

Influence of Gender on Long-term Prognosis of Patients With Chronic Heart Failure Seen in Heart Failure Clinics

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ABSTRACT

Background: Controversy exists concerning the influence of gender in the prognosis of patients with heart failure and no evidence is available from specific heart failure clinics.

Hypothesis: Women with ambulatory heart failure are managed differently than men, although their prognosis might be better than men.

Methods and Results: We analyzed the clinical characteristics, complementary test results, treatment, and prognosis in 4720 patients with chronic heart failure seen in 62 specialized clinics forming part of a multicenter registry during a mean follow-up of 40 months. The mean age was 65 ± 12 years and 71% were men. The men were younger than the women and more often had a history of hyperlipidemia and ischemic heart disease. The men had a more advanced heart failure New York Heart Association (NYHA) functional class (III-IV) than the women and a greater frequency of systolic ventricular dysfunction. The men more often received treatment with β -blockers, vasodilators, and antiplatelet aggregators as well as higher mean doses as compared with the women. The overall survival after the follow-up was similar for both genders, although the women had lower rates of survival free of admission for heart failure.

Conclusions: Despite the mortality of women and men with heart failure being similar, the rate of readmission for heart failure is greater in women in specialized heart failure clinics. These results may be associated with the pharmacological treatment differences observed.

Introduction

Heart failure represents one of the greatest public health problems due to its high rates of death and disease, its social and economic impact, and its increasing prevalence in relation to the gradual aging of the population and better control of cardiac diseases causing heart failure, especially ischemic heart disease.¹

Given the greater life expectancy of women in the developed world, the overall impact of heart failure is even greater in this gender. The number of hospital admissions continues to rise in women² compared with men and the total number of deaths from heart failure may even be twice that of men.³ However, despite the important repercussion in women of the prognosis of heart failure, most available scientific evidence regarding the influence of gender on the prognosis of patients with chronic heart failure derives from observational studies and retrospective analyses, and women are known to be underrepresented in clinical trials.⁴ These studies report divergent findings concerning the management and prognosis of patients with chronic heart failure according to gender, mainly attributable to the study characteristics, etiology of heart failure, and the type of population studied.^{5–8} Nevertheless, women with heart

failure tend to have a better survival rate than the men.⁴ Few reports deal with the differences with patients in specialized heart failure clinics or units.

The aim of this study was to determine the influence of gender on the diagnostic and therapeutic management and long-term prognosis of patients with heart failure seen in specific heart failure clinics.

Methods

During the years 2000–2003 the Working Group on Heart Failure, Heart Transplantation and Other Therapeutic Alternatives of the Spanish Society of Cardiology set up a voluntary registry of heart failure units, the BADAPIC registry, which included 62 centers from all over Spain with specific heart failure units or clinics. The only requirement to participate in this registry is the existence of a specific clinic or unit for patients with heart failure and the inclusion of all the patients seen in a common database, agreed by consensus of all the participating centers. This database includes over 100 variables dealing with the main demographic, clinical, and analytical characteristics, as well as functional tests, pharmacological and nonpharmacological therapy, and patient evolution. The

participating centers and researchers are shown in the Appendix.

Characteristics of the Participating Units

Of the 62 hospitals, 14 (22%) are community hospitals and 48 (78%) general hospitals; 21% of the patients were from the community hospitals and 79% from the general hospitals. Only 10 (16%) of the participating hospitals have a heart transplantation program. Although most units are integrated in cardiology services or areas, 8 (13% of the total) depend on an internal medicine service.

Inclusion Criteria and Definition of the Variables

The diagnostic criteria for heart failure and the definition of the terms and variables included in the database were agreed on by all the participating units and drawn up in a common written protocol and in the BADAPIC database. The diagnosis of heart failure was made according to the criteria of the European Society of Cardiology,⁹ after agreement of the participating researchers. The units included the data concerning the first visit to the heart failure clinic by each patient diagnosed with heart failure, as well as the annual follow-up data. The database does not include patients who were diagnosed with heart failure in each hospital but not studied by the heart failure unit or patients who were referred to the units for study and in whom heart failure was excluded. The protocols for the diagnosis and treatment of the patients, as well as the methods of exclusion of other diseases causing symptoms indicative of heart failure, were decided by each unit. The etiology of heart failure was established in each case by the researcher in charge at each center. Although more than 1 etiological cause may have been present in the same patient, the researcher selected the cause considered to be the most important in that particular patient. Valvular disease was considered to be important and causative of heart failure when echocardiography or cardiac catheterization showed the presence of stenosis or at least moderate valvular failure. Hypertension was established as the cause of heart failure when no data suggested ischemic heart disease or other important heart disorders. Idiopathic dilated cardiomyopathy was diagnosed when the left ventricle was dilated and the ejection fraction was below 45%, in the absence of other cardiac disorders. Heart failure with preserved systolic function was diagnosed when the ejection fraction was equal to or higher than 45% and with depressed systolic function when the ejection fraction was below 45% (whatever the etiology). Concerning the complementary tests, and in accordance with the registry protocol, a patient was considered to have had a test when the test was undertaken during the initial visit to the heart failure unit or during the previous 6 months if the researcher in charge considered that no important clinical changes had taken place during the period. In the case of repeat

tests, the result included in the database was that of the last test performed during the specific time period. The data regarding pharmacological treatment are those of the treatment planned after the initial visit.

Follow-up

The frequency of the revisions depended on the clinical judgment of each participating physician, although the follow-up data (changes in treatment and clinical events) were provided annually by each center. The follow-up data analyzed included mortality, admissions for heart failure, acute myocardial infarction, coronary revascularization, valvular surgery, or heart transplant. Analyses were made, according to the methods and tests mentioned in the section on statistical study, of the likelihood of survival, admission due to heart failure, and survival free of important cardiac events; this latter variable referred to the first important cardiac event suffered by a patient. The mean follow-up of all the patients included in the study was 40 ± 12 months.

Statistical Analysis

The descriptive analysis was made using percentages for the qualitative variables and the mean \pm SD for quantitative variables. Comparison of the differences between the various subgroups of patients was made using the χ^2 test for qualitative variables and the Student *t* test for quantitative variables. The probability of survival and events during the follow-up was calculated by the Kaplan-Meier test, using Mantel's log rank test to compare the survival curves between subgroups. The results were analyzed with the statistical program SPSS, Ver 11.0 (Chicago, IL). A test was considered statistically significant if $P < .05$.

Results

Baseline Characteristics

We studied 4720 patients in 62 heart failure units or clinics. The mean age of the patients was 65 ± 12 years; 71% ($n = 3351$) were men and 29% ($n = 1369$) were women. Table 1 shows the epidemiological, clinical, and exploratory characteristics according to gender. The men were younger than the women (64 ± 12 y vs 70 ± 12 y). Fewer men had a history of hypertension and diabetes, but more had hyperlipidemia. A total of 50% of the men had a history of ischemic heart disease compared with 30% of the women. More men had an advanced New York Heart Association (NYHA) functional class (III-IV) than women (53% vs 35%). Table 2 shows the tests undertaken during the initial visit or during the previous 6 months according to gender. No significant differences were found with Doppler echocardiography (90% in men vs 88% in women). Other tests, such as endomyocardial biopsy or electrophysiological studies, were very uncommon.

Table 1. Baseline Characteristics of the Study Patients According to Gender

	Men	Women	<i>P</i>
Age	64 ± 12 y	70 ± 12 y	<.001
Community hospital	17%	23%	<.05
Hypertension	35%	50%	<.001
Hyperlipidemia	42%	34%	NS
Diabetes	29%	39	<.001
Ischemia	50%	30%	<.001
AMI	41%	19%	<.001
Coronary revascularization	20%	9%	<.01
Prior admission HF	69%	72%	NS
NYHA class III-IV	53%	35%	.0002
LVEF (%)	38% ± 17%	47% ± 24%	<.001
% EF <45%	73%	40%	<.001
Sinus rhythm	68%	62%	<.05
Ischemic etiology heart failure	48%	26%	<.001
Etiology hypertension	12%	29%	<.001
Etiology DCM	18%	6%	<.05

Abbreviations: AMI, acute myocardial infarction; DCM, dilated cardiomyopathy; EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction; NS, not significant; NYHA, New York Heart Association.

Table 2. Tests Undergone by the Patients at the Initial Evaluation According to Gender

	Men	Women	<i>P</i>
Echocardiogram	90%	88%	NS
Ergometry	22%	9%	<.05
Radioisotope studies	21%	13%	<.05
Holter	25%	20%	NS
Catheterization	49%	30%	<.01
Known LVEF	97%	93%	NS

Abbreviations: LVEF, left ventricular ejection fraction; NS, not significant.

Pharmacological Therapy

Table 3 shows the pharmacological treatment after the initial visit to the heart failure clinic according to gender. No significant differences were found between the men and women in the prescription of diuretics, digitalic agents, spironolactone, or anticoagulation agents. More

Table 3. Pharmacological Therapy After the Initial Visit According to Gender

	Men	Women	<i>P</i>
Diuretics	85%	90%	NS
Digoxin	48%	49%	NS
ACE inhibitors	82%	70%	<.001
ARA II	27%	18%	<.01
Spironolactone	43%	43%	NS
β-Blockers	75%	62%	<.001
Calcium antagonists	12%	16%	NS
Anticoagulation agents	44%	44%	NS
Antiplatelet aggregating agents	47%	41%	.011

Abbreviations: ACE, angiotensin-converting enzyme; ARA II, angiotensin II receptor antagonists.

Table 4. Mean Dose of the Most Commonly Used Drugs at the End of the Follow-up Period (mg/d) According to Gender

	Men	Women	<i>P</i>
Enalapril	16 ± 11	14 ± 12	<.05
Carvedilol	22 ± 16	19 ± 16	.011
Furosemide	51 ± 21	55 ± 23	NS
Spironolactone	29 ± 22	31 ± 27	NS

Abbreviations: NS, not significant.

men, however, took β-blockers (75% vs 62% of the women, *P*<.001), angiotensin-converting enzyme (ACE) inhibitors (82% vs 70%, *P*<.001), angiotensin II receptor antagonists (ARA-II; 27% vs 18%, *P* = .01), and antiplatelet aggregators (47% vs 41%, *P* = .011). Only slight changes were made during the follow-up period in the percentages of the drugs used, and the pharmacological profile at the end of the study was similar to that shown in Table 3. Table 4 shows the doses at the end of the follow-up period for the most commonly used drugs, expressed in milligrams/day. Of note were the significantly higher mean doses of enalapril and carvedilol in the men (16 ± 11 mg/d of enalapril in the men vs 14 ± 12 mg/d in the women and 22 ± 16 mg/d of carvedilol in the men vs 19 ± 16 mg/d in the women).

Morbidity and Mortality During the Follow-up

Figure 1 shows the overall rates of survival according to gender after a mean follow-up of 40 ± 12 months; the rates were similar for men and women (73% and 70%, respectively, *P* = not significant). Significant differences were found, however, in the overall rates of survival free of readmission

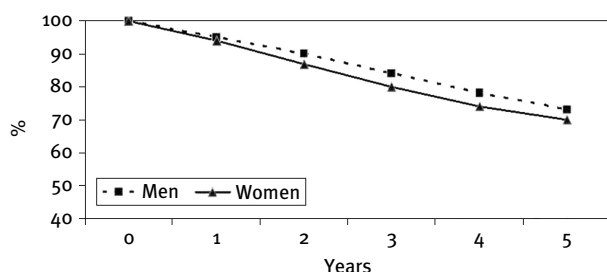


Figure 1. Probability of overall survival during the follow-up period, according to gender.

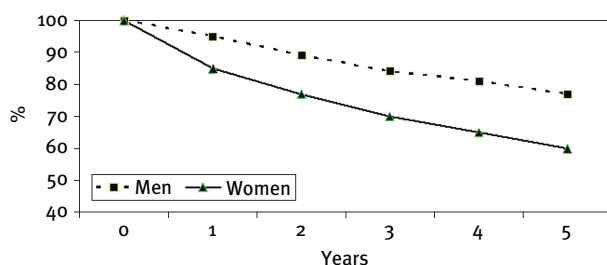


Figure 2. Probability of survival free of readmission for heart failure during the follow-up period, according to gender.

due to heart failure during the follow-up (Figure 2); 77% of the men did not require readmission due to heart failure compared with 60% of the women ($P < .001$). Likewise, the men had a significant reduction in cardiovascular event-free survival (defined as percentage of deaths, admissions due to heart failure, acute myocardial infarction, coronary revascularization, valvular surgery, or heart transplant during the follow-up period), with a likelihood of 62% vs 45% in the women ($P < .001$).

Discussion

This registry provides a true picture of the differences according to gender in the clinical characteristics, diagnostic and therapeutic management, and long-term prognosis of patients with chronic heart failure seen in specific heart failure units. No differences were found in death according to gender, but the rate of readmissions for heart failure and the rate of cardiovascular events were greater among the women. These findings could be associated with the differences noted in pharmacological therapy between the men and women.

The differences in the diagnosis and treatment of women with heart failure have been the subject of debate over recent years.^{6–8,10,11} Most studies have been undertaken in hospitalized patients^{6,10,11} and have found a less favorable clinical profile and the performance of fewer complementary tests, which could be related mainly with a different etiology of heart failure in women. However, these studies lack a

follow-up and scientific knowledge of long-term follow-up derives from post hoc analyses of clinical trials,⁴ in which women are known to be underrepresented.

Most studies examining the differences between men and women in the treatment of patients with heart failure have detected unmistakable differences in the use of various groups of drugs,^{5,7,10,11} especially ACE inhibitors and β -blockers. These differences have been explained by the different etiology of heart failure according to gender and even by the results of a meta-analysis that seem to suggest fewer benefits with certain drug groups,¹² as well as more adverse effects (such as cough) in women who took ACE inhibitors.¹³

Recently, specific clinics for management of patients with heart failure have been developed leading to a better prognosis.¹⁴ These patients, like those in our study, are treated in accordance with recent pharmacological advances; 60% received β -blockers. Of note in our study was the low rate of death and readmission for heart failure after a follow-up of over 3 years (mean, 40 ± 12 mo) compared with the prognosis of patients admitted for heart failure in general hospitals. This improvement in prognosis could be explained by differences in study populations and to the fact that the specific heart failure clinics in our study were managed only by cardiologists.¹⁵

Only one recent study analyzes the prognostic differences in patients currently receiving drugs (60% with β -blockers).⁸ The patients, 116 men and 52 women, were seen in specific heart failure clinics. No differences were detected in this contemporaneous series in 1 year mortality between men and women. Another earlier study⁵ in 6428 ambulatory patients with chronic heart failure involving a similar percentage of women and similar etiology to our study, but with a lower mean age and a low percentage of patients using β -blockers, showed no differences in mortality or hospital readmission for heart failure after 1 year of follow-up.

The main limitation of this study is that it is observational, which may introduce a certain selection bias. Despite this, however, the results from such a high number of patients may help to resolve the controversy over the existence of a gender bias in the management of these patients, as well as the prognostic repercussion associated with patient gender.

Mortality in women with heart failure followed up at specialized clinics was low and similar to that of the men. However, the rate of readmissions for heart failure was greater in the women. These findings could, in part, be explained by the differences detected in the pharmacological therapy of the 2 groups. However, this treatment of the patients seen in specific heart failure clinics was very well adapted to the recommendations in heart failure guidelines.

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Appendix

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Hospital Mutua de Terrassa: Leandro Saenz, Amparo Alvarez. Hospital Sant Pau de Barcelona: Domingo Ruiz Hidalgo, Josep Antón Montiel Dacosta. Hospital Clinic i Provincial de Barcelona: Eulalia Roig Monguell, Alfredo Cupoletti Beange. Hospital Sacrat Cor de Barcelona: Francesc Rossell Abaurrea, Cesar Morcillo Serra. Hospital de Basurto de Bilbao: Nekane Murga Eizagaechaverria, Inmaculada Lluís Serret. Hospital San Pedro de Alcántara de Cáceres: Concepción de la Concepción Palomino, Yolanda Porras Ramos. Hospital General de Castellón: José Luis Diago Torrent, Alex Navarro Bellver. Hospital Reina Sofía de Córdoba: Manuel Anguita Sánchez, Soledad Ojeda Pineda. Hospital de Elche, Alicante: Fernando García de Burgos y de Rico, Alejandro Jordá Torrent. Hospital de Galdakao, Vizcaya: Javier Zumalde Otegui, Alberto Salcedo Arruti.

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