Heart Failure in Women

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ABSTRACT: Heart failure is an important cause of morbidity and mortality in women, and they tend to develop it at an older age compared to men. Heart failure with preserved ejection fraction is more common in women than in men and accounts for at least half the cases of heart failure in women. When comparing men and women who have heart failure and a low left ventricular ejection fraction, the women are more symptomatic and have a similarly poor outcome. Overall recommendations for guideline-directed medical therapies show no differences in treatment approaches between men and women. Overall, women are generally underrepresented in clinical trials for heart failure. Further studies are needed to shed light into different mechanisms, causes, and targeted therapies of heart failure in women.

EPIDEMIOLOGY OF HEART FAILURE IN WOMEN

According to the 2017 American Heart Association (AHA) Heart Disease and Stroke Statistics Update, heart failure (HF) prevalence has increased to 6.5 million in Americans ≥ 20 years of age.[1] By 2030, the incidence of HF is projected to rise by 46%, affecting more than 8 million individuals. Heart failure affects both genders equally and is a leading cause of morbidity and mortality.

Whereas the lifetime risk of developing coronary heart disease is 1 in 2 for men and 1 in 3 for women, by the age of 40, men and women have equal lifetime risks of developing HF. At 40 years of age, the lifetime risk of developing HF for both men and women is 1 in 5.[2,3] At 80 years of age, the remaining lifetime risk for developing new HF remains at 20% for men and women even in the face of a much shorter life expectancy.[2] Occurrence of HF increases with advancing age, and women at older age are at greater risk than men.[4]

Incidence rates of HF in men approximately double with each 10-year increase in age from 65 to 85 years; however, the HF incidence rate triples for women between ages 65 to 74 and 75 to 84 years.[2] Likewise, at younger ages, the cumulative prevalence of HF is higher in men compared to women, but it equalizes between the two genders after age 80.[3,5,6]

In the Atherosclerosis Risk in Communities Study (ARIC), the age-adjusted incidence rate per 1,000 person-years was lowest for white women (3.4) compared to all other groups including white men (6.0), black women (8.1), and black men (9.1).[7] Incidence rates in black women were more similar to those of men than of white women.[7] The lifetime risk of developing HF differs between genders and races. Data from the National Heart, Lung, and Blood Institute-sponsored Chicago Heart Association Detection Project in Industry, ARIC, and Cardiovascular Health Study (CHS) cohorts indicate that lifetime risks for HF were 30% to 42% in white males, 20% to 29% in black males, 32% to 39% in white females, and 24% to 46% in black females.[8]

Patients with HF and preserved ejection fraction (HFpEF) are more often female and older compared to those with HF and reduced systolic function.[9,10] According to the 2017 AHA Heart Disease and Stroke Statistics Update, white females had the highest proportion of hospitalized HFpEF (59%), whereas black males had the highest proportion of hospitalized HF with reduced ejection fraction (HFrEF) (70%).[1] Among all patients with HF-related hospitalizations, 53% of the patients had HFrEF and 47% had HFpEF. Age-adjusted hospitalization and readmission rates are similar between women and men.[2,11]

Over the past 50 years, the incidence of HF appears to have declined among women but not among men, whereas survival after the onset of HF has improved in both sexes.[12] Data from Olmsted County, MN, indicate that the age- and sex-adjusted incidence of HF declined substantially over 10 years—from 315.8 per 100,000 in 2000 to 219.3 per 100,000 in 2010—with a greater rate reduction for HFrEF than for HFpEF.[13]

ETIOLOGY OF HEART FAILURE IN WOMEN

Common causes of HF in women, especially in postmenopausal women, include hypertension, valvular heart disease, diabetes, and coronary artery disease.[14] Women with HFpEF are less likely to have coronary artery disease and more likely to have hypertension.[9,10] However, it should be noted that once women develop coronary heart disease, the risk of HF is high. In fact, women in the Framingham cohort had a greater risk of symptomatic HF after myocardial infarction than men.[3] Hypertension and diabetes play a greater role in the development of coronary artery disease in women than in men;

thus, they also directly or indirectly play a significant role in the development of HF in women.

Other etiologies of HF include peripartum cardiomyopathy, autoimmune disorders, collagen vascular disorder, cardiotoxicity (such as chemotherapy with doxorubicin, trastuzumab, or other toxins), or genetic cardiomyopathies in select populations. Less-common causes include viral myocarditis and cardiomyopathies induced by alcohol/toxins, tachycardia, and stress. Stress-induced cardiomyopathy has a predilection for postmenopausal women, and it is usually a reversible cause of HF with better long-term outcomes.[15] The stressors are different between genders, with emotional stress being the main driver in women and physical stress/trauma being the main driver in men.

In the Heart and Estrogen/Progestin Replacement Study (HERS) trial, nine factors were independently associated with the development of HF. These included atrial fibrillation, history of myocardial infraction, creatinine clearance < 40 mL/min, systolic blood pressure > 120 mm Hg, active smoking, body mass index > 35 kg/m^2, left bundle branch block, left ventricular hypertrophy, and diabetes, which was the strongest risk factor for development of HF.[16]

There are also physiologic differences in the cardiovascular systems of women and men (Table 1). Compared to men, women have lower left ventricular (LV) mass, greater LV contractility, more preserved LV mass with aging, a lower rate of myocyte apoptosis, smaller coronary vessels, a faster resting heart rate, and less catecholamine-mediated vasoconstriction.

PRESENTATION OF HEART FAILURE IN WOMEN

Women tend to develop HF at an older age compared to men.[10] Heart failure with preserved ejection fraction is more common in women than in men, and it accounts for at least half the cases of HF in women.[10] When men and women with HF and a low LV ejection fraction are compared, the women are more symptomatic and have a similarly poor outcome.

Overall signs and symptoms of HF are similar between men and women.[17] However, compared to men, women have higher frequency rates of dyspnea on exertion, difficulty exercising, and edema.[12,18] Despite controlling for age, ejection fraction, and New York Heart Association classification, women tend to have worse quality of life ratings than men for intermediate activities of daily living and social activity.[19] Depression is also more common in women with HF than in men.[20] Women usually present with HF at an older age than men and more frequently develop left bundle branch block on ECG than men. Furthermore, women are less likely to be referred for specialty care or diagnostic testing, and they undergo fewer procedures including revascularization, implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), or mechanical circulatory support.

	WOMEN COMPARED TO MEN
Left ventricular mass	Lower
Contractility	Greater
Cell turnover/apoptosis	Lower
Coronary vessel caliber	Smaller
Blood pressure	Lower
Resting heart rate	Higher
Catecholamine-mediated vasoconstriction	Less

Table 1.
Compared to men, women with heart failure have these unique anatomical and physiologic features.

MECHANISMS OF HEART FAILURE IN WOMEN

Women tend to have lower LV end diastolic volumes at similar LV end diastolic pressures compared to men, suggesting that diastolic dysfunction is one explanation for the paradox of women having more frequent HF symptoms despite better preserved LV systolic function.[21] It should be noted, however, that women with HF symptoms are usually older and have a higher prevalence of hypertension, both of which are known to be associated with diastolic dysfunction.[22] In addition, myocardial remodeling with age or mechanical load is different in both genders. Women with aortic stenosis tend to have smaller, thicker-walled ventricles than men despite having similar degrees of outflow obstruction, implying differences in physiological and biological responses other than diastolic dysfunction.[23,24] Women also have better systolic cardiac performance as measured by LV fractional shortening despite similar degrees of clinical impairment in women and men.[25]

Compared to men, women have lower LV mass, greater LV contractility, preserved LV mass with aging, a lower rate of apoptosis, small coronary vessels, lower blood pressure, faster resting heart rate, and less catecholamine-mediated

vasoconstriction.[23] Left ventricular hypertrophy has a greater impact on survival in women than in men.[26]

Diagnosis

Although the same tests are used to diagnose HF in women and men, the results may not be the same. Reports of echocardiographic and other imaging dimensions for cardiac structures such as LV size and volume measurements should be indexed to body surface area (BSA) for women and men since the normal values differ according to gender, age, and BSA.[27]

Regarding biomarkers, natriuretic peptide levels are usually higher in women than in men but can vary by gender and age.[28,29] The "normal" values for natriuretic peptides in women are higher than for men.[29,30] Similarly, peak VO_2 appears to be lower for women than men.[31] This may be related to the adjustment for body weight, not for lean body mass, as women usually have a higher percentage of body fat than men.[32]

Prognosis

Survival after a HF diagnosis has significantly improved between 1979 and 2000.[33,34] However, the death rate still remains high: Approximately 50% of people diagnosed with HF will die within 5 years.[33] Survival is significantly reduced in both women and men with HFpEF or HFrEF compared to those without HF.[21]

Over the past 50 years, the incidence of HF has declined among women but not among men, whereas survival after the onset of HF has improved in both sexes.[12] It is important to note that men and younger persons have experienced larger survival gains compared to women and the elderly.[33]

Overall, women with HF tend to survive longer than their male counterparts.[35-40] This is more apparent when the etiology is unrelated to ischemia; women with HF due to nonischemic causes have significantly better survival than men with or without coronary disease as their primary cause of HF.[40] Interestingly, the mortality rates of women and men are similar when HF evolves from coronary artery disease. In fact, women are much more likely to develop HF after a myocardial infraction than men. Some evidence suggests that the reasons may include a less aggressive treatment approach for women.[33] In studies involving patients with coronary artery disease, the prevalence of HF in women is approximately twice that of men, although LVEF is similar or better in women.[41,42] Even though the clinical manifestations of HF appear to be more severe in women with HFpEF, after adjustment for baseline differences, HF hospitalizations are not increased and survival expectancy is better for women compared to men.[43]

Regarding ethnicity and racial disparities, though the respective death rates are lower compared to men, death rates for women are highest among non-Hispanic black women. In 2014, death rates in men were 103.7 per 100,000 for non-Hispanic whites, 108.0 for non-Hispanic blacks, and 61.8 for Hispanics. For women, the rates were 75.3 per 100,000 for non-Hispanic whites, 80.4 for non-Hispanic blacks, and 47.0 for Hispanics.[44]

Due to their unique pathophysiology and etiology, differences in cardiovascular physiology and neurohormonal mechanisms, drug pharmacokinetics, and metabolism, women need to be more proportionately represented in research studies. In all major HF studies, females on average constitute less than approximately 25% of enrolled subjects (Table 2).[45-61] To date, there are no prospective HF studies dedicated only to women with HF. Until prospective trial data prove otherwise, HF treatment guidelines should be uniformly applied to both women and men.[62-64]

Guideline-directed medical therapies show no differences in the overall recommendations for standard medical therapy approaches between men and women. The main contraindication for using angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or ARBs and neprilysin inhibitors in females is pregnancy due to the risk of birth defects associated with these drug classes.

In terms of benefit with standard therapies, evidence reveals that ACE inhibitors and ARBs have similar effects on men and women.[49,65,66] Despite low enrollment rates, especially in earlier randomized clinical trials, data from 30 ACE inhibitor studies involving 1,587 women with HF demonstrate improved survival with the use of ACE inhibitors and a favorable trend in the combined end point of survival and hospitalization in women.[37] Physician adherence to guidelines in the diagnosis and treatment of HF is less strict in women than in men, leading to undertreatment with inhibitors of the renin-angiotensin system. Similarly, despite the under-enrollment of women compared to men, multiple studies evaluating the role of β-blockers in patients with HF yielded beneficial results for survival and HF hospitalizations by subgroup analyses for women.[36,37,67]

Mineralocorticoid receptor antagonists are also beneficial in women. In the RALES study, which analyzed 446 women participants retrospectively, women had significant survival benefit with spironolactone.[52] In the EPHESUS study, eplerenone was used in a very select population that included 1,918 women. Those women taking eplerenone had a better overall survival than those not using the drug.[51]

The safety and efficacy of digoxin therapy appears to differ between men and women. In the Digitalis Investigation Group trial, post hoc subgroup analysis demonstrated a higher rate

TRIAL	% WOMEN REPRESENTED	MORTALITY REDUCTION IN SUBGROUP ANALYSIS
A-HeFT[59]	40	HR 0.33 (0.16-0.71)
CIBIS II[45]	19	RR 0.52 (0.30-0.89)
COMET[46]	20	HR 0.97 (0.73-1.27)
COMPANION[47]	32	NA
CONSENSUS[48]	20	RR 1.14 (0.68-1.90)
EMPHASIS-HF[50]	22	HR 0.65 (0.4-0.9)
EPHESUS[51]	29	NA
MADIT II[53]	16	HR 0.57 (0.28-1.16)
MERIT-HF[54]	23	RR 0.93 (0.58-1.49)
PARADIGM-HF[55]	21	HR 0.92 (0.6-1.1)
RALES[52]	27	NA
SCD HeFT[56]	24	HR 0.96 (0.58-1.61) ICD arm HR 1.17 (0.72-1.90) Amiodarone
SHIFT[57]	23	NA
SOLVED[58,60]	20	RR 1.15 (0.74-1.78) Prevention RR 0.86 (0.67-1.09) Treatment
TOPCAT[61]	51	HR 0.89 (0.71-1.12)
Val-HeFT[49]	20	NA
V-HeFT I, V-HeFT II[49]	0	0

*** Composite HR for primary outcomes that included death from cardiovascular cause, aborted cardiac arrest, or hospitalization for heart failure management.**

Table 2.
Female representation in key heart failure trials and survival benefit. HR: hazard ratio; RR: relative risk; NA: not available; ICD: implantable cardioverter defibrillator

of death with digoxin treatment in women with LVEF < 45% but no increased risk in women with normal LVEF.[68,69] The median serum digoxin level was slightly higher in women than in men, suggesting that digitoxicity may have played a role in this association. Interpreting this data should be done with great caution since there are many limitations with this study design.

The initial Veterans Administration Cooperative Studies (I, II, and III) evaluating hydralazine and isosorbide dinitrate excluded women from the trials.[70,71] In the most recent A-HeFT study, which included 40% women, the combination drug hydralazine/isosorbide was shown to improve survival in both male and female African American patients with HFrEF and moderate-to-

severe HF symptoms without a significant treatment interaction by gender.[59,72]

Additionally, based on the SOLVD trial, ejection fraction appears to be independently associated with thromboembolic risk in women.[73] Although women in this trial had a higher tendency to develop stroke and thromboembolic events, they were also less likely than men to be taking blood thinners.[73]

Studies of CRT that include a majority of male participants demonstrated that biventricular pacing can reduce symptoms, reduce the need for hospitalization, increase exercise tolerance, and increase survival. In studies with female representation, there was evidence of fewer deaths/hospitalizations in women with CRT.[74-78] Likewise, ICD therapy can prevent death and is recommended in women as in men.[62]

Mechanical circulatory devices are used as a bridge-to-transplant or destination therapy for both male and female patients who are not candidates for transplantation. According to the International Society for Heart and Lung Transplantation (ISHLT), 77% of heart transplant recipients between 2002 and 2008 were male.[79] Current criteria for matching a heart based on body weight, blood type, and tissue typing are likely to account for the lower rates of transplantation in females. Parous females tend to have elevated panel reactive antibodies, which can further decrease their chances of receiving a transplant.[79]

The same ISHLT report indicated that women had an increased risk of death one year after heart transplantation. Continuous-flow LV assistance as a bridge to transplantation is associated with similar survival rates in women and men.[80] However, the devices have minimum weight/height requirements in order to fit properly. Since women tend to have smaller frames, their options are limited. Traditionally, women with a BSA < 1.5 m^2, or > 1.5 m^2 but with a small thoracic cavity, were unable to get a ventricular assist device due to anatomical constraints. With the advent of newer technologies and smaller continuous-flow devices, the hope is that more females will be eligible for these therapies.[81]

CONCLUSION

Although HF is an important cause of morbidity and mortality for women, only 20% to 25% of subjects in randomized clinical trials are women.[82-85] The reasons for the low enrollment of women have not been clear. Overall, women are generally underrepresented in clinical trials of HF, and gender-specific analyses have been neglected in older large trials. Further studies are needed to shed light on the different mechanisms, causes, and targeted therapies of heart failure in women.

KEY POINTS

- Heart failure is an important cause of morbidity and mortality in women.
- Women tend to develop heart failure at an older age compared to men.
- Heart failure with preserved ejection fraction is more common in women than in men and accounts for at least half the cases of heart failure in women.
- Overall recommendations for guideline-directed medical therapies show no differences in treatment approaches between men and women. However, women are generally underrepresented in clinical trials for heart failure. Further studies are needed to shed light into different mechanisms of, causes of, and targeted therapies for heart failure in women.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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