Current perspectives

Heart failure woman: does she make any difference?

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Significant differences between sexes may influence the prevalence, incidence and severity of the heart failure syndrome. These differences may also interfere with treatment and management.

In this review sex differences and similarities have been analyzed focusing on epidemiology, drug therapy and psychological implications.

Pathophysiological differences but also a selection bias are evident; such differences bear an influence on clinical management. Gender differences exist even in the health-related quality of life, depression and coping ability. No studies have been specifically designed to investigate gender differences and the exclusion of elderly persons (mainly women) from large trials may compromise the quality of their care.

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Introduction

Heart failure is a serious health problem that is becoming increasingly common, particularly in the elderly and in women.

Gender-related differences have been reported and they may affect the prevalence, incidence, severity and psychological impact of the heart failure syndrome[1]. These differences may also interfere with treatment and management.

In this review topic sex differences and similarities have been analyzed focusing on epidemiology, drug therapy and psychological implications.

Data obtainable from clinical trials, health registries and personal experiences have been considered in order to elucidate the relevant aspects and their impact on health care in the real world.

Epidemiology

Prevalence: data from the community. Considering comparable age groups (age 65-74 years), the prevalence of heart failure among males varies from 23/1000 (Rochester, 1986[2]) to 53/1000 (Liverpool, 1994[3]) while in women it ranges from 0/1000 (Rochester, 1986[2]) to 45/1000 (Liverpool, 1994[3]).

In summary results show that:
- the prevalence increases with age in both men and women;
- differences between sexes are not constant and the higher prevalence observed among men in some studies[4-8] tends to vanish in the highest age groups;
- the association between age and the prevalence of heart failure is particularly evident in women. In fact, for a population of 4842 males and females aged ≥ 65 years, the prevalence of heart failure increased more than 2-fold from the age group 65-69 years (6.6%) to the age group ≥ 85 years (14%), while the same data for men were 12 and 18.1% in the two age groups respectively[9].

Incidence: data from the community. The incidence of heart failure had been reported to be higher in men than in women in the total population and specifically in every age group in almost all studies conducted in the community between 1962 and nowadays. There are a few exceptions to this constant rule showing, for elderly subjects, incidence rates which are higher for women than for men[4,10,11]. Actually, in most of the studies the gap between the incidence rates of women and men decreases with increasing age. The gender ratio of incidence rates is therefore influenced by the

age distribution of the study population. The dramatic increase in the incidence rates observed in men starting from the seventh decade of life, is delayed in women until the eighth decade of life[12]. The Framingham study enrolled a population aged between 28 and 62 years[13] and only a few patients were very old at the time of the observation period[14]. In a paper showing data on the 30-year follow-up of the Framingham study[15], the incidence rates for the age group 85-94 years are about 54‰ for men and 88‰ for women.

Prevalence and incidence data from hospitals. Studies conducted in hospitals cannot easily provide prevalence and incidence data due to the lack of a population denominator. Most of these studies provide information that is biased by the selection of the specialties observed, usually the most severe cases and younger patients being referred to specialists[16,17]. Furthermore, some studies considered the diagnosis at admission, other studies that at discharge. It is important to note that a patient with a first-time admission is not necessarily a new heart failure, incident case.

Both in Sweden[18] (data from the National Board of Health, at the time of admission for heart failure and cardiomyopathy) and in France[19] (EPICAL, data at the time of admission for severe heart failure to all primary care and referral centers in Lorraine) the incidence rates were more than double in men than in women in each age group, with the exception of the age groups < 30 years in Sweden and 30-40 years in France where similar rates were observed in both genders.

On the contrary, according to the Scottish Morbidity Records the first-time admission rates for heart failure were higher in women than in men, in the entire population > 25 years of age in 1984, 1988 and 1992[20].

In the REACH study[21], the incidence of heart failure admission in Detroit was consistently higher for men than for women from 1989 until 1998 and vice versa, it was higher for women than for men in 1999.

With regard to Italy, the results of the TEMISTOCLE study (Heart Failure Epidemiological Study in Italian people), coordinated by the Association of Italian Hospital Cardiologists (ANMCO) and the Italian Federation of Hospital Internists (FADOI), have been recently presented[22]. The aim of the study was to identify differences in the clinical profile, use of resources, management and outcome in a large population of real world patients with heart failure consecutively admitted for worsening heart failure to cardiology or internal medicine departments. In brief, the study was conducted in a network of 167 cardiology and 250 internal medicine units. Between February 14 and 25, 2000, 2127 consecutive heart failure patients were enrolled. Of these, 1000 (47%) were women. The percentage of female patients who were admitted to medicine units was significantly higher than that of women who were admitted to cardiology units (70 v 30%, $p < 0.0001$). On the whole, it may be said that even in hospital-based studies, the incidence rates increase with age in both genders and are higher in men.

Etiology. Etiology is an even foggier topic than incidence, since it is influenced by differences not only in the methods employed to diagnose heart failure but also in the criteria used to determine the etiological factors (history or objective identification), their definition and classification and the presence of concomitant etiological pathologies which may not be mutually exclusive. It is also difficult to clearly distinguish between etiological and risk factors. The issue relates to the step at which the cascade of the pathophysiological process of heart failure is observed: several risk and etiological factors act in a synergistic and interrelated way in inducing heart failure. Diabetes is a typical condition that is usually described as a risk factor for heart failure. However, it could also be considered, just as hypertension, a true etiological determinant[23]. The identification of the etiological factors in women and men is also affected by the possibly different application of technological diagnostic procedures that result in a better detection of some pathological conditions [i.e. ischemic heart disease (IHD) with coronary angiography].

Both in women and in men, IHD and hypertension are the two most common etiologies of heart failure. IHD is reported to be a more common etiology in men than in women in community and hospital studies, but women who had a myocardial infarction are more likely to develop heart failure than men[24-27]. In studies conducted in the community, hypertension is not constantly more common in women than in men while this datum seems to be more constant in studies conducted in hospitals. Hypertension and IHD are often combined and hypertension could be also considered an etiological factor for IHD itself. It is therefore not definitively clear which one is the most common cause of heart failure. Valvular etiology is constantly more common in women than in men in both studies in the community and in hospitals. In Sweden, no significant differences were found between genders concerning etiology[28].

Quite important changes in the prevalence of preexisting conditions among patients with heart failure and aged 50-89 years have been observed in the Framingham cohort, from 1950 to 1987. The prevalence of IHD increased by 41 and 25% in men and women respectively, that of hypertension decreased by 10 and 27% and that of valvular heart disease decreased by 45 and 32% in men and women respectively[29].

Baseline characteristics. Most data on the baseline characteristics of patients with heart failure derive from studies conducted in hospitals on prevalent cases. The results regarding the differences between genders were not quite concordant. However, according to the net majority of studies, in comparison with men, women are older, have a lower incidence of IHD and present more frequently with hypertension and a preserved left

ventricular ejection fraction. On the whole, diabetes seems to be more common among women than among men, with most studies indicating either a higher prevalence of the disease among women or no difference, while a minority of studies suggests a higher prevalence among men. On the contrary, summarizing published data, women seem to be less prone to atrial fibrillation, a third heart sound, an increased jugular venous pressure and pulmonary congestion but more commonly present with effort dyspnea (without differences in dyspnea at rest) and an increased cardiothoracic ratio and heart rate. As summarized in table I, the clinical observations reported above may be attributed to the several differences occurring between the cardiovascular systems of women and men[30-37].

Mortality and survival. The mortality rates reported in the literature are quite variable: the differences in the studied populations (i.e. in the mean age, sex distribution, inclusion/exclusion criteria), diagnostic criteria and follow-up (considering the in-hospital mortality, the long-term mortality of hospital survivors or the long-term mortality comprehensive of the in-hospital mortality) make the reported results incomparable.

Table I. Gender-related differences in the cardiovascular system: women vs men.

Structural
Smaller body size
Smaller coronary arteries
Smaller muscle fibers
Lower left ventricular volume
Prone to develop concentric hypertrophy and to preserve the systolic function in response to conditions of overload
Better preservation of the myocardial structure with less myocardial loss with aging
Functional
Different physiologic outcome as a consequence of the same genetic alterations
More vasospasm
Higher resting heart rate (probably due to sympathetic hyperactivity)
More heart rate variability (due to higher parasympathetic tone)
Higher resting ejection fraction
Lower left ventricular end-diastolic pressure
Lack of increment in the ejection fraction with exercise
Higher end-diastolic and stroke volumes with exercise
Longer early diastolic left ventricular filling
Electrical
Longer QT interval with a higher risk for torsades de pointes
Pharmacological
Possible different drug metabolism
Different clearance rates
More common drug side effects
Other
Estrogen effect
Possible effect on receptors on the blood vessel walls
Effect on plasma lipoproteins (↑HDL, ↓LDL)

Some general conclusions can anyway be drawn: in both women and men, the mortality increases with age and in incident cases it is particularly high within the first 90 days of the diagnosis[38-42]. Of 26 studies reporting mortality data related to gender in patients with heart failure, 13, including the two largest epidemiological studies in the community, Framingham[43] and NHANES-1[44] (in 9 studies a multivariate analysis was performed), observed a lower mortality among women than among men, 8 did not find any significant difference and in 5 studies there were discordant results depending on the type of analysis performed (i.e. whether the data were adjusted or not adjusted for age or other risk factors)[19,40,45]. In two studies, conducted in hospital on prevalent cases, the survival was better for women with a non-ischemic etiology but it did not differ in ischemic patients[46,47]. Table II[38,43,45-54] shows the odds ratios or the relative risks for death related to gender in patients with heart failure.

It seems that the lack of the protection link to the female gender, that is usually seen in the community and in most published studies, is related to a) the selection of very severe cases[19,50,55]; b) the old age of the population studied[38,51], even in case of an ischemic etiology[56]; c) the conduction of the study in highly specialized structures[31,52]; d) the inclusion of the in-hospital mortality[57,58].

On the basis of the available data, it seems that the short-term mortality (90-day[59] and in-hospital[38,58]) does not differ between women and men. MacIntyre et al.[53] observed a highly significant interaction between age and gender in the 30-day case fatality. Women < 64 years of age had a worse outcome than men at 30 days while women aged ≥ 65 years had a better outcome. No age-gender interaction was observed in the long term, with a better survival for women.

Quite discordant results are seen regarding patients with a preserved or impaired left ventricular ejection fraction. Several issues had been raised by the results of the SOLVD trial, in which the 1-year mortality rate was 22% in women and 17% in men ($p = 0.05$)[60]. As observed by Petrie et al.[61], the worse prognosis reported for women in the SOLVD study is not surprising considering that all patients had a reduced left ventricular ejection fraction, that there was a higher proportion of women with IHD than in the other studies and that women complained of more signs and symptoms and had more severe cardiomegaly than men.

According to the results of the Framingham study, over a 6-year period sudden death occurred in 9% of men and in 4% of women with symptomatic heart failure[29].

Prognostic factors. Only a few studies separately evaluated for each gender the impact of the various prognostic factors in patients with heart failure. Generally, no differences were observed between women and men in the risk evaluation of the common prognostic factors.

Table II. Relative risk and odds ratio for dying in women vs men with heart failure.

Study	Study period	No. patients	Cases	Age (M/F, years)	Follow-up	Notes	RR/OR	95% CI	Adjustment
Scotland[53]	1986-1999	66 547	Prevalent cases Hospital	72/78*	5 years		*0.87*	*0.85-0.89*	Multivariate
Netherlands[45]	1996-1998	181	Prevalent cases Community	77	6 years		*0.53*	*0.34-0.83*	Age
UK[50]	1995-1997	220	Incident cases Community	76	1.5 years		1.14	0.74-1.75	
US[46]	1984-1994	557	Prevalent cases University	52/49	10 years	No IHD	*0.42*	*0.28-0.62*	
						IHD	1.18	0.62-2.2	
US[38]	1994-1995	2445	Prevalent cases Hospital	65	30 days		0.90	0.70-1.20	Age
					1 year		*0.82*	*0.71-0.95*	Age
					1 year		0.90	0.75-1.08	Multivariate
US[48]	1984-1992	231 245	1st admission Medicare	77/79	8 years		*0.72*	*0.71-0.73*	Age, race
Italy[52]	1995-1998	3327	Prevalent cases Hospital, outpatients	62/65	1 year		0.93	0.75-1.14	Multivariate
US[43]	1948-1998	652	Incident cases Community	70	10 years		*0.64*	*0.54-0.77*	Age
Sweden[49]	1987-1995	432	Prevalent cases Hospital		10 years		*0.73*	*0.56-0.94*	Age, cohort
US[51]	1993-1996	1720	1st admission Medicare	78	1 year	LVEF ≤ 40%	1.26	0.81-1.95	
						LVEF > 40%	0.97	0.63-1.50	
US, Europe[47]		471	Prevalent severe cases	64/64	1.5 years		0.68	0.44-1.04	
							0.40	*0.23-0.70*	Multivariate
			FIRST trial			No IHD	*0.32*	*0.16-0.64*	
						IHD	0.61	0.32-1.15	
US[54]	1995	45 894	Prevalent cases Hospital		≈10 days		*0.88*	*0.81-0.91*	Multivariate

CI = confidence interval; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; OR = odds ratio; RR = relative risk. * median age. In italics the results in favor of women.

Differences had been observed in the Framingham study[43], where valvular heart disease was not significantly related to the 5-year mortality in women while it was in men, and both diabetes mellitus and signs of left ventricular hypertrophy at ECG were significantly related to mortality in women but not in men. In a study conducted on hospitalized patients in Scotland[53], atrial fibrillation was significantly related to the long-term (5 years) mortality in women but not in men while a history of cerebrovascular or of respiratory disease was associated with an increased 30-day mortality in men but not in women.

Hospitalization. Admission rates for heart failure are higher in men than in women[61,62] and women tend to be less referred to hospital than men[63]. In comparison with men, women with heart failure tend to be more commonly admitted to geriatric and general medicine departments, where diagnostic procedures are less often performed[64,65] than in cardiology wards[28,65,66]. The length of hospitalization is generally reported to be longer in women than in men[54,62,67-69], with some exceptions[28], even though this datum is partially influenced by the specialty of ward to which the patient is admitted. Some data suggest that diagnostic procedures are less performed in women than in men[28,54,70] and that, after discharge, men are more often referred to a hospital outpatient clinic and women to general practitioners[28]. Other data suggest that there are no gender differences in the use of diagnostic procedures[38] or that the differences are related to the older age of women[71].

Drug therapy

From the trials. The percentage of women enrolled in the main heart failure trials is reported in table III where it may be seen that women are not adequately represented in the therapeutic trials. Many women did not enter the trials because they did not meet the inclusion criterion regarding the lower ejection fraction required. Since heart failure predominates in older women, this under-representation is exacerbated by the exclusion of older participants. Women, having a longer life expectancy, often present multiple health problems that may create additional risks and confound the results of the trial.

However, women do differ from men and some of their characteristics may influence the response to drugs (Table I). They have a smaller heart, smaller coronary arteries and a higher ejection fraction[33,34]. Women are more likely to present with side effects to drugs than men. Drug clearance rates may differ between sexes for a variety of drugs[72] and different dosages may be re-

Table III. Women presentation in the main heart failure clinical trials.

Trials	Year	Gender	
		Women	Men
ACE-inhibitors/AT_2 inhibitors			
SOLVD Prevention Enalapril vs placebo	1992	486 (11.5%)	3802 (88.5%)
SOLVD Treatment Enalapril vs placebo	1990	594 (23%)	1975 (77%)
CONSENSUS Enalapril vs placebo	1992	75 (30%)	178 (70%)
V-HeFT II Enalapril vs hydralazine	1991	0	0
ELITE Losartan vs captopril	1997	240 (33%)	482 (67%)
ELITE II Losartan + captopril vs placebo	2000	966 (30.5%)	2185 (69.5%)
ATLAS Lisinopril vs placebo	1999	648 (20%)	2516 (80%)
RESOLVD Candesartan vs enalapril vs both	1999	127 (15%)	641 (85%)
SPICE Patients intolerant to converting enzyme	2000	2421 (26%)	6789 (26%)
Val-HeFT Valsartan vs placebo	2001	1000 (20%)	4010 (80%)
Beta-blockers			
US Carvedilol Carvedilol	1996	57 (25.5%)	309 (84.5%)
MDC Metoprolol vs placebo	1993	105 (28%)	278 (72%)
CIBIS Bisoprolol vs placebo	1994	112 (17%)	529 (83%)
CIBIS II Bisoprolol vs placebo	1999	515 (29%)	2132 (80%)
PRECISE Carvedilol vs placebo	1996	74 (34%)	204 (66%)
MOCHA Carvedilol vs placebo	1996	109 (24%)	245 (76%)
ANZ Carvedilol Carvedilol vs placebo	1997	Not specified	Not specified
MERIT-HF Metoprolol vs placebo	2000	898 (22.5%)	3093 (77.5%)
RESOLVD Metoprolol vs placebo	2000	76 (18%)	350 (82%)
COPERNICUS Carvedilol vs placebo	2001	452 (20%)	1837 (80%)
BEST Bucindolol vs placebo	2001	593 (22%)	2115 (78%)
Amiodarone and ICD			
GESICA Amiodarone	1994	56 (11%)	460 (89%)
MADIT Implanted defibrillator vs medical	1996	16 (9%)	184 (91%)
DIAMOND Dofetilide vs placebo	1999	404 (26.5%)	1114 (73.5%)
MADIT II Implanted defibrillator vs medical	2002	190 (15.5%)	1042 (84.5%)
Other			
V-HeFT I Prazosin, hydralazine + nitrates vs placebo	1986	0	0
PROMISE Milrinone vs placebo	1991	232 (21.4%)	853 (88.6%)
RADIANCE Digoxin vs placebo	1993	42 (24%)	136 (76%)
PROVED Digoxin withdrawal	1993	75 (85%)	13 (15%)
PRAISE Amlodipine vs placebo	1996	556 (24%)	1750 (76%)
FIRST Epoprostenol vs placebo	1997	123 (24%)	348 (76%)
DIG Digitalis vs placebo	1997	1520 (22.4%)	5280 (77.6%)
PRIME II Ibopamide vs placebo	1997	374 (20%)	1532 (80%)
RALES Spironolactone vs placebo	1999	446 (27%)	1217 (73%)
REMATCH Left ventricular device vs medical	2001	26 (20%)	103 (80%)
MUSTIC Atrio-biventricular pacemaker	2001	17 (25%)	50 (75%)

quired. Specific enzymatic factors involved in drug metabolism respond differently in men and women. In addition, body size and hormones are factors that may account for gender differences. Fluctuating hormone levels and risk factors related to menopause may play a role in heart failure in women[73,74] and may modify the metabolism of various drugs[75].

Reading clinical trials, one may be led to uncertain conclusions on the efficacy of drugs. For instance, some data suggest that ACE-inhibitors may be of less benefit in women than in men. Subgroup analysis of the CONSENSUS study revealed a statistically significant reduction in mortality with enalapril in men but not in women[25]: a 51% reduction in the 6-month mortality was observed for men treated with enalapril, whereas only a 6% reduction was found for women ($p < 0.001$). The SOLVD investigators revealed that enalapril therapy was associated with a greater reduction in mortality, in the rate of first heart failure hospitalization and in the onset of new worsening heart failure in men than in women[76,77]. In the SAVE trial, which included patients with asymptomatic post-infarction left ventricular dysfunction, treatment with captopril was associated with a 2% decrease in the risk of death in women and with a 22% decrease in men. The risk for the combined endpoint consisting of cardiovascular death and morbidity was reduced by 4% in women and by 28% in men[78]. The CONSENSUS II study presents an even more surprising result: 13.5% of women treated with enalapril died compared with 11.2% of women treated with placebo[79].

It should be noted, however, that all these trials included relatively few women and did not have sufficient statistical power to examine gender differences; the lack of a direct comparison with men limits the interpretation of the data[61,80].

An overview of 30 randomized controlled trials of ACE-inhibitor treatment in patients with heart failure identified a total of 5399 men and 1991 women. Significant reductions for mortality and for the combined endpoint of all-cause mortality and hospitalizations for heart failure were observed only in men. Even in this case, however, there was no evidence of a statistical heterogeneity, and the apparent lack of response most likely reflects, once more, the relatively small number of women recruited in each study[81].

In any case, in most trials women were treated with ACE-inhibitors less often than men. Of interest, more adverse events, such as skin rash, taste disorders, gastrointestinal upset and a greater increase in serum creatinine levels have been reported in women than in men[82,83]. In the SPICE trial and in the SOLVD study, in comparison with men, women were more likely to present with side effects due to ACE-inhibitors and to discontinue the treatment (women more often complained of cough and symptomatic hypotension)[84-86].

Similarly, the under-representation of women in beta-blocker trials (< 21%) maintains the uncertainty about the effects of such treatment in women. In CIBIS II, the survival benefit was higher in women, in COPERNICUS it was the same in both sexes, in MERIT-HF where women constituted only 23% of the whole population, the mortality benefit was not demonstrated[87-89]. Again questions arise about the different benefits or the small number of women and about the limited number of events. Pooled mortality data from COPERNICUS, CIBIS II and MERIT-HF (with consequently a larger number of deaths for analysis) showed a comparable and statistically significant survival benefit in women (relative risk 0.69, 95% confidence interval 0.51-0.93) and men (relative risk 0.66, 95% confidence interval 0.58-0.75).

Of interest, the trials seem to suggest an apparent absence of any gender effects on hospitalizations. This aspect may be worthy of future studies.

Although the benefit of additive therapy with spironolactone was reported for NYHA functional class IV patients, the outcomes for the 27% of women participants were not specified[90].

Diuretic-induced hypokalemia has been reported to be more common in women than in men. This gender-specific effect leads to the hypothesis that there would be more arrhythmic consequences related to hypokalemia in women compared to men because of the longer basal QTc intervals[91].

No gender-based differences have been reported in the beneficial responses to or in the side effects of digoxin[91].

In the real world. In daily clinical practice, it has been shown that among hospitalized women and elderly patients with heart failure, the use of efficacious drugs is less than optimal[92]. For example, women appear to receive ACE-inhibitors less often than men, even in the absence of contraindications[92,93].

From the TEMISTOCLE study focusing on the drug differences related to sex, it can be observed that in-hospital females were less frequently treated with inotropic agents, spironolactone, amiodarone, nitrates, statins and antiplatelet agents[22]. However, digoxin was more often prescribed to women during hospitalization and at the time of discharge. At discharge, moreover, ACE-inhibitors, amiodarone and spironolactone were less frequently prescribed to females (Table IV). Thus, even in Italy women receive ACE-inhibitors/angiotensin II receptor antagonists less often than men (79 vs 84%). In the TEMISTOCLE study physicians were asked why they did not prescribe ACE-inhibitors. A clinical reason was given for almost all patients. Among these, the concomitance of aortic stenosis was more frequent in women (in accordance with the older age and with the higher rate of a valvular heart failure etiology), while renal impairment was more common among men (Table V). Of note, while cough limits ACE-inhibitor treatment in more than 30% of heart failure patients, in this study angiotensin II receptor an-

Table IV. Medical treatment during hospital stay and at discharge in women and men.

	In-hospital			Discharged alive		
	Women (n = 1000)	Men (n = 1127)	p	Women (n = 935)	Men (n = 1072)	p
Inotropic agents (%)	15.5	21.1	0.0009	4.9	6.0	NS
ACE-inhibitors (%)	71.0	73.0	NS	71.8	76.0	0.0298
Digoxin (%)	71.1	65.3	0.0042	63.3	58.8	0.0373
Furosemide (%)	95.0	96.1	NS	87.2	86.9	NS
Spironolactone (%)	37.9	43.7	0.0062	35.2	40.3	0.0186
Beta-blockers (%)	9.1	11.6	NS	10.9	13.1	NS
ARB therapy (%)	6.6	6.7	NS	7.0	7.7	NS
Amiodarone (%)	13.0	19.3	< 0.0001	9.1	17.5	< 0.0001
Other antiarrhythmic agents (%)	3.0	2.7	NS	1.4	2.2	NS
Nitrates (%)	49.1	53.9	0.0283	43.9	47	NS
Other vasodilators (%)	4.9	3.8	NS	4.4	3.4	NS
Calcium channel blockers (%)	16.4	16.8	NS	14.8	16.0	NS
Statins (%)	4.1	6.3	0.0234	4.6	6.6	NS
Oral anticoagulants (%)	27.8	28.2	NS	23.5	24.7	NS
Antiplatelet agents (%)	36.1	41.4	0.0117	38.6	41.8	NS

ARB = angiotensin-receptor blocker. Data from the TEMISTOCLE study[22].

Table V. Reasons why ACE-inhibitors were not prescribed to women and men admitted in medicine and cardiology departments.

	Women (n = 935)			Men (n = 1072)		
	Medicine (n = 697, 69.7%)	Cardiology (n = 303, 30.3%)	p	Medicine (n = 641, 56.9%)	Cardiology (n = 486, 43.1%)	p
Reason specified (%)	94.7	100	0.022	94.8	100	0.001
Renal artery stenosis (%)	0.0	1.1	NS	2.2	0.0	NS
Aortic valve stenosis (%)	5.3	10.5	NS	0.0	2.5	NS
Skin rush (%)	1.8	1.1	NS	0.7	0.8	NS
Dizziness (%)	5.9	2.1	NS	3.0	4.1	NS
Renal failure (%)	10.7	13.7	NS	17	26.2	NS
Neutropenia (%)	0.0	0.0	NS	0.0	0.8	NS
Hypotension (%)	13.6	15.8	NS	8.2	19.7	0.0072
Cough (%)	33.1	30.5	NS	34.8	31.2	NS
ARB therapy (%)	9.5	4.2	NS	10.4	9.0	NS
Other (%)	23.1	27.4	NS	25.9	17.2	NS

ARB = angiotensin-receptor blocker. Data from the TEMISTOCLE study[22].

tagonists were, regardless of gender, prescribed to less than 10%. When cardiologist and internal medicine departments were compared, no significant difference in the reasons limiting ACE-inhibitor prescription was evident in female patients.

The reasons why amiodarone and spironolactone are less prescribed to women are less clear. At entry atrial fibrillation was more frequent among women, but no difference in atrial fibrillation procedures or in the percentage of atrial fibrillation at discharge was evident. For both males and females, the severity of symptoms at entry was similar.

Beta-blockers were not routinely prescribed, not even at discharge. However, no gender-related difference in the rate of prescription was noted. Comparing women and men, hypotension and chronic obstructive pulmonary disease were the most frequent limits to beta-blocker therapy in men, while older age and the absence of left ventricular systolic dysfunction were the main reasons why beta-blockers were prescribed more often to women than men (Table VI). If provider-differences are highlighted, one may observe that diabetes and older age more significantly limited the internist in prescribing women a beta-blockers. Hypotension limited more the cardiologist, who treated more severe heart failure females.

Worthy of notice is the fact that the rate of prescription of oral anticoagulants did not differ between sexes, even if atrial fibrillation was more frequent in females and although a greater risk of thrombotic events in women in sinus rhythm (2.4 vs 1.8%, from SOLVD trials), proportional to the decline in left ventricular dys-

Table VI. Reasons why beta-blockers were not prescribed to women and men admitted in medicine and cardiology departments.

	Women (n = 935)			Men (n = 1072)		
	Medicine (n = 697, 69.7%)	Cardiology (n = 303, 30.3%)	p	Medicine (n = 641, 56.9%)	Cardiology (n = 486, 43.1%)	p
Reason specified (%)	100	100	NS	100	100	NS
Bradycardia (%)	2.4	4.2	NS	2.7	7.0	0.0007
Hypotension (%)	4.4	8.4	0.0306	4.5	14.4	< 0.0001
COPD (%)	30.0	33.4	NS	52.7	37.2	< 0.0001
Diabetes (%)	7.2	3.4	0.034	7.0	3.7	0.033
PAD (%)	1.0	0.8	NS	2.3	1.1	NS
NYHA IV (%)	13.1	16.7	NS	11.3	16.5	0.0234
Older age (%)	51.5	32.6	< 0.0001	28.4	17.3	< 0.0001
Not indicated (%)	2.5	4.2	NS	0.5	2.1	0.0276
Other (%)	10.9	17.2	0.0150	12.0	20.7	0.0015

COPD = chronic obstructive pulmonary disease; PAD = peripheral artery disease. Data from the TEMISTOCLE study[22].

function decline has been reported[94]. Among the reasons of non-prescription, again older age affects women more significantly than men (Table VII).

Psychological implications

So far, not much attention has been paid to the gender differences in the psychological responses to heart failure. Only few studies are available, often enrolling small samples and using different assessment procedures, so that results can be hardly compared.

In a general perspective, women with heart failure seem to complain of more psychological distress, in terms of depression, quality of life or satisfaction with physical functioning.

In a prospective study on the gender differences in patients with congestive heart failure, Chin and Goldman[95] found that at 1-year follow-up patients' quality of life improved from admission, but was generally low, particularly in the physical dimensions in women. Furthermore, women rated the quality of their inpatient and outpatient care lower than men. The authors suggest that these results could be related to the women's reported need of more help at home, and that in order to improve the health-related quality of life, women's special needs should be identified and managed through home nursing assistance.

These suggestions found further confirmation in a more recent study conducted on a very large sample of patients with heart failure by Riedinger et al.[96] within the SOLVD trials. In this study it clearly emerged that the lower quality of life of women was due to the worse physical functioning, in terms of the ability to perform the so-called "intermediate" activities such as shopping and housekeeping. Probably related to these impairments, is the reduction in social activity. Together, these two factors lower the total life satisfaction. Interestingly, women's emotional distress (defined in terms of anxiety and depression) did not differ from that of men.

Preliminary unpublished data of a study on female patients (n = 44) enrolled in the Heart Failure Unit of the Scientific Institute of Montescano by means of SF

Table VII. Reasons why anticoagulants were not prescribed to women and men admitted in medicine and cardiology departments.

	Women (n = 935)			Men (n = 1072)		
	Medicine (n = 697, 69.7%)	Cardiology (n = 303, 30.3%)	p	Medicine (n = 641, 56.9%)	Cardiology (n = 486, 43.1%)	p
Reason specified (%)	100	100	NS	100	100	NS
Not indicated (%)	45.1	55.2	0.0185	46.6	59.6	0.0003
History of cerebral bleeding (%)	0.4	1.6	NS	0.2	0.3	NS
History of gastrointestinal bleeding (%)	3.8	4.4	NS	3.0	3.9	NS
Poor compliance (%)	15.0	15.9	NS	20.1	17.5	NS
Hypertension (%)	1.7	0.6	NS	2.6	1.0	NS
Peptic ulcer (%)	1.5	0.0	NS	4.0	1.9	NS
Bleeding diathesis (%)	2.1	0.6	NS	2.0	1.9	NS
Older age (%)	38.2	25.1	0.0014	21.1	12.0	0.001
Other (%)	9.2	13.1	NS	10.9	9.4	NS

Data from the TEMISTOCLE study[22].

36, confirms the lower functional and health statuses of patients compared to age-matched healthy subjects: the differences were found to be statistically significant in all the dimensions.

The study by Murberg et al.[97] reaches the same conclusions with regard to the fact that the limitations in physical activity are more pronounced in women than in men. However, in contrast to Riedinger et al.[96], Murberg et al. found a higher level of depression in women than in men, although depression is explained by the limitations in physical activity only in men, and not in women. This could be related to underlying social cognitive factors: men perceive their symptoms as more psychologically invasive than women, since among men a positive well-being depends more on the strenuous activities they are able to perform.

The nature of depression in heart failure women has not yet been completely understood. In the experience of the heart failure unit of Montescano, female heart failure patients were found to be more depressed and more neurotic than male patients (Fig. 1). On the other hand, no differences emerged between female patients and healthy subjects, although there was a trend in this direction. Trait anxiety scores did not differ. Both women and men were in NYHA functional class II or III, so that results could be considered independent of functional capacity. In heart failure as well as in other chronic illnesses and in healthy samples[98-101] higher scores of depression are more frequent among women than among men. In a recent review[102] the female preponderance in depression was called "the big fact". It has not yet received a complete explanation, although several models and theories are now under examination. Anyway, nowadays it is widely held that depression should always be assessed together with the coping abilities. The latter play a fundamental mediating role between stressful situations and outcomes. Gender differences do however exist, making sense of some clinical observations made in daily clinical practice. For example, men manifest more avoidant and women more vigilant coping[103]: this might explain why men report less distress. On the other hand, women pay more attention to their physical well-being, thus increasing the likelihood of preventing serious illness.

The implications of gender differences in coping with chronic illnesses deserve more attention in future, since coping is an emerging issue in the study of the adaptive mechanisms which are involved in dealing with the stressors stemming from severe health threats. Coping refers to a complex process that involves personality characteristics, personal relationships and situational parameters. Perceived supportive relationships undoubtedly play a fundamental role in protecting patients from the illness-related burden. The absence of emotional support was found to be a strong independent predictor of the occurrence of fatal and non-fatal cardiovascular events in elderly heart failure female patients[104].

Coyne et al.[105] demonstrated that heart failure patients with a higher marital quality live longer than patients with a low marital quality. The association between marital functioning and survival was found to be stronger for females than for males. It is necessary that these results be fully explained. It can be argued that supportive relatives or spouses can make it easier for the patient to follow the complex prescription regimens. All the same, the relationship between patient compliance, social support and the medical outcome is still puzzling clinicians and researchers.

On the whole, these studies seem to suggest that women and men adopt different criteria to rate the burden of their heart failure and the consequent physical limitations. They also react differently to illness-related stress and activate different coping strategies.

Whilst awaiting specific trials, some suggestions deriving from small size, qualitative studies deserve to be taken into account. One of them[106] analyzed how female

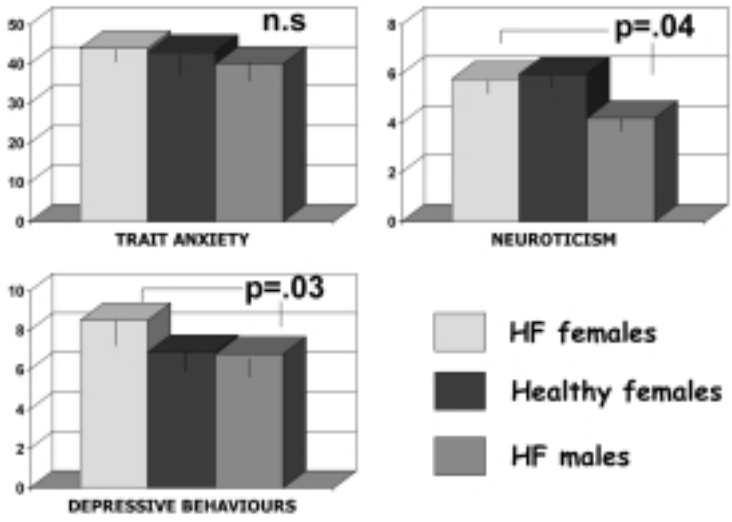

Figure 1. *Comparison among some psychological characteristics of heart failure (HF) women, healthy female subjects and HF men.*

patients with heart failure conceive their life situation. Five dimensions emerged: feeling content, feeling a sense of support, feeling a sense of limitation, feeling anxiety, and feeling powerless. Results could be considered a step towards the comprehension of the reasons why social support is so protective in female patients' life.

In spite of these difficulties, and confirming the need of always assessing problems and resources together, women ascribe positive meanings to their heart failure (illness as a challenge; illness as a value) more often than men. One woman stated: "It is a challenge, but we all know what is best for us. It is sometimes hard for us to understand. We need to struggle to find an inner meaning in all our trials and tribulations. I know that things will never be the same in my life again and I have accepted that. We can only make the best of what we have left in life to live"[107].

Conclusions

If heart failure is a disease of the elderly, this is particularly true for women. The cardiovascular system of women is different to that of men in terms of anatomy, physiology and aging; this is likely to be the same also for pathology. Such differences may also contribute to the reduced responsiveness or tolerance to treatments.

Data on etiology and hospitalization suggest that some selection bias occurs in diagnosing heart failure in women, who are likely to be referred to less "invasive" specialties (i.e. internal medicine and geriatrics) when they are not very severe cases.

This selection bias results in a possible under-treatment of women with heart failure (confirmed in the Italian scenario), and also undermines the validity of the available results on mortality, as no studies have been specifically designed to investigate gender differences. Most of the published data on heart failure, especially those from the community, suggest a better survival in women than in men but this advantage vanishes if the analysis is performed on specific groups of patients: ischemic, very severe and very old cases.

Gender differences also exist in terms of the psychological impact of the disease: women perceive a lower and more severe health-related quality of life than men. Besides, they activate different coping strategies.

Finally, in view of the fact that in heart failure sex does matter, data are required to tailor comprehensive management regimens for women. The exclusion of elderly persons (mainly women) from large trials may compromise the quality of their care.

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