REVIEW

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Heart failure in women is different than in men; should treatment be different?

ABSTRACT

Women with heart failure differ from their male counterparts in a number of ways, including etiology, pattern of cardiac remodeling, and prognosis. They may even respond differently to medical therapy. But until prospective, sex-specific studies show that we should do otherwise, we recommend that women with heart failure be treated the same as men, according to established guidelines.

KEY POINTS

Women tend to develop heart failure at an older age and with better left ventricular systolic function compared with men.

Women are more likely than men to have hypertension and diabetes as underlying risk factors for heart failure and are less likely to have coronary artery disease. However, when they have coronary artery disease, it is a strong risk factor for the development of heart failure.

The morbidity associated with heart failure in women is significant, but the prognosis is better than in men, since women with heart failure generally survive longer.

Current guidelines for heart failure therapy are not sex-specific, since there are no large, prospective, randomized, blinded, sex-specific heart failure therapeutic trials.

RIGHT NOW, WE KNOW more about how heart failure is different in women than whether it should be treated differently.

Studies of heart failure treatment have included mostly men, and the results have been generalized to women even though there are pharmacologic and pathophysiologic differences between the sexes. In fact, most of our current knowledge about treating heart failure in women is based on post hoc analyses. Until prospective sex-specific studies are performed, however, we recommend following current guidelines and treating women with heart failure the same as we treat men.

WOMEN DEVELOP HEART FAILURE LATER

Heart failure affects nearly 5 million people in the United States, and more than 50% of them are women.[1] Compared with men, women tend to develop heart failure at an older age[1] and with better left ventricular systolic function.[2] Heart failure with preserved left ventricular function is also more common in women.[3,4]

RISK FACTORS ARE SIMILAR, BUT RELATIVE RISKS ARE DIFFERENT

The risk factors for heart failure are similar in women and men, but the relative risks are different. Below is a discussion of the risk factors for heart failure from the perspective of women, and a brief discussion of peripartum cardiomyopathy.

Coronary artery disease

Women are less likely than men to have coronary artery disease as the cause of their heart failure,[5–7] but it still remains a significant risk factor. Compared with women with nonischemic cardiomyopathy, those with coronary artery disease appear to have a poorer prognosis with a higher risk of death[8]; the reason is unclear, but it may be due to a higher incidence of comorbidities, acute coronary syndromes, or arrythmias.

Diabetes mellitus

Diabetes mellitus is a strong risk factor for heart failure in women,[1,9] and especially in younger women.[9] In the Framingham Heart Study,[10] the incidence of heart failure in young diabetic women (age 35–64 years) was twice as high as in young diabetic men. Diabetes is also one of the strongest predictors of heart failure in postmenopausal women with coronary artery disease.[11]

Although the mechanism remains unknown, it is interesting to note that diabetes mellitus is an independent predictor of increased left ventricular mass and wall thickness.[12,13] This is important, since left ventricular hypertrophy is considered an early pathologic feature of heart failure,[10] and it frequently leads to diastolic dysfunction.[14]

In Framingham, hypertension preceded heart failure in 59% of women vs 39% of men

Obesity

Obesity is associated with heart failure in both women and men. It contributes to hypertension, diabetes mellitus, coronary artery disease, and dyslipidemia, which all in turn play a key role in the pathogenesis of heart failure.

In Framingham women,[15] the risk of heart failure increased by 7% with each increment of 1 kg/m^2 in body mass index after adjusting for known risk factors (compared with 5% in men). Overweight women had a 50% greater risk of heart failure than did women of normal weight.

Hypertension

The prevalence of hypertension increases with age, and hypertension is an important risk factor for heart failure in women and men.[7,14] However, more women than men had hypertension before they had heart failure.[7,8,14,16,17] For instance, in the Framingham study,[14] hypertension preceded the development of heart failure in 59% of women vs 39% of men. Although hypertension may be a more common cause of heart failure in women due to the high prevalence of this disease, a woman's individual risk of developing heart failure is still greater with coronary artery disease.[7]

Valvular heart disease

There is little information about valvular disease as a risk factor for heart failure in women. The Framingham study suggested that more women than men with heart failure had valvular disease, but this distinction was based on clinical examination and was not verified by echocardiography.[6]

Idiopathic cardiomyopathy

Idiopathic cardiomyopathy appears to be less common in women than in men.[18,19] However, it is a diagnosis of exclusion, and its prevalence depends on whether an extensive workup was done. For instance, in one tertiary care center, 50% of patients who were initially thought to have idiopathic cardiomyopathy were later found to have an identifiable cause of their heart failure. Fewer women than men in that center received the final diagnosis of idiopathic cardiomyopathy, suggesting that the true prevalence is less in women than in men.[18]

Chemotherapy

With new chemotherapeutic regimens for advanced breast cancer that are based on anthracyclines such as doxorubicin (Adriamycin), the incidence of heart failure in breast cancer patients (who are mostly women) has increased. The risk appears to be dose-dependent, but the mechanism remains unclear.[20]

Some breast cancer patients treated with trastuzumab (Herceptin), a humanized monoclonal antibody against the HER2 protein, also develop impaired left ventricular function, but this adverse effect is more frequent when trastuzumab is combined with anthracyclines,[21,22] and it may not occur if anthracyclines are not used.[21,23]

Peripartum cardiomyopathy

Heart failure can occur in the absence of a preexisting cardiac condition in the last month of pregnancy or within 5 months postpartum.

This condition is known as peripartum cardiomyopathy; the cause remains unknown.

The incidence is approximately 1 per 3,000 to 4,000 live births in the United States. Risk factors include multiparity, advanced maternal age, multifetal pregnancy, preeclampsia, gestational hypertension, and African American race.[24]

SEX DIFFERENCES IN PATHOPHYSIOLOGY

Sex differences have been noted in the pathophysiology of heart failure, but the reasons have not been fully elucidated.

Women often have higher ejection fractions

Heart failure with preserved left ventricular function is more common in women,[3,4] and diastolic abnormalities have been noted on cardiac catheterization.[25]

In one study,[25] more women than men referred for cardiac catheterization had heart-failure symptoms, even though they had higher systolic left ventricular ejection fractions. The pressure-volume relationship was notable: the left ventricular end-diastolic pressure was similar in women and in men, but women had a smaller left ventricular end-diastolic volume.

Signs and symptoms do not tell you the ejection fraction

Women have more hypertrophy

Sex differences have also been noted in cardiac remodeling during pressure-overload states. In severe aortic stenosis, women tend to develop more cardiac hypertrophy, while men have less hypertrophy but greater left ventricular cavity size and reduced left ventricular function.[26]

The reason may be that women have a smaller myocyte volume at baseline.[27] Their myocyte volume can therefore increase more, so that the heart can compensate longer, delaying the progression to heart failure.

Sex differences in ventricular remodeling are also apparent histologically, with less fibrosis, apoptosis, and myocyte necrosis in women than in men.[28] These differences probably account for the sex differences in cavity size and left ventricular function. However, very little is known about differences at the molecular level.

Estrogen may have beneficial effects

Sex hormones may affect cardiac remodeling. Estrogens reduce left ventricular mass, fibrosis, and renin levels and enhance vasodilation, while androgens have the opposite effects.[29] 17-Beta-estradiol attenuates the development of pressure-overload cardiac hypertrophy,[30] and this effect may be mediated by the beta-estrogen receptor.[31]

Few human studies have assessed the role of hormone therapy in the development of heart failure. However, in a retrospective analysis of a beta-blocker study,[32] significantly fewer postmenopausal women with impaired systolic left ventricular function died if they were on hormone replacement therapy.

On the other hand, the HERS[33] and WHI[34,35] studies found no difference in the number of hospital admissions for heart failure in women receiving hormone therapy (estrogen alone or estrogen and progestin) vs placebo. Possible reasons for the lack of benefit: heart failure was a secondary end point, and too few heart failure events occurred for the studies to detect a difference; another possibility is that hormone replacement therapy may not prevent heart failure (few participants in HERS or WHI had underlying heart failure), but it might improve the prognosis after heart failure develops. (See **TABLE 1** for a glossary of studies discussed in this paper.)

WOMEN HAVE MORE DYSPNEA, EDEMA

Heart failure is a clinical diagnosis based on symptoms and signs. The symptoms and signs are the same in women and men, but women are more likely to have dyspnea, edema, elevated jugular venous pressure, and an audible third heart sound.[5]

EVALUATION FOR HEART FAILURE

One cannot always tell whether a heart failure patient's systolic function is impaired or preserved on the basis of symptoms and physical examination. Therefore, tests such as echocardiography are often necessary.

The evaluation should also include electrocardiography, chest radiography, complete blood cell count, and thyroid function tests.

TABLE 1

Glossary of heart failure studies

A-HeFT—African-American Heart Failure Trial[72,73]

BEST—Beta-Blocker Evaluation of Survival Trial[8]

CHARM—Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity[63,64,91–93]

CIBIS II—Cardiac Insufficiency Bisoprolol Study II[56]

COMPANION—Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure[76]

COPERNICUS—Carvedilol Prospective Randomized Cumulative Survival Study[54]

DIG—Digitalis Investigation Group[74,75]

ELITE-II—Losartan Heart Failure Survival Study[65]

EPHESUS—Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study[68]

HERS—Heart and Estrogen/Progestin Replacement Study[33]

MERIT-HF—Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure[55]

MIRACLE—Multicenter InSync Randomized Clinical Evaluation[78]

MUSTIC—Multisite Stimulation in Cardiomyopathy[77]

RALES—Randomized Aldactone Evaluation Study[67]

SAVE—Survival and Ventricular Enlargement[89]

SOLVD—Studies of Left Ventricular Dysfunction[5,57,94]

TRACE—Trandolapril Cardiac Evaluation[90]

Val-HEFT—Valsartan Heart Failure Trial[62]

V-HeFT—Vasodilator-Heart Failure Trial[70,71,95]

WHI—Women's Health Initiative[34,35]

Cardiac catheterization or a stress test may be performed to assess for coronary artery disease as the cause of heart failure. Measurement of neurohormones such as B-type natriuretic peptide may aid in the diagnosis of heart failure, but women have a higher "normal value" than men.[36,37]

Metabolic stress testing, which measures oxygen uptake during exercise, is often used to help determine when ambulatory patients should be considered for heart transplantation.[38] Women with impaired systolic function may have a lower peak oxygen uptake (peak V_{O_2}) than men do.[39–41] Yet, for any given peak V_{O_2} value, women appear to have a better survival rate.[41,42]

WOMEN ARE SICKER, BUT LIVE LONGER

More women than men are hospitalized for congestive heart failure,[1,43,44] and many studies suggest that women with heart failure have a worse quality of life,[45–47] more dyspnea,[5] worse functional status,[46–48] and more depression[49] than men do. Yet, they have a lower age-adjusted mortality rate.[50,51]

It remains unclear why women with heart failure live longer than men with heart failure. The data noting a better life expectancy for women with heart failure[50,51] did not differentiate between those with preserved and impaired left ventricular systolic function. Although sex differences in survival may reflect differences in left ventricular function, it is unlikely, since recent population studies indicate that the mortality rates are similar in patients with preserved vs impaired left ventricular function.[3,4] Most likely, sex differences in survival are due to sex differences regarding the underlying cause. For instance, in the BEST study,[8] women with ischemic cardiomyopathy and impaired left ventricular function had a poor prognosis, with a mortality rate similar to that in men.

Women have higher normal BNP values than men do

Therefore, the survival advantage for women may be due to the lower prevalence of ischemic cardiomyopathy in women than in men.

DRUG TRIALS: MOSTLY MEN WITH LOW EJECTION FRACTIONS

Current guidelines for heart failure therapy are not sex-specific,[38] since there have been no large, prospective, randomized, blinded studies in women with heart failure.

All the information below is from either retrospective studies or post hoc analyses of major trials. In these studies women were

TABLE 2

Studies of heart failure therapy: Few women, few patients with preserved systolic function

STUDY	% WOMEN	NUMBER OF WOMEN	LEFT VENTRICULAR EJECTION FRACTION	TREATMENT EVALUATED
A-HeFT[72,73]	40	421	≤ 35%[a]	Hydralazine-isosorbide dinitrate
CHARM-Overall[93]	32	2,400	Any	Candesartan (Atacand)
CHARM-Preserved[92]	40	1,212	≥ 40%	Candesartan (Atacand)
CIBIS II[56]	19	515	≤ 35%	Bisoprolol (Zebeta)
COMPANION[76]	32	493	≤ 35%	Cardiac resynchronization
COPERNICUS[54]	20	469	≤ 25%	Carvedilol (Coreg)
DIG[74,75]	22	1,519	≤ 45%	Digoxin (Lanoxin)
ELITE-II[65]	31	966	≤ 40%	Losartan (Cozaar), captopril (Capoten)
MERIT-HF[55]	23	898	≤ 40%	Metoprolol succinate (Toprol XL)
MIRACLE[78]	32	145	≤ 35%	Biventricular pacing
MUSTIC[77]	26	47	≤ 35%	Biventricular pacing
RALES[67]	27	446	≤ 35%	Spironolactone
SAVE[89]	17	390	≤ 40%	Captopril
SOLVD prevention[94]	13	548	≤ 35%	Enalapril (Vasotec)
SOLVD treatment[57]	20	2,568	≤ 35%	Enalapril
TRACE[90]	29	501	≤ 35%	Trandolapril (Mavik)
Val-HEFT[62]	20	1,033	≤ 40%	Valsartan (Diovan)
V-HeFT I[70]	0	0	≤ 45%	Hydralazine-isosorbide dinitrate
V-HeFT II[71]	0	0	≤ 45%	Enalapril
V-HeFT III[95]	0	0	≤ 45%	Felodipine (Plendil)

[a]Or < 45% with left ventricular dilation

NOTE: See **TABLE 1** for the full names of the studies

underrepresented,[52] and many of the studies included only patients with impaired systolic function (**TABLE 2**), despite the fact that heart failure with relatively preserved left ventricular systolic function is common among elderly women. Therefore, the data should be interpreted with caution.

We suggest that women with heart failure receive the same medications that men do until prospective studies enable us to recommend sex-specific therapy. Our discussion below will review the literature for the treatment of patients with impaired systolic function but not preserved systolic function (previously called diastolic heart failure). Treatment for preserved systolic function remains limited and often requires therapy for the underlying cause. We also recommend that patients with peripartum cardiomyopathy be referred to a heart failure specialist for therapeutic decisions and sensitive discussions regarding subsequent pregnancies, since the ideal management remains unknown because no randomized, prospective studies have been done.

DRUGS REDUCE DEATHS, HOSPITALIZATIONS

Beta-blockers

Three beta-blockers have been proven in multicenter, prospective, randomized studies to reduce the rates of morbidity and death in patients with heart failure and impaired systolic function when added to therapy with an angiotensin-converting enzyme (ACE) inhibitor: carvedilol (Coreg), bisoprolol (Zebeta), and metoprolol succinate (Toprol-XL). However, in the United States, only carvedilol and metoprolol succinate have been approved by the US Food and Drug Administration for treating heart failure,

and therefore our discussion will be limited to these two drugs.

Carvedilol is a nonselective beta-adrenergic antagonist with alpha-blocking and antioxidant properties, and metoprolol succinate is a beta-1-selective adrenergic antagonist. Both drugs have been shown in post hoc analyses to be beneficial to women with heart failure despite the relatively small number of female participants in each study. Carvedilol has survival benefits in women with moderate heart failure and systolic dysfunction,[53] and appears to reduce the hospitalization rate for women with severe heart failure and impaired systolic function.[54] Metoprolol succinate has not been shown to affect survival for women with heart failure and impaired systolic function, but can reduce hospitalizations by 42% ($P = .021$).[55]

It is unclear why metoprolol succinate did not improve survival for women with heart failure and impaired systolic function, since a survival benefit for women was noted with bisoprolol, which is also a beta-1-selective adrenergic antagonist. The reason may be that metoprolol is a less potent beta-1-selective adrenergic antagonist than bisoprolol. Another reason may be that the MERIT-HF study (of metoprolol succinate)[55] included women with a better functional status and a higher ejection fraction than did the CIBIS II study (of bisoprolol).[56]

Since there were few women in the beta-blocker trials, and many of the trials were terminated early, the beneficial effects of beta-blockers in women are likely underestimated.

ACE inhibitors

Current guidelines recommend ACE inhibitors for all patients with symptomatic heart failure and impaired systolic function.[38]

ACE inhibitors have lowered morbidity and mortality rates in multicenter, prospective, randomized trials.[57,58] Although women participated in most of these trials, the percentage in each study was small, and the benefit of this class of drugs remains unclear even when data are pooled from multiple studies.

Garg and Yusuf[59] performed a meta-analysis of 30 ACE inhibitor studies involving a total of 1,587 women with heart failure and found a trend towards a lower mortality rate in women taking ACE inhibitors (13.4% vs 20.1%) and a lower rate of the combined end point of death or hospitalization (20.2% vs 29.5%). Another meta-analysis, involving 2,373 women, revealed similar trends. Women with symptomatic heart failure appeared to benefit more from ACE inhibitors than those who had no symptoms.[60]

However, there is some doubt about the actual benefit of ACE inhibitors in women, since both meta-analyses had wide confidence intervals that included 1.0. Moreover, there may be sex differences in side effects, since women have a higher frequency of cough with use of these drugs.[61]

Angiotensin receptor blockers

Current guidelines support the use of the angiotensin receptor blockers (ARBs) candesartan (Atacand), losartan (Cozaar), or valsartan (Diovan) either as alternatives to an ACE inhibitor (especially if the patient cannot tolerate an ACE inhibitor because of cough or angioedema) or in addition to an ACE inhibitor.[38] Studies in heart failure patients with impaired left ventricular function have found lower rates of hospitalization for heart failure and, in some studies, lower mortality rates when these drugs are used.[62–65]

Carvedilol and metoprolol both have beneficial effects in women with heart failure

However, ARBs have not been shown to be superior to ACE inhibitors. Furthermore, there are very few data supporting the use of an ARB in women with heart failure. Only candesartan has been shown to reduce hospitalizations and improve survival for women with heart failure and impaired left ventricular systolic function.[63] Although other ARBs have been studied, the benefit in women remains unclear because the hazard ratios had wide confidence intervals that crossed the 1.0 line.[62,65,66]

Aldosterone antagonists

Aldosterone antagonists, also known as potassium-sparing diuretics, include spironolactone (Aldactone) and eplerenone (Inspra). They are one of the few classes of medications deemed by subgroup analysis to reduce the mortality rate in women with heart failure and impaired systolic function, based on both the RALES and EPHESUS trials.[67,68]

Although the investigators of the RALES and EPHESUS trials did not explore the potential mechanisms, the Framingham

Heart Study found higher levels of aldosterone in women than in men before the onset of heart failure. It also found a correlation between increased aldosterone levels and increased ventricular wall thickness in women.[69] This association is important, since left ventricular hypertrophy is a risk factor for heart failure.

In view of the Framingham data, it is tempting to suggest that aldosterone antagonists may have greater survival benefit for women than for men with heart failure; however, prospective clinical studies have not been performed to address this issue.

Hydralazine-isosorbide dinitrate

For men, hydralazine (Apresoline) and isosorbide dinitrate (eg, Isordil) have been proven to be acceptable substitutes for ACE inhibitors, based on V-HeFT, which demonstrated a survival benefit with these drugs. However, V-HeFT included no women.[70,71]

Some doubt the benefit of ACE inhibitors in women

The only large clinical trial of these drugs that included a large percentage of women was A-HeFT.[72,73] All participants were African American and had moderate to severe heart failure with impaired systolic function; 40% were women. Patients received, in addition to their standard medical regimen, hydralazine and isosorbide dinitrate in a fixed-dose combination (now available as BiDil) or placebo. The trial was stopped early because the survival rate was significantly higher in the active treatment group,[72] and the benefit appears to apply to the subgroup of women as well as to men.[73]

Digoxin

Digoxin (eg, Lanoxin) decreases hospitalizations in patients with heart failure but does not improve survival.[74]

In fact, some worried that digoxin might even *increase* the risk of death in women, in view of the results of the DIG trial. In that study, more women with impaired systolic function died if they received digoxin than if they didn't, but the trend was not statistically significant.[17]

The increase in deaths was presumed to be due to digoxin toxicity, since the risk of death increased at higher serum drug levels. A drug level between 0.5 and 0.9 ng/mL was considered safe, but levels between 1.2 and 2.0 ng/mL were associated with more deaths in both women and men.[75]

Anticoagulation and antiplatelet therapy

In the SOLVD trial,[16] women with impaired systolic function had a higher risk of thromboembolic events (mostly pulmonary emboli) than their male counterparts. However, in that study women were less likely than men to be taking antiplatelet agents or anticoagulation therapy. Therefore, these women may have been at higher risk because of inadequate prophylactic therapy. In fact, the women who used antiplatelet agents in that study had a significantly reduced likelihood of thromboembolic events.

Diuretics

There are not enough data to comment on the use of loop diuretics (eg, furosemide [Lasix]) in women with heart failure. Aldosterone antagonists appear to be beneficial.

LIMITED SEX-SPECIFIC DATA ON DEVICES AND SURGERY

Biventricular pacing

Biventricular pacing, also called cardiac-resynchronization therapy (CRT), has been shown in large, prospective, randomized multicenter studies to improve symptoms, left ventricular ejection fraction, and mortality rates. Candidates include those with a left ventricular ejection fraction less than 35%, New York Heart Association functional class III or IV symptoms, and a wide QRS interval.[76–79]

Although few studies reported sex-specific data, biventricular pacing appears to be beneficial for both women and men.[76,79]

Implantable cardioverter-defibrillators

An implantable cardioverter-defibrillator (ICD) is recommended for primary prevention of sudden death in patients with mild to moderate heart failure symptoms (New York Heart Association class II or III), a left ventricular ejection fraction less than 30% to 35%, and a life expectancy of at least 1 year.[38,80] These devices can also be considered in patients with functional class IV symptoms if they are also eligible for cardiac resynchro-

nization therapy.[80] Of note, patients with ischemic cardiomyopathy should wait at least 3 months after revascularization and at least 40 days after a myocardial infarction before an ICD is implanted, in hopes that the left ventricular ejection fraction will improve and a device may no longer be necessary.[80,81]

The above recommendations are based on many multicenter studies,[76,82,83] but few studies provided sex-specific data. Unfortunately, the limited post hoc analyses available do not clearly demonstrate that ICDs prevent death in women[76,82] except possibly in the subgroup of women with ischemic cardiomyopathy.[84] It remains unclear if this is because too few women were enrolled, because only subgroups of women (ie, those with ischemic cardiomyopathy) are at risk of sudden death, or because women truly do not benefit from ICDs.

Ventricular assist devices

Ventricular assist devices are often used in critically ill heart failure patients for whom medical therapy has failed. They can be used as a "bridge" to heart transplantation or as "destination therapy" for those who are ineligible for heart transplantation because of age or comorbidities.

The surgical technique for implanting these devices is the same in women as in men, but since many of these devices are large, they require a minimum body surface area to fit properly. Therefore, small women tend not to be good candidates for this therapy.[85] Unfortunately, there are very limited data comparing outcomes in women and men who received one of these devices.

Heart transplantation

In the United States, in 2005, women donated 30% of the available hearts and received 28% of the hearts transplanted. Women had a shorter wait on the transplant list compared with men (142 days vs 177 days). The overall survival rate after transplantation was slightly worse for women than for men: 84.6% vs 86.4% at 1 year, 76.1% vs 78.9% at 3 years, and 68.5% vs 72.1% at 5 years.[86]

An international database also found a higher 1-year mortality rate for female recipients and a slightly higher risk if there was a donor-recipient mismatch (ie, if the donor was male and the recipient female).[87] However, many factors affect survival, including allograft vasculopathy, rejection, and infection, and it remains uncertain whether the sex of the donor affects the survival of the female recipient. One large international study involving 4,159 patients concluded that women can receive a heart from either sex without an effect on survival.[88]

FOR MORE INFORMATION

For more information about heart failure in women, please visit our Web site at **www.clevelandclinic.org/heartcenter/pub/guide/disease/heartfailure/hfwomen/default.htm**.

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