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Influence of gender on ischemic times and outcomes after ST-segment elevation myocardial infarction

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ABSTRACT

Aims

Previous studies investigating the influence of gender on ST-segment elevation myocardial infarction (STEMI) have reported conflicting results. The aim of this study was to assess the influence of gender on ischemic times and outcomes after STEMI in patients treated with primary percutaneous coronary intervention (PCI) in modern practice.

Methods

The present multicenter registry included consecutive STEMI patients treated with primary PCI at three hospitals. Adjusted mortality rates were calculated using Cox proportional-hazards analyses.

Results

In total, 3,483 patients were included, of whom 868 were women (25%). Women were older, had a higher risk factor burden and more frequently had a history of malignancy. Men suffered more often from previous cardiac history and peripheral vascular disease. Ischemic times were longer in women (median 192 min (IQR 141-286) vs. 175 min (128-279) in men, p=0.002). However, multivariate linear regression showed that this was due to age and comorbidity. All-cause mortality was higher at both seven days (6.0% in women vs. 3.0% in men, p<0.001) and one year (9.9% in women vs. 6.6% in men, p=0.001). After adjustment, female gender predicted seven day all-cause mortality (hazard ratio 1.61, 95% CI 1.06-2.46) and cardiac mortality (hazard ratio 1.58, 95% CI 1.03-2.42) but not 1-year mortality. Moreover, gender was an independent effect modifier for cardiogenic shock, leading to substantially worse outcome in women.

Conclusions

Ischemic times remain longer in women because of age and comorbidity. Female gender independently predicted early all-cause and cardiac mortality after primary PCI and a strong interaction between gender and cardiogenic shock was observed.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in men and women in the Western world.[1] In 2003, the total cost of CAD in the European Union was an estimated €45 billion, with approximately 1 million working years lost because of CAD mortality.[2] To reduce the huge burden of CAD, research aimed at the optimal recognition and treatment of CAD in both men and women is essential. Nonetheless, women are underrepresented in clinical trials of CAD.[3] It is known that risk factors for CAD bear different weight between men and women and that women with anginal symptoms more frequently show non-obstructive CAD on coronary angiography compared to men.[4-7] Moreover, women have consistently shown higher mortality rates after acute coronary syndromes (ACS), due to higher age and comorbidities.[8,9] However, in the specific ST-segment elevation myocardial infarction (STEMI) population, conflicting results have been reported.[8-14] Furthermore, previous studies lacked guideline-recommended treatment with primary percutaneous coronary intervention (PCI) or excluded high-risk patients commonly encountered in daily practice. Our goal was to investigate the influence of gender on ischemic times and outcomes after STEMI in patients treated with primary PCI in modern practice.

METHODS

The present Dutch multicenter registry prospectively included consecutive patients treated with primary PCI for STEMI at three tertiary centers in the Netherlands. Two high-volume centers in the north of the Netherlands, Medical Center Alkmaar and Medical Center Leeuwarden, provide 24/7 cardiac care for area's of 450,000 and 650,000 inhabitants, respectively. The Leiden University Medical Center serves an area of approximately 750,000 inhabitants.

Patients

Consecutive patients who underwent primary PCI for STEMI from January 2006 to December 2009 were included in the analysis. Interventions included passing of a guidewire through thrombus, thrombosuction, and/or percutaneous coronary balloon angioplasty with or without the placement of coronary stents. In case of out-of-hospital cardiac arrest (OHCA), only patients with return of spontaneous circulation at the moment of arrival at the catheterization laboratory were included. Furthermore, patients permanently living outside the Netherlands were excluded to make follow-up through municipality records possible. STEMI was defined as symptoms of angina lasting >30 minutes along with typical electrocardiographic (ECG) changes (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V_1 through V_3 or ≥0.1 mV in other leads or presumed new left bundle branch block).

Pre-hospital protocols included triage by 12-lead electrocardiographic findings in the field faxed to the operator on call and in-ambulance treatment with aspirin, intravenous heparin bolus and a loading dose of clopidogrel. Glycoprotein IIb/IIIa inhibitors were administered frequently, using up-front administration at the Leiden University Medical Center and periprocedural administration at the other hospitals. On arrival at the hospital, patients were transferred as soon as possible to the catheterization laboratory. Procedures were performed according to current clinical guidelines. Patients treated at the Leiden University Medical Center were treated according to the institutional MISSION! protocol, a standardized pre-hospital, in-hospital and outpatient clinical framework for decision making and treatment.[15] After hospital discharge, these patients were intensively monitored and managed in the outpatient clinic for one year, after which they were referred back to the general practitioner or referred to regular, generally regional, cardiological outpatient clinics. At the other centers, local residents were managed in the outpatient clinics, and patients referred from regional hospitals were referred back for further management after primary PCI by regional cardiologists.

Data collection and follow-up

Hospitals prospectively included patients treated with primary PCI, registering baseline- and procedural data. Definitions of variables were synchronized among centers. Cardiogenic shock was defined as systolic blood pressure <90 mmHg with signs of tissue hypoperfusion requiring treatment in form of resuscitation, inotropic agents or assistant devices. Symptom-to-balloon time was defined as the time between the onset of symptoms and balloon inflation. Diagnosis-to-balloon time was defined as the time between the first diagnostic ECG, mostly the ambulance triage ECG, and balloon inflation. Door-to-balloon time was the time between patient arrival at the tertiary hospital and balloon inflation. Close cooperation with regional emergency medical system providers supplied pre-hospital times. Vital status was obtained using municipality records.

Statistical analysis

The three databases were pooled into a patient-level database and stratification was done according to gender. Continuous variables are presented as mean with standard deviation or median with interquartile ranges and were compared using Student's t-test in case of mean and non-parametrical tests in case of medians. Categorical variables are expressed as counts and percentages and were compared using Pearson's χ^2 test. All statistical tests were 2-tailed and a p-value <0.05 was considered statistically significant. Time to endpoint was analyzed using Kaplan-Meier plots and the log-rank test was applied to compare cumulative incidences of the endpoint between groups. Linear regression models were used to analyze variables predictive of log-transformed treatment delay. Univariate predictors of delay were added into multivariate linear regression models using a cut-off p-value of 0.10.

To evaluate the effect of gender as an independent predictor of mortality, multivariate Cox proportional-hazards models were constructed using a forward stepwise method. A cut-off p-value of <0.10 was applied to enter significant univariate predictors of outcome into the multivariate models. Gender was forced to stay in the multivariate models to allow calculation of adjusted hazard ratios (HR) for all outcomes.

RESULTS

During the inclusion period, 3483 consecutive STEMI patients were treated with primary PCI, of whom 868 were women (24.9%) and 2615were men (75.1%). Baseline characteristics (**Table 1**) showed that women were on average older and had a higher risk factor burden with a higher prevalence of insulin-dependent diabetes mellitus and hypertension.

Table 1. Baseline characteristics

Variable	Male (N=2615)	Female (N=868)	p-Value
Age (years ± standard deviation)	61.8 ± 11.9	67.6 ± 13.1	<0.001
Body mass index (kg/m^2 ± standard deviation)	26.6 ± 3.7	26.3 ± 4.8	0.110
Risk factors			
Diabetes mellitus, non-insuline dependent	214 (8.3%)	80 (9.3%)	0.346
Diabetes mellitus, insuline dependent	50 (1.9%)	42 (4.9%)	<0.001
Hypertension*	841 (32.5%)	394 (45.9%)	<0.001
Hypercholesterolemia†	608 (23.6%)	187 (21.8%)	0.282
Family history of cardiovascular disease‡	994 (40.2%)	335 (41.2%)	0.646
Current smoker	1222 (47.8%)	344 (40.6%)	0.001
Mean risk factors ± standard deviation	1.52 ± 1.05	1.60 ± 1.10	0.036
Previous myocardial infarction	314 (12.1%)	61 (7.1%)	<0.001
Previous percutaneous coronary intervention	238 (9.2%)	52 (6.0%)	0.004
Previous coronary artery bypass grafting	76 (2.9%)	9 (1.0%)	0.002
Prior peripheral vascular disease	136 (5.3%)	28 (3.3%)	0.016
Prior cerebrovascular disease	157 (6.1%)	59 (6.9%)	0.418
Prior malignancy	142 (5.5%)	68 (8.0%)	0.011
Prior renal insufficiency§	86 (3.3%)	41 (4.8%)	0.053
Anemia on admission, moderate to severe‖	41 (1.6%)	14 (1.6%)	0.911
Out of hospital cardiac arrest	176 (6.7%)	48 (5.5%)	0.212
Cardiogenic shock	162 (6.2%)	65 (7.5%)	0.181
Intra-aortic balloon pump placement	144 (4.4%)	35 (4.0%)	0.680
Creatine phosphokinase peak (median U/l, IQR)	1420 (649-2715)	1170 (566-2335)	<0.001
Symptom-to-balloon time (median minutes, IQR)	175 (128-279)	192 (141-286)	0.002
Diagnosis-to-balloon time (median minutes, IQR)	78 (64-99)	81 (66-101)	0.037
Door-to-balloon time (median minutes, IQR)	46 (33-67)	46 (33-68)	0.405

* Blood pressure ≥140/90 mmHg or previous pharmacological treatment; † Total cholesterol ≥190 mg/dl or previous pharmacological treatment; ‡ First degree family member suffering cardiovascular disease before the age of 60 years; § eGFR<60 ml/min/1.73m^2; ‖Admission hemoglobin <9.7 g/dl for women and <10.5 g/dl for men.

Furthermore, women more often had histories of malignancy. In contrast, men had suffered a previous myocardial infarction more frequently and a larger proportion of men had undergone PCI or bypass surgery. Additionally, peripheral vascular disease was more common in men, and the median peak of creatine kinase was higher compared to women.

Ischemic times

Time between onset of symptoms and balloon inflation (ischemic time) was significantly longer in women (**Table 1**). In addition, time between first diagnosis of STEMI and balloon inflation was marginally longer. Multivariate linear regression analysis of log-transformed ischemic time revealed that age per 10-year increase (beta 0.03, 95% confidence interval [CI] 0.01-0.05, p=0.001), history of diabetes mellitus (beta 0.10, 95% CI 0.03-0.18,

Table 2. Procedural characteristics

Variable	Male (N=2615)	Female (N=868)	p-Value
Coronary culprit vessel			0.049
Left anterior descending	1026 (39.3%)	381 (43.9%)	0.016
Left circumflex	435 (16.6%)	118 (13.6%)	0.033
Right	1082 (41.4%)	352 (40.6%)	0.657
Left main	36 (1.4%)	11 (1.3%)	0.807
Bypass graft	34 (1.3%)	6 (0.7%)	0.144
Number of vessels narrowed >50%			0.152
1	1204 (46.1%)	433 (49.9%)	
2	837 (32.0%)	257 (29.6%)	
3	571 (21.9%)	178 (20.5%)	
Stenting	2503 (95.8%)	828 (95.4%)	0.616
Drug-eluting stents	1806 (72.6%)	603 (73.6%)	0.584
Bare-metal stents	688 (27.7%)	221 (27.0%)	0.701
Multivessel intervention	282 (10.8%)	97 (11.2%)	0.743
Abciximab treatment	1964 (75.9%)	596 (69.2%)	<0.001
TIMI flow pre-procedure*			0.078
0	1809 (69.3%)	566 (65.2%)	
1	274 (10.5%)	112 (12.9%)	
2	298 (11.4%)	100 (11.5%)	
3	229 (8.8%)	90 (10.4%)	
TIMI flow ≥2 post-procedure	2558 (98.0%)	846 (97.6%)	0.488
Admission duration (mean days ± standard deviation)	3.7 ± 6.2	4.0 ± 6.9	0.415
Discharge medication			
Aspirine / warfarin derivative	2502 (99.2%)	808 (99.1%)	0.766
Clopidogrel	2472 (98.1%)	798 (97.9%)	0.745
Beta-blocker	2277 (90.7%)	714 (88.0%)	0.029
Ace-inhibitor / Angiotensin II antagonist	1791 (71.4%)	578 (71.3%)	0.938
Statin	2345 (93.4%)	743 (91.6%)	0.093

* TIMI = Thrombolysis In Myocardial Infarction

p=0.006) and history of renal insufficiency (beta 0.15, 95% CI 0.02-0.27, p=0.020) were independent predictors of longer ischemic time, whereas gender was not (beta 0.03, 95% CI -0.03-0.08, p=0.295).

Procedurally, a higher percentage of women presented with left anterior descending coronary artery as the culprit vessel, balanced by a lower percentage of circumflex artery as the culprit vessel (**Table 2**). Abciximab treatment was more common in men and Thrombolysis In Myocardial Infarction (TIMI) flow before and after the procedure was similar between men and women. Beta-blocking agents were more frequently prescribed in men; other medications were balanced between the genders.

Mortality

One-year survival status was known in 3479 patients. Both all-cause and cardiac mortality were more common in women compared to men during the entire follow-up period (**Table 3**). Landmark analysis, with a cut-off point at seven days (**Figure 1**), showed that this was due to higher early mortality, with a similar prognosis for men and women after this period.

Multivariate Cox modeling showed that female gender predicted 7-day all-cause mortality (**Figure 2**) and 7-day cardiac mortality (T**able 3**). The association between ischemic time and 7-day mortality was investigated separately, resulting in an HR of 1.01 (95% CI 1.00-1.01) for every 10-minute increase in ischemic time.

After one year, gender no longer influenced all-cause (**Figure 3**) and cardiac (T**able 3**) mortality. The interaction of gender with predictors of all-cause mortality was investigated through multivariate modeling. After correction for confounders, female gender modified

Table 3. All-cause and cardiac mortality

Variable	Male (N=2615)	Female (N=868)	p-Value
All-cause mortality			
Seven day	78 (3.0%)	52 (6.0%)	<0.001
Unadjusted HR (95% CI)	0.49 (0.35-0.70)	2.04 (1.43-2.89)	<0.001
Adjusted HR (95% CI)	0.62 (0.41-0.95)	1.61 (1.06-2.46)	0.027
One year	173 (6.6%)	86 (9.9%)	0.001
Unadjusted HR (95% CI)	0.65 (0.50-0.84)	1.54 (1.19-1.99)	0.001
Adjusted HR (95% CI)	0.98 (0.73-1.32)	1.02 (0.76-1.37)	0.900
Cardiac mortality			
Seven day	77 (2.9%)	50 (5.8%)	<0.001
Unadjusted HR (95% CI)	0.50 (0.35-0.72)	1.98 (1.39-2.83)	<0.001
Adjusted HR (95% CI)	0.63 (0.41-0.97)	1.58 (1.03-2.42)	0.037
One year	132 (5.1%)	75 (8.7%)	<0.001
Unadjusted HR (95% CI)	0.57 (0.43-0.76)	1.75 (1.32-2.32)	<0.001
Adjusted HR (95% CI)	0.79 (0.57-1.10)	1.26 (0.91-1.75)	0.168

HR (hazard ratios) were calculated using cox proportional hazards models. CI = confidence interval.

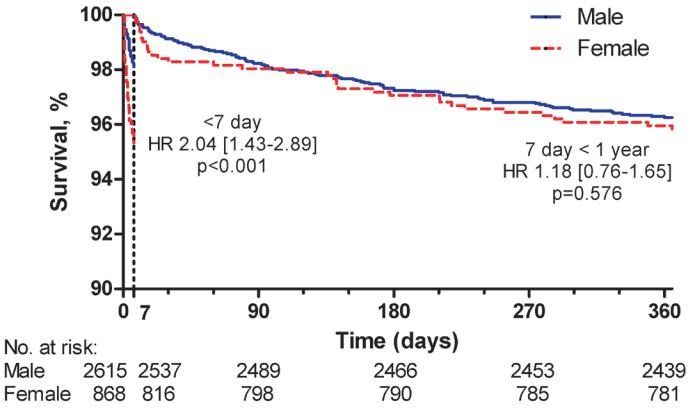

Figure 1. Landmark analysis of 1-year survival with 7-day cut-off
HR = hazard ratio.

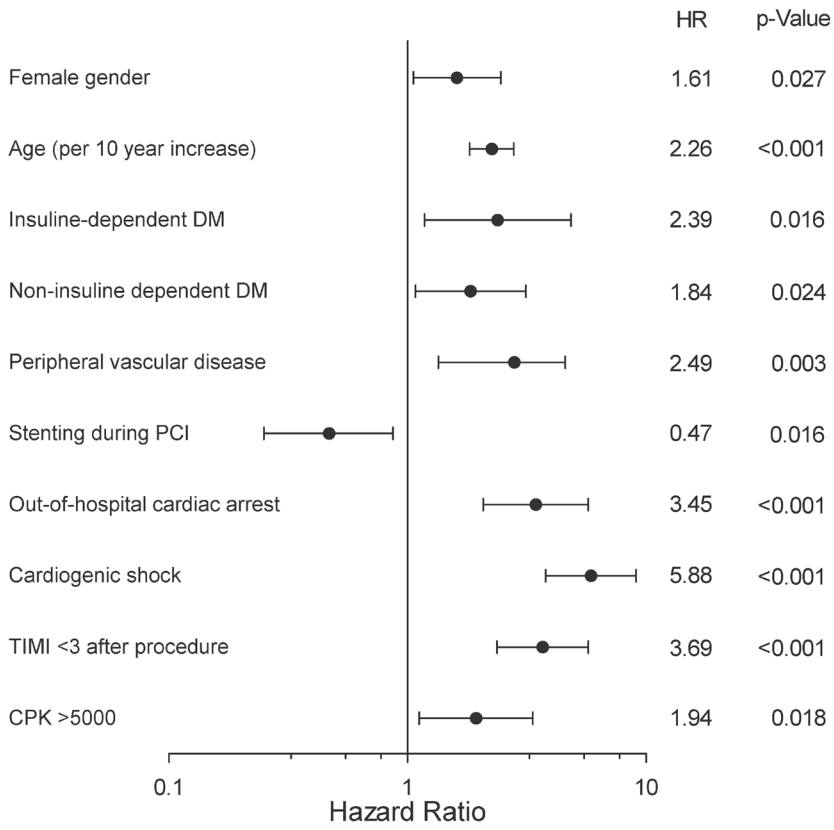

Figure 2. Independent multivariable predictors of 7-day all-cause mortality.
CPK = creatine phosphokinase; DM = diabetes mellitus; TIMI = thrombolysis in myocardial infarction. Other abbreviations as in figure 1.

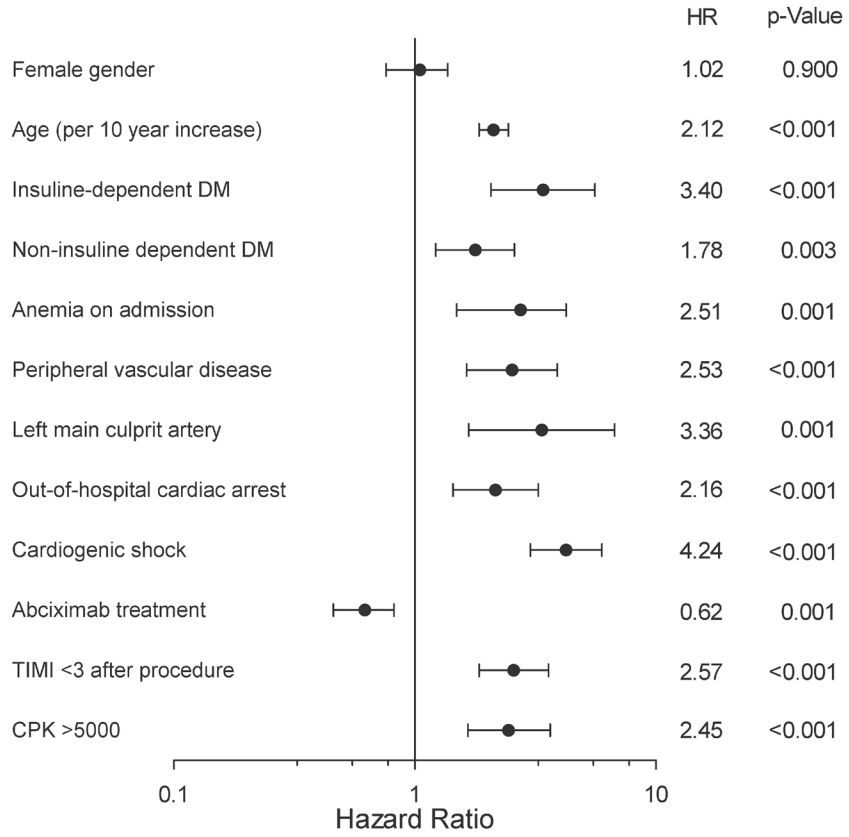

Figure 3. Independent multivariable predictors of 1-year all-cause mortality.
LAD = left anterior descending artery; LM = left main artery; MI = myocardial infarction; RCA = right coronary artery = RCX = ramus circumflex; other abbreviations as in figure 1 and 2.

the effect of cardiogenic shock on 1-year mortality with an HR of 1.94 (95% CI 1.04-3.62, p=0.038). For men with cardiogenic shock, an HR of 0.52 (95% CI 0.28-0.96) or an approximately 50% lower hazard of dying from the developed cardiogenic shock was observed during one year compared to women. Gender did not influence other predictors of all-cause mortality.

DISCUSSION

Key findings of the present multicenter registry comparing men and women treated with primary PCI for STEMI are as follows: 1) Female gender independently predicted early all-cause and cardiac mortality. Following this early period, prognoses were identical between men and women up to one year. 2) Ischemic times continue to be longer in

women, explained by a higher prevalence of comorbidity and older age. 3) Women with cardiogenic shock had substantially worse outcomes compared to men.

The influence of gender on CAD has long been a topic of debate.[16] Traditional risk factors for CAD bear different weight between men and women, and female-specific risk factors influence the development of CAD.[4,5,6] While women are more likely to present with atypical symptoms of ischemia, lower rates of obstructive CAD are observed.[7,17,18] In contrast, women show longer delay to treatment in the setting of STEMI, underlining the difficulties that exist regarding appropriate referral for coronary angiography.[19] Moreover, women consistently show higher short-term mortality after ACS.[8,9] Although confounding factors were found to be responsible for this, focus on the STEMI population has produced conflicting results. In the present analysis, women were older than men and had a higher prevalence of risk factors, mirroring previous observations.[20] After adjustment, female gender predicted short-term mortality. The difference in outcome was due to particularly high mortality in the first days of admission. Similarly, Jneid et al.[10] found that higher early mortality in women was due to the first day after infarction. Two other studies observed that female gender predicted short- but not long-term mortality.[11,12] Contradicting this, Berger et al. reported that female gender predicted 30-day mortality but observed that this effect disappeared when only patients undergoing angiography were selected.[8] Also, a recent study found no effect of gender on survival, although a strong trend toward higher mortality in women was observed.[13] Moreover, a registry resembling our population found no effect of gender on early mortality.[14] Closer examination of these studies reveals that a substantial portion of patients did not undergo reperfusion therapy,[10,11] or that patients received thrombolysis only.[8] Furthermore, high-risk patients who would normally be encountered in daily practice were excluded because of longer ischemic times or transfer from referring hospitals.[13,14] In contrast, the present analysis included patients from three centers incorporating modern systems of care with short times to treatment delay, full use of primary PCI, and no exclusion based on delay or angiographic factors, following guideline recommended treatment and reflecting a population faced in daily practice.

Explanations for the higher early mortality in women remain speculative. It has been suggested that less aggressive treatment is applied in women.[18] In the present study, women were treated less often with abciximab, but this did not explain the mortality difference. Women have also been shown to experience more bleeding complications during admission, events that are associated with mortality.[13,21,22] However, female gender also predicted cardiac mortality in the present analysis, excluding bleeding as a cause. Besides this, longer ischemic times negatively influence the prognosis of STEMI.[23,24] In our population, ischemic times were longer in women due to higher age and greater prevalence

of diabetes mellitus and renal insufficiency. These factors have been previously linked to painless myocardial infarction, most likely explaining the longer delays in the present analysis.[25] The observation that gender by itself did not predict, but age and comorbidity did predict longer delay suggests that the focus should be on recognition of STEMI in these sub-groups in men and women. As the association of ischemic time and mortality was small in this study, the delay failed to explain the mortality gap. Since the difference in outcome lay in the early days of hospital admission, the previous observation that more men die before reaching the hospital might explain the difference between men and women, because of a sicker female population being admitted to the hospital.[26] Therefore, pre-hospital mortality rates should be incorporated in future investigations.

The predictors of mortality established in the current study reflect those found in previous investigations.[27-30] Strikingly, female gender was found to modify the effect of cardiogenic shock on mortality, causing higher mortality due to cardiogenic shock in women compared to men. It has been noted that women developing cardiogenic shock have higher rates of ventricular septal rupture and severe mitral regurgitation, possibly explaining the difference in outcome between men and women.[31] Supporting this, Engström et al found that severe mitral regurgitation was more common in female STEMI patients and identified it as a predictor of mortality. [32] However, the clinical implications of these findings are unclear, and additional research is required to uncover the optimal treatment for these patients.

Limitations

The present analysis had several limitations. The study was observational and thus shares the limitations of all observational analyses. Additionally, since left ventricular ejection fractions were not available for all patients, peak creatine phosphokinase during admission was used as a surrogate for infarction size, which may not reflect the actual infarction size. There may have been other measured or unmeasured confounding variables that, had they been adjusted for, might have modified the relationship between gender and outcome. Finally, because our cohort included only patients treated with primary PCI, it cannot be ruled out that a disproportionate number of men and women died before arrival at the hospitals.

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