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# Oral abstracts

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## 2A.01. Disruption of STE20/SPS1-related Proline/Alanine-rich Kinase (SPAK) binding lowers blood pressure and recapitulates Gitelman syndrome in mice

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The salt-wasting hypotensive phenotype of Gitelman syndrome is caused by low $Na^+$-$Cl^-$ Cotransporter (NCC) activity. In the kidney WNK4 phosphorylates SPAK (p-SPAK) at threonine residue 243. This activated p-SPAK increases NCC phosphorylation (p-NCC) and thus NCC activity. Previously we demonstrated SPAK T243A mutant mice recapitulate Gitelman syndrome, thus confirming the integral role of SPAK activity in blood pressure control. For signalling to occur WNK4 and NCC bind to SPAK at leucine residue 502 in the conserved C-terminal. To test this *in vivo* we generated homozygous SPAK L502A mice which we hypothesised would exhibit a Gitelman syndrome phenotype.

To investigate renal salt-wasting, wildtype and SPAK L502A mice ($n=14$) were fed a 3% w/w sodium diet for 10 days and switched to a 0.03% w/w sodium diet with urine electrolytes measured at 0hr, 3hr, 6hr, 12hr, 24hr and 96hr post-switch and normalised to urine creatinine. Two weeks post-switch blood pressure was measured by catheterisation of the right carotid artery under anaesthesia (isoflurane). After sacrifice by exsanguination, the kidneys were harvested for western blot analysis. All data are mean ± SEM.

$Na^+$ wasting at 6hr was observed in SPAK L502A versus wildtype mice [$77 \pm 17$ vs $41 \pm 7$ arbitrary units; $P<0.05$]. Mean arterial blood pressure was also strikingly lower in the SPAK L502A [$62 \pm 1$ mmHg vs $78 \pm 1$ mmHg; $P<0.001$] and the inhibition of SPAK binding resulted in a 3-fold decrease in levels of p-NCC in SPAK L502A.

In conclusion, SPAK binding is crucial for blood pressure maintenance and pharmacological inhibition of this binding is an attractive antihypertensive strategy.

## 2A.02. Microarray and Transfection Studies Reveal DACH1 as an Inhibitor of Aldosterone Production in Human Adrenals

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**Background**: Common somatic mutations may define a sub-group of smaller, zona glomerulosa (ZG)-like aldosterone producing adenomas (APAs).[1] We have therefore sought signature 'ZG-genes' which may provide insight to ZG-like APAs.

**Methods**: A microarray was performed of 14 trios of ZF, ZG and APA, and 7 pairs of ZF and ZG adjacent to phaeochromocytoma. Expression of most up-regulated genes in ZG *vs* ZF was validated. Their exome sequence was examined in germline and APAs of 13 patients. The regulation of aldosterone production and apoptosis was assessed.

**Results**: Seven genes were >10-fold more abundant in ZG than ZF ($P<10^{-23}$). All have been confirmed as highly ZG-selective by qPCR and immunohistochemistry. Among the seven genes, *DACH1* was the only up-regulated gene to have a common, germline variant. Its expression was 14.4 fold higher in ZG than ZF ($P=1.4\times10^{-21}$) and 3.0 higher in ZG than APA ($P=2.2\times10^{-7}$); on qPCR the fold-changes were 30.3 and 4.1, respectively. On IHC, there was dense nuclear staining of ZG and APAs in all 13 adrenals. Western blot supported IHC. Knockdown of *DACH1* resulted in a 1.5-fold increase in aldosterone ($P=1.0\times10^{-9}$). Reversely, *DACH1* overexpression reduced aldosterone by 2.4-fold ($P=4.2\times10^{-6}$); this was partially attributable to a 5.9-fold increase in apoptotic cells ($P=0.008$).

**Conclusion**: Several unexpected genes are markedly over-expressed in human ZG. We postulate that [i] inhibition of aldosterone secretion by *DACH1* reflects human over-exposure to salt; [ii] a pro-apoptotic role of up-regulated human ZG-genes contributes to the small size of ZG-like APAs.

1. Azizan *et al.* (2013). *Nature Genetics*.

## 2A.03. Putative calcium-sensitive genes, *vsnl1* and *ano4*, are upregulated in human zona glomerulosa cells and may play a role in regulation of aldosterone production

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**Objective**: Somatic mutations in genes encoding $Ca_v1.3$ and $Na^+/K^+$-ATPase delineate a zona glomerulosa (ZG) subtype of aldosterone producing adenomas (APA), and point to the central role of ion traffic in regulating aldosterone secretion.[1] This role was further emphasized by our microarray comparison of healthy ZG with ZF, in which two out of three genes upregulated 20-fold in ZG are putative ion-channels or regulators: anoctamin 4 (*ANO4*) and visinin-like-1 (*VSNL1*). Our aim was to quantify these changes by qPCR and investigate the role of ANO4 by transfection into adrenocortical cells.

**Design and method:** 1) RNA isolated by laser capture microdissection from ZF and ZG of 20 adrenals was quantified by qPCR. 2) VSNL1 distribution was analysed by immunohistochemistry. 3) Subcellular localisation of ANO4 was determined by immunofluorescence microscopy of transfected HEK293 cells. 4) ANO4's role in regulating steroidogenesis was studied by transfection of H295R cells.

**Results:** 1) qPCR found 168- and 54-fold up-regulation, respectively, of *VSNL1* and *ANO4* in ZG vs. ZF. 2) IHC showed selective staining of both VSNL1 and ANO4 in ZG. 3) Steroidogenesis regulator nuclear factor *NR4A2* expression increased 42-fold, while *CYP11B2* mRNA expression increased 8-fold. 4) HA-tagged *ANO4* was localized to plasma membrane.

**Conclusions:** *ANO4* and *VSNL1* are confirmed as highly selective ZG proteins. ANO4 appears to be a positive regulator of aldosterone synthesis, whose membrane disposition and analogy to $Ca^{++}$ activated chloride channels suggest a role in regulating membrane depolarisation. *VSNL1* may protect normal ZG cells from $Ca^{2+}$ activation.[2]

1. Azizan EA *et al. Nat Genet* 2013 Sep; **45**(9): 1055–1060.
2. Williams TA *et al. Hypertension* 2012 Apr; **59**(4):833–839.

## 2A.04. Highly-selective expression of *Nephronectin (NPNT)* delineates a common subtype of aldosterone-producing adenoma (APA), and a putative role in aldosterone production

**Ada ED Teo[1], Elena AB Azizan[1], Lalarukh Haris Shaikh[1], Junhua Zhou[1], Diane Walters[2], Sudeshna G Neogi[3], Ian McFarlane[3] and Morris J Brown[1]**

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**Objective:** Over 5% of hypertension is due to adrenal aldosterone-producing adenomas (APAs), potentially curable by unilateral adrenalectomy. Although adrenal zona glomerulosa (ZG) is the site of physiological aldosterone production, classical APAs paradoxically resemble cells of the cortisol-secreting zona fasciculata (ZF). Our finding of gain-of-function mutations in a distinct group of smaller APAs resembling ZG cells [1] prompted investigations that ZG-like APAs have a different origin from classical APAs.

**Methods:** A microarray comparison was performed of 5 ZG-like APAs, with somatic mutations in *CACNA1D* or *ATP1A1,* and 8 ZF-like APAs with mutations in *KCNJ5.* Differences were validated by quantitative PCR (qPCR) and immunohistochemistry. Expression of selected genes was compared between normal ZF and ZG, using laser capture microdissection for RNA extraction.

**Results:** Microarray identified 43 genes with differential expression in ZG-like and ZF-like APAs. The top gene was *Nephronectin (NPNT)* (x12.2, $P = 2.97E-08$), a secreted matrix protein, recently reported to regulate cell invasion in malignant melanoma. *NPNT* was down-regulated in the ZG adjacent to an APA. qPCR confirmed that *NPNT* was 29.9-fold upregulated in ZG-like vs ZF-like APAs ($P = 0.00034$), and 25.3-fold more abundant in

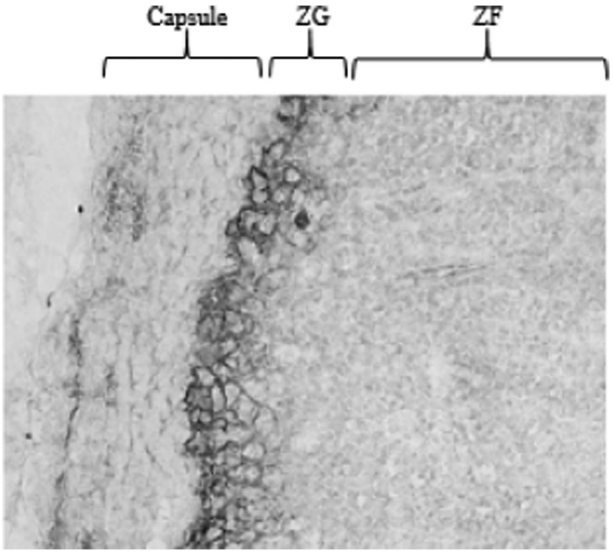


**Figure 1** Highly selective immunohistochemistry NPNT staining of ZG in normal adrenal gland.

normal ZG vs ZF ($P=0.0001$). Immunohistochemistry showed highly-selective staining of ZG (Fig. 1),

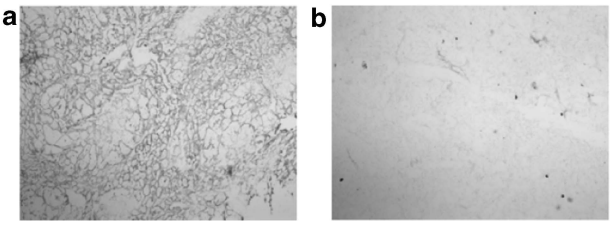


**Figure 2** (**a**) NPNT staining in a ZG-like tumour and (**b**). NPNT staining in a ZF-like tumour, both mounted on the same slide.

and confirmed that NPNT was more abundant in ZG-like tumours (Fig. 2).

**Conclusion:** Small NPNT-rich APAs probably resolve the paradox of the 'missing' APAs of ZG-origin. The striking peri-glomerular distribution suggests a role in facilitating cell-clustering into functional units. Switch-off of NPNT may play a key role in the negative feedback on aldosterone production.

1. Azizan EAB *et al. Nature Genetics* 2013; **45**(9):1055–1060.

## 3A.01. Bilirubin: a novel endogenous hypolipidaemic and hypotensive agent preventing cardiovascular disease

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**Background:** A clear relationship exists between circulating bilirubin and coronary atherosclerotic disease, with mildly elevated bilirubin being protective. Despite bilirubin's well-known antioxidant effects possibly contributing to atheroprotection, the effect of bilirubin on lipid status and systolic heart function remains unknown.

**Aim:** To determine whether elevated bilirubin is associated with hypotension and hypolipidaemia in mutant hyperbilirubinaemic (Gunn) rats and in patients with benign hyperbilirubinaemia.

**Methods:** Eight Gunn rats and normo-bilirubinaemic controls underwent cardiac ultrasound and catheterisation for assessemnt of aortic and left ventricular developed pressures. Hearts were subsequently mounted and perfused on a Langendorff perfusion apparatus for assessment of *ex vivo* heart function. 44 human volunteers, half of whom possessed mild hyperbilirubinaemia (Gilbert's Syndrome) were matched to controls. Blood pressure and serum lipid status were assessed using sygmomanometry and biochemistry, respectively.

**Results:** Aortic Doppler analysis revealed Gunn rats experienced a marked reduction in peak blood velocity and rate of velocity development (AoVTI peak/slope; $P<0.001$) whilst maintaining stroke volume, fractional shortening and ejection fraction. Millar catheterisation indicated the rate of aortic systolic pressure development ($\Delta p \Delta t$) was reduced in Gunn rats, which was mirrored by reduced developed pressures and rate of pressure development *ex vivo* (all $P<0.05$). No difference in systolic or diastolic pressures were noted in Gilbert's Syndrome versus control subjects, however, hyperbilirubinaemic rodents and humans demonstrated significantly reduced circulating total cholesterol and lipoprotein concentrations ($P<0.01$).

**Conclusion:** Hyperbilirubinaemia may induce negative inotropic effects in the heart, reducing the rate of pressure development *in vivo*. This, combined with the lipid lowering effects of bilirubin, provides a new hypothesis to explain protection from ischaemic heart disease in hyperbilirubinaemic individuals.

## 3B.01. Cuff-based assessment of carotid-femoral pulse wave velocity: comparison with the SphygmoCor device

**Jean Woodcock-Smith, Jane Smith, Karen Miles and Carmel McEniery**

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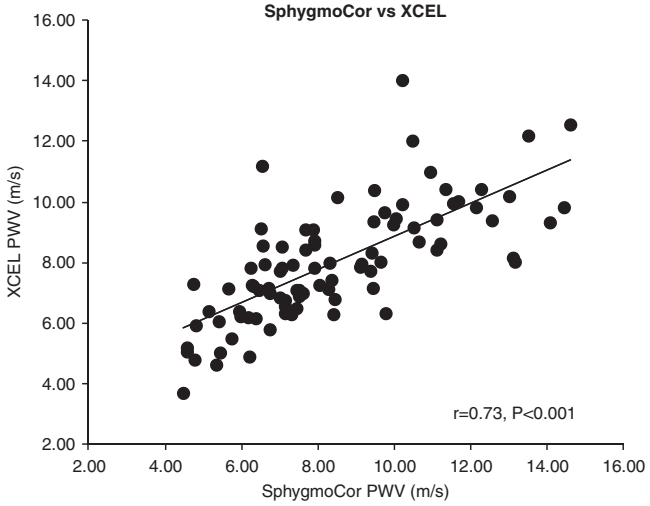
Pulse wave velocity (PWV) is a robust marker of arterial stiffness and independently predicts cardiovascular outcome. New cuff-based devices for assessing PWV have recently become available, making the measurement less operator-dependent and potentially more suitable to the non-specialist setting. The aim of the current study was to compare measurements of carotid-femoral PWV using two cuff-based devices (Vicorder and XCEL), with a widely-used tonometric method (SphygmoCor).

Comparative measurements of PWV were made using the SphygmoCor, XCEL and Vicorder devices in 91 individuals (mean ± SD age 62 ± 18 years; range 20-89 years). All path length and PWV measurements were made as per manufacturers' instructions, following at least 10 min supine rest. Readings were made in triplicate with each device and the average values compared. The order in which devices were used was random. Since the Vicorder includes an optional algorithm to adjust for the influence of the additional femoral segment on measured PWV, both unadjusted (Vicorder) and adjusted (Vicorder_adj) values were analysed.

PWV ranged from 4.47m/s-14.60m/s (SphygmoCor), 3.70m/s-14.03m/s (XCEL), 4.40m/s-14.20m/s (Vicorder) and 3.60m/s-16.63m/s (Vicorder_adj). The XCEL and Vicorder PWV values were significantly correlated with SphygmoCor values (($r = 0.73$, $P < 0.001$ and ($r = 0.70$, $P < 0.001$, respectively). PWV measured with the XCEL was significantly lower than SphygmoCor-derived PWV (mean ± SD of difference 0.42m ± 1.74m/s, ($P = 0.03$), whereas Vicorder (−0.21 ± 1.88m/s) and Vicorder_adj (0.07 ± 2.21m/s) were not significantly different from SphygmoCor, albeit with somewhat higher SDs.

Cuff-based devices provide reasonable estimates of PWV when directly compared with a widely used tonometric method. Use of the correction algorithm in the Vicorder device resulted in a closer estimate of the average PWV as measured with SphygmoCor, but a greater spread of values around the mean.




## 3B.02. Effect of kidney donation on clinic and ambulatory blood pressure: a feasibility study

**Jane Smith, Carmel McEniery, Ian Wilkinson and Laurie Tomlinson**

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Rates of living-donor nephrectomy are increasing since renal transplantation offers improved health and quality of life for the growing pool of people requiring dialysis. Observational evidence suggests that living kidney donors are at no greater risk of cardiovascular disease (CVD) or dialysis than the general population, and, as a result, kidney donation is currently being extended to a broader population including older people and those with hypertension. However the long-term

risks to these donors are unknown. The aim of the current study was to determine the feasibility of examining clinic and 24 h ambulatory blood pressure (BP) in people undergoing donor nephrectomy, prior to, and 12 months following, donation.
48 living donors (20 male) were recruited over a 3 year period. The average age was 51 ± 13 years and there were 3 current smokers. Glomerular filtration rate (eGFR) was estimated and clinic and ambulatory BP assessed using standard techniques.
As expected, eGFR fell from 85 ± 18 ml/min at baseline to 59 ± 12 ml/min, 12 months post-donation ($P<0.001$). Clinic BP was 123 ± 15/79 ± 9 mmHg at baseline and 126 ± 14/80 ± 9, 12 months post-donation ($P=0.08$ and ($P=0.1$ for systolic and diastolic, respectively) and ambulatory daytime BP was 125 ± 9/80 ± 9 mmHg at baseline and 123 ± 8/80 ± 8, 12 months post-donation ($P=0.5$ and ($P=0.3$, respectively).
These data demonstrate that it is feasible to recruit patients undergoing living-donor nephrectomy and to examine the effects on BP in the clinic and ambulatory settings up to 12 months following donation. Moreover, the results provide important data on which to base larger studies aimed at investigating longer-term effects of kidney donation.

## 3B.03. Assessment of drug adherence prior to carrying out sympathetic renal denervation for resistant hypertension in the drug efficacy clinic

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Resistant hypertension is common amongst the hypertensive population with reported prevalence of 5–30%. These patients have higher cardiovascular risk and consequently poorer cardiovascular prognosis. Compliance with antihypertensive medication is notoriously poor with adherence of only 57% after median of 2 years reported in a recent meta-analysis. We report our experience from the drug efficacy clinic (DEC) where patients with resistant hypertension were given their medications under direct observation. Patients had 24 h ambulatory blood pressure (ABP) monitoring prior to DEC appointment. At the DEC visit, patients were fitted with a 24 h ABP monitor and each drug, at currently prescribed dose, was administered by a nurse; the first drug one hour after arrival and thereafter at 60-minute intervals and patient observed for 7 hours. All symptoms were recorded.
Forty seven out of 53 patients had complete data on the ABP. Twenty four were females and a mean [ ± SD] age of 62 [ ± 10.7] years. Mean [ ± SD] 24 hr ABP prior to the clinic visit was 158 [ ± 19]/87 [ ± 13] mmHg and on the day of clinic was 155 [ ± 21]/85 [ ± 14] mmHg. Ten (21.3%) patients reported symptoms of hypotension suggesting non-adherence. Twenty eight (59.6%) patients were truly resistant (24hr systolic BP fall $<10$ mmHg). Nineteen (40.4%) patients had clinically significant non-adherence (24 systolic BP fall $\geq 10$ mmHg). For patients with a clinically significant drop in their 24 hr systolic BP, the mean drop was 21.2 mmHg (95% CI −16.7 to −25.7; $P<0.001$). Similarly a clinically significant drop in the diastolic BP was observed; 10.1 mmHg (95% CI −6.8 to −13.5; $P<0.001$).
Our results suggest that drug efficacy clinic can be an effective method of identifying the truly resistant hypertensive patients who should be considered for renal denervation. Every effort should be made to address potential barriers to adherence in patients identified as non-adherent to improve their compliance and consequently improve their blood pressure control.

## 3B.04. Audit of lifestyle advice provision in patients with hypertension attending a secondary care cardiovascular risk clinic

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**Background:** Current guidelines recommend that all patients undergoing assessment or treatment for hypertension should receive lifestyle advice (1).
**Aim:** To determine whether patients with hypertension attending a secondary care cardiovascular risk clinic are receiving advice regarding lifestyle changes that might improve their blood pressure control and cardiovascular health.
**Methods:** An audit was carried out over a one week period. All patients with hypertension attending cardiovascular risk clinics in our hospital were asked to complete a short anonymous questionnaire by a clinic nurse after their appointment with the clinic doctor. Patients were asked whether they had received lifestyle advice, who had given this advice, the timing of the most recent advice and the lifestyle topics covered in the advice.

**Results:** 30 patients (67%) (out of a potential total of 45) completed audit questionnaires. 25 patients (83.3%) reported having received lifestyle advice. The reported sources of advice were: Hospital doctor $n=17$, GP $n=16$, Practice nurse $n=11$, Hospital clinic nurse $n=3$. 14 patients reported receiving lifestyle advice from one source, 8 from two sources, 3 from three sources and 2 from four sources. 19 patients (63.3%) reported having received lifestyle advice at least within the last 6 months, and 22 patients (73.3%) at least within the last year. The most common topic of lifestyle advice received was salt reduction, followed by exercise, weight loss, reduction in alcohol intake and stopping smoking.

**Conclusions:** The results suggested that we should improve our provision of lifestyle advice to patients with hypertension. A written lifestyle information leaflet was introduced to the clinic, and clinic doctors and nurses were reminded to give lifestyle advice. Our provision of lifestyle advice following these changes will be re-audited later this year.

1. NICE clinical guideline 127: Hypertension: clinical management of primary hypertension in adults. 2011.

## 4A.01. Urinary tetrahydroladosterone excretion correlates with placental growth factor in normal and pre-eclamptic pregnancy

**Gemma Currie[1], Nicole Eisele[2], Heather Small[1], Genevieve Escher[2], Carine Gennari-Moser[2], David Carty[1], Markus Mohaupt[2] and Christian Delles[1]**

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**Background:** Aldosterone levels are elevated in pregnancy but fall despite volume contraction in pre-eclampsia. Vascular endothelial growth factor (VEGF) and soluble fms-like tyrosine kinase 1 (sFlt-1) have been implicated in this phenomenon in vitro and in animal work. Low placental growth factor (PlGF), which is closely linked to VEGF signalling, identifies women at risk of pre-eclampsia between 20 and 35 weeks gestation. We aimed to examine these relationships in human subjects in early pregnancy.
**Methods:** We measured aldosterone and PlGF at gestational week 14-16 in women who had previously taken part in the Proteomics in Pre-eclampsia (PIP) Study; a longitudinal study of 4000 pregnancies investigating biomarkers for early detection of pre-eclampsia. Stored samples were obtained from 48 cases and 48 matched pregnant controls. Urinary tetrahydroaldosterone (THAldo) excretion was measured by gas chromatography-mass spectrometry (GC-MS) and PlGF by enzyme linked immunosorbent assay (ELISA).
**Results:** Booking diastolic blood pressure was higher among women who went on to develop pre-eclampsia (72 mmHg, IQR 54-82 cf 70 mmHg, IQR 56-78 by Mann Whitney, $P=0.0452$). Urinary THAldo/creatinine ratio was significantly lower among cases than controls (9.22μg/mmol, IQR 1.41–16.6 cf 15.96μg/mmol, IQR 2.76-22.61 by *t*-test, $P=0.024$). Whilst the groups did not show any significant difference in early pregnancy PlGF level we identified a linear relationship between PlGF and THAldo (Spearman's rank 0.415, $P=0.001$).
**Conclusion:** THAldo and PlGF are closely linked in early pregnancy. Given the critical role of THAldo in pregnancy, these data suggest that in women destined to develop preeclampsia low THAldo rather than PlGF is causal.

## 4A.02. Pregnancy-unmasked aldosterone-producing adenomas (APAs) are caused by a distinct genotype and gene transcript

**Ada ED Teo[1], Lalarukh Haris Shaikh[1], Junhua Zhou[1], Fiona E Karet Frankl[2], Mark Gurnell[3], Lisa Happerfield[4], Alison Marker[4], Elena AB Azizan[1] and Morris J Brown[1]**

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**Objective:** Detection of somatic mutations in APAs permits recognition of sub-types with different clinical and biochemical phenotypes.[1,2] A recent patient enabled discovery of a further, clinically significant sub-type.

**Methods:** A 34-year old pregnant woman presented with weakness, hypokalaemia and elevated plasma aldosterone. This fell by half post-pregnancy even after hypokalaemia was corrected. A unilateral APA was diagnosed by Magnetic Resonance Imaging and

adrenal vein sampling. Post-adrenalectomy studies showed a zona glomerulosa (ZG)-type APA, with much higher ratio of CYP11B2/CYP11B1 than classical zona fasciculata (ZF)-like APA. The clinical presentation and APA analyses recalled previous women included in our exome-sequencing and/or microarray analyses.[1,2] These led to recognition of a common underlying genotype and transciptome, confirmed by Sanger sequencing and quantitative PCR (qPCR).
**Results:** Exome sequencing revealed a gain-of-function mutation in *CTNNB1*, encoding the key Wnt protein, beta-catenin. Sanger sequencing confirmed three APAs with mutations which prevent phosphorylation of exon 3, causing nuclear translocation and aberrant gene activation. Microarray showed *LHCGR*, encoding the luteinizing hormone/choriogonadotropin receptor, to be the most over-expressed gene (x119) *cf* 13 other ZF- and ZG-type APAs. Over-expression was confirmed by qPCR in all three *CTNNB1*-mutant APAs (x146, x128, x66).
**Conclusion:** Overexpression of G protein-coupled receptors, and the presentation in pregnancy of ZG-type APAs, have been previously observed.[3,4] Our patients link these observations, and explain the unmasking by pregnancy. Since adrenal and gonads share a common progenitor cell, it is unsurprising that Wnt activation by *CTNNB1* mutation results in aberrant adrenal *LHCGR* expression.

1. Azizan EAB *et al. Nature Genetics* 2013; **45**(9):1055-1060.
2. Azizan EAB *et al. JCEM* 2012; **97**(5):E819–E829
3. Albiger *et al. Eur J Endocrinol* 2011; **164**:405–12.
4. Shigematsu K *et al. Endocr Pathol* 2009; **20**(1): 66–72.

## 4A.03. Spatial and socio-economic variation in salt intake in Britain 10 years after a national salt reduction program

**Chen Ji and Francesco Cappuccio**

*University of Warwick, Coventry, UK*

**Background**: In the 2000–2001 British National Diet and Nutrition Survey there were significant socio-economic inequalities in the distribution of salt intake, independent of the south-north gradient. Since then the UK has implemented a national salt reduction programme. The impact of such a programme on social inequalities remains unknown.
**Objectives**: To examine the spatial and socio-economic variations in salt intake in the 2008–2011 British National Diet and Nutrition Survey and to compare them with those before the programme was implemented.
**Design & Setting**: Cross-sectional survey in Great Britain.
**Participants:** 1,027 white male and female participants, aged 19 to 64 years, from the British National Diet and Nutrition Survey 2008-11.
**Primary outcome**: Participants' dietary sodium intake measured with a 4-day food diary. Bayesian geo-additive models were used to assess the spatial and socio-economic patterns of sodium intake while accounting for socio-demographic, anthropometric and behavioural confounders.
**Results**: Dietary sodium intake varied significantly across socio-economic groups, even when adjusting for geographical variations. Higher dietary sodium intake was found in people with the lowest educational attainment (coeff: 0.252 [90% credible intervals 0.003, 0.486]) and in low levels of occupation (coeff: 0.109 [−0.069, 0.288]). Those with no qualification had, on average, a 5.7% [0.1, 11.1] higher dietary sodium intake than the reference group. Compared to 2000-01 the gradient of higher dietary sodium intake from south to north still remained but it was no longer significant when adjusted for socio-economic status and other confounders. Estimated dietary sodium consumption from food sources (not accounting for discretionary sources) was reduced by 366 mg of sodium ($\sim$0.9 g of salt) per day during the 10-year period, likely the effect of national salt reduction initiatives. However, the social inequalities remained.
**Conclusions**: Understanding the socio-economic pattern of salt intake is crucial. Efforts are needed to minimise the gap between socio-economic groups for an equitable delivery of cardiovascular prevention.

## 4A.04. PRedicting Out-of-OFfice Blood Pressure in the clinic (PROOF-BP): Derivation and validation of a tool to improve blood pressure measurement in Primary Care

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**Background:** Patients often have lower (white coat effect) or higher (masked effect) blood pressure at home compared to the clinic, potentially resulting in misdiagnosis and sub-

optimal management of hypertension. This study assessed whether patient characteristics and changes in clinic blood pressure (BP) with repeated measurement on a single occasion predict subsequent differences between clinic and home measurements.

**Methods:** Data were analysed from five previous studies measuring both clinic and out-of-office BP. Candidate predictors for the home-clinic BP difference were pre-specified following a systematic review of the literature and then tested in a model derived using linear regression with backwards stepwise selection in two datasets ($n = 991$). Validation was undertaken in the remaining three cohorts ($n = 968$) using calibration plots and Pearson's Correlation.

**Results:** Age, sex, mean clinic BP, clinic pulse pressure, clinic BP change over multiple measurements, history of hypertension, duration of hypertension and smoking status were all significant predictors of the home-clinic BP difference. Goodness-of-fit did not change between models examining 3 or 6 clinic BP readings (Adjusted $R^2$ 0.50–0.52). The final model showed good calibration across all validation datasets (Pearson's correlation 0.54–0.81; $P < 0.001$).

**Conclusions:** Patient characteristics and multiple BP measurements taken over a short period of time at a single clinic can reasonably predict patient's subsequent out-of-office blood pressure. Utilisation of this prediction tool in clinical practice could allow for better targeting of out-of-office monitoring for those patients with a suspected white coat or masked effect.

## 5A.01. Pharmacogenetic GWAS meta-analysis of LDL cholesterol response to statins

**Iris Postmus[1], Stella Trompet[1], Helen R Warren[2], J Wouter Jukema[1] and Mark J Caulfield[2] on behalf of the GIST consortium**

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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, it is also established that there is inter-individual variability in LDL-C 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 LDL-C response to statins, we formed the Genomic Investigation of Statin Therapy (GIST) consortium and conducted a pharmacogenetic meta-analysis of genome-wide association studies of LDL-C response to statins, which is the largest, most comprehensive study of its kind conducted to date.

**Methods:** The meta-analysis comprises GWAS datasets from both randomized controlled trials (RCTs) and observational studies, including approximately 40,000 statin-treated subjects overall, divided into a first discovery stage and a second validation stage.

The response variable analysed is the difference between the natural log transformed LDL-C levels on- and off-treatment, and is adjusted for baseline LDL-C, in order to eliminate the confounded effect of association between the genetic variant and baseline LDL-C levels. Further adjustment was made for the type and dose of statins used, in order to combine several different types of statins across the contributing trials and within the observational studies.

**Results:** Overall, at genome-wide significant level, 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, such as conditional, eQTL and pathway analyses. For example, the genome-wide conditional analysis highlighted 14 independent SNPs explaining 5% of the variance, of which 6 SNPs reached genome-wide significance in our combined meta-analysis. Collectively our functional and pathway analysis confirmed a strong biological and functional role in statin response for several strongly associated gene loci, including *APOE*, and *SORT1/CELSR2/PSRC1*. Furthermore, a genetic risk score including our 4 lead SNPs was significantly associated with coronary disease risk in the CARDIoGRAM and C4D consortium.

**Conclusions:** 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.

## 5A.02. All-cause and cardiovascular mortality in West African villages: a 10-year follow-up using verbal autopsies

**Francesco Cappuccio[1], Federico Fratelli[1], Chen Ji[1], Frank Micah[2], Sally Kerry[3], Iain McPhee[4], John Eastwood[4] and Jacob Plange-Rhule[2]**

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**Objectives:** To assess predictors of death in a community-based population study in rural and semi-urban West Africa

**Design & Methods:** In a 10-year prospective community-based population study 1,013 participants randomly selected from 12 villages (628 women, 481 rural dwellers) in the Ashanti region of Ghana, West Africa were recruited and screened between June 2001 and June 2002. Very few were on drug therapy for hypertension or other chronic condition. Follow-up was completed by December 31st, 2011. They were screened at baseline for cardiovascular and metabolic risk factors. They were then followed-up for the ascertainment of vital status using verbal autopsies (WHO 2007). All-cause and cardiovascular (CV) (VA04 & VA07) deaths were recorded. Time to death was used in a Cox regression model to estimate hazard ratios (HR) and 95% C.I.

**Results**: After a 10-year follow-up, vital status was collected for 1,006 (99.3%) participants. During 9,118 person-years of follow-up, we documented 198 deaths (19.7%) including 64 (6.4%) from CV causes. After adjustment for age, BMI, smoking and locality, men were more likely to die from both all (HR: 1.83 [1.35, 2.48]; $P<0.001$) and CV causes (2.06 [1.21, 3.51]; $P=0.008$). After further adjustment for sex, significant independent predictors of deaths from all causes were smoking (1.56 [1.01, 2.42]; $P=0.049$), living in rural areas (0.73 [0.55, 0.98]; $P=0.038$), systolic BP above median (1.39 [1.03, 1.88]; $P=0.029$), HDL-cholesterol above median (0.59 [0.44, 0.79]; $P<0.001$), serum uric acid above median (1.43 [1.05, 1.95]; $P=0.023$). Similar estimates were found for CV deaths with the exception of a much stronger relationship between higher serum uric acid and CV death (2.48 [1.37, 4.48]; $P=0.003$). When deaths within the first 2 years of follow up were excluded, the estimates did not vary substantially.

**Conclusions:** This is the first prospective cohort study of a West African population. The findings indicate that alongside some traditional risk (smoking, higher BP) and protective (living in rural areas, higher HDL-cholesterol) factors, higher serum uric acid, even in this lean population, is a strong risk factor not only for all-cause death but especially for CV death.

## 5A.03. Obesity-related perivascular adipose tissue damage is partially reversed following diet-induced weight loss

**Charlotte Bussey, Sarah Withers, Gillian Edwards and Anthony Heagerty**

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The damaging effects of obesity on perivascular adipose tissue (PVAT) function have recently been shown to be reversed following bariatric surgery. However, PVAT function has not previously been characterised following weight loss induced by caloric restriction, often the first line treatment for obesity. This study investigated the role of PVAT in control of vascular function in rat models of diet-induced obesity and weight loss.

Male rats were fed high-fat diet for 16 weeks to induce obesity, they were then split into 2 groups; obese rats maintained on the diet and weight loss rats subjected to 50% caloric restriction for a further 4 weeks. A control group was also provided with a 10% fat diet during the 20 week period. The effect of PVAT on the contractility of isolated rat mesenteric arteries in response to noradrenaline ($1\times10^{-5}$–$3\times10^{-9}$ mol.l$^{-1}$) was investigated using wire myography. Data were expressed as mean ± SEM.

In control animals, the vasoconstrictor response to noradrenaline was reduced in the presence of PVAT and this anticontractile effect was abolished in obesity with an accompanying increase in systolic blood pressure. The PVAT anticontractile effect was partially restored following diet-induced weight loss with a reduction in obesity-induced hypertension. The vasoconstrictor response was unaltered between the groups in the absence of PVAT suggesting that changes in body weight do not affect vascular smooth muscle or endothelial cell function. Overall, our data indicate that obesity-induced hypertension may be a consequence of PVAT damage and this can be partially reversed following diet-induced weight loss.

## 5A.04. Long term changes in blood pressure and risk of mortality, stroke and myocardial infarction in the EPIC-Norfolk prospective population study

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**Background**: Longitudinal changes in blood pressure (BP) and how these are associated with mortality and CV incidence is less well researched.
**Methods:** We examined the association between longitudinal changes in BP and these outcomes in the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort participants (aged 40-79 years at the baseline) who attended more than one health examination over the follow-up. The categories of BP change were $\geq -10$, $-9.9$ to $+9.9$ and $\geq +10$ mmHg for systolic and $\geq -5$ mmHg, $-4.9$ to $+4.9$ and $\geq +5$ mmHg for diastolic BP. Adjusted Cox proportional hazard models were constructed to estimate the risk of mortality and incident stroke and myocardial infarction (MI) using inter-visit BP change categories as predictor variables.
**Results:** 14,184 participants (55% women) were included in post second health check (HC) and 6,445 participants (56% women) were included in the post third HC analysis with mean follow ups of 11.7 and 3.2 years, respectively. Adjustments were made for age, sex, BMI, cholesterol, prevalent MI, stroke, diabetes, social class, education, alcohol consumption, smoking status, physical activity, family history of stroke and MI, aspirin therapy, other medications including diuretics, beta blockers, ACE inhibitors and calcium channel blocker therapies. An increase in SBP $\geq +10$ mmHg between 1st HC and 2nd HC was associated with increased risk of both stroke (HR 1.27;95%CI: 1.01–1.59) and myocardial infarction (1.30;1.05–1.62) but not mortality (1.05;0.95–1.17). There was no significant increased risk of any of the outcomes assessed in any other categories with regard to SBP especially a fall in BP between visits did not have major predictive value. Between 1st HC and 3rd HC, an increase in mortality was observed with a change in SBP of $\geq +10$ mmHg (HR 1.67; 95%CI 1.19–2.34). Changes in DBP between health checks were not associated with an increased risk of mortality or stroke incidence but there was an increased risk of incident myocardial infarction with an increase in DBP of $\geq +5$ mmHg (HR 1.35; 95%CI:1.09–1.68) between 1st and 2nd HC and a decrease in DBP of $\geq -5$ mmHg between 1st and 3rd HC (HR 6.65; 95%CI 1.43–30.9).
**Conclusions:** Changes in BP in middle and older age are variably associated with future risk of cardiovascular events and mortality depending on length of follow up and may also depend on changing health status.

## 5A.05. Inter-arm blood pressure difference and differences in arterial stiffness

**Christopher Clark, Francesco Casanova, Kim Gooding, Nicola Pamphilon, Kunihiko Aizawa, David Mawson, Damilola Adingupu, Clare Ball, Francesca Worthington, Salim Elyas, David Strain, Phillip Gates, Angela Shore and John Campbell**

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**Introduction:** Inter-arm differences in systolic blood pressure (IADs) are attributed to upper limb arterial disease, but subclavian stenoses have only been radiologically confirmed with large differences ($>35$ mmHg). The associations of IAD with increased mortality could be causally related to non-homogenous arterial stiffness. We examined associations between IAD, pulse pressures, and carotid-femoral pulse wave velocity.
**Methods:** Volunteers with and without cardiovascular risk factors underwent vascular assessments to determine arterial stiffness and blood pressure (BP). Pulse wave velocity and central arterial pressure were derived using arterial tonometry. Bilateral brachial BP was measured simultaneously six times using a repeated cross-over method. BPs were recorded as the mean of six consecutive measurements.
**Results:** For 554 subjects, 106 (19.1%) had a mean systolic IAD $\geq 5$ mmHg and 20 (3.6%) were $\geq 10$ mmHg. On multivariate analysis (adjusted for age, smoking and diabetes status, systolic BP, total cholesterol and renal function) systolic IADs were positively correlated with pulse wave velocity (($r=0.11$, $P=0.02$) and right (but not left) brachial pulse pressure (($r=0.091$, $P=0.04$). IAD was strongly correlated with brachial pulse pressure difference (($r=0.86$, $P<0.001$).
For the subgroup of 100 control subjects without diabetes, cardiovascular disease or hypertension, systolic IAD was moderately correlated with pulse

wave velocity ($r=0.38$, $P<0.001$) and strongly correlated with pulse pressure difference ($r=0.95$, $P<0.001$).
**Discussion:** These results suggest a potential association of arterial stiffness with IAD. Therefore, aetiology of IAD may involve localised changes to the mechanical and/or physiological properties of proximal arteries. We believe this to be the first European study to suggest these associations.

### 5A.06. Cardiovascular events in women with a history of pre-eclampsia in the Generation Scotland: Scottish Family Health Study

**David Carty[1], Catriona Brown[1], Scott Robinson[1], Marcus Schneider[1], Shona Kerr[2], Pamela Linksted[2], Archie Campbell[2], Anna Dominiczak[1], Sandosh Padmanabhan[1], Christian Delles[1] and Generation Scotland Scottish Family Health Study[3]**

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Women with a history of pre-eclampsia are reported to have increased risk of future cardiovascular (CV) disease and death; monitoring and early treatment of affected women have been proposed. We aimed to determine the frequency of CV events in women with a history of pre-eclampsia from the Generation Scotland: Scottish Family Health Study (GS:SFHS). Over 24,000 adults were recruited between 2006-11 for GS:SFHS, a Scotland-wide population-based study. Data on hospital admissions (SMR-01) and maternity admissions (SMR-02) dating back to 1980 were obtained from Information Services Division NHS Scotland. ICD-9 and -10 codes for moderate and severe hypertension with proteinuria were used to define pre-eclampsia; primary diagnosis codes for ischaemic heart disease, cerebrovascular disease, hypertension, pulmonary vascular and peripheral vascular disease were used to classify CV outcomes. CV event rates were compared between women with and without a history of pre-eclampsia.
Record linkage analysis was available for 11,410 pregnancies between 1980 and 2013 (in 6,040 women), of which 364 (3.2% of pregnancies, occurring in 329 women) were complicated by pre-eclampsia. Of the 329 women with a history of pre-eclampsia, 238 (72%) were primigravidae; their offspring were of lower birthweight ($P<0.001$), born at earlier gestation ($P=0.015$), and were more likely to be delivered by Caesarean Section ($P<0.001$). Of the 6,040 women, 278 had a subsequent CV event. 26 of the 329 women with a history of pre-eclampsia (7.9%) had a CV event compared to 252 of the 5,711 women (4.4%), with a history of normotensive pregnancy (OR 1.86 (95% CI 1.22 to 2.83,$P=0.004$). There was no difference in age at time of first CV event (44 yrs ± 10 vs 47 yrs ± 11, $P=$ ns), nor of time between first pregnancy and first CV event between women with and without a history of pre-eclampsia (19 ± 9 yrs vs 20 ± 11 yrs $P=$ ns).
In the current study we have seen that even in relatively young women from an unselected population cohort, those with a history of pre-eclampsia have a nearly 2-fold increased risk of cardiovascular disease. Women with pre-eclampsia should be targeted for more intensive cardiovascular risk reduction measures.

## Poster abstracts

### PA.01. RCT of different systolic blood pressure targets for people with a history or stroke or transient ischaemic attack: the PAST-BP (Prevention After Stroke – Blood Pressure) study

**Jonathan Mant[1], Richard McManus[2], Andrea Roalfe[3], Kate Fletcher[3], Clare Taylor[3], Una Martin[3], Satnam Virdee[3], Sheila Greenfield[3] and Richard Hobbs[2]**

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**Background**: Blood pressure lowering is effective at lowering risk of stroke recurrence in people who have had a cerebrovascular event, but it is uncertain how low blood pressure should be lowered in this population. We assessed whether intensive blood pressure targets could be achieved in a community population of people with prevalent cerebrovascular disease.
**Methods:** In this randomised open label trial, patients with a history of stroke or transient

ischaemic attack whose blood pressure was ≥125 mmHg and who were not already on three or more antihypertensive drugs were recruited from 99 General Practices in England during 2009–2011. Participants were randomly assigned to an intensive systolic blood pressure target (130 mmHg or 10 mmHg reduction from baseline if this was <140 mmHg) or a standard target (140 mmHg). Apart from the different target, patients in both arms were managed in the same way with regular reviews by the primary care team. The primary end-point was at twelve months. All randomised patients who attended the twelve month follow up visit were included in the analysis.

**Findings**: 529 patients, mean age 72, were enrolled, 266 to the intensive target arm and 263 to the standard target arm, of whom 379 were included in the primary analysis (182, 68% intensive arm; 197, 75% standard arm). 84 patients withdrew from the study during the follow up period (52 intensive arm; 32 standard arm). Mean systolic blood pressure dropped by 16.1 mmHg to 127.4 mmHg in the intensive target arm and by 12.8 mmHg to 129.4 mmmHg in the standard arm (difference between groups 2.9 mmHg, 0.2 to 5.7; $P = 0.03$).

**Interpretation**: Aiming for a 130 mmHg or lower target for systolic blood pressure in people with cerebrovascular disease in primary care rather than a 140 mmHg target leads to a small additional reduction in systolic blood pressure. Active management of systolic blood pressure in this population using a 140 mmHg target leads to a clinically important reduction in blood pressure. Management of blood pressure in this population should focus on achieving a <140 mmHg target.

**Funding:** National Institute for Health Research

## PA.02. New Onset Diabetes - predictors and outcomes in 15,111 treated hypertensive patients with 40 year follow-up

**Stefanie Lip, Panniyammakal Jeemon, Linsay McCallum, Scott Muir, Anna Dominiczak, Gordon McInnes and Sandosh Padmanabhan**

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**Objective:** Hypertension and diabetes mellitus (DM) synergistically increase cardiovascular(CV) risk. It is unclear if new onset DM (NOD) poses a significantly higher risk in hypertensive patients.

**Methods:** The Glasgow BP Clinic population consists of 15,111 patients. NOD status was based on the first hospital admission or prescription receipt for a diabetes related diagnosis. This was classified into early and late (diagnosis <10 yrs or >10years from first clinic visit). Cox proportional hazards (Cox-PH) models were used to study cause-specific morality and composite end point of all-cause mortality + NOD (to address any competing risk introduced due to the long follow-up period.

**Results:** Of 2521(17%) patients with DM, 2061(14%) had NOD. The incidence rate of NOD was 9.2 per 1000 person-years. Prevalence of early NOD was 898(6%) and late NOD 1163(8%). The total time at risk was 239,952 person-years with a median survival time of 28 years (IQR:16.2–39.9). There were 5225 deaths (52% from cardiovascular causes) during the follow-up period. Independent predictors of NOD were baseline glucose, BMI, age, alanine transaminase, alkaline phosphatase, gamma glutamyl transpeptidase and bilirubin. Age, glucose, BMI and alkaline phosphatase remained top predictors for NOD + all-cause-death. The mortality risk was the highest in prevalent DM (HR = 1.5[95%CI = 1.2;1.9]) and lowest in those with late NOD (0.79[0.68;0.92]). Early NOD and non-diabetic subjects had similar risks.

**Conclusions:** Indices of liver function tests, BMI and baseline glucose predict the risk of NOD and mortality. The risk posed by NOD is primarily related to duration of diabetes, and efforts to delay the onset of NOD are warranted.

## PA.03. Sex, drugs, cigarettes and alcohol: a systematic review of factors which predict the white coat and masked effect

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**Background:** Patients often have lower (white coat effect) or higher (masked effect) blood pressure at home compared to the clinic, potentially resulting in misdiagnosis and suboptimal management of hypertension. There is little consensus on what (if any) factors make a patient more susceptible to a large home-clinic blood pressure difference. This study aimed to systematically review the literature and

establish the most important predictors of a significant home-clinic blood pressure difference.
**Methods:** A systematic review was conducted using a MEDLINE search strategy which was replicated in 5 other literature databases. Studies examining factors which predict the home-clinic blood pressure difference were included in the review. Mean values for home-clinic blood pressure difference and coefficients/odds ratios describing the association between patient characteristics and this difference were extracted.
**Results:** The search strategy identified 3,743 articles of which 22 were eligible for this review. The mean home-clinic blood pressure across all studies was −6.6/−2.2 mmHg (95% CI −6.9 to −6.3/−2.4 to −1.9). Studies reported a total of 31 predictors for the white coat or masked effect. The most commonly cited predictors included increasing age, male sex, office blood pressure, number of prescribed antihypertensives, smoking status and alcohol consumption.
**Conclusions:** A number of common patient characteristics predict the home-clinic blood pressure difference. There is scope to incorporate such predictors into a clinical prediction tool which could be used to aid identification of those patients displaying a significant white coat or masked effect in routine clinical practice.

## PA.04. A double blind, randomised trial investigating if arterial stiffness can be reduced independently of blood pressure in participants with or at risk of type 2 diabetes

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Arterial stiffness is a powerful independent predictor for cardiovascular events and all cause mortality and is a common complication associated with Type 2 diabetes. This double-blind, randomised, factoral designed trial tests whether aortic pulse wave velocity (PWV) can be reduced independently of blood pressure (BP) in participants with or at risk of Type 2 diabetes. The broad criteria excludes only those with intercurrent illness or eGFR $<45$ mls/min. The effect of a daily intervention of spironolactone ($\leq 50$ mg) or doxazosin ($\leq 16$ mg) along with a nitrate donor ($\leq 0.4$ g nitrate), or identical but nitrate free placebo, juice is being assessed baseline, three and six months, using SphygmoCor, Arteriograph, Vicorder and VaSera. Circulating nitrite will also be assessed.

To date 70 of the 100 participant target have been screened, 65 randomised and 25 have completed six months (excluding four drop-outs). A 'masked' outline analysis of all four arms shows a decrease in systolic BP after three months from $136 \pm 16$ mm Hg to $130 \pm 17$ mm Hg, ($n = 38$, 61% male, mean ± SD; age $58 \pm 13$ years and BMI $33.0 \pm 5.6$).
For those who have completed ($n = 25$), systolic BP fell between baseline and six months from $134 \pm 16$ mmHg to $128 \pm 17$ mmHg with a slight reduction in PWV ($9.00 \pm 2.03$ ms$^{-1}$ to $8.82 \pm 1.55$ ms$^{-1}$), with a reduced standard deviation noted. The data to date suggest that, a trial focused on PWV with BP as a secondary component is feasible within our target population, with relatively simple recruitment and a low drop-out rate.

## PA.05. Patterns of short- and long-term treatment persistence and adherence of seven antihypertensive drug classes in the Glasgow BP Clinic

**Linsay McCallum, Christin Schulz, Abdulaziz AlQadi, Scott Muir and Sandosh Padmanabhan**

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**Background:** Adherence and persistence to antihypertensive therapy are important predictors of adverse outcomes and treatment resistance in hypertensive patients.
**Methods:** We analysed 3417 hypertensive patients newly referred to the Glasgow BP Clinic from 1994 onwards. Antihypertensive drug refill prescription data was obtained from the NHS Scotland Information and Statistics Division from 2003 to March 2013. New antihypertensive prescription was defined as first prescription atleast 30 days after the clinic appointment. Drug discontinuation was determined if the last refill prescription of the drug was picked up more than 60 days before the March 2013. Persistence for each class of antihypertensive drug was calculated for 1–5 year and >5year periods. Early non-persistence were determined for <1year and 1–5 years. Adherence was calculated using two metrics - the annual refill rate and the coefficient of variation of the inter-pick-up interval of prescriptions.
**Results:** Patients with new prescriptions included 1133 (thiazides), 1071 (ACEI), 1048 (ARB), 1454 (CCB), 393 (Spironolactone), 730 (alpha-blockers)

and 880 (beta-blockers) during the study period. Early non-persistence defined by the 1-year discontinuation rates were alpha-blockers (32%), Spironolactone (30%), ACEi (25%), beta-blockers (21%), thiazides (19%), CCB (15%), ARB (14%). The 1–5 year non-persistence rates were 10% for ACEi, ARB and beta-blockers followed by CCB (13%), spironolactone (15%), alpha-blockers (18%) and thiazides (19%). Long-term persistence (>5 years) were >35% for all drugs except spironolactone (21%) and alpha-blockers (25%), while the 1–5year persistence was 25–35% for all drugs. Amongst long-term persisters (>5 years) adherence to therapy was poorest for ACEi (coeff va($r$=38%), spironolactone (34%) and alpha-blockers (33%). Thiazides, ARB and CCB showed similar adherence levels (~20%).

**Conclusion:** ARB and CCB have the best long-term adherence and persistence profile and should be considered as first-line therapy in hypertensive patients.

## PA.06. An Audit of Appropriate Use of Antithrombotic Therapy in Patients Presenting with Suspected Acute Coronary Syndrome

**Alan Cameron and L McCallum**

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**Background:** Chest pain presentations are common although most patients do not have an acute coronary syndrome (ACS). We hypothesised that many low-risk patients are treated with potent antithrombotic therapy for ACS due to the current NHS GG&C guideline.

**Methods**: We conducted a prospective analysis of patients presenting with suspected ACS to the Western Infirmary Glasgow between 6/10/13–3/11/13. We collated data on demographics, investigation, initial management and final diagnosis. We conducted sensitivity, specificity and a-ROC analyses for the current NHS GG&C guideline, SIGN guideline and a new proposed guideline.

**Results**: We studied 126 patients: 74 (59%) male and mean (SD) age 61 years. Anti-thrombotic agents patients were taking on admission and administered on presentation are detailed in tables 1 and 2. Amongst 117 patients not taking warfarin, full antithrombotic therapy for ACS was recommended in 54 patients (46%) according to the NHS GG&C guideline, 29 (25%) by the SIGN guideline and 13 (11%) by our new proposed guideline. The final diagnosis was ACS in 39 patients (33%). The current NHS GG&C guideline had a sensitivity of 69%, specificity 57% and a-ROC 0.63 (95% CI 0.47–0.79) (Figure 1). The respective values were 62%, 80% and 0.71 (95% CI 0.54–0.87) for the SIGN guideline and 46%, 93% and 0.70 (95% CI 0.52–0.89) for our new proposed guideline.

**Conclusions**: Only one-third of patients presenting with suspected ACS had this as their diagnosis. The current NHS GG&C guideline should be revised as both the SIGN guideline and our new proposed guideline have improved diagnostic accuracy.

## PA.07. Costs of hypertension detection within the NHS Health Check programme compared to opportunistic detection

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**Introduction:** The NHS Health Check Programme (NHSHC) offers 5 yearly assessments to adults (40 to 74 years) without established vascular disease. The programme's evidence base id debated, and its cost-effectiveness assumes an uptake rate of 75%. We have prospectively audited new diagnoses of hypertension; findings from our practice's first 6 months of checks are presented.

**Methods:** Eligible patients were identified from the practice database and invited to nurse-run clinics. During a 30 minute appointment they received targeted health advice based on lifestyle history and clinical measurements. Blood pressure (BP) was recorded as the mean of three readings with an automated sphygmomanometer after five minutes rest. Patients with mean BP >140/90 were followed up by nurses and doctors according to NICE hypertension diagnostic guidelines. We used published UK figures to estimate costs incurred in confirming a new diagnosis of hypertension, and compared these with estimated costs of detecting the same cases with an opportunistic approach.

**Results:** 278 patients were invited, 86 (31%) attended, and 26 (30%) required follow up of an elevated BP; six (23%) did not re-attend and hypertension was diagnosed in seven (27%). The cost per diagnosis through NHSHC was £547.78; an additional cost of £318.43 compared to opportunistic detection.

**Discussion:** NHSHC uptake is low, but comparable with the county-wide rate (34%). Estimated costs of diagnosing hypertension with NHSHCs are double those for an opportunistic approach. If this finding is replicated in a larger sample of practices it may challenge one of the cost-effectiveness assumptions of the NHSHC Programme.

## PA.08. Auditing compliance with the NICE guidelines for initial investigations upon primary hypertension diagnosis

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**Background:** The complications associated with hypertension are usually related to target organ damage. Our previous audit to assess compliance in a primary care setting with investigations for target organ damage, as outlined by the 2011 National Institute of Health and Clinical Excellence (NICE) hypertension guideline, found that none of the patients had all the recommended investigations. ECG, urinalysis and fundoscopy were performed in 33%, 8.3% and 0% of cases respectively. Therefore, we recommended: a hypertension investigation checklist, use of local ophthalmology services, continuing professional development events for general practitioners (GPs) on hypertension, and more patient education centred strategies.
**Aim:** To re-audit compliance with investigations for target organ damage in hypertension as detailed in 2011 NICE guidelines following prior audit recommendations.
**Method:** Records of patients placed on the primary hypertension register between June 2013 and March 2014 were analysed and the investigations conducted at diagnosis of hypertension were noted.
**Results:** $n = 21$, compliance rate = 0%. While no patient had all the investigations conducted, a trend favouring increased compliance was observed. Improvements were noted in ECG (52% versus 33%), urinalysis (13% versus 8%) and fundoscopy (5% versus 0%). There was a decrease in plasma glucose (24% versus 92%), lipid profile (91% versus 100%) and urine ACR measurements (13% versus 33%). All patients had their HbA1c measured. GPs described the various issues surrounding the lack of compliance.
**Conclusion:** GPs need to become familiar with the recommended investigations for improved compliance with NICE guidance. HbA1c may be a suitable alternative to plasma glucose measurement.

## PA.09. Prevalence and management of hypertension in patients with gout enrolled in the Febuxostat versus Allopurinol Streamlined Trial (FAST)

**Claudine Jennings[1], Isla Mackenzie[1], Rob Flynn[1], Ian Ford[2], George Nuki[3] and Thomas MacDonald[1]**

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**Introduction:** Patients with gout have increased cardiovascular morbidity and mortality compared with the general population therefore management of cardiovascular risk factors, including hypertension, is important in this population. The Febuxostat versus Allopurinol Streamlined Trial (FAST) is evaluating the long term cardiovascular safety of febuxostat versus allopurinol in patients with gout. Recruited patients must be aged over 60 years, already taking allopurinol and have at least one additional cardiovascular risk factor.
**Methods:** We reviewed pre-randomisation data for the first 1490 patients recruited into the FAST trial to assess prevalence and management of hypertension in this high risk patient group. Screening data included patient demographics, clinic blood pressure (mean of 3 readings, seated), cardiovascular history and current medication.
**Results:** Mean patient age was $71 \pm 6$ years, 85% were male and mean BMI was $31 \pm 5\,kg/m^2$. 26% had established IHD, 11% had cerebrovascular disease, 25% were diabetic and 13% had chronic kidney disease. 78% of FAST patients had a history of hypertension and mean screening blood pressure in this group was 138/74 ($\pm$18/11) mmHg. 43% of patients with a history of hypertension had clinic blood pressure above 140/90 mmHg at screening. 41% of patients with no history of hypertension also had screening blood pressure above 140/90 mmHg. Patients with a history of hypertension were taking on average 2.3 antihypertensive medications (52% diuretic, 51% ACEi, 24% ARB, 45% B-blocker, 44% CCB). Systolic BP $>140$ mmHg at the screening visit was significantly associated with a past history of IHD or stroke.

**Limitations:** Observational data of a selected patient group, using a single set of clinic blood pressure readings.
**Conclusion:** Our data shows that clinic blood pressure is often sub-optimal in this patient group despite most patients taking a number of anti-hypertensive medications. Gout and hypertension share many risk factors. Whether improving hyperuricaemia will impact on blood pressure control is currently being studied in a sub-study of the FAST trial.

## PA.10. 'Real life' experience of renal denervation for resistant hypertension from two NHS Hospital Foundation Trusts in Birmingham

**Mohammed Hameed[1], Mark Pucci[2], Una Martin[2], Richard Watkin[1], Sagar Doshi[2], Jonathan Freedman[1], Peter Riley[2], John Townend[2], Lisa Tebbit[1], Louise Beesley[2], Paul Crowe[1] and Indranil Dasgupta[1]**

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Resistant hypertension is common in the hypertensive population with reported prevalence of 5–30%. Renal denervation has been a promising new treatment option for such patients, however, the recently published SIMPLICITY HTN-3 trial did not meet its primary (change in office systolic blood pressure at 6 months) or secondary (change in mean 24-hour ambulatory systolic blood pressure) efficacy endpoints, but has been shown to be safe.
We report our experience of renal denervation from combined data of two specialist hypertension clinics in Birmingham. Patients who were identified to have truly resistant hypertension (by careful exclusion of secondary causes and non-adherence) underwent renal denervation. Baseline demographics, clinic BP, ambulatory BP and medications were recorded. Patients were followed up for six months with repeat measurements.
Thirty Three patients have completed the six months follow up. Eighteen were males. The mean age [±SD] was 53.7 [±11.3] years. On average patients were taking 4.40 [±1.79] medications at baseline and 4.30 [±1.66] medications at six months. Mean [±SD] clinic systolic BP at baseline was 184.3 mmHg [±23.6] and mean daytime ambulatory systolic BP was 163.4 mmHg [±18.3]. There was a significant reduction in clinic systolic BP of 13.5 mmHg at six months (95% CI −4.54 to −22.5; $P=0.005$). There was a statistically non-significant drop in daytime ambulatory systolic BP (11.4 mmHg; 95% CI +4.76 to −27.6; $P=0.159$). 42% of patients had a clinically significant reduction in clinic BP of 10 mmHg or more (mean 30.2 mmHg; 95% CI −19.6 to −40.9; $P<0.001$) and 39% had reduction in daytime ambulatory systolic BP of 5 mmHg or more (mean 19.5 mmHg; 95% CI −13.0 to −25.9; $P<0.001$).
Our 'real life' data suggest that renal denervation does appear to be an effective treatment option for some patients with resistant hypertension, whilst in others it has no effect. Further research is warranted to improve our understanding of which patients might benefit from the procedure so that treatment can be targeted more effectively.

## PA.11. Catheter Ablation for Ischaemic VT: The effect on VT burden, ICD shocks and psychological sequelae in a North of Scotland population

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**Background**: Ischaemic VT carries significant morbidity and mortality. ICD-delivered shocks – appropriate or not – increase the risk of death up to fivefold. Shocks are also associated with psychological distress including PTSD. In the past two decades, catheter ablation has been used to treat ischaemic VT resistant to conventional therapy, with variable success.
**Methods and Results**: Between 2004–2014, 20 patients (age 46–88 years at time of intervention, 19 men) with IHD and moderately to severely impaired LV function, underwent catheter ablation at Aberdeen Royal Infirmary for recurrent/incessant drug-refractory VT or shock storm. All patients were on antiarrhythmics (Class I–III). ICD data for 6 months prior ablation and 6 months following was retrospectively compared for number of ATPs and shocks delivered for VT. Patients were also contacted to explore quality of life and mental health before and after ablation, as well as experience of the procedure. Two patients had more than one ablation. One patient was considered a failed ablation. Four patients were excluded - two patients had missing records, one patient died of a coronary embolus during mapping prior to RF ablation, one patient did not have an ICD at ablation for comparison ($n=16$). The mean +/−standard deviation ATP reduction was 63.6% +/−66.6%, with 87.5% of patients experiencing 48–100% reduction. Mean shock reduction was 57.3% +/−50.9%, with

81.3% of patients experiencing 11–100% reduction. For all patients ($n = 20$), all cause cardiology readmission post-ablation was 45%, all cause 1 year mortality 25% and 5 year mortality 50%. Of the 8 contactable patients, 7 were positive about the ablation and described improved symptoms, most importantly being less shocks. One of these patients however requires ongoing psychological support following shock storm, despite objectively improved arrhythmia and shock burden, advocating early psychological support in such cases. A shared anxiety was the length and complexity of the procedure. One patient could not express their views due to advanced dementia.

**Conclusions**: Catheter ablation, for the majority of patients, can reduce ischaemic VT ATP and shock burden. However, substrate for arrhythmia persists in this high risk group and ablation can therefore be considered a palliative procedure. This may be the only option if VT is drug-resistant, incessant or the patient is in shock storm. The majority of contactable patients have found ablation beneficial and described an improved quality of life.

## PA.12. Anti-hypertensive medicine intolerance – an overlooked and important cause of failed compliance

**Manish Saxena[1], Sotiris Antoniou[2], Nadya Hamedi[2], Romana Chowdhury[2], Satnam Lidder[1], Timothy Brier[1], Paul Robinson[1], Vikas Kapil[1] and Mel Lobo[1]**

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**Aim:** Poor compliance is increasingly recognised as a major cause of failure to attain BP control in hypertension (HTN). Simultaneously referrals of patients with failed compliance due to multiple medication intolerances are rising. Current guidance offers no strategies to help manage these patients. We sought to characterise this medication intolerant hypertensive cohort and develop a potential treatment protocol.

**Methods and Results:** We retrospectively analysed case records for patients referred with uncontrolled HTN and with multiple medicines intolerance. 60 (39 female) patients (mean age $66.5 \pm 8.4$ yrs) of whom 98% are Caucasian, were intolerant of $7.3 \pm 3.9$ medicines at first visit with baseline clinic BP of $170 \pm 21/98 \pm 15$ mmHg. This sub-group has high cardiovascular risk: prior cardiovascular events ($n = 21$, 35%), LVH ($n = 18$, 30%) and hypercholesterolemia ($n = 25$, 41%). Only 10 patients (16.6%) had atopic allergic disorders and the most common co-morbidities in this subgroup are gastro-intestinal disorders (e.g. gastro-oesophageal reflux disease, $n = 22$, 36.6%). A stratified protocol has been developed to utilise fractional tablet dosing, liquid formulations, transdermal patches and unlicensed medications to attain BP control.

**Conclusion:** Medication intolerance can arise due to hypersensitivity reactions, typical (known) side effects of drugs or unspecified adverse effects of drugs (ICD-9-CM 995.2.) Regardless of cause, the adverse effects are distressing and incapacitating enough to significantly affect quality of life and warrant discontinuation of therapy which poses a substantial challenge to clinicians. There is need for better awareness, greater empathy and further research into this condition.

## PB.01. Home Blood Pressure Monitoring - what is the optimal schedule? A systematic review

**James Hodgkinson[1], Sabrina Grant[1], Emma Bray[3], Sarah Stevens[2], Una Martin[1], Rafael Perera-Salazar[2], Bryan Williams[4], Richard McManus[2]**

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**Background**: Self-monitoring of blood pressure (SMBP) has the potential to better estimate underlying blood pressure (BP), is increasingly popular with patients, and is endorsed in hypertension guidelines worldwide. However, there is little agreement as to the optimal self-monitoring schedule. Updating a NICE systematic review, we reviewed the literature regarding the optimum schedule for SMBP in terms of both prediction of future cardiovascular events and the relationship between the number of readings taken and ''true'' underlying BP, considering the number, timing and frequency of self-monitoring measurements.

**Methods**: Six electronic databases were searched and data were extracted independently by two reviewers from each included paper. For prognostic

studies reporting hazard ratios (HR), the adjusted HRs per 1 mmHg increase in BP were summarised along with the associated outcome. For reliability/reproducibility studies, correlations reported between SMBP and ambulatory BP measurement (ABPM) were summarised. Methodological quality was assessed using three adapted validated checklists and monitor validation status.

**Results**: From 2,530 unique papers identified, 10 met the inclusion criteria. A further 11 studies were included from the NICE review. In 7/8 prognostic studies, SMBP had predictive value. In 13 reliability/reproducibility studies, all six reporting correlations with ABPM showed strong associations (R = 0.70–0.89) for systolic BP for the best proposed home monitoring schedule. However, there was considerable heterogeneity in population, study quality, and clinical outcomes considered in these studies, and meta-analysis was not possible. 12 studies suggested an optimal number of days to monitor per week (mean 4.75 [SD 1.8]; range 3–7); 12 an ideal number of measurements to be taken each day, (mean 3.7 [SD 1.4]; range 2–6); 10 recommended a total number of measurements to be taken per week (mean 19.8 [SD 9.2]; range 6–30), with some also suggesting how many measurements should be discarded (mean 6.4 [SD 6.8], range 0–18) and how many used (mean 12.2 [SD 6.9], range 5–24). 10 papers advocated taking readings in both the morning and evening, though evidence even here was mixed and marginal. Only one paper assessed the best particular time interval (one minute) to rest between measures.

**Conclusions:** There was limited consensus across the studies identified, other than advocating both morning and evening measurements. Whilst these findings provide a partial endorsement of current guideline recommendations for SMBP, the extent of heterogeneity and concerns over the methodological quality of included studies highlights that further research is necessary before we can recommend a particular schedule to ensure underlying blood pressure is measured adequately.

## PB.02. Changes in Systolic Blood Pressure (SBP) on Repeated Measurements may be due to local arm factors and not just accimatisation to stress

**Jonathan Elliott[2], Maureen Holland[1] and Philip Lewis[1]**

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To investigate how and why SBP changes with repeated measurements, we analysed patterns of change in 32 normotensive (M = 12, F = 20) subjects aged 21 to 80 (mean 50.2) years. SBP was measured with an upper arm cuff by brachial artery Doppler return-to-flow in randomised sequence both at rest (with restful music played into earphones) and under stress (induced by mental arithmetic). To assess the contribution of the number of inflations as well as the effect of time and sequence, 5 readings every 2 minutes and 9 readings every 1 minute were taken in randomised order for stress and rest. Changes in the circumference of the mid-forearm distal to the blood pressure cuff were measured by a Hokansen strain gauge prior to cuff inflation. Stress was measured using Galvanic Skin Response (GSR) electrodes on the contralateral ring and index fingers and continuous SBP was also measured in the contralateral middle finger (Portapres).

**Results:** Mean rest SBP was 14.0 mmHg lower than under stress ($P < 0.001$). In 8 minutes, SBP decreased with 9 readings at rest by 3.25% ($P = 0.009$) and 1.85% with 5 readings ($P = 0.049$) whilst contralateral finger SBP increased by 0.12% with 9 readings ($P = 0.949$) and by 2.11% with 5 readings ($P = 0.208$). At rest, basal forearm circumference decreased by 0.33% with 9 readings ($P = 0.003$) and by 0.54% with 5 readings ($P = 0.025$). SBP under stress decreased by 2.41% with 5 readings ($P = 0.164$) and increased on average by 0.35% with 9 readings ($P = 0.845$) whilst contralateral finger SBP increased by 1.91% with 9 readings ($P = 0.288$) and decreased by 0.59% with 5 readings ($P = 0.709$). Under stress, basal forearm circumference decreased by 0.11% with 9 readings ($P = 0.589$) and by 0.62% with 5 readings ($P = 0.045$). Higher stress GSR and pulse rate [6.4 bpm] (both $P < 0.001$) cf. rest did not correlate with SBP differences. A reduction in GSR with 5 readings at rest (but not with more readings or stress) correlated with the fall in SBP.

**Conclusion:** The bigger reduction in blood pressure and ipsilateral forearm circumference when more readings were taken over the same time period at rest, the lack of a concomitant decrease in contralateral finger blood pressure and little correlation between stress measures and SBP changes suggest that local arm factors as well as stress contribute to the decrease in blood pressure.

## PB.03. Smartphone applications for the monitoring of hypertension: a systematic review

**Christopher Floyd, Kevon Parmesar and Albert Ferro**

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**Introduction:** Smartphone applications (apps) have become integrated with many aspects of modern life, with >100,000 apps currently available for use in healthcare. Apps are unregulated and potentially place patients at risk if the information they contain is inaccurate. Additionally, any app that transforms clinical data (e.g. calculating a mean blood pressure (BP)) is a Class 1 medical device and should be registered with the MHRA. Here we present a systematic review of blood pressure (BP) monitoring apps available in the UK.
**Methods:** The Apple App Store (UK) was searched on 15th March 2014 using the terms ''hypertension'' OR ''blood pressure''. Inclusion criteria were iPhone compatibility, free to use, English language, targeted for patient use, ability to record multiple BP readings and app functionality independent of other medical devices. Data were extracted from each app according to a predefined protocol: conformity to guidelines, presence of data transformation, limits to data input and data protection policy.
**Results:** Following the removal of duplicates, 608 apps were identified of which 96 met the inclusion criteria. Five apps provided advice on how to measure BP, of which four claimed conformity to national and/or international guidelines. A further 11 apps providing advice unrelated to BP measurement technique also claimed conformity to guidelines (15 apps in total; 16%). No apps stated approval by recognised societies. Data transformation was performed by 24 apps (25%), none of which displayed regulatory approval. Three apps did recommend using a specific approved sphygmomanometer, with one providing formulae used for subsequent data transformation. Data input was subject to checks in 60% (58 apps) to ensure that diastolic values were lower than systolic. 25% (24 apps) required a passcode to access stored data, but it was unclear where data was stored (e.g. locally on device or on a server) in 89% of apps.
**Conclusions:** There are many apps freely available to patients that enable them to record BP measurements. These unregulated apps conform poorly to recognised guidelines and have the potential to harm if their advice or data transformations are inaccurate.

## PB.04. Determinants of systolic blood pressure differ between normal weight and overweight young adults

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The positive association between body size and blood pressure (BP) is well recognised. However, not all hypertensive individuals are overweight and vice versa. This study aimed to examine the influence of body size on the haemodynamic mechanisms driving systolic BP (SBP) at rest and during exercise, in young adults.
Detailed anthropometric, biochemical and haemodynamic measurements including BP, cardiac index (CI) and peripheral vascular resistance (PVR) were obtained in 2497 untreated individuals ($23 \pm 6$ years) at rest. A sub-set of 50 individuals undertook steady-state, sub-maximal cycling exercise, with detailed haemodynamic measurements re-assessed. Subjects were stratified according to gender-specific tertiles of body mass index (BMI); the lower tertile deemed normal weight (NW) and the upper tertile, overweight (OW).
Overall, there was a positive association between SBP and CI, at rest in males (($r=0.27$, $P<0.001$) and females (($r=0.25$, $P<0.001$). However, this was significantly stronger in NW versus OW individuals ($P<0.001$). In contrast, there was a positive association between SBP and PVR in OW males (($r=0.21$, $P<0.001$) and females (($r=0.28$, $P<0.001$), but not in NW. During exercise, the increase in CI was positively associated with the increase in SBP in NW males (($r=0.62$, ($P=0.02$). However, in OW males, the reduction in PVR was inversely associated with the increase in SBP (($r=-0.56$, ($P=0.03$). Similar patterns were observed in females, though none were significant.
The primary haemodynamic mechanisms driving SBP differ depending on body size in young adults, emphasising the need for differential approaches in understanding and treating high BP in young individuals.

## PB.05. Variability of Blood Pressure readings - Thoughts from a Telemetry Study

**Paul Padfield[1], Rob Elton[1], Janet Hanley[2], Mary Paterson[1] and Brian McKinstry[1]**

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Variability of BP can be measured in time; from seconds to months and may in and of itself determine clinical outcome. A simple assessment of 'variability status' (VS) could become important in future risk stratification. We have examined data from our recently published, randomised trial of Telemetry of Home Monitoring in patients with uncontrolled BP which confirmed superiority of telemetry for BP control (*BMJ* 2013;346:f3030 doi: 10.1136/bmj.f3030).

After clinic measurement (3 readings with second and third recorded) All patients ($n=359$) underwent daytime ABPM, half (182), thereafter, home monitored with telemetry for 6 months. ABPM and clinic measurements were repeated after 6 months. The calculated measure of variability (Standard Deviation) was related to several other parameters. Data are presented for SBP only.

Self reported adherence to medication was positively associated with the level of clinic BP and to a lesser extent ABPM ($P<0.003$). Subjects with high clinic variability (between second and third readings) tended to be those with high daytime ABP variability (($r=+\ 0.20$, $P<0.001$). The 'white coat effect' correlated with the overall daytime ABP variability on both occasions (($r=0.33$, $P<0.001$); there was no seasonal variability of the WC effect.

Variability during both ABPM periods was positively correlated with age (($r=0.3$), female sex (($r=0.12$) and depression scores (($r=0.11$), $P<0.001$, $<0.02$ and 0.03. Importantly ambulatory 'variability' was closely reproduced on repeat assessment (($r=0.45$, $P<0.001$) suggesting that VS may be a feature of individuals. Variability of ABPM was affected by the 'white coat window' with SBP in the 2 h period after commencement being 3 mm Hg greater than the average for the rest of the day ($P<0.001$) on both occasions. For the group who home monitored there was a high degree of correlation between the variability noted during the first week (unaffected by treatment changes) and either clinic or ABPM variability ($r\sim0.3$, $P<0.001$).

Whilst these data do not establish a true 'variability status', they do suggest that several measures of variability may be common within individuals, supporting the idea that future research could be profitably directed towards defining a measure of VS.

## PB.06. Home blood pressure monitoring: What is the most feasible and acceptable schedule? – A qualitative study

**Sabrina Grant[1], Siobhan Milner[1], James Hodgkinson[1], Sheila Greenfield[1], Una Martin[1] and Richard McManus[2]**

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**Background:** Self-monitoring of blood pressure (SMBP) has the potential to better estimate underlying blood pressure (BP), is increasingly popular with patients, and is endorsed in hypertension guidelines worldwide. Despite the growing popularity of home blood pressure monitoring there is currently no evidence based schedule that is recommended for patient use and little is known about the feasibility and acceptability of available self-monitoring schedules. This qualitative study explored the views and experiences of patients and health care professionals (HCPs) on acceptable and feasible self-monitoring schedules, informed by a recent systematic review and national clinical guidelines.

**Methods:** 14 focus groups: 10 primary care [4 with HCPs, 6 with patients, with and without experience of self-monitoring], and 4 secondary care [1 HCP, 3 patients] plus 3 interviews with secondary care HCPs. Interviews and focus groups, supported by field notes, were recorded, transcribed verbatim and analysed by constant comparative method.

**Results:** Preliminary analysis suggests patients generally supported structured schedules, preferred a 3-day monitoring schedule (2x daily) over a longer 7-day period, but felt schedules must have a degree of flexibility to adapt to individual routines. HCPs made a clear distinction between 7-day schedules which were considered better for diagnosis and 3-day schedules which were considered adequate for follow up. HCPS thought that a formalised schedule could reduce panic about one-off high readings but expressed concern how compliance with schedules could be monitored.

**Conclusions:** This qualitative study provided an insight into patients' and HCPs' views and experiences about schedules for self-monitoring.

## PB.07. Accuracy of hypertension diagnosis using clinic blood pressure measurement in CKD patients with proteinuria: a pilot study

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**Introduction:** Hypertension is a modifiable risk factor for disease progression and cardiovascular complications in chronic kidney disease (CKD). Recommendations for hypertension management in CKD rely on blood pressure (BP) to be ''consistently'' below 140/90 and 130/80 for patients without and with proteinuria, respectively. We examined the diagnostic utility of clinic BP relative to the most consistent measure of daytime average BP from ambulatory monitoring (ABPM).
**Method:** Data were collected from 49 patients (31 male) aged $68 \pm 15$y (mean ± SD) with eGFR of $30 \pm 8\,\mathrm{ml.min^{-1} \cdot 1.73m^{-2}}$. Nineteen patients presented with proteinuria. Following measurement of clinic BP, patients underwent ABPM monitoring for 48 hours. Receiver Operating Characteristic (ROC) analysis was employed to derive optimal cut-points of clinic BP, with sensitivity and specificity equally weighted.
**Results:** The prevalence of systolic hypertension in the proteinuria sample was 12/19. The ROC area-under-the-curve (AUC) was 0.89 (95% CI: 0.67–0.99) with a clinic cut-point of $>137$ mmHg (sensitivity = 75%, specificity = 100%). The prevalence of diastolic hypertension was 6/19. The ROC AUC was 0.89 (95% CI, 0.66 to 0.99) with a clinic cut-point of $>75$ mmHg (sensitivity = 100%, specificity = 77%). There was disagreement between systolic clinic and ABPM measurements in the 'no proteinuria' group, which precluded any ROC analysis.
**Conclusion:** These pilot data on 19 proteinuric patients with clinic cut-points that best discriminate hypertension (average daytime AMPB at a threshold of 130/80) are 137 mm Hg for systolic and 75 mm Hg for diastolic BPs. Clinic measurements of BP are not useful for reliable diagnosis of hypertension in patients without proteinuria.

## PC.01. Prevalence of an inter-arm blood pressure difference and survival implications in community based populations: an updated analysis

**Christopher Clark, Angela Shore, Rod Taylor and John Campbell**

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**Background:** Different prevalence rates for inter-arm differences in blood pressure (IADs) may be associated with differing vascular risks. To explore this we undertook a meta-analysis of prevalences, and updated our previous review's survival findings, for studies representative of primary care or community cohorts.
**Methods:** We updated literature searches for our reviews of cross-sectional and cohort studies reporting IADs (to March 2014). We extracted study level estimates of prevalences of IAD $\geq 10$ mmHg measured by repeated simultaneous methods, and prospective survival differences associated with IADs $\geq 10$ mmHg measured by simultaneous or sequential methods. Pooled prevalence estimates grouped by diabetic and hypertensive status, and hazard ratios (HRs) for systolic IADs, were calculated using random effects meta-analysis models.
**Results:** Pooled prevalences of systolic IADs $\geq 10$ mmHg were 13.6% (95%CI 8.6 to 18.5; $I^2 = 43\%$) for three hypertensive cohorts (323 participants); 7.0% (5.1 to 9.0; $I^2 = 45\%$) for five diabetic cohorts (1363 participants); and 4.4% (3.6 to 5.2; $I^2 = 0\%$) for six studies (2594 participants) of general populations. Prevalences differed between the three groups ($P < 0.001$). For survival studies pooled HRs were 1.5 (1.2 to 1.9; $I^2 = 0\%$) for cardiovascular deaths from seven cohorts (16369 participants), and 1.4 (1.1 to 1.7; $I^2 = 0\%$) for all-cause mortality from eight cohorts (16452 participants) for systolic IADs $\geq 10$ mmHg.
**Discussion:** Prevalence of IAD varies in association with population cardiovascular risk; this should be acknowledged in future studies. Recent cohort studies are consistent with previous survival findings and strengthen evidence for increased cardiovascular and all-cause mortality with a systolic IAD $\geq 10$ mmHg.

## PC.02. Circulating levels of a dicarboxylic acid associate with blood pressure, predict mortality and response to antihypertensive drugs. A multi-omics study

**Sandosh Padmanabhan[1], Cristina Menni[2], Safaa Alsanosi[1], Gabi Kastenmüller[3], Martin McBride[1], Massimo Mangino[2], Julia Brosnan[5], Jeff Trimmer[5], Robert Mohney[6], Karsten Suhre[3], Christian Geiger[3], Olle Melander[4], Anna Dominiczak[1], Tim Spector[2] and Ana Valdes[2]**

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**Objective:** The aim of the current study was to use a systems approach combining omics and epidemiology to discover molecular markers associated with blood pressure regulation and response to antihypertensive drugs.
**Methods:** We tested the association between 280 known metabolites and blood pressure in 3980 adult female from the TwinsUK cohort after adjustment for conventional covariates. We run replication replication in the independent KORA study comprising both males and females. Survival analysis was performed using Cox proportional hazards model. We tested gene expression and metabolite correlations in 586 adipocyte samples. We then tested SNPs within the metabolite-associated genes for association with hypertension and drug response in the BP-extremes GWAS (1621/1699 cases/hypercontrols) and the Nordic Diltiazem study ($n = 4039$) respectively.
**Results:** We identified a dicarboxylic acid associated with SBP (Beta[95%CI] = 1.31 [0.83; 1.78], ($P = 6.81 \times 10^{-8}$) and DBP (0.81[0.5;1.11], ($P = 2.96 \times 10^{-7}$) in the Twins study and KORA study (SBP:1.42[0.37; 2.47], ($P = 0.01$; DBP:0.64 [0.09,1.19], ($P = 0.02$). In Twins, the highest tertile was also associated with 50% higher mortality compared to the lowest tertile (HR [95%CI] = 1.49[1.08; 2.05], ($P = 0.02$). Levels of the acid correlated with adipocyte gene-expression levels of a gene on chromosome 11 (−0.15 [−0.2;−0.11]; $P < 1.01 \times 10^{-9}$). The minor T allele of an intronic SNP on that gene was associated with high metabolite levels (0.03[0.002; 0.02], ($P = 0.04$), hypertension (0.22[0.08; 0.36], ($P = 0.01$), poorer DBP response to calcium channel blockers (CCB) (−2.16[−3.65; −0.67], ($P = 0.005$) and consequent higher cardiovascular mortality (HR = 2.68[1.04; 6.9]; ($P = 0.04$).
**Conclusions:** Our findings indicate a novel pathway and potential biomarker for hypertension, involving a dicarboxylic acid and influenced by CCB. This can potentially be used for diagnosis and stratification for hypertension management.

## PC.03. Glyceryl trinitrate for acute stroke: Main results from the Efficacy of Nitric Oxide in Stroke (ENOS) Trial

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**Background:** High blood pressure (BP) is common during the acute phase of stroke and is associated with a poor outcome. Although small and medium-sized trials have assessed the effect of altering BP on outcome, the management of high BP remains unclear. We tested whether transdermal glyceryl trinitrate (GTN), a nitric oxide that lowers BP, is safe and effective in improving outcome after acute stroke.
**Methods:** ENOS is an international multicentre prospective randomised single-blind blinded-endpoint trial. Patients with acute ischaemic stroke (IS) or intracerebral haemorrhage (ICH) and systolic BP 140–220 mmHg were randomised to GTN or no GTN (and, where relevant, to continue or stop pre-stroke antihypertensive therapy - results reported separately). The primary outcome is shift in modified Rankin Scale at 3 months. Patients or relatives gave written informed (proxy) consent and all sites had research ethics approval. Analysis is by intention-to-treat.
**Results:** 4,011 patients were enrolled from 173 sites in 23 countries across 5 continents between July 2001 and October 2013 (with 79% patients recruited from start of 2008). At baseline: mean age 70 (SD 12); male 57%; recruitment from Asia 14%, Europe 16%, UK 64%; prior hypertension 65%; prior stroke 15%; diabetes 17%; atrial fibrillation 17%; mean BP 167 (19)/90 (13) mmHg; severity (Scandinavian Stroke Scale) 34 (13)/58; total anterior circulation syndrome 30%; IS 81%, ICH 16%; stroke-recruitment time <12 hours 18%.
**Summary:** The main results will be available for presentation in quarter 2 2014. ENOS is large enough to influence clinical practice.

## PC.04. A systematic review and meta-analysis of thiazide-induced hyponatraemia: time to reconsider electrolyte monitoring regimens after thiazide initiation?

**Jenny Barber[1], Tricia McKeever[1], Sarah McDowell[3], Jenny Clayton[5], Robin Ferner[3], Richard Gordon[4], Michael Stowasser[4], Kevin O'Shaughnessy[2], Ian Hall[1] and Mark Glover[1]**

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Thiazide and thiazide-like diuretics are one of the most widely used and cost-effective class of antihypertensive agents worldwide. Thiazide-Induced Hyponatraemia (TIH) is one of their major adverse effects and the leading cause of drug-induced hyponatraemia requiring hospitalisation in the UK. Greater understanding of thiazide-induced hyponatraemia could improve both clinical practice and our understanding of the pathophysiology of this paradigm of disordered sodium and water handling in the kidney. We report a systematic review and proportions meta-analysis of the clinical and laboratory characteristics of patients with thiazide-induced hyponatraemia.

Medline, Embase, Web of Science and PubMed were searched to identify relevant articles published before October 2013. Results are presented as mean (95% confidence interval). Confidence intervals were determined with a random effects model using the DerSimonian and Laird method to calculate weights.

100 articles detailing 4204 patients with TIH were identified. Meta-analysis showed that patients, 78% (74–82) of whom were women, of average age 75 (73–77) years and body mass index 25 (20–30) kg/m$^2$ presented 19 (8–30) days after starting thiazide treatment with a trough sodium concentration of 117 (114–120) mmol/L. Serum potassium and urinary sodium concentrations were 3.3 mmol/L (3.0–3.5) and 62 (45–80) mmol/L respectively; serum and urine osmolalities were 242 (238–246) and 400 (366–434) mOsm/kg. The most frequently implicated agents were hydrochlorothiazide, bendroflumethiazide and indapamide.

Patients with TIH were characterised by advanced age, female gender, inappropriate saliuresis and mild hypokalaemia. Low BMI could not be substantiated despite previous suggestions. Time to diagnosis of TIH suggests that the recommended practice of performing a single investigation of serum biochemistry 7–14 days after thiazide initiation may be suboptimal. The poor quality and heterogeneous nature of many reports highlights the need for larger and more systematic studies of this important condition.

## PC.05. Hypertension and the brain: which treatments could improve cerebral blood flow?

**Tom Coope[1], Angus Nightingale[2], Laura Ratcliffe[2], Amy Burchell[2], Richard Wise[3], Julian Paton[1] and Emma Hart[1]**

*[1]University of Bristol, Bristol, UK; [2]University Hospitals Bristol NHS Foundation Trust, Bristol, UK and [3]Cardiff University, Cardiff, UK*

Many patients with dementia have a preceding history of hypertension. Animal work suggests that angiotensin converting enzyme inhibitors (ACEi) prevents pathological remodelling of the cerebral vessels when administered to young, spontaneously hypertensive rats [1]. We measured whether cerebral blood flow was higher in hypertensive humans taking ACEi ($n = 13$, 8 men, age; $57 \pm 8$ yrs) compared to hypertensives taking other treatments ($n = 9$, 6 men, age; $54 \pm 6$ yrs, 5 calcium channel blockers, 4 angiotensin receptor blockers). Blood flow in the left and right internal carotid and vertebral arteries was measured using magnetic resonance (MR) phase contrast imaging. Total cerebral blood flow was the sum of the mean blood flow in all vessels. Total cerebral vascular conductance (CVC) was calculated as total flow/mean arterial pressure. Average 24hr ambulatory systolic and diastolic blood pressures in both treated groups were comparable; $131 \pm 4$, $81 \pm 4$ mmHg vs. $134 \pm 3$, $82 \pm 3$ mmHg. There was a near significant trend towards higher total cerebral blood flow in the ACEi group compared to non ACEi group ($627 \pm 118$ vs. $512 \pm 139$ ml/min, $P = 0.06$). CVC was higher in the ACEi group vs. the non ACEi group ($5.4 \pm 1.1$ vs. $4.1 \pm 0.9$ ml/min/mmHg, $P = 0.05$). These preliminary data indicate that ACEi might help to prevent a reduction in CVC in hypertensive humans.

1. Harrap SB. Angiotensin converting enzyme inhibitors, regional vascular hemodynamics, and the development and prevention of experimental genetic hypertension. *Am J Hypertens* 1991; **4**: 212S–216S.

## PC.06. Statin therapy does not significantly alter microvascular function in grade 1 hypertension

**Caroline Bleakley, Vivienne McClenaghan, Aaron McCann, Rick Plumb, Mark Harbinson and Gary McVeigh**

*Queen's University Belfast, Northern Ireland, UK*

**Background:** Young patients with uncomplicated hypertension are frequently exempt from statin therapy as they generally fall below current treatment thresholds. This study examined whether there may be evidence of improved microvascular function in young patients with grade 1 hypertension following 12 weeks of statin therapy.
**Methods:** This was a randomised double blind placebo controlled crossover study in which 42 statin naïve subjects with grade 1 hypertension were randomized to receive either simvastatin 40 mg or a placebo for 12 weeks, followed by a four week washout period, after which the arms crossed for a further 12 weeks. Measures of vascular function were recorded at the beginning and end of each study period equating to four measures in total. The brachial artery was studied by flow-mediated dilatation (FMD) together with the resistive and pulsatility indices and mean velocity of flow.
**Results:** Statin therapy did not significantly alter the change in FMD seen in the brachial artery (standardised differential mean 0.02 (0.23), confidence interval −0.45 to 0.48, $P=0.932$). No significant changes were seen in the brachial artery mean velocity (CI −9.68 to 11.51, $P=0.861$), resistive index (CI −0.11 to 0.12, $P=0.903$), or pulsatility index (CI −5.82 to 4.91, $P=0.864$).
**Conclusion:** This study did not demonstrate any significant changes in established measures of microvascular function after treatment with a statin in a young hypertensive population with no antecedent cardiovascular disease. This may indicate that either the intervention was insufficiently vasoactive to produce a clinically detectable improvement in vascular function, or that the means used to assess the microvasculature were insufficiently sensitive to detect what may have been quite minor changes.

## PC.07. Effect of glyceryl trinitrate on outcome in acute stroke by time to treatment: an individual patient data meta-analysis

**Philip MW Bath, Lisa Woodhouse and Kailash Krishnan**

*University of Nottingham - Stroke, Division of Clinical Neuroscience, Nottingham, UK*

**Background:** Nitric oxide (NO) is a candidate treatment for acute stroke due to its multimodal activity, including vasodilator, blood pressure lowering and neuroprotection. Glyceryl trinitrate (GTN), a NO donor, has been studied in several trials in patients with ultraacute, hyperacute, acute or subacute stroke.
**Methods:** Randomised controlled trials of GTN versus control were identified through electronic searches of databases and individual patient data collated. The effect of GTN on outcome (modified Rankin Scale, mRS; Barthel Index, BI) and blood pressure were assessed both overall and in pre-specified subgroups, including by time to treatment. Data are number (%) or mean (standard deviation).
**Results:** Five trials (4 phase II, 1 phase III) were identified, these involving 4,197 patients (GTN 2113, no GTN 2084) treated with acute or subacute stroke: age 70 (12) years, male 57%, Scandinavian Stroke Scale 32 (12), patients enrolled within 6 hours 314 (7%). Individually, GTN significantly improved the mRS in one small trial ($n=41$) of ultra-acute treatment (<4 hours) and had no effect on mRS in 3 other small trials when administered later than 6 hours. The primary results of the large ENOS trial ($n=4{,}011$, including $n=273$ enrolled <6 hours) have yet to be presented thereby precluding reporting of outcome data at this stage.
**Conclusion**: The overall results of this individual patient data meta-analysis will be available to present in September 2014.

## PD.01. Chemerin: more than just a chemokine

**Amanda Kennedy, Rhoda Kuc, Janet Maguire and Anthony Davenport**

*University of Cambridge, Cambridge, UK*

Targeting G-protein coupled receptors (GPCRs) has made significant advances in cardiovascular disease treatment, but there is still no cure. Orphan GPCRs with unknown functions could prove to be successful drug targets. Hypertension is a risk factor for coronary artery disease and the single most important cause of stroke. The GPR1 gene has been linked to hypertension. It has been proposed to be a

receptor for the endogenous peptide chemerin. Chemerin is also known to act through a second GPCR, CMKLR1. This study will localise GPR1 and CMKLR1 in the human vasculature, and understand the function of these novel transmitter systems.
Using a β-arrestin binding assay, chemerin was found to bind to either GPR1- or CMKLR1-transfected CHO-K1 cells with sub-nanomolar potency, and the antagonist CCX832 was confirmed to be CMKLR1-selective. Immunofluorescence double staining of human vessels showed GPR1 and CMKLR1 have a similar expression pattern; present in both vascular smooth muscle cells and endothelial cells. qPCR analysis revealed that there was more CMKLR1 than GPR1. Vascular reactivity of chemerin(145–157) was investigated using endothelium-denuded human saphenous vein, in organ baths, and caused constriction with $pD_2 = 10.69 \pm 0.18$, $n = 18$.
This work reveals widespread expression of GPR1 and CMKLR1 in human vessels. Chemerin binds to both receptors, and has been shown for the first time to cause potent constriction of saphenous vein. The selective antagonist provides a useful tool to investigate which receptor is involved in the transmission of the chemerin vascular response. This will direct further research into a possible new therapeutic target for hypertension.

## PD.02. Blood serum concentrations of vasoregulators CNP and ET-1 in women with Essential Hypertension after menopause with PPAR-γ different genes inheritance

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Blood serum concentrations of vasodilator CNP and vasoconstrictor ET-1 are largely controlled by peroxisome proliferator-activated receptor gamma (PPARG).
**Aim:** To evaluate levels of CNP and ET-1 in blood serum at inheritance of different genes that control properties and expression of polymorphysm PPAR-γ in women with Essential Hypertension.
**Methods:** The study population consisted of 181 women after menopause at 45–65 years who live in Vinnitsa region, Ukraine. All patients were divided into three groups: I -control group consisted of 80 women without any evidences of HT, II group- 51 women with I stage, III group – 50 women with II-III uncomplicated Essential Hypertension. Genotyping of PPAR-γ gene was amplified by polymerase chain reaction (PCR). Concentrations of CNP and ET-1 in blood serum was conducted with immunoassey.
**Results:** PPAR-γ allele Ala was twice frequent in females in menopause with Essential HT of I-II-III stages versus practically healthy subjects (20.59%, 20% Ta 9% respectively, $P<0.05$) and seldom – allele Pro (respectively 79.41%, 80% Ta 91%, $P<0.05$).
Women with Essential HT had higher levels of CNP and ET-1 versus healthy subjects ($P<0.05$). CNP level at I stage Essential HT patients with PRO/PRO genotype was lower versus carries of Ala genotype ($P<0.05$). ET-I concentration was higher and CNP-lower in II-III stage Essential HT patients versus I stage Essential HT that indicated imbalance in the system of vasoconstrictor/vasodilator without any prevalence in certain PPAR-γ genotype inheritance.

## PE.01. The Stem Cell Gene, LGR5, is the most specific marker of Human Adrenal Zona Glomerulosa, and may drive loss of aldosterone through Non-Canonical Wnt Activation

**Lalarukh Haris Shaikh[1], Ada Teo[1], Grahame McKenzie[2], JunHua Zhou[1], Sudeshna Guha Neogi[3], Ian McFarlane[3], Nichola Figg[4], Elena Azizan[1], Anthony Davenport[1] and Morris Brown[1]**

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**Background:** Zona glomerulosa (ZG)-like aldosterone-producing adenomas, with common somatic mutations in *CACNA1D* or *ATP1A1*, may be a consequence of high turnover of adrenocortical cells (1). We aimed to compare by microarray the transcriptomes of ZG vs zona fasciculata (ZF) and to examine effects on aldosterone production of up-regulated genes in the Wnt signalling pathway.
**Methods:** RNA from ZG and ZF of 20 human adrenals was analysed by Affymetrix microarray. Genes up-regulated in ZG were validated by qPCR and immunohistochemistry. Functional analysis

was performed using Wnt-pathway proteins. Measurements included aldosterone secretion and luciferase activity in cells transfected by constructs carrying either canonical or noncanonical Wnt promoters.
**Results:** LGR5, a Wnt signaling target and stem cell marker, was the most up-regulated gene in ZG (x25.0, ($P=10^{-23}$) vs. paired ZF. Its cognate ligand, RSPO3, (x5.27, ($P=10^{-11}$) was also expressed in ZG. Immunohistochemistry confirmed localisation of LGR5 in ZG (Figure 1). Inhibition of the canonical WNT pathway reduced aldosterone ($P=10^{-5}$). RSPO3 and over transfection of LGR5 caused inhibition of aldosterone ($P<0.05$). Wnt non-canonical AP1 signalling showed a 5.7 fold increase in LGR5 transfected cells ($P=0.001$).
**Conclusion:** LGR5 is the most ZG-selective gene in human adrenal. Our results suggest that LGR5 switches Wnt signaling from canonical to noncanonical, and that this results in cell loss and inhibition of aldosterone production. The switch may be a protective response to high salt intake, and is reversed by some of the somatic mutations causing constitutive production of aldosterone in adrenal adenomas.

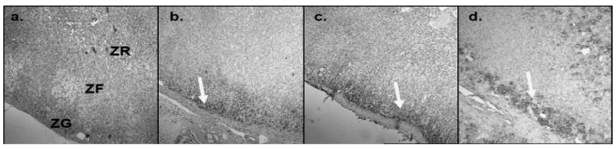


**Figure 1.** Staining of the human adrenal, where ZG: zona glomerulosa, ZF: zona fasciculate, ZR: zona reticularis. (**a**) Haemotoxylin and Eosin staining showing human adrenal histology. Commercial antibodies for LGRS used are the following (**b**) Novus Biologicals (NBP1-28904) polyclonal rabbit (**c**) Abcam (ab75732) polyclonal rabbit (**d**) Origene (TA503316) monoclonal mouse.

1. Azizan *et al. Nat Genet* 2013; **45**(9):1055–1060.

## PE.02. Continue or stop pre-stroke antihypertensive therapy in acute stroke: Main results from the Efficacy of Nitric Oxide in Stroke (ENOS) Trial

**Philip MW Bath, Lisa Woodhouse, Sally Utton and Nikola Sprigg**

*University of Nottingham - Stroke, Division of Clinical Neuroscience, Nottingham, UK*

**Background:** A majority of patients are taking antihypertensive medication before their stroke. However, management of such treatment(s) remains unclear and is the subject of the ENOS trial.
**Methods:** ENOS is an international multicentre prospective randomised open-label blinded-endpoint trial. Patients with acute ischaemic stroke (IS) or intracerebral haemorrhage (ICH), systolic BP 140–220 mmHg, and taking antihypertensive therapy immediately before their stroke were randomised to continue or stop this for 7 days; all patients were also randomised to transdermal glyceryl trinitrate (GTN) or no GTN (single-blind, results reported separately). The primary outcome is shift in modified Rankin Scale at 3 months. Patients or relatives gave written informed consent and all sites had research ethics approval. Analysis is by intention-to-treat.
**Results:** 2,097 patients were enrolled from 152 sites in 23 countries across 5 continents between July 2001 and October 2013 (with 82% patients recruited from start of 2007). At baseline: age 73 (SD 11); male 51%; recruitment from Asia 10%, Europe 19%, UK 65%; number of BP drugs before stroke, 1: 44%, 2: 35%, 3: 16%, 4: 4%, >4: 1% (median 2); angiotensin modifier 64%, beta-blocker 39%, calcium channel blocker 35%, diuretic 35%, alpha-blocker 7%,; prior stroke 20%; diabetes 23%; atrial fibrillation 22%; mean BP 167 (19)/88 (13) mmHg; severity (Scandinavian Stroke Scale) 33 (13)/58; total anterior circulation syndrome 33%; IS 85%, ICH 12%; median time to recruitment 26 (IQR 20) hours.
**Summary:** The main results will be available for presentation in quarter 2 2014. ENOS is large enough to influence clinical practice.

## PE.03. The Potential Contribution of Vascular Growth Factors in relation to previous Maternal Malaria Exposure to Change in Blood Pressure (BP) in Nigerian Children over the first 3 Years of Life

**OO Ayoola[1], AJ Whatmore[1], J Farikullah[1], O Omotade[2], I Butcher[1], H Soran[3], PE Clayton[1] and Kennedy Cruickshank[4]**

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Where malaria is endemic in sub-Saharan Africa, hypertension is common. In our Nigerian cohort, maternal malaria resulted in smaller babies with lower blood pressure (BP) at birth,

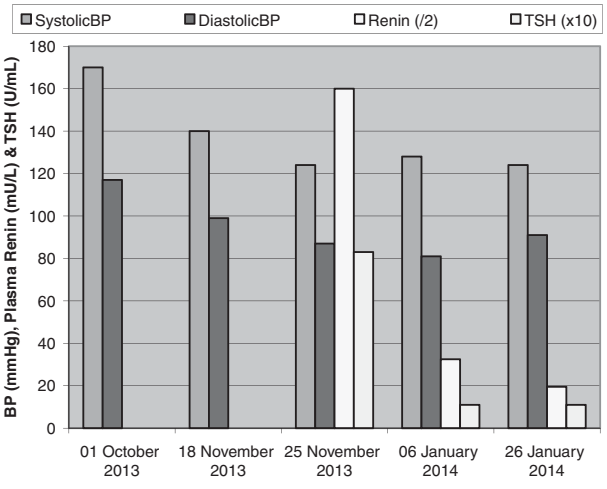
but greater change(Δ) in BP to 12 months independent of growth. We tested whether effects from malarial exposure persisted to age 3y and whether it could be mediated via vascular growth factors (VascGFs).
Height, weight and BP were measured on 164 babies (89 female) at all 4 time points - birth, 12, 24 and 36 months. Vasc GFs, epidermal (EGF), prominent in malignant vascular growth, hepatocyte GF(HGF)and placental GF (PlGF)s, were measured at 12 months, Effects of malaria (52% exposed) on BP and ΔBP were compared via backward regression for independence from growth, adjusting for regression to the mean.
ΔsysBP over 0–12 m was higher in babies exposed to malaria ($19 \pm 14$ vs $14 \pm 17$ mmHg, no malaria; $P = 0.03$) and persisted to 36 months ($25 \pm 13$ vs $18 \pm 15$ mmHg; $P = 0.002$). ΔsysBP over 0–36 months was lower in females (Δ20 mmHg) than males (Δ23 mmHg) but the impact of malaria was more pronounced in females ($+8.7$ mmHg with malaria; $P = 0.003$) than males ($+5.0$ mmHg; $P = 0.15$).
ΔsBP over 0–36 m was no longer positively related to malarial exposure but was inversely to EGF levels when included in the regression (β (SE) −0.17 (0.007)mmHg/pg/ml, $P = 0.012$) independent of growth.
Changes in systolic BP are greater in children exposed to maternal malaria than those not, more pronounced in girls than boys. This increased ΔsysBP may be mediated in part by lower EGF levels.

## PE.04. Subacute hypertension caused by hypothyroid-induced endothelial dysfunction unmasking presumed fibromuscular dysplasia of the renal artery

**Morris Brown and Jackie Salsbury**

*University of Cambridge, Cambridge, UK*

**Objective:** Hypothyroidism is associated with recent smoking cessation, and may be an under-recognised cause of hypertension as a result of endothelial dysfunction.
**Methods**: A 44 year-old woman presented with severe headache and BP 150/110 mmHg. Six months earlier BP was 100/60 mmHg. She had stopped smoking 10 months earlier, and complained of weight gain, alopecia, and fatigue.
The GP confirmed hypertension (BP 170/117 mmHg), and prescribed bisoprolol 5 mg. This caused extreme fatigue with syncope, and was changed to lisinopril 5 mg.
On clinic referral, BP was 140/99. No bruits were audible. Fundoscopy showed reduced branching angulation. Treatment was changed to losartan/HCTZ 50/12.5 mg. Two weeks later, BP was 124/87 mmHg.
**Results and Outcome**: Renin 320 mU/L (5–60) Aldosterone 222pmol/L (100–450), TSH 8.3 (0.35–5.5), FT4 13.1 (10–19.8), Anti Thyroid Peroxidase 300 (0–100).
Thyroxine 25–50 micrograms was prescribed. MR of the renal arteries showed a possible stenosis on the left, suggestive of fibromuscular dysplasia (FMD). Renal angioplasty (if stenosis confirmed) was planned. However, symptoms were much improved, BP remained low, and the HCTZ was discontinued. Repeat TFTs and renin were normal (T4 17.1, TSH 1.1, renin 65 mU/L on losartan/HCTZ, 39 mU/L on losartan). A MAG3 renogram after captopril showed slight reduction in uptake on the left, not present on the baseline scan. Angioplasty was cancelled.
**Conclusion:** We believe that subacute onset of hypothyroidism unmasked renal artery stenosis by impairing function of abnormal endothelial cells covering an area of FMD. The increase in renin/angiotensin would further impair function, setting up a 'vicious spiral' that explains the rapid onset of symptomatic hypertension, and reversal by thyroxine and low-dose losartan. The case illustrates the value of plasma renin and TFT analysis.



## PE.05. Frequency of Haematomata following Pacemaker Insertion on Warfarin

**Helen Parry and Douglas Elder**

*Ninewells Hospital and Medical School, Dundee, UK*

**Introduction:** Traditionally warfarin has been stopped several days prior to permanent pacemaker insertion due to the increased risk of haematoma formation and haemopericardium. Recent studies have shown relatively low risk of haematoma formation following pacemaker insertion in patients with high stroke risk who continue wafarin therapy relative to those who were bridged with heparin during the peri-procedural period.

**Objectives:**
(1) To determine the rate of haematoma formation in patients undergoing pacemaker insertion whilst taking warfarin in Ninewells Hospital Dundee
(2) To determine whether haematoma formation on warfarin was associated with an INR outside the therapeutic range.
**Methods:** All individuals with an INR $>1.8$ at the time of pacemaker insertion were identified for the 2 year period 01 April 2012 to 31 March 2014. Records of all complications following pacemaker insertion in Ninewells Hospital during this period were reviewed to identify all patients who developed haematoma post-pacemaker insertion. The rate of post-procedural haematoma formation for individuals continuing warfarin was calculated.
**Results:** A total of 599 pacemaker procedures were performed during this period and 45 of these procedures were in patients taking warfarin with therapeutic INR. Two of these 45 individuals (4.4%) developed haematomata following pacemaker insertion. Both these patients had an INR between 2 and 3 at the time of the procedure. Our complication rates compare well with the previously published rate of 3.5% (1). The overall rate of post-pacemaker haematoma formation at Ninewells was 1.5% during this period.
**Conclusions:** Haematoma formation in patients who continue warfarin at the time of pacemaker insertion is uncommon and is not related to over-anti-coagulation.

1. Birnie *et al.* Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013; 368:2084–2093:

## PE.06. The cardiovascular consequences of Pre-eclampsia Study (COPS) - a summary of the vascular studies to date

**Catriona Brown[1], Joanne Flynn[1], Gemma Currie[1], David Carty[1], Generation Scotland[2] and Christian Delles[1]**

*[1]University of Glasgow, Glasgow, UK and [2]Generation Scotland, Scotland, UK*

**Background:** Women with a history of pre-eclampsia are at higher risk of cardiovascular diseases later in life. We evaluate the cardiovascular health of women who had pre-eclampsia in comparison with women who had normotensive pregnancies.
**Methods:** Women (target: $n=160$) are being recruited from the previous Proteomics in Pre-eclampsia (PIP) study, the Generation Scotland Scottish Family Health Study and the Glasgow Blood Pressure Clinic (pregnancies 1–5, 10–30 and 1–30 years ago, respectively). We assess carotid intima-media thickness (CIMT), brachial flow-mediated dilatation (FMD), carotid-femoral pulse wave velocity (PWV) and heart rate-adjusted augmentation index (AIx).
**Results:** To date 90 women (62 cases, 28 controls) have participated. Age ($46 \pm 10$ *vs* $43 \pm 5$ years; $P=0.06$), BMI ($29.7 \pm 6.7$ *vs* $27.7 \pm 4.7\,kg/m^2$; $P=0.17$), systolic ($129 \pm 14$ *vs* $122 \pm 11$ mmHg; $P=0.04$) and diastolic blood pressure ($82 \pm 9$ *vs* $78 \pm 8$ mmHg; $P=0.08$) are similar in cases and controls and current diagnosis of hypertension is 31% and 11% ($P=0.06$). There is no significant difference in CIMT (*P*-values 0.07, 0.13 and 0.61 at the CCA, bulb and ICA, respectively), and in the first 23 cases and 20 controls there is no difference in FMD ($P=0.92$). AIx is similar ($P=0.10$) whereas PWV is different between cases and controls ($7.7 \pm 1.5$ *vs* $7.0 \pm 0.9$ m/s; $P=0.02$) but not on age-adjusted analysis ($P=0.15$).
**Conclusions:** We are currently unable to demonstrate significant differences in vascular function and structure parameters between women with and without history of pre-eclampsia. Further studies will explore whether altered biomarker profiles in this cohort of women 1–30 years post pre-eclampsia could explain their higher cardiovascular risk.

## PE.07. Management of uncontrolled blood pressure in patients referred to a specialist hypertension clinic with multiple medicines intolerance

**Sotiris Antoniou[1], Nadya Hamedi[2], Romana Choudhury[2], Satnam Lidder[1], Manish Saxena[1], Timothy Brier[3], Paul Robinson[1], Vikas Kapil[3] and Melvin Lobo[1]**

*[1]Barts Hypertension Clinic, St Bartholomew's Hospital, Barts Health NHS Trust, London, UK; [2]Department of Pharmacy, London Chest Hospital, Barts Health NHS Trust, London and UK, [3]William Harvey Research Institute, Centre for Clinical Pharmacology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK*

**Introduction:** Many patients report intolerance to anti-hypertensive medicines at standard doses. We developed a protocol to manage multiple medicines intolerance with *n-of-1* trials of: fractional tablet dosing, liquid formulations and trans-dermal formulations of standard anti-hypertensive medicines. We report the blood pressure (BP) control of patients referred to our hypertension clinic with uncontrolled BP due to multiple medicines intolerance.
**Methods:** We retrospectively analysed clinic letters for the first 25 patients with a diagnosis of multiple medicines intolerance who had at least 3 clinic visits. Clinic BP and any modification to treatment were extracted. Changes in clinic BP from baseline through to subsequent visits was analysed. Data are expressed as mean ± SD.
**Results:** 25 (15 female) patients (mean age 62.1 ± 12.0 yrs) were intolerant of 6.3 ± 3.6 anti-hypertensive medicines at first visit with baseline clinic BP of 170 ± 21/98 ± 15 mmHg. Patients had 4.6 ± 1.5 follow-up visits over 1.2 ± 1.0 yrs. Clinic systolic/diastolic BP (SBP/DBP) were reduced compared to baseline over entirety of follow-up ($P<0.001$, $P=0.05$ respectively, Table 1).
**Discussion:** Fractional tablet dosing may target multiple physiological pathways but minimise dose-dependent adverse effects. Liquid formulations avoid excipients that may contribute to adverse effects and trans-dermal patches overcomes gastro-intestinal intolerance associated with tablets. This is the first dedicated anti-hypertensive protocol for high risk patients with multiple medicines intolerance and application of our novel strategy demonstrated improved BP control consistently over subsequent visits.

**Table 1.** Change in clinic systolic and diastolic BP compared to baseline

| Visit (n) | 2 (25) | 3 (25) | 4 (19) | 5 (13) | 6 (8) |
|---|---|---|---|---|---|
| ΔSBP (mmHg) | −3.9 ± 17.9 | −14.6 ± 28.1 | −20.0 ± 20.8 | −27.2 ± 21.9 | −25.6 ± 31.7 |
| ΔDBP (mmHg) | −0.9 ± 13.1 | −5.2 ± 15.0 | −8.6 ± 17.5 | −13.3 ± 19.3 | −7.1 ± 21.1 |

## PE.08. Highly variable response to renal denervation for resistant hypertension – real world experience from 2 UK centres

**Amy Burchell[1], Kenneth Chan[2], Laura Ratcliffe[1], Emma Hart[1], Manish Saxena[2], David Collier[2], Ajay Jain[3], Anthony Mathur[3], Charles Knight[3], Mark Caulfield[2], Julian Paton[1], Angus Nightingale[1], Andreas Baumbach[1] and Melvin Lobo[2]**

*[1]Bristol Heart Institute, Bristol, UK; [2]William Harvey Research Institute, London, UK and [3]London Chest Hospital, London, UK*

**Objective:** Renal denervation (RDN) is aimed at treating resistant hypertension (rHTN). Symplicity HTN-1&2 studies reported response rates of 92% at 24 months and 84% at 6 months post RDN, respectively. We investigate the real world outcomes of RDN from two UK centres.
**Methods:** Rigorous screening of 352 patients identified 29 patients with rHTN (office blood pressure (OBP) >160/90 mmHg, ≥3 antihypertensives) suitable for RDN. Following RDN (Symplicity (Medtronic) catheter), patients were reviewed at 1, 3, 6 and 12 months with outcome measures of both OBP and ambulatory BP (ABPM).
**Results:** Six months post RDN 52% of patients (15/29) responded with a mean change in OBP of −13/−5 [−25,−2/−12,1] mmHg. Significant correlations between change in office SBP and baseline ($R=-0.47$, $P=0.01$) and number of ablations ($R=-0.56$, $P=0.002$). Change in mean 24hr ABPM at six months ($n=13$) −12/−7 [−24,0/−14,1] mmHg. ABPM correlation between baseline daytime diastolic BP and change in 24 hr SBP ($R=-0.69$, $P=0.009$).
**Conclusions:** RDN is a safe treatment for rHTN but ~90% response rates from the Symplicity studies could not be replicated. Individual responses to

RDN are highly variable with non-responders/reverse responders identified. Baseline oSBP best predicts BP response, whilst diastolic ABPM predict a reduction in 24hr BP post RDN. Reverse responders had fewer ablations which should impact on future catheter design. Markers of procedural success and improved patient selection parameters are key research aims.

## PE.09. The high prevalence of Primary Amyloidosis among Afro Caribbean Heart Disease

**Sukhneet Randhawa[1], Girish Dwivedi[3], Desley Neal[2], Rick P Steeds[2] and Robert J MacFadyen[4]**

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**Background**: Primary amyloid (A) is a rare infiltrative disease in late adult life affecting the heart and other tissues diagnosed by tissue analysis of the affected organ. We reviewed our echocardiographic database of hypertensive Afro Caribbean (AC) patients seen with heart failure symptoms to define prevalence of this disease using accepted biopsy and/or MRI criteria.
**Method**: From ethnicity specific heart failure service records (from $n = 106$ total subjects) we identified 86 AC subjects with a complete trans-thoracic (TT) echo dataset. A was defined by typical TT echo criteria and confirmed by positive RV septal tissue histology at biopsy and or typical features on late gadolinium MRI (reported independently). Cases positive for A (28) were compared to negative (58) controls (C) by multivariate regression (MVr).
**Results**: We found a high prevalence (33%) of A($n = 29$;18male;$68 \pm 17$ yr;Y $\pm$ Ykg) compared to C($n = 58$;39male;$71 \pm 16$ yr;Y $\pm$ Ykg) in this sample. Both demographic criteria (age;gender;body mass;blood pressure) and a range of standard TT echo measures of morphology (LVDDd LVDDs) or function (ePAP; Simpsons LVEF) were similar on MVr. Only septal (IVSs;A,$1.86 \pm 0.77$;C,$1.45 \pm 0.39$; IVSd A,1.7(1.4–1.9 cm);C,1.1 (1.0–1.4 cm)$P = 0.033$) and PW thickness (LVPWs A,$1.89 \pm 0.69$;C,$1.44 \pm 0.61$;LVPWd A $1.63 \pm 0.38$;C,$1.23 \pm 0.55$ $P = 0.002$ ) were significantly higher in A. LV internal diameters (d and s) were lower in A than C. Renal function was poorer in A cases (Urea A,13.5,7.9–21.3 mM; C 8.5, 6.5–12.9 mM $P = 0.02$; Creat A,188,115–401; C,119, 98–155 μM; $P = 0.004$). Notably in our series neither atrial volume nor inter atrial septal wall thickness were recorded routinely despite their known sensitivity and specificity in the TT echo diagnosis of A.
**Conclusion**: We have recorded an unusually high retrospective prevalence of A in elderly AC heart disease patients with HF symptoms. Given the development of specific treatments for this condition all clinicians seeing AC patients with abnormal TT echo should consider biopsy and/or MRI in suspicious cases.

## PE.10. Results of the REPAIR Randomised Controlled Trial - Renal Protection Against Ischaemia Reperfusion in Transplantation

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Long-term kidney allograft survival has remained unchanged in recent years despite immunosuppressive and surgical advances. Ischaemia reperfusion (IR) injury sustained at the time of transplantation contributes to graft fibrosis which limits allograft lifespan. Interventions to reduce IR injury may therefore prolong graft life, delaying the need for a return to dialysis, with its incumbent risks and reduction in patient quality of life. Remote ischaemic preconditioning (RIPC), is a whole-body protective reflex that is activated in humans by non lethal ischaemia applied to the arm or leg. It has been reported to prevent tissue IR injury in small-scale clinical trials. REPAIR (Renal Protection Against Ischaemia Reperfusion in Transplantation), a multicentre, multinational randomised trial, investigated

whether RIPC improves kidney function and other clinical outcomes following renal transplantation.
REPAIR recruited 406 live donor/recipient pairs (original target 400). Each pair was randomised using a factorial design to four groups: control (sham RIPC), RIPC immediately prior to surgery, RIPC 24 hours pre-surgery or dual RIPC. The RIPC stimulus consisted of four 5 minute inflations of a blood pressure cuff on the upper arm to 40 mmHg above systolic blood pressure separated by 5 minute deflations. The sham procedure consisted of four inflations to 40 mmHg separated by 5 minute deflations.
By May 2014 all patients will have completed 12 month follow up. Results will be presented on the primary endpoint of glomerular filtration rate (GFR) using iohexol clearance at 12 months post-transplant together with the pre-specified secondary endpoints. The findings of REPAIR will establish whether this simple, non-invasive and virtually cost free intervention can improve graft function, and ultimately lead to prolonged allograft life in these patients, with resultant economic and quality of life benefits. The findings will also have implications for the use of RIPC in other ischaemic syndromes.

## PE.11. Early reduction in blood pressure and heart rate variability following multi-electrode radio-frequency renal denervation in medicines intolerant patients

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**Aim:** Percutaneous sympathetic renal artery denervation(RDN) is a novel treatment for patients with resistant hypertension (HTN). Trials to date have excluded patients with medication intolerance as they do not meet criteria for resistance, so this group has not been studied, despite high CV risk, but few treatment options. We studied the safety & efficacy of RDN using a multi-electrode catheter ablation system in patients with essential HTN & multiple drug intolerances at our centre, a previously unstudied group.
**Methods & results:** This is a substudy of the EnligHTNII study which is a postmarket study evaluating safety & effectiveness of EnligHTN RDN System in patients with uncontrolled HTN. Subjects with uncontrolled HTN (office systolic BP $\geq$ 140 mmHg and daytime mean systolic ambulatory BP $\geq$ 135 mmHg) were suitable for the study. As of 1/2/14, 8 patients from our centre, with multiple drug intolerance in this substudy of EnligHTNII study have been treated with the EnligHTN RDN system. Currently there are 6 patients in the intolerant group with 3 month follow-up data (not a scheduled protocol visit). The average age is $62.6 \pm 5.2$ years; average BMI is 25; average numbers of antiHTN medications is 0.7 for this sub-group. Of the 6 subjects, 5 are female, 5 Caucasians & 1 south Asian. None had known CAD, but 5 had GORD, 3 had previous cancers (breast, thyroid, melanoma) & 2 had chronic lower back pain. Baseline office systolic BP (OBP) averaged $183.1 \pm 20$ mmHg & baseline average 24 hour ambulatory systolic BP was $155.8 \pm 13.1$ mmHg. At 3 months, the average reduction of systolic OBP was 6.7 mmHg ($P$ = n.s.) & 24hr ABPM daytime systolic 2.8 mmHg ($P$ = n.s.). At 3 months,the SD of daytime SBP on 24hour ABPM was reduced by 3.2 mmHg ($P < 0.05$,CI 0.5 to 5.8) & the average fall in the SD of daytime HR on 24 h ABPM was 1.1 bpm ($P < 0.05$ CI 0.1 to 2.0). So far in this sub-group, there have been no procedure related events or any complications.
**Conclusions:** This study demonstrates that the EnligHTN RDN system is safe in the treatment of medication intolerant patients with uncontrolled HTN. Whilst, in this small cohort, the mean clinic & 24 h ABPM averages are not significantly reduced at 3 months, the reduced variability in daytime systolic ABP is encouraging. Reduction of BP variability has been associated with reduced CV events especially stroke. This cohort represents a high risk subset of the hypertensive population and this is the first study of its kind to address the critical issue of how to improve BP control in those patients for whom no pharmaco-therapeutic options are available.

## PE.12. Appropriateness of remote electrocardiographic monitoring in a District General Hospital setting

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**Introduction:** Remote electrocardiographic monitoring (''telemetry'') can identify life threatening arrhythmias in patients. Published guidelines for the use of telemetry are available, although their application is not universal. This study aimed to identify use of telemetry in a

large district general hospital in comparison to established guidelines.

**Methods**: Prospective single centre study of telemetry requests in a 2-month period for patients admitted to a general medical or surgical bed. We established patient demographics, indications for the request, clinical outcome and the duration of recording. Each request was categorised into class I (definitely indicated), class II (may be indicated) or class III (not indicated), according to the American Heart Association (AHA) guidelines.

**Results:** There were 48 patients (19 male, 29 female) with median age 77.8 years. Mean duration of monitoring was 3.6 days with a mean gap in recording of 11 hours. 21% of patients with no significant findings were kept on telemetry longer than the recommended 72 hours. 60.5% of requests were class I, 12.5% class II and 27% class III. Only 1/18 patients in the class II and III groups had a rhythm disturbance that required active treatment. In 14% of patients on telemetry cardiopulmonary resuscitation was not deemed to be appropriate by the team looking after them.

**Conclusion:** Telemetry is requested inappropriately in almost 1 in 3 patients and unplanned gaps in monitoring are considerable. Clear local guidelines and a formal education programme on the use of telemetry may improve this, and should be the subject of further study.