

Heart Failure in Women

Biykem Bozkurt, M.D., Ph.D.; Shaden Khalaf, M.D.

WINTERS CENTER FOR HEART FAILURE RESEARCH, CARDIOVASCULAR RESEARCH INSTITUTE, BAYLOR COLLEGE OF MEDICINE, HOUSTON, TEXAS

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 \geq 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 infarction, creatinine clearance < 40 mL/min, systolic blood pressure > 120 mm Hg, active smoking, body mass index > 35 kg/m², 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

| | 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.

specialty care or diagnostic testing, and they undergo fewer procedures including revascularization, implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), or mechanical circulatory support.

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 infarction 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 EPHEUS 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 m², or > 1.5 m² 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.

Keywords:

heart failure, women, female, gender, sex

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017 Mar 7;135(10):e146-e603.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016 Jan 26;133(4):e38-360.
3. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002 Dec 10;106(24):3068-72.
4. Goldberg RJ, Spencer FA, Farmer C, Meyer TE, Pezzella S. Incidence and hospital death rates associated with heart failure: a community-wide perspective. *Am J Med*. 2005 Jul;118(7):728-34.
5. Braunwald E. Heart failure. *JACC Heart Fail*. 2013 Feb;1(1):1-20.
6. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*. 2012 Jan 3;125(1):e2-e220.
7. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol*. 2008 Apr 1;101(7):1016-22.
8. Huffman MD, Berry JD, Ning H, et al. Lifetime risk for heart failure among white and black Americans: cardiovascular lifetime risk pooling project. *J Am Coll Cardiol*. 2013 Apr 9;61(14):1510-7.

9. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*. 2004 Feb 4;43(3):317-27.
10. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol*. 2003 Jan 15;41(2):217-23.
11. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol*. 2008 Aug 5;52(6):428-34.
12. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002 Oct 31;347(18):1397-402.
13. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015 Jun;175(6):996-1004.
14. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med*. 2001 Apr 9;161(7):996-1002.
15. Sharkey SW, Lesser JR, Zenovich AG, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation*. 2005 Feb 1;111(4):472-9.
16. Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Predictors of heart failure among women with coronary disease. *Circulation*. 2004 Sep 14;110(11):1424-30.
17. Lund LH, Mancini D. Heart failure in women. *Med Clin North Am*. 2004 Sep;88(5):1321-45.
18. Johnstone D, Limacher M, Rousseau M, et al. Clinical characteristics of patients in studies of left ventricular dysfunction (SOLVD). *Am J Cardiol*. 1992 Oct 1;70(9):894-900.
19. Riedinger MS, Dracup KA, Brecht ML, Padilla G, Sarna L, Ganz PA. Quality of life in patients with heart failure: do gender differences exist? *Heart Lung*. 2001 Mar;30(2):105-16.
20. Gottlieb SS, Khatta M, Friedmann E, et al. The influence of age, gender, and race on the prevalence of depression in heart failure patients. *J Am Coll Cardiol*. 2004 May 5;43(9):1542-9.
21. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol*. 1999 Jun;33(7):1948-55.
22. Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. *N Engl J Med*. 1985 Jan 31;312(5):277-83.
23. Carroll JD, Carroll EP, Feldman T, et al. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. *Circulation*. 1992 Oct;86(4):1099-107.
24. Aurigemma GP, Silver KH, McLaughlin M, Mauser J, Gaasch WH. Impact of chamber geometry and gender on left ventricular systolic function in patients > 60 years of age with aortic stenosis. *Am J Cardiol*. 1994 Oct 15;74(8):794-8.
25. Gerds E, Zabalgoitia M, Bjornstad H, Svendsen TL, Devereux RB. Gender differences in systolic left ventricular function in hypertensive patients with electrocardiographic left ventricular hypertrophy (the LIFE study). *Am J Cardiol*. 2001 Apr 15;87(8):980-3.
26. Liao Y, Cooper RS, Mensah GA, McGee DL. Left ventricular hypertrophy has a greater impact on survival in women than in men. *Circulation*. 1995 Aug 15;92(4):805-10.
27. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015 Jan;28(1):1-39.
28. Keyzer JM, Hoffmann JJ, Ringoir L, Nabbe KC, Widdershoven JW, Pop VJ. Age- and gender-specific brain natriuretic peptide (BNP) reference ranges in primary care. *Clin Chem Lab Med*. 2014 Sep;52(9):1341-6.
29. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002 Sep 4;40(5):976-82.
30. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol*. 2002 Aug 1;90(3):254-8.
31. Daida H, Allison TG, Johnson BD, Squires RW, Gau GT. Comparison of peak exercise oxygen uptake in men versus women in chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1997 Jul 1;80(1):85-8.
32. Richards DR, Mehra MR, Ventura HO, et al. Usefulness of peak oxygen consumption in predicting outcome of heart failure in women versus men. *Am J Cardiol*. 1997 Nov 1;80(9):1236-8.
33. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004 Jul 21;292(3):344-50.
34. Barker WH, Mullooly JP, Getchell W. Changing incidence and survival for heart failure in a well-defined older population, 1970-1974 and 1990-1994. *Circulation*. 2006 Feb 14;113(6):799-805.
35. Adams KF Jr, Sueta CA, Gheorghiade M, et al. Gender differences in survival in advanced heart failure. Insights from the FIRST study. *Circulation*. 1999 Apr 13;99(14):1816-21.
36. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the

- Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation*. 2001 Jan 23;103(3):375-80.
37. Ghali JK, Pina IL, Gottlieb SS, Deedwania PC, Wikstrand JC. Metoprolol CR/XL in female patients with heart failure: analysis of the experience in Metoprolol Extended-Release Randomized Intervention Trial in Heart Failure (MERIT-HF). *Circulation*. 2002 Apr 2;105(13):1585-91.
 38. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993 Jul;88(1):107-15.
 39. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. *J Am Coll Cardiol*. 1992 Aug;20(2):301-6.
 40. Adams KF Jr, Dunlap SH, Sueta CA, et al. Relation between gender, etiology and survival in patients with symptomatic heart failure. *J Am Coll Cardiol*. 1996 Dec;28(7):1781-8.
 41. Greenland P, Reicher-Reiss H, Goldbourt U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. *Circulation*. 1991 Feb;83(2):484-91.
 42. Fisher LD, Kennedy JW, Davis KB, et al. Association of sex, physical size, and operative mortality after coronary artery bypass in the Coronary Artery Surgery Study (CASS). *J Thorac Cardiovasc Surg*. 1982 Sep;84(3):334-41.
 43. Deswal A, Bozkurt B. Comparison of morbidity in women versus men with heart failure and preserved ejection fraction. *Am J Cardiol*. 2006 Apr 15;97(8):1228-31.
 44. Centers for Disease Control and Prevention [Internet]. Atlanta, GA: U.S. Department of Health and Human Services; 2017. National Center for Health Statistics; National Vital Statistics System, 2015 [cited 2017 Aug 14]. Available from: <https://www.cdc.gov/nchs/nvss/index.htm>
 45. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999 Jan 2;353(9146):9-13.
 46. Pool-Wilson PA, Swedberg K, Cleland JG, et al.; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003 Jul 5;362(9377):7-13.
 47. Bristow MR, Saxon LA, Boehmer J, et al.; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004 May 20;350(21):2140-50.
 48. CONSENSUS Trial study group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987 Jun 4;316(23):1429-35.
 49. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001 Dec 6;345(23):1667-75.
 50. Zannad F, McMurray JJ, Krum H, et al.; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011 Jan 6;364(1):11-21.
 51. Pitt B, Remme W, Zannad F, et al.; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003 Apr 3;348(14):1309-21.
 52. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999 Sep 2;341(10):709-17.
 53. Moss AJ, Zareba W, Hall WJ, et al.; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002 Mar 21;346(12):877-83.
 54. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999 Jun 12;353(9169):2001-7.
 55. McMurray JJ, Packer M, Desai AS, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014 Sep 11;371(11):993-1004.
 56. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005 Jan 20;352(3):225-37.
 57. Swedberg K, Komajda M, Böhm M, et al.; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010 Sep 11;376(9744):875-85.
 58. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991 Aug 1;325(5):293-302.
 59. Taylor AL, Lindenfeld J, Ziesche S, et al. Outcomes by gender in the African-American Heart Failure Trial. *J Am Coll Cardiol*. 2006 Dec 5;48(11):2263-7.
 60. Schekelle PG, Rich MW, Morton SC, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials. *J Am Coll Card*. 2003 May 7;41(9):1529-38.

61. Pitt B, Pfeffer MA, Assman SF. Spironolactone for Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2014 Apr 10;370(15):1383-92.
62. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013 Oct 15;128(16):e240-e327.
63. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017 Apr 28.
64. Wenger NK. Women, heart failure, and heart failure therapies. *Circulation*. 2002 Apr 2;105(13):1526-8.
65. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003 Sep 6;362(9386):759-66.
66. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000 May 6;355(9215):1582-7.
67. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001 May 31;344(22):1651-8.
68. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med*. 2002 Oct 31;347(18):1403-11.
69. Jones RC, Francis GS, Lauer MS. Predictors of mortality in patients with heart failure and preserved systolic function in the Digitalis Investigation Group trial. *J Am Coll Cardiol*. 2004 Sep 1;44(5):1025-9.
70. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991 Aug 1;325(5):303-10.
71. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986 Jun 12;314(24):1547-52.
72. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004 Nov 11;351(20):2049-57.
73. Dries DL, Rosenberg YD, Waclawiw MA, Domanski MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. *J Am Coll Cardiol*. 1997 Apr;29(5):1074-80.
74. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004 May 20;350(21):2140-50.
75. Mooyaart EA, Marsan NA, van Bommel RJ, et al. Comparison of long-term survival of men versus women with heart failure treated with cardiac resynchronization therapy. *Am J Cardiol*. 2011 Jul 1;108(1):63-8.
76. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol*. 2002 Jul 3;40(1):111-8.
77. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002 Jun 13;346(24):1845-53.
78. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005 Apr 14;352(15):1539-49.
79. Taylor DO, Stehlik J, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Heart Transplant Report-2009. *J Heart Lung Transplant*. 2009 Oct;28(10):1007-22.
80. Bogaev RC, Pamboukian SV, Moore SA, et al. Comparison of outcomes in women versus men using a continuous-flow left ventricular assist device as a bridge to transplantation. *J Heart Lung Transplant*. 2011 May;30(5):515-22.
81. Morgan JA, Weinberg AD, Hollingsworth KW, Flannery MR, Oz MC, Naka Y. Effect of gender on bridging to transplantation and posttransplantation survival in patients with left ventricular assist devices. *J Thorac Cardiovasc Surg*. 2004 Apr;127(4):1193-5.
82. Lindenfeld J, Krause-Steinrauf H, Salerno J. Where are all the women with heart failure? *J Am Coll Cardiol*. 1997 Nov 15;30(6):1417-9.
83. Petrie MC, Dawson NF, Murdoch DR, Davie AP, McMurray JJ. Failure of women's hearts. *Circulation*. 1999 May 4;99(17):2334-41.
84. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*. 2001 Aug 8;286(6):708-13.
85. Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med*. 2002 Aug 12-26;162(15):1682-8.