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ORIGINAL PAPER

Short-term prognosis of contemporary interventional therapy of ST-elevation myocardial infarction: does gender matter?

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Abstract
Background A higher mortality risk for women with acute ST-elevation myocardial infarction (STEMI) has been a common finding in the past, even after acute percutaneous coronary intervention (PCI). We set out to analyze whether there are gender differences in real-world contemporary treatment and outcomes of STEMI.
Patients and methods A retrospective analysis of all consecutive patients with STEMI and acute coronary angiography with the intention of performing a PCI at our center 6/1999-6/2006 was carried out ($n = 566$). Data were examined for gender-specific differences regarding patients' characteristics, referral patterns, timing of acute symptoms, angiographic findings, procedural details, and adverse events at 30 days after PCI.
Results Women ($n = 161$) were on average 8 years older than men ($n = 405$), had higher co-morbidity, were more often transported to the hospital by ambulance and presented less often to the emergency room on their own (4.2% vs. 12.6% in men, $P = 0.02$). The pre-hospital delay from symptom onset to admission was significantly longer for women (median 185 vs. 135 min, $P < 0.02$). There was no gender difference in time from admission to PCI (median 46 min vs. 48 min, $P = 0.42$). Both genders received PCI with similar frequency (88.8% vs. 92.4%, $P = 0.19$), with similar success rates (83.2% vs. 85.3%, $P = 0.68$). Thirty-day overall mortality for women was not significantly higher than for men (8.7% vs. 7.2%, $P = 0.6$). Re-infarction or stroke within 30 days were rare for both genders without gender-specific differences whereas bleeding necessitating blood replacement was significantly more frequent in women (16.8% vs. 5.9%, $P < 0.001$). In multivariate analysis, female gender was not independently associated with a higher risk of 30-day mortality (OR 0.964, $P = 0.93$).
Conclusions Women underwent PCI therapy for STEMI with the same frequency and the same angiographic success as men. Despite their more advanced age and the higher prevalence of co-morbidities, they did not have a significantly higher 30-day mortality rate than men. Female gender was not an independent risk factor of 30-day mortality. Longer pre-hospital delays before hospital admission in women indicate that awareness of risk from coronary artery disease should be further raised in women.

Keywords ST-elevation myocardial infarction · Primary coronary intervention · Gender differences · Outcomes

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Introduction

Strategies for treatment of acute ST-elevation myocardial infarction (STEMI) have rapidly evolved in recent years, resulting in a marked decrease in mortality [12, 15, 22]. Short-term mortality has been reported to be higher for women than men [4–6, 9, 18–20]. This has been attributed in part to higher average age and higher co-morbidity of

women with STEMI [9, 10, 21]. Another reason put forward has been less aggressive treatment of women with this condition [3, 5, 8, 15, 18]. However, even in studies where all patients underwent acute percutaneous coronary intervention (PCI), women frequently had increased short-term mortality [9, 17, 20].

We set out to analyze whether "real-life" contemporary acute interventional therapy of unselected STEMI patients ("all comers") shows gender-specific differences in treatment, complications and outcomes.

Patients and methods

We retrospectively analyzed all consecutive patients admitted to our hospital with acute STEMI in the period from 6/1999 to 6/2006 who underwent acute coronary angiography with the intention of primary PCI. STEMI was defined as persisting ST-elevation at hospital admission >0.1 mV in at least two standard leads or >0.2 mV in at least two contiguous precordial leads, or previously unknown left bundle branch block, and a creatine kinase elevation >170 U/l and/or a troponin I elevation >0.5 ng/ml within the first 6 h after admission. Primary PCI is our standard treatment of STEMI and is available at all times in our institution. During the study period, primary PCI was delivered by five experienced interventional cardiologists. Patients with symptom duration over 24 h were excluded. Impaired renal function was not considered a contraindication for interventional STEMI treatment. Data were extracted by review of records from emergency room, cath lab, intensive care, and other hospital units. Follow-up data were obtained by questionnaire or telephone contact with patients or their primary care physicians, registering the following complications: re-infarction, stroke, bleeding, and death.

The following definitions applied:

- *Successful primary PCI*: <30% residual stenosis of culprit lesion and TIMI grade 3 coronary flow, as assessed visually.
- *Multivessel disease*: at least one additional ≥70% stenosis in a major coronary vessel besides the culprit lesion.
- *Cardiogenic shock*: clinical diagnosis based on tachycardia, hypotension, pulmonary edema, and clinical signs of low cardiac output.
- *Re-infarction*: recurrent ischemic symptoms and/or ECG signs after the index STEMI with a second CK or troponin I peak ≥50% higher than the previous value.
- *Ejection fraction*: visual estimate from echocardiography performed within the first 4 h after admission.
- *Creatinine clearance*: calculated according to the simplified Modification of Diet in Renal Disease (MDRD) formula [11]: Renal impairment was defined as GFR < 60 ml/min/1.73 m^2.
- *Stroke*: clinical signs of cerebral ischemia together with compatible findings on cranial computed tomography.

Primary PCI and adjunctive therapy

All patients received 500 mg aspirin and 5,000 IU unfractionated heparin intravenously before or at hospital admission. Patients undergoing stent placement during primary PCI received an oral loading dose of 300 mg clopidogrel immediately before or after PCI. During PCI, another 5,000 IU of unfractionated heparin were routinely given. Procedural details of PCI, including the use of glycoprotein IIb/IIIa inhibitors, were determined individually by the interventionalist. After PCI, clopidogrel 75 mg was maintained for 4 weeks to 6 months. Aspirin 300 mg was given for 4 weeks and followed by 100 mg per day indefinitely.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), unless indicated otherwise. Time intervals and age were compared by unpaired Mann–Whitney *U* test. Categorical variables were compared by Fisher's exact test. Multivariate analysis of predictors of mortality was performed by multiple logistic regression. In addition, a propensity score analysis [14, 16] based on logistic regression modeling for gender with risk adjustment for covariates was performed: patients were divided into quintiles defined by their gender probabilities (propensity scores). Balance of the covariables across the two groups was achieved after adjustment for the propensity scores. Results of multivariate analysis and propensity score analysis were presented as odds ratios (ORs) with 95% confidence intervals (CIs). P values < 0.05 were considered significant. All P values are results of two-tailed tests. All statistical calculations were carried out using SPSS version 14.01 (SPSS Inc., Chicago, USA).

Results

Patient characteristics

Of 566 included patients, 161 (28.4%) were females (Table 1). Women on average were 8 years older than men, more frequently had a history of hypertension, and had a higher rate of renal impairment. In contrast, men more frequently had a history of smoking. The following

Table 1 Hospital admission characteristics of 566 patients with STEMI

Characteristics (percentages in parentheses)	Total ($n = 566$)	Male ($n = 405$)	Female ($n = 161$)	P
Baseline data				
Age (median), years	63 ± 13 (65)	61 ± 13 (62)	69 ± 13 (72)	<0.001
Hypertension	381 (67.3)	254 (62.7)	127 (78.9)	<0.001
Diabetes	176 (31.1)	116 (28.6)	60 (37.3)	0.056
Smoking	322 (56.9)	267 (65.9)	55 (34.2)	<0.001
Dyslipoproteinemia	379 (66.9)	271 (66.9)	168 (67.1)	1.000
Creatinine clearance <60 ml/min/1.73 m^2	172 (30.4)	97 (23.9)	75 (46.6)	<0.001
Prior myocardial infarction	71 (12.5)	50 (12.3)	21 (13)	0.888
Prior PCI	69 (12.2)	52 (12.8)	17 (10.6)	0.569
Prior CABG	15 (2.7)	12 (2.9)	3 (1.9)	0.573
Prior stroke	51 (9.0)	30 (7.4)	21 (13)	0.050
Prodromal angina				
Progressive angina within the last 2–14 days	127 (22.4)	89 (21.9)	38 (23.6)	0.738
Progressive angina >14 days	23 (4.1)	14 (3.5)	9 (5.6)	0.246
Stable angina	36 (6.4)	26 (6.4)	10 (6.2)	1.000
Infarction without prodromal angina	369 (65.2)	269 (66.4)	100 (62.1)	0.330
Symptoms unknown	11 (1.9)	7 (1.7)	4 (2.5)	0.517
Referral patterns				
Referred from other hospital	184 (32.5)	119 (29.4)	65 (40.4)	0.013
Primarily admitted to our institution	382 (67.5)	286 (70.6)	96 (59.6)	0.013
Patients admitted by ambulance	342 (89.5)	250 (87.4)	92 (95.8)	0.020
Patients presenting directly to emergency dept	40 (10.5)	36 (12.6)	4 (4.2)	0.020
Clinical status at admission				
Pre-hospital cardiac arrest	44 (7.8)	33 (8.2)	11 (6.8)	0.728
Cardiogenic shock	46 (8.1)	32 (7.9)	14 (8.7)	0.736
Anterior infarction	229 (40.5)	160 (39.5)	69 (42.9)	0.507
Ejection fraction <30%	59 (10.4)	44 (10.8)	15 (9.3)	0.650

PCI percutaneous coronary intervention, *CABG* coronary artery bypass grafting

characteristics did not significantly differ by gender: 12.5% of patients had a history of previous myocardial infarction, 12.2% of a previous coronary intervention, and 2.7% of previous coronary bypass surgery. At admission, 8.2% of men and 6.8% of women had undergone cardiopulmonary resuscitation during the index STEMI ($P = 0.73$). Of all patients, 8.1% presented with cardiogenic shock, 40.5% had an anterior myocardial infarction, and 10.4% had a severely impaired left ventricular function by echocardiography. Features of intensive care treatment also did not differ significantly (Table 2).

Referral patterns

A total of 184 patients (32.5%) were referred from other hospitals (Table 1). Of the remaining 382 patients who were primarily admitted to our institution, 40 patients (10.5%) presented directly to the hospital's emergency department. In this group, the percentage of female patients was much lower than male patients (4.2% vs. 12.6%, $P = 0.02$). Accordingly, women were more often admitted via the emergency ambulance service (95.8% vs. 87.4%) than by self-referral. Furthermore, women waited longer after the onset of symptoms before seeking medical treatment (median time, 185 min vs. 135 min in men, $P < 0.02$).

Symptoms

There was no difference in the incidence of prodromal angina between men (31.8%) and women (35.4%). During the 2 weeks before the index infarction, 21.9% (men) and 23.6% (women), respectively, had experienced an increase in angina (Table 1).

Timing of acute symptoms

Infarct symptoms started most frequently in the morning between 6:00 and 12:00 (35% in men and 36% in women), followed by the interval between 12:00–18:00 and 18:00–24:00 (Fig. 1).

Table 2 Treatment characteristics

Characteristics (percentages in parentheses)	Total ($n = 566$)	Male ($n = 405$)	Female ($n = 161$)	P
Time intervals (minutes)				
Symptom—door (median)[a]	244 ± 255 (150)	236 ± 263 (135)	262 ± 235 (185)	<0.02
Door—angiography (median)	61 ± 54 (47)	63 ± 58 (48)	57 ± 45 (46)	0.420
Intensive care characteristics				
Temporary pacemaker	34 (6.0)	25 (6.2)	9 (5.6)	1.000
Intra-aortic balloon pump	33 (5.8)	25 (6.2)	8 (4.9)	0.676
Mechanical ventilation	87 (15.4)	62 (15.3)	25 (15.5)	1.000
Inotropic therapy	88 (15.5)	63 (15.6)	25 (15.5)	1.000
Duration of intensive care (median)		4 ± 4 (3)	5 ± 7 (3)	0.869
Infarction related coronary vessel				
LM	5 (0.9)	4 (1.0)	1 (0.6)	1.000
LAD	230 (40.6)	157 (38.8)	73 (45.3)	0.156
CX	59 (10.4)	41 (10.1)	18 (11.2)	0.761
RCA	248 (43.8)	186 (45.9)	62 (38.5)	0.112
CABG	8 (1.4)	6 (1.5)	2 (1.2)	1.000
Unclear	17 (3)	12 (3.0)	5 (3.1)	1.000
Presence of multivessel disease	250 (44.2)	181 (44.7)	69 (42.9)	0.708
Procedural data				
PCI attempted	517 (91.3)	374 (92.4)	143 (88.8)	0.187
Successful	439 (84.9)	319 (85.3)	120 (83.2)	0.682
Stent implantation	460 (88.9)	332 (88.8)	128 (89.5)	0.876
Conservative treatment	35 (6.2)	20 (4.9)	15 (9.3)	0.079
Emergency CABG	14 (2.5)	11 (2.7)	3 (1.9)	0.766
Use of GPIIb/IIIa-antagonists	382 (67.5)	281 (69.4)	101 (62.7)	0.136
Creatinine kinase (median), IU/l	2,085 ± 2,219 (1,300)	2,104 ± 2,288 (1,290)	2,035 ± 2,041 (1,338)	0.740

LM left main coronary artery; *LAD* left anterior descendent artery; *CX* circumflex artery; *RCA* right coronary artery; *CABG* coronary artery bypass grafting; *PCI* percutaneous coronary intervention

[a] Symptom-door-time: missing values overall $n = 33$ (5.8%)

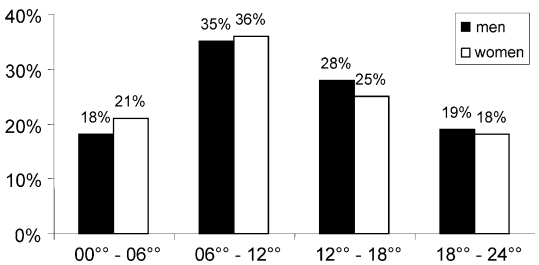

Fig. 1 Frequency of onset of symptoms according to circadian time interval; role of gender

Angiography

There were no significant gender differences in the anatomic distribution of culprit lesions or the incidence of multivessel disease (Table 2).

Procedural details

PCI was performed in similar frequency in both men (92.4%) and women (88.8%; $P = 0.19$), and was successful in a similar proportion (85.3% vs. 83.2%, respectively). 88.9% of patients undergoing PCI received a stent, without gender difference. 2.5% of patients were referred to cardiac surgery for emergency coronary bypass operation and 6.7% of patients were managed conservatively after angiography, with a trend to higher frequency among women (9.3% vs. 4.9% in men, $P = 0.08$). Registered maximum creatine kinase levelswere similar in both genders ($P = 0.740$) (Table 2).

Thirty-day mortality

Thirty-day mortality in all patients (including conservatively or surgically treated patients) did not differ significantly between women and men ($n = 566$; 8.7% vs. 7.2%, respectively), in particular between patients after PCI ($n = 517$; 8.4% vs. 5.6%, respectively; Table 3), or after successful PCI ($n = 438$; 5.0% vs. 3.8%, respectively). In patients in whom PCI was unsuccessful or a conservative management was chosen, 30-day mortality was considerably higher independently of gender: 21.1% (women) and 19.7% (men); $P = 1.00$.

Table 3 Major adverse events within 30 days after PCI

Adverse events (%)	Total ($n = 517$)	Male ($n = 374$)	Female ($n = 143$)	P
Death	33 (6.4)	21 (5.6)	12 (8.4)	0.314
Cardiac death	30 (5.8)	19 (5.1)	11 (7.7)	0.293
Non-cardiac death	3 (0.6)	2 (0.5)	1 (0.7)	1.000
Myocardial infarction	18 (3.5)	13 (3.5)	5 (3.5)	1.000
Stroke	6 (1.2)	3 (0.8)	3 (2.1)	0.354
Bleeding necessitating blood transfusion	46 (8.9)	22 (5.9)	24 (16.8)	<0.001
Without shock symptoms	39 (7.5)	19 (5.1)	20 (14.0)	<0.002
With shock symptoms	7 (1.4)	3 (0.8)	4 (2.8)	0.096

Table 4 Overall mortality (unadjusted and model adjusted)

	Mortality		
	Male ($n = 405$)	Female ($n = 161$)	P
1. Overall mortality unadjusted	7.2%	8.7%	0.598
	OR (CI 95%): 1.235 (0.634; 2.403)		
2. Overall mortality adjusted, based on logistic regression with propensity score (PS)	8.0%	6.2%	0.595
	OR (CI 95%): 0.852 (0.415; 1.752)		0.664
3. Logistic regression with PS and symptom-door time (min)[a]	OR (CI 95%): 0.927 (0.441; 1.948)		0.841

OR odds ratio, *CI* confidence interval, *PS* propensity score analysis based on logistic regression modeling for gender with risk adjustment for covariates: reanimation/shock, EF < 30%, diabetes, blood transfusion, no reperfusion, age > 65 years, anterior infarction, GFR < 60 ml/min/1.73 m^2, multi-vessel disease

[a] Symptom-door-time: missing values overall $n = 33$ (5.8%)

Adverse events at 30 days after PCI

Reinfarction and stroke occurred with similar low frequency in both genders. Although the use of glycoprotein IIb/IIIa-inhibitors was not different between men and women (69.4% vs. 62.7%; $P = 0.14$), blood transfusions were given significantly more often in women than in men (overall 16.8% vs. 5.9%; $P < 0.001$). Bleeding events with symptoms of hemorrhagic shock, however, were relatively rare for both genders (2.8% vs. 0.8%; $P = 0.096$) (Table 3).

Predictors of 30-day mortality

Univariate significant predictors of 30-day mortality were entered in a multivariate logistic regression analysis (Fig. 2). In the multivariate model, the following characteristics emerged as significant independent predictors of 30-day mortality, in the order of strength: pre-hospital resuscitation or cardiogenic shock, left ventricular ejection fraction < 30%, diabetes, blood transfusion, no coronary reperfusion, age, anterior infarction, and impaired renal function. Female gender clearly was no independent predictor of 30-day mortality (OR 0.964, $P = 0.930$). After adjustment for the confounding factors by the propensity score risk-adjusted overall mortality rates still do not differ significantly by gender, but some trend favoring female patients is apparent (6.2% vs. male 8.0%; $P = 0.5954$); female vs. male adjusted OR (CI 95%): 0.852 (0.415; 1.752), $P = 0.852$ (Table 4). We extended our logistic regression model using propensity score in combination with the factor "Symptom-Door-Time" (Table 4): there was no influence on 30-day mortality female vs. male: adjusted OR (CI 95%) 0.927 (0.441; 1.948) (Table 4).

Discussion

In the large multicenter German MITRA Registry of STEMI treatment, in-hospital mortality in the years 1994–1997 was 20.9% in women vs. 12.3% in men [5]. A recently published registry [18] from 25 Berlin hospitals from the years 1999–2002 also showed distinctly higher mortality in females (18.6% vs. 8.4%, respectively). However, in both registries women had received significantly less frequently reperfusion therapy than men. Furthermore, several studies have reported higher short-term mortality in women even if all analyzed patients had

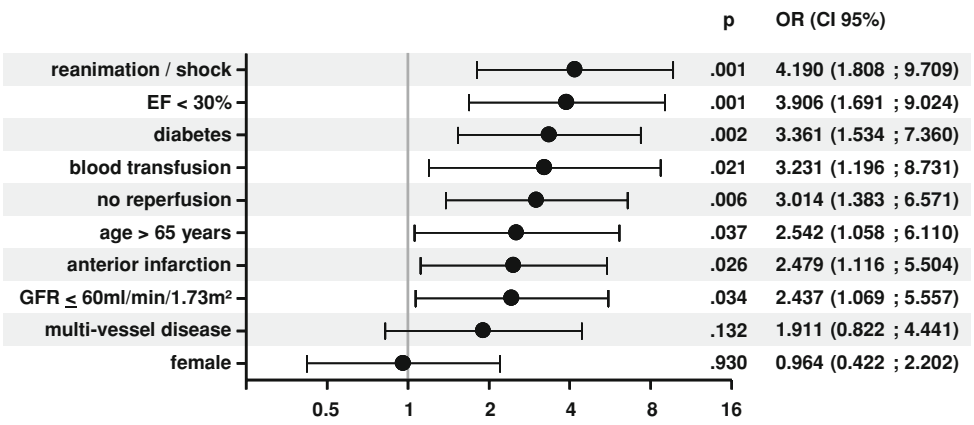

Fig. 2 Multivariate logistic regression analysis: predictors of 30-day mortality after STEMI; *OR* odds ratio; *CI* confidence interval

undergone reperfusion therapy with similar success rates [9, 20].

In the present registry, all patients underwent emergency angiography with the intention to treat, which is our standard therapy in all patients with acute STEMI. In our group, women constituted 28.4% of patients. They were older and had more risk factors and co-morbidities such as hypertension or renal impairment. This is in line with previously published data [1, 5, 8–10]. However, their clinical characteristics at admission did not differ significantly from those of men, nor did their management in the cath lab or the duration of intensive care.

In contrast, the pattern of referral to our hospital differed between men and women. Women less often presented directly to the emergency department, and more often were transported to the hospital by emergency ambulance service. Importantly, women waited significantly longer after the onset of symptoms before seeking medical treatment. Similar observations have been made by other authors [5, 18]. Both observations may indicate delayed recognition of a medical emergency by the female patients themselves, fostered by lack of awareness of the risk of CAD in women.

The multivariate predictors of 30-day mortality in our study (pre-hospital resuscitation or cardiogenic shock, impaired left ventricular function, diabetes, blood transfusion, no coronary reperfusion, age, anterior infarction, and impaired renal function) correspond to those identified in other studies [7, 13, 21, 23].

In this study, no significant gender-related differences in contemporary hospital management of STEMI were detected. In particular, door-to-angiography-time did not differ (median time, 46 min in women and 48 min in men). Women underwent PCI as often as men and with similar success. This is in strong contrast to older data showing significantly less stent implantations in women, e.g., in the GUSTO-IIb Angioplasty substudy [17] spanning the years 1990–1993 (14.7% vs. 36.4% in men, $P = 0.018$).

Thirty-day mortality in our study was not significantly higher in women, whether all patients were analyzed or only those undergoing PCI (Table 3), or those with successful PCI. This is in contrast to earlier studies that described an increased short-term mortality in women after interventionally treated STEMI [9, 17, 20], even with success rates similar to ours [9, 20]. Re-infarction or stroke within 30 days also did not occur more often in women than men.

Even if severe bleeding with signs of hemorrhagic shock rarely occurred in both genders, blood replacement was clearly more frequent in women (16.8% vs. 5.9% in men, $P = 0.001$). This finding is in line with other studies [1, 2, 15]. Possible reasons include fixed dosages of anticoagulants and antiaggregatory drugs, leading to higher bleeding rates due to lower body weight and reduced glomerular filtration rates in women. In our analysis, the factor "blood transfusion" emerged as an independent risk factor of 30-day mortality.

Limitations of the study

This study is retrospective and details a one-center experience. Nevertheless, it reflects contemporary and homogeneous STEMI treatment characteristics and outcomes in "all comers" at a referral center.

Conclusion

No major differences in STEMI treatment and outcomes were observed between men and women at our center in recent years, except for more bleeding complications in women. In spite of higher age and co-morbidity, 30-day mortality was not significantly higher in women than in men, particularly after successful PCI. Female gender was not an independent predictor of mortality. To achieve

shorter pre-hospital delays, awareness of CAD and education about the signs and consequences of myocardial infarction should be systematically promoted especially in women.

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