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Sex differences in acute myocardial infarction: Is it only the age?☆

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ABSTRACT

Background: Several studies have shown that, after an acute myocardial infarction, women have worse prognosis than males. However, it is not clear if female sex is an independent predictor of mortality risk. Our aim was to analyse sex influence on the prognosis of these patients.
Methods: Retrospective registry of patients with ST segment elevation myocardial infarction (STEMI) from January 2010 to April 2015.
Results: From 1111 patients, 258 (23.2%) were women. Compared with men, they presented higher risk profiles with older age (70.1 ± 14.4 years vs. 62.3 ± 13.4, $P < 0.001$), more cardiovascular risk factors (except smoking), longer time from symptoms onset to hospital arrival (5.2 ± 4.1 h *vs.* 4.2 ± 3.7), higher Killip classification (1.6 ± 1.1 *vs.* 1.4 ± 0.8), fewer complete revascularizations (175 [67.8%] *vs.* 662 [77.9%] in men) and higher in-hospital mortality (26 [10.1%] *vs.* 34 [4.0%]); all p values <0.003. At discharge, women less frequently received ACE inhibitors (189 [81.1%] *vs.* 702 [85.8%], $p = 0.045$) and presented more major adverse events (death, bleeding, infection, myocardial infarction, stent thrombosis or heart failure) during the first month after discharge (10.5% vs. 4.5%, $p < 0.001$) and higher long-term mortality (hazard ratio [HR] 1.6, 95% CI 1.1–2.2). After adjusting by age, most of the differences disappeared, and sex was not an independent factor of in-hospital (odds ratio 1.71, 95% CI 0.97–2.99) or long-term mortality (HR 1.0, 95% CI 0.7–1.5).
Conclusions: In patients with acute STEMI, the association of female sex with poor prognosis is mainly explained by age. Sex does not seem to be an independent prognostic factor.

Cardiovascular disease is the most common cause of death in the world [1,2]. Myocardial infarction has been traditionally considered a man's disease, but the prevalence of coronary heart disease and acute coronary syndrome is only slightly superior in men than in women [3]. Moreover, women have a higher mortality rate within the first year of an acute myocardial infarction [4] and most studies observe higher unadjusted short-term mortality in women than in men [5]. However, this difference could be explained, at least in part, by differences in age, prevalence of risk factors and comorbidity [6].

Previous data in younger women without comorbid conditions also suggested higher female-related risk, even after adjustment for other variables [7]. On the other hand, sex influence on the prognosis of these patients is not clear, as large studies have been unable to find an independent effect of sex in the prognosis of these patients [8] and some authors have suggested that female sex could even be a protective factor [9]. Our aim was to analyse the independent influence of sex on the prognosis of acute ST segment elevation myocardial infarction (STEMI) in a contemporary, single-centre population, in order to add new data to existing evidence and help to clarify this issue.

1. Methods

Our data come from the DIAMANTE (*Descripción del Infarto Agudo de Miocardio: Actuaciones, Novedades, Terapias y Evolución*—Description of Acute Myocardial Infarction: Management, New Therapies and Evolution) database. This database includes prospectively collected consecutive patients with STEMI admitted to the Coronary Intensive Care Unit of the Gregorio Marañon General Hospital (Madrid, Spain), a primary PCI-capable tertiary centre offering service "24/7", between January 2010 and April 2015.

Inclusion criteria: Eligible patients were 18 years of age or older who had a STEMI diagnosis performed by a cardiologist, according to the

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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presence of chest pain and current ST-segment elevation criteria [10]. All subjects underwent urgent reperfusion therapy, both primary PCI and pharmacological fibrinolysis (mainly receiving the fibrin-specific agent tenecteplase). Patients presenting within 12–24 h of symptoms onset who persisted with clinical and electrocardiographic evidence of ongoing ischemia were also included. In case of failed fibrinolysis (ST-segment resolution <50% at 60–90 min; absence of typical reperfusion arrhythmia and/or chest pain), rescue PCI was immediately indicated. According to the "pharmacoinvasive" strategy currently recommended [11], early angiography after successful fibrinolysis was routinely conducted within the first 24 h. The decision of which reperfusion therapy was conducted was up to the clinicians that decided on a case-by-case basis.

Exclusion criteria: patients presenting with more than 24 h of symptom onset or who did not undergo any reperfusion therapy; out-of hospital cardiac arrest patients regardless of the first electrocardiogram rhythm; subjects who required endotracheal intubation prior to hospital arrival; and patients with non-obstructive coronary artery disease and no evidence of cardiac emboli as the cause of the STEMI (e.g. Takotsubo syndrome or coronary vasospasm).

1.1. Definitions

Kidney disease: creatinine clearance <60 mL/1.73 m^2/min at admission. Anaemia: defined by the World Health Organization criteria [12]; haemoglobin <13 g/dL in men and <12 g/dL in women. Smoking: active smoker at admission. Significant coronary stenosis was defined as 70% or greater coronary lumen stenosis of any coronary vessel (>50% in the case of left main coronary artery). Complete revascularization at discharge: all epicardial coronary artery significant stenosis treated. Major adverse events: death, bleeding, infection, myocardial infarction, stent thrombosis or heart failure within the first 30 days after discharge. Acute renal failure: increase in serum creatinine level by more than 50%.

1.2. Endpoints and outcomes

Our primary endpoint was all cause mortality (in-hospital and long-term). The secondary endpoints were the development of high-degree atrioventricular block (second- and third-degree AV block), complete revascularization at the time of discharge and fatal and non-fatal major adverse events in the first 30 days. We also collected data regarding the evolution and complications during hospitalization, like acute renal failure, ventricular arrhythmias, paroxysmal atrial fibrillation, pericarditis, pericardial effusion, cardiac tamponade, puncture-related complications, stroke, heart failure, infection and acute stent thrombosis. Long-term outcomes were determined through medical record review and, when necessary, through telephonic follow-up.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañon, Madrid, Spain.

1.3. Statistical analysis

Continuous variables are presented as means (±SD) and categorical variables are presented as frequencies and percentages. Continuous variables were tested by using a Student t-test and categorical variables by using the χ^2 test. Univariate relations between variables and the primary endpoint were assessed by logistic regression analysis. Multiple logistic regression and Cox regression analysis were performed to identify predictor variables. Kaplan–Meier methods were used to estimate survival curves for follow-up events. The following variables were entered in the multivariate model when they were significantly related to mortality at univariate analysis: age, body mass index, sex, hypertension, diabetes, hypercholesterolemia, smoking, peripheral arterial disease, chronic kidney disease, previous history of atrial fibrillation, previous stroke/transient ischemic attack, anticoagulation treatment, previous coronary artery bypass graft surgery, chronic pulmonary obstructive disease, anaemia, active cancer, chronic heart failure, basic activities of daily living dependence, systolic/diastolic blood pressure and heart rate on arrival, infarct location, time-to-treatment, Killip class at presentation, angiography approach (radial or femoral), early ventricular fibrillation (0–24 h), acute atrioventricular block, type of reperfusion therapy, preprocedural and postprocedural thrombolysis in myocardial infarction (TIMI) flow, multivessel disease, procedural success, type and use of stent, serum creatinine and haemoglobin levels, left ventricular ejection fraction, presence of pericardial effusion, right ventricular dilatation/dysfunction and mitral insufficiency (grade 0–4) on echocardiography (performed within the first 24–48 h of hospitalization). The interaction for sex and all the significant variables was tested.

Statistical analysis was performed with the SPSS 20.0 statistical package (IBM Corp., Armonk, NY, USA).

2. Results

The registry included 1111 patients (258 women; 23.2%). Mean age was 64.1 ± 14.0 years. The proportion of women increased with age (from 14.7% in the first quartile [<53 years] to 40.4% in those in the last one [>76]). Nine patients were missing at 30 days of follow-up (0.8%), and long-term follow-up data could not be recorded in 22 patients (2.0%). Mean follow-up was 23.8 ± 19.4 months.

Baseline characteristics according to sex are shown in Table 1A, 1B. Mean age in women was 8 years higher than men. Diabetes was more frequent in women than in men, as were hypertension and anaemia. However, women were less frequently active smokers. At admission, women had a worse risk profile than men, with higher Killip class, more atrioventricular block and longer time from symptom onset (Table 1B). A radial approach was less frequent in women than in men, and females were discharged more often without complete revascularization (31.9% vs. 22.3%, respectively, $p = 0.002$). The rate of cardiogenic shock was higher in women than in men as was in-hospital mortality (Table 2).

The unadjusted odds ratio for in-hospital mortality for female sex was 2.7 (95% confidence interval 1.6–4.6). Fatal and non-fatal major adverse events in the first 30 days were more frequent in women (10.5% vs. 4.5% in men, $p < 0.001$). A total of 147 patients (13.2%) died at the end of follow-up. Long-term mortality was higher in women (Fig. 1A). However, multivariable analysis did not show an association between sex and in-hospital mortality nor long-term mortality (Table 3). The comparison of long-term mortality in men and women in the different age quartiles showed no relevant differences (Fig. 1B). In fact age adjustment was enough to make sex-related differences in mortality disappear (in-hospital mortality odds ratio 1.71, 95% CI 0.97–2.99; long-term mortality hazard ratio 1.0, 95% CI 0.7–1.5). The rate of female patients increased with age and this was also the case for hypertension, diabetes, chronic renal disease and Killip class >I (Appendix A).

3. Discussion

Our study confirms that in patients with STEMI, women have higher unadjusted in-hospital and long-term mortality than men. However, this difference is mainly due to age. In fact, the differences in mortality between men and women disappeared only by performing age adjustment.

In the first 30 days, major adverse events were more frequent in women than in men, but women presented more frequently with cardiovascular risk factors (except smoking) and a more severe clinical presentation; factors that are associated with both age and poor prognosis. This is consistent with previous data that showed no sex differences in major adverse cardiovascular events after matching patients by diabetes and age [13]. Previous studies have also focused on the influence of sex in the mortality after myocardial infarction. The Variations in Recovery: Role of Gender on Outcomes of Young AMI Patients

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