

Review

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

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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



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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 (**HF_{rEF}**) 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” (**HF_{pEF}**) [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.









Risk factors for HF		
CAD		
T2DM		
Fat		
Cancer related HF		
PPCM	Only in women.	

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 CHA₂DS₂-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.









Cardiovascular System		
Stroke Volume		
Systolic and diastolic stiffness		
Inflammaging		

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 β 1-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 β 2-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 \leq 40%), HFmrEF (midrange LVEF 41-49%), and HFpEF (LVEF \geq 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 \geq 55-year-old individuals, the prevalence rises to 5% and seems slightly more frequent in men. In \geq 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 \geq 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.









HF Phenotype		
HFpEF		
HFmEF		
HFrEF		

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.	Less atrial fibrillation.
Higher lifetime risk of HF.	Less socioeconomic disadvantages.
More atrial fibrillation.	
More socioeconomic disadvantages.	
Pathophysiology/Risk Factors	

More coronary microcoronary dysfunction.	
More arterial dysfunction and hypertension.	
More concentric left ventricular remodeling.	More traditional cardiovascular risks factors (e.g., CAD).
More left ventricular dilation and cardiomyopathies.	More apoptosis.
More T2D, hypertension and obesity.	More eccentric LV remodeling.
More Inflammation.	
Adipose tissue (risk factor only in women).	

Phenotypes of HF

More HFpEF than HFmrEF and HFrEF.	More HFrEF and HFmEF than HFpEF.
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Clinics

Older, more co-morbidities.	Younger. Less co-morbidities.
Higher LVEF and NT-proBNP values.	Lower LVEF and NT-proBNP values.
More atypic symptoms.	Less atypic symptoms.

Outcomes

Better survival (unless with T2DM).	Higher mortality.
Poorer quality of life and greater disability.	Better quality of life.

Treatment

Underrepresented in clinical trials.	
More adverse effects with drugs therapies.	More men in clinical trials.
Less likely to get non-pharmacologic therapies and more complications.	More rehabilitation.
Greater benefit from ICDs and CRT-Ds but less frequently received.	More likely to get non-pharmacologic therapies, with less complications.
Receive less intensive care at end of life.	More likely to get cardiac transplantation.
Less cardiac transplantation, less risk factors but receive hearts from high-risk patients.	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.
HFrfEF	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.

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