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POSITION PAPER

Differences in presentation, diagnosis and management of heart failure in women. A scientific statement of the Heart Failure Association of the ESC

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Despite the progress in the care of individuals with heart failure (HF), important sex disparities in knowledge and management remain, covering all the aspects of the syndrome, from aetiology and pathophysiology to treatment. Important distinctions in phenotypic presentation are widely known, but the mechanisms behind these differences are only partially defined. The impact of sex-specific conditions in the predisposition to HF has gained progressive interest in the HF community. Under-recruitment of women in large randomized clinical trials has continued in the more recent studies despite epidemiological data no longer reporting any substantial difference in the lifetime risk and prognosis between sexes. Target dose of medications and criteria for device eligibility are derived from studies with a large predominance of men, whereas specific information in women is lacking. The present scientific statement encompasses the whole scenario of available evidence on sex-disparities in HF and aims to define the most challenging and urgent residual gaps in the evidence for the scientific and clinical HF communities.

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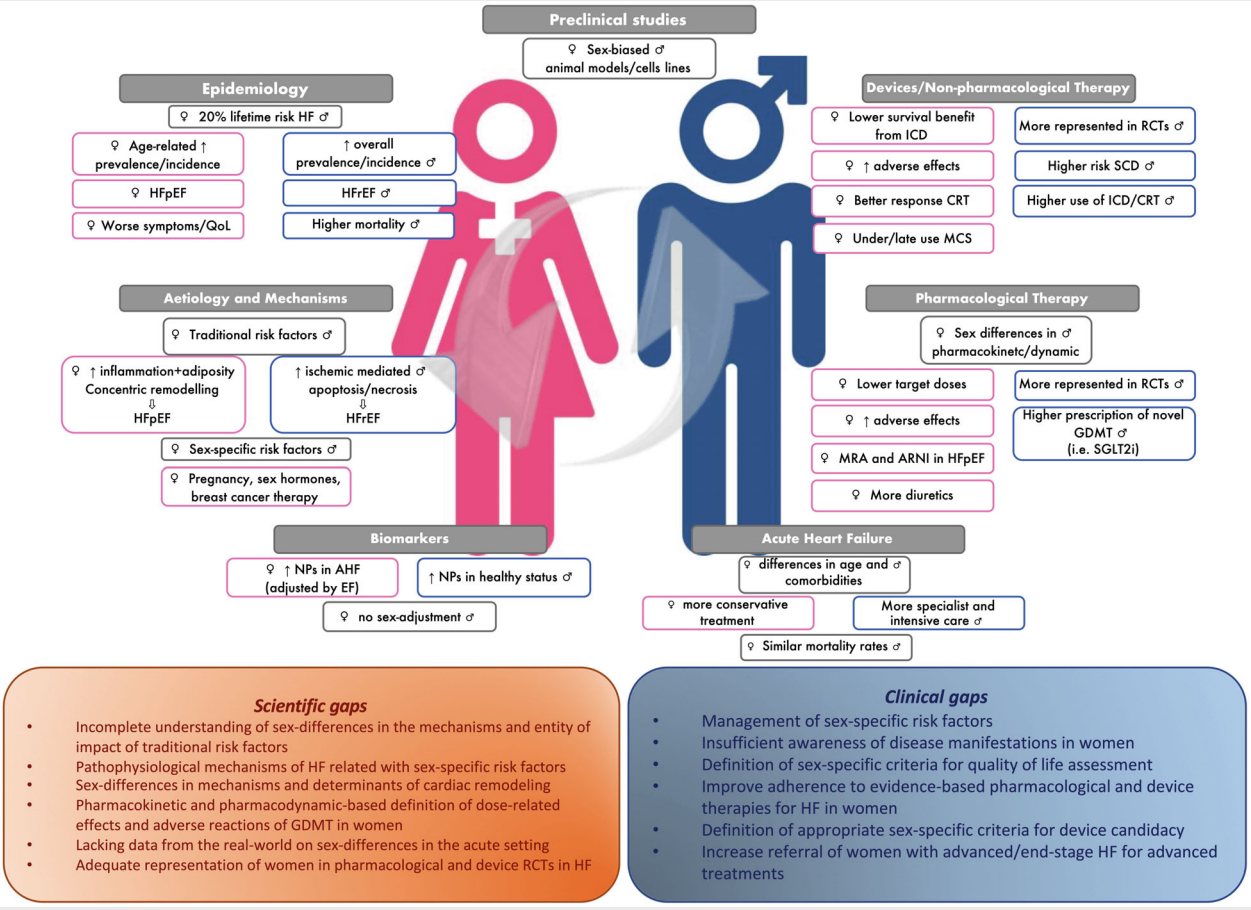
Graphical Abstract



Sex-based differences in heart failure (HF) encompass the complete scenario of the disease, from pre-clinical studies to advanced therapeutic strategies. The progresses in knowledges made available multiple information for researchers and clinicians, which aids to understand the underlying mechanisms and to define how to apply information to clinical-decision making. However, several residual scientific and clinical gaps must be filled in order to finally eliminate sex disparities in the management of HF. AHF, acute heart failure; ARNI, angiotensin receptor–neprilysin inhibitor; CRT, cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed medical therapy; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NP, natriuretic peptide; QoL, quality of life; RCT, randomized clinical trial; SCD, sudden cardiac death; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Keywords Sex • Heart failure • Women • Risk factor • Medical therapy • Device

Introduction

Heart failure (HF) is a global pandemic affecting more than 64 million people worldwide with a steadily growing prevalence.[1] Despite improvements in treatment, mortality in HF remains high and the burden of HF-related hospitalizations is increasing.[2–4] Several inequalities are reported within the global management of the syndrome, related to different factors, of which biological sex remains one of the most prominent.[5–8] HF represents the paradigm of a medical condition with profound differences between sexes which span across the entire disease process, from presentation to pathophysiology and finally outcome.

This scientific statement aims to provide a complete overview of the available evidence on sex-related differences in HF, including the pathophysiological background, the epidemiological distribution, the response to treatments by sex, and differences in outcome. Gaps in knowledge, including under-representation of women in landmark randomized clinical trials (RCTs), are analszed and future perspectives for closing these gaps examined.

Animal and cellular models

Heart failure shows sex dimorphisms in prevalence, presentation, and outcomes. Despite this evidence and the ability of animal and cellular models to be used as a platform for evaluating sex-specific differences in HF, pre-clinical studies are mainly sex-biased. Young male animals and/or the derived tissues and cells are usually used, and many animal studies either provide combined data obtained from males and females or do not report the sex of the animals and of the primary cells or cell lines used for *in vitro* experiments.[9]

The ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines have suggested the minimum criterion is reporting the sex of the animals used in the experimental studies,[10] this is now also requested by most scientific journals. Similarly, the sex of primary cells and cell lines should also be reported. These criteria are further in line with the recommendations for best practice and ethical standards.[11] In the case of primary or stabilized cell lines being derived from animals of unknown sex, the sex of the cell/tissue donor can be determined identifying specific fragments of the X and Y chromosomes.[12] In addition, cell culture media composition should be reported since it may contain sex steroid hormones.[13]

Beyond these minimum criteria, scientists are advised to use and compare male and female animals/tissues/cells in their experiments.[12] If not, researchers should justify the use of appropriate sex and age of mice/cells according to disease and therapy. This further applies to cells, for which additionally the use of hormone-neutral cell culture media is advised.

Pre-clinical studies should also evaluate the effect of risk factors and comorbidities in a sex-specific manner.[12] Once sex dimorphisms on HF are identified, the relative contributions of sex hormones and sex chromosomes can be determined.[12,14]

Epidemiology of heart failure

The overall lifetime risk of developing HF is reported to be approximately 20% in both sexes,[15] but with some important differences related to age. The overall prevalence of HF is higher in men compared with women between the ages of 20–79 years, after which prevalence is higher in women, mostly mediated by the steepest increase in the prevalence of HF with preserved ejection fraction (HFpEF).[16] In the United Kingdom (UK), the age-standardized prevalence of HF in the period 2002–2014 was higher in men than in women.[17] *Table 1* summarizes the prevalence of HF in major population studies according to sex.[16–23]

The incidence of HF in Europe and the United States of America is 2–3 cases per 1000 population.[5,17,20,24] Increases in the incidence rates of HF in women are larger than in men at older ages (>65 years).[25] Several reports suggest that incidence might be stable or even declining over time in the general population.[17] In a large UK population-based study, the overall incidence was higher in men than in women (incidence rate ratio 1.52, 95% confidence interval [CI] 1.50–1.54), particularly in the younger age groups, but the total number of incident cases was only 9% higher in men due to the larger proportion of older women.[17] In a Dutch community-based cohort study, the incidence rates were 3.7/1000 person-years in men and 2.4/1000 person-years in women.[26] In the 2000–2010 decade, a larger decrease in HF incidence was observed in women from the Olmsted County.[5] More contemporary data report greater increases in HF hospitalization in women versus stable rates in men, which might be explained by the progressive increase in age and in the proportion of individuals with HFpEF.[27–29]

More consistent sex differences can be found in the phenotype distribution of HF.

Men exhibit a higher risk of HF with reduced ejection fraction (HFrEF) compared to women,[30] but HFpEF affects women more.[5]

Table 1 Reported prevalence of heart failure in the major population studies according to sex

Study (country; years of inclusion)	Study population	HF prevalence in men vs. women
EPICA study (Portugal; 1998)[16]	5434 subjects in primary care	Men 4.3%; Women 4.4%
PRICE study (Spain; 2004–2005)[18]	1776 subjects aged ≥45 years in primary care	Men 6.5%; Women 7%
Swedish National Patient (Sweden; 2014)[19]	Overall Swedish population	Men 1.94%; Women 1.42%
Zarrinkoub *et al.* (Sweden; 2010–2014)[20]	2.1 million inhabitants in Stockholm (Sweden)	Men and Women 2.2% decreasing in women, stable in men
Norwegian Prescription Database (Norway; 2013–2016)[21]	Nationwide population	Men 3.7%; Women 2.1%
Clinical Practice Research Datalink (UK; 2002–2014)[17]	4 million individuals	Men 1.8%; Women 1.2%
Health Search IMS Health Longitudinal Patient Database (Italy; 2002–2013)[22]	1.1 million subjects in primary care	Men 1.25%; Women 1.24%
Public Health Agency of Canada (Canada; 2012–2013)[23]	Nationwide population	Men 4%; Women 3%

HF, heart failure.

In Sweden, women represented 55% of patients with HFpEF, 39% of those with HF with mildly reduced ejection fraction (HFmrEF), and 29% of patients with HFrEF.[31] Race and ethnicity related disparities in outcome have been reported also in women.[32]

Aetiology and mechanisms of heart failure

Traditional risk factors

Traditional risk factors for HF are, in general, the same in both women and men, but their interaction with sex-specific risk factors and the differences in pathophysiological mechanisms concur to explain the differences in phenotype expression, clinical manifestations and outcomes (*Figure 1*).

Obstructive coronary artery disease (CAD) is less frequently present in women. They also express less extensive apoptosis and necrosis of myocytes and less adverse remodelling after myocardial infarction, partially explaining the lower frequency of HFrEF in women compared to men.[33–36] However, after menopause, CAD also becomes the most frequent cause of HFrEF in both sexes.[37] Moreover, in women with HFrEF the presence and extent of CAD more strongly affect survival compared with men.[38] Hypertension and diabetes are the modifiable risk factors with the highest attributable risk of HFrEF in both women and men, mainly as determinants of CAD.[39]

Although the lifetime risk of HFpEF has been reported to be similar in women and men, suggesting that the higher prevalence of HFpEF in women might be in large part explained by differences in ageing,[30,36,40,41] the contribution of risk factors to structural remodelling in HFpEF differs between the two sexes. Women with HF are older, with a higher prevalence of diabetes and hypertension, and they are more likely to be obese. Furthermore, diabetes had the strongest impact as risk factor for HF in women and was more associated with concentric remodelling, which predisposes to HFpEF.[42–44]

The two risk factors accounting for about two-thirds of the attributable risk of HFpEF in women are hypertension and obesity.[39] Women exhibit greater concentric remodelling and heightened load-induced impairment of left ventricular (LV) relaxation, features that are strongly related with systemic hypertension.[45–47] In women, obesity was associated with the risk of HFpEF, whereas weaker or no association was observed with HFrEF. Of note, a similar observation was reported when waist circumference was used as a measure of adiposity.[39,48,49] Systemic microvascular inflammation appears as a key aspect relating obesity with HFpEF.[50] Impaired microvascular response is associated with higher risk of HFpEF in women with diabetes.[51] Inflammation is also considered an important pathophysiological mediator of the association between frailty and HF in women.[52] Given that women, especially post-menopausal women, are more likely to have inflammatory illnesses, they may be at higher risk for developing concurrent inflammatory syndromes such as frailty and HF.

According to the inflammatory-metabolic hypothesis, an expanded epicardial adipose tissue mass, microvascular endothelial dysfunction, and enhanced activity of adipocyte-associated inflammatory mediators, may predispose obese women to greater risk of HFpEF by mediating interstitial fibrosis and oxidative stress, culminating in myocardial stiffness and concentric remodelling.[53,54] Enhanced expression of biomarkers associated with lipid metabolic pathways has been observed in women.[55] Additional mechanisms include the overproduction of aldosterone and neprilysin mediated by adipocytes, which results in sodium retention, plasma volume expansion and rising filling pressures.[54,56] Finally, among the cardiomyopathies presenting with an HFpEF phenotype, transthyretin cardiac amyloidosis and Fabry disease, which is an X-linked genetic disease, have lower incidence and later onset in women than in men.[57–59]

Sex-specific risk mediators

Women carry specific risk factors for HF which are partially linked to their sex-hormonal background. In addition, these are also frequently related to other causes that preferentially or exclusively affect women, such as breast cancer and associated chemotherapy/radiation therapy and chronic inflammatory (auto-immune) diseases.

Pregnancy

Pregnancy represents a stressful condition for the cardiovascular system and can be a trigger for the onset of latent HF. Hypertensive disorders of pregnancy, such as pre-eclampsia and HELLP syndrome, a severe form of pre-eclampsia (H: haemolysis, EL: elevated liver enzyme, LP: low platelet count), have been associated with endothelial dysfunction and distortion in the nitric oxide pathway.[39,60] Although the aetiology remains to a considerable degree unknown, there is a close link between pre-eclampsia and peripartum cardiomyopathy, partially explained by a shared genetic background but also involving common pathophysiological mechanisms related to inflammatory and autoimmune processes, haemodynamic stress, altered oxidative stress-mediated cleavage of prolactin and induction of antiangiogenic factors.[61–64] Peripartum cardiomyopathy is a life-threatening condition complicating pregnancy, or the first months after delivery, characterized by acute or progressive, but generally reversible, LV systolic dysfunction and HF. Pathogenesis is mediated by a genetic predisposition, with titin variants as the more frequently mutations encountered, but is probably in large part determined by the central role of inflammation and autoimmune reactions.[64]

Sex hormones

Oestrogens exert a widespread protective effect on the cardiovascular system. The less intense inflammatory and immune-mediated response to myocardial injury has been linked with the lower incidence of myocarditis and cardiovascular disease in fertile women.[65] Women have a higher density of vascular oestrogen receptors, which contributes to protect against atherosclerotic degeneration,[66] enhance the production of nitric oxide with vasodilating and anti-inflammatory properties.[67] The lower activity of the renin–angiotensin–aldosterone system mediated by oestrogens might contribute to explain some sex-related differences in HF therapies.[68]

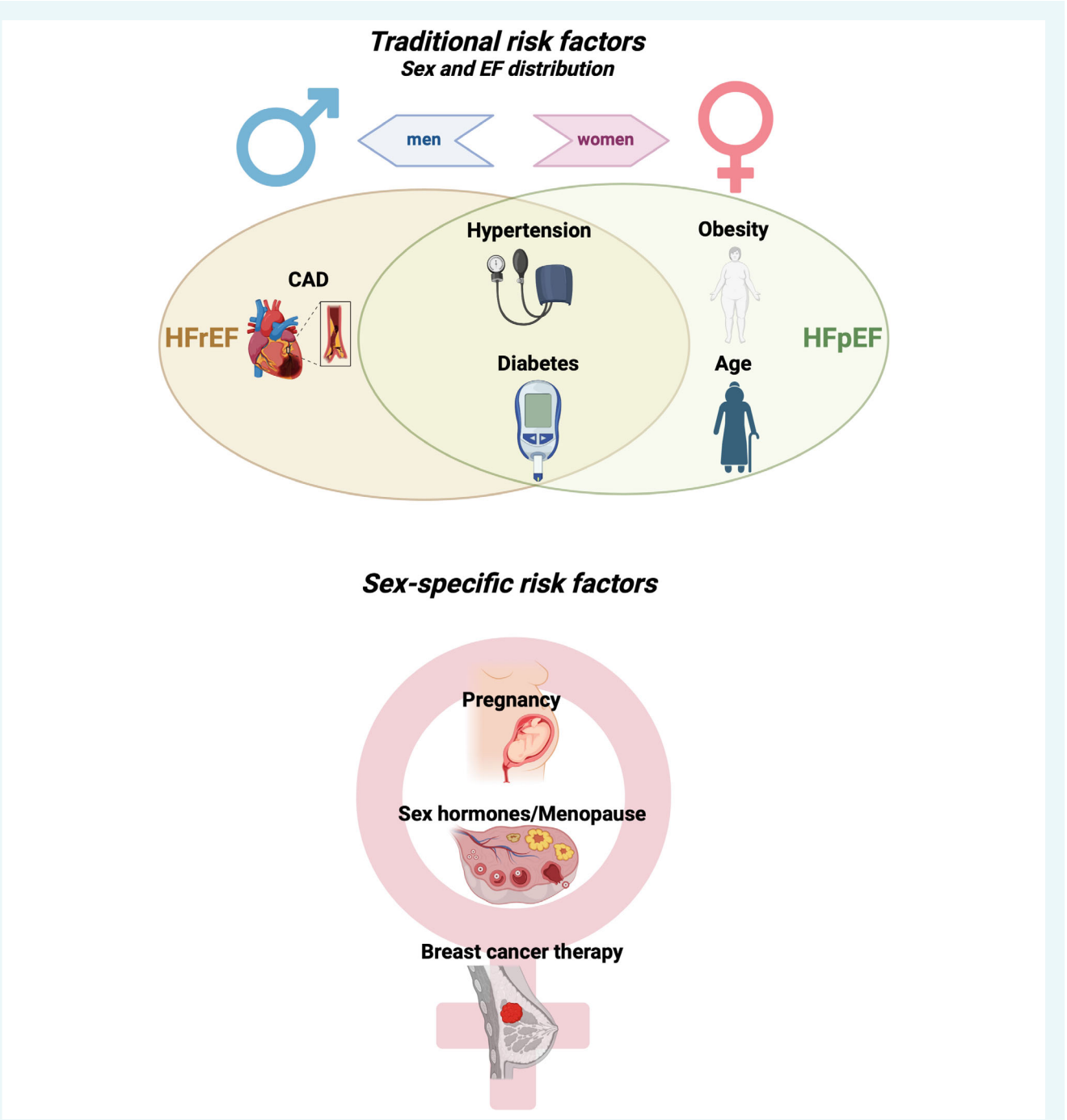


Figure 1 Main traditional and sex-specific risk factors involved in the pathogenesis of heart failure with reduced and/or preserved ejection fraction (HFrEF/HFpEF). CAD, coronary artery disease; EF, ejection fraction.

The loss of hormonal protective effects with menopause may predispose to the increasing prevalence of HF with ageing in women, and particularly of HFpEF, through different mechanisms. Poor activation of the endothelial nitric oxide pathway and release of pro-angiogenic factors are triggers of microvascular dysfunction.[69,70] In women there is also an immune-mediated predisposition to endothelial inflammation. Markers of inflammation are indeed more expressed in females compared with males.[71] Nevertheless, post-menopause replacement therapy with equine oestrogens and synthetic progestins has not demonstrated a protective cardiovascular effect in late post-menopausal women.[72,73] The same study, however, demonstrated a cardiovascular benefit of oestrogen replacement therapy when started in early post-menopause.

Overall and age-adjusted impaired diastolic dysfunction is more prevalent in women, in particular with ageing,[45,74] and it is

paired with a more altered ventriculo–arterial coupling.[75,76] An impaired ventriculo–arterial coupling might also involve the right ventricle–pulmonary circulation axis.[77] Although type 1 pulmonary hypertension, including the subtype associated with connective tissue disease, is more frequent in women, the severity of right ventricular impairment and of right HF is worse in men.[77,78] Finally, metabolic syndrome and obesity are more prevalent in women after menopause and are additional factors promoting the pathogenesis of HFpEF.[79] Early natural menopause, before 40 years of age, is associated with a higher individual cardiovascular risk, whereas this is uncertain after surgical menopause.[80]

Breast cancer therapy

Prolonged survival of women with breast cancer has led to a growing population exposed to the long-term cardiotoxic effects of anti-cancer therapies.[81,82] Cardiotoxicity manifests more frequently with HFrEF and the higher exposure in breast cancer compared to other sites is linked with the concomitant treatment with radiations and the use of multiple chemotherapeutic agents. In breast cancer, the use of anthracyclines and trastuzumab has also been correlated with a very high rate of diastolic dysfunction in subjects with normal or unknown diastolic function before initiating the treatment.[83]

Baseline cardiovascular risk stratification is pivotal in determining women at risk of cardiotoxicity and HF. Serial echocardiographic monitoring, including novel deformation imaging and repeated biomarker sampling, are useful to guide early recognition of anthracycline-induced cardiotoxicity.[84–88] Dexrazoxane and liposomal anthracyclines can be used for cardiotoxicity prevention in high or very high-risk patients.[89,90] Anti-neurohormonal HF therapy reduced the incidence of LV dysfunction in patients treated with combination of anthracyclines and anti-human epidermal growth receptor 2 (HER2) therapy, but data on primary prevention of overt HF are less robust.[91–93] HER2-targeted therapy (i.e. trastuzumab) is an alternative cause of LV dysfunction, with potential reversibility, increased by the combination with anthracyclines.[94–96] Endocrine therapy, that includes oestrogen receptor modulators and aromatase inhibitors, is associated with increased risk of metabolic syndrome, ischaemic heart disease but also HF.[97]

Biomarkers for the diagnosis of heart failure

Natriuretic peptides are released by the myocardium in response to stretch and promote natriuresis, vasodilatation, and myocardial relaxation. The natriuretic peptides in clinical use include B-type natriuretic peptide (BNP), the N-terminal pro-B-type natriuretic peptide (NT-proBNP), and mid-regional pro-atrial natriuretic peptide (MR-proANP). Concentrations of each of these natriuretic peptides tend to be higher in healthy women than in healthy men of a similar age.[98–102]

The precise mechanism for higher natriuretic peptide levels in women is not established, but is likely related to sex hormones. Investigators in large observational studies have identified

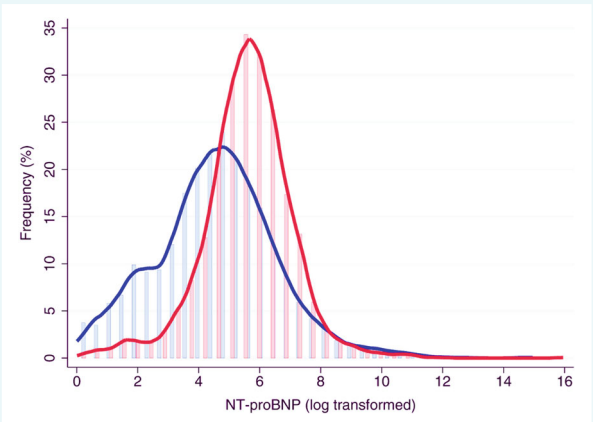


Figure 2 Distribution of N-terminal pro B-type natriuretic peptide (NT-proBNP) in the general population (i.e. free of heart failure) in both sexes. Blue, men; pink, women. Reproduced with permission from Suthahar *et al.*[105]

an association between hormone replacement therapy in women and increased natriuretic peptide levels,[99,103] whereas others have noted an inverse association between circulating androgen levels and natriuretic peptide levels.[103,104] In addition, the inverse relationship between NT-proBNP and obesity is more pronounced among females than males (*Figure* 2).[102,105]

However, sex-specific differences appeared to be less pronounced in the setting of acute dyspnoea and HF. Some studies have demonstrated that women with HF have similar or lower levels of natriuretic peptides than men.[106–108] This might be related to the higher relative prevalence of HFpEF in women than in men, which is associated with less-marked increases in natriuretic peptides than HFrEF.[109] Accordingly, when patients are stratified according to ejection fraction, women with acute HF tend to have higher levels than men.[109]

Despite the differences in natriuretic peptide levels between the sexes, their performance for diagnosing HF among acutely dyspnoeic patients in the emergency department is similar, and adjustment of cut-off points is not advised.[106–108]

Sex-differences in acute heart failure

There is a persisting low rate of sex-specific reporting in clinical studies on acute decompensated HF and a broad variability in sex distribution across registries, from 37% women in ALARM-HF to 52% women in ADHERE.[110–114] Each dataset reports that women are older and that LV ejection fraction is higher.[111–113] Sex differences in comorbidities and precipitating factors also characterize the acute setting.[111,113] Atrial fibrillation is reported as proportionally more frequent in women, while ventricular arrhythmias are more typical for men in acute HF registries.[111,113,114] Stress-induced cardiomyopathy is a cause of acute HF and has a nine-fold higher incidence in women compared with men.[115]

Specialist care is less frequent for women and this is consistent across continents—the UK National Confidential Enquiry into Acute HF Inpatient Deaths showed that 44% of women versus 55% of men (https://www.ncepod.org.uk/2018ahf.html) were admitted to cardiology wards, with less women admitted to cardiology or general intensive care units in the other main registries on acute HF. All registries showed lower rates of revascularization, device therapy and direct current cardioversion in women compared to men.[110–114] Nonetheless, mortality rates were similar between sexes in all studies, perhaps due to the confounding effects of older age and less pro-active management versus less CAD and higher LV ejection fraction.[111–114] Extending the timeline of follow-up after hospitalization for acute HF in the Get With The Guidelines-HF registry, women demonstrated lower adjusted 5-year mortality versus men. However, they experienced a significantly greater loss in survival time when compared with the median age- and sex-matched US population and had higher risk of 5-year rehospitalization.[116] Sex disparities have also been reported in cardiogenic shock due to acute HF. Women were treated more often conservatively, including the use of percutaneous mechanical circulatory support (MCS), and experienced higher in-hospital (30 days) but comparable 1-year mortality.[117–120]

Although the proportion of women with HF approaches half of all diagnosed patients, the disappointingly low rates of trial inclusion also affects acute HF trials, ranging between 20% and 40%.[121–123] As acute HF trials have shown largely neutral results, sex-related outcomes are not usually explored, but the EVEREST trial, which tested the effect of the vasopressin antagonist tolvaptan on long-term outcome in acute HF and was globally neutral, did show a trend towards favouring tolvaptan for women.[124]

Sex differences in pharmacological therapy

Pharmacokinetic and pharmacodynamics

Registry and post-hoc analyses from RCTs noted that women, differently from men, achieve the plateau of risk reduction with renin–angiotensin system inhibitors (RASi) and beta-blockers at lower than 100% of target doses, without any additional benefit at higher doses.[125–127] Studies on pharmacokinetics of classical anti-neurohormonal drugs demonstrated a more than two-fold higher plasma concentration of the drugs in women.[128,129] Digoxin has been associated with higher mortality risk in women in the DIG trial, but women displayed higher plasma concentrations of digoxin, although men were treated with higher doses.[130–132] Women were therefore more exposed to drug toxicity and drug-related adverse effects. In general, adverse effects appear to occur at a higher rate in women than men with all the HF medications.[127] Differences in pharmacokinetic of drugs may originate from differences in body composition, plasma protein binding, metabolizing enzymes and transporters, excretion activity, hormonal differences. Oral absorption can also be influenced by several mechanisms. However, despite these differences related to gender, they do not generate differences in drug absorption between sexes. Drug distribution depends on many variables. The different ratio between per cent body fat (higher in women) and body weight (lower in women) explains the faster onset and longer effect duration of lipophilic drugs and the more rapid and greater effect of hydrophilic drugs observed in women.[129,133,134] Different activity of metabolic liver enzymes, along with the differences in liver blood flow, and physiological lower glomerular filtration rate may determine significant gender differences in the metabolism and elimination of molecules. However, differences in renal excretion become trivial after normalization for body weight.[135] Finally, sex hormones have significant influences on the amount and activity of serum-binding globulins.[127,129,133–135]

Randomized controlled trials

With few exceptions, and despite similar eligibility in registry populations,[136] women have been under-represented in largest HF RCTs, raising concerns regarding generalizability of results.[137–139] No studies have been specifically dedicated to women nor defined thresholds for female inclusion in their design.

Despite the under-representation of women,[140–143] more recent and more representative RCTs and meta-analyses supported consistent benefit in women compared to men for treatment with beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers and mineralocorticoid receptor antagonists, with no concerns for differences in safety.[144–155]

Novel therapies have changed the management and perspectives of patients with HFrEF in the last years. Although US national policies advocate the appropriate representation of women in clinical research the limited recruitment of women in recent RCTs is still a burning issue, with persistent inclusion rates below 25%.

Regarding efficacy in HFrEF (*Figure 3*), in the PARADIGM-HF trial, sacubitril/valsartan determined a consistent mortality/morbidity reduction regardless of sex,[156] although in a subgroup analysis of the PROVE-HF trial, women exhibited more rapid NT-proBNP reduction and earlier LV reverse remodelling.[157] The impact of sodium–glucose cotransporter 2 inhibitors (SGLT2i) on mortality and HF events was comparable in females and males in the two landmark RCTs on HFrEF.[158,159] Pre-specified subgroup analyses did not identify different response according to sex for the two drugs vericiguat and omecamtiv mecarbil.[160–162]

In RCTs on HFpEF/HFmrEF the proportion of women is higher compared to RCTs in HFrEF, and this is explained by the differential epidemiology of HFpEF (*Figure 3*).[163] Among neutral RCTs on HFpEF, controversial data on treatment interaction by sex have been observed for mineralocorticoid receptor antagonists since only women showed survival benefit in a post-hoc analysis of the TOPCAT Americas, whereas no interaction by sex was found in a pooled data analysis of three large RCTs.[164,165] Differently from the PARADIGM-HF, in the pre-specified sex-based analysis of the PARAGON-HF study, only women appeared to benefit from treatment with sacubitril/valsartan (p for interaction = 0.017).[166] Underlying reasons for the different impact of treatment are

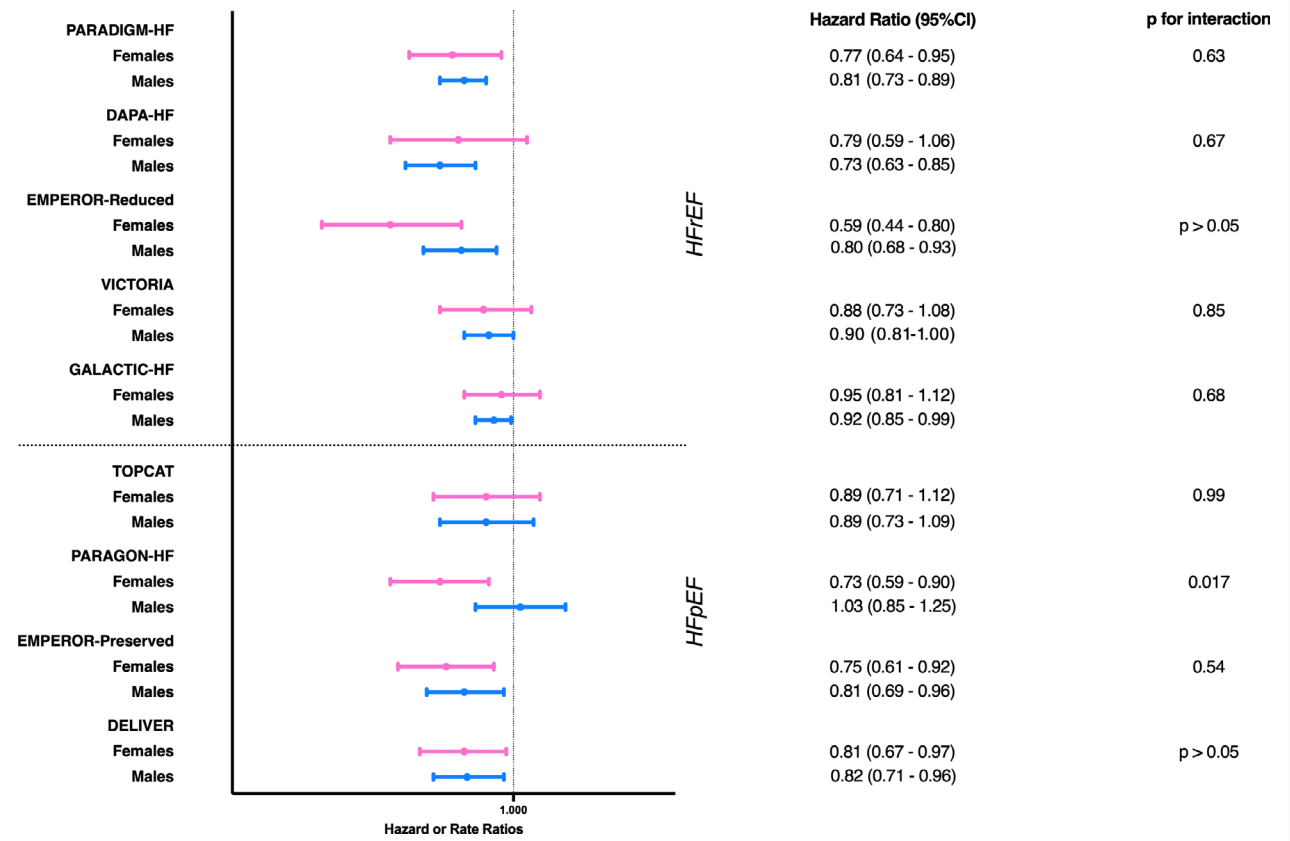


Figure 3 Recent pharmacological randomized controlled trials in heart failure: results (primary endpoints) in females versus males. Data from PARADIGM-HF were estimated. CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

unclear, it has been hypothesized a deficit in a cGMP-protein kinase G signalling pathway linked with lower natriuretic peptide levels observed in women.[167] Finally, benefit from SGLT2i was similar across sexes in both the major RCTs on HFpEF/HFmrEF.[168,169]

The borderline interaction for sex subgroup analysis observed in two large RCTs,[170,171] paired with the larger prevalence of iron deficiency in women,[172] claims for specific investigations on the actual benefit of iron supplementation in women with HF.

Finally, the importance of high-intensity medical implementation in hospitalized patients with acute HF was consistent across sexes in terms of feasibility, safety and risk reduction.[173]

Data from the real world

Data on the underuse of guideline-recommended therapies in women with HFrEF in real-world studies are discordant. Women are more likely treated with diuretics, probably due to the worse symptomatic status they present at index evaluation.[31,138,174–176] Several factors including older age, comorbidities, less specialty care and more deprived socio-economic status can contribute to affect the rate of prescription.[8,177–179] In the Swedish HF registry, the extensive adjustment for all these confounders limited the potential bias and demonstrated similar use of RASi and diuretics, higher use of beta-blockers and digoxin perhaps linked with the higher required doses in women to achieve successful rate control, but lower use of SGLT2i.[31,180]

Sex differences in non-pharmacological therapy

Implantable cardioverter-defibrillator

Implantable cardioverter-defibrillator (ICD) implantation rates for primary prevention of sudden cardiac death have been reported to be lower in women.[31,174,181–183] Besides the common reasons limiting implementation of guideline-directed medical therapy, higher ICD implantation-related adverse event rates have been observed in women which may also discourage clinicians from procedure referral.[184] ICD counseling seems also to be less frequently offered to women.[183] The representation of women in RCTs on primary prevention ICD has been even lower compared to pharmacological studies, leading to questions regarding the measure of the impact of ICD on overall survival and risk of sudden death in women (*Table 2*).[185–191,201] Conflicting results on efficacy were also

Table 2 Sex-differences in randomized controlled trials of implantable cardioverter-defibrillator and cardiac resynchronization therapy

Study	Specific population	Published (year)	Females (%)	Primary endpoint	Sex-specific outcome, HR (95% CI)	*p*-value for interaction
Implantable cardioverter-defibrillator						
MADIT-II[185]	Previous MI	2002	16	Mortality	Females 0.57 (0.28–1.18) Males 0.66 (0.48–0.91)	0.72
AMIOVIRT[186]	NICM	2003	29	Mortality	Not provided	Not reported
DEFINITE[187]	NICM	2004	29	Mortality	Females 1.14 (0.50–2.64) Males 0.49 (0.27–0.90)	0.18
DINAMIT[188]	Recent MI	2004	24	Mortality	Not provided	0.82
SCD-HeFT[189]	NYHA class II–III	2005	23	Mortality	Females 0.96 (0.56–1.61) Males 0.57 (0.73–0.93)	0.54
IRIS[190]	Recent MI	2009	23	Mortality	Not provided	0.85
DANISH[191]	NICM	2016	30	Mortality	Females 1.03 (0.57–1.87) Males 0.85 (0.64–1.12)	0.66
Cardiac resynchronization therapy						
MUSTIC[192]	NYHA class III, QRS >150 ms	2001	25	6MWD	Not provided	Not reported
MIRACLE[193]	NYHA class III–IV, QRS ≥130 ms	2002	32	NYHA class, QoL score, 6MWD	Not provided	Not reported
MIRACLE-ICD[194]	NYHA class III–IV, QRS ≥130 ms	2003	23	NYHA class, QoL score, 6MWD	Not provided	Not reported
COMPANION[195]	NYHA class III–IV, QRS ≥120 ms	2004	32	Mortality or all-cause hospitalization	Not provided	>0.05
CARE-HF[196]	NYHA class III–IV	2005	27	Mortality or CV hospitalization	Females 0.64 (0.42–0.97) Males 0.62 (0.49–0.79)	>0.05
REVERSE[197]	NYHA class I–II, QRS ≥120 ms	2008	21	HF clinical composite response	Females 0.75[a] (0.26–2.19) Males 0.69[a] (0.43–1.11)	Not reported
MADIT-CRT[198]	NYHA class I–II, QRS ≥130 ms	2009	25	Mortality or non-fatal HF event	Females 0.37 (0.22–0.60) Males 0.76 (0.59–0.97)	0.01
RAFT[199]	NYHA class II–III, QRS ≥120 ms	2010	17	Mortality or HF hospitalization	Not provided	0.09
SMART-AV[200]	NYHA class III–IV, QRS ≥120 ms	2010	32	Left ventricular reverse remodelling	Higher benefit in women vs. men	< 0.02

6MWD, 6-min walking distance; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; NICM, non-ischaemic cardiomyopathy; NYHA, New York Heart Association; QoL, quality of life.
[a]Odds ratio.

derived from previous studies.[202–204] Results of two meta-analyses grouping data from primary prevention ICD RCTs concluded there was an absence of survival benefit in women,[204–206] but with only 934 and 1145 women were included, confirming the limited current available evidence. Rates of appropriate ICD interventions, and of sudden cardiac death, are lower in women.[182,207,208] Underlying aetiology may play a role, since non-ischemic is more frequent than ischaemic cardiomyopathy in women and is less prone to major ventricular arrhythmias.[209] In the DANISH study, the risk of overall cardiovascular and non-sudden cardiovascular mortality was lower in women, and having an ICD had no impact on mortality nor sudden cardiac death irrespective of sex.[210] Besides the higher prevalence of non-ischemic aetiology, there are other reasons behind the different electrical variability, including the influence of sex-specific hormones.[211] Women are also less prone to the progression of myocardial fibrosis, and consequently of myocardial scar during cardiac magnetic resonance imaging.[212]

Cardiac resynchronization therapy

The sex gap in the implementation of device therapy, persists also for CRT (*Table 2*).[31,174,192–200,213] This is particularly concerning given that women generally exhibit better responses to CRT. Left bundle branch block and dyssynchrony are more common in females than in males, who also have a higher proportion of non-ischaemic cardiomyopathy and less severe fibrotic burden.[212,214] Better characteristics of women are paired with evidence of increased benefit derived from observational studies and RCTs sub-analyses, that involves symptoms, reverse remodelling and prognosis.[215–217] A recent study suggested that smaller body size and cardiac dimensions may be the predominant reason explaining the sex disparities in response to CRT.[218] Strategies for correct application of guideline recommendations on CRT, regardless of sex, are advised. In addition, in women less permissive QRS intervals may be appropriate for eligibility

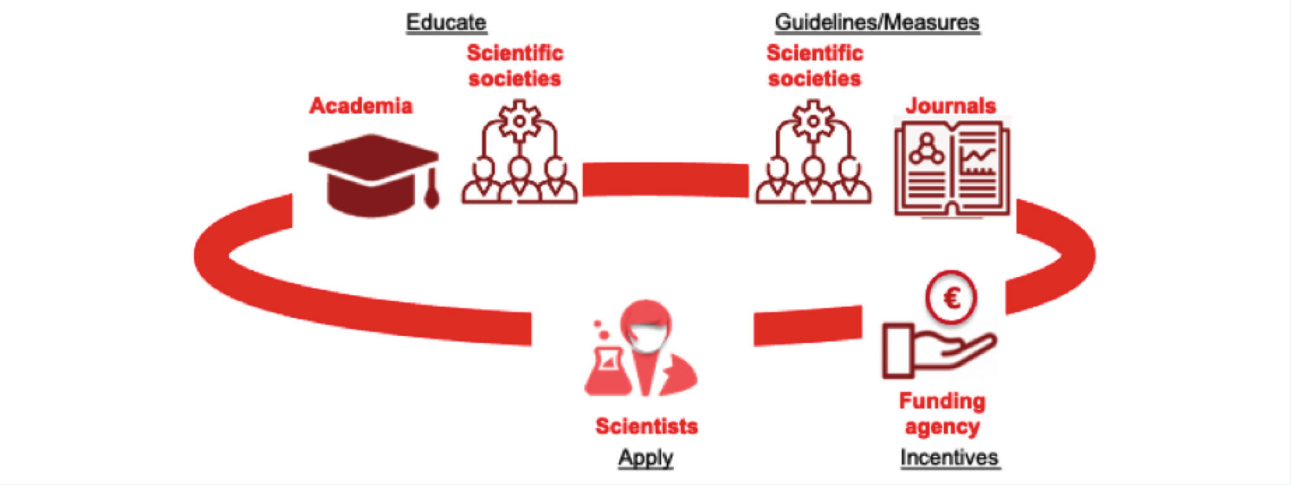


Figure 4 Raising awareness of the relevance to study sex-specific differences in heart failure via concerted action on the part of scientists, trial sponsors, universities, scientific societies, journal editors, peer reviewers, and funding agencies.

to treatment.[3,219] In an important individual-level meta-analysis, women but not men benefited from CRT at intermediate QRS prolongation.[214]

Transcatheter mitral valve repair

Similarly to pharmacological RCTs, rate of enrolment of women in the two RCTs testing transcatheter mitral valve repair for the treatment of secondary mitral regurgitation in HFrEF was low.[220,221] Differences were observed in the two RCTs in the magnitude of effect according to sex. Neutral results of the MITRA-FR were consistent in men and women in the subgroup analysis, whereas in the COAPT trial, even though women presented with more symptoms and more impaired functional capacity, the benefit gained by transcatheter mitral valve repair was less pronounced compared to men (hazard ratio 0.78; 95% CI 0.57–1.05 vs. hazard ratio 0.43; 95% CI 0.34–0.54, p for interaction = 0.002).[222] In large international registries, procedural success and association with mortality reduction was similar across sexes.[223]

Mechanical circulatory support and heart transplantation

Temporary and long-term MCS is guideline-indicated for patients with cardiogenic shock and end-stage HF.[3] Some sex differences with higher mortality of women treated with intra-aortic balloon pump were reported, however after multivariable adjustment, this was no longer statistically significant.[224,225] Similarly, during MCS with veno-arterial extracorporeal membrane oxygenation (VA-ECMO), as well as LV unloading with the Impella microaxial pump, no significant survival differences related to sex emerged, although women may have somewhat higher complication rates.[226–229] In peripartum cardiomyopathy and cardiogenic shock, immediate LV support with Impella CP and bromocriptine treatment were associated with LV recovery, whereas ECMO support appeared to be associated with less favourable outcomes.[230–232]

Durable MCS such as LV assist devices (LVAD) are increasingly used in patients with end-stage HF. In parallel to the higher rates of this condition in males, the LVAD implant ratio between males and females is around 4:1, suggesting underutilization and late referral.[233,234] Although there seemed to be a slightly higher complication rate in women, in recent years survival is not different between sexes after LVAD placement.[233,235] Nevertheless, LVAD implantation is also an option for severe peripartum cardiomyopathy in the absence of recovery during short-term MCS. Use of LVAD has led to haemodynamic stabilization and facilitated LV recovery in one third of these young female patients.[236]

Women are just as likely as men to survive after a heart transplant despite often getting poorer-quality donor hearts. Long-term results of heart transplants are equal for both men and women.[237]

Sex differences in cardiac rehabilitation

Cardiac rehabilitation programmes have been demonstrated to favourably impact the outcome and the quality of life of patients with HF.[238] In a previous meta-analysis, women were 36% less likely to enrol in a rehabilitation programme.[239] More recently, in the REHAB-HF trial enrolling patients ≥60 years old hospitalized for acutely decompensated HF, more than 50% were women. Benefit from rehabilitation was similar, or slightly better in women.[240] Nevertheless, exercise programmes are frequently underutilized by women[241–243] and adherence to prescribed rehabilitative sessions is lower, suggesting also that person-centred interventions are urgently needed to maximize the benefits derived from physical rehabilitation programmes.[244] Understanding these sex differences may help in developing more effective and tailored cardiac rehabilitation programmes for women with HF.

Conclusions, unmet needs and future perspectives

Extensive sex-mediated differences exist in HF that span throughout the overall spectrum of the disease (*Graphical Abstract*). Although this should lead to a dedicated approach to the understanding of their nature and for a more individualized treatment, a wide gap persists in research, pre-clinical studies, RCTs, and within clinical practice. HFrEF is more predominant in men, whereas HFpEF is more prevalent in women. This is mediated by the diversity in aetiological background and classical risk factors. Sex-specific risk factors exclusive for women, also have an essential role in the genesis of sex-related differences in HF. The existing evidence, which demonstrates similar benefits from pharmacological and interventional treatments for HF in both men and women, should incentivize the full implementation of all treatment strategies regardless of sex. Multiple strategies of action are strongly warranted to improve the future approach in the treatment of women with HF. A careful analysis, and a complete understanding, of the mechanisms behind the different characteristics of HF between sexes is key to progress towards the practical application of precision medicine. Hereto, awareness of the relevance to study sex-specific differences in HF should be raised via concerted action on the part of scientists, universities, scientific societies, journal editors, peer reviewers, and funding agencies (*Figure 4*). Inclusive strategies for promoting the early referral and the specialty care of women with symptoms suggestive of HF should be implemented in practice. Education to sex neutral implementation of treatments should also cover the knowledge of the fields of different or incremental benefits that women can gain from treatments. Specific thresholds for inclusion of women in future RCTs, or dedicated RCTs, are definitively needed to allow powered sex-based analysis for creating rigorous evidence on the sex disparities, or equalities, for treatments.

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