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WOMEN AND HEART DISEASE (C LINDE, SECTION EDITOR)

Sex Differences in Heart Failure—Female Representation in Heart Failure Studies

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Abstract

Purpose of Review The prevalence of heart failure (HF) continues to grow in the USA, and approximately 50% of these patients are women. Despite this, there has been an underrepresentation of women in HF clinical trials, which has led to limitations in understanding of sex-related differences in HF pathophysiology, diagnosis, and treatment. The purpose of this review is to highlight the differences between men and women in various heart failure trials conducted in the last century and emphasize new findings from recent trials in the management of, and outcomes in, women with HF.

Recent Findings HF trials have shown that women have improved survival with guideline-directed medical therapy, and the most recent analysis from PARADIGM-HF showed women had lower mortality and hospitalization rate compared with men. Furthermore, despite comprising only 20% of subjects in cardiac resynchronization therapy (CRT) trials, we now know that women are likely to benefit from a CRT device, in particular those with left bundle branch block. Advanced therapies for heart failure including durable mechanical circulatory support remain underused in women, and female patients are less likely to undergo heart transplantation when compared with men of similar risk profiles. The latest studies have shown women receiving continuous-flow left ventricular assist device support had lower chances of heart transplantation, increased risk of waitlist mortality, and higher rates of delisting for worsening clinical status. However, post transplantation, women have better survival when compared with men.

Summary Although several studies have shown that women with HF live longer than men, they experience greater self-reported psychological and physical disability and poorer overall quality of life. The cause of sex differences in morbidity and mortality remains unknown, but as the therapeutic options for HF expand, sex-based differences in treatment would need to be considered.

Keywords Sex differences · Women · Heart failure · Clinical trials · Medical therapy · Device therapy

Introduction

The prevalence of heart failure (HF) continues to rise and is now a major and important cause of morbidity and mortality in the USA. According to the 2019 American Heart Association statistical update, HF has increased to 6.5 million and is projected to rise by 46% in 2030, affecting over 8 million Americans [1, 2]. Furthermore, it is the leading cause of hospital admissions in the USA, and women constitute approximately one-half of the patients hospitalized for HF [3].

HF affects men and women equally, and the prevalence of the disease increases with age [3]. Compared with men, women with HF are older and have greater clinical severity as demonstrated by more frequent symptoms and signs of HF [4]. Women also report more functional capacity impairment, lower quality of life, and increased signs of depression. Women with HF are less likely to die than men, and mode of death is less likely to be sudden death [5]. The cause of sex differences in morbidity and mortality remains unknown, but could be in part due to the etiology of HF and the difference in systolic dysfunction [6].

Although 50% of patients with heart failure are women, only 30% of all cardiovascular disease (CVD) clinical trials enrolled women. In HF trials, that number is even

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lower, approximately 17–23%, limiting our understanding of gender-related differences in HF pathophysiology, diagnosis, and treatment [3, 7].

Epidemiology

Based on data from 2005 to 2014 community surveillance of the Atherosclerosis Risk in Communities (ARIC) study, there were one million new HF cases annually and of those 505,000 were women. There has been an increased incidence of HF in the elderly and improved survival leading to an increased HF prevalence. The lifetime risk for heart failure is approximately 30 to 42% in white men, 20 to 29% in black men, 32 to 39% in white women, and 24 to 46% in black women [1]. Women tend to have heart failure with preserved ejection fraction (HFpEF) almost twice as much as men. The disparity in mortality between men and women may be due to the higher incidence of HFpEF, suggesting that patients with HFpEF have an overall better prognosis. HF hospitalization rates are similar between men and women, although women have shown to have better survival than men [8]. Women with ischemic heart disease and heart failure have a similar mortality to men.

Etiology

The risk factors influencing the development of heart failure such as obesity, hypertension, coronary artery disease (CAD), and diabetes differ among women and men. Hypertension and diabetes are common comorbidities in women with HF, whereas men tend to have more CAD and peripheral vascular disease [3]. Women with HFpEF are less likely to have CAD and more likely to have hypertension, and once they develop CAD, the risk of HF is high [2]. Women with CAD and ischemic HF are usually more symptomatic and have lower functional capacity and worse quality of life. CAD is the leading cause of death in women > 65 years of age [4], and obese women tend to have worse outcome than men. In the Framingham Heart Study, obesity increased the risk of CAD in women by 64% as opposed to 46% in men [9].

Diabetes is known to be a particularly strong risk factor for the development of HF in women. Diabetic women have a poor baseline risk profile and experience an almost twofold increase in cardiac mortality despite development of the smallest infarct size during the index event. In the setting of acute myocardial infarction, diabetic women are more likely to develop subsequent heart failure. Additionally, studies have suggested that diabetes may promote the development of heart failure independently of obstructive coronary disease [10–12].

Other etiologies of HF that are predominantly seen in women include stress-induced cardiomyopathy in postmenopausal women, comprising 90% of the cases, and spontaneous coronary dissection in premenopausal women, comprising 80% of the cases [13]. Peripartum cardiomyopathy presenting in late pregnancy and up to 6 months postpartum is a rare but potentially lethal complication of pregnancy. Women with black ancestry seem to be at greatest risk. Other risk factors include preeclampsia, advanced maternal age, and multiple gestation pregnancy [14].

Sex Differences in Medical Therapy for Heart Failure

Guideline-directed medical therapies recommend standard medical therapy in the management of women with HF. Past studies have shown that women were less likely to be prescribed evidence-based pharmacological therapies; however, most recent data from the American Heart Association's Get With the Guidelines-Heart Failure registry indicate this treatment gap appears to be closing [15, 16].

Sex differences in pharmacokinetics, pharmacodynamics, and physiology exist and may affect drug safety and effectiveness [17, 18]. Data from HF guidelines are not gender specific due to underrepresentation of women in clinical trials. As therapeutic options for HF continue to grow, sex-based differences in treatment will need to be considered. To date, multiple multicenter HF studies have been conducted and on average included 27% of women (see Table 1). The U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) now require all sponsors to include efficacy and safety data in women in applications for regulatory approval of drugs and devices, which has led to an increase in the representation of women in contemporary clinical trials of HF. Furthermore, the proportion of trials that have reported sex-specific outcomes continues to grow from 57.1% in 2001 to 71.9% in 2013–2016 [19].

The major beta-blocker trials MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Heart Failure), CIBIS II (Cardiac Insufficiency Bisoprolol Study II), and COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Trial) showed a similar survival benefit in men and women with beta blockade [20]. The early HF trials with ACE inhibitors (CONCENSUS [Cooperative North Scandinavian Enalapril Survival Study], SAVE [Survival and Ventricular Enlargement], SOLVD [Studies of Left Ventricular Dysfunction]) showed reduction in mortality and hospitalization in men but not in women; however, these trials were underpowered due to small sample size [21–23]. Subsequent meta-analyses with ACE inhibitors have demonstrated comparable benefit in survival and reduced hospitalization among men and women. Furthermore, the angiotensin II receptor blocker (ARB) trials showed similar benefit in women and men.

Table 1 Heart failure trials: number and percentage of women enrolled

Study	% women	Number of women
A-HeFT	40	420
CHARM-Overall	32	2400
CHARM-Preserved	40	1212
CIBIS II	19	515
COAPT	36	221
COMPANION	32	493
CONCENSUS	30	75
COPERNICUS	20	469
DIG	22	1520
ELITE-I	33	240
ELITE-II	31	966
MADIT-II	16	192
MERIT-HF	23	898
MIRACLE	32	145
MITRA-FR	24	73
PARADIGM-HF	22	1832
RALES	27	446
SCD HeFT	23	588
SOLVD-Prevention	11	484
SOLVD-Treatment	20	505
TRED-HF	33	17
Val-HEFT	20	1003
V-HeFT I, II, III	0	0
WARCEF	20	339
HF-ACTION	29	653

Adapted from Eisenberg et al. [13]

A more recent study which analyzed women ($n = 3357$) and men ($n = 12{,}058$) with HF enrolled in PARADIGM-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) found women had a significantly lower rate of mortality and hospitalization compared with men [24•]. The aldosterone antagonist trials (RALES [Randomized Aldactone Evaluation Study] and EPHESUS [Eplerenone Post-myocardial Infarction Heart Failure Efficacy and Survival Study]) demonstrated a mortality benefit in women in post hoc subgroup analysis [25, 26]. In addition, in A-HeFT (African-American Heart Failure Trial), which included 40% women, the combination of hydralazine and isosorbide dinitrate leads to improved survival in both male and female African-American patients with HFrEF and moderate-to-severe HF symptoms [27, 28]. While several studies have shown women with HF have fewer comorbidities, better survival, and lower rates of hospitalization, they have more symptoms and worse quality of life than men do [24, 29, 30].

Sex Differences in Device Therapy for Heart Failure

Implantable Cardioverter-Defibrillators

In 2015, approximately 75,000 patients died from advanced heart failure and 55% were women [1]. Implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT) are believed to improve clinical outcomes and reduce sudden death in patients with HF [31]. Primary prevention with an ICD is a class I recommendation for symptomatic HF patients who despite medical therapy have NYHA functional class II or III symptoms with ischemic cardiomyopathy > 40 days after myocardial infarction or nonischemic cardiomyopathy with left ventricular ejection fraction ≤ 35%. In the landmark trials that have shown this benefit, women were underrepresented and the studies were not designed to prospectively analyze the female cohort [6, 32•]. In one meta-analysis utilizing 5 primary prevention trials (DEFINITE [Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation], SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial], DINAMIT [Defibrillation in Acute Myocardial Infarction Trial], MUSTT [Multicenter Unsustained Tachycardia Trial], and MADIT-II [Multicenter Automatic Defibrillator Implantation Trial II]), ICD therapy for primary prevention of sudden cardiac death in women was not shown to reduce all-cause mortality [33]. Further studies are needed to investigate this observation and to define the population of women who may benefit from ICD therapy.

Cardiac Resynchronization Therapy

CRT through biventricular pacing has been shown in many randomized clinical trials to improve exercise capacity, quality of life, cardiac left ventricular function, ventricular remodeling, and survival [32•, 34, 35]. Studies suggest CRT results in at least equivalent, if not greater, clinical therapeutic outcomes in women compared with men. The COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [women 33%]) and CARE-HF (Cardiac Resynchronization-Heart Failure [women 25%]) studies found that CRT was associated with significant clinical benefit in both men and women and there was no difference between genders [36–38]. On the other hand, numerous studies have also demonstrated greater clinical benefit of CRT in women. The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) showed that cardiac resynchronization therapy defibrillator (CRT-D) therapy was associated with a greater benefit in the composite outcome of mortality and nonfatal HF events in women compared with men [39]. The reason women benefit more than men from CRT remains unclear but may have to do with women having

more left bundle branch block (LBBB) at shorter QRS duration [32•]. Based on data from the National Cardiovascular Data Registry, women had an 18% lower mortality risk compared with men after CRT-D implantation. In multivariable analyses controlling for comorbidities, left bundle branch block was associated with a 26% reduction in mortality in women (HR 0.74 [95% CI 0.71 to 0.77]) and a 15% reduction in mortality in men (HR 0.85 [95% CI 0.83 to 0.87]) [40, 41].

Transcatheter Mitral Valve Repair

Studies have shown that patients with left ventricular dysfunction and secondary mitral regurgitation (MR) have worse prognosis. Previously, guideline-directed medical therapy targeting left ventricle–related diseases and CRT were the only management strategies to reduce severity of MR. Two recent trials, MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation), were conducted in Europe and in the USA/Canada, respectively, to assess whether transcatheter mitral valve repair reduced the risk of death and hospitalization for heart failure patients. The MITRA-FR trial (women 25%) showed no significant difference in mortality benefit or length of hospitalization in both men and women. On the other hand, the COAPT trial (women 36%) showed a significantly lower rate for hospitalization at 2 years and significantly lower all-cause mortality at 2 years in the device group for both genders [42, 43•]. The difference between these two studies was in part attributed to patient selection. Comparing the patients in the COAPT trial with those in the MITRA-FR trial, the mitral valve effective orifice area was approximately 30% higher whereas the LV volumes were approximately 30% smaller in the COAPT trial, indicating that patients with degrees of MR that are disproportionately greater than might be expected from the degree of LV enlargement respond favorably to transcatheter mitral valve repair [44]. Furthermore, medical management before and after enrollment may have differed between the two trials [45]. Once again, the number of women enrolled in these trials was substantially low and further investigation is needed to assess outcomes in women and identify those who have the greatest chance of benefiting.

Mechanical Circulatory Support and Transplant

The use of circulatory support continues to rise over time for women and men with advanced HF. From 2006 to 2016, > 22,000 patients received an FDA-approved mechanical circulatory support. Over 95% of these durable mechanical circulatory support devices are continuous-flow left ventricular assist devices (LVADs) with the majority implanted in men (79%) [32•, 46, 47]. Even in the current era, women are less likely to receive durable mechanical circulatory support [48••]. Initially, enrollment of women in trials involving first-generation pulsatile-flow LVAD ranged from 8 to 20%, primarily due to small body size [49–51]. With the development of smaller continuous-flow devices, slightly more women have been implanted (21% women and 79% men in 2006–2009 versus 22% women and 78% men in 2014–2017) [32•]. Women receiving continuous-flow LVAD support have lower chances of heart transplantation. Among patients with LVAD, women are at greater risk of stroke and neurological events and have increased risk of waitlist mortality compared with men [48••]. The reason for these sex differences remains unknown. More research is needed to fully understand these differences and whether device management strategies should be tailored based on gender [52–54].

According to the Scientific Registry of Transplant Recipients (SRTR) and Organ Procurement and Transplantation Network (OPTN), more than 3200 heart transplants were performed in the USA in 2016. Furthermore, the number of new active listings for heart transplant increased to 57% between 2005 and 2016 [55]. Women are less frequently transplanted than men, despite shorter waiting time. Of the patients who underwent heart transplant between 2005 and 2010, only 23% were women. The number increased slightly in 2017, with women receiving only 26% of the donor hearts [32•, 48••, 56]. The criteria for matching a heart are based on body weight, blood type, and tissue typing which makes identifying a suitable donor in women more challenging. The lower rate of transplantation in women may be partly explained by the higher levels of panel-reactive antibodies on parous women [2, 57, 58] or by lower referral rates. Women have worse survival while awaiting heart transplantation, but slightly better survival than men post transplantation. In addition, women have lower risk of coronary allograft vasculopathy and malignancy but a higher risk of antibody-mediated rejection [32•, 59]. One well-studied risk factor for decreased survival in men and women is donor–recipient cardiac size mismatching. Worst survival has been reported among the male recipients receiving female donor hearts and those with undersized hearts [60].

Conclusions

Although HF remains a significant healthcare concern for women, less than 25% of subjects in randomized clinical trials are women and the reasons for the low enrollment rate are not clear. This underrepresentation of women in clinical trials has limited our understanding of sex-related differences in HF pathophysiology, diagnosis, and treatment. Currently,

recommendations for guideline-directed medical therapy show no difference in treatment approaches between genders despite the sex differences in pharmacokinetics and pharmacodynamics that may affect drug safety and effectiveness. As the therapeutic options for HF expand, sex-based differences in treatment would need to be considered. Based on multiple studies with advanced heart failure, there are many sex differences including greater benefit with CRT in women compared with men, similar LVAD survival, but worse neurological complications and better survival than men post transplantation. Further studies are needed to understand the sex differences in heart failure etiology, pathophysiology, and treatment response in order to improve care in women.

Compliance with Ethical Standards

Conflict of Interest Edlira Tam DO, MS, declares that she has no conflict of interest. Ileana L. Piña MD, MPH, declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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