

# Sex-based differences in clinical and angiographic outcomes in patients with ST-elevation myocardial infarction treated with concomitant use of glycoprotein IIb/IIIa inhibitors

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## Abstract

**Background:** *The widespread use of primary coronary intervention (PCI) has significantly improved the prognosis of men presenting with acute coronary syndromes, but the cardiovascular event rate among women has either levelled off or increased. The purpose of the present prospective study was to compare the clinical outcome of women and men presenting with ST-elevation myocardial infarction (STEMI) undergoing primary PCI with concomitant usage of GP IIb/IIIa inhibitors.*

**Methods:** *Between January 2006 and December 2007, 297 consecutive patients presenting with STEMI were prospectively included in this single center investigation. Overall, 82 (27.6%) women and 215 (72.4%) men were treated by PCI with additional bare metal stent implantation and a GP IIb/IIIa inhibitor.*

**Results:** *Women were significantly older ( $65 \pm 10$  vs  $60 \pm 12$  years,  $p = 0.04$ ), presented with a smaller reference luminal diameter ( $2.83 \pm 0.51$  vs  $2.94 \pm 0.43$ ,  $p = 0.03$ ) and had a higher prevalence of hypertension (68% vs 53%,  $p = 0.025$ ) and obesity (30% vs 18%,  $p = 0.03$ ). The incidence of major adverse cardiac events (MACE, defined as death, re-myocardial infarction, target lesion revascularization and coronary artery bypass graft) during long-term follow-up was similar in women and men (20% vs 26%,  $p = 0.29$ ). Age, C-reactive protein, platelet count and cardiogenic shock were identified as independent predictors for MACE, whereas gender was not predictive.*

**Conclusions:** *In this study, female gender did not emerge as an independent predictor for MACE, but women presenting with STEMI had a higher cardiovascular risk profile; this emphasizes the need for a more extensive therapeutic strategy. Combination therapy with primary PCI and GP IIb/IIIa inhibitors might mitigate gender-related differences in clinical outcomes. (Cardiol J 2010; 17, 6: 580–586)*

**Key words:** STEMI, acute coronary syndrome, myocardial infarction, GP IIb/IIIa, gender

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## Introduction

Acute coronary syndromes (ACS), especially ST-elevation myocardial infarction (STEMI), still represent the commonest cause of death in the western world [1]. The widespread use of primary coronary intervention (PCI) has significantly improved the prognosis of men, but, astonishingly, the cardiovascular event rate among women has either levelled off or increased [2–4]. In the case of thrombolysis, female sex is in fact associated with a worse outcome compared to men [5–7]. The reason for the discrepancy between men and women concerning the benefit of reperfusion therapy in ACS remains enigmatic and there is conflicting data on the impact of the sex of a patient on outcomes in those with acute myocardial infarction [8–12].

The administration of glycoprotein IIb/IIIa receptor (GP IIb/IIIa) inhibitors is a frequent treatment for patients undergoing primary PCI. According to the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the management of patients with STEMI [13], there is a class IIa recommendation (treatment reasonable) for the GP IIb/IIIa inhibitor abciximab and a class IIb recommendation (treatment may be considered) for the GP IIb/IIIa inhibitors tirofiban and eptifibatide.

Nevertheless, there is little data available about gender-related differences in clinical outcome in patients presenting with STEMI, and no data focusing on gender-related differences for patients presenting with STEMI who are treated with GP IIb/IIIa inhibitors. Therefore, the purpose of the present prospective study was to compare the clinical outcome of women and men presenting with STEMI undergoing primary PCI with concomitant use of GP IIb/IIIa inhibitors.

## Methods

### Patient selection

Between January 2006 and December 2007, 297 consecutive patients presenting with STEMI were included in this study. In-hospital and long-term follow-up data were prospectively collected. Patients with intravenous pre-hospital thrombolysis and patients with contraindications for a GP IIb/IIIa inhibitor were excluded. Hemodynamically stable patients, as well as patients with cardiogenic shock, were included. STEMI management was carried out according to the AHA/ACC guidelines [13]. All patients were treated by PCI with additional bare metal stent implantation and received

a GP IIb/IIIa inhibitor before the intervention. Written informed consent was obtained from all patients.

### Procedural details and angiographic analysis

PCI was performed by the femoral approach. Standard 5, 6 or 7 F guiding catheters and 0.014-inch floppy guide wires were used. Implantation technique, balloon size and stent type were chosen at the discretion of the physician. Predilation was performed with a single low-pressure inflation (8 atm) followed by stent implantation. High pressure stent deployment (> 12 atm) was recommended. All patients received unfractionated heparin (UFH) (70 U/kg body weight) and 500 mg acetylsalicylic acid before the procedure. Repeated 2,500 U bolus doses of UFH were given during the procedure to maintain an activated clotting time of > 250 s. After diagnostic angiography, treatment with a GP IIb/IIIa inhibitor (abciximab [ReoPro®] 0.25 mg/kg body weight, followed by a 12 hour infusion at 0.125 µg/kg/min, eptifibatide [Integrilin®] 180 µg/kg body weight, followed by a 18–24 hour infusion at 2.0 µg/kg/min, or tirofiban [Aggrastat®] 10 µg/kg body weight, followed by an 18 hour infusion at 0.1 µg/kg/min) was initiated and followed by a 12–24 hour infusion with concomitant UFH infusion. A loading dose of 600 mg of clopidogrel was given before the procedure, followed by 75 mg daily for the four weeks using bare metal stents. Long-term treatment with acetylsalicylic acid (100 mg/daily) was initiated in all patients. Angiograms were obtained in multiple projections at baseline and immediately after stent placement. The angiograms were analyzed by quantitative coronary angiography (QCA) evaluated by two independent observers. QCA was performed by analyzing the digitally stored images before and after stent implantation, using Quantcor-software (Siemens Medical Systems, Munich, Germany). The coronary perfusion was graded using the Thrombolysis In Myocardial Trial (TIMI) classification [14]. In the case of total occlusions (TIMI 0), the infarct-related lesion was clearly identified and characterized after a guide wire was passed through the thrombus (TIMI ≥ 1). The length of the stenosis was estimated with an electronic calliper and the catheter tips were used for calibration. The diameters of the proximal and distal reference segments were averaged by the system to yield the reference luminal diameter. The minimal luminal diameter and the percentage of diameter stenosis were calculated. The 'door-balloon-time', quantity of contrast agent as well as stent- and balloon-parameter were recorded.

**Table 1.** Baseline clinical characteristics.

	Female (n = 82)	Male (n = 215)	P
Age (years)	65 ± 10	60 ± 12	<b>0.04</b>
Risk factors			
Smoking	34 (41%)	103 (48%)	0.36
Hypercholesterolemia	48 (59%)	139 (65%)	0.35
Hypertension	56 (68%)	115 (53%)	<b>0.025</b>
Diabetes mellitus	16 (20%)	50 (23%)	0.54
Obesity	25 (30%)	39 (18%)	<b>0.03</b>
Family history of CAD	10 (12%)	41 (19%)	0.17
Medical history			
Cardiogenic shock	7 (9%)	32 (15%)	0.18
Prior myocardial infarction	9 (11%)	21 (10%)	0.83
Previous angioplasty	4 (5%)	33 (15%)	<b>0.02</b>
Previous bypass surgery	3 (4%)	12 (15%)	0.77
Laboratory parameters			
CK max [U/L]	1347 ± 1742	1359 ± 1978	0.89
TNI max [ug/L]	50.6 ± 75.2	84.1 ± 484.6	0.80
CRP [mg/L]	12.12 ± 21.1	25.62 ± 46.0	0.10
PLT [10 <sup>9</sup> /L]	274.5 ± 69.3	261.6 ± 81.6	0.21

Data is presented as mean ± standard deviation or as number (%); CAD — coronary artery disease; CK — creatine kinase; TNI — troponin I; CRP — C-reactive protein; PLT — platelet count

### Clinical data

STEMI was diagnosed according to the presence of two of the following criteria: persistent angina pectoris for > 20 min; ST-segment elevation of ≥ 0.1 mV in at least two standard leads or ≥ 0.2 mV in at least two contiguous precordial leads; or the presence of a new left bundle branch block. In-hospital serial electrocardiograms, coronary risk factors, as well as peak creatine kinase (CK), troponin I (TNI), C-reactive protein (CRP) and platelet count (PLT) levels were recorded. Long-term follow-up was obtained by hospital consultation or telephone contact and completed in all patients. Major adverse cardiac events (MACE) were defined as target lesion revascularization (TLR), coronary artery bypass graft, re-myocardial infarction and death.

### Statistical analysis

Data is presented as mean ± standard deviation (SD) for continuous variables and number and percentage for categorical variables. Comparisons of continuous variables between the groups were performed using the unpaired Student *t* test (two tailed) for normally distributed data and the Mann-Whitney U test for nonparametric data. Comparisons of categorical variables were carried out by  $\chi^2$  and Fisher's exact tests. A value of *p* < 0.05 was considered to be significant. To evaluate potential

confounding factors on patients with and without MACE, multivariate logistic regression analysis with backward elimination was performed. Age, gender, smoking, hypercholesterolemia, hypertension, diabetes mellitus, obesity, familiar history of coronary artery disease, cardiogenic shock, prior myocardial infarction, previous angioplasty, previous bypass surgery, CK, TNI, CRP and PLT were selected as independent variables. Cumulative survival rates of female and male patients are presented by Kaplan-Meier curves. The calculations were performed using InStat (GraphPad Software, San Diego, California, USA) and SPSS software (SPSS-Software GmbH, Munich, Germany).

## Results

### Baseline clinical data

The baseline clinical and laboratory data are shown in Table 1. Eighty two females (27.6%) and 215 males (72.4%) presenting with STEMI and undergoing PCI were included. There was a moderate but statistically significant difference in mean age (women: 65 ± 10 years, men: 60 ± 12 years, *p* = 0.044). Arterial hypertension was more common in the women included (56 [68%] *vs* 115 [53%], *p* = 0.025). Obesity also was a more common finding in the women (25 [30%] *vs* 39 [18%], *p* = 0.027). Men had undergone a previous angioplasty more

often (4 [5%] vs 33 [15%],  $p = 0.02$ ), but the medical history concerning prior myocardial infarction and previous bypass surgery did not differ between groups. The rate of patients with cardiogenic shock was similar in both groups (7 [9%] vs 32 [15%],  $p = 0.180$ ), as were the maximum peak elevations of CK, TNI, CRP and PLT (Table 1).

### Angiographic characteristics and procedural outcome

There was no difference between the allocation of the target vessel and the incidence of 1-, 2- or 3-vessel disease (Table 2). The rate of administration of the respective GP IIb/IIIa inhibitors (ab-ciximab, eptifibatid, tirofiban) was similar in both groups, as were procedural details such as quantity of contrast agent, number of stents, stent length, stent diameter and maximal inflation pressure. QCA results as diameter stenosis, minimal luminal diameter and length of stenosis were comparable in both groups, but women had a smaller reference luminal diameter at baseline ( $2.83 \pm 0.51$  vs  $2.94 \pm 0.43$ ,  $p = 0.03$ , Table 3). The rate of post-interventional major bleeding complications including intracranial hemorrhage (0 vs 1 [0.5%]), hematoma (6 [7%] vs 13 [6%],  $p > 0.05$ ), pseudoaneurysm (2 [2%] vs 3 [1%],  $p > 0.05$ ), and the rate of blood product

**Table 2.** Angiographic characteristics.

	Female (n = 82)	Male (n = 215)	P
Target vessel			
LAD	40 (49%)	79 (37%)	0.06
Left circumflex	8 (10%)	30 (14%)	0.44
Right	32 (39%)	98 (46%)	0.36
Saphenous vein graft	0 (0%)	5 (2%)	0.33
1-vessel disease	34 (41%)	78 (36%)	0.42
2-vessel disease	23 (28%)	66 (31%)	0.78
3-vessel disease	24 (29%)	69 (32%)	0.91
Baseline TIMI flow*			
0–1	72 (88%)	198 (92%)	0.26
2	10 (12%)	17 (8%)	0.26
Final TIMI flow*			
3	72 (88%)	91 (89%)	0.84

\*According to the Thrombolysis In Myocardial Infarction (TIMI) trial; LAD — left anterior descending

transfusion (6 [7%] vs 14 [7%],  $p > 0.05$ ) did not differ significantly between females and males.

### Clinical outcome

The in-hospital incidence of MACE (9 [11%] vs 33 [15%],  $p = 0.46$ ) did not differ significantly between women and men (Table 4). Long-term fol-

**Table 3.** Procedural characteristics and quantitative coronary angiography.

	Female (n = 82)	Male (n = 215)	P
Procedural characteristics			
Door-to-balloon time [min]	$2.79 \pm 0.69$	$2.73 \pm 0.53$	0.72
Abciximab	50 (60%)	127 (59%)	0.79
Eptifibatid	16 (20%)	38 (18%)	0.74
Tirofiban	16 (20%)	50 (23%)	0.54
Number of stents used	97	250	1.00
Stent diameter [mm]	$3.14 \pm 0.27$	$3.14 \pm 0.28$	0.94
Stent length [mm]	$16.9 \pm 3.5$	$17.3 \pm 3.9$	0.49
Max. inflation pressure [atm]	$14.6 \pm 1.8$	$15.1 \pm 1.9$	0.09
Quantity of contrast agent [mL]	$205 \pm 80$	$214 \pm 88$	0.19
Baseline			
Reference luminal diameter [mm]	$2.83 \pm 0.51$	$2.94 \pm 0.43$	<b>0.03</b>
Minimal luminal diameter [mm]	$0.28 \pm 0.43$	$0.26 \pm 0.41$	0.69
Diameter stenosis [%]	$87 \pm 15$	$89 \pm 18$	0.84
Length of stenosis [mm]	$11.2 \pm 6.4$	$10.8 \pm 4.8$	0.47
After stent implantation			
Reference luminal diameter [mm]	$3.1 \pm 0.3$	$3.2 \pm 0.5$	0.86
Minimal luminal diameter [mm]	$2.7 \pm 0.6$	$2.8 \pm 0.5$	0.74
Luminal gain [mm]	$2.4 \pm 0.8$	$2.4 \pm 0.7$	0.32
Diameter stenosis [%]	$10.8 \pm 16.2$	$11.4 \pm 14.7$	0.86

Data is presented as mean  $\pm$  standard deviation or as number (%)

**Table 4.** Clinical outcome.

	Female (n = 82)	Male (n = 215)	P
In-hospital follow-up			
Re-MI	0	2 (1%)	1.00
Death	6 (7%)	23 (11%)	0.51
CABG	2 (2%)	5 (2%)	1.00
TLR	1 (1%)	3 (1%)	1.00
<b>MACE</b>	<b>9 (11%)</b>	<b>33 (15%)</b>	<b>0.46</b>
Long-term follow-up*			
Re-MI	0	8 (4%)	0.11
Death	6 (7%)	28 (13%)	0.22
CABG	2 (2%)	6 (3%)	1.00
TLR	8 (10%)	14 (7%)	0.33
<b>MACE</b>	<b>16 (20%)</b>	<b>56 (26%)</b>	<b>0.29</b>

\*Cumulative data including in-hospital follow-up; MI — myocardial infarction; CABG — coronary artery bypass graft; TLR — target lesion revascularization; MACE — major adverse cardiac events

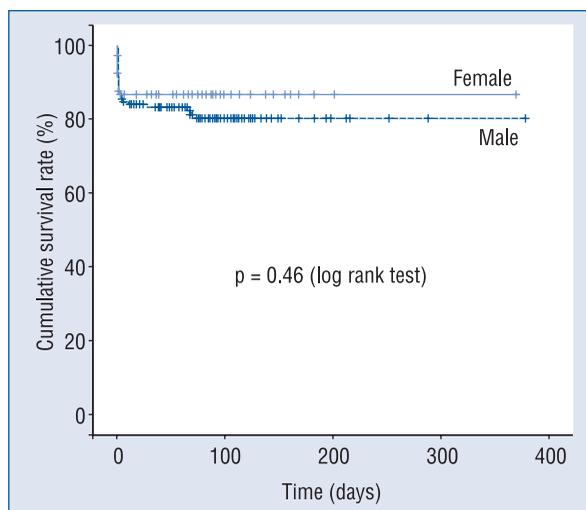
low-up was obtained for all patients  $213 \pm 68$  days after stent implantation. The incidence of MACE during long term follow-up was similar in both patient groups (16 [20%] vs 56 [26%],  $p > 0.29$ ). Figure 1 shows the Kaplan-Meier survival curves according to gender.

### Patients developing MACE

At univariate analyses, patients developing MACE were significantly older ( $65 \pm 10$  vs  $60 \pm 12$ ,  $p = 0.003$ ), had a higher incidence of obesity (19 [26%] vs 27 [12%],  $p = 0.005$ ), presented with cardiogenic shock more frequently (28 [39%] vs 11 [5%],  $p < 0.0001$ ) and displayed a higher CRP and PLT level. Female gender was not predictive for MACE (16 [22%] vs 66 [29%],  $p = 0.29$ ) (Table 5). Following multivariate analysis, after adjustment with the variables mentioned in the section on statistical analysis, the association of age (OR 1.03, 95% CI 1.00–1.07,  $p = 0.033$ ), CRP (OR 1.00, 95% CI 1.00–1.02,  $p = 0.022$ ), PLT (OR 1.00, 95% CI 1.00–1.01,  $p = 0.020$ ) and cardiogenic shock (OR 9.17, 95% CI 3.68–22.89,  $p < 0.001$ ) with MACE remained significant.

### Discussion

This is the first study comparing the clinical outcome of women and men presenting with STEMI undergoing primary PCI with concomitant use of GP IIb/IIIa inhibitors. According to the present results, female gender was not associated with a higher rate of MACE or other complications.



**Figure 1.** Kaplan-Meier survival curves according to gender. Kaplan-Meier analysis estimates the rates of death during in-hospital days and long-term follow-up. Rates of death between women and men were not significantly different ( $p = 0.46$ , log rank test). Small vertical tick-marks indicate when patients dropped out of the study.

There have been several studies reporting that women treated with thrombolysis and presenting with ‘acute myocardial infarction’ have a worse outcome than men [5–7]. In studies investigating patients presenting with ACS (patients with STEMI, NSTEMI or instable angina) randomized controlled trials have yielded conflicting results. Whereas the TACTICS TIMI-18 trial suggested a clear benefit of an early invasive approach without any obvious gender-related difference [15], the FRISC-II [16] and RITA-3 [17] trials reported that an early invasive strategy resulted in a beneficial effect in men that was not seen in women. From these studies, no direct conclusions can be drawn concerning the impact of GP IIb/IIIa inhibitors on gender. In the FRISC-II and RITA-3 trials, only 10% of patients received abciximab, whereas in the TACTICS TIMI-18 trial, all patients received the GP IIb/IIIa inhibitor tirofiban. Likewise, in our study, all patients received a GP IIb/IIIa inhibitor and no gender-related difference in outcome was found. Importantly, our results focus on the field of STEMI in real clinical practice.

So far, there have been many fewer studies investigating the impact of gender in patients presenting with STEMI than in patients presenting with ACS. One of these studies was performed by De Luca et al. [18]. The authors reported a higher mortality rate in women, but as in our study, female

**Table 5.** Incidence of major cardiac events during in-hospital and long-term follow-up.

Patient characteristic	With MACE (n = 72)	Without MACE (n = 225)	RR	95% CI	P
Age <sup>†</sup>	65.0 ± 10.4	60.3 ± 11.8			< 0.01*
Female	16 (22%)	66 (29%)	0.75	46–1.23	0.29
Risk factors					
Smoking	29 (40%)	111 (49%)	0.75	0.50–1.14	0.22
Hypercholesterolemia	48 (67%)	144 (64%)	1.09	0.71–1.68	0.78
Hypertension	46 (64%)	125 (56%)	1.30	0.85–1.99	0.22
Diabetes mellitus	20 (28%)	46 (20%)	1.35	0.87–2.08	0.20
Obesity	19 (26%)	27 (12%)	1.96	1.29–2.97	< 0.01**
Familiar history of CAD	9 (13%)	42 (19%)	0.69	0.37–1.29	0.28
Medical history					
Cardiogenic shock <sup>†</sup>	28 (39%)	11 (5%)	4.21	3.02–5.88	< 0.01***
Prior MI	9 (13%)	21 (9%)	1.27	0.71–2.29	0.50
Previous angioplasty	12 (17%)	25 (11%)	1.41	0.84–2.35	0.22
Previous bypass surgery	6 (8%)	9 (4%)	1.71	0.89–3.29	0.21
Laboratory parameters					
CK max [U/L]	1829 ± 2740	1205 ± 1575			0.71
TNI max [ug/L]	166 ± 853	49 ± 89			0.37
CRP [mg/L] <sup>†</sup>	37.27 ± 61.0	17.54 ± 32.2			0.05
PLT [10 <sup>9</sup> /L] <sup>†</sup>	288.1 ± 99.1	257.8 ± 69.4			0.02

Data is presented as mean ± SD or as number (%); <sup>†</sup>p = 0.003; \*\*p = 0.005; \*\*\*p < 0.0001; <sup>†</sup>Independent predictors of MACE at multivariate analyses; RR — relative risk; CI — confidence interval; CAD — coronary artery disease; MI — myocardial infarction; CK — creatine kinase; TNI — troponin I; CRP — C-reactive protein; PLT — platelet count

sex did not emerge as an independent predictor of death. Similarly in other studies, female sex did not emerge as an independent predictor of MACE [9, 10]. De Luca et al. [18] explained the higher mortality rate in women by the smaller reference luminal diameter and the higher prevalence of cardiovascular risk factors in women, a difference in presentation which has been confirmed by many other studies [5–9, 12]. We also found a consistently smaller reference luminal diameter and a higher cardiovascular risk profile in women. Unlike our study, the use of GP IIb/IIIa inhibitors was not reported or discussed. Previous data has suggested that the greatest benefit from GP IIb/IIIa inhibitors is derived by patients presenting at high risk (elevated troponin levels) [19]. Further, it has been reported that in patients with cardiogenic shock, the benefit of GP IIb/IIIa inhibitors persists through long-term follow-up [20]. It is possible that both of these attributes have contributed to our results, considering that in the present study the incidence of cardiogenic shock was relatively high (13%) and only patients presenting with STEMI were included. Further studies are necessary to confirm this beneficial effect, and to clarify whether GP IIb/IIIa inhibitors might be able to reduce gender-related dif-

ferences in women < 50 years old (which is a separate risk factor for mortality in women presenting with ACS [7]). In this study, only five women with this characteristic pattern could be included.

In general, patients with ACS display increased platelet activation and increased levels of inflammatory mediators, both correlating with the degree of myocardial damage [21–23]. GP IIb/IIIa inhibitors suppress platelet aggregation [24] and have anti-inflammatory effects [25, 26]. Both mechanisms may also have contributed to the beneficial effects of GP IIb/IIIa inhibitors in this study and may have mitigated gender-related differences in the vascular risk factor profile of the investigated patient cohort. It remains to be clarified by further studies whether these beneficial effects might also significantly improve the clinical outcome in patients already pre-treated with prasugrel.

In patients presenting with ACS, advanced age, female sex, history of bleeding and renal insufficiency are independently associated with a higher risk of bleeding [27]. In this study, the incidence of major bleeding complications did not differ between women and men. Nevertheless, we emphasize the importance of adjusting antiplatelet medication dose for body surface area to minimize bleeding complications.

### Limitations of the study

The non-randomized design of this single center investigation may have influenced the comparative analysis. Similar to other studies, a higher pre-hospital mortality of women and the exclusion of patients receiving pre-hospital thrombolysis could have affected our results. Therefore, caution is needed in the interpretation of our data. Nonetheless, we consider it improbable that these limitations have significantly influenced our main findings.

### Conclusions

In this study, female gender did not emerge as an independent predictor for MACE. But women presenting with STEMI had a higher cardiovascular risk profile, which emphasizes the need for a more extensive therapeutic strategy. Combination therapy with primary PCI and GP IIb/IIIa inhibitors might mitigate gender-related differences in clinical outcome. New studies investigating patients pre-treated with prasugrel should be performed, to evaluate the clinical influence of the beneficial effects of GP IIb/IIIa inhibitors.

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