Gender and Myocardial Salvage After Reperfusion Treatment in Acute Myocardial Infarction

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OBJECTIVES
The aim of this study was to investigate whether there are gender-associated differences in the amount of myocardial salvage after primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI).

BACKGROUND
Despite having a more adverse cardiovascular risk profile, women with AMI have similar or even better outcomes after primary PCI compared with men. The reasons for these findings are unclear.

METHODS
In this study we included 202 women and 561 men with AMI who underwent primary PCI in the setting of three randomized trials. The primary end point of the study was myocardial salvage index (proportion of initial perfusion defect salvaged by reperfusion therapy), obtained by paired scintigraphic studies performed 7 to 10 days apart.

RESULTS
The amount of myocardium at risk or initial perfusion defect (median [25th, 75th percentiles]) did not differ significantly between women and men (22.0% [12.0, 40.0] vs. 24.0% [14.0, 39.0] of the left ventricle [LV], p = 0.26). Final infarct size, measured in the follow-up scintigraphy, was significantly smaller in women than in men (6.0% [0.71, 18.7] vs. 10.0% [3.9, 21.8] of the LV, p = 0.001). Myocardial salvage index was 0.64 (0.35, 0.95) in women versus 0.50 (0.26, 0.77) in men (p < 0.001). After adjustment for baseline characteristics, female gender was an independent predictor of greater myocardial salvage after PCI (p = 0.002).

CONCLUSIONS
The efficacy of primary PCI in patients with AMI appears to be gender-dependent. Myocardial salvage achieved by primary PCI is greater in women than in men. (J Am Coll Cardiol 2005;45:828–31) © 2005 by the American College of Cardiology Foundation

Despite the fact that women, by the time of acute myocardial infarction (AMI), are older and have a more adverse cardiovascular risk profile, studies investigating the influence of gender on the outcome after primary percutaneous coronary intervention (PCI) have reported no differences in the short- or long-term mortality between the genders (1,2). In a recent study that included more than 2,000 patients with AMI treated mostly with primary PCI, we demonstrated similar short- and long-term prognosis in both genders; however, after adjustment for age, female gender was associated with a 35% reduction in mortality (2). To date, no studies have addressed whether there are gender-related differences in the amount of jeopardized myocardium that is salvaged by mechanical reperfusion in patients with AMI. Therefore, we undertook this study to assess the impact of gender on the myocardial salvage achieved by primary PCI with adjunct antiplatelet therapy in patients with AMI.

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Manuscript received October 1, 2004; revised manuscript received November 16, 2004, accepted November 22, 2004.

METHODS

Patients and study protocol. We included in this study 763 patients with AMI within the first 48 hours of symptom onset receiving primary PCI as reperfusion therapy between December 1997 and February 2002, in the setting of three randomized trials: Stent Versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOPAMI)-1 and -2, and Stent or Percutaneous Transluminal Coronary Angioplasty for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Ineligible for Thrombolysis (STOPAMI)-3 trial (3–5). In the STOPAMI-1 and -2 trials, patients with AMI eligible for thrombolysis were randomized to receive coronary stenting plus abciximab (152 patients), or thrombolysis applied as alteplase alone (69 patients) or as half-dose alteplase plus abciximab (81 patients) (3,4). In the STOPAMI-3 trial, patients with AMI ineligible for thrombolysis were randomly assigned to undergo coronary stenting (305 patients) or plain balloon angioplasty (306 patients) (5). All included patients provided written informed consent for participating in the three trials.

Detailed information about patient enrollment and study designs has been previously published (3–5). Shortly, all patients received 500 mg of aspirin and a bolus of 60 U/kg of heparin intravenously. In addition, they received an
intravenous injection of 27 mCi of $^{99m}$Tc-sestamibi required for the baseline scintigraphic study. In patients without contraindications, abciximab was used as adjunct therapy. Post-interventional oral antiplatelet therapy consisted of ticlopidine, given at a dose of 250 mg twice daily, or clopidogrel, given at a dose 75 mg daily, for four weeks, and aspirin given at a dose of 100 mg twice a day indefinitely. Qualitative and quantitative assessment of digital angiograms was performed off-line using the automated edge detection system CMS (Medis Medical Imaging Systems, Nuenen, the Netherlands) in the Angiographic Core Laboratory. Classification of anterograde coronary flow in the infarct-related artery was done according to Thrombolysis In Myocardial Infarction (TIMI) classification (6). Collateral circulation was quantified according to Rentrop et al. (7). Post-discharge clinical follow-up consisted of telephone interviews at one month and a hospital visit at six months after the initial procedure.

The first scintigraphy was performed within six to eight hours after injection of 27 mCi (1,000 MBq) of $^{99m}$Tc-sestamibi. A follow-up scintigraphy was scheduled 7 to 10 days after intervention. Paired scintigraphic examinations were used to calculate three parameters: initial perfusion defect and final infarct size, both expressed as a percentage of the left ventricle (LV), as well as myocardial salvage, calculated as initial perfusion defect minus final infarct size divided by initial perfusion defect. The measurement of scintigraphic images was performed off-line in the scintigraphic core laboratory by operators unaware of patients’ treatment and characteristics.

Of the 763 patients receiving primary PCI in the STOPAMI trials, 634 (83.0%) had technically satisfactory paired $^{99m}$Tc-sestamibi scintigraphic studies needed for determination of salvage index. No gender-dependent difference in the rate of completed paired scintigraphic studies was observed (161 women, 80.0% vs. 473 men, 84.3%, $p = 0.14$). The primary end point of the study was the salvage index.

Statistical analysis. The data are presented as median (25th, 75th percentiles) or as counts or proportions. The differences between women and men were assessed with Table 1.

<table>
<thead>
<tr>
<th>Table 1. Patients’ Demographics, Cardiovascular Risk Profile, and Infarct Characteristics</th>
<th>Women (n = 202)</th>
<th>Men (n = 561)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>72.9 [60.7, 87.6]</td>
<td>60.0 [51.5, 80.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>158 (78.2)</td>
<td>358 (63.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50 (24.8)</td>
<td>109 (19.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>On insulin therapy</td>
<td>15 (7.4)</td>
<td>20 (3.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Current smoker</td>
<td>51 (25.2)</td>
<td>249 (44.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol level (mg/dl)</td>
<td>200 [173, 240]</td>
<td>199 [170, 234]</td>
<td>0.12</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>21 (10.4)</td>
<td>89 (15.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>4 (2.0)</td>
<td>24 (4.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>6 (7.6)</td>
<td>56 (10.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
<td>88 (44.0)</td>
<td>238 (42.6)</td>
<td>0.78</td>
</tr>
<tr>
<td>Pre-infarct angina</td>
<td>98 (49.0)</td>
<td>224 (40.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Killip class</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>1</td>
<td>132 (65.4)</td>
<td>396 (70.6)</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>44 (21.8)</td>
<td>109 (19.4)</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>12 (5.9)</td>
<td>15 (2.7)</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>14 (6.9)</td>
<td>41 (7.3)</td>
<td>—</td>
</tr>
<tr>
<td>Time to admission (h)</td>
<td>10.3 [4.4, 40.9]</td>
<td>8.0 [2.4, 37.1]</td>
<td>0.004</td>
</tr>
<tr>
<td>Time door-to-balloon (h)</td>
<td>1.58 [1.3, 2.0]</td>
<td>1.59 [1.3, 1.9]</td>
<td>0.52</td>
</tr>
<tr>
<td>Initial perfusion detect, % of the LV*</td>
<td>22.0 [12.0, 40.0]</td>
<td>24.0 [14.0, 39.0]</td>
<td>0.26</td>
</tr>
<tr>
<td>Therapy at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>170 (84.7)</td>
<td>489 (87.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>182 (91.1)</td>
<td>515 (92.3)</td>
<td>0.56</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>176 (88.1)</td>
<td>500 (89.7)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Data are presented as number (percentage) or median [25th, 75th percentiles]. *Available in 161 women and 473 men.

Abbreviations and Acronyms

- **AMI** = acute myocardial infarction
- **LV** = left ventricle
- **PCI** = percutaneous coronary intervention
- **SPECT** = single-photon emission computed tomography
- **STOPAMI** = Stent Versus Thrombolysis for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction trial
- **STOPAMI-3** = Stent or Percutaneous Transluminal Coronary Angioplasty for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction Ineligible for Thrombolysis trial
- **Tc** = technetium
- **TIMI** = Thrombolysis In Myocardial Infarction

**Gender and Myocardial Salvage**

**Thrombolysis In Myocardial Infarction (TIMI)** classification (6). Collateral circulation was quantified according to Rentrop et al. (7). Post-discharge clinical follow-up consisted of telephone interviews at one month and a hospital visit at six months after the initial procedure.

**99mTc-sestamibi scintigraphy.** The first scintigraphy was performed within six to eight hours after injection of 27 mCi (1,000 MBq) of $^{99m}$Tc-sestamibi. A follow-up scintigraphy was scheduled 7 to 10 days after intervention. Paired scintigraphic examinations were used to calculate three parameters: initial perfusion defect and final infarct size, both expressed as a percentage of the left ventricle (LV), as well as myocardial salvage, calculated as initial perfusion defect minus final infarct size divided by initial perfusion defect. The measurement of scintigraphic images was performed off-line in the scintigraphic core laboratory by operators unaware of patients’ treatment and characteristics.

Of the 763 patients receiving primary PCI in the STOPAMI trials, 634 (83.0%) had technically satisfactory paired $^{99m}$Tc-sestamibi scintigraphic studies needed for determination of salvage index. No gender-dependent difference in the rate of completed paired scintigraphic studies was observed (161 women, 80.0% vs. 473 men, 84.3%, $p = 0.14$). The primary end point of the study was the salvage index.

**Statistical analysis.** The data are presented as median (25th, 75th percentiles) or as counts or proportions. The differences between women and men were assessed with
two-sided chi-square test for categorical data or nonparametric Wilcoxon rank sum test for continuous data. Differences in clinical outcome data between women and men were assessed by the use of Mantel-Haenszel analysis with stratification by STOPAMI trial. Multiple linear regression analysis was used to assess the independent impact of gender on myocardial salvage while adjusting for other variables. The following parameters were entered into the model: age, diabetes, arterial hypertension, cholesterol level, smoking, previous myocardial infarction, previous coronary angioplasty, previous coronary bypass graft surgery, Killip class, anterior infarction, time-to-admission interval, initial coronary TIMI flow grade, and pre-infarct angina. A two-tailed p < 0.05 was considered to indicate statistical significance.

RESULTS

Of the 763 patients receiving primary PCI as reperfusion therapy in the STOPAMI-1, -2, and -3 trials, 202 (26.0%) were women and 561 (74.0%) were men. Patient characteristics are shown in Table 1. Women were older, had arterial hypertension and pre-infarct angina more often, and presented later in the hospital after symptom onset as compared to men. Furthermore, there was a trend for a higher incidence of diabetes in women than in men.

With the exception of vessel size and final minimal lumen diameter, no other significant differences were observed between the genders with regard to the angiographic or procedural characteristics (Table 2).

Gender and myocardial salvage. Initial perfusion defect or myocardium at risk did not differ significantly between women and men (22.0% [12.0, 40.0] vs. 24.0% [14.0, 39.0] of the LV, p = 0.26). Final infarct size was significantly smaller in women than in men (6.0% [0.71, 18.7] vs. 10.0% [3.9, 21.8] of the LV, p = 0.001). Salvage index was 0.64 (0.35, 0.95) in women versus 0.50 (0.26, 0.77) in men (p < 0.001) (Fig. 1). This advantage of female gender regarding salvage index remained even when subgroups of patients with first AMI (0.69 [0.37, 0.96] in women vs. 0.52 [0.27, 0.8] in men, p = 0.001) or patients eligible for thrombolysis (0.70 [0.49, 0.91] in women vs. 0.52 [0.31, 0.69] in men, p = 0.005) were analyzed separately. In the subgroup of patients with pre-infarct angina, women had a trend for higher salvage index (0.71 [0.32, 0.97]) than men (0.57 [0.29, 0.83], p = 0.08). After adjustment in the multivariate model, female gender (p = 0.002) and pre-infarct angina (p = 0.03) were identified as independent factors associated with a higher salvage index. A higher Killip class at presentation (p < 0.001), a longer symptom onset-to-admission interval (p = 0.01), and a history of previous myocardial infarction (p = 0.02) were independently associated with a lower salvage index.

Clinical outcome at six months. Six female and 15 male patients experienced recurrent myocardial infarction (3.0% vs. 2.7%, respectively; p = 0.82). Stroke occurred in five women and in two men (2.5% vs. 0.4%, respectively; p = 0.02). Eighteen women and 42 men died within this period (8.9% vs. 7.5%, respectively; p = 0.64). Nonstroke-related mortality was 6.9% in women (n = 14) and 7.3% in men (n = 41), p = 0.97. Twelve women (5.9%) and 37 men (6.6%) died of cardiac causes (p = 0.74).

DISCUSSION

This study demonstrates for the first time a significant gender difference in the degree of myocardial salvage after...
mechanical reperfusion in AMI, with women having a greater amount of myocardium at risk salvaged than men. The degree of anterograde coronary flow before and after reperfusion and the presence of coronary collateral vessels, which have been proposed as predictors of the degree of myocardial salvage by reperfusion (8,9), were not different between the genders in our study and thus cannot explain the observed differences.

In the present study, more than 90% of the patients received aggressive antiplatelet therapy with abciximab as an adjunct to PCI. Platelets of women have been demonstrated to show a greater sensitivity to aggregating stimuli (10,11). Thus, women may benefit to a greater degree from effective antiplatelet inhibition by abciximab. Women presenting with AMI in our study reported pre-infarction angina more frequently than men. Pre-infarct angina may have protective effects leading to limitation of the infarct size, a greater myocardial viability upon reperfusion, and an improvement in the long-term survival and left ventricular function (12,13). Ischemic pre-conditioning and enhancement of spontaneous thrombolysis due to adenosine-related platelet aggregation inhibition during angina, leading to an increase in the hypoxic tolerance of the myocardial tissue, have been suggested as underlying explanatory mechanisms. Experimental studies have provided evidence that the hypoxic tolerance and its underlying mechanisms are gender-specific (14,15). Female cells present a higher basal expression of the survival-associated protein Bcl-2, showing a higher inherited hypoxic tolerance than male cells. Moreover, upon pre-conditioning, female cells—because of a significant lower activation of signaling pathways that control cell apoptosis—develop a higher tolerance to induced hypoxia than do male cells (16). Another factor possibly playing a role with respect to the increase in hypoxic tolerance seems to be the activation of estrogen receptor in cardiac cells upon pre-conditioning. Because of more functional and a higher density of estrogen receptors, even low blood levels of estrogen may confer resistance to female, but not male, cardiomyocytes against intracellular Ca^{2+} loading induced by hypoxia-reoxygenation (15).

These gender-related differences in the hypoxia tolerance may result in a better local myocardial response to ischemic injury in women and may explain the greater myocardial salvage in women than in men.

In conclusion, women with acute myocardial infarction treated with mechanical reperfusion and adjunct platelet glycoprotein IIb/IIIa receptor inhibitors show a higher degree of myocardial salvage than men. This may improve the chances of survival of women, despite their more adverse cardiovascular profile.

REFERENCES