Cardiovascular Disease in Women (V)

Heart Failure. Are Women Different?

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The clinical syndrome of heart failure is very common in women. In fact, the majority of heart failure patients in the general population are female, in particular elderly women and women with a preserved ejection fraction. There are differences between heart failure in women and men in terms of epidemiology, pathogenesis, treatment response, and quality of care. The incidence is greater in men, but the prevalence at more advanced ages is higher in women. Prognosis seems to be better in women, although the mechanism responsible is not well understood. Clinical trials of heart failure have included fewer women than men, and this has limited our understanding of the efficacy of heart failure treatment in this group of patients.

Key words: *Cardiovascular disease. Heart failure. Woman.*

Insuficiencia cardíaca. ¿Son diferentes las mujeres?

El síndrome clínico de la insuficiencia cardiaca (IC) es muy frecuente en la mujer y, de hecho, la mayor parte de los pacientes con IC en la población general son mujeres, particularmente mujeres de edad avanzada y con fracción de eyección conservada. La IC en la mujer presenta diferencias con respecto a la del varón en algunos aspectos como epidemiología, etiopatogenia, respuesta al tratamiento y calidad de los cuidados. La incidencia es mayor en varones, aunque la prevalencia en edades avanzadas es superior en mujeres. El pronóstico parece ser un poco mejor en mujeres, aunque el mecanismo no es del todo conocido. Los ensayos clínicos de IC han incluido un menor número de mujeres que de varones, lo que ha limitado el conocimiento en cuanto a la eficacia del tratamiento de este grupo de pacientes.

Palabras clave: *Enfermedad cardiovascular. Insuficiencia cardiaca. Mujer.*

HEART FAILURE IN WOMEN

The clinical syndrome of heart failure (HF) has a high prevalence and elevated mortality, even in our era. There are differences in HF between women and men in terms of epidemiology, etiology, risk factors, pathogenesis, treatment response, and prognosis.[1] The potential mechanisms that could cause these observed differences can be classified into 3 main groups[2]: *a)* inherent biological alterations, i.e., gender-related differences in manifestation of the disease, treatment response, and the natural history of the disease; *b)* unmeasured clinical variations, such as confounding factors (e.g., disease severity or comorbidity) which have a different, but unknown frequency between the 2 sexes; and *c)* differences in care, for instance, when clinical guidelines are applied differently according to sex. The implications associated with the type of mechanism are important for both the overall and individualized approach to the problem as well as to define research needs. The present article reviews the available information, in an attempt to clarify the extent to which HF may vary according to sex and which aspects are relevant.

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EPIDEMIOLOGY

Epidemiological studies have suggested that there are important differences between men and women with regard to HF. These differences are not consistently observed between studies and vary according to several factors that include the diagnostic

criteria, setting and era in which the study was performed, and patient characteristics.

Various tools have been used to determine the extent of the problem of HF and its distribution among the various population strata, both in Spain and abroad. Information is available from sources of data collected routinely for other reasons (death registries, hospital discharge records, etc) and other information from specific studies on prevalence or incidence. All of these sources provide valuable information to help define the problem; nevertheless it is important to remember that some sources may have important limitations, which are added to the difficulties inherent to the study of HF.

Studies on the prevalence, and even more so, the incidence of HF are difficult to perform. The available data on HF incidence are generally found in government health surveys[3] or large cohort studies, such as the Framingham study,[4] and have long follow-up periods. Prevalence is obtained from cross-sectional population studies. Because of the above-mentioned difficulties involved in studying a large sample of the general population (necessary to obtain accurate estimates), whenever the reference population (denominator of prevalence) can be identified, medical histories at primary care centers have been used to identify HF cases (numerator). Nevertheless, this approach, although reasonable, tends to underestimate actual prevalence, as not all patients with HF see a physician and therefore, only the most serious or most advanced cases are considered. Other problems of studies that attempt to estimate the extent of the problem include the fact that the studies are sometimes based on self-reports[5] and sometimes on diagnoses at hospital discharge; in the latter case, the information is based on events (hospitalizations) instead of patients and therefore, does not reflect the incidence.

Incidence

No incidence studies are available for Spain. In the U.S., studies on the incidence of HF have yielded somewhat disparate results. According to the Framingham study,[4] the incidence of HF in the U.S. between 1950 and 1999 was higher in men than women. Over time, the incidence remained essentially unchanged in men, but decreased in women. Survival improved in both sexes. In the present study, which included 1075 patients with HF (51% women) the cases were classified according to the date of onset, from 1950 until 1999 (divided into decades). The age-adjusted annual incidence of HF was higher in men than women (for the first decade, 1950-1959, 627 men per 100 000 person-years versus 420 women per 100 000 person-years), with no significant changes over 50 years (in the past decade, age-adjusted annual incidence was 564 per 100 000 in men versus 327 per 100 000 in women). When 1950-1959 was taken as a reference and compared to the following 3 decades, it was found that the incidence of HF in men remained unchanged, whereas in women it dropped from 31% to 40%. Nevertheless, this study only included the white population and there might have been some bias in selecting a more privileged population with better access to preventive and therapeutic measures. The increase in the use of antihypertensive therapy, with the resulting decrease in the prevalence of hypertension, could favorably affect the incidence of heart failure in women even more than men. In men, the higher incidence of HF could be explained by the higher prevalence and incidence of arteriosclerosis and ischemic heart disease (IHD).

The REACH (Resource Utilization Among Congestive Heart Failure) study,[6] also conducted in the U.S., found that age- and sex-adjusted incidence remained stable from 1989 to 1999. The methodology of this study was different, as it used data from a comprehensive health system covering more than 5 million people and included hospitalized HF patients and outpatients of all ages and various ethnic groups; almost 30 000 cases of HF were detected. Survival following the diagnosis of HF increased by 12% in each decade for both sexes.

In a Rochester Epidemiology Project population study conducted in the county of Olmsted, Minnesota[7] between 1979 and 2000, 4537 HF patients (57% women) were identified based on the Framingham criteria and clinical evidence. The incidence of HF was higher in men (378 men per 100 000 vs 289 women per 100 000) and remained stable in both sexes over the 2 decades. Survival improved with time (age-adjusted 5-year survival increased from 43% [1979-1984] to 52% [1996-2000], $P<.001$). Although survival was poorer in men than women, the long-term survival increase was greater in men.

In a historic cohort study comparing the incidence of HF between 2 periods (1970-1974 and 1990-1994) among individuals over 65 years, Barker et al[8] found a 14% increase in the age-adjusted incidence (95% confidence interval [CI], 2-43), that was more noticeable among older patients and men. After 5 years of follow-up, the mortality risk decreased by 33% (95% CI, 14-48) in men and 24% (95% CI, 1-43) in women, after adjusting for age and comorbidity. According to this study, the increase in HF among the elderly population (65 years of age or older) between 1970 and 1990 was associated with an increase in incidence and an improvement in survival; both effects are higher in men.

Prevalence

The prevalence studies also show some differences. In Spain, according to data from the PRICE study

(unpublished data, from a personal communication with M. Anguita), the prevalence of HF in individuals over age 45 is 7% (95% CI, 5.6-8.3) and increases with age, from 1.7% (95% CI, 0.1-3.3) in the age group of 45-54 years to 18.7% (95% CI, 13.9-23.4) among those over age 75, with no overall differences between men and women. In the U.S., in an analysis of the Cardiovascular Health Study[9] of 4842 individuals residing in a community and between 66 and 103 years of age, the prevalence of HF was 8.8% and increased with age, particularly among women. In particular, prevalence rose from 6.6% in women aged 65-69 to 14% in those over age 85. In patients with HF, women were more likely to have a preserved ejection fraction (EF) than men (67% vs 42%, *P*<.01) and among women with HF, elderly patients were more likely to have a preserved EF than younger cohorts.[10] According to data from the REACH study[6] mentioned above, from 1989 to 1999 there was a greater yearly secular increase in the prevalence of HF among women than men (1 per 1000 for women vs 0.9 per 1000 for men, *P*=.001).

Information from other sources, such as cohort studies investigating mortality, also show diverse results with respect to sex. A Danish study[11] analyzed whether survival varied according to sex in 5491 consecutive HF patients (40% women) admitted to 34 hospitals between 1993 and 1996. Differences were found according to sex, with older women less likely to have IHD and more likely to have preserved EF. In contrast, men received angiotensin-converting enzyme inhibitors (ACE inhibitors) more often than women. After a follow-up of 5-8 years, 72% of men and women had died. When adjusted for age, male sex was associated with an increased risk of death (hazard ratio [HR]: 1.25; 95% CI, 1.17-1.34). Therefore, this study showed that among hospitalized patients for HF, male sex was an independent risk factor for long-term mortality. In Spain several longitudinal studies have analyzed prognostic differences according to sex. In a series of 1560 patients (38.7% women) admitted for HF at a third-level referral hospital, Varela Román et al[12] found no sex-related differences in survival after a median follow-up of 2.3 years. In that study, the women were older than the men, and had a higher proportion of preserved EF and a lower percentage of IHD. There were no differences in survival between subgroups with preserved or depressed EF. In another Spanish study[13] of 1065 hospitalized HF patients, survival was better in women among the population with EF less than 30%, but there were no differences between the sexes in the population with preserved EF. When considering HF in patients with preserved EF, however, it should be noted that the prognosis may vary according to the etiology of the heart disease.[14]

In Spain, according to data obtained by Rodríguez-Artalejo[15] using overall information from routine sources (death records), the number of deaths due to HF was higher in women than men. In 2000, HF was the cause of 4% of all deaths among men and 10% of cardiovascular deaths, whereas among women these values were 8% and 18%, respectively. Mortality due to HF decreased gradually in both sexes from 1997 to 2004, and was found to be stabilized in individuals aged 85 years or older. Despite the drop in mortality rates, the total number of deaths for HF increased in women from 1980 to 2000 because of the larger size of the population and progressive ageing. However, these studies have the limitation that HF coding as the cause of death is not entirely accurate (among other aspects, it might not be the primary cause of death and therefore, would not be recorded).

Several factors can affect the epidemiology of HF. Better control of cardiovascular risk factors, such as hypertension (HT), diabetes mellitus (DM), and dyslipidemia, as well as the management of acute coronary syndromes (thrombolysis and angioplasty) prolong patients' lives, but also make it possible for them to develop HF over time and thus, increase the incidence and prevalence of HF. Additionally, risk factor control has prevented HF in many patients, thereby reducing its prevalence and incidence. Population ageing and improvements in medical treatment (because of decreasing mortality) have increased the prevalence. Finally, a deeper understanding of the pathology by physicians and the availability of diagnostic techniques (in particular, noninvasive) that allow an earlier, more accurate diagnosis may have contributed to an increase in the incidence and prevalence, which is actually spurious, as there are no more cases, but rather more of the existing cases are diagnosed.

In summary, there are epidemiological differences related to sex, although they vary according to the study. Incidence appears to be higher among men than women, but some studies find no differences. The trend is for HF incidence to gradually decrease over time in women, but to remain unchanged among men. The prevalence increases with age, with some studies finding no sex-related differences, whereas others have observed that the prevalence is higher in women in the older age groups. Survival appears to be poorer in men; however, the trend over time is for survival to improve in men and for this improvement to be less pronounced in women.

ETIOLOGY

Heart failure has a multifactorial etiology. The most common causes in both sexes are IHD, HT, idiopathic dilated cardiomyopathy, and valve disease; however, the relative role of these diseases may vary according to sex. The combination of HT and IHD is present in

many patients. The population-attributable risk (PAR)[16] is defined as

$$([RR-1]\times P)/([RR-1])\times P+1)\times 100\%$$

where P is the percentage of population with the risk factor and RR, the relative risk in individuals with a risk factor versus individuals without the risk factor. The PAR is a public health measurement, which, assuming the causality of the factor being considered for the disease under study, estimates what percentage of existing disease among the population would be eliminated if this factor were to disappear completely (i.e., what percentage of cases would not develop). It depends not only on the intensity of the relationship between the factor and the disease (relative risk), but also, on how common the factor is among the population (factor prevalence). This measurement estimates the potential impact of certain interventions, but should be viewed with caution because it generally does not consider potential interactions between factors. According to the NHANES I Epidemiologic Follow-up Study,[17] coronary disease was the most common cause of HF among the general population. The PAR in HF stratified by sex showed the following differences: for men, the PAR values for IHD, smoking, HT, low level of education, excess weight, valve disease, and diabetes were 67.9%, 15.5%, 9%, 8.7%, 5.6%, 3.2%, and 3%, respectively, and for women, the respective estimations were 55.9%, 21.5%, 12.1%, 9.5%, 9.6%, 1.8%, and 3.1%. Additionally, physical inactivity was associated with a PAR of 13.2% in women. A noteworthy finding of this study was the considerable contribution of IHD; however, this is not likely to be reproducible in Spain, given the lower prevalence of IHD compared to the U.S.

Hypertension

Women have been found to have a higher risk of HF in association with HT than men. Levy et al[18] observed that age-adjusted risk and other risk factors for HF development in hypertensive patients as compared to normotensive subjects is almost twice as high in men and three times higher in women (much higher estimates than those offered by the NHANES I Follow-up Study mentioned above[17] and that would also affect PAR calculations). In the Framingham Heart Study,[19] the risk of developing HF over one's lifetime was investigated in 3757 men and 4472 women without HF at baseline and followed-up from 1971 to 1996. The overall risk of developing HF was found to be 20% in both sexes and twice that level if HT was also present. When considering only patients who developed HF but had no prior history of acute myocardial infarction (AMI), the risk was 1 of 9 men and 1 of 6 women, suggesting that the risk attributable to HT is high.

Obesity

The ratio between body mass index (BMI) and the incidence of HF was analyzed by Kenchaiah et al[20] in a cohort of 5881 participants (55% women). After a mean follow-up of 14 years, there were 496 cases of HF, and after adjusting for known risk factors, the risk increased by 5% in men and 7% in women for each unit of increased BMI. Obese subjects were twice as likely as patients of normal weight to have heart failure, with the hazard ratio higher in women than men (2.12 vs 1.90).

Diabetes

In a study[21] of 2623 participants without HF or AMI who underwent glucose tolerance testing and left ventricular echocardiographic measurements, ventricular mass and wall thickness were found to be higher when glucose intolerance was higher, with this effect more evident among women than men.

Ischemic Heart Disease

The incidence, prevalence, and contribution of IHD to mortality in the population is lower in women than men; however, the decrease in cardiovascular mortality in the last 20 years in the U.S. is lower among women.[16] In recent years the prevalence of IHD has increased in both sexes, although it is still less frequent in women than men, with a range of 8%-74% in women versus 17%-84% in men, respectively.[16] The Euro Heart Survey of Stable Angina[22] examined the impact of sex on the diagnosis, treatment, and clinical progress of patients with stable angina. A total of 3779 (42% women) patients from 179 European hospitals followed up for 1 year were included. An important adverse bias was found for both diagnostic and therapeutic procedures. Women were less likely to undergo stress testing (odds ratio [OR] =0.81; 95% CI, 0.69-0.95) or coronary angiography (OR=0.59; 95% CI, 0.48-0.72) and were less likely to receive antithrombotic therapy or statins, both at the initial assessment (for similar incidences of hyperlipidemia between sexes) and at 1 year of follow-up, even when the diagnosis of coronary disease had been confirmed. Women with coronary disease underwent revascularization less often than men and, finally, the risk of death or myocardial infarction after 1 year of follow-up was twice as high among women than men in the multivariate analysis (hazard ratio, 2.09; 95% CI, 1.13-3.85), even after adjusting for age, ventricular dysfunction, severity of coronary disease, and diabetes. The extent to which this European study is

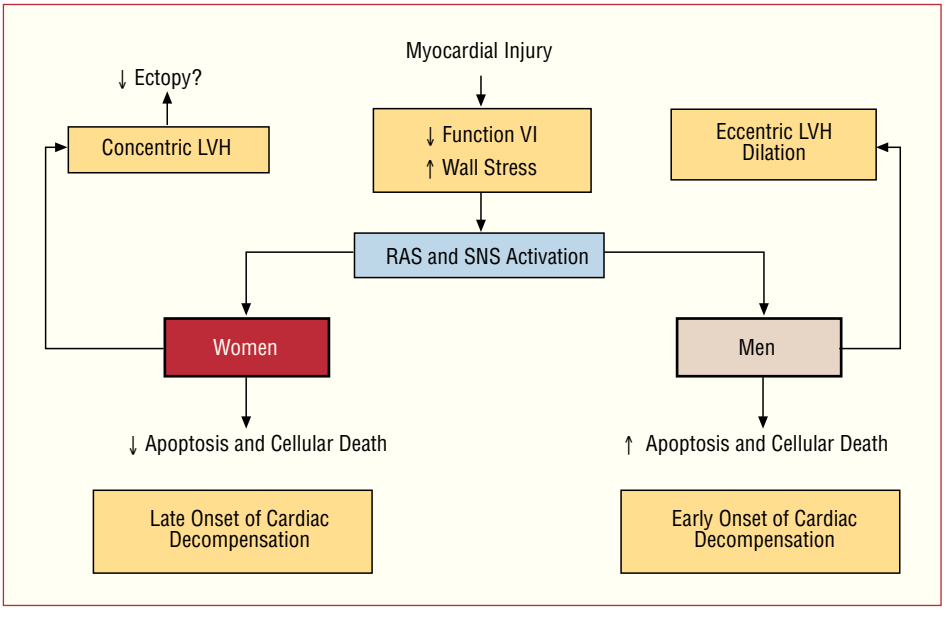

Figure. A theory on how the differences in survival of heart failure (HF) among men and women could be influenced by differences in the pathophysiological mechanisms of HF. RAS indicates renin-angiotensin system; SNS, sympathetic nervous system; LVH, left ventricular hypertrophy; LV, left ventricle. Adapted from Jessup and Piña.[25]

actually representative of European cardiologic practice is unknown, although investigations with fewer patients in the U.S. and the United Kingdom also support this observation.[23] The results of this study suggest routine underutilization of treatments and diagnostic procedures among women as compared with men. This may mean that more advanced disease is present at the time of myocardial infarction because of less rigorous prevention and the bias related to the fact that only women with more advanced coronary disease or more severe symptoms are finally diagnosed and treated.[23] As a result, inadequate treatment of IHD in women in the past may be the cause for a higher incidence and prevalence of HF in elderly women at the present time.

PATHOPHYSIOLOGY

The pathophysiology of HF between men and women appears to be dissimilar. In order to better understand the link between gender and the left ventricular pressure/volume relation, Mendes et al[24] studied the clinical characteristics, left ventricular EF, and end-diastolic volume and pressure in 1081 men and 586 women who had undergone cardiac catheterization. Women had a higher prevalence of HT, diabetes, and HF. At the time the procedure was performed, the women had a higher LVEF (61% vs 56% for men), but a lower prevalence of 3-vessel coronary disease. The end-diastolic volume index was lower in women than men, despite a similar left ventricular end-diastolic pressure. When the patients were stratified according to left ventricular end-diastolic pressure (LVEDP), women had a lower end-diastolic volume than men (74 vs 86 mL/m^2; P=.0001) for a LVEDP greater than or equal to 18 mm Hg. The authors suggested that LV response to pressure overload, as occurs with HT, could be gender-related and that the differing effects of sexual hormones on hypertrophic myocardium may be the cause of a higher incidence of HF with normal EF in women. In normal subjects, left ventricular mass and ventricular size are smaller in women than men; however, with aging, the LV mass increases in women and decreases in men. Moreover, when there is injury and/or work overload, the LV mass becomes hypertrophic to a greater extent in women than among men.[16] Jessup and Piña[25] suggest a possible scheme to explain the pathophysiological response to myocardial injury (Figure) in which women develop greater concentric hypertrophy and have a later clinical presentation.

Heart failure with normal EF is on the rise, its prevalence increases with age, and it is more commonly seen among elderly women.[26]

The BARI study[27] showed that women had better results as compared to men following coronary revascularization. Some studies[28] suggest that sexual hormones affect cardiac function by several mechanisms (Table 1). In particular, estrogens protect against HT, in part because they reduce renin activity, have a vasodilator effect, and reduce fibrosis, whereas testosterone has the opposite effect.

Ventricular arrhythmias are interpreted in relation to dispersion of conduction tissue through nonhomogeneous myocardial tissue that facilitates repetitive ventricular rhythms. The incidence of sudden death among individuals with HF is 6- to 9-fold higher[29] and is more common among men than women, being almost 2-fold in 1 study.[30] Other risk

factors for arrhythmias in HF are alterations in cardiac autonomic control. In a study[31] that examined the variability of heart rate in patients with nonischemic HF, women were found to have attenuation of sympathetic activation and increased vagal activity in comparison with men; it was postulated that this could be an advantage. In a later study[32] with 24-h Holter monitoring among patients admitted for HF decompensation, the same authors observed that the prevalence of complex ventricular extrasystoles and ventricular tachycardia was greater in men than women. Advanced age and male sex were independent risk factors for complex ventricular arrhythmia.[33]

Muscular alterations in relation to HF may vary in magnitude according to sex. Along this line, a study[34] investigated oxygen consumption to assess whether a cardiac rehabilitation program might improve alterations in the heavy-chain isoforms of myosin, enzyme activity, and capillarity (all of them factors that contribute to exercise intolerance in chronic HF). It was observed that at baseline, these alterations were more severe among men, but that after rehabilitation, the improvement was also greater in men than women.

Another study[35] suggested that the heart might be better protected against necrosis and the signs of cellular death by apoptosis among women than men. In the explanted hearts of 7 women and 4 men who underwent heart transplantation, the degree of myocyte necrosis and apoptosis was found to be smaller in the hearts of women as compared to men. In addition, this smaller degree of cellular death was associated with lengthier duration of cardiomyopathy, later onset of decompensation, and a longer interval between HF and transplantation. In another study[36] of 50 explanted hearts from transplantation patients, there were no sex-related remodeling differences in hearts affected by dilated cardiomyopathy, but hearts with ischemic disease showed more favorable remodeling and less hypertrophy in women. Nevertheless, these data are taken from small observational studies and should be viewed with caution.

TABLA 1. **Different Effects of the Sexual Hormones**

Site	Androgens	Estrogens
Heart		
Contractility	↑	↔
Left ventricular mass	↓	↓
Fibrosis	↓	↓
Vessels	Vasoconstriction	Vasodilation
Musculoskeletal	↑	↔
Kidneys		
Glomerulosclerosis	↑	↔
Renin	↑	↔

Taken from Lund and Mancini.[16]

TREATMENT

The capacity to discern whether women respond differently than men to HF treatment is limited by the smaller number of women included in clinical trials on HF. The percentages of women in such trials are indicated in Table 2 and vary between 20% and 40%, with a mean of 30%, including pharmacological[37-54] and nonpharmacological treatments.[51,55]

The study that enrolled the highest proportion of women (40%) was A-HeFT54, which evaluated the effect of a combination of isosorbide dinitrate and hydralazine versus conventional therapy among patients with HF exclusively among the black population. The low enrollment of women is partly due to a higher percentage of HF with preserved EF in women, who are therefore ineligible for clinical trials on HF (largely conducted among patients with HF and depressed EF). Moreover, in many clinical trials the exclusion criteria include advanced age (HF is more prevalent among women), women in the childbearing years, pregnancy, and breastfeeding. The SENIORS[56] study, which assessed the effect of nebivolol in elderly patients (>70 years) with HF, both with preserved and depressed EF (35% of the patients had EF>35%), included 37% of women, a percentage clearly higher than most earlier HF studies.

Details on whether there is any evidence to suggest that the efficacy of drug therapy could vary according to sex are provided below.

Angiotensin-Converting Enzyme Inhibitors

In HF with depressed EF, ACE inhibitors have been shown to reduce hospitalization and improve survival, and in high-risk patients to prevent the development of HF. In CONSENSUS-I,[57] men had a significant, 51% reduction in the HR for 6-month mortality, whereas this value was 6% and nonsignificant in the case of women.

In the SOLVD studies on treatment[38] and prevention,[39] enalapril reduced mortality and hospitalizations in both sexes, although the decrease was lower in women. In the SAVE[48] and TRACE[49] studies, the decrease in the HR of mortality among men was 22% and 26%, whereas among women the reduction was not significant (2% and 10%, respectively). In a meta-analysis[58] of 12 763 patients from five clinical trials that studied the effect of ACE inhibitors on patients with HF or ventricular dysfunction (SAVE, AIRE, TRACE, SOLVD-T, and SOLVD-P), ACE inhibitors were more beneficial than placebo with regard to death and/or rehospitalizations for HF. However, when analyzed according to sex, the OR for death was 0.79 (0.72-0.87) for men versus 0.85 (0.71-1.02) for women. With these data, it could appear that there is less evidence for the benefit of

TABLE 2. **Participation of Women in Clinical Trials on Heart Failure With Depressed Ejection Fraction**

Study	No. of Patients	No. of Women	Women, %
CONSENSUS-I[37]	253	75	30
SOLVD-T[38]	2569	504	23
SOLVD-P[39]	4228	476	31
ELITE-I[40]	722	240	31
ELITE-II[41]	3152	966	30
MERIT-HF[62]	3991	451	23
CIBIS-II[43]	2647	515	20
COPERNICUS[44]	2287	465	28
BEST[45]	2708	593	22
Val HeFT[46]	5010	1002	20
RALES[47]	1663	446	27
SAVE[48]	2231	390	29
TRACE[49]	1749	501	22
CHARM[50]	7599	243	32
SCD HeFT[51]	2521	580	23
DIG[52]	6800	1520	22.4
EPHESUS[53]	6642	1918	28.8
A-HeFT[54]	1050	420	40
CARE-HF[55]	813	216	26.5

ACE inhibitors in women than in men. However, we should consider that many women with HF do not have systolic dysfunction, a requirement for most trials with ACE inhibitors. In addition, women had not been analyzed prospectively and separately. Therefore, if a trial reveals an overall benefit, it would not be appropriate to conclude that women do not benefit, since this subgroup could be limited due to a smaller sample size. In fact, the above meta-analysis showed that the benefit of treatment was independent of sex and age.[58] In the SAVE study (captopril in HF and post-AMI), an analysis with a proportional risk model showed that the benefits of captopril were independent of many variables and, after adjusting for sex, the benefits were still significant.[59]

Angiotensin-II Receptor Blockers (ARBs)

In the ELITE II study (captopril vs losartan), captopril was associated with a nonsignificant decrease in mortality among both sexes.[41] In the Val-HefT study (valsartan plus standard therapy, which often included an ACE inhibitor), women were analyzed separately and showed similar benefit in the combined endpoint of mortality and morbidity than men, although this was not statistically significant.[46]

Beta-Blockers

The U.S. carvedilol study[60] was halted prematurely following a dramatic decrease in mortality among the carvedilol group in both sexes; the HR was even more beneficial for women than for men (0.23; 95% CI, 0.07-0.69 vs 0.41; 95% CI, 0.22-0.8). A meta-analysis of CIBIS I and CIBIS II[61] showed greater benefit of bisoprolol compared to placebo among women versus men (HR=0.61 vs 0.71; $P<.05$ in both cases). In the MERIT-HF study,[62] the 23% of women included was the only subgroup in which no favorable effect on mortality was observed. The women in this study were 37% less likely to die than men, after adjusting for potential confounding factors, such as IHD. However, a post-hoc analysis of the MERIT-HF study,[63] which reassessed the benefit of metoprolol CR/XL in the subgroup of women, found that metoprolol was beneficial in women, including those with severe HF. Metoprolol CR/XL therapy in women led to a 21% decrease in the risk for the primary combined endpoint (total mortality/all-cause hospitalization), a 29% decrease in hospitalizations, and a 42% decrease in hospitalizations for HF decompensation. This same study undertook a joint analysis of three clinical trials on beta-blockers (MERIT-HF, CIBIS-II, and COPERNICUS, that looked at metoprolol CR/CX, bisoprolol and carvedilol, respectively), finding benefit for the total mortality among both men and women. The recommendation of the latest guidelines on HF (AHA/ACC)[64] for underrepresented subgroups in clinical trials is that the benefits demonstrated for the overall population should be assumed.

Digitalis

The DIG[52] study, the largest clinical trial on digoxin in HF, randomized 6800 patients with HF and systolic dysfunction under diuretic and ACE inhibitor therapy to receive digoxin (mean dose, 0.25 mg/day) or placebo. This study showed that at 37 months of follow-up, overall mortality was 35%, with no differences between the placebo group and the digoxin group. There was a 12% decrease in the incidence of pump failure in the digoxin group, which was offset by an increase in the incidence of arrhythmic death. However, digoxin reduced the incidence of hospitalizations for HF and the combined objective of death or hospitalization for HF. A post-hoc analysis of subgroups,[65] in which women and men were analyzed separately, showed that by the end of 5 years, women under digoxin therapy had a higher mortality than those under placebo treatment (33.1% vs 28.9%; absolute difference 4.2%; 95% CI, –0.5 to 8.8), whereas this difference was not observed in men. Furthermore, in the multivariate analysis, digoxin was associated with a statistically significant increase in the risk of death among women (HR of 1.23 vs placebo (95% CI, 1.02-1.47), whereas this risk was not observed among men. Although this was a post-hoc analysis, these findings caused considerable debate and some concern regarding the risk/benefit of using

digoxin among women,[66-68] with the impression that digoxin toxicity could have been the cause. The serum concentration of digoxin was equal to or greater than 2 ng/mL in 2.3% of the men and 3.4% of the women 1 month after randomization.[65] Because the incidence of digoxin-induced arrhythmias rises as serum values of this drug increase (from 10% for 1.7 ng/mL to 50% for 2.5 ng/mL) digoxin toxicity observed in the DIG clinical trial could have been the cause for the excess number of deaths among women, as well as for deaths not attributable to HF. For correct use of digoxin, Rahimtoola[69] recommends serum values between 0.7 and 1.1 ng/mL, with the level not to exceed 1.3 ng/mL. Nevertheless, the recommendations of the latest guidelines on HF of the AHA/ACC[64] are still more restrictive and establish the upper limit for the blood digoxin concentration at 1 ng/mL, given the lack of evidence that higher values are beneficial and may even be harmful.

There are other aspects that suggest gender-related differences in treatment. In the BEST study,[45] bucindolol (nonselective beta-blocker with mild vasodilator action) was shown to offer no benefit over placebo in patients with advanced HF (NYHA III or IV) and reduced EF (<35%). A subsequent analysis of this clinical trial[70] to assess possible gender-related differences found that women (22% of all patients enrolled) had a better survival than the men, although only when the etiology of the heart disease was not ischemic. In this study, the women were younger, more likely to be black, with higher EF, lower prevalence of atrial fibrillation, lower concentration of plasma norepinephrine and lower prevalence of ischemic etiology. Heart failure and ischemic etiology were the 2 factors with the most prognostic value in both sexes; nevertheless, there were gender-related differences in the magnitude of these 2 prognostic predictors, with this greater among women. These observations support the existence of gender-related differences and that the prognostic predictive value of some variables may differ in magnitude according to sex.

A retrospective analysis of the BEST study[71] found hormone replacement therapy in women over age 50 was associated with marked improvement in survival, although this was only observed when the etiology of the HF was nonischemic. This benefit, however, is still not proven in clinical trials.

DIFFERENCES IN CARE

Various studies have found that women receive less optimal care than men. These differences in care could be caused by the limited inclusion of women in clinical trials, meaning that the information in this population is less sound and the clinicians are less convinced of the efficacy of certain measures.

One study[72] assessed the presence of bias according to patient sex and physician specialty on the drug therapy of patients with HF and EF <45%. It was observed that, after adjusting for age, race, coronary disease, and LVEF, there was a higher use of combined therapy (ACE inhibitors, diuretics, vasodilators, and digoxin) by cardiologists among men (OR=2.07; 95% CI, 1.09-3.95) and a greater use of digoxin by non-cardiologist physicians among (OR=5.5; 95% CI, 1.4-22.2). Data from the EuroHeart Women Failure Survey Program,[73] which studied a total of 11 327 discharges or deaths for HF at 115 hospitals in 24 countries of the European Society of Cardiology, found differences in the diagnostic methods according to sex. Thus, LVEF was measured in only 41% of women, but in 57% of men.

The ADHERE registry,[74] which is the largest database available on patients hospitalized for acute decompensated HF and includes more than 100 000 patients admitted for HF at 274 hospitals in the U.S., collected information on patient characteristics, treatments, and results from admission to hospital discharge. Quality indicators[75] were also evaluated to determine the suitability and variability between the various sites to these indicators, in accordance with the 4th Joint Commission on Accreditation of Health Care Organizations (4th JCAHO), and four indicators were identified: *a)* recommendations at discharge, *b)* determination of EF (either at admission or scheduled at discharge), *c)* use of ACE inhibitors in patients with LV dysfunction, and *d)* recommendation to stop smoking. One of the aspects assessed was the impact of sex in terms of clinical history data, clinical characteristics, and recommendations at discharge,[76], and survival.[77] Women comprised 51% of all hospital admissions, were older than the men (74.5 vs 70.1 years), and were more likely to have normal EF (51% vs 28%). Regarding their medical history, women were less likely to have coronary disease (51% vs 64%), smoking (10% vs 17%), and dyslipidemia (32% vs 37%), but more likely to have HT (75% vs 69%). Three of the four JCAHO quality indicators showed sex-related differences, with lower adherence among women. A significantly lower number of women received instructions at discharge regarding diet, weight control, and medications (30.1% vs 32.8%), measurement of EF (81.5% vs 85.6%), and the recommendation of an ACE inhibitor when indicated (72.6% vs 73.9%). Nevertheless, there were no differences in hospital stay or in-hospital mortality between the 2 sexes.

CONCLUSIONS

Although many doctors consider HF to be a primarily male disease because coronary risk factors are more common in males and women are less likely

to be included in clinical trials on HF, most patients with HF in the general population are women, particularly, elderly women with preserved EF. The incidence appears to be higher among men, although the prevalence at advanced ages is greater in women. Although women have a better survival than men, the benefit observed in the improvement of HF survival among men in recent years is less evident in women. Moreover, some studies have identified differences in care, in particular, that it was lower/less stringent/meticulous in women. Our understanding of the pathophysiological mechanisms of HF in both sexes should be improved, and the inclusion of more women in clinical trials should be encouraged.

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