STATE-OF-THE-ART PAPER

Heart Failure in Women

A Need for Prospective Data

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Heart failure affects 5 million Americans, and nearly 50% of these are women. Sex differences have been noted regarding the underlying etiology, pathophysiology, and prognosis. Women are less likely to have coronary artery disease and more likely than men to have hypertension and valvular disease as the underlying etiology. They often present at an older age with better systolic function than men. For both sexes, there is significant morbidity, but age-adjusted data reveal that women have a better survival. Despite these known sex differences, medical management recommendations are the same for women and men, because prospective sex-specific clinical trials have not been performed. However, our review raises some concerns that women might respond differently to therapy. (J Am Coll Cardiol 2009;54:491–8) © 2009 by the American College of Cardiology Foundation

More women die every year of cardiovascular disease (CVD) than of breast or uterine cancer. Although nearly 50% of the female CVD mortality is due to coronary heart disease, heart failure (HF) contributes 35% of the total female CVD mortality (1). Despite this fact, HF in women remains a poorly recognized and poorly understood syndrome and has not received the same public awareness as coronary heart disease. The objective of this work is to review sex differences in epidemiology, etiology, diagnosis, and prognostic testing and discuss sex-specific results from the landmark HF trials that have shaped our current medical practice. In addition, to guide practitioners when caring for women with HF, this review will offer practical suggestions. For sex differences in HF pathophysiology, we refer readers to the excellent review by Konhilas and Leinwand (2).

Epidemiology/Prognosis/Etiology

Heart failure affects 5.3 million Americans, and nearly 50% of these are women (1). The prevalence of HF increases with age for both sexes, with more women than men having HF after 79 years of age (1). Women with acute decompensated HF tend to have HF with preserved left ventricular (LV) function almost twice as often as men (3,4), and those with impaired LV systolic function tend to present with a higher left ventricular ejection fraction (LVEF) when compared with men (3). Additionally, comorbidities are common. Women with HF tend to have more hyperten-

sion compared with men, who have more smoking and coronary artery disease (CAD) (5). Thyroid disease is more frequent in women with acute decompensated HF, whereas chronic obstructive lung disease, peripheral vascular disease, and renal insufficiency are more common in men (3,4).

Age-adjusted HF incidence is higher in men than in women, yet the prevalence is similar, because men with HF have shorter survival than women (6,7). The incidence of HF from 1979 to 2000 rose 8% (95% confidence interval [CI]: −5% to 23%) in women and 3% (95% CI: −11% to 20%) in men according to the Olmsted County data (6), which validated 4,537 cases of new onset HF. Similarly, the Framingham investigators also reported an increase in the incidence of HF for both women and men between 1980 and 1999 (7). During those time periods, age-adjusted, 5-year mortality improved for both sexes (6,7).

There is significant morbidity associated with HF, and women have been shown to have a lower quality of life than men, with more functional capacity impairment (8), more HF hospital stays (1,3,8), and depression (9). Nonetheless, survival is better for women (6,7). The cause for sex differences in mortality remains unknown, but 2 leading hypotheses are differences in systolic function and in etiology. Women are more likely than men to have HF with preserved LV systolic function, which was believed to have a better prognosis than impaired LV function. However, 2 recent observational studies showed a similar mortality rate for HF patients with preserved or impaired systolic function (10,11). Women also have less ischemic cardiomyopathy, and survival might be related to sex differences in etiology (12). Although the CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) study noted that sex differences in survival were not entirely

explained by LV systolic function or by etiology, there was a worse prognosis for both women and men with ischemic cardiomyopathy (Fig. 1) (5).

Tests used for survival prediction might require sex-specific interpretation. For example, brain natriuretic peptide >500 pg/ml might be a stronger predictor of death in women with HF than in men (13). Cardiopulmonary exercise testing, often used to determine optimal timing for listing for heart transplantation, seems to be an excellent predictor of death in both women and men (14), but for any given peak oxygen consumption women have a better survival (14,15). However, women with an ischemic cardiomyopathy have a worse prognosis compared with those women with a nonischemic cardiomyopathy for any given peak oxygen consumption (Fig. 2) (14).

Heart failure is associated with many risk factors with some sex differences. Women are more likely than men to have hypertension and valvular disease as the
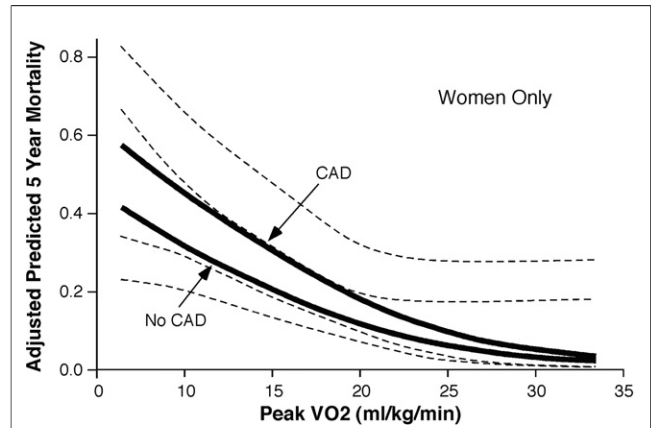
Figure 2   **Adjusted Predicted Mortality**

Adjusted predicted mortality in women with heart failure and impaired systolic function on the basis of peak oxygen consumption (VO$_2$) and the presence or absence of coronary artery disease (CAD). Adapted from Hsich et al. (14).

underlying etiology for HF and less likely to have CAD (3–5). Although CAD is less common, it is such a significant risk factor that women are more likely to develop HF with CAD than with hypertension. For example, in the NHANES (National Health and Nutrition Examination Survey) I survey—which included 8,098 women without HF—27% had hypertension and only 3% had CAD, but the relative risk (RR) of developing HF for women was significantly higher if they
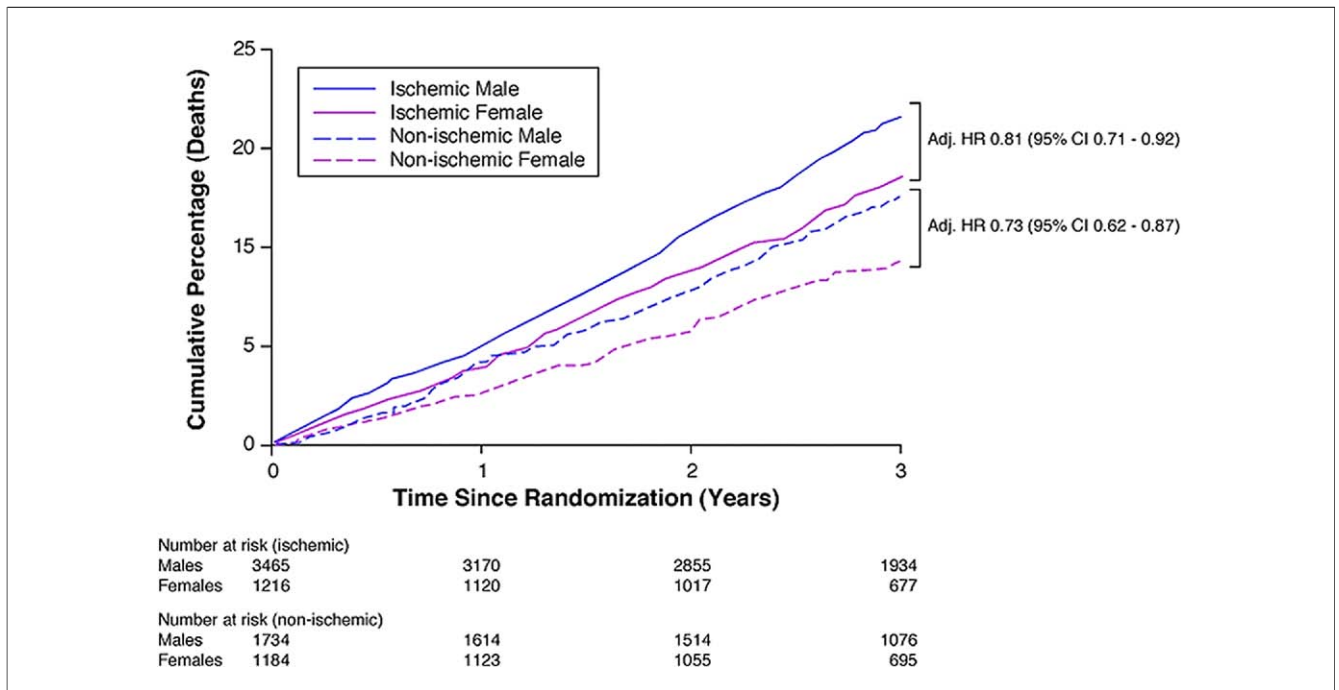
Figure 1   **Kaplan-Meier Curves for All-Cause Mortality in the CHARM Study**

Kaplan-Meier curves for all-cause mortality in the CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) study for women and men with heart failure on the basis of the presence or absence of an ischemic cardiomyopathy. Adapted from O'Meara et al. (5).

had CAD (RR: 8.16; 95% CI: 6.79 to 9.8; p < 0.001) than if they had hypertension (RR: 1.51; 95% CI: 1.29 to 1.77; p < 0.001) (16). Diabetes mellitus is common in both sexes (i.e., 44%) (3) and is one of the strongest additional risk factors for the development of HF in women with CAD (17). Other causes of HF include cardiac toxicity from chemotherapeutic agents used to treat breast malignancy and peripartum cardiomyopathy (PPCM).

PPCM

PPCM is the development of HF with impaired systolic function in the last month of pregnancy or within 5 months post-partum with no pre-existing cardiac disease or identifiable cause (18). The incidence varies on the basis of the population studied, with an estimated occurrence in 1 of 4,000 pregnancies in the U.S. (18). The etiology remains unknown, but potential causes include myocarditis, abnormal immune response to pregnancy, increased myocyte apoptosis, genetic predisposition, and proteolytic cleavage of prolactin during oxidative stress. Risk factors include advanced maternal age, African descent, high parity, twin pregnancy, usage of tocolytics, and poverty (19). Approximately one-half of PPCM patients recover normal systolic function within 6 months (20). Another 20% deteriorate and either die or require heart transplantation (21). The degree of LV systolic dysfunction at presentation might predict recovery. In 1 study involving 33 patients with PPCM, those who recovered LV systolic function had a higher LVEF at presentation (LVEF 35 ± 4% vs. 25 ± 4%, p = 0.001) (22). In another study involving 98 patients from Haiti with PPCM, a similar finding was noted, with recovery more likely in patients with less severe systolic dysfunction (LVEF 28%, 95% CI: 15% to 41% vs. LVEF 23%, 95% CI: 11% to 35%, p < 0.001) (23). There are limited data regarding the risk of subsequent pregnancies. One retrospective study noted that the average LVEF after subsequent pregnancy was reduced both in patients who had recovered systolic function before pregnancy (n = 28; LVEF 56 ± 7% reduced to 49 ± 10%, p = 0.002) and in those with persistent LV systolic dysfunction (n = 16; LVEF 36 ± 9% reduced to 32 ± 11%, p = 0.08). All 3 patients who died in this series had LV systolic dysfunction before the subsequent pregnancy (24). Preliminary data involving animal research and 12 PPCM patients suggest that bromocriptine, which inhibits prolactin secretion, might help prevent death and deterioration of LV function upon subsequent pregnancies by preventing the formation of a 16-kDA prolactin fragment. An imbalance of oxidative stress during pregnancy or in the peripartum period can cause prolactin to be cleaved by cathepsin D into a 16-kDA prolactin fragment, which can destroy the cardiac microvasculature and lead to LV cavity dilation and systolic dysfunction (25). The 16-kDA prolactin fragment induces endothelial apoptosis (26), inhibits vascular endothelial growth factor-induced proliferation of endothelial cells, and impairs

nitric oxide-mediated vasorelaxation (27). Although this is potentially an exciting breakthrough in the pathophysiology of PPCM, the data are preliminary, and the usage of bromocriptine in the post-partum period to suppresses lactation has been associated with increased incidence of cardiovascular events, hypertension, and thrombus formation (19). Therefore, it is reasonable to await the results of larger studies with usage of bromocriptine and to counsel women who have a diagnosis of PPCM about subsequent pregnancies and the need to remove angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy should a new pregnancy occur.

Diagnosis

The diagnosis of HF is a clinical diagnosis based on a constellation of symptoms and signs (28). According to the SOLVD (Studies Of Left Ventricular Dysfunction) database, women with impaired systolic LV function are more likely than men to have dependent edema, jugular venous distension, and an S3 gallop (29). In contrast, according to ADHERE (Acute Decompensated Heart Failure National Registry) (impaired and preserved systolic function), there were no clinically important differences in the frequency of HF symptoms/signs between women (n = 54,674) and men (n = 50,713) (3). This apparent difference in symptom observation might be related to the fact that the ADHERE registry was derived from patients hospitalized for acute decompensation compared with most clinical trials where patients present with chronic symptoms.

Diagnostic tests to assess LV function are frequently used to further classify HF patients into those with impaired or preserved LV systolic function and to assess for other structural heart disease. From both the Framingham and the Olmstead County databases, more women than men have HF with preserved LV function (30,31) as depicted in Figure 3. Coronary angiography might determine who has
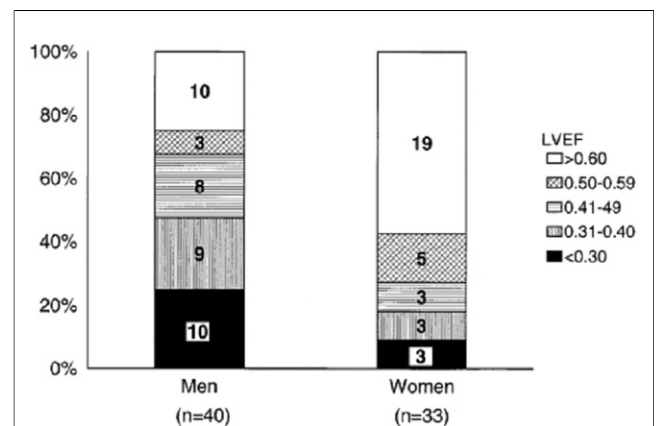
Figure 3   **LVEF**

Left ventricular ejection fraction (LVEF) in women and men with congestive heart failure. Reprinted from Vasan et al. (31).

Table 1	Female Participants in Chronic Heart Failure Trials		
Study (Ref #)	**% Women**	**Number of Women**	**LVEF**
A-HeFT (47)	40	420	≤35%
BEST (12)	22	593	≤35%
CARE-HF (55)	26	215	≤35%
CHARM-low LVEF (37)	26	1,188	≤40%
CIBIS II (41)	19	515	≤35%
COMPANION (52)	32	493	≤35%
CONSENSUS (63)	30	75	Any
COPERNICUS (40)	20	469	<25%
DIG (48)	22	1,520	≤45%
ELITE-II (61)	31	966	≤40%
EPHESUS (45)	29	1,918	≤40%
MADIT II (55)	16	192	≤30%
MERIT-HF (42)	23	898	≤40%
RALES (43)	27	446	≤35%
SCD HeFT (54)	23	588	≤35%
SOLVD prevention (29)	13	548	≤35%
SOLVD treatment (29)	20	514	≤35%
U.S. Carvedilol (40)	23	256	≤35%
Val-HeFT (38)	20	1,003	<40%
V-HeFT I (45)	0	0	<45%
V-HeFT II (46)	0	0	<45%

LVEF = left ventricular ejection fraction.

an ischemic cardiomyopathy. Brain natriuretic peptide, a biomarker, is being used more frequently to identify patients with symptoms of HF and to risk stratify. However, "normal" brain natriuretic peptide values are higher in women versus men (32). More studies are needed that will address sex differences in biomarker levels and strategies to intervene on outcomes. Sufficient women need to be enrolled so that analyses can be carried out by sex.

Therapy

Most clinical trials have not planned to prospectively analyze the female cohort or enroll a certain percentage of women. One exception is BEST (Beta-Blocker Evaluation of Survival Trial), which stratified patients by sex (12). Consequently, current guidelines for HF therapy (28,33) are not sex specific due to under-representation of women (Table 1) and lack of sex-specific, prospective, randomized clinical trials. The summaries that follow refer mostly to HF with impaired systolic function and should be interpreted with caution, because they have been derived from retrospective studies or post hoc analyses.

ACEI. ACEIs are currently recommended for all patients with HF and impaired systolic function, because of the known morbidity and mortality benefits (28,34). Unfortunately, few women participated in these landmark HF clinical trials, and therefore the benefits in women remain unclear. A meta-analysis consisting of 30 ACEI studies involving a total of 1,587 women with HF demonstrated a trend toward improved survival in the group taking ACEIs compared with those not taking the drug (13.4% vs. 20.1%) and a favorable trend in the combined end point of survival and hospital stay in the group of women taking an ACEI (20.2% vs. 29.5%) (35). Another meta-analysis involving 2,373 women revealed similar trends and noted that women who were symptomatic benefited more than those who were asymptomatic (36). However, both meta-analyses had wide CIs that crossed 1.0, raising some uncertainty about the actual benefit (Table 2).

ARBs. Angiotensin receptor blockers are used in ACEI-intolerant HF patients or in addition to an ACEI (28). Sex-specific data for ARBs are limited, but candesartan and valsartan seem beneficial in women. Pooled data from the CHARM-Alternative (ARB for patients intolerant of ACEI) and CHARM-Added trials (ARB added to an ACEI) that included 1,188 women, New York Heart Association (NYHA) functional class II to IV with LVEF ≤40%, showed that candesartan reduced the combined end point of cardiovascular death or HF hospital stay in women (37). In the Val-HeFT (Valsartan Heart Failure Trial), which included 1,003 women with NYHA functional class

Table 2	Risk of Mortality and/or Hospital Stay in Female HF Patients		
		HR, RH, or OR (95% CI)	
Study (Ref #)	**End Point***	**Women**	**Men**
U.S. Carvedilol HF Study (39)	Mortality	HR: 0.23 (0.07–0.69)	HR: 0.41 (0.22–0.80)
A-HeFT (47)	Mortality	HR: 0.33 (0.16–0.71)	HR: 0.79 (0.46–1.35)
ACEI meta-analysis (35)	Mortality	OR: 0.79 (0.59–1.06)	OR: 0.76 (0.65–0.88)
ACEI meta-analysis (35)	Mortality or HF hospital stay	OR: 0.78 (0.59–1.04)	OR: 0.63 (0.55–0.73)
BEST (12)	Mortality	HR: 0.82 (0.60–1.13)	HR: 0.85 (0.73–0.99)
CIBIS II (41)	Mortality	RH: 0.53 (0.42–0.67)	RH: 0.37 (0.19–0.69)
Val-HeFT†	Mortality	HR: 0.93 (0.68–1.27)	HR: 1.04 (0.90–1.19)
Val-HeFT†	HF hospital stays	HR: 0.74 (0.55–0.98)	HR: 0.73 (0.62–0.86)
ELITE II (61)	Mortality	HR: 1.14	HR: 1.12
SCD-HeFT (amiodarone) (54)	Mortality	HR: 1.17 (0.72–1.90)	HR: 1.04 (0.83–1.30)
SCD-HeFT (ICD) (54)	Mortality	HR: 0.96 (0.58–1.61)	HR: 0.73 (0.57–0.93)
CARE-HF (53)	Mortality + hospital stay	HR: 0.64 (0.42–0.97)	HR: 0.62 (0.49–0.79)

*End point for sex-specific results and not necessarily primary end point of trial. †Unpublished data provided by the principal investigators.
HF = heart failure; HR = hazard ratio; OR = odds ratio; RH = relative hazard.

II to IV and LVEF <40%, valsartan when compared with placebo did not significantly reduce mortality in women but did reduce HF hospital stay (hazard ratio [HR]: 0.74, 95% CI: 0.55 to 0.98) and first morbid event (HR: 0.79, 95% CI: 0.63 to 0.99) (I. Anand, personal communication, April 22, 2008), which was defined as cardiac arrest, HF hospital stay, or administration of intravenous inotrope/vasodilator therapy (Table 2) (38).

Beta-blockers. Three beta-blockers are proven in multicenter, prospective, randomized studies to reduce mortality and morbidity in HF patients with impaired systolic function: carvedilol, bisoprolol, and metoprolol succinate. Post hoc analyses suggest that these agents, when added to an ACEI, are beneficial in women with HF despite the relatively small number of female participants in each study.

Carvedilol is a nonselective beta-adrenergic antagonist with alpha-blocking and antioxidant properties. Carvedilol improved survival in the 256 women participating in the U.S. Carvedilol Heart Failure Study of HF patients with moderate symptoms and LVEF ≤35% (HR: 0.23, 95% CI: 0.07 to 0.69) (39), although this was not a mortality trial. In the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study) study, carvedilol reduced the combined end point of death or hospital stay in the 469 women studied with LVEF <25% and severe HF symptoms. Most of this benefit was due to a reduction in hospital stays, because the mortality data had a wide CI and the HR crossed 1.0 (40).

Bisoprolol and metoprolol succinate are beta$_1$-selective adrenergic antagonists. In the European CIBIS II (Cardiac Insufficiency Bisoprolol Study), bisoprolol improved survival in the 515 women studied who were NYHA functional class III or IV and had LVEF ≤35% (relative hazard: 0.37, 95% CI: 0.19 to 0.69) (41). In the MERIT-HF (Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure) trial, metoprolol succinate had no survival benefit for women (6.9% vs. 7.5%, p = NS) but did reduce HF hospital stay by 42% (p = 0.021) in the 898 women studied with LVEF <40% who were NYHA functional class II to IV. This effect was even more dramatic with a 72% reduction in HF hospital stays (0.54 vs. 0.15; p = 0.0004) in the subgroup of women (n = 183 patients) with LVEF <25% (42).

Aldosterone antagonists. Aldosterone antagonists are one of the few medications deemed by subgroup post hoc analysis to have a total mortality benefit for women with systolic HF on the basis of both the RALES (Randomized Aldactone Evaluation Study) and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trials (43,44). The RALES trial included 446 women and studied the effects of spironolactone in ischemic and nonischemic cardiomyopathy patients with NYHA functional class III to IV and LVEF ≤35% (43). The EPHESUS trial included 1,918 women participants and studied the effects of eplerenone after an acute myocardial infarction in patients with LVEF ≤40% (44).

Hydralazine/isosorbide dinitrate. The combination of hydralazine and isosorbide dinitrate has been commonly used in HF patients who cannot tolerate an ACEI or ARB. The original data supporting the use of this combination by demonstrating a survival benefit included only men (45,46). In fact there remain no published data for women using hydralazine and isosorbide dinitrate as a substitute for an ACEI or ARB. Added to ACEI/ARB and beta-blockers, this combination has been studied in the A-HeFT (African-American Heart Failure Trial), which included 420 women participants who were NYHA functional class III to IV. The trial was prematurely stopped because of the significant survival benefits that were noted for both women (HR: 0.33, 95% CI: 0.16 to 0.71, p = 0.003) and men (HR: 0.79, 95% CI: 0.46 to 1.35, p = 0.385) with no significant treatment interaction by sex. There were also fewer first hospital stays for HF in both women (HR: 0.62, 95% CI: 0.41 to 0.96, p = 0.03) and men (HR: 0.60, 95% CI: 0.42 to 0.89, p = 0.005) (47).

Digoxin. Digoxin reduces HF hospital stay but has no beneficial effect on survival (48).

In women with impaired systolic function, there was an initial concern of increased mortality (adjusted HR: 1.23, 95% CI: 1.02 to 1.47) that was not observed in men (adjusted HR: 0.93, 95% CI: 0.85 to 1.02) on the basis of a post hoc subgroup analysis of the Digitalis Investigation Group trial (49). The increased mortality was presumed to be due to digoxin toxicity, because the risk of death increased at higher serum drug levels. Drug levels between 1.2 and 2.0 ng/ml were associated with increased mortality (HR: 1.33, 95% CI: 1.001 to 1.76, p = 0.049), and levels between 0.5 and 0.9 ng/ml were considered safe for both women and men (HR: 0.8) on the basis of a retrospective analysis (50).

Antiplatelet agents and anticoagulation. In a retrospective analysis of the SOLVD trial, women with HF had an increased risk of thromboembolic events compared with men. Although women had more thromboembolic events (mostly pulmonary embolic events) they were also less likely than men to be taking antiplatelet agents or anticoagulation therapy. In fact, the use of an antiplatelet agent in women significantly reduced the likelihood of this complication (51). Further information regarding this topic might be provided by the ongoing WARCEF (Warfarin Versus Aspirin in Reduced Ejection Fraction) trial.

Cardiac resynchronization therapy (CRT). CRT is recommended for HF patients with LVEF ≤35%, NYHA functional class III to IV symptoms in spite of optimal medical therapy, and a wide QRS (QRS ≥120 ms), on the basis of large, prospective, randomized multicenter studies that demonstrated improvement in symptoms, functional capacity, and mortality (52,53). Although few studies have reported sex-specific data, it seems that CRT is beneficial for both women and men. In the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) study, which included 299 women, women

with CRT had a greater reduction in the combined end point of total mortality or hospital stay for any cause compared with women given just medical therapy (52). A retrospective analysis of the CARE-HF (Cardiac Resynchronization–Heart Failure) data—a study that included 215 women—suggested that CRT was preferable to medical therapy alone in women for the combined end point of total mortality and hospital stay for major cardiovascular events (Table 2). All patients were functional NYHA functional class III or IV, had LVEF ≤35%, LV end-diastolic diameter ≥30 mm as indexed for height, and QRS >120 ms with evidence of dyssynchrony if QRS was 120 to 149 ms (53).

Implantable cardioverter-defibrillator (ICD). The recommendations for an ICD to prevent sudden death are based on many multicenter studies, but few have provided sex-specific data (52,54). Unfortunately, the limited post hoc analyses available for women with an ICD do not clearly demonstrate a mortality benefit (52,54,55). In the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), which included 588 women in NYHA functional class II to III with LVEF ≤35% (ischemic and nonischemic cardiomyopathy), the benefits of an ICD were not clear, although the trial was not powered to detect sex differences (women HR: 0.96, 95% CI: 0.58 to 1.61). In the MADIT (Multicenter Automatic Defibrillator Implantation Trial) II, which included 119 women with an ischemic cardiomyopathy LVEF ≤30%, there was a nonsignificant trend toward lower mortality in women with an ICD (adjusted HR: 0.57, p = 0.132), suggesting that this subgroup (ischemic cardiomyopathy) might benefit. However, this analysis was limited by too few women participants (55).

Ventricular assist device (VAD). VADs are used in critically ill HF patients as a "bridge" to heart transplantation or as "destination therapy" for those who have failed medical therapy and are ineligible for heart transplantation. There is no sex difference in the surgical technique for implanting these devices. However, small women have limited options, because devices like implantable left VADs require a minimum body surface to fit properly.

The VAD outcome data comparing women and men remain limited (56,57). One study noted that women were more likely than men to require a right VAD after implantation of a left VAD, but there were few women participants and pre-VAD implantation data were not analyzed (56). In another study in which women had a worse prognosis, women were clinically more unstable than men before VAD implantation. Survival after VAD correlated best with the degree of medical severity before VAD implantation and not sex (57). The recent Food and Drug Administration approval of the HeartMate II (Thoratec Corporation, Pleasanton, California) a small continuous flow device, will allow the implantation of more VADs in women and enable data analysis in a more consistent prospective manner, because it will be added to the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) National Heart, Lung, and Blood Institute patient registry for VADs.

Heart transplantation. In the U.S. for 2007, women donated 28% of the available hearts and received 26% of the hearts transplanted. The overall survival after transplantation on the basis of UNOS (United Network of Organ Sharing) data from 1997 to 2004 was slightly worse for women (i.e., survival rate female vs. male: 1 year 86% vs. 88%, 3 years 76% vs. 79%, 5 years 68% vs. 72%) (58). The most recent data (2007) from the International Society for Heart and Lung Transplantation (59) showed that the sex of the donor or recipient did not significantly affect 1-year mortality but that the RR of 5-, 10-, and 15-year mortality was slightly increased for male recipients who received female hearts (5-year RR: 1.2, 95% CI: 1.05 to 1.37, p = 0.0093; 10-year RR: 1.08, 95% CI: 1.01 to 1.17, p = 0.0309; 15-year RR: 1.13, 95% CI: 1.01 to 1.25, p = 0.0334). With respect to coronary allograft vasculopathy, the RR within 5 years was highest for recipients who received male donor hearts and lowest for female recipients who received female donor hearts (59).

Conclusions

Approximately 2.7 million women have HF. Heart failure affects women at an older age with better LV systolic function, compared with men. Women are more likely to have hypertension and valvular disease as the etiology and less likely to have CAD. However, CAD is such an important risk factor that a woman with CAD is more likely to develop HF than a woman with hypertension. Survival for women with HF is better than for men, and the reason remains unclear but might in part be related to sex differences in etiology, with a worse survival in both women and men with ischemic cardiomyopathy.

Since the landmark HF in women review article by Petrie et al. (60) in 1999, which was striking mainly because of the lack of sex-specific data, we have learned more regarding epidemiology, prognostic testing, and the rare disease PPCM. We continue to know little sex-specific information regarding therapy. At least 9 multicenter HF studies have been published since Petrie's article (i.e., RALES [43], EPHESUS [44], A-HeFT [47], CHARM [37], ELITE II [Losartan Heart Failure Survival Study] [61], Val-HeFT [38], COPERNICUS [40], COMPANION [52], and CARE-HF [53]) and on average included 28% women. This is an improvement in enrollment compared with the 19% reported by Petrie et al. but still an under-representation for a disease that has approximately 40% women with impaired systolic function and 60% women with preserved LV function (3). Our current HF guidelines are not sex specific because of insufficient data, but our review of the published reports raises concern that sex differences might exist regarding the degree of benefit of any given therapy. For instance, retrospective analysis revealed a morbidity and/or mortality benefit for HF women treated with beta-

blockers, aldosterone antagonists, or CRT but did not show the same benefit with ACEI or ICD, despite all studies having a paucity of female participants.

What do we need to do to change the future? Since 1986 the National Institutes of Health (NIH) has requested that women be included in clinical trials, and in 1993 an NIH Revitalization Act was passed that stipulated that a sufficient number of women be included in NIH-sponsored trials to report meaningful sex-specific results. Despite the NIH attempts, there continues to be a low rate of sex-specific reporting in cardiovascular trials (62). Although journal editors could require sex-specific results, it does not change the fact that most clinical HF trials were not designed to even determine sex differences. Changes need to be made, but who should accept this responsibility and how to enforce it remains controversial.

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