Influence of Sex on Mortality in Hospitalized Patients With Congestive Heart Failure and Preserved or Depressed Systolic Function

Alfonso Varela Román, Lilian Grigorian Shamagian, Manuel A. Bandín Diéguez, Pedro Rigueiro Veloso, and José R. González-Juanatey

Servicio de Cardiología y Unidad Coronaria, Hospital Clínico Universitario, Santiago de Compostela, A Coruña, Spain.

Introduction and objectives. There is some controversy about the impact of sex on mortality in patients with heart failure. Moreover, little is known about its influence on prognosis in patients with preserved systolic function. The objective of this study was to investigate the influence of sex on survival in patients with heart failure, including subgroups with preserved or depressed left ventricular ejection fraction (LVEF).

Patients and method. The study included 1252 patients (767 male, 61.3%) who were admitted with heart failure to the cardiology department of a tertiary hospital. The median follow-up period was 2.3 years, with the mortality rate rising to 41% after 12 years of follow-up. A LVEF less than 50% was observed in 60.2% of patients. Female patients were older (73.4 ± 10.0 years vs 66.8± 11.9 years; *P*<.001), a higher proportion had preserved systolic function (52.2% vs 31.9%; *P*<.001), and fewer had ischemic cardiopathy (44.1% vs 53.2%; *P*<.001).

Results. In the group as a whole, the influence of sex on prognosis did not reach statistical significance: the hazard ratio in males compared with females was 1.253 (95%CI, 0.978-1.605; *P*=.074). In addition, no influence of sex on survival was observed in subgroups with preserved or depressed systolic function.

Conclusions. In a large cohort, we did not observe any influence of sex on mortality in hospitalized patients with heart failure, either in the group as a whole or in subgroups with preserved or depressed left ventricular systolic function, despite a tendency towards higher mortality in males.

Key words: *Heart failure. Prognosis. Sex.*

Correspondence: Dr. J.R. González-Juanatey.
Servicio de Cardiología. Hospital Clínico Universitario.
Choupana, s/n. 15706 Santiago de Compostela. A Coruña. España.
E-mail: jose.ramon.gonzalez.juanatey@sergas.es

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Influencia del sexo en la mortalidad a largo plazo de pacientes hospitalizados por insuficiencia cardíaca con función sistólica conservada o deprimida

Introducción y objetivos. Hay una relativa controversia sobre el impacto del sexo en la mortalidad de los pacientes con insuficiencia cardíaca y es escasa la información acerca de su influencia en el grupo de pacientes con función sistólica ventricular izquierda conservada. El objetivo es estudiar la influencia del sexo en el pronóstico de la insuficiencia cardíaca, así como en los subgrupos con función sistólica conservada y deprimida.

Pacientes y método. Se incluyó a 1.252 pacientes, 767 varones (61,3%), ingresados con insuficiencia cardíaca en un servicio de cardiología de un hospital terciario. La mediana del seguimiento ha sido de 2,3 años, con una mortalidad total al final de los 12 años de seguimiento de un 41%. El 60,2% presentaba una fracción de eyección < 50%. Las mujeres tuvieron mayor edad (73,4 ± 10,0 frente a 66,8 ± 11,9 años; p < 0,001), mayor proporción de función sistólica conservada (el 52,2 frente al 31,9%; p < 0,001) y menor proporción de cardiopatía isquémica (el 44,1 frente al 53,2%; p < 0,001).

Resultados. La influencia del sexo en el pronóstico no alcanzó significación estadística en el análisis multivariable en el grupo global (varón frente a mujer *hazard ratio* [HR] = 1,253; intervalo de confianza [IC] del 95%, 0,978-1,605; p = 0,074). Tampoco se objetivaron diferencias significativas en la supervivencia entre ambos sexos cuando se analizaron los subgrupos de función sistólica conservada y deprimida.

Conclusiones. En nuestro estudio no observamos influencia significativa del sexo en la mortalidad de los pacientes hospitalizados por insuficiencia cardíaca ni tampoco en los subgrupos de función sistólica conservada y deprimida, a pesar de la tendencia hacia una mayor mortalidad en el grupo de los varones.

Palabras clave: *Insuficiencia cardíaca. Pronóstico. Sexo.*

ABBREVIATIONS

CHF: congestive heart failure.
LVEF: left-ventricular ejection fraction.
PSF: preserved systolic function.
DSF: depressed systolic function.
LVSF: left ventricular systolic function.
ACEI: angiotensin-converting enzyme inhibitor.

INTRODUCTION

Congestive heart failure (CHF) is a major cause of mortality, morbidity, and health expenditure.[1-3] Although several studies have described demographic markers with prognostic value in this condition, only age has shown to be a strong predictor of survival in virtually all of them.[4-7] In contrast, there is some controversy regarding the impact of sex on mortality in patients hospitalized for CHF. In some studies, most of which involve patients with depressed left ventricular systolic function (CHF-DSF), male sex was shown to be an independent predictor of mortality during follow-up,[8-11] whereas in others no differences in survival were found according to this variable.[12,13] In fact, among the patients included in the SOLVD study, mortality in women was significantly higher than in men.[14] Martínez-Sellés et al[15] recently reported that mortality in men with CHF-DSF is significantly higher than in women, with no differences between sexes in the group with CHF and preserved systolic function. Despite these efforts, the current information regarding the influence of sex on the prognosis of patients with CHF is scant and discordant, particularly in the population with preserved left ventricular systolic function (CHF-PSF).

The characteristics of the patients included in the available studies may have played a part in conditioning the results. In some of them only a limited percentage of women are included,[9,10] and this is in line with what is observed in nearly all the clinical trials in CHF. Additionally, many of them offer no information on ventricular function[8] or limit the study only to patients with CHF-DSF.[9,10] Furthermore, differences in the clinical profile, with a higher percentage of ischemic heart disease in men,[16] in the use of drugs with recognized prognostic benefit,[17] and in the quality of the clinical monitoring and follow-up,[18] as well as a potential difference in the natural history of the disease between men and women could justify the differences in the findings obtained.

Our aim was to study the influence of sex (women vs men) on long-term survival in patients hospitalized for CHF, in both the total population with this condition and in the subgroups with CHF-PSF or CHF-DSF.

PATIENTS AND METHOD

Study population

Data were compiled from the medical records of all patients admitted for CHF and discharged from the Cardiology Department of Hospital Clínico Universitario de Santiago de Compostela, Spain, between 1 January 1991 and 31 December 2002. The present analysis includes all patients who underwent an electrocardiogram with assessment of left-ventricular systolic function (LVSF) during the first days after hospital admission. The patients who were not included in the analysis because echocardiography was not available (407 patients) were older (73.0±11.4 vs. 69.2±11.8 years; $P<.001$); no other statistically significant differences with respect to those undergoing echocardiography were observed.

A modification of the Framingham criteria was used to define CHF. Major criteria included nocturnal paroxysmal dyspnea, orthopnea, crepitant rales, jugular vein enlargement, third heart sound, and radiological evidence of pulmonary congestion and cardiomegaly; minor criteria were exertional dyspnea, edema, hepatomegaly, and pleural effusion. A diagnosis of CHF was established when at least 2 of the major criteria, or 1 major and 2 minor criteria, were met. When selection of a patient was based on minor criteria, other possible causes for the signs or symptoms were ruled out.

Systolic function was considered to be preserved when the left-ventricular ejection fraction (LVEF) as determined by echocardiography was ≥50% and depressed when LVEF was <50%.

Data were compiled on the main clinical characteristics, additional examinations performed, treatment prescribed at hospital discharge, and duration of the hospital stay. Among patients admitted more than once for CHF during the 12-year study period, only the first admission with echocardiographic data on LVSF was included in the analysis.

Clinical data were recorded prospectively over the entire period of the study. However, information for the survival analysis was obtained from the hospital's general files and a telephone interview performed in April 2003.

Selection of patients for inclusion in the study and data collection were carried out by staff mem-

bers of the Cardiology Department with extensive experience in CHF.

Etiology

A patient was considered to have ischemic heart disease when one of the following factors was present: diagnosis of ischemic heart disease, prior hospitalization for an acute coronary event (acute myocardial infarction or unstable angina), prior surgical or percutaneous myocardial revascularization, presence of pathological Q-waves on the electrocardiogram (ECG) performed during hospitalization, or coronary angiography showing ≥50% stenosis in at least 1 coronary vessel. The diagnosis of valve disease was established on the basis of clinical criteria and findings from the echocardiographic or cardiac catheterization studies. Most of the patients were not eligible for a surgical procedure because they had advanced heart disease and comorbid conditions. Patients with valvular heart disease amenable to surgical or percutaneous correction were excluded. Hypertension (HT) was established in cases with a prior diagnosis of this condition and in patients requiring antihypertensive drugs for blood pressure control. The diagnosis of idiopathic dilated cardiomyopathy was reserved for patients with depressed systolic function and left ventricular enlargement, and no evidence of the etiologic conditions mentioned above.

Statistical Analysis

Categorical and dichotomous variables were compared with the chi-square or Fisher exact text and expressed as a percentage. Continuous variables were compared with the Student *t* test for between-group comparisons and expressed as the mean ± standard deviation.

Survival curves were obtained with the Kaplan-Meier method in the total patient population and in the CHF-DSF and CHF-PSF subgroups, for women and for men. The log rank test was used to assess differences in survival between the groups.

A univariate analysis was performed to determine which variables had an influence on prognosis in the overall group of patients studied. Lastly, multivariate analysis of variance was done using the Cox proportional hazards model, which simultaneously included all the significant variables from the univariate analysis as well as those considered necessary to adjust the model (HT, sex, and LVSF). In addition, independent multivariate analyses were performed in the subgroups of patients with CHF-PSF and CHF-DSF hospitalized during the years 1991-1996 and 1997-2002, in which sex was adjusted by variables with potential prognostic influence (age, etiology, diabetes mellitus, HT, hyperlipidemia, left bundle branch block, NYHA functional class, and angiotensin converting enzyme inhibitor [ACEI], or beta-blocker treatment prescribed at hospital discharge).

RESULTS

Characteristics of the Sample

The population sample consisted of 1252 patients hospitalized for CHF during the study period, in whom an echocardiographic study with LVSF determination was performed during the hospital stay. Mean age was 69.4±11.7 years (range, 16-98 years) and median hospital stay was 12.0 days. At the time of admittance, 41.7% of the patients were in NYHA functional class IV. Chest radiography showed cardiomegaly in 79.4% of the cases and alveolar edema in 19.4%. The most prevalent arrhythmia was atrial fibrillation, present in 33.9%. Left ventricular systolic function was depressed in 60.2% of the patients. The main clinical characteristics of the sample are shown in Table 1.

TABLE 1. **Clinical Characteristics of 1252 Heart Failure Patients***

Variable	n	%
Age, years	69.4±11.7	
<65	415	33.1
65-74	423	33.8
>75	414	33.1
Sex		
Men	767	61.3
Women	485	38.7
Hospital stay, days	14.4±12.1	
NYHA IV	522	41.7
Crepitant rales	958	76.5
JVE	562	44.9
Hepatomegaly	292	23.3
Third sound	165	13.2
Chest x-ray		
Cardiomegaly	994	79.4
Flow redistribution	808	64.5
Interstitial edema	623	49.8
Alveolar edema	152	12.1
Pleural effusion	243	19.4
Electrocardiogram		
Sinus rhythm	675	53.9
Atrial fibrillation	424	33.9
Pathologic Q-waves	260	20.8
Left bundle branch block	196	15.7
Echocardiogram		
LVEF<50%	754	60.2
LVEF≥50%	498	39.8

*LVEF indicates left ventricular ejection fraction; JVE, jugular vein enlargement; NYHA IV, New York Heart Association functional class IV.

TABLE 2. **Cardiovascular Risk Factors and Etiology***

	n	%
Cardiovascular risk factors		
HT	693	55.4
Hyperlipidemia	419	33.5
Diabetes mellitus	335	26.8
Smoking	390	31.2
Ischemic heart disease	616	49.2
Valvular heart disease	260	20.8
Dilated cardiomyopathy	116	9.2
Others	260	20.8

*HT indicates arterial hypertension.

TABLE 3. **Treatment Prescribed at the Time of Discharge in 1252 Patients With Heart Disease***

Variable	n	%
Digoxin	386	30.8
Diuretics	948	75.7
ACEIs	785	62.7
Spironolactone	162	12.9
Nitrates	545	43.5
Calcium antagonists	237	18.9
Beta-blockers	351	28.0
Antiplatelet agents	710	56.7
Coumarin derivatives	336	26.8

*ACEIs indicates angiotensin converting enzyme inhibitors.

Etiology

The most prevalent cardiovascular risk factor was HT, present in 56% of the patients. The most frequent type of cardiac condition was ischemic heart disease, diagnosed in 48.6% of the cases; 66.8% of these patients also presented concurrent HT. The prevalence of the different risk factors and etiologies analyzed are shown in Table 2.

Treatment

Diuretic treatment, administered in 75.7% of the patients, was the most common drug therapy prescribed at hospital discharge, followed by ACEIs in 62.7% of the cases. Beta-blockers were given in 28% of the patients and digoxin in 30.8%. Pharmacological treatment prescribed at hospital discharge is summarized in Table 3.

Sex

Among the total population studied, 767 patients were men (61.3%) and 485 women (38.7%). Mean age was significantly higher in the group of women (73.4±10.0 vs 66.8±11.9 years; *P*<.001) (Table 4). Differences in the clinical characteristics between the 2 groups were limited to the presence of a third heart sound, jugular venous enlargement, and hepatomegaly, which were more frequent among men. There were significant between-group differences in the LVSF, with a predominance of depressed LVSF in men (68.1%) and preserved LVSF in women (52.2%). Significant differences in the etiology between the groups included a higher percentage of HT and diabetes mellitus in women, whereas smoking was more frequent among men. No significant differences were found for hyperlipidemia. Ischemic disease was the most frequent type of cardiac pathology in both men and women, although its prevalence was higher in men (54.2% vs 44.1%); valvular disease was more predominant in women (28.9% vs 15.6%) and occupied the second place after ischemic disease. Idiopathic dilated cardiomyopathy was more frequent among men (12.0% vs 5.4%), and no significant differences were found in the percentages of the remaining heart diseases.

With respect to the drug treatment given at the time of discharge, there were significant differences in ACEI and beta- blocker prescription, which were more frequent in men than women (65.6% vs 58.1%; *P*=.01, and 30.4% vs 24.3%; *P*=.02, respectively). There were no significant between-group differences relative to the remaining pharmacological groups analyzed. Pharmacological treatment and differences according to sex are shown in Table 5.

Survival

Reliable survival data were available for 1133 patients (90.5%). Median follow-up in these patients was 2.3 years. At completion of follow-up, 668 patients had died (41.0%); one-year, three-year and five-year mortality was 16.0%, 33.3%, and 49.1%, respectively, with a median survival of 5.1±0.4 years (95% confidence interval [CI], 4.3-5.9 years). In the univariate analysis assessing the various clinical variables and cardiovascular risk factors, age (hazard ratio [HR]=1.044; 95% CI, 1.035-1.054; *P*<.001), presence of crepitant rales on pulmonary auscultation (HR=1.326; 95% CI, 1.048-1.677; *P*=.019), jugular vein enlargement (HR=1.218; 95% CI, 1.011-1.467; *P*=.038), radiological alveolar edema (HR=1.779; 95% CI, 1.390-2.277; *P*=.001), diabetes mellitus (HR=1.597; 95% CI, 1.311-1.945; *P*<.001), and ischemic or valvular heart disease (as compared to idiopathic dilated cardiomyopathy and other heart diseases; *P*<.001) were significantly associated with lower survival. Male sex (HR=1.142; 95% CI, 0.950-1.373; *P*=.158) and the remaining variables showed no

TABLE 4. **Clinical and Etiological Differences Between Men and Women, in 1252 Patients With Heart Failure***

Variable	Men, n	(n=767), %	Women, n	(n=485), %	*P*
Age, years	66.8±11.9		73.4±10.0		<.001
Hospital stay, days	14.6±11.6		14.2±13.0		.65
NYHA IV	301	39.1	221	45.6	.06
Crepitant rales	580	75.6	378	77.9	.72
JVE	360	46.9	202	41.6	.04
Hepatomegaly	208	27.1	84	17.3	<.001
Third sound	116	15.1	49	10.1	.01
Chest x-ray					
Cardiomegaly	616	80.3	378	77.9	.45
Flow redistribution	503	65.6	305	62.9	.37
Interstitial edema	370	48.2	253	52.2	.17
Alveolar edema	90	11.7	62	12.8	.59
Pleural effusion	142	18.5	101	20.8	.46
Electrocardiogram					
SR	419	54.6	256	52.8	.56
AF	253	33.0	171	35.3	.43
Q-wave	171	22.3	89	18.4	.07
LBBB	124	16.2	72	14.8	.52
Echocardiogram					<.001
LVEF<50%	522	68.1	232	47.8	
LVEF≥50%	245	31.9	253	52.2	
Cardiovascular risk factors					
HT	388	50.6	305	62.9	<.001
HLP	246	32.1	173	35.7	.20
DM	178	23.2	157	32.4	<.001
Smoking	374	48.8	16	3.3	<.001
Etiology					<.001
Ischemic heart disease	402	53.2	214	44.1	
Valvular heart disease	120	15.6	140	28.9	
Dilated cardiomyopathy	92	12.0	26	5.4	
Others	153	19.9	105	21.6	

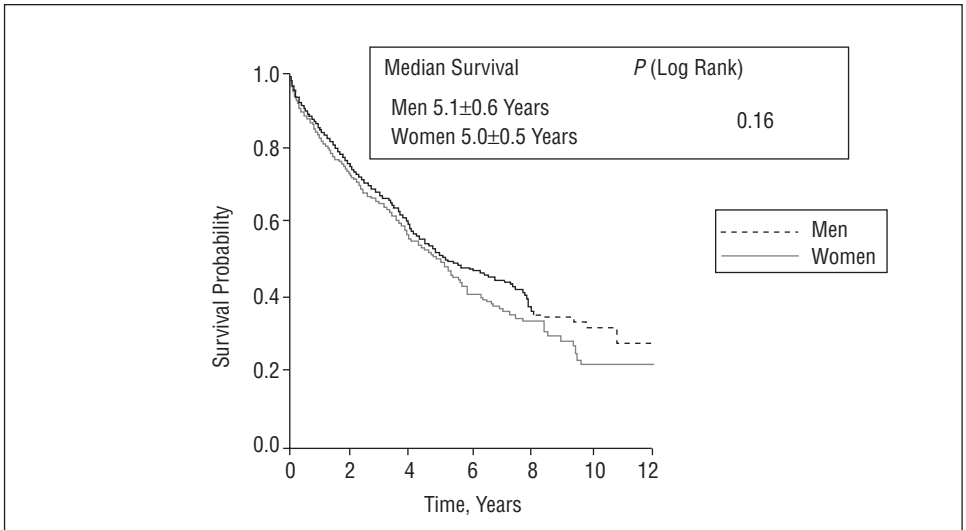
*AF indicates atrial fibrillation; DM, diabetes mellitus; HLP, hyperlipidemia; HT, arterial hypertension; JVE, jugular vein enlargement; LBBB, left bundle branch block, bundle of His; NYHA IV, New York Heart Association functional class IV; SR, sinus rhythm

significant association with the prognosis. When the influence of treatment prescribed at discharge was assessed in the univariate analysis, diuretics (HR=1.360; 95% CI, 1.058-1.748; *P*=.017), digoxin (HR=1.267; 95% CI, 1.023-1.569; *P*=.030) and nitrates (HR=1.422; 95% CI, 1.154-1.741; *P*=.001) were associated with lower survival, whereas ACEI (HR=0.592; 95% CI, 0.480-0.730; *P*<.001), beta-blockers (HR=0.662; 95% CI, 0.499-0.879; *P*=.004) and anticoagulants (HR=0.582; 95% CI,

TABLE 5. **Differences in Pharmacological Treatment Prescribed at the Time of Admission Between Men and Women in 1252 Patients With Heart Failure**

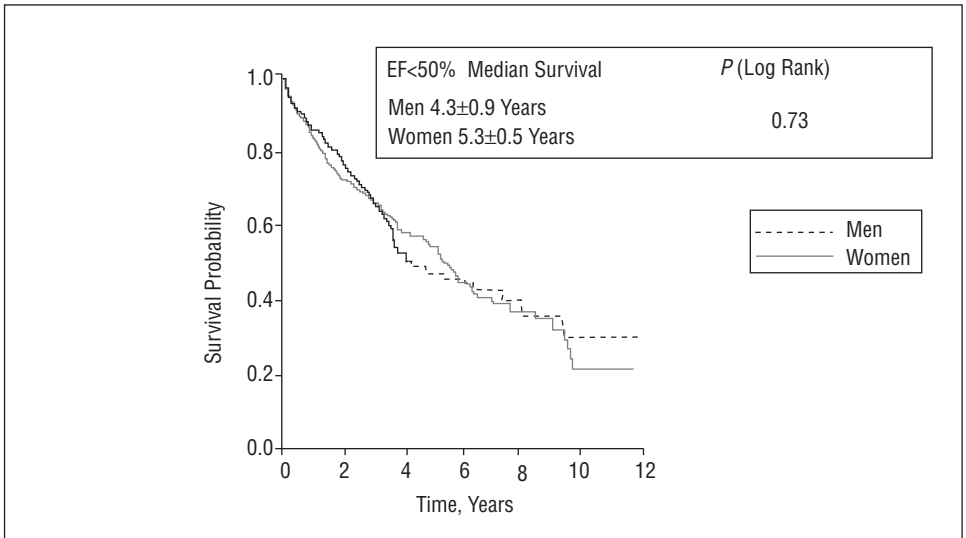
Variable	Men, n	(n=767), %	Women, n	(n=485), %	*P*
Digoxin	237	30.9	149	30.7	.89
Diuretics	574	74.8	374	77.1	.42
ACEIs	503	65.6	282	58.1	.01
Spironolactone	107	13.9	55	11.3	.24
Nitrates	334	43.5	211	43.5	.95
Calcium agonists	133	17.3	104	21.4	.11
Beta-blockers	233	30.4	118	24.3	.02
Antiplatelet agents	444	57.9	266	54.8	.37
Coumarin derivatives	215	28.0	121	24.9	.32

*ACEIs indicates angiotensin-converting enzyme inhibitors.



Men	No. of Patients	682	392	187	109	39	13	0
	Cumulative Events	1	149	216	249	265	269	270
Women	No. of Patients	439	233	116	62	27	11	1
	Cumulative Events	1	108	152	177	186	194	194

Figure 1. Survival curves (Kaplan-Meier) for men and women in the total sample.



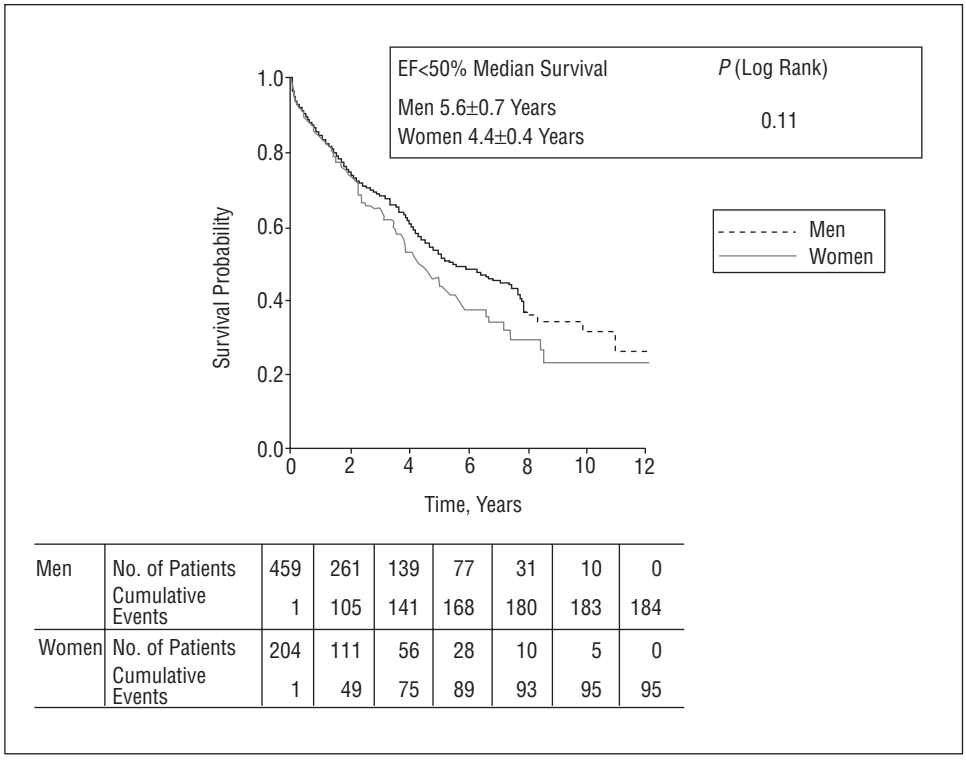
Men	No. of Patients	222	130	47	31	8	4	0
	Cumulative Events	1	44	76	82	85	86	86
Women	No. of Patients	234	122	60	34	16	6	0
	Cumulative Events	1	59	77	88	93	99	99

Figure 2. Survival curves (Kaplan-Meier) for men and women in the group with preserved systolic function (ejection fraction ≥50%). EF indicates ejection fraction.

0.441-0.768; *P*<.001) were associated with a more favorable prognosis.

In the univariate analysis performed in the CHF-PSF and CHF-DSF subgroups, male sex again showed no significant influence on survival (HR=0.950; 95% CI, 0.711-1.269; *P*=.727, and HR=0.817; 95% CI, 0.638-1.047; *P*=.111, respectively).

Similarly, in the Kaplan-Meier analysis performed to determine the influence of sex on the periods 1991-1996 and 1997-2002, no significant differences



Men	No. of Patients	459	261	139	77	31	10	0
	Cumulative Events	1	105	141	168	180	183	184
Women	No. of Patients	204	111	56	28	10	5	0
	Cumulative Events	1	49	75	89	93	95	95

Figure 3. Survival curves (Kaplan-Meier) for men and women in the group with depressed systolic function (ejection fraction <50%).

in survival were found between men and women; median survival was 5.6 years (95% CI, 3.8-7.3) for men and 5.0 years (95% CI, 3.9-6.1) for women (*P*=.221) in the first period and 4.3 years (95% CI, 3.3-5.3) versus at 5.3 years (95% CI, 4.1-6.4), respectively (*P*=.439) in the second period.

Overall survival curves for men and women (Figure 1) showed no significant differences. Nor were there differences between sexes in the individual survival analyses of patients with CHF-PSF (Figure 2) or CHF-DSF (Figure 3).

In the multivariate analysis for the overall group according to Cox's proportional hazards model, which included all the significant clinical variables found in the univariate analysis as well as those considered necessary to adjust the model (HT, sex, and LVSF), sex showed no significant influence on the prognosis. Results of the multivariate analysis to determine the variables with an independent influence on the prognosis are summarized in Table 6. There were no statistically significant findings.

DISCUSSION

The results of our study, which included a large number of patients hospitalized for CHF and a lengthy follow-up, indicate that sex did not significantly influence survival, either in the univariate analysis or after adjustment for other variables with prognostic influence (particularly for age). Moreover, the absence of prognostic value for this factor was also observed in the CHF-PSF or CHF-DSF patient subgroups. It is important to highlight that, despite the lack of significant differences in survival between sexes in the overall population of patients, the HR for mortality in men vs. women was 1.3

TABLE 6. **Multivariate Cox Analysis to Determine the Variables With an Independent Influence on Prognosis in the Overall Group***

Variable	HR	95% CI, HR	*P*
Age	1.041	1.028-1.054	<.001
ACEIs	0.649	0.513-0.822	<.001
Digoxin	1.392	1.059-1.831	.018
DM	1.340	1.030-1.742	.029
Nitrates	1.275	0.994-1.637	.056
Male sex	1.253	0.978-1.605	.074
Coumarin derivatives	0.754	0.546-1.041	.086
Alveolar edema	1.292	0.906-1.844	.158
Diuretics	1.240	0.915-1.680	.166
JVE	1.120	0.883-1.421	.351
Beta-blockers	0.868	0.628-1.201	.392
Ischemic heart disease	0.799	0.470-1.359	.407
HT	0.954	0.740-1.232	.718
Crepitant rales	1.030	0.770-1.378	.843
LVSF	0.993	0.767-1.287	.959

*ACEIs indicates angiotensin converting enzyme inhibitors; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HT, hypertension; LVSF, left ventricular systolic function; JVE, jugular vein enlargement

TABLE 7. **Multivariate Cox Analysis in the Subgroups With Preserved and Depressed LVSF in the Periods 1991-1996 and 1997-2002***,†

Variable	HR	95% CI, HR	*P*
Preserved systolic function			
Male sex	1.260	0.898-1.770	.181
Age	1.055	1.035-1.076	<.001
ACEIs	0.602	0.429-0.847	.004
Depressed systolic function			
Male sex	1.250	0.926-1.687	.144
Age	1.038	1.024-1.051	<.001
Diabetes mellitus	1.652	1.226-2.226	.001
ACEIs	0.638	0.482-0.845	.002
Period 1991-1996			
Male sex	1.161	0.921-1.464	.205
Age	1.044	1.033-1.056	<.001
NYHA class IV	1.701	1.353-2.138	<.001
Period 1997-2002			
Male sex	1.144	0.888-1.473	.298
Age	1.043	1.030-1.057	<.001
Ischemic heart disease	1.405	1.015-1.945	.040
ACEIs	0.619	0.483-0.795	<.001

*ACEIs indicates angiotensin converting enzyme inhibitors; CI, confidence interval; HR, hazard ratio; LVSF, left ventricular systolic function; NYHA, New York Heart Association.
†The variable sex was adjusted by age, etiology, diabetes mellitus, hypertension, hyperlipidemia, left bundle branch block, bundle of His, NYHA functional class, and treatment with ACEIs and beta-blockers. The Table only shows the statistically significant variables and sex.

with a 95% CI at the lower end of virtually 1 (0.98-1.60), a fact indicative of the trend toward lower survival among men.

Nevertheless, the similarity of the survival curves for men and women in the first years, when the number of patients lost to follow up was lower, is quite striking, particularly in the overall analysis, a fact that reinforces the lack of association between patient sex and prognosis in our study.

The series studied included only hospitalized patients. This might limit the applicability of our findings to the overall CHF population, and we cannot rule out that other variables which were not included in the analysis might have had an effect on the results. It should be kept in mind that our series was comprised exclusively of patients admitted to the Cardiology Department of our Hospital, accounting for about 40% of all the hospitalizations for this disease (60% of the patients are admitted to the Internal Medicine Service, and information was not available for them). In addition, changes in the therapeutic approach used during follow-up might have had an influence on the patients' prognosis. Lastly, the loss to follow-up of 9.5% of the patients in the total group is another of the limitations of our study, particularly because the main finding (HR for mortality in men vs women of 1.3 [95% CI, 0.98-1.60]) has a value at the limit of statistical significance.

The characteristics of the patients included in our series are similar to those described in other studies,[4,6,11,15] with a higher percentage of men hospitalized for CHF. The women were older and had a higher prevalence of HT and diabetes mellitus than men. Moreover, in women there were more cases of CHF-PSF, which among other reasons, could be due to the fact that the proportion of patients with ischemic cardiomyopathy (in particular, a history of myocardial infarction) was significantly higher in men. These facts could suggest that the absence of differences in the prognosis between men and women included in our series might be because the women were older and presented CHF-PSF in a higher proportion. Even though age is the main determining factor of mortality in all the studies, one could speculate that a possibly better prognosis in patients with CHF and preserved systolic function would balance the mortality. Nevertheless, we found no significant differences in mortality between the patient groups with CHF-PSF or CHF-DSF and, after adjusting for age, sex still was not a determinant of differences in the prognosis.

Several factors justify the higher percentage of women among the group of patients with CHF-PSF. The larger number of cases of ischemic heart disease in men and HT in women could have exerted a certain influence. It has been described both in animals and humans that women develop a greater degree of concentric hypertrophy in situations of pressure overload as compared to men.[19,20] Furthermore, in men in this situation, the left ventricle is more prone to dilation and progressive deterioration of systolic function.[21] These facts, together with the higher prevalence of ischemic heart disease in men,[16] could explain the differences in the pathophysiologic pattern of CHF in relation to sex (CHF-PSF vs CHF-DSF), at least in patients with CHF secondary to HT.

There is some controversy as to the influence of sex on the prognosis of patients with CHF. Several studies have described a poorer prognosis in men,[8-11] both in the univariate analysis and following adjustment for factors with a potential influence, such as age. Gustafsson et al[11] reported that male sex was an independent predictor of mortality in a large series of hospitalized CHF patients. Although sex did not determine differences in the univariate analysis, after adjusting for other variables, particularly age, male sex was a strong determinant of mortality. The elevated prevalence of clinical ischemic heart disease (57% of women and 65% of men) and the surprisingly small num-

ber of HT cases (26% of women and 21% of men) could determine the differences with respect to our findings. In our setting, the study by Martínez-Sellés et al[15] in a series of 1065 patients hospitalized with CHF yielded similar results for survival between women and men whose LVEF was >30%. Worse prognosis for men in that study was limited to the group with severely depressed LVSF, suggesting that systolic dysfunction is a long-term predictor of mortality in men but not in women with CHF. Several mechanisms might account for the impact of sex on the relationship between LVEF and the prognosis of patients with CHF. Women may possess protective mechanisms against CHF due to systolic dysfunction; differences have been observed between men and women in ventricular remodeling, myocardial ion channel activity, skeletal muscle adaptation, ventricular arrhythmias and neurohormonal activity, as well as the higher incidence of myocyte apoptosis in women with CHF.[22] The differences in survival between men and women in our series did not reach statistical significance in either the CHF-PSF or CHF-DSF group. However, the LVEF value (>50% or <50%) used to classify the patients might have had an effect on the results in the group of patients with systolic dysfunction.

In contrast to reports showing an influence of sex on mortality in CHF patients[8-11] and in line with our data, several studies have observed no significant impact of sex on the prognosis of patients with CHF.[7,12,13] In some of them significance in the univariate analysis was lost after adjusting for other variables. Notably, in the SOLVD series, mortality was higher in women than men.[14] It has been speculated that exclusion of patients with CHF-PSF might have played a part in determining these results; nevertheless, this justification is not consistent with the findings of Martínez-Sellés et al.[15] It has also been suggested that the scant number of women included (in some studies <20% of the sample) might be an obstacle to obtaining significant differences; however, our data do not seem to confirm this hypothesis since the size of our group of women was similar to that of men.

We believe that efforts should be intensified to achieve more effective prevention of CHF through better control of hypertension and ischemic heart disease, and that each individual patient should receive the therapeutic strategy that has been shown to prolong and improve the quality of life in this population. In this respect, less extensive use of ACEI has been described in women with CHF, even though there is no evidence of differences in the efficacy of this treatment according to sex.

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