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REVIEW

Sex, drugs, and heart failure: a sex-sensitive review of the evidence base behind current heart failure clinical guidelines

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Abstract

Heart failure (HF) is a complex disease, almost as common in women as in men. Nonetheless, HF clinical presentation, prognosis, and aetiology vary by sex. This review summarizes the current state of sex-sensitive issues related to HF drugs included in treatment guidelines and suggests future directions for improved care. Heart failure presentation differs between female and male patients: females more often show with hypertensive aetiology and the preserved ejection fraction phenotype, while men more often show ischaemic aetiology and the reduced ejection fraction phenotype. Yet the HF clinical guidelines in Europe, the United States, and Canada do not reflect the sexual dimorphism. Further, in randomized clinical trials of HF medication, women are largely underrepresented, typically consisting of ≥70% men. Given the knowledge that some adverse drug reactions, such as torsade de pointes and angiotensin-converting enzyme inhibitor-induced cough, occur more frequently in women, we emphasize the need to test medications thoroughly in both sexes and explore sexual dimorphisms. To better represent all of the targeted patient population and provide better care for all, two kinds of change must come about: recruitment methods to randomized clinical trial samples need to evolve and the participation needs to seem more attractive to women.

Keywords Heart failure; Sexual dimorphism; Randomized clinical trial; Clinical guidelines

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Introduction

Heart failure (HF) is a complex cardiovascular (CV) syndrome, for which the global burden of disease is increasing while the prognosis for patients remains poor.[1,2] The global prevalence of HF is over 25 million, and increasing.[3] In Europe and North America, approximately 75% of HF cases are of hypertensive or ischaemic aetiology. This increasing prevalence is partly due to improved survival.[1,2] The long-term prognosis for HF patients is poor and patients present multiple co-morbidities.[1] Mortality is high among HF patients, and more than 50% of HF patients are expected to die within 5 years of diagnosis.[1,4]

Observational studies using registry, community, or hospital data indicate that the incidence of HF in Europe and North America is similar in both men and women.[5,6] On the other hand, there may be significant differences between the sexes regarding clinical presentation, safety, and efficacy of treatment, as well as prognosis. Because women form approximately half the HF population, it is extremely concerning that women are underrepresented in randomized clinical trials (RCTs) and that investigations in the subgroup of women and sex-drug interactions are likely underpowered in RCTs.[7,8] Further, because women are underrepresented in the initial phases of drug development, they are also largely ignored in defining drug dosing.[9] Women have a higher risk of experiencing some adverse drug reactions, and more severe adverse drug reactions, than men.[10] This could be the result of differences in drug pharmacokinetics (absorption, distribution, metabolism, excretion[10]), pharmacodynamics (PD), or behaviour (such as drug compliance). Sex differences in drug metabolism by the cytochrome P450 isoenzymes have been

the focus of many studies[11]; yet their clinical impact is uncertain. Also, women's drug response is affected by hormonal levels, which vary during a woman's life.[12] Thus, the current 'one size fits all' approach puts underrepresented patient groups, including women, at increased risk due to under-investigated differences in pharmacokinetics and PD.[9]

This review aims to adapt a sex-sensitive perspective while depicting the current state of chronic HF research and the evidence base of existing clinical practice guidelines.

Sexual dimorphism in heart failure

There are well-established sex differences in the clinical presentation of HF, and the risk factor effect size varies with both sex and disease phenotype. For example, women tend to be older than men at diagnosis[13] and women tend to have higher body mass index.[14,15] Diabetes is a stronger risk factor for the reduced ejection fraction phenotype (HFrEF) in women than in men.[16] While a diabetic woman has three times the risk of a non-diabetic woman to develop ischaemic heart disease and subsequent HF, the risk is only doubled in diabetic men compared with non-diabetic men. Overall, women with HF are more likely than men to present with hypertension[13–15,17] that leads to a pattern of pressure overload concentric cardiac hypertrophy and ultimately HF with preserved ejection fraction (HFpEF).[6,17] The most frequent HF aetiology in men is a prior myocardial infarction that leads to a pattern of volume overload eccentric cardiac hypertrophy and dilatation and eventually HFrEF.[18,19] Ultimately, female sex in itself is considered a protective factor in HF mortality. This was clearly established in a large meta-analysis.[20] Suggested mechanisms behind this effect have generally included women's generally higher left ventricular ejection fraction (LVEF), and the fact that women tend to be less likely to present ischaemic heart disease-caused HF.[14] Yet data from most cohorts have shown otherwise and found that the sex-outcome associations were independent of LVEF and HF aetiology.[21,22]

In addition to differences in HF aetiology, the phenotypic differences in HF presentation and prognosis between women and men may be the result of progressive, sex-specific changes in cardiac and vascular physiology. This process of 'CV ageing' is the end result of years of interaction between traditional risk factors, such as hypertension, and an individual's intrinsic predisposition to develop CV diseases, such as inherited (genetic) factors.[23,24]

With ageing, the heart progressively develops sex-specific patterns of remodelling. In women, HF aetiology is often hypertension, and women demonstrate greater body-size adjusted increases in LV wall thickness and concentric remodelling than men, which predispose to myocardial stiffness and diastolic dysfunction. Furthermore, the age-related increase in LVEF is more pronounced in women.[24] In addition, animal models indicate that female rats are more likely to develop concentric myocardial hypertrophy.[25] These differences in LV remodelling are consistent with the highest likelihood of women to present HFpEF. On the other hand, men are more likely to show age-related increases in LV cavity dimension and LV systolic dysfunction, which are hallmarks of HFrEF.[24] Consistent with these observations, male rats generally develop eccentric myocardial hypertrophy and fibrosis.[25]

Despite one sex being more represented in each specific phenotype, both types of HF occur in patients of both sexes. However, if women with HFrEF have different underlying disease processes compared with men with HFrEF, this may contribute to a difference in efficacy between therapeutic interventions. This argues for a differentiation in treatment not only depending on phenotype but also on sex.

Advances in the treatment of HF, and other CV diseases, have lowered the HF mortality rate, indicating that HF patients, especially males, live longer.[17] Despite these advances, men still tend to have a worse prognosis than women. A register study of 32 028 HF patients in Sweden 1987–2003 showed a 63% decline in 3-year mortality for ischaemic HF males aged 35–64 during 1999–2001 compared with 1987–89.[17] The decline in non-ischaemic HF males for the same periods was 50%. The 3-year mortality rate for women aged 35–64 decreased by 47% for ischaemic aetiology and 37% for non-ischaemic, for the same years. The study also showed several interaction effects involving sex. Sex and year of hospitalization has a significant interaction effect on survival, with the strongest survival improvement seen in younger male patients. The sex difference decreased with increasing age and interaction between sex, year of hospitalization, and age was also significant. Male 3-year survival has improved more than female for both ischaemic and non-ischaemic aetiology, but females still show better survival than males, and ischaemic aetiology does not seem to be the key.

Death registry data from seven European countries showed that the absolute number of female HF deaths per year was approximately double that of male.[26] However, the age at death was on average 5 years older among women compared with men and when the death rate was age-standardized, the rate for women was consistently lower than the rate for men.[26] Presumably, older women were more likely to have developed age-related co-morbidities contributing to the mortality risk.[27] As most regression analyses of time to event in HF adjust for age, age alone cannot explain all the variation in women's hazard ratios.

Approximately half of HF deaths are due to sudden death, or arrhythmia.[28] Among the causes for ventricular arrhythmia in HF patients are underlying structural disease, mechanical factors, neurohormonal factors, ischaemia, and drugs. In Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), a study of 7141 acute

decompensated HF patients of which 34% women,[29] male sex was shown to be a risk factor for sudden cardiac death and tachycardia in both HFrEF and HFpEF.[30,31] The higher risk of sudden cardiac death in men compared with women in this population of individuals with decompensated HF has also been observed in patients with chronic HF.[32]

Pharmacological treatment of heart failure

At baseline in the ESC-HF-LT registry, 89.2% of patients used angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), 88.9% used beta-blockers, 60.9% used statins, and 8.4% used ivabradine.[1] Less than a third (28.8%) of the registry patients were women. In the clinical setting, both men and women will present as HF patients and therapeutic drugs will be administered to patients of both sexes. Clinical guidelines based on results from RCTs give recommendations on the management of HF. Due to the inherent differences dictated by sex in HF aetiology and clinical presentation, HF patients may benefit from sex-specific recommendations. Sex differences are also relevant for PD as the process depends partly on sex hormones, which may affect drug efficiency, and consequently effective dosage.[27] In addition to differences in efficacy, there are safety issues, with as many as two-thirds of drug-induced torsade de pointes occurring in women, highlighting different tolerability and possibly drug metabolizing pathways between sexes. Women also have a higher risk of ACEI-induced cough.[33]

Heart failure with reduced ejection fraction has seen the most progress with respect to research and development of therapeutic interventions. RCTs have shown significant reductions in mortality and hospitalizations with the use of ARBs, ACEIs, beta-blockers, mineralocorticoid receptor antagonists, and angiotensin receptor neprilysin inhibitors in HFrEF patients.[34]

Advances with respect to HFpEF have not been as clear, and RCTs have yet to show consistent results of effective therapies targeted to HFpEF.[6,34] RCTs testing ARBs, ACE inhibitors, and beta-blockers have shown inconclusive results in HFpEF patients. Data from the TOPCAT trial have suggested a potential benefit of spironolactone in HFpEF in patients randomized in the Americas, with significant reductions in CV mortality and HF hospitalizations, but most guidelines have not routinely recommended its use because the reduction in the overall population was not significant.[35]

Treatment recommendations in clinical guidelines: heart failure with reduced ejection fraction

The latest versions of the clinical guidelines for diagnosis and treatment of chronic HF issued by the European Society of Cardiology,[6] the American Heart Association,[36,37] and by the Canadian Cardiovascular Society[38,39] make recommendations for the management of HF patients according to LVEF and HF functional class. Guidelines state that beta-blockers and ACE inhibitors should be started immediately after diagnosis and, in patients with EF $\leq$ 35%, complemented by an aldosterone antagonist. Large RCTs have shown that ACEIs reduce mortality and morbidity in HF patients regardless of degree of symptoms.[37]

Studies Of Left Ventricular Dysfunction (SOLVD) included 20% women when testing enalapril, but no sex-stratified analyses were reported in the main article.[40] CONSENSUS was a small (n = 253) Scandinavian RCT where 29% of participants were female.[41] The group treated with enalapril had significantly fewer deaths, but no sex-stratified analyses were presented in the main article. To our knowledge, none of the sub-analyses done in CONSENSUS has focused on sex differences. Yet a subsequent meta-analysis of ACEI trials in HF showed consistent benefit between women and men.[42] In addition, a sub-analysis of sex differences in adverse effects of enalapril in the studies of left ventricular dysfunction RCT showed that women reported more adverse effects than men, especially in the treatment arm, which is not mentioned in the treatment guidelines.[33] Treatment with ACEIs has been connected with increased risk of angioedema, especially in women.[37] This emphasizes the need for implementing sex-stratified analyses in the main methodology of ACEI trials.

The clinical trial ATLAS tested a high dose vs. a low dose of an ACEI in 3164 individuals, although only 20% were women.[43] Although the primary endpoint of all-cause mortality was not significantly different between treatment groups (P = 0.128), the secondary endpoint of death or hospitalizations was lowered in the high-dose group. Interestingly, in analyses stratified by sex, the high-dose lisinopril showed a beneficial effect on all-cause mortality or any hospitalization only in men (P = 0.053).

Underlying the recommendation for β-blocker use in HFrEF are the RCTs Metoprolol CR/XL Randomized Intervention Trial-HF (MERIT-HF), CIBIS II (Cardiac Insufficiency Bisoprolol Study II) COPERNICUS, and SENIORS. MERIT-HF enrolled 3991 participants and stopped early after 1-year follow-up. Significant treatment effect {relative risk [RR] 0.66 [95% confidence interval (CI) 0.53–0.81]} was reported for the full study population. Sex-stratified analyses showed that the treatment effect was significant in both men and women.[44,45] CIBIS II reported sex-stratified results, independent treatment effect RR 0.53 (95% CI 0.42–0.67) for men and RR 0.37 (95% CI 0.19–0.69) for women.[46] COPERNICUS tested the effect of beta-blocker treatment in severe chronic HF and found a significant treatment effect in both sexes on both endpoints 'Death or hospitalization for cardiovascular reason' and 'Death or hospitalization for HF'.[47] Of the 2289 participants, one-fifth were women. Another clinical trial testing the effect of a beta-blocker on mortality and hospitalization for CV reasons (SENIORS) recruited elderly patients

that resulted in a higher proportion of female participants (37%). A significant treatment effect on the primary endpoint 'Death or cardiovascular hospital admission' was detected in women only.[48]

The recommendation for treatment with aldosterone antagonists is based on two trials, Randomized Aldactone Evaluation Study (RALES) and Eplerenone in Mild Patients Hospitalization And SurvIval Study-HF (EMPHASIS-HF)[49,50] RALES tested spironolactone vs. placebo in 1663 participants, of which only 27% were women. Results showed better survival with spironolactone for both male and female subgroups, but adverse events were only analysed in the full sample and in men. EMPHASIS-HF tested eplerenone vs. placebo in 2743 participants including only 22% women, and results showed overall beneficial effect of eplerenone on CV death or HF hospitalization. Sex-stratified analysis of treatment effect was reported, showing a significant treatment effect on CV death or HF hospitalization in both sexes.[51]

According to guideline recommendations, patients intolerant to ACE inhibitors are to be prescribed ARBs. Valsartan Heart Failure Trial (Val-HeFT) tested an ARB against placebo and also found a significant treatment effect in men only.[52] However, the CHARM program tested an ARB against placebo in three different trials and found no difference in treatment effect between the two sexes.[53] Nevertheless, women had a significantly lower all-cause mortality. Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) tested high vs. low dose of an ARB and found a beneficial effect of the higher dose in men only.[54]

The new combination agent, valsartan/sacubitril (LCZ696), is recommended in replacement of ACEI or an ARB in patients who remain symptomatic despite standard drug therapy. Valsartan/sacubitril is an angiotensin receptor neprilysin inhibitor, that is, a composite drug consisting of an ARB and a neprilysin inhibitor. Valsartan/sacubitril was tested against enalapril, an ACEI, on the composite outcome of CV death or HF hospitalization in 8399 HFrEF patients. Analyses showed a beneficial effect of valsartan/sacubitril in both sexes for the composite outcome, but adverse events were not analysed stratified by sex.

Digoxin is used in HF patients to reduce the risk of hospitalization.[6] Yet as the RCTs supporting these benefits predates the use of most drugs and all devices now commonly used to treat HF, its current benefits are uncertain and its place in HF treatment is more limited. The available literature on sex differences in response to digoxin is narrow, which explains why sex-specific treatment guidelines are lacking. Rathore *et al*.[8] concluded from a sub-study of the Digitalis Investigation Group trial that women with HF who were randomly assigned to digoxin had a higher death rate than women randomized to placebo. A follow-up retrospective analysis of the Digitalis Investigation Group study provided further insight into this observation and highlighted that this association may have been attributable to modestly higher digoxin concentrations in women than in men,[55] which have been associated with an increased risk of death.[56] Specifically, women with serum concentration 1.2–2.0 ng/mL had a significant increase in death of 33%.[55]

Several studies cited in the guidelines, investigating several types of treatments, have under closer inspection revealed significant treatment effects in women only. One such trial is Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which showed a reduction of all-cause mortality in women only and a reduction of 'CV death or CV hospitalization' in men only, although neither interaction terms were significant (all-cause mortality: $P = 0.44$; CV death and CV hospitalization, $P = 0.08$).[57]

Diuretics are commonly administered to manage fluid retention in HF patients. However, their effects on mortality and morbidity have not been studied in large RCTs.[6] Dose is determined according to weight, previous use/dosing of diuretics, renal function, and symptoms of congestion, with no sensitivity to sex.

Treatment recommendations in clinical guidelines: heart failure with preserved ejection fraction

The data supporting the benefit of any drug to treat HFpEF are much more limited than for HFrEF, and consequently guidelines are briefer. HFpEF deaths are more often non-CV deaths compared with HFrEF deaths, and patients should be conscientiously screened for co-morbidities. The majority of treatments given to HFpEF patients are aimed at symptoms, risk factors, and co-morbidities.[36] Digoxin has shown inconclusive effects in HFpEF patients and is recommended with caution. American Heart Association guidelines recommend blood pressure control using ACE inhibitors, ARBs, and beta-blockers, and European Society of Cardiology guidelines recommend treatment aimed towards increasing patients' quality of life.[6]

Common for the three sets of guidelines is that the evidence base consists of RCTs where treatment effects and adverse events either have not been analysed with attention to sex or the recommendations do not reflect the sex-specific results. Further, when analyses stratified by sex are performed, the power of such subgroup analyses has not been ascertained. Clinical trials are costly, and investment in CV drug development shows a declining trend,[58,59] with pressure to minimize the sample size. Because RCTs' power calculations are conducted for the full patient sample, subgroup samples are often too small to provide reliable results. *Table 1* lists the key RCTs referenced in either set of guidelines. The PARADIGM-HF[60] trial is the largest study listed ($n = 8399$), with only one-fifth of the sample as women. Because the disease profile varies between men and women, the inclusion criteria may by design be favouring one sex over the other, and too often result in a younger, predominantly male study

Table 1 Frequency and percentage of women in randomized clinical trials in heart failure (HF) patients 1985–2016, referenced in guidelines for management of HF

Study	Drug[a] (type)	HF phenotype	Year	Sample *n*	Women *n* (%)	Sex-stratified analyses	Treatment effect estimates stratified analyses[b]
I-PRESERVE	Irbesartan (ARB)	HFpEF	2002–6	4133	2480 (60%)	Yes	Similar and insign. treatment effect estimates in both sexes
PARAMOUNT	LCZ696 (ARNI) vs. valsartan (ARB)	HFpEF	2009–12	301	170 (56%)	Yes	Sign. treatment effect only in women
TOPCAT	Spironolactone (AA)	HFpEF	2006–13	3445	1775 (52%)	Yes	Women better health-related QoL at baseline but sex was not predictor of longitudinal change in QoL
ATLAS	Lisinopril (ACEI)	HFrEF	1992–97	3164	648 (20%)	Yes	Sign. lower all-cause mortality in men, sign. lower 'death or any hospitalization' in both sexes
CONSENSUS	Enalapril (ACEI)	HFrEF	1985–86	253	75 (29%)	No	—
COPERNICUS	Carvedilol (β-blocker)	HFrEF	1997–2000	2289	469 (20%)	Yes	Similar and sign. risk reduction for 'death or CV hospitalization', and 'death or HF hospitalization', in both sexes
EMPHASIS-HF	Eplerenone (AA)	HFrEF	2006–10	2743	611 (22%)	Yes	Sign. higher risk of 'CV death or HF hospitalization' in men compared with women
EPHESUS	Eplerenone (AA)	HFrEF	1999–2002	6642	1918 (29%)	Yes	All-cause mortality reduction only sign. in women. 'CV death or CV hospitalization' only sign. reduced in men
HEAAL	Losartan (ARB)	HFrEF	2001–9	3846	1155 (30%)	Yes	Sign. lower event rate for higher drug dose in men only
OVERTURE	Enalapril (ACEI) vs. omapatrilat (NEP + ACEI)	HFrEF	2000–2	5770	1212 (21%)	Yes	No sign. benefit of omapatrilat over enalapril in either sex
PARADIGM-HF	LCZ696 (ARNI) vs. enalapril (ACEI)	HFrEF	2009–14	8399	1832 (22%)	Yes	Similar sign. risk reduction for primary endpoint in both sexes
RALES	Spironolactone (AA)	HFrEF	1995–98	1663	446 (27%)	Yes	Lower mortality for both men and women, but adverse events not analysed in women
SAVE	Captopril (ACEI)	HFrEF	1987–92	2231	390 (18%)	No	—
SENIORS	Nebivolol (β-blocker)	HFrEF	2000–3	2128	785 (37%)	Yes	Sign. lower risk of primary endpoint in women only
SHIFT	Ivabradine (I_f blocker)	HFrEF	2006–10	6505	1535 (24%)	No	—
SOLVD-TREATMENT	Enalapril (ACEI)	HFrEF	1985–90	2569	514 (20%)	No	—
TRACE	Trandolapril (ACEI)	HFrEF	1990–94	1749	490 (28%)	No	—
Val-HeFT	Valsartan (ARB)	HFrEF	1999–2001	5010	1002 (20%)	Yes	Sign. treatment effect in men only
CHARM—OVERALL	Candesartan (ARB)	HFrEF & HFpEF	1999–2003	7601	2398 (32%)	Yes	Women had sign. lower all-cause mortality. No difference in treatment effect between sexes
—ALTERNATIVE	Candesartan (ARB)	HFrEF	1999–2003	2028	648 (32%)		Women had sign. lower all-cause mortality
—ADDED	Candesartan (ARB)	HFrEF	1999–2003	2548	535 (21%)		Women had sign. lower all-cause mortality
—PRESERVED	Candesartan (ARB)	HFpEF	1999–2003	3023	1209 (40%)		Women had sign. lower all-cause mortality

AA, aldosterone antagonist; ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker neprilysin inhibitor; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; I_f, funny channel inhibitor; NEP, neutral endopeptidase; QoL, quality of life.

[a]If only one drug is listed, drug was tested against placebo.

[b]Unless otherwise specified, outcome tested is the study primary endpoint. Assessment is given from the tested drug or dose's perspective, for example, 'sign. lower mortality in women' = for the women subgroup, significantly lower mortality in the treatment arm.

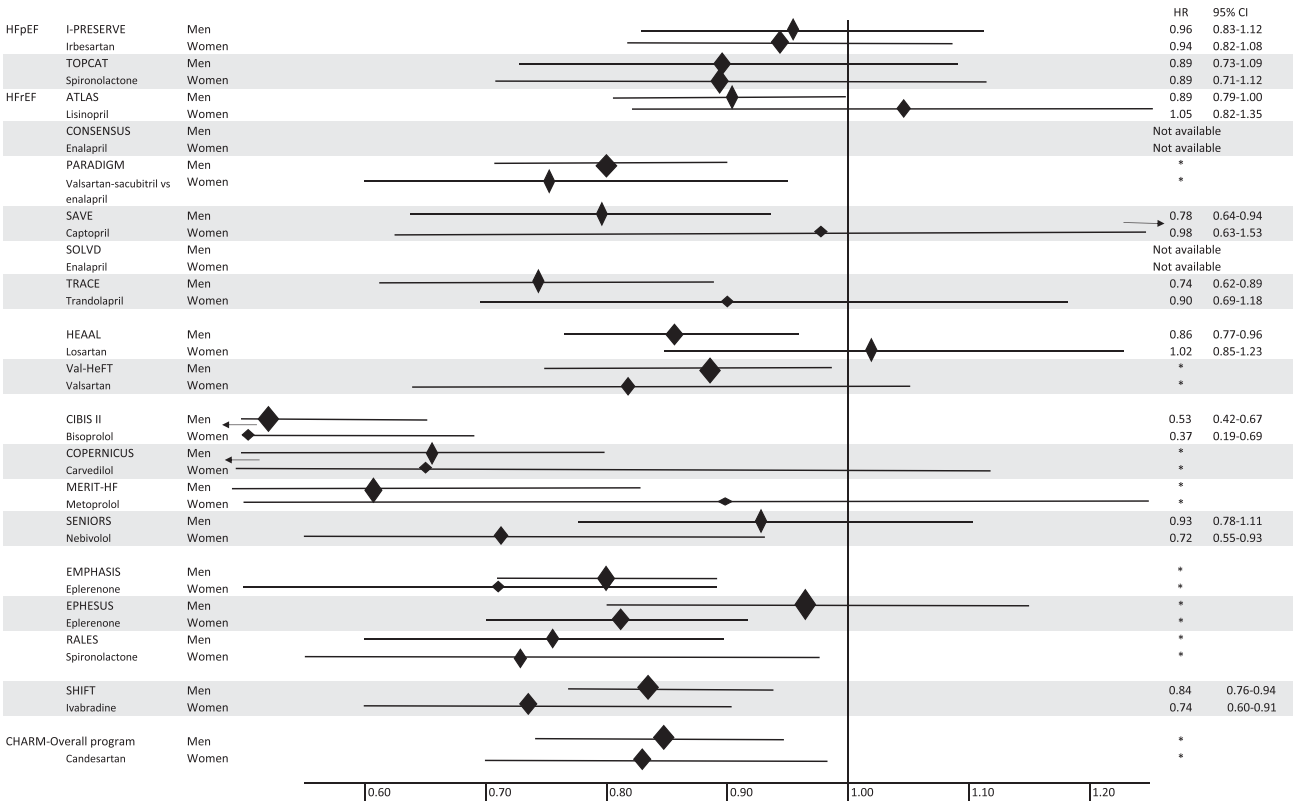
sample.[27,61] Elderly tend to have more co-morbidities, which makes them less attractive for trials that generally aim for sample homogeneity,[27] and may contribute to the lesser success in drug development for HFpEF relative to HFrEF. HFpEF studies will more likely favour a higher percentage of women, for example, I-PRESERVE[62] (60%), TOPCAT[63] (52%), and PARAMOUNT[64] (56%). We have captured in *Figure 1* the efficacy evidence derived from the listed clinical trials stratified by sex. Studies where the inclusion rate of women does not mirror the prevalence in the general population suffer from sample selection bias, where the participants of an RCT are not representative of the patient population, but rather a subgroup of the patient population defined by the inclusion and exclusion criteria of the trial.[65] Such bias can greatly hamper the generalizability of the RCT results.

Just as concerning is that RCTs are not powered to detect sex–drug interactions, to test the benefit in the subgroup of women, or to identify a drug that would only be effective in women. Let us consider a clinical trial sample including 30% women, and for which the number of women is too small for separate analysis. If the drug has an effect only in women, then it is likely that the overall trial results will be of no effect. If the effect only exists in men, however, the overall trial result will likely be positive as the null effect in women may be overshadowed by the effect seen in men. As a proof of principle, we performed data simulations for a 1:1 placebo controlled RCT with 5000 study participants including 30% of women for a drug causing a 25% reduction of the primary outcome at the term of the trial. Each simulation can either be a success = a significant drug effect, that is, a reduction in the primary outcome, is detected, or a failure = no significant effect is detected. The simulation was run 25,000 times for each of the two scenarios. In a situation where the benefit is only occurring in women ($HR_f = 0.75$) but not in men ($HR_m = 1.0$), the study was successful at detecting an overall drug effect 55% of the time. If the benefit was only in men ($HR_m = 0.75$) but not in women ($HR_f = 1.0$), then the overall study was successful 90% of the time. In this latter scenario, the sex-by-treatment interaction effect was only found to be significant 68% of the time.

Summary and future perspective

In the present review, we have revisited the current evidence base underlying clinical guidelines for HF with a sex-sensitive

Figure 1 Forest plot depicting the sex-stratified main endpoint results of randomized clinical trials in heart failure referenced in guidelines for management of heart failure. The presented trials are those referenced in clinical guidelines, for which sex-stratified results were available, in the main or subsequent RCT publications.



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perspective. Although not a systematic literature review, we have focused on the articles upon which the current HF clinical guidelines in the USA, Canada, and Europe are based, specifically looking for sex-specific evidence. HF is a heterogeneous disease in terms of aetiology, clinical presentation, and prognosis as well as progression. Survival rates have increased over the last 30 years, and consequently HF patients spend more time alive with the disease. Therapeutic treatment for HFrEF has enabled important progress both in terms of disease progression and mortality, while an effective treatment for HFpEF remains to be found. Nevertheless, there are HF patients of both sexes in both HF types, and patients of both sexes use the therapeutics available to them. Further, the clinical guidelines on treatment of HF in both men and women are constructed using results from RCTs, which often include only 30% or less women. The reason for the low percentage of women is multifaceted, but one of the factors is the restrictions put on women entering RCT that often leads to a homogeneous sample with limited hormonal fluctuation,[27] while women present a more heterogeneous HF disease than men.

The main incentive to increase the number of women in HF RCTs is to enable a systematic assessment of drug safety and efficacy in the full target population, instead of one that is dictated by the effect in men. In addition to differences in clinical presentation between the two sexes, there are biological differences that may lead to different responses to the same drug.[66] Thus, verifying effects in both sexes should be considered an essential part of the clinical testing process.

Both the US National Institute of Health and the Canadian Institute of Health Research have tried to address the sex gap in medicine by adding a sex/gender requirement to all applications for funding. As health care advances towards personalized medicine, the current lack of sex-specific medicine will have to be solved, or it will become a roadblock. Similar to how advertisement agencies adapted to customer desires in the 1960s, recruitment strategies and research methodology will have to adapt to attract and maintain women's interest in clinical trials participation. While sex and gender are not synonymous, they are often mistakenly used in that manner. Sex is a biological characteristic (male or female) while gender refers to a range of socially constructed characteristics related to roles, behaviours, and identity. We suggest that clinical trial recruitment strategies assess the approaches that are sensitive to gender roles and social structures as they have previously been successfully established in advertisement strategies. Women perceive greater risks and smaller benefits than men from participating in RCT, and because women according to gender roles tend to be more risk-averse than men, this discourages participation.[67] Thus, the benefits of participation, for example, close monitoring of health changes, must be emphasized. Additional strategies should also include to target advertisement of clinical trials in places frequented by women, to include and display female researchers working in the clinical trial,[68] and to provide transportation to and from study visits.[69] In addition, in order to provide the necessary sex-sensitive evidence for treatment efficacy, future studies may have to consider establishing predetermined target female ratios.

Conflict of interests

Drs. Tardif and Dubé have an equity interest in DalCor. Dr. Tardif has received research support from Amarin, AstraZeneca, DalCor, Eli-Lilly, Hoffmann-LaRoche, Merck, Pfizer, Sanofi, and Servier, and honoraria (to his institution) from Hoffmann-LaRoche, Pfizer, Servier, and Valeant. Dr. Dubé has received research support from AstraZeneca, DalCor, Pfizer, Servier and honoraria from DalCor.

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