

Original Article

The influence of biological age and sex on long-term outcome after percutaneous coronary intervention for ST-elevation myocardial infarction

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Abstract: Background: Outcome following ST-segment elevation myocardial infarction (STEMI) is thought to be worse in women than in age-matched men. We assessed whether such differences occur in the UK Pan-London dataset and if age, and particularly menopause, influences upon outcome. Methods: We undertook an observational cohort study of 26,799 STEMI patients (20,633 men, 6,166 women) between 2005-2015 at 8 centres across London, UK. Patient details were recorded at the time of the procedure into local databases using the British Cardiac Intervention Society (BCIS) PCI dataset. Primary outcome was all-cause mortality at a median follow-up of 4.1 years (IQR: 2.2-5.8 years). Results: Kaplan-Meier analysis demonstrated a higher mortality rate in women versus men (15.6% men vs. 25.3% women, $P < 0.0001$). Univariate Cox analysis revealed that female sex was a predictor of all-cause mortality (HR: 1.69 95% CI: 1.59-1.82). However, after multivariate adjustment, this effect of female sex diminished (HR: 1.05 95% CI: 0.90-1.25). In a sub-group analysis, we compared the sexes separated by age into the ≤ 55 and the > 55 year olds. Age-stratified Cox analysis revealed that female sex was a univariate predictor of all-cause mortality (HR: 1.60 95% CI: 1.25-2.05) in the ≤ 55 group and in the > 55 group (HR: 1.38 95% CI: 1.28-1.47). However, after regression adjustment incorporating the propensity score into a proportional hazard model as a covariate, whilst female sex was not a significant predictor of all-cause mortality in the ≤ 55 group it was a predictor in the > 55 group. Moreover, whilst age did not influence outcome in < 55 group, this effect in the > 55 group was correlated with age. Conclusions: Overall women have a worse all-cause mortality following primary PCI for STEMI compared to men. However, this effect was driven predominantly by women > 55 years of age since after adjusting for co-morbidities the risk in younger women did not differ significantly from that in men. These observations support the view that as women advance past the menopausal years their risk of further events following revascularization increases substantially and we suggest that routine assessment of hormonal status may improve clinical decision-making and ultimately outcome for women post-PCI.

Keywords: Primary PCI, sex, myocardial infarction

Introduction

Despite the year-on-year decrease over the past 2 decades, coronary heart disease (CHD)

remains the leading cause of mortality worldwide amongst women [1]. Most CHD-related mortality is a consequence of acute myocardial infarction (AMI), with ST-segment elevation

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myocardial infarction (STEMI) thought to account for 25-47% of this [2-5]. This is true not only in low middle-income countries but also in those countries considered high income and with universal access to healthcare (i.e. with a per capita of \$12,000 or more [4]).

These statistics are surprising considering the well-established fact that women, at least during the pre-menopausal years, enjoy innate protection against cardiovascular diseases and particularly CHD [6]. More surprising is the evidence indicating that outcome for women following a STEMI is worse than for age-matched men; an observation first demonstrated in data collated across 15 different countries in the GUSTO-I study [7] and also supported by large scale meta-analyses [8]. In the latter increased risk of vascular complications, 30-day mortality and co-morbidities were implicated in the outcomes. More recently, a European study conducted across 41 heart attack centres in 12 countries including 8834 patients, 2657 of whom were women, demonstrated increased 30-day mortality post-percutaneous coronary intervention (PCI) in younger women. In this study, as age increased this risk progressively decreased and indeed was absent in the over 60s, suggesting that the worse outcome for women post-PCI is driven by differences between the sexes in the younger years. These data, however, conflict with recent evidence from the USA [9, 10] demonstrating increased risk for older women compared to men post-PCI in both STEMI and NSTEMI groups.

There has been considerable interest in determining why women might fare worse than men with differences in treatment and presentation having been implicated. Studies in the USA and Europe have shown that women receive revascularisation less, experience greater delays when revascularisation is applied, i.e. longer call-to-balloon, and experience delays in treatment i.e. longer door-to-balloon times [11]. However reassuringly, use of a standardised protocols such as in STEMI eliminates the sex differences in time to treatment and is associated with proportional improvements post-PCI in mortality rates [12]. However, despite this, differences still persist and whether this difference might pertain specifically to younger or older women (i.e. pre or post-menopausal) is not clear.

Since the incidence of STEMI in women is generally low compared to men it is difficult to interpret apparent differences in risk with confidence. The British Cardiac Intervention Society (BCIS) dataset of 26,799 patients merging information from 8 heart attack centres in cosmopolitan London, including 6098 women of varied ethnicity, provides us with an excellent opportunity to robustly assess the influence of sex on outcome post-PCI in a true STEMI UK-based population eliminating differences due to other factors which may confound outcomes.

Methods

The data collected were part of a mandatory national cardiac audit and all patient identifiable fields were removed prior to merging of the datasets and analysis. The authors declare that all supporting data are available within the article. In addition, the data can be provided on request from Dr. Andrew Wragg.

In this study, STEMI was defined as per the European Society of Cardiology (ESC) guidelines as patients presenting with persistent chest discomfort and ST-segment elevation in at least two contiguous leads as STEMI [13]. The latest ESC guidelines describe further management of patients presenting with STEMI [13].

This was a retrospective observational cohort study designed to investigate the relationship between sex and outcome after primary PCI in patients with STEMI. We analysed the merged databases of the 8 London Heart Attack Centres that collect data into the BCIS dataset. The BCIS audit is part of a national mandatory audit that all UK PCI centres participate in.

Study database

The UK BCIS audit collects data from all hospitals in the UK that perform PCI, recording information about every procedure performed in a standardized manner [14]. PCI is defined as the use of any coronary device to approach, probe or cross one or more coronary lesion, with the intention of performing a coronary intervention [14]. The database is part of the suite of datasets collected under the auspices of the National Cardiac Audit Programme (NCAP), and is compliant with UK data protection legislation. Data

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are collected prospectively at each hospital, electronically encrypted and transferred online to a central database. Each patient entry offers details of the patient journey, including the method and timing of admission, inpatient investigations, results, treatment and outcomes. Repeat admissions were removed from the analysis. Patients' survival data is obtained by linkage of patients' National Health Service (NHS) numbers to the Office of National Statistics, which records live status and the date of death for all deceased patients.

Population study and design

We examined an observational cohort of consecutive patients with STEMI treated with primary PCI between January 2005 and July 2015 at all 8 tertiary cardiac centres in London, UK. There are no other centres in London that undertake primary PCI. Patient and procedural details were recorded at the time of the procedure and during the admission into each Centre's local BCIS database. Anonymous datasets with linked mortality data from the Office of National Statistics were merged for analysis from the 8 centres. Patients with cardiogenic shock on presentation were included in the study.

STEMI was defined as per ESC STEMI guidelines criteria [15]. All patients with onset of symptoms of <12 h and at least 1 mm ST-segment elevation in 2 or more contiguous limb leads or at least 2 mm in 2 or more contiguous precordial leads or left bundle branch block or a posterior myocardial infarction were considered for primary PCI. Coronary angiography was performed via the radial or femoral artery. The culprit lesion was identified and crossed with an angioplasty guidewire. Manual thrombus aspiration was performed at the discretion of the operator followed by conventional percutaneous coronary intervention to the culprit vessel.

Patient classification

Initially, patient data was grouped into Men or Women and then a further sub-analysis performed in the following age groups: ≤55 or >55 years. The age cut-off selected for the impact upon outcome was chosen based upon clinical data and recommendations in the UK as well as precedent in other large registry studies (e.g.

[16]). The average age for menopause is 51 however the range at which menopause can occur is 45-55 years [17]. To ensure that the post-menopause group represent a cohort of women that are likely to be post-menopausal and have low circulating concentrations of female sex hormones we elected to use 55 as the cut-off category. This age characteristic was used as the defining classification of women into pre and post-menopausal groups for analysis.

Clinical outcomes

Patient clinical and demographic data, procedural characteristics, bleeding complications, procedural complications, all cause in-hospital mortality, non-fatal myocardial infarction (MI), re-intervention and stroke were recorded during the admission. For the baseline demographics, cardiogenic shock was defined as systolic blood pressure <90 mmHg due to cardiac insufficiency with clinical signs of hypoperfusion (cold extremities, oliguria, altered mental state etc.), not responsive to fluid resuscitation for more than 30 minutes, with a cardiac index below 1.8 l/min/m² without support or 2.0 to 2.2 l/min/m² with support. Hypertension and hypercholesterolemia were a pre-hospital diagnosis as was diabetes status. Furthermore, diabetes status included Type I and Type II diabetics. Smoking status included those currently smoking or had smoked in the past. Poor left ventricle (LV) function included anyone with an ejection fraction of <35% during their hospital stay. In hospital Major Adverse Cardiac Events (MACE) was defined as death, MI (new pathologic Q waves in the distribution of the treated coronary artery with an increase of creatine kinase-MB to ≥2 times the reference value or significant rise in Troponin biomarkers-which includes a troponin T cut-off of <15 ng/dl), stroke or target vessel revascularisation. Procedural complications recorded included MI, emergency coronary artery bypass grafting (CABG), arterial complications, aortic/coronary dissection, side branch occlusion, and arrhythmia. Following discharge, long-term all-cause mortality was obtained by linkage to the Office of National Statistics. Successful primary PCI result was defined as final TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 and residual stenosis <20% in the infarct-related artery at the end of the procedure.

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Socioeconomic status

The Index of Multiple Deprivation (IMD) 2015 is the official measure of relative deprivation for small areas (or neighbourhoods) in England. The socio-economic status of each patient was assessed from their residential postal code using the 2015 version of the English IMD score [18].

IMD score

This robust index of deprivation divides England into 32,482 small geographical areas, each of which contains about 1,500 residents, and awards them a score for seven domains (income, employment, health and disability, education and training, housing and services, living environment, and crime) according to information obtained from the 2010 national census. The domains were weighted and then combined to provide a single measure of deprivation for each geographical area. IMD scores have been widely used to study relationships between socio-economic factors and health outcomes, such as equity of access to care [19], disease presentation [20], life expectancy [21], and post-surgical mortality [22].

The English IMD score has several limitations which arise from the methodology involved in its derivation. The score incorporates seven domains into an overall quantification of deprivation, which is assigned based on defined geographical area rather than on an individual subject's characteristics. Individuals who live in one particular area will obviously experience different levels of deprivation [23]. IMD scores are not a linear measure of deprivation and do not incorporate information on duration of residence. Therefore, we could not assess the contribution of deprivation exposure time to mortality. Nevertheless, the IMD score is the best available means for quantifying deprivation in England [24]. Within this study, patients were analysed by quintile of IMD score (Q1, least deprived; Q5, most deprived).

Ethics

The data was collected as part of a national cardiac audit and all patient identifiable fields were removed prior to analysis. The local ethics committee advised us that formal ethical approval was not required.

Statistical analysis

Clinical characteristics of men versus women (overall between the sexes and within the two age groups: ≤ 55 or > 55 years) were compared using the Pearson Chi Square test for categorical variables and Student t test for continuous variables. Normality of distribution was assessed using the Shapiro-Wilks test. We calculated Kaplan-Meier product limits for cumulative probability of reaching end point and used the log rank test for evidence of a statistically significant difference between the groups. Time was measured from the first admission for a procedure to outcome (all-cause mortality). Cox regression analysis was used to estimate hazard ratios (HR) for the effect of sex in age-adjusted and fully adjusted models (including sex, ethnicity, cardiogenic shock, diabetes, hypertension, hypercholesterolaemia, previous MI/PCI/CABG, history of smoking, renal dysfunction, poor LV function, glycoprotein (GP) IIb/IIIa inhibitor use, procedural success, radial access and multivessel disease), based on covariates ($P < 0.05$) associated with the outcome. The proportional hazards assumption was evaluated by examining log (-log) survival curves and additionally was tested with Schoenfeld's residuals. The proportional hazard assumption was satisfied for all outcomes evaluated.

A propensity score analysis was conducted using a non-parsimonious logistic regression model comparing Men and Women (overall between the sexes and within the two age groups: ≤ 55 or > 55 years). Multiple variables were included in the model, including age, diabetes, hypertension, hypercholesterolaemia, previous CABG, previous PCI, previous MI, multivessel disease, chronic renal failure, pre-procedure TIMI flow, procedural success (defined by TIMI 3 flow at the end of the case) and GP IIb/IIIa use. We then undertook a regression adjustment incorporating the propensity score into a proportional hazard model as a covariate. We used SPSS for Mac version 22.0 for all analyses.

For the socioeconomic status analysis, Patients were analysed by quintile of English IMD score [18].

Interaction between age and sex was examined in the multivariable models, first using a linear

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model for age and then by fitting p-splines to examine the non-linear associations [25]. Models with spline terms were compared to non-linear models using likelihood ratio tests and a final model was fitted including spline by age interaction terms. Spline models were fitted using the survival package in R (version 3.6.0).

Results

The study population consisted of 26,799 patients with a mean age of 62.2 years, (60.20±12.6 men and 68.54±13.4 women) 23.0% of which were women. Of these 43.2% of the patients had hypertension, 38.7% had dyslipidemia, 52.1% were active or ex-smokers, and 16.5% had diabetes. Furthermore, 31.3% of PCI procedures were performed through the radial route and 7.4% of patients had cardiogenic shock in the study. In the whole cohort, there were 20,701 men and 6,098 women. Separation according to presumed menopausal status according to an age of 55 gave 1095 of the 6098 (~18%) women in the <55 years versus 7950 men of 20701 (~38%).

Patient characteristics

Women were more likely to be Caucasian, individuals with hypertension and diabetes and present in cardiogenic shock compared to men (**Table 1**). There were higher rates of men who were smokers or ex-smokers compared to the women and also higher rates of previous MI, previous CABG and previous PCI. There were no differences in left ventricular function (assessed during the index hospitalisation). These differences between the sexes were present irrespective of age in terms of ≤55 or >55 years stratification (**Tables 2 and 3**). As expected, however, in the individuals >55 year men were more likely to have suffered a previous MI and been treated with PCI or CABG (**Table 2**).

Response, procedural characteristics and outcomes

There was a higher average call-to-balloon time in women compared to men, in both age groups i.e. ≤55 or >55 years, but no statistically significant differences in door-to-balloon times. There were lower rates of radial access, multi-vessel disease, multi-vessel intervention and GPIIb/IIIa use in the women compared to the men

(**Table 4**) and again this was evident irrespective of the age group (**Table 4**). In addition, overall there were lower rates of left main coronary artery, left anterior descending artery, left circumflex coronary artery and saphenous vein graft intervention in the women compared to the men. However, there were higher rates of right coronary artery disease and intervention in the women compared to men. Segregation of the data according to age demonstrates that these differences are driven primarily by the >55 years group with no differences between those ≤55 years. Finally, procedural success was greater in men than women, although the difference was small (i.e. 0.5%) and an effect evident in both age categories with no differences in mean stent lengths/widths.

In-hospital outcomes

Unadjusted in-hospital major adverse cardiac events (MACE) rates were higher in women overall compared to the men (7.5% vs. 5.7%, $P<0.0001$), and mainly due to death (5.0% vs. 3.3, $P<0.0001$) and Q wave MI (0.5% vs. 0.2%, $P<0.0001$). In addition, there were higher rates of bleeding complications in the women compared to the men (1.0% vs. 0.4%, $P<0.0001$, **Table 5**). As with the baseline characteristics and procedures these differences in mortality and bleeding rates were driven by increased rates in the >55 group with no evidence of worse outcomes for the ≤55 years (**Table 5; Figure 1**).

Long term outcomes

Patients were followed-up for a median of 4.1 years (IQR range: 2.2-5.8 years). Kaplan-Meier analysis over a five-year period demonstrates a higher mortality rate in the women compared to the men (25.3% in the women vs. 15.6% in the men, $P<0.0001$) (**Figure 2A**). In both the ≤55 group (5.0% men vs. 6.8% women, $P=0.002$) (**Figure 2B**) and the >55 years group (21.6% men group vs. 28.4% for women, $P<0.0001$) (**Figure 2C**) the rate in women was greater than in the men, however the adjusted difference was statistically significant only in the >55 years group.

Predictors of all-cause mortality

Univariate Cox analysis revealed that female sex was a significant predictor of all-cause mortality (HR: 1.69 (95% confidence intervals (CI)

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Table 1. Baseline characteristics according to biological sex

Characteristic	Men (n=20701)	Women (n=6098)	P Value	Men ≤55 (n=7950)	Women ≤55 (n=1095)	P Value	Men >55 (n=12751)	Women >55 (n=5003)	P Value
Age (yrs)	60.20±12.76	68.54±13.4	<0.0001	47.40±5.91	47.56±6.05	0.822	68.16±8.93	73.32±9.63	<0.0001
Ethnicity (Caucasian)	9432 (45.6%)	3167 (51.9%)	<0.0001	3296 (41.5%)	542 (50.3%)	<0.0001	6564 (51.5%)	2693 (53.8%)	<0.0001
Previous MI	3398 (16.4%)	864 (14.2%)	<0.0001	866 (10.9%)	103 (10.8%)	0.188	2161 (16.9%)	619 (12.4%)	<0.0001
Previous CABG	884 (4.3%)	199 (3.3%)	<0.0001	225 (2.8%)	38 (3.7%)	0.212	874 (6.9%)	207 (4.1%)	<0.0001
Previous PCI	2580 (12.5%)	581 (9.5%)	<0.0001	739 (9.3%)	90 (8.4%)	0.312	1767 (13.9%)	433 (8.7%)	<0.0001
Cardiogenic Shock	1533 (7.4%)	520 (8.5%)	0.008	436 (5.5%)	79 (6.9%)	0.014	1135 (8.9%)	462 (9.2%)	0.448
Hyperchol esterolaemia	7866 (38.0%)	2499 (41.0%)	<0.0001	2584 (32.5%)	352 (33.3%)	0.944	5088 (40.0%)	2018 (40.3%)	0.65
Diabetes mellitus	3155 (15.2%)	1161 (19.0%)	<0.0001	952 (12.0%)	228 (21.2%)	<0.0001	2221 (17.4%)	919 (18.4%)	0.118
Hypertension	8319 (40.2%)	3067 (50.3%)	<0.0001	2432 (30.6%)	386 (35.3%)	0.001	5912 (46.4%)	2672 (53.4%)	<0.0001
Smoking History	11443 (55.3%)	2521 (41.3%)	<0.0001	5091 (64.0%)	631 (57.7%)	<0.0001	6391 (50.1%)	1820 (36.4%)	<0.0001
PVD	418 (2.0%)	123 (2.0%)	0.914	62 (0.8%)	14 (1.4%)	0.107	306 (2.4%)	96 (1.9%)	0.058
CKD (Creat >200)	32 (0.2%)	12 (0.2%)	0.477	56 (0.7%)	21 (1.9%)	<0.0001	306 (2.4%)	92 (1.8%)	0.033
Poor Left ventricular function	899 (0.4%)	257 (4.1%)	0.48	259 (3.3%)	37 (3.4%)	1	625 (4.9%)	202 (4.0%)	0.027
Direct Transfer	12405 (59.9%)	3645 (59.8%)	0.417	5166 (65.0%)	674 (55.6%)	0.173	8414 (66.0%)	3305 (66.1%)	0.625
Call to Balloon Time (mins)*	104 [97-138]	142 [118-189]	0.042	109 [85-148]	158 [124-194]	0.021	98 [77-131]	125 [102-181]	0.035
Door to Balloon Time (mins)*	49 [26-120]	57 [30-144]	0.369	53 [24-115]	62 [39-158]	0.188	46 [31-124]	53 [28-139]	0.285

MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; Creat, creatinine concentration; Hypertension (systolic BP≥140 mmHg), Hypercholesterolemia (total cholesterol ≥5.0 mmol/L), poor left ventricular function (EF<35%), CKD (eGFR<60 ml/min/1.73 m²) *median (interquartile range).

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Table 2. Cox proportional model of univariate and multivariate analysis of predictors of mortality in the ≤55 group

Variable	Comparator	Univariate	Multivariate*
Age (per year)		1.02 (1.002-1.04)	1.05 (0.98-1.16)
Female	Male	1.60 (1.25-2.05)	1.72 (0.84-4.10)
Ethnicity (Asian)	Caucasian	1.02 (0.81-1.27)	1.88 (0.93-3.80)
Cardiogenic Shock	No Cardiogenic Shock	6.44 (5.03-8.26)	6.74 (2.15-14.85)
Diabetes	No diabetes	2.55 (2.02-3.21)	1.85 (0.62-4.85)
Previous MI	No previous MI	1.41 (1.09-1.83)	1.41 (0.32-6.58)
Previous CABG	No Previous CABG	2.58 (1.67-3.96)	3.025 (0.58-15.12)
Previous PCI	No previous PCI	1.58 (1.20-2.08)	1.20 (0.38-4.51)
Hypertension	No hypertension	1.45 (1.17-1.79)	2.48 (1.25-4.98)
Hypercholesterolaemia	No hypercholesterolaemia	1.22 (0.99-1.51)	1.43 (0.68-3.02)
History of smoking	Never smoked	1.05 (0.82-1.35)	1.59 (0.81-3.14)
eGFR<60 ml/min/1.73 m ²	eGFR>60	6.18 (3.68-10.37)	1.39 (0.25-10.25)
EF<35%	EF>35%	3.11 (2.14-4.52)	3.92 (1.38-7.29)
GP IIb/IIIa inhibitor use	No GP IIb/IIIa inhibitor use	0.78 (0.64-0.96)	0.81 (0.41-2.37)
Procedural success	Procedural failure	0.56 (0.40-0.80)	0.57 (0.32-0.98)
Access route (femoral)	Radial	0.57 (0.44-0.75)	0.82 (0.31-1.97)
Multi-vessel disease	Single-vessel disease	1.69 (1.37-2.08)	3.52 (1.88-4.81)

*Adjusted for age, sex, previous MI, eGFR<60 ml/min/1.73 m², EF<35%, Hypertension (systolic BP≥140 mmHg), Hypercholesterolemia (total cholesterol ≥5.0 mmol/L) procedural success, multivessel disease, GP IIb/IIIa use, multivessel disease and IABP use. Legend: MI = myocardial infarction, PCI = percutaneous coronary intervention, GP IIb/IIIa = glycoprotein II/IIIa inhibitor, CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, NA = Not applicable.

Table 3. Cox proportional model of univariate and multivariate analysis of predictors of mortality in the >55 group

Variable	Comparator	Univariate	Multivariate*
Age (per year)		1.08 (1.07-1.08)	1.07 (1.06-1.08)
Female	Male	1.38 (1.28-1.47)	1.20 (1.09-1.41)
Ethnicity (Asian)	Caucasian	1.14 (1.05-1.23)	1.14 (0.95-1.35)
Cardiogenic Shock	No Cardiogenic Shock	4.03 (3.70-4.42)	3.87 (2.69-4.17)
Diabetes	No diabetes	1.37 (1.26-1.48)	1.41 (1.20-1.58)
Previous MI	No previous MI	1.45 (1.34-1.57)	1.25 (0.85-1.53)
Previous CABG	No Previous CABG	1.48 (1.32-1.67)	1.19 (0.73-1.69)
Previous PCI	No previous PCI	1.27 (1.16-1.40)	0.85 (0.67-1.38)
Hypertension	No hypertension	1.22 (1.14-1.31)	0.97 (0.84-1.13)
Hypercholesterolaemia	No hypercholesterolaemia	1.05 (0.98-1.12)	1.08 (0.69-1.26)
History of smoking	Never smoked	1.13 (1.05-1.22)	1.49 (1.25-1.63)
eGFR<60 ml/min/1.73 m ²	eGFR>60	3.55 (3.06-4.13)	2.65 (1.88-3.91)
EF<35%	EF>35%	1.86 (1.63-2.13)	1.93 (1.67-2.84)
GP IIb/IIIa inhibitor use	No GP IIb/IIIa inhibitor use	0.72 (0.67-0.77)	0.62 (0.49-0.86)
Procedural success	Procedural failure	0.53 (0.48-0.59)	0.72 (0.56-0.95)
Access route (femoral)	Radial	0.79 (0.72-0.86)	0.84 (0.72-1.34)
Multi-vessel disease	Single-vessel disease	1.53 (1.43-1.64)	1.48 (1.20-1.77)

*Adjusted for age, sex, previous MI, eGFR<60 ml/min/1.73 m², EF<35%, Hypertension (systolic BP≥140 mmHg), Hypercholesterolemia (total cholesterol ≥5.0 mmol/L), procedural success, multivessel disease, GP IIb/IIIa use, multivessel disease and IABP use. Legend: MI = myocardial infarction, PCI = percutaneous coronary intervention, GP IIb/IIIa = glycoprotein II/IIIa inhibitor, CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, NA = Not applicable.

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Table 4. Procedural characteristics according to biological sex

Procedural Characteristic	Men (n=20701)	Women (n=6098)	P Value	Men ≤55 (n=7950)	Women ≤55 (n=1095)	P Value	Men >55 (n=12751)	Women >55 (n=5003)	P Value
Access for PCI									
Radial	5829 (28.2%)	1446 (23.7%)	<0.0001	2791 (35.1%)	346 (31.6%)	0.024	4085 (32.0%)	1380 (27.6%)	<0.0001
No. of diseased vessels									
Multi-vessel	7351 (35.5%)	2005 (32.9%)	<0.0001	2139 (26.9%)	225 (20.5%)	<0.0001	4948 (38.8%)	1678 (33.5%)	<0.0001
Mean Vessels	1.24±0.67	1.20±0.60	<0.0001	1.13±0.41	1.09±0.34	<0.0001	1.16±0.46	1.13±0.42	<0.0001
Target vessel									
Right coronary artery	7816 (37.8%)	2728 (44.7%)	<0.0001	2898 (36.5%)	407 (37.2%)	0.662	4808 (37.7%)	2297 (45.9%)	<0.0001
Left main coronary artery	563 (2.7%)	144 (2.4%)	0.104	246 (3.1%)	34 (3.1%)	1	680 (5.3%)	196 (3.9%)	<0.0001
Left anterior descending	9796 (47.3%)	2681 (44.0%)	<0.0001	3944 (49.6%)	542 (49.5%)	0.948	5793 (45.4%)	2041 (40.8%)	<0.0001
Left circumflex coronary	3678 (17.8%)	953 (15.6%)	<0.0001	1262 (15.9%)	158 (14.4%)	0.231	2210 (17.3%)	746 (14.9%)	<0.0001
Saphenous vein graft	445 (2.1%)	71 (1.2%)	<0.0001	59 (0.7%)	3 (0.3%)	0.08	307 (2.4%)	52 (1.0%)	<0.0001
Multi-vessel intervention	2855 (13.8%)	726 (11.9%)	<0.0001	895 (11.3%)	87 (7.9%)	0.001	1749 (13.7%)	571 (11.4%)	<0.0001
Vessel diameter	4.06±17.50	3.93±9.74	0.78	4.12±10.68	4.16±12.87	0.218	4.07±20.61	3.88±9.27	0.954
Vessel length	22.09±10.03	21.68±10.23	0.151	22.00±9.27	21.62±9.39	0.272	22.39±10.67	21.97±10.55	0.683
TIMI Pre-angiography									
TIMI 3	2594 (12.5%)	780 (12.8%)	0.722	843 (10.6%)	113 (10.3%)	0.636	1265 (9.9%)	501 (10.0%)	0.757
TIMI 0	10120 (48.9%)	2988 (49.0%)	0.716	4332 (54.5%)	618 (56.4%)	0.683	5687 (44.6%)	2599 (51.9%)	0.408
DES	8851 (42.8%)	2502 (41.0%)	0.011	3892 (49.0%)	535 (48.9%)	0.291	5810 (45.6%)	2226 (44.5%)	0.387
GP IIb/IIIa inhibitor	11224 (54.2%)	2879 (47.2%)	<0.0001	4578 (57.6%)	565 (51.6%)	<0.0001	6517 (51.1%)	2256 (45.1%)	<0.0001
Procedural Success	15007 (72.5%)	4388 (72.0%)	0.034	6000 (75.5%)	819 (74.8%)	0.057	9176 (72.0%)	3546 (70.9%)	0.999

TIMI, thrombolysis in myocardial infarct; DES, Drug-eluting stent; GP: Glycoprotein.

Sex differences following PPCI for STEMI

Table 5. In-hospital outcomes and complications post PCI according to biological sex and < or >55 years of age

In Hospital	Men (n=20701)	Women (n=6098)	P Value	Men ≤55 (n=7950)	Women ≤55 (n=1095)	P Value	Men >55 (n=12751)	Women >55 (n=5003)	P Value
MACE	1172 (5.7%)	461 (7.6%)	<0.0001	318 (4.0%)	39 (3.6%)	0.509	982 (7.7%)	450 (9.0%)	0.004
Death	675 (3.3%)	306 (5.0%)	<0.0001	122 (1.5%)	19 (0.9%)	0.604	620 (4.9%)	305 (6.1%)	0.001
Q wave MI	41 (0.2%)	32 (0.5%)	<0.0001	17 (0.2%)	2 (0.2%)	1	23 (0.2%)	25 (0.5%)	<0.0001
Re-intervention	174 (0.8%)	49 (0.8%)	0.745	54 (0.7%)	9 (0.8%)	0.563	109 (0.8%)	41 (0.8%)	0.851
CVA	32 (0.2%)	15 (0.2%)	0.164	7 (0.1%)	3 (0.2%)	0.112	27 (0.2%)	12 (0.2%)	0.723
Emergency CABG	32 (0.2%)	13 (0.2%)	0.375	13 (0.1%)	2 (0.2%)	0.703	16 (0.1%)	11 (0.2%)	0.196
Arterial Complications	74 (0.4%)	54 (0.9%)	<0.0001	22 (0.3%)	5 (0.5%)	0.368	40 (0.3%)	38 (0.8%)	<0.0001
Bleeding Complications	83 (0.4%)	58 (1.0%)	<0.0001	28 (0.4%)	10 (0.9%)	0.475	46 (0.4%)	57 (1.1%)	<0.0001

Legend: MI = myocardial infarction, PCI = percutaneous coronary intervention, MACE = major adverse cardiac events, CABG = coronary artery bypass grafting.

1.59-1.82) (Table 6) but this association was lost after multivariate adjustment. Separation according to age indicated that whilst there was no statistically significant effect of sex on mortality rates in the ≤55 years, female sex did predict a worse outcome in the >55 years group (Tables 2 and 3).

After regression adjustment incorporating the propensity score (variables mentioned above) into a proportional hazard model as a covariate, female sex was still not a predictor of all-cause mortality in the overall cohort (HR: 0.98 95% CI: 0.84-1.14), whilst after separation of the sexes according to the age cut-offs sex remained a significant predictor in the >55 year group. After adjustment for covariates there was no statistically significant age by sex interaction (P=0.21) (Table 7) indicating that the sex differences evident between the two groupings were not driven by age.

Spline plot

Figure 3 demonstrates the spline plot of the association between age and log hazard for all-cause mortality. This indicates that there is a non-linear effect (P=0.009) with risk accelerating at older ages. There is significant interaction in the non-linear term between sexes (P=0.011). The plot of the curves reveals that whilst risk is higher in younger women, that risk in men and women becomes similar with respect to the influence of age above 50 years. Whilst women start at higher risk age does not impact upon risk until 55 years of age, whereas the increase with age in men is steeper and more consistent than that seen in the women over life time.

Comparison of ethnicity and socioeconomic status on long-term outcome

Assessment of the impact of ethnicity demonstrated that the differences between men and women were equally present in both the Caucasians (13.2% men vs. 6.8% for women, P<0.0001) (Figure S1A) and Asians (16.7% men vs. 26.4% for women, P<0.0001) (Figure S1B).

Categorisation by quintiles 1 to 5 of socioeconomic status was this further stratified by above and below 55 even if you combine quintiles 1-4 demonstrated that whilst there were higher mortality rates in the women compared to the men in quintiles 1 to 4, there was no difference between the two groups in quintile 5 (i.e. the most affluent) (16.4% men vs. 27.5% for women, P=0.192, Figure S2). This data was not further split by age due to the low numbers within each quintile.

Discussion

This analysis of the ethnically and socioeconomically diverse large Pan-London dataset has demonstrated that women, in London, have a worse outcome post-PCI in a true STEMI cohort (~50% more in-hospital and ~40% more death in 4 year follow-up) compared to men, irrespective of race. This observation is in keeping with other cohorts [26-30]. However, in our sub-group analysis where patients were divided into before and after the average menopausal age we found that, following adjustment for co-variables, only women in the >55 age group had a significantly greater likelihood of poorer outcome. No significant difference in rates were found between women and men <55 years of age; and importantly in the

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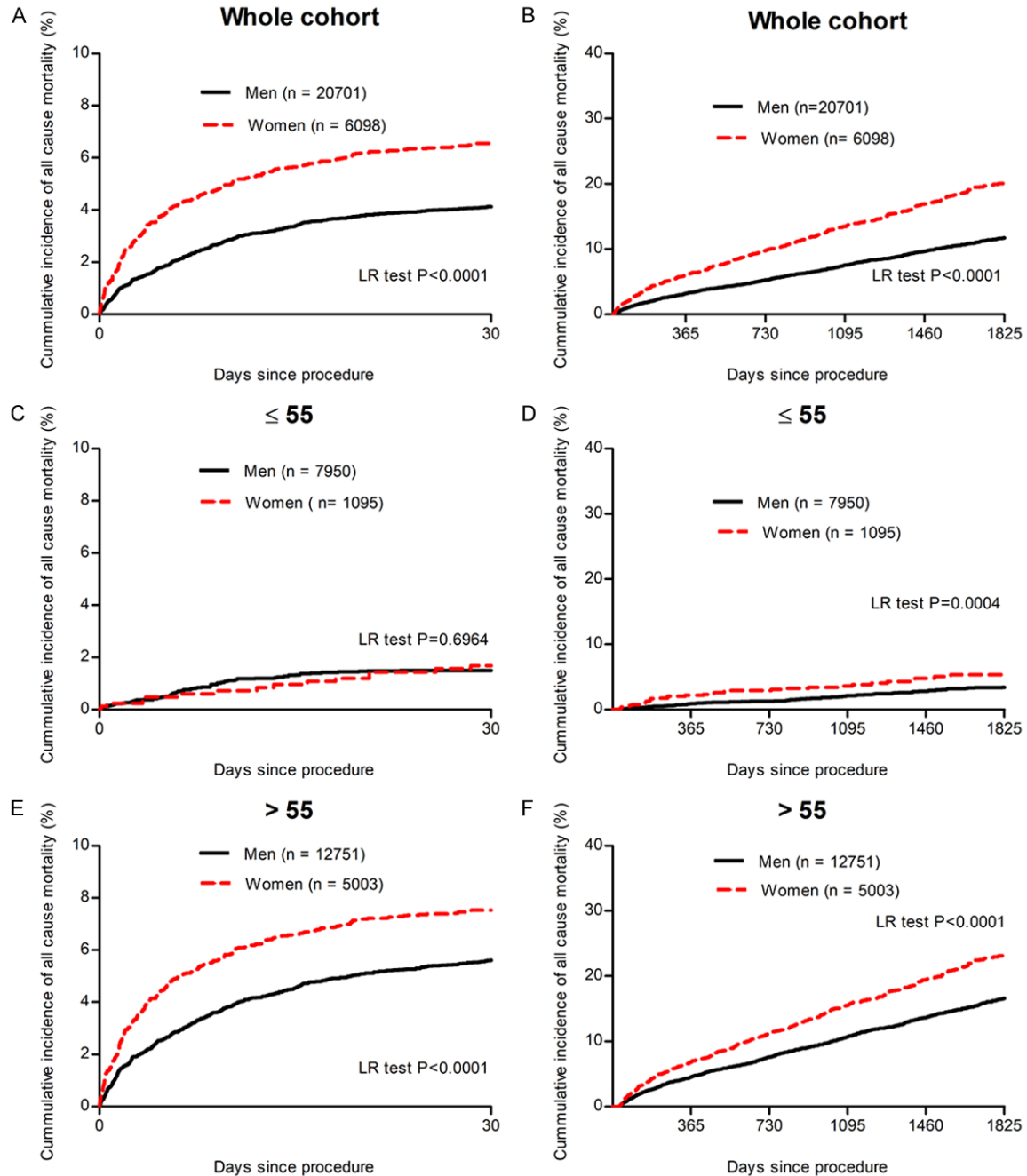


Figure 1. Survival rates in patients over the study period: Kaplan Meier curves showing cumulative probability of all-cause mortality after PCI according to group at 5 years, (A) landmark analysis up to 30 days in the whole cohort, (B) from 30 days to 5 years in the whole cohort, (C) landmark analysis up to 30 days in the less than 55 age group, (D) from 30 days to 5 years in the less than 55 age group, (E) landmark analysis up to 30 days in the greater than 55 age group, (F) from 30 days to 5 years in the greater than 55 age group.

whole cohort when accounting for co-variables the influence of sex was lost. In contrast to men, increasing age did not influence risk in younger women, however at the approximate time of menopause, age did influence outcome for women. We suggest that these results, in a true STEMI cohort, intimate that whilst female

sex itself predisposes to a worse outcome than men that this phenomenon is worse in older women where the benefits of female sex hormones no longer apply.

Once age-matched the evidence, to date, suggests that women suffering a STEMI not only

Sex differences following PPCI for STEMI

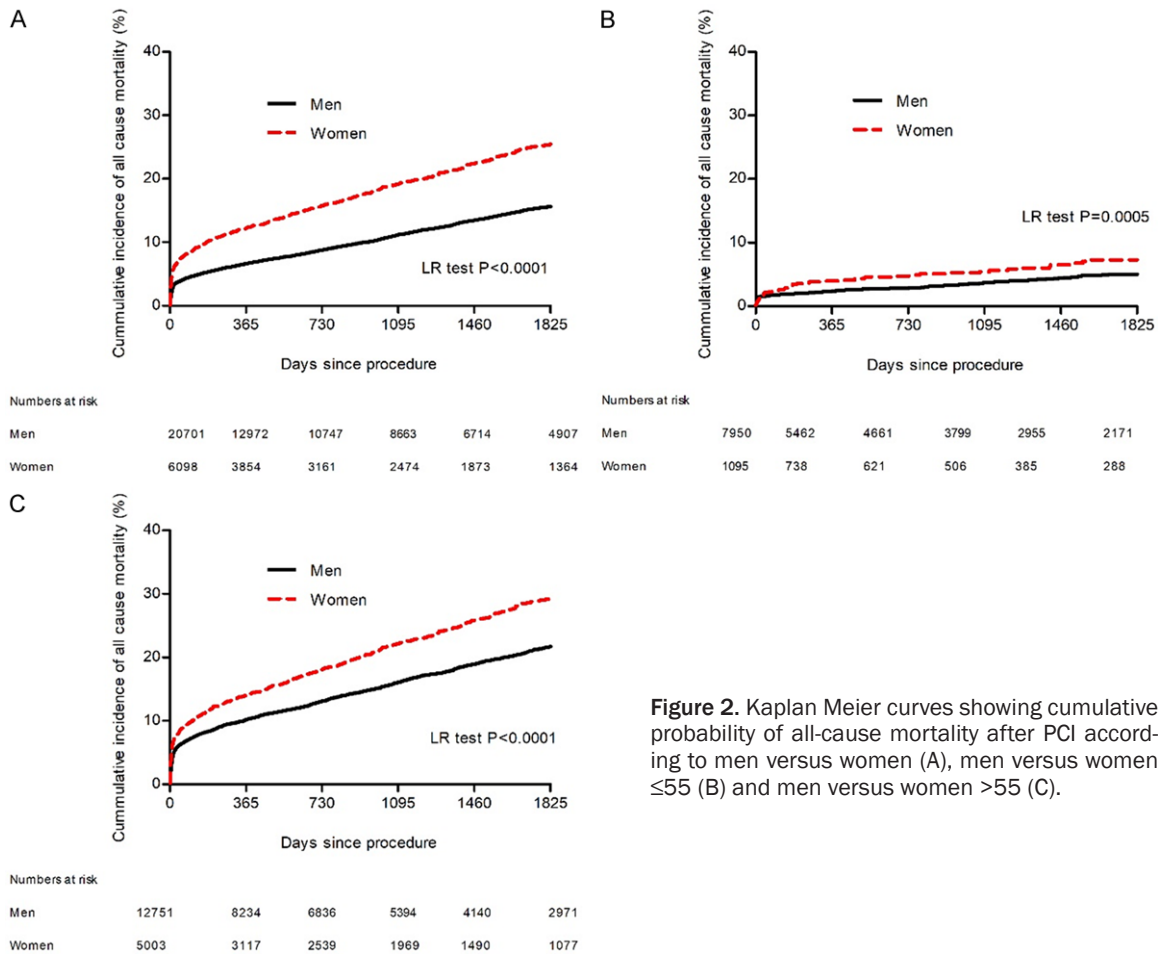


Figure 2. Kaplan Meier curves showing cumulative probability of all-cause mortality after PCI according to men versus women (A), men versus women ≤55 (B) and men versus women >55 (C).

have a worse prognosis with in-hospital mortality rates overall being higher [31, 32], but also have a greater risk of events following optimal therapy post-PCI [9]. Most importantly, and perhaps more worryingly, in sizeable cohorts the evidence suggests that this is particularly true for younger patients and less relevant for older women [8, 33-35]. A number of reasons have been cited as possible causes for this including: risk factors [36] and differences in clinical presentation resulting in delays in treatment [37]. Although mortality after primary PCI is decreasing, the 30-day mortality in women is still high (i.e. 13.7% in 1995 compared to 4.4% in 2010 in the US); our data with 5% in-hospital mortality in the women and 3.3% in men and higher cardiogenic shock concurs with this, although it is substantially less than in recent European cohorts (7.1%) [35]. However, where our data differ is that this difference is driven by women in the post-menopausal years, whilst this cannot be said for younger women.

It is unlikely that the above increased mortality in women >55 years compared to men is due to differences in the care pathway. Women in the Pan-London cohort, as in many other cohorts, are more likely to breach the recommended time of reperfusion (call-to-balloon times) compared to men [34], whether they were younger or older women. In addition, there were no statistically significant differences in the door-to-balloon times within either age group between the sexes. The "Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients2" (VIRGO) study found sex differences in 1,238 young patients (<55 years of age) presenting with STEMI, who were eligible for reperfusion therapy between 2008-2012 in the USA [34], observations replicated in another large US database of 632,930 patients who were less than 60 years of age presenting with STEMI between 2004 and 2011 [38]. However, in these studies it was shown that women were much less likely to

Sex differences following PPCI for STEMI

Table 6. Cox proportional model of univariate and multivariate analysis of predictors of mortality in overall cohort of men versus women

Variable	Comparator	Univariate	Multivariate*
Age (per year)		1.07 (1.07-1.08)	1.07 (1.06-1.08)
Women	Men	1.69 (1.59-1.82)	1.05 (0.90-1.25)
Ethnicity (Asian)	Caucasian	1.27 (1.17-1.37)	1.05 (0.89-1.25)
Cardiogenic Shock	No Cardiogenic Shock	4.38 (4.02-4.77)	3.51 (2.87-4.29)
Diabetes	No diabetes	1.57 (1.45-1.69)	1.43 (1.20-1.71)
Previous MI	No previous MI	1.58 (1.47-1.70)	1.13 (0.92-1.39)
Previous CABG	No Previous CABG	1.87 (1.67-2.09)	1.17 (0.89-1.54)
Previous PCI	No previous PCI	1.39 (1.27-2.51)	1.03 (0.80-1.32)
Hypertension	No hypertension	1.49 (1.40-1.60)	1.01 (0.86-1.18)
Hypercholesterolaemia	No hypercholesterolaemia	1.15 (1.07-1.23)	1.001 (0.86-1.18)
History of smoking	Never smoked	1.31 (1.22-1.40)	1.30 (1.12-1.51)
eGFR<60 ml/min/1.73 m ²	eGFR>60	4.37 (3.79-5.05)	2.37 (1.67-3.36)
EF<35%	EF>35%	2.11 (1.85-2.39)	1.84 (1.50-2.24)
GP IIb/IIIa inhibitor use	No GP IIb/IIIa inhibitor use	0.67 (0.63-0.72)	0.78 (0.68-0.91)
Procedural success	Procedural failure	0.49 (0.44-0.54)	0.77 (0.62-0.96)
Access route (femoral)	Radial	0.74 (0.68-0.81)	0.95 (0.81-1.11)
Multi-vessel disease	Single-vessel disease	1.75 (1.64-1.86)	1.40 (1.21-1.62)

*Adjusted for age, sex, previous MI, eGFR<60 ml/min/1.73 m², EF<35%, Hypertension (systolic BP≥140 mmHg), Hypercholesterolemia (total cholesterol ≥5.0 mmol/L), procedural success, multivessel disease, GP IIb/IIIa use, multivessel disease and IABP use. Legend: MI = myocardial infarction, PCI = percutaneous coronary intervention, GP IIb/IIIa = glycoprotein II/IIIa inhibitor, CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, NA = Not applicable.

Table 7. The effect of age on the sex association by including an age*sex interaction with age centred at the median (62) after adjustment for covariates. After adjustment for covariates there is no significant age by sex interaction (P=0.21)

t	Hazard Ratio	Standard Error	Z	P> [z]	[95% Confidence Interval]	
Ethnicity	1.06	0.95	0.68	0.500	0.89	1.27
Cardiogenic Shock	3.06	0.32	10.57	0.000	2.49	3.77
Diabetes	1.39	0.12	3.63	0.000	1.16	1.65
Previous CABG	1.24	0.17	1.54	0.123	0.94	1.63
Previous PCI	0.08	0.12	0.68	0.494	0.87	1.33
Hypertension	1.01	0.08	0.16	0.872	0.87	1.18
Hypercholesterolaemia	1.01	0.08	0.14	0.886	0.87	1.18
History of Smoking	1.30	0.10	3.42	0.001	1.12	1.51
EGFR<60 ml/min/1.73 m ²	2.45	0.43	5.10	0.000	1.74	3.46
EF<35%	2.19	0.27	6.43	0.000	1.73	2.78
GP IIb/IIIa inhibitor use	0.78	0.06	-3.07	0.002	0.66	0.91
Procedural success	0.74	0.08	-2.80	0.005	0.59	0.91
Access route (radial)	0.90	0.08	-1.26	0.207	0.76	1.06
Multivessel disease	1.30	0.10	3.39	0.001	1.12	1.51
Female	1.16	0.13	1.28	0.200	0.92	1.46
Age 62	1.07	0.004	17.36	0.000	1.06	1.08
Sex x Age 62	0.99	0.01	-1.24	0.214	0.98	1.01

eGFR<60 ml/min/1.73 m², Hypertension (systolic BP≥140 mmHg), Hypercholesterolemia (total cholesterol ≥5.0 mmol/L).

undergo coronary angiography, and hence receive revascularisation therapy, compared to

men, and that those women who underwent revascularisation suffered from significant

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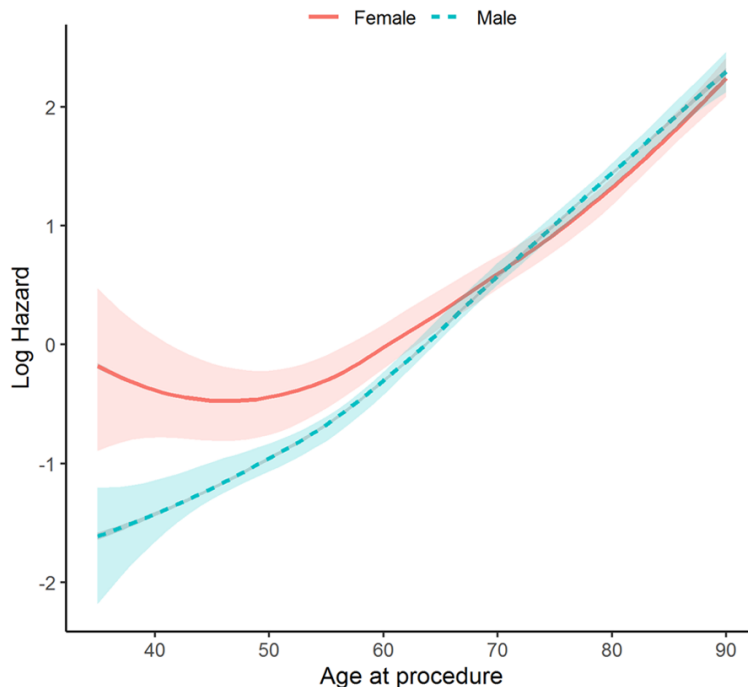


Figure 3. Spline plot for a non-linearly related risk factor. Association between age and log hazard (of overall all-cause mortality). The cut-points used are the age at procedure (40, 50, 60, 70, 80 and 90). The shaded regions show 95% CIs.

delays in both door-to-needle time for fibrinolytic therapy and door-to-balloon time for treatment with PCI [34]. Factors are not the case in the Pan-London Cohort.

There are many possible explanations for the longer call-to-balloon times. These include bias in the response to emergency calls, the possibility that women underestimate their symptoms and denial, but also that there are acknowledged differences in presentation between the sexes. Atypical symptoms are more common in women experiencing MI [39, 40], and although retrosternal chest pain is found in approximately 70% of patients of both sexes, women have higher rates of other symptoms such as shortness of breath, nausea, back pain or palpitations which can lead to a delay in the diagnosis of MI. Additionally, for women <55 years at least, their sex appears to be an independent predictor of not diagnosing an AMI or unstable angina [41]. Improved awareness of the underestimation of symptoms by both caller [42] and those receiving the call may offer opportunities to improve this. Investigating the underlying cause for the differences in call-to-balloon times between the

two sexes is an important finding that warrants further investigation.

Risk factor profile in women

It has been suggested that women have more co-morbidities as well as risk factors compared to their male counterparts, despite CHD appearing 5-10 years later than men. After the age of 50, women have higher cholesterol and triglyceride levels and therefore higher risk of CAD [43-46]. Women are also more likely to suffer from hypertension and diabetes [33, 47-50], and some evidence suggests that women with diabetes have a higher event rate post-PCI [51]. Indeed, there was a higher incidence of diabetes in women in the >55 group but not the <55, and diabetes remains an independent predictor of outcome post-PCI in

the older group with multivariate analysis. Importantly, our analysis shows no significant interaction between age and sex supporting the view that sex and not age in older women underlies the negative influence over outcome.

Although the rates of smoking are lower in women compared to men, in London, in both age groups the trends of smoking rates are alarmingly high (~41 versus 55% respectively), and smoking remained a predictor of risk with multivariate analysis for both sexes. In the FAST-MI study, whilst 40% of the cohort were smokers in 1995 by 2010 the percentage had risen to more than 70% [52]; similar rates to those identified in the VIRGO [34] study. Furthermore, there is evidence indicating that the harmful effects of tobacco are greater in women; smoking associated with a 1.57 increase in risk of MI in women compared to men, a risk that was even higher in women <55 years [53]. Stratification of the Pan-London cohort by age demonstrated herein, that whilst smoking did not influence outcome in younger men or women that the negative effect of smoking upon outcome post-PCI was driven by the >55 s group. This link between smoking and

age confirms recent observations in a single Centre South Yorkshire (UK) study [54].

Socioeconomic status and outcome

Two of the domains contributing to the English IMD score are 'income' and 'education, skills and training' deprivation. These variables have a potentially important influence on behaviour related to outcome in patients with vascular disease. Change leading to risk factor modification, uptake of cardiac rehabilitation, and compliance with medications are likely to be affected by these variables which may affect cardiovascular and non-cardiovascular mortality [55-57]. However, within our study, we found that women had a worse outcome post-PCI compared to men regardless of socioeconomic status. It was only in Quintile 5, the least deprived in our society, where there was no difference between the sexes, although the numbers of individuals in this category were very small and so substantially underpowered for statistical analysis. Our observations are in keeping with a recent large systematic review and meta-analysis investigating more generally whether sex differences exist in the association of socioeconomic status and cardiovascular disease. In a study of over 22 million adults (35% women), with 1,078,459 events identified (701,617 had CHD), lower socioeconomic status was associated with increased risk of CHD in women and men. In this study women with the lowest level of education had a 24% higher excess risk of CHD compared with men (age-adjusted ratio of the RR [RRR], 1.24 [1.09-1.41]) [58]. Whether this observation also holds true for those experiencing a second event was not assessed. In agreement with our observations others have shown that older women in lower socioeconomic status have worse outcomes compared to men [59]. However, with regards to ethnicity, previous studies demonstrate no differences in MACE or mortality in women, or in South Asian patients following primary PCI despite adjustment in univariable or multivariable analyses [60, 61].

Differences in the treatment pathway and pathophysiology

Differences in the atherosclerotic process between the sexes have been observed. This fact is in part reflected by the observation that non-obstructive coronary disease is more common in women compared to men [62-64]. Stu-

die have also found differences in the composition of atheromatous plaques according to sex and age [65]. These studies show greater calcium, plaque volume and fibroatheromas with age but that in women <65 these indices are more marked compared to men, with a loss of these apparent differences in the over 65 s. In agreement with these findings, is the Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty (OCTAVIA) study, where both men and women (with a mean age of 67.8 ± 10.4 years and thus post-menopausal) presenting with a STEMI, had plaque rupture that was associated with the usual risk factors [66]. In addition, in a sub-study of the PROSPECT trial those women with thin cap fibroatheroma (TCFA) had greater plaque vulnerability with a predilection for rupture compared to men [65, 67], suggesting fundamental differences in the pathophysiology of plaque formation between the sexes. In addition, evidence suggests more plaque erosions and more vulnerable plaque in post-menopausal women versus pre-menopausal women [68]. Whether these differences underlie the differences evident post-PCI in the >55 cohort in the present study is unknown.

Much evidence supports the view that female sex hormones, particularly oestrogen, are protective [69, 70]. Our analysis whilst possibly supporting this view, does not provide definitive proof due to the absence of any measurements of menopausal status, hormonal levels or hormone therapy use. However, our data inevitably raises the question of whether restoring sex hormone levels with replacement therapy in post-menopausal women could procure benefits both from a clinical as well as a health economic point of view. In the UK the negative backlash from the outcome of the Women's Health Initiative study [71] is still being felt despite efforts by NICE and the NHS supporting the use of hormone replacement therapy for the treatment of menopausal symptoms. The routine assessment of hormonal levels in patients and the collection of this data could help to provide valuable information that would add to the discussion assessing the potential of therapeutics based upon oestrogen for secondary prevention post-PCI and enable analysis comparing the outcomes of women on hormone replacement therapy with men.

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Further analysis using spline terms suggested that there is a non-linear effect, with risk accelerating at older ages. Furthermore, the data revealed that although the risk is higher in younger women, that this risk does not increase with age up until approximately 51 years [72]. This profile is very different to that in men where the risk in men increases in a linear fashion with age. These results suggest that at least prior to the menopausal years women are protected from the negative effects of ageing. The causes of this difference are uncertain but likely relate to the positive effects of female sex hormones against the effects of those lifestyle stimuli (e.g. unhealthy diet, lack of exercise, exposure to environmental pollutants) thought to precipitate damage to the coronary endothelium through triggering of the synthesis of for example excessive reactive oxygen species and pro-hypertrophic mediators [73, 74].

Strengths and limitations of this study

A key strength of this study is that it includes patients from 8 different centres in a large metropolitan city with a diverse ethnic and social make up. Perhaps the key limitation of our study design is that it is observational, and as such the results may be biased if the two groups are different in ways other than their sex. Although we adjusted for certain characteristics using extensive multivariable models, residual confounding due to selection and adherence biases may still be present.

The study also includes patients with cardiogenic shock, previous bypass surgery, and other co-morbidities and is thus representative of the broad range of patients encountered in day-to-day clinical practice. Whilst inclusion of such patients may result in bias, the baseline characteristics were similar and any differences were adjusted for in the multivariate analyses. To further account for confounding variables and bias, propensity analyses was performed. Mortality tracking in England is particularly robust and based on official UK Office of National Statistics data and hence our mortality end point is reliable.

Whilst the multivariate analyses highlight the quality of the data this study has all the limitations of a registry and all the potential bias and unmeasured confounding associated with non-randomised studies.

The absence of any quantifiable measures of menopause and hormonal status limit our ability to identify the role of sex hormones in any effects seen. This point is of particular importance since our results suggest a difference in outcome for those women who should have reduced levels of sex hormones precipitated by the menopause. Introduction of measurements of hormonal status in patients presenting with STEMI, as a standard of care, would allow assessment of the potential link between endogenous sex hormone levels and outcome. But perhaps more importantly this information could support clinical decision-making and advice to patients post-PCI regarding the additional risks that may come with reduction of female sex hormones precipitated by the menopause.

An important limitation that should also be considered is that this database provides incomplete data on procedure medications, discharge medications as well as data regarding optimal medical therapy. This information would have been of value in assessing further risk for future cardiac events and thus we cannot rule out the possibility that differences here may also have impacted upon outcome.

It is also important to note that the rates of emergency CABG and CVA in our cohort are lower than other studies investigating sex differences in patients post-PCI with STEMI [75, 76] and possibly due to London being far more metropolitan compared to other cities and other Western Populations. We feel that this aspect of this cohort adds greater interest since it describes a group of broader diversity in ethnicity and social status reflecting modern large urbanised and cosmopolitan cities. However, there have been studies demonstrating similar rates of CABG and CVA to ours from large metropolitan cities [77].

Finally, despite the size of the overall cohort of just over 20,000, only 6098 were women with only 1095 aged under 55 and only 78 events overall in this age group. Thus, it is possible that our observations in this group relate to a type II error caused by insufficient power. We suggest that further studies assessing sex differences in larger cohorts will be important to corroborate our observations.

Conclusion

Although there are a number of differences between women and men in terms of risk factors, symptomology as well as treatment care pathway in STEMI, there must be other factors resulting in the poor outcome seen in women post-PCI. We take this view since our analysis found worse prognosis in women >55 years even after adjusting for confounding variables. This suggests that characteristics of premenopausal women may protect against worse outcome following PCI. An attractive mechanism for this protection relates to beneficial effects of the female sex hormones, particularly oestrogen. We suggest that hormone levels measured as a standard of care and assessment of use of hormone replacement therapy becomes standard practice for all patients presenting with AMI. Without this information to inform large database collections, or large multi-centre trials assessing why the risk in women increases substantially post-menopause, women will continue to be inadequately served by modern health systems.

Our data do not concur with the large studies assessing similar outcomes in the USA, suggesting that regional differences apply. Interestingly, race or socioeconomic status is not the driver of the regional differences indicating that the cosmopolitan nature of London may have undescribed benefits. Our evidence indicates that continued vigilance in equity of treatment is required but that better targeted approaches in secondary prevention, as well as for primary prevention post STEMI and PCI, are needed for women. Identification of what these targeted approaches might be remain uncertain but can only be developed following a better understanding of the pathophysiology underlying these inequalities.

Disclosure of conflict of interest

None.

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References

[1] GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific

mortality for 264 causes of death, 1980&-2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2017; 390: 1151-1210.

[2] Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G, Gitt A, Hasdai D, Hasin Y, Marrugat J, Van de Werf F, Wallentin L and Behar S; Euro Heart Survey Investigators. The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the mediterranean basin in 2004. *Euro Heart J* 2006; 27: 2285-2293.

[3] Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV and Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med* 2010; 362: 2155-2165.

[4] Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M and Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 2016; 37: 3232-3245.

[5] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS and Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation* 2019; 139: e56-e528.

[6] Lerner DJ and Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1986; 111: 383-390.

[7] Weaver WD, White HD, Wilcox RG, Aylward PE, Morris D, Guerci A, Ohman EM, Barbash GI, Betti A, Sadowski Z, Topol EJ and Califf RM. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. GUSTO-I investigators. *JAMA* 1996; 275: 777-782.

[8] Lansky AJ, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, Aymong ED, Stuckey TD, Garcia E, Tchong JE, Mehran R, Negoita M, Fahy M, Cristea E, Turco M, Leon MB, Grines CL and Stone GW. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the controlled

Sex differences following PPCI for STEMI

- abciximab and device investigation to lower late angioplasty complications (CADILLAC) trial. *Circulation* 2005; 111: 1611-1618.
- [9] Iantorno M, Torguson R, Kolm P, Gajanana D, Suddath WO, Rogers T, Bernardo NL, Ben-Dor I, Gai J, Satler LF, Garcia-Garcia HM, Weintraub WS and Waksman R. Relation of sex and race to outcomes in patients undergoing percutaneous intervention with drug-eluting stents. *Am J Cardiol* 2018; 123: 913-918.
- [10] Ezekowitz Justin A, Savu A, Welsh Robert C, McAlister Finlay A, Goodman Shaun G and Kaul P. Is there a sex gap in surviving an acute coronary syndrome or subsequent development of heart failure? *Circulation* 2020; 142: 2231-2239.
- [11] Scholz KH, Maier SKG, Maier LS, Lengenfelder B, Jacobshagen C, Jung J, Fleischmann C, Werner GS, Olbrich HG, Ott R, Mudra H, Seidl K, Schulze PC, Weiss C, Haimerl J, Friede T and Meyer T. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. *Eur Heart J* 2018; 39: 1065-1074.
- [12] Wei J, Mehta PK, Grey E, Garberich RF, Hauser R, Bairey Merz CN and Henry TD. Sex-based differences in quality of care and outcomes in a health system using a standardized STEMI protocol. *Am Heart J* 2017; 191: 30-36.
- [13] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P and Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; 39: 119-177.
- [14] Ludman PF; British Cardiovascular Intervention Society. British cardiovascular intervention society registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart* 2011; 97: 1293-1297.
- [15] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R and Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2018; 40: 87-165.
- [16] Angeja BG, Shlipak MG, Go AS, Johnston SC, Frederick PD, Canto JG, Barron HV and Grady D; National Registry of Myocardial Infarction 3 Investigators. Hormone therapy and the risk of stroke after acute myocardial infarction in postmenopausal women. *J Am Coll Cardiol* 2001; 38: 1297-1301.
- [17] NHS. Menopause. <https://www.nhs.uk/conditions/menopause/> accessed April 2020.
- [18] Department for Communities and Local Government. The english index of multiple deprivation (IMD) 2015-guidance. 2015
- [19] Maunder P, Landes DP and Steen N. The equity of access to primary dental care for children in the North East of England. *Community Dent Health* 2006; 23: 116-119.
- [20] Bello AK, Peters J, Rigby J, Rahman AA and El Nahas M. Socioeconomic status and chronic kidney disease at presentation to a renal service in the United Kingdom. *Clin J Am Soc Nephrol* 2008; 3: 1316-1323.
- [21] Maheswaran R, Elliott P and Strachan DP. Socioeconomic deprivation, ethnicity, and stroke mortality in Greater London and south east England. *J Epidemiol Community Health* 1997; 51: 127-131.
- [22] Leigh Y, Seagroatt V, Goldacre M and McCulloch P. Impact of socio-economic deprivation on death rates after surgery for upper gastrointestinal tract cancer. *Br J Cancer* 2006; 95: 940-943.
- [23] Greenland S and Robins J. Invited commentary: ecologic studies—biases, misconceptions, and counterexamples. *Am J Epidemiol* 1994; 139: 747-760.
- [24] Inclusion. OCfS. Why the indices of deprivation are still important in the open data era. 2011.
- [25] Eilers PHC, Rijnmond DM and Marx BD. Flexible smoothing with B-splines and penalties. *Stat Sci* 1996; 11: 89-121.
- [26] Chung SC, Gedeberg R, Nicholas O, James S, Jeppsson A, Wolfe C, Heuschmann P, Wallentin L, Deanfield J, Timmis A, Jernberg T and Hemingway H. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet* 2014; 383: 1305-1312.
- [27] Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M and Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015; 36: 1163-1170.
- [28] Johnston N, Jonelid B, Christersson C, Kero T, Renlund H, Schenck-Gustafsson K and Lagerqvist B. Effect of gender on patients with ST-elevation and non-ST-elevation myocardial infarction without obstructive coronary artery disease. *Am J Cardiol* 2015; 115: 1661-1666.

Sex differences following PPCI for STEMI

- [29] Lam CS, McEntegart M, Claggett B, Liu J, Skali H, Lewis E, Kober L, Rouleau J, Velazquez E, Califf R, McMurray JJ, Pfeffer M and Solomon S. Sex differences in clinical characteristics and outcomes after myocardial infarction: insights from the valsartan in acute myocardial infarction trial (VALIANT). *Eur J Heart Fail* 2015; 17: 301-312.
- [30] Redfors B, Angeras O, Ramunddal T, Petursson P, Haraldsson I, Dworeck C, Odenstedt J, Ioaness D, Ravn-Fischer A, Wellin P, Sjolund H, Tokgozoglu L, Tygesen H, Frick E, Roupe R, Albertsson P and Omerovic E. Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish web system for enhancement of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *J Am Heart Assoc* 2015; 4: e001995.
- [31] Vaccarino V, Krumholz HM, Yarzebski J, Gore JM and Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001; 134: 173-181.
- [32] Vaccarino V, Parsons L, Every NR, Barron HV and Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National registry of myocardial infarction 2 participants. *N Engl J Med* 1999; 341: 217-225.
- [33] Champney KP, Frederick PD, Bueno H, Parashar S, Foody J, Merz CN, Canto JG, Lichtman JH and Vaccarino V; NRM I Investigators. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. *Heart* 2009; 95: 895-899.
- [34] D'Onofrio G, Safdar B, Lichtman JH, Strait KM, Dreyer RP, Geda M, Spertus JA and Krumholz HM. Sex differences in reperfusion in young patients with ST-segment-elevation myocardial infarction: results from the VIRGO study. *Circulation* 2015; 131: 1324-1332.
- [35] Cenko E, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Krljanac G, Kalpak O, Ricci B, Milicic D, Manfrini O, van der Schaar M, Badimon L and Bugiardini R. Sex differences in outcomes after STEMI: effect modification by treatment strategy and age. *JAMA Intern Med* 2018; 178: 632-639.
- [36] Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S and Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008; 29: 932-940.
- [37] Canto AJ, Kiefe CI, Goldberg RJ, Rogers WJ, Peterson ED, Wenger NK, Vaccarino V, Frederick PD, Sopko G, Zheng ZJ and Canto JG. Differences in symptom presentation and hospital mortality according to type of acute myocardial infarction. *Am Heart J* 2012; 163: 572-579.
- [38] Khera S, Kolte D, Gupta T, Subramanian KS, Khanna N, Aronow WS, Ahn C, Timmermans RJ, Cooper HA, Fonarow GC, Frishman WH, Panza JA and Bhatt DL. Temporal trends and sex differences in revascularization and outcomes of ST-segment elevation myocardial infarction in younger adults in the United States. *J Am Coll Cardiol* 2015; 66: 1961-1972.
- [39] Gallagher R, Marshall AP and Fisher MJ. Symptoms and treatment-seeking responses in women experiencing acute coronary syndrome for the first time. *Heart Lung* 2010; 39: 477-484.
- [40] Shin JY, Martin R and Suls J. Meta-analytic evaluation of gender differences and symptom measurement strategies in acute coronary syndromes. *Heart Lung* 2010; 39: 283-295.
- [41] Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, Griffith JL and Selker HP. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000; 342: 1163-1170.
- [42] Benamer H, Bataille S, Tafflet M, Jabre P, Dupas F, Laborne FX, Lapostolle F, Lefort H, Juliard JM, Letarnec JY, Lamhaut L, Lebaill G, Boche T, Loyeau A, Caussin C, Mapouata M, Karam N, Jouven X, Spaulding C and Lambert Y. Longer pre-hospital delays and higher mortality in women with STEMI: the e-MUST registry. *EuroIntervention* 2016; 12: e542-549.
- [43] Hokanson JE and Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 1996; 3: 213-219.
- [44] Tremollieres FA, Pouilles JM, Cauneille C and Ribot C. Coronary heart disease risk factors and menopause: a study in 1684 French women. *Atherosclerosis* 1999; 142: 415-423.
- [45] Brown SA, Hutchinson R, Morrisett J, Boerwinkle E, Davis CE, Gotto AM Jr and Patsch W. Plasma lipid, lipoprotein cholesterol, and apoprotein distributions in selected US communities. The atherosclerosis risk in communities (ARIC) study. *Arterioscler Thromb* 1993; 13: 1139-1158.
- [46] Davis CE, Pajak A, Rywik S, Williams DH, Broda G, Pazucha T and Ephross S. Natural menopause and cardiovascular disease risk factors. The Poland and US collaborative study on cardiovascular disease epidemiology. *Ann Epidemiol* 1994; 4: 445-448.
- [47] Hvelplund A, Galatius S, Madsen M, Rasmussen JN, Rasmussen S, Madsen JK, Sand NP,

Sex differences following PPCI for STEMI

- Tilsted HH, Thayssen P, Sindby E, Hojbjerg S and Abildstrom SZ. Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. *Eur Heart J* 2010; 31: 684-690.
- [48] Jakobsen L, Niemann T, Thorsgaard N, Nielsen TT, Thuesen L, Lassen JF, Jensen LO, Thayssen P, Ravkilde J, Tilsted HH, Mehnert F and Johnsen SP. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention* 2012; 8: 904-911.
- [49] Schiele F, Meneveau N, Seronde MF, Descotes-Genon V, Chopard R, Janin S, Briand F, Guignier A, Ecarnot F and Bassand JP. Propensity score-matched analysis of effects of clinical characteristics and treatment on gender difference in outcomes after acute myocardial infarction. *Am J Cardiol* 2011; 108: 789-798.
- [50] Velders MA, Boden H, van Boven AJ, van der Hoeven BL, Heestermans AA, Cannegieter SC, Umans VA, Jukema JW, Hofma SH and Schalij MJ. Influence of gender on ischemic times and outcomes after ST-elevation myocardial infarction. *Am J Cardiol* 2013; 111: 312-318.
- [51] Bundhun PK, Pursun M and Huang F. Are women with type 2 diabetes mellitus more susceptible to cardiovascular complications following coronary angioplasty?: a meta-analysis. *BMC Cardiovasc Disord* 2017; 17: 207.
- [52] Puymirat E, Simon T, Steg PG, Schiele F, Guéret P, Blanchard D, Khalife K, Goldstein P, Cattan S, Vaur L, Cambou JP, Ferrières J and Danchin N; USIK USIC 2000 Investigators; FAST MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA* 2012; 308: 998-1006.
- [53] Prescott E, Hippe M, Schnohr P, Hein HO and Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998; 316: 1043-1047.
- [54] Steele L, Palmer J, Lloyd A, Fotheringham J, Iqbal J and Grech ED. The impact of smoking on mortality after acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: a retrospective cohort outcome study at 3 years. *J Thromb Thrombolysis* 2019; 47: 520-526.
- [55] Beauchamp A, Worcester M, Ng A, Murphy B, Tatoulis J, Grigg L, Newman R and Goble A. Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. *Heart* 2013; 99: 620-625.
- [56] Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, Masoudi FA and Rumsfeld JS. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J* 2008; 155: 772-779.
- [57] Jaber WA, Lennon RJ, Mathew V, Holmes DR Jr, Lerman A and Rihal CS. Application of evidence-based medical therapy is associated with improved outcomes after percutaneous coronary intervention and is a valid quality indicator. *J Am Coll Cardiol* 2005; 46: 1473-1478.
- [58] Backholer K, Peters SAE, Bots SH, Peeters A, Huxley RR and Woodward M. Sex differences in the relationship between socioeconomic status and cardiovascular disease: a systematic review and meta-analysis. *J Epidemiol Community Health* 2017; 71: 550-557.
- [59] Jenkins KR and Ofstedal MB. The association between socioeconomic status and cardiovascular risk factors among middle-aged and older men and women. *Women Health* 2014; 54: 15-34.
- [60] Edmund Anstey D, Li S, Thomas L, Wang TY and Wiviott SD. Race and sex differences in management and outcomes of patients after ST-elevation and non-ST-elevation myocardial infarct: results from the NCDR. *Clin Cardiol* 2016; 39: 585-595.
- [61] Krishnamurthy A, Keeble C, Burton-Wood N, Somers K, Anderson M, Harland C, Baxter PD, McLenachan JM, Blaxill JM, Blackman DJ, Malikin CJ, Wheatcroft SB and Greenwood JP. Clinical outcomes following primary percutaneous coronary intervention for ST-elevation myocardial infarction according to sex and race. *Eur Heart J Acute Cardiovasc Care* 2019; 8: 264-272.
- [62] Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, Simes RJ, White HD, Van de Werf F, Topol EJ, Hochman JS, Newby LK, Harrington RA, Califf RM, Becker RC and Douglas PS. Sex differences in mortality following acute coronary syndromes. *JAMA* 2009; 302: 874-882.
- [63] Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Lerman A, Quyyumi AA and Sopko G; WISE Investigators. Insights from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006; 47 Suppl: S21-29.
- [64] Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, Pena-Sing I, Axel L, Attubato MJ, Yatskar L, Kalhorn RT, Wood DA, Lobach IV and Hochman JS. Mechanisms of myocardial

Sex differences following PPCI for STEMI

- infarction in women without angiographically obstructive coronary artery disease. *Circulation* 2011; 124: 1414-1425.
- [65] Ruiz-Garcia J, Lerman A, Weisz G, Maehara A, Mintz GS, Fahy M, Xu K, Lansky AJ, Cristea E, Farah TG, Teles R, Botker HE, Templin B, Zhang Z, de Bruyne B, Serruys PW and Stone GW. Age- and gender-related changes in plaque composition in patients with acute coronary syndrome: the PROSPECT study. *EuroIntervention* 2012; 8: 929-938.
- [66] Guagliumi G, Capodanno D, Saia F, Musumeci G, Tarantini G, Garbo R, Tumminello G, Sirbu V, Coccato M, Fineschi M, Trani C, De Benedictis M, Limbruno U, De Luca L, Niccoli G, Bezerra H, Ladich E, Costa M, Biondi Zoccai G and Virmani R; OCTAVIA Trial Investigators. Mechanisms of atherothrombosis and vascular response to primary percutaneous coronary intervention in women versus men with acute myocardial infarction: results of the OCTAVIA study. *JACC Cardiovasc Interv* 2014; 7: 958-968.
- [67] Dohi T, Mintz GS, McPherson JA, de Bruyne B, Farhat NZ, Lansky AJ, Mehran R, Weisz G, Xu K, Stone GW and Maehara A. Non-fibroatheroma lesion phenotype and long-term clinical outcomes: a substudy analysis from the PROSPECT study. *JACC Cardiovasc Imaging* 2013; 6: 908-916.
- [68] Burke AP, Farb A, Malcom G and Virmani R. Effect of menopause on plaque morphologic characteristics in coronary atherosclerosis. *Am Heart J* 2001; 141 Suppl: S58-62.
- [69] Vitale C, Mendelsohn ME and Rosano GM. Gender differences in the cardiovascular effect of sex hormones. *Nat Rev Cardiol* 2009; 6: 532-542.
- [70] Arnold AP, Cassis LA, Eghbali M, Reue K and Sandberg K. Sex hormones and sex chromosomes cause sex differences in the development of cardiovascular diseases. *Arterioscler Thromb Vasc Biol* 2017; 37: 746-756.
- [71] Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM and Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the women's health initiative randomized controlled trial. *JAMA* 2002; 288: 321-333.
- [72] Juhan N, Zubairi YZ, Zuhdi AS, Khalid ZM and Wan WA. Gender differences in mortality among ST elevation myocardial infarction patients in Malaysia from 2006 to 2013. *Ann Saudi Med* 2018; 38: 1-7.
- [73] Shufelt CL, Pacheco C, Tweet MS and Miller VM. Sex-specific physiology and cardiovascular disease. In: Kerkhof PLM, Miller VM, editors. *sex-specific analysis of cardiovascular function*. Cham: Springer International Publishing; 2018. pp. 433-454.
- [74] Stanhewicz AE, Wenner MM and Stachenfeld NS. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. *Am J Physiol Heart Circ Physiol* 2018; 315: H1569-H1588.
- [75] Gnani R, Rusciani R, Dalmaso M, Giammaria M, Anselmino M, Roggeri DP and Roggeri A. Gender, socioeconomic position, revascularization procedures and mortality in patients presenting with STEMI and NSTEMI in the era of primary PCI. Differences or inequities? *Int J Cardiol* 2014; 176: 724-730.
- [76] Worrall-Carter L, McEvedy S, Wilson A and Rahman MA. Gender differences in presentation, coronary intervention, and outcomes of 28,985 acute coronary syndrome patients in Victoria, Australia. *Womens Health Issues* 2016; 26: 14-20.
- [77] Heer T, Hochadel M, Schmidt K, Mehilli J, Zahn R, Kuck KH, Hamm C, Bohm M, Ertl G, Hoffmeister HM, Sack S, Senges J, Massberg S, Gitt AK and Zeymer U. Sex differences in percutaneous coronary intervention-insights from the coronary angiography and PCI registry of the German Society of Cardiology. *J Am Heart Assoc* 2017; 6: e004972.

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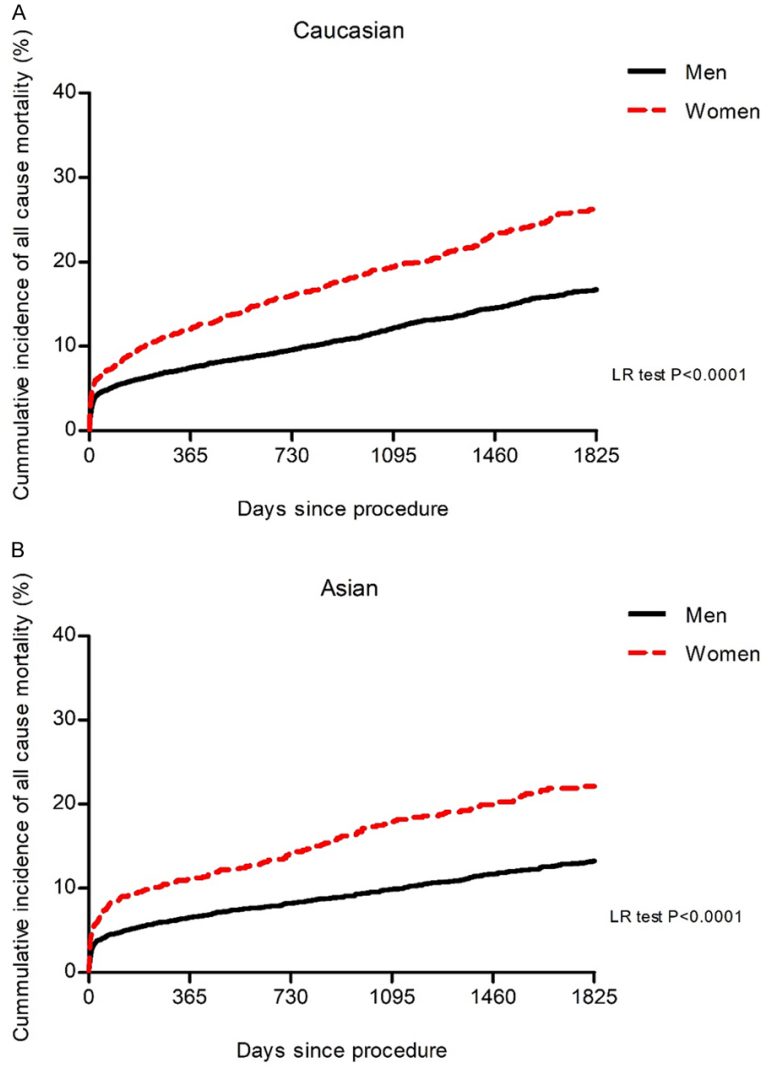


Figure S1. Kaplan Meier curves showing cumulative probability of all-cause mortality after PCI according to ethnicity (A) Caucasian and (B) Asian.

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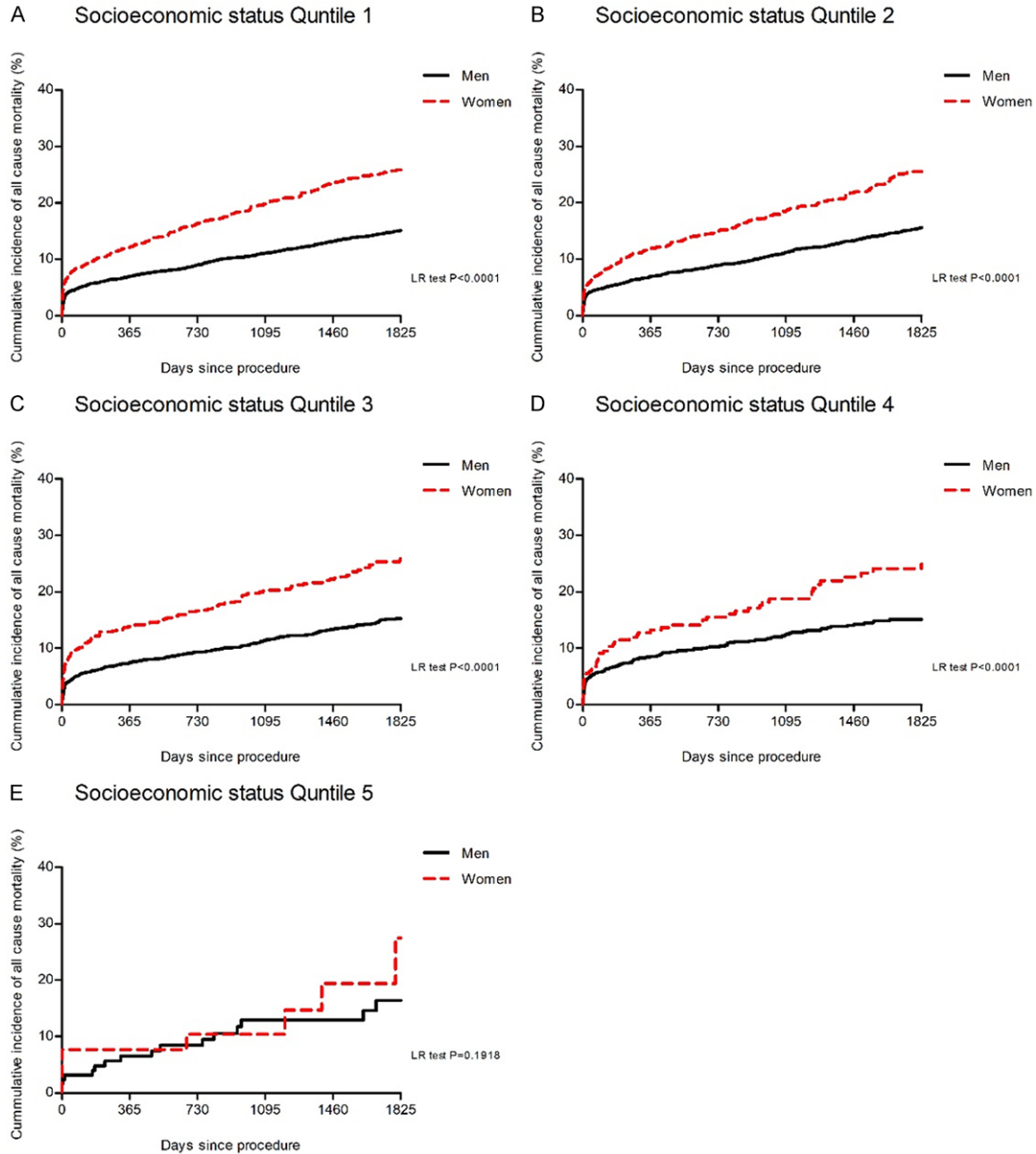


Figure S2. Kaplan Meier curves showing cumulative probability of all-cause mortality after PCI according to socio-economic status (A-E) Quintile 1-Quintile 5.