

Gender differences in management and outcome of patients with acute myocardial infarction[☆]

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Abstract

Background: The study objectives were to assess any gender differences in the application of diagnostic and therapeutic procedures and their impact on outcome in patients with acute myocardial infarction (AMI).

Methods: Prospective cohort study of patients in the PRIAMHO II registry. 58 randomly selected public hospitals in Spain included 6209 patients with AMI admitted to Coronary/Critical Care Unit from May 15 to December 15 2000 with 1-year follow-up. Data were gathered on use of coronary angiography and reperfusion procedures, on a combined outcome variable (including death, reinfarction, postinfarction angina, and stroke during hospital stay), and on 28-day and 1-year mortality rates.

Results: 4641 (74.75%) of the patients were male and 1568 (25.5%) female. No gender differences in coronary angiography or reperfusion therapy use were found. However, female sex alongside age, use of reperfusion therapy, diabetes mellitus, previous revascularization, previous AMI, and higher Killip class were predictors of the combined outcome variable, with an adjusted OR of 1.21 (CI 95% 1.02–1.42).

Conclusions: No association was observed between the gender of patients with AMI and the application of diagnostic or therapeutic procedures. Nevertheless, female sex behaved as an independent adverse short-term prognostic factor.

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1. Introduction

Men and women share the same coronary risk factors except for the exclusively female experience of menopause and oral contraceptive use. However, as evidenced by the Framingham study [1], ischemic heart disease appears later

in women than in men, although this difference reduces and disappears in older age groups. There have been reports of a higher mortality risk in women that is not always explained by other studied variables. In fact, apart from some isolated studies [2], the female sex has been found to be an independent predictor of worse prognosis in patients with coronary heart disease. This has been a consistent finding in a wide range of studies of first acute myocardial infarction [3] (AMI) and post-AMI periods [4] across numerous countries [5–11] and in reports of atypical presentation forms [12]. However, it remains unclear whether this higher mortality is explained by the higher age of females or presence of other risk factors, notably diabetes [13].

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It is also known that diagnostic and therapeutic procedures are less used in women [14], even taking account of the profile of the attending physician [15]. This situation has also been reported in other populations, including elderly patients [16], ethnic minorities [17], and some financial [18] and socio-economic [19] subpopulations, despite the higher morbidity and mortality rates in these patients. Similar circumstances have been documented in Spain [20], although not in relation to diagnosis or therapeutic management or since publication of new clinical practice guidelines in 2004.

Randomized clinical trials have demonstrated a strong relationship between post-AMI mortality and early myocardial reperfusion, although other treatment strategies (e.g., antiplatelet drugs, betablockers, ACE-inhibitors) have also shown a positive effect on outcome. Our initial working hypothesis was that a lesser use of diagnostic and therapeutic procedures in women may in part explain their worse postinfarction prognosis compared with men. Therefore, the objectives of this study were to assess differences in management between men and women with AMI and to determine the impact of any differences on short and long-term prognoses.

2. Materials and methods

The study used the database from the PRIAMHO II registry [21], designed by the working group on ischemic heart disease of the Spanish Society of Cardiology with the collaboration of the intensive cardiological care group of the Spanish Society of Critical and Coronary Care. Out of the 168 public hospitals in Spain with a coronary or critical care unit (CCU), 58 were randomly selected for the study. Selected centers obtained approval for the study from their corresponding institutional review board. Patients with AMI admitted to these CCUs between May 15 and December 15 2000 were prospectively recruited. Verbal informed consent was obtained from each patient to collect and use their data for research purposes.

Demographic, diagnostic, therapeutic, and clinical data were collected from hospital medical records. Coronary risk factors and previous conditions were assessed by a specific questionnaire administered to patients or their relatives. All variables were precisely defined and their collection was standardized. The CCU application of various diagnostic and therapeutic procedures was also recorded, including coronary angiography and reperfusion procedures (fibrinolysis or primary, rescue, or subacute percutaneous coronary intervention [PCI]). Patients were followed at 1 year by personal interview at an outpatient clinic or by telephone contact when this was not possible.

The end-point of the study was a combined variable including death, reinfarction, postinfarction angina, and stroke during hospital stay. Mortality for any cause at 28 days and 1 year was also considered.

Continuous variables are presented as means (\pm standard deviation) and categorical variables as percentages. Gender

differences were assessed by the chi-square test for categorical variables and by Student's *t*-test or Mann–Whitney *U*-test, as appropriate, for continuous variables. Survival curves were constructed by the Kaplan–Meier method and differences in survival were assessed with the log-rank test. Multivariate analyses were performed by using Cox proportional models. The models included factors that showed univariate gender differences with a $p < 0.10$. All *p* values were two-tailed. A *p* value < 0.05 was considered significant.

3. Results

The study included 6209 patients with AMI: 4641 (74.75%) males and 1568 (25.25%) females. Table 1 lists patient characteristics by gender, including age, history, AMI features, and mortality rates.

The women were significantly older than the men (71 years vs. 64 years). A significantly higher proportion of women than men had a history of diabetes (41.2% vs. 25.5%), hypertension (61.1% vs. 41%), and revascularization (12% vs. 7.2%) but a lower percentage had a history of smoking (15.7% vs. 53.6%) and previous AMI (13% vs. 16.6%). The women more frequently had an AMI with non-ST elevation or LBBB and an AMI of anterior localization, and they had a

Table 1
Patient demographics, cardiovascular risk profile, infarction (AMI) characteristics, and mortality rates

	Men (<i>n</i> =4641)	Women (<i>n</i> =1568)	<i>p</i>
Age	64 (13)	71 (12)	<0.01
Diabetes	1181 (25.5%)	643 (41.2%)	<0.01
Smoking	2486 (53.6%)	245 (15.7%)	<0.01
Dyslipidemia	1845 (39.8%)	651 (41.9%)	0.13
Hypertension	1905 (41.0%)	953 (61.1%)	<0.01
Prior myocardial infarction	772 (16.6%)	202 (13.0%)	<0.01
Prior Revascularization	335 (7.2%)	186 (12.0%)	<0.01
<i>AMI characteristics</i>			
ECG at admission			<0.01
ST elevation	3074 (66.5%)	1005 (65.7%)	
Non-ST elevation	778 (16.6%)	286 (18.7%)	
LBBB	130 (2.8%)	61 (4.0%)	
Not determined	641 (13.9%)	177 (11.6%)	
AMI location			<0.01
Anterior	1953 (42.2%)	707 (45.9%)	
Inferior	2089 (45.2%)	613 (39.8%)	
Not determined	583 (12.6%)	219 (14.0%)	
Killip class at admission			<0.01
I	3742 (81.2%)	1106 (72.3%)	
II	467 (10.1%)	208 (13.6%)	
III	244 (5.3%)	119 (7.8%)	
IV	155 (3.4%)	96 (6.3%)	
Coronary angiographies in CCU	562 (12.3%)	182 (12.4%)	
Reperfusion procedures	2344 (50.8%)	656 (42.9%)	
CCU mortality	358 (7.7%)	235 (15.0%)	<0.01
28-day mortality	440 (9.5%)	265 (16.9%)	<0.01
1-year mortality	666 (14.4%)	357 (22.8%)	<0.01

AMI: Acute myocardial infarction; LBBB: left bundle branch block; CCU: coronary or critical care unit.

Table 2
Adjusted odds-ratio for coronary angiography during CCU stay

	95% CI			p
	OR	Lower	Upper	
Age	0.98	0.98	0.99	<0.01
Sex: women	1.08	0.89	1.32	0.42
Diabetes	0.97	0.81	1.17	0.78
Smoking	0.88	0.74	1.06	0.18
Prior myocardial infarction	1.06	0.85	1.33	0.59
Prior Revascularization	1.93	1.45	2.56	<0.01
ECG at admission (*)				
Non ST elevation	1.32	1.07	1.64	<0.01
LBBB	1.37	0.82	2.29	0.22
Not determined	1.27	0.97	1.66	<0.07
AMI location (¶)				
Inferior	0.80	0.67	0.95	<0.01
Not determined	0.75	0.55	1.01	<0.06
Killip class at admission (§)				
II	1.27	1.00	1.63	<0.05
III	0.98	0.69	1.39	0.91
IV	1.15	0.78	1.71	0.48

(*) Reference category: ST elevation.

(¶) Reference category: Anterior.

(§) Reference category: Killip I.

significantly higher Killip class at admission (Killip ≥ II; 27.7% vs. 18.8%) compared with the men. No significant gender differences were observed in the CCU use of coronary angiography. The factors significantly predicting performance of coronary angiography in the multivariate analysis were lesser age, history of revascularization, non-ST elevation on admission, and anterior location of the AMI (Table 2).

A reperfusion procedure (fibrinolysis or primary, rescue, or subacute PCI) was performed in 42.93% of women (656/1528 with available data) compared with 50.82% of men (2344/4612 with data), a significant difference ($p < 0.0001$). This is an issue of special importance, because patients who underwent some kind of reperfusion had a significantly

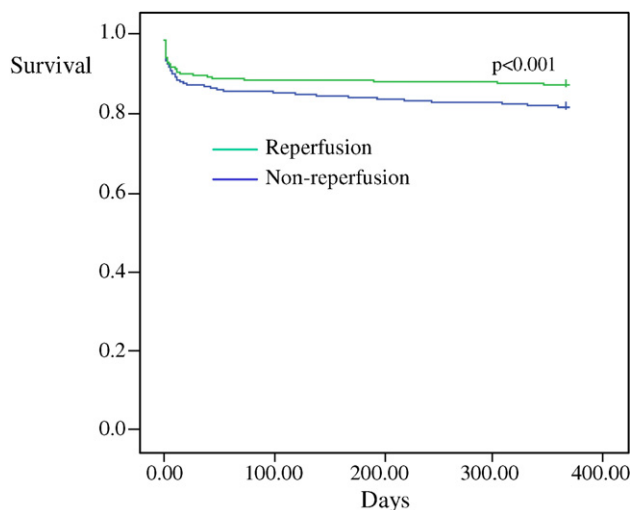


Fig. 1. Survival at 1 year among patients who underwent reperfusion and among those who did not.

Table 3
Adjusted odds-ratios for reperfusion

	95% CI			p
	OR	Lower	Upper	
Age	0.98	0.97	0.98	<0.01
Sex: women	0.87	0.75	1.01	<0.07
Diabetes	0.76	0.67	0.88	<0.01
Smoking	1.16	1.00	1.34	<0.05
Prior myocardial infarction	1.04	0.86	1.26	0.66
Prior Revascularization	1.13	0.87	1.47	0.34
ECG at admission (*)				
Non-ST elevation	0.06	0.05	0.08	<0.01
LBBB	0.28	0.17	0.44	<0.01
Not determined	0.04	0.03	0.06	<0.01
AMI location (¶)				
Inferior	1.02	0.89	1.16	0.78
Not determined	0.45	0.32	0.64	<0.01
Killip class at admission (§)				
II	0.89	0.73	1.09	0.26
III	0.57	0.43	0.76	<0.01
IV	0.65	0.51	0.94	<0.01

(*) Reference category: ST elevation.

(¶) Reference category: Anterior.

(§) Reference category: Killip I.

higher 1-year survival rate versus those who did not (Fig. 1). In the multivariate analysis, the factors significantly predicting performance of reperfusion procedure were lesser age, absence of diabetes, no smoking history, ST segment elevation on admission ECG, anterior localization of AMI, and Killip class I on admission (Table 3). In this analysis, the female sex variable was only close to statistical significance.

The women received significantly less treatment with IIb/IIIa glycoprotein inhibitors (10.6% vs. 13.1%) despite their higher frequency of AMI with non-ST elevation at admission, lower frequency of lipid-lowering therapy at discharge (36.4% vs. 42.6%), and their similar history of hypercholesterolemia. Furthermore, a significantly lower proportion of women was receiving antiplatelets and betablockers at discharge in comparison with the men, although a higher proportion was taking ACEIs and nitrates (Table 4).

Mortality in the CCU and at 28 days was significantly higher in women (Table 1), with an OR at hospital discharge of 1.95; this difference was established early during CCU

Table 4
Drug therapy during hospital stay

	Men (n=4641)	Women (n=1568)	p
<i>Treatment during hospital stay</i>			
GPIIb-IIIa inhibitors	602 (13.1%)	161 (10.6%)	<0.01
Aspirin	3536 (76.4%)	1078 (70.5%)	<0.01
Ticlopidine	496 (10.7%)	114 (7.5%)	<0.01
Clopidogrel	665 (14.4%)	182 (11.9%)	<0.01
Betablockers	2424 (52.4%)	674 (44.1%)	<0.01
ACEIs	1759 (38.0%)	645 (42.2%)	<0.01
Lipid-lowering drugs	1971 (42.6%)	556 (36.4%)	<0.01
Nitrates	1520 (32.8%)	568 (37.1%)	<0.05
Calcium-channel blockers	658 (14.5%)	183 (13.1%)	<0.1

ACEIs=angiotensin-converting enzyme inhibitors.

stay and persisted until the 1-year follow-up. Table 5 shows the variables significantly related to 28-day mortality in the bivariate analysis, which showed worse 28-day and 1-year survival prognoses for the women. In the multivariate analysis of this end-point (28-day mortality), female sex preserved its strong significance with an OR of 1.36 (95% CI 1.09–1.69), diabetes emerged as an adverse prognostic factor, and some of the treatments applied (betablockers, lipid-lowering drugs) were shown to be protective factors (Table 6). Finally, multivariate analysis of the combined end-

Table 5
Mortality at 28 days

	Alive (n=5515)	Dead (n=705)	p
<i>History</i>			
Age	64 (13)	73 (11)	<0.01
Sex: women	1305 (23.7%)	265 (37.6%)	<0.01
Diabetes	1539 (28.0%)	285 (40.5%)	<0.01
Smoking	2525 (45.9%)	207 (29.4%)	<0.01
Dyslipidemia	2258 (41.1%)	239 (34.0%)	<0.01
Hypertension	2507 (45.6%)	352 (50.1%)	<0.01
Prior myocardial infarction	841 (15.3%)	133 (18.9%)	<0.01
<i>AMI data</i>			
ECG admission			<0.01
Elevated ST	3580 (65.7%)	500 (71.3%)	
Non-elevated ST	956 (17.5%)	108 (15.4%)	
LBBB	153 (2.8%)	37 (5.3%)	
Without change	762 (14.0%)	56 (8.0%)	
AMI location			<0.01
Anterior	2304 (42.2%)	357 (50.9%)	
Inferior	2453 (44.9%)	248 (35.3%)	
Not determined	705 (12.6%)	97 (13.8%)	
Killip class at admission			<0.01
I	4566 (83.9%)	283 (40.5%)	
II	541 (9.9%)	134 (19.2%)	
III	255 (4.7%)	108 (15.5%)	
IV	77 (1.4%)	173 (24.8%)	
<i>Reperfusion</i>			
Reperfusion (of any type)	2695 (49.4%)	307 (43.9%)	<0.01
Primary reperfusion			<0.01
Fibrinolysis	2242 (41.1%)	245 (35.0%)	
PCI	37 (0.7%)	12 (1.7%)	
PCI-stent	249 (4.6%)	25 (3.6%)	
Rescue revascularization			<0.01
Fibrinolysis	35 (0.7%)	8 (1.2%)	
PCI balloon	21 (0.4%)	5 (0.8%)	
PCI stent	97 (1.9%)	11 (1.7%)	
CABG	0 (0.0%)	2 (0.3%)	
<i>CCU treatments</i>			
ASA	5080 (93.3%)	601 (85.9%)	<0.01
Ticlopidine	364 (6.7%)	32 (4.6%)	<0.05
Clopidogrel	421 (7.7%)	27 (3.9%)	<0.01
GPIIb-IIIa Antagonists	700 (12.9%)	63 (9.0%)	<0.05
Non-fractionated heparin	2997 (56.1%)	335 (48.1%)	<0.01
Low-molecular-weight heparin	2769 (51.7%)	254 (37.0%)	<0.01
Betablockers	3007 (55.3%)	127 (18.2%)	<0.01
ACEIs	2357 (43.4%)	198 (28.3%)	<0.01
Lipid-lowering drugs	1168 (21.5%)	52 (7.5%)	<0.01
Calcium antagonists	550 (10.1%)	38 (5.4%)	<0.01

Table 6
Adjusted odds-ratio for mortality at 28 days

	OR	CI 95%		p
		Lower	Upper	
Age	1.04	1.03	1.05	<0.01
Sex: women	1.36	1.09	1.69	<0.01
Diabetes	1.33	1.09	1.62	<0.01
Smoking	1.06	0.84	1.34	0.60
Hypertension	1.05	0.87	1.27	0.62
Prior myocardial infarction	1.12	0.88	1.43	0.36
ECG admission (*)				<0.01
Non-elevated ST	0.50	0.37	0.67	<0.01
LBBB	0.54	0.31	0.93	<0.05
Without change	0.45	0.30	0.69	<0.01
AMI location (¶)				<0.01
Inferior	0.58	0.47	0.72	<0.01
Not determined	1.04	0.71	1.52	0.84
Killip class at admission (§)				<0.01
II	2.90	2.26	3.72	<0.01
III	5.22	3.88	7.03	<0.01
IV	18.75	13.35	26.33	<0.01
ASA	0.82	0.60	1.13	0.23
Heparin	0.54	0.42	0.70	<0.01
Betablockers	0.42	0.34	0.53	<0.01
ACEIs	0.38	0.30	0.46	<0.01
Lipid-lowering drugs	0.56	0.41	0.77	<0.01
Reperfusion	0.94	0.75	1.16	0.54

(*) Reference category: ST elevation.

(¶) Reference category: Anterior.

(§) Reference category: Killip I.

point showed higher age, history of diabetes, previous revascularization, anterior AMI localization, advanced Killip class, reperfusion (primary, rescue or subacute), and female

Table 7
Adjusted odds-ratio for combined outcome variable (death, reinfarction, postinfarction angina and stroke) during hospital stay

	OR	CI 95%		p
		Lower	Upper	
Age	1.02	1.02	1.03	<0.01
Sex: female	1.21	1.02	1.42	<0.02
Diabetes	1.18	1.02	1.36	<0.03
Smoking	0.86	0.74	1.01	<0.07
Previous myocardial infarction	1.07	0.88	1.29	0.50
Previous revascularization	1.71	1.29	2.26	<0.00
ECG at admission (*)				
Non-elevated ST	1.04	0.84	1.28	0.75
LBBB	0.80	0.52	1.24	0.32
Not determined	1.07	0.81	1.42	0.62
AMI location (¶)				
Inferior	0.74	0.64	0.86	<0.01
Not determined	1.15	0.85	1.52	0.32
Killip class at admission				
II	1.69	1.38	2.05	<0.01
III	2.64	2.02	3.37	<0.01
IV	13.32	9.45	18.41	<0.01
Reperfusion	1.27	1.08	1.50	<0.01

(*) Reference category: ST elevation.

(¶) Reference category: Anterior.

(§) Reference category: Killip I.

sex to be significant and independent predictive variables of worse prognosis at hospital discharge with an OR of 1.21 (95% CI 1.02–1.42) (Table 7).

4. Discussion

The clinical history (especially age and frequency of diabetes), AMI type, and clinical situation at admission of the women in this study implied *a priori* a worse prognosis than the men, indicating the need for a more interventionalist approach. However, a similar percentage of women as men underwent coronary angiography and significantly fewer women than men underwent primary reperfusion procedures. Moreover, a smaller percentage of women received treatment with IIb/IIIa glycoprotein inhibitors despite their higher rate of AMIs with non-ST elevation at admission. Although use of antiplatelet and lipid-lowering drugs appears to have been below clinical guideline recommendations in both sexes, the women were even less likely to be receiving them at discharge despite their more frequent history of hypercholesterolemia, and they were less likely to be receiving betablockers despite their higher rate of HTA. On the other hand, the women appeared more likely to receive nitrates and calcium antagonists, therapeutic measures of a dubious clinical utility, although the difference did not reach statistical significance.

As anticipated, given the worse AMI prognosis of these women at admission, their short-term and long-term mortality rates were significantly higher than those of the men, and this difference emerged within the first 28 days. It is well documented and is confirmed in this study that initial therapeutic measures, especially pharmacological and/or interventional reperfusion, have a major influence on mortality. Therefore, part of this gender difference in mortality may be due to a difference in therapeutic approach, since women less frequently received primary reperfusion techniques. In fact, the multivariate analysis showed that the simple fact of being a woman was practically an independent predictive factor for not receiving a primary reperfusion.

This issue is rarely addressed in clinical trials, which by their very nature ensure equality between compared groups. Moreover, the relatively low proportion of women in trials of AMI therapies raises suspicions of a gender bias in the selection process [22,23]. In registry-based studies, which more accurately reflect daily clinical practice, similar gender differences to the present findings are commonly reported, despite the fact that hospital-based registries are also liable to a possible selection bias because of women's lesser accessibility to hospitals [24,25]. Indeed, the registry used in the present study may reflect this phenomenon, since only 25.5% of the patients were female, a low percentage for this type of registry.

Most studies that reported a significantly higher mortality in women with AMI [26–28] found, in common with the present study, that higher age, greater presence of comorbidities, and type of AMI presentation played a role in this

gender difference. Many authors have also observed that women less frequently receive treatments known to be equally beneficial to both sexes, including betablockers, ACEIs, antiplatelets, and fibrinolysis [29–32]. Indeed, the largest AMI registry to date, the American NRMI, showed that women less frequently received coronary angiography, PCI, or revascularization surgery compared with men [14]. In the present study, the higher mortality of the women is in part explained by the different treatment they received, especially the lesser use of reperfusion techniques (not itself explained by differences in studied variables), as well as by their age, comorbidities, and form of presentation of the disease. Thus, in the bivariate analysis, the women presented a higher risk of worse prognosis at hospital discharge than the men, with an OR of 1.95, and this difference remained significant when other risk factors were considered in the multivariate analysis, although with a lower OR of 1.2.

5. Conclusions

Women have a worse prognosis after an AMI largely as a function of clinical factors. However, there appears to be a gender difference in AMI management that is not explained by these factors and may contribute to this worse prognosis.

Clinical registries closely reflect reality and appear to be an ideal method to demonstrate this variation and to assess the effects of any remedial action taken.

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