial infarction, whereas the analogous data in patients with stable coronary artery disease (CAD) are scarce. The aim of this study was to assess the prevalence of AF in outpatients with CAD, and to determine clinical and laboratory correlates associated with the higher prevalence of this comorbid arrhythmia. Further, we compared the indications for antithrombotic therapy using the older CHADS2 and the modern CHA2DS2-VASc scale.

Methods: We investigated a representative sample of 2578 Polish patients with stable CAD participating in the multicenter RECENT study (age: 65 ± 10 years; men: 55%; Canadian Cardiovascular Society [CCS] class I/II/III: 38/48/14%). These patients were consulted by the primary care physicians and the specialists on an outpatient basis and the detailed medical history was obtained using a dedicated questionnaire.

Results: AF was present in 19% of patients with stable CAD. In simple comparisons patients with AF were older, had more comorbidities, higher resting heart rate, lower total cholesterol, higher creatinine, and declared the greater severity of angina (as assessed using CCS scale) and the longer history of CAD (all $P < 0.05$). In a multivariable logistic regression model, advanced age (prevalence of AF according to age: >65 [median] vs. ≤ 65 years – 26 vs. 12%, $P < 0.001$), the longer history of CAD (>6 [median] vs. ≤ 6 years: 24 vs. 15%, $P < 0.001$) and concomitant heart failure (HF) (with vs. without HF: 31 vs. 13%, $P < 0.001$) were independently associated with the higher prevalence of AF (all $P < 0.05$). In patients aged >65 years, with CAD history of >6 years, and with coexistent HF, the prevalence of AF was 40%. In patients with CAD and AF, according to CHADS2 scale 73% of subjects required antithrombotic therapy (score ≥ 2) and according to CHA2DS2-VASc scale – 94% (score ≥ 2). 47% of patients with a CHADS2 score of 0 and 85% with a CHADS2 score of 1 had a CHA2DS2-VASc score ≥ 2 . In summary, 21% of patients with CAD and AF did not have clear indications for antithrombotic therapy according to CHADS2 scale (score: 0–1), while they required oral anticoagulation according to CHA2DS2-VASc scale (score ≥ 2).

Conclusions: AF affects every fifth ambulatory patient with CAD and in patients with advanced age, longer history of CAD and HF the prevalence is doubled. According to CHA2DS2-VASc scale almost all patients with CAD and AF require antithrombotic management, which makes the additional antiplatelet therapy challenging.

P2690 | BEDSIDE

Contribution of good control of cardiovascular risk factors or optimal medical treatment on quality of life in patients with stable angina. The AVANCE study. A national survey

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Purpose: To assess whether a good control of cardiovascular risk factors (CVRF) was associated with quality of life (QOL) in a national-wide survey of patients with stable coronary artery disease (SCAD).

Methods: Two thousand and twenty-four patients with SCAD were consecutively recruited in an observational, multicentric, transversal registry. Good control of CVRF was defined as: blood pressure $<140/90$ mmHg; glycaemic control, <111 mg/dL for non-diabetic and <126 mg/dL in diabetic patients; LDL cholesterol <100 mg/dL, heart rate <70 beats per minute. Seattle angina questionnaire (SAQ) questionnaire was filled by the patients.

Results: No CVRF or HR good control was present in only 25 patients. The number of well controlled CVRF was associated with younger age, male gender, heart failure, and had no association with stroke, optimal medical treatment (OMT, 52% of patients). Beta blockers (78% of patients), calcium channel blockers (40%), and statins (93%) were associated with better CVRF control, but not with antiplatelet therapy (96%), ACEI (41%) or ARB (32%). Bivariate analysis of all items of the SAQ questionnaire were associated with the number of well controlled CVRF (QOL improved as more CVRF were controlled). On multivariate analysis, the number of well controlled CVRF had an independent association with satisfaction with treatment, stability of angina SAQ domains, but not on perception of disease, frequency of angina and physical limitation SAQ domains. OMT had no independent association with QOL. In fact, the proportion of OMT was similar among all groups of control of CVRF (between 48.4% and 57.5%).

Conclusions: Despite reasonable rates of use of secondary prevention drugs, there is room for improvement among patients with SCAD in terms of good control of CVRF. Good control of CVRF rather than optimal medical treatment is independently associated with QOL as assessed with the SAQ.

P2691 | BEDSIDE

5-year-mortality and quality of life in the elderly with stable angina and documented coronary artery disease (CAD): Results of the STAR-Registry

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Background: First angiographic diagnosis of CAD is made at different ages dependent on onset of angina symptoms. Little is known about the 5-year-mortality and quality of life in the elderly compared to younger patients with newly diagnosed CAD.

Methods: Between Sept 2001 and March 2003, a total of 2,002 consecutive patients with angina pectoris and first angiographic diagnosis of CAD were enrolled in the STAR-Registry (50 centers). We compared outcome and quality of life in the elderly (≥ 75 years) and in younger (<75 years) patients at five years follow-up.

Results: Elderly patients more often were female, had more concomitant diseases as well as 3-vessels CAD. There were no differences in the use of PCI during the 5 years follow-up. The elderly showed a significantly higher 5-year-mortality. In the group of survivors more than half of the elderly complained of impaired quality of life (EuroQol D5-Score).

	Patients ≥ 75 years (18.9%)	Patients <75 years (81.1%)	p-value
Mean age	77.0%	64.0%	<0.0001
Females	49.2%	25.5%	<0.0001
Prior MI >4 weeks	7.9%	8.3%	=0.81
Prior stroke	7.4%	4.0%	<0.01
Creatinin >2 mg/dl	2.1%	0.5%	<0.01
Diabetes	30.4%	25.5%	<0.05
3-vessel disease	33.9%	24.0%	<0.0001
PCI	38.1%	47.8%	<0.001
5-year-mortality	34.1%	15.3%	<0.0001
MACCE (death, MI, stroke) @ 5 years	40.6%	21.6%	<0.0001
EQoL d5-score (some to severe problems)			
Mobility	53.8%	23.9%	<0.0001
Self care	22.3%	7.2%	<0.0001
Pain/discomfort	56.1%	38.4%	<0.0001
Anxiety/depression	25.3%	23.3%	=0.56
Condition today worse than last year	28.3%	17.6%	<0.001

Conclusion: 5-years-mortality was more than doubled in the elderly with stable angina. More than 50% of the elderly suffered from impaired mobility and quality of life.

P2692 | BEDSIDE

Fifteen years survival of patients with nonsignificant atherosclerotic changes of coronary arteries

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Hemodynamically nonsignificant atherosclerotic plaques are often found in patients indicated for coronary angiography. The aim of our study was to compare the fifteen years survival among patients with nonsignificant stenoses of coronary artery disease, patients with significant coronary artery stenoses and individuals with smooth coronary arteries diagnosed by coronary angiography.

Elective coronary angiography was performed in 671 consecutive patients with symptoms of coronary artery disease in 1998. Patients with other cardiac diseases were excluded from the trial. So, the final sample consisted of 600 individuals, of whom 489 had angiographic evidence of significant coronary artery disease (at least one diameter stenosis $\geq 50\%$), 42 minor atherosclerotic changes (diameter stenosis $<50\%$) and 69 smooth coronary artery. Gehan - Wilcoxon test with Bonferroni correction and the Cox proportional hazards model were used to compare the survival rates in 3 groups of patients.

We have found statistically significantly higher fifteen years survival for individuals with smooth coronary arteries (87%), compared with patients with significant coronary artery stenoses (61%) ($P_{\text{corr}} < 0.0001$) and also with coronary artery irregularities (62%) ($P_{\text{corr}} < 0.01$). In contrast, there was no statistical difference in survival between patients with significant atherosclerotic coronary artery disease and patients with insignificant changes. The differences were statistically significant even after including the effects of age and gender (smooth coronary arteries vs significant stenoses: $p < 0.05$, HR 2.25; smooth coronary artery vs insignificant atherosclerotic changes: $p < 0.05$, HR 2.57).

The results of our study indicate that long-term prognosis of patients with insignificant atherosclerotic changes is significantly worse than in individuals with smooth coronary arteries and roughly corresponds to patients with significant coronary artery disease. This finding supports the need for aggressive anti-atherosclerotic drug therapy in such individuals.

P2693 | BEDSIDE**Heart rate and quality of life in stable angina patients. AVANCE study. A national survey**

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Purpose: To assess whether heart rate (HR) was associated with quality of life (QOL) in a national-wide survey of patients with stable coronary artery disease (SCAD).

Methods: Two thousand and thirty-nine patients with SCAD were consecutively recruited in an observational, multicentric, transversal registry. There were 85 patients where HR was not available. Therefore 1954 patients were studied. Good heart rate control was considered when HR was <70bpm. Seattle angina questionnaire (SAQ) was filled by the patients.

Results: See Table. Patients with HR >70 bpm were more frequently women, had a higher rate of atrial fibrillation (AF), DM, hypertension, were more symptomatic (both angina episodes and number on GTN per week), and had a higher prevalence of comorbidities (i.e. stroke, COPD). There were also some baseline differences in medical treatment. HR <70 bpm was achieved in a 63% of patients. After adjustment with covariates significant at bivariate analysis, HR >70 bpm was independently associated with worse QOL (all items of SAQ but physical limitation).

	HR <70 bpm (n=1213)	HR >70 bpm (n=741)	p
Age, years	67.4±10.2	68.0±10.6	0.19
Male, %	76	68	<0.005
Heart rate, bpm	59.6±5.6	77.7±8.1	<0.005
Atrial fibrillation, %	9	15	<0.005
Heart failure, %	12	17	0.001
Diabetes mellitus, %	32	39	0.002
Beta blockers, %	80	72	0.001
Ivabradine, %	11	12	0.77
SAQ domains (healthy person = 100)			
Physical limitation	56.5±21.0	53.1±21.3	0.002
Angina stability	68.5±30.0	62.7±30.6	<0.005
Frequency of angina	84.8±19.8	80.4±21.8	<0.005
Treatment satisfaction	76.7±15.0	72.8±16.5	<0.005
Perception of disease	61.4±22.7	56.4±23.1	<0.005

Conclusions: HR <70 bpm was achieved in a 63% despite of extensive beta blocker use. HR <70 bpm is independently associated with QOL in patients with SCAD.

P2694 | BEDSIDE**Gender-related differences in coronary atherosclerosis severity in patients with premature coronary disease**

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Background: Coronary artery disease (CAD) remains the leading cause of death in Western and developing countries. Despite the advances in interventional and pharmacological treatment, in the group of young women with CAD mortality is even increasing. Reasons for this discrepancy remains unclear.

The aim of this study was to assess disease severity in women with premature CAD in comparison with men with premature CAD.

Materials and methods: The study prospectively included women and men with premature onset of CAD ≤55 and ≤45 yrs of age respectively. CAD was defined as presence of stenosis ≥50% in a major epicardial coronary artery on coronary angiography.

The disease severity was assessed by the modified Duke Coronary Artery Disease Index which classifies ≥50% stenosis as clinically significant and evaluates the number of vessels involved and the location of stenosis.

An obstructive coronary artery stenosis was defined as ≥75% stenosis in a major epicardial coronary and/or ≥50% stenosis in the left main (LM).

Results: The study included 283 women (mean age 46.7±5.4yrs) and 240 men (mean age 39.6±4.4yrs).

The mean value of modified Duke Coronary Artery Disease Index for entire group was 48.4±17.7; median 48. The mean value of the Index was higher in women as compared with men (49.9±17.9 vs 46.6±17.4; p=0.035).

There was no gender-related difference in number of patients who had at least one obstructive (≥75%) stenosis in coronary arteries (91.2% of women vs 94.2 of men; p=0.24).

However, in women the obstructive stenosis was more frequently located in the proximal left anterior descending coronary artery (LAD) and/or LM than in men (53.7% vs 44.6%; p=0.044).

Female gender was a significant predictor of the higher (≥median) modified Duke Coronary Artery Disease Index and of the presence of obstructive stenosis in proximal LAD and/or LM after adjustment for age, sex, hyperlipidemia, hypertension, diabetes and smoking (OR 2.14; p=0.002 and OR 2.2; p=0.0006 respectively).

Conclusions: Women with premature CAD as compared with men have more severe coronary disease burden. In patients with premature CAD women present with greater frequency of high-risk anatomy as compared with men, including significant proximal LAD and LM involvement.

P2695 | BEDSIDE**Long-term clinical outcomes in patients with coronary artery disease and moderate angina pectoris treated with enhanced external counterpulsation therapy**

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Background: Enhanced External Counterpulsation (EECP) therapy is a non-invasive circulatory assist device used commonly in the treatment of refractory angina. There are limited data on the long term outcomes of EECP therapy in patients with Class II angina. This study compares the efficacy, and 2-year survival rates free of major adverse cardiovascular events (MACE: CABG; PCI, MI, death) for patients with moderate angina (Class II) and severe angina (Class III/IV) treated with EECP.

Methods: Methods: The International EECP Patient Registry enrolled patients from 90 centers. Patients were divided into two groups; Moderate Angina Group (MAG: Class II: N=257) and Severe Angina Group (SAG: Class III/IV; N=2848). Comparisons between groups were analyzed using chi-square and t-tests. Follow-up events were analyzed using survival methods.

Results: Average age was 67 years in MAG; 66 in SAG. The previous invasive revascularization rate was lower in MAG (p<0.001); 81% in MAG and 90% in SAG had prior PCI or CABG. MAG had less hypertension, multivessel disease, congestive heart failure, prior MI and had lower rates of nitroglycerin usage and lower angina frequency (p<0.001). In both groups, patients were on optimal medical therapy as tolerated. After a mean treatment course of 34 hours, both groups showed a significant reduction in the severity of angina (78% vs 61%) Discontinuation of nitroglycerin usage was similar in both groups (>50%). MACE during the treatment period was low in both groups (<2%). Compliance with the treatment course was better in MAG (p<0.01).

At 2 year follow up 80% of MAG and 78% of SAG had maintained the improvement in angina class; 44% in MAG and 30% in SAG had no angina; discontinuation of nitro usage was maintained in both groups. Survival rate was 95% in MAG and 90% in SAG (p<0.01). MACE free survival rate was 82% in MAG vs 72% in SAG (p<0.001).

Conclusion: Patients presenting for EECP treatment with class II angina had different baseline profiles compared with Class III and IV angina. However, both cohorts achieved substantial reduction in angina with high event free survival rates at 2 years. For patients with stable Class II angina pectoris who were not candidates for further revascularization the best treatment options have not been fully defined. EECP appears to offer a safe and effective treatment option.

P2696 | BEDSIDE**N-3 to N-6 polyunsaturated fatty acid ratio is associated with atheroma progression in patients achieving very low levels of low-density lipoprotein cholesterol**

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Background: An aggressive reduction in low-density lipoprotein cholesterol (LDL-C) with statins produces regression or stabilization of coronary artery plaques. However, after achieving very low levels of LDL-C, atheroma regression is not observed in all patients. The purpose of the present study was to evaluate the determinants of atheroma progression despite achieving very low levels of LDL-C.

Methods: The effects of 8-month statin therapy on coronary atherosclerosis were evaluated using virtual histology intravascular ultrasound in the TRUTH study. Of these, 33 patients who achieved an on-treatment LDL-C level of <70 mg/dl were divided into 2 groups according to increase (progressors) or decrease (regressors) in plaque volume.

Results: At the 8-month follow-up, serum LDL-C and apolipoprotein B levels were significantly lower in progressors than in regressors; however, significant increases in high-density lipoprotein cholesterol and apolipoprotein AI and decreases in high-sensitivity C-reactive protein and oxidized LDL were observed only in regressors. The changes in the N-3 to N-6 polyunsaturated fatty acid ratios significantly differed between the 2 groups. Multivariate regression analysis showed that a decrease in the EPA + DHA/AA ratio was a significant predictor associated with atheroma progression ($\beta = -0.512$, $p=0.004$).

Conclusions: N-3 to N-6 polyunsaturated fatty acid ratios affected coronary artery plaque progression and regression in patients who achieved very low levels of LDL-C during statin therapy.

CORONARY ARTERY DISEASE AND COMORBIDITIES

P2698 | BEDSIDE

Prevalence of cerebrovascular events, associated clinical profile and treatment of patients with stable coronary artery disease: the results of the multicentre RECENT study

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Introduction: Atherosclerosis is a chronic systemic disease, which often takes the multifocal form, occupying more than one distinct vascular areas. The magnitude of concomitant symptomatic coronary artery disease (CAD) and cerebrovascular disease (i.e. transient ischemic attack (TIA) and/or stroke) remains unclear.

Methods: We analyzed data on 2,593 patients with stable CAD participating in the RECENT registry, constituting a representative group of the Polish outpatient CAD population.

Results: The prevalence of previous TIA and stroke among patients with stable CAD was 6.1% and 4.6%, respectively. Patients with atrial fibrillation (AF) accounted only for 19% of this group. TIA and/or stroke occurred in 8% vs 17% of patients without vs with AF ($p<0.0001$).

Patients without AF with previous TIA and/or stroke were older, more often suffered from heart failure (HF), arterial hypertension, dyslipidemia in comparison with those without TIA and/or stroke (all $p<0.05$). Patients with AF and a history of TIA and/or stroke were older, more often had angina in CCS class III/IV, HF and peripheral artery disease (PAD) as compared to those without TIA and/or stroke (all $p<0.05$).

We identified the following independent risk factors of higher prevalence of previous TIA and/or stroke in patients with stable CAD in a sinus rhythm: age of 65 years and more (11% vs. 6%), family history of CAD (12% vs. 7%), angina in CCS III/IV class (17% vs. 14%), hypertension (9% vs. 5%), dyslipidemia (10% vs. 6%) and PAD (17% vs. 7%) (all $p<0.05$). In patients with stable CAD and AF, the following risk factors were independently associated with the higher prevalence of previous TIA and/or stroke: angina in CCS III/IV class (29% vs. 27%) and PAD (35% vs. 15%) (all $p<0.05$).

Patients in a sinus rhythm with a history of TIA and/or stroke were more likely to receive angiotensin converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics and short-acting nitrates as compared to patients without neurological complications (all $p<0.05$). In the group of patients with AF, the history of TIA and/or stroke did not differentiate the applied treatment.

Conclusions: In a stable CAD population, almost every tenth patient in a sinus rhythm has suffered from cerebrovascular events, such as TIA and/or stroke, and among those with AF the risk has been almost doubled.

The presence of peripheral vascular disease and more severe angina symptoms are associated with the higher prevalence of previous neurological complications, regardless of the presence of AF and other classical cardiovascular risk factors.

P2699 | BEDSIDE

Coronary artery disease complications depend on pulse pressure dipping in old hypertensives

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Purpose: Pulse pressure, particularly estimated according to Ambulatory Blood Pressure Monitoring has recently played an increasing role in the cardiovascular risk assessment. The goal of our study was to evaluate the impact of diurnal pulse pressure profile on cardiovascular events in different age-groups of hypertensive patients with significant atherosclerosis established in coronary angiography. The present study is a part of PROGNOSIS study.

Methods: We enrolled 891 patients with coronary artery disease confirmed in angiography, 63.7±9.4 years of age. Clinic blood pressure measurement was performed and 24-hour ambulatory BP monitoring was obtained with BP readings set at 20-minute intervals (06:00 AM – 06:00 PM) and at 30-minute intervals (06:00 PM – 06:00 AM). Pulse pressure was calculated as difference between systolic and diastolic blood pressure values. Pulse pressure dipping was calculated as percentage of decrease in nighttime pulse pressure in relation to daytime pulse pressure values. The studied subjects were divided into three age groups: <65 years of age, 65-74 years of age and ≥75 years of age. During a follow-up period of 6.7 years in total, cardiovascular events were assessed.

Results: In the group ≥75 years of age in comparison to group <65 years of age were observed: higher values of 24 hour pulse pressure (60.7±12.3 mmHg vs. 49.4±9.9 mmHg, $p<0.01$), daytime (60.4±12.9 mmHg vs. 49.5±9.9 mmHg, $p<0.01$) and nighttime (61.3±12.4 mmHg vs. 49.2±10.6 mmHg, $p<0.01$). Moreover, nighttime pulse pressure/ daytime pulse pressure dipping ratio was signif-

icantly higher in patients ≥75 years of age in comparison to <65 years of age (1.1±0.1 mmHg vs. 49.2±10.6 mmHg, $p<0.01$). In the group ≥75 years of age in comparison to group <65 years of age higher total mortality (20% vs. 11%, $p<0.05$) and prevalence of major advanced cardiovascular event (42% vs. 30%, $p<0.05$) were observed. Only in the group ≥75 years of age pulse pressure dipping was associated with a hazard ratio of major advance cardiovascular events of 0.98 (95%CI 0.96-0.99, $p<0.03$), and revascularization (percutaneous coronary angioplasty or coronary by-pass grafting) with a hazard ratio of 0.98 (95% CI 0.97-0.99, $p<0.04$).

Conclusions: Pulse pressure dipping is a good indicator is related to major advance cardiovascular events and coronary revascularization in older hypertensive patients with coronary artery disease.

P2700 | BEDSIDE

Impact of coronary artery fixed lesion on 3-years clinical outcomes in vasospastic angina patients with myocardial bridge

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Background: It is not known whether the presence of angiographic fixed coronary lesion (FCL) can negatively impact on long-term major clinical outcomes in vasospastic angina patients (pts) with myocardial bridge (MB).

Methods: A total 5,882 patients (pts) underwent coronary angiography with acetylcholine (Ach) provocation test from Nov 2004 to Oct 2010. Among them, total 563 pts who had MB and documented significant coronary artery spasm (CAS) by Ach provocation test were enrolled. Study populations were categorized into two groups; the fixed coronary lesion (FCL) group (n=216) and the non-FCL group (n=347). Cumulative major clinical outcomes were compared between the two groups up to 3 years.

Results: Baseline characteristics were similar between the two groups except the incidence of elderly, hypertension, diabetes, and dyslipidemia were higher in the FCL group. In univariate analysis, only the composite end-point consisted of cardiac death, de Novo percutaneous coronary intervention (PCI), myocardial infarction (MI), and cerebrovascular accident (CVA) was higher in FCL group (Table). However, in multivariate regression analysis, the incidences of cardiac death, PCI, MI, CVA, recurrent chest pain, and other composite end-points were similar between the two groups up to 3 years.

Table. Three-year clinical outcomes

Variables, N (%)	Total (n=563)	FCL (n=216)	Non-FCL (n=347)	p-value
Cardiac death	1 (0.1)	1 (0.4)	0 (0.0)	0.381
Percutaneous coronary intervention (PCI)	1 (0.1)	1 (0.4)	0 (0.0)	0.384
Myocardial infarction (MI)	4 (0.7)	3 (1.3)	1 (0.2)	0.160
Cerebrovascular accident (CVA)	1 (0.1)	1 (0.4)	0 (0.0)	0.381
Recurrent chest pain	35 (6.2)	16 (7.4)	19 (5.4)	0.356
Cardiac death, PCI, MI	5 (0.8)	4 (1.8)	1 (0.2)	0.071
Cardiac death, PCI, MI, CVA	6 (1.0)	5 (2.3)	1 (0.2)	0.033
Cardiac death, PCI, MI, CVA, Recurrent chest pain	37 (6.5)	18 (8.3)	19 (5.4)	0.181

Conclusions: In our study, the presence of angiographic fixed coronary lesion in vasospastic angina pts with MB was not a predictor of adverse long-term clinical outcomes.

P2701 | BEDSIDE

Spontaneous coronary artery dissection single centre experience with systematic angiographic followup

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Introduction: Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome. Evidence is based on single case reports, whereas only few larger case series have been published. In particular, there are no studies with systematic angiographic follow-up. We describe clinical characteristics, treatment, and angiographic follow-up of a contemporary SCAD population

Method: Over a 15 years period we systematically collected patients presenting with SCAD at our institution. A follow-up angiography was offered to all patients.

Results: There were 56 patients with SCAD (mean age 51±11 years, 93% females, three patients with peripartum SCAD). All patients had acute coronary syndrome. The following vessels were affected: left main (n=1), left anterior descending artery (n=25), left circumflex artery (n=28), right coronary artery (n=2). One patient underwent coronary bypass grafting, five patients underwent percutaneous coronary intervention (PCI), and 51 patients were treated medically. One patient with peripartum left main SCAD died from cardiogenic and hemorrhagic shock during emergency PCI. All other patients were discharged in a stable condition. Twenty-nine patients (three of them after PCI) underwent a follow-up angiogram (median 6 (interquartile range, 5-19) months after the index event: one patient with SCAD of the posterior descending artery of the right coronary artery who was treated conservatively developed out-of-hospital cardiac arrest a few

days after the first angiogram, was found to have a persistent dissection at the second angiogram which was still treated medically, had a complicated clinical course including multiorgan failure but finally survived with only minimal neurological sequelae. Two medically treated patients presented with a second event more than a year after the first event and were found to have SCAD in a second vessel, while the initially affected vessel was angiographically normal. In all other patients (n=26), there was a good angiographic result after PCI (n=3), or the vessel was angiographically normal after medical therapy (n=23).

Conclusion: In the majority of cases, SCAD can be treated medically with a good clinical result and complete angiographic resolution of the dissection after months. However, rarely SCAD is a catastrophic event resulting in death, and in some patients, the dissection persists leading to additional events, and some patients have SCAD in a second vessel.

P2702 | SPOTLIGHT

Anemia prognosis significance on admission in patients undergoing percutaneous coronary intervention; up to 4 years of follow up

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Purpose: Anemia is common before percutaneous coronary intervention (PCI). Numerous studies have shown the prognostic value of anemia in patients with acute coronary syndrome (ACS). Few studies have investigated the long-term impact and in-hospital prognosis of anemia on admission in patients undergoing PCI and constitutes the aim of this study.

Methods: We performed a single-center observational study with prospective follow-up of 759 consecutive patients undergoing PCI between 2007 and 2011. Anemia was defined according to OMS's criteria (hemoglobin <13 g/dl in men and <12 g/dl in women). We evaluated the relationship between anemia on admission with cardiovascular events and long-term mortality (mean follow-up 26.5±14.4 months).

Results: Anemia on admission was observed in 226 (29.8%) patients. Patients with anemia on admission were older (72±10 vs 64±11 years, p<0.001), female (23.5 vs 15.2%, p=0.006), and diabetic (47.3 vs 31.5%, p<0.001) hypertension (76.1 vs 63.4%, p=0.001). Most often patients were previously treated with anticoagulants (14.2 vs 7.3%, p=0.003) antiplatelets (58.4 vs 44.1%, p<0.001) had increased prevalence of acute myocardial infarction on admission (59.7 vs 49.2%, p=0.008), lower creatinine clearance (66.5±29.6 vs 78.9±23 ml/min/1.73m², p<0.001) and higher levels of C reactive protein (35.5±54.5 vs 13.2±25.6 mg/l, p<0.001). While hospitalized had a higher incidence of contrast-induced acute kidney injury (15 vs 6%, p<0.001), bleeding complications (19.5 vs 8.6%, p<0.001), need for transfusion (6.6 vs 6%, p<0.001) and mortality (5.3 vs 1.5%, p=0.003). During long-term follow-up patients with anemia on admission had a higher incidence of readmissions (59.7 vs 47.7%, p=0.002), acute myocardial infarction with ST segment elevation (4.5 vs 1.7%, p=0.027), stroke (5.8 vs 2.1%, p=0.008) cardiac mortality (8 vs 2.8%, p<0.001) as well as all cause mortality (20.4 vs 4.9%, p<0.001). Lastly, anemia on admission was associated to lower survival at follow up (45.3±1.5 vs 52.1±0.5 months, log-rank p<0.001). Cox regression analysis showed that the anemia was an independent predictor of all cause mortality (adjusted hazard ratio = 2.1, 95% confidence interval 1.1 to 4.1, P=0.028).

Conclusion: Patients with anemia on admission are numerous and have both poorer in hospital and long term prognosis as well as increased long-term mortality.

P2703 | BEDSIDE

Low high-density lipoprotein cholesterol level on admission was predictor of in-hospital mortality in patients with acute coronary syndrome

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Background: In-hospital mortality of patients with acute coronary syndrome (ACS) is desired to be predicted at the timing of hospital admission. Previous reports had shown that patient's backgrounds and physical findings predicted in-hospital mortality in patients with ACS (e.g. GRACE score). However, association between lipid profile on admission and in-hospital mortality was unclear.

Methods: Consecutive 638 ACS patients (including ST-elevated myocardial infarction, non-ST-elevated myocardial infarction and unstable angina), who admitted to our hospital from October 2010 to July 2013, were retrospectively surveyed and possible determinants associated with in-hospital mortality were assessed.

Results: Overall in-hospital mortality was 5.9%. Multivariable analysis demonstrated that low HDL cholesterol level, elevated troponin T and high Killip class were independent predictors of in-hospital mortality (Table). In-hospital mortality in ACS patients with low HDL cholesterol level on admission was significantly worse compared with those with high HDL cholesterol level (P<0.05 by Log rank test). In ACS patients with multi-vessel coronary artery disease, HDL levels were significantly lower than those with single-vessel coronary disease (47.0mg/dl vs. 49.5mg/dl, P<0.05).

Table 1. Logistic regression analysis

	Univariate analysis			Multivariate analysis		
	P value	OR	95%CI	P value	OR	95%CI
Age	0.027	1.035	1.004–1.066	0.746	1.006	0.970–1.044
Male sex	0.693	1.286	0.509–2.763			
Smoking	0.005	0.368	0.184–0.737	0.371	0.686	0.300–1.567
Elevated Troponin T	0.028	3.830	1.159–12.652	0.028	4.045	1.159–14.114
Killip class ≥3	<0.001	14.414	6.945–29.917	<0.001	13.545	6.240–29.398
Defibrillation in out-of-hospital	0.857	0.829	0.108–6.368			
ST elevation	0.095	1.980	0.889–4.410			
Chronic kidney disease	0.300	1.427	0.728–2.794			
HDL cholesterol level	0.017	0.964	0.936–0.993	0.038	0.967	0.936–0.998
LDL cholesterol level	0.114	0.993	0.984–1.002			
TG level	0.168	0.996	0.991–1.002			

Conclusions: Besides well-known determinants, low HDL cholesterol level on admission was an independent predictor of in-hospital mortality in ACS patients.

P2704 | BEDSIDE

Troponin-I level after major noncardiac surgery and its association with long-term mortality: A retrospective cohort study with seven year period

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Purpose: The purpose of this study was to evaluate the long-term impact of cardiac troponin elevation on clinical outcome after major noncardiac surgery. Individuals with intermediate to high cardiac risk for major noncardiac surgery suffer from perioperative myocardial ischemic injury.

Methods: Patients (n=750) aged ≥50 years who underwent major noncardiac surgery were eligible for the study. Postoperative cardiac troponin-I data were collected retrospectively. The primary outcome measure was all-cause mortality.

Results: Up was 1727 days in all patients. Among 750 patients, 92 (12.2%) showed elevated postoperative troponin-I above 0.10 ng/mL. Operative mortality was 4.1% (31 subjects), and patients with perioperative troponin-I elevation showed a higher operative mortality rate (Odds ratio [OR] = 5.85, 95% confidence interval [CI]: 2.76 – 12.40, p<0.001). In multivariate regression, postoperative troponin-I concentration above 0.10 ng/mL was associated with all-cause mortality (OR = 1.70, 95% CI 1.05 – 2.74, p=0.030). It should be noted that there was a significant difference between patients with elevated and non-elevated troponin-I in the rate of mortality until 6 months. However, these differences disappeared after 6 months. In addition, age over 70 years, male sex, presence of chronic kidney disease, lower hemoglobin level, and heart rate more than 80 beats per minute were independent predictors of long-term mortality in major noncardiac surgery.

Conclusion: I level confers increase in mortality during the 7 year follow-up period after major noncardiac surgery. This difference of mortality was mainly derived from the result within the first six months.

P2705 | BEDSIDE

Vein grafts and progression of atherosclerotic disease after coronary artery bypass surgery

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Background: We sought to characterise patterns of native coronary artery disease progression after primary CABG and to examine the effects of conduit type on disease behaviour.

Methods: 405 patients enrolled into a randomized study of coronary bypass conduits underwent surveillance angiography as determined by trial protocol irrespective of symptoms. Mean duration of follow up was 6.2±3.1 years. Each major native coronary vessel was interrogated and assigned a grade; Grade 0 is a non-flow-limiting lesion of 0-39%, grade 1 is a moderate lesion of 40-69%, grade 2 is a flow-limiting lesion of 70-80%, grade 3 is a severe lesion (81-99%) and grade 4 represents total occlusion (100%). Native vessel disease progression (NVDP) is defined as an increase of two or more grades of stenosis or progression to occlusion between the pre and post-operative angiograms. The presence of disease progression was correlated with vessel location and conduit type.

Results: NVDP occurred in 19.5% of all coronary vessels analysed and was similar across territories at 18.9%, 21.4% and 19.8% for the anterior, lateral and inferior territories respectively. Native arteries which were diseased at the time of surgery were more likely to progress than their un-diseased counterparts (27.9% vs. 12.4%, p<0.001). The presence of a saphenous vein graft was associated with significantly increased risk of progression, both when compared to analogous vessels receiving arterial conduits and to diseased vessels which were left ungrafted. Freedom from NVDP at 1, 5 and 10 years is estimated at 98.8%, 86.5% and 46.2% for territories bypassed with a SVG compared with 97.5%, 85.3% and 57.3% for the RA (p=0.043); with 99.6%, 93.1% and 64% for the RITA (p<0.001) and with 98.2%, 88.6% and 58.7% for ungrafted vessels (p=0.018).

Discussion: Vein grafts are associated with increased risk of NVDP in addition to their poorer long term patencies compared with arterial grafts, making them an inferior conduit choice for revascularization.

P2706 | BEDSIDE**Factors associated with CPAP acceptance in the patients with sleep apnea and cardiovascular disease**

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Background: Although excessive daytime sleepiness (EDS) is one of the main treatment target of continuous positive airway pressure (CPAP), many of patients with sleep apnea syndrome (SAS) and cardiovascular disease (CVD) does not have subjective daytime sleepiness. We examined the acceptance rates of CPAP in CVD patients with an AHI greater than 20 and the factors associated with CPAP acceptance.

Methods: Data were collected from consecutive adult patients referred to our department of cardio-vascular medicine, university school of medicine unit from May 2010 to October 2012. We prospectively screened 309 patients with CVD for SAS using full polysomnography, and offered CPAP to 168 patients (54.4%) who meet the clinical criteria for CPAP therapy (AHI $\geq$ 20) regardless of their clinical symptoms and complaints. To determine the differences between acceptors and refusers, demographic variables, subjective sleepiness (Epworth Sleepiness Scale), polysomnographic variables, the types of sleep apnea, depressive symptoms (Patient Health Questionnaire-9), sleep habits (PSQI), QOL (EQ-5D) and echocardiographic evaluation of cardiac function were compared. Regression analysis was performed to identify factors associated with acceptance.

Results: Most of subjects (91.1%) did not complain of EDS. Of the 168 patients, 70 patients (41.7% acceptance rates) were prescribed CPAP. Of the 98 refusers, 67 did not even try the CPAP titration, and the rest of 31 patients refused to use CPAP after one night of CPAP titration. CPAP acceptance was associated with higher EDS, lower QOL, higher subjective sleep disturbance (PSQI: C5) and higher obstructive apnea index, but not age, AHI, PHQ-9, sleep architecture and any cardiac function.

Conclusion: CPAP acceptance is low in Japanese patients with CVD. The absence of subjective sleepiness in CVD patients may reduce the acceptance rate of CPAP.

P2707 | BEDSIDE**Time-dependent impact of pre-infarction angina pectoris and intermittent claudication on mortality from myocardial infarction as measures of endogenous local and remote ischemic preconditioning**

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Purpose: Local and remote ischemic preconditioning are cardioprotective mechanisms. We examined the time-dependent impact of pre-infarction angina pectoris and intermittent claudication on short- and long-term mortality following myocardial infarction.

Methods: We conducted a nationwide population-based cohort study using medical registries. We identified all first-time hospitalizations for myocardial infarction in our country between 1996 and 2012. We used Cox regression to compute mortality rate ratios (MRRs) within 30 days, 31-365 days, 1-5 years, and 6-10 years comparing patients with and without previous angina or intermittent claudication. We repeated the analyses according to time between first diagnosis of angina or intermittent claudication and subsequent myocardial infarction ($\leq$ 7 days, 8-14 days, 15-30 days, 31-90 days, and $>$ 90 days). We adjusted for age, sex, calendar period of diagnosis, and comorbidities.

Results: We identified 150,480 patients with first-time myocardial infarction, among whom 23,705 (15.8%) had previously been diagnosed with stable angina, 3,806 (2.5%) with unstable angina, and 3,740 (2.5%) with intermittent claudication. Compared to patients without previous stable or unstable angina, the adjusted 30-day MRR was 0.85 (95% CI: 0.82-0.88) for patients with prior stable angina and 0.67 (95% CI: 0.61-0.74) for patients with prior unstable angina. The mortality reduction was higher the shorter time interval between angina presentation and myocardial infarction and higher for unstable than stable angina. Thus, the 30-day MRR was 0.33 (95% CI: 0.20-0.55) for patients presenting with unstable angina within 7 days before myocardial infarction compared to myocardial infarction patients without previous angina. Beyond 30-days of follow-up, there was no additional survival benefit of pre-infarction angina. Independent of time to myocardial infarction, patients with intermittent claudication had increased short and long-term mortality.

Conclusions: Pre-infarction angina, but not intermittent claudication, improved 30-day mortality following myocardial infarction. The dependency of time and angina type, suggests an effect of endogenous local ischemic preconditioning. The results for intermittent claudication may reflect an absent remote preconditioning effect or the higher comorbidity burden among these patients.

P2708 | BEDSIDE**Lipid profile after acute coronary syndrome in HIV-infected individuals. Results from the PACS-HIV case-control study**

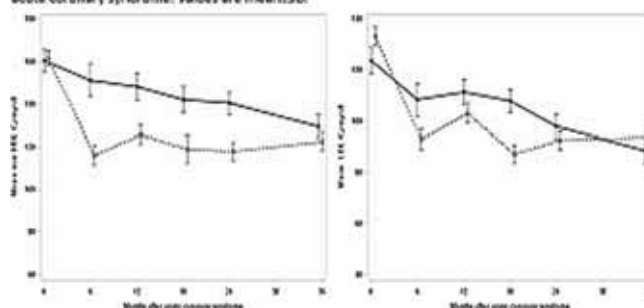
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Purpose: To compare the lipid parameters evolution and goals achievement between HIV-infected (HIV+) and uninfected individuals (HIV-) under statin therapy after acute coronary syndrome (ACS).

Methods: Fasting lipid parameters (Total Cholesterol, LDLc, HDLc, Non-HDLc, triglycerides, Total Chol/HDLc ratio) were collected during the prespecified 3-year follow up of the PACS-HIV study (Prognosis of Acute Coronary Syndrome In HIV-infected patients). The lipid goals were assessed using the updated NCEP-ATP III guidelines. A mixed model for repeated measures was used to compare the evolution of lipid values over the entire follow-up between the two groups. Logistic regression was used to compare the probability of achieving the goal of lipid control.

Results: 95 HIV+ and 187 HIV- enrolled prospectively in the PACS-HIV study (mean age of the cohort 49 years, 94% men) received statin therapy at month 1. At baseline, lipid parameters were similar in both groups except for a higher level of triglycerides in HIV+ (238.9 $\pm$ 179.7 mg/dL vs 166.9 $\pm$ 125.1 mg/dL, p=0.001). Six months after ACS a significant decrease of LDL-C was observed in the HIV-group (p<0.0001), while in the HIV+ group the decrease was not significantly different (p=0.06) (Figure 1). Concomitantly, the NCEP ATPIII goals for all atherogenic lipid lipoproteins were less frequently achieved in the HIV+ group as compared to the HIV- group during the first 18 months. At 18 months, NECP ATPIII LDL goal was reached by 43% of HIV+ and 72% HIV- patients, p=0.002 while at 36 months no significant difference was observed.

Figure 1. Lipids level among HIV-infected (continuous line) and HIV-uninfected (dotted line) individuals who were prescribed statin medication in the first month following an acute coronary syndrome. Values are means $\pm$ SD.



Conclusions: Both LDL decrease and LDL goal attainment are less frequently achieved in HIV+ as compared to HIV- during the first 18 months after ACS. This early higher residual cardiovascular risk warrants particular attention.

P2709 | BEDSIDE**Low LDL cholesterol in acute myocardial infarction patients: friend or foe?**

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Introduction: High LDL cholesterol is both an etiologic and a prognostic factor in acute myocardial infarction (AMI). There is scarce literature concerning patients with ACS and low levels of LDL cholesterol (and not on statin therapy).

Objective: The aim of this study was to describe the rare population of patients with AMI and LDL below 100 mg/dL and to compare several clinical and analytical variables between this population and those with LDL levels $\geq$ 100 mg/dL or on statin therapy.

Methods: Retrospective observational study that included all AMI patients admitted to a single Coronary Care Unit at a tertiary hospital between January 2004 and August 2013. Patients were divided into two groups according to LDL cholesterol levels and previous statin therapy: group 1) patients with LDL $<$ 100 mg/dL and no previous statin therapy; group 2) patients with LDL $\geq$ 100 mg/dL or previous statin therapy.

Results: Retrospective analysis of 1169 AMI patients with clinical data concerning LDL cholesterol levels and previous statin therapy. 123 patients had LDL below 100 mg and were not on statins (group 1) and the remaining 1046 patients either had LDL levels equal or above 100 mg/dL or were on statin therapy (group 2). Group 1 patients were older (73 $\pm$ 11 vs. 69 $\pm$ 11; p<0.001) and had a higher BMI (27.0 $\pm$ 4.4 vs. 28.1 $\pm$ 4.5; p=0.012). Regarding past medical history, patients with lower LDL had a higher prevalence of Type 1 Diabetes Mellitus (11.6 vs. 4.0; p<0.001). Prevalence of other cardiovascular risk factors like hypertension, smoking, family history of coronary artery disease and type 2 Diabetes mellitus

were not statistically different between groups. Patients with lower LDL had higher scores on GRACE score (156 ± 40 vs. 142 ± 34 ; $p < 0.001$) and higher admission troponin (21.1 ± 41.2 vs. 16.8 ± 0.87 ; $p = 0.002$) but coronary anatomy was not different between groups. Group 1 patients had higher creatinine levels (1.40 ± 0.92 vs. 1.23 ± 0.87 ; $p = 0.008$) and lower estimated glomerular filtration rate (56.9 ± 34.0 vs. 68.8 ± 36.8 ; $p < 0.001$). In hospital mortality rates were similar in both groups (6.5% vs. 4.4% , $p = 0.292$).

Conclusion: This exploratory study found some intriguing associations in the rare population of patients with low LDL levels and acute coronary syndrome. In fact, as this population had a higher prevalence of type one diabetes mellitus and lower glomerular filtration rates, it is possible that the beneficial role of a low LDL level was superimposed by a higher prevalence of the former cardiovascular risk factors or blunted by the pleiotropic effects in the statin-treated cohort.

ACUTE CORONARY SYNDROMES – INTERESTING TOPICS

P2711 | BENCH

Age and gender differences in occurrence of ST-elevation myocardial infarction: a population based cohort study

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Purpose: Efficient and cost-effective coverage of 24/7 primary PCI service for ST-elevation myocardial infarction (STEMI) is problematic to establish and should be based on the STEMI risk of serviced population. We studied age- and gender specific risks of STEMI at the population level.

Methods: Age and gender differences in STEMI occurrence were studied using a nationwide, population based ($n = 26\,723\,956$ person-years) registry of hospital admissions in patients aged ≥ 30 during 2001–2008. We included admissions with STEMI as primary (91%), secondary (7%) or tertiary (2%) discharge diagnosis. Hospitals with coronary angiography that treat emergency patients ($n = 22$) were included in study. Hospital transfers (14% of admissions) during the same treatment period were combined as one admission. Incidence was calculated using age and gender matched population data.

Results: The study period included 27 993 STEMI admissions of which 66.0% (95%CI 65.0–66.9%) occurred to men and 34.0% (95%CI 33.4–34.7%) to women, RR 2.37 (95%CI 2.05–2.74, $p < 0.0001$). Female patients were significantly older than men (74.3 ± 11.7 vs. 64.7 ± 12.4 years, $p < 0.0001$). Age-standardized incidence of STEMI admission was 91.8 (95%CI 90.6–92.9) /100 000 person-years overall, 140.1 (95%CI 138.0–142.1)/100,000 in men and 52.1 (95%CI 50.9–53.3)/100,000 in women. Men had a 3.03 (95%CI 2.86–3.21; $p < 0.0001$) fold age-adjusted relative risk of STEMI compared to women with highest risk difference in population under 55 years of age (RR 5.94; 95%CI 5.36–6.58, $p < 0.0001$). Incidence increased with age up to 90 years-old, with estimated gender-adjusted increase rate of 41% (95%CI 40%–42%; $p < 0.0001$) per 5-year increase in age. STEMI incidence had a slowly declining trend (-2.2% ; 95%CI -3.4 to -1.0% per year, $p < 0.001$) during the study period.

Conclusions: Men have a tripled overall risk for STEMI compared to women with highest relative risk in younger adults. Incidence of STEMI admissions increases with age by estimated rate of 41% per 5-years of age.

P2712 | BEDSIDE

Gender differences in the cardiovascular risk profile of patients admitted with ST-elevation myocardial infarction – results from the Bremen STEMI registry

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Introduction: While the importance of cardiovascular risk factors in the pathogenesis of coronary artery disease is well established there is few data on their association with gender in patients with acute myocardial infarctions. Aim of this study was to analyze gender differences of the cardiovascular risk profile in patients presenting with acute ST-elevation myocardial infarctions (STEMI).

Methods and results: Between 2006 and 2013 a total of $n = 5620$ patients with STEMI were admitted to the Bremen heart center and then documented in the Bremen STEMI registry (BSR). 4056 (72%) of patients were male and 1564 (28%) were of female gender. Since at time of STEMI women were on average older than men (69.3 ± 13 yrs. vs. 61.5 ± 13 yrs., $p < 0.01$) all data had to be adjusted for age. Patients were assigned to two groups: those with a first coronary event (first event, $n = 4505$ (80%)) and those with previously known coronary artery disease (known CAD, $n = 1115$ (20%)). In patients with a first event women were more likely to show hypercholesterolemia (total cholesterol ≥ 240 mg/dl) and to be obese ($\text{BMI} > 30 \text{ kg/m}^2$) than male patients while the prevalence of diabetes mellitus was lower in women and the proportion of active smokers showed no gender bias (Table). In patients with known CAD however the proportion of active smokers was lower in women than in men while the prevalence of hypercholesterolemia as well as obesity remained higher in women. However women were less often

on medication with HMG-CoA reductase inhibitors ("statins") prior to STEMI than men (18 vs. 23%, OR 0.74, 95% CI 0.67–0.81, $p < 0.01$).

Table 1. Age adjusted risk profile of female vs male patients with STEMI

		Hyperchol. (TC ≥240 mg/dl)		Obesity (BMI > 30 kg/m ²)		Smoking		Diabetes mellitus				
		%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)			
First event												
Female	30	1.61	(1.4–1.8)	29	1.28	(1.2–1.4)	46	1.0	(0.9–1.2)	17	0.8	(0.6–0.9)
Male	21		24	47		19						
Known CAD												
Female	24	2.65	(2–3.5)	31	1.68	(1.3–2.1)	27	0.7	(0.6–0.9)	31	1.79	(1.4–2.2)
Male	11		21	35		21						

Conclusions: Age adjusted data from the Bremen STEMI registry demonstrates that women with ST-elevation myocardial infarctions (STEMI) show a more severe cardiovascular risk profile: In comparison to men they present with higher rates of hypercholesterolemia and obesity while being less often on premedication with HMG-CoA reductase inhibitors ("statins").

P2713 | BEDSIDE

Acute coronary syndromes in women of reproductive age

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Objectives: Data about younger women with Acute Coronary Syndromes (ACS) is very limited. The aim of this study was to compare women with ACS in the reproductive age compared with older women using a 20-year national registry.

Methods: Retrospective analysis of all women hospitalized with ACS in our country from 1991 through 2010 was made. Patients were divided into two groups according to age. Clinical characteristics and outcomes were compared.

Results: During the 20-years period; 2472 women were hospitalized with ACS; 359 patients aged 15–49 years and 2113 patients aged 50 years and above. There was a significantly lower prevalence of diabetes mellitus, hypertension, chronic renal impairment and underlying ischemic heart disease in younger women compared to older women. Heart failure and atrial fibrillation were significantly more common complications in elderly women [table]. The in-hospital mortality rate was significantly lower in women in the reproductive age compared to older women (7% vs. 11.2%; $P = 0.02$).

Table 1

Variable	Women 15–49 yrs	Women 50 & above	P value
Age in year (mean $\pm$ SD)	43 $\pm$ 5.5	65 $\pm$ 10	0.001
Body mass index (kg/m^2) (mean $\pm$ SD)	31 $\pm$ 7.5	30 $\pm$ 7	0.09
Current smoker	21 (5.8)	68 (3.2)	0.01
Hypertension	179 (49.9)	1503 (71.1)	0.001
Diabetes mellitus	184 (51.3)	1441 (68.2)	0.001
Chronic renal impairment	12 (3.3)	152 (7.2)	0.007
Dyslipidemia	95 (26.5)	576 (27.3)	0.75
Prior myocardial infarction	43 (12)	440 (20.8)	0.001
Atrial fibrillation	3 (0.8)	94 (4.4)	0.001
Heart failure	26 (7.2)	323 (15.3)	0.001
Valvular heart disease	1 (0.3)	18 (0.9)	0.25
Total hospital stay (days, mean $\pm$ SD)	4.7 $\pm$ 3.7	6 $\pm$ 4.6	0.001
In-hospital Mortality	25 (7)	236 (11.2)	0.02

Data are expressed in numbers (%) of patients unless otherwise indicated.

Conclusions: Although women in the reproductive age have more favorable cardiac risk profiles, the observed mortality remains high. The current study underscores the need to study women in this age group in other ethnicities.

P2714 | BEDSIDE

Association of pre-infarction angina and total ischemic time with long-term survival in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Purpose: The cardioprotective effects of pre-infarction angina in ST-segment Elevation Myocardial Infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) are still controversial. This study aimed to investigate the influence of pre-infarction angina on clinical outcomes and assess the association of pre-infarction angina and total ischemic time with long-term survival in STEMI patients undergoing primary PCI.

Methods: The CREDO-Kyoto AMI Registry is a multicenter registry enrolling consecutive 5429 patients with acute myocardial infarction undergoing primary PCI from January 2005 to December 2007. Pre-infarction angina was defined as angina within 48 hours of hospital arrival for the index STEMI. The current study consisted of 3476 patients who underwent primary PCI within 24 hours of

symptom onset and in whom the data on pre-infarction angina was available. The median follow-up period was 1845 days.

Results: Pre-infarction angina was present in 675 patients (19%). The infarct size estimated by peak creatinine phosphokinase was significantly smaller in patients with pre-infarction angina than in patients without pre-infarction angina (median: 2141 IU/L versus 2462 IU/L, $p < 0.001$). The cumulative 5-year incidence of death was significantly lower in patients with pre-infarction angina compared with patients without pre-infarction angina (12.4% versus 20.7%, $p < 0.001$). After adjustment for confounders, pre-infarction angina was independently associated with a lower risk for death (adjusted hazard ratio 0.69, 95% confidence interval 0.54–0.86, $p = 0.001$). According to total ischemic time (≤ 3 hours: short, 3–6 hours: mid, or 6–24 hours: long), the cumulative incidence of death in patients with pre-infarction angina was consistently lower than that in patients without pre-infarction angina. Furthermore, the cumulative incidence of death in patients with pre-infarction angina in both mid and long total ischemic time was almost equal to that in patients without pre-infarction angina in short total ischemic time.

Conclusions: Pre-infarction angina was independently associated with lower 5-year mortality in STEMI patients undergoing primary PCI. The presence of pre-infarction angina as well as total ischemic time might be important as the determinants of long-term survival in STEMI patients.

P2715 | BEDSIDE

Identification of acute, spontaneous myocardial infarction in patients with atrial fibrillation and chest pain by use of a contemporary sensitive troponin I assay

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Introduction and aim: Introduction of more sensitive troponin assays has facilitated diagnosis of acute myocardial infarction due to improved sensitivity with corresponding loss of specificity. Atrial fibrillation is associated with elevated troponin levels independent of coronary status. The aim of the present study was to evaluate the diagnostic performance of troponin I in patients with suspected acute coronary syndrome and prevalent atrial fibrillation.

Material and methods: Contemporary sensitive troponin I (99th percentile cut-off 0.032 ng/mL) was assayed in a validation cohort of 90 patients with suspected acute coronary syndrome and prevalent atrial fibrillation to establish diagnostic cut-off values. These thresholds were then tested in an independent validation cohort of 314 patients with symptoms suggestive of a myocardial infarction and atrial fibrillation upon presentation. Additionally, changes in troponin I concentration within 3 h after admission were used as a diagnostic criterion.

Results: In the derivation cohort an unweighted optimized diagnostic threshold (0.04 ng/mL) as well as cut-offs for a rule-out strategy with high sensitivity (0.019 ng/mL) and for a rule-in strategy with high specificity (0.09 ng/mL) were established. Application of the unweighted and the specificity-optimized cut-offs in the validation cohort upon admission led to a positive predictive value of 73% and 88% compared with 71% if using the 99th percentile cut-off. The sensitivity-optimized and the unweighted cut-offs were associated with a negative predictive value of 99% and 100% in the validation cohort 3 h after admission. In patients with troponin I levels above the specificity-optimized threshold upon admission, additional use of the 3-h change in absolute/relative concentrations yielded a positive predictive value of 96%/100% compared with application of the 99th percentile upon admission with 71%.

Conclusion: The concentration of troponin I, including 3-h changes in its concentration, provides valid diagnostic information in patients with suspected acute, spontaneous myocardial infarction and prevalent atrial fibrillation. Due to atrial fibrillation-associated elevation of troponin I levels, application of diagnostic cut-offs other than the 99th percentile might be beneficial.

P2716 | BEDSIDE

Painless myocardial ischemia frequency in patients with unstable angina and attendant subclinical hypothyroidism

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Background: Subclinical hypothyroidism (SH) is a strong indicator of risk for atherosclerosis and myocardial infarction in elderly woman, it is associated with a moderately elevated risk of heart failure events and increased risk for cardiovascular mortality among older adults.

Purpose: To assess the role of SH in ischemic damage of myocardium and development of painless myocardial ischemia by acute coronary syndrome without ST-segment elevation.

Design: The study includes 24 patients (F/M: 18/6, mean age 60.4±3.2 years)

with acute coronary syndrome without ST-segment elevation (unstable angina) and attendant SH. Control group includes 22 patients (F/M: 16/6, mean age 61.1±3.4 years) with acute coronary syndrome without ST-segment elevation (unstable angina) with normal thyroid function. All patients determined concentration of cardiac troponin T (cTnT), underwent electrocardiography, echocardiography, Holter monitoring, and most of them (61%) – coronary angiography.

Results: The patients with unstable angina and attendant SH showed significantly higher median concentrations of cTnT than patients with normal thyroid function (0.6±0.2 versus 0.4±0.1 ng/ml, $p < 0.01$). Also significant but inverse and weaker correlation was obtained between cTnT level and left ventricular ejection fraction ($r = -0.61$, $p < 0.01$). Painless myocardial ischemia in patients with unstable angina and attendant SH was observed 2.2 times more frequent than in control (54.5% versus 25.2%; $p < 0.001$).

Conclusion: In patients with acute coronary syndrome without ST-segment elevation (unstable angina) and subclinical hypothyroidism are more expressed manifestation of ischemic damage indices, that can be additional risk factor for development of myocardial infarction and cardiac complications. Our data seems to indicate close relationship between subclinical hypothyroidism and painless myocardial ischemia.

P2717 | BEDSIDE

Novel dual-biomarker strategy and clinical judgment in the detection of exercise-induced myocardial ischemia

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Background: Assessment of coronary artery disease (CAD) currently is a resource-intensive process. The aim of this study was to investigate whether a dual-biomarker strategy quantifying two complementary pathophysiological signals (subclinical cardiomyocyte injury and hemodynamic cardiac stress) by measuring B-type natriuretic peptide (BNP) and either high-sensitivity cardiac troponin (hs-cTn) T or hs-cTnI can be used to diagnose exercise-induced myocardial ischemia in patients without known CAD.

Methods: We included 234 patients without previously known CAD referred for rest/stress myocardial perfusion single photon emission tomography (SPECT). BNP, hs-cTnT and hs-cTnI were obtained immediately before stress-testing in a blinded manner, followed by exercise stress testing. All clinical information available to the treating cardiologist was used to quantify the clinical judgment regarding the presence of myocardial ischemia using a visual analogue scale (VAS) twice: once prior and once after exercise stress testing. The VAS was then compared to the AUC obtained by logistic regression to combine the values of both biomarkers. The presence of myocardial ischemia was adjudicated based on perfusion SPECT combined with coronary angiography findings.

Results: Myocardial ischemia was detected in 49 (21%) participants. Median levels of biomarkers were significantly higher in patients with myocardial ischemia: BNP 60 [IQR 31–106] vs 112 [63–187] pg/ml, hs-cTnT 4 [2–10] vs 7 [4–19] ng/ml and hs-cTnI 2.3 [1.5–4] vs 3.4 [2.8–9.3] ng/ml. Diagnostic accuracy as quantified by the area under the ROC curve was 0.698 (95%CI 0.635–0.756) for BNP, 0.664 (0.599–0.724) for hs-cTnT, 0.719 (0.657–0.775) for hs-cTnI, as well as 0.726 (0.665–0.783) for the combination of BNP and hs-cTnT and 0.743 (0.683–0.798) for the combination of BNP and hs-cTnI.

Combining clinical judgment prior to exercise testing (AUC 0.661 (0.596–0.721)) with the dual marker information increased the AUC to 0.752 (0.691–0.806) for BNP/hs-cTnT and 0.751 (0.690–0.805) for BNP/hs-cTnI ($p < 0.05$ for both combinations). These were comparable to the AUC of clinical judgement incorporating exercise test results 0.752 (0.692–0.806). Adding the information gained from the dual biomarkers, the AUC further increased significantly to 0.794 (0.736–0.844) for hs-cTnT ($p = 0.03$) and showed a trend towards improvement for hs-cTnI (0.774 (0.715–0.826)).

Conclusion: The dual-biomarker approach provides incremental value to clinical judgment in the diagnosis of suspected exercise-induced myocardial ischemia.

P2718 | BEDSIDE

Role of CHADS2 and CHA2DS2-VASc scores for predicting subsequent myocardial infarction, stroke and death in patients with acute coronary syndrome

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Aims: Patients with acute coronary syndrome (ACS) present with a wide spectrum of risks for subsequent cardiovascular ischemic events and death. No simple and common scoring system is used to identify patients at high risk of adverse outcome. The aim of the study was to investigate whether the CHADS2 and CHA2DS2-VASc scores were useful risk assessment tools for adverse events in patients with ACS.

Methods and results: This observational, prospective study was conducted at 39 hospitals in Taiwan. Patients with ACS who were admitted were enrolled after informed consent. We calculated the CHADS2 and CHA2DS2-VASc scores from the data collected. The primary end point was the occurrence of adverse event, including subsequent myocardial infarction (MI), stroke and death at one year post-discharge. Of the 3183 patients enrolled, 1,665 (52.3%) patients were

diagnosed with ST elevation MI. The rates of MI, stroke or death continuously increased with increasing CHADS2 and CHA2DS2-VASc scores. The CHADS2 and CHA2DS2-VASc scores were significant predictors of adverse events in separate multivariate regression analysis. After adjustment, the hazard ratio of the CHADS2 or CHA2DS2-VASc score for predicting future MI, stroke or death was 1.44 (95% CI 1.30-1.58, $p < 0.001$) and 1.36 (95% CI 1.26-1.46, $p < 0.001$), respectively. The Kaplan-Meier analysis based on the CHADS2 and CHA2DS2-VASc scores ≥ 2 obtained a higher rate of adverse events than when based on scores < 2 (both log rank, $P < 0.001$). In addition, CHA2DS2-VASc score improved diagnostic performance in predicting subsequent adverse events when compared with the CHADS2 score with the area under the receiver operating characteristic curve increased from 0.66 to 0.70 ($p < 0.001$). The CHA2DS2-VASc scores could be used to further stratify the patients with CHADS2 scores of 0 or 1 into 2 groups with different rates of adverse events at a cutoff value of 2 (4.1% vs. 10.7%, $P < 0.001$).

Conclusions: CHADS2 and CHA2DS2-VASc scores are useful predictors for subsequent adverse events in ACS patients and may be helpful for identifying high-risk patients.

P2719 | BEDSIDE

De novo atrial fibrillation during acute coronary syndromes: which is the best therapeutic strategy?

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Introduction: De novo atrial fibrillation (nAF) is frequent during acute coronary syndromes (ACS), being associated with morbidity and mortality. The current literature concerning the best therapeutic approach to nAF in this context is meager.

Objective: Describe and compare nAF therapeutic strategies during ACS, namely the rate (RaM) versus rhythm management (RyM) and the antithrombotic treatment.

Methods and results: We performed a prospective study including 902 consecutive patients (P; aged 64.0 ± 13.2 years, 77.5% male) admitted in a Coronary Unit for the period of 2 years, with a 6 month follow-up. The atrial fibrillation (AF) rhythm was identified in 13.8% P, from whom 73.3% presented nAF and 26.8% previously known AF. From the 84 P with nAF, 27.4% were submitted to RaM and 72.6% to RyM. Between those which RyM strategy was applied, 30.0% went home with antiarrhythmic therapy to maintain sinus rhythm. Age ($p = 0.045$), significant mitral regurgitation (grade $\geq II/IV$; $p = 0.026$) and left atrium diameter > 45 mm ($p = 0.022$), risk factors for AF recurrence described in literature, constituted predictors of RaM strategy choice. Regarding antithrombotic treatment, by virtue of ACS, the majority of P went home medicated with double antiplatelet therapy (100% with acetylsalicylic acid and 97.6% with clopidogrel). Additionally, anticoagulant therapy was introduced in 69.6% P oriented to RaM and 18.0% oriented to RyM. P submitted to RaM strategy that did not receive oral anticoagulants had a superior mortality in follow-up when compared to those who did receive ($p = 0.049$). Anticoagulant therapy did not show any benefit in the P submitted to RyM. The RaM strategy was associated with higher mortality, when compared to RyM ($p = 0.007$).

Conclusion: nAF diagnosed in the context of acute myocardial ischemia and with less than 48 hours of evolution is, in the majority of cases, possible to revert to sinus rhythm. In this study, there was a tendency to the superiority of RyM over RaM and of anticoagulant therapy in the last group (results of univariate analysis). To validate these conclusions, randomized trials evaluating effects of RyM and RaM strategies, antithrombotic and antiarrhythmic management should be designed and executed.

P2720 | BEDSIDE

Acute coronary syndrome with prolonged hospitalization

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Purpose: To determine the clinical characteristics that influence hospital length of stay in patients with acute coronary syndrome.

Methods: We examined a cohort of patients admitted consecutively to a university hospital with a diagnosis of unstable angina or acute myocardial infarction. We selected those that did not require coronary artery bypass surgery and analyzed the variables associated with length of stay (LOS) of 10 days or more using a logistic regression analysis.

Results: Between January 2007 and December 2010, our hospital admitted 1912 patients with acute coronary syndrome. 1537 of these (age 64 (54-74) years, 70.3% male) were not undergoing surgery, forming the study group. 82.4% of them received invasive management and the overall hospital mortality was 6.6%. Patients with a LOS of 10 days or more (corresponding to the 75th percentile, $n = 464$ (30.2%)) were older (68 (58-75) vs 63 (52-73) years, $p < 0.001$), with greater comorbidity (diabetes: 37.9% vs 31%, $p = 0.008$; peripheral artery disease: 11.2% vs 5.9%, $p < 0.001$; chronic obstructive pulmonary disease: 7.1% vs 4.1%, $p = 0.013$) and more frequently had multivessel disease (56.7% vs 41.7%, $p < 0.001$). The multivariable analysis showed that the presence of chronic kid-

ney disease (OR 1.70; 95% CI 1.08-2.68, $p < 0.023$), anemia at admission (OR 2.14; 95% CI: 1.55-2.96, $p < 0.001$), cerebrovascular disease (OR 1.84; 95% CI: 1.04-3.24, $p = 0.035$), presence of Q-wave infarction (OR 1.88; 95% CI: 1.40-2.54, $p < 0.001$), moderate or severe mitral regurgitation (OR 3.27; 95% CI: 1.45-7.37, $p = 0.004$), and age (OR 1.02; 95% CI: 1.01-1.03, $p < 0.001$) were associated with a longer income. Complete revascularization during the episode was associated with a lower risk (OR 0.64; 95% CI: 0.46 - 0.89, $p = 0.008$).

Conclusions: Prolonged hospitalization after an acute coronary syndrome is related to the presence of anemia, chronic renal disease and mitral insufficiency independently of other related patient comorbidity factors. Complete revascularization is a protective factor.

TRANSPLANT NEWS

P2722 | BEDSIDE

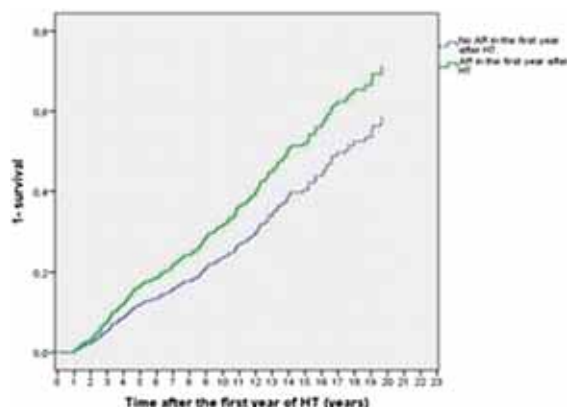
Prognostic impact of acute rejection episodes during the first year after heart transplantation on long-term post-transplant survival

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Purpose: Acute rejection (AR) is a major complication after heart transplantation (HT). It is more common in the first year following HT, a period in which infection and graft failure have a decisive impact on patient's prognosis. Our aim was to evaluate the prognostic implications of first-year AR, and its implication on one-year-conditioned long-term survival.

Methods: Retrospective study of patients who underwent HT in our center between April 1991 and December 2012. Patients younger than 18 years and those who survived less than 24 hours were excluded. AR was defined by any clinically relevant event leading to an intensification of immunosuppressive treatment that included intravenous therapy. One-year-conditioned long-term survival of patients with or without AR during the first post-transplant year was compared by means of the Kaplan-Meier method (univariable analysis) and the Cox's proportional hazards method (multivariable analysis).

Results: 609 patients (83% male, mean age 54 ± 12 years) were studied over a mean follow-up of 8.3 years. 373 patients (61%) had at least one AR episode during the first post-transplant year. 47.8% of patients died during the follow-up of those 61% died within the first year. Patients with AR had significantly reduced non-adjusted one-year-conditioned long-term survival (log rank $p = 0.019$) than patients without AR (graph). After multivariable adjustment, the presence of AR during the first post-transplant year remained as an independent predictor of one-year-conditioned long-term mortality (HR 1.42, 95% CI 1.07-1.91).



1-survival conditioned 1st year survival.

Conclusions: AR during the first post-transplant year has a negative impact on one-year-conditioned long-term survival. Therefore it is critical to prevent rejection, something still unresolved.

P2723 | BEDSIDE

Echocardiographic assessment of left ventricular longitudinal function at rest for detection of significant coronary artery stenosis in heart transplant recipients

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Purpose: Cardiac allograft vasculopathy (CAV) and late graft failure (usually secondary to CAV) are the most common causes of death in long-term heart trans-

plant (HTx) recipients. Currently available non-invasive tests show low diagnostic value, therefore invasive coronary angiography (ICA) is frequently performed. Left ventricular longitudinal function parameters at rest may be abnormal in patients with significant coronary artery stenosis, which might be used to evaluation of CAV. The aim of this study was to estimate their diagnostic performance in HTx patients versus a reference standard of quantitative ICA.

Methods: We enrolled prospectively 87 consecutive patients (mean age 53.1 ± 13.3 years, 75 men) at least one year after transplant, who underwent resting echocardiography, annual routine ICA and myocardial biopsy. Mean post-transplant time was 6 ± 4.0 years. All studies were analysed conventionally and quantitatively using tissue Doppler and speckle tracking techniques. We evaluated regional and global myocardial tissue longitudinal displacement, velocity and strain parameters. A 50% or greater stenosis by ICA was considered significant.

Results: ICA excluded CAV in 45 (51.7%) patients. In 19 (21.8%) patients significant stenosis was detected, of whom 8 patients needed stent implantation. Segmental wall motion abnormalities in the standard echocardiography occurred in 13 patients. Speckle tracking was possible in 97.6% of 1530 attempted segments from the 85 studies with technically adequate images. Analysis of all 18 left ventricular segments was possible in 69 (79.3%) patients. In multivariate regression analysis only post-systolic shortening index (PSSI), tricuspid annular systolic velocity (RV S') and post-transplant time remained independent predictors of significant stenosis. The area under the receiver-operating-characteristic curve was not significantly greater for PSSI than for RV S' (0.90 vs. 0.75, $P=0.06$). Sensitivity, specificity, positive and negative predictive value for significant stenosis detection (PSSI threshold $\geq 25\%$) was calculated as 89.5%, 93.9%, 81.0% and 96.9%, respectively. Diagnostic accuracy was 92.9%.

Conclusions: Among the left ventricular longitudinal function parameters only PSSI might be used to evaluation of CAV. Low PSSI virtually rule out significant stenosis due to CAV. Therefore assessment of PSSI might avoid a significant proportion of invasive coronary angiography studies in heart transplant recipients.

P2724 | BEDSIDE

Achieving eligibility for heart transplantation: the role of sildenafil in advanced heart failure patients with pulmonary vascular disease

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Background: Pulmonary hypertension (PH) is a frequent complication of chronic heart failure (HF) and elevated pulmonary vascular resistance (PVR) remains a major problem for heart transplant (HTx) candidate selection. In this setting, a simple therapy to modulate severe PH and allow HT without compromising patient outcomes would be of great value. Our aim was to (1) assess the effect of pre-HTx sildenafil administration on pulmonary hemodynamics before and early after HTx and (2) in long-term mortality after HTx in high-risk patients because of established pulmonary vascular disease (PVD).

Methods: We performed a monocentric, retrospective study including 236 consecutive patients who underwent HTx between November 2003 and December 2013. Thirty (Group A) received sildenafil therapy due to the presence of PVD (elevated transpulmonary gradient or PVR) and 206 patients (Group B) did not receive sildenafil due to the absence of PVD. Pulmonary hemodynamics were evaluated before sildenafil initiation in all patients, early after HTx during the first endomyocardial biopsy at 1 week and 1 year after HTx in both groups. Survival after HTx was compared between the groups using the Log-Rank test.

Results: The mean age of group A was 54 ± 11 years and of group B 53 ± 13 years. Mean pulmonary artery pressure (mPAP), systolic pulmonary pressure (sPAP), PVR and transpulmonary pressure gradient (TPG) were respectively 40 ± 12 mmHg, 63 ± 17 mmHg, 435 ± 180 dyn·s/cm⁵ and 13 ± 1 mmHg in group A before sildenafil. Regarding group B, these values before HTx were 29 ± 10 mmHg, 45 ± 15 mmHg, 254 ± 183 dyn·s/cm⁵ and 9 mmHg. Early after HTx, no differences were found regarding sPAP - 40.2 ± 7.9 mmHg in group A vs 36.5 ± 11.5 mmHg in group B ($p=0.1$) and right ventricular end-diastolic pressure 7.9 ± 5.8 mmHg vs 6.9 ± 7 mmHg ($p=0.5$). One year after transplantation, group A sPAP was 32.4 ± 6.3 vs 30.5 ± 8.2 in group B ($p=0.3$). Survival after HTx was similar between the groups. With a median follow-up of 53 months (range 28 - 87 months), 55 patients died (23.3% in group A and 23.4% in group B, $p=0.5$).

Conclusions: Although patients treated with sildenafil had significantly worse pre-HTx hemodynamics markers, signaling for preexisting PVD, no differences were found after-HTx hemodynamic variables. These findings support the concept that sildenafil can rescue previously ineligible HTx patients due to severe, fixed PVD.

P2725 | BENCH

Bacteria and bacteriophages in the myocardium are related with resistance to pulse therapy in myocardial rejection

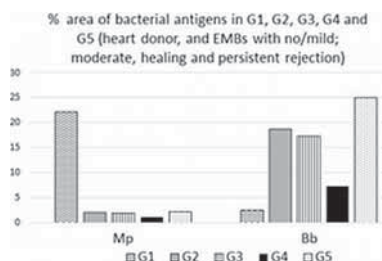
M.M. Reis, R.N. Ikegami, R.R.A. Ferreira, J.T. Kawakami, S.A.P. Palomino, P. Pomerantzeff, S. Mangini, E.A. Bocchi, M.L. Higuchi. *Heart Institute (InCor) - University of Sao Paulo Clinics Hospital, Sao Paulo, Brazil*

Purpose: Cardiotropic bacteria and many viral DNAs were described in Dilated Cardiomyopathy (DCM). In previous study we found in DCM biopsies, human vi-

ral and bacterial antigens and at electron microscopy, viral microparticles in the cytoplasm of bacteria, suggesting that these are bacteriophages. In the present paper we studied if these infectious agents proliferated in the donor heart after heart transplantation (HT), during episodes of myocardial rejection (MR) and caused resistance to pulse therapy (PT).

Methods: 13 patients with DCM had their endomyocardial biopsies (EMBs) revised in 60 days post HT to determine by immunohistochemistry the % antigens' area against *Borrelia burgdorferi* (Bb), *Mycoplasma pneumoniae* (Mp), HBs, HCV, PVB19, and HHV6. EMBs were grouped in: G1 - donor heart zero time after HT; G2 - absent or mild MR, G3 - moderate MR, G4 - healing MR and G5 - persistent MR.

Results: The mean % area of bacterial antigens in groups G1, G2, G3, G4 and G5 were: of Bb 2.51, 18.73, 17.22, 7.26 and 24.93 and of Mp: 22.13, 1.95, 1.82, 1.1 and 2.17. There was an increase in Bb and viral levels in G3 than in G1 ($P<0.01$) and decrease after PT in G4. In G5 occurred increase in Bb ($P<0.01$) and Mp ($P=0.09$) levels; there were Mp correlations with levels of many viral antigens: HBs, HCV and HHV6 and also correlations between viruses HHV6 vs PVB19 ($r=0.7$, $P<0.05$) and HHV6 vs HCV ($r=0.90$, $P<0.001$). In G4, correlation occurred only between Bb vs HHV-6 ($r=0.78$, $P=0.02$).



Conclusion: Beyond autoimmunity, MR seems to be a myocarditis associated with Bb and HHV-6, which regresses with PT. In persistent MR occurs increase in levels of Bb and Mp in correlation with many viruses, suggesting that these are bacteriophages and may have a role in PT resistance in treatment of MR.

P2726 | BEDSIDE

The importance of the diastolic pulmonary gradient in the characterization of pulmonary hypertension in a cardiac transplant population

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Background: Pulmonary hypertension (PH) is a frequent complication of left heart disease due to backward transmission of the elevated left atrial pressure (LAP) and a small subset even develops PH with elevated transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR). Severe PH is a contraindication for heart transplantation (HTx) since the right ventricle will fail due to the high PVR. The risk has been described to be directly proportional to PVR and TPG. However, TPG is sensitive to changes in cardiac output and LAP. Therefore, we analyzed the diastolic pulmonary gradient (DPG) (difference between diastolic pulmonary arterial pressure and mean pulmonary capillary wedge pressure) in an HTx population as a parameter to better characterize patients in whom PH is potentially reversible and wherein the Tx may be more successful.

Methods and results: We retrospectively examined 127 patients with pre and post HTx hemodynamic measurements. Patients were predominantly male (79%) and the mean age was 53 ± 12 years. As expected, HTx had a significant effect in hemodynamics, with normalization of LV and RV filling pressures and a significant increase in cardiac output (CO). Before HTx mPAP was 38 ± 9 mmHg, PCW 21 ± 8 mmHg, PVR 374 ± 154 dyne/s/cm⁵·m² and the TPG 17 ± 4 mmHg. After Tx mPAP was 22 ± 7 mmHg, PCW 11 ± 5 mmHg, PVR 184 ± 138 dyne/s/cm⁵·m² and the TPG 9 ± 5 mmHg. The mean DPG before HTx was 4.1 ± 6.3 . Then we examine the subpopulation of 37 patients with established pulmonary vascular disease, i.e., with TPG > 12 and divided them into two groups: DPG ≥ 4 (40.5%) and DPG < 4 (59.5%). The right atrial pressure post HTx was significantly lower in the group with DPG < 4 ($p<0.05$) as well as PVR ($p<0.05$). Despite the lack of statistical significance, we also found a favorable trend toward increased CO in the group with DPG < 4 .

Conclusions: DPG could be a better discriminator instead TPG to identify patients with greater reversibility of pulmonary vascular disease after HTx and may help in the selection of HTx candidates.

P2727 | BEDSIDE

Surgical techniques and clinical spectrum of indications for permanent pacemaker implantation after heart transplantation

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Background: Two surgical techniques are currently used in heart transplantation (HTX): the atrial technique (BA) involves removal of both recipient and donor

heart at the midatrial level and the bicaval technique (BC) with resection of the superior and inferior vena cavae, preserving the integrity of right atrium. BA technique has been associated with atrial dysrhythmias and sinus node dysfunction. BC technique has the advantage of preservation of atrial contractility and sinus node function, but this procedure takes longer to complete and prolongs ischemic time. Permanent pacemakers (PM) are generally indicated only for bradycardia that does not resolve and is associated with symptoms. PM implantation is required after orthotopic HTX in 4–29% of transplant recipients. The aim of this study is to describe changes in spectrum of clinical indications for posttransplant PM placement with two different surgical techniques of HTX.

Methods: The HTX database, medical records and pacing database/records were reviewed for all patients undergoing de novo orthotopic HTX (n=934) at our institution between January 1984 and December 2013. BA surgical technique of HTX was used until 1993. Since 1993 BC technique has been employed at our institution in all patients.

Results: A total of 48 patients (5.3%) received a PM after HTX. Mean age was 54±8 years, 10 patients were females. Clinical indication for PM was sick sinus syndrome in 9 cases (19%), in all 4 pts with biatrial technique. Atrioventricular block was an indication for PM in 37 pts (77%). In 30 of them, PM was implanted early after HTX (7–49 days). In remaining 2 pts (4%), the reason for PM implant was syncope and bundle branch block. BA surgical technique was used in 89 pts, 4 of them (4.5%) received PM, all of them for clinical indication of sick sinus syndrome. BC procedure was performed in 845 pts, 44 of them (5.3%) were indicated for PM placement, most of them for AV block.

Conclusions: In our study, PM was implanted after HTX in 5.3% pts. With bicaval surgical technique of HTX the need for pacing has not changed, but in the spectrum of clinical indications for PM placement atrioventricular block became predominant.

P2728 | SPOTLIGHT

Vectorcardiographic predictors of pediatric heart transplant acute graft rejection

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Introduction: The vectorcardiographic (VCG) parameter, the spatial QRS-T angle and its vector components have been shown to be predictive of arrhythmias in adults with ischemic heart disease. We hypothesized that the spatial QRS-T angle and its vector components (tested along with QTc measurements) would be associated with endomyocardial biopsy (Bx) proven moderate acute cellular rejection (ACR) in a pediatric population of orthotopic heart transplant (OHT) recipients.

Methods: A blinded, retrospective evaluation of patients (pts) with available Bx data was performed. Resting 12-lead electrocardiograms (ECGs) done on the day of Bx and clinical data were collected. The following parameters were calculated: QTc interval measurements, the spatial QRS-T angle, principle QRS-wave and T-wave vector components (root mean square of the X, Y and Z components of the QRS and T-wave complexes, respectively). Student t-tests and the Mann-Whitney U test were used as appropriate to assess significant differences between pts with and without ACR (defined as ISHLT grade ≥2R).

Results: There were 97 biopsies reviewed in 83 pts. The mean age was 13.9±5.0yr, the median time from transplant was 8.0 yr [IQR 3.2–11.9], and 52% were male. Pre-OHT diagnosis was cardiomyopathy in 50 (52%), congenital heart disease in 37 (38%), and repeat-OHT in 10 (10%). There were 33 cases with and 64 without ACR. The principle QRS-wave vector component was significantly lower in those with ACR (1.17±0.39 mV vs 1.54±0.69 mV; p=0.003). There were no significant associations between ACR and the repolarization parameters of spatial QRS-T angle, T-wave vector components, and the QTc.

Conclusion: A lower principle QRS-wave vector component was associated with heart transplant rejection in this pediatric OHT patient population. This suggests that depolarization abnormalities may be predictive of acute moderate cellular rejection in this population.

P2729 | SPOTLIGHT

Phosphodiesterase-5 inhibitor in pulmonary hypertension due to left heart disease with pre-capillary component: hemodynamic and functional impact

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Introduction: Pulmonary hypertension (PH) in chronic heart failure results from passive backward transmission of high left heart pressures, frequently associated with a component of pulmonary vascular disease (PVD), defined by an increase in vasomotor tone and/or obstructive remodelling of vessels' wall. PH carries a poor prognosis and may preclude heart transplant in end-stage cardiac disease. Phosphodiesterase-5 inhibitor is recommended for group 1 PH; however, its value in group 2 PH is still controversial. This study evaluates the clinical and hemodynamic utility of sildenafil in patients (pts) with advanced heart failure (AHF) and PH with a pre-capillary component.

Methods: Retrospective unicentric study of pts with AHF referred for heart transplant over the past 10 years. Clinical, laboratorial and hemodynamic (right heart catheterization) data were collected from pts with out-of-proportion PH, in whom sildenafil was prescribed "off-label".

Results: 55 pts had complete hemodynamic evaluation before and during treatment with sildenafil. Mean age was 45±17 years and 69.5% were men. The majority had severely compromised functional capacity, half being in NYHA class IV; peak VO₂ was 15.1 (IQR 12.4–17.3) mL/kg/min. Median values of BNP were significantly elevated (540 (IQR399–1035) pg/dL). Before the treatment, hemodynamic data reflected this severe clinical status, with mean pulmonary artery pressure (mPAP) of 46±11 mmHg, mean pulmonary capillary wedge pressure (PCWP) of 27.48±8.89mmHg, cardiac output (CO) of 3.19±0.84L/min and high pulmonary vascular resistance (PVR): 547.25±467.39 dynes·s⁻¹·cm⁻⁵. After 3 months (median) of therapy patient's functional capacity, BNP levels and hemodynamic profile improved significantly. By then, only 19.7% of pts were still in NYHA functional class IV. BNP reduced on average 6% (p=0.046) and mean peak VO₂ increased to 17.8 mL/kg/min (+17%, p=0.048). Regarding hemodynamic parameters, there was a mean reduction of mPAP of 21% (p<0.001) and of PCWP in 22% (p<0.001), an increase of CO in 24% (p<0.01) and a reduction of 39% in PVR (p=0.001); these changes were most visible in pts with a transpulmonary gradient (TPG) >12 mmHg. No significant side effects were reported with the use of sildenafil, namely systolic arterial pressure decrease during treatment.

Conclusion: Sildenafil improved significantly the clinical and hemodynamic profile of pts with advanced heart failure and PH with a reactive component, and also showed to be safe. Its use may be of particular interest in rescuing pts with established PVD for eligibility for heart transplant.

P2730 | BEDSIDE

Superior rejection profile during the first 24 months after heart transplantation under tacrolimus as baseline immunosuppressive regimen

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Background: The use of tacrolimus in heart transplant patients increased during the last years.

Aim: In this retrospective study, we evaluated the effects of a tacrolimus (TAC) based immunosuppressive therapy regarding rejection profile in comparison to a Cyclosporine A (CsA) based regimen in patients after heart transplantation (HTx).

Patients: The data of 233 patients who underwent HTx at our Heart Transplantation Center from May 1998 until November 2010 were retrospectively analyzed. Primary immunosuppressive therapy was changed from a CsA (n=114) to a TAC (n=119) based regimen in February 2006. Follow-up period was two years post HTx. Primary end-point was time to first rejection requiring therapy. In all patients routine follow-up at our Center was mandatory.

Results: No statistical significant differences regarding recipient age, donor age, recipient gender, ischemic time, and diagnosis leading to HTx were found between the two groups (all p=ns). Time to first biopsy proven rejection requiring therapy was significantly longer in the TAC group (logrank analysis, p=0.0003) in all patients still on baseline immunosuppressive schedule two years after HTx (n=150). Likewise, in the remaining patients, who underwent a change in immunosuppressive regimen also a significant longer time to first biopsy proven rejection was found in the primary TAC subgroup (logrank analysis, p=0.0002). Further subgroup analysis in the TAC subgroup showed a longer time to biopsy proven rejection under prolonged release TAC compared to conventional TAC, however the level of statistical significance was not met (logrank analysis, p=0.1736).

Conclusion: Our study demonstrated that a TAC based primary immunosuppressive therapy is superior to a CsA based immunosuppressive regimen in patients after HTx regarding time to first biopsy proven rejection requiring rejection.

P2731 | BEDSIDE

The impact of human leukocyte antigen matching on rejection after heart transplantation

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Background: The main antigenic stimulus for allograft rejection is the major human leukocyte antigen (HLA) system. HLA matching is not considered in current allocation policies in heart transplantation. The aim of our study was to assess the impact of HLA matching on rejection after heart transplantation.

Patients and methods: Forty patients transplanted between November 2011 and July 2013 were analyzed retrospectively. The shortest follow-up time was 6 months. The mean follow-up time was 14.17±5.65 months (6–26 months). Immunosuppressive therapy was used according to our protocol; for induction therapy patients were treated with ATG, corticosteroid and mycophenolate mofetil. Maintenance therapy was performed using tacrolimus, mycophenolate mofetil and corticosteroid. HLA mismatches on the major antigen loci HLA-A, -B and -DR

were calculated (zero to six mismatches). All patients were routinely monitored for cellular rejection with scheduled endomyocardial biopsies.

Results: During the follow-up period 11 patients (27.5%) suffered from grade 2R acute cellular rejection. Fifteen patients (37.5%) had 2 HLA-DR mismatches, 21 patients (51.2%) had 1 HLA-DR mismatch, while 4 patients (10%) were without HLA-DR mismatch. We found a significant positive correlation between the number of HLA-DR mismatches and grade 2R acute rejection ($p=0.03$). HLA-DR identical recipients didn't have grade 2R cellular rejection during the follow-up period.

Conclusions: The investigation of HLA matching can be useful clinical parameter to predict rejection episode after heart transplantation. Patients with better HLA compatibility might require lower immunosuppressive therapy.

P2732 | BEDSIDE

Long-term experience with heart transplantation in children and patients with congenital heart disease

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This study is to assess the long-term outcome of heart (HTx) and heart-lung transplantation (HLTx) in patients with congenital heart disease (CHD) and children with non-congenital cardiac or pulmonary disease.

Methods: The study is a retrospective single-centre analysis of long-term outcome after heart transplantation of children and adults with CHD, and children with non-congenital cardiac disease.

Results: From 1984 to 2013, 111 first-HTx, 5 HLTx and 6 second-HTx were performed (62 males), in patients aged 11.7 ± 8.2 y (med 12y): 96 (79%) were aged <18y at transplant. Cardiac diseases included 61 cardiomyopathies (50.8%), 50 CHD (41.7%), 6 retransplants (5%). HLTx included 1 Eisenmenger syndrome, 1 primitive pulmonary hypertension, and 2 pulmonary diseases. Patients with cardiomyopathy were younger than those with CHD (8.7y vs 14.9y). Seventeen (14%) patients were under circulatory mechanical support as a bridge to transplant. Immunosuppression was achieved by tritherapy in the majority of cases. Acute rejection occurred more frequently within the first year post-transplant or late after transplant (>5th year) in teenagers because of non-compliance. Overall mortality was 27%: 33 patients died, 3.5 ± 4.6 y post-HTx (1 day to 16.4y, med 1.5 months), due to: early multivisceral failure in 6 (18%), Pulmonary hypertension in 3 (9%), acute rejection in 7 (21%), graft coronary disease in 6 (18%), sepsis in 5 (15%) and miscellaneous in 6. Graft coronary disease occurred in 15 cases (12.4%), of them 4 had 2nd HTx, 6 died and 5 are alive. Five posttransplant lymphoma occurred, 4 months to 14y after HTx and were successfully cured in 4 (1 died). Patients survival was 85% at 1y, 81% at 5y, 70% at 10y and 61% at 20y post-transplant. Graft survival rates were respectively 82%, 68% and 52% at 5y, 10y and 20y post-transplant. Survival did not differ with pretransplant disease, age, gender, pretransplant mechanical support. Mortality was higher in patients with graft coronary disease (40%) than those free from (25%). The majority of survivors (97%) are in NYHA class I.

Conclusion: Our experience with HTx and HLTx is favourable with acceptable long-term prognosis in patients with end-stage disease. Graft coronary disease is the main cause of failure, less frequent than in the adult non-CHD heart-transplanted population.

P2733 | BEDSIDE

Decreased circulating and neutrophils mediated VEGF release in stable long-term cardiac transplant recipients

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Purpose: A chronic state of inflammation may contribute to the long-term cardiac and vascular complications following cardiac transplantation (CTx). Vascular endothelial growth factor (VEGF) possess angiogenic and pro-inflammatory properties. The measure of circulating levels of VEGF, interleukin 8 (IL-8), interleukin 1 receptor antagonist (IL-1ra) concomitantly with the assessment of neutrophil pro-inflammatory responses have not been investigated in long-term CTx recipients.

Methods: Eighteen CTx recipients aged 14.6 ± 3.1 years, 145 ± 20 months fol-

lowing transplantation and 35 age-matched healthy control (HC) subjects were recruited. Seven (39%) patients exhibited coronary allograft vasculopathy (all CAV1). VEGF, IL-8 and IL-1ra were measured in resting state. Circulating neutrophils were isolated, purified and stimulated by vehicle (PBS), N-Formyl-Met-Leu-Phe (fMLP, 10^{-7} M), bacterial lipopolysaccharide (LPS, $10 \mu\text{g/mL}$), or tumor necrosis factor alpha (TNF- α , 10 ng/mL).

Results: Results are presented in the figure below. There were no differences in the circulating levels of IL-8 and IL-1ra. Neutrophils from CTx exhibited significant decreases in the release of IL-8 and IL-1ra in response to LPS and TNF- α ($p < 0.001$) - data not shown. There were no differences in patients with CAV vs non CAV.

Conclusions: Long-term CTx recipients exhibit a marked reduction in the circulating levels of VEGF, as well as neutrophils mediated release of VEGF, and the pro- and anti-inflammatory cytokines IL-8 and IL-1ra. The mechanisms and physiologic impacts of these findings in relationship with various severities of CAV deserve additional investigations.

CARDIAC SURGERY AND DEVICES

P2735 | BEDSIDE

Pacemaker lead impedance monitoring in heart failure patients

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Purpose: The purpose of this study was to determine the correlation between conventional pacemaker (PM) lead impedance and degree of congestion at the time of heart failure (HF) hospitalization. Intrathoracic impedance, measured using specialist equipment, falls, as the amount of conductive intrathoracic fluid increases with pulmonary congestion. We hypothesized that monitoring of conventional PM lead impedance, may also provide an early warning means of congestion.

Methods: Twenty-four patients with NYHA class III/IV HF and previously implanted PM for bradyarrhythmia indications, were admitted to our department with acute decompensation of chronic HF. All enrolled patients had signs of pulmonary congestion, increased jugular venous pressure and peripheral edema. The right JVP was assessed at admission and before discharge with the patient reclining at 45°.

The lead impedance was measured in VVI mode with unipolar pacing at 5V with the PM analyzer. A pre-discharge value of PM impedance was established as the "reference impedance" and used to quantify the magnitude of any impedance change. At 3 month follow-up, PM impedance and a JVP were measured.

Results: PM impedance correlated with changes in clinical congestion assessed by JVP. Impedance was low on admission (mean value 340 ± 40 Ohms) and increased after intensive diuresis (mean value 420 ± 50 Ohms). JVP was high (mean value 20cm H2O), and decreased after treatment (mean value 14cm H2O). During the 3 month follow up visit the PM impedance was comparable to the reference impedance in most (21) patients, (mean difference 20 Ohms), whereas 3 patients who had worsening HF, had lower than reference impedance (mean decrease 60 Ohms). This was considered an "early warning" and we admitted these patients to hospital, where impedance went up again after treatment. A major finding in this study was the correlation between conventional PM lead impedance and clinical fluid status evaluation.

Conclusions: The findings from this study suggest that monitoring of PM impedance at regular intervals during HF therapy may provide quantitative information on the severity of volume overload and a warning sign of impending HF decompensation. Further studies are needed to determine whether such an early warning can facilitate preemptive therapy to reduce hospital admissions.

P2736 | BEDSIDE

Pediatric ventricular assist device: a single centre preliminary experience

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Objective: Pediatric ventricular assist device (VAD) is currently used as mechanical circulatory support device for adolescents, infants and small children with advanced heart failure. We report our preliminary experience (a third level centre of Paediatric Cardiology and Cardiac Surgery) with VAD.

Methods: Between April 2009 and February 2014, 8 children (4 male and 4 female) followed in our Department of Paediatric Cardiology underwent pediatric VAD implantation at the Cardiac Surgery Division of our hospital. The diagnosis was myocarditis in 6 patients, idiopathic dilated cardiomyopathy in a single case and heart failure secondary to valve disease in one of them. Two cycles of i.v. inotropic therapy (dobutamine and levosimendan) were undertaken before im-

Circulating levels and release of VEGF by activated neutrophils

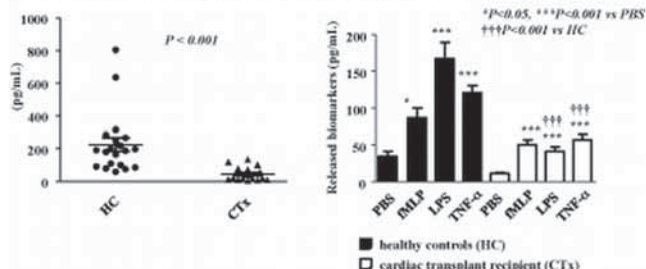


Figure 1

plantation. In addition, all patients underwent imaging evaluation (including cardiac Magnetic Resonance Imaging (MRI) in 3 patients), cardiac catheterization, endomyocardial biopsy (EMB) and viral genome PCR at VAD implantation.

Results: The median age at implantation was 8.8 years (2 to 15 years), the mean weight was 40 kg (13 kg to 64 kg), and the median support time was 121 days (5–459 days). Four pts received a BIVAD and 4 pts a LVAD. In three pts, MRI showed diffuse subepicardial enhancement without signs of intracellular and interstitial edema, capillary leakage and hyperemia. On the other hand, EMB showed diffuse fibrotic replacement without signs of active inflammation in all pts while at PCR only in one case a viral etiology (CMV) was revealed. Out of our 8 pediatric pts, 6 were bridged to heart transplantation, 1 died on support, and 1 is still waiting for heart transplantation. After heart transplant, 3 pts needed an Extra Corporeal Membrane Oxygenation (ECMO), 3 pts had chest wound infection and one had hyperacute rejection and bleeding problems. These complications occurred only in patients that underwent implantation in I-II INTERMACS level, while patients implanted at an early stage had no complications.

Conclusions: In agreement with literature, our experience confirmed that paediatric VAD could provide satisfactory and safe circulatory support for children with end-stage heart diseases. Further studies are needed to better define the prognostic impact of timing of device implantation and choice between univentricular vs biventricular support in pts with end stage disease.

P2737 | BEDSIDE

Preoperative hemodynamic and echocardiographic predictors of right ventricular failure after left ventricular assist device implantation

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Objectives: Although preoperative prediction of Right Ventricular Failure (RVF) after Left Ventricular Assist Device (LVAD) implantation is a frequently laboured entity, there isn't a consensus about any hemodynamic or echocardiographic parameter. In this trial, we aimed to detect new pre-operative hemodynamic and echocardiographic parameters in order to predict RVF after continuous flow LVAD implantation.

Methods: From March to November 2013, 26 continuous flow LVAD implanted patients (23 male, 3 female; mean age 49±12) were included in our single center, prospective, observational study. Patients' pre-operative Right Heart Catheterisation (RHC) and echocardiographic findings were evaluated. Post-operative RVF was defined as inotropy dependence for more than 14 days and/or need for RVAD implantation.

Results: 15 patients included in the study had ischemic and 11 patients had non-ischemic etiology. 22 patients had HeartWare and 4 patients had HeartMate II. Functional classes were defined according to INTERMACS classification. 3 patients were in INTERMACS I-II, 18 patients were in INTERMACS III-IV and 6 patients were in INTERMACS V-VII class. 3 patients (11%) had RVF. In 2 patients in INTERMACS I-II and 1 patient in INTERMACS III-IV, RVF was stated. No RVF was developed in INTERMACS V-VII group. Among echocardiographic data; low TAPSE (p=0.04), low FAC (p=0.03), low right ventricular outflow tract-SE (RVOT-SE) (p=0.04) and increased RV diameter (p=0.01) were found statistically significant to be associated with RVF. Among RHC findings increased RAP (p=0.04), diastolic RV pressure (RVDd) (p=0.04) and low diastolic pulmonary gradient (DPG) (p=0.01) was found statistically significant to predict RVF.

Conclusions: Increased RAP, RVPd, low DPG, low TAPSE, FAC, RVOT-SE measurements and increased RV diameters were detected to predict RVF. Despite our small study population, we think that DPG, RVOT-SE and other parameters found to be associated with post-operative RVF will be a pathfinder for bigger prospective trials with larger study populations.

P2738 | BEDSIDE

New generation left ventricle assist device does not affect microvascular endothelial tone regulation and vWF production

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Purpose: Left Ventricular Assist Device (LVAD) is a promising new therapy for patients with advanced heart failure. Previous studies suggest that continuous blood flow impairs endothelial function. Effects of last generation LVAD device on microvascular endothelial function, endothelial nitric oxide (NO) bioavailability and vWF metabolism are not known.

Methods: We compared LVAD-supported patients (n=13) with age/BMI matched patients with chronic heart failure (CHF, n=13) and healthy subjects (Control, n=15). All patients were implanted with a HeartWare® LVAD. Skin microvascular endothelial function was assessed with Laser Doppler Imager by hyperemic testings using acetylcholine (ACh) and sodium nitroprusside (SNP) iontophoresis. NO-mediated vasodilation was further evaluated by comparing heating hyperemic response in skin area pretreated either by a specific NO-synthase inhibitor (L-

NAME) or a control saline solution. Monomeric and high molecular weight multimeric (HMWM) vWF antigens and vWF activity were also measured.

Results: Compared to control, CHF patients have both reduced ACh and SNP-induced vasodilation (all p<0.05; Fig. 1), whereas LVAD patients have no significant differences in ACh and SNP responses. Endothelial NO bioavailability did not differ between LVAD, CHF and control group. Compared to CHF, LVAD did not affect vWF endothelial production or vWF activity. However, we observed in 2 LVAD-supported patients a loss of HMWM vWF and no abnormality in other groups.

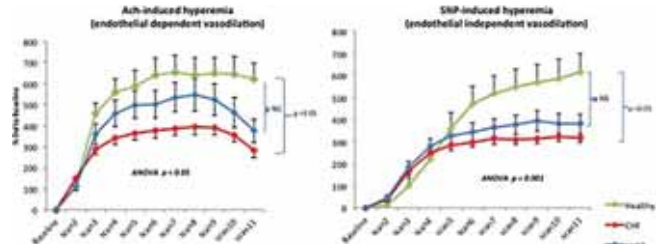


Figure 1

Conclusion: LVAD therapy tends to normalize microvascular endothelial tone regulation impairment present in CHF population and does not affect endothelial NO bioavailability or endothelial regulation of vWF. However, LVAD is associated with a loss of HMWM vWF, which could favor bleeding complications.

P2739 | BEDSIDE

How long is too long? Extended biventricular assist device support as a bridge to heart transplantation in a low organ donation environment

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Purpose: Low organ donation combined with delayed referral of advanced-stage cardiomyopathy patients necessitates biventricular assist device (BiVAD) support for extended periods of time. Reliable devices and close patient follow-up increase the survival likelihood. We report our experience with the Berlin Heart Excor BiVAD.

Methods: Sixty-three biventricular Berlin Heart Excor devices have been implanted since 2004. Patients' ages ranged from 11 to 60 years (median age 35 years). Diagnoses included dilated (74.5%), ischemic (17%) and others (8.5%) cardiomyopathies (fulminant myocarditis, restrictive cardiomyopathy, Amyloidosis, ARVC). All patients presented in severe biventricular failure (intravenous inotropes, 40; ventilated, 10; IABP, 35; mean: CI 1.9 L/min/m²; CVP 19 mmHg; total bilirubin 3.75 mg/dl; NT-proBNP, 25,500 pg/ml). Two patients needed a BiVAD after left ventricular assist device support of 439 and 295 days, respectively. Anticoagulation consisted of heparin, Vitamin K antagonist, aspirin, dipyridamole and clopidogrel.

Results: Thirty day, 180 day, and 1 year survival after implantation (excluding transplanted patients) was 95%, 87% and 82% respectively. Thirty-two were transplanted and nine are ongoing. Mean time on support was 681 days and 58 out of 63 patients with adult-sized pumps were discharged home with a mobile driver. Thirty patients exceeded 2 years of uncomplicated support before they were transplanted. Five patients were on support for more than 3 years when transplanted. One patient with renal failure and dialysis dependence lives at home 3.5 years after implantation. Complications included infection (n=15), bleeding requiring reexploration (n=5), and thromboembolic events (n=10). Patients died, 1 of an accidentally ruptured cannula (after 365 days), 6 of sepsis, 5 of multiorgan system failure.

Conclusions: Reliability of components and strict utilization of patient-care protocols leads to excellent survival in this extremely sick population. Meticulous multi-disciplinary management by experienced personnel is essential.

P2740 | BEDSIDE

Pre-operative hepatic dysfunction could predict postoperative mortality and morbidities in patients undergoing open-heart surgery; utilization of the MELD scoring system

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Background: Patients who require open-heart surgery frequently suffer from hepatic dysfunction due to the underlying right ventricular failure. The Model of End-Stage Liver Disease (MELD) score allows risk-stratification of patients undergoing major cardiac and non-cardiac surgery.

Purpose: The aim of this study is to evaluate the impact of pre-operative MELD score on postoperative outcomes following open-heart surgery.

Methods: We analyzed 532 consecutive patients (67.9% male, mean age 67.8±12.9 year-old) undergoing open-heart surgery between January 2013 and October 2013 at our institution. Associations between liver dysfunction estimated by the MELD score and post-operative clinical courses were analyzed.

Results: The mean value of the MELD score obtained from the total cohort was 9.4 ± 4.3 . Patients with high MELD scores (>12) were associated with longer intubation time (24.9 ± 60.5 vs. 12.3 ± 26.8 hours, $p=0.0087$), longer length of stay in the intensive care unit (3.7 ± 4.5 vs. 2.1 ± 2.5 days, $p<0.0001$) and longer hospital stay (16.9 ± 15.9 vs. $>13.8 \pm 11.6$ days, $p=0.0289$) as compared to those with low MELD scores (≤ 12). The MELD score was correlated with the total length of stay in hospital ($r=0.201$, $p<0.0001$). Multivariate analysis revealed that the MELD score was independently associated with >30 days length of stay in hospital (odds ratio 1.08, $p=0.0495$), which was predictive of >30 days post-operative stay with a sensitivity of 71.9% and a specificity of 51.7%. Regarding mortality and morbidity, high MELD score was associated with higher mortality rate (>3.75 vs. 0.82%, $p=0.0337$) as well as higher incidences of atrial fibrillation (37.5 vs. 34.0%, $p=0.0013$), hemodiafiltration or hemodialysis (43.4 vs. 4.9%, $p<0.0001$) and stroke (>4.0 vs. 0.9%, $p=0.0020$) after surgery. The Kaplan-Meier analysis showed lower survival rates in patients with a MELD score >12 as compared to those with a MELD ≤ 12 (90 >days survival, 95.9 vs. 99.4%, log-rank $p=0.0125$).

Conclusion: Assessment of liver dysfunction using the MELD scoring system provides additional risk information and is useful for predicting post-operative mortality and morbidity in patients undergoing open-heart surgery.

P2741 | BEDSIDE

Outcomes of the arterial switch operation for transposition of the great arteries

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Background: The arterial switch operation (ASO) is currently the standard surgical procedure for transposition of the great arteries (TGA). The purpose of this study is to evaluate the early and late outcomes of ASO and the incidence of and risk factors for transcatheter or surgical re-intervention.

Methods: A total of 223 Patients (162 boys and 61 girls), with median age of 29 days (3-1074) and mean weight of 3.68 kg (2.1-15 kg) at operation, underwent ASO in our institution from 1998 to 2012. Patients were divided into three groups according to the indication for the ASO: group A, TGA with intact ventricular septum ($n=135$); group B, TGA with ventricular septal defect (VSD) ($n=72$); and group C, Taussig-Bing anomaly (TBA) ($n=16$). Balloon atrial septostomy (BAS) were done in 160 (72%) patients before the surgery. 64 (28.7%) patients had abnormal coronary artery patterns. 16 (7.2%) patients had an aortic anomaly which included coarctation of the aorta (CoA) ($n=12$, 5.4%), interrupted aortic arch (IAA) ($n=3$, 1.3%) and CoA with right aortic arch (RAA) ($n=1$, 0.4%). The median follow-up period was 5.81 years (range 0 to 14.06 years). Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL USA).

Results: Early mortality included one patient from group A who had an extracorporeal membrane oxygenation (ECMO) implanted intra-operatively. Late mortality contains two patients who died after discharge on the twenty-fifth and thirty-eighth postoperative day. Pulmonary stenosis (PS) developed in 44 (20%) patients, of which, 17 (39%) patients underwent re-interventions. The median time to re-interventions was 4.68 years (range 0 to 14.06 years). Re-interventions ($n=31$, 14%) included balloon angioplasties ($n=16$, 7%), reoperations ($n=5$, 2%) and a combination of both ($n=10$, 5%). Balloon angioplasties were performed in 7 (5.2%), 5 (6.9%) and 4 (25%) patients in groups A, B and C, respectively. Two reoperation each was performed in groups A and B. One reoperation was in group C. A combination of balloon angioplasty and reoperation was performed in 3 (2.2%), 5 (6.9%) and 2 (12.5%) patients in groups A, B and C, respectively. Univariate Cox analysis identified TBA ($p=0.001$), VSD ($p=0.008$), pulmonary stenosis ($p<0.001$), presence of aortic anomalies ($p=0.005$), BAS ($p=0.046$) and abnormal coronary artery ($p=0.03$) as potential risk factors for re-intervention.

Conclusion: The arterial switch operation can be performed with excellent outcomes. However, a large population of patients requires re-intervention. A regular life-long cardiac follow-up is, therefore, recommended.

P2742 | BEDSIDE

Single center experience with heartware left ventricular assist device: outcome in high risk patients

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Purpose: To present our experience with the HeartWare ventricular assist device (VAD) (HeartWare, Framingham, MA) and its clinical outcome in critically sick patients (pts).

Methods: Outcome of HeartWare VAD implantations performed at single institution from 01.2010- 02.2014 was studied. The study design was a retrospective review of the prospectively collected data.

Results: 58 pts with a mean age of 55 ± 12 years were included. Fifty pts were male (86%). The preoperative INTERMACS profile of the pts was I 26 (45%), II 7 (12%), III 7 (12%) and IV 18 (31%). Twenty-two pts (38%) were on extracorporeal life support (ECLS) prior to VAD implantation. The median duration of VAD support was 204 days (2-1250 days). With a total support duration of 37 pts year, Kaplan-Meier analysis revealed a survival of 77%, 74% and 74% at 180 days, 1 year and 2 years respectively. Nineteen pts (33%) were successfully bridged

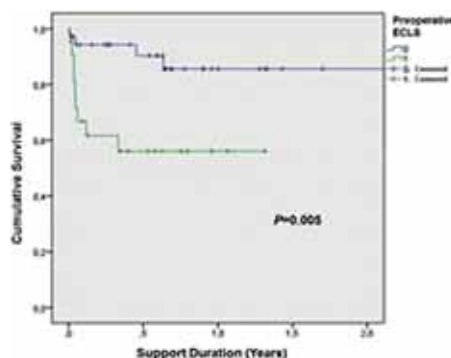


Figure 1

to heart transplantation. Device explantation was performed in four pts (7%) after recovery of the left ventricle. Postoperative complications included right heart failure in 23 pts (40%), respiratory failure in 19 (33%), renal failure in 18 (31%), gastrointestinal bleeding in 14 (24%), 11 reoperation for bleeding (19%), 8 neurologic dysfunctions (14%), 7 driveline infections (12%), and 7 events (12%) of pump thrombosis. A significantly lower survival rate and higher postoperative complications were observed in pts with preoperative ECLS ($p=0.005$) (Fig. 1).

Conclusions: Considering the sick pt population included in this study, the outcome following HeartWare VAD implantation is very satisfactory with survival to 180 days and/or transplantation of 77%. The outcome in pts with preoperative ECLS is significantly lower and associated with higher postoperative complications.

P2743 | BEDSIDE

Left ventricle endocardial leads for cardiac resynchronization therapy. Long term follow up

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Aim: Aim of the study is to analyze long term effects of biventricular pacing in patients with cardiac resynchronization devices where left ventricle leads were placed endocardially by using transseptal or transapical approach.

Methods and materials: 136 cardiac resynchronization devices were implanted from 11 January to 1 September in our Centre, 80 CRT – D devices and 56 CRT – P. In 13 patients of this group left ventricle lead was placed alternatively due to features of coronary sinus – 3, or high thresholds in target branches of coronary sinus – 4, or diaphragmatic nerve stimulation – 3, continuous lead dislodgement from venous system of heart – 3: whether by using left thoracotomy – 3, or thoracoscopic approach – 1, or transseptal approach – 6, or transapical approach – 3.

Endocardial left ventricle lead placement was performed by using transseptal or transapical approach. All left ventricle endocardial leads (9) were implanted in patients with permanent atrial fibrillation and warfarin was already administered in this cohort of patients before CRT-P/D implantation. All patients underwent TEE 24 hours before the procedure to exclude the presence of thrombus in left chambers.

Results: All left ventricle leads were implanted successfully from the first attempt without major complications. Acute thresholds for the left ventricle leads were in normal range. No thromboembolic events were revealed in these patients during follow up period. No dislodgements or other left ventricle lead failure were diagnosed.

According to echo 3D strain examination this cohort of patients had more homogeneous and effective contractile function of left ventricle when compared with cohort of patients with routine technique of left ventricle lead implantation.

Conclusion: 1) Alternative methods of endocardial left ventricle lead placement could be methods of choice in patients with previous unsuccessful attempts of lead placement into the branch of coronary sinus. 2) Left ventricle endocardial lead placement is safe and gives an operator a possibility to choose the region of lead implantation.

P2744 | BEDSIDE

The variation of left ventricular strain after aortic valve replacement by three-dimensional speckle tracking echocardiography

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Objective: To investigate the variation of left ventricular strain by three-dimensional speckle tracking echocardiography in patients underwent surgical aortic valve replacement (AVR)

Methods: Twenty patients with severe aortic stenosis (AS) and 16 patients with severe aortic incompetence (AI) were enrolled. All patients underwent AVR with LVEF $\geq 55\%$ before the operation. Global longitudinal strain (GLS) and global circumferential strain (GCS) were evaluated by three-dimensional speckle tracking echocardiography before AVR, 1 week and 1 month after AVR.

Results: The change of LVEF achieved no significance at 1 week and 1 month after AVR compared with baseline in two groups (all $p > 0.05$). Both GLS and GCS in AS patients after AVR were decreased at 1 week compared to that before surgery (GLS: -9.0% vs. -13.1%, $p = 0.046$; GCS: -8.8% vs. -14.5%, $p = 0.022$) and recovered at 1 month compared to that before surgery (GLS: -10.1% vs. -13.1%, $p = 0.14$; GCS: -11.4% vs. -14.5%, $p = 0.16$). While in AI patients, there were no significant difference of GLS and GCS at 1 week after AVR compared to that before AVR (GLS: -11.5% vs. -11.8%, $p = 0.93$; GCS: -15.0% vs. -17.6%, $p = 0.562$). However, GLS and GCS were significantly increased in AI patients at 1 month after AVR (GLS: -14.0% vs. -11.8%, $p = 0.463$; GCS: -18.0% vs. -17.6%, $p = 0.953$).

Conclusions: Strains measured by three-dimensional speckle-tracking echocardiography are useful for the sensitive evaluation of global cardiac function compared with the conventional echocardiographic index. The GLS and GCS were influenced by AVR and recovered in 1 month in AS patients, while no similar phenomenon was detected in AI patients after AVR.

P2745 | BEDSIDE

Predictors of hospital readmission for sternal wound infection after coronary artery bypass grafting surgery

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Introduction: Readmission after surgery is one of the indicators for quality of care and resources utilization. Sternal wound infection after coronary artery bypass grafting operations with median sternotomy increases mortality, morbidity, hospital stays and the cost. The aim of this study is to investigate the predisposing factors for hospital re admission because of sternal wound infection in order to develop strategies to minimize this problem.

Patients and methods: A retrospective study of prospectively collected data base included all patients admitted for first time, isolated Coronary artery bypass grafting surgery during 3 years period from May 2007 to may 2010. Redo patients and combined surgery are excluded from the study. Univariate and multi variate analysis were used to identify incidence and Predictors of Hospital readmission for sternal wound infection after discharge following coronary artery bypass grafting surgery are identified.

Results: Out of 2121 patients who had first time isolated CABG in 3 years period; 76 patients were readmitted after discharge for sternal wound infection. Those patients represent 57.5% of readmission for any reason. The age of the patients who required admission was 64.97 ± 9.93 compared with 62.32 ± 10.21 for those who did not require readmission ($p = 0.02$). Female are more likely need readmission. Predictors for readmission for sternal wound infections are care score (odds ratio: 1.03 CI: 0.63-1.70) BITA (odds ratio: 1.40 CI: 0.64-3.05) BMI (odds ratio: 1.03 CI: 0.97-1.09) Gender (odds ratio: 0.26 CI: 0.13-0.52) Age years (odds ratio: 0.95 CI: 0.91-0.98) and hypertension (odds ratio: 1.07 CI: 0.30-3.71).

Conclusion: This study showed that although readmission rate for sternal wound infection is small (3.5%), but it represented more than half of the rate of readmission for any reason within the 30 day after discharge. Patients who at high risk of readmission are most likely to be older, obese, hypertensive, with high Care score female and had bilateral mammary grafts.

P2746 | BEDSIDE

Outcomes of the arterial switch operation for transposition of the great arteries for coronary anomaly

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Background: The arterial switch operation (ASO) for transposition of the great arteries (TGA) in patients with coronary anomalies is associated with an increased risk of coronary events and mortality. The purpose of this study is to evaluate the early and late outcomes of ASO and the incidence of and risk factors for transcatheter or surgical re-intervention.

Methods: A total of 64 patients with TGA and coronary anomaly (47 boys and 17 girls), with median age of 29 days (3-364) and mean weight of 3.62 kg (2.1-6.7 kg) at operation, underwent ASO in our institution from 1998 to 2012. Patients were divided into three groups: group A, TGA with intact ventricular septum ($n = 33$); group B, TGA with ventricular septal defect ($n = 22$); and group C, Taussig-Bing anomaly (TBA) ($n = 9$). Balloon atrial septostomy (BAS) was performed in 38 (59%) patients before surgery. 6 (10%) patients had an aortic anomaly which included coarctation of the aorta (CoA) ($n = 5$, 8%) and interrupted aortic arch (IAA) ($n = 1$, 2%). Secondary thorax closure was performed in 36 patients (56%). The median follow-up period was 6.41 years (range 0.10 to 14.25 years). Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL USA).

Results: There was no early mortality. Late mortality included one patient from group B who died after discharge on the thirty-eighth postoperative day. Pulmonary stenosis (PS) developed in 16 (25%) patients, of which 9 patients underwent re-interventions. The median time to re-intervention was 4.37 years (range 0.01 to 14.25 years). Re-interventions ($n = 14$, 22%) included balloon angioplasties ($n = 6$, 9%), re-operation ($n = 2$, 3%) and a combination of both ($n = 6$, 9%). Balloon angioplasties were performed in 4 (12%), 2 (9%) and 2 (22%) patients in groups A, B and C, respectively. One reoperation each was performed in groups A and C.

A combination of balloon angioplasty and reoperation was performed in one (3%), 3 (14%) and 2 (22%) patients in groups A, B and C, respectively.

Univariate Cox analysis identified TBA ($p = 0.03$), preoperative BAS ($p = 0.05$), presence of aortic anomalies ($p = 0.01$), single coronary artery ($p = 0.025$) and PS ($p = 0.006$) as potential risk factors for re-intervention. However, only the latter two ($p = 0.03$ and $p = 0.008$, respectively) were the predictors of late re-intervention as confirmed by Cox multivariate analysis.

Conclusion: The ASO in patients with coronary anomalies can be performed with excellent outcomes. However, a large population of patients requires re-interventions. A regular life-long cardiac follow-up is, therefore, recommended.

HEART FAILURE MANAGEMENT

P2748 | BEDSIDE

Beta-2 adrenergic receptor gene polymorphism Gln27Glu is associated with the clinical status, heart rate and blood pressure history in chronic heart failure patients

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Purpose: Prior studies have shown that β -adrenergic receptor (β -AR) single nucleotide polymorphisms (SNP) affect outcomes in patients with heart failure and after acute coronary syndrome. Our aim was to estimate relationship of β 2-AR gene polymorphism Gln27Glu with severity of clinical symptoms, renal and cardiovascular function in CHF.

Methods: β 2-AR gene polymorphism Gln27Glu was genotyped in genomic DNA from blood isolated from 66 CHF pts with I-IV NYHA functional class (FC) without primary renal, endocrine, autoimmune and oncological diseases. We analysed their echocardiography left ventricular ejection fraction (LVEF, Simpson's method), transmitral flow and tissue Doppler parameters of the medial and lateral parts of the mitral annulus, 24-hour ECG and blood pressure (BP) monitoring, 6-minute walking test, estimated glomerular filtration rate (e-GFR, MDRD and CKD-EPI equation), 24-hour urinary albumin excretion (UAE), history and clinical data. All pts were stable on medical therapy in accordance with current guidelines. The median of age was 63.0 (interquartile range 57.0-69.0) years; of LVEF - 34.0 (26.7-39.0)%. 91% were men, 85.5% had coronary artery disease, 9.1% - arterial hypertension (AH) heart disease, 5.4% - dilated cardiomyopathy.

Results: 25.8% of pts had Glu/Glu, 45.5% - Glu/Gln, 28.8% - Gln/Gln genotype. The carriers of the Gln/Gln genotype had more severe CHF (mean NYHA FC in the Glu/Glu was 2.5 ± 0.5 , in the Glu/Gln - 2.6 ± 0.6 , in the Gln/Gln - 2.8 ± 1.1 , $p = 0.003$). The duration of AH in anamnesis was longer in the Glu/Glu genotype (14 (6.5-26), 10 (1-14) and 0 (0-7) years in the Glu/Glu, Glu/Gln and Gln/Gln, respectively, $p = 0.028$). 57.7% of pts had sinus rhythm, others - permanent atrial fibrillation without differences within genotype groups. Minimal 24-hour ECG heart rate was lower in the Glu/Glu genotype (40 (36-42), 47 (43-49) and 49 (44-61) per minute in the Glu/Glu, Glu/Gln and Gln/Gln, respectively, $p = 0.015$). Maximal 24-hour ECG RR interval was longer in the Glu/Glu genotype (2248 (1736-2960), 1760 (1624-1888) and 1564 (1488-1728) ms in the Glu/Glu, Glu/Gln and Gln/Gln, respectively, $p = 0.05$). No association was found between Gln27Glu SNP and other 24-hour ECG parameters, BP monitoring, 6-minute walking test, LVEF, transmitral E/A and E/Ea ratio, e-GFR and UAE in the Glu/Glu, Glu/Gln and Gln/Gln genotype groups.

Conclusions: We found that the Gln/Gln genotype of β 2-AR gene is associated with severity of CHF and the Glu/Glu genotype - with lower trend for heart rate and longer duration of arterial hypertension before CHF development.

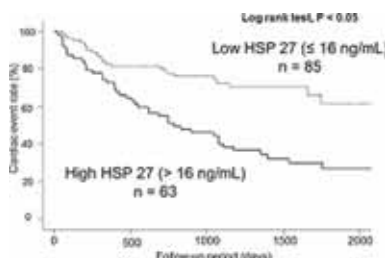
P2749 | BEDSIDE

Association of plasma HSP 27 level with severity and prognosis in patients with heart failure secondary to ischemic or dilated cardiomyopathy

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Background: Heat shock protein 27 (HSP 27) belongs to the small heat shock protein family member, which is induced by a variety of stressors and functions as chaperone in the heart. Recently, circulating HSP 27 was reported to be associated with cardiovascular disease such as acute coronary syndrome and atherosclerosis. However, it remains to be determined whether circulating HSP 27 level can predict cardiac prognosis in patients with chronic heart failure (CHF).

Methods and results: We measured plasma HSP 27 level in consecutive 148 patients with CHF due to ischemic or dilated cardiomyopathy, and 24 control subjects. Plasma HSP 27 was increased with advancing New York Heart Association functional class. Patients were prospectively followed during a mean follow-up period of 1029 days. There were 68 cardiac events, including 18 cardiovascular deaths and 50 re-hospitalization due to worsening heart failure or serious arrhythmia. In the multivariate Cox proportional hazard analysis, HSP 27 level was independently associated with poor outcomes in patients with CHF. A Kaplan-Meier analysis demonstrated that the cardiac event rate was higher in patients with high HSP 27 than in those with low HSP 27.



Kaplan-Meier analysis.

Conclusion: Plasma HSP 27 level was associated with severity and cardiac prognosis in patients with CHF secondary to ischemic and dilated cardiomyopathy.

P2750 | BEDSIDE

Use of new echocardiographic parameters to predict acute rejection after heart transplantation. A way to reduce the number of endomyocardial biopsies

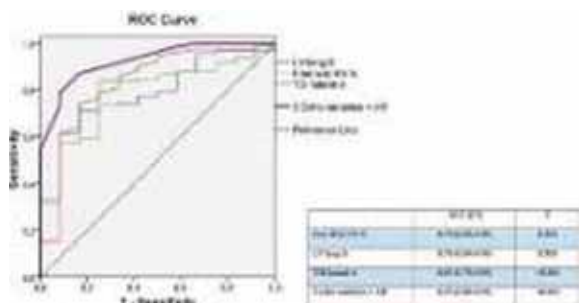
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Objective: To analyze the usefulness of conventional and new echocardiographic parameters to exclude acute rejection (AR) after heart transplantation (HT).

Background: AR is a limiting factor of survival after HT. The only validated method to detect AR is endomyocardial biopsy (EB). Recent advances in 2D-strain imaging may allow early detection of AR.

Methods: We included 34 HT performed at our institution between 2010 and 2012. A median of 7 (IQR 6-8) EB and echocardiograms/patient were performed simultaneously along the first year after HT. We analyzed classic echocardiographic parameters and speckle-tracking derived left ventricular (LV) longitudinal (Long), radial and circumferential strain, and Free wall Right ventricular (RV) Long strain.

Results: We analyzed 235 paired EBs and echocardiograms, 62 EBs presented AR (50 1R, 9 2R and 3 3R). Variables independently related to the absence of AR $\geq 2R$ were: Free wall RV Long strain $<-17\%$, global LV Long strain $<-15.5\%$ and Lateral Tissue Doppler Imaging (TDI) A >4.5 cm/s. C-statistic measure to exclude AR $\geq 2R$ based on the combination of them was 0.93 (0.86-0.99), with sensitivity 100%, specificity 54.8% and negative predictive value 100%. ROC curves are shown in the figure below.



ROC curves related with absence of AR.

Conclusions: We propose the combination of three echocardiographic measures, namely LV and free wall RV global Long-strain and lateral TDI A velocity, to exclude AR after HT. They are simple and reproducible parameters, and in case of external validation its routine measure could be a reliable tool to exclude high degree AR and it may alleviate the burden of repeated EB.

P2751 | BEDSIDE

Immune status in patients with decompensated heart failure: clinical implications

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Purpose: To analyze immune status in patients hospitalized with decompensated chronic heart failure.

Abstract P2751 – Table 1. Results

	IgA	IgG	CD25	IL-6	CIC	CRP	BNP	EF	Mortality	ASK
D1	2.8±0.4°	21.2±2.2°	27.7±3.5°	35.3±7.7°	31.1±6.3°	19.4±4.7°	1125±131°	30.6±2.5°	0%	162±4°
D4	2.7±0.2°	23.4±2.5°	31.7±2.9°	28.5±6.7°	38.0±6.5°	16.5±2.9°	831±43°	32.3±1.4°	2%	161±7°
DDis	3.5±0.4°	22.6±2.3°	26.4±3.4°	26.4±7.2°	42.1±6.8°	20.1±5.5°	423±21°	36.1±2.0°	4%	109±3°
12 months	No data	No data	No data	No data	No data	11.3±1.2	412±22°	38.4±3.2°	12%°	No data
Control	2.0±0.4	12.4±3.5	12.7±5.3	2.5±1.1	11.2±1.8	4.6±0.9	23±3	56.3±3.7	0%	45±2°

CIC, circulating immune complexes; ASK, antistreptokinase.

To assess contribution of systemic inflammation as one of important pathogenic mechanisms leads patients to hospitalization and immune status towards clinical presentation and 1-year follow-up prognosis.

Methods: Dynamics of a number of haematological and biochemical parameters of peripheral blood were studied. The parameters measured were GFR, hs-CRP, BNP, leucogram, amount of CD 4, CD 25, levels of Ig A,G,M, interleukins 2,6,10, circulating immune complexes, antistreptokinase and antisterptolysine-O and antiphospholipids antibodies, antioxidant plasma activity, and LV function by echocardiography. A total of 52 patients (male -34, female- 18) were studied with average age 60.8±3.6 years and EF<35%. The patients were hospitalized with diagnosis of decompensated CHF due to non-valvular causes without any evident signs of inflammation or infection. Patients were assessed at admission, day 4, day of discharge from hospital and 12 months follow-up. Control group included 40 patients without CHF.

Results: See Table 1. Patients with the highest levels of the above mentioned parameters were also characterized by poor clinical indicators, such as longer hospital stay, slower normalization of clinical signs and lab parameters and higher mortality (2 patients died in hospital, 4 during 1-st year after discharge)).

Conclusion: Patients with acute decompensation of CHF demonstrated clear immunological signs of chronic infection and/or systemic inflammation. This signs and their severity may have an important prognostic value for both in-patient and follow-up phase of management of patients with decompensated CHF. Some of the possible sources of antigen stimulation in this case maybe intestinal discirculation, altered wall penetrability of colon, severe edema of lower extremities with poor circulation or progression of atherosclerosis.

P2752 | BEDSIDE

Monitoring of intrathoracic impedance can reduce heart failure hospitalization

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Background: A major cause of heart failure (HF) related hospitalizations is fluid accumulation. Recent studies have suggested that intrathoracic impedance (ITI) may be a useful parameter to track daily changes in pulmonary fluid status. OptiVol alert, which is a fluid status algorithm calculated from ITI, can detect impending fluid accumulation at an early stage. However, the clinical utility of this method is not well established. Therefore, we sought to examine whether OptiVol alerts can reduce HF hospitalization.

Methods: We conducted two arms. One was a prospective, multicenter study. HF patients who had been implanted with a high-energy devices with an OptiVol feature were included in this study (OptiVol arm). All patients in OptiVol arm were followed by a wireless remote monitoring system and asked to visit to outpatient clinic after OptiVol alert. Patients took some examinations at enrollment, at OptiVol alert and at HF hospitalization. If we would notify HF sing in outpatient clinic, we intervene along with HF guideline. The other was a retrospective, multicenter study. HF patients who had been implanted with a high-energy devices without an OptiVol feature (Control arm). We compared HF hospitalization rate per year and HF hospitalization free survival rate. And also, we examined the reasons why some patients in OptiVol arm could not avoid HF hospitalization.

Results: One hundred ninety seven patients were enrolled in OptiVol arm and 436 patients were enrolled in Control arm. There was no significant difference in patient characteristics between two arms. HF hospitalization rate per year was significantly lower in OptiVol arm than that in Control arm (0.08±0.39 vs. 0.22±0.61, p<0.01). And HF hospitalization free survival rate was also significantly higher in OptiVol arm than that in Control arm (p<0.05). In OptiVol arm, there were 23 HF hospitalizations. The value of ITI at HF hospitalization was decreased ~10% compared with that at baseline (63.4±8.8 Ω vs. 70±7.4 Ω, p=0.001). In 15 of 23 HF hospitalizations, OptiVol alerts were notified before HF hospitalization. However, some patients refused visiting hospitals after experience of repetitive false positive OptiVol alert events, which was one reason. Sometimes, ITI acutely decreased after the false positive OptiVol alert events. However, in these cases, we could not notify acutely decreased ITI, because OptiVol alert did not have function of remainder, which was another reason.

Conclusions: Monitoring of ITI can reduce HF hospitalization. However, OptiVol index and OptiVol alert system would not be enough for clinical use.

P2753 | BEDSIDE

Response to cardiac resynchronization therapy is improved by combining radial dyssynchrony and contractility of the late activated segment

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Background: Speckle tracking echocardiography (STE) has the potential to assess mechanical dyssynchrony, and to evaluate viability of the latest activated segment (LAS) by measuring its peak radial strain. The aim of this study was to assess the predictive value of a simple prediction index (Radial Prediction Index - RPI), based on the combination of radial dyssynchrony and contractility of LAS.

Methods: Two-dimensional speckle tracking echocardiography was performed in 100 heart failure (HF) patients before undergoing CRT, to assess LV radial dyssynchrony (anteroseptal to posterior wall delay >130 msec), and residual myocardial viability (>16% peak radial strain) of the LAS. Concordance between LV lead position (by chest x-ray) and LAS was also evaluated. The RPI was obtained by multiplying radial dyssynchrony by peak radial strain of the LAS. Two end-points were considered: 1) >15% reduction in LV end-systolic volume index at 6 months, and 2) combined all-cause mortality and hospitalizations for HF in long-term follow-up.

Results: Three patients were classified as echo responders. RPI was significantly greater in responders than in non-responders (56.5±50 vs 14.7±14, p<0.0001). After correction for other clinical and echocardiographic predictors, logistic regression analysis revealed that RPI was independently associated with the likelihood of response to CRT (P<0.0001). By ROC analysis, a cut-off value of RPI ≥25.6% showed a significantly greater area under the curve than dyssynchrony indices alone (p<0.001). This predictive value significantly increased when concordance between LV lead position and LAS was present, since prevalence of echo-responders increased to 89% versus 67% when only radial dyssynchrony was considered. After a mean follow-up of 19±15 months there were 35 combined events. Cox proportional regression analysis showed that RPI was an independent predictor of worse outcome (log-rank test 10.6, P<0.01) after adjusting for other clinical and echocardiographic predictors.

Conclusions: This novel combined index by radial strain echocardiography might be able to predict response to CRT, either in terms of reverse remodeling or long-term prognosis. The discriminatory value of this index in the identification of responders seems to be better than time-delay indexes alone.

P2754 | BENCH

Adenosine receptors transcriptomic profiling in leukocytes and cardiac fibroblast of patients with valvular disease undergoing prosthetic implantation

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Purpose: Adenosine is a potent extracellular messenger produced in high concentrations under metabolically unfavourable conditions. It restores tissue homeostasis through the interaction with its G-protein coupled membrane receptors (A1R, A2aR, A2bR and A3R), all with a cardioprotective role. ARs are expressed on multiple cardiac cells, including fibroblasts, endothelial cells, smooth muscle cells and leukocytes however the modulation of these receptors is still not fully understood. Aim of this study was to assess changes of transcriptomic profiling of A1R, A2aR, A2bR and A3R in human leukocytes of patients with HF due to valvular disease (HF-V) as compared to healthy subjects (C) and in cardiac fibroblast (CF) obtained by human atrium (auricle) fragments of patients undergoing cardiac surgery for prosthetic implantation. A human CF atrial cell line (NHCF-A) was used as control (cc).

Methods: Total RNA was extracted from leukocytes of C (n=7) and of Vlv pts (n=6, NYHA III-IV) with PAXgene Blood RNA Kit and by acid guanidinium thiocyanate-phenol-chloroform from CF (n=13). To avoid changes in the original phenotype, the experiments were conducted at the third passage in fibroblast cultures. Real-time PCR was performed and optimized for each AR primer. CD39 and CD73 mRNA expression was also evaluated.

Results: For each receptor analyzed higher levels of mRNA expression were observed in patients with respect to C both at peripheral and cardiac level: Leukocytes A1R: C=1.97±0.72, HF-V=10.9±3.27, p=0.0098; A2aR: C=0.45±0.15, HF-V=3.19±0.94, p=0.0057; A2bR: C=0.43±0.16, HF-V=5.00±2.98, p=0.05; A3R: C=1.39±0.26, HF-V=2.9±0.71, p=0.04; CD39:C=0.33±0.05, HF-V=2.37±0.40 p<0.0001; CD73:C=1.34±0.38, HF-V=6.77±1.91, p=0.01. CF A1R: cc=0.33±0.004, CF=4.24±1.72; A2aR: cc=1.01±0.006, CF=2.77±0.67; A2bR: cc=0.07±0.03, CF=3.04±1.3; A3R: cc=0.74±0.26, CF=2.9±0.71, p=0.04; CD39 cc=0.66±0.002 CF=9.6±3.06; CD73: cc=0.32±0.01, CF=4.71±2.22. In the subgroup of patients (n=4) in which simultaneous cardiac biopsy and blood sample were obtained, AR leukocytes transcriptomic profile mimed that of CF showing the previously reported trend.

Conclusions: These results demonstrated that all ARs are activated both in peripheral leukocytes and at tissue cardiac level in HF-V pts. These preliminary data show, for the first time, that human circulating blood cells may express the same alterations occurring in the heart, thus suggesting their application for the study

of the adenosinergic system in greater populations and in different pathologic conditions.

P2755 | BEDSIDE

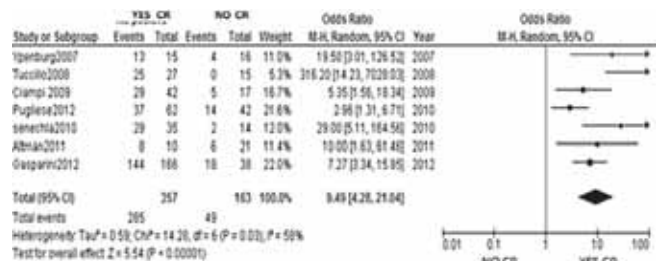
Meta analysis echocardiography cardiac resynchronization therapy positive contractile myocardial reserve as a predictor of response

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Purpose: The cardiac resynchronization therapy (CRT) in patients with dilated cardiomyopathy (DCMP) could no response in 40%. Our aim is to determinate if the presence of contractile reserve (CR) determined by pharmacology stress echocardiography (SECHO) can predict a clinical positive (Clin-R) and echocardiography response (Echo-R) to CRT in ischemic and non-ischemic DCMP.

Methods: Condition to investigate was DCMP with ejection fraction (EF) <25%, New York Health Association functional class (FC) ≥ III and QRS ≥120 ms. The prognostic measure was RC estimated by SECHO. Clin-R was defined as improvement in at least I FC and Echo-R as increases ≥5% in EF or reduce >15% in left ventricle end systolic volume (LVESV). Every step was made by two authors independently and the discordances solved by consensus. The searching was made by two authors in PUB med; Chocrane library, EBSCO, Proquest and Lilacs, just for adults humans prospective observational studies. The publication bias was assessed with the funnel plot. The bias risk assessment was done with the chek liste STROBE. The data was assessed with de Parmar method.

Results: We found 196 articles, 8 were included in the quality analysis. The funnel plot didn't show published bias. 3 studies included for Clin-R, and 7 for the Echo-R. There was consensus in CRT therapy Echo -R between studies. We found that echo CR positive predict Clin-R with an OR 4.42 IC 95% (1.52-12.85). The echo CR predicts Echo-R (fig1) with OR 9. One study reported 38 patients lost, the analysis in the worst scenario showed that Echo-R the OR 8.37 IC 95% (5.58-15.12).



Contractile reserve (CR) yes/no in Echo-R.

Conclusion: The presence of contractile reserve measure by echocardiography is a parameter important in the detection of good CRT clinical and echocardiography response.

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Acute heart failure with preserved or reduced ejection fraction: is it bimodal or overlapping multiple phenotypes?

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Purpose: Whether heart failure with preserved or reduced left ventricular ejection fraction (LVEF) represents distinct or overlapping syndromes and whether they are associated with different outcomes remain unsettled. The different cut offs of ejection fraction used to dichotomize the two syndromes contributed to the confusion surrounding this issue. We sought to characterize further the importance of LVEF in patients hospitalized with acute heart failure stratified according to a spectrum of LV function strata rather than two dichotomized groups.

Methods: We conducted a prospective registry in 18 hospitals in between October 2009 and December 2010, and followed mortality rates till January 2013. In this sub-study we describe the baseline characteristics and outcomes in this patient population stratified into 4 groups according to LVEF; normal (>50%), mild LV dysfunction (41-50%), moderate LV dysfunction (31-40%) and severe LV dysfunction (≤30%).

Results: A total of 2,610 patients were enrolled in this study with mean age (SD) of 61.3 (14.9) and 65.6% were men. Patients with normal LV systolic function and those with severe systolic dysfunction presented two distinct groups. Compared to those with severe systolic dysfunction, patients with normal LVEF were older (64.9 vs. 58.7, p<0.001) with those above 70 years constituted 40% vs 24% (p<0.001), more likely to be female (60.4% vs 23.3%, p<0.001) and have higher body mass index (32.6 vs 28, p<0.001). They also have higher prevalence of hypertension (83.2% vs 63.6%, p<0.001), diabetes (66.9% vs 59.2%, p<0.001), atrial fibrillation (27.7% vs 13.9%, p<0.001) and anemia (33.1% vs

17.9%, $p < 0.001$). Ischemia and ventricular arrhythmias were less reported in this group (27.3% and 0.9% vs 56.4% and 5.2%, $p < 0.001$ respectively). The other two groups with mild and moderate LV systolic dysfunction showed an overlapping spectrum between the normal and severe LV dysfunction groups. All-cause cumulative mortality rates at 30 days, 1 year and 3 years were 8.3%, 19.5% and 24.3%, and were similar in the 4 groups.

Conclusion: Classifying acute heart failure patients according to LVEF uncovers two distinct groups with normal LV function and severe dysfunction with a spectrum of phenotypes in between; however, short-term and long-term mortality was similar across these groups. The higher age and comorbidities in the normal LVEF patients may explain the observed similar mortality in the normal and severe LV systolic dysfunction groups.

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Assessment of right ventricular adaptability to load allows prediction of transplant free outcome with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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Purpose: Finding predictors of transplant (Tx) free survival with severe precapillary pulmonary hypertension and timing of Tx listing are main challenges with prolongation in Tx waiting time. Right ventricle (RV) function is highly load-dependent and RV failure (RVF) due to pressure overload is a main cause of death in pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTPH). Assessment of RV adaptability to load has proved useful for other surgical decisions. Now we assessed its predictive value for outcomes with severe PAH and CTPH aiming to provide new tools for the timing of Tx listing.

Methods: At selection and each follow-up control, all Tx candidates with PAH (except congenital heart diseases) and CTPH (not suitable for embolectomy), without RVF at first evaluation performed in 2006-2012, underwent echocardiography (with tissue Doppler and strain imaging) plus NT-ProBNP and 6 min walk distance (6MWD) measurements. At selection patients (pts) underwent right heart catheterization. For assessment of RV adaptability to load we used a recently validated "load adaptation index" (LAI) based on the relationship between RV load and RV dilation, taking also RA pressure into account. Collected data were tested for ability to predict short- (1 year) and mid-term (3 years) RV stability and Tx-free survival.

Results: During a 22 to 94 months follow-up, 27 of 102 evaluated pts developed irreversible RVF (16 died before Tx) although initially these unstable pts showed similar pulmonary arterial pressure, 6MWD, RV size and RVEF in comparison to pts remaining stable and there were also no differences in medication between these 2 patient groups. However, those with subsequent RVF had initially a lower LAI and RV afterload-corrected peak global longitudinal systolic strain rate (PSSrL), and also higher RV dyssynchrony (for all $p < 0.01$). LAI and afterload-corrected PSSrL stability showed high predictive values for 1 and 3 year freedom from RV failure (85-89% and 81-86%, respectively) and 3 year Tx-free survival (83-90%). LAI reduction of $\geq 20\%$ in clinically stable pts with tricuspid regurgitation $\geq$ grade 2 revealed 86% predictive value for short term (< 6 months) development of severe RVF. NT-Pro-BNP, TAPSE and Tei Index were initially also more altered in unstable pts but their predictive value for RVF was low.

Conclusion: Serial echo follow-up assessment of RV adaptability to load in pts referred for Tx because of severe PAH and CTEPH allow the prediction of RV stability and Tx-free patient survival during the next 1 to 3 years. This can be helpful for timing of Tx listing.

P2758 | BEDSIDE

The mean apnoea hypopnea index as a diagnostic criterion for sleep disordered breathing in patients with heart failure

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Purpose: Sleep Disordered Breathing (SDB) is diagnosed in patients with Heart Failure (HF) by calculating the Apnoea Hypopnea Index (AHI) typically from a single overnight Polysomnography (PSG) study. Repeated PSG studies over 2-4 nights have, however, shown that the AHI may vary in type and severity in these patients.

We hypothesized that due to alveolar fluid changes in HF patients, the AHI would be highly variable over a prolonged period of monitoring and therefore a single sleep study may be insufficient for the diagnosis of SDB. We therefore investigated an alternative diagnostic criterion for SDB - meanAHI - calculated from the SleepMinderTM (SM) device, which is a non-contact bedside nocturnal respiratory monitor that can be used for weeks to months and that we have previously validated for this purpose.

Methods: 39 adult HF patients consented to have nightly SM recordings in their homes for 12 months. We calculated the variability of the AHI using the Intra Class Correlation Co-efficient (ICC) together with the 95% confidence interval and the Co-efficient of Variation (CoV). Further we compared the proportion of patients with a mean AHI > 15 over a 2-week, 3-month and 12-month period using a Monte Carlo simulation. In addition, we calculated the misclassification rate of

SDB based on severity (MRsev) and treatment group (MRT for AHI > 15) compared with a single baseline diagnostic study.

Results: The mean (SD) age, ejection fraction, and Body Mass Index were 77 (9) years, 38 (13.7)%, and 28 (5) kg/m² respectively. The ICC for the AHI over consecutive nights in all patients was 0.33 (95% CI 0.23-0.49). The CoV was 54%.

The mean (SD) 2wkAHI was (20) events/hour in all patients and the AHI was consistently above treatment threshold (AHI > 15) in 57% of these patients, which compares with 60% and 74% over a 3mth and 12mth FU period and 62% (95% CI 33-85) from a Monte Carlo simulation. The meanAHI was higher in non-survivors (n=8) vs survivors (n=31) (33 vs 22 events/hour), without adjustment for potential confounders). The mean MRsev and MRT for all patients was 35% and 21%, respectively, over a 2-week period.

Conclusion: The AHI is highly variable in patients with HF and a single night's value may be insufficient for the diagnosis of SDB. The meanAHI over a 2-week period from non-contact monitoring may provide an alternative and realistic approach for more accurate diagnosis and therapeutic decision-making in this patient group.

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Assessment of the subjectivity of the NYHA classification: use of the 6 minute walk test

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Purpose: The New York Heart Association (NYHA) functional class status has been used in the vast majority of heart failure studies as well as in many guidelines. However, the NYHA class status includes an element of subjectivity. We aim to review the literature on all studies done with correlation between 6 Minute Walk Test Distance (6MWT) and New York Heart Association (NYHA) functional class and thus determine the objectivity of the NYHA criteria in assessing functional class in heart failure patients.

Methodology: The search terms "Comparison of NYHA to 6MWT", "NYHA and 6MWT" and "heart failure and 6MWT" were entered into the PubMed database, yielding 328 papers. 48 studies comparing 6MWT in each NYHA class were included. 280 papers were excluded, with 81 studies describing 6MWT values in combined NYHA classes and 199 studies failing to compare NYHA to 6MWT. We then obtained the mean and standard deviation of 6MWT for each NYHA class for each paper and compared them across each NYHA class.

Results: The 48 studies consisted of 28 from Europe, 13 from the USA, 5 from Asia and 2 from South America. A total of 11014 patients (7502 males, mean age 59.3 $\pm$ 10.6 years old) were studied. Mean 6MWT was 446.1 $\pm$ 123.1m in NYHA I patients, 401.5 $\pm$ 95.0m in NYHA II patients, 328.3 $\pm$ 80.7m in NYHA III patients and 232.0 $\pm$ 31.5m in NYHA IV patients. There was no significant difference between 6MWT values in each NYHA class, with much overlap in 6MWT distances among all 4 groups (see Fig. 1).

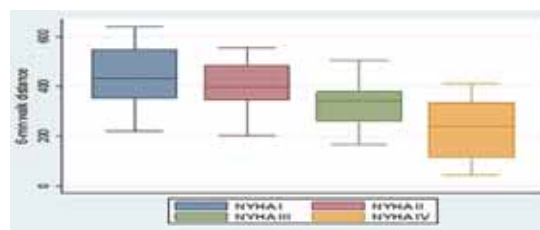


Figure 1. Mean 6MWT in each NYHA class.

Conclusion: The NYHA criteria has an element of subjectivity that may be influenced by multiple factors. More objective measures such as the 6MWT may be included in studies to provide better definition of the patient's functional status.

HEART FAILURE NEWS

P2761 | BEDSIDE

Left ventricular diastolic dysfunction is independently associated with cerebral white matter lesion in elderly patients without ischemic heart disease and stroke

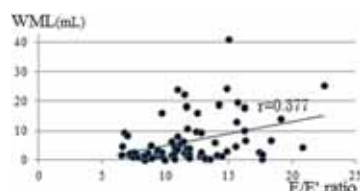
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Background: Left ventricular (LV) diastolic dysfunction with normal contraction is known to increase with age and may cause systemic hypoperfusion at terminal stage. Cerebral white matter lesions (WMLs) on magnetic resonance imaging (MRI), mainly caused by ischemia, have also been established to increase with age, and are associated with heightened risks of stroke. Although aging is a common risk factor of these diseases, the relationship between them is not fully understood. The aim of this study was to clarify it.

Subjects and method: Subjects comprised 75 patients between 65 and 75

years old with normal LV contraction and no signs or history of symptomatic heart failure, ischemic heart diseases, atrial fibrillation, stroke, or cognitive dysfunction. For the estimation of LV diastolic function, E/E' measured by tissue Doppler echocardiography offers an indicator of the severity of LV diastolic dysfunction, reflecting both diastolic LV stiffness and diastolic LV filling pressure. The volume of cerebral WMLs was quantified on brain MRI.

Results: Mean age was 69.3 ± 3.4 years, E/E' ratio 11.8 ± 3.5 , and the volume of cerebral WMLs 6.4 ± 7.6 mL. Linear regression analysis showed the positive association between E/E' ratio and the volume of WMLs ($r=0.377$, $p=0.0009$). Then, we re-evaluated the association between E/E' ratio and the volume of WMLs, using another multivariate linear regression analysis adjusted for confounding factors such as age, hypertension, diabetes, and sex. As a result, a direct association between E/E' ratio and the volume of WMLs was confirmed ($p=0.0057$).



Relationship between WML and E/E'

Conclusions: This investigation identified a direct association between LV diastolic dysfunction and cerebral WMLs. Further investigation is needed to clarify the mechanisms.

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Abnormal fibrin clot structure in chronic heart failure

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Background and purpose: Chronic Heart Failure (CHF) is an overwhelming healthcare burden with poor clinical outcomes and high mortality rates. One reason for these poor outcomes is the abnormal haemostatic balance leading to stroke, venous thrombosis, bleeding and sudden death. Abnormal fibrin clot properties in CHF may explain the phenomenon of the prothrombotic and increased haemorrhagic state in these patients. Coagulation and clot lysis can be assessed by Thrombelastography (TEG), fibrinolysis and turbidimetric assays.

Methods: Whole blood and plasma from 15 CHF patients and 15 healthy controls were analysed by TEG, fibrinolysis and turbidimetric assay. Data were compared by t-test.

Results: Using TEG, no statistically significant differences were seen in whole blood from CHF subjects compared to controls: mean R-time (10.2 minutes vs. 8.5 minutes, $p=0.414$) and K-time (1.9 minutes vs. 2.1 minutes, $p=0.8$), α -angle (64.0° vs. 60.2° , $p=0.3$) Maximum Amplitude (66.7mm vs. 66.9mm, $p=0.9$) and LY60 (2.4% vs. 3.9%, $p=0.3$). Turbidimetric analysis revealed increased absorbance of light through fibrin clot in CHF patients (0.6 vs 0.5, $p=0.003$). Fibrinolysis assay showed no difference in time to lyse 50% of clot (16.3 mins vs. 18.4 minutes, $p=0.3$) but a significantly steeper slope of fibrin clot lysis in CHF subjects (-2.5 vs -1.8 , $p=0.01$).

Indices of CHF vs. control

	CHF	Control	P value
TEG: R-time (min)	10.2 (7.5)	8.5 (1.9)	$P=0.4$
TEG: K-time (min)	2.0 (1.2)	2.1 (0.5)	$P=0.8$
TEG: α -angle	64.0 (12.4)	60.2 (7.4)	$P=0.3$
TEG: Maximum amplitude (mm)	66.7 (7.1)	66.9 (9.8)	$P=0.9$
TEG: LY60 (%)	2.5 (2.1)	3.9 (4.4)	$P=0.3$
Turbidimetric analysis: Absorbance	0.6 (0.1)	0.5 (0.07)	$P=0.003$
Fibrinolysis: Time to lysed 50% of fibrin clot (min)	16.3 (5.3)	18.4 (5.6)	$P=0.3$
Fibrinolysis: Slope	-2.5 (0.8)	-1.8 (0.7)	$P=0.01$

Conclusions: Thicker fibrin clots are formed in CHF (as demonstrated by increased absorbance), followed by an increased rate of fibrin clot lysis in CHF. TEG shows no evidence of abnormal clot kinetics in patients with CHF. This may potentially explain the increased haemorrhagic risk associated with CHF patients on warfarin seen in recent trials.

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The association between cerebral blood flow, oxidative stress, inflammation and quality of life in older heart failure patients

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Purpose: Diminished quality of life (QoL) is reported to predict mortality and hospitalizations in heart failure (HF) patients, though the physiological mechanisms

underlying diminished QoL in older HF patients are unclear. The objective of this study was to investigate the relationship between QoL and biomarkers known to be impaired in older HF patients that may be useful as guides to therapy.

Methods: Patients with HF (N=36; NYHA class II, III or IV) and healthy controls (N=40) matched for age (≥ 60 years) and sex completed the Short Form 36-item health survey (SF-36). The SF-36 measures eight health domains (physical and mental functioning, role limitations due to physical and emotional problems, vitality, bodily pain, social functioning and general health) with higher scores depicting better health functioning. Biomarkers included cerebral blood flow (Transcranial Doppler ultrasound), oxidative stress (determinable reactive oxygen metabolites; d-ROMs) and systemic inflammation (high sensitive C-reactive protein; hs-CRP).

Results: HF patients and controls were well matched for age (68 ± 7 versus 67 ± 5 years, $p>0.05$) and sex ($p>0.05$). The expected pattern of results were observed between groups on QoL and biomarker measures. However, in new findings Spearman's correlations (ρ) demonstrated that reduced common carotid arterial blood flow velocity in HF patients was weakly-moderately associated with role limitations due to physical ($r=0.36$, $p<0.05$) and emotional ($r=0.35$, $p<0.05$) functioning, vitality ($r=0.40$, $p<0.05$) and social functioning ($r=0.40$, $p<0.05$). Additionally, reduced middle cerebral arterial blood flow velocity in HF patients was moderately-strongly related to lower vitality ($r=0.53$, $p<0.01$), and physical and mental functioning ($r=0.51$, $p<0.05$ and $r=0.45$, $p<0.05$, respectively). Finally, hs-CRP was negatively correlated with vitality ($r=-0.40$, $p<0.05$). These relationships were not observed in the control group. Oxidative stress as determined by d-ROM was not significantly related to QoL in HF patients.

Conclusions: Reduced cerebral blood flow and increased inflammation are associated with reduced physical and mental QoL in older HF patients. Addressing these mechanisms with interventions that increase cerebral blood flow velocity and reduce systemic inflammation may improve QoL in older HF patients.

P2764 | BEDSIDE

Dilated inferior vena cava at admission is a prognostic factor for cardiovascular events in heart failure patients with preserved ejection fraction

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Purpose: Heart failure (HF) with preserved ejection fraction (HFpEF) has been increasing in recent years, with poor prognosis. However, few studies report on the risk factors for readmission for HFpEF. Hence, We investigated the risk factors for readmission of HF, particularly those with preserved EF (pEF).

Method: We retrospectively studied the medical records of 416 first-onset HF patients admitted to our hospital from 2009–2013. In this study, 171 of whom were classified as pEF. The study endpoint was readmission due to heart failure. HF-pEF was defined as LVEF $\geq 50\%$ and according to ESC guidelines. Data regarding medical history, vital signs, electrocardiogram, chest X-rays, blood tests, and echocardiograms were collected and compared between patients with pEF and those with reduced EF (rEF). The chi-square test, Student's t-test, and Kaplan–Meier survival curves were used to compare variables between the patients, as appropriate. Univariate analysis was performed on all items, and those with statistical significance were selected. Multivariate analysis was performed on variables with a value of $P<0.05$ using the stepwise multiple regression approach (step-up method).

Results: Of the 171 pEF patients, 49 reached the endpoint over 1 year. Multivariate analysis revealed high blood urea nitrogen (BUN) level at admission [hazard ratio (HR): 1.045], dilated inferior vena cava (IVC) at admission (HR: 1.088), medical history of old myocardial infarction (HR: 3.033), and old cerebral infarction (HR: 3.006) as independent risk factors for readmission. In contrast, 64 of 245 rEF patients reached the endpoint. Risk factors for rEF patient readmission were low systolic blood pressure at discharge (HR: 0.977), high blood urea nitrogen level (HR: 1.049), low albumin level (HR: 0.307) at discharge, and absence of beta-blocker use (HR: 0.489). We calculated the Kaplan–Meier survival curves and compared them using log-rank tests. Significant differences were shown for all factors.

Conclusion: Our study suggests dilated inferior vena cava at admission was a predictor of readmission for HFpEF patients.

P2765 | BENCH

Increased volume load due to stimulation of renal beta1-adrenoceptors by beta1-adrenoceptor antibodies contributes to the progression of dilated immune-cardiomyopathy

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Stimulating antibodies (abs) targeting the 2nd extracellular loop (ECII) of the β_1 -adrenoceptor (β_1 -AR) induce cardiac dilatation & failure in rats. Within the first 6 months of immunization antibody-positive rats develop a hypertensive phenotype (increased RR, LV hypertrophy), which then evolves into a DCM-phenotype. As β_1 -ARs are also highly expressed in the kidney, we hypothesized that the initial

hypertensive phenotype may, at least in part, rely on an antibody-induced stimulation of renal β 1-ARs.

Methods: N=40 Lewis rats were monthly immunized with a β 1-ECII/GST fusion protein, n=20 NaCl (0.9%)-injected rats served as controls. Antibody titers & cardiac function were followed every 3 months by ELISA & by echocardiography. In addition, every month we analyzed plasma renin activity, drinking behavior, serum electrolytes, and 24h-urine samples. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were assessed invasively before harvesting the kidneys for further histological and molecular analysis.

Results: Chronic stimulation of the kidney by anti- β 1-ECII abs results in an initial increase in renin mRNA levels, indicating activation of β 1-ARs in the membrane of renin producing granular cells within the juxtaglomerular apparatus. In the course of our study renin mRNA levels decreased. These findings fit well with the observed transient increase in plasma renin activity and the increase in GFR in immunized versus control rats suggesting renin-mediated hyperfiltration. In addition, β 1-ECII antibody-induced stimulation of β 1-ARs in the distal tubules resulted in a significant increase in sodium and chloride reabsorption. Physiologically this initiates a decrease in aldosterone secretion and, hence, negatively affects potassium secretion. This cascade further enhances sodium and (passive) water reabsorption, thus by volume overload contributing to the initial hypertensive phenotype.

In conclusion we show here that stimulating anti- β 1-ECII appear in fact to be able to modulate renal function, in particular through β 1-ARs localized (a) on renin-producing macula densa cells, and (b) on distal tubular cells, which might –by volume overload– indirectly accelerate switching of the hypertensive to the DCM phenotype.

P2766 | BEDSIDE

Impaired gas diffusion correlates with right heart-pulmonary circulation uncoupling and ventilation inefficiency during exercise in heart failure

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An altered gas diffusing capacity for carbon monoxide (DLCO) is a marker of lung capillary injury that bears relevant clinical and prognostic information in heart failure (HF) patients. It is unknown whether right heart-pulmonary circulation (RH-PC) uncoupling abnormalities in gas diffusion are linked and may become synergic in causing exercise limitation and ventilation inefficiency.

Methods: 12 HFrEF patients (mean age 64 ± 11 ; male 75%; NYHA II-III; mean left ventricular (LV) ejection fraction $34 \pm 11\%$) underwent DLCO measurements by single breath technique and maximal cardiopulmonary exercise testing (CPET, tilt-ergometer, personalized ramp protocol) combined with Echo-Doppler assessment. The RH-PC coupling was assessed by monitoring the ratio of tricuspid annular peak systolic excursion (TAPSE)/pulmonary systolic arterial pressure (PASP) and the entity of their changes during exercise.

Results: Patients exhibited an abnormal gas diffusion (mean DLCO 17 ± 4.1 ml/min/mmHg) elevated PASP (mean 43.5 ± 9.4 mmHg) and depressed TAPSE (mean 15.9 ± 4.2 mm) along with significant functional limitation (mean peak VO₂ 11.6 ± 2.9 ml/kg/min) and ventilatory inefficiency (mean VE/VCO₂ slope: 35.7 ± 7.7 and mean end-tidal of CO₂ mean 31.6 ± 5.8 mmHg). The figure below show the correlations existing between DLCO and other ventilatory or echo-derived parameters.

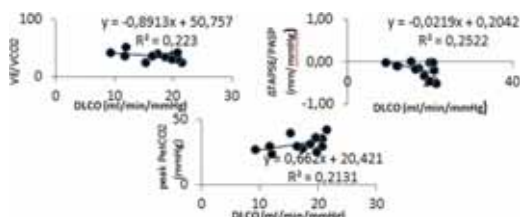


Figure 1. Correlations.

Conclusions: Our findings suggest a link between the RV-PH uncoupling with gas diffusion abnormalities suggesting that interventions aimed at targeting the right heart and functional performance have to combine a modulatory effect on the alveolar-capillary gas diffusion capacity.

P2767 | BENCH

Endothelial protein tyrosine phosphatase 1b deficiency reduces both endothelial and cardiac dysfunction of in a mouse model of heart failure

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Purpose: Chronic heart failure (CHF) is associated with an endothelial dysfunction, and especially a decrease in nitric oxide (NO) production, however the direct link between endothelial dysfunction and aggravation of CHF is not established. We reported previously a new potent therapeutic approach of CHF, based on

inhibition of protein tyrosine phosphatase 1B (PTP1B), which both increases NO production (via restored PI3K/Akt/eNOS signaling) and reduces adverse Left Ventricular (LV) remodeling and LV dysfunction. To address the direct link between endothelial protection and reduction of CHF, we evaluate the cardiac and vascular consequences of endothelial PTP1B deficiency (endoPTP1B^{-/-}) in a mouse model of CHF.

Methods: EndoPTP1B^{-/-} mice, developed by crossing LOX-P PTP1B mice with mice expressing CRE under the control of the endothelial promoter Tie2, or wild-type (WT) were subjected to left coronary artery ligation or sham surgery, and the development of CHF was assessed by echocardiography at 2 weeks, and 1, 2 and 3 months, and endothelial function at 3 months.

Results: WT CHF mice showed a markedly impaired flow-mediated dilatation of isolated mesenteric arteries (sham: $40 \pm 4\%$; CHF: 5 ± 5 ; $p < 0.001$), which was improved in endoPTP1B^{-/-} mice ($30 \pm 5\%$; $p < 0.001$ vs. WT CHF). These responses were reduced by a NO-synthase inhibitor, showing the implication of NO.

In WT, CHF increased LV diameters and decreased LV fractional shortening (at 3 months: sham: 49 ± 2 ; CHF: $12 \pm 1\%$; $p < 0.001$) while these parameters were improved in endoPTP1B^{-/-} mice ($20 \pm 2\%$; $p < 0.01$). LV pressure-volume curves showed that endoPTP1B^{-/-} mice with CHF had reduced LV end-systolic (sham: $22.5 \pm 1.2\%$; CHF WT: $14.9 \pm 1.9\%$, $p < 0.05$) and increased end-diastolic pressure-volume relationships (sham: $2.1 \pm 0.9\%$; CHF WT: $4.9 \pm 0.7\%$, $p < 0.05$) demonstrating impaired systolic and diastolic dysfunction, respectively, which were both improved in endoPTP1B^{-/-} mice (end-systolic: $20.6 \pm 2.3\%$, $p > 0.05$; end-diastolic: $2.3 \pm 0.9\%$, $p < 0.05$). Histological analysis showed cardiomyocytes hypertrophy and increased collagen density in WT CHF mice, which were reduced in endoPTP1B^{-/-} mice, at identical infarct size. These beneficial cardiovascular effects were associated with a significant increase in survival (CHF WT: 44%, CHF endoPTP1B^{-/-}: 87%, $p < 0.001$).

Conclusions: Thus, in this mouse model of CHF, endoPTP1B deficiency not only induced an improvement of endothelial function, but also of cardiac function, adverse LV remodeling and survival. These results provide a direct demonstration of the beneficial effect of endothelial protection in the treatment of CHF.

P2768 | BEDSIDE

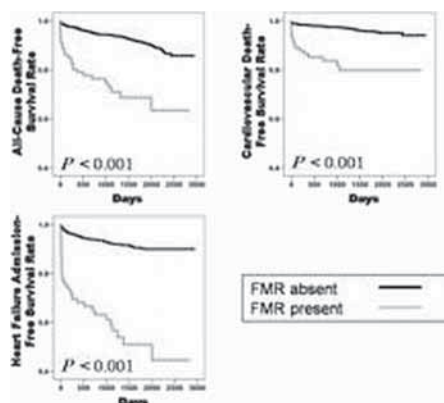
Prevalence and long-term prognosis of functional mitral regurgitation in Asian symptomatic heart failure in recent era of cardiovascular clinical practice

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Purpose: Previous studies performed in Western countries in 1980s to 1990s demonstrated that functional MR (FMR) was a common and critical condition in HF patients. However, sophisticated patients care improved the prognosis of HF and the epidemiology of HF in Asia is different from that in Western countries. In the present study, we aimed to clarify the prevalence and prognosis of FMR in Asian HF patients in contemporary era.

Methods: With a single hospital-based cohort in the Shinken Database 2004–2011, which comprised all new patients (n=17,517) who visited our institute, we followed symptomatic HF patients (NYHA $\geq$ II).

Results: A total of 1,701 patients were included: 104 FMR patients [who had moderate – severe FMR]; 1,597 non-FMR patients [who had none or mild FMR]. FMR patients had lower rates of hypertension, but had higher rates of DCM, AF, and NYHA III/IV. FMR patients had higher BNP level and lower LVEF. Use of cardiovascular drugs was more common in patients with FMR patients. Kaplan-Meier curves revealed that the incidences of all-cause death, cardiovascular death, and HF admission were significantly higher in FMR patients. The adjusted multivariate Cox regression analysis showed that significant functional MR was associated with higher incidences of all cause death (HR 2.179, 95% CI 1.266–3.751, $p=0.005$), cardiovascular death (HR 2.371, 95% CI 1.157–4.858, $p=0.018$), and HF admission (HR 1.819, 95% CI 1.133–2.920, $p=0.013$). In subanalysis, there was no significant difference in the mortality of FMR patients between with and without surgical MR intervention.



Conclusion: FMR was common in Asian symptomatic HF patients and was

still associated with adverse outcomes in contemporary era. Establishing optimal therapeutic strategies for FMR is strongly warranted.

P2769 | SPOTLIGHT

The HDL proteome analyses of chronic heart failure reveals new insights in disease related HDL function

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Background: High density lipoproteins (HDL) exerts endothelial-protective effects via stimulation of endothelial cell (EC) NO production. An abnormality in endothelium-dependent vasodilatation is a key phenomenon in patients with chronic heart failure (CHF). To test the hypothesis that HDL particles are remodelled under the CHF conditions we characterized the proteome of HDL of healthy controls compared with CHF patients with impaired endothelial-protective function by 2D LC-MS.

Material and method: HDL was isolated from 5 healthy controls (HDLcontrol) and 5 patients with CHF-NYHA-IIIb (HDLNYHA-IIIb). First, EC were incubated with HDL and phosphorylation of eNOS-Ser1177, eNOS-Thr495, PKC- β II-Ser660 and p70S6K-Ser411 was evaluated. Secondly, in-depth proteome characterization of HDL particle was performed by online strong cation exchange fractionation coupled with reverse phase liquid chromatography (2D LC-MS).

Results: Incubation of EC with HDL-NYHA-IIIb triggered a lower stimulation of phosphorylation at eNOS-Ser1177 and a higher phosphorylation at eNOS-Thr495 when compared to HDL-healthy. The 2d-nano-LC-MS/MS shotgun proteome analysis of HDL particles identified 494 distinct proteins, whereas 118 proteins were commonly found in more than 50% of each group indicating a high variability among the HDL particles and sample types. Several proteins varied between NYHA III patients compared to healthy controls. Those proteins may exert a specific biological function related to the pathophysiology of chronic heart failure.

Conclusion: These results demonstrate that HDL-function is impaired in CHF and mass spectrometric applications increase tremendously our understanding of proteome complexity and their functional diversity in HDL-NYHA-IIIb.

P2770 | BENCH

Cardiomyocytes and myocyte cells contain the molecular system of intracellular iron metabolism and respond to environmental iron changes in vitro conditions

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Background: There are premises that iron plays a critical role in the functioning of cardiomyocytes and skeletal myocyte cells. The presence of the molecular system of proteins involved in intracellular iron metabolism in these cells is anticipated.

Methods: H9C2 rat adult cardiomyocytes and L6G8C5 (L6) rat myocyte cells were cultured for 24 hours: a) during the optimal conditions (optimal oxygen partial pressure, optimal iron concentration in a medium); b) during the reduced iron concentration in the medium (iron chelation - 50 μ M or 100 μ M deferoxamine, DFO); c) during the increased iron concentration in the medium (added ammonium ferric citrate 100 μ M or 200 μ M). We analysed the expression of mRNA of the following genes: HIF-1 α (hypoxia and iron depletion indicator), ferritin heavy and light chain (FTH and FTL; iron storage), myoglobin (MB; oxygen storage), ferroportin (FPN1; cellular iron exporter), transferrin receptor type 1 (TfR1; cellular iron uptake), hepcidin (HAMP; iron metabolism regulator) using qPCR, and the level of respective proteins using Western Blot.

Results: H9C2 cells (cardiomyocytes) exposed to gradually reduced iron concentrations in the medium demonstrated an increased expression of HIF-1 α as compared to cells cultured in control conditions ($r=0.96$, $p<0.0001$), and a decrease in expression of FTH ($r=-0.91$, $p<0.0001$), FTL ($r=-0.91$, $p<0.001$), FPN1 ($r=-0.96$, $p<0.0001$), MB ($r=-0.75$, $p<0.05$) and HAMP ($r=-0.75$, $p<0.05$). All these changes confirmed the induction of depleted iron status in examined cells. As a consequence, the expression of TfR1 ($r=0.70$, $p<0.05$) was increased, reflecting a facilitating entrance of iron to the cells. The inverse changes occurred in H9C2 cells exposed to increased iron concentrations in the medium in comparison to cells cultured in control conditions. The same pattern of changes in gene expression was observed in L6 cells (myocyte cells), and there was a strong correlation between analogous genes in both cell lines (all genes $r>0.90$, $p<0.0001$). The WB analysis of proteins encoded by aforementioned genes revealed the same pattern of changes as that seen in the gene expression profile.

Conclusions: Both rat cardiomyocytes and myocyte cells contain the set of genes involved in the intracellular iron metabolism, and both types of investigated cells response to changing iron concentrations in the cultured environment. These changes in gene and protein profiles reflect the physiological adaptive mechanism aiming to counteract the unfavourable iron status occurring in the environment and affecting the cultured cells.

P2771 | BEDSIDE

Relationship of serum erythropoietin level to short-term clinical outcome in patients with acute decompensated heart failure

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Purpose: High serum erythropoietin (EPO) level has been reported to be associated with adverse events in chronic heart failure (HF). However, its prognostic significance in patients with acute decompensated HF (ADHF) remains unknown.

Methods: We examined 280 consecutive ADHF patients who admitted to our institution between January 2013 and December 2013 from prospective registry. Patients who had acute coronary syndrome, without accessible EPO level at admission and/or failed to be followed-up over 60 days were excluded. Finally, 173 patients were divided into two groups according to higher serum EPO level (above 34 mIU/ml, the median) or lower serum EPO level (below 34 mIU/ml) at admission. Adverse events were defined as re-exacerbation of HF and death within 60 days after admission.

Results: Adverse events were occurred in 19 patients (11%). Higher serum EPO group had significantly higher incidence of adverse events compared with lower serum EPO group (18.2% vs 3.5%, $P=0.001$). Patients with higher serum EPO level had lower hemoglobin level and higher serum creatinine, plasma brain natriuretic peptide (BNP) levels on admission than those without. There were no significant differences between the two groups in terms of age, gender, blood pressure, etiology of ADHF, cardiovascular medications, left ventricular ejection fraction, serum troponin-T, C-reactive protein (CRP) levels on admission, and early management for HF. Multivariate logistic regression analyses showed that higher serum EPO level (odds ratio 5.0, 95% CI 1.5-22.6, $P=0.0065$) was an independent determinant for adverse events within 60 days after admission, among variables including age, gender, blood pressure, serum creatinine, hemoglobin, and plasma BNP levels on admission.

Conclusions: Higher serum EPO level might be a predictor for short-term adverse events in patients with ADHF.

HEART FAILURE MATTERS

P2773 | BEDSIDE

Congestive heart failure with concomitant tachyarrhythmia: predictors for tachycardiomyopathy

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Introduction: Differential diagnosis of tachycardiomyopathy (TC) from other cardiomyopathies remains challenging in patients presenting with new onset congestive heart failure (CHF) and concomitant tachyarrhythmia. Given the benign prognosis of TC defining clinical associates that predict complete resolution of left ventricular systolic dysfunction (LVSD) after rhythm/rate control are utterly needed. Therefore, the aim of this study was to determine the factors that predict complete resolution of LVSD in patients with new onset CHF and concomitant tachyarrhythmia.

Methods: Using an institutional echo database we screened for patients with new onset LVSD (LV ejection fraction (LVEF) $\leq 40\%$) in the presence of tachyarrhythmia (non-sinus rhythm ≥ 100 beats per minute (bpm)). Hospital charts of 71 patients meeting inclusion criteria were reviewed with respect to patient characteristics and pharmacologic and non-pharmacologic management. After six months follow-up, baseline characteristics of patients with normalized LVEF $\geq 50\%$ (suspected TC patients) were compared with those of patients with persistent LVSD (LVEF $< 50\%$).

Results: Patients were 58 (IQR 51-67) years old, mostly symptomatic (89% NYHA $\geq$ II), with a median heart rate of 118 bpm (IQR 100-130) and a median LVEF of 30% (IQR 25-38). Arrhythmias included atrial fibrillation (80%), atrial flutter (16%) and ectopic atrial tachycardia (4%). Besides recommended heart failure medication, patients were treated with electroconversion (44%), radiofrequency ablation (31%) and amiodarone (41%). After a median follow-up time of six months median LVEF improved to 50% (IQR 44-55) and median heart rate was 65 bpm (IQR 55-77). Rhythm control (sinus rhythm) was achieved in 48 (68%) patients and adequate rate control in 23 (32%) patients. Thirty-seven (52%) patients exhibited complete normalization of LVEF ($\geq 50\%$). The following baseline parameters were significantly associated with LVEF normalization at follow-up: lack of hypertension ($p<0.05$), younger age ($p<0.02$), presence of atrial flutter ($p<0.05$), better LVEF ($p<0.001$) and less LV remodeling ($p<0.05$).

Conclusion: Half of the patients presenting with first onset CHF in the context of significant LVSD and concomitant tachyarrhythmia normalize their LVEF within six month under appropriate therapy. The absence of hypertension or significant LV remodeling and the presence of atrial flutter are strong predictors of LVEF normalization and thus may identify patients with TC.

P2774 | BEDSIDE**Resting heart rate and real life treatment modality in outpatients with left ventricular systolic dysfunction (REALITY HF) study**

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Purpose: Resting heart rate (HR) is referred as a target of therapy and important predictor of prognosis in chronic heart failure (HF) and HR reduction is associated with improved outcomes in randomized clinical trials. However, less is known about resting HR and related treatment modalities in real life practice. Resting Heart Rate and Real Life Treatment Modality in Outpatients with Left Ventricular Systolic Dysfunction (REALITY HF) study was a multicenter, prospective, observational registry aimed to evaluate resting HR and the effects of current treatment modalities in real life clinical practice.

Methods: REALITY HF enrolled 1054 patients (mean age 61±12 years, 76% male, from 16 centers) admitted to the outpatient clinic with the diagnosis of HF and LVEF <40%. Clinical characteristics, HR and medications were noted (enrollment phase). 487 patients with sinus rhythm and HR ≥70 bpm were included in further 4-month follow-up (FU) program (V0). Adjustment of HF medication was left to physician discretion. Changes in HR and medications were reevaluated at 1-month (V1) and 4-month (V2) FU. Health-related quality of life (QoL) was assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (OSS) scale at V0 and at V2.

Results: During enrollment, 93% of patients were receiving evidence-based HF medication and 82% were on ≥2 drug therapy including ACEI (61.7%) or ARB (12.7%), beta blocker (BB) (81%), aldosterone blocker (35.4%) or digoxin (12.6%). 794 patients (75%) were in sinus rhythm, in which mean HR was 76±14 bpm and 68% of these patients had a resting HR ≥70 bpm. Mean HR was lower in patients receiving BB (75.8±13 vs 80.4±16 bpm, p=0.001), however, 66% of those had a resting HR ≥70 bpm.

In patients participating 4-m FU, BB therapy was uptitrated in 43.7% of patients at V0 and 12.9% at V1, ivabradine was initiated in 7.6% of patients at V0 and 11.5% at V1, and digoxin was initiated or adjusted in 3.9% at V0 and in 1.8% at V1 by the clinicians. Mean HR significantly reduced from 83.6±12 bpm at V0 to 78.6±13 bpm at V1 (p<0.001) and further decreased to 73.0±11 bpm at V2 (p<0.001). Proportion of patients achieving a resting HR <70 bpm was 21.7% at V1 (p<0.001) and 39.9% at V2 (p<0.001). KCCQ OSS significantly increased from 59.7±23 at V0 to 73.1±18 at V2 (p<0.001). Also, proportion of patients with NYHA-I increased from 24.4% at V0 to 29.3% at V1 and 39.3% at V2.

Conclusions: In real life clinical practice, treatment modalities targeting HR in patients with chronic HF significantly reduce resting HR and reduction in resting HR is associated with improved health related QoL.

P2775 | BEDSIDE**Elevated resting heart rate is associated with impaired health status in patients with chronic heart failure: results from REALITY HF Study**

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Purpose: Resting heart rate (HR) and health related quality of life (QoL) have emerged as important determinants of prognosis and targets of therapy in chronic heart failure (HF). However less is known about the resting HR levels in relation to health related QoL. REALITY HF (Resting Heart Rate and Real Life Treatment Modality in Outpatients with Left Ventricular Systolic Dysfunction) study data were analyzed for the evaluation of any relationship of resting HR with health status as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ).

Methods: REALITY HF was a multicenter, prospective, observational, national registry designed to evaluate HF patients' clinical characteristics and the effects of current treatment modalities on resting heart rate (HR) and other clinical variables and enrolled 1057 patients (mean age 61.9±12 years, 76% male) from 16 centers who were admitted to the outpatient clinic with the diagnosis of chronic HF, LVEF <40% and >18 years of age. 395 patients in sinus rhythm who have completed KCCQ scales were included in this analysis. Resting HR was obtained from 12-lead ECG. Selected study population was divided into four groups according to the baseline KCCQ overall summary score (OSS) (<25, 26-49, 50-74 and 75-100), in which higher scores show better patient's self-reported health status.

Results: At the time of enrollment, 93% of patients were receiving evidence-based HF medication and 82% were on ≥2 drug therapy including ACEI or ARB, beta blocker, aldosterone blocker, diuretic or digoxin. Out of 1057 patients, 794 patients (75%) were in sinus rhythm and 263 patients (25%) had atrial fibrillation or flutter. In patients with sinus rhythm, mean resting HR was 76±14 bpm (78.4±15 bpm in females and 76.2±14 bpm in males) and 68% of the patients had a resting HR ≥70 bpm. In 395 patients with sinus rhythm who have completed KCCQ scales, mean resting HR was 81.8±13 bpm and mean KCCQ OSS was 61.04±22.3. Mean resting HR was found to be 86.9±12 bpm in those with OSS ≤25 (n=31), 83.1±12 bpm in those with OSS 26-49 (n=99), 81.5±13 bpm in those with OSS 50-74 (n=141) and 79.9±12 bpm in those with OSS 75-100

(n=124) and overall, mean resting HR levels significantly increased across worse KCCQ OSS categories (Kruskal-Wallis, p<0.022). Also, a statistically significant negative correlation was found between resting HR and KCCQ OSS (p<0.003).

Conclusions: These results suggest that majority of chronic HF patients who receive evidence-based therapy have a resting HR ≥70 bpm and elevated resting HR is associated with impaired health related QoL.

P2776 | BEDSIDE**The relationship between left atrial emptying function and exercise capacity in heart failure**

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Background and aim: Six minute walking test (6-MWT) is introduced as a reproducible test for assessing exercise capacity in heart failure (HF) patients, as is the case with several echocardiographic indices. We aimed in this study to assess the role of left atrial (LA), in addition to left ventricular (LV) indices, in predicting exercise capacity in patients with HF.

Methods: This study included 88 consecutive patients (60±10 years) with stable HF. LV end-diastolic and end-systolic dimensions, ejection fraction (EF), mitral and tricuspid annulus peak systolic excursion (MAPSE and TAPSE), myocardial velocities (s', e' and a'), LA dimensions, LA volume and LA emptying fraction were measured. A 6-MWT distance was performed on the same day of the echocardiographic examination.

Results: Patients with limited exercise performance (≤300 m) were older (p=0.01), had higher functional NYHA class (p=0.004), higher LV mass index (p=0.003), larger LA (p=0.002), lower LV EF (p=0.009), larger LV end-systolic dimension (p=0.007), higher E/A ratio (p=0.03), reduced septal MAPSE (p<0.001), larger LA end-systolic volume (p=0.03), larger LA end-diastolic volume (p=0.005) and lower LA emptying fraction (p<0.001) compared with good performance patients. In multivariate analysis, only LA emptying fraction [0.944 (0.898-0.993), p=0.025] independently predicted poor exercise performance. A LA emptying fraction <60% was 68% sensitive and 73% specific (AUC 0.73, p<0.001) in predicting poor exercise performance.

Conclusion: In heart failure patients, the impaired LA emptying function is the best predictor of poor exercise capacity. This finding highlights the need for routine LA size and function monitoring for better optimization of medical therapy in HF.

P2777

ABSTRACT WITHDRAWN

P2778 | BEDSIDE**Predictors of exercise-induced pulmonary hypertension in patients with preserved left ventricular ejection fraction**

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Purpose: Exercise-induced pulmonary hypertension (EIPH) is not uncommon in patients with preserved LVEF. However, there is limited data on predictors of EIPH in these subjects, and its clinical implications are unclear. Our study attempted to analyze EIPH predictors in patients with preserved LVEF and to investigate its association with exercise capacity.

Methods: Overall 1,404 patients were referred for exercise stress echocardiography. PASP was estimated from the systolic trans-tricuspid PG, adding an assumed RA pressure of 10mmHg. EIPH was defined as PASP $\geq$ 50mmHg at exercise. Patients with positive exercise stress echocardiography, significant valvular heart disease, atrial fibrillation, or LVEF lower than 50% were excluded.

Results: EIPH did developed in 447 patients (32%). Those subjects were older, more often male, and had higher BMI and had shorter exercise duration. In the multivariable analysis, independent predictors of EIPH were age ($p<0.001$), RVSP at rest ($p<0.001$), E/e' ratio at exercise ($p=0.022$), and maximal SBP at exercise ($p=0.014$). However, this multivariable model did not show any significant differences of exercise capacity (exercise duration or metabolic equivalents) between the two groups.

Predictors of exercise-induced PH

Variable	Univariable analysis		Multivariable analysis	
	β Coefficient	p Value	β Coefficient	p Value
Age (years)	0.215	<0.001	0.113	<0.001
BMI (kg/m ²)	0.179	0.048		
Systolic BP rest (mmHg)	0.085	<0.001		
Systolic BP stress (mmHg)	0.049	<0.001	0.029	0.014
Exercise time (sec)	-0.009	<0.001		
METs	-0.435	0.001		
LVEF (%)	0.201	<0.001		
LA diameter (mm)	0.364	<0.001		
E/e' rest	0.793	<0.001		
E/e' stress	0.790	<0.001	0.230	0.022
PASP rest (mmHg)	1.050	<0.001	0.922	<0.001

Conclusion: In this large cross-sectional study, exercise-induced pulmonary hypertension in patients with preserved LVEF is independently associated with age, RVSP at rest, E/e'ratio and maximal SBP at exercise.

P2779 | BEDSIDE**Clinical significance of hypoxapnea in patients with stable chronic heart failure**

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The clinical significance of hypoxapnea in stable chronic heart failure (CHF) has not been fully investigated so far. Accordingly, we sought to clarify the significance in patients with stable CHF. We prospectively performed arterial blood gas analysis, cardiac iodine-123 metaiodobenzylguanidine (123I-MIBG) scintigraphy and polysomnography in 107 patients with CHF (NYHA functional class II/III and left ventricular ejection fraction [LVEF] <50%). The patients were divided into the 2 groups according to the presence (group A, n=17) or absence (group B, n=90) of hypoxapnea (partial pressure of arterial carbon dioxide [PaCO₂] <35 Torr). Group A had an older age (71.1 $\pm$ 7.6 years vs. 64.2 $\pm$ 12.7 years, $p=0.04$), a higher arterial pH (7.45 $\pm$ 0.03 vs. 7.41 $\pm$ 0.03, $p<0.001$), a lower HCO₃⁻ (22.8 $\pm$ 1.5 mmol/L vs. 25.6 $\pm$ 2.4 mmol/L, $p<0.001$), a higher plasma brain natriuretic peptide (BNP) level (439 $\pm$ 486 pg/ml vs. 194 $\pm$ 274 pg/ml, $p=0.001$), a higher central apnea index (8.2 $\pm$ 12.2 vs. 2.7 $\pm$ 6.0, $p=0.005$) and a higher cardiac washout rate of 123I-MIBG (52.5 $\pm$ 15.6% vs. 44.9 $\pm$ 12.6%, $p=0.03$) than group B. PaCO₂ was significantly correlated with age ($r = -0.20$, $p=0.04$), log BNP ($r = -0.28$, $p=0.003$), cardiac washout rates of 123I-MIBG ($r = -0.31$, $p=0.001$) and central apnea index ($r = -0.24$, $p=0.01$). A logistic multivariate analysis revealed that log BNP was significantly associated with hypoxapnea (odds ratio 4.7, 95% confidence interval 1.5 - 14.2, $p=0.006$), and a multiple regression analysis showed that cardiac washout rates of 123I-MIBG were significantly associated with PaCO₂ ($\beta = -0.31$, $p=0.001$). In conclusion, this study suggests that hypoxapnea in stable CHF is associated with its severity and resultant activated cardiac sympathetic nervous system, both of which can cause hyperventilation and thereby contribute to the occurrence of central sleep apnea.

P2780 | BEDSIDE**Haemodynamic response to exercise one year after heart transplantation**

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Purpose: Heart transplantation (HT) is the ultimate therapy for end-stage heart failure. Despite the normal magnitudes of haemodynamic parameters are well defined in healthy individuals, there is scarce knowledge on their magnitudes

after HT, especially with regards to the response to exercise. The impact of the age dependent differences, seen in healthy subjects, furthermore needs evaluation after HT. We haemodynamically characterized our patients at rest and during exercise one year after HT, to observe the haemodynamic response to exercise and investigate potential age dependent differences in the exercise response.

Methods: We analyzed 32 adults (31% women; mean age 51 yrs), evaluated with right heart catheterization, at our lab, at rest and during exercise one year after HT performed 1988-2010. Men exercised at 50 W and women at 30 W. The most common diagnosis was dilated cardiomyopathy (66%). 12 patients were $\leq$ 50- and 20 were >50 yrs of age. Paired t- or Wilcoxon Signed rank tests were performed when analyzing the response to exercise. T- or Mann-Whitney Rank Sum tests were performed when comparing the groups. $P<0.05$ was considered significant.

Results: Resting total pulmonary vascular resistance (TPVR) was higher ($p<0.03$) in patients >50 yrs. Exercise in patients $\leq$ 50yrs increased ($p<0.05$) mean pulmonary artery pressure (MPAP) by 14.8 $\pm$ 4.6 mmHg (114%), pulmonary artery wedge pressure (PAWP) by 12.1 $\pm$ 4.3 mmHg (191%), transpulmonary gradient (TPG) by 2.8 $\pm$ 3.3 mmHg (43%), mean right atrial pressure (MRAP) by 8.8 $\pm$ 5.8 mmHg (463%), cardiac output (CO) by 5.8 $\pm$ 3.4 L·min⁻¹ (89%) and TPVR by 0.2 $\pm$ 0.4 WU (10%), whereas PVR decreased ($p<0.003$) by 0.4 $\pm$ 0.3 WU (27%). Exercise in patients >50 yrs increased ($p<0.008$) MPAP by 19.6 $\pm$ 6.2 mmHg (122%), PAWP by 15.3 $\pm$ 5.9 mmHg (228%), TPG by 4.3 $\pm$ 2.8 mmHg (53%), MRAP by 10.6 $\pm$ 3.5 mmHg (447%), CO by 5.2 $\pm$ 1.6 L·min⁻¹ (89%) and TPVR by 0.5 $\pm$ 0.8 WU (12%), whereas PVR decreased ($p<0.001$) by 0.3 $\pm$ 0.3 WU (16%). MPAP, PVR and TPVR were higher ($p<0.05$) in patients >50 yrs during exercise. The percentage change in these parameters during exercise did, however, not differ ($p=ns$) between the groups.

Conclusion: There was no age dependent difference in exercise response one year after HT. Although the response to exercise was adequate, there was an exaggerated increase in MPAP, MRAP and, in particular, PAWP. This response was true both for patients aged $\leq$ 50 yrs and >50 yrs. As a result of the exaggerated increase in PAWP, the PVR response to exercise "normalized" after HT, whereas the TPVR response remained deranged. This suggests that TPVR may be more adequate than PVR for evaluations post-HT.

P2781 | BENCH**Characterization of phase analysis of gated myocardial perfusion SPECT in patients with heart failure**

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Introduction: The QRS morphology and duration on the electrocardiogram (ECG) are markers of electrical dyssynchrony and the best predictors of response to cardiac resynchronization therapy (CRT). Mechanical dyssynchrony is not always accompanied with electrical dyssynchrony as was demonstrated in the Echo-CRT trial. Moreover, a great number of patients who meet the criteria for CRT do not improve and additional criteria for best selection are needed. Left ventricular mechanical dyssynchrony (LVMD) assessed by phase analysis of gated SPECT myocardial perfusion imaging (MPI) may be a useful tool for predicting response to CRT.

Methods: We retrospectively evaluated heart failure (HF) patients (pts) with LV ejection fraction <50% who underwent SPECT - MPI. We obtained parameters of dyssynchrony by phase analysis i.e. histogram bandwidth (hb) and standard deviation (sd) for each pt. ECG was analyzed according to QRS duration and morphology. Cardiac events as sudden death, heart transplantation and hospitalization due to decompensated heart failure were registered.

Results: One-hundred and one patients (78 males; mean age 63 $\pm$ 9 years) underwent SPECT-MPI with phase analysis. Forty pts (39%) were classified as having ischemic cardiomyopathy and 61 pts (61%) were classified as having non-ischemic cardiomyopathy. Complete left bundle branch block was present in 51 patients at baseline. Mean QRS duration was 140 $\pm$ 33ms, with no significant difference between ischemic VS non-ischemic cardiomyopathy ($P=0.165$). Mean histogram bandwidth (hb) was 168 $\pm$ 77 degrees in ischemic cardiomyopathy and 99 $\pm$ 64 degrees in non-ischemic cardiomyopathy (normal values of $\sim$ 38 degrees; $p<0.001$), and standard deviation (sd) measures were 53 $\pm$ 21 degrees in ischemic cardiomyopathy and 33 $\pm$ 18 degrees in non-ischemic cardiomyopathy (normal values of 14 degrees; $P<0.001$). Mean ejection fraction was 29.9 $\pm$ 9.2%, with no significant difference between ischemic VS non-ischemic cardiomyopathy ($P=0.155$). Eighteen pts (17, 8%) had cardiac events: 2 pts were submitted to heart transplantation, 7 pts had cardiac sudden death or where resuscitated from lifethreatening arrhythmias and 9 pts were hospitalized due to acute heart failure.

Discussion: Although mean ejection fraction and mean QRS duration were not different between groups, left ventricle dyssynchrony, assessed with SPECT-MPI phase analysis appears to be significantly different in patients with ischemic cardiomyopathy compared to non-ischemic cardiomyopathy. Further studies are needed to determine the role of SPECT-MPI phase analysis on management of heart failure patients.

P2782 | BEDSIDE**Atorvastatin treatment mobilizes endothelial progenitor cells in early stages of ischemic heart failure**

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Purpose: Patients with heart failure (HF) manifest endothelial dysfunction. Circulating endothelial progenitor cells (EPC) contribute to reendothelialization and repair of damaged endothelium in HF. Statins with anti-inflammatory and pleiotropic properties can restore endothelial function in HF. Aim of the present study was to examine the effects of different doses of atorvastatin treatment and clinical status, on mobilization of EPC and endothelial function in patients with ischemic HF.

Methods: We studied the effect of 4 weeks atorvastatin treatment in 23 subjects with ischemic HF at New York Heart Association (NYHA) functional class II and III. The study was carried out on two separate arms, one with atorvastatin 40mg/d and one with atorvastatin 10mg/d (randomized, double-blind, cross-over design). Endothelial function was evaluated by flow-mediated dilation (FMD) of the brachial artery. Serum levels of tumor necrosis factor alpha (TNFa) were measured by ELISA. The number of circulating CD34(+)/CD133(+)/KDR(+) EPCs were evaluated by flow cytometry.

Results: From the study population, 15 subjects were categorized as NYHA II and 8 subjects as NYHA III. Compared to baseline, treatment with 40 mg/d of atorvastatin improved FMD ($3.16 \pm 2.98\%$ vs. $6.05 \pm 2.45\%$, $p=0.001$), TNFa levels [1.08 (0.79 - 1.35) pg/ml vs. 0.85 (0.68 - 1.24) pg/ml, $p=0.01$] and circulating EPC [362 (209 - 456) cells/ml vs. 175 (143 - 232) cells/ml, $p=0.002$]. Similarly, compared to baseline, treatment with atorvastatin 10mg/d also improved FMD ($3.24 \pm 3.12\%$ vs. $4.20 \pm 2.09\%$, $p=0.08$), TNFa [1.11 (0.73 - 1.37) pg/ml vs. 0.99 (0.64 - 1.12) pg/ml, $p=0.01$] and EPC [201 (151 - 309) cells/ml vs. 169 (115 - 228) cells/ml, $p=0.01$]. The increase in EPC ($p=0.02$) and FMD ($p=0.001$) was greater with the dose of 40 mg/d. Moreover, in the 40 mg/day atorvastatin treatment group we found an association between baseline FMD and increased EPC numbers ($r=0.48$, $p=0.03$). Importantly, in the 40 mg/day atorvastatin treatment group, the increase in EPC was higher in NYHA II subjects compared to NYHA III subjects (217 ± 142 cells/ml vs. 60 ± 150 cells/ml, $p=0.03$).

Conclusions: In ischemic HF subjects, both high and low dose atorvastatin treatment mobilizes EPC and improves endothelial function with a parallel anti-inflammatory effect. This improvement is more pronounced in subjects with better clinical status and better functional endothelium. These findings shed some light on the pleiotropic effects of statins in patients with ischemic HF.