Gender-related differences among patients with STEMI: a propensity score analysis

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ABSTRACT

Introduction and objectives: Female sex is believed to be a significant risk factor for mortality among patients with ST-segment elevation myocardial infarction [STEMI] undergoing primary percutaneous coronary interventions [pPCI].

Methods: We collected data on all consecutive STEMI patients treated with pPCI within 12 hours and compared the males vs the females. The primary endpoint was long-term mortality one month after hospital discharge. The secondary endpoint was 30-days mortality.

Results: From March 2006 to December 2016, 1981 patients underwent pPCI at our hospital, 484 (24.4%) were females. Compared with men, women were older [mean age 71.3 ± 11.6 vs 62.9 ± 11.8 years, P < .001], less smokers [26.7% vs 72.7%; P < .001], more diabetic [28.0% vs 22.3%; P < .002], more hypertensive [69.6% vs 61.3%; P < .001], presented more often with shock at baseline [13.2% vs 9.0%; P = .006], had longer symptoms-to-balloon time frames [5.36 ± 3.97 vs 4.47 ± 3.67 hours; P < .001]. Also, women were less likely to receive glycoprotein IIb-IIIa inhibitors [59.5% vs 71.4%; P < .001] and stents [79.5% vs 86.6%; P = .01]. During the 30-day and long-term follow-up [mean 4.9 ± 3.2 years] the female sex was associated with a higher mortality rate [8.9% vs 4.0%, P < .001 and 23.8% vs 18.4%, P = .01, respectively]. After propensity score matching, 379 men and 379 women were selected. Female sex continued to be associated with a higher death rate at 30 days [9.5% vs 5.5%; P = .039] but not in the long term among survivors [25.6% vs 21.4%; P = .170].

Conclusions: Compared to men, women with STEMI undergoing pPCI had higher 30-day mortality rates. However, among survivors, the long-term mortality rate was similar. Even if residual confounding cannot be ruled out, this difference in the outcomes may be partially explained by biological sex-related differences.

Keywords: ST-segment elevation myocardial infarction. Primary angioplasty. Sex differences. Outcomes.

Diferencias relacionadas con el sexo en pacientes con IAMCEST: análisis por puntuación de propensión

RESUMEN

Introducción y objetivos: El sexo femenino se considera un importante factor de riesgo de mortalidad en el infarto agudo de miocardio con elevación del segmento ST [IAMCEST] tratado con intervención coronaria percutánea primaria [ICPp].

Métodos: Se analizó a todos los pacientes consecutivos con IAMCEST tratados con ICPp dentro de las primeras 12 horas, y se compararon varones y mujeres. El objetivo principal fue la mortalidad a largo plazo en los supervivientes después del primer mes del alta, y el objetivo secundario fue la mortalidad a los 30 días.

Resultados: Desde marzo de 2006 hasta diciembre de 2016 se trató con ICPp 1.981 a pacientes, de los cuales 484 (24,4%) eran mujeres. En comparación con los varones, las mujeres tenían mayor edad [edad media 71,3 ± 11,6 frente a 62,9 ± 11,8 años, p < 0,001] y la frecuencia de fumadoras era más baja [26,7 frente a 72,7%; p < 0,001], mientras que era más alta la frecuencia de diabetes [28,0 frente a 22,3%; p < 0,002], hiperpresión arterial [69,6 frente a 61,3%, p < 0,001] y shock al ingreso [13,2 frente a 9,0%; p = 0,006], y más largo el tiempo desde el comienzo de los síntomas hasta la intervención con balón [5,36 ± 3,97 frente
bECOMING THE TREATMENT OF CHOICE IN THIS FIELD. 4 However, the use of abciximab was extended for another 12 hours after the procedure or ticagrelor (180 mg) was administered before or immediately after the PCI, unless patients were already on chronic maintenance therapy, and then followed by a maintenance dose of clopidogrel (75 mg once a day), prasugrel (10 mg once a day), or ticagrelor (90 mg twice a day) for 12 months when possible.

Repeated revascularization was only performed in the presence of symptom recurrence or proven ischemia related to the treated lesion.

Data on the 30-day follow-up were available for all patients at our center database. Information beyond the first month was collected through outpatient visits, telephone calls or by reviewing any available medical records to obtain the longer follow-up for each patient. All data were entered into a dedicated database.

The men vs women outcomes before and after the propensity score matching were compared. The primary endpoint was long-term mortality after hospital discharge. The secondary endpoint was 30-day mortality rate, 30-day and long-term Bleeding Academic Research Consortium bleeding type ≥ 2. 2 Long-term events were evaluated starting from day 31 after discharge until the longer available follow-up. The rate of procedural efficiency (defined a Thrombolysis in Myocardial Infarction [TIMI] III grade flow and residual stenosis < 30%) and ST-segment resolution of more than 50% 60–90 minutes after the PCI was also collected and reported.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median (Q1-Q3), according to the normality of their distribution. Qualitative variables were expressed as frequencies and percentages. The Fisher’s exact test or the chi-square test were used for qualitative variables while the Student’s t test or the Mann-Whitney U test were used for quantitative variables as appropriate. Survival data were represented and analyzed using the Kaplan-Meier curves and the Cox regression analysis. All statistical tests were 2-sided. Results were considered significant if P values < .05. Given the baseline differences between female and male patients and in order to reduce selection bias, we used propensity score matching. The logistic regression model was used based on the baseline and peri-percutaneous coronary intervention characteristics. Thus, P values < .20 were defined to include the selected variables in the final model. The selected variables were...
Table 1. Baseline features

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 1981)</th>
<th>Female (n = 944; 24.4%)</th>
<th>Male (n = 1037; 75.6%)</th>
<th>P</th>
<th>Female (n = 379)</th>
<th>Male (n = 379)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65.0 ± 12.3</td>
<td>71.3 ± 11.6</td>
<td>62.9 ± 11.8</td>
<td>&lt; .001</td>
<td>68.5 ± 11.9</td>
<td>69.2 ± 11.6</td>
<td>.43</td>
</tr>
<tr>
<td>Age &gt; 80 years</td>
<td>262 (13.2)</td>
<td>134 (27.7)</td>
<td>128 (8.6)</td>
<td>&lt; .001</td>
<td>69 (18.2)</td>
<td>75 (19.8)</td>
<td>.58</td>
</tr>
<tr>
<td>Diabetes mellitusa</td>
<td>469 (23.7)</td>
<td>135 (27.9)</td>
<td>334 (22.3)</td>
<td>.002</td>
<td>63 (18.6)</td>
<td>74 (19.5)</td>
<td>.29</td>
</tr>
<tr>
<td>Hypertensionb</td>
<td>1254 (63.3)</td>
<td>337 (68.6)</td>
<td>917 (61.3)</td>
<td>.001</td>
<td>227 (59.9)</td>
<td>240 (63.3)</td>
<td>.33</td>
</tr>
<tr>
<td>Dyslipidemiac</td>
<td>742 (37.5)</td>
<td>182 (37.6)</td>
<td>560 (37.4)</td>
<td>.93</td>
<td>134 (35.4)</td>
<td>142 (37.5)</td>
<td>.54</td>
</tr>
<tr>
<td>Obesityd</td>
<td>307 (15.5)</td>
<td>113 (23.3)</td>
<td>194 (13.0)</td>
<td>&lt; .001</td>
<td>64 (16.9)</td>
<td>66 (17.4)</td>
<td>.85</td>
</tr>
<tr>
<td>Chronic kidney failure e</td>
<td>53 (2.7)</td>
<td>17 (3.5)</td>
<td>36 (2.4)</td>
<td>.19</td>
<td>23 (6.1)</td>
<td>23 (6.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoking (current or former smoker)</td>
<td>1217 (61.4)</td>
<td>129 (26.7)</td>
<td>1088 (72.7)</td>
<td>&lt; .001</td>
<td>129 (34.0)</td>
<td>129 (34.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cardiogenic shock at presentation</td>
<td>198 (10.0)</td>
<td>64 (13.2)</td>
<td>134 (9.0)</td>
<td>.006</td>
<td>56 (14.8)</td>
<td>43 (11.3)</td>
<td>.16</td>
</tr>
<tr>
<td>Oral intubation</td>
<td>116 (5.9)</td>
<td>31 (6.4)</td>
<td>85 (5.7)</td>
<td>.56</td>
<td>26 (6.9)</td>
<td>23 (6.1)</td>
<td>.56</td>
</tr>
<tr>
<td>Cardiac resuscitation at presentation</td>
<td>21 (1.1)</td>
<td>8 (1.7)</td>
<td>13 (0.9)</td>
<td>.14</td>
<td>7 (1.8)</td>
<td>8 (2.1)</td>
<td>.79</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>48.4 ± 10.0</td>
<td>46.8 ± 10.0</td>
<td>48.5 ± 10.0</td>
<td>.007</td>
<td>47.5 ± 9.4</td>
<td>47.3 ± 9.6</td>
<td>.83</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt; 35%</td>
<td>202 (10.2)</td>
<td>69 (14.3)</td>
<td>133 (8.9)</td>
<td>.001</td>
<td>43 (11.3)</td>
<td>44 (11.6)</td>
<td>.91</td>
</tr>
<tr>
<td>Total ischemia time</td>
<td>4.7 ± 3.8</td>
<td>5.4 ± 4.0</td>
<td>4.5 ± 3.7</td>
<td>&lt; .001</td>
<td>4.4 ± 3.7</td>
<td>4.6 ± 4.0</td>
<td>.13</td>
</tr>
<tr>
<td>Anterior wall infarct location</td>
<td>877 (44.3)</td>
<td>217 (44.8)</td>
<td>660 (44.1)</td>
<td>.82</td>
<td>165 (43.5)</td>
<td>165 (43.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

a American Heart Association Guidelines definition.
b Arterial systemic pressure > 140/90 mmHg.
c Total cholesterol > 200 mg/dL; low density lipoproteins ≥ 130 mg/dL; triacylglycerol > 175 mg/dL.
d Body mass index > 30.
e Dialysis or serum creatinine > 2 mg/dL.
Values are expressed as mean ± standard deviation or frequencies (percentages).

RESULTS

From March 2006 to December 2016, among the 1981 patients who underwent pPCIs at our hospital, 484 (24.4%) were females (table 1). Compared to men, women were older (mean age 71.3 ± 11.6 vs 62.9 ± 11.8 years; P < .001), there were fewer female smokers (26.7% vs 72.7%; P < .001), they were more diabetic (28.0% vs 22.3%; P < .002), more hypertensive (69.6% vs 61.3%; P < .001), and they presented more frequently with cardiogenic shock at admission (13.2% vs 9.0%; P = .006). They also had longer symptoms-to-balloon time (5.36 ± 3.97 vs 4.47 ± 3.67 hours; P < .001) and lower left ventricular ejection fractions (46.8 ± 10% vs 48.5 ± 10%; P = .007). Also, as shown on table 2, women were less likely to be treated with glycoprotein IIb-IIIa inhibitors (59.5% vs 71.4%; P < .001), thrombus aspiration devices (48.3% vs 58.0%, P < .001) and stents (79.5% vs 86.6%, P = .01). Procedural efficiency and ST-resolution were significant lower in the female cohort (93.0 vs. 97.1%, P < .001 and 60.0 vs 65.8%, P = .033, respectively, and table 3).

At the 30-day and long-term follow-up (mean 4.9 ± 3.2 years, completed in 1634, 82.5% patients) the female sex was associated with a higher mortality rate (8.9% vs 4.0%, P < .001 and 23.8% vs 18.4%, P = .01, respectively) and a higher rate of major bleedings at 30 days (4.5% vs 1.4%; P = .039) and a higher rate of major bleedings and death at 30 days (9.5% vs 5.5%, P = .039 and 4.2% vs 1.6%, P = .007). Conversely, in the matched cohort no significant differences were found in the long-term...
mortality rate among survivors (25.6% vs 21.4%, \( P = .170 \), table 3; and log-rank \( P = .23 \), figure 3). The multiple Cox regression analysis revealed that age (hazard ratio [HR], 1.09; (1.06 – 1.12); \( P < .001 \)), cardiogenic shock at presentation (HR, 6.82 (3.84 – 12.12); \( P < .001 \)), the left ventricular ejection fraction < 35% (HR, 1.98 (1.11 – 3.54); \( P = .022 \)) and procedural efficacy (HR, 0.46 (0.23 – 0.89); \( P = .022 \)) have an effect on mortality when included together with female sex (HR, 0.68 (0.42 – 1.09); \( P = .106 \)), which is not significant as stated before (table 4).

Main outcome analysis was performed based on a 2-time period (2006-2010 and 2011-2016) without underlining any differences among the groups (table 2 of the supplementary data).

**DISCUSSION**

Our large single-center registry showed that in a high PCI volume center, women admitted with STEMI undergoing pPCI have a higher 30-day and long-term mortality rate compared to men. This difference persists after propensity score adjustment regarding the 30-day mortality.

A drop in cardiovascular mortality has been observed over the last few decades, but cardiovascular disease is still the leading cause of death. The findings that women with STEMI have a lower procedural efficacy and higher mortality rate when compared with men may explain the higher mortality rates observed in women, despite the improved overall survival. This is in line with the results from previous studies that have shown lower procedural efficacy in women undergoing PCI, which could contribute to the higher mortality rates in this group. However, further research is needed to understand the underlying mechanisms and factors contributing to these differences.
cause of mortality in women worldwide. Cardiovascular mortality remains higher in women compared to men.\textsuperscript{5} So far, the reasons of this difference have been mainly justified by the higher prevalence of traditional risk factors (higher mean age, hypertension, diabetes, and renal failure) in the female cohort.\textsuperscript{6} Also, women who experience myocardial infarction often present with atypical symptoms like dyspnea, fatigue, nausea/vomiting and atypical chest pain, which can lead to delayed diagnosis and treatment.\textsuperscript{6}

Another factor associated with a higher mortality rate to be taken into account is represented by bleeding and mechanical complications, more common in women compared to men.\textsuperscript{6,11} Our study confirms all these data: in our population, women were significantly older, with more traditional risk factors (except for smoking), longer ischemic time frames and higher-risk presentations. Also, they had a significantly higher rate of bleeding and mechanical complications.

After propensity score adjustment, our study showed that female sex was independently associated with 30-day but not long-term mortality. These findings are similar to those of a recent large meta-analysis led by Conrotto et al.,\textsuperscript{12} that included 98,778 patients (73,559 men and 25,219 women) and could be explained, at least in part, by the different pathophysiology of coronary disease in women: the rupture of the plaque surface, the leading cause of coronary occlusion in men, happens only in around 50% of women,\textsuperscript{13} the remaining percentage being represented by the erosion of the plaque,\textsuperscript{14} coronary spasm leading to thrombus generation,\textsuperscript{15} and spontaneous coronary artery dissection.\textsuperscript{16} Particularly spontaneous coronary artery dissection seems to play an important role in younger women (< 60 years of age) and is associated with a high rate of major adverse cardiac events.\textsuperscript{17} Therefore, these findings may explain why, in our population, women had lower rate of thrombus aspiration, use glycoprotein IIb-IIIa inhibitors, and stent implantation, which in turn may justify, along with the clinical features, the lower procedural success and ST-segment resolution observed in our study. These factors, associated with the higher rate of bleedings and mechanical complications and other psychological factors, like depression, more prevalent in women compared to men in the general population,\textsuperscript{18,19} may be phenotypes of a higher frailty in the female sex, and may definitely explain the worse outcomes, at least in the short-term. At long-term, other factors, like the lower in-stent restenosis rate and the resulting lower need for target vessel revascularization observed in women, and already shown in some studies,\textsuperscript{20-23} may explain the similar outcomes observed in the propensity score analysis.
WHAT IS KNOWN ABOUT THE TOPIC?

- Women have a higher ACS-related mortality rate but there is no consensus on whether to consider female sex as a risk factor of poor outcomes. This is due to the fact that many authors explain this sex difference by the atypical onset of symptoms in women and the lower recurrence to cath. lab procedures and angioplasties performed in females. However, only a limited number of studies have reported medium or long-term mortality results and even fewer studies have had clear inclusion criteria (ie, the entire acute coronary syndrome spectrum or only the STEMI subset) or reported on the treatment strategies used.

WHAT DOES THIS STUDY ADD?

- Our large single-center registry showed that in a high PCI volume center, women admitted with STEMI to undergo pPCI have a higher rate of 30-day and long-term mortality compared to men. This difference persisted even after propensity score adjustment on the the 30-day mortality, which may be justified by the higher frailty of the female sex, which could in turn explain the worse outcomes seen, at least, in the short-term.

CONCLUSIONS

In conclusion, in our single-center cohort of patients and after propensity score adjustment, women with STEMI undergoing pPCI seem to have a higher 30-day mortality rate but similar long-term outcomes after discharge compared to men. Even if residual confounding cannot be ruled out, this difference in the outcomes may be partially explained by biological sex-related differences.

CONFLICT OF INTERESTS

None of the authors have declared any conflicts of interests related to the present article.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.24875/RECICE.M19000061.
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