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Review

Impact of Sex and Gender Differences on Heart Failure, Especially in Elderly Patients

Giuseppe Cocco [1,*], Hans Peter Hofmann [2], Stefano Pandolfi [3]

1. Cardiology Office, Weiermattstrasse 41, CH 4153 Reinach/BL, Switzerland; E-Mail: praxis@cocco.ch
2. Praxis Museumstrasse 3, CH-6060 Sarnen/Switzerland; E-Mail: nh.hofmann@bluewin.ch
3. Salina Medizin AG, Roberstenstrasse 31, CH-4310 Rheinfelden/Switzerland; E-Mail: Stefano.Pandolfi@parkresort.ch

* **Correspondence:** Giuseppe Cocco; E-Mail: praxis@cocco.ch

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Abstract

Heart failure is one of the major health threats in Western societies, and its prevalence is steadily increasing. Many data show the important impact of sex (biological) and gender (sociocultural) differences on most aspects (diagnosis, etiology, treatments, and outcomes) of heart failure. For example, compared to men, women with heart failure are older, have more co-morbidities, and develop different phenotypes of heart failure. Postpartum cardiopathy is unique in women. The iatrogenic effects of cancer therapies are more frequent among women compared to men. Currently, the integration of sex and gender differences into the therapy of heart failure is rare. Consequently, women derive disadvantages from a nonspecifically adapted therapy for heart failure, get worse outcomes, and have more iatrogenic adverse effects than men. This situation is medically unfortunate and increases medical expenditures. A sex-guided approach to the correct evaluation of patients with heart failure should become the cornerstone for the correct management of these patients.

Keywords

Heart failure; sex differences; gender differences

1. Introduction

Biological sex differences exist in animals and humans due to the expression of specific chromosomes that control sex hormones with specific expression and function in many organs [1]. Gender differences are unique to humans and are due to socioeconomic inequalities. Women and men encounter distinct environmental influences (e.g., income, lifestyle, competition) and exhibit varying behaviors, including differential attitudes toward medical prevention and adherence to therapeutics [1]. It is almost impossible to distinguish appropriately between the effects of sex and gender differences (**S&GDs**). However, it is established that both exert significant and specific effects on cardiovascular diseases (**CVDs**) and heart failure (**HF**) [1-3]. The paper reviews the most important effects of S&GDs on clinical characteristics, outcomes, and therapy in chronic HF.

2. S&GDs and HF-Prevalence

HF is one of the major health threats in Western societies, at present affecting more than 64 million people globally, and in the elderly, the incidence is about 10% [1, 4-9]. Aging is an important factor in the occurrence of HF, which in absolute numbers is more frequent among women than among men. In 40-year-old individuals, the prevalence of HF is less than 3% and is similar in both sexes [1, 7-9]. In 45-year-old individuals, the prevalence rises up to 5%, and S&GDs are detectable because the phenotype HF with reduced ejection fraction (**HFrEF**) is more frequent among men than in women [1, 7-9]. In later lifetime, the S&GDs become more evident because the prevalence of HF is higher in women, and compared to men, women usually develop the phenotype "HF with preserved ejection fraction" (**HFpEF**) [1, 10-13].

3. S&GDs and HF-Epidemiology

Substantial S&GDs are detectable in the HF-epidemiology. Compared to men, in women, HF occurs later, the ischemic etiology is less frequent, and the outcomes are different [1, 10-15]. Moreover, in women only, the density and distribution of fat is a risk for major cardiovascular adverse events (**MACEs**) and all-cause mortality, and this risk is unrelated to classic cardiovascular risk factors (**CVRFs**) [16, 17]. Compared to men, women generally have a lower risk for MACEs and all-cause mortality. However, in older women who get a myocardial infarction (**MI**), the risk for MACEs becomes higher than in similarly aged men.

Postpartum cardiomyopathy (**PPCM**) is an idiopathic cardiopathy unique to women, which is characterized by left ventricular (**LV**) dysfunction with a LV ejection fraction (**LVEF**) <45% [18]. PPCM develops in women without a previously documented cardiac disease, either in the last month of pregnancy or in the five months following delivery [18]. In industrialized countries, its incidence amounts to 1:1,000-4,000 live births. Its incidence appears to increase in some countries, probably due to better medical knowledge of the pathology [18]. Predisposing factors for the PPCM include a genetic disposition, black ethnicity, maternal age >30 years, multiparity, multiple gestation pregnancies (often following hormonal therapies for infertility), the presence of preeclampsia or hypertension, infections during pregnancy, low selenium level, autoimmune reactions, and large bleeding in the peripartum phase [19]. 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 [20].

An increased incidence of breast cancer, combined with a longer survival in treated women, has resulted in a rising number of women who develop cardiotoxicity from anticancer therapies. Indeed, in women with breast cancer, late HF mortality now exceeds cancer mortality [21]. Several factors cause cardiotoxicity in anticancer therapies. Bilateral radiotherapy seems to increase the risk of HFpEF [22]. Anthracyclines (e.g., doxorubicin) play a major role in the occurrence of cardiotoxicity, especially because women seem to be more susceptible than men to anthracycline-induced cardiotoxicity, probably due to unfavorable pharmacokinetics in women versus men [22]. Doxorubicin at standard dosages induces a significant decrease in LVEF in up to 15% of patients [23]. Similarly, trastuzumab, a humanized antibody used to treat HER2-positive breast cancer, induces a significant LVEF decline in up to 13% of treated women [24].

Figure 1 summarizes the most important S&GDs risk factors in HF.

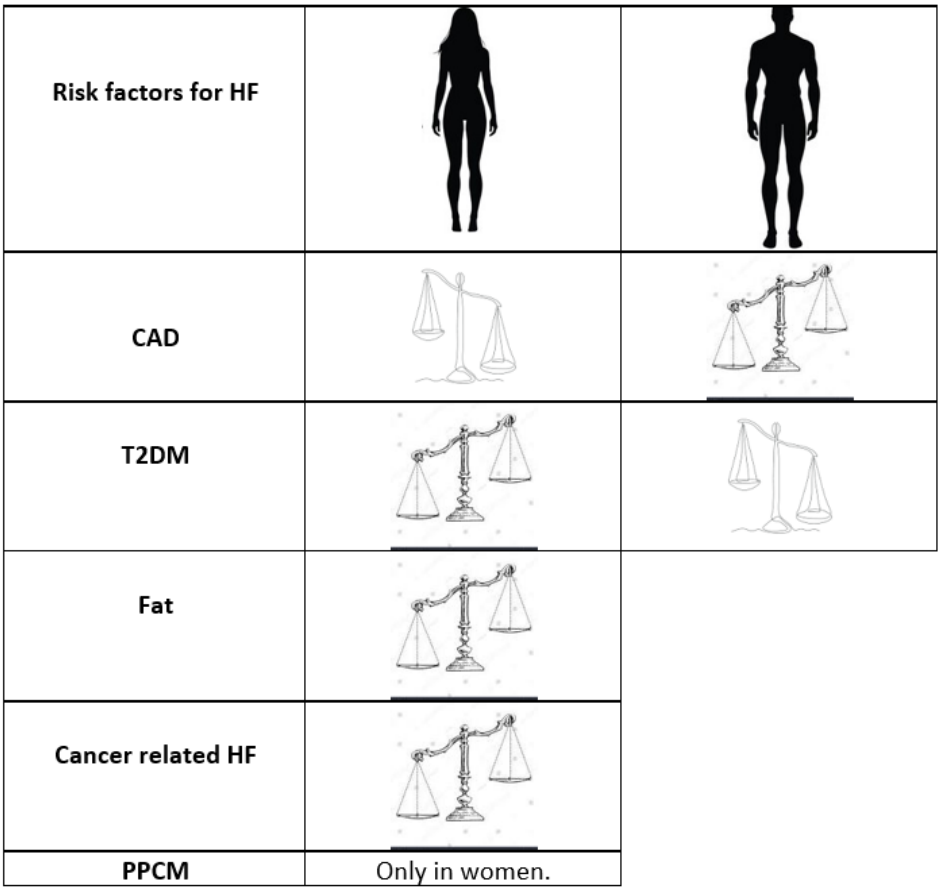

Figure 1 S&GDs in risk factors of HF. Compared to men, coronary artery disease is less frequent, except for elderly postmenopausal obese women with T2DM. Compared to men, in women, T2DM induces less adverse cardiovascular events and HF. However, in the post in elderly obese women with T2DM, the risk is as high as in men. The peculiar fat density and distribution of fat are risks for HF and CVDS in women only. Cancer therapies for breast cancer exert a significant risk of HF in women. Postpartum cardiomyopathy is unique to women.

4. S&GDs and Pathologic Cardiovascular Changes in HF

S&GDs differences in cardiovascular structures and function exist in healthy people and increase with aging [25-27].

In healthy people, the cardiac index is similar in both sexes [1]. However, compared to men, women show smaller indexed LV stroke volumes and higher systolic and diastolic LV stiffness, and the increase of LV stiffness is markedly steeper in older women than in similarly aged men [1, 28-30]. Due to the smaller aortic root and stiffer aortic arch, the pulse pressure and pulsatile afterload are higher in women than men. Consequently, older women have a higher risk of myocardial ischemia and diastolic dysfunction than older men [31, 32].

Moreover, compared to men, women often present the HF phenotype "preserved ejection fraction" (**HFpEF**), characterized by higher indexed LV wall thicknesses and diastolic dysfunction [1, 33, 34]. Also, the age-related rise in systolic blood pressure is steeper in women versus men. Therefore, the prevalence of arterial hypertension is higher in postmenopausal women than in similarly aged men [1, 33, 34]. Consequently, the Cardiology, Geriatric, Hypertension, and Nephrology Societies have included arterial hypertension as a CVRF for HFpEF in older women [25, 32, 35, 36].

The combined effects of hypertension and obesity favor the occurrence of eccentric LV hypertrophy in older men and induce concentric LV hypertrophy in postmenopausal women [25, 34].

The prevalence of atrial fibrillation is lower among women than in men. However, women with atrial fibrillation have a higher risk of stroke than similarly-aged men, possibly due to a smaller atrial size [36]. Therefore, the female sex is included as a CVRF in the CHA_2DS_2-VASC score of atrial fibrillation [37].

S&GDs are also present in the compensatory mechanisms occurring in HF. Historically, an increased LV afterload was considered the key mechanism for the occurrence of HF, especially the phenotype HFpEF. However, recent data highlight the significant role of chronic inflammation, endothelial dysfunction, and subsequent microvascular dysfunction, ischemia, fibrosis, and cardiac hypertrophy in the pathophysiology of CVDs and HF [38-40]. Compared to men, older women have significantly higher chronic inflammation (inflammaging), a stronger immune response, and a higher expression of proinflammatory myocardial genes [38-42]. This should be due to a dysfunction in endothelial nitric oxide signaling. These pathologic changes represent a high risk of developing microvascular dysfunction and autoimmune diseases. Compared to women, men have a higher activation of the proinflammatory and profibrotic pathways combined with a dysfunction of the myocardial calcium handling and energy metabolism [38, 40-42]. These pathologies favor the occurrence of HFrEF.

The higher body fat index in women versus men should contribute to the occurrence of different HF phenotypes and the different occurrences of MACEs and all-cause mortality in women and men [17]. This "fat density" risk factor is unrelated to other established CVRFs.

While the impact of sex on the assessment of congestion in HF is still a matter of debate, the female sex is independently associated with different levels of the biomarkers of congestion, such as the N-terminal prohormone of brain natriuretic peptide (**NT-proBNP**) [43-45].

Resuming existing S&GDs have a relevant impact on the different occurrences and outcomes of HF in women and men. The impact of fat as a risk in HF is unique to women. Aging increases the impact of S&GD differences on HF.

Figure 2 summarizes the different cardiovascular changes of HF between women and men.

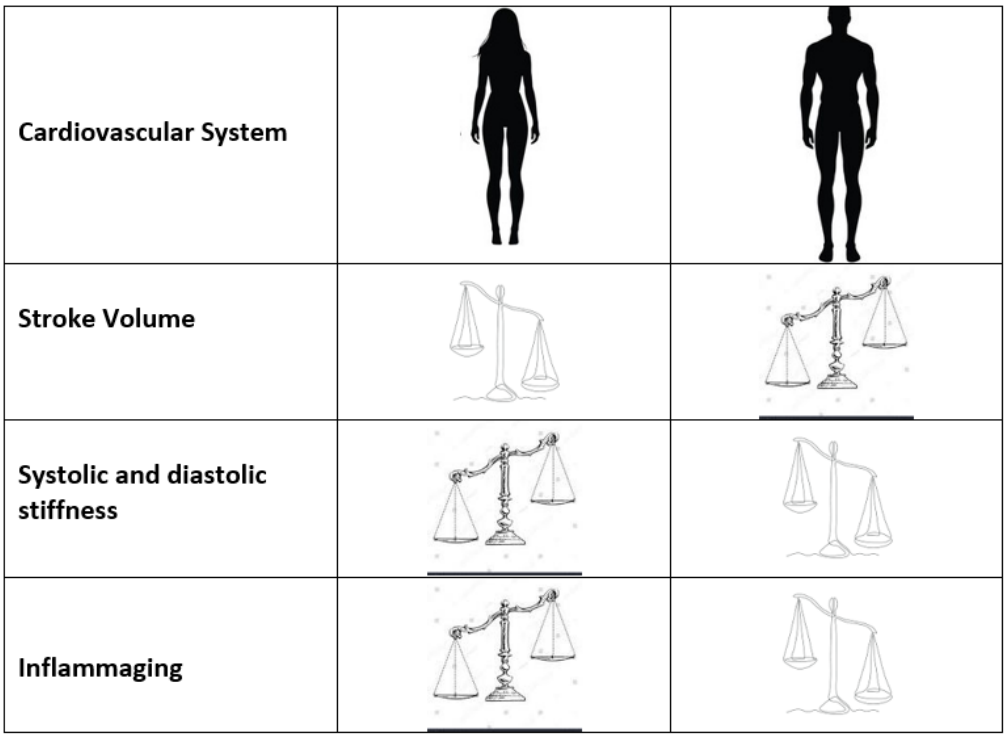

Figure 2 Cardiovascular differences related to sex and gender in HF are notable. In women with HF, compared to men, there are observed differences such as a smaller stroke volume, increased systolic and diastolic stiffness, and higher levels of aging-related inflammatory changes.

5. S&GDs and Heart Rate

Under normal conditions, at rest, the heart rate is higher in women versus men [44]. Studies in young animals and healthy individuals have consistently highlighted that the sympathetic and vagal systems function better in females than males under physiologic conditions [46-48]. During psychic and physical stress, men activate the Starling mechanism and react by increasing stroke volume and blood pressure [46]. Women react to stress with lower sympathetic response, greater vasodilation, and increased peripheral oxygen extraction [46]. Compared to men, women have a lower density of β1-adrenoreceptors in cardiomyocytes [1, 34, 38-40], and this different density of receptors impacts stress's effect on the cardiovascular system. Stress induces more fibrosis (collagen deposition) and favors eccentric LV-remodeling and dilatation in women than men [1, 34, 38-40]. These changes, in turn, favor the occurrence of HFpEF.

6. S&GDs and Sex Hormones

Sexual hormones significantly affect cardiomyocytes, electric-conducting cardiac cells, endothelial cells, and vascular smooth muscle cells [1].

Testosterone (**TE**) has many effects on the cardiovascular system (**CVS**) [49]. Low endogenous TE levels are associated with higher rates of all-cause and cardiovascular-related mortality. A significant association between TE deficiency, HF, and exercise capacity might exist. Men with type 2 diabetes mellitus (**T2DM**) have statistically significant lower levels of total TE compared with those in nondiabetics. In men receiving antiandrogen therapy, there is a significant increase in the rate of MI, stroke, sudden cardiac death, and development of CVDs. In men with coronary artery disease (**CAD**) TE increases angina threshold by causing vasodilation of coronary arteries and has significant antianginal effects. TE may play an important role in the regulation of ventricular repolarization. Between the two sexes prior to the onset of puberty there is no difference in ventricular repolarization patterns between the two sexes before the onset of puberty. However, after puberty, men experience a gradual shortening of their QTc interval from approximately age 9 until around age 50, which corresponds to the highest levels of circulating TE in normal men. In addition, castrated men have QTc intervals that are longer than the QTc interval in non-castrated men, and virilized women have shorter QTc intervals compared with those in normal women. Low endogenous TE levels are associated with worsening cardiovascular mortality, T2DM, and obesity. Finally, there is an association between TE levels and carotid intima-media thickness with an inverse correlation between these two variables.

Estrogen (**ES**) may increase β2-adrenergic receptor responses [1-3, 50], promotes vasodilation, reduces catecholamine-induced vasoconstriction, has anti-inflammatory and antioxidant effects [44, 50]. Despite numerous animal studies demonstrating the beneficial cardioprotective effects of ES, large clinical trials failed to support the effectiveness of ES replacement therapy in reducing CVDs. Therefore, the presumed protective role of ES in CVDs and, consequently, the use of ES replacement in women is still a matter of debate [51]. It is, however, unknown if the lack of evidence of cardiovascular protection was due to the initiation of replacement long after the start of menopause, the dose, and the combination of ES and progestin. Despite unclarified aspects of ES on the CVS in postmenopausal women, the decreased ES levels affect the function of the sympathetic and vagal system and increase the sensitivity to circulating catecholamines, favoring the occurrence of cardiac microvascular dysfunction and, consequently, of HFpEF and stress induced (Takotsubo) cardiomyopathy [1, 25, 47].

A recent clinical trial [52] detected that the breast fat density in premenopausal women is a CVRF, which is not linked to other traditional CVRFs. Premenopausal women with fatty breasts had statistically more MACEs than women with non-fatty breasts due to overexpressed sodium-glucose transporter 2 (**SGLT2**), inflammatory cytokines, and down-regulated breast sirtuins. This discovery could be the starting point for new trials on the SGLT2 inhibitor therapy in women with different classes of HF, and screening mammography could be proposed in overweight women to stage breast density and predict MACEs [53].

7. S&GDs and Symptoms of HF

Perhaps women tend to have more atypical HF symptoms, but otherwise, clinical symptoms do not differ significantly between women and men [1-3, 10-13]. Following the onset of HF, depression manifests with greater frequency, and the quality of life is observed to be diminished in women compared to men, potentially attributable to gender inequalities [54-56].

8. S&GDs and HF-Phenotypes

HF-phenotypes are classified according to the LVEF: HFrEF (LVEF ≤ 40%), HFmrEF (midrange LVEF 41-49%), and HFpEF (LVEF ≥ 50%) [10-15, 25, 57]. S&GDs have a strong impact on the occurrence of HF phenotypes.

In 40-year-old individuals, the prevalence of HFpEF is low and similar in both sexes, but in ≥55-year-old individuals, the prevalence rises to 5% and seems slightly more frequent in men. In ≥60-year-old women, the prevalence is slightly higher than in men, and from this age, it increases steadily, reaching up to 8% in the ≥80-year-old women [1, 3, 7, 25]. The HFpEF phenotype is more frequent in women than men [1, 11-15], and microvascular cardiac dysfunction is detected in 75% of patients with HFpEF [38, 41]. The high frequency of HFpEF in women is explained, at least in part, by the fact that women versus men adapt to cardiovascular stress by maintaining LVEF but developing concentric LV hypertrophy and diastolic dysfunction with less LV systolic dysfunction and eccentric dilation [1, 15, 25-34]. Due to the increasing human aging, the prevalence of HFpEF should increase by 1% per year, and it will become the most common phenotype of HF in the future [1, 3, 4, 12, 25]. Due to the higher life expectancy among women compared to men, a majority of HFpEF cases are anticipated to be prevalent among older women [1, 3, 4, 12, 25].

The levels of circulating NT-proBNP are higher in postmenopausal women versus similarly aged men due to higher cardiac stretching [43-45], and the greater visceral adipose tissue increases neprilysin activity, which counteracts the microvascular inflammation [56]. Other studies [17, 52, 53] found that in women, the amount of central fat and density of fat in the breasts plays a role as a CVRF in the occurrence of MACEs and outcomes in HF and also that this CVRF is unrelated to the other established CVRFs.

HFmrEF is a heterogeneous disease that accounts for about one-third of the HF phenotypes [1, 3, 4, 12-15, 25]. Its prevalence is higher among men than women, and in two-thirds of patients, HFmrEF is associated with a macrovascular CAD [4, 57, 58].

HFrEF in Europe affects more men than women and is usually also due to CAD, often following MI [1, 11, 12, 25, 28]. The high prevalence of HFrEF in men is explained, at least in part, by the fact that men adapt to HF by developing eccentric LV-hypertrophy and dilation [1, 11-13, 27, 59, 60]. It is unknown how frequently HFpEF changes into HFrEF [1]. The transition from a hypertrophic to a dilated, hypocontractile HF phenotype has been described in a woman with hypertrophic cardiomyopathy [61]. The autosomal underlying gene defects of the dilated and hypertrophic cardiomyopathy appear to be distributed equally in both sexes. However, in old studies, these CVDs were slightly more frequent in men [62, 63].

Figure 3 summarizes the different prevalence of HF-phenotypes in women and men.

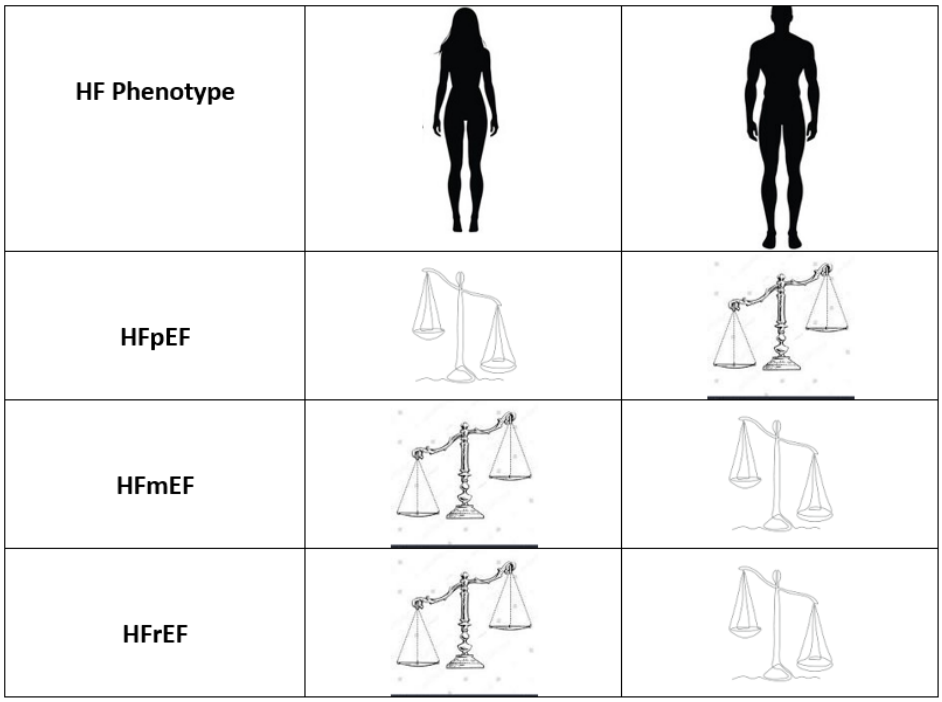

Figure 3 S&GDs and HF-Phenotypes. In women, HFpEF is the most frequent type (except for postmenopausal women with T2DN; HFrEF is as frequent as in men). HFmEF and HFrEF are more frequent in men than in women.

9. S&GDs and HF-Risk Factors

S&GDs are detected in non-modifiable HF-risk factors (e.g., ethnicity, epigenetics, genetics, family history, and aging) and modifiable risk factors. HF and T2DM show a growing prevalence and are strongly interrelated, especially in older people. T2DM is a chronic disease associated with micro- and macrovascular complications, including myocardial ischemia, and with a specific and intrinsic cardiac dysfunction called diabetic cardiomyopathy (**DCM**) [64-66]. Both clinical and animal studies demonstrate significant sex differences in the prevalence, pathophysiology, and outcomes of CVDs and DCM [67]. Endothelial dysfunction, atherosclerosis, coagulation, and fibrosis are differentially sex modulated in the diabetic cardiovascular system, and impairment of energy metabolism also emerged as a determinant of multiple CVDs associated with diabetes [67]. The global prevalence of T2DM presents large regional, age-related, and socioeconomic variations but is higher among men [64]. Premenopausal women with T2D tend to develop fewer cardiometabolic complications than men. However, due to hormonal changes, postmenopausal women tend to become obese with changed visceral and central fat distribution. The changed fat distribution favors the occurrence of MACES and HF [17, 34, 52, 53]. If elderly postmenopausal women develop T2DM, the prevalence of HF is higher than in similarly aged men, and the incidence of MACEs increases largely [64]. Of note, HFpEF is the most frequent HF phenotype in postmenopausal non-diabetic women. However, frequently in postmenopausal women with T2DM, LV hypertrophy, and remodeling become frequent, and these changes induce poorer outcomes than in similarly aged diabetic men [64, 65]. As discussed later, in cardiac patients with T2DM, the therapy with glucagon-like peptide 1 receptor agonists (**GLP-1 RA**) exerts a profound impact on T2DM and also on the effect of cardiac resynchronization therapy devices (**CRT-Ds**).

S&GDs are detected in arterial hypertension because the pathology induces more LV remodeling and more HF among postmenopausal women than in age-related men [27, 31-35, 68]. In many CVRFs, more men than women develop a macrovascular CAD and HFrEF [27, 31-35, 68-70]. However, there is an exception because, in postmenopausal women, the risk of developing CAD and HFrEF is at least as high as in men [68-70].

S&GDs are detected in metabolic and inflammatory disorders related to visceral and general obesity [16, 17, 34, 52, 53, 71]. While obese men are prone to develop HFrEF, postmenopausal obese women usually develop HFpEF [57, 71, 72]. In women, fat density and distribution are a CVRF risk for MACES and HF [16, 17, 34, 52, 53].

Tobacco use is a substantial risk for many diseases and the occurrence of HF in all people. At present, in high-income countries, young women are smoking more than in the past [73, 74], and tobacco's negative effects are more frequent among women than in men [1, 73]. Also, tobacco is a risk factor for PPCM [74].

Gender inequalities vary among the nations concerning regional social, economic, and religious practices and play a significant role in CVDs and HF [1]. Compared to a good-high income, low-income increases twofold the risk of in-hospital mortality and post-discharge MACEs in both sexes; however, there is a gender difference because low-income is much more frequent in women than in men [75]. Consequently, women have a higher HF risk. Moreover, low-income is frequently combined with poor education, and people in this situation have a significantly higher incidence of HF than those with better income and education [75-77]. Since more women than men are in this situation, women have a higher HF risk. Furthermore, lacking social support is also associated with an increased rate of hospitalizations for HF, a worse prognosis, and a lower quality of life. Since men under 65 years reported the lowest social support among all demographic groups, the risk of MACEs in HF is higher in men [78]. Lastly, widowhood represents an independent risk of increased hospitalization for HF [79]. Since widowhood is more frequent among women than in men, HF risk is higher in women.

In women, the amount and localization of fat are risk factors for HF. This might be a starting point for developing effective therapies, e.g., with SGLT2 inhibitors and/or GLP-1 RA, especially in postmenopausal women. There are insufficient data to accept that socioeconomic factors can fully explain the higher risk of HF in women who had a MI. However, many data indicate that gender inequalities interplay with the occurrence and outcomes of HF.

Table 1 summarizes the most significant S&GDs in HF.

Table 1 S&GDs in HF.

Women versus Men	**Men versus Women**
Etiology/Socioeconomic Disadvantages	
PPCM (unique to women) More HF due to cancer therapies. Higher lifetime risk of HF. More atrial fibrillation. More socioeconomic disadvantages.	Less atrial fibrillation. Less socioeconomic disadvantages.
Pathophysiology/Risk Factors	

More coronary microcoronary dysfunction. More arterial dysfunction and hypertension. More concentric left ventricular remodeling. More left ventricular dilation and cardiomyopathies. More T2D, hypertension and obesity. More Inflammation. Adipose tissue (risk factor only in women).	More traditional cardiovascular risks factors (e.g., CAD). More apoptosis. More eccentric LV remodeling.
Phenotypes of HF	
More HFpEF than HFmrEF and HFrEF.	More HFrEF and HFmEF than HFpEF.
Clinics	
Older, more co-morbidities. Higher LVEF and NT-proBNP values. More atypic symptoms.	Younger. Less co-morbidities. Lower LVEF and NT-proBNP values. Less atypic symptoms.
Outcomes	
Better survival (unless with T2DM). Poorer quality of life and greater disability.	Higher mortality. Better quality of life.
Treatment	
Underrepresented in clinical trials. More adverse effects with drugs therapies. Less likely to get non-pharmacologic therapies and more complications. Greater benefit from ICDs and CRT-Ds but less frequently received. Receive less intensive care at end of life. Less cardiac transplantation, less risk factors but receive hearts from high-risk patients.	More men in clinical trials. More rehabilitation. More likely to get non-pharmacologic therapies, with less complications. More likely to get cardiac transplantation. Receive more intensive care at end of life.

10. S&GDs and Pharmacologic Therapy in HF

The modern medical therapy of HF comprises angiotensin-converting enzyme inhibitors (**ACEIs**), angiotensin II-receptor blockers (**ARBs**), β-blockers, and sacubitril/valsartan (**ARNI**, i.e., the neprilysin inhibitor sacubitril plus the ARB valsartan), mineralocorticoid receptor antagonists (**MRAs**), and SGLT2 inhibitors [80-82]. All these drugs reduce morbidity and mortality in HFrEF [12, 80, 81], and the SGLT2 inhibitors are the first class with beneficial effects in HFmrEF and HFpEF [82, 83]. To reduce morbidity and mortality, the actual guidelines in HF recommend titrations to target doses for the drugs without giving sex-specific recommendations [12, 80-83]. The absence of sex-specific recommendations is due to several factors. Most experimental dose-finding studies preferentially used male laboratory animals. The underrepresentation of females in experimental studies reduced the possibility of finding sex-specific dosing in women [84]. Years ago, in the USA, six drugs had to be withdrawn from the market because they posed greater health risks to women than to men [85]. The calculation revealed that the prevention of some drug withdrawals, achieved through improved targeting of drugs and doses for women, could have saved several billion US dollars in 2010 [86]. Furthermore, women are underrepresented among the participants in available

randomized clinical trials across all HF-phenotypes, often comprising less than one-fourth of the study population [87, 88]. On the other hand, it is established that the pharmacokinetics and pharmacodynamics of cardiovascular drugs differ significantly between women and men. Men benefit most from the guidelines-recommended target doses of ACEIs, ARBs, and β-blockers, whereas submaximal doses may be more effective and safer in women [89, 90].

Clinical trials on ACEIs in HF therapy gave discording results. In a meta-analysis in HFrEF (women were less than 40% of the tested patients), ACEIs reduced mortality and hospitalization in men but not in women [90]. However, two analyses of trials with ACEIs in patients with MI found that ACEIs mortality and progression to HF were similarly reduced in both sexes [91, 92]. Another meta-analysis of trials with ACEIs and β-blockers in HFrEF (women were 25% of the studied patients) found that mortality was reduced in men but not in women [93]. Of note, these clinical trials were performed more than 20 years ago. In those years, the results were analyzed without sex specificity [94, 95].

Clinical studies in HFrEF-patients demonstrated that ARBs reduce mortality in both sexes [96-102]. Interestingly, higher doses of losartan were more effective in women than men [102]. However, data on the safety of ARBs is discordant. In the HF-therapy ARBs, the mortality reduction was similar in women and men. However, women experienced significantly fewer adverse effects, raising the consideration that their better tolerance may have contributed to the prescription of higher doses of ARBs [102]. On the other hand, in a trial with irbesartan, the adverse effects and reduction of mortality were similar in both sexes [103].

Clinical HF trials with ARNI gave discording results for efficacy and safety. In a trial with ARNI in patients with HFpEF and HFmrEF, the composite endpoints of HF hospitalization or cardiovascular death were significantly reduced only in women [104]. In the PARADIGM trial in HFrEF-patients (women were 22% of the participants), ARNI reduced mortality similarly in both sexes [105]. In another trial in HFrEF-patients, ARNI reversed cardiac remodeling, improved the health status, and reduced the level of NT-proBNP among women only [106]. Furthermore, in HFpEF patients, women responded to treatment with ARNI at higher LVEF ranges than men [107]. The different efficacy in women and men was justified because postmenopausal women had greater visceral adipose tissue with increased neprilysin activity and lower NO synthases, microvascular inflammation, and bradykinin production [108]. However, a meta-analysis found that the safety profile was similar in both sexes in patients treated with ACEIs [109].

It is assumed that in HF, most β-blockers improve survival similarly in both sexes [110, 111]. However, there is a significantly different β-adrenergic receptor activity between women and men [1, 33, 35, 37, 41]. Women exhibit higher oral bioavailability, a smaller volume of distribution, and slower clearance of β-blockers through CYP2D6 compared to men [112, 113]. Indeed, the bradycardic and hypotensive effects of β-blockers are more pronounced in women versus men [114]. Also, in a HFrEF study with β-blockers and either ACEIs or ARB, in women, the lowest risk of death or hospitalization was detected with β-blockers taken at half the guideline-recommended dose [93]. Furthermore, in a trial, the anti-ischemic effect of 100 mg metoprolol was significantly less pronounced in women than in men [115].

Experimental studies have shown that the effect of the mineralocorticoid receptor on ventricular remodeling and gene expression is sex-specific [116]. However, a pooled analysis of trials in patients with HFpEF and HFrEF found that the positive effect of MRAs was the same in both sexes and was LVEF-independent [117]. In the old RALES trial in HFrEF, the efficacy of spironolactone, added to an ACEI and a loop diuretic, was similar in both sexes [118]. Also, in the EMPHASIS-HF trial, eplerenone

was similarly effective in both sexes [119]. On the other hand, in a study of HF in post-MI patients with cardiac dysfunction, eplerenone reduced cardiovascular mortality or HF hospitalization in men only, whereas all-cause mortality was reduced in women only [120]. Moreover, in the TOPCAT trial in HFmrEF and HFpEF, spironolactone reduced the mortality across the entire spectrum of LVEF in women. However, in men, the reduction was seen in lower LVEF only [121, 122].

Diuretics are prescribed in HFrEF to reduce congestive symptoms. They are used more frequently in women than men [123, 124]. In rats, ES enhances the NaCl cotransporter density in the apical plasma membrane of the distal convoluted tubule. Thus, the natriuretic and kaliuretic effects of loop and thiazide diuretics are more potent in females than males [124, 125]. However, in HFrEF-patients, the diuretic effect of torsemide was significantly smaller among women than in men [126].

The Swedish HF Registry reports that, despite known more adverse effects of digoxin in women, in all HF phenotypes, women were more likely to be treated with digoxin than men, the titration was the same in both sexes, and the mortality was higher among women than in men [127].

The recent ESCHF guidelines recommend SGLT2 inhibitors for all patients with HFrEF who are already receiving treatment with ACEIs or ARBs, ARNI, β-blockers, and MRAs, irrespective of their diabetic status [81, 82, 128, 129]. Of note, in available clinical trials, less than 40% of patients treated with SGLT2 inhibitors were women. In clinical trials of T2DM patients (36% of the patients were women), the beneficial effects of SGLT2 inhibitors were similar in both sexes. However, women reported more adverse effects, such as urinary tract and genital mycotic infections [130, 131]. Lastly, in trials on HFrEF [130, 131] and on HFpEF [132], SGLT2 inhibitors reduced the worsening of HF or cardiovascular death to a similar extent in both sexes.

Resuming, at present, guidelines in the therapy of HF recommend drugs without differential dosage schedules for women and men. On the other hand, compared to men, especially older women usually have a smaller body size and surface, a higher body fat content, or a lower hepatic and kidney function [133]. Also, compared to men, women often have more risk factors for iatrogenic effects, such as older age, frailty, morbidities, polytherapy, and depression [134]. Adverse drug events represent a source of greater health concern in women than in men because 60% of patients admitted to hospitals for adverse drug events are women [135-139].

11. S&GDs and Non-Pharmacologic HF-Therapies

Cardiac rehabilitation improves quality of life and outcomes in HFrEF-patients. Compared to men, women get more benefits from rehabilitation [140]. Nevertheless, a significantly lower proportion of women than men participate in cardiac rehabilitation programs, a disparity attributed to women frequently reporting greater familial obligations compared to men [141]. In HFpEF patients, lifestyle interventions increase physical work capacity, reduce diastolic dysfunction and hypertension, and ameliorate quality of life. The effects are similar in women and men; however, this intervention is significantly less frequently offered to women [142, 143]. For reasons yet unidentified, during the final six months of life for patients with advanced HF, fewer women than men are hospitalized and receive critical care and invasive procedures upon admission [144].

There are no data on the sex-specific use of wearable cardioverter-defibrillators (**WCDs**). WCDs were used in 107 women with PPCM and in 159 matched nonpregnant women with nonischemic dilated cardiomyopathy. No PPCM women received an appropriate shock for ventricular tachycardia/ventricular fibrillation. A woman with dilated cardiomyopathy received 2 successful

shocks [145]. Implantable cardioverter defibrillators (**ICDs**) and cardiac resynchronization therapy devices (**CRT-Ds**) are effective in the HF-therapy. Less than 20% of published trials on ICDs and CRT-Ds report data differentiating women and men [146]. S&GDs significantly influence the efficacy of ICDs and CRT-Ds. Women versus men have better benefits, such as improved quality of life and overall survival, more reduction of LV-remodeling, and less hospitalization [147, 148]. It is hypothesized that the better outcomes in women are due to smaller bodies and cardiac size, consequently with shorter distance and time for cardiac electric conduction [149], and to less frequent CAD etiology and minor myocardial scars [150]. Indeed, the sex differences decrease when the size of the heart and cardiac scars are similar in women and men, supporting this explanation's validity [149, 151]. However, for reasons incompletely understood, even when adjusting the results for age and co-morbidities, the outcomes of the therapy with ICDs and CRT-Ds are still different between women and men [152]. Indeed, after ICDs and CRT-Ds implantation, iatrogenic complications, such as bleeding, pneumothorax, tamponade, infection, or lead dislodgement, are more frequent among women than in men [153]. Also, women are less likely to receive appropriate anti-tachycardia pacing or ICD shocks [154] because the occurrence of ventricular arrhythmias is less frequent among women versus men, probably due to fewer and smaller myocardial scars [151]. Furthermore, in women, the QRS duration is shorter than in men, and after CRT-Ds implantation, women need lower cut-off values for QRS duration than men [154-157]. Finally, ICDs implantation should reduce sudden cardiovascular death in both sexes, but a clear benefit regarding overall mortality was not found in women [149, 155]. Therefore, sex-specific data would help implement CRT-Ds [157, 158].

The term metabolic syndrome (**MS**) refers to a clustering of specific CVRFs whose underlying pathophysiology is thought to be related to insulin resistance. While there is no question that certain CVRFs are prone to cluster, it has been found that the MS has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVRF marker [159]. Even if the definition is imprecise, clustering CVRFs called MS can affect clinical outcomes in CRT-D patients. A study [160] compared CRT-Ds' effects in patients with MS and those without MS. The results show a significant difference in the percentage of CRT-Ds responders regarding the sensing, pacing, and impedance thresholds of the right atrium, right ventricle, and left ventricle leads since there were more responders in non-MS patients. Therefore, the clustering of CVRFs defined as MS may affect the functionality of CRT-D leads and, in the end, clinical outcomes in HF-patients. MS may predict hospitalization for HF worsening in CRT-D patients [160]. Furthermore, both clinical and animal studies demonstrate that the occurrence of an acute MI in women with T2DM increases the risk of MACEs and mortality by 50%, while the risk is unchanged in men with T2DM [67]. Clinical studies also reveal a sexual dimorphism in the incidence and outcomes of DCM [67]. Indeed, HF and T2DM exhibit a well-established interrelationship and a growing prevalence, particularly in elderly patients. Reports on CRT-Ds in diabetic elderly patients are limited and controversial. A study [161] investigated the functional role of T2DM (37.5% of diabetic patients were treated with insulin) on CRT-Ds' effectiveness in elderly patients who underwent CRT-Ds implantation. After 1 year, in >75-year-old patients, CRT-Ds improved myocardial LV geometry and functional capacity in a comparable proportion of diabetic and non-diabetic patients and a similar functional status amelioration. Another study [162] investigated the effects of GLP-1 RA and conventional hypoglycemic therapy in T2DM patients with HF treated by CRT-Ds. GLP-1 RA therapy, in addition to standard hypoglycemic drugs versus standard hypoglycemic drugs,

significantly reduced inflammation and NT-proBNP values in diabetic HF patients treated by CRT-Ds. GLP-1 RA exerts anti-inflammatory and hemodynamics effects linked to significant improvement of LVEF, the reduction of the NYHA class, arrhythmic burden, and hospitalization for HF-worsening. Intriguingly, GLP-1 RA therapy, in addition to standard hypoglycemic drugs, was associated with a 3.7-fold higher rate of CRT-D responders versus other conventional hypoglycemic drugs. Therefore, GLP-1 RA therapy and standard hypoglycemic drugs may improve CRT-D responder rate and clinical outcomes in diabetic patients. Moreover, GLP-1 RA therapy, in addition to standard hypoglycemic drugs, may be recommended in T2DM HF patients treated by CRT-Ds [162].

Advanced HF mechanical circulatory support devices (**MCSDs**) allow bridging to cardiac transplantation. S&GDs are also present in this therapy because MCSDs reverse LV remodeling more often among women than in men [163-168]. However, despite a more critical state at admission, women account for at most 33% of patients treated with MCSDs, and this sex difference is increasing over time [163-168]. Several factors contribute to the underutilization of MCSDs in women. Compared to men, women needing MCSDs have higher mortality scores of the Society of Thoracic Surgery, a higher incidence of right ventricular failure, are older, have more co-morbidities, often have a smaller body surface area, a greater susceptibility to bleeding, vascular complications, and neurologic events, and last but not least, their survival rate following MCSDs implantation is worse [169-173]. New techniques and smaller MCSDs seem to reduce the sex difference due to a different body surface area. Indeed, in HF patients, the outcomes with continuous flow LV MCSDs were similar in patients with small and larger body sizes [174, 175]. Also, with the use of the newer generation MCSDs Heart Ware or HeartMate III, the disadvantage of women in short and long-term survival rates vanished [176]. Of note, in 2021, the novel sex-specific risk score was found to allow excellent mortality risk prediction in outcomes of both sexes after MCSD implantation [177].

When all other therapies have failed, in the absence of contraindications, heart transplantation is an option for HF treatment [12]. At present, compared to men, women listed for heart transplantation are less likely to have a CAD pathology but more likely to have DCM, hypertension, or an ICD [173]. Compared to men, heart-transplanted women tend to have a lower risk of coronary allograft vasculopathy and malignancy and show better long-term survival; however, they have a higher risk of antibody-mediated rejection. Despite having fewer cardiac risks than men, women receive hearts from higher-risk donors [174]. Outcomes are generally better in sex-matched than in sex-mismatched transplants [173-178]. However, in 2021, women represented 37% of heart donors but less than 30% of heart recipients [174, 175]. Consequently, compared to men, women had lower chances of getting heart transplantation, increased risk of waitlist mortality, and delisting for worsening clinical status at two years post-implantation [178].

12. Conclusions

A large amount of data shows the presence and important impact of S&GDs in most aspects of HF. The most important S&GDs are summarized in the enclosed table. While the S&GDs are known, there are large knowledge gaps in their impact on occurrence (etiology, phenotypes), outcomes, and therapy of HF. Till now, we had very sex-specific research studies, and women were underrepresented in clinical trials. Consequently, current HF guidelines cannot offer sex-specific recommendations. With the present therapeutic guidelines, the efficacy is less, and adverse effects are more frequent in women than men. This situation is unfortunate and also increases medical

expenditures. A sex-guided approach to the correct evaluation of patients with HF should become the cornerstone for the correct management of these patients.

Abbreviations

ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin II-receptor blockers
ARNI	Sacubitril/Valsartan
CRT-Ds	Cardiac resynchronization devices
DCM	Diabetic cardiomyopathy
ES	Estrogen
LV	Left ventricular
MS	Metabolic syndrome
MCSDs	Mechanical circulatory support devices
MRAs	Mineralocorticoid receptor antagonists
SGLT2	Sodium glucose transporter 2 inhibitors
TE	Testosterone
GLP-1 RA	Glucagon-like peptide 1 receptor agonists
WCDs	Wearable cardioverter defibrillators
CAD	Coronary artery disease
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction.
HFmrEF	Heart failure with mid-range ejection fraction.
HFrEF	Heart failure with reduced ejection fraction.
LVEFF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro B-type natriuretic peptide
PPCM	Postpartum cardiomyopathy
S&GDs	Sex and gender differences

Author Contributions

All authors collected the references. GC and HPH selected the references, and wrote the paper, table and figures. SP checked and discussed the written manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. EUGenMed, Cardiovascular Clinical Study Group, Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, et al. Gender in cardiovascular diseases: Impact on clinical manifestations, management, and outcomes. Eur Heart J. 2016; 37: 24-34.
2. Oertelt-Prigione S, Regitz-Zagrosek V. Sex and gender aspects in clinical medicine. Berlin, Germany: Springer Science & Business Media; 2011.

3. Schenck-Gustafsson K, DeCola PR, Pfaff DW, Pisetsky DS. Handbook of clinical gender medicine. Basel, Switzerland: Karger Medical and Scientific Publishers; 2012.
4. Goyal A, Norton CR, Thomas TN, Davis RL, Butler J, Ashok V, et al. Predictors of incident heart failure in a large insured population: A one million person-year follow-up study. Circ Heart Fail. 2010; 3: 698-705.
5. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: Lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014; 63: 1123-1133.
6. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. Eur J Prev Cardiol. 2021; 28: 1682-1690.
7. Cocco G, Amiet P. Known-unknowns in geriatric cardiology. OBM Geriatr. 2020; 4: 111.
8. Cocco G, Amiet P. Epigenetics and medicine. OBM Geriatr. 2021; 5: 133.
9. Cocco G, Pandolfi S. Age-related pathologies and life span. OBM Geriatr. 2023; 7: 253.
10. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002; 347: 1397-1402.
11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC committee for practice guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. Eur Heart J. 2012; 33: 1787-1847.
12. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J. 2023; 44: 3627-3639.
13. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: Prevalence, therapies, and outcomes. Circulation. 2012; 126: 65-75.
14. Lopatin Y. Heart failure with mid-range ejection fraction and how to treat it. Card Fail Rev. 2018; 4: 9-13.
15. Pandey A, Omar W, Ayers C, LaMonte M, Klein L, Allen NB, et al. Sex and race differences in lifetime risk of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Circulation. 2018; 137: 1814-1823.
16. Peters SA, Colantonio LD, Chen L, Bittner V, Farkouh ME, Rosenson RS, et al. Sex differences in incident and recurrent coronary events and all-cause mortality. J Am Coll Cardiol. 2020; 76: 1751-1760.
17. Sardu C, Paolisso G, Marfella R. Impact of sex differences in incident and recurrent coronary events and all-cause mortality. J Am Coll Cardiol. 2021; 77: 829-830.
18. Bauersachs J, König T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, et al. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: A position statement from the heart failure association of the European society of cardiology study group on peripartum cardiomyopathy. Eur J Heart Fail. 2019; 21: 827-843.

19. Kolte D, Khera S, Aronow WS, Palaniswamy C, Mujib M, Ahn C, et al. Temporal trends in incidence and outcomes of peripartum cardiomyopathy in the United States: A nationwide population-based study. J Am Heart Assoc. 2014; 3: e001056.
20. Kerpen K, Koutrolou-Sotiropoulou P, Zhu C, Yang J, Lyon JA, Lima FV, et al. Disparities in death rates in women with peripartum cardiomyopathy between advanced and developing countries: A systematic review and meta-analysis. Arch Cardiovasc Dis. 2019; 112: 187-198.
21. Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, et al. A population-based study of cardiovascular mortality following early-stage breast cancer. JAMA Cardiol. 2017; 2: 88-93.
22. Saiki H, Petersen IA, Scott CG, Bailey KR, Dunlay SM, Finley RR, et al. Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. Circulation. 2017; 135: 1388-1396.
23. Drafts BC, Twomley KM, D'Agostino R, Lawrence J, Avis N, Ellis LR, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging. 2013; 6: 877-885.
24. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Coll Cardiol. 2012; 60: 2504-2512.
25. Regitz-Zagrosek V, Brokat S, Tschope C. Role of gender in heart failure with normal left ventricular ejection fraction. Prog Cardiovasc Dis. 2007; 49: 241-251.
26. Lam CS, Carson PE, Anand IS, Rector TS, Kuskowski M, Komajda M, et al. Sex differences in clinical characteristics and outcomes in elderly patients with heart failure and preserved ejection fraction: The irbesartan in heart failure with preserved ejection fraction (I-PRESERVE) trial. Circ Heart Fail. 2012; 5: 571-578.
27. Lam CS, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. Eur Heart J. 2019; 40: 3859-3868c.
28. Hayward CS, Kalnins WV, Kelly RP. Gender-related differences in left ventricular chamber function. Cardiovasc Res. 2001; 49: 340-350.
29. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age-and gender-related ventricular-vascular stiffening: A community-based study. Circulation. 2005; 112: 2254-2262.
30. Chung AK, Das SR, Leonard D, Peshock RM, Kazi F, Abdullah SM, et al. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume: The Dallas heart study. Circulation. 2006; 113: 1597-1604.
31. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: A report of the American college of cardiology foundation task force on clinical expert consensus documents developed in collaboration with the American academy of neurology, American geriatrics society, American society for preventive cardiology, American society of hypertension, American society of nephrology, Association of black cardiologists, and European society of hypertension. J Am Coll Cardiol. 2011; 57: 2037-2114.
32. Nichols WW, Denardo SJ, Davidson JB, Huo T, Merz CN, Pepine CJ. Association of aortic stiffness and wave reflections with coronary flow reserve in women without obstructive coronary artery disease: An ancillary study from the national heart, lung, and blood institute-sponsored women's ischemia syndrome evaluation (WISE). Am Heart J. 2015; 170: 1243-1254.

33. Gori M, Lam CS, Gupta DK, Santos AB, Cheng S, Shah AM, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. Eur J Heart Fail. 2014; 16: 535-542.
34. Kuch B, Muscholl M, Luchner A, Döring A, Riegger GA, Schunkert H, et al. Gender specific differences in left ventricular adaptation to obesity and hypertension. J Hum Hypertens. 1998; 12: 685-691.
35. Aurigemma GP, Gaasch WH. Gender differences in older patients with pressure-overload hypertrophy of the left ventricle. Cardiology. 1995; 86: 310-317.
36. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: The Framingham heart study. JAMA. 1994; 271: 840-844.
37. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a $CHADS_2$ score 0-1: A nationwide cohort study. Thromb Haemost. 2012; 107: 1172-1179.
38. Aslam F, Bandeali SJ, Khan NA, Alam M. Diastolic dysfunction in rheumatoid arthritis: A meta-analysis and systematic review. Arthritis Care Res. 2013; 65: 534-543.
39. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016; 16: 626-638.
40. Cocco G, Jerie P, Amiet P, Pandolfi S. Inflammation in heart failure: Known knowns and unknown unknowns. Expert Opin Pharmacother. 2017; 18: 1225-1233.
41. Shah SJ, Lam CS, Svedlund S, Saraste A, Hage C, Tan RS, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J. 2018; 39: 3439-3450.
42. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013; 62: 263-271.
43. Taki M, Ishiyama Y, Mizuno H, Komori T, Kono K, Hoshide S, et al. Sex differences in the prognostic power of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide for cardiovascular events-the Japan morning surge-home blood pressure study. Circ J. 2018; 82: 2096-2102.
44. Rossi A, Mikail N, Bengs S, Haider A, Treyer V, Buechel RR, et al. Heart-brain interactions in cardiac and brain diseases: Why sex matters. Eur Heart J. 2022; 43: 3971-3980.
45. Scicchitano P, Paolillo C, De Palo M, Potenza A, Abruzzese S, Basile M, et al. Sex differences in the evaluation of congestion markers in patients with acute heart failure. J Cardiovasc Dev Dis. 2022; 9: 67.
46. Wheatley CM, Snyder EM, Johnson BD, Olson TP. Sex differences in cardiovascular function during submaximal exercise in humans. Springerplus. 2014; 3: 445.
47. Delco A, Portmann A, Mikail N, Rossi A, Haider A, Bengs S, et al. Impact of sex and gender on heart failure. Cardiovasc Med. 2023; 26: 88-94.
48. Mühl A, Asatryan B, Tanner H. Sex-specific aspects of cardiac electrophysiology and arrhythmias. Cardiovasc Med. 2023; 26: 169-172.
49. Oskui PM, French WJ, Herring MJ, Mayeda GS, Burstein S, Kloner RA. Testosterone and the cardiovascular system: A comprehensive review of the clinical literature. J Am Heart Assoc. 2013; 2: e000272.

50. Loyer X, Damy T, Chvojkova Z, Robidel E, Marotte F, Oliviero P, et al. 17β-estradiol regulates constitutive nitric oxide synthase expression differentially in the myocardium in response to pressure overload. Endocrinology. 2007; 148: 4579-4584.
51. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biol Sex Differ. 2017; 8: 33.
52. Sardu C, Gatta G, Pieretti G, Viola L, Sacra C, Di Grezia G, et al. Pre-menopausal breast fat density might predict MACE during 10 years of follow-up: The BRECARD study. Cardiovasc Imaging. 2021; 14: 426-438.
53. Sardu C, Gatta G, Pieretti G, D'Onofrio N, Balestrieri ML, Scisciola L, et al. SGLT2 breast expression could affect the cardiovascular performance in pre-menopausal women with fatty vs. non fatty breast via over-inflammation and sirtuins' down regulation. Eur J Intern Med. 2023; 113: 57-68.
54. Riedinger MS, Dracup KA, Brecht ML, Padilla G, Sarna L, Ganz PA. Quality of life in patients with heart failure: Do gender differences exist? Heart Lung. 2001; 30: 105-116.
55. Kendel F, Gelbrich G, Wirtz M, Lehmkuhl E, Knoll N, Hetzer R, et al. Predictive relationship between depression and physical functioning after coronary surgery. Arch Intern Med. 2010; 170: 1717-1721.
56. Sorimachi H, Omote K, Omar M, Popovic D, Verbrugge FH, Reddy YN, et al. Sex and central obesity in heart failure with preserved ejection fraction. Eur J Heart Fail. 2022; 24: 1359-1370.
57. Gouda P, Alemayehu W, Rathwell S, Paterson DI, Anderson T, Dyck JR, et al. Clinical phenotypes of heart failure across the spectrum of ejection fraction: A cluster analysis. Curr Probl Cardiol. 2022; 47: 101337.
58. Bhambhani V, Kizer JR, Lima JA, Van Der Harst P, Bahrami H, Nayor M, et al. Predictors and outcomes of heart failure with mid-range ejection fraction. Eur J Heart Fail. 2018; 20: 651-659.
59. Kararigas G, Dworatzek E, Petrov G, Summer H, Schulze TM, Baczko I, et al. Sex-dependent regulation of fibrosis and inflammation in human left ventricular remodelling under pressure overload. Eur J Heart Fail. 2014; 16: 1160-1167.
60. Crea F, Bairey Merz CN, Beltrame JF, Kaski JC, Ogawa H, Ong P, et al. The parallel tales of microvascular angina and heart failure with preserved ejection fraction: A paradigm shift. Eur Heart J. 2017; 38: 473-477.
61. Regitz-Zagrosek V, Erdmann J, Wellnhofer E, Raible J, Fleck E. Novel mutation in the α-tropomyosin gene and transition from hypertrophic to hypocontractile dilated cardiomyopathy. Circulation. 2000; 102: e112-e116.
62. Codd MB, Sugrue DD, Gersh BJ, Melton 3rd LJ. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984. Circulation. 1989; 80: 564-572.
63. Coughlin SS, Comstock GW, Baughman KL. Descriptive epidemiology of idiopathic dilated cardiomyopathy in Washington County, Maryland, 1975-1991. J Clin Epidemiol. 1993; 46: 1003-1008.
64. Estoppey P, Clair C, Auderset D, Puder JJ. Sex differences in type 2 diabetes. Cardiovasc Med. 2023; 26: 96-99.

65. Galderisi M, Anderson KM, Wilson PW, Levy D. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham heart study). Am J Cardiol. 1991; 68: 85-89.
66. Clemens KK, Woodward M, Neal B, Zinman B. Sex disparities in cardiovascular outcome trials of populations with diabetes: A systematic review and meta-analysis. Diabetes Care. 2020; 43: 1157-1163.
67. Fourny N, Beauloye C, Bernard M, Horman S, Desrois M, Bertrand L. Sex differences of the diabetic heart. Front Physiol. 2021; 12: 661297.
68. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996; 275: 1557-1562.
69. Goyal P, Paul T, Almarzooq ZI, Peterson JC, Krishnan U, Swaminathan RV, et al. Sex-and race-related differences in characteristics and outcomes of hospitalizations for heart failure with preserved ejection fraction. J Am Heart Assoc. 2017; 6: e003330.
70. Núñez J, Lorenzo M, Miñana G, Palau P, Monmeneu JV, López-Lereu MP, et al. Sex differences on new-onset heart failure in patients with known or suspected coronary artery disease. Eur J Prev Cardiol. 2021; 28: 1711-1719.
71. Savji N, Meijers WC, Bartz TM, Bhambhani V, Cushman M, Nayor M, et al. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. JACC Heart Fail. 2018; 6: 701-709.
72. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: A metaanalysis. Am J Obstet Gynecol. 2019; 221: 393-409.e50.
73. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001; 161: 996-1002.
74. Haghikia A, Podewski E, Libhaber E, Labidi S, Fischer D, Roentgen P, et al. Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol. 2013; 108: 366.
75. Hung CL, Chao TF, Su CH, Liao JN, Sung KT, Yeh HI, et al. Income level and outcomes in patients with heart failure with universal health coverage. Heart. 2021; 107: 208-216.
76. Christensen S, Mogelvang R, Heitmann M, Prescott E. Level of education and risk of heart failure: A prospective cohort study with echocardiography evaluation. Eur Heart J. 2011; 32: 450-458.
77. Lawson CA, Zaccardi F, Squire I, Ling S, Davies MJ, Lam CS, et al. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: A population-based study. Lancet Public Health. 2019; 4: e406-e420.
78. Bennett SJ, Perkins SM, Lane KA, Deer M, Brater DC, Murray MD. Social support and health-related quality of life in chronic heart failure patients. Qual Life Res. 2001; 10: 671-682.
79. Zhu W, Wu Y, Zhou Y, Liang W, Xue R, Wu Z, et al. Living alone and clinical outcomes in patients with heart failure with preserved ejection fraction. Psychosom Med. 2021; 83: 470-476.
80. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. The Euroheart failure survey programme-a survey on the quality of care among patients with heart failure in Europe: Part 1: Patient characteristics and diagnosis. Eur Heart J. 2003; 24: 442-463.
81. Burnett H, Earley A, Voors AA, Senni M, McMurray JJ, Deschaseaux C, et al. Thirty years of evidence on the efficacy of drug treatments for chronic heart failure with reduced ejection fraction: A network meta-analysis. Circ Heart Fail. 2017; 10: e003529.

82. Tadic M, Sala C, Saeed S, Grassi G, Mancia G, Rottbauer W, et al. New antidiabetic therapy and HFpEF: Light at the end of tunnel? Heart Fail Rev. 2021; 27: 1137-1146.
83. Meyer P, Massie E, Poku N. SGLT-2 inhibition in heart failure with mildly reduced and preserved ejection fraction. Cardiovasc Med. 2023; 26: 186-188.
84. Klein SL, Schiebinger L, Stefanick ML, Cahill L, Danska J, De Vries GJ, et al. Sex inclusion in basic research drives discovery. Proc Natl Acad Sci. 2015; 112: 5257-5258.
85. United States General Accounting Office (GAO). Drug safety: Most drugs withdrawn in recent years had greater health risks for women. Washington, D.C.: United States General Accounting Office (GAO); 2001.
86. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al. How to improve R&D productivity: The pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010; 9: 203-214.
87. Ramirez FD, Motazedian P, Jung RG, Di Santo P, MacDonald Z, Simard T, et al. Sex bias is increasingly prevalent in preclinical cardiovascular research: Implications for translational medicine and health equity for women: A systematic assessment of leading cardiovascular journals over a 10-year period. Circulation. 2017; 135: 625-626.
88. Whitelaw S, Sullivan K, Eliya Y, Alruwayeh M, Thabane L, Yancy CW, et al. Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: A systematic review. Eur J Heart Fail. 2021; 23: 15-24.
89. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, et al. Identifying optimal doses of heart failure medications in men compared with women: A prospective, observational, cohort study. Lancet. 2019; 394: 1254-1263.
90. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA. 1995; 273: 1450-1456.
91. Franzosi MG, Santoro E, Zuanetti G, Baigent C, Collins R, Flather M, et al. Indications for ACE inhibitors in the early treatment of acute myocardial infarction-systematic overview of individual data from 100,000 patients in randomized trials. Circulation. 1998; 97: 2202-2212.
92. Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. Lancet. 2000; 355: 1575-1581.
93. Shekelle PG, Rich MW, Morton SC, Atkinson CS, Tu W, Maglione M, et al. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: A meta-analysis of major clinical trials. J Am Coll Cardiol. 2003; 41: 1529-1538.
94. Seeland U, Regitz-Zagrosek V. Sex and gender differences in cardiovascular drug therapy. In: Sex and gender differences in pharmacology. Berlin, Heidelberg: Springer; 2012. pp. 211-236.
95. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: Randomised trial-the losartan heart failure survival study ELITE II. Lancet. 2000; 355: 1582-1587.
96. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003; 349: 1893-1906.

97. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: Angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Ann Intern Med. 2004; 141: 693-704.
98. JB Y. Candesartan in heart failure assessment of reduction in mortality and morbidity (CHARM) investigators and committees. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: Results of the CHARM low-left ventricular ejection fraction trials. Circulation. 2004; 110: 2618-2626.
99. Majahalme SK, Baruch L, Aknay N, Goedel-Meinen L, Hofmann M, Hester A, et al. Comparison of treatment benefit and outcome in women versus men with chronic heart failure (from the valsartan heart failure trial). Am J Cardiol. 2005; 95: 529-532.
100. Hudson M, Rahme E, Behlouli H, Sheppard R, Pilote L. Sex differences in the effectiveness of angiotensin receptor blockers and angiotensin converting enzyme inhibitors in patients with congestive heart failure-a population study. Eur J Heart Fail. 2007; 9: 602-609.
101. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Piña IL, Granger CB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: Results of the candesartan in heart failure: Assessment of reduction in mortality and morbidity (CHARM) program. Circulation. 2007; 115: 3111-3120.
102. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): A randomised, double-blind trial. Lancet. 2009; 374: 1840-1848.
103. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008; 359: 2456-2467.
104. McMurray JJ, Jackson AM, Lam CS, Redfield MM, Anand IS, Ge J, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: Insights from PARAGON-HF. Circulation. 2020; 141: 338-351.
105. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371: 993-1004.
106. Ibrahim NE, Piña IL, Camacho A, Bapat D, Felker GM, Maisel AS, et al. Sex-based differences in biomarkers, health status, and reverse cardiac remodelling in patients with heart failure with reduced ejection fraction treated with sacubitril/valsartan. Eur J Heart Fail. 2020; 22: 2018-2025.
107. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation. 2020; 141: 352-361.
108. Nuechterlein K, AlTurki A, Ni J, Martínez-Sellés M, Martens P, Russo V, et al. Real-world safety of sacubitril/valsartan in women and men with heart failure and reduced ejection fraction: A meta-analysis. CJC Open. 2021; 3: S202-S208.
109. Kostis WJ, Shetty M, Chowdhury YS, Kostis JB. ACE inhibitor-induced angioedema: A review. Curr Hypertens Rep. 2018; 20: 55.
110. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. Circulation. 1994; 90: 1765-1773.
111. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001; 344: 1651-1658.

112. Luzier AB, Killian A, Wilton JH, Wilson MF, Forrest A, Kazierad DJ. Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. Clin Pharmacol Ther. 1999; 66: 594-601.
113. Jochmann N, Stangl K, Garbe E, Baumann G, Stangl V. Female-specific aspects in the pharmacotherapy of chronic cardiovascular diseases. Eur Heart J. 2005; 26: 1585-1595.
114. Eugene AR. Gender based dosing of metoprolol in the elderly using population pharmacokinetic modeling and simulations. Int J Clin Pharmacol Toxicol. 2016; 5: 209-215.
115. Cocco G, Chu D. The anti-ischemic effect of metoprolol in patients with chronic angina pectoris is gender-specific. Cardiology. 2006; 106: 147-153.
116. Kanashiro-Takeuchi RM, Heidecker B, Lamirault G, Dharamsi JW, Hare JM. Sex-specific impact of aldosterone receptor antagonism on ventricular remodeling and gene expression after myocardial infarction. Clin Transl Sci. 2009; 2: 134-142.
117. Rossello X, Ferreira JP, Pocock SJ, McMurray JJ, Solomon SD, Lam CS, et al. Sex differences in mineralocorticoid receptor antagonist trials: A pooled analysis of three large clinical trials. Eur J Heart Fail. 2020; 22: 834-844.
118. Rales Investigators. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the randomized Aldactone evaluation study [RALES]). Am J Cardiol. 1996; 78: 902-907.
119. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011; 364: 11-21.
120. Pitt B. Eplerenone post-acute myocardial infarction heart failure efficacy and survival study investigators: Eplerenone, a selective aldsterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348: 1309-1321.
121. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014; 370: 1383-1392.
122. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: A secondary analysis of TOPCAT trial. JACC Heart Fail. 2019; 7: 228-238.
123. 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; 24: 871-884.
124. Verlander JW, Tran TM, Zhang L, Kaplan MR, Hebert SC. Estradiol enhances thiazide-sensitive NaCl cotransporter density in the apical plasma membrane of the distal convoluted tubule in ovariectomized rats. J Clin Invest. 1998; 101: 1661-1669.
125. Brandoni A, Villar SR, Torres AM. Gender-related differences in the pharmacodynamics of furosemide in rats. Pharmacology. 2004; 70: 107-112.
126. Werner U, Werner D, Heinbüchner S, Graf B, Ince H, Kische S, et al. Gender is an important determinant of the disposition of the loop diuretic torasemide. J Clin Pharmacol. 2010; 50: 160-168.
127. Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U, Lund LH. The Swedish heart failure registry: A living, ongoing quality assurance and research in heart failure. Ups J Med Sci. 2019; 124: 65-69.
128. Tamargo J. Sodium-glucose cotransporter 2 inhibitors in heart failure: Potential mechanisms of action, adverse effects and future developments. Eur Cardiol. 2019; 14: 23-32.

129. Rådholm K, Zhou Z, Clemens K, Neal B, Woodward M. Effects of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes in women versus men. Diabetes Obes Metab. 2020; 22: 263-266.
130. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383: 1413-1424.
131. Butt JH, Docherty KF, Petrie MC, Schou M, Kosiborod MN, O'Meara E, et al. Efficacy and safety of dapagliflozin in men and women with heart failure with reduced ejection fraction: A prespecified analysis of the dapagliflozin and prevention of adverse outcomes in heart failure trial. JAMA Cardiol. 2021; 6: 678-689.
132. Solomon SD, McMurray JJ, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022; 387: 1089-1098.
133. Catananti C, Liperoti R, Settanni S, Lattanzio F, Bernabei R, Fialova D, et al. Heart failure and adverse drug reactions among hospitalized older adults. Clin Pharmacol Ther. 2009; 86: 307-310.
134. Franconi F, Campesi I. Pharmacogenomics, pharmacokinetics and pharmacodynamics: Interaction with biological differences between men and women. Br J Pharmacol. 2014; 171: 580-594.
135. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. BMJ. 2004; 329: 15.
136. Gurwitz JH. The age/gender interface in geriatric pharmacotherapy. J Womens Health. 2005; 14: 68-72.
137. Patel H, Bell D, Molokhia M, Srishanmuganathan J, Patel M, Car J, et al. Trends in hospital admissions for adverse drug reactions in England: Analysis of national hospital episode statistics 1998-2005. BMC Clin Pharmacol. 2007; 7: 9.
138. Sikdar KC, Alaghehbandan R, MacDonald D, Barrett B, Collins KD, Donnan J, et al. Adverse drug events in adult patients leading to emergency department visits. Ann Pharmacother. 2010; 44: 641-649.
139. Franconi F, Campesi I. Sex and gender influences on pharmacological response: An overview. Expert Rev Clin Pharmacol. 2014; 7: 469-485.
140. Colbert JD, Martin BJ, Haykowsky MJ, Hauer TL, Austford LD, Arena RA, et al. Cardiac rehabilitation referral, attendance and mortality in women. Eur J Prev Cardiol. 2015; 22: 979-986.
141. Supervía M, Medina-Inojosa JR, Yeung C, Lopez-Jimenez F, Squires RW, Pérez-Terzic CM, et al. Cardiac rehabilitation for women: A systematic review of barriers and solutions. Mayo Clin Proc. 2017; 92: 565-577.
142. Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E, Zhu S, et al. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. Circ Heart Fail. 2013; 6: 1165-1171.
143. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: A randomized clinical trial. JAMA. 2016; 315: 36-46.
144. Van Spall HG, Hill AD, Fu L, Ross HJ, Fowler RA. Temporal trends and sex differences in intensity of healthcare at the end of life in adults with heart failure. J Am Heart Assoc. 2021; 10: e018495.

145. Saltzberg MT, Szymkiewicz S, Bianco NR. Characteristics and outcomes of peripartum versus nonperipartum cardiomyopathy in women using a wearable cardiac defibrillator. J Card Fail. 2012; 18: 21-27.
146. Dewidar O, Podinic I, Barbeau V, Patel D, Antequera A, Birnie D, et al. Integrating sex and gender in studies of cardiac resynchronization therapy: A systematic review. ESC Heart Fail. 2022; 9: 420-427.
147. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, et al. Cardiac resynchronization therapy is more effective in women than in men: The MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) trial. J Am Coll Cardiol. 2011; 57: 813-820.
148. Zabarovskaja S, Gadler F, Braunschweig F, Ståhlberg M, Hörnsten J, Linde C, et al. Women have better long-term prognosis than men after cardiac resynchronization therapy. Europace. 2012; 14: 1148-1155.
149. Linde C, Cleland JG, Gold MR, Claude Daubert J, Tang AS, Young JB, et al. The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: An individual-patient data meta-analysis. Eur J Heart Fail. 2018; 20: 780-791.
150. Beela AS, Duchenne J, Petrescu A, Ünlü S, Penicka M, Aakhus S, et al. Sex-specific difference in outcome after cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging. 2019; 20: 504-511.
151. Lee AW, O'Regan DP, Gould J, Sidhu B, Sieniewicz B, Plank G, et al. Sex-dependent QRS guidelines for cardiac resynchronization therapy using computer model predictions. Biophys J. 2019; 117: 2375-2381.
152. Ghanbari H, Dalloul G, Hasan R, Daccarett M, Saba S, David S, et al. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: A meta-analysis of randomized controlled trials. Arch Intern Med. 2009; 169: 1500-1506.
153. Santangeli P, Pelargonio G, Russo AD, Casella M, Bisceglia C, Bartoletti S, et al. Gender differences in clinical outcome and primary prevention defibrillator benefit in patients with severe left ventricular dysfunction: A systematic review and meta-analysis. Heart Rhythm. 2010; 7: 876-882.
154. Lampert R, McPherson CA, Clancy JF, Caulin-Glaser TL, Rosenfeld LE, Batsford WP. Gender differences in ventricular arrhythmia recurrence in patients with coronary artery disease and implantable cardioverter-defibrillators. J Am Coll Cardiol. 2004; 43: 2293-2299.
155. Russo AM, Daugherty SL, Masoudi FA, Wang Y, Curtis J, Lampert R. Gender and outcomes after primary prevention implantable cardioverter-defibrillator implantation: Findings from the national cardiovascular data registry (NCDR). Am Heart J. 2015; 170: 330-338.
156. Mohamed MO, Contractor T, Zachariah D, van Spall HG, Parwani P, Minissian MB, et al. Sex disparities in the choice of cardiac resynchronization therapy device: An analysis of trends, predictors, and outcomes. Can J Cardiol. 2021; 37: 86-93.
157. Varma N, Manne M, Nguyen D, He J, Niebauer M, Tchou P. Probability and magnitude of response to cardiac resynchronization therapy according to QRS duration and gender in nonischemic cardiomyopathy and LBBB. Heart Rhythm. 2014; 11: 1139-1147.

158. Butt JH, Yafasova A, Elming MB, Dixen U, Nielsen JC, Haarbo J, et al. Efficacy of implantable cardioverter defibrillator in nonischemic systolic heart failure according to sex: Extended follow-up study of the DANISH trial. Circ Heart Fail. 2022; 15: e009669.
159. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: Time for a critical appraisal. Arterial Hypertens. 2006; 12: 99-116. doi: 10.18705/1607-419X-2006-12-2-99-116.
160. Sardu C, Santamaria M, Funaro S, Sacra C, Barbieri M, Paolisso P, et al. Cardiac electrophysiological alterations and clinical response in cardiac resynchronization therapy with a defibrillator treated patients affected by metabolic syndrome. Medicine. 2017; 96: e6558.
161. Sardu C, Marfella R, Santulli G. Impact of diabetes mellitus on the clinical response to cardiac resynchronization therapy in elderly people. J Cardiovasc Transl Res. 2014; 7: 362-368.
162. Sardu C, Paolisso P, Sacra C, Santamaria M, de Lucia C, Ruocco A, et al. Cardiac resynchronization therapy with a defibrillator (CRTd) in failing heart patients with type 2 diabetes mellitus and treated by glucagon-like peptide 1 receptor agonists (GLP-1 RA) therapy vs. conventional hypoglycemic drugs: Arrhythmic burden, hospitalizations for heart failure, and CRTd Responders rate. Cardiovasc Diabetol. 2018; 17: 137.
163. Sherazi S, Kutyifa V, McNitt S, Papernov A, Hallinan W, Chen L, et al. Effect of gender on the risk of neurologic events and subsequent outcomes in patients with left ventricular assist devices. Am J Cardiol. 2017; 119: 297-301.
164. Magnussen C, Bernhardt AM, Ojeda FM, Wagner FM, Gummert J, de By TM, et al. Gender differences and outcomes in left ventricular assist device support: The European registry for patients with mechanical circulatory support. J Heart Lung Transplant. 2018; 37: 61-70.
165. DeFilippis EM, Truby LK, Garan AR, Givens RC, Takeda K, Takayama H, et al. Sex-related differences in use and outcomes of left ventricular assist devices as bridge to transplantation. JACC Heart Fail. 2019; 7: 250-257.
166. Alasnag M, Truesdell AG, Williams H, Martinez SC, Qadri SK, Skendelas JP, et al. Mechanical circulatory support: A comprehensive review with a focus on women. Curr Atheroscler Rep. 2020; 22: 11.
167. Gruen J, Caraballo C, Miller PE, McCullough M, Mezzacappa C, Ravindra N, et al. Sex differences in patients receiving left ventricular assist devices for end-stage heart failure. Heart Fail. 2020; 8: 770-779.
168. Kenigsberg BB, Majure DT, Sheikh FH, Afari-Armah N, Rodrigo M, Hofmeyer M, et al. Sex-associated differences in cardiac reverse remodeling in patients supported by contemporary left ventricular assist devices. J Card Fail. 2020; 26: 494-504.
169. Zafar F, Villa CR, Morales DL, Blume ED, Rosenthal DN, Kirklin JK, et al. Does small size matter with continuous flow devices? Analysis of the INTERMACS database of adults with BSA ≤ 1.5 m^2. JACC Heart Fail. 2017; 5: 123-131.
170. Mariani S, Li T, Bounader K, Boethig D, Schöde A, Hanke JS, et al. Sex differences in outcomes following less-invasive left ventricular assist device implantation. Ann Cardiothorac Surg. 2021; 10: 255-267.
171. Huckaby LV, Seese LM, Aranda-Michel E, Mathier MA, Hickey G, Keebler ME, et al. Sex-based heart transplant outcomes after bridging with centrifugal left ventricular assist devices. Ann Thorac Surg. 2020; 110: 2026-2033.
172. Nayak A, Hu Y, Ko YA, Steinberg R, Das S, Mehta A, et al. Creation and validation of a novel sex-specific mortality risk score in LVAD recipients. J Am Heart Assoc. 2021; 10: e020019.

173. Hsich EM, Blackstone EH, Thuita L, McNamara DM, Rogers JG, Ishwaran H, et al. Sex differences in mortality based on united network for organ sharing status while awaiting heart transplantation. Circ Heart Fail. 2017; 10: e003635.
174. Moayedi Y, Fan CP, Cherikh WS, Stehlik J, Teuteberg JJ, Ross HJ, et al. Survival outcomes after heart transplantation: Does recipient sex matter? Circ Heart Fail. 2019; 12: e006218.
175. Ayesta A. Influence of sex-mismatch on prognosis after heart transplantation. Front Cardiovasc Med. 2021; 8: 617062.
176. ISHLT TTX Registry. International thoracic organ transplant (TTX) registry data slides: 2022 slides [Internet]. Chicago, IL: ISHLT TTX Registry; 2022. Available from: https://ishltregistries.org/registries/slides.Asp.
177. U.S. Department of Health & Human Services. OPTN: Organ procurement and transplantation network [Internet]. Washington, D.C.: U.S. Department of Health & Human Services; 2022. Available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#.
178. Hsich EM. Sex differences in advanced heart failure therapies. Circulation. 2019; 139: 1080-1093.