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RESEARCH ARTICLE

Sex-based differences in chronic heart failure: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Sex-based disparities in patient enrolment and treatment effects in heart failure (HF) randomized controlled trials (RCTs) have been reported. We aim to systematically analyse sex-based enrolment and treatment effect differences in HF RCTs over time.

Methods RCTs enrolling patients with chronic HF were systematically searched on PubMed-MEDLINE. Eligible trials included pharmacological or device-based interventions with a hard primary endpoint (mortality and hospitalization) and reporting enrolment of women. Sex-specific treatment effects (hazard ratio [HR] or risk ratio [RR]) were extracted. Meta-analyses were performed using random-effects models, and pre-specified subgroup analyses were performed.

Results A total of 56 RCTs (39 drug, 17 device) were included. The pooled proportion of women enrolment was 27.0% (95% confidence interval [CI]: 22.0%–32.4%) in drug trials and 25.3% (95% CI: 21.0%–29.9%) in device trials. Women were more underrepresented in HF with reduced ejection fraction (HFrEF) than in HF with preserved EF (HFpEF) trials (21.0% vs 49.6%, $P < .001$). Among drug trials reporting sex-specific effects, the pooled sex interaction for RCTs reporting HR was 0.94 (95%CI 0.89–1.01) and RR was 0.81 (95% CI 0.68–0.96), suggesting potentially greater benefit for women. No interaction was observed between HFrEF and HFpEF trials (HR: $P = 0.44$; RR: $P = .95$). The pooled interaction estimate on event counts was 0.90 (95%CI 0.84–0.96). For devices, the pooled sex interaction for RCTs reporting HR was 1.05 (95% CI 0.90–1.22) and RR was 0.68 (95% CI 0.50–0.93).

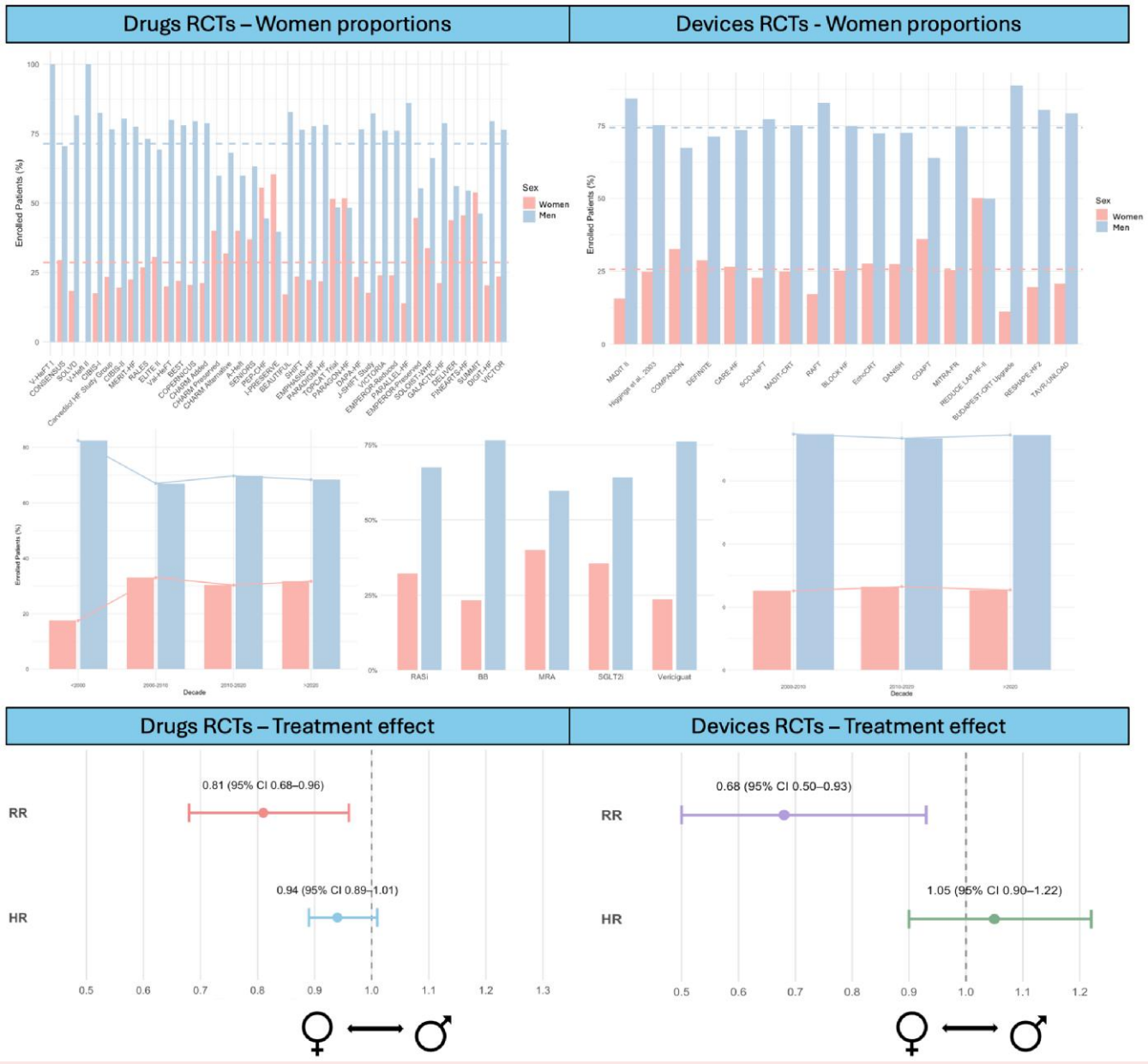
Conclusion Women remain underrepresented in HF RCTs. Sex-stratified analyses suggest a potentially greater relative benefit of drug intervention in women, which might inform future RCTs. Further studies are required to investigate the mechanisms of these differences.

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Graphical abstract



Keywords Heart failure • Randomized controlled trials • Chronic heart failure • Sex differences • Guideline-directed medical therapy • Meta analysis

Introduction

Heart failure (HF) remains a leading cause of morbidity and mortality worldwide, with substantial clinical and economic burden.[1] Over the past 3 decades, randomized controlled trials (RCTs) have demonstrated the benefit of evidence-based pharmacological and device therapies to improve outcomes in patients with HF.[2,3] However, women have historically been underrepresented in HF clinical trials, contributing to sex-based HF care disparities.[4,5] In addition, whether sex differences exist in the response to HF therapies remains an area of ongoing investigation, with some studies suggesting differential treatment effects between men and women.[5–7]

Contemporary evidence emphasizes the importance of understanding and addressing sex-related disparities in HF care and research.[8,9] Yet, comprehensive evidence quantifying the underrepresentation of women and elucidating potential sex-specific differences in treatment efficacy across both drug and device-based therapies in HF is limited. Moreover, the evolution of enrolment of women in HF trials over time and the consistency of treatment effects across HF phenotypes and drug classes remain incompletely characterized.

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Therefore, we conducted a systematic review and meta-analysis of RCTs enrolling patients with chronic HF to (a) quantify sex differences in trial enrolment over time, (b) evaluate potential sex-specific treatment effects, with a specific focus on pharmacological therapies belonging to guideline-directed medical therapy (GDMT), as well as device-based interventions and (c) explore these differences across HF phenotypes and therapeutic subgroups. By focusing the RCT selection on therapies incorporated into contemporary HF guideline-directed treatment, we aimed to assess whether sex may modify the efficacy of interventions. Our findings aim to inform future trial design and enhance the effectiveness and equity of HF care.

Methods

Two reviewers systematically searched PubMed-MEDLINE electronic databases up to November 2025 for RCTs enrolling patients with chronic HF. The search strategy used was ['heart failure' AND (stable OR chronic OR ambulatory OR outpatient OR severe OR class OR symptomatic)]. The PubMed-MEDLINE filter for RCTs was applied.

All records were imported into the citation manager software; duplicate entries were removed using the deduplication tool. The literature obtained from the searches was independently filtered by two authors, L.F. and L.P., using titles/abstracts first, and full text when deemed appropriate; discrepancies were resolved by the senior author (A.C.). This review was registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO, CRD42024612520) and performed in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.[10]

Inclusion criteria

Studies were eligible for inclusion in this meta-analysis if they met all of the following criteria: (1) randomized trials enrolling patients with chronic HF; (2) trials evaluating a hard primary endpoint[11]; (3) trials testing either a pharmacological class within GDMT or device-based interventions; and (4) trials reporting the proportion of enrolled women. However, those that did not report sex-specific treatment effects were excluded from the pooled treatment effect meta-analysis. We excluded studies with (1) other study designs than randomized; (2) soft primary endpoints (e.g. NYHA class, exercise capacity, echocardiographic changes), and (3) head-to-head randomized trials testing drugs from the same category (e.g. lisinopril vs captopril), avoiding comparative effectiveness designs that do not test active therapy versus control and therefore are not informative for sex-specific treatment benefit relative to no treatment or standard care.

Data extraction

Once the studies were selected, two authors (L.F. and L.P.) extracted data from the identified literature. The extracted data were collected in a dedicated electronic database. The name of the trial, first author, publication year, HF phenotype, intervention arm (drugs and devices), sample size, proportion of women enrolled, and treatment effects were collected.

Objective and subgroup analysis

The aim of our study was (1) to determine the enrolment sex differences in the randomized trials including patients with chronic HF over time, and describe if the proportion of women enrolled changed over time, (2) to evaluate sex differences in treatment effect in drug- and device-based RCTs, overall and by HF phenotype and drug class.

Statistical analysis

The overall proportion of women (single proportion) was estimated using a random-effects model (DerSimonian and Laird method) with inverse-variance weighting. To address the likely skewness in the distribution of observed proportions, the variance-stabilizing double arcsine transformation was applied to the proportions collected. The heterogeneity across studies was evaluated by using the I^2 and Tau^2. The I^2 index describes the percentage of total variation across the studies that is due to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% are attributed to small, moderate, and large heterogeneity. A subgroup meta-analysis was performed to compare the proportion of women enrolled between trials enrolling patients with HF with reduced ejection fraction (HFrEF) and those with HF with preserved ejection fraction (HFpEF). Between-group differences were assessed using the Q-test for subgroup differences. We conducted a sex-stratified analysis of treatment effect estimates reported in RCTs of HF therapies. For each included study, we extracted the hazard ratio (HR) or risk ratio (RR) for the primary outcome separately in men and women, along with their corresponding 95% confidence intervals (CIs). HRs and RRs were transformed to their natural logarithms, and standard errors were derived from the 95% CIs. To facilitate visual comparison of sex-specific treatment effects, we constructed forest plots displaying the log-transformed effect sizes for men and women as separate rows within each trial. For each study, the sex interaction was defined as the ratio of treatment effects in women versus men, expressed on the log scale as $log\left(\frac{RR_{women}}{RR_{men}}\right)$ or $log\left(\frac{HR_{women}}{HR_{men}}\right)$, depending on the effect measure reported. After exponentiation, values <1 indicated a greater relative treatment benefit in women, values >1 a greater relative benefit in men, and 1.00 indicated no sex-related difference. Interaction estimates were pooled using random-effects meta-analysis with a random-effects model (REML method). Leave-one-out analysis comprising RCTs testing class I recommended drugs was performed. As HR and RR reflect different effect measures, primary analyses were performed separately. To address the challenge of combining these different effect measures, a secondary unified analysis was conducted using reconstructed sex-specific event counts by treatment arm whenever available. All analyses were performed using R version 4.2.2 (R Core Team [2022]. R: A language and environment for statistical computing, Vienna, Austria).

Results

Trial selection and characteristics

The initial search yielded 6579 results (Supplementary Figure S1). After removing duplicate records and ineligible trials, 64 remained and were fully reviewed based on the inclusion criteria. Of these, a total of 56 studies were included, comprising 39 RCTs testing drugs and 17 RCTs testing devices. Specific RCTs' primary endpoints are reported in Supplementary Tables S1 and S2.

Sex-based enrolment in heart failure drug trials over time

Over time and overall, men were significantly more represented than women in HF trials testing drugs, 71.4% vs 28.6%, respectively.

The pooled proportion of women enrolled in drug trials was 27.0% (95% CI: 22.0%–32.4%).

Substantial heterogeneity with low between-study variance was observed ($I^2 = 99.6$, $Tau^2 = 0.02$) (*Figure 1A*). Women's enrolment was significantly lower in HFrEF trials (pooled proportion: 21.0%, 95% CI: 17.0%–25.4%) compared with HFpEF trials (pooled proportion: 49.6%, 95% CI: 44.6%–54.6%), with a statistically significant subgroup difference ($P < .001$) (*Figure 2*).

Analysing the trials by pharmacological class, the proportion of women was the highest for MRA RCTs (40.2%) and the lowest for beta-blockers and soluble guanylate cyclase stimulator RCTs (23.4%, 23.7%, respectively).

Analysing the trials by decade, women's enrolment appeared higher after 2000 and then relatively stable thereafter (<2000: 17.5%, 2000–2010: 33%, 2011–2020: 30.3%, >2020: 31.7%). Heterogeneity was still significant among each decade group (I^2 from 99.2 to 99.7%), with Tau^2 consistently low.

Sex-based enrolment in heart failure device trials over time

Over time and overall, men were significantly more represented in HF trials testing devices than women, 74.3% vs 25.7%, respectively.

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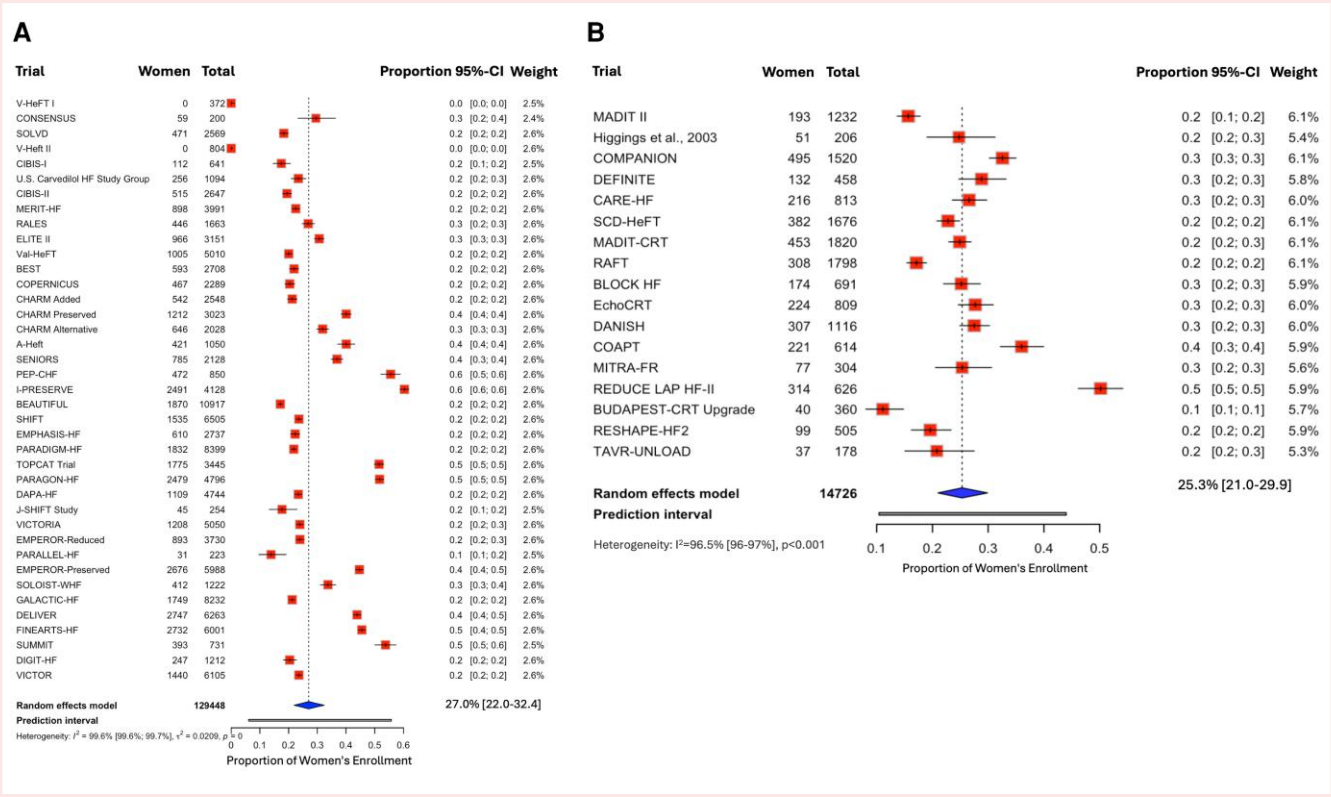


Figure 1 Forest plots of estimated women enrolment proportions in the randomized trials testing drugs (A) and testing devices (B)

The pooled proportion of women enrolled in device trials was 25.3% (95% CI: 21.0% to 29.9%). Substantial heterogeneity with low between-study variance was observed ($I^2 = 96.5$, $Tau^2 < 0.01$) (*Figure 1B*).

Analysing the trials by decade, the mean proportion of women enrolment was 25.2% in the 2000 to 2010 decade, 26.5% in the 2010 to 2020 decade, and 25.4% in studies published after 2020. Heterogeneity was still significant among each decade group (I^2 from 94.9 to 98.7%), with Tau^2 consistently low.

Sex-specific interaction of treatment effects in trials testing drugs

A total of 23 RCTs reporting sex-specific HRs and 4 RCTs reporting RRs were included. The pooled interaction effect of trials reporting HRs was 0.94 (95% CI 0.89–1.01), while the pooled interaction effect of trials reporting RRs was 0.81 (95% CI 0.68–0.96), potentially indicating a greater benefit in women compared to men (*Figure 3*). The sex-specific treatment effects of trials reporting HRs and RRs are presented for individual studies in Supplementary Figures S2 and S3. We did not observe a significant difference in interaction effect across trials enrolling patients with HFrEF compared to trials enrolling patients with HFpEF in either trials reporting HRs ($P = .44$) or reporting RRs ($P = .95$) (Supplementary Figure S4). Specifically, the pooled interaction effect of HFrEF trials reporting treatment effect as HR was 0.93 (95% CI 0.86–1.00), while the pooled interaction effect of HFpEF trials reporting treatment effect as HR was 0.98 (95% CI 0.87–1.10). Among the classes of drugs included in the GDMT, the SGLT2 inhibitors group was the only one for which all RCTs reported treatment effects as hazard ratios. We found no evidence of sex-based differences in interaction effects when comparing trials conducted in HFrEF versus HFpEF populations ($P = .66$) (Supplementary Figure S5). In additional analyses stratified by major GDMT drug class, sex-treatment interaction estimates were separately pooled for renin-angiotensin-aldosterone inhibitors, beta-blockers, and SGLT2 inhibitors, consistently showing a non-significant interaction term trend towards greater benefit in women within the classes. (Supplementary Figure S6). Although beta-blockers showed the numerically lowest women-to-men interaction ratio, there was no significant difference in interaction effects across drug classes (P for subgroup differences = .52).

Given the high heterogeneity in RCTs reporting sex-specific HRs and RRs, we performed different sensitivity analyses, including (1) RCTs enrolling more than 2000 patients, (2) RCTs testing class I recommendation drugs, and (3) a leave-one-out analysis among RCTs testing class I recommendation drugs, which confirmed the trend towards a greater benefit in women compared to men (Supplementary Figures S7–S9).

Based on reconstructed sex-specific event counts, the pooled interaction estimate (RR women/RR man) was 0.90 (95% CI 0.84–0.96), indicating a greater magnitude of treatment effect in women (*Figure 4A*). Although observed in HFrEF trials as well, this signal appeared to be primarily driven by trials enrolling patients with HFpEF (*Figure 4B*). Results were consistent in leave-one-out analyses and when restricting the analysis to studies evaluating GDMT (Supplementary Figures S10 and S11).

Sex-specific interaction of treatment effects in trials testing devices

A total of 10 RCTs reporting sex-specific HRs and 3 RCTs reporting RRs were included. The pooled interaction effect of trials reporting HRs was 1.05 (95% CI 0.90–1.22), while the pooled interaction effect

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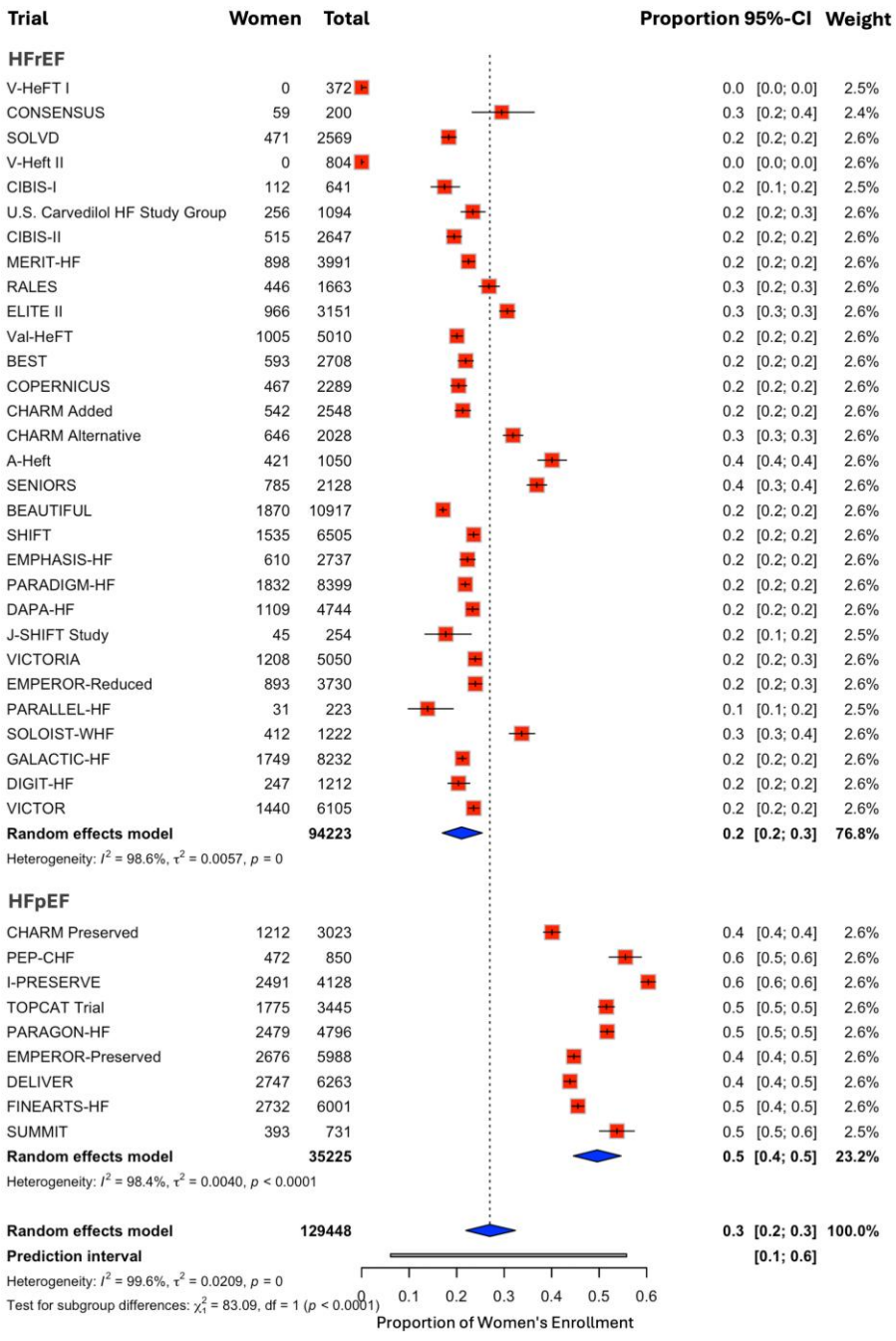


Figure 2 Forest plot of estimated women enrolment proportions in the randomized trials testing drugs according to the phenotype of heart failure subgroup analysis: HFrEF vs HFpEF

of trials reporting RRs was 0.68 (95% CI 0.50–0.93) (*Figure 5*). No significant differences were observed when splitting device trials according to device type (Supplementary Figure S12). The REDUCE LAP HF-II Trial mostly drives the greater benefit for women in RCTs reporting RR, precluding conclusions.

Only five trials (EchoCRT, DANISH, and trials testing mitral transcatheter edge-to-edge repair) reported event counts. No significant differences in treatment effect were observed (Supplementary Figure S13).

Publication bias

The presence of publication bias was evaluated using a funnel plot and Egger's test for asymmetry for RCTs' primary endpoint. Visual inspection of the funnel plot, including drug RCTs, revealed no substantial asymmetry. Egger's test did not demonstrate significant asymmetry ($Z = 0.61$, $P = .54$), indicating no evidence of publication bias. Heterogeneity among the included studies was negligible ($I^2 = 0\%$, $\tau^2 = 0$) (Supplementary Figure S14). Visual inspection of the funnel

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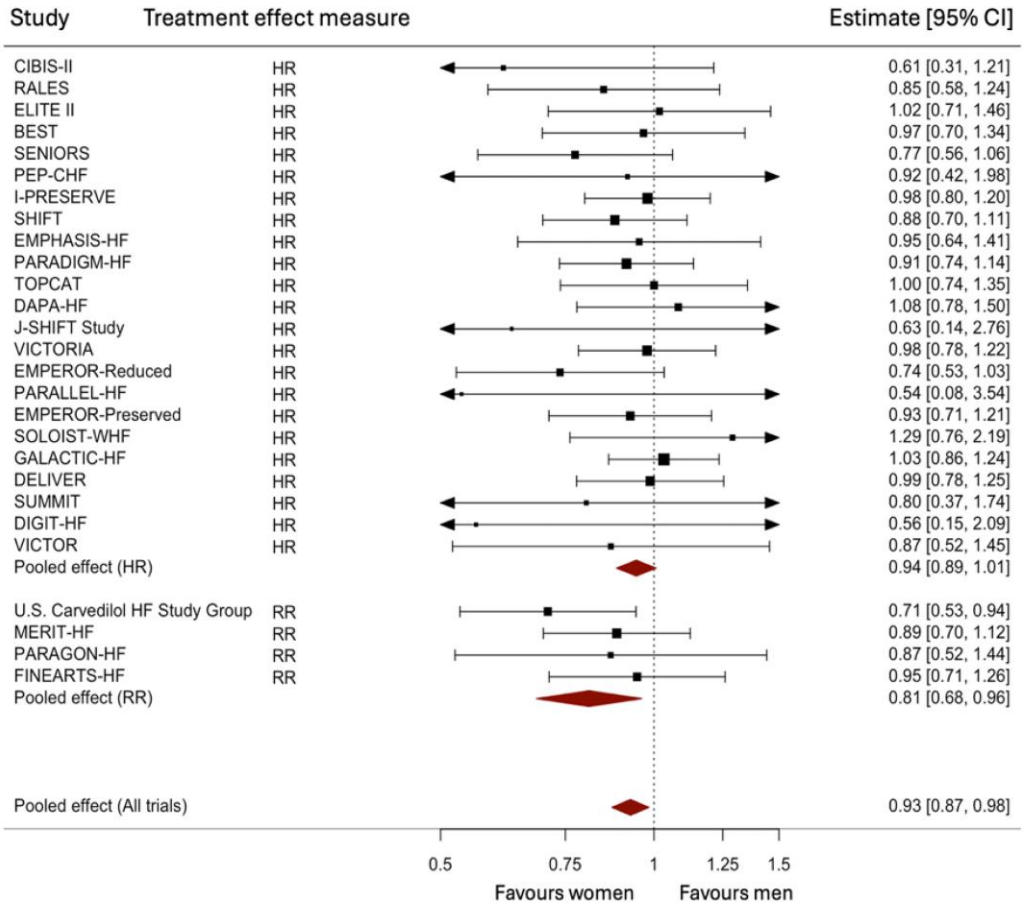


Figure 3 Forest plots showing the study-specific and pooled interaction effect of trials testing drugs. Studies are presented separately according to the treatment effect measure used (HR/RR)

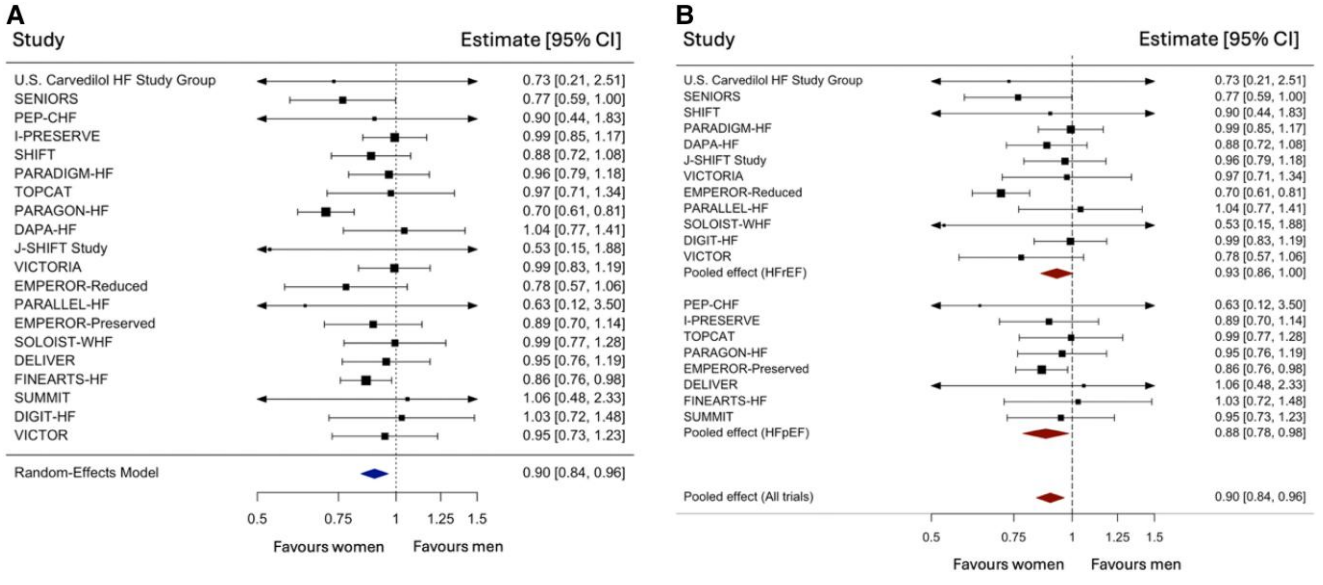


Figure 4 Forest plot showing the pooled interaction estimate based on reconstructed sex-specific event counts overall (A) and according to heart failure phenotype (B)

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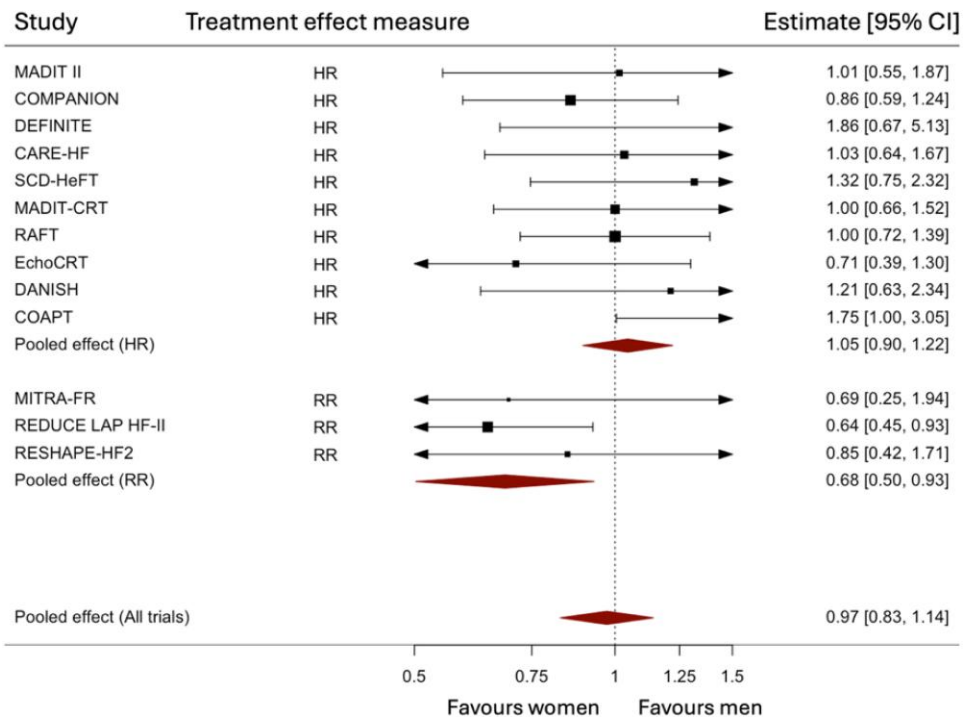


Figure 5 Forest plots showing the study-specific and pooled interaction effect of trials testing devices. Studies are presented separately according to the treatment effect measure used (HR/RR)

plot, including device RCTs, revealed no substantial asymmetry. Egger's test did not demonstrate significant asymmetry ($Z = 1.12$, $P = .26$), indicating no evidence of publication bias. Heterogeneity among the included studies was low to moderate ($I^2 = 20.4\%$, $\tau^2 = 0.017$) (Supplementary Figure S15).

Discussion

In this systematic review and meta-analysis of RCTs in chronic HF, we investigated sex differences in trial enrolment and treatment effects over time. We found that women remain underrepresented in both drug and device trials, with enrolment proportions consistently below 30%, and observed a signal towards a potentially greater relative benefit of pharmacological therapies in women, although the magnitude and consistency of this association differed according to HF phenotype and analytical approach. In particular, in the analysis based on reconstructed event counts, this signal appeared to be predominantly driven by trials enrolling patients with HFpEF. These findings emerged in the context of substantial heterogeneity across studies, likely reflecting the diverse designs, populations, and interventions evaluated.

Addressing sex disparities in HF clinical trials has been a hot topic for decades.[12] Several reasons were hypothesized as underlying the sex disparities, including sex-specific exclusion criteria, particularly those concerning pregnancy potential, which are often applied without clear justification for the specific intervention[13]; moreover, HF overall prevalence and incidence are higher in men,[8] women are more likely to be excluded due to characteristics such as cognitive impairment and frailty,[4] and the lack of sex diversity within trial leadership.[14] According to all these reasons, the 'implementation science' has developed, offering a valuable framework for addressing disparities in HF and cardiovascular care.[9] A recent narrative synthesis highlighted foundational principles to guide equity-focused implementation strategies, including promoting fair access to care, which requires coordinated efforts across sectors beyond health care alone, and highlighting that the social and organizational context in which care is delivered plays a critical role and must be considered when designing equitable interventions.

There are multiple pathophysiological reasons why sex-specific analyses are essential in HF treatment research. First, women and men differ fundamentally in their biological and physiological profiles, encompassing cardiovascular structure and function, hormonal regulation, and immune responses, thereby warranting dedicated and tailored considerations in both research and clinical practice.[15] Second, while the overall prevalence and incidence are higher in men with higher mortality, women are more likely to develop HFpEF with higher symptom burden and worse quality of life.[8] Third, women are naturally exposed to a distinct set of HF risk factors and inflammatory pathways, many of which are influenced by their hormonal profile.[16,17]

Fourth, women present structural differences, including smaller ventricles, higher EF, and smaller mitral annular dimensions.[15] Beyond these intrinsic factors, women are also more likely to present with conditions associated with HF development, including breast cancer treatments, chronic autoimmune and inflammatory disorders, which disproportionately impact the women's cohort, and pregnancy.[18,19] Even within dilated cardiomyopathy, emerging data suggest sex-related differences in genetics, response to therapy, and ultimately in outcomes.[20,21] These biological distinctions, along with social and clinical factors, justify a dedicated focus on women in HF research and trial design. Future HF trials should therefore aim for sex representation that reflects the epidemiology of the HF phenotype under investigation according to the geographic regions being enrolled and prospectively set adequately powered sex-specific analyses and pre-specified sex-by-treatment interaction testing.

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Recently, a meta-analysis reported no differences in the efficacy of pharmacological treatment for HF between sexes, concluding that the historical underrepresentation of women in HF trials was unlikely to have masked clinically relevant differences in treatment efficacy.[22] The apparently different findings of that study and our analysis should be interpreted in light of important differences in study scope, trial selection, and methodology. First, van der Bijl *et al.* evaluated a broad spectrum of pharmacological HF interventions, including trials conducted in acute HF, head-to-head comparisons, and interventions not belonging to contemporary GDMT (iron supplementation, calcium-channel blockers, vasodilators, and others), whereas our pharmacological analysis specifically focused on therapies incorporated into guideline-directed treatment of chronic HF. Thus, the two studies address partially different clinical questions. Second, the methodology differed. They harmonized different reported relative effect measures on the logarithmic scale and investigated the relationship between women enrolment and treatment efficacy through meta-regression, whereas we estimated within-trial women-to-men ratios of treatment effects and analysed HRs and RRs separately because of their different statistical interpretation. Third, we performed a complementary analysis based on reconstructed sex-specific event counts supporting the signal observed in the primary analyses. Fourth, trials testing devices were not included by van der Bijl *et al.* Therefore, our findings should not be interpreted as disproving the absence of sex differences reported by van der Bijl *et al.*, but rather as identifying a potential signal within a more specifically selected group of GDMT trials. Taken together, the different conclusions emphasize the need for prospectively powered sex-specific analyses and, ideally, individual patient-data meta-analyses.

The effectiveness of GDMT in women is derived from RCTs in which women are underrepresented. Evidence from multiple RCTs shows that key pharmacological therapies for HFrEF, including renin-angiotensin system inhibitors, beta-blockers, and SGLT2 inhibitors, are equally effective in men and women, with no apparent sex-based differences in mortality or cardiovascular outcomes.[4] However, it was recently hypothesized that women may achieve similar clinical benefit with lower doses of GDMT than men,[23] aligning with the trend of a potential greater relative benefit of drug intervention in women, which might be suggested by our work.

The reasons underlying such a potentially greater benefit might be only hypothesized. First, sex-related differences in pharmacokinetics and pharmacodynamics, including lower body weight, smaller volume of distribution, reduced renal and hepatic clearance, and greater systemic drug exposure, result in higher plasma drug concentrations at equivalent doses in women.[23] Accordingly, evidence from BIOSTAT-CHF and ASIAN-HF cohorts has shown that in women with HFrEF the risk of death or HF hospitalization is already reduced at approximately half of the guideline-recommended dose of ACE inhibitors/ARBs and beta-blockers, with no additional benefit observed at higher doses.[23,24] Second, women also appear to exhibit greater clinical sensitivity to cardiovascular pharmacotherapy, potentially mediated by sex hormones and differences in cardiac receptor expression.[23] Third, women with HFrEF may derive greater benefit from lower drug doses because of sex-related differences in HF phenotype and pathophysiology, including a lower burden of ischaemic heart disease, less extensive myocardial fibrosis, and a higher prevalence of non-ischaemic aetiologies. These features may confer greater myocardial responsiveness to neurohormonal modulation and reverse remodeling.[6,7] In the present study, although all class-specific interaction estimates numerically favoured a greater relative treatment effect in women, none reached statistical significance, and the available data do not allow definitive conclusions regarding whether a specific pharmacological class primarily drove the overall observed signal.

HFpEF is one of the cardiovascular syndromes in which sex differences have been most extensively studied. The PARAGON-HF Trial is one of the largest RCTs enrolling patients with HFpEF. Notably, it suggested a greater treatment benefit from sacubitril-valsartan in reducing HF hospitalizations among women compared to men.[25] This observed sex difference was explained through several hypotheses. Women tend to have higher baseline EF and more frequent subclinical systolic dysfunction, which could make them more responsive to neprilysin inhibition. Hormonal changes after menopause, particularly reduced oestrogen levels, may impair natriuretic peptide signalling, potentially enhancing the effect of sacubitril-valsartan in women. Additionally, differences in visceral adiposity, arterial stiffness, and neprilysin-related peptide metabolism, including bradykinin, were hypothesized to play a role.[25] However, the trial reported treatment effects using RRs rather than HRs (see limitation section below), which limits the comparability of its findings with those of other RCTs in HFpEF that report HRs. This methodological heterogeneity complicates the inclusion of PARAGON-HF in quantitative syntheses and pooled analyses assessing sex-treatment interactions. To address this limitation, we performed an analysis restricted to RCTs in which the sex-specific event count was available for each arm of randomization, which supported our observations.

Regarding device treatment, the apparent greater benefit in women in device trials was largely driven by a single study and should be interpreted cautiously. Interatrial shunts seem to have a significantly different treatment effect in the REDUCE LAP HF II Trial.[26] This was a RCT testing an interatrial shunt device to lower left atrial pressure in patients with HF with EF above 40%, which showed increased risk of the event in men, while a trend towards a clinical benefit in women was observed. Men may have experienced less favourable outcomes due to larger right atrial size and impaired right ventricular function, possibly limiting effective left atrial decompression and exacerbating subclinical right-sided dysfunction when exposed to left-to-right shunting. This trial's findings further support sex-specific considerations in trial design. Similarly, the RELIEVE-HF Trial tested an interatrial shunt in symptomatic HF with any left ventricular EF.[27] This RCT was excluded since a sex-specific treatment effect was not available. Given the trend towards a clinical benefit in women in the REDUCE LAP HF II Trial, it would have been interesting to pool these populations.

RCTs testing mitral transcatheter edge-to-edge repair (TEER) were included. Functional mitral regurgitation differs among sexes, and accordingly, sex-related differences in TEER use and outcomes have been observed.[28,29] Women remain underrepresented in clinical trials and registries and are often referred for intervention at a more advanced stage of disease.[28] Despite these disparities, short-term outcomes following TEER appear largely comparable between men and women. However, emerging evidence suggests a potential signal towards reduced clinical efficacy in women at longer-term follow-up, highlighting the need for more sex-specific evaluation of patient selection and treatment response.[29]

Limitations

Our systematic review and meta-analysis have several important limitations that must be acknowledged. First, not all RCTs reported sex-stratified treatment effect estimates, thereby restricting our pooled analyses to those studies that published sex-specific data. For instance, the CHARM studies explicitly state that no sex-related difference in treatment effect was observed, yet they do not provide sex-specific HRs, precluding their inclusion in quantitative synthesis. Second, the enrolment analyses were characterized by high between-trial heterogeneity. Such heterogeneity likely reflects the clinical, methodological, geographical, design, and temporal diversity of the included trials. Indeed, sex heterogeneity is also largely described in real-world registries.[30] The primary aim of this work was not to derive a single pooled estimate but rather to provide a broad perspective on sex-related enrolment patterns and treatment effects across HF trials, including trial-by-trial analysis to inform future study design. Third, another

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important limitation relates to the use of different effect measures across trials, HR and RR. These measures are not directly comparable, as HR reflect time-to-event dynamics accounting for censoring and varying follow-up durations, whereas RR are based on cumulative event proportions over a fixed period. As a result, pooling HR and RR within a single meta-analysis introduces methodological bias and misinterpretation of treatment effects. For this reason, our primary analyses were conducted separately according to the reported effect measure, which precluded a unified quantitative synthesis across all trials. Although we attempted to address this limitation through a secondary analysis based on reconstructed event counts, this approach is dependent on data availability. Fourth, there was variability in the trial outcomes across RCTs. To ensure consistency, we restricted our analysis to the primary clinical endpoint reported in each trial. Studies that evaluated only soft endpoints, such as changes in NYHA class, quality of life, or echocardiographic parameters, were excluded. Fifth, the search strategy was conducted using PubMed as an electronic database. This approach was chosen based on the assumption that the pivotal RCTs in HF testing hard endpoints, particularly those that have informed guideline recommendations, are published in high-impact journals and are consistently indexed in PubMed and cited in major clinical guidelines. Restricting the search to PubMed may have missed secondary reports indexed differently, although the authors believe the most influential HF RCTs were likely captured. Sixth, although the participation-to-prevalence ratio could provide a more informative assessment of women representation in HF trials, we were unable to calculate it because no robust and universally applicable estimate of the proportion of women within HFrEF and HFpEF populations is currently available. Contemporary epidemiological data show substantial variation across registries, geographical regions, populations, and HF phenotype definitions, making the selection of a single prevalence denominator inherently arbitrary.[30] Seventh, pharmacological RCTs were often placebo-controlled (88% of the trials), whereas device trials were mostly open-label. Differences in blinding and control design may influence co-interventions, outcome ascertainment, and the magnitude of observed treatment effects, particularly for nonfatal endpoints such as hospitalization. This may have contributed to between-study heterogeneity and should be considered when interpreting pooled sex-specific treatment effects. Finally, caution is warranted when interpreting the pooled findings for device-based interventions, given the considerable heterogeneity in the type of device, intervention modality, and underlying clinical context across included studies.

Conclusion

Women remain significantly underrepresented in HF RCTs over time. Although our findings should be interpreted in the context of substantial heterogeneity, sex-stratified analyses suggest a potential difference in the relative benefit of pharmacological therapies between women and men. This should be considered a signal since the number of studies and variability in treatment effect reporting limited definitive interpretations according to HF phenotype. In contrast, the apparent greater benefit observed in device trials appears to be largely driven by a single study, precluding conclusions. These findings support the need for sex-balanced enrolment and pre-specified sex-specific analyses in future HF trials.

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Supplementary data

Supplementary data are available at *European Journal of Heart Failure* online.

Declarations

Disclosure of Interest

M.S. Reports consultancy agreements with Novo Nordisk, Bayer AG, Cardurion, Boehringer Ingelheim, Amgen, AstraZeneca, Merck, MSD, Reprieve Cardiovascular, and CPC Clinical Research; has served on advisory boards for AstraZeneca, Novo Nordisk, Bayer AG, Merck, Boehringer Ingelheim, Cardurion, and Amgen; and has received speaker fees from Merck, MSD, Bayer AG, Novo Nordisk, AstraZeneca, Cardurion, and Amgen.

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Data Availability

Data underlying the results described in this manuscript are published and available in indexed journals.

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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