

Original article

Sex-based Differences in Clinical Features, Management, and 28-day and 7-year Prognosis of First Acute Myocardial Infarction. RESCATE II Study

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ABSTRACT

Introduction and objectives: To analyze sex-based differences in clinical characteristics, management, and 28-day and 7-year prognosis after a first myocardial infarction.

Methods: Between 2001 and 2003, 2042 first myocardial infarction patients were consecutively registered in 6 Spanish hospitals. Clinical characteristics, management, and 28-day case-fatality were prospectively recorded. Seven-year vital status was also ascertained by data linkage with the National Mortality Index.

Results: The registry included 449 women and 1593 men with a first myocardial infarction. Compared with men, women were older, had a higher prevalence of hypertension and diabetes, and were more likely to receive angiotensin-converting enzyme (ACE) inhibitors but were less likely to receive beta-blockers or thrombolysis. No differences were observed in use of invasive procedures. More women had non-ST-segment elevation and unclassified myocardial infarction than men (37.9% vs 31.3% and 9.8% vs 6.1%, respectively; both $P < .001$). Case-fatality at 28 days was similar in women and men (5.57% vs 4.46%; $P = .39$). After multivariate adjustment, the odds ratio of 28-day mortality for men was 1.06 (95% confidence interval: 0.49–2.27; $P = .883$) compared with women. After multivariate adjustment, men had higher 7-year mortality than women, hazard ratio 1.93 (95% confidence interval: 1.46–2.56; $P < .001$).

Conclusions: There are demographic and clinical differences between men and women with a first myocardial infarction. The short-term prognosis of a first myocardial infarction in this century is similar in both sexes. However, the long-term vital prognosis after a first myocardial infarction is worse in men than in women. These results are observed in both ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction events.

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Diferencias en función del sexo en las características clínicas, tratamiento y mortalidad a 28 días y 7 años de un primer infarto agudo de miocardio. Estudio RESCATE II

RESUMEN

Introducción y objetivos: Analizar las diferencias en función del sexo en las características clínicas, tratamiento y mortalidad a los 28 días y a los 7 años de un primer infarto de miocardio.

Métodos: Entre 2001 y 2003, 2.042 pacientes con un primer infarto de miocardio ingresaron consecutivamente en seis hospitales españoles. Se recogen prospectivamente las características clínicas, el tratamiento y la mortalidad a los 28 días. Se dispone del estado vital a los 7 años mediante consulta del Índice Nacional de Defunciones.

Resultados: Se incluyó a 449 mujeres y 1.593 varones con un primer infarto de miocardio. En comparación con los varones, las mujeres eran mayores y tenían mayor prevalencia de hipertensión y diabetes mellitus; también recibieron más tratamiento con inhibidores de la enzima de conversión de la angiotensina, pero menos bloqueadores beta y trombolisis. No hubo diferencias en el uso de procedimientos invasivos. Las mujeres tuvieron más infartos de miocardio sin elevación del segmento ST o no clasificables (el 37,9 frente

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al 31,3% y el 9,8 frente al 6,1% respectivamente; $p < 0,001$). La mortalidad a los 28 días era similar en mujeres y varones (el 5,57 y el 4,46%; $p = 0,39$). Tras el ajuste multivariable, la *odds ratio* de mortalidad a los 28 días de los varones fue 1,06 (intervalo de confianza del 95%, 0,49–2,27; $p = 0,883$). Los varones tuvieron mayor mortalidad a los 7 años que las mujeres (*hazard ratio* = 1,93; intervalo de confianza del 95%, 1,46–2,56; $p < 0,001$).

Conclusiones: Hay diferencias clínicas y demográficas entre varones y mujeres que ingresan por un primer infarto de miocardio. El pronóstico a corto plazo es similar en ambos sexos. La mortalidad a 7 años de un primer infarto de miocardio es peor en varones que en mujeres. Estos resultados se observan en infartos agudos de miocardio con y sin elevación del segmento ST.

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Abbreviations

AMI: acute myocardial infarction
 NSTEMI: non-ST-elevation myocardial infarction
 STEMI: ST-segment elevation myocardial infarction

INTRODUCTION

During the last 3 decades a large number of studies have focused on the differences between men and women in ischemic heart disease characteristics.^{1,2} One of the main areas of research has been the differences between the sexes in ischemic heart disease prognosis. Women have a worse short-term prognosis after an acute myocardial infarction (AMI) in most of these studies^{3–12} but not in all.¹³ This poorer short-term prognosis has been mainly observed in ST-segment elevation myocardial infarction (STEMI) cases, particularly in younger women, and seems to be attenuated with age.¹⁴ In other studies, the worse prognosis of AMI in women was mainly related to higher age and comorbidity and to differences between the sexes in the pathophysiology^{15–17} and clinical presentation of the disease,^{15,18–20} as well as to a lower use of effective drugs and procedures during the acute phase of the disease in women.^{15,21–26} However, this mortality gap has been decreasing.²⁷

A few studies have analyzed differences between sexes in long-term prognosis after AMI, with conflicting results. Compared with men, women have been reported to have better,^{28,29} worse,^{30,31} and similar long-term prognosis.^{13,32–35}

We reported that in the 1990s women had more lethal first AMI than men regardless of age and comorbidity.¹² The present study had 3 aims: to determine whether this difference persisted in the first decade of the 21st century, whether there are differences between men and women in 1-year and 7-year mortality after a first AMI and, if so, whether these differences are present in both STEMI and non-ST-segment elevation myocardial infarction (NSTEMI)

METHODS

Study Design

This is a prospective register of patients with a first AMI undertaken in 6 public hospitals in Spain, with a long-term follow-up of vital status. All patients over 18 years of age who were admitted with a first AMI within 72 h of symptom onset from September 2001 to June 2003 were prospectively and consecutively included.

The study was approved by the local ethics committee and all participants were informed and provided signed consent.

Study Population

The diagnosis followed the European Society of Cardiology/American College of Cardiology (ESC/ACC) definition³⁶ that AMI is a

myocardial necrosis secondary to ischemia. Myocardial necrosis is defined as elevated levels (according to the normal levels as defined in each center) of troponin T or I, or of the creatine phosphokinase-MB fraction, in the presence of symptoms related to myocardial ischemia. Exclusion criteria were a history of previous AMI, residence outside the center's catchment area, and serious illness unrelated to the admission episode that limited the patient's life expectancy.

Variables of Interest

A standardized questionnaire administered by trained personnel was used to prospectively gather demographic variables and comorbidities. History of classical risk factors was based on previous diagnosis or treatment or de novo diagnosis during hospital stay using the following criteria: hypertension (systolic blood pressure greater than or equal to 140 or diastolic blood pressure greater than or equal to 90 mmHg), diabetes (2 fasting glucose determinations greater than or equal to 126 mg/dL or 1 glucose determination greater than or equal to 200 mg/dL), dyslipidemia (low-density lipoprotein cholesterol greater than 160 mg/dL or high-density lipoprotein cholesterol lower than 35 in men, or 45 mg/dL in women). Information related to previous smoking and angina was also recorded by self-report.

Clinical characteristics of the event were recorded, including the delay between symptom onset and hospital monitoring, AMI location, presence of ST-segment elevation on the admission electrocardiogram, appearance of Q waves, and complications such as the development of pulmonary edema or cardiogenic shock or the presence of malignant ventricular arrhythmias within the first 48 h (defined as the appearance of ventricular fibrillation or sustained ventricular tachycardia requiring immediate medical attention). Finally, management of the acute event was recorded, including pharmacological treatments during hospital stay and at discharge, reperfusion (thrombolysis or primary percutaneous coronary intervention), and other procedures such as pharmacological or stress-testing techniques to assess the presence of ischemia, echocardiography, coronary angiography to determine the number of vessels with severe lesions, and elective surgical or percutaneous coronary revascularization.

Each participating hospital followed its own protocols for the clinical management of the patients. All of the hospital protocols followed national and international clinical practice guidelines in force at the time of the study.^{36–38}

Events of Interest

Events of interest were defined as 28-day, 1-year, and 7-year mortality, with a follow-up of vital status until December 31, 2009. An individual follow-up was performed in all patients (most of them with a clinical visit and the rest by phone call) to assess 28-day events (angina, reinfarction, stroke, death). Fatal cases were identified through access to the Spanish National Death Registry, an exhaustive and mandatory official database collecting individual

data of all deaths in Spain since 1987. This database, made available by the Spanish Health Ministry to public institutions (health care administrations, research centers), provides information on vital status and date of death and can be manually linked with individual patient data in our hospital registries. Patients who did not appear in the Spanish National Death Registry were assumed to be alive at the end of the follow-up.

Statistical Analysis

Student's *t* test or the Mann-Whitney U test were used to compare continuous variables and the chi-square test was used to compare categorical variables between 2 groups. Logistic regression and Cox regression were used to determine associations between sex and 28-day or long-term mortality, with adjustment for the confounding variables identified. In the multivariate analyses, different models were built to assess the influence on mortality of different sets of variables, such as age and electrocardiogram pattern (model 1), comorbidities (model 2), the severity of AMI (model 3), management (medical therapy during admission [for 28-day case-fatality] or at discharge [for intermediate and long term mortality]—model 4a—or invasive procedures—model 4b—), and all mentioned variables (model 5). We also tested for the interaction between sex and the electrocardiographic patterns (STEMI and NSTEMI) on 28-day, 1 year, and 7-year prognosis.

In the multivariate analyses, multiple imputation methods³⁹ were performed, using “mi” and “mitools” (R statistical package, version 2.11.1),⁴⁰ to replace missing values in the adjustment variables and avoid potential selection bias and loss of statistical power. A *P*-value <.05 was considered as statistically significant.

RESULTS

The study included 2042 consecutive first AMI patients, 21.99% of them female (n=449). The flow-chart corresponding to the selection of the patients included in the study is shown in Figure 1.

Baseline Characteristics and Clinical Management

The demographic and clinical characteristics of the patients are presented in Table 1. Women were older, less likely to smoke, and had a higher prevalence of hypertension and diabetes. STEMI was more common in men; the presence of non-Q-wave AMI and Killip III-IV at admission was more frequent in women. Women also showed a longer delay in arriving at the hospital after symptom onset.

The use of drug therapies and invasive diagnostics or therapeutic procedures by sex is shown in Table 2. The use of beta-blockers and reperfusion (related to a lower use of fibrinolysis) was lower, although the use of angiotensin-converting enzyme inhibitors was higher, in women than in men. No differences between sexes were observed in ejection fraction or the use of invasive procedures, antiplatelets, statins, or optimal pharmacological therapy (defined as a combination of antiplatelets+betablockers+ACE inhibitors+statins). Medical treatments (antiplatelets, statins, ACE inhibitors, or beta-blockers) at discharge were similar to those administered during admission. Men showed a higher proportion of multivessel disease (Table 2).

In-hospital Prognosis and 28-day Case-fatality

Table 3 shows in-hospital outcome and 28-day case-fatality, stratified by sex. Women showed a higher proportion of

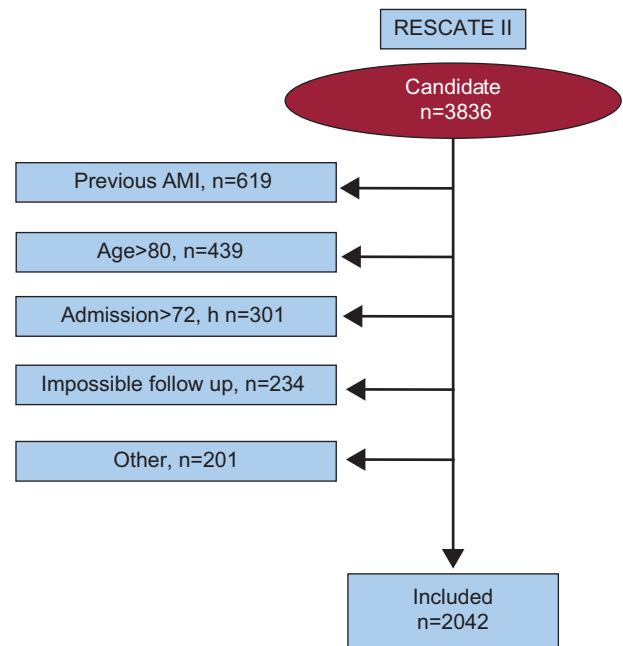


Figure 1. Flowchart of registered and included patients in the RESCATE II Registry. AMI, acute myocardial infarction.

pulmonary edema or cardiogenic shock and post-AMI angina than men; 28-day case-fatality was similar in men and women.

Sex was not significantly associated with 28-day case fatality in the different multivariate models defined (Table 4), and there was no interaction (*P*=.943) between sex and electrocardiographic patterns (STEMI and NSTEMI) relevant to 28-day case-fatality.

Table 1

Baseline Characteristics of the Patients Included in this Register, by Sex

	Men (n=1593)	Women (n=449)	<i>P</i> -value
Age, years	60.2±11.7	66.8±10.8	<.001
ECG at admission			<.001
STEMI	996 (62.5)	235 (52.3)	
NSTEMI	499 (31.3)	170 (37.9)	
Unclassified AMI	98 (6.15)	44 (9.8)	
Hypertension	750 (48.1)	314 (71.0)	<.001
Diabetes	399 (25.9)	165 (37.4)	<.001
Dyslipidemia	696 (45.5)	208 (48.0)	.383
Current Smoker	819 (53.4)	80 (18.5)	<.001
Previous angina	651 (42.1)	197 (45.7)	.201
Admission Killip III-IV	120 (7.7%)	54 (12.6)	.002
Delay symptoms-monitoring	120 [60-240]	155 [52-287]	.002
ECG at discharge			<.001
Anterior Q-wave	326 (21.9)	76 (18.5)	
Inferior Q-wave	478 (32.1)	85 (20.7)	
Lateral Q-wave	34 (2.3)	10 (2.4)	
Q-wave several locations	101 (6.8)	29 (7.1)	
Non-Q-wave	509 (34.1)	194 (47.2)	
Unclassified	43 (2.9%)	17 (4.1)	

AMI, acute myocardial infarction; ECG, electrocardiogram; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

Table 2
Pharmacological Therapies In-hospital and at Discharge and Procedures Undertaken During Hospital Admission, by Sex

	Men N=1593	Women N=449	P-value
<i>Acetylsalicylic acid</i>			.238
In-hospital	1439 (93.1)	397 (91.3)	<.001
At discharge	1324 (91.6)	343 (85.3)	
<i>Clopidogrel</i>			.197
In-hospital	595 (38.5)	152 (34.9)	.204
At discharge	563 (37.0)	150 (33.8)	
<i>GPIIb-IIIa inhibitors in hospital</i>	386 (25.0)	124 (28.5)	.153
<i>Beta-blockers</i>			
In-hospital	1208 (78.0)	309 (71.0)	.003
At discharge	1033 (71.2)	260 (64.5)	.011
<i>ACE-inhibitors</i>			
In-hospital	946 (61.1)	289 (66.4)	.049
At discharge	801 (55.2)	235 (58.3)	.298
<i>Statins</i>			
In-hospital	1128 (72.8)	321 (74.5)	.532
At discharge	1062 (73.2)	292 (73.2)	1
<i>OMT*</i>			
In-hospital	545 (35.3)	141 (32.6)	.318
At discharge	405 (28.0)	95 (23.7)	.102
<i>Primary PCI</i>	111 (11.5)	27 (12.1)	.908
<i>Rescue PCI</i>	83 (8.60)	14 (6.3)	.314
<i>Elective PCI</i>	208 (21.6)	50 (22.4)	.847
<i>Thrombolytic</i>	536 (55.5)	104 (46.4)	.017
<i>Reperfusion therapy (PCI or thrombolytic)</i>	647 (67.0)	131 (58.5)	.019
<i>Delay symptoms-reperfusion, min</i>	180 [120-255]	195 [120-270]	.108
<i>Delay monitoring-reperfusion, min</i>	55 [33-102]	60 [30-120]	.501
<i>CABG</i>	160 (10.3)	50 (11.5)	.546
<i>Ejection fraction, %</i>			.673
<30	117 (7.39)	35 (7.83)	
31-45	343 (21.7)	89 (19.9)	
46-60	665 (42.0)	182 (40.7)	
>60	458 (28.9)	141 (31.5)	
<i>Number of affected vessels</i>			<.001
0	47 (4.43)	32 (10.5)	
1	403 (38.0)	123 (40.3)	
2-3	611 (57.6)	150 (49.2)	

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; GPIIb-IIIa, GlicoproteinIIb-IIIa inhibitors; OMT, Optimal Medical Therapy; PCI, percutaneous coronary intervention.

Data are expressed as No. (%) or median [interquartile range].

*Optimal medical therapy in-hospital, combination of acetylsalicylic acid, statins, beta-blockers and angiotensin-converting enzyme inhibitors

Intermediate and Long-Term Mortality: 1-year and 7-year Mortality in 28-day Survivors

This study achieved 100% follow-up (median, 7.16 years) of patients who survived the acute phase. In the bivariate analysis, there were no sex-related differences in intermediate and long-term mortality (Table 3). The Kaplan-Meier 7-year survival curves for men and women, with their corresponding confidence intervals, are shown in Figure 2.

However, in the multivariate Cox regression models for 7-year mortality, among 28-day survivors a clear association was observed between being male and higher 7-year mortality (Table 5). Depending on the model considered, the probability of death during the 7-year follow-up was 70% higher to more than 200% higher in men than in women. The interaction between sex and the electrocardiographic patterns on 7-year

mortality in survivors was not statistically significant (interaction, $P=.522$).

We also analyzed 1-year mortality and the results were similar (Tables 3 and 5).

Overall Mortality (Acute, Intermediate and Long-term)

The overall 7-year mortality, from symptom onset until the end of follow-up, was similar in men and women (Table 3). However, in the multivariate Cox regression models for 7-year mortality, there was a clear association between male sex and higher overall 7-year mortality (Table 5). The probability of death during the 7-year follow-up was 57% higher to 93% higher in men than in women, depending on the model considered. The results for 1-year mortality were similar (Table 5).

Table 3

Twenty-eight-day Prognosis and 1- and 7-year Mortality Among Patients Included in this Register, by Sex

	Men (n=1593)	Women (n=449)	P-value
<i>28-day prognosis</i>			
Maximum Killip III-IV	126 (8.45)	69 (16.5)	<.001
AMI recurrence	53 (3.43)	21 (4.85)	.220
Angina post-AMI	145 (9.45)	58 (13.3)	.025
VT/VF<48 h	108 (6.91)	21 (4.73)	.122
VT/VF 48 h-28 day	24 (1.58)	6 (1.38)	.942
Mechanical complications	16 (1.0)	6 (1.4)	.514
Complete AVBlock	54 (3.45)	18 (4.07)	.636
Stroke	12 (0.8)	3 (0.7)	.873
28-daycase-fatality	71 (4.46)	25 (5.57)	.392
<i>1-year prognosis</i>			
In 28-day survivors	4.01	3.88	.963
In the whole period	9.35	8.16	.486
<i>7-year prognosis</i>			
In 28-day survivors	18.2	18.4	.819
In the whole period	21.9	22.9	.810

AMI, acute myocardial infarction; AV, atrioventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

Data are expressed as No. (%).

The interaction between sex and the electrocardiographic patterns on overall 7-year and 1-year mortality was not statistically significant.

DISCUSSION

In this study, the short-term prognosis after a first AMI in the present century was similar in men and women. The women in our registry were older, had greater comorbidity and arrived later at the hospital, although the management of AMI in the acute phase was similar for men and women. Men had a worse long-term prognosis after a first AMI, with a higher 7-year mortality than women. These results were observed in both STEMI and NSTEMI.

Table 4

Association Between Sex and 28-day Case Fatality Rate, Adjusted by Various Covariables in Logistic Regression Models

	Women (n=449)	Men (n=1593) OR (95%CI)	P-value
Model 1	1	1.23 (0.76-2.01)	.399
Model 2	1	1.43 (0.75-2.32)	.277
Model 3	1	1.50 (0.74-3.05)	.257
Model 4a	1	1.14 (0.53-2.43)	.736
Model 4b	1	1.36 (0.66-2.80)	.403
Model 5	1	1.06 (0.49-2.27)	.883

95%CI, 95% confidence interval; OR, odds ratio.

Model 1: adjusted for age and electrocardiographic pattern.

Model 2: model 1 plus diabetes, hypertension, smoking, and angina.

Model 3: model 2 plus Killip 3-4, ejection fraction, and number of vessels.

Model 4a: model 3 plus acetylsalicylic acid, clopidogrel, beta-blockers, statins, angiotensin converting enzyme inhibitors, and reperfusion.

Model 4b: model 3 plus elective percutaneous coronary revascularization or coronary artery by-pass.

Model 5: model 3 plus acetylsalicylic acid, clopidogrel, beta-blockers, statins, angiotensin converting enzyme inhibitors, elective percutaneous coronary revascularization or coronary artery by-pass, and reperfusion

Acute Phase Prognosis

Although direct comparison is not possible because the definition of AMI changed in 2000, a similar study undertaken in 1992-1994 (RESCATE I study) in 4 of the 6 hospitals participating in this study reported that women had a greater short-term risk of death at 28 days and at 6 months after a first AMI than men.¹² Moreover, as we showed in a previous study, considering only the patients in RESCATE II with the same diagnostic criteria as RESCATE I, in-hospital mortality decreased by 25% and the 6-month prognosis also improved in the second registry.⁴¹

Several factors could contribute to explaining the observed reduction of acute case-fatality, mainly in women, and therefore to the disappearance of the differences between sexes^{12,41}: the mean age of women in the current study was 2 years younger than in the earlier study; although women still arrived later at the hospital than men, the gap between sexes was reduced from 60 min to 35 min; a lower proportion of women receive reperfusion therapy, but the gap was also reduced, and the proportion of patients

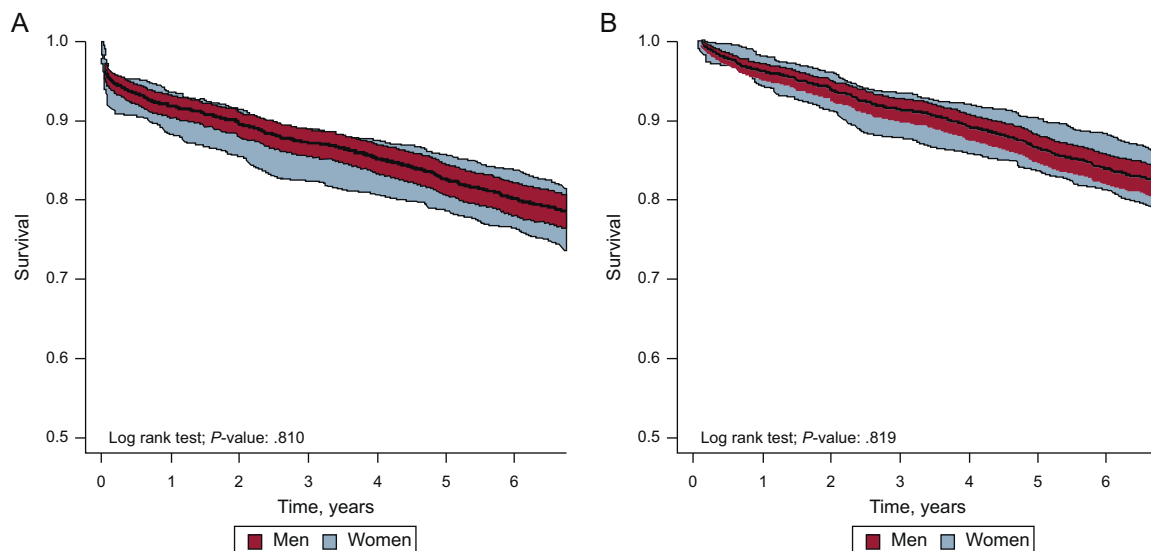


Figure 2. Kaplan-Meier curves. 7-year survival by sex from admission (A) and among 28-day survivors (B).

Table 5
Association Between Sex and 1-year and 7-year Mortality Rate Adjusted by Various Covariables in Cox Regression Models

	In 28-day survivors			Including 28-day case-fatality		
	Women (N=424)	Men (N=1522) HR (95%CI)	P-value	Women (N=449)	Men (N=1593) HR (95%CI)	P-value
<i>1-year mortality</i>						
Model 1	1	1.66 (0.94-2.91)	.080	1	1.39 (0.97-2.00)	.069
Model 2	1	1.97 (1.02-3.78)	.042	1	1.68 (1.07-2.64)	.024
Model 3	1	2.20 (1.12-4.33)	.022	1	1.83 (1.14-2.95)	.013
Model 4a	1	2.45 (1.19-5.05)	.015	1	2.11 (1.21-3.66)	.008
Model 4b	1	2.39 (1.19-4.82)	.014	1	1.82 (1.12-2.96)	.016
Model 5	1	2.53 (1.20-5.32)	.015	1	2.14 (1.21-3.77)	.008
<i>7-year mortality</i>						
Model 1	1	1.68 (1.30-2.17)	<.001	1	1.57 (1.25-1.96)	<.001
Model 2	1	1.81 (1.36-2.41)	<.001	1	1.74 (1.34-2.26)	<.001
Model 3	1	1.90 (1.42-2.55)	<.001	1	1.84 (1.41-2.41)	<.001
Model 4a	1	2.11 (1.55-2.88)	<.001	1	1.92 (1.45-2.53)	<.001
Model 4b	1	2.01 (1.49-2.72)	<.001	1	1.91 (1.45-2.52)	<.001
Model 5	1	2.12 (1.55-2.90)	<.001	1	1.93 (1.46-2.56)	<.001

95%CI, 95% confidence interval; HR, hazard ratio.

Model 1: adjusted for age and electrocardiographic pattern.

Model 2: model 1 plus diabetes, hypertension, smoking, and angina.

Model 3: model 2 plus Killip 3-4, ejection fraction.

Model 4a: model 3 plus acetylsalicylic acid, clopidogrel, beta-blockers, statins, angiotensin-converting enzyme inhibitors, and reperfusion.

Model 4b: model 3 plus elective percutaneous coronary revascularization or coronary artery by-pass.

Model 5: model 3 plus acetylsalicylic acid clopidogrel, beta-blockers, statins, angiotensin-converting enzyme inhibitors, elective percutaneous coronary revascularization or coronary artery bypass, and reperfusion.

treated with thrombolysis or primary percutaneous coronary intervention significantly increased for both men and women, from less than 50% overall (23.9% in women) to almost 66% (58.5% in women); perhaps the most important improvement for women was the one-third decline in pulmonary edema or cardiogenic shock, from 24.8% to 16.5%.

In our study, we observed no differences between the sexes in the management of AMI during hospital stay, unlike other studies.^{22,23,42} The proportion of patients receiving “optimal pharmacological therapy” (antiplatelets+beta-blockers+ACE inhibitors+statins) and invasive procedures was similar in men and women. However, there were some differences in pharmacological treatments: a lower use of thrombolysis in women, which could be related to the longer delay in arriving at the hospital, and more ACE inhibitors and fewer beta-blockers in women, which could be explained by their higher rate of pulmonary edema and cardiogenic shock.

All these data suggest that the use of evidence-based therapies, including a more invasive approach, in the treatment of AMI in both men and women is associated with a better 28-day prognosis and with the disappearance of the differences between sexes in the acute phase. This similarity in prognosis has been reported in some recent studies^{13,32} but not in others,^{31,33} including a recent registry in Chile, which included nearly 50 000 patients. In this registry, younger women have a higher risk of in-hospital mortality due to AMI.⁴⁴ Moreover, recent Spanish registries have shown higher acute phase mortality rates for women, although men had more readmissions in the long-term follow-up.⁴⁵ On the other hand, in a large registry in Sweden, the SWEDEHEART study, including more than 46 000 patients admitted with non-ST-segment elevation acute coronary syndrome, outcome with an invasive strategy was similar in men and women, although the follow-up was limited to 1 year.⁴³

Intermediate and Long-term Mortality

In our study, intermediate and long-term (1-year and 7-year) mortality was approximately twice as high in men as in women. Although most studies have not reported mortality differences by sex at 1-year^{13,32,33,43} or at 3- to 5-year follow-up,^{30,31,34} higher long-term mortality in men has been reported in other studies with a 3-year²⁸ or a 5-year follow-up.²⁹ Despite the contrasting results, several possible factors could be involved in higher long-term mortality in men. First, there are differences in atherosclerosis progression, especially in the coronary arteries.⁴⁶ When patients with clinical coronary artery disease are included, women show a lower atheroma burden at the coronary tree than men⁴⁷ and more often show single-vessel lesion disease; men usually show greater extent of the disease.³³ Second, the different coronary atherosclerosis pattern could explain the higher risk of reinfarction in men.³³ Finally, we analyzed total mortality. Men have a lower life expectancy than women and causes of mortality other than cardiovascular diseases could also be a factor, especially mortality causes related to smoking, such as pulmonary diseases and certain cancers.

Although the cause of death was not available, we consider that 1-year mortality after an AMI is mainly related to cardiovascular causes, as reported in other studies,⁴⁸ especially in a young population such as that in our study. We analyzed and compared 1-year and 7-year mortality and observed that the excess of mortality rates in men were similar at 1- and 7-years, suggesting that this excess could be related to cardiovascular causes.

Strengths and Limitations

Our study has several limitations. We have data on in-hospital management and discharge treatment but no information on changes in pharmacological therapy, risk factor exposure or

control during the follow-up, or outcomes other than death. Furthermore, although we determined overall 7-year mortality, the specific cause of death was not available. One of the strengths of the study is that the results are based on an exhaustive and consecutive register of hospitalized first AMI patients, with a long follow-up and with detailed clinical information obtained during the hospital stay.

CONCLUSIONS

There are demographic and clinical differences between men and women with a first myocardial AMI. The short-term prognosis of a first AMI in this century is similar in both sexes. However, the long-term vital prognosis after a first AMI is worse in men than in women. These results are observed in both STEMI and NSTEMI.

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CONFLICTS OF INTEREST

None declared.

REFERENCES

- Vaccarino V, Badimon L, Corti R, De Wit C, Dorobantu M, Hall A, et al. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors. *Cardiovasc Res*. 2011;90:9–17.
- Vaccarino V. Ischaemic heart disease in women: many questions, few facts. *Circ Cardiovasc Qual Outcomes*. 2010;3:111–5.
- Vaccarino V, Krumholz HM, Berkman LF, Horwitz RJ. Sex differences in mortality after myocardial infarction: is there any evidence for an increased risk for women? *Circulation*. 1995;91:1861–71.
- Køber L, Torp-Pedersen C, Ottesen M, Rasmussen S, Lessing M, Skagen K; TRACE study group. Influence of gender on short- and long-term mortality after acute myocardial infarction. *Am J Cardiol*. 1996;77:1052–6.
- Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes II Investigators. *N Engl J Med*. 1999;341:226–32.
- Koek HL, De Bruin A, Gast F, Gevers E, Kardaun JW, Reitsma JB, et al. Short- and long-term prognosis after acute myocardial infarction in men versus women. *Am J Cardiol*. 2006;98:993–9.
- Jneid H, Fonarow GC, Cannon CP, Hernandez AP, Palacios IF, Maree AO, et al. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118:2803–10.
- Halvorsen S, Eritsland J, Abdelnoor M, Holst Hansen C, Riscøe C, Mittdø K, et al. Gender differences in management and outcome of acute myocardial infarctions treated in 2006–2007. *Cardiology*. 2009;114:83–8.
- Benamer H, Tafflet M, Maitaille S, Escolano S, Livarek B, Fourchard V, et al.; CARDIO-ARHIF Registry Investigators. Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. *Eurointervention*. 2011;6:1073–9.
- Sadowski M, Gasior M, Gierotka M, Janion M, Polonski L. Gender-related differences in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry. *Eurointervention*. 2011;6:1068–72.
- Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Miura F, Nakana Y, et al. Comparison of gender-specific mortality in patients < 70 years versus > 70 years with acute myocardial infarction. *Am J Cardiol*. 2011;108:772–5.
- Marrugat J, Sala J, Masiá R, Pavesi M, Sanz G, Valle V, et al.; RESCATE Investigators. Mortality differences between men and women following first myocardial infarction. *JAMA*. 1998;280:1405–9.
- Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 years trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ*. 2012;344:e356.
- Canto JG, Rogers W, Goldberg R, Peterson E, Wenger N, Vaccarino V, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307:813–22.
- Shaw LJ, Bugiardini R, Bairey-Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol*. 2009;54:1561–75.
- Arslasian-Engoren C, Engoren M. Physiological and anatomical bases for sex differences in pain and nausea as presenting symptoms of acute coronary syndromes. *Heart Lung*. 2010;39:386–93.
- Bairey-Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol*. 2006;47(3 Suppl):S21–9.
- Kirchberger I, Heier M, Kucj B, Wende R, Meisinger C. Sex differences in patients reported symptoms associated with myocardial infarction (from the population based MONICA/KORA Myocardial Infarction Registry). *Am J Cardiol*. 2011;107:1585–9.
- Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. *Eur Heart J*. 2011;32:3107–14.
- Ladwig KH, Meisinger C, Hymer H, Wolf K, Heire M, Von Scheidt W, et al. Sex and age specific time patterns and long term time trends of pre-hospital delay of patients presenting with acute ST-segment elevation myocardial infarction. *Int J Cardiol*. 2011;152:350–5.
- Anand SS, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol*. 2005;46:1845–51.
- Fang J, Alderman MH. Gender differences of revascularization in patients with acute myocardial infarction. *Am J Cardiol*. 2006;97:1722–6.
- Johnston N, Schenck-Gustafsson K, Lagerqvist B. Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain? *Eur Heart J*. 2011;32:1331–6.
- Bugiardini R, Yan AT, Yan RT, Fitchett D, Langer A, Manfrini O, et al. Canadian Acute Coronary Syndrome Registry I and II Investigators. Factors influencing underutilization of evidence-based therapies in women. *Eur Heart J*. 2011;32:1337–44.
- Schiele F, Meneveau N, Seronde MF, Descotes-Genon V, Chopard R, Janin S, et al. Propensity score-matched analysis of effects of clinical characteristics and treatment on gender difference in outcomes after acute myocardial infarction. *Am J Cardiol*. 2011;108:789–98.
- Alfredsson J, Lindbäck J, Wallentin L, Swahn E. Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Eur Heart J*. 2011;32:3128–36.
- Grau M, Sala C, Sala J, Masia R, Vila J, Subirana I, et al. Sex-related differences in prognosis after myocardial infarction: changes from 1978 to 2007. *Eur J Epidemiol*. 2012;27:847–55.
- Hurtado-Martínez J, Pinar-Bermúdez E, Teruel-Carrillo F, Gimeno-Blanes JR, Lacunza-Ruiz J, Valdesuso R, et al. Mortalidad a corto y largo plazo en mujeres con infarto de miocardio tratado con angioplastia primaria. *Rev Esp Cardiol*. 2006;59:1113–22.
- Koek HL, De Bruin A, Gast F, Gevers E, Kardaun JW, Reitsma JB, et al. Short- and long-term prognosis after acute myocardial in men versus women. *Am J Cardiol*. 2006;98:993–9.
- D'Ascenzo F, Gonella A, Quadri G, Longo G, Biondi-Zoccai G, Moretti C, et al. Comparison of mortality rates in women versus men presenting with ST-segment elevation myocardial infarction. *Am J Cardiol*. 2011;107:651–4.
- Machón M, Basterretxea M, Martínez-Cambor J, Aldasoro E, María San Vicente J, Larrañaga N. Diferencias por sexo en la supervivencia relativa y los factores pronósticos de pacientes con un primer infarto agudo de miocardio en Guipúzcoa. *Rev Esp Cardiol*. 2010;63:649–59.
- Woo JS, Kim W, Ha SJ, Kim SJ, Kang WY, Jeong MH. Impact of gender differences on long-term outcomes after successful percutaneous coronary intervention in patients with acute myocardial infarction. *Int J Cardiol*. 2010;145:516–8.
- Lawesson SS, Stenestrand U, Lagerqvist B, Wallentin L, Swahn E. Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST-elevation myocardial infarction. *Heart*. 2010;96:453–9.
- Sjauw KD, Stegenga NK, Engstrom AE, Van der Schaaf RJ, Wis MM, Macleod A, et al. The influence of gender on short- and long-term outcome after primary PCI and delivered medical care for ST-segment elevation myocardial infarction. *Eurointervention*. 2010;5:780–7.
- Norhammar A, Stenestrand U, Lindbäck J, Wallentin L. Women younger than 65 years with diabetes mellitus are a high-risk group after myocardial infarction: a report from the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admission (RIKS-HIA). *Heart*. 2008;94:1565–70.
- The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J*. 2000;21:1502–13.
- Ryan TJ, Anderson JL, Antman EM, Braniff BA, Brooks NH, Califf RM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol*. 1996;28:1328–428.
- Braunwald E, Antman EM, Beasley JW, Califf RM, Chaitlin MD, Hochman JS, et al.; Committee Members Task Force Members. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—2002: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice

- Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation*. 2002;106:1893–900.
39. Abayomi K, Gelman A, Levy M. Diagnostics for multivariate imputations. *Applied Statistics*. 2008;57:273–91.
 40. R Development Core Team (2010). R: A language and environment for statistical computing. Viena: R Foundation for Statistical Computing [accessed 2013 Jun 18]. Available at: <http://www.R-project.org>
 41. García-García C, Sanz G, Valle V, Molina LL, Sala J, Subirana I, et al. Evolución de la mortalidad intrahospitalaria y el pronóstico a seis meses de los pacientes con un primer infarto agudo de miocardio. Cambios en la última década *Rev Esp Cardiol*. 2010;63:1136–44.
 42. Riesgo A, Miró O, López-de-Sá E, Sánchez M. Comparación del manejo del infarto de miocardio sin elevación del ST durante la asistencia urgente en función del sexo del paciente. *Rev Esp Cardiol*. 2011;64:1060–4.
 43. Alfredsson J, Lindbäck J, Wallentin L, Swahn E. Similar outcome with an invasive strategy in men and women with non-ST-elevation acute coronary syndromes: from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *EurHeart J*. 2011;32:3128–36.
 44. Nazzari C, Alonso FT. Las mujeres jóvenes en Chile tienen elevado riesgo de muerte intrahospitalaria por infarto de miocardio. *Rev Esp Cardiol*. 2013;66:104–9.
 45. Andrés E, Cordero A, Magán P, Alegría E, León M, Luengo E, et al. Mortalidad a largo plazo y reingreso hospitalario tras infarto agudo de miocardio: un estudio de seguimiento de ocho años. *Rev Esp Cardiol*. 2012;65:414–20.
 46. Kardys I, Vliegthart R, Oudkerk M, Hofman A, Wittemam JC. The female advantage in cardiovascular disease: do vascular beds contribute equally? *Am J Epidemiol*. 2007;166:403–12.
 47. Nicholls SJ, Wolski K, Sipahi I, Schoenhagen P, Crowe T, Kapadia SR, et al. Rate of progression of coronary atherosclerotic plaque in women. *J Am Coll Cardiol*. 2007;49:1546–51.
 48. Wallentin L, Becker R, Budaj A, Cannon C, Emmanuelson H, Held C, et al.; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–57.