Sex differences in heart failure with preserved ejection fraction: From traditional risk factors to sex-specific risk factors

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Abstract

Heart failure with preserved ejection fraction has a higher prevalence in women versus men. There are several proposed mechanisms to explain this sex discrepancy including differences in cardiovascular adaptation to comorbidities and potential underlying etiologic mechanisms. In this review, we summarize sex differences in traditional risk factors, such as obesity, diabetes, hypertension, and coronary artery disease, which contribute to the development of heart failure with preserved ejection fraction in women. Furthermore, we explore female-specific risk factors, such as sex hormones, adverse pregnancy outcomes, and other reproductive factors, which may explain the predominance of heart failure with preserved ejection fraction in women. Beyond sex differences in risk factors, there are also significant sex differences in outcomes with women reporting lower quality of life but overall better survival versus men. Finally, while treatment options for patients with heart failure with preserved ejection fraction are still limited, sex differences have also been reported for the available therapies, with suggestion of preferential benefit of specific heart failure with preserved ejection fraction therapies in women. Further work is required to better understand sex differences in heart failure with preserved ejection fraction, including deeper understanding of pathophysiological mechanisms, derivation of more accurate risk stratification models, and increased representation of women in clinical trials.

Introduction

Heart failure (HF) affects approximately six million Americans above the age of 20, with a projected prevalence of more than eight million by 2030.[1,2] HF encompasses a broad range of phenotypes and is further subdivided into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), both of which have unique epidemiology, risk factors, and treatment options. Secular trends from the Framingham Heart Study have demonstrated a declining incidence for HFrEF, but an increasing incidence for HFpEF over two decades (1990–1999 versus 2000–2009).[1] Significant sex differences exist in the realm of HF, particularly when considering HFpEF. For example, the odds of HFpEF were 2.8-fold higher in women than in men within the Framingham Heart Study.[3,4] The prevalence of HFpEF has also been demonstrated to be higher in women and increases with age (8%–10% in women and 4%–6% in men for individuals ≥ 80 years of age).[5] Epidemiologic analyses from large

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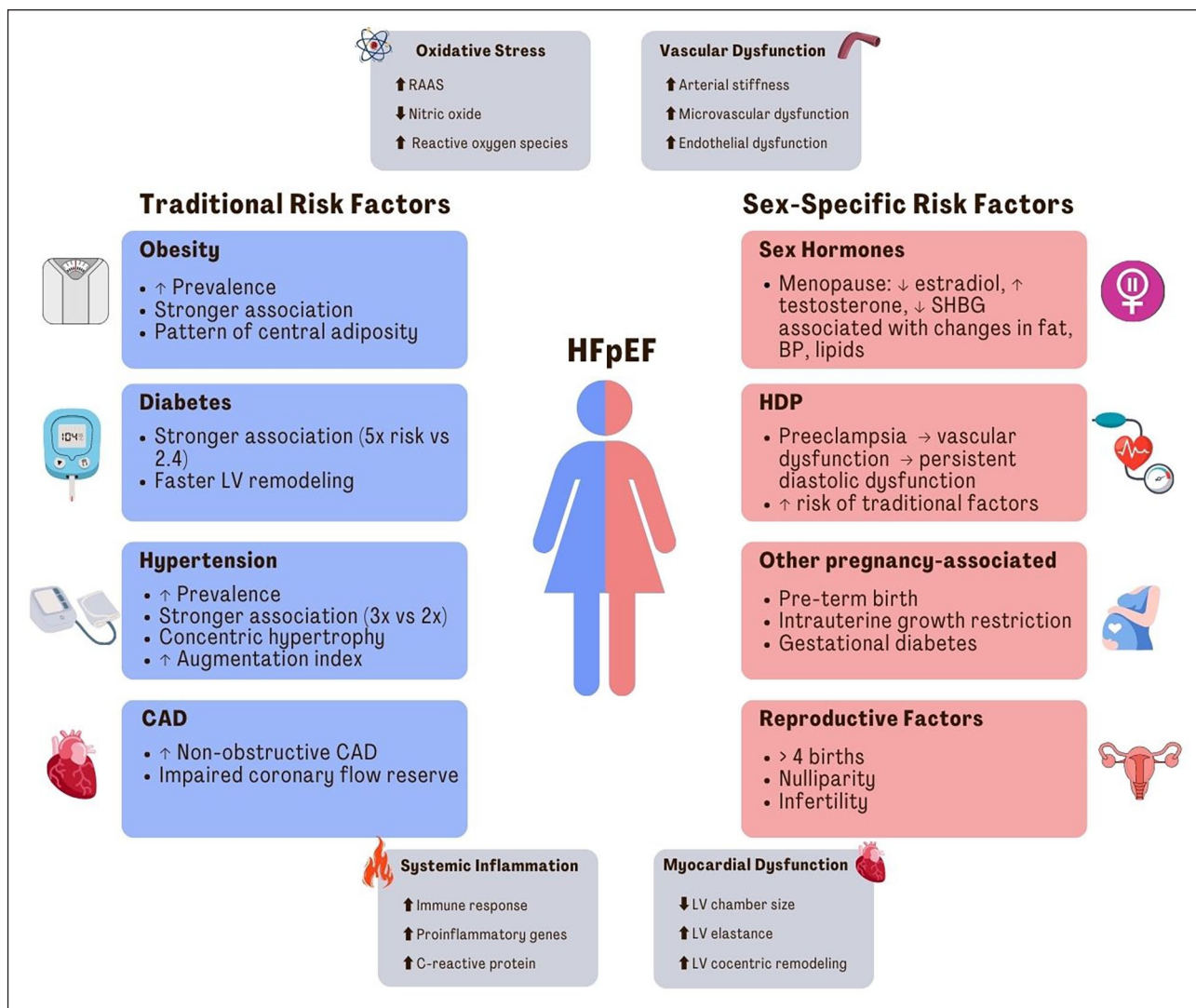Email: elau6@mgh.harvard.edu

Oxidative Stress

↑ RAAS

↓ Nitric oxide

↑ Reactive oxygen species

Vascular Dysfunction

↑ Arterial stiffness

↑ Microvascular dysfunction

↑ Endothelial dysfunction

Traditional Risk Factors

Obesity
- ↑ Prevalence
- Stronger association
- Pattern of central adiposity

Diabetes
- Stronger association (5x risk vs 2.4)
- Faster LV remodeling

Hypertension
- ↑ Prevalence
- Stronger association (3x vs 2x)
- Concentric hypertrophy
- ↑ Augmentation index

CAD
- ↑ Non-obstructive CAD
- Impaired coronary flow reserve

HFpEF

Sex-Specific Risk Factors

Sex Hormones
- Menopause: ↓ estradiol, ↑ testosterone, ↓ SHBG associated with changes in fat, BP, lipids

HDP
- Preeclampsia → vascular dysfunction → persistent diastolic dysfunction
- ↑ risk of traditional factors

Other pregnancy-associated
- Pre-term birth
- Intrauterine growth restriction
- Gestational diabetes

Reproductive Factors
- > 4 births
- Nulliparity
- Infertility

Systemic Inflammation

↑ Immune response

↑ Proinflammatory genes

↑ C-reactive protein

Myocardial Dysfunction

↓ LV chamber size

↑ LV elastance

↑ LV cocentric remodeling

Figure 1. Risk factors and pathophysiology for HFpEF in women.
Summary of proposed pathophysiological mechanisms for HFpEF in women, including oxidative stress, vascular dysfunction, systemic inflammation, and myocardial dysfunction. Summary of traditional and sex-specific risk factors for HFpEF in women. HFpEF: heart failure with preserved ejection fraction; RAAS: renin angiotensin aldosterone system; LV: left ventricular; CAD: coronary artery disease; SHBG: sex hormone binding globulin; HDP: hypertensive disorders of pregnancy.

registries found that women comprise 55% of patients with HFpEF, but only 29% of patients with HFrEF.[6]

There is no clear consensus on the exact pathophysiological mechanisms to explain sex differences in prevalence, but hypotheses include greater inflammation and chronic microvascular dysfunction in women, two purported mechanistic drivers of HFpEF (Figure 1).[7,8] Furthermore, traditional risk factors (obesity, diabetes, hypertension, and coronary artery disease (CAD)) preferentially contribute to development of HFpEF in women, and emerging data show that sex-specific risk factors including early menopause, adverse pregnancy outcomes (APOs), and other reproductive factors are also important risk factors for HFpEF in women. Finally, HFpEF is a clinical syndrome with considerable phenotypic heterogeneity, in part related

to differences in patient profiles in men versus women. For example, previous studies have demonstrated notable phenotypic differences based on sex—women have more concentric left ventricular (LV) remodeling and more severe diastolic dysfunction with impaired LV relaxation versus men.[9,10] A previous study analyzing data from three large HFpEF trials showed age-related differences in HFpEF: Younger patients were more often obese men and older patients were more often women with higher prevalence of comorbidities.[11] Novel phenotyping tools are now able to identify distinct groups of HFpEF patients that differ in risk profile, outcomes, and clinical trajectories. One study leveraging these novel phenotyping tools found three separate phenogroups among a US-based cohort of 397 patients with HFpEF: (1) younger females with less

adverse remodeling, (2) predominately females with obesity and diabetes, and (3) older men and women with chronic kidney disease and adverse LV remodeling.[12] Beyond the sex differences in prevalence and clinical profile, there are also sex differences in outcomes within the HFpEF population, with women reporting lower quality of life (QOL) as compared to men[13] but overall better survival.[14]

In this review, we summarize sex differences in traditional risk factors and explore female-specific risk factors, which may explain the predominance of HFpEF in women. We also review sex differences in outcomes and response to treatment options, while acknowledging existing gaps in knowledge and areas for future research.

Sex differences in traditional risk factors for HFpEF

Prediction models from longitudinal community-based cohorts have demonstrated important risk factors for the development of HFpEF including age, blood pressure, body mass index (BMI), and previous myocardial infarction (MI).[15] Given that inflammation is thought to be central to the development of HFpEF, sex differences in prevalence of comorbidities that drive inflammation such as obesity, diabetes mellitus, and hypertension may explain the disproportionate risk in women.[16,17] Cardiovascular risk factors are strongly associated with incident HF— both HFpEF and HFrEF—in both women and men, as demonstrated by a large analysis compiling data from four community-based cohorts; however, in this analysis, there were subtle sex-related differences with age (women: hazard ratio (HR) 2.07 (95% confidence interval (CI): 1.89–2.28) versus men: HR 1.80 (95% CI: 1.67–1.95)) and hypertension (women: HR 1.98 (95% CI: 1.68–2.34) versus men: HR 1.67 (95% CI: 1.45–1.93)) more strongly associated with HF risk in women.[18] In this section, we review important differences between women and men in both the prevalence and the overall HFpEF risk conferred by traditional risk factors (Figure 1).

Obesity

Obesity has been an established risk factor for HF for many decades,[19] and more recently has been associated with the risk of HFpEF in particular.[15,16,20] Obesity is more common among women than men with existing HFpEF (46% versus 35%), as seen in baseline data from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial.[21] It is also more strongly associated with risk of HFpEF. In a study of 22,681 patients, obesity was more strongly linked with the risk of HFpEF than HFrEF (HR 1.34 per 1 standard deviation increase in BMI (95% CI: 1.24–1.45) versus HR 1.18 (95% CI: 1.10–1.27)), and notably, this association was more pronounced among women versus men (p for difference HFpEF versus HFrEF = 0.01 in women and p = 0.34 in women).[22] The proposed model for the relationship between obesity and HFpEF includes cardiometabolic factors, such as insulin resistance, leading to a state of systemic inflammation, endothelial dysfunction, and subsequent myocyte remodeling.[23] Furthermore, the relative distribution of fat mass differs between women and men. Pre-menopausal women have more subcutaneous adiposity and less visceral adiposity than men.[24] However, during the peri-menopausal transition, there is a rise in visceral adiposity due to the decline in estrogen levels.[25] Estrogen may mediate signaling pathways that attenuate reactive oxygen species leading to downstream anti-inflammatory effects. Furthermore, estrogen may exert regulatory effects on adipocyte and cardiomyocyte gene expression at the post-transcriptional level by driving expression of non-coding ribonucleotide acids (RNA), such as microRNAs (miRNAs) and long-non-coding RNAs.[26] Therefore, a decline in estrogen levels during menopause may result in loss of protective miRNAs and contribute to a state of systemic inflammation.[26]

Visceral adipose tissue, in particular, is associated with concentric LV remodeling[27] and can also affect exercise intolerance which is a hallmark symptom of HFpEF. Haykowsky et al.[28] found that intra-abdominal fat was significantly higher in patients with HFpEF when compared with healthy controls and was the strongest predictor of peak oxygen consumption (a marker of exercise performance). There were inverse associations between intra-abdominal fat with all measurements of physical function, including peak oxygen consumption and 6-min walk distance. This highlights the importance of specific management strategies aimed at not only promoting weight loss in general but also targeting specific fat stores, especially intra-abdominal.

Diabetes mellitus

Diabetes mellitus is another traditional risk factor that has been established as having a more pronounced effect on HF in women as compared to men, with a fivefold associated increase in risk in women versus 2.4-fold increase in risk in men.[29] The prevailing HFpEF hypothesis proposes that diabetes and other cardiometabolic risk factors contribute to HFpEF pathogenesis via systemic vascular inflammation and endothelial dysfunction.[30] The production of reactive oxygen species[31] and decreased bioavailability of nitric oxide leads to downstream lowering of soluble guanylate cyclase and protein kinase G (PKG) activity in cardiomyocytes. Deficient PKG activity subsequently impairs myocardial relaxation and induces cardiomyocyte hypertrophy.[32] This process appears to occur earlier in the disease course in women versus men.[33] Metabolic syndrome, thought to be a clinical precursor to

diabetes, has been shown to be associated with echocardiographic measures of diastolic dysfunction.[8,34]

Hypertension

Hypertension is more prevalent among females with HFpEF versus males, especially in individuals age 75 years or older,[14] and also confers greater risk of HF in women (threefold increase in risk in women versus twofold increase in men).[35] Potential explanations include differential remodeling in these two populations. Hypertension more frequently leads to concentric hypertrophy in women, but eccentric remodeling in men.[36,37] There are also intrinsic physiological characteristics in women that predispose them to HFpEF, including increased arterial stiffness and more pronounced age-related increase in arterial stiffness.[9,38] In an analysis of 279 participants from the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fraction (PARAMOUNT) study, women had higher arterial stiffness compared with men, though the difference was not significant after adjusting for height.[38] In addition, Higashi et al.[39] investigated the relationship between arterial stiffness and LV diastolic dysfunction in 446 participants and found higher carotid augmentation index (a parameter of arterial stiffness) was more strongly correlated with measures of LV diastolic function in women than men, even after controlling for confounding factors such as age and blood pressure. Overall, this hints toward a differential impact of aging and hypertension on cardiac structure and endothelial function between the sexes. Augmentation of blood pressure due to arterial stiffness increases LV systolic load and cardiac afterload, therefore, worsening myocardial oxygen demand, all of which can influence LV diastolic function. Additionally, elderly women with isolated systolic hypertension have sex-specific alterations of pulse wave reflection (related to increased LV systolic load) and LV remodeling, which may amplify the increased risk of HFpEF.[40] Another study reported greater difference between central and peripheral blood pressure, or a higher augmentation index, in women compared to men (7.4 ± 5.2 versus 1.0 ± 6.9; $p < 0.001$), which may put women at a higher risk for end-organ damage such as LV hypertrophy.[41]

While hypertension contributes to HFpEF development via concentric hypertrophic in response to increased myocardial afterload, it has also been linked to increased microvascular inflammation which is known to promote downstream myocardial remodeling associated with HFpEF.[30]

Coronary artery disease

CAD and myocardial ischemia can lead to diastolic dysfunction and HFpEF. In a retrospective study of 376 patients with HFpEF, those with CAD were more likely to be men as compared to those without CAD (57% versus 25%).[42] Several studies, including the I-PRESERVE study and the PARAMOUNT study, have demonstrated that women are less likely to have CAD versus men (38% versus 43% stable angina in I-PRESERVE and 22% versus 11% MI in PARAMOUNT).[21,38] However, women are more likely to have non-obstructive CAD and coronary microvascular dysfunction, which has a high prevalence in HFpEF.[7,43] In Proteomic Evaluation of the Comorbidity-Inflammation Paradigm in Heart Failure With Preserved Ejection Fraction, a prospective, multi-center study comprised of 263 patients, the prevalence of coronary microvascular dysfunction in HFpEF patients was 75% and was associated with systemic endothelial dysfunction as measured by peripheral arterial tonometry testing.[7] Furthermore, in a study of 201 patients without obstructive CAD, impaired coronary flow reserve (a marker of chronic microvascular dysfunction) was associated with diastolic dysfunction (adjusted odds ratio (OR) 2.58, 95% CI: 1.22-5.48) and HFpEF hospitalizations (adjusted HR 2.47, 95% CI: 1.09-5.62).[44] Finally, an analysis from the Multiethnic Study of Atherosclerosis (MESA), comprised of 6,809 healthy participants, reported that coronary artery calcium (CAC) scores greater than 300 were associated with increased risk of HFpEF, but only in women.[45] Notably, after excluding participants who developed coronary heart disease events before HFpEF hospitalization, CAC greater than 300 was no longer a significant contributor to estimating risk of HFpEF in women, suggesting that ischemia and microvascular dysfunction may be mediators in women.[45]

Atrial fibrillation

Atrial fibrillation (AF) is prevalent in 25%–39% of HFpEF patients, and the two conditions share common risk factors including age and hypertension.[46] Studies have also demonstrated an association between AF with death and HF hospitalization in HFpEF patients, an association that has not been observed in HFrEF patients.[47] While AF is more common in men versus women with HFpEF, outcomes are worse in women with HFpEF and AF. For example, among participants enrolled in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, the association between AF and hospitalization was stronger in women with HFpEF (HR 1.63, 95% CI: 1.40–1.91) versus men (HR 1.37, 95% CI: 1.18–1.58), p-interaction = 0.032.[48]

Iron deficiency and anemia

Anemia is a common comorbidity in HF and has been independently associated with greater risk of death and HF hospitalization across a range of ejection fractions,[49,50] Potential mechanisms include adverse LV remodeling,

neurohormonal activation, and higher levels of systemic inflammation.[51] Previous studies have shown a prevalence of 21%–68% within the HFpEF population, with higher prevalence is HFpEF than HFrEF.[49,52–54] Within the Get With the Guidelines-Heart Failure registry, prevalence of anemia was higher in women versus men for both HFrEF and HFpEF subgroups.[55] Greater prevalence of iron deficiency in women in the general population has been hypothesized to predispose to HFpEF due to adverse effects on oxidative metabolism and immunological responses.[56] Furthermore, in the Acute Decompensated Heart Failure Syndromes registry in Japan, there were sex-specific differences in the association between anemia and outcomes. Anemia was an independent predictor of all-cause death and cardiac death in women with HFpEF, but not in women with HFrEF, while the opposite was observed in men.[57]

Female-specific risk factors

Beyond sex differences in prevalence and conferred risk related to traditional risk factors, emerging data suggest that sex-specific risk factors may also contribute to the predominance of HFpEF in women (Figure 1).

Sex hormones

Patients with HFpEF are more likely to be older females,[21] with postmenopausal women having a higher incidence of LV diastolic dysfunction. This observation has led to the hypothesis that the decline in estradiol at menopause may contribute to the pathogenesis of HFpEF.[58,59] Estradiol is an important regulator of inflammation, reactive oxygen species, nitric oxide signaling, and endothelial function.[59] The decline in estradiol levels at menopause is associated with changes in body fat, blood pressure, and lipids, all of which are implicated in development of HFpEF.[59] Furthermore, in a study from MESA, a more androgenic pattern of hormones with lower estradiol, higher free testosterone, and lower sex hormone binding globulin was associated with greater increase in LV mass in both women and men, but associated with concentric remodeling only in women.[60]

Pregnancy

Hypertensive disorders of pregnancy, such as preeclampsia, are risk factors for future cardiovascular disease including HFpEF.[61,62] In a meta-analysis of twenty-two studies, preeclampsia was associated with a fourfold increase in future incident HF.[63] Furthermore, in a Norwegian cohort study, preeclampsia was associated with HF with HR of 2 (95% CI: 1.50–2.68, $p < 0.001$).[64] While most previous studies did not distinguish between HFrEF and HFpEF, a recent retrospective cohort study utilizing New York and Florida state data found that preeclampsia was independently associated with greater risk of HFpEF with an adjusted HR of 2.09 (95% CI: 1.80–2.44).[62] Additionally, there is likely to be reciprocal interplay between traditional cardiovascular risk factors and sex-specific risk factors. For example, women with preexisting hypertension and diabetes are at increased risk of developing preeclampsia, and patients with preeclampsia are more likely to develop downstream hypertension and diabetes.[62] Preeclampsia and resultant endothelial dysfunction can lead to diastolic dysfunction that persists up to 1 year postpartum in 51% of patients,[65] highlighting the importance of identifying and monitoring these high-risk women for downstream cardiovascular complications. Endothelial dysfunction with low nitric oxide bioavailability and LV remodeling is the leading hypothesis explaining these associations.[30] Breetveld et al.[66] reported that women with former preeclampsia have lower endothelium-dependent flow-mediated dilation, a marker of endothelial dysfunction, compared with women with normal gestation along with threefold higher prevalence of HF. Another study demonstrated impaired coronary flow reserve in patients with preeclampsia.[67] In addition, evidence of persisting vascular dysfunction has been described in women following pregnancy complicated by hypertensive disorder of pregnancy.[68]

Beyond hypertensive disorders of pregnancy, APOs that include pre-term birth, preeclampsia, and intrauterine growth restriction portent increased risk for future hypertension, LV hypertrophy, and vascular dysfunction. Proteomic analyses show that pathways of inflammation and coagulation are increased in both women with APOs and in HFpEF.[69] Furthermore, normotensive pregnancies with fetal growth restriction also have impaired myocardial relaxation with one specific study showing a third of women with history of fetal growth restriction to have diastolic dysfunction.[70] However, Hansen et al.[71] revealed that in a population of 10,292 women, women with any APO had higher prevalence of hypertension, diabetes, coronary heart disease, but only hypertensive disorders of pregnancy were significantly associated with HFpEF (OR, 1.87; 95% CI: 1.32–2.65).

Gestational diabetes has been associated with future risk of HF among women, though the data are mixed. In a large population-based cohort study, women with gestational diabetes had a 62% higher risk of HF (HR 1.62, 95% CI: 1.28–2.05) even after adjustment for confounders.[72] However, in an analysis from the Women's Health Initiative, there was no association seen between gestational diabetes and HF. This may be due to the low prevalence of gestational diabetes in that study's population (2.5% versus 7.6% prevalence in the United States).[71,73]

Reproductive factors

Other pregnancy-related features, including parity, are also associated with diastolic function. A study of 710 women

demonstrated grand parity, which was defined as greater than four births, to be an independent risk factor for LV diastolic dysfunction. The exact mechanism remains to be elucidated.[74] On the other end of the spectrum, nulliparity and a shorter total reproductive duration have also been shown to portend a higher risk of HFpEF.[75,76] Potential explanations include shorter total reproductive duration and therefore lower cumulative exposure to endogenous sex hormones. Another sex-specific risk factor related to reproductive health is infertility. In a large prospective cohort from the Women's Health Initiative, infertility was shown to be significantly associated with incident HFpEF (20% increased risk). This risk was not explained by established cardiovascular risk factors.[77]

Sex differences in outcomes

Studies have shown HFpEF outcomes differ by sex. In general, women with HFpEF have better outcomes than men,[21,78] including lower in-hospital mortality (4.2% versus 4.6%, $p < 0.01$).[14] However, a post hoc analysis of the TOPCAT trial showed no difference in cardiovascular and all-cause mortality between women and men, though women had worse patient-reported outcomes.[79] Other studies have also demonstrated lower QOL in women with HFpEF, which was independent of age and HF severity.[80]

One potential explanation for worse QOL in women versus men with HFpEF is that women have lower exercise capacity, which is a quintessential feature of HFpEF. In a study of participants from the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trial, women with HFpEF had worse exercise capacity than men, despite comparable resting cardiac function.[81] Furthermore, a cross-sectional observational study using invasive hemodynamic exercise measures demonstrated that women have lower exercise peripheral oxygen extraction and ventricular reserve compared to men in spite of lower burden of cardiometabolic disease among women in that study's population.[82] Additionally, Beale et al.[9] revealed that women had poorer diastolic reserve with higher measurements of LV filling pressures with exercise as well as systemic and pulmonary vascular dysfunction in a group of 161 patients with HFpEF. These sex differences in exercise hemodynamics highlight the need for further investigation into related pathophysiology to explain differences in muscle and vascular responses to exercise in women versus men with HFpEF.

While exercise capacity may be one explanation to explain variances in QOL, another study demonstrated no association between exercise capacity with QOL in women with HFpEF. In this study which examined echocardiographic and QOL data from the RELAX and NEAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trials in men versus women, diastolic dysfunction, ischemic heart disease, and exercise capacity predicted QOL in men with HFpEF, while only age and BMI predicted QOL for women. More investigation is required to ascertain these differences, including potential contributions from psychosocial factors and other social determinants of health.[83]

Sex differences in treatment

While treatment options for HFpEF are not as widespread as for HFrEF, sex differences have been reported for the available HFpEF therapies (Table 1). In a post hoc analysis of the TOPCAT trial, there was a reduction in all-cause mortality for spironolactone in women (HR 0.66; 95% CI: 0.48–0.9; $p = 0.01$), but not in men (sex–treatment interaction $p = 0.02$). These results were only hypothesis generating, but warrant further studies on the use of spironolactone in women with HFpEF. The authors of the analysis hypothesized that differential effects of mineralocorticoid antagonists on cardiac remodeling in women versus men may have explained the sex-specific finding.[79] In a prespecified subgroup analysis of the Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction (PARAGON-HF) trial, sacubitril-valsartan reduced the risk of HF hospitalization by 26% in women, but no effect was seen in men.[84,85] Similar to TOPCAT, there is no clear mechanistic evidence to explain these findings, but sex differences in natriuretic peptide (NP) biology and crosstalk with sex hormones have been proposed.[85] Specifically, the authors hypothesize that sacubitril-valsartan-induced NP production may preferentially benefit women versus men with HFpEF given lower baseline levels of NP in women with HFpEF.[85] Lower NP levels are associated with reduced cyclic guanosine monophosphate-protein kinase (cGMP) signaling. This reduction in signaling may be further accentuated by loss of estrogen-dependent endothelial nitric oxide synthase activation of cGMP pathway following menopause. NP activation by sacubitril-valsartan may explain preferential benefit in women with HFpEF who are cGMP deficient. Sodium glucose transporter-2 inhibitors (SGLT2i) are another class of medications that have emerged as treatment options for HFpEF. SGLT2i do not lead to NP activation, but rather work through several distinct mechanisms. Most recently, in the EMPEROR-PRESERVED (Empagliflozin in Heart Failure with a Preserved Ejection Fraction) trial and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial, which investigated the SGLT2 inhibitors empagliflozin and dapagliflozin, respectively, there was no difference in treatment effect among women versus men.[86,87]

Conclusion and gaps in knowledge

The disproportionate prevalence of HFpEF in women stems from a myriad of factors, including higher rates of

Table I. Sex differences in recent HFpEF treatment trials.

Trial (year)	Number of patients	% female	Intervention	EF cut-off	Type of analysis	Baseline differences (women versus men)	Sex-specific results
TOPCAT (2019)	1767	49.9%	Spironolactone	45%	Post hoc, non-pre-specified	Older Fewer comorbidities Higher LVEF, BP, BMI Lower GFR, Hgb Higher NYHA class Lower KCCQ score	• Rates of primary outcome and HF hospitalization not different • Significant reduction in all-cause mortality w/ spironolactone in women (HR 0.66; 95% CI: 0.48–0.9; p=0.01), but not in men; sex-treatment interaction p=0.024.
PARAGON-HF (2020)	4796	51.7%	Sacubitril-valsartan	45%	Prespecified subgroup	Older More obesity Fewer comorbidities Lower median NT-proBNP level Lower GFR Higher LVEF Higher NYHA class Lower KCCQ score Less likely on MRA	• In control group, women had higher rates of HF hospitalization and lower rates of CV death • Rate ratio for primary outcome was 0.73 (95% CI: 0.59–0.90) in women and 1.03 (95% CI: 0.84–1.25) in men with p interaction=0.017, predominately related to HF hospitalization (33% RRR, p interaction=0.005)
EMPEROR-PRESERVED (2021)	5988	44.7%	Empagliflozin	40%	Prespecified subgroup	–	• No difference between women and men • HR for male: 0.81 (95% CI: 0.69–0.96) and for female: 0.75 (95% CI: 0.64–0.92)
DELIVER (2022)	6263	43.9%	Dapagliflozin	40%	Prespecified subgroup	–	• No difference between women and men • HR for male: 0.82 (95% CI: 0.71–0.96) and for female: 0.81 (95% CI: 0.67–0.97)

Summary of sex-specific results in recent HFpEF treatment trials, including TOPCAT, PARAGON-HF, and EMPEROR-PRESERVED.
TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with Aldosterone Antagonist; PARAGON-HF: Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction; EMPEROR-PRESERVED: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EF: ejection fraction; CAD: coronary artery disease; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; BP: blood pressure; BMI: body mass index; GFR: glomerular filtration rate; Hgb: hemoglobin; NYHA: New York Heart Association; KCCQ: Kansas City Cardiomyopathy Questionnaire; NT-proBNP: N-terminal pro brain natriuretic peptide; MRA: mineralocorticoid; HR: hazard ratio; CI: confidence interval; RRR: relative risk reduction.

traditional risk factors, unique pathophysiological consequences that put women at higher risk from these traditional risk factors, and distinct sex-specific effects. While women represent the majority of patients with HFpEF, there is still a lack of adequate representation in clinical trials. Given the heterogeneity of HFpEF, further work is needed to create more accurate risk stratification models that encompass both traditional and sex-specific risk markers. Additionally, we are yet to thoroughly understand the differences in pathophysiological mechanisms as well as responses to comorbidities between women and men.

Given these challenges, we propose a series of future directions to address the higher prevalence of HFpEF in women and improve outcomes:

- Existing evidence suggests that sex-specific miRNA networks may mediate the relationship between comorbidity-induced inflammatory activation and HFpEF pathogenesis in women. Future research on miRNA-induced mechanisms may shed light on unique pathways that contribute to HFpEF development in women.
- Improved mechanistic understanding of sex-specific inflammatory cascades and effects of sex hormones may enable greater precision of targeted therapies for women with HFpEF. Specifically, identification of novel circulating biomarkers related to tissue remodeling, inflammation, and neurohormonal regulation may refine risk prediction in women with HFpEF.
- Baseline sex differences in LV ejection fraction and steeper trajectories with age in women are well established, but diagnostic cutoffs remain sex-agnostic.[88] We propose sex-specific diagnostic cutoffs in ejection fraction.[8]
- A preventive strategy should be adopted to decrease the rising incidence and prevalence of HFpEF in women.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Gurleen Kaur: Conceptualization; Writing – original draft; Writing – review & editing.
Emily Lau: Conceptualization; Writing – original draft; Writing – review & editing.

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