Gender Differences in Patients with Suspected Non-ST-Segment Elevation Acute Coronary Syndromes. Implications for Invasive Management

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Sex differences have been observed in the clinical profile, prognosis, and treatment of patients with unstable ischemic heart disease. Men tend to receive more invasive management. We assessed these differences in 823 consecutive patients (543 men) with possible acute coronary syndrome without ST-segment elevation who were seen since our chest pain unit opened. A protocol for the management of unstable ischemic heart disease was followed. Women had a worse baseline clinical profile but men more frequently had a positive exercise stress test. Univariate analysis showed that angiography and revascularization procedures were performed more often in men. However, multivariate analysis did not confirm male sex as an independent predictor of the need for a more invasive strategy. The inauguration of a chest pain unit and application of a protocol for the management of unstable ischemic heart disease has helped to correct case stratification and optimize the application of invasive treatments.

Key words: *Unstable angina. Sex. Catheterization. Revascularization.*

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Diferencias entre sexos en pacientes con sospecha de síndrome coronario agudo sin elevación del segmento ST. Implicaciones en el tratamiento intervencionista

Se han observado diferencias entre sexos en las características clínicas, el pronóstico y el tratamiento de los pacientes con cardiopatía isquémica inestable, con una tendencia hacia un manejo más intervencionista en los varones. Hemos analizado estas diferencias en 823 pacientes consecutivos (543 varones) con sospecha de síndrome coronario agudo sin elevación del segmento ST desde el desarrollo de una unidad de dolor torácico y de un protocolo de asistencia a la cardiopatía isquémica inestable. Las mujeres presentaron unas características clínicas más desfavorables, pero demostraron con menor frecuencia un test de esfuerzo positivo. En el análisis univariado se observó un mayor porcentaje de coronariografía y revascularización en varones. Sin embargo, en el análisis multivariado estas diferencias desaparecieron. El desarrollo de una unidad de dolor torácico y un protocolo de manejo de la cardiopatía isquémica inestable ayudan a una correcta estratificación de los casos y a la adecuada utilización del intervencionismo.

Palabras clave: *Angina inestable. Sexo. Cateterismo cardíaco. Revascularización.*

INTRODUCTION

Previous studies of a large number of patients have shown gender differences in clinical profiles, prognosis, and treatment of patients with acute ischemic cardiopathy.[1-6]

Over the past years we have seen the development of treatment that is increasingly protocolized of patients with possible unstable ischemic cardiopathy; the introduction and application of new recommendations, among these the use of chest pain units,[7] may change the previous tendency toward under-utilization of interventional procedures in women.

Our aim in this study is to analyze gender differences with regard to clinical characteristics, treatment, and short-term prognosis (intrahospital for patients admitted to the hospital or during the first week for patients discharged early), as well as the use of interventional treatment in patients with suspected non-ST segment elevation acute coronary

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ABBREVIATIONS

ECG: electrocardiogram.
95% CI: 95% confidence interval.
NS: not significant.
OR: odds ratio.
NSSEACS: non-ST segment elevation acute cardiac syndrome.

syndrome (NSSEACS), starting with the development of a chest pain unit and an action protocol for unstable ischemic cardiopathy.

PATIENTS AND METHODS

Study group

We studied 823 consecutive patients (543 men and 280 women) evaluated in our chest pain unit from January 15, 2001, to April 15, 2002 for chest pain with suspected NSSEACS. We excluded from our study patients with chest pain clearly of non-cardiac origin and patients with ST segment elevation. The general characteristics of the patients and characteristics according to sex are shown in Tables 1 and 2.

Action protocol

Following the chest pain unit action protocol which we have reported previously,[8,9] we performed clinical evaluation, an electrocardiogram (ECG), and serial determinations of markers of myocardial damage. Following the action protocol of our service for unstable ischemic cardiopathy, those patients with dynamic ECG changes (ST segment decline >1 mm or T-wave peak >1 mm), with elevation of markers for damage or patients considered high risk or with a high probability of NSSEACS as determined by the attending cardiologist were admitted to our hospital. For these patients we followed a conservative strategy, with catheterization and revascularization (if anatomically possible) performed in those patients with recurrent angina or a positive pre-discharge stress test. According to our action protocol[8] a definite diagnosis of NSSEACS was given to those patients with an infarct (elevation of CK-MB mass >5 ng/mL) or unstable angina (without enzyme elevation but with evidence of ischemia on stress test or angiography).

If the ECG and serial analysis of markers were negative and the patients remained stable, performance of ergometry was recommended: if the stress test was conclusive and negative, the patient was discharged and followed for 7 days in the outpatient chest pain clinic; if the test was positive, the patients was admitted for performance of catheterization; if the test was inconclusive or unreadable, the patient was admitted for the study to be completed.

The incidence of major events was evaluated during the intrahospital period (for patients admitted) or following a week of outpatient followup (for patients with early discharge). We recorded deaths (all of cardiac origin) and complicated infarcts (new episodes of chest pain with new elevation of CK-MB mass >5 ng/mL).

Statistical analysis

Quantitative variables are expressed as mean#+standard deviation and were compared via the Student *t* test for non-paired data. Qualitative data are expressed as percentages and compared via the χ^2 test. Multivariate analyses to determine variables that were independently related to the performance of catheterization or revascularization were performed by logistical regression, including those variables that on univariate analysis had a value of $P<.2$. In the definitive model we calculated the odds ratio (OR) and 95% confidence intervals for those variables that were shown to be independent. In all cases a value of $P<.05$ was considered significant. For statistical analysis we used the SPSS version 9.0 statistical package (Chicago, Illinois, USA).

RESULTS

Study group

We studied 823 consecutive patients (543 men and 280 women) with possible NSSEACS. The women had a higher probability of having diabetes mellitus, arterial hypertension, and were of a greater age, and were less likely to be smokers (Table 1).

Among the women fewer stress tests were performed, but a similar amount of early ergometry was performed and the ergometry results were more frequently negative or inconclusive than in the group of men. There was a tendency to perform more stress tests with imaging (isotopes or magnetic resonance) in woman than in men (Table 2).

A definite diagnosis of NSSEACS was made more frequently in men. The percentage of patients with a diagnosis of infarct was identical for both sexes, but the diagnosis of unstable angina was more frequent in men, while a final diagnosis that ruled out NSSEACS was more frequent in women (Table 1). We did not observe differences between the sexes with regard to the incidence of major events (death or infarct) during the intrahospital followup period (for patients admitted) or after 1 week (in the case of pa-

TABLE 1. **Study group. Gender differences with regard to clinical characteristics and events**

	All	Men	Women	*P*
Number	823	543	280	
Clinical characteristics				
Previous ischemic cardiopathy	49%	50%	47%	NS
Dyslipemia	48%	46%	52%	NS
Diabetes mellitus	29%	24%	40%	<.0001
Smoker	20%	28%	4%	<.0001
Hypertension	63%	61%	68%	.04
Age, years	67±12	64±12	70±11	<.0001
Troponin I>0.5 ng/mL	41%	40%	43%	NS
Diagnosis NSSEACS	56%	61%	47%	<.0001
Diagnosis infarct	36%	36%	36%	NS
Diagnosis unstable angina	20%	25%	11%	<.0001
Diagnosis non-NSSEACS	44%	39%	53%	<.0001
Early discharge (<24 h)	15%	15%	15%	NS
Events				
Recurrent angina	14%	15%	13%	NS
Infarct*	2%	2%	1%	NS
Death	3%	3%	3%	NS
Infarcta/death	5%	5%	5%	NS

*Complicating infarct (new episode of chest pain with new elevation of markers for cardiac damage).
NS indicates not significant (in all cases *P*>.2); NSSEACS, non-ST segment elevation acute coronary syndrome.

TABLE 2. **Study group. Gender differences with regard to electrocardiogram, stress test, and interventional treatment**

	All	Men	Women	*P*
Number	823	543	280	
ECG-ergometry				
Left branch block	7%	6%	9%	.2
Unreadable ECG	11%	10%	14%	.1
Negative T-wave	11%	10%	11%	NS
ST decline	23%	23%	24%	NS
Ergometry	42%	45%	37%	.03
Early ergometry	23%	24%	21%	NS
Positive ergometry[a]	35%	39%	26%	.02
Inconclusive ergometry[a]	28%	24%	38%	.009
Imaging test	7%	6%	9%	.2
Interventional treatment				
Catheterization	35%	40%	26%	<.0001
Normal coronary arteries[b]	17%	16%	22%	NS
Angioplasty	11%	12%	8%	.1
Surgery	7%	9%	4%	.02
Revascularization	18%	21%	12%	.002

[a]Refers exclusively to patients with ergometry (n=346). Ergometry was positive in 35% of these cases (n=121) and inconclusive in 28% (n=97). [b]Refers to patients with catheterization (n=288). 17% of cases had normal coronary arteries (n=49). ECG indicates electrocardiogram; NS, not significant (in all cases *P*>.2).

tients discharged early) (Table 1). In the patients discharged early there were no major events detected.

Cardiac catheterization

Cardiac catheterization during admission was performed in 288 patients (35%). On multivariate analysis, the variables that were independently related to performance of catheterization during admission were lesser age, recurrent angina, positive stress test, and not performing ergometry (Table 3). Overall, a higher percentage of catheterizations were performed on men but the masculine sex was not an independent predictor for performance of cardiac catheterization.

Revascularization

Revascularization (percutaneous or surgical) was performed during admission on 146 patients (18%). On multivariate analysis the variables with an independent relationship with revascularization during admission were lesser age, recurrent angina, troponin I elevation, a positive stress test, and not performing ergometry (Table 4).

A greater percentage of revascularizations was performed on men, but masculine sex was not an independent predictor for revascularization. Of the 288 patients in whom catheterization was performed during admission, we did not observe differences with regard to the percentage of revascularizations among men and women (49% vs 44%; *P*=NS).

Five major events occurred (3.4% of procedures) related to revascularization, 1 among men and 4 among women (*P*=NS). With regard to percutaneous revascularization, there were 2 deaths and 1 Q-wave infarct, and with regard to surgery, 1 death and 1 Q-wave infarct.

DISCUSSION

Previous studies have shown clear differences between the sexes in unstable ischemic cardiopathy with regard to clinical characteristics (women generally present with a higher risk baseline profile), treatment (more interventional treatment in men), and prognosis (more unfavorable in women in the short term).[1-6] In general, these are findings from broad retrospective population studies,[1,3,4] and, therefore, it is difficult to collect the variables of interest from them. In fact, on multivariate analyses it can be seen that gender differences appear to diminish and depend to a great extent on the differences in baseline clinical characteristics between men and women.[1-3,5]

Our study prospectively collects data from a consecutive series of patients with suspected NSSEACS evaluated by a chest pain unit in a tertiary hospital and treated according to a homogenous and actualized assistance protocol for ischemic cardiopathy. We analyzed whether or not the differences observed between

TABLE 3. **Percentage of patients who underwent cardiac catheterization as a function of whether a variable was present (yes) or not (no). Univariate and multivariate analysis**

	Univariate			Multivariate	
	Yes	No	*P*	OR (95% CI)	*P*
Clinical characteristics					
Previous ischemic cardiopathy	37%	34%	NS		
Dyslipemia	38%	33%	NS		
Diabetes mellitus	39%	34%	.1		NS
Smoker	43%	33%	.03		NS
Hypertension	35%	37%	NS		
Age, years	64±11	68±13	<.0001	0.94 (0.92-0.96)	<.0001
Troponin I>0.5 ng/mL	38%	33%	.2		NS
Recurrent angina	84%	27%	<.0001	16.9 (9.5-30.2)	<.0001
Male	40%	26%	<.0001		NS
ECG-Ergometry					
Left branch block	29%	36%	NS		
Unreadable ECG	29%	36%	NS		
Negative T-wave	38%	35%	NS		
ST decline	48%	32%	<.0001		NS
Ergometrya	29%	40%	.001	0.09 (0.05-0.2)	<.0001
Positive ergometry[a]	70%	29%	<.0001	48.6 (24.2-97.5)	<.0001
Inconclusive ergometry[a]	26%	29%	NS		

[a]Patients with ergometry (n=346).
OR (95% CI) indicates odds ratio with 95% confidence interval of those variables that on multivariate analysis were independent variables to predict performance of catheterization (we included in this analysis all variables with a value of *P*<.2 on univariate analysis).
«Yes» indicates that a variable is present and «No» that it is absent. Thus, for example, in patients with a history of dyslipidemia (yes) catheterization was performed in 38%of cases while in those without a history of dyslipidemia (no) catheterization was performed in 33%.
In the case of the variable Age (continuous variable) this was expressed as mean±standard deviation (years) in cases in which catheterization was performed (yes) and those in whomit was not performed (no). ECG indicates electrocardiogram; NS, not significant (in all cases *P*>.2).

TABLE 4. **Percentage of patients in whom revascularization was performed as a function of whether a variable was present (yes) or absent (no). Univariate and multivariate analysis**

	Univariate			Multivariate	
	Yes	No	*P*	OR (95% CI)	*P*
Clinical characteristics					
Previous ischemic cardiopathy	20%	16%	NS		
Dyslipemia	21%	15%	.04		NS
Diabetes mellitus	21%	16%	.1		NS
Smoker	23%	17%	.09		NS
Hypertension	17%	18%	NS		
Age, years	64±11	67±13	.02	0.96 (0.94-0.98)	<.0001
Troponin I>0.5 ng/mL	23%	14%	.001	1.5 (1.01-2.3) .04	
Recurrent angina	55%	11%	<.0001	9.1 (5.6-14.7)	<.0001
Male	21%	12%	.002		NS
ECG-Ergometry					
Left branch block	9%	18%	.1	NS	
Unreadable	ECG	13%	18%	NS	
Negative T-wave	18%	18%	NS		
ST decline	28%	15%	<.0001		NS
Ergometry	13%	21%	.002	0.2 (0.07-0.4)	<.0001
Positive ergometry[a]	31%	15%	<.0001	13.7 (6-31.6)	<.0001
Inconclusive ergometry[a]	11%	13%	NS		

«Yes» indicates that a variables is present and «No» absent. Thus, for example, in patients with a history of dyslipemia (yes) revascularization was performed in 21% of cases while in those without a history of dyslipemia (no) revascularization was performed in 15%.
In the case of the variable Age (continuous variable) this was expressed as mean±standard deviation (years) in cases in which catheterization was performed (yes) and those in whom it was not performed (no). ECG, indicates electrocardiogram; NS, not significant (in all cases *P*>.2).
[a]Patients with ergometry (n=346).
ECG indicates electrocardiogram; NS, not significant (in all cases P>.2); OR (95% CI), odds ratio with 95% confidence interval of those variables that on multivariate analysis were independent for predicting the performance of revascularization (we included in this analysis all variables with a value of *P*<.2 on univariate analysis).

the sexes in population studies continue to exist in our work environment.

In accordance with previous studies,[1-3,5,6] women were shown to be a group at higher cardiovascular risk (greater age, diabetes, and hypertension). Nevertheless, a heterogeneous population is involved, as, in spite of the baseline risk profile, a smaller percentage of women present with ischemia on ergometry and are finally diagnosed with NSSEACS.[6] Probably due to this fact, and in accordance with previous studies,[1-3] the incidence of events observed is identical to that in men (although it was expected to be higher due to their clinical characteristics).

Strict treatment in the chest pain unit was identical for both sexes (there was no difference with regard to early ergometry or speedy discharge). Generally a lower percentage of ergometry procedures were performed in women, which is a result of the greater frequency of non-readable ECGs and greater age of the female patients, and compensated for in part by the more frequent use of imaging tests in women.

Interventional treatment (both catheterization and revascularization) was used less in women. Nevertheless, multivariate studies reveal that this is not a function of under-utilization in the female sex but can be explained by a difference in clinical profiles.[6] In fact, the variables that were shown to be independent predictors of interventional treatment were:

– Lesser age. In previous registries more conservative treatment has been reported in patients of advanced age.[10] The greater overall age of the women explains, in part, the less aggressive treatment.

– Refractory angina. Application of an overall conservative strategy is obviously related to interventional treatment.

– The non-performance of ergometry. This is probably because more unstable patients were involved.

– Positive ergometry results. Since these were observed less frequently in women, this also explains the lesser use of interventional treatment. Female sex was not an independent predictor for the under-utilization of catheterization or revascularization (probably because some of the non-invasive tests were discarded with greater frequency when ischemia was present, and, for another, in some cases it is greater patient age and not patient gender that tends to result in more conservative treatment).

In conclusion, in the context of a chest pain unit and a treatment protocol for unstable ischemic cardiopathy, we have confirmed that there is a different baseline clinical profile between the sexes. The female sex is not related in an independent manner with under-utilization of interventional treatment. Protocolized action and the development of chest pain units may contribute to an adequate stratification of cases and avoid previously observed biases.

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