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HEART FAILURE IN WOMEN SPECIAL ISSUE

STATE-OF-THE-ART REVIEWS

Primary Prevention of Heart Failure in Women

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CME/MOC/ECME Objectives for This Article: Upon completion of this activity, the learner should be able to: 1) identify the major risk factors and preventive targets for heart failure with reduced ejection fraction in women; 2) the major risk factors and preventive targets for heart failure with preserved ejection fraction in women; and 3) discuss interventions to optimize sex-specific prevention of heart failure.

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Primary Prevention of Heart Failure in Women

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ABSTRACT

The incidence of heart failure (HF) is increasing, particularly among women, and constitutes a rapidly growing public health problem. The primary prevention of HF in women should involve targeted, sex-specific strategies to increase awareness, promote a heart healthy lifestyle, and improve treatments that optimally control the risk factors for HF with reduced ejection fraction and HF with preserved ejection fraction. Epidemiological and pathophysiological differences in both HF subtypes strongly suggest that sex-specific preventive strategies and risk factor reduction may be particularly beneficial. However, significant gaps in sex-specific knowledge exist and are impeding preventive efforts. To overcome these limitations, women need to be adequately represented in HF research, sex differences must be prospectively investigated, and effective sex-specific interventions should be incorporated into clinical practice guidelines. This review summarizes the existing evidence that supports the primary prevention of HF in women and identifies potential strategies that are most likely to be effective in reducing the burden of HF among women. (J Am Coll Cardiol HF 2019;7:181–91)

Of the 6.5 million adults with heart failure (HF) in the United States, 3.6 million (55.4%) are women (1). Although HF-related death rates have been declining for both men and women since 2000, the incidence of HF is increasing and is disproportionately affecting women across the lifespan (**Figure 1**). Between the ages of 65 and 85 years, it is estimated that the incidence of HF doubles in men with each 10-year increase, whereas the rate of incidence of HF triples in the same time frame among women (2). By 2030, the prevalence of HF is projected to increase by 46% unless widespread effective strategies are implemented for HF prevention (1). Unfortunately, there are little randomized trial data that have documented the effectiveness of interventions to prevent HF in women. This review summarizes the limited existing evidence and identifies potential strategies most likely to be effective in reducing the burden of HF in women (**Table 1**).

Epidemiological differences in HF between men and women may provide important insights for guiding effective sex-specific preventive strategies (**Central Illustration**). Compared with men, women with HF are typically older, have a higher body mass index (BMI), a higher ejection fraction (EF), and a greater prevalence of hypertension, diabetes, and kidney dysfunction (3–5). Hypertension is the most common risk factor in women (**Figure 2**) and confers the highest risk for developing HF among women, whereas coronary artery disease (CAD) confers the greatest risk in men (6,7). In studies of new-onset HF, women develop HF later in life than men and are more likely to have HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF) (8–10). In addition, atrial fibrillation has been shown to have sex-specific predictive value for the development of HFpEF in women (7,8). Interventions targeted at maintaining or achieving a healthy body weight and reducing the number of risk factors, particularly hypertension and atrial fibrillation, may be successful in lowering the rate of incident HF among women. HF risk factors disproportionately affect racial and ethnic minorities, specifically hypertension, obesity, and diabetes, and impart a higher risk of HF in African American and Hispanic women (7,11). The extent to which these risk factors can be modified may make them particularly impactful targets for HF prevention. However, differences in the efficacy of specific preventive interventions among women of different racial and ethnic backgrounds has not been well studied.

The critical importance of prevention is underscored in the American College of Cardiology and the American Heart Association Heart Failure Staging Classification Schema (12). Stage A includes asymptomatic patients with risk factors for HF; stage B patients have pathological structural heart changes, but no symptoms of HF; stage C includes patients with HF symptoms; and stage D is defined by end-stage disease (13). This classification recognizes that there are established risk factors and structural prerequisites for the development of HF, and that therapeutic interventions introduced before the appearance of left ventricular dysfunction or clinical symptoms may reduce the morbidity and mortality associated with HF (14). To truly prevent HF, targeted primary prevention efforts must focus on patients with stage A

disease and incorporate aggressive, sex-specific risk factor control. However, there are no sex-specific recommendations for the prevention of HF, nor do guidelines use different criteria for the diagnosis or treatment of HF in men and women. In this review, we explore the unique risk factors and pathobiology of HF in women and the evidence, or lack thereof, for incorporating sex-specific strategies and interventions into clinical care for the primary prevention of HF in women.

HFrEF IN WOMEN

ISCHEMIC CARDIOMYOPATHY. CAD and ischemic cardiomyopathy are present in 63% of women with HFrEF (11). Although this proportion is smaller than that of men, CAD is still the most common etiology of HFrEF in women, and primary prevention should focus on effectively treating CAD risk factors (**Central Illustration**). Modifiable risk factors for CAD and subsequent HFrEF include hypertension, hyperlipidemia, diabetes, obesity, and physical inactivity (15). Although these traditional risk factors are common in both men and women, many of these risk factors impart a differential risk in women compared with men. In addition, there are sex-specific risk factors and mechanisms of disease that are unique or that predominate in women, such as complications of pregnancy, hormonal changes associated with menopause, autoimmune disease, psychosocial stress, and a variety of cancer treatments, including radiation and chemotherapy (16,17).

Among the modifiable risk factors, hypertension has the highest attributable risk (42.7%) for the development of HFrEF in women (**Figure 3**) (7). It is estimated that >50 million women in the United States have hypertension, and the most recent data from the National Health and Nutrition Examination Survey has revealed that after age 65 years, more women have hypertension than men (1,18). Despite receiving treatment, women are less likely to achieve blood pressure control compared with men (44.8% vs. 51.1%), and this lack of control is more prevalent with advancing age, such that only 29% of women aged older than 70 years have adequate blood pressure control (19,20). The potential reasons for poor blood pressure control in women are multiple and have been explained by lack of medication uptitration (treatment inertia), increased arterial stiffness, overactivation of the renin-angiotensin system, hormonal influences on vascular reactivity, salt–water regulation, and autonomic control (20,21). In addition, sex hormones interact with metabolizing enzymes, which result in differences in drug exposure, elimination, efficacy, and adverse effects. Compared with men, women have better responses to similar doses of diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and beta-blockers, and often need lower doses than men do to have the same effect (22). Importantly, women also have more side effects that may adversely affect treatment, such as electrolyte disturbances with diuretics, ACEI-induced cough, and limiting fatigue with beta-blockade, which may contribute to lower adherence rates (18,22).

Adequately treating blood pressure in women may be one of the most effective ways of preventing HF in women. In the SPRINT (Systolic Blood Pressure Intervention Trial) study, intensive blood pressure treatment (systolic target <120 mm Hg) in women was associated with fewer acute decompensated HF events than standard treatment (systolic target <140 mm Hg), but this did not reach statistical significance (hazard ratio: 0.76; 95% confidence interval: 0.44 to 1.31) perhaps because of the small sample size (only 35% women) (23). Yet, there was a significant reduction in acute HF events among men who received intensive blood pressure treatment compared with standard treatment (hazard ratio: 0.57; 95% confidence interval: 0.39 to 0.83). However, SPRINT was not powered to detect an interaction between the treatment arm and any subgroup. Nonetheless, antihypertensive therapy needs to be individualized in women to ensure target blood pressure levels are achieved with medications that minimize side effects and maximize compliance.

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitors

BMI = body mass index

CAD = coronary artery disease

HF = heart failure

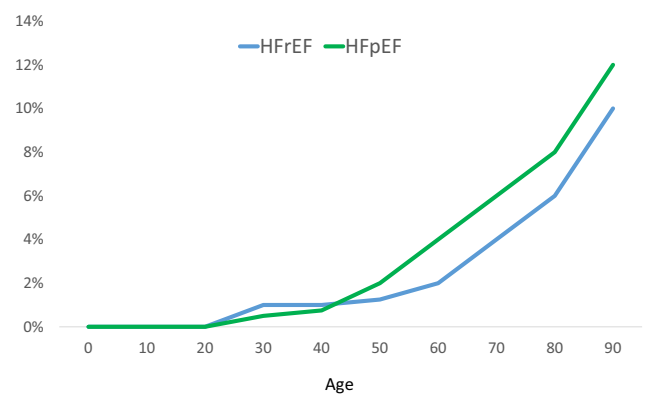
HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

PPCM = peripartum cardiomyopathy

SGLT2 = sodium-glucose cotransporter-2

FIGURE 1 Prevalence of HF in Women Across the Lifespan



The proportion of women affected by heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) increases across the lifespan. Created from data from Benjamin et al. (1), Kao et al. (47), and Mehta and Cowie (71).

TABLE 1 Prevention of HF in Women by HF Stage

Primary →		Secondary →	
Stage A	**Stage B**	**Stage C**	**Stage D**
HFrEF			
CAD risk factor management Exercise/physical activity	Treat HTN, HLD, DM2 Exercise/physical activity Smoking cessation ACEI/ARB and BB*	ACEI/ARB and BB Sodium restriction Diuretics Mineralocorticoid-receptor antagonist Neprilysin inhibition* Cardiac rehabilitation	Cardiac resynchronization therapy Inotropes Left ventricular assist device Heart transplant
HFpEF			
Maintain a healthy weight Weight loss for overweight and obese women Statin* Blood pressure control Exercise/physical activity	Treat HTN Weight loss for overweight and obese women Glucose control in women with DM2, pre-diabetes or history of GDM Physical activity	Treat HTN Diuretics Sodium restriction Use of new antiglycemic agents* Neprilysin inhibition*	Treat HTN Diuretics Supportive care

*Potential benefit, but limited sex-specific evidence to support recommendation.

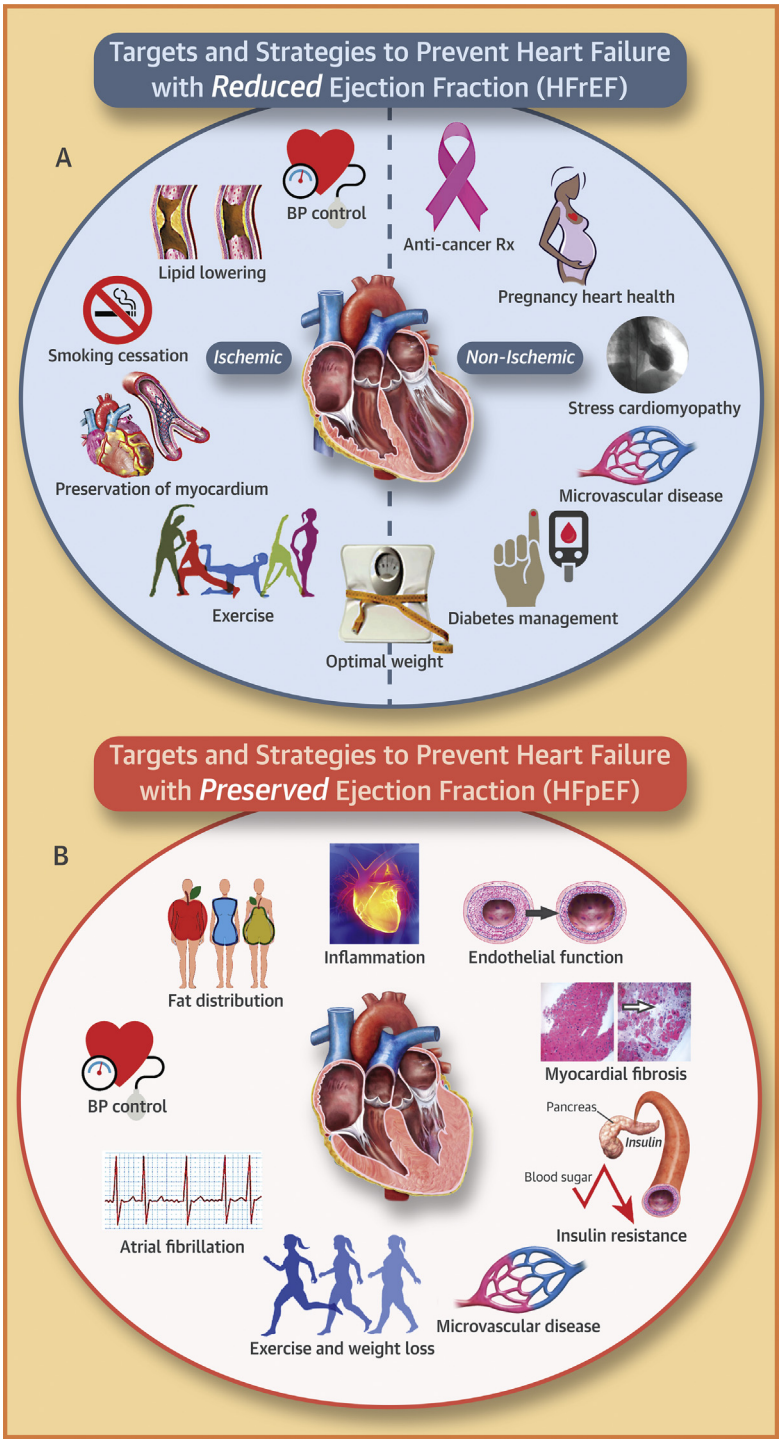
ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BB = beta blocker; CAD = coronary artery disease; DM2 = type 2 diabetes mellitus; GDM = gestational diabetes mellitus; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HLD = hyperlipidemia; HTN = hypertension.

Although hypertension imparts the greatest risk for the development of HF in women, treatment of this risk factor alone may be insufficient to decrease the incidence of HF. A comprehensive approach that includes the effective treatment of hypertension and other coexisting CAD risk factors is key to the primary prevention of HF in women.

Diabetes imparts the second highest risk for the development of HFrEF in women (7). Increasing evidence suggests that biologic differences affect the expression of diabetes and imparts a 4- to 5-fold greater risk for ischemic heart disease and HFrEF in women than that in men, even after adjusting for age, race, education, BMI, smoking, hypertension, cholesterol levels, and medical therapy (24). Even in the absence of significant CAD, diabetes is associated with a greater risk of developing HF, with pathogenic and epidemiological evidence supporting direct cardiac damage. Two distinct phenotypes have been described: 1) coronary microvascular endothelial dysfunction that results in a restrictive HFpEF phenotype with concentric left ventricular remodeling and diastolic dysfunction; and 2) cardiomyocyte cell death that results in a dilated HFrEF phenotype with eccentric left ventricular remodeling and systolic dysfunction (25). Although diabetic cardiomyopathy does not appear to predominate in women, poorer diabetic control can predispose to the development of diabetic cardiomyopathy. Unfortunately, women with diabetes are less likely to have a hemoglobin A_{1c} of <7% compared with men with diabetes, and women also have poorer control of other risk factors (e.g., hypertension and hyperlipidemia) (26). Taken together, women with diabetes are at greatly increased risk for developing CAD, ischemic heart disease, and HFrEF, and may also be at increased risk for either diabetic cardiomyopathy phenotype. Early and aggressive treatment of diabetes in women is needed to prevent the microvascular and macrovascular coronary complications that contribute to HFrEF development. New antidiabetic agents, particularly sodium-glucose cotransporter-2 (SGLT2) inhibitors, that have reduced HF exacerbations in patients with diabetes may also be effective in preventing HF (27–29). Women were <40% of the study population in the SGLT2 inhibitor trials, which limited the results of sex-based subgroup analyses. However, because of the greater risk of ischemia and HF among women with diabetes, a meta-analysis of the SGLT2 inhibitor trials may demonstrate a more significant benefit and even greater potential for HF prevention compared with men with diabetes.

Among women, physical inactivity contributes to a similar number of cardiovascular deaths (approximately 70,000/year) as tobacco smoking and is inversely associated with HF incidence (18,30). It is estimated that 28.6% of men and 31.0% of women are physically inactive (19). Guidelines for the prevention of cardiovascular disease in women recommend 150 min of moderate activity per week (15); however, even lesser amounts of physical activity can have considerable benefit. Among post-menopausal women, each increase in physical activity (equivalent to approximately 60 min of brisk walking per week) has been associated with an average risk reduction for HFrEF of 10% (31). Similarly, the

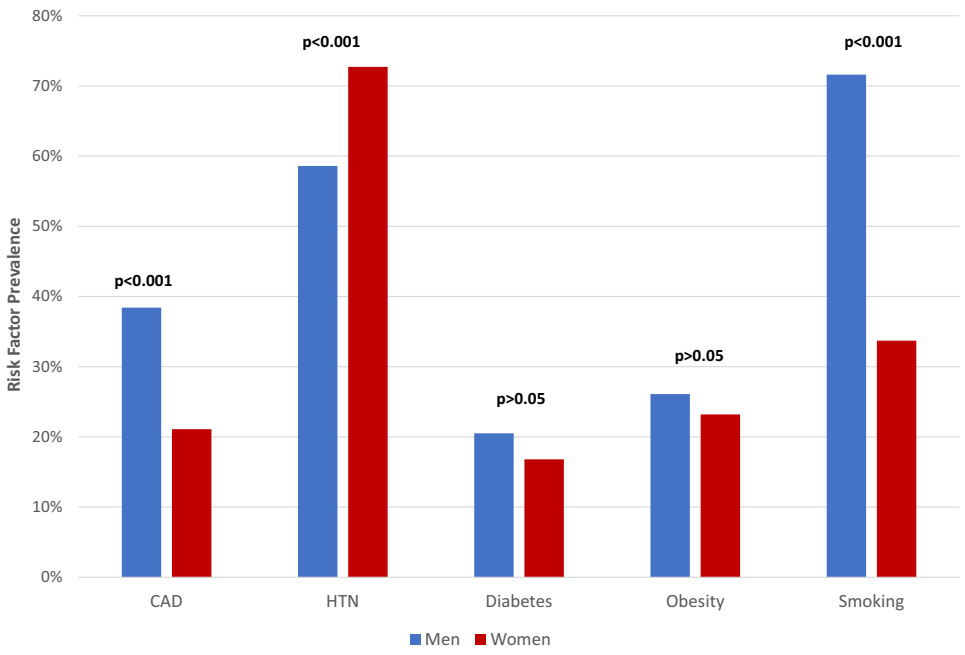
CENTRAL ILLUSTRATION **Targets and Strategies to Prevent HFrEF and HFpEF in Women**



Daubert, M.A. et al. J Am Coll Cardiol HF. 2019;7(3):181–91.

The primary prevention of HF in women should involve targeted, sex-specific strategies to increase awareness, promote a heart healthy lifestyle, and improve treatments that optimally control the risk factors for **(A)** heart failure with reduced ejection fraction (HFrEF) and **(B)** heart failure with preserved ejection fraction (HFpEF). BP = blood pressure.

FIGURE 2 Prevalence of Risk Factors for HF in Men and Women



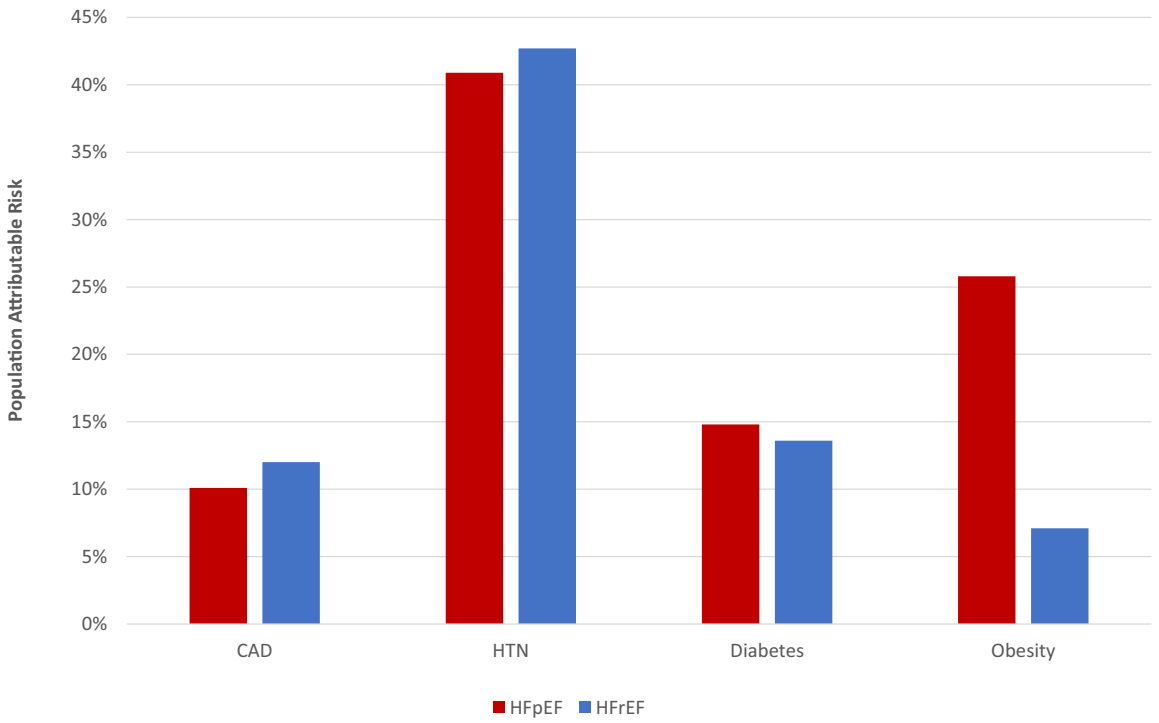
Numerous risk factors contribute to the development of heart failure (HF) (subtype not specified), but the prevalence and attributable risk differs between men and women. Created from data from Dunlay et al. (6).

INTERHEART study demonstrated that the protective effects of exercise on future cardiovascular disease were even greater for women than that for men (32). Regular physical activity in combination with optimal control of other CAD risk factors decreased the incidence of HF in women in the Atherosclerosis Risk in Communities (ARIC) study (33). Greater adherence to the American Heart Association's Life's Simple 7 guidelines for physical activity, diet, body mass, cholesterol, blood pressure, smoking and glucose control in the ARIC study was associated with a lower lifetime risk of HF in women—13.0% in women with optimal adherence compared with 48.7% in women with inadequate adherence. Although the ARIC study was not analyzed by HF subtype, greater adherence was associated with a 50% reduction in systolic dysfunction, or presumably stage B HFrEF. Therefore, along with effective risk factor treatment, a critical component of preventing HFrEF in women is to prescribe regular physical activity, assess for compliance, and encourage ongoing efforts.

There is increasing recognition that pregnancy complications, including gestational diabetes, premature birth, and pre-eclampsia, are early indicators of increased cardiovascular risk in women (34). Gestational diabetes, which is on the rise due to the obesity epidemic, is associated with a significantly increased risk of developing type 2 diabetes mellitus and confers a 59% higher risk of myocardial infarction compared with women without gestational diabetes during pregnancy (32). Women with a history of pre-eclampsia have a 4-fold higher incidence of essential hypertension, are at twice the risk for CAD and stroke, and are nearly 80% more likely to develop HF than women without hypertension during pregnancy (35–37). This underscores the importance of obtaining a comprehensive reproductive history when evaluating cardiovascular risk in women. Pregnancy complications can identify women at high risk who might benefit from the early application of preventive interventions and risk factor modification.

NONISCHEMIC CARDIOMYOPATHY. HFrEF due to nonischemic dilated cardiomyopathy contributes significantly to the global burden of cardiovascular disease and is related to a variety of etiologies (**Central Illustration**). Myocarditis, which is defined as inflammation of the myocardium with or without necrosis, has a slightly greater prevalence in men than women (reported female-to-male ratio between 1:1.5 and 1:1.7), which may be due to sex differences in genetics and the influence of sex hormones on the acute response of the heart to injury (38). Sex

FIGURE 3 Population Attributable Risk of Comorbidities for HFpEF and HFrEF in Women



Hypertension (HTN) has the highest attributable risk for HFrEF in women followed by diabetes. Hypertension and obesity confer the highest attributable risk for HFpEF in women. Created from data from Eaton et al. (7).

hormones have a profound influence on the immune and cardiovascular systems and may explain some of the sex differences in HF. Through estrogen receptor membrane signaling, estrogen has been shown to regulate arterial tone and blood pressure, as well as protect against vascular injury and atherosclerosis. Women have higher estrogen receptor expression on their arteries than men, but this decreases with age and menopause, which partially explains the loss of cardioprotection in older adult and post-menopausal women (39). However, studies have failed to demonstrate a protective effect with supplemental estrogen therapy for primary or secondary cardiovascular prevention (40,41). Further evidence of sex differences in nonischemic HFrEF pathophysiology is illustrated by stress-induced cardiac dysfunction and cardiomyopathy (also called takotsubo cardiomyopathy, broken heart syndrome, and apical ballooning syndrome), which most commonly occurs in post-menopausal women (42,43). Although most women recover within 6 weeks, relapses are common, with an average recurrence rate of 2% to 4% per year and up to 20% at 10 years (43). Meta-analyses of standard HF therapies, including beta-blockers, ACEIs, and angiotensin receptor blockers, have yielded conflicting evidence regarding the efficacy of reducing recurrent episodes of stress-induced dysfunction (43-46).

Peri-partum cardiomyopathy (PPCM), a cause of nonischemic cardiomyopathy and HFrEF unique to women, occurs in the last month of pregnancy or within 5 months of delivery, and may have genetic underpinnings as evidenced by familial clustering (38). Risk factors for PPCM include age ≥30 years, African-American race, hypertension, pre-eclampsia and/or eclampsia, multiple gestations, asthma, anemia, autoimmune disease, and substance abuse (47). In addition, the occurrence of PPCM exponentially increases with each additional risk factor (47). Therefore, targeting modifiable conditions such as hypertension and substance abuse could have a marked impact on decreasing the incidence of PPCM.

Another cause of nonischemic cardiomyopathy with a greater burden in women is cardiotoxicity from cancer treatments, which manifest as asymptomatic systolic dysfunction or overt HFrEF (48). The greatest

risk is in breast cancer because of its high prevalence and long survivorship, concomitant radiation, and use of cardiotoxic drugs in combination. Secondary prevention treatment with beta-blockers and ACEIs, or angiotensin receptor blockers during treatment with anthracyclines with and/or without trastuzumab have shown improvement in EF in nonrandomized studies; however, clinical trials that have evaluated the use of neurohormonal blockade for primary prevention of HFrEF have yielded mixed results. Additional trials are ongoing (48–50).

Women have been included in <30% of the study population in most HFrEF clinical trials (51). Thus, current HF treatment guidelines are not sex-specific due to under-representation of women and a lack of prospective, randomized data for sex-specific analyses of safety and treatment efficacy. As an example, the SOLVD (Studies of Left Ventricular Dysfunction) prevention trial showed that patients with asymptomatic left ventricular dysfunction (stage B HF) who were treated with enalapril and beta-blockers had a reduced risk of developing HFrEF (52,53). Less than 12% of the participants in this trial were women, which limited the applicability of sex-specific analyses or assessment of interaction by sex, but suggested that early recognition and treatment of stage B HF might prevent the future development of symptomatic HFrEF in women. The significant gaps in sex-specific knowledge are impeding preventive efforts. The National Institutes of Health have enacted policies to promote the inclusion of women in clinical trials and require sex to be factored into research design and analyses (54). Specifically, women need to be adequately represented in HF research, sex differences have to be prospectively investigated, and effective sex-specific interventions should be incorporated into clinical practice guidelines.

HFpEF IN WOMEN

Although HFrEF predominates in men, HFpEF is much more common among women (1,55,56). The difference in the prevalence of HF subtypes may be explained, at least in part, by the fact that women live longer and are a larger proportion of the older adult population. However, fundamental sex differences in HF etiology, risk factors, and cardiac remodeling also contribute to the differential risk for HFpEF in women compared with that in men. This suggests that there may be underlying sex-specific pathophysiology that can be targeted to ameliorate the disproportionate burden of HFpEF among women (**Central Illustration**).

A study of incident HF in the Women's Health Initiative found that hypertension and obesity accounted for approximately two-thirds of the attributable risk for HFpEF in women (**Figure 3**); these 2 risk factors contributed to an even greater proportion of the risk among minority women (7). Unlike hypertension, which was a major risk factor for both HFrEF and HFpEF in women, obesity was only associated with an increased risk of HFpEF, and this risk increased with increasing BMI (7). A similar association between obesity and HFpEF in women was observed in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial (57) and a large cohort study by Savji et al. (58) that showed that increased BMI predicted HFpEF, particularly in women.

The pathophysiological mechanisms by which obesity yields higher rates of incident HFpEF include systemic inflammation, insulin resistance, coronary microvascular dysfunction, and myocardial remodeling and fibrosis that result in diastolic dysfunction (58–60). Increased adiposity promotes systemic inflammation that can affect myocardial remodeling via a signaling cascade of coronary microvascular endothelial dysfunction, myocardial infiltration by activated macrophages, interstitial fibrosis, and increased oxidative stress in cardiac myocytes, which culminates in concentric hypertrophy and myocardial stiffness (60). Although these findings are not specific to women, they are highly relevant because more than one-third of U.S. women are obese, and obesity has been more prevalent among women than men since 1960 (1,61). In addition, obese patients with HFpEF have been shown to overproduce adipocyte-derived, cell-signaling molecules, including aldosterone and neprilysin, which results in sodium retention, plasma volume expansion, and increased cardiac filling pressures that further promotes cardiac and systemic inflammation, as well as fibrosis (60,62).

Fortunately, there is evidence that weight loss can lead to dissipation of this deleterious inflammatory response. In a small study of obese post-menopausal women, weight loss by caloric restriction resulted in reduced levels of systemic inflammatory biomarkers and improvement in insulin resistance (63). Because the inflammation and insulin resistance associated with obesity is believed to predispose to HFpEF, weight loss could be a potentially effective method of preventing HFpEF in women. To test this hypothesis, Sundstrom et al.

(64) studied obese patients who received either intensive lifestyle modification or underwent bariatric surgery, and found that the rate of incident HF was significantly reduced, particularly among those receiving bariatric surgery. The importance of a weight loss strategy is underscored by the finding that a 10-kg weight reduction by either strategy reduced the risk of HF by 23%, although no sex-specific analyses were performed. Greater recognition of the contribution of adipocytes to the inflammatory derangements, sodium retention, and plasma volume expansion seen in HFpEF has suggested that mineralocorticoid receptor antagonists, neprilysin inhibitors, and SGLT2 inhibitors, which counteract the previously mentioned pathobiology, may be effective. These treatments have shown promise in the management of obese HFpEF phenotypes (60,62). Obviously, treating obesity and maintaining a healthy weight would be the preferred initial strategies for preventing HFpEF in women, but the novel use of these adjunctive therapeutic interventions in stage B patients with obesity would be an intriguing area of study.

In addition to obesity, elevated blood pressure, higher fasting glucose, increased waist-to-hip ratio and greater insulin resistance, all hallmarks of the metabolic syndrome, predict incident HFpEF among women (58,65). Taken together, this suggests that the pathogenesis of HFpEF may be a complication of the metabolic syndrome, which is significantly more prevalent among women compared with men (35.6% vs. 30.3%; $p < 0.001$) (66). In addition, menopause increases the prevalence of the metabolic syndrome and truncal obesity, both of which contribute to HF development, particularly HFpEF (44,67). These important sex differences may underlie the higher prevalence of HFpEF among women. Future investigations of the preventive potential of treating the metabolic syndrome on reducing HFpEF incidence are critically needed.

Given the pro-inflammatory state in HFpEF, the pleiotropic effects of statin therapy could also be beneficial in the prevention of HFpEF. Statins improve endothelial redox balance and restore nitric oxide bioavailability, independent of their lipid-lowering properties (60). Alehagen et al. (68) demonstrated that statin use reduced death and cardiovascular hospitalizations in patients with HFpEF (68). An observational study of statin-treated HFpEF patients revealed a lower incidence of atrial fibrillation (69). Because atrial fibrillation has been independently identified as a sex-specific risk factor for HFpEF in women, and statin therapy may lower the risk of developing atrial fibrillation, then it is possible that the primary prevention of HFpEF in women may also include statin therapy. However, whether statins and other novel approaches for treating systemic inflammation are effective in preventing HFpEF requires further study. In addition to inflammation, mitochondrial dysfunction and impaired contraction–relaxation coupling in cardiomyocytes are also believed to contribute to the development of HFpEF. Clinical trials that are assessing the effect of mitochondrial-targeting agents and partial adenosine-A1 receptor agonists are currently ongoing (70). If an adequate number of women are enrolled, these studies may provide additional insight on sex-specific strategies for the prevention and treatment of HFpEF in women.

FUTURE DIRECTIONS

HF in both men and women should be considered a preventable disease. The epidemiological and pathophysiological differences in both HF subtypes strongly suggest that sex-specific preventive strategies and risk factor reduction may be particularly beneficial in women, but significant questions remain (**Table 1**). In HFpEF, because there are no proven therapies, identification and implementation of effective preventive strategies in women is particularly urgent. In HFrEF, additional research is needed to generate evidence to support whether sex-specific primary and secondary treatment interventions are advantageous. To accomplish this, women need to be adequately represented in clinical research and sex differences need to be prospectively investigated. In the meantime, incorporating specific recommendations for women into clinical guidelines when data are sufficient will likely improve HF outcomes and decrease health disparities in women.

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