Targeting elderly women: delay time between symptom onset of an acute ST elevation myocardial infarction and hospital arrival.

Findings from the multicentre MEDEA Study.

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Abstract

Background: Early administration of reperfusion therapy in acute myocardial infarction is crucial to reduce AMI mortality. Although female sex and old age are key factors contributing to an inadequate long prehospital delay time, little is known whether elderly women are a particular risk population.

Objectives: We studied the interaction of sex and age (<65y/≥65y) and the contribution of the absence of chest pain to delay time during acute ST-elevation myocardial infarctions (STEMI).

Patients and Methods: Bedside interview data were collected in 619 patients with STEMI from the *Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction (MEDEA) study*.

Results: Sex and age group stratification disclosed an excess delay risk for elderly women accounting for a 2.39 (95% CI, 1.39-4.10) -fold higher odds to delay longer than two hours compared to all other patient groups including younger women ($p \leq 0.002$). Median delay time was 266 min in elder and 148 min in younger women ($p< 0.001$). Chest pain during STEMI had the lowest frequency both in elderly women (81%) and older men (83%) and highest frequency (95%) in younger women. Elderly women's risk of non-chest pain was 2.32 fold (95% CI 1.20-4.46, $p<0.05$) higher compared to all other patients. Mediation analysis disclosed that the effect accounted for only 9% of the variance.

Conclusion: Age specific educational strategies targeting elderly women at risk are urgently needed. In order to tailor adequate strategies more research is required to understand specific age and sex driven barriers to timely identification of ischemic symptoms.

Condensed Abstract:

In order to study the interaction of sex and age as contributing factors to prehospital delay time in acute ST-elevation myocardial infarction (STEMI) patients, we analysed bedside interviews data from 619 patients immediately post STEMI. Women per se were at not at greater risk to delay their hospital admission and did not present more "atypical" symptoms. Although they experienced more non-chest pain infarctions, this contributed marginally to delay time variance. The combined effect of older age (≥65y) and female sex created a particular risk population: elderly women experienced an excess summit in delay time compared to men and even stronger compared to younger women.

Key words: ST-elevation myocardial infarction; prehospital delay time, sex and age differences, symptom pattern, non-chest pain infarction

Abbreviations:

STEMI: ST-elevation myocardial infarction
MEDEA: Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction Study
PHD: prehospital delay
CPC: chest pain characteristics

Introduction

Early administration of reperfusion therapy in acute myocardial infarction (AMI) is crucial to reduce AMI mortality and morbidity [1]. A major barrier to early treatment is the time that patients take to decide seeking appropriate medical care. Estimates point to a proportion of about 75% of pre-hospital delay time which may be caused by deficits in the patients' subjective decision making [2].

Female sex and old age are widely acknowledged as major key factors contributing to an inadequate long prehospital delay time. A systematic review on this topic disclosed that female sex and old age were significant contributors to arrive at the hospital with substantial delay [3] although the authors also ascertained a substantial number of studies which did not confirm these findings. Surprisingly, a paucity of studies focused on the effect of the interaction between age and sex on delay time. It remains widely unexplored whether women per se are at greater risk to delay longer or whether a synergistic effect of female sex in combination with older age creates the vulnerable target population at greater risk for prolonged delay to hospital arrival after onset of an AMI.

Most research to date on barriers to react adequately in the face of an acute event has been dedicated to sex differences in acute symptom presentation [4]. Systematic reviews showed that women are more likely than men to report shortness of breath, nausea or vomiting and jaw and neck pain [5,6] which has prompted many clinicians to believe that women may report more “atypical” symptoms of AMI. However, more recent work failed to find discernible patterns of non-chest pain symptoms in AMI between men and women [7]. Possibly more important are findings showing that significantly more women than men may experience an AMI *without* chest pain [7,8]. However, the clinical relevance of an AMI without chest pain and its impact on delay time remains questionable [9] and may even be in part due to a reporting bias [10,11].

Therefore, the first aim of the present investigation was to investigate whether a synergistic effect of female sex in combination with older age creates the highly vulnerable target population. The second aim was to disentangle whether a particular symptom pattern or the absence of chest pain in the most critical sex and age stratified subpopulation contributes substantially to delay.

Patients and Methods

The multicentre, cross-sectional MEDEA study (*Munich Examination of Delay in Patients Experiencing Acute Myocardial Infarction*) was conceived with the aim to document the prehospital delay of patients with STEMI, and the factors which may contribute to prolonged delay.

Study design

The patients were recruited from eight different university or municipal hospitals with coronary care units, belonging to the Munich emergency system network clinics. The MEDEA study was approved by the Ethic Commission of the Faculty of Medicine of the Technische Universität München (TUM) on 10.12.2007 and the consent of the Munich Institut für klinische Forschung (IKF) for the participating four municipal hospitals (9.4.2008). The main inclusion criterion was diagnosis of STEMI as evidenced by typical clinical symptoms, ECG changes and myocardial biomarkers levels. Exclusion criteria were: In-hospital STEMI, resuscitation at AMI-onset and language barriers or cognitive impairment impeding patients to answer the questionnaires properly. There were no age restrictions.

Standardized operation procedures (SOPs) were implemented to ensure the consecutive referral of eligible patients into the study. All patients were informed of the aim and procedures of the study and also that taking part in the study would have no effect on their treatment. All patients were required to sign a declaration of consent.

Sample

From 12.12.2007 until 31.05.2012, data on 619 patients who were capable of taking part in the study were collected. There were few dropouts in the study since physicians did not inform MEDEA study personnel of AMI patients who were unable to answer the study questionnaire due to their critical condition (e.g. coma). Approximately 18% of patients were excluded: 4% due to not meeting inclusion criteria and 14% due to absence of consent or missing data. Comparison of included and excluded patients showed no significant differences in age, sex, sociodemographic, clinical and other relevant covariates. However, included patient were more likely to have a high-education level and being employed.

Data collection

The data collection process was divided into three sections. Firstly, a bedside interview was conducted with trained personnel within 24 hours after referral from intensive care. Secondly, a self-administered questionnaire was completed by the patient in a calm and non-supervised environment. Thirdly, somatic risk factors were derived from the medical records and assessed by the medical personal of the cardiology departments.

Measures

Pre-hospital Delay (PHD)

Patients were asked to recall at what time acute symptoms began. Following the procedure as proposed by [12], we assisted patients during the bedside interview to triangulate the time of symptom onset by placing it in the context of their daily activities. The time difference between symptom-onset and first ECG in the hospital constitutes "prehospital delay" (PHD), measured in minutes. PHD time in min was heavily left-skewed and did not approximate a normal-distribution after transformations. Following recent guideline recommendations [1], we dichotomized PHD time into 2 groups (<120, and ≥120 minutes.) (Table 4)

Baseline, clinical and behavioural measures

The hospital patient charts and bedside patient-interviews provided data on socio-demographic variables (educational level, employment status, living conditions and marital status), metabolic risk factors (hypertension, hypercholesterinaemia, obesity, and diabetes mellitus), and life style factors (smoking, physical inactivity). Prodromal and presenting symptoms were coded following the KORA format [13]. Important clinical measures on the acute course after admission to the coronary care unit were transferred from the patients chart.

Data analysis

Differences by sex and age group ((<=65y vs >65y) for dichotomous variables were assessed using the chi-square test. When comparing ordinal variables with more than two categories, the Mantel-Haenszel chi-square test was used. Differences in age were assessed using the t-test. The non-parametric Wilcoxon test was used for assessing differences in median prehospital delay times.

Logistic regression models were used to assess relative risk of perceived symptom patterns of old women compared with all the other age and sex groups. Mediation models were calculated in order to assess the intermediate effect of chest pain in the association between old women and prehospital delay. Mediation analyses were conducted in R, using the mediation package which calculated boot-strapped confidence intervals using 1000 simulations in order to increase the power of estimates. All other statistical analyses were run in SAS (Version 9.3, SAS-Institute Inc., Cary, NC, USA). The significance level α was set at .05. The analysis and the description in this paper follow the STROBE guidelines for cross-sectional studies [14].

Findings

A total of 619 STEMI patients were enrolled in the present investigation, among them 457 (73.8 %) men and 162 (26.2%) women. As displayed in Table 1, gender differences in clinical characteristics were marginal except that women were less likely to be smokers (31% vs. 42%; p=0.02). However, regarding sociodemographic factors, women were significantly older, less often employed and more likely to live alone (Table 1).

Prehospital delay time

The median delay time for men was 194 min and was 231 min for women (p=0.27). Stratification into sex and age specific subgroups disclosed an excess delay risk for elderly women (>65 years old) with a median of 266 min versus 148 min in younger women (p< 0.001). Median delay in older men was 222 min compared to 183 min in younger men (p<0.01).

As can be seen in Figure 1, elderly women had a 2.39 fold (95% CI, 1.39-4.10) higher odds to delay longer than two hours compared to all other patients (p ≤ 0.0016). The unfavourable odds for a longer delay time remained in a similar effect size compared to older and younger men. Remarkably, the comparison with younger women yielded an excess OR of 3.33 (95%

CI, 1.62-6.87; p<0.002). As displayed in the sum-percent curve (cumulative frequency) in Figure 2, the delayed arrival of the elderly women was particularly pronounced in the most critical time window up to approximately 300 min after AMI onset (p=0.01).

Symptom patterns of STEMI patients, stratified for sex and age

The symptom presentation during the acute STEMI event across all four study groups under investigation is shown in Table 2. The majority of patients experienced chest pain as a key symptom with the highest frequencies in younger women and men (94%; 95%) corresponding with lower frequencies in elderly women and men (81%; 83%), respectively. Age was also associated with chest pain perception: a significantly higher proportion of older men experienced more severe chest pain strength compared to younger men. However, sex and age attributable differences in chest pain frequency disappeared when a strict conservative measure of chest pain indicative of an AMI (with a duration of >20 min) was applied – which was experienced by only about one third of all patients.

Diaphoresis was the second most frequent AMI symptom (reaching a proportion of 65% in younger men) followed by nausea (particularly prevalent in women). Approximately one in three patients experienced new onset of dyspnoea during AMI which was least frequent in older men (22%). Only a minority of 12 to 16% of patients reported fatigue with no sex or age driven differences. Gastro-intestinal symptoms (heartburn, epigastric pain, nausea and vomiting) were more frequent in younger compared to older female patients. Except chest pain, all major AMI symptoms did not show preponderance in elderly women. Against expectation, this was also not the case for a combined gastrointestinal and sympathetic symptoms cluster – only in comparison to older men, elderly women reported a higher risk to perceive gastrointestinal symptoms (1.53 95% CI 1.07-2.19, p<0.05) (see Table3).

Non-chest pain AMI

Table 3 shows that elderly women displayed significantly increased odds to experience an AMI without chest pain compared to all other patients. Overall median delay time in patients without chest pain was 153 min and 204 min in patients with chest pain. As can be seen in Figure 3, a stratified analysis disclosed the longer delay was particularly significant in younger patients ($p \leq 0.05$).

Instead of chest pain, these patients experienced sweating (54 %), nausea (42%), dizziness (37%) and dyspnoea (30%) as the most prevalent symptoms. However, the frequency of single symptoms or its scoring (0-4) did not differ significantly between chest pain and non-chest pain patients (data not shown).

In order to investigate the reason behind the impact of sex and age differences on delay time, we conducted a mediation analysis with chest pain as a possible mediator and confirmed non-chest pain as a significant contributor to the process underlining the relationship between sex and age differences and delay time (when comparing old women to all the other patients). However, the mediation effect accounted for only 9% ($p \leq 0.08$) of the total effect. When comparing elderly women to younger women or younger men respectively, the mediation effects did not remain significant (see Table 5).

Discussion

The independent impact of sex and age as major contributing factors on delay time in arrival at an intensive care facility in face of an AMI is uniformly acknowledged in recent guidelines and scientific statements [1,2,4] as well as in systematic reviews and meta-analyses [3,5]. Notwithstanding, the present investigation evidenced that women per se are not at greater risk to delay longer, rather a synergistic combination of female sex with older age creates the vulnerable target population at greater risk for prolonged delay to hospital arrival after AMI onset. Thus, elderly women in this investigation not only reached the peak level of 266 min median delay time but also experienced the highest odds to delay compared to all other sex and age groups. It is of note that particularly compared to younger women, the target population of older women yielded the most pronounced risk of delay longer than two hours. Specifically, the risk of delay was more than three folds higher.

A surprisingly low number of investigations have provided data on this issue - except one study by Moser et al. [15] with a small sample of 194 AMI patients assessed more than one decade ago Overall this study failed to show a difference between male and female AMI patients in PHD time. However, the division of the sample into patients younger and older than 55 years disclosed an excess risk of elderly women (3.7 h) while in the younger age stratum, women in consensus with the present investigation experienced an even significantly lower delay time than men [15]. In consequence, Moser's and our findings point to a synergistic effect of age and sex as contributing to delay and clearly question the singular effect of female sex as an independent risk factor for delay per se.

Clinical presentation of chest pain during AMI

Chest pain was the most prevalent AMI symptom in the present investigation evidencing that angina pectoris is the hallmark of AMI and imperative to initiate urgent lifesaving procedures. Sex differences in clinical presentation of chest pain during AMI have been widely advocated as one major reason for a longer delay in women [4]. However, the empirical basis for this assumption is not very strong. In the present investigation, no sex or age related differences were found for chest pain duration, pain radiating into arms, neck or jaw and pain strength (the latter being somewhat least intensive in younger men). These findings are in congruence with earlier studies, among them an analysis of the Myocardial

Infarction Triage and Intervention (MITI) Project Registry with 1,097 consecutive MI patients which was unable to discern distinguishable findings in the presentation of AMI symptoms [16]. In a database registry of 4,497 consecutive patients admitted to 16 King County hospital coronary care units, also no differences in chest pain presentation between men and women were observed [17].

Kreatsoulas et al. [11] mapped a continuum of angina associated symptoms in 128 male and 109 female cardiac patients and evidenced that angina-type symptoms were remarkable similar across sexes suggesting that the clinical construct of “atypical angina in women” is incorrect. The authors confirmed this finding in a recent study reasoning that there is more overlap of shared experiences between men and women than conventionally thought [18]. In line with these findings, Gimenez et al. [19] assessed 34 predefined chest pain characteristics (CPC) in 143 women and 369 men with AMI in the emergency setting and disclosed that only an evanescent minority of 9% of CPCs showed a sex specific diagnostic performance. It is of note that studies which found differences in chest pain frequency or characteristics mostly relied on less homogenous ACS samples including patients with acute conditions and sustained instable angina [20].

The perception of angina symptoms during the acute event is an important survival mechanism alerting the need for urgent medical care [21]. Therefore, it is of major concern that a clinically meaningful subpopulation of about 20% of elderly women experienced no chest pain during AMI in the present investigation. This risk is four fold higher compared to 5% of younger women and 6% of younger men without chest pain. Evidence from large scale registry studies point to a higher incidence of women experiencing no chest pain during AMI [8] while more recent clinical studies question different rates of chest pain between sexes

[22]. It is of note that that the marked difference in the present investigation became apparent only after sex and age stratification.

Contrary to the US National Registry of Myocardial Infarction database findings [8] which reported a female preponderance in younger female patients to suffer a AMI without chest pain, our age and sex stratified analyses disclosed an marked disadvantage for elderly women with an odds ratio of 2.4 compared to all other patients. However, this difference although highly significant and often labelled as "*defective anginal warning system*" [23] did not contribute substantially to the excess delay in this patient group: a mediation analysis disclosed that compared to male and female patients <65 years, not more than 9% of the variance accounted for non-chest pain contributing to the excess delay in old elderly women.

"Atypical" symptoms during AMI

Symptoms which may be mistaken as being musculoskeletal, gastro-intestinal or neurologic in origin are often viewed as "atypical" symptoms of AMI. There is evidence showing that women experience more "atypical" symptoms of AMI than men among them a study carried out in over 10.000 adults in the USA presenting to the emergency department with symptoms suggestive of AMI which found that women were more likely to present with nausea or vomiting, shortness of breath [24,25]. Kahn et al. [7] in a more recent study of about 1000 patients in a younger age range of 18-55 years hospitalized for AMI were unable to identify a consistent pattern of symptoms for AMI presentation with or without chest pain in both sexes. Here, we confirm these findings for age stratified patient groups and show that, contrary to expectation; the present data do not support a gender gap in atypical symptom presentation: elderly women were not likely to experience more dyspnoea, fatigue, gastrointestinal and sympathetic symptoms.

Limitations

There are a few study limitations that are worth considering. The retrospective data assessment may favour a potential for recall bias. However, data were collected at bedside within a very narrow time frame after STEMI. Furthermore, we have no data on symptom patterns of STEMI patients who died prior to hospital admission. Vice versa, a number of patients might have avoided hospital admission and thus cannot be accounted for. We had relatively small numbers of women, so replications of these results in larger datasets are warranted.

Conclusions

Women per se are at not at greater risk to delay their hospital admission in the setting of a STEMI. Women are also not at greater risk to present more "atypical" symptoms. Although they experience more acute events without chest pain, the impact on delay is negligible – it only accounts for 9% of the variance in delay time. Therefore, the conclusion already formulated by Canto et al. [9] in 2007 saying that potential differences in pain perception between men and women are not significant enough to *"warrant a separate or different message for awareness of ACS symptoms in women compared to men*" (p.2411) remains true. However, our investigation discloses that the combined effect of older age and female sex creates a particular risk population: elderly women experience an excess summit in delay time compared to men and even stronger compared to younger women. Therefore, more precisely educational strategies targeting old women at risk are urgently needed.

Perspectives:

Core Clinical Competencies: Contrary to recent guidelines and scientific statements which generally acknowledge the independent impact of sex and age as major contributing factors on delay time in arrival at an intensive care facility in face of a STEMI, the present investigation shows that women per se are at not at greater risk to delay their hospital admission and are also not at greater risk to present more “atypical” symptoms. Women experience more acute events without chest pain - yet, the impact on delay is negligible as it only accounts for 9% of the variance in delay time. However, the combined effect of older age *and* female sex creates a particular risk population to experience an excess summit in delay time compared to men and even stronger compared to younger women.

Translational Outlook: Heart foundations and health agencies should seriously consider to develop educational strategies more precisely targeting elder women at risk. In routine consultations, family physicians and cardiologists are advised particularly with their elderly female patients to repeatedly share knowledge on symptom patterns and subsequent adequate behaviour when faced with an STEMI.

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Tables and Figures

Study or Subgroup	Odds Ratio IV, Random, 95% CI
Older women vs. All the other patients	2.39 [1.39, 4.10]
Older women vs. Older men	2.13 [1.16, 3.90]
Older women vs. Younger women	3.33 [1.62, 6.85]
Older women vs. Younger men	2.37 [1.62, 3.47]

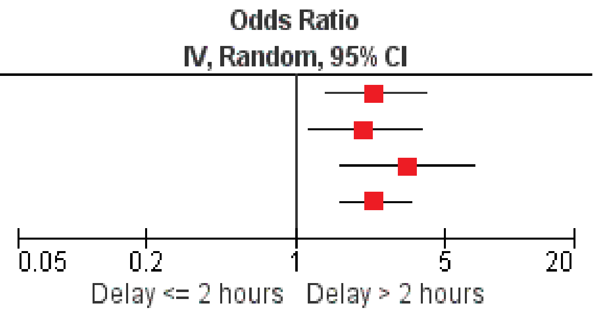

Figure 1: Odds ratio and 95% CI for demonstrating the chance of delay more than 2 hours for elder women compared to sex and age stratified sub-study populations

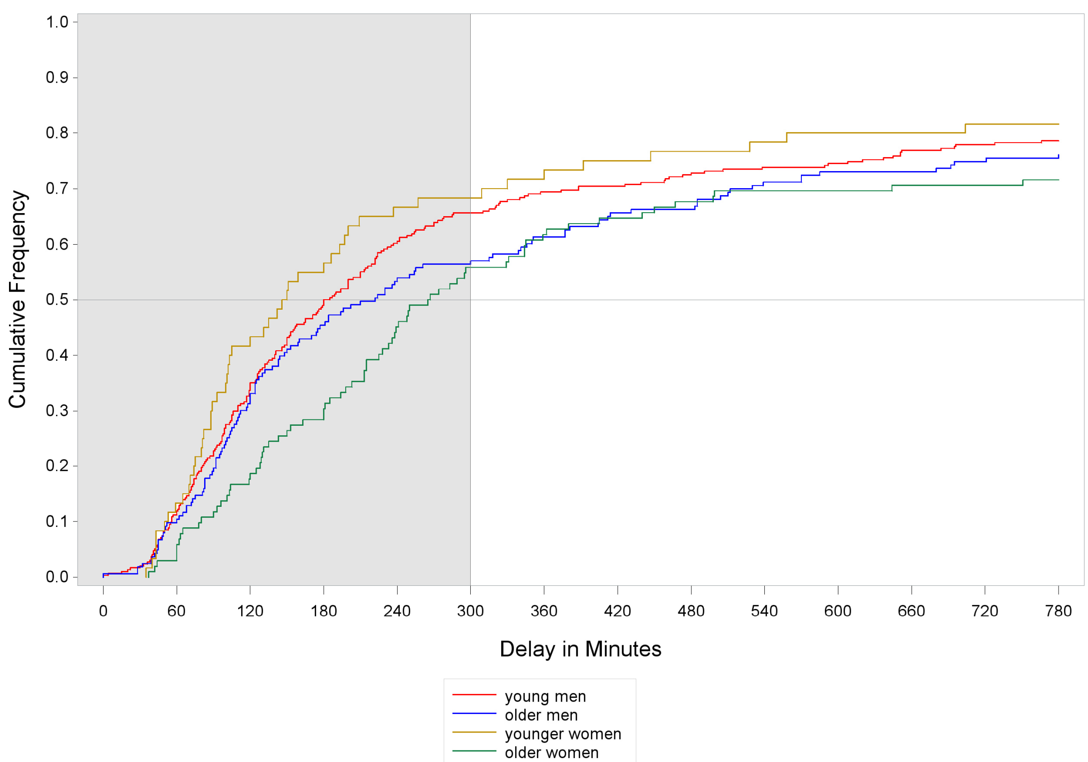

Figure 2: Sum-Percent Curve (cumulative frequency) of delay time in MEDEA patients (n=619), stratified for two age groups(>65/≤65 years) and sex (male/female)

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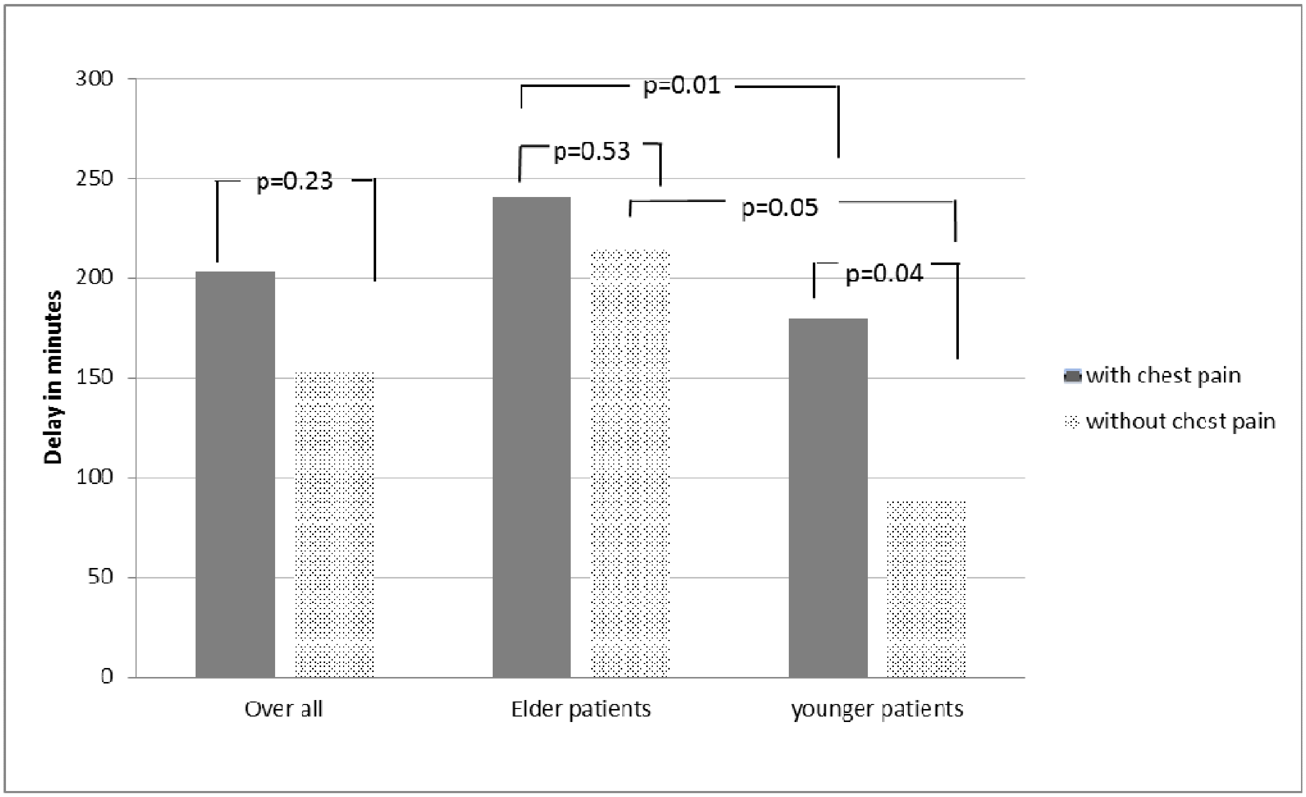

Figure 3: Median delay times (in min) for all patients with and without chest pain and stratified for older (>65y) and younger (<65y) patients

Table 1: Social demographic and clinical characteristics of 619 acute STEMI patients stratified by sex

Sociodemographic Data	**Men (n=457)**	**Women (n=162)**	**P - Value*)**
Age	60.5±11.4	68.1±12.5	**<.0001**
Employed	252 (55)	52 (32)	**<.0001**
Well educated	180 (39)	76 (47)	0.10
Living alone	113 (25)	69 (43)	**<.0001**
Hypertension	275 (45)	98 (61)	0.88
Hypercholesterolemia	173 (38)	55 (34)	0.36
Diabetes Mellitus	95 (21)	34 (21)	0.98
Smoking	193 (42)	51 (31)	**0.02**
Obesity (BMI >30)	153 (34)	51 (32)	0.65
Family History MI	219 (48)	81 (50)	0.68
Physical inactivity	220 (48)	103 (64)	**0.0007**

*) all analyses we performed by chi-squared tests except calculation of age differences by t test. Values are n (%) or mean ± SD. Bold means significant p values at <0.05 level.

Table 2: Symptom characteristics during acute STEMI in 457 male and 162 female patients, stratified by age (<=65y; >65y)

Symptoms	**Younger men (n=294) n (%)**	**Older men (n=163) n (%)**	**P value**	**Younger women (n=60) n (%)**	**Elderly women (n=102) n (%)**	**P value**
Chest pain						
Prevalence	276 (94)	136 (83)	**0.0006**	57 (95)	83 (81)	**0.03**
○ duration (> 20 mins)	201 (69)	114 (69)	0.95	44 (73)	70 (69)	0.53
○ Radiating pain	183 (63)	93 (56)	0.37	47 (78)	72 (71)	0.46
○ severity (high vs. low)	156 (40)	65 (55)	**0.0023**	36 (61)	54 (53)	0.35
Dyspnoea						
Shortness of breath	105 (36)	35 (22)	**0.0021**	23 (38)	31 (30)	0.39
Sympathetic (autonomic symptoms						
Dizziness	68 (23)	40 (24)	0.84	23 (38)	32 (31)	0.46
Faint	16 (5)	7 (4)	0.75	4 (7)	8 (8)	1.00
Racing heart	24 (8)	7 (4)	0.16	8 (13)	15 (15)	0.99
Diaphoresis	189 (65)	80 (49)	**0.0019**	34 (57)	50 (49)	0.44
Exhaustion (Fatigue)	48 (16)	19 (12)	0.22	9 (15)	14 (14)	1.00
Gastro-intestinal symptoms						
Heartburn	19 (7)	5 (3)	0.18	9 (15)	5 (5)	**0.05**
Nausea	105 (36)	54 (33)	0.63	32 (53)	50 (49)	0.71
Epigastric pain	20 (7)	10 (6)	0.93	10 (17)	6 (6)	**0.05**
Vomiting	40 (14)	17 (10)	0.40	14 (23)	18 (18)	0.50

Bold means significant p values at <0.05 level.

Table 3: Relative risks of perceived symptom patterns during acute MI of elderly women compared to all other patients and for sex and age subgroups (n=619)

Elderly women vs. all other patients	OR (95% CI)		**vs. older Men**	OR (95% CI)	
No chest pain vs. chest pain	2.32	1.20-4.46*	No chest pain vs. chest pain	0.87	0.58-2.63
Dyspnea	1.01	0.62-1.65	Dyspnea	1.73	0.93-3.20
Fatigue	0.86	0.47-1.75	Fatigue	0.96	0.43-2.16
Gastrointestinal symptoms	1.21	0.93-1.57	Gastrointestinal symptoms	1.53	1.07-2.19*
Sympathetic symptoms	1.01	0.78-0.32	Sympathetic symptoms	1.21	0.87-1.65
vs. younger women	OR (95% CI)		**vs. younger men**	OR (95% CI)	
No chest pain vs. chest pain	4.52	1.12-15.87*	No chest pain vs. chest pain	2.98	1.41-6.28*
Dyspnea	0.64	0.31-1.41	Dyspnea	0.82	0.48-1.40
Fatigue	0.98	0.35-2.68	Fatigue	0.81	0.41-1.64
Gastrointestinal symptoms	0.70	0.46-1.05	Gastrointestinal symptoms	1.27	0.95-1.71
Sympathetic symptoms	1.02	0.67-1.55	Sympathetic symptoms	0.93	0.69-1.25

*) significant p values at <0.05 level

Table 4: Mediation analysis of non-chest pain in elderly women in comparison to study population on delay time

Exposure (X)	Natural direct effect (β) (X→Y)	p	Natural in-direct effect (β) (mediated effect)	p	a (X→M)	p	b (M→Y)	p	% mediated
Chest pain (M), Delay ≤ 2hrs or > 2hrs (Y)									
Elder women vs. all patients	-0.17	**<0.001**	0.02	**0.02**	0.43	**0.01**	-0.36	**0.03**	10.1%
Elder women vs. all younger patients	-0.19	**<0.001**	0.02	0.16	0.67	**<0.001**	-0.19	0.37	10.7%
Elder women vs. younger women	-0.23	**<0.001**	-0.01	0.72	0.75	**0.01**	-0.36	**0.03**	3.0%
Elder women vs. younger men	-0.17	**<0.001**	0.01	0.20	0.65	**<0.001**	-0.17	0.43	7.8%

Bold means significant p values at <0.05 level.