Received: 19 December 2017 | Revised: 24 January 2018 | Accepted: 2 February 2018

DOI: 10.1002/clc.22917

WILEY CLINICAL CARDIOLOGY

REVIEW

Sex differences in heart failure

Evann Eisenberg[1] | Katherine E. Di Palo[2] | Ileana L. Piña[3]

[1]Department of Cardiology, Cedars–Sinai Medical Center, California, Los Angeles

[2]Department of Cardiology, Montefiore Medical Center, New York

[3]Albert Einstein College of Medicine, New York

Correspondence
Katherine DiPalo, PharmD, 1825 Eastchester Road, Bronx, NY 10461-2301
Email: kdipalo@montefiore.org

Heart failure (HF) numbers continue to grow in the United States and approximately 50% of patients living with HF are women. For the provider, it is critical to understand the role that gender plays in recognition, diagnosis, and management. The purpose of this literature review is to highlight the prevalence of heart failure in women and discuss gender variations in epidemiology, symptoms, pharmacology, and treatment as well as examine the representation of women in clinical trials.

KEYWORDS

Gender Differences, Heart Failure, Women

1 | INTRODUCTION

For the provider, it is critical to understand the role that gender plays in the recognition, diagnosis, and management of heart failure (HF). HF numbers continue to grow in the United States, and approximately 50% of patients living with HF are women. The Framingham cohort gives a glimpse into the epidemiology of HF in women. In the 1950s and 1960s, the HF incidence rate/10 000 person-years of follow-up was 42 (95% confidence interval [CI]: 34-50) in women and 63 (95% CI: 48–78) in men.[1] Subsequently, the incidence rate declined in women but not in men. One could hypothesize that the decline could have been related to the earlier recognition and treatment of rheumatic heart disease. In the 1990s, as mortality from myocardial infarction (MI) dropped, the 5-year incidence of HF increased to 32% from a rate of 23% in the 1970s. For both men and women who survived the first 30 days following MI, the rates of incident HF did not change.[2] Over the 50 years from 1948 to 1988, median survival for women was better than men, although both sexes had higher mortality with increasing age. Nonetheless, after adjusting for age, the women in Framingham had a better survival than the men. In spite of these observations, if patients were diagnosed in the 1990s, the 5-year mortality was greater than 50%.[3] The lifetime risk of HF without a prior MI is 15% at age 40 years for women and 11% for men, with the risk rising rapidly with age.[4]

2 | SYMPTOMS AND DIAGNOSIS

The symptoms of HF are similar between men and women. However, women often present with more symptom burden, including more dyspnea, bronchitis-like symptoms, edema, fatigue, and worse quality of life. Provider perceptions of HF being a "man's syndrome" often lead to delay in diagnosis and treatment, instead treating a presumed upper respiratory syndrome without further investigating the source. Thus, symptoms of HF can often be missed or misinterpreted in women. It is estimated that the prevalence of undiagnosed HF in primary care patients ≥65 years old with concomitant chronic obstructive pulmonary disease (COPD) is 20%.[5] Additionally wheezing, coughing, and shortness of breath can be misinterpreted as bronchial asthma instead of cardiac asthma caused by congestive HF,[6] resulting in treatment with nebulizers and inhalers. On presentation, older women with HF are more likely to have heart failure with preserved ejection fraction (HFpEF) and a background of hypertension (HTN). The NHANES (National Health and Nutrition Examination Survey) study found that before age 45 years, men are more likely to have HTN, but that after age 65 years, the incidence is higher in women. Additionally, women are more likely to develop heart failure after an MI.[7]

Some HF etiologies are singular to women, such as peripartum cardiomyopathy, which can present up to 6 months after delivery and be confused with the early demands of an infant on the mother.[8] Stress cardiomyopathy is also more common in women and composes approximately 90% of cases. Additionally, 80% of patients who present with spontaneous coronary artery dissection are female,[9] and should be considered in perimenopausal patients with chest pain. These patients can present with an HF-like syndrome.

The interpretation of cardiac biomarkers should vary between genders. In a recent study, high-sensitivity troponin I was shown to significantly increase the diagnosis of acute myocardial infarction in women (11%–22%) but not men (19%–22%).[10] The role of B-type

natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has been well validated for both diagnostic and therapeutic assessment of HF.[11,12] Although the clinical correlations of these measurements are similar, the baseline values have significant gender differences.[3] Women have a 1.6-fold increase in baseline circulating plasma BNP levels and a 1.3-fold increase in NT-proBNP levels when compared to men.[13] Additionally, because BNP has been validated in nonischemic cardiomyopathy, this test is critical in the assessment of women with HF.[14]

3 | HEART FAILURE WITH REDUCED EJECTION FRACTION

In 2012, an estimated 5.8 million or 2.4% of the total US population had heart failure.[7,15,16] Current guidelines differentiate HF classes by both functional capacity and left ventricular ejection fraction (LVEF). Despite the fact that the cumulative incidence of HF is similar between both genders, women are approximately 65% less likely to develop heart failure with reduced ejection fraction (HFrEF) (LVEF ≤40%) than men, particularly in their younger years.[1,3,17,18] Although cardiovascular (CV) risk factors predispose both genders to HFrEF, diabetes and obesity significantly increases the risk of HFrEF in women compared to men. From 1971 to 2000, mortality rates from diabetes have decreased by 43% in men, whereas women's mortality are unchanged.[12,13] Additionally, women are less likely to achieve a glycated hemoglobin level < 7 than men, and are less frequently prescribed primary preventative therapy such as aspirin or statins (odds ratio: 0.75, $P < 0.05$).[14] Obesity appears to have a worse outcome in women than men. The Framingham Heart Study reported that obesity increased the relative risk of coronary artery disease (CAD) in women by 64%, as opposed to only 46% in men.[1]

In large datasets or clinical trials, women with HFrEF have a higher prevalence of nonischemic cardiomyopathy when compared to men.[19,20] Although, in general, women have a better overall survival with HFrEF than men,[16] and women who have an ischemic etiology for HFrEF may have a mortality similar to or worse than men with ischemic HFrEF.

Despite comprising only 20% of subjects enrolled in the initial cardiac resynchronization therapy (CRT) clinical trials, we now know that women are more likely to have a mortality benefit after CRT.[21,22] National Cardiovascular Data Registry data published in 2014 found that women had an 18% lower mortality risk after cardiac resynchronization therapy–defibrillator implantation (hazard ratio [HR]: 0.82, 95% CI: 0.78-0.87, $P < 0.0001$).[23] In those with a left bundle branch block (LBBB), women had a 21% lower mortality risk than men (HR: 0.79, 95% CI: 0.74-0.84, $P < 0.001$). Although there was no significant gender difference in mortality among patients with a QRS >140 ms, women had a higher mortality benefit than those with a QRS duration of 120 to 129 ms (HR: 0.73, 95% CI: 0.60-0.88, $P = 0.001$). There was no observed sex difference in patients without a LBBB. These studies highlight the importance of the accurate recognition of LBBB and symptomatic left ventricular (LV) dysfunction in women, and potentially a role for earlier CRT implantation than male patients.[24] Yet, women are less likely to receive an indicated CRT, or implantable cardioverter defibrillator, or both. Medical therapy will be discussed below.

4 | HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF (LVEF ≥55%) is twice as common in women than men, which results from physiologic differences between the 2 genders.[25] In the presence of hemodynamic stress, female myocardium is more likely to remodel in a concentric pattern compared to men who experience eccentric hypertrophy.[26] The HFpEF phenotype is heterogeneous, encompassing various degrees of LV systolic and diastolic function, pulmonary hypertension, and comorbid conditions. Specific risk factors for developing HFpEF include HTN, obesity, and atrial fibrillation, but it is important to note that roughly 50% of patients with HFpEF have 5 or more major comorbidities.

There is no single diagnostic test with adequate predictive characteristics for the diagnosis of HFpEF. Symptoms of HFpEF are often nonspecific, and thus, diagnosis is often supported with the addition of biomarkers, echocardiography, and right heart invasive catheterization.[16] In the decompensated patient, BNP and NT-proBNP can rule out HFpEF, but its utility is limited in obese patients and those with renal dysfunction.[14] Patients with HFpEF will uniformly have a LVEF >40%, but many will have echocardiographic evidence of diastolic dysfunction, elevated filling pressures, and pulmonary HTN. In the patient with exertional symptoms and normal filling pressures at rest, diastolic stress testing can be utilized.[27]

Over the past decade, data have emerged demonstrating the high morbidity and mortality of HFpEF. In-hospital mortality rates range from 2.4% to 4.9%,[16] with 90-day mortality rates estimated as high as 9.5%. One-year mortality is estimated at 29% in patients who were hospitalized at the time of diagnosis, whereas patients who were diagnosed as outpatients have annual mortality rates of roughly 5%. Not surprisingly, the mortality of HFpEF increases with age and comorbid conditions. Higher mortality rates are also observed in patients with right ventricle dysfunction and pulmonary HTN. Most deaths are noncardiac. Finally, the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial uncovered that 43% patients with HFpEF report a low health-related quality of life.[28]

5 | CARDIOMYOPATHIES

5.1 | Ischemic cardiomyopathy

CAD in women remains a distinct entity than in men. Women who have ischemic cardiomyopathies are older, have multiple comorbidities, and are less likely to have obstructive epicardial coronary stenosis (>50% obstruction), and have more comorbidities than men.[9,29,30] Although more common in patients who present with HFrEF, the prevalence of CAD in patients with HFpEF ranges from 20% to 76%.[9] However, despite the lack of obstructive CAD, women who present with symptoms of angina have a higher mortality than

asymptomatic females. The WISE (Women's Ischemic Syndrome Evaluation) study demonstrated that women experience symptoms of obstructive CAD differently than men, with older women more likely to present in a typical pattern.[24,31,32] During their event, women may present with symptoms of shortness of breath (58%), weakness (55%), unusual fatigue (43%), diaphoresis (39%), and dizziness (39%).[26] For decades, common teaching was that chest pain had a typical presentation: substernal pain brought on by exertion, relieved by rest or nitroglycerin.[33] Unfortunately, these criteria have a low sensitivity for ischemic heart disease in women, most notably in women less than 55 years old.

Despite frequent atypical symptoms, it is important to note that the most common symptom in women with acute coronary syndrome (ACS) is still chest pain.[9] Although most present with acute symptoms, some report a prodrome of unique symptoms up to 1 month prior including increased fatigue (70%), sleep disturbance (47.8%), and shortness of breath (42.1%).[19] The 10-year follow-up from the WISE study demonstrated a 20% mortality rate in women referred for invasive angiography for symptoms of ischemia. In those who did not have obstructive disease, the 10-year mortality was 13%, significantly greater than asymptomatic age-matched controls (2.8%).[27,32]

Women are far more likely than men to have evidence of coronary microvascular dysfunction (CMD) on invasive testing.[19,20,31] Although less likely than obstructive epicardial CAD to result in HFrEF, CMD diagnosis should be considered in patients presenting with HFpEF. In a postmortem analysis of subjects with HFpEF, there was strong correlation between CMD and myocardial fibrosis. Interestingly, patients who had CMD had similar levels of fibrosis as patients with HFrEF and epicardial stenosis.[34] In an analysis of women with suspected CMD, a reduced coronary flow reserve was associated with a significantly higher risk of hospitalization for HF, even without obstructive CAD. Additionally, CMD in women has negative prognostic implications in hypertrophic cardiomyopathy and dilated cardiomyopathy.[35,36]

5.2 | Nonischemic cardiomyopathy

The etiology of nonischemic cardiomyopathies (NICM) has important gender differences. Stress-induced or takotsubo cardiomyopathy predominantly affects postmenopausal women.[37] Patients will present with an ACS, nonobstructive CAD, and reduced LVEF. On echocardiography, the classic finding is apical akinesis with preserved basal wall motion.[38] Patients may report a recent stressful event, although this is not required for diagnosis. Most patients will recover within 3 months, and recurrence rate is low (2%–5%).[39]

Peripartum cardiomyopathy (PPCM) presents in women within 6 months of delivery, although the majority of diagnoses are within the first week postpartum.[40] Risk factors include advanced maternal age, preeclampsia, and multiple gestations. The prognosis of PPCM is generally favorable, with more than 70% of patients having full recovery of LVEF at 6 months.[41] Treatment includes standard American College of Cardiology/American Heart Association (ACC/AHA) guideline-based medical therapy, although small nonrandomized trials have reported a benefit from bromocriptine administration at the time of diagnosis (58% LV recovery vs 27%, $P = 0.012$),[42,43] and future pregnancies should be avoided as recurrence is common.[44]

With over 2.2 million women in the United States having undergone therapy for breast cancer, the cardiotoxicity of adjuvant chemotherapy is increasingly recognized as a risk factor for NICM in women.[45] The incidence of cardiotoxicity varies depending on the type of chemotherapy administered. In women who receive adjuvant chemotherapy, the adjusted 3-year incidence of HF is as high as 42% for patients receiving anthracycline and trastuzumab, 32% for patients receiving trastuzumab alone, compared to 18% with no adjuvant therapy.[46] Current guidelines recommend long-term surveillance in women who have undergone anthracycline-based therapy or mediastinal radiation therapy with symptom-based echocardiography at 5 and 10 years.[45,47]Additionally, high-risk patients should receive a functional noninvasive stress test at 5 or 10 years, based on symptoms.

6 | SEX DIFFERENCES IN PHARMACOLOGY AND TREATMENT OF HEART FAILURE

Gender differences in the pharmacokinetics (PK) and pharmacodynamics (PD) exist and may result in disparities among drug absorption, distribution, metabolism, and excretion, as well as drug concentration at the site of action and resulting effect of common HF therapies. Table 1 summarizes some of the distinct variations between the sexes.[29,30,48]

Clinically relevant PK and PD gender differences in HF pharmacotherapy include captopril, digoxin, torsemide and metoprolol succinate. Captopril is better absorbed when administered on an empty

TABLE 1 Variations in PK properties of drugs in women

PK Property	Effect in Women	Cause
Absorption	Less oral drug absorption	Less gastric acid secretion Slower GI motility and transit time
Distribution	Larger for lipophilic drugs Smaller for hydrophilic drugs	Greater body fat Lower total body water
Metabolism	Phase I Increased activity of CYP2B6, CYP2D6, CYP3A4 Decreased activity of CYP1A2, CYP2E1 Phase II Increased activity of xanthine-oxidases Decreased activity of N-acetyltransferases, sulfotransferases, methyltransferases	Variations in enzyme activity due to pregnancy, menopause, OC use and menstruation
Excretion	Lower but marginal difference when normalized for body weight	Decreased renal blood flow, GFR, and tubular secretion and reabsorption

Abbreviations: CYP, cytochrome P(450); GI, gastrointestinal; GFR, glomerular filtration rate; OC, oral contraception; PK, pharmacokinetic.

stomach, and women should wait longer after eating, as prolonged gastrointestinal transit may decrease absorption. Serum digoxin concentrations are higher in woman due to reduced volume of distribution (Vd) and lower clearance (Cl); lower doses and target serum concentrations should be used to avoid toxicity.[49] The peak plasma concentration and area under the curve of plasma levels of torsemide are significantly higher in women resulting in reduced elimination and noted gender differences in the frequency of hospitalizations secondary to diuretic use.[50] A reduced Vd and slower Cl of metoprolol succinate via CYP2D6 can result in a greater reduction in blood pressure and heart rate at lower doses in women.

The incidence of adverse drug effects (ADEs) among women is 1.5- to 1.7-fold higher than men. Hospitalizations due to ADEs also occur more frequently in women.[51] Electrolytes should be monitored closely, as women with HF receiving diuretic therapy are more likely to experience hyponatremia, hypokalemia, and subsequent severe arrhythmias. Angiotensin-converting enzyme (ACE) inhibitor–induced cough occurs more frequently in women than men by a factor of ~1.5 to 2.[51]

Because women are under-represented in clinical trials, the current guidelines for HF are not gender specific. Early landmark trials with ACE inhibitors suggested that reductions in mortality and HF hospitalizations were observed in men and not women with HFrEF. However, a small percentage of women were enrolled in the CONSENSUS (The Effects of Enalapril on Mortality in Severe Congestive Heart Failure), SAVE (Survival And Ventricular Enlargement Trial), and SOLVD (Effects of Enalapril on Survival in Patients With Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure) trials. Furthermore, the teratogenic effects of ACE inhibitors may preclude women of child bearing age from receiving this therapy. Subsequent meta-analyses have demonstrated comparable benefits of ACE inhibitors survival and HF hospitalization in both men and women with HFrEF.[52]

In addition, the landmark trials with angiotensin II receptor blockers (ARBs) have achieved similar benefit on survival and HF hospitalization in men and women with HFrEF. Aldosterone antagonists, such as spironolactone and epleronone, demonstrated a total mortality benefit among women with HFrEF in post hoc subgroup analysis of the RALES (Randomized Aldactone Evaluation Study) and EPHESUS (Eplerenone Post-Ami Heart Failure Efficacy and Survival Study) trials.[52] Pooled mortality data by sex from the MERIT-HF (Metoprolol Cr/Xl Randomized Intervention Trial in Congestive Heart Failure), CIBIS (Cardiac Insufficiency Bisoprolol Study)-II, and COPERNICUS (Effect of Carvedilol on Survival in Severe Chronic Heart Failure) trials showed similar and significant survival benefits in women and men with HFrEF receiving metoprolol succinate, bisoprolol, and carvedilol, respectively.[53] Given the morbidity and mortality benefits of renin-angiotensin-aldosterone system inhibitors along with guideline-specific β-blockers, triple therapy should not be withheld from women with HFrEF.

Both men and women with HFrEF who self-identify as African American with New York Heart Association class III to IV symptoms benefited from combination hydralazine and isosorbide dinitrate when added to ACE inhibitor/ARB and β-blocker therapy as evidenced by A-HeFT (African-American Heart Failure Trial).[54] However, there are no published data for women to support substituting hydralazine and isosorbide dinitrate for an ACE inhibitor/ARB among intolerant patients. An increase in all-cause mortality among women with HFrEF was noted in a post hoc analysis of the DIG (Digoxin Investigation Group) study. However, a second retrospective analysis concluded that there was a beneficial effect on morbidity in women and no excess mortality between concentrations between 0.5 and 0.9 ng/mL.[52] Newer agents for HFrEF, such as ivabradine and sacubitril/valsartan, appear to have similar effects in both men and women.

The 2017 focused update of the HF guidelines included a recommendation for aldosterone antagonists to reduce HF hospitalizations in patients with HFpEF.[55] A subgroup analysis of the TOPCAT trial that included the Americas had a study population where women composed 50%.[56] An existing recommendation suggests ARB use to decrease HF hospitalizations based on the CHARM (The Effects of Candesartan for the Management of Patients With Chronic Heart Failure)–Preserved trial where 40% of the 3025 study participants were women.[57] Both the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction Study) and the CHARM-Preserved trials identified specific subgroups with different clinical features, outcomes, and response to treatment.[58–60] Worse outcomes were noted in elderly women with renal dysfunction and a group of 44% women with multiple CV comorbidities. Interestingly, the latter population was the only one that had a significant reduction in adverse events with irbesartan compared to placebo (HR: 0.72, 95% CI: 0.52-0.91).

As HFpEF continues to represent a disease of older women, and in the setting of limited pharmacotherapy treatments, it is critical that future clinical trials reflect the patient population. The limited data on women due to low enrollment in clinical trials make analysis of sex-specific data extremely difficult. Although the National Institutes of health and other funding agencies continue to ask for better recruitment, the numbers are still inadequate.[57] Table 2 provides a list of well-known HF trials and the percent of women enrolled.

7 | EXERCISE TRAINING AS THERAPY

The ACC/AHA guidelines recommend exercise training as another therapeutic modality for patients with HF. The data on the benefits are derived from the National Heart, Lung, and Blood Institute trial HF-ACTION (Heart Failure–A Randomized Controlled Trial Investigating Outcomes of Exercise Training), which randomized 2231 patients with HFrEF to a control group or an exercise group of aerobic training at 70% of heart rate reserve. The percent of women recruited was 29%, with more nonischemics than ischemics. The population was well medicated, with a mean ejection fraction of 25%. Post hoc subgroup analysis by sex showed that the women had a greater benefit related to the primary endpoint of all-cause mortality or all cause hospitalization.[16] Based on the totality of the data with safety and improvement in health-related quality of life, the Centers for Medicare and Medicaid Services now covers cardiac rehabilitation for patients with HFrEF. Therefore, sex should not limit referral to exercise training.

TABLE 2 Heart failure trials: number and percent of women enrolled in each and LVEF for entry

Study	% Women	No. of Women	LVEF
A-HeFT	40	420	≤35%
CHARM–Overall	32	2400	Any
CHARM–Preserved	40	1212	>40%
CIBIS II	19	515	≤35%
COMPANION	32	493	≤35%
CONSENSUS	30	75	Unknown
COPERNICUS	20	469	<25%
DIG	22	1520	≤45%
ELITE-I	33	240	≤40%
ELITE-II	31	966	≤40%
MADIT II	16	192	≤30%
MERIT-HF	23	898	≤40%
MIRACLE	32	145	≤35%
PARADIGM	22	1832	≤40%
RALES	27	446	≤35%
SCD HeFT	23	588	≤35%
SOLVD-Prevention	11	484	≤35%
SOLVD-Treatment	20	505	≤35%
Val-HEFT	20	1003	<40%
V-HeFT I II III	0	0	<45%
WARCEF	20	339	<40%
HF ACTION	29	653	≤35%

Abbreviations: A-HeFT, African-American Heart Failure Trial; CHARM, Effects of Candesartan for the Management of Patients With Chronic Heart Failure; CIBIS, Cardiac Insufficiency Bisoprolol Study; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure; CONSENSUS, Effects of Enalapril on Mortality in Severe Congestive Heart Failure; COPERNICUS, Effect of Carvedilol on Survival in Severe Chronic Heart Failure; DIG, Digoxin Investigation Group; ELITE, Evaluation of Losartan in the Elderly; HF-ACTION, Heart Failure—A Randomized Controlled Trial Investigating Outcomes of Exercise Training; LVEF, left ventricular ejection fraction; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MERIT-HF, Metoprolol Cr/Xl Randomized Intervention Trial in Congestive Heart Failure; MIRACLE, Multicenter Insync Implantable Cardioversion Defibrillation Randomized Clinical Evaluation; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomized Aldactone Evaluation Study; SCD HeFT, Sudden Cardiac Death in Heart Failure Trial; SOVLD, Effects of Enalapril on Survival in Patients With Reduced Left Ventricular Ejection; Val-HEFT, Valsartan Heart Failure Trial; V-HeFT, Effects of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure; WARCEF, Warfarin and Aspirin in Patients With Heart Failure and Sinus Rhythm.

8 | CONCLUSION

It is important for the clinician to recognize the prevalence of HF in women and not to confuse symptoms of HF with those of other disorders, such as COPD or asthma. Medical therapy should be offered to female patients the same as to male patients using evidence based-care and not preconceived notions. There also needs to be a larger number of women represented in HF clinical trials so that appropriate and statistically sound conclusions can be made in analyses by sex. Until then, and as discussed above, extrapolation of results in women are often relegated to post hoc analyses of small numbers with all its pitfalls.

Conflicts of interest

The authors declare no potential conflicts of interest.

ORCID

Katherine E. Di Palo http://orcid.org/0000-0003-1558-4718

REFERENCES

1. Kenchaiah S, Vasan RS. Heart failure in women—insights from the Framingham Heart Study. *Cardiovasc Drugs Ther.* 2015;29:377–390.
2. Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. *Circulation.* 2008;118:2057–2062.
3. 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;347:1397–1402.
4. Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation.* 2002;106:3068–3072.
5. Rutten FH, Cramer MJ, Grobbee DE, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J.* 2005;26:1887–1894.
6. Jorge S, Becquemin MH, Delerme S, et al. Cardiac asthma in elderly patients: incidence, clinical presentation and outcome. *BMC Cardiovasc Dis.* 2007;7:16.
7. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121:586–613.
8. Arany Z, Elkayam U. Peripartum cardiomyopathy. *Circulation.* 2016;133:1397–1409.
9. Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. *Circ Res.* 2016;118:1273–1293.
10. AlBadri A, Lai K, Wei J, et al. Inflammatory biomarkers as predictors of heart failure in women without obstructive coronary artery disease: a report from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE). *PLoS One.* 2017;12:e0177684.
11. Januzzi JL, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol.* 2005;95:948–954.
12. Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J.* 2005;27:330–337.
13. Doyle M, Pohost GM, Bairey Merz CN, et al. Use of bio-informatics assessment schema (BIAS) to improve diagnosis and prognosis of myocardial perfusion data: results from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE). *Cardiovasc Diagn Ther.* 2016;6:424–431.
14. Felker GM, Whellan D, Kraus WE, et al. N-terminal pro-brain natriuretic peptide and exercise capacity in chronic heart failure: data from the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study. *Am Heart J.* 2009;158(4 suppl):S37–S44.
15. 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. *J Am Coll Cardiol. 2013;62*:e147–e239.
16. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* 2017;14:591–602.
17. Ho JE, Gona P, Pencina MJ, et al. Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the community. *Eur Heart J.* 2012;33:1734–1741.
18. Ho JE, Lyass A, Lee DS, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. *Circ Heart Fail.* 2013;6:279–286.

19. Leuzzi C, Modena MG. Coronary artery disease: clinical presentation, diagnosis and prognosis in women. *Nutr Metab Cardiovasc Dis*. 2010; 20:426–435.
20. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol*. 2009;54:1561–1575.
21. Zusterzeel R, Curtis JP, Caños DA, et al. Sex-specific mortality risk by QRS morphology and duration in patients receiving CRT: results from the NCDR. *J Am Coll Cardiol*. 2014;64:887–894.
22. Zusterzeel R, Spatz ES, Curtis JP, et al. Cardiac resynchronization therapy in women versus men: observational comparative effectiveness study from the National Cardiovascular Data Registry. *Circ Cardiovasc Qual Outcomes*. 2015;8(2 suppl 1):S4–S11.
23. Loring Z, Caños DA, Selzman K, et al. Left bundle branch block predicts better survival in women than men receiving cardiac resynchronization therapy: long-term follow-up of ~145,000 patients. *JACC Heart Fail*. 2013;1:237–244.
24. Bairey Merz CN, Regitz-Zagrosek V. The case for sex- and gender-specific medicine. *JAMA Intern Med*. 2014;174:1348–1349.
25. Piña IL, Kokkinos P, Kao A, et al. Baseline differences in the HF-ACTION trial by sex. *Am Heart J*. 2009;158(4 suppl):S16–S23.
26. Stock EO, Redberg R. Cardiovascular disease in women. *Curr Probl Cardiol*. 2012;37:450–526.
27. Romero J, Husain SA, Holmes AA, et al. Non-invasive assessment of low risk acute chest pain in the emergency department: a comparative meta-analysis of prospective studies. *Int J Cardiol*. 2015;187: 565–580.
28. Lewis EF, Kim HY, Claggett B, et al. Impact of Spironolactone on Longitudinal Changes in Health-Related Quality of Life in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial. *Circ Heart Fail*. 2016;9:e001937.
29. Jochmann N, Stangl K, Garbe E, Baumann G, Stangl V. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. *Eur Heart J*. 2005;26:1585–1595.
30. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. *Pharmacol Res*. 2007;55:81–95.
31. Gulati M, Shaw LJ, Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. *Clin Cardiol*. 2012;35:141–148.
32. Kenkre TS, Malhotra P, Johnson BD, et al. Ten-year mortality in the WISE study (Women's Ischemia Syndrome Evaluation). *Circ Cardiovasc Qual Outcomes*. 2017;10(12).
33. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. 1979;300: 1350–1358.
34. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. 2015;131:550–559.
35. Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med*. 2003;349:1027–1035.
36. Neglia D, Michelassi C, Trivieri MG, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. *Circulation*. 2002;105:186–193.
37. Murakami T, Yoshikawa T, Maekawa Y, et al. Gender differences in patients with Takotsubo cardiomyopathy: multi-center registry from Tokyo CCU network. *PLoS One*. 2015;10:e0136655.
38. Kagiyama N, Okura H, Matsue Y, et al. Multiple unfavorable echocardiographic findings in takotsubo cardiomyopathy are associated with increased in-hospital events and mortality. *J Am Soc Echocardiogr*. 2016;29:1179–1187.
39. Kurisu S, Kihara Y. Tako-tsubo cardiomyopathy: clinical presentation and underlying mechanism. *J Cardiol*. 2012;60:429–437.
40. Sliwa K, Fett J, Elkayam U. Peripartum cardiomyopathy. *Lancet*. 2006; 368:687–693.
41. Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: diagnosis, prognosis, and management. *J Am Coll Cardiol*. 2011;58:659–670.
42. Jahns BG, Stein W, Hilfiker-Kleiner D, Pieske B, Emons G. Peripartum cardiomyopathy—a new treatment option by inhibition of prolactin secretion. *Am J Obst Gynecol*. 2008;199:e5–e6.
43. Sliwa K, Blauwet L, Tibazarwa K, et al. Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation*. 2010;121:1465–1473.
44. Elkayam U, Tummala PP, Rao K, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med*. 2001;344:1567–1571.
45. Francis SA, Cheng S, Arteaga CL, Moslehi J. Heart failure and breast cancer therapies: moving towards personalized risk assessment. *J Am Heart Assoc*. 2014;3:e000780.
46. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol*. 2012;60:2504–2512.
47. Sawaya H, Sebag IA, Plana JC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging*. 2012;5:596–603.
48. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2009;48:143–157.
49. 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;347:1403–1411.
50. Werner U, Werner D, Heinbuchner S, et al. Gender is an important determinant of the disposition of the loop diuretic torasemide. *J Clin Pharmacol*. 2010;50:160–168.
51. Rosano GM, Lewis B, Agewall S, et al. Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC. *Eur Heart J*. 2015;36:2677–2680.
52. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. *Eur Heart J*. 2017;3:163–182.
53. Ghali JK, Krause-Steinrauf HJ, Adams KF, et al. Gender differences in advanced heart failure: insights from the BEST study. *J Am Coll Cardiol*. 2003;42:2128–2134.
54. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med*. 2004; 351:2049–2057.
55. 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;136:e137–e161.
56. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.
57. McMurray J, Ostergren J, Pfeffer M, et al. Clinical features and contemporary management of patients with low and preserved ejection fraction heart failure: baseline characteristics of patients in the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur J Heart Fail*. 2003;5:261–270.
58. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail*. 2011;4:27–35.
59. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359: 2456–2467.
60. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362: 777–781.

How to cite this article: Eisenberg E, Di Palo KE, Piña IL. Sex differences in heart failure. *Clin Cardiol*. 2018;41:211–216. https://doi.org/10.1002/clc.22917