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Sex differences in treatment and prognosis of acute coronary syndrome with interventional management

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ABSTRACT

Objective: Female sex has been associated with differences in diagnostic and management of acute coronary syndrome (ACS). Our aim was to analyze sex differences in ACS with interventional management in a tertiary care hospital.
Methods: Patients with ACS admitted to a Spanish tertiary care referral center were included prospectively and consecutively. All patients included in the study underwent a coronary angiography.
Results: From the total cohort of 1214 patients, 290 (24%) were women. Women were older (71 ± 12.8 vs 64 ± 13.4 years, $p < 0.001$) and showed lower ischemic risk and higher hemorrhagic risk scores (GRACE 159 ± 45 vs 171 ± 42, $p = 0.005$; CRUSADE 41 ± 19 vs 28 ± 17, $p < 0.001$). There were no significant differences in time to coronary angiography and revascularization rates between sex groups. A lower proportion of women received high-potency antiplatelet agents (29% vs 41.3%, $p = 0.004$). In-hospital evolution and one-year mortality were similar between groups.
Conclusions: In our population, there were no gender differences in management and prognosis of ACS. Differences in risk profile among groups could have an influence on antiplatelet therapy.

1. Introduction

Despite advances in current therapeutic strategies in acute coronary syndrome (ACS) have led to a significant improvement in patients' survival in our country [1] and globally, female gender continues to be associated with a worse prognosis after ACS [2–4]. Several hypotheses have been proposed to explain these differences, such as an unfavorable risk profile on women, and differences in clinical presentation, therapeutic approach and clinical outcomes, both in the acute phase and during the follow-up [4–7]. Thus, atypical presentation of symptoms and misdiagnosis may result in delayed revascularization and differences in medical treatment in women [2–4, 7]. These results come from studies including heterogeneous populations, from a great variety of centers with different management protocols and facilities. One of the most significant difference is a higher rate of medical (non-interventional) treatment in women [4]. However, it is unknown if this difference continues once the diagnosis has been made and an interventional management has been decided.

Our goal was to analyze whether these gender differences in treatment and prognosis of ACS persist once invasive management has been decided in a population from a tertiary care referral hospital.

2. Methods

From January 2013 to January 2016, 1214 consecutive patients with ACS admitted to a tertiary care referral hospital were recruited prospectively and included in a multipurpose database. Under the term of ACS were included patients with ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) [8]. All patients underwent at least one coronary angiography. Catheterization timing was decided according to the recommendations included in current guidelines for clinical practice [9].

For purposes of analysis and comparison patients were classified by gender. One-year follow up was completed in all patients after discharge. Ischemic and hemorrhagic risks were calculated using validated GRACE [10] and CRUSADE [11] scores. High-risk ACS was considered when GRACE score exceeded 140 and high hemorrhagic risk when CRUSADE score was higher than 40.

Patients with non-confirmed or rejected coronary origin for ACS were excluded from the analysis, such as patients without coronary angiogram, those with diagnosis of myocarditis, pericarditis, stress cardiomyopathy (Takotsubo syndrome) or type 2 myocardial infarction [8].

Differences between men and women for clinical and procedural variables were explored. The primary outcome is in-hospital mortality. Incidence and differences of ACS-related complications was assessed.

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Quantitative variables are expressed as mean (±standard deviation), and differences were analyzed with the Student's *t*-test. Categorical variables are reported as a frequency (percentage) and were compared with the Chi-squared test and Fisher's exact test when appropriate. Differences were considered statistically significant with a p value < 0.05, Gender, together with variables with statistically significant differences, were entered into a binomial logistic regression model to search for independent predictors for the primary outcome and for those complications where unadjusted differences existed. *P*-values are two-tailed. All analyses were performed using IBM SPSS Statistics, version 24.0 (Chicago, Illinois, USA).

3. Results

Baseline characteristics and angiographic findings are shown in Tables 1 and 2. Twenty-four percent ($n = 290$) of the entire population were women. STEMI was present in 684 patients (56%). Females were 6.5 (±0.9) years older, had higher prevalence of hypertension and diabetes and showed a higher hemorrhagic risk scoring. On the other hand, fewer women had ever smoked or suffered from coronary artery or peripheral vascular disease. Women presented less often with cardiac arrest, they had a lower GRACE score and a lower peak of cardiac markers (but with no significant differences in terms of left ventricular function).

There were no gender differences in time to coronary angiography and revascularization rates. All patients were treated with dual antiplatelet therapy (DAPT). Women received less high-potency antiplatelet agents (ticagrelor and prasugrel). After excluding patients with absolute or relative contraindications for high-potency antiplatelet agents, such as patients receiving chronic anticoagulation (11%) or those with previous stroke (8%), these differences in antiplatelet treatment were still present. There were no significant differences in statins, beta-blockers and ACE inhibitors administration between groups (Table 3).

A multivariate analysis showed that gender was not an independent predictor of in-hospital mortality. Only age (hazard ratio –HR– 1.03, 95% confidence interval –CI– 1.006–1.06 for every additional year, $p = 0.02$), hemoglobin (HR 0.85, 95% CI 0.74–0.98, for every point of g/dL, $p = 0.02$), creatinine clearance (HR 0.97, 95% CI 0.96–0.98 for every point of mL/min, $p < 0.001$) and cardiac arrest at admission (HR 7, 95% CI 3.33–14.66, $p < 0.001$). Similar results were obtained when removing hemoglobin and kidney function from the analysis to prevent interaction since both are directly related to gender.

Clinical evolution and prognosis at discharge were similar between groups. There were no significant differences in complications (heart failure, major bleeding, stroke, stent thrombosis, kidney failure or ventricular arrhythmias), in-hospital mortality (Fig. 1) or one-year follow up (Fig. 2).

Table 1
Baseline epidemiological and clinical variables.

	Males ($n = 924$)	Females ($n = 290$)	*p*-value
Age (years)	64,7 ± 13,5	71,1 ± 12,6	<0,001
Hypertension	554 (60%)	205 (71%)	0,001
Diabetes	227 (25%)	103 (36%)	<0,001
Dyslipidemia	439 (48%)	153 (53%)	0,119
Smoke habit	577 (62%)	91 (31%)	<0,001
Family history of early IHD	40 (4%)	6 (2%)	0,079
Weight (kg)	79,9 ± 13,2	69,3 ± 12,9	<0,001
Hemoglobin (g/dL)	14,2 ± 4,6	12,6 ± 1,6	<0,001
Creatinine clearance (ml/min)	75,9 ± 26,1	70,1 ± 25,8	0,001
Known CAD	186 (20%)	33 (11%)	0,001
Previous PCI	178 (19%)	39 (13%)	0,024
Peripheral vascular disease	104 (11%)	18 (6%)	0,013
Previous stroke	61 (7%)	24 (8%)	0,33
Atrial fibrillation	86 (9%)	31 (11%)	0,486
Liver disease	44 (5%)	8 (3%)	0,142
Previous treatment			
Anticoagulation	69 (8%)	34 (12%)	0,02
ASA	280 (30%)	72 (25%)	0,073
ACEI	543 (60%)	173 (60%)	0,788
ADP inhibitors	84 (9%)	23 (8%)	0,543
Beta blockers	202 (22%)	52 (18%)	0,151
Statins	413 (45%)	142 (49%)	0,203
Clinical variables at admission			
Systolic blood pressure	127,9 ± 25,3	126,7 ± 27,5	0,51
Heart rate	77,4 ± 18	78,6 ± 16,5	0,31
STEMI	509 (55%)	175 (60%)	0,115
Killip class			
I	691 (77%)	214 (75%)	0,472
II	101 (11%)	38 (13%)	
III	45 (5)	17 (6)	
IV	65 (7%)	15 (5%)	
Cardiac arrest	83 (9%)	10 (3%)	0,002
Infarct territory			
Anterior	303 (33%)	99 (34%)	0,643
Inferior/posterior	351 (38%)	110 (38%)	
Lateral	63 (7%)	24 (8%)	
Undefined	206 (22%)	56 (19%)	
RV acute failure	57 (6%)	20 (7%)	0,657
GRACE score	160,3 ± 45,2	171,2 ± 41,4	0,009
CRUSADE score	28,3 ± 17	41,1 ± 19,4	<0,001

ACEI: angiotensin converting enzyme inhibitors; ASA: acetylsalicylic acid; CAD: coronary artery disease; CK: creatine kinase; Cx: circumflex; IHD: ischemic heart disease; LAD: left anterior descending; LM: left main; RCA: right coronary artery; RV: right ventricle; STEMI: ST elevation myocardial infarction;

4. Discussion

Gender differences in the treatment and prognosis of patients with ACS have been reported in several studies with a large number of patients [3, 4]. However, explanations to these differences are not entirely understood. Some hypotheses point to clinical presentation variability as a potential contributor to increased mortality of ACS in women. According to this, delayed diagnosis and treatment caused by atypical presentation of symptoms and lesser rates of interventional management with coronary angiography might have an influence over prognosis [4]. However, as these results come from studies with a highly variable level of expertise and where therapeutic are not usually standardized, such gender differences could not be applicable to other populations.

In the present study, there were no significant differences according to sex in treatment and prognosis of patients with ACS invasively managed. A lower proportion of women received high-potency antiplatelet agents. However, this finding had not prognostic relevance. Differences in the ischemic and hemorrhagic risk profiles, with greater hemorrhagic risk scores among women could have contributed to this distinction in pharmacological prescriptions. In addition, in our series several relative contraindications to high-potency antiplatelet drugs, such as advanced age, hypertension, and small body size, were more common among women. Therefore, both a higher hemorrhagic risk and the presence of relative contraindications could explain some differences in the use of antiplatelet agents.

Table 2
Characteristics of coronary angiograms.

		Males ($n = 924$)	Females ($n = 290$)	*p*-value
Culprit vessel	LAD	343 (37%)	119 (41%)	0,328
	Cx	182 (20%)	44 (15%)	
	RCA	304 (33%)	101 (35%)	
	LM	22 (2%)	4 (1%)	
	Unclear	73 (8%)	22 (8%)	
Coronary dominance	Right	828 (90%)	270 (93%)	0,057
	Left	82 (9%)	20 (7%)	
	Codominant	14 (2%)	0	

Table 3
Procedural management and outcomes.

	Males ($n = 924$)	Females ($n = 290$)	p-value
Catheterization timing			
Emergent	115 (25%)	44 (32%)	0,283
First 24 h	215 (47%)	55 (40%)	
24–72 h	83 (18%)	63 (10%)	
>72 h	46 (10%)	44 (32%)	
Radial access	699 (76%)	223 (77%)	0,787
PCI	725 (93%)	209 (88%)	0,082
Fibrinolysis	10 (1%)	2 (1%)	0,742
Anti-IIb/IIIa	42 (5%)	15 (5%)	0,66
CK (peak)	1581 ± 2066	1302 ± 1640	0,025
LVEF at discharge (%)	49 ± 12	50 ± 13	0,083
Revascularization			
PCI	794 (86%)	243 (84%)	0,595
CABG	52 (6%)	17 (6%)	
None	78 (8%)	30 (10%)	
Treatment at discharge			
Ticagrelor/Prasugrel	272 (41%)	58 (30%)	0,004
ACEI	629 (81%)	196 (80%)	0,58
Beta blockers	665 (86%)	210 (86%)	0,95
Statins	753 (97%)	237 (96%)	0,51

ACEI: angiotensin converting enzyme inhibitors; CABG: coronary artery bypass grafting; CK: creatine kinase; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

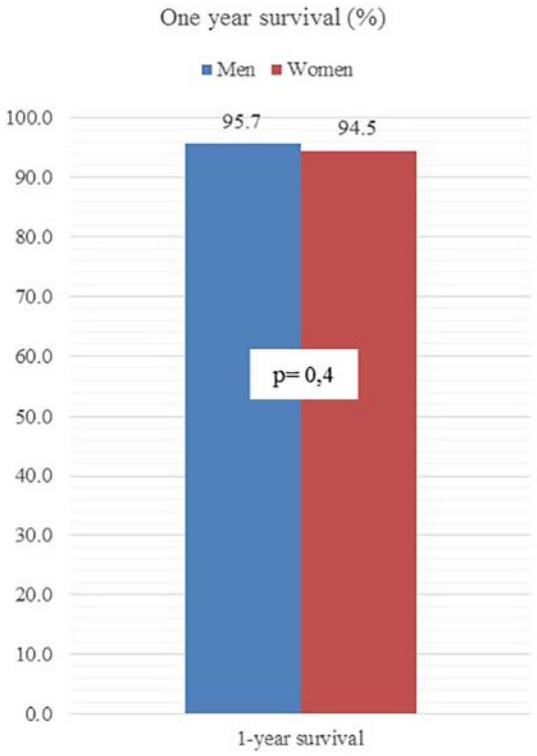

Fig. 2. One year follow-up.

Our study has certain qualities that should be mentioned: first, it includes a large population of patients with ACS treated with an invasive strategy. All patients underwent close clinical follow-up up to one year after hospital discharge. Moreover, the study was conducted in a tertiary care referral center with high volume and experience in the treatment of ischemic heart disease. Thus, potential confounding factors relating to treatment variability between centers with a different degree of experience are eliminated in the present study.

It is well known that certain factors such as high-sensitivity diagnostic tests (high sensitive troponin and echocardiography), the availability of urgent 24/7 angioplasty and admission to high-experienced centers, have a great impact on ACS prognosis [9, 12, 13]. Some differences

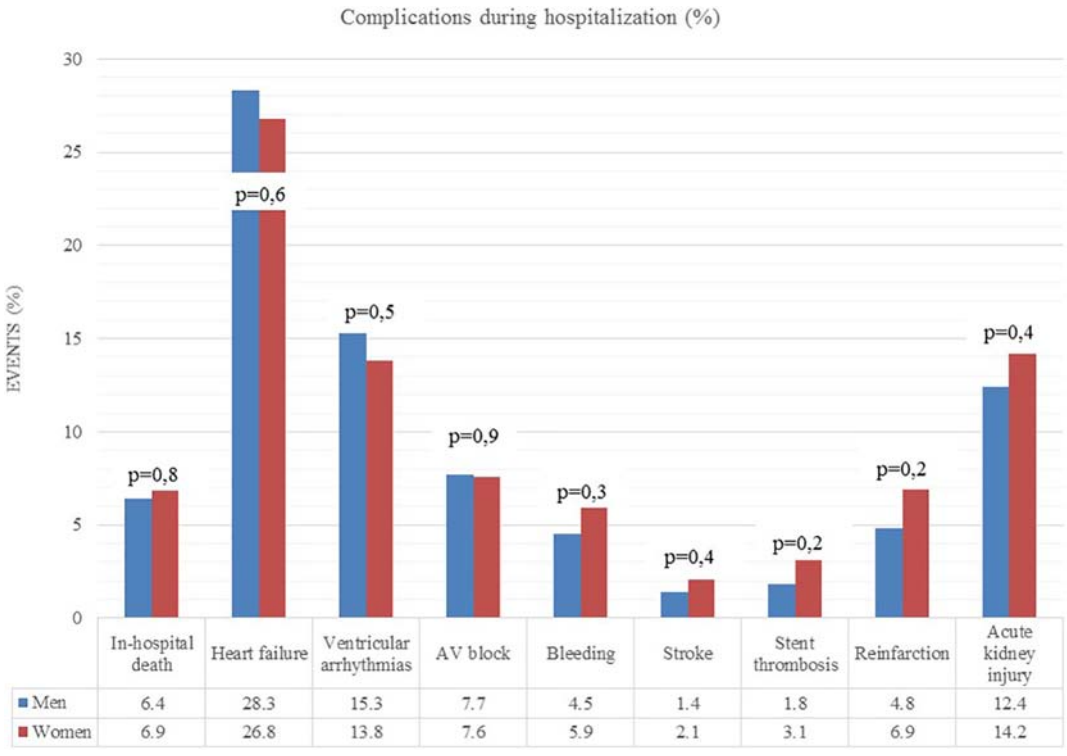

Fig. 1. Events and complications during hospitalization (Arrhythmias V: ventricular arrhythmias).

between our results and those from previous studies could be related to these factors.

Unification and improvement of current protocols for diagnosis and treatment of patients with ACS is mandatory. Adherence to evidence-based recommendations should be encouraged in order to overcome those previously reported sex differences in the management of ACS patients [9]. It is essential to maintain a high level of suspicion as well as close communication between out-of-hospital emergency services, who first receive the patient, and the clinical cardiologist. In addition, continuous training in the interpretation of diagnostic tests, especially the electrocardiogram, and constant updating of knowledge and recommendations are desirable to keep a high level of excellence in the management of ACS. As evidenced in our study, all these aspects can play an important role over prognosis of this highly prevalent pathology.

5. Limitations

The present study has several limitations that must be considered when interpreting the results. Although it includes a large population of patients with ACS, recruitment was performed in a single center, so the conclusions may not be applicable to other centers with different characteristics. However, as previously mentioned our results highlight the need to unify protocols in order to improve the diagnostic and therapeutic approach to ACS. Patients with ACS who were treated conservatively were not included in the present study, since the coronary origin of ACS could not be confirmed by coronary angiography. In our center all patients with ACS undergo a coronary angiography, except in those cases of contraindication, or those with a clear non-coronary origin of symptoms.

Finally, unfortunately, for this study only creatine kinase could be used as a biomarker. Some patients were referred from other secondary hospitals that used different troponin measurements, with a different scale and normality threshold, thus preventing direct comparison.

6. Conclusion

In our population of patients with ACS there were no gender differences in management and prognosis. A different risk profile could influence the use of high-potency antiplatelet agents in women.

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