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Review Article

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Sex and Gender Differences in Heart Failure

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Conflict of Interest
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ABSTRACT

Heart failure (HF) phenotypes differ according to sex. HF preserved ejection fraction (EF) has a greater prevalence in women and HF reduced EF (HFrEF) in men. Women with HF survive longer than men and have a lower risk of sudden death. Ischemia is the most prominent cause in men, whereas hypertension and diabetes contribute to a greater extent in women. Women with HF have a greater stiffness of the smaller left ventricle and a higher EF than men. This higher stiffness of women's hearts may be based on an increase in fibrosis at old age. In younger women estrogen reduces collagen production in female cardiac fibroblasts, but stimulates it in males. Lipid and energy metabolism is better maintained in female than in male stressed hearts. Pulse pressure is a key determinant of outcome in HF women but not in men. Takotsubo and peripartum cardiomyopathy are rare diseases affecting predominantly or exclusively women. Sudden cardiac arrest affects more men than women, but women are less adequately treated. New findings in HF therapy indicate that women with HFrEF need lower doses of beta-blockers and angiotensin-converting enzyme inhibitors than men for optimal effects. The combined neprilysin inhibitor/angiotensin II receptor blockers sacubitril-valsartan led to a significant reduction in event rate versus valsartan in women, which was not observed in men. Unfortunately, only less than 10% of recent randomized controlled trial report effects and adverse drug reactions for women and men separately. More research on sex differences in pathophysiology and therapy of HF is needed.

Keywords: Heart failure; Women; Sex; Gender; Drug therapy; Pharmacology

INTRODUCTION

Heart failure (HF) is one of the major health threats to women and men, particularly at old age. In western populations, HF preserved ejection fraction (HFpEF) has a greater prevalence in women and HF reduced ejection fraction (HFrEF) in men. A number of studies agree that women with HF, with HFpEF and HFrEF, usually survive longer than men.[1)] Cleland reported data from a cross sectional European study, where in most cases of hospitalizations for HFpEF, women were affected, whereas in most cased of hospitalization for HFrEF, men.[2-7)]

In the following review we discuss the role of biological sex and the sociocultural dimension gender for risk factors, disease manifestation, pathophysiology and prevention of HF

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syndromes. We also discuss some specific features of HF in women as well as sex and gender differences in medical therapy.

EPIDEMIOLOGY AND RISK FACTORS

As recently reviewed, risk factors for HF differ in women and men, even though HF in both sexes is driven by aging, hypertension, diabetes mellitus, obesity, and ischemic heart disease (IHD).[8-10] Ischemia is the most prominent cause in men, whereas hypertension and diabetes contribute to the risk for HF in women to a greater extent. Acute coronary syndromes (ACS) occur 3–4 times more often in men than in women below age 60, but after 75 years women represent the majority of patients. IHD seems to carry a relatively higher risk for HF in women than in men. As in IHD, diabetes mellitus type 2 was associated with a higher risk of all-cause mortality in women with HFpEF than in men.[11] Takotsubo cardiomyopathy (TTC) is rare but a life- threatening syndrome and affects more women than men in western societies.[12] Other sex specific risk factors include endocrine disorders, rheumatic diseases, depression, socioeconomic state that all affect women more than men. Peripartum cardiomyopathy (PPCM) is a life threatening syndrome in women.[13]

Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are more frequent causes of HF in men than in women. Sudden cardiac death is a frequent event in HF, more common in men than in women.

Along with these considerable differences between men and women in determinants of cardiac structure and function, lie similarities in HF epidemiology and pathophysiology. Sex specific risk prediction models have been developed for HFpEF and HFrE. Adjusting for these sex specific risk factors abolishes the sex difference in HFpEF incidence. However, male sex remained an important predictor of HFrEF, with a hazard ratio (HR) of 2.[9]

GENDER DIMENSION

In addition to biological sex, gender, which results from a socio-cultural process that programs differences among men and women, gender is an equally important variable as biological sex in human health, and impacts the behavior of the community, doctors and patients and thereby outcome of diseases.[10][14] Gender has 4 main dimensions: gender roles, identity, relations, and institutionalized gender. Gender roles represent the behavioral norms applied to men and women in society, which influence individuals' everyday actions, expectations, and experiences, including diets, exposures and physical activity, and affects health and disease susceptibility. Gender identity describes how a person sees him/herself as a woman or a man.

Gender-related variables of men and women can influence health differently from biological sex. Gender determine help-seeking behavior, access to healthcare, and individual use of the healthcare system. Being perceived as a man or a woman triggers different responses from doctors and medical staff who may diagnose and suggest interventions differently, biased by gender.

Mortality 1 year after an acute coronary event was recently found to be more strongly associated with gender than with biological sex.[15] A gender score was constructed by the

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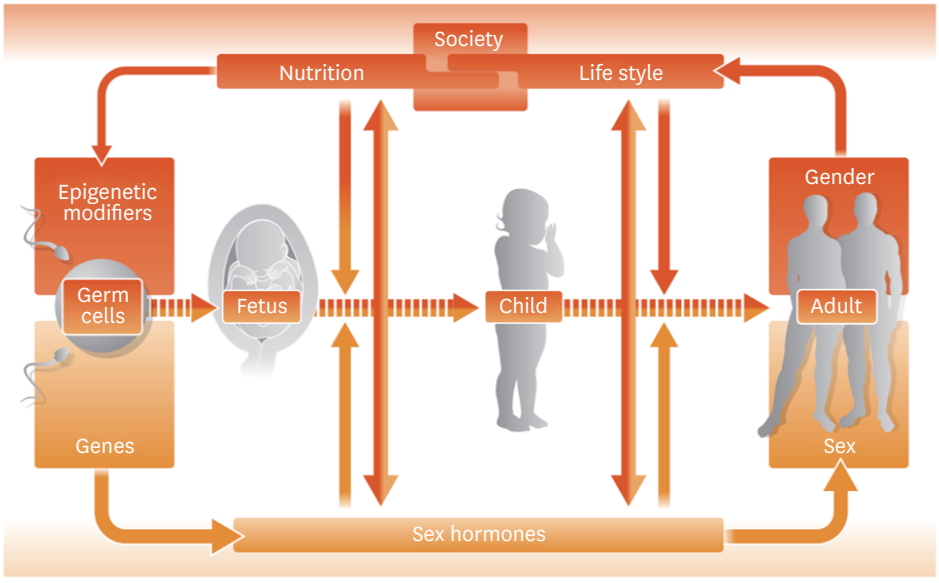


Figure 1. Interaction of sex and gender during lifetime. Adapted from Regitz-Zagrosek.[14]

authors, based on sociocultural variables and it was tested whether the gender score or biological sex was better associated with clinical outcomes. Indeed, 1 year mortality was more closely associated with gender than with sex. Female biological sex reduced mortality, whereas female gender score increased it. Anxiety was a major driver to impair outcomes in women. Similarly control of cardiovascular risk factors (hypertension, diabetes, depressive symptoms), was better predicted by gender than by biological sex. Thus, the interaction of sex and gender should be taken into account during lifetime (**Figure 1**).[14] Including a gender dimension into clinical studies and practice will improve understanding of different clinical manifestations and outcomes of diseases in women and men.

DISEASE MANIFESTATIONS

Major clinical manifestations in HFrEF are not different in women and men.[16] Minor differences have been described in the expression of symptoms. In a single center study, women with severe systolic HF had lower exercise tolerance, worse pulmonary function and poorer kidney function than men in the presence of similar age and ejection fraction (EF).[17]

In some but not all studies, women with HF had a lower prevalence of atrial fibrillation (AF) than men which may be due to smaller left atrial size. However, as in the general population, women with HF and AF have a higher risk for stroke than men, for yet unknown reasons. Therefore, female sex is included as an independent risk factor in the CHA_2DS_2-VASC score.[18]

Symptoms and outcomes in women and men with HFpEF were compared in a recent meta analysis of the largest HFpEF trials, i.e. Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved (EF≥45%), Irbesartan in heart failure with Preserved ejection fraction (I-Preserve), and Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)-Americas. Women had worse symptoms, more congestion, and lower quality of life, nevertheless similar rates for HF

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hospitalization compared to men, but a lower risk of cardiovascular death. The higher risk for congestion in HF in women is very similar to our findings in IHD in 2004, when we looked at outcomes after coronary artery bypass grafts surgery in women and men and found more congestion in women, among others.[19] The lower risk of cardiovascular death in women, compared with men, was in part explained by a substantially lower risk of sudden death compared to men and a higher rate of non-cardiovascular mortality.[2]

Women with heart disease also have more depression than men. Women exhibit a worse quality of life after diagnosis of HF and exhibit more frequently depression.[20][21] Because of the high prevalence of depression in women with HF, systematic screening may be considered.

PATHOPHYSIOLOGY

Myocardial function and metabolism

We already described >10 years ago that the hallmark of HFpEF in women is a greater stiffness of the smaller left ventricle, compared to men.[22] Under stress, women develop smaller hearts with thicker walls than men (**Figure 2**).[23] Since women have smaller left ventricular (LV) chambers and accordingly lower stroke volumes they need a higher resting heart rate to maintain cardiac output than men.[3][17][24] With exercise, stiffness increase more in women than in men, the stroke volume in women is smaller and therefore they depend even more on an increase in heart rate to raise cardiac output. Thus, chronotropic incompetence is a more severe event in women than in men. This may partially explain the higher sensitivity of women to beta blockers[25] and more adverse effects with those.

Women hearts are stiffer and increases in LV stiffness with aging are more pronounced in women than in men. This occurs even though women do have a lower tendency to develop

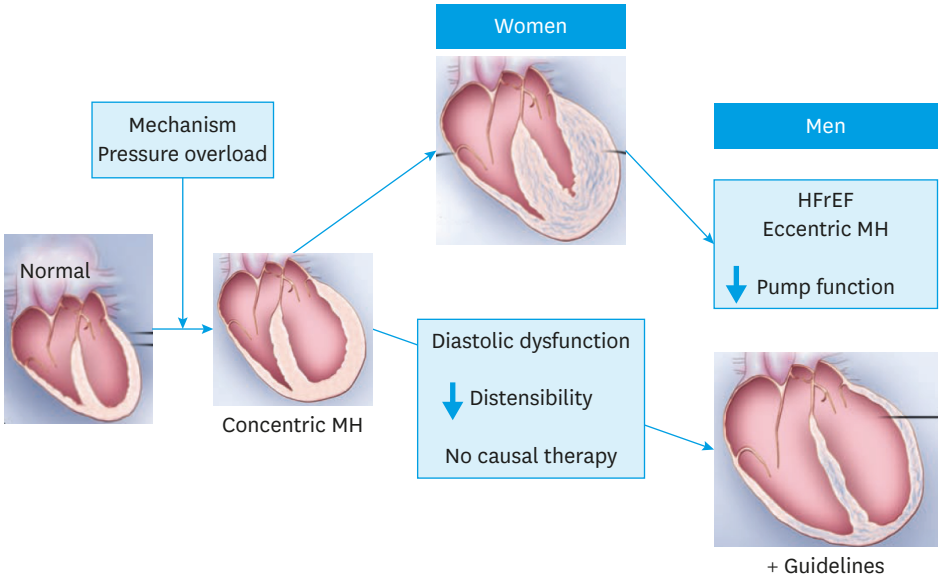


Figure 2. Paradigmatic changes in male and female hearts under pressure overload: both genders respond primarily with concentric MH, but women stay more in concentric MH with maintained diastolic function, whereas men develop more easily eccentric MH. Adapted from Regitz-Zagrosek and Kararigas G.[23]
HFrEF = heart failure reduced ejection fraction; MH = myocardial hypertrophy.

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myocardial fibrosis than men.[26] In contrast, men do develop more fibrosis under stress, i.e. pressure overload.[27][28] This is probably due to a direct effect of estrogen, that reduces collagen production in female cardiac fibroblasts, but stimulates it in males. Female hearts may have a higher stiffness based on more titin related mechanisms, as discussed recently.[29]

Part of the sexual dimorphism in HF and other cardiovascular diseases is linked to energy metabolism and mitochondrial function. In pressure overload, an important precursor of myocardial hypertrophy and HF, downregulation of lipid and energy metabolism related genes is more pronounced in the male than in the female hearts from mice and humans.[30][31] Thus, a better preservation of mitochondrial function and content in female heart under stress and subsequently, a better ability to handle calcium and to decrease reactive oxygen species production participate in the lesser sensitivity of females to HF.

The role of estrogens on glucose and lipid homeostasis and diabetes recently received more attention and it was shown that genetic mechanisms contribute to sex specific body fat distribution in women and men.[32][33] Aromatase activity in the white adipose tissue increases estrogen levels in elderly or obese men above those in women.[34] These estrogens are important for cardiometabolic disorders in men. In HFrEF, men with estrogen levels in the lowest and in the highest quintile had poorer outcomes than those with normal estrogen levels.[35]

In pressure overload, female, but not male, human hearts exhibit an upregulation of peroxisome dependent lipid utilization genes which may represent an alternative pathway to cover greater energy demand.[36] Moreover, estrogens stimulate mitochondrial respiration in female and male hearts. In women, estrogen treatment reversed the mitochondrial dysfunction associated with menopause.[37][38] Mechanisms of estrogen protection of mitochondria include increased expression of proteins that are part of the respiratory chain or the tricarboxylic citric acid cycle and mitochondrial DNA binding to regulate mitochondrial encoded genes.[39][40] These protective mechanisms are not only active in pressure overload but also in ischemia/reperfusion injury,[41][42] and injury induced by oxidative stress.[43-45] Maintaining mitochondrial function under stress requires more efficient dealing with free radicals resulting from high turnover of oxidative phosphorylation. Higher amounts of proteins that can capture free radicals have already been documented in the female heart.[46] Estrogen increased expression of the antioxidative enzyme glutathione peroxidase, and stimulated the activity of the mitochondrial antioxidant manganese sodium dismutase in the hearts of ovariectomized animals and repressed superoxide generation in neonatal rat cardiomyocytes subjected to oxidative stress.[47][48]

Sex differences in lipid metabolism are important for arrhythmia and its treatment. In women, arachidonic acid is metabolized to epoxyeicosanoids (EET) under the influence of estrogen, whereas in men, it is metabolized to hydroxyeicosatetraenoic (HETE) under the influence of androgens. EET are antiarrhythmic and cardioprotective, whereas HETE are proarrhythmic. EET analogues are now developed for the use in human AF. Thus, a protective mechanism in females is used to treat men and women.[49][50]

Sex differences in lipid metabolism occur also in the skeletal muscle. A recent landmark study showed that in the skeletal muscle, high density lipoprotein (HDL) via its major protein component apolipoprotein A-I stimulates mitochondrial respiration.[32] HDL levels are higher in premenopausal women than in age-matched men, but decrease after menopause. Women with diabetes have lower HDL than non-diabetic women or men and may lose

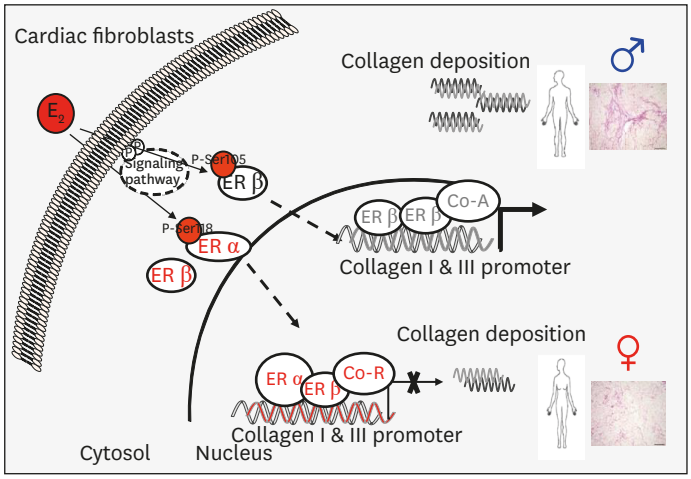
this stimulatory function of apolipoprotein A-I. Diabetes and the decrease in HDL after menopause may predisposes women to reduced muscular strength, sarcopenia and frailty. In the Strong Heart Study, sarcopenic women had greater probability of hypertension and abnormalities of glucose metabolism compared to women with normal fat free mass.[51]

Female myocytes appear to have a lower tendency to develop apoptosis during lifetime. The number of cardiomyocytes are similar between sexes at birth, but men develop more apoptosis and cardiomyoyte loss during lifetime than women.[52] Interestingly, very similar observations have been made in IHD. Women have an apparently greater resistance to cardiomyocyte loss in the context of myocardial infarction (MI) than men.[53] This may explain that women have greater salvage with percutaneous coronary intervention, lower rates of apoptosis and necrosis, and lower rates of infarct re-expansion and delayed healing after acute coronary ischemia.[54] This relative resistance to cardiomyocyte death in women results in less eccentric LV remodeling after MI and protection against the development of HFrEF.

Even though a lot is known about sex hormones in the pathophysiology of HF, the mechanisms are not fully understood. Estrogens and androgens affect myocardial calcium handling and myocardial growth.[23] Both may contribute to sex differences in diastolic function. Men with very low or very high estrogen levels are at greater risk[35] for a worse outcome in HFrEF. We identified a potential interaction between estrogen, myosin regulatory light chain interacting protein (MYLIP) and contractile function as a potential risk factor in men.[55] MYLIP has a double function as a regulator of myosin light chain and low density lipoprotein receptor (LDLR). After ex-vivo estradiol exposure of human heart tissues from women and men, the MYLIP gene was only induced in tissues of men. Exposure of estrogen treatment in isolated mouse cardiomyocytes led to impaired contractile function in male cardiomyocytes only. Further analysis showed that MYLIP expression levels rose with increasing age in hearts of men, potentially leading to dysregulation of myosin regulatory light chain function and contributing to poor outcomes of cardiometabolic HF in men. Moreover, MYLIP has a completely independent second function – it acts as an inducible degrader of the LDLR, also called Idol. The LDLR is a critical factor in the regulation of blood cholesterol levels that are altered in different human diseases. Both mechanisms may be related to the development or progression of cardiovascular disease in elderly and obese men and MYLIP/Idol may even offer a novel treatment target. Complete understanding of the role of this protein will contribute to better understanding of sex differences in contractile function.

Furthermore, pathomechanisms of cardiac inflammation, leading to myocarditis or coronary artery disease (CAD) appear to differ between men and women. [36] Cardiac inflammation is supposed to play a crucial role in the initiation of cardiac fibrosis and diastolic stiffness in HFpEF patients.

Cardiac fibrosis is strongly associated with progression of HF in a sex specific manner. Myocardial fibrosis affects males to a greater degree than females (**Figure 3**).[27][28] This may partially be due to greater induction of renin angiotensin system (RAS) related genes in men compared to women.[56] Or it may be due to decrease of RAS by oestrogens in women.[57] After exposure to pressure overload, men and male mice activate more profibrotic genes and generate more collagen and fibrous tissue in the myocardium than women or female animals.[27] This difference is partly due to the effects of estrogens: they stimulate collagen synthesis in male cardiac fibroblasts from different species, like human, mouse and rat, and inhibit collagen synthesis in the female cells and in engineered connective heart tissues.[26]



Clinical implications

- Aortic stenosis
- Hypertension
- Arteriosclerosis

Figure 3. Sex-specific E2/ER mediated collagen regulation underlies sex differences in cardiac fibrosis. Interaction of E2, ER α and ER ß with pro- and anti-fibrotic pathways in women and men. E2 activates ER α and ER ß in a sex specific manner, leading to a stronger transcriptional activation of pro-fibrotic pathways in men than in women. Adapted from Regitz-Zagrosek and Kararigas G.[23]
ER = estrogen receptor.

More precisely, both estrogen receptors (ER α and ER ß) are phosphorylated differently and at different sites in the male and female cells. Once phosphorylated, they bind to the collagen promoters in a sexually dimorphic manner. In a simplified manner, ER α represses and ER β induces collagen synthesis. In engineered connective heart tissues, E2 via ER modulates cardiac tissue function in a sex dependent manner. Engineered heart tissues from male cells showed an increased condensation and stiffness upon E2-treatment, analysed by rheological measurements, whereas impaired condensation was found in females.

Whereas at young age, men have a greater propensity towards inflammation and fibrosis than women, cardiac aging leads to more fibrosis and inflammation in women than in men.[58] Cardiac aging predisposes elderly women to HFpEF, as LV concentric remodeling and diastolic dysfunction are hallmarks of HFpEF, and are present to a greater degree in women with HFpEF compared with men with HFpEF. Thus, a female predisposition to diastolic dysfunction and HFpEF may result from activation of inflammatatory mechanisms due to a loss of estrogens in old age.

Summarizing the sex differences in myocardial pathophysiology described above, it becomes evident that a number of changes are induced by sex hormones, that occur in parallel (**Figure 4**). Therefore, a search for a superior regulatory mechanisms was started. MicroRNAs (miRNAs) regulate a number genes by binding to their 3 prime regions. They therefore could represent one of these overall coordinators of sex specific changes. We recently showed that some miRNA in the human heart, that are related to mitochondrial function, are regulated by ER ß.[59] Thus, the sex-specific regulation of these miRNAs and corresponding downregulation of downstream protein targets may contribute to sex-specific remodelling in pressure overload-induced LV hypertrophy.[59]

Vascular pathophysiology

Finally, vascular dysfunction is known to be a major contributor to the development, progression and treatment of HF.[60] Sex differences in vascular dysfunction are due to sex differences in vascular biology. Microvascular disease primarily affects postmenopausal

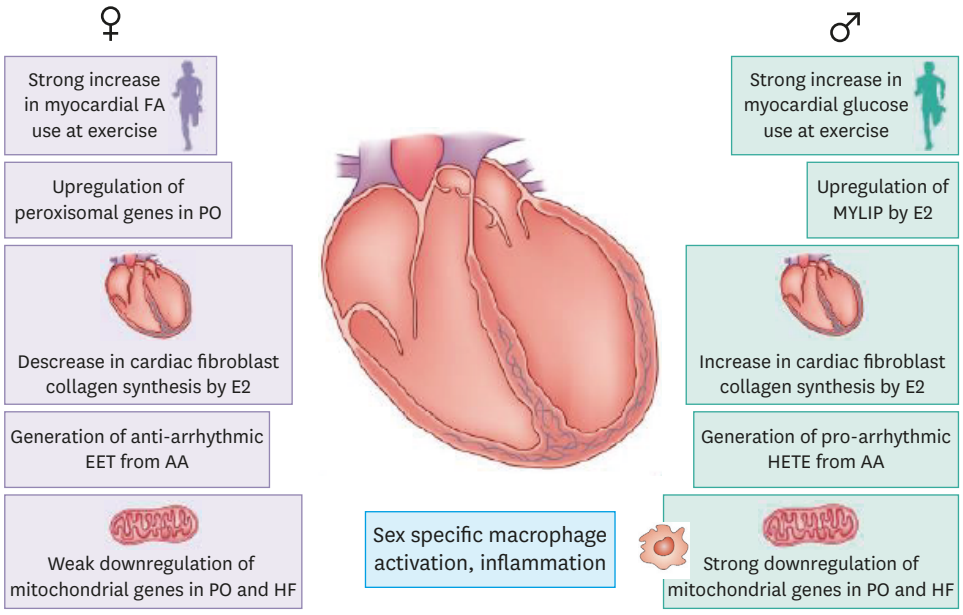


Figure 4. Summary of sex differences in myocardial pathophysiology. Adapted from Gerdts and Regitz-Zagrosek.[29]
AA = arachidonic acid; EET = epoxyeicosanoids; FA = fatty acid; HETE = hydroxyeicosatetraenoic; HF = heart failure; MYLIP = myosin regulatory light chain interacting protein; PO = pressure overload.

women due to changes in hormonal exposure as well as to accumulation of risk factors and to intrinsic biological sex specific factors. The sex-specific alterations in biomechanical properties of the arteries have deleterious sex-specific effects on LV diastolic function. In conclusion, sex differences in vascular dysfunction play a multifactorial and crucial role in the pathophysiology of the HF syndrome.

An association between arterial stiffness and LV diastolic function in relation to gender and age was found in elderly women but not in younger women or men. The data suggest, that increased arterial stiffness plays an important role in the development of HFpEF as well as LV diastolic dysfunction (LVDD) in elderly women.[61]

Investigations from Korea suggest that the effects of earlier wave reflection on central pressure may contribute to greater susceptibility to HF with preserved LV EF in women.[62] Moreover, an association of LVDD and IHD severity was observed only in women. Myocardial ischemia may be a potential pathophysiology for higher prevalence of HFpEF in women.[63]

An impact of sex on ventricular-vascular stiffness and long-term outcomes in HFpEF was also confirmed in the TOPCAT trial substudy. The aim of the substudy to TOPCAT was to characterize sex differences in vascular and ventricular structure and function, and to investigate the impact on the primary outcome in the TOPCAT trial.[64] Echocardiography revealed higher arterial, systolic, and diastolic ventricular elastance and worse ventricular-vascular coupling in women. Women had better overall survival and HF hospitalization outcomes. Pulse pressure was a key determinant of outcome in women whereas in men heart rate and B-type natriuretic peptide were associated with poorer outcome. Thus, outcomes in patients with HFpEF appear to be differentially influenced by key physiological factors according to sex. In women, ventricular-vascular stiffening was the most significant determinant of outcome.

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PREVENTION

Unfortunately, not much is known about sex specific aspects in prevention of HF.[65] One of the few trials that investigated Dietary Patterns and Incident HF in U.S. Adults without Known Coronary Disease was the REasons for Geographic and Racial Differences in Stroke trial. This was a prospective cohort of black and white adults followed from 2003 to 2007 through 2014. Inclusion criteria included completion of a food frequency questionnaire and no baseline coronary heart disease or HF. Five dietary patterns (convenience, plant-based, sweets, Southern, and alcohol/salads) were derived from principal component analysis. The primary endpoint was incident HF hospitalization. After a median of 8.7 years of follow-up, 363 participants had incident HF hospitalizations. In brief, adherence to a plant-based dietary pattern, more frequently found in women, was inversely associated with incident HF risk, whereas the Southern dietary pattern was positively associated with incident HF risk.

Opportunistic screening models for high-risk men and women to detect diastolic dysfunction and HFpEF in the community were developed in an European group.[66] The group aimed to develop sex-specific diagnostic models to enable the early identification of men and women at high-risk of LVDD with or without symptoms of HF who require more aggressive preventative strategies. Individual patient data from 4 primary care HF-screening studies were analysed. Eleven candidate predictors were entered into logistic regression models to be associated with the presence of HFpEF in men and women separately. Increased age and β-blocker therapy remained as predictors in both the models for men and women. The model for men additionally consisted of increased body mass index, moderate to severe shortness of breath, increased pulse pressure and history of ischaemic heart disease. The models performed moderately and similarly well in men and women and the performance improved significantly following the addition of N-terminal pro B-type natriuretic peptide. Thus, the authors provide an easy-to-use screening tool for use in the community, which can improve the early detection of HFpEF in high-risk men and women and optimise tailoring of preventive interventions. More development of is needed for specific aspects in women and men.

TTC

In contrast to HCM and DCM, the TTC is a rare disease affecting predominantly women, approximatively 70–90% women in most registries.[67-70] An altered brain heart axis and a decrease in estrogen levels post-partum probably contributes to the altered sensitivity of the heart to circulating catecholamines. TTC is often preceded by acute massive psychological or physical stress. The patients frequently recover with normalized EF.[71][72]

TTC in almost all cases is preceded by severe emotional stress. It is characterized by angina symptoms, accompanied by ECG changes and cardiac enzyme elevations. During first phase of TTC an acute, reversible, regional systolic dysfunction involving the LV apex and mid-ventricle with hyperkinesias of the basal LV segments in the absence of obstructive epicardial CAD is found. TTC constitutes ca. 6–10% of all women presenting with ACS. Despite the overall favorable prognosis, TTC remains a life-threatening condition that has a mortality rate up to 8%. and recurrence is estimated to 5%.

Mechanism of TTC remains still unclear. Existing hypotheses comprise the catecholamine spillover, microcirculatory dysfunction, epicardial spasm, etc. The microcirculatory dysfunction has been demonstrated after acute episodes and under psychological stress in

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patients with TTC. Few data are known explaining the impaired peripheral endothelium-dependent vasodilation, excessive vasoconstriction, and augmented sympathetic activation after acute mental stress in TTC patients.

Severe activation of the sympathetic nervous system with catecholamine release caused by a dysfunctional limbic system has been proposed as a potential mechanism. Recently it was shown that altered limbic and autonomic processing occurs which supports the role of a brain-heart axis in TTC.[73] Using brain functional magnetic resonance imaging, resting state functional connectivity was measured in subjects with TTC and healthy controls. The authors found parasympathetic- and sympathetic-associated subnetworks with reduced functional connectivity in TTC patients compared with controls. Important brain regions included the amygdala, hippocampus, and insula as well as cingulate, parietal, temporal, and cerebellar regions. These findings suggest that autonomic-limbic integration might play an important role in the pathophysiology and contribute to the understanding of TTC.

Since TTC occurs predominantly in postmenopausal women, decreased estrogen availability may contribute to the pathophysiology of the disease. Reduction of estrogen levels following menopause may augment the reactivity to stress via modulation of autonomic functions and down-regulation of cardioprotective substances in the heart, i.e. ANP, resulting in the high incidence of TTC in postmenopausal women. Furthermore, the occurrence of TTC in post-menopausal women may support the hypothesis of stress-mediated vasoconstriction enhanced by estrogen depletion through i.e. the hormonal control of nitric oxide production.

PPCM

The 2018 European Society of Cardiology guidelines provide fundamental information on this life-threatening condition.[13]

PPCM presents with HF secondary to LV systolic dysfunction towards the end of pregnancy and in the months following delivery, with the majority diagnosed post-partum. Careful history-taking is necessary to identify and exclude other causes of HF. The LV may be non-dilated, but the EF is usually <45%. Symptoms and signs are often typical for HF with numerous phenotypes reported. Patients frequently present with acute HF, but also with ventricular arrhythmias and/or cardiac arrest. Echocardiography is the imaging modality of choice. Initial LVEF <30%, marked LV dilatation (LV end diastolic diameter ≥6.0 cm), and RV involvement are associated with adverse outcomes.

Important predisposing factors include multiparity, African ethnicity, smoking, diabetes, pre-eclampsia, malnutrition, advanced age, and teenage pregnancy. The cause is uncertain, but potential aetiologies include inflammation and angiogenic imbalance, inducing vascular damage. The biologically active 16-kDa prolactin and other factors such as soluble fms-like tyrosine kinase 1 may initiate and drive PPCM.[74][75]

Prospective larger cohort studies have focused mainly on 6-month outcomes, reporting a mortality ranging from 2.0% in Germany, to 12.6% in a large cohort of 206 patients with PPCM from South Africa. A prospective study over 24 months from Turkey reported a 24% mortality. Frequently, but not always, the EF normalizes after the first episode. However, the patients are in danger of a second and even more severe event in a subsequent pregnancy. When the EF has not recovered to >50–55%, subsequent pregnancy should be discouraged. Even with normalized EF, counselling is required due to potential recurrence. With expert interdisciplinary

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management and immediate bromocriptine treatment post-delivery, successful subsequent pregnancies especially in patients with recovered EF have been reported.[76]

Sudden cardiac arrest (SCA)

Epidemiology and risk factors

SCA is a hallmark of HF and affects women less frequently than men.[77-79] HF phenotypes and genotypic predisposition combine and lead to sex specific phenotypes. Arrhythmogenic phenotypes can be caused by pathophysiological mechanisms affecting ion channels or factors related to regulatory pathways of ion channels in a sex-specific manner. Electrophysiological differences between men and women include faster resting heart rates and longer rate-corrected QT intervals in women. In the case of long QT syndromes (LQTS), the sudden cardiac death during adolescence is equally common among boys and girls; after puberty, the rate increases significantly in women, but not in men. The influence of the localization of the mutation in the gene, in a channel-forming loop or in another localization has a much greater influence in men than in women. Thus, men with a mutation in the canal-forming region belong to a high-risk group. Other high-risk groups are women, patients with a previous syncope or with an extremely long QT time. Women die more from torsade de point tachycardia in LQTS, whereas men are more affected by Brugada syndrome.[77-79]

Genetic defects leading to LQTS are located on autosomes. Mutations in 13 genes have been associated with LQTS, but most of the LQTS are due to mutations in 3 ion channels. LQTS-induced tachycardia occurs with equal frequency in boys and girls. However, after puberty, arrhythmias are more frequent in women than men. Women are at higher risk than men for Torsade de Pointes with LQTS type 1 and type 2, but LQTS type 3 occurs with equal frequency between men and women.[79] It has been hypothesized that testosterone contributes to shortening of the QT interval in men, whereas estrogen prolongs the QT in women.[80][81]

95% of SCA victims in sports in large studies are men. This is not only a question of exposure. Targeted examinations have shown that women exposed to stress are relatively better protected against SCA than men. This may also protect them from arrhythmogenic death in HF. Sex specific switches in adrenergic signalling under stress conditions could represent an endogenous protective mechanism in women. Furthermore, women may generate protective metabolites in the arachidonic acid pathways under the influence of oestrogen, whereas men, under the influence of testosterone, generate more pro-arrhythmic and pro-hypertrophic metabolites. However, the precise mechanisms underlying protection in women are still unknown. We discuss this entity since it may be important to identify protective mechanisms in women. Furthermore, women and men are not equally treated with defibrillators. Women receive less for the same indications, in primary as well as in secondary prevention and the reasons for this are not yet clear.

Clinical manifestation

Women and men differ in their presentation with SCA. According to the large Oregon heart study, women are more often alone at the time of the event, and have less shockable rhythm, i.e. ventricular tachycardia and more frequently asystole.[82] Duration of reanimation in women are shorter than in men, in US and Europe. The phenomen is not really understood, but it is generally believed that men are reluctant to touch women for reanimation purposes. Nevertheless, women have better survival rates.

SCA and sex hormones

The influence of sex hormones on the incidence of events in women and men is based on

their effects on ion currents. Estrogen inhibits the repolarizing potassium inward flow and prolongs the action potential, leading to prolonged action potential duration which is more harmful in patients with pre-existing prolongation. In contrast, testosterone in men stimulates the potassium inward flow and thereby shortens the action potential and reduces risk for LQTS tachycardia.

Sudden cardiac death in sports is mainly a disease of men. 95% of those affected in large studies are men. Only in cycling, jogging, swimming and hiking, significant numbers of SCA are reported in women. There is no good explanation why SCA in sports is so much less frequent in women.

The current concept in the development of sudden cardiac death is that either IHD or HF results in a vulnerable substrate, which then facilitates the occurrence of ventricular fibrillation in combination with a specific trigger. The interaction between the vulnerable substrate and the trigger, which can be influenced by different mechanisms, some of which may be sex- or gender-specific, plays a central role.[83]

Potential mechanisms include nutrition, lipid metabolism, psychosocial determinants as well as sex hormones, modulators of ion channels, genetic factors and calcium. Possible protective factors in women are a Mediterranean diet, which is more frequently chosen by women than men, a favourable profile of lipid metabolites, higher concentrations of polyunsaturated fatty acids, low concentrations of lipoprotein a, which is downregulated by estrogens.

Metabolites in the metabolism of arachidonic acid can also play an important role. Arachidonic acid is degraded to eicosanoids and this occurs in the myocardium differently under the influence of androgens and estrogens, in men and women. Estrogens affect the cytochrome P 450 isoenzyme CYP 2J2 pathway toward the formation of EET and block the degradation of EET by inhibiting the soluble epoxide hydroxylase. Higher levels of protective EET are the result. In men, on the other hand, the cytochrome P450 pathway is driven towards the formation of 20 hydroeicosanoids (20 HETE) by the isoenzyme CYP4.[49]

20 HETE and EET have varying, almost opposite effects on cardiac remodeling. EET have strong anti-apoptotic, anti-inflammatory and antiarrhythmic effects. They regulate the L-type calcium channel and ATP-dependent potassium channels. In a model of the pressure load of the heart, the increase in the concentration of EET induced by overexpression of the epoxygenase CYP2J2 significantly reduces the deaths after pressure overload in male animals. In addition, EET also inhibit the onset of ventricular fibrillation after electrical stimulation of the heart. Equally favourable effects were found in a model of catecholamine overstimulation.[49] Accordingly, EET analogues are now the starting point for the development of new antiarrhythmic drugs.

Further important protective mechanisms are found in beta-adrenergic signal transduction and some of them are related to sex or sex hormones.[84-88] In the heart, beta 1 and beta 2 adrenergic receptors are expressed (ß1AR, ß2AR). They are regulated by sex hormones on expression and activity levels. ß1AR is down-regulated by estrogen whereas beta 2AR can be activated by estrogen. Both receptor types couple to stimulatory G proteins and lead to the formation of cAMP, activation of protein kinase A and sarcoplasmic calcium release, leading to positive inotropy, arrhythmias and apoptosis. However, after adrenergic overstimulation, the beta 2AR may switch from Gs to GI protein coupling and beta 2AR may act suddenly in a

negative inotropic, anti-apoptotic and anti-arrhythmic manner. This switch seems to be more easily activated in women than in men and may be related to TTC. Its activation under stress conditions could represent an endogenous protective mechanism in women against SCA.

Several authors also described significant sex differences in calcium signaling in HF. We found an up regulation of calcium dependent signaling in men with HF.[23] In addition, we found significant sex differences in L-type calcium channel activities. In men, activation of the channel leads to a stronger calcium inward current then in women.

In summary, potential mechanisms for sex differences in the genesis of arrhythmia have been located to lipid metabolism, to arachidonic acid metabolism and to eicosanoids and to calcium signaling. Alltogether, they result in the protection of women.

Implantable cardioverter defibrillator (ICD) therapy

Different studies found that ICD in the field of primary and secondary prevention in ischemic and non-IHD obtained similar results related to sex and gender, but was underused in women. In general, women represented only a small part of study cohorts, between 10 and 20%. Based on the small number of women in the studies it is difficult to assess results for them.[89]

In an analysis of the national register of the US in which 90% of pacemaker and ICD implant patients in the United States are included, >38,000 implantations, only 25% of women, were included. Women had more comorbidities and more severe HF and more frequently non-ischemic cardiomyopathies then men. ICD related complications occured more frequently in women than in men.[90]

Data from a Multicenter French Registry in primary prevention describe a large multicenter cohort of consecutive patients referred for ICD implantation for primary prevention (2002–2012), in ischemic and non-ischemic cardiomyopathy (CMP). Of 5539 patients, only 837 (15.1%) were women. Compared to men, women presented with a significantly higher proportion of non-ischemic CMP (60.2% vs. 36.2%, p<0.001), wider QRS complex width (QRS >120 ms: 74.6% vs. 68.5%, p=0.003), higher New York Heart Association functional class, and lower prevalence of AF. During a 16 786 patient-years follow-up, overall, fewer appropriate therapies were observed in women. By contrast, no sex-specific interaction was observed for inappropriate shocks, ICD complications, and all-cause mortality. Thus, in this real-life registry, women accounted for the minority of ICD recipients and presented with a different clinical profile.[89] They were less likely to experience sustained ventricular arrhythmias in comparison with men.

Further analysis in secondary prevention, i.e. in patients that had already experienced a SCA event confirmed that women benefit as much as men, if they are treated. Curtis et al.[91] analysed a 5% national sample of patients from the US Centers for Medicare & Medicaid Services eligible for ICD therapy and found, that in the secondary prevention ICD cohort, there was a statistically significant mortality benefit for both sexes even after adjustment for other factors.[92]

Nevertheless, women were less likely to be referred for ICD therapy despite current guideline recommendations. To understand the underlying mechanisms, Hernandez et al.[93] analysed data from the get with the guidelines (GWTG)-HF programme and studied 13,034 patients with HF who were eligible for ICD therapy. The study revealed that while around 44% of

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eligible (white) men received ICDs, only around 28% of eligible women received ICD therapy. The study by Curtis et al.[91] mentioned above showed that only 8.6 per 1,000 women received an ICD compared with 32.3 per 1,000 men within 1 year of known eligibility for a primary prevention ICD. The rates of ICD implantation for secondary prevention of SCD were also equally disproportionate in women (38.4 per 1,000) compared to men (102.2 per 1,000).

Other studies reported similar results: Among 9,246 eligible secondary prevention patients (age 66.3±14.3 years; 3,577 women [39%]) with cardiac arrest, men were more likely to undergo ICD implantation, with an age-, comorbidity-, and arrhythmia-adjusted HR of 1.92 (95% confidence interval [CI], 1.66–2.23).

Among 105,516 patients with MI (age 68.3±12.7 years; 42,987 women [41%]), men were threefold more likely to undergo ICD implantation, with an adjusted HR of 3.00 (95% CI, 2.53–3.55).[94]

The studies clearly reveal there is an ongoing need to improve ICD therapy in women. Over the past few years there have been ongoing efforts to improve utilisation of implantable cardiac device therapy in eligible female patients.

The IMPROVE HF20 study evaluated whether a programme to provide clinical decision-making support tools and educational materials to healthcare providers would lead to similar improvements in adherence to clinical practice guidelines for both male and female patients.[95] This was a prospective study where high-risk patients with HF with reduced EF (<35%) eligible for treatment with an ICD, cardiac resynchronization therapy (CRT) or several other guideline-recommended therapies were identified and hospitals were provided with clinical algorithms, pocket cards, patient educational materials and patient assessment forms and were followed for 24 months. The study included a total of 15,170 patients of whom 4,383 (28.9%) were women. At the end of 2 years, rates of ICD use went up from 40–50% to 75–80% and CRT use from 35–40% to 65–75% in both men and women. Thus, providing clinical decision-making support and education can lead to better ICD therapy utilisation in eligible patients irrespective of sex. Similarly, Al-Khatib et al.[96] analysed 11,880 patients enrolled in the GWTG-HF program for trends in ICD implantation rates over the past decade and found that with the implementation of the GWTG-HF program, rates of ICD implantation went up overall (around 30% in 2005 to 42% in 2007).

In conclusion, there are significant biological differences in cardiac electrophysiology and in arrhythmia in women and men. Protective mechanisms were identified in women and serve as a basis for anti-arrhythmic drug development in men. Treatment with ICD has significant benefits in women and men even though women have less arrhythmic events. However, there is a gender bias leading to less treatment in women. More studies are needed to establish sex and gender sensitive guidelines for ICD treatment in women.

MEDICAL THERAPY

Current guidelines do not stratify HF for women and men. However, there is a lot of recent evidence that women may need different doses for some drugs, that they benefit more or less from others than men. Reporting of sex and gender differences from clinical trials is still underdeveloped.

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Digoxin

In 1997, the Digitalis Investigation Group confirmed the efficiency of digoxin therapy for patients with HF.[97] Thereafter, guidelines strongly endorsed the use of digoxin in HFrEF, without considering sex. However, in a post hoc subgroup analysis, digoxin was associated with a significantly higher mortality among women taking digoxin compared with those taking placebo, an effect that was not observed in men.[98] Subsequently, higher drug serum levels in the upper normal range were held responsible for the unfavorable survival effects reported in women. More studies are needed to clarify is there is a pharmacokinetic or pharmacodynamics sex difference in the effect of digoxin. In the absence of definitive evidence, digoxin plasma concentration should be below 0.8 ng per ml in women and men.[99]

Beta-blockers

Beta-blockers are cornerstones in the treatment of HF. Two major trials, the metoprolol CR/XL (MERIT)-HF study and the carvedilol prospective randomized cumulative survival (COPERNICUS) trial, failed to find a beneficial effect on mortality in the small subgroups of women.[100][101] In the cardiac insufficiency bisoprolol study II (CIBIS II) study, women profited significantly from treatment with bisoprolol.[102][103] Pooling of mortality results from MERIT-HF, CIBIS II, and COPERNICUS showed survival benefits in both women and men.[104] The lack of evidence in some large beta-blocker studies is therefore probably due to the under-representation of women in the trials and beta-blockers are an effective treatment in women.

However, optimal doses for beta-blockers may well differ in women and men. A recent analysis in the BIOlogy Study to TAilored Treatment (BIOSTAT) in Chronic HF study performed in 11 European countries, found that women with HFrEF needed lower doses of beta-blockers and angiotensin-converting enzyme inhibitors (ACEI) (see below) than men for optimal effects (**Figure 5**).[25] Women achieved optimal effects with half the doses of men and increasing the doses further did not improve the outcomes. The results from the European study were confirmed in an Asian cohort.[25] In this cohort, women needed lower doses for optimal effect and did not improve with increasing doses. This may be explained by sex differences in the pharmacokinetics of beta-blockers. Metoprolol and propranolol are primarily metabolized by liver cytochrome CYP2D6 which has a lower activity in women than in men.[105][106] Propranolol reaches plasma levels that are up to 80% higher in women compared to men. The optimal effect of the beta-blocker metoprolol may be achieved in lower doses in women than in men: a 50 mg metoprolol dose in adult women provided an approximately similar drug exposure to a 100 mg dose in adult men.[107] Oral contraceptives can interact with metoprolol metabolism and further increase its plasma levels.[108] Since women experience more frequently adverse effects with beta-blockers than men, it may be useful to keep doses low and more studies on optimal dosing of beta-blockers in women are needed.

ACEI

In early multicentre studies, e.g. CONSENSUS I, SAVE, and SOLVD, ACEI led to much smaller mortality reductions in women compared with men. The later trials AIRE and HOPE, as well as a number of smaller studies, showed a significant benefit of ACEI in women, suggesting that they benefit from treatment as much as men. However, the "Second Australian National Blood Pressure Study" (ACEI vs diuretics) demonstrated a significant reduction in cardiovascular events in men, but not in women, despite similar reductions in blood pressure in both sexes.[109] Most recently, the BIOSTAT HF trial suggested that women with HFrEF reach the same treatment effects, i.e. mortality and reduction of cardiovascular events, with

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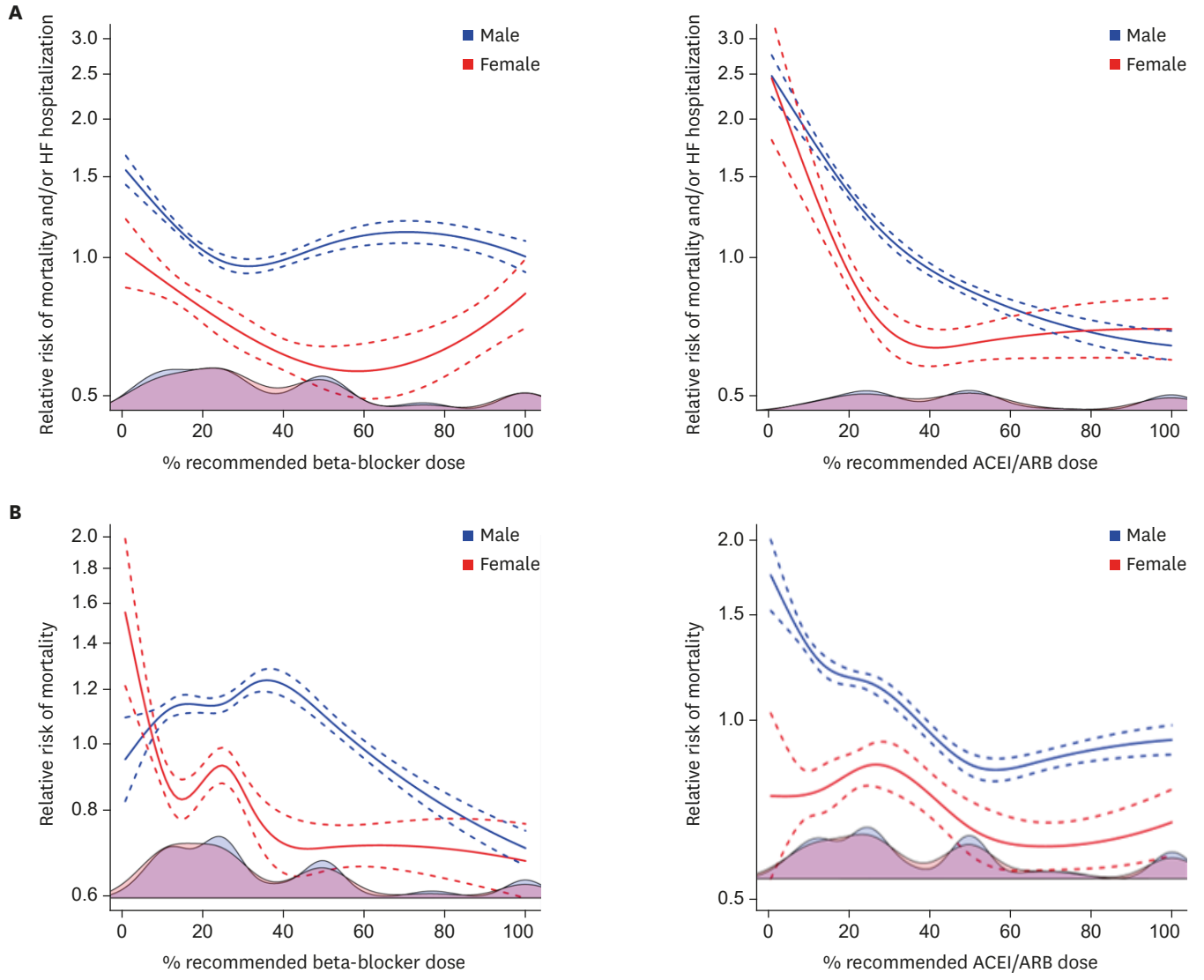


Figure 5. Women with HFrEF needed lower doses of beta-blockers and ACEI than men for optimal effects. (A) Results from BIOlogy Study to TAilored Treatment in Chronic HF, (B) results from Asian HF see text for details.[25]
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; HF = heart failure; HFrEF = heart failure reduced ejection fraction.

lower doses than men, and do not benefit from up-titrating to guideline recommended doses (**Figure 5**).[25] It is unclear, whether the underlying pathophysiology interferes with treatment results in a sex specific manner or if pharmacokinetic aspects play a role. Adverse effects of ACEI, especially a typical dry cough, that occurs early with treatment and seems to be dose independent, are more frequent in women than in men.[110] Cardiology societies should urge industry to do more studies to find out about optimal ACEI doses in women.

Angiotensin II receptor blockers (ARB)

Major ARB studies in patients with hypertension, after MI and HF found no sex- or gender-related differences and showed the same safety profile in both sexes. This was true for Losartan Intervention for Endpoint Reduction in Hypertension, Evaluation of Losartan in the Elderly, Optimal Trial in Myocardial infarction with Angiotensin II Antagonist Losartan, Valsartan Antihypertensive Long-Term use Evaluation, Valsartan Heart Failure Trial,

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I-Preserve, CHARM. Thus, we assume that these drugs are equally effective in women and men and may be used in the same doses.

Sacubitril-valsartan

Recently, completely unsuspected sex differences were found in a large randomized controlled trial (RCT), comparing the combined Neprilysin inhibitor/ARB sacubitril-valsartan and the ARB valsartan in patients with HFpEF.[111][112] Neprilysin inhibition augments endogenous biologically active natriuretic peptides and other vasoactive compounds, with increased generation of cGMP, a signaling molecule that is reduced in HFpEF, and is beneficial in HFEF.[113][114] Sacubitril-valsartan did not result in a significantly lower rate of total hospitalizations for HF and death from cardiovascular causes in a mixed sex cohort of patients with HFpEF/HFmEF.[112] However, it led to a significant reduction in event rate versus valsartan in women, which was not observed in men (0.73 in women and 1.03 in men; p interaction=0.017).[111] Thus, the drug was effective in women, but not in men. The study could not provide a definite mechanistic basis for this finding. This is a challenge for guideline committees – will the recommend the use of this drug in women only?

Renin inhibitors

Aliskiren, the first non-peptide active renin inhibitor, provided equally effective, dose-dependent blood pressure lowering in women and men with mild-to-moderate hypertension, also in the elderly, obese or those with metabolic syndrome.[115] The drug can also be used in HF. Sex specific analysis are not available.

Aldosterone receptor antagonists

A first trial found no difference in the effect of spironolactone on symptomatic HF between men and women.[116] However just 30% of the patients enrolled have been women and the trial was not powered to detect sex differences. The major clinical trial of eplerenone in patients with acute MI and LV dysfunction, EPHESUS, showed a trend towards a greater benefit for women, treated with eplerenone, at 30 days which was not confirmed at 16 months.[117] Furthermore, in an exploratory, post hoc, non-pre-specified analysis of the TOPCAT trial, evidence for sex differences were found. In TOPCAT, subjects with symptomatic HF and a LV EF ≥45% were randomized to spironolactone or placebo. In a post-hoc subgroup analysis, in which only subjects enrolled from the Americas were analyzed, spironolactone therapy was associated with reduced all-cause mortality in women (HR, 0.66; p=0.01) but not in men (p interaction= 0.02).[118] Thus, even though the interaction between spironolactone and sex in TOPCAT overall and in the present analysis was non significant for the primary cardiovascular outcome, there was a reduction in all-cause mortality associated with spironolactone therapy in women, with a significant interaction between sex and treatment arm. More prospective studies are needed for confirmation and mechanistic understanding.

Antiarrhythmic drugs

A number of antiarrhythmic drugs prolongs cardiac repolarization. Women have longer rate corrected QT intervals than men and are more prone to adverse effects with such drugs. For all of the following QT-prolonging drugs, women consistently had a higher incidence of QT prolongation and torsades de pointes than men: amiodarone, bepridil, disopyramide, quinidine, erythromycin, halofantrine, ibutilide, probucol, sotalol, and terfenadine.[77] There are no sex-related recommendations in the guidelines, but it may be wise, if doctors check for changes in the QT intervals when initiating treatment of women with these drugs.

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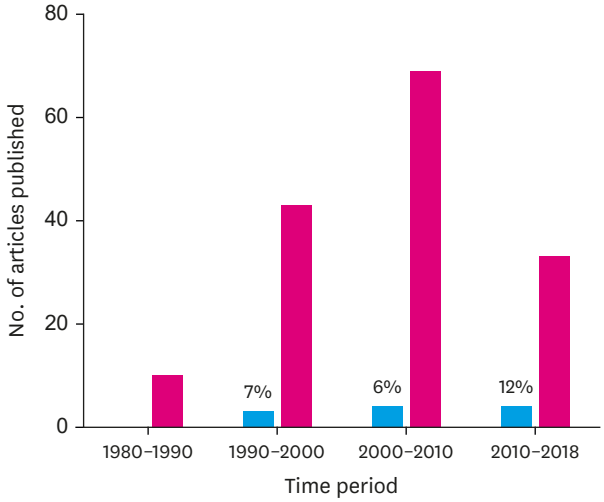


Figure 6. Sex-specific ADR reporting across the past 4 decades. Low use of sex specific reporting of adverse drug effects. Adapted from Bots et al.[121] The total number of articles that reported ADR data (pink) and the number of articles that reported sex-specific ADR data (blue). The articles have been divided by decade of publication. The percentage of sex-specific ADR papers of all ADR papers published that period are presented on top of the blue bars. ADR = adverse drug reaction.

Calcium-channel blockers

The major hypertension trials with calcium antagonists revealed no evidence for gender differences in outcomes.[119] Only the Amlodipine Cardiovascular Community Trail trial therapy with amlodipine resulted in more pronounced blood pressure reduction in women than in men. Women also had a higher incidence of edema. The sex differences were small and further evidence is needed to support clinical relevance. No sex differences of verapamil treatment were confirmed.

Sex specific reporting of effects and adverse effects

Knowledge on sex differences in effects and adverse effects in RCT is crucial for understanding mechanisms in women and men and optimizing therapy. However, most RCT do not present their results in a sex-disaggregated manner. A recent RCT reporting positive effects of colchicine for MI included only 20% women and did not present results in a sex-specific manner.[120] We recently performed a systematic search of PubMed and Embase to collect all available information on adverse drug reactions (ADRs) to ACEI, beta-blockers, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, ivabradine, and digoxin in both women and men with HF.[121] We identified 155 eligible records, of which only 11 (7%) reported ADRs data for women and men separately. Sex-stratified reporting of ADRs did not increase over the last decades (**Figure 6**). Three of the 11 studies reported a higher risk of angiotensin-converting enzyme inhibitor–related ADRs in women, 1 study showed higher digoxin-related mortality risk for women.

These results underline the scarcity of ADR data stratified by sex. The study investigators call for a more comprehensive reporting of ADR data for women and men separately.[121]

CONCLUSION

Women are at greater risk than men of experiencing an adverse reaction to most cardiovascular drugs and effects of cardiovascular drugs in women and men can be

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different. Underlying causes are yet unknown, but genetic mechanisms like polymorphisms modifying drug response to ACEI, beta-blockers and calcium-channel blockers interfering with the effect of sex hormones and menstrual cycle, with age, underlying pathophysiology, comorbidities, co-medication and self-medication can all play a role.

Significant sex and gender differences still exist. Clinical and basic investigators, industrial study managers, cardiology societies, guideline committees urgently need to pay attention to the fair inclusion of women in research projects and guidelines for management. Considering women and men equally will make medicine more efficient and reduce number of failed diagnosis and ADR. It is a step forward towards precision medicine and improvement of clinical research. Cardiology societies should urge industry to do more studies to find out about optimal doses of cardiovascular drugs in women.

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