Influence of Gender on the Clinical Characteristics and Prognosis of Patients Hospitalized for Heart Failure

Belén Redondo-Bermejo, Domingo A. Pascual-Figal, José A. Hurtado-Martínez, Pablo Peñafiel-Verdú, Daniel Saura-Espin, Iris P. Garrido-Bravo, Juan Martínez-Sánchez, and Mariano Valdés-Chávarri

Unidad de Insuficiencia Cardiaca, Servicio de Cardiología, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

Background and objectives. The natural history of heart failure (HF) may be different in women due to their clinical characteristics, treatment and prognosis being distinct. Our aim was to describe the differential characteristics of women hospitalized with HF.

Methods. We prospectively studied consecutive patients who were discharged with a diagnosis of HF (n=412). Clinical, laboratory, echocardiographic, and therapeutic variables were recorded at discharge. During follow-up (16 [9] months), all-cause mortality and the need for rehospitalization were recorded.

Results. Compared with men, women (n=157, 38%) were older (75 [12] years vs 71 [18] years, P<0.001), had a higher prevalence of arterial hypertension (71% vs 51%, P<0.001), had more frequently been previously hospitalized for HF (36% vs 25%, P=0.02), had a higher prevalence of HF with a preserved left ventricular ejection fraction (LVEF) (44% vs 21%, P<0.001), had less coronary disease (34% vs 49%, P=0.07), had more hypertensive cardiomyopathy (17% vs 8%, P=0.006), had worse renal function (52 [25] vs 58 [25] mL/min per 1.73m², P=0.02), and had lower hemoglobin levels (12.1 [1.7] vs 12.9 [1.9] g/dL, P<0.001). This clinical profile resulted in less use of coronary angiography (22% vs 37%, P=0.001), antiplatelet drugs (45% vs 62%, P=0.001), and beta-blockers (39% vs 50%, P=0.03). In addition, women received statin treatment less often (31% vs 45%, P=0.003); Nevertheless, mortality (23% vs 18%, P=0.036) and the rehospitalization rate (44% vs 46%, P=0.81) were similar. In women, age (hazard ratio [HR]=1.05; 95% confidence interval [CI] 1.01–1.09; P=0.036) and anemia (HR=2.43; 95% CI, 1.16–5.12; P=0.015) were independent predictors of death.

Conclusions. Women hospitalized for HF had a distinct clinical profile: their LVEF was greater and they more frequently had comorbid conditions. This led to different treatment, though prognosis was similar to that in men.

Key words: Women. Heart failure. Prognosis.

Influencia del sexo en el perfil clínico y pronóstico de la insuficiencia cardíaca tras el alta hospitalaria

Introducción y objetivos. La historia natural de la insuficiencia cardíaca puede ser distinta en mujeres, debido a su diferente perfil clínico, terapéutico y pronóstico. Nuestro objetivo fue definir las características diferenciales de mujeres hospitalizadas por insuficiencia cardíaca.

Métodos. Estudiábamos prospectivamente a los pacientes consecutivos dados de alta con el diagnóstico de insuficiencia cardíaca (n = 412). Al alta, se registraron las variables clínicas, analíticas, ecocardiográficas y terapéuticas. Durante el seguimiento (16 ± 9 meses) se registraron mortalidad y reingreso hospitalario.

Resultados. Respecto a los varones, las mujeres (n = 157; 38%) presentaron: mayor edad (75 ± 12 y 71 ± 18 años; p < 0.001), hipertensión arterial (el 71 y el 51%; p < 0.001) e ingresos previos por insuficiencia cardíaca (el 36 y el 25%; p = 0.02); mayor prevalencia de fracción de eyecisión del ventrículo izquierdo (FEVI) preservada (el 44 y el 21%; p < 0.001); menor prevalencia de cardiopatía isquémica (el 34 y el 49%; p = 0.007) y mayor de hipertensiva (el 17 y el 8%; p = 0.006); peor función renal (52 ± 25 y 58 ± 25 mL/min/1.73 m²; p = 0.002) y menos hemoglobina (12.1 ± 1.7 y 12.9 ± 1.9; p < 0.001). Este perfil clínico conllevó menos coronariografías (el 22 y el 37%; p = 0.001), antiplaquetarios (el 45 y el 62%; p = 0.001) y bloqueadores beta (el 39 y el 50%; p = 0.03); el sexo femenino tiene relación con menos uso de estatinas (el 31 y el 45%; p = 0.003). Sin embargo, su mortalidad (el 23 contra el 18%; p = 0.26) y sus reingresos hospitalarios (el 44 y el 46%; p = 0.81) fueron similares. En mujeres, los predictores independientes de muerte fueron edad (p = 0.036; hazard ratio [HR] = 1.05 [1.01-1.09]) y anemia (p = 0.015; HR = 2.43 [1.16-5.12]).

Conclusiones. Las mujeres hospitalizadas por insuficiencia cardíaca presentan un perfil clínico diferente, con FEVI más preservada y mayores comorbilidades, que conlleva un manejo terapéutico distinto. Su pronóstico es similar al de los varones.

Palabras clave: Mujeres. Insuficiencia cardíaca. Pronóstico.
INTRODUCTION

Heart failure is an important public health problem, a consequence of its high prevalence (it affects some 10% of people over 70 years of age and is responsible for some 80 000 hospitalizations per year in Spain) and elevated comorbidity. It is the primary cause of hospitalization in people aged over 60 years (with an associated mortality of 20%-30%) and its treatment accounts for some 2% of health budget spending in industrialized countries; hospitalization accounts for some 60% of this spending. Improving of our knowledge of its epidemiology, diagnosis, and treatment is therefore vital.

Recent records show the prevalence of heart failure to be similar in men and women. About 1 in 5 people develop heart failure over their lifetime, a risk that is independent of sex according to the Framingham study.

Cardiovascular disease continues to be one of the main causes of death in women, with heart failure the overall third most common. There appear to be sex-related differences with respect to the presentation of this disease, its etiology, its clinical profile, diagnosis, and treatment. Given the smaller numbers of women included in clinical trials, however, our knowledge of the clinical profile of heart failure in women at presentation is reduced. Further, the data available on sex-related prognosis are contradictory and certainly the prognostic markers for use with women patients are less well identified than those for use with men. It should therefore be established whether there are any differences between men and women in terms of the risk of developing heart failure, its clinical presentation, management, course, and prognostic determinants. Strategies can then be developed that might facilitate its prevention, and that can correct and potentiate its treatment.

The aims of the present work were to investigate mortality among women hospitalized due to heart failure, to determine the mid-term prognostic markers associated with the disease, and to study the differences between men and women in terms of risk factors, the clinical presentation of this problem, its diagnostic management and its treatment.

ABBREVIATIONS

GFR: glomerular filtration rate
HR: hazard ratio
LVEF: left ventricular ejection fraction
LVSD: left ventricular systolic dysfunction
NYHA: New York Heart Association

METHODS

Study Population

This observational study involved 412 patients who had been released from the cardiology department of a university, tertiary hospital with a main diagnosis of heart failure. Patients were enrolled consecutively between January 2002 and April 2004. A diagnosis of heart failure was arrived at according to the clinical guidelines in force. On the day of release, all patients’ baseline clinical variables (age, sex, presence of diabetes, hypercholesterolemia or high blood pressure, use of tobacco, New York Heart Association [NYHA] functional class, associated comorbidities, etiology of cardiomyopathy, previous hospitalizations due to heart failure, heart rhythm, the presence of complete bundle branch block, diagnostic tests and treatment during hospitalization, and medication prescribed for use after release) were prospectively recorded.

Heart failure etiology was established as follows: ischaemic cardiomyopathy – when patients had a history of acute coronary syndrome, showed coronary angiographic evidence of coronary disease, or had undergone coronary revascularization; valvular – when at least moderate valve disease was the primary cause; hypertensive – when blood pressure was high, the patient reported episodes of poor control, and where myocardial involvement was clear; and dilated cardiomyopathy – where dilation was clear and where left ventricular systolic dysfunction (LVSD) could not otherwise be explained after a complete cardiological examination. Patients in whom different etiologies were apparent were classified according to the main clinical cause of their heart failure.

Echocardiographic and Blood Test Variables

All patients underwent a complete echocardiographic study using a Sonos 5500 apparatus (Philips, Andover, Massachusetts, USA) once the phase of acute decompensation was over (at least 72 h after admission) and again before release. The variables recorded were those established by current clinical guidelines. The left ventricular ejection fraction (LVEF) was measured using the Simpson biplane method. Left ventricular systolic dysfunction was defined as an LVEF of <45%. Blood was taken before release after an overnight fast; all patients rested for 10 min before blood was drawn. All samples were immediately analyzed. Hemoglobin and hematocrit concentrations were determined using an automated XE-2100 analyzer (Symex, Kobe, Japan). Biochemical determinations were made using a Roche/Hitachi Modular Analyzer (Roche Diagnosis, Manheim, Germany). Anemia was defined according to criteria established by the World Health Organization (WHO): hemoglobin <13 g/dL in men, and <12 g/dL in women.
Kidney function was determined by measuring creatinine and urea concentrations, and the glomerular filtration rate (GFR) calculated using the simplified MDRD formula \(186.3 \times \frac{\text{plasma creatinine}}{\text{age}}^{0.154} \times \frac{1}{\text{weight}^{0.849}} \times \frac{\text{height}^{0.229}}{1.61} \). The correction factor for women was adjusted by multiplying the result by 0.742. Results were validated by the creatinine clearance using the Cockroft-Gault formula. Other analytical variables recorded included the concentrations of plasma sodium, uric acid, C-reactive protein, albumin, total proteins, and fibrinogen. The lipid profile was also determined.

**Events and Follow-up**

The main event recorded was death by any cause, which was classified as non-cardiac, cardiovascular, due to heart failure, or sudden death. Patients who underwent a transplant were censored on the day of surgery. The secondary event recorded was readmission and its causes; these were classified as non-fatal heart failure or as other causes depending on the hospital release data available in the patients medical histories and hospital records.

Follow-up was performed via personal interviews at clinics and hospitals, by telephone, and by the review of clinical histories, hospital records and official death registers. The duration of follow-up was 16 (9) months; 2 patients (0.5%) were lost to follow-up.

**Statistical Analysis**

Normally distributed quantitative variables are expressed as means (standard deviations [SD]). Asymmetrically distributed variables are expressed as medians and interquartile ranges. Categorical variables are presented as frequencies (percentage).

Differences between quartiles for the different clinical variables recorded were determined by analysis of variance and the Kruskal-Wallis test (for continuous variables) or the Pearson \(\chi^2\) test (for categorical variables). Kaplan-Meier analysis was used to investigate event-free survival; log-ranks were used to compare survival curves. Univariate and multivariate analysis of event predictors was performed using the Cox proportional hazards test. Univariate analysis included all the clinical, echocardiographic and analytical variables measured. Those that showed a significance of \(P<.1\) were then included in multivariate analysis.

Hazard ratios (HR) are shown with their 95% confidence intervals (CI). Logistic regression analysis was used to identify the independent predictors associated with being subjected to coronary angiographic study and treatment with antiaggregants, beta-blockers, statins, and oral anticoagulants (including in multivariate analysis those variables with a significance of \(P<.1\) in univariate analysis). All calculations were performed using SPSS v.12.0 software (SPSS Inc, Chicago, Illinois, USA).

**RESULTS**

**Study Population**

Of the 412 consecutive patients enrolled, 157 (38.1%) were women and 255 (61.9%) were men. Tables 1 and 2 show their baseline clinical characteristics. Feminine sex was associated with presentation at an older age. A higher proportion of women patients had high blood pressure and a lower proportion smoked. In addition, proportionately fewer women suffered chronic bronchial disease or peripheral vascular disease. Fewer women patients presented with de novo heart failure (64% compared to 75% of men; \(P=.017\)); the women showed a greater prevalence of prior admission for heart failure. Hypertensive and valvular cardiomyopathy were more common among the women patients, while ischaemic cardiomyopathy was less common. In this context, echocardiography revealed a better preserved systolic function; the LVEF was higher and the end-diastolic volume lower (Table 1 and Figure 1).

Hemoglobin and hematocrit concentrations were lower in women (Table 2), although no significant differences were seen in terms of anemia (as defined by the WHO). All kidney function variables were worse in women.

Compared to men, fewer women underwent a coronary angiographic study at admission (Table 3); this was true for both the sample as a whole (21.6% of women compared to 36.5% of men; \(P=.001\)) and among the subsamples diagnosed with ischaemic cardiomyopathy (40.7% compared to 58.2%; \(P=.035\)). Among those patients who underwent coronary angiography, no significant differences were seen in terms of the numbers of women and men who received revascularization treatment (61.8% and 65.6% respectively; \(P=.835\)). Female sex was not an independent predictor of being subjected to coronary angiography. However, the following factors were predictive: age (HR=0.962; 95% CI, 0.944-0.982; \(P<.001\)), a diagnosis of acute coronary syndrome at admission (HR=5.380; 95% CI, 3.660-7.909; \(P<.001\)), and the presence of diabetes mellitus (HR=1.672; 95% CI, 1.2796; \(P=.05\)). Feminine sex was also significantly associated with a reduced use of antiaggregants, statins, and beta-blockers in treatment. Among those patients with heart failure of ischemic origin (n=176; 54 [30%] women), fewer women again received treatment with antiaggregants (72% compared to 91% of men; \(P=.001\)) or statins (48% compared to 66%; \(P=.03\)), and a trend was seen towards fewer being treated with beta-blockers (46.3% compared to 58.2%; \(P=.14\)). In multivariate analysis, feminine sex was independently associated with a lower probability of receiving statin treatment (HR=0.484; 95% CI, 0.288-0.815; \(P=.006\)), while lower rates of treatment with beta-blockers or antiaggregants were associated with age (HR=0.943; 95% CI, 0.904-0.985; \(P=.008\)) and ischaemic cardiomyopathy (HR=7.352; 95% CI, 2.476-21.826; \(P<.001\)).
Eighty one (19.7%) patients died during follow-up (16 [9] months), with no difference between the proportion of women and men involved (23% and 18% respectively; \( P = .26 \)). Feminine sex was not a predictor of mortality in univariate (HR=1.372; 95% CI, 0.883-2.132; \( P = .160 \)) or multivariate analysis (HR=1.053; 95% CI, 0.720-1.539; \( P = .790 \)). Figure 2 shows the survival curves for the sexes; no differences were apparent (log rank, 0.213). No significant differences were seen between women and men with respect to deaths due to heart failure (50% compared to 49%), sudden death (6.3% compared to 5.4%), other cardiovascular causes (19% compared to 24%), or non-cardiovascular causes (25% compared to 22%) (\( P = .96 \)). A total of 183 patients were readmitted to hospital, with no significant difference between the numbers of women and men involved (44.4% compared to 45.6%; \( P = .815 \)). At 18 months, readmission-free survival was 51% compared to 52% (log rank, 0.89), and
readmissions due to non-fatal heart failure reached 79% and 81% respectively (log rank, 0.725). Figure 3 shows the survival curves with reference to the combination death and/or readmission for any cause (log rank, 0.676).

Prognostic Factors

Cox univariate analysis identified the following as independent predictors of death among the women patients: age (HR=1.056; 95% CI, 1.012-1.102; \( P < .013 \)), anemia (HR=2.929; 95% CI, 1.410-6.086; \( P < .004 \)), and GFR (mL/min/1.73 m\(^2\); HR=0.98; 95% CI, 0.961-0.999; \( P < .042 \)). In multivariate analysis, however, only age (HR=1.046; 95% CI, 1.010-1.093; \( P < .036 \)) and anemia (HR=2.43; 95% CI, 1.161-5.121; \( P < .015 \)) were independent predictors. Figure 4 shows the mortality rate and relative risk of death with respect to the presence of anemia and age above and below the median. In men, age was the only independent predictor of death (HR=1.029; 95% CI, 1.002-1.058; \( P < .035 \)).

DISCUSSION

There were fewer women than men in this sample of patients hospitalized in a cardiology unit because of heart failure. However, these women presented with a higher...
risk clinical profile and more advanced disease than their male counterparts, but showed a better preserved LVEF and had disease of different etiology (more commonly due to high blood pressure and less commonly due to ischemia). The differences in the treatment (with the exception of statin treatment) received by the sexes was a consequence of these different clinical profiles. During follow-up, morbidity/mortality and the need for readmission were similar in both sexes, despite the greater age and more serious risk profile of the women patients. Age and anemia were the main predictors of mortality among women patients.

Earlier reports mention a similar prevalence and incidence of heart failure among men and women, but
in the present work, in which the patient sample came from a cardiology unit, the proportion of women was significantly smaller. This might indicate that a significant proportion of women with heart failure are admitted to other units, which might also determine their undergoing different types of monitoring and their receiving different treatments. This possibility is supported by the fact that women patients are older and have a better preserved systolic function. In the present sample, as in those of other studies, the mean age of the women presenting with heart failure was very high, and clearly much higher than in men presenting for the same reason. In addition, these women presented with different clinical profiles (largely hypertensive cardiomyopathy), had a better preserved systolic function, and were more symptomatic then the men. The reason for these differences may lie in inherent biological characteristics of the female sex that favor a later development of heart failure. Estrogens help protect the myocardium from systolic overload through their vasodilatory effect, the reduction of renin activity, and the attenuation of myocardial fibrosis. In addition, they help protect against apoptosis as a result of myocardial damage. In women, the greater prevalence of hypertension, plus the different response of the left ventricle to pressure that appears with age, favor the development of concentric hypertrophy and diastolic dysfunction, reducing functional capacity and quality of life. After the menopause the protective effect of estrogen disappears and non-treated risk factors become more apparent, making women more vulnerable.

The present women showed more advanced disease, poorer functional capacity, suffered a greater number of readmissions because of heart failure, and greater deterioration of the affected organs than their male counterparts; their kidney function was worse and a greater proportion of women suffered anemia. Anemia was found to be the main independent predictor of disease severity and mortality; this has been reported in other studies. Anemia was not a predictor of death in men. This difference has not been analyzed before, and may indicate women to be more susceptible to hemoglobin deficit and hyperdynamia as a result.

Owing to their worse clinical profiles, the risk of developing symptoms of heart failure after an acute cardiac event would appear to be greater in women. However, the progress of the present women was no worse than that of men during follow-up; no significant differences were seen between men and women with respect to mortality and readmissions (either in general or for non-fatal heart failure). The epidemiological data available suggest that sex differences in the development and prognosis of heart failure are difficult to establish, and that they can be obfuscated by the different etiologies of heart failure associated with each sex. Clearly these differences imply death is the outcome of different mechanisms. The discrepancies in sex-associated mortality reported by different authors may be due to the different profiles of the populations studied.

Several studies have shown different diagnostic tests, such as echocardiography and ergometry, to be less often...
used in women than in men hospitalized because of heart failure.\textsuperscript{4,5,14,34} In the present study, fewer women underwent a coronary angiographic study. Differences were also seen with respect to the treatment prescribed at discharge, with women showing a distinct therapeutic deficit compared to men. These differences in management were due, however, to the different clinical profiles of these groups of patients (the women were older and their disease was less commonly associated with an ischemic etiology) rather than to their sex. Feminine sex was related only to a reduced number of patients receiving statin treatment.

Limitations of the Study

The main limitation of this study is the inclusion of patients with heart failure admitted to a cardiology department; this might have introduced some bias into the selection process. However, the advanced age of the women patients suggests less selection bias than in other studies.

The assessment of kidney function in elderly patients is limited, and controversy exists regarding which formula should be used to calculate the glomerular filtration rate.\textsuperscript{35,36} Finally, this study is exploratory in nature; its findings therefore need to be confirmed in larger cohorts. This would improve our understanding of the differences between men and women with respect to the clinical characteristics of heart failure, the markers of prognosis, and management of the disease.

CONCLUSIONS

Women hospitalized because of heart failure have a different clinical profile to that of men. They are older, more commonly suffer high blood pressure, are more likely to have a history of hospitalization due to heart failure and have poorer functional class scores. In addition, their systolic function is better preserved, the etiology of the disease is more likely to be hypertensive than in men, and less likely to be ischaemic. Although women receive different treatment, this is due to the clinical profiles with which they present rather than a consequence of their sex – except in the case of treatment with statins. Despite their having a more serious risk profile, the long-term prognosis for women with heart failure is similar to that of men. Age and anaemia are independent predictors of death.

REFERENCES


