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Large knowledge gaps remain

Impact of sex and gender on heart failure

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Summary

The prevalence of heart failure (HF) is increasing mainly due to population aging. There are important biological (sex) and sociocultural (gender) differences in epidemiology, pathophysiology, phenotype, prognosis and treatment of HF between women and men. While the overall lifetime risk of HF is similar between men and women, women with HF are older, have more comorbidities and a higher incidence of heart failure with preserved ejection fraction (HFpEF) than men. Men instead present a predisposition to the development of heart failure with reduced ejection fraction (HFrEF) due to their higher incidence of coronary artery disease. Sex differences are also notable in the penetrance of genetic cardiomyopathies, HF risk factors as well as in sex-specific conditions such as peripartum cardiomyopathy (PPCM), cancer treatment-induced cardiomyopathy and Takotsubo cardiomyopathy. Although women with HF have a better age-adjusted prognosis than men they experience a worse quality of life. Underpinning current sex disparities in HF, HF treatment is limited by a profound underrepresentation of women in clinical trials, which has resulted in a lesser understanding of disease behaviour in female patients and in treatment guidelines that are predominantly based on male-derived data. In addition, a full understanding of the impact of sociocultural gender on HF management and disease course is lacking. This review outlines the key sex differences with respect to clinical characteristics, pathophysiology and therapeutic responses to HF treatments. Finally, we address existing knowledge gaps in sex-specific mechanisms, optimal drug doses for women and sex-specific criteria for device therapy and heart transplantation.

Keywords: HFrEF; HFmrEF; HFpEF; sex; gender

Introduction

With more than 64 million affected individuals globally, chronic heart failure (HF) is a leading global public health problem with increasing prevalence due to the worldwide aging of the population [1]. Chronic HF represents the final stage of virtually all adult cardiovascular risk conditions and diseases such as ischaemic heart disease, arterial hypertension, diabetes mellitus, obesity, and atrial fibrillation. The prevalence and risk burden of these conditions differ between women and men resulting in sex differences in the pathophysiology, clinical presentation and prognosis of HF phenotypes [2, 3].

HF phenotypes are categorised based on left ventricular ejection fraction (LVEF): HF with reduced LVEF (≤40%, HFrEF), HF with mildly reduced LVEF (41–49%, HFmrEF, previously HF with midrange EF) and HF with preserved LVEF (≥50%, HFpEF) [4]. While the overall lifetime risk of HF amounts to about 20% in 40 years old individuals and is comparable between women and men, the epidemiology and type of HF differs substantially between women and men. While men encounter a higher lifetime risk of HFrEF at index age of 45 years, the lifetime risk of HFpEF is higher amongst women [5]. The prevalence of HFpEF is very low in individuals aged 55 years or younger, but increases sharply with age affecting 5% of the general population aged ≥60 years and >8% of women over 80 years [6]. Given the aging of the population and higher life expectancy of women, the prevalence of HFpEF is predicted to increase at a rate of 1% per year and will become the most common type of HF in the future [7]. HFmrEF patients are a heterogeneous group accounting for about one-third of the entire HF population [8]. There is a higher percentage of males in the HFmrEF group and the condition is associated with macrovascular coronary artery disease in two-thirds of patients [9].

While guideline-directed medical therapy has reduced HF-related mortality by an estimated 63%, this mortality decrease is slower in women than in men and morbidity from HF remains high in both sexes, particularly in women [10, 11]. The sex disparity in HF outcomes most likely reflects an absence of effective drug and device therapies for HFpEF and the lack of female-specific recommendations for HF therapies, which can be attributed, at least in part, to a persisting underrepresentation of women in randomised clinical HF tri-

als. This review aims to summarise most recent data on sex and gender differences in pathophysiology, clinical characteristics, diagnosis, management and outcome of HF. We further highlight current knowledge gaps and outline future areas of investigation to reduce sex and gender disparities.

Sex differences in heart failure pathophysiology

Several mechanisms and hypotheses explain the asymmetric incidence of HF subtypes in women and men (fig. 1). These include sex differences in cardiac structure and function, the influence of sex steroids on cardiomyocytes, fibroblasts, endothelial cells and vascular smooth muscle cells, sex-specific gene expression and immune responses as well as gender differences in HF risk conditions and comorbidities. Normal left ventricular (LV) geometry differs substantially between women and men, with women having smaller indexed LV volumes, but a similar cardiac index than men as well as a higher systolic and diastolic LV stiffness, which increases steeper with age in woman than in men [12, 13]. Accordingly, as compared to men, women, in general, have higher circulating natriuretic peptide levels, a prognostic cardiovascular biomarker (with a stronger predictive value in women) indicating atrial or ventricular wall stretch (tab. 1) [14]. These characteristics have all been suggested to account for the female predisposition to develop HFpEF rather than HFrEF. Also, female and male hearts respond differently to afterload stress. Women more often maintain LVEF than men and develop LV hypertrophy and diastolic dysfunction, while men are more likely to develop eccentric remodelling [15, 16]. In addition, female cardiomyocytes have a lower density of β1-adrenergic receptors than male ones, which may account for the fact that chronic β-adrenergic stimulation leads to an increase in collagen deposition in males but not in females, making males more prone to LV dilation and eccentric remodelling [17]. Finally, women have a smaller (non-indexed) aortic root and a smaller and stiffer aortic arch, leading to a higher pulse pressure, increased pulsatile afterload and impaired coronary flow contributing to diastolic dysfunction [13, 18, 19]. Also, the age associated rise in systolic blood pressure is steeper in women than in men, resulting in a higher prevalence of hypertension, a risk factor for HFpEF, in older women, which was recently addressed in a consensus statement of the European Society of Cardiology [20, 21].

However, while an increased LV afterload has historically been considered the key mechanism of HFpEF, increasing evidence highlights the central role of chronic inflammation, endothelial dysfunction and subsequent microvascular dysfunction, ischaemia, fibrosis and cardiomyocyte hypertrophy in the pathophysiology of HFpEF [22]. In fact, microvascular dysfunction is present in up to 75% of HFpEF patients and is more frequently observed in women [23, 24]. The anti-inflammatory and antioxidant effects of oestradiol (E2) on the endothelium, which are lost after menopause, have been suggested to account for the higher incidence of microvascular dysfunction in older women [25]. Sex differences in endothelial nitric oxide (NO) signalling and a systemic proinflammatory state might further predispose older women for the development of microvascular dysfunction [26, 27]. Systemic inflammation is more commonly observed in women, who generally exert stronger immune responses than men, show a higher expression of proinflammatory genes in the myocardium and face a higher risk to develop autoimmune diseases than men [28–30].

In summary, besides gender differences in the prevalence of cardiovascular disease (CVD) risk factors, sex differences in cardiac and vascular structure and function, differential adaptations to injury and aging, enhanced inflammatory responses in women and the effects of sex hormones on vascular and myocardial cells may explain, at least in part, the differential predisposition to HF phenotypes in women and men (fig. 1).

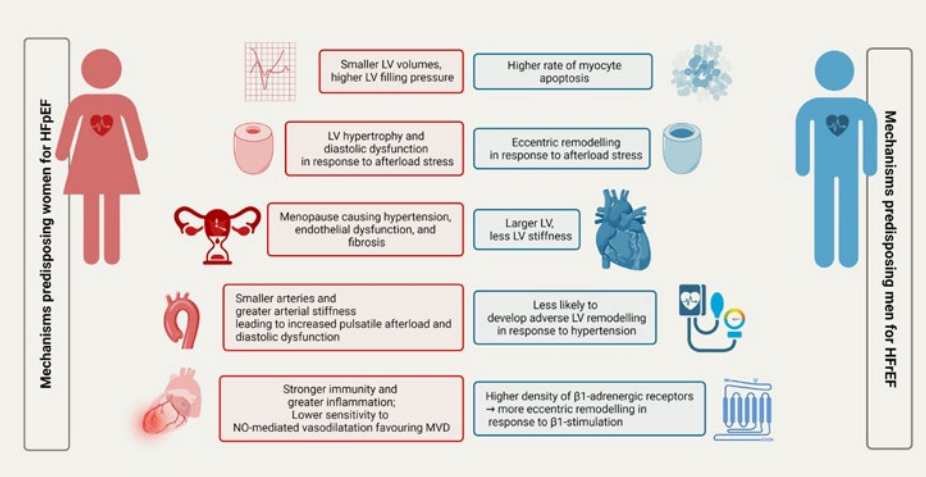

Figure 1: Impact of sex on the pathophysiology of heart failure.

HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LV, Left ventricular; MVD, Microvascular disease; NO, Nitric oxide.

Sex and gender differences in heart failure risk factors

In addition to traditional modifiable risk factors such as arterial hypertension, diabetes mellitus, obesity, smoking, and renal impairment, the risk for incident HFrEF includes some non-modifiable factors such as age, family history of CVD, and ethnicity. In fact, it was recently shown that among older persons free of HF, black men exhibit the highest risk for the development of HFrEF [31]. All the modifiable HF risk factors are also risk factors for the development of coronary artery disease. However, while men have a higher prevalence of macrovascular coronary artery disease, the risk of developing HFrEF in the presence of coronary artery disease is greater in women than in men (fig. 2) [32].

The importance of type II diabetes and hypertension in the context of HF has long been recognised. Although underrepresented in clinical trials, the prevalence and relative risk to develop HF is greater amongst diabetic or hypertensive women than amongst men [33]. Women with type II diabetes also appear to be especially vulnerable to the development of HFpEF, which can be attributed to the fact that worsening glucose tolerance has a stronger association with adverse LV remodelling and increased LV wall thickness in women than in men [34, 35]. Similarly, hypertensive women are more likely to develop adverse LV remodelling and HF than hypertensive men (fig. 2) [36]. The mechanisms accounting for this sex discrepancy are described in the previous paragraph.

The prevalence of general and central obesity, a stronger risk factor for the development of HFpEF than HFrEF, is higher in women, particularly after menopause and has a greater impact on women in terms of risk for metabolic diseases and HFpEF [37–39]. Also, pericardial fat volume and visceral adipose tissue have recently been attributed an important role in the pathophysiology and/or adverse disease course of HFpEF, particularly in

Table 1: Areas of future heart failure research due to gaps in sex- and gender-specific knowledge

HF phenotype	Knowledge Gap/Problem	Intervention	Benefit
All	Optimal drug doses for women. Information on drug efficacy and safety in women.	Randomised clinical trials need to include participants proportionate to the sex-specific distribution of the disease. An approach targeted at current barriers for female participation (e.g., increasing the number of female trial leaders) alongside an awareness programme on the benefits of the study drug, might increase the participation of women in HF trials.	Increasing female representation in HF clinical trials is essential to decreasing sex disparities in clinical care of all HF patients.
	Lack of sex-specific criteria for advanced HF therapy/devices: Women are less likely than men to receive a cardiac device in clinical practice, although they show better responses. Women account for a minority of patients on the waiting list for heart transplantation.	Implementation of sex-specific prediction models and identification of barriers impeding advanced HF therapies in women.	Overcoming barriers impeding advanced HF therapies in women alongside technological advances in mechanical circulatory support will likely increase their implantation in women.
	Impact of sociocultural gender on access to HF health care. Women with HF are referred for health care services less frequently than men.	An increased understanding how society, family and environment affect health care and prognosis of female and male HF patients is needed.	Studies focusing on sociocultural gender will help clinicians to provide more appropriate levels of care and understand HF as a multifaceted disease.
HFpEF	Sex-specific prevention strategies are lacking. Hypertension, obesity, and type II diabetes, the most common HFpEF antecedents, are less well controlled in women.	Greater efforts in primary prevention of HFpEF are needed through aggressive treatment of risk factors.	Sex-specific prevention strategies will reduce the medical and societal impact of this disorder.
	Women are more often affected by HFpEF, but outcomes are worse in men. Sex-specific disease mechanisms in HFpEF are unknown.	Suitable female/male preclinical HFpEF models to study HFpEF disease mechanisms are required. Age needs to be incorporated in preclinical HFpEF models.	Exploring mechanisms that predispose men for worse outcomes. Gaining insights into the age-related derangements that predispose women and the elderly to HFpEF will advance the development of new therapies for HFpEF
	NT-proBNP levels are higher in women than men across the LVEF spectrum.	Implementation of sex-specific thresholds for natriuretic peptides.	Sex-specific thresholds for natriuretic peptides may improve their diagnostic utility for HFpEF.
HFsnEF	Evidence suggests that the association between LVEF and mortality shows a U-shaped relationship. Patients with an LVEF >70% face a higher mortality than patients with preserved LVEF. Mechanisms are unknown.	More research is necessary to identify clinical relevance and prevention/treatment strategies of HFsnEF.	Identification of prevention/treatment strategies of HFsnEF might particularly benefit women who have a higher LVEF than men.
HFmrEF	Lack of sex-specific outcome data.	More research is necessary to identify sex-specific predictors for treatment responses and adverse outcomes.	Sex-specific risk prediction will enable early preventive and therapeutic measures.

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFsnEF, heart failure with supranormal ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide.

women, thereby indicating that women with HFpEF might specifically benefit from weight loss interventions [40, 41].

While fewer women than men use tobacco, the risk of HF is substantially higher in smoking women than in smoking men [42]. Given the increasing prevalence of smoking among women in high-income countries, particularly among younger women, awareness campaigns are needed to combat this alarming trend. Notably, smoking is an established risk factor for incident HF, independent of the presence of coronary artery disease and increases the risk of PPCM in women [42, 43].

Although there are substantial sex and gender differences in the prevalence and weighting of these risk factors for the development of HF, it is notable that atrial fibrillation is the only HF risk factor exhibiting an increased HF risk in women, but not in men [44].

There is increasing evidence that, besides clinical-biological risk factors, sociocultural variables are powerful determinants of HF risk. As sociocultural factors ('gender') vary between women and men, their social determinants of health also differ substantially depending on country and geographic region. In fact, low-income patients with HF have a nearly twofold risk of in-hospital mortality and post-discharge adverse events compared to

high-income HF patients, with the low-income group being more likely to be female [45]. Similarly, education level and family income, both of which were lower in women, have been inversely associated with HF risk in the Copenhagen City Heart Study [46]. Further, the absence of social support, a known prognostic indicator for health outcomes, was associated with a lower quality of life, worse HF prognosis and increased rate of HF hospitalisations [47]. Notably, men under the age of 65 years reported the lowest social support amongst all demographic groups [47]. Finally, living alone and/or being widowed was associated with an independent increase in HF hospitalisation in women, who were also more frequently widowed than men, in two recent studies [48].

Sex and gender differences in heart failure outcomes

HF prognosis is determined by HF phenotype, pre-existing comorbidities and age, timing of diagnosis, treatment initiation, treatment adherence, and response to treatment. Contemporary epidemiology indicates that adjusted HF mortality and hospitalisation rates are consistently higher in men than in women for all HF phenotypes (fig. 2) [49]. However, although women with HF live longer than men, their additional years of life are of poorer quality. Indeed, women across all HF subtypes report greater psychological and physical disability, more HF-related symptoms and higher rates of anxiety and depression [50]. In addition, health-related quality of life (HRQL) is much worse in women after accounting for variation in demographics, functional status and symptom burden [51]. It is notable, however, that gender disparity in HRQL is not unique to patients with HF and HRQL and has been shown to be worse in other chronic disease such as diabetes mellitus, coronary artery disease and colorectal cancer [52-54]. It is also noteworthy that the survival benefit in women is attenuated in the presence of atrial fibrillation, renal dysfunction, advanced New York Heart Association Class III/IV symptoms or stable angina pectoris [55]. In addition, women with HFpEF are more likely than men to develop pulmonary hypertension during their disease course, which is associated with a worse prognosis [56]. The higher incidence of pulmonary hypertension in women with HFpEF may be attributed to their higher LV filling pressures, higher arterial stiffness [57] or an increase in pulmonary vasoreactivity following menopause [58].

There is a complete lack of sex-specific data on disease outcomes in HFmrEF, however, current evidence suggests that mortality risk in patients with HFmrEF is higher than in HFpEF and similar to HFrEF [9].

Impact of sex and gender on heart failure treatment

Pharmacological therapies

Current HFrEF treatments comprise the use of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta blockers, mineralocorticoid receptor antagonists (aldosterone antagonists) or an angiotensin receptor and neprilysin inhibitor (ARNI) as well as the sodium-glucose transport protein 2 (SGLT2) inhibitors. While these treatments have shown to reduce morbidity and mortality in HFrEF, there is much less evidence regarding the pharmacological therapy

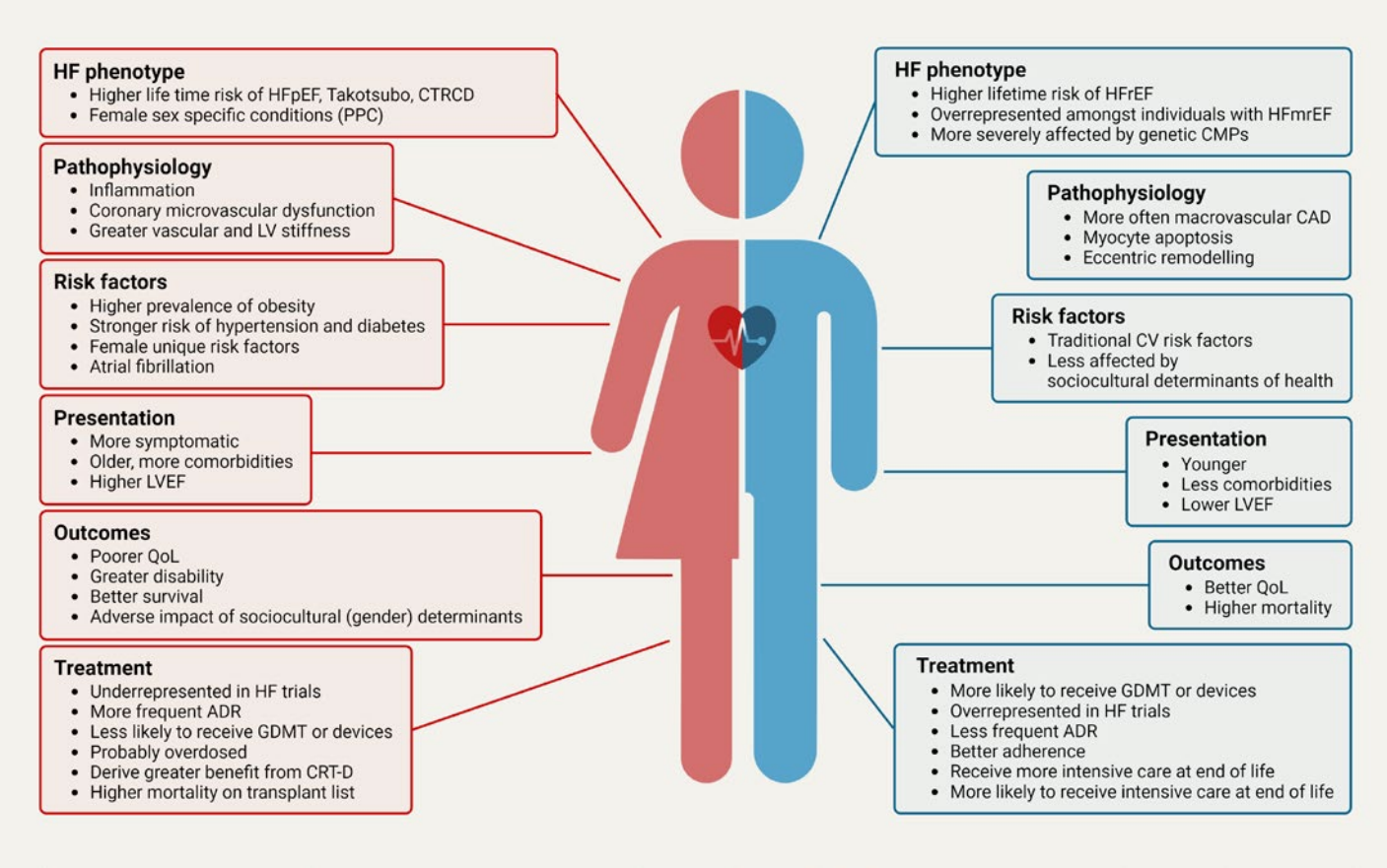

Figure 2: Sex and gender differences in heart failure.
ADR, Adverse drug reactions; CAD, Coronary artery disease; CMP, Cardiomyopathy; CRT-D, Cardiac resynchronisation therapy with defibrillator; CTRCD, Cancer treatment related cardiac dysfunction; CV, Cardiovascular; GDMT, Guideline-directed medical therapy; HF, Heart failure; HFmrEF, Heart failure with mildly reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LV, Left ventricular; LVEF, Left ventricular ejection fraction; PPC, Peripartum cardiomyopathy; QoL, quality of life.

for HFpEF and HFpEF. In fact, although SGLT2 inhibitors have shown beneficial effects across the whole spectrum of LVEF [59-61], the guideline recommendations for these compounds are absent or weak (class II) in HFpEF and HFmrEF [4]. Thus, recommended therapies are restricted to treating symptoms and underlying comorbidities.

Despite increasing evidence demonstrating that sex differences in pharmacokinetics and pharmacodynamics of cardiovascular drugs exist and may contribute to differences in drug efficacy and safety between men and women, current HF guidelines do not provide sex-specific recommendations [4, 62]. Instead, uptitration to target doses that are similar in men and women is recommended, even if sex-specific drug effects are known, which is the case for digoxin, which increased mortality in women with HF by 4.2% [4, 63]. As a consequence, women with HF experience more adverse reactions when these drugs are prescribed and are less often treated with guideline-recommended HF drugs than men (fig. 2) [64]. In addition, recent data from the Swedish HF Registry (SwedeHF) indicate that women were more likely than men to be treated with digoxin across the whole EF spectrum of HF, despite the known adverse effects of digoxin in the female population [65].

Information on drug safety and efficacy in women is very limited because women represent less than one-fourth of study participants in more than 70% of HFpEF and HFrEF trials [66]. Similarly, the preferential use of male animals, with no significant change over time, has the potential to skew our understanding of disease processes and the effectiveness of potential therapies [67, 68]. The female underrepresentation in experimental and clinical studies is particularly concerning as increasing evidence suggests that women, given to sex differences in body weight and height, body fat percentage and distribution, and renal and hepatic drug metabolism and clearance, need lower doses of HF drugs than men. Indeed, several studies indicate that men benefit most from recommended target doses of beta blockers, ACEIs or ARBs, whereas submaximal doses may be more effective and safer in women [69, 70].

Consistent with this observation, a meta-analysis of 34 randomised HF trials (37% women) showed that ACEIs significantly reduced the combined endpoint of mortality or HF hospitalisation in men, but not in women, while overall mortality was reduced in both sexes [71]. A later meta-analysis of six HF trials (25% women) indicated that women with HFrEF did not achieve a mortality benefit when treated with recommended doses of ACEIs [72]. It is notable, however, that in patients with myocardial infarction, ACEIs seem to reduce mortality and progression to HF in both sexes according to two meta-analyses [73, 74]. However, all these trials were published more than 20 years ago and were not designed to examine mortality in women and men separately [75]. Ever since, sex-specific effects of ACEIs have not been re-evaluated in randomised clinical trials.

The effect of ARBs (candesartan, valsartan, losartan) in patients with HFrEF has been studied in several randomised clinical trials. Overall, a mortality benefit with ARBs in both sexes was seen in these trials, although it was evident that women, unlike men, do not profit from higher doses of ARBs (losartan) [70, 76-82]. In some of these trials an even greater survival benefit was observed in women, which has been attributed to a lower frequency of adverse effects with ARBs as compared to ACEIs and, thus, a higher treatment adherence in women [82]. In HFpEF, which only has a few therapeutic options, no heterogeneity in the treatment effect of ARBs (irbesartan) by sex was found [83].

While the PARADIGM-HF trial (HFrEF patients, 22% women) demonstrated a similar mortality reduction in male and female HFrEF patients being treated with an ARNI (sacubitril/valsartan) as compared to ACEI [84], the PARAGON-HF trial, conducted in HFpEF and HFmrEF patients, showed a significant reduction of the composite endpoint of HF hospitalisation or cardiovascular death only in women, suggesting a relevant sex–treatment interaction [85]. The beneficial effect in women was driven by a reduction in HF-related hospitalisations in the ARNI treatment arm. In addition, treatment with sacubitril/valsartan was associated with a significant N-terminal prohormone of brain natriuretic peptide (NT-proBNP) reduction, health status improvement, and reverse cardiac remodelling in women with HFrEF in a post hoc analysis of the PROVE-HF trial [86]. It is also notable that women with HFpEF seem more responsive to treatment with ARNIs at higher LVEF ranges than men [87]. Potential mechanisms accounting for this more favourable response in women comprise their lower natriuretic peptide levels after menopause, sex-dependent regulation of the constitutive NO synthases, sex differences in microvascular inflammation, increased neprilysin activity from relatively greater visceral adipose tissue or dose–response relationships [40]. Notably, bradykinin production after neprilysin inhibition is higher in women than in men, which might account for the fact that women are more likely to develop angioedema following ARNI treatment [88]. A recent meta-analysis, however, showed a similar safety profile of sacubitril/valsartan in women and men with HFrEF [89].

Animal and human studies have consistently highlighted that, under physiological conditions, men have a higher baseline sympathetic activity, whereas women display a more pronounced parasympathetic tone while maintaining sympathovagal balance. This difference attenuates with increasing age, possibly resulting from changes in E2 concentrations in women [90]. Accordingly, while beta blockers seem to produce significant survival benefits in both women and men with HF, several studies have shown greater pharmacodynamic effects of beta blockers in women resulting in a larger decrease in heart rate and blood pressure [72, 91-95]. Also, women have a higher oral bioavailability, a lower volume of distribution (Vd) and a slower clearance via CYP2D6 of beta blockers compared to men [96]. Consistent with this observation, women with HFrEF had the lowest risk of death or hospitalisation when taking beta blockers plus either ACEIs or ARBs at half the guideline-recommended dose [69].

There is evidence that treatment responses to MRAs (spironolactone, eplerenone) differ between women and men, possibly due to a different sensitivity to mineralocorticoid receptor inhibition observed in an experimental study [97]. Indeed, an exploratory subgroup analysis of the recent TOPCAT trial described a reduction of mortality in the spironolactone arm in women with HFmrEF or HFpEF across the entire spectrum of LVEF, in men only at a lower LVEF [98, 99], while other trials report a similar treatment efficacy in women and men with HFrEF [100, 101]. Conversely, in post-myocardial infarction patients, a reduction in cardiovascular mortality or HF hospitalisation was noted in men only, while women, but not men, experienced a reduction in all-cause mortality [102]. Finally, a recent pooled analysis of three trials comprising patients with HFpEF and HFrEF reported similar benefits in women and men independent of LVEF; however, the heterogeneous study population makes it difficult to draw any conclusions [103].

The 2021 update of the ESC guidelines on HF recommends the SGLT2 inhibitors dapagliflozin or empagliflozin for all patients with HFrEF already treated with an ACEI/ARNI, a beta-blocker, and an MRA, regardless of whether they have a diabetes or not [4]. Although women encounter more frequent side effects of SGLT2 inhibition, such as urinary tract and genital mycotic infections, SGLT2 inhibition seems to provide similar efficacy and safety in diabetic women and men according

to a pooled analysis of four randomised clinical trials (36% women) [104, 105]. Likewise, treatment with the SGLT2 inhibitors dapagliflozin or empagliflozin resulted in a similar or greater benefit in women with HFrEF as compared to men regarding the composite endpoint of worsening HF events or cardiovascular death [106, 107]. It is notable, however, that these trials are limited by a profound underrepresentation of women (23-24%). In patients with HFpEF a subgroup analysis of the DELIVER trial, albeit underpowered to test sex-treatment interactions, revealed similar treatment benefits of dapagliflozin in women and men [59].

Diuretics are recommended to reduce the signs and symptoms of congestion in patients with HFrEF and are more frequently prescribed in women, most likely because of their greater perception of dyspnoea [4, 65]. While their sex-specific efficacy and safety profile in HF patients has not been studied, it is known that the renal excretion of torasemide is significantly reduced in women with HFrEF as compared to men [108]. In addition, experimental studies indicate that the diuretic, natriuretic and kaliuretic effects of loop and thiazide diuretics are stronger in females than in males due to sex differences in ion transporters in kidney tubules [109, 110]. Consequently, women treated with thiazide and loop diuretics experience electrolyte disturbances more often, which, in turn, increase the risk of long QT-associated arrhythmias [62].

Non-pharmacological therapies and palliative care

Cardiac rehabilitation as well as lifestyle modifications such as salt reduction, weight loss and exercise, have been shown to improve quality of life and outcomes in patients with HFrEF. However, women with HFrEF participate less often than men in cardiac rehabilitation programs, despite achieving greater benefits from it [111]. This gender difference might be attributed to the older age and higher amount of comorbidities of women with HF, their poorer cardiorespiratory fitness, less social support and higher burden of care giver and family responsibilities [112]. Similar to HFrEF, in HFpEF patients, lifestyle changes led to improvement in diastolic function, arterial elastance, physical function and quality of life [113, 114]. Also, gastric bypass surgery in twelve obese women with HFpEF resulted in improved symptoms, reduced LV mass and increased LV relaxation [115].

In end-stage HF, sex-related differences in palliative care for HF patients have been described: Women with HF have fewer hospitalisations, critical care admissions and invasive procedure in the last six months of life than men and lower odds of dying in a hospital setting [116]. The reasons for these gender differences in end-of-life health care warrant further investigation.

Devices and advanced heart failure therapies

Implantable cardioverter-defibrillators and cardiac resynchronisation therapy

The range of devices for HF therapy includes implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy (CRT) and CRT with defibrillators (CRT-D). Benefits from CRT-D therapy have been shown to be greater in women than in men in terms of improved reverse remodelling, quality of life, cardiovascular hospitalisation and overall survival [117, 118]. The greater benefit of CRT-D therapy in women has been attributed to their lower rate of ischaemic aetiology of HF and less scar tissue compared to men [119]. Also, it seems that shorter patients, of whom a greater proportion were women, have the most benefit from CRT, which might be reflective of smaller body and heart size in women associated with a shorter distance of conduction travel across the myocardium [120]. Accordingly, the gender gap in CRT-D outcomes seems to narrow when sex differences in heart and scar size are being considered [119, 121]. However, women are less likely to receive an ICD or CRT-D device than men, also after adjustment for known clinical confounders such as age and comorbidities (fig. 2) [122]. The reason for this gender disparity remains elusive, but it has been suggested that sex-specific indication for CRT implantation might be needed. In fact, women respond to CRT therapy at QRS durations that are shorter than in men, indicating the need for lower cut-off values for QRS duration in women [123].

ICD implantation seems to reduce sudden cardiovascular death in both women and men, while there is no clear benefit regarding overall mortality in women [124-127]. Women also encounter higher rates of implantation-related complications like pneumothorax, infection, bleeding, tamponade or lead dislodgement and are less likely to receive appropriate antitachycardia pacing or ICD shocks compared with men [122, 124]. The latter might be attributed to the fact that women are less likely to encounter ventricular arrhythmias than men, most likely due to their lower myocardial scar burden [128]. Similar to other HF studies, there is incomplete reporting of sex in CRT cohort studies and clinical trials, with only 17% of studies reporting sex-disaggregated data [129].

Mechanical circulatory support devices

Although mechanical circulatory support (MCS) devices successfully bridge women and men to transplant and even lead to more favourable reverse remodelling in women than in men, women are less likely than men to receive ventricular assist device (VAD) support, despite eligibility and a more critical HF state at admission (fig. 2) [130-132]. In fact, women account only for 20-33% of patients receiving MCS devices with this gender gap widening over time [133, 134]. The reasons accounting for the underutilisation of MCS devices in women most likely include their greater susceptibility to bleeding, vascular complications and neurologic events as well as their lower survival rates following MCS device implantation, which might hinder operator confidence [130, 131, 133-135]. The use of MCS in women with advanced HF might further be limited by the fact that women have a smaller body surface area, are older at the time of implantation, have more comorbidities and higher Society of Thoracic Surgery (STS) mortality scores than men [133]. In addition, women seem to require temporary or permanent right ventricular support due to a higher incidence of right ventricular failure more often than men [130]. Nevertheless, technical refinements resulting in device miniaturisation and less invasive left ventricular assist device (LVAD) implantation techniques might help to overcome this gender gap. In fact, a post hoc analysis of the INTERMACS trial showed a similar outcome in individuals with small body size as compared to larger ones following implantation of the continuous flow LVAD (CF-LVAD) [136]. The latter was also associated with a decrease in complication rates in women alongside an increase of implantation rates over time [137]. Similarly, the disadvantage of women in short and long-term survival rates vanished following less-invasive LVAD implantation or newer-generation HeartWare or HeartMate III LVADs [138, 139]. A novel sex-specific risk score providing excellent mortality risk prediction in both male and female LVAD recipients might further help to optimise utilisation and outcomes in women with advanced HF [140].

Heart transplantation

Heart transplantation remains the gold standard for the treatment of advanced HF in the absence of contraindications [4]. Factors affecting transplantation include sex of the donor and recipient, blood type, human leukocyte antigens, matching body size and heart transplant waitlist priority status. Post-transplant one-year survival is around 90% with a median survival of 12.5 years [141]. Women

tend to have better long-term survival than men post-transplantation, lower risk of coronary allograft vasculopathy and malignancy, but a higher risk of antibody-mediated rejection [142]. In general, outcomes are better in sex-matched transplants than in sex-mismatched transplants, with hormonal factors, immunologic factors, cardiac size mismatch and subsequent right ventricular failure most likely accounting for these differences [143]. Accordingly, data from the International Thoracic Organ Transplant (TTX) Registry shows that one-year unadjusted survival was best for male recipients receiving male donor hearts, intermediate for female recipients receiving either female or male donor hearts and worst for male recipients receiving female donor hearts [144]. Women represent 37% of heart donors but only 26% (international, 2010-2018) to 28% (U.S, 2021) of heart recipients [144, 145]. Accordingly, female patients receiving MCS have lower chances of being listed for heart transplantation, increased risk of waitlist mortality and delisting for worsening clinical status at two years post-implantation (fig. 2) [131]. Nevertheless, if women are listed for transplantation, they are more likely than men to be younger or have dilated cardiomyopathy and less likely than men to have an ischaemic cardiomyopathy, diabetes mellitus, hypertension, tobacco usage or an ICD [146]. Consequently, despite having lower risk features than males, women receive hearts from higher risk donors [147]. Additional efforts such as the consideration of sex-specific transplant candidacy criteria are needed to address current gender disparities in heart transplantation.

Female sex-specific conditions

There are some HF aetiologies that are unique to women, such as PPCM, or more often affect women, such as cancer therapy-induced cardiomyopathy or Takotsubo (stress) cardiomyopathy, with 90% of Takotsubo cases occurring in postmenopausal women (fig. 2) [148, 149].

Takotsubo cardiomyopathy is usually precipitated by acute emotional or physical stress and mimics an acute coronary syndrome. It is accompanied by transient LV apical ballooning in the absence of angiographically significant coronary artery stenosis. The exact mechanisms by which a stressful life event translates into the onset of Takotsubo cardiomyopathy in postmenopausal women and much less so in men, are not fully understood. However, an attenuating influence of oestrogen on sympathetic responses to mental stress, catecholamine-mediated vasoconstriction and the upregulation of endothelial NO synthase activity by oestrogen have been suggested to account for the observed sex differences in Takotsubo cardiomyopathy [150, 151].

The incidence of PPCM amounts to one per 1,000-4,000 live births in industrialised countries and appears to be rising in some countries, most likely due to increased awareness, rising maternal age and increasing numbers of multiple gestation pregnancies [152]. PPCM develops either in the last month of pregnancy or in the five months following delivery in women with no previously documented cardiac disease and is defined as an idiopathic LV dysfunction with LVEF <45% [153]. Predisposing factors include multiparity and multiple gestation pregnancy, advanced age (>30 years), black ethnicity, the presence of preeclampsia or hypertension, a genetic disposition, low selenium level, infections during pregnancy, autoimmune reactions as well as extensive bleeding in the peripartum phase [153]. PPCM is usually reversible within six months after delivery, although acute mortality can be as high as 4% in high-income countries and 14% in low- and middle-income countries [154].

An increase in breast cancer incidence alongside a decrease in breast cancer related mortality has resulted in a rising population of breast cancer survivors at risk for cardiotoxicity from anti-cancer therapies. Consequently, late cardiovascular mortality has exceeded oncologic mortality in breast cancer patients [155]. Exposure to anthracyclines (e.g., doxorubicin) play a major role in cancer therapy-induced cardiomyopathy as a doxorubicin-induced LVEF decrease occurs in approximately 10–15% of patients at standard dosages [156]. Women seem to be more susceptible to anthracycline-induced cardiotoxicity than men, most likely due to sex differences in pharmacokinetics. Similarly, about 13% of patients being treated with trastuzumab, a humanised monoclonal antibody used to treat HER2-positive breast cancer, encounter a decline in LVEF [157]. Radiation therapy for breast cancer also imposes a risk to cardiac structures and seems to increase the risk of HFpEF according to a recent study [158].

Conclusion

Sex and gender affect almost every aspect of HF, from epidemiology and risk factors, to pathophysiology, phenotype, response to medical, non-medical and device therapy and ultimate outcomes. However, despite an increasing awareness of sex and gender differences in HF, large knowledge gaps persist in sex-specific disease mechanisms, optimal drug doses for women and therapeutic interventions in HFpEF as well as sex-specific criteria for advanced HF therapy (table 1). Such knowledge gaps can only be closed with a systematic approach to ensure that sex-specific analyses are prospectively considered from study design, trial recruitment, statistical analysis plan and reporting. Higher quality data on sex and gender differences in HF could facilitate tailored treatment for men and women, which is absent from current European HF guidelines.

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Recommended references

3 Lam CS, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. Eur Heart J. 2019 Dec;40(47):3859-3868c.
4 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep;42(36):3599-726.
64 Tamargo J, Caballero R, Delpón E. Sex-related differences in the pharmacological treatment of heart failure. Pharmacol Ther. 2022 Jan;229:107891.
65 D'Amario D, Rodolico D, Rosano GM, Dahlström U, Crea F, Lund LH, et al. Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry. Eur J Heart Fail. 2022 May;24(5):871-884.
69 Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, et al.; ASIAN-HF investigators. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. Lancet. 2019 Oct;394(10205):1254-63.

References

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