Optimization of care for ST-elevation myocardial infarction

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CHAPTER 2

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

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Abstract

Previous studies investigating the influence of gender on ST-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 ST-elevation myocardial infarction in patients treated with primary percutaneous coronary intervention (PCI) in modern day practice. The present multicenter registry included consecutive patients with ST-elevation myocardial infarction treated with primary PCI at 3 hospitals. Adjusted mortality rates were calculated using Cox proportional-hazards analyses. In total, 3483 patients were included, of whom 868 women (25%). Women were older, had a higher risk factor burden and more frequently had histories of malignancy. Men more often had cardiac histories 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, multivariable linear regression showed that this was due to age and co-morbidity. All-cause mortality was higher at 7 days (6.0% in women vs. 3.0% in men, p<0.001) and 1 year (9.9% in women vs. 6.6% in men, p=0.001). After adjustment, female gender predicted both 7 day all-cause mortality (HR 1.61, 95% CI 1.06-2.46) and cardiac mortality (HR 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. In conclusion, 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 Western men and women.[1] In 2003, the total cost of CAD in the European Union was an estimated 45 billion euro, with approximately 1 million working years lost due to CAD mortality.[2] To reduce the huge burden of CAD, research aimed at the optimal recognition and treatment of CAD in 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 among men and women and that women with anginal complaints 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 more co-morbidities.[8,9] However, in the specific ST-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 treated with primary PCI in modern day practice.

Methods

The present Dutch multicenter registry prospectively included consecutive patients treated with primary percutaneous coronary intervention (PCI) for STEMI in 3 tertiary centers in the Netherlands. Two high-volume centers in the north of the Netherlands, the Medical Center Alkmaar and the Medical Center Leeuwarden, provide 24/7 cardiac care for an area of 450.000 and 650.000 inhabitants respectively. The Leiden University Medical Center serves an area of approximately 750.000 inhabitants.

Consecutive patients who underwent primary PCI for STEMI between January 2006 and December 2009 were included in the analysis. Interventions included passing of guidewire through a thrombus, thrombosuction and/or percutaneous coronary balloon angioplasty with or without placement of coronary stents. In case of out-of-hospital cardiac arrest, only patients with return of spontaneous circulation on 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 electrocardiographical changes (ST-segment elevation ≥0.2 mV in ≥2 contiguous leads in V1 through V3 or ≥0.1 mV in other leads or presumed new left bundle branch block). Pre-hospital protocols included triage by 12-lead electrocardiogram 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 in the Leiden University Medical Center and

periprocedural administration in 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 in the Leiden University Medical Center were treated according to the institutional MISSION! protocol, a standardized prehospital, in-hospital and outpatient clinical framework for decision making and treatment.[15] After hospital discharge, these patients were intensively monitored and managed at the outpatient clinic for 1 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.

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 prehospital times. Vital status was obtained using municipality records.

The 3 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 as medians with interquartile range and were compared using Student's t-test for means and nonparametric tests for medians. Categorical variables are expressed as counts and percentages and were compared by means of Pearson's χ^2 test. All statistical tests were 2-tailed and p-values <0.05 were 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. Univariable predictors of delay were added into multivariable linear regression models using a cut-off p-value of 0.10. To evaluate the effect of gender as an independent predictor of mortality, multivariable cox proportional hazards models were performed using a forward stepwise method. A cut-off p-value of <0.10 was applied to enter significant univariable predictors of outcome into the multivariable models. Gender was forced to stay in the multivariable models to allow calculation of adjusted hazard ratios 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 2615 were 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. Furthermore, women more often had histories of malignancy. In contrast, men had had previous myocardial infarctions more frequently and a larger proportion of men had undergone PCI or bypass surgery. Additionally, peripheral vascular disease was more common in men, and their median peak creatine kinase level was higher compared to women.

Table 1. Baseline characteristics

Variable	**Men** (N=2615)	**Women** (N=868)	p-Value
Age (yrs)	61.8 ± 11.9	67.6 ± 13.1	<0.001
Body mass index (kg/m^2)	26.6 ± 3.7	26.3 ± 4.8	0.110
Risk factors			
Diabetes mellitus, non-insulin dependent	214 (8.3%)	80 (9.3%)	0.346
Diabetes mellitus, insulin 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
Number of risk factors	1.52 ± 1.05	1.60 ± 1.10	0.036
Previous myocardial infarction	314 (12.1%)	61 (7.1%)	<0.001
Previous PCI	238 (9.2%)	52 (6.0%)	0.004
Previous coronary artery bypass grafting	76 (2.9%)	9 (1.0%)	0.002
Previous peripheral vascular disease	136 (5.3%)	28 (3.3%)	0.016
Previous cerebrovascular disease	157 (6.1%)	59 (6.9%)	0.418
Previous malignancy	142 (5.5%)	68 (8.0%)	0.011
Previous 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 (U/l)	1420 (649-2715)	1170 (566-2335)	<0.001
Symptom-to-balloon time (minutes)	175 (128-279)	192 (141-286)	0.002
Diagnosis-to-balloon time (minutes)	78 (64-99)	81 (66-101)	0.037
Door-to-balloon time (minutes)	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.

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. Multivariable linear regression analysis of log transformed ischemic time revealed that age per 10 year increase (beta 0.03, 95% CI 0.01-0.05, p=0.001), history of diabetes mellitus (beta 0.10, 95% CI 0.03-0.18, 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).

Table 2. Procedural characteristics

Variable	**Men** (N=2615)	**Women** (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
Abciximab treatment	1964 (75.9%)	596 (69.2%)	<0.001
Preprocedural TIMI flow grade*			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%)	
Postprocedural TIMI flow grade ≥2	2558 (98.0%)	846 (97.6%)	0.488
Admission duration (days)	3.7 ± 6.2	4.0 ± 6.9	0.415
Discharge medication			
Aspirine / warfarin derivative	2438 (96.7%)	782 (96.0%)	0.305
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.

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

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 7 days (Figure 1), showed that this was due to higher early mortality, with similar prognoses for men and women after this period.

Table 3. All-cause and cardiac mortality

Variable	**Men** (N=2615)	**Women** (N=868)	p-Value
All-cause mortality			
Seven days	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 days	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 were calculated using Cox proportional-hazards models. CI = confidence interval.

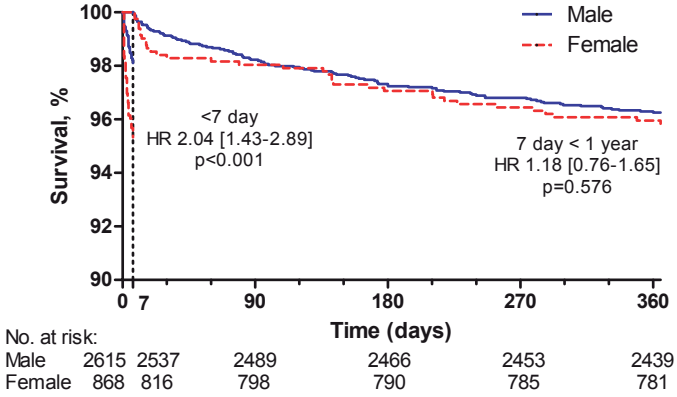

Figure 1. Landmark analysis of 1-year survival with 7-day cut-off.

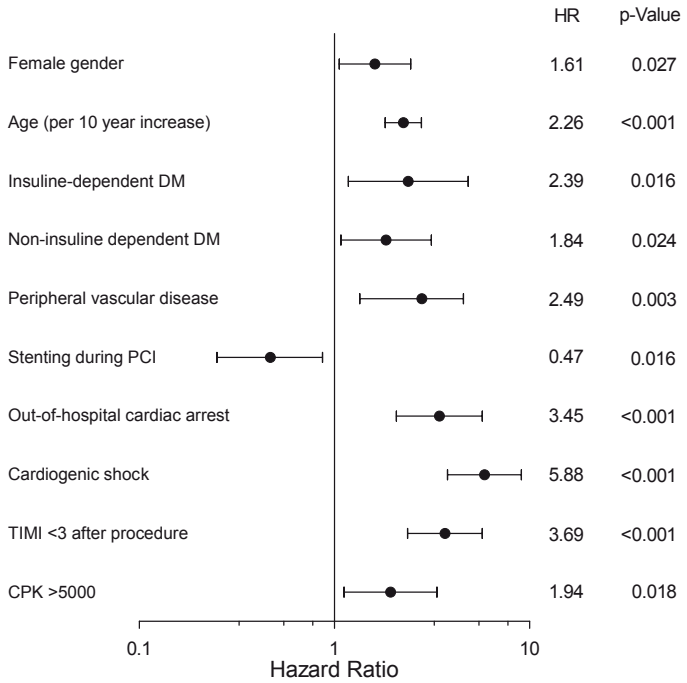

Figure 2. Independent multivariable predictors of 7-day all-cause mortality. (CPK = creatine phosphokinase; DM = diabetes mellitus; TIMI = thrombolysis in myocardial infarction.).

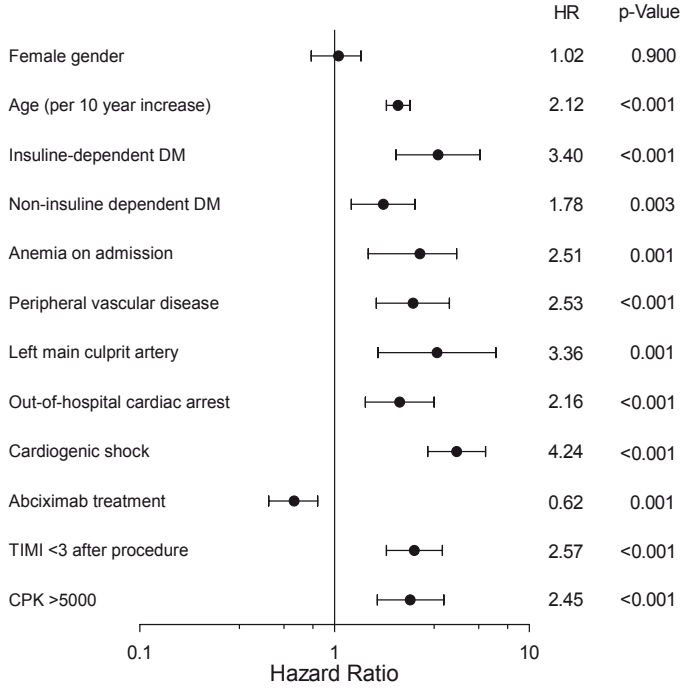

Figure 3. Independent multivariable predictors of 1-year all-cause mortality. (LAD = left anterior descending artery; LM = left main artery; MI = myocardial infarction; RCA = right coronary artery; RCX = ramus circumflex.).

Multivariable Cox modeling showed that female gender predicted 7-day all-cause mortality (Figure 2) and 7-day cardiac mortality (Table 3). The association between ischemic time and 7 day mortality was investigated separately, resulting in a HR of 1.01 (95% CI 1.00-1.01) for every 10 minute increase in ischemic time. After 1 year, gender no longer influenced all-cause (Figure 3) and cardiac mortality (Table 3). The interaction of gender with predictors of all-cause mortality was investigated through multivariable modeling. After correction for confounders, female gender modified 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 1 year compared to women. Gender did not influence other predictors of all-cause mortality.

Discussion

The 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. After this early period, prognoses were identical between men and women up to 1 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.[4-6] Although 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 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 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-term 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 who underwent angiography were selected.[8] Also, a recent study found no effect of gender on survival, although a strong trend for 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 current analysis included patients from 3 centers incorporating modern systems of care with short time to treatment delays, 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 suffer more bleeding complications during admission, events that are associated with mortality.[13,21,22] However, female gender also predicted cardiac mortality in the current analysis, excluding bleeding as a cause. Besides this, longer ischemic times negatively influence prognosis of STEMI.[23,24] In our population, ischemic times were longer in women because of older 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 current analysis.[25] The observation that gender by itself did not predict but age and comorbidity did predict longer delay suggests that focus should be on recognition of STEMI in these subgroups in men and women. Because the association of ischemic time and mortality was small in this study, the delay failed to explain the mortality gap. Because 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, prehospital mortality rates should be incorporated in future investigations.

The predictors of mortality established in the present 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 women with STEMIs 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. The present analysis had several limitations. The study was observational and thus shares the limitations of all observational analyses. Additionally, because 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 have underestimated actual infarction size. There may have been other measured or unmea-

sured confounding variables that, had they been adjusted for, might have modified the relation between gender and outcome. Finally, because our cohort only included 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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