

Women with Acute Coronary Syndromes are less Invasively Treated than Men in the Acute Phase in an Argentine Population

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ABSTRACT

Background

Previous studies have reported that women with acute coronary syndromes have worse outcomes compared to men and also undergo less diagnostic tests and interventions. It would thus be useful to establish whether this trend occurs in our country and which are the possible associations of prognostic value.

Objective

The aim of this study was to evaluate the clinical characteristics, treatments and outcomes of an Argentine cohort of patients with acute coronary syndromes at 2-year follow-up.

Methods

The Argentine cohort of the GRACE study included 4708 men and 2027 women with non-ST segment elevation acute coronary syndromes. The clinical history, type of presentation, final diagnosis, pharmacological treatments, revascularization and cumulative incidence of mortality and reinfarction were analyzed during hospitalization and at 6-month and 2-year follow-up.

Results

Women were older (69.4 ± 12.3 vs. 63.1 ± 11.9 years; $p < 0.01$), and had greater prevalence of heart failure and hypertension. The proportions of ischemic electrocardiographic changes and abnormal cardiac enzymes were similar in both sexes. Use of aspirin, clopidogrel and beta blockers was significantly lower in women, who had 50% chance of undergoing either percutaneous coronary intervention (OR= 0.55;95% CI 0.48-0.62) or coronary artery bypass graft surgery (OR= 0.49; 95% CI 0.36-0.67) than men. The crude incidences of mortality and reinfarction during hospitalization and at two-year follow up were higher in women with no differences in the relative risk of major events after adjusting for age and other covariates.

Conclusions

Despite similar risk than men to that of men, women were exposed to fewer interventions during hospitalization. Our results should alert physicians to indicate anti-ischemic treatments and interventions adjusted to risk in women.

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Key words > Acute coronary syndromes - Female sex - Gender gap.

Abbreviations > ACS Acute coronary syndrome | ECG Electrocardiogram

INTRODUCTION

Cardiovascular diseases are the leading cause of death in Western and developed countries in both sexes regardless of race or ethnic group, (1) Studies performed in other countries have shown that one out of three women dies of coronary artery disease, which means

that more women die of heart disease than of stroke, lung cancer, chronic obstructive pulmonary disease and breast cancer put together.(2)However, there is data indicating that women are less likely to be diagnosed with coronary artery disease and to receive interventions. (3,4) It is hence of interest to inves-

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tigate whether the same trend exists in our country and which are the possible associations of prognostic value. The goal of the present study is to evaluate the differences in the use of diagnostic and therapeutic methods between men and women with non-ST segment elevation acute coronary syndromes and the incidence of major events at 2 years.

METHODS

We analyzed the Argentine cohort of the collaborative GRACE study. The design and the definitions of this registry have been previously published (5). Briefly, the registry is a large, prospective, multinational observational study of ≥ 18 year old patients, enrolled between 1999 and 2007, hospitalized with presumptive diagnosis of non-ST-segment elevation acute coronary syndromes (ACS) and with at least one of the following features: ECG changes suggestive of ACS increased cardiac enzymes and previous history of coronary artery disease.

The present study is a post-hoc analysis evaluating the cohort of 6772 patients identified in six centers representative of private, public and social security medical care, to attain a reasonable external sample representation.

The study population was consecutively enrolled until the same number of cases was obtained per site each month. Once the maximum number of patients was reached, enrollment was stopped until the following calendar month in order to balance the relative weight of the volume of patients treated by each participating center. The variables were determined from the clinical records of each site by trained study coordinators who completed case report forms (CRF). Printed forms were filled at the early stages of the registry and subsequently, data were entered into an electronic, web-based CRF, providing three versions of data collected over the course of 10 years. The variables were coded according to the standardized definitions of the registry (6). Once patient data recruitment ended, follow-up was completed at 2 years of the index event and the database was closed. Data at 6 and 2 years were obtained, if possible, from medical visits or new hospitalizations registered in the medical records, or by telephone contacts.

For the purposes of the present study, the Argentine cohort was treated individually and data analysis was performed independently of the central database. The following diagnostic tests were recorded: physical examination, electrocardiogram (ECG), laboratory tests including biomarkers of myocardial damage, standard exercise stress test or imaging stress test and coronary angiography. Invasive approaches included percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG).

Statistical Analysis

The variables coded and reviewed were entered in a space delimited text worksheet and then analyzed using STATA 11.0 software package (STATA Corp, CollegeStation, Texas).

Continuous variables were expressed as mean \pm standard deviation and categorical variables as percentage. The Mann-Whitney U test was used to compare the distribution of continuous variables. Categorical variables were compared using Pearson's test or Fisher's exact test, as applicable. To determine the strength of the association between female gender and interventions and events, odds ratio (OR) were calculated with their corresponding 95% confidence intervals (95% CI). A multiple logistic regression analysis was performed to adjust for covariates included in the

GRACE risk score using a backward elimination procedure for removing confounders and goodness-of-fit testing in each stage. Alpha value of 0.05 was considered as statistically significant.

The study was observational and no interventions or changes were introduced to the standard medical care each center adopted for individual patients. Therefore, according to valid regulations in Argentina, patients were not asked to sign an informed consent form. The registry was approved by the Teaching and Ethics Committees of each center.

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RESULTS

The study included 2027 women and 4708 men with non-ST segment elevation ACS. Patients' characteristics at presentation are summarized in Table 1. Women were older (69.4 vs. 63.1; $p < 0.01$) and had more prevalence of heart failure (9.9 vs. 6.1%; $p < 0.01$) and hypertension compared to men. Revascularization was more frequent in men, either with PCI (13.2% vs. 10.6%; $p < 0.01$) or CABG (11.3% vs. 8.4%; $p < 0.01$).

Both men and women had the same ratio of ECG changes suggestive of ischemia at admission. Cardiac enzymes were elevated in about 40% of men and women (Table 2). However, the frequency of coronary angiography in women was significantly lower compared to men (41% vs. 51.9%), and among those women undergoing coronary angiography, the prevalence of 2- and 3-vessel disease was lower (Table 2).

Treatment with aspirin and clopidogrel within 24 h of admission was significantly lower in women (93.7% vs. 96.6% and 21.4% vs. 25.9%, respectively; $p < 0.01$ in both cases). Likewise, they received significantly lower treatment with beta blockers (Table 3).

Table 4 shows patient outcomes and procedures, demonstrating that the likelihood of undergoing PCI and CABG was lower in women compared to men (OR= 0.55; 95% CI = 0.48 - 0.62 and OR= 0.49; 95% CI = 0.36 - 0.67, respectively). Mortality was greater in women during the initial hospitalization (OR= 1.36; 95% CI: 1.09 - 1.16; $p = 0.005$) and at 2 years (OR= 1.28; 95% CI 1.05 - 1.57; $p = 0.01$) (Figure 1). However, the risk of reinfarction at two years was similar in both genders (OR=1.06; 95% CI 0.72 - 1.54; $p = 0.73$).

After adjusting for age, heart failure, diabetes, chronic kidney failure, previous revascularization and ST-segment deviation, there were no differences in mortality and/or new infarction between both genders at 6 months and 2 years, mainly due to the effect of age as covariate (Figure 2).

DISCUSSION

Over the last decades, significant data indicate that women with ACS receive fewer therapeutic interventions and present worse outcomes (7,8). The Argentine cohort of the GRACE study is contemporary, from the end of the nineties until a couple of years ago when follow-up was completed.

Table 1. Demographic characteristics and clinical presentation

Variables	Women (n=2027)	Men (n=4708)	p
Age (mean ± standard deviation)	69.4 ±12.3	63.1 ±11.9	< 0.01
	n (%)	n (%)	
Clinical history			
HT	1585 (78.5)	3061 (65.5)	< 0.01
Dyslipidemia	964 (47.9)	2238 (47.9)	0.992
Diabetes	478 (23.8)	981 (20.9)	0.01
Smoking	659 (32.8)	3218 (68.7)	< 0.01
Previous AMI	454 (22.6)	1313 (28.1)	< 0.01
CHF	199 (9.9)	282 (6.1)	< 0.01
Previous angina	589 (29.13)	1388 (29.59)	0.705
Previous coronary artery disease †	450 (22.48)	1392 (29.93)	< 0.01
Peripheral vascular disease	160 (7.97)	494 (10.6)	< 0.01
Use of ASA	717 (35.4)	1739 (36.97)	0.222
Coronary artery bypass graft surgery	168 (8.4)	526 (11.3)	< 0.01
Previous PCI	213 (10.6)	619 (13.2)	< 0.01
History of venous thromboembolism	5 (0.4)	9 (0.3)	0.636
Kidney failure	86 (4.3)	204 (4.4)	0.9
BMI (kg/m ²)	27.5 ± 4.74	28.13 ± 4.39	< 0.01
Diagnosis at admission			
AMI	616 (30.39)	1781 (37.83)	< 0.01
Unstable angina	1246 (61.47)	2569 (54.57)	< 0.01
Other ‡	165 (8.1%)	358 (7.6)	0.165

BMI=body mass index, HT= hypertension, AMI= acute myocardial infarction, CHF= congestive heart failure, ASA= acetyl salicylic acid.

† History of myocardial infarction, heart failure secondary to ischemia or ischemic sudden death, history of positive exercise stress test or imaging stress test, previous coronary angiography with significant coronary artery stenosis, or previous myocardial revascularization.

‡Atypical chest pain, excluding myocardial infarction or other cardiac symptoms.

Table 2. Diagnostic tests during hospitalization

Variables	Women (n=2021) n (%)	Men (n=4708) n (%)	p
Ischemia in ECG	1750 (86.8)	4053 (86.6)	0.8
ST-segment elevation	541 (26.69)	1601 (34.01)	< 0.01
ST-segment depression	717 (35.37)	1547 (32.86)	0.045
Increased levels of markers of necrosis	857 (42.28)	1938 (41.16)	0.394
Exercise stress test	436 (21.87)	1088 (23.38)	0.179
Coronary angiography	828 (40.85)	2444 (51.91)	< 0.01
Two-vessel disease	201 (24.27)	674 (27.58)	< 0.01
Three-vessel disease	189 (22.83)	636 (26.03)	< 0.01
Left main coronary artery disease	50 (6.04)	149 (6.1)	0.121

ECG: Electrocardiogram

Table 3. Pharmacological treatment during hospitalization

Variables	Women n (%)	Men n (%)	p
Aspirin	1898 (93.73)	4497 (95.60)	< 0.01
Clopidogrel	330 (21.40)	920 (25.94)	< 0.01
Heparins	1240 (61.17)	2932 (62.28)	0.393
Oral beta blockers	1523 (75.14)	3778 (80.25)	< 0.01
Statins	934 (52)	2706 (64.09)	< 0.01

Variables	Women	Men	p
PCI*	372 (18.35)	1362 (28.93)	< 0.01
Coronary artery bypass graft surgery*	55 (2.73)	250 (5.37)	< 0.01
In-hospital mortality	145 (7.15)	253 (5.37)	< 0.01
Mortality at 6 months	194 (9.57)	349 (7.41)	< 0.01
Mortality at 2 years	217 (10.71)	405 (8.60)	< 0.01
Reinfarction at 6 months	55(2.73)	116 (2.46)	0.551
Reinfarction at 2 years	71 (3.50)	151 (3.21)	0.533

* During initial hospitalization

Table 4. Interventions and events

The present study revealed that despite women were older and had an unfavorable risk profile, most of them underwent a conservative diagnostic and therapeutic approach compared to men. Previous studies have reported that age is associated with adverse outcomes in women (9); yet, our cohort presented other risk variables, as heart failure and hypertension at admission which could have improved the threshold to indicate an interventional approach. The risk profile and the distribution of the baseline characteristics of our cohort are similar to those published in multinational studies over the past decade, indicating that a defined pattern exists and has not varied across the years.

Surprisingly, the gap for early interventions expanded early and adversely for women, who were less frequently treated with anti-ischemic and antiplatelet agents within the first 24 hours after an ACS. Thus, the administration of aspirin, clopidogrel and oral beta blockers was lower than in men. Moreover, the indication of coronary angiography and revascularization therapy by PCI or CABG was also lower compared to men.

Several hypotheses arise to explain the different approaches between men and women. Firstly, this might be due to the different clinical presentation in women attributed to a greater proportion of atypical or confusing symptoms (11). However, in our study the proportion of atypical symptoms was similar in both groups and, although the presumptive diagnosis of infarction was lower in women, unstable angina was more prevalent in women (61%) than in men (55%) (Table 1). With this combination of characteristics at presentation, the threshold of suspicion and therapeutic decision should have been at least equivalent in both genders.

Age is an omnipresent risk factor for most non-communicable chronic diseases (2), and coronary artery disease is not the exception. As expected, mean age of women was higher compared to men, yet far from life expectancy at birth which is of 77 years for this group in Argentina. Therefore, this factor should have promoted more interventions in women. However, during the acute stage of the disease, women had 50% chance of undergoing PCI or CABG compared to men, which is markedly opposite to their risk pro-

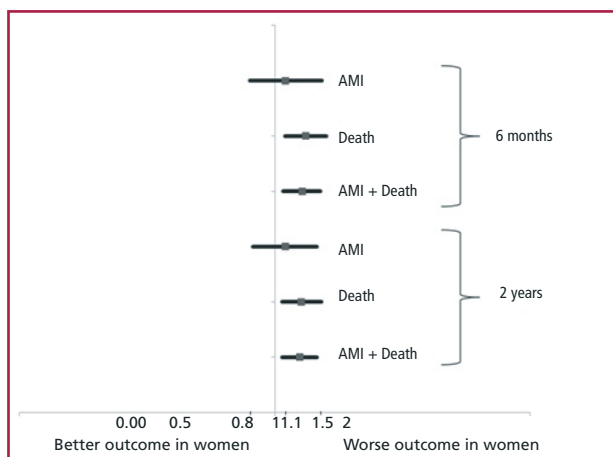


Fig. 1. Relative risks of mortality, reinfarction and combined mortality and reinfarction at 6-month and 2-year follow-up, with the corresponding 95% confidence intervals.

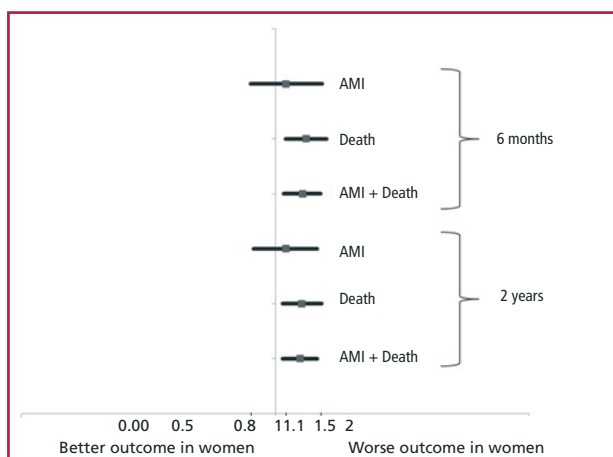


Fig. 2. Relative risks of mortality, reinfarction and combined mortality and reinfarction at 6-month and 2-year follow-up, with their corresponding 95% confidence intervals, adjusted for age, heart failure, diabetes, chronic kidney failure, previous revascularization and ST-segment deviation

file. In line with these observations, the cumulative incidence of mortality during hospitalization and at 2-year follow-up was significantly greater in women compared to men. However, age emerged as the main

confounder after multivariate adjustment, which, in combination with other covariates, neutralized the sex-related effect for the endpoints mortality and/or new myocardial infarction.

Another explanation may be that women are not considered at high risk according to Braunwald's classification or to TIMI, PURSUIT or GRACE risk scores. (12) Thus, they would not have an indication of invasive strategy, or the decision would be more conditioned by the availability of a catheterization laboratory or an operation room than by the presence of clinical risk indicators or patient characteristics. However, this explanation loses significance by the fact that the proportion of women with markers of myocardial necrosis was similar to that of men (42% vs. 41%), as well as the presence of ST-segment deviations. Hence, the number of interventions should have been comparable.

On the other hand, women wait longer before seeking medical attention. This behavior may produce adverse outcomes, though the analysis of this behavior was not part of our study (13).

Another possibility is the presence of bias due to medical issues as doctors may underestimate the risk in women. Coronary artery disease has been traditionally considered a condition affecting men, and concomitantly with their higher risk, men have received a greater number and proportion of coronary interventions (14,15). The risk of coronary artery disease in women has been increasing over the last years due to the high prevalence of smoking habits, obesity and sedentary lifestyle in women (16). In addition, their increased participation in the job market has led them to stress, poor eating habits and less physical activity equivalent to those of men, so medical behavior should be reevaluated to avoid gender-related biases.

It would be important to shorten the delay to presentation in women and increase clinical suspicion among health care professionals. At this point, the role of health promotion is relevant, as women should know that ischemic heart disease is not a condition affecting only men and that they are more likely to present atypical symptoms and should seek medical advice as soon as possible.

Finally, a limitation of this study is information bias, as it was based on a post-hoc analysis of a cohort with lack of information of the reasons for medical decisions or for the treating physicians' preferences to indicate invasive tests or treatments.

CONCLUSION

Despite having greater clinical risk or at least equivalent to that of men, coronary angiography, PCI, CABG, antiplatelet therapy and beta blockers were less frequently indicated to women. However, the adjusted relative risk of mortality and/or reinfarction at 6 months was similar in both sexes and mainly associated with higher age in women. In women with acute coronary events, the risk determined by age and the

similar clinical risk profile identified by markers of necrosis and ECG changes should alert physicians to indicate anti-ischemic treatments and interventions. Actions should be taken to promote cardiovascular health in women as well as to improve the detection and alert threshold of the health care team. It is hence advisable to review any gender gap influencing medical behavior.

RESUMEN

Las mujeres con síndromes coronarios agudos reciben menos intervenciones en la fase aguda que los hombres en una población argentina

Introducción

Existen antecedentes en la bibliografía científica que indican que las mujeres con enfermedad coronaria tienen peor pronóstico que los hombres y se observa asimismo una utilización menor de métodos diagnósticos e intervenciones en ellas, por lo que resulta de interés establecer si esta tendencia existe en nuestro país y las posibles asociaciones de valor pronóstico.

Objetivo

Investigar en una cohorte argentina de síndromes coronarios agudos las características clínicas, los tratamientos y la evolución a 2 años de seguimiento.

Material y métodos

Componente argentino del estudio cooperativo GRACE de 4.708 hombres y 2.027 mujeres con síndromes coronarios agudos sin supradesnivel persistente del segmento ST. Se analizaron antecedentes, tipo de presentación, diagnóstico definitivo, tratamientos farmacológicos, aplicación de revascularización e incidencia acumulativa de muerte e infarto recurrente en la etapa hospitalaria y a los 6 meses y a los 2 años de seguimiento.

Resultados

Las mujeres fueron mayores ($69,4 \pm 12,3$ vs. $63,1 \pm 11,9$ años; $p < 0,01$), con mayor prevalencia de insuficiencia cardíaca e hipertensión. La proporción de signos de isquemia miocárdica en el electrocardiograma, así como la de enzimas miocárdicas en rango anormal fue similar para ambos géneros, con un uso significativamente menor de aspirina, clopidogrel y betabloqueantes en las mujeres, quienes tuvieron la mitad de chance de angioplastia (OR: 0,55, IC 95% 0,48-0,62) y de cirugía de revascularización (OR: 0,49, IC 95% 0,36-0,67), con mayores incidencias crudas de muerte e infarto en agudo y a los 2 años, pero sin diferencia en el riesgo relativo de eventos mayores una vez ajustado por edad y otras covariables.

Conclusiones

A pesar de un riesgo clínico similar en mujeres y hombres, las primeras recibieron menos intervenciones durante la fase hospitalaria. Nuestros resultados llaman a un adecuado alerta e intervenciones ajustadas al riesgo para el sexo femenino.

Palabras clave > Síndromes coronarios agudos - Sexo femenino - Brecha de géneros

Conflicts of interest

None declared.

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