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SHORT COMMUNICATION

Sex differences in efficacy of pharmacological therapies in heart failure with reduced ejection fraction: a meta-analysis

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Abstract

Aims Recent studies have suggested potential sex differences in treatment response to pharmacological therapies in heart failure (HF). We performed a systematic review and meta-analysis of studies comparing treatment effects between men and women with HF and reduced ejection fraction (HFrEF) using established guideline-directed medical therapy and other emerging pharmacological treatments.

Methods and results Systematic search was performed on PubMed, Embase, and Cochrane Library for randomized controlled trials published in 1990–2021. Outcomes were all-cause mortality and combined outcome of all-cause mortality and/or hospitalization for HF. Of 618 articles identified, 25 articles and 100 213 patients (mean age 62 ± 1.7 years, women 23.1%, mean left ventricular ejection fraction 26.6 ± 1.3%) were included in the systematic review and meta-analysis. For the outcome of all-cause mortality, there was no evidence of treatment heterogeneity by sex for renin-angiotensin system inhibitors (RASi) [hazard ratio (HR) 0.86 (95% confidence interval 0.75–0.99) in men; HR 0.97 (0.77–1.23) in women; $P_{\text{interaction}}$ = 0.288], or for beta-blockers (BB) [HR 0.71 (0.59–0.86) in men; HR 0.87 (0.73–1.03) in women; $P_{\text{interaction}}$ = 0.345]. Similarly, for the composite outcome of death or HF hospitalization, there was no evidence of treatment heterogeneity by sex for RASi [HR 0.84 (0.77–0.93) in men; HR 0.94 (0.81–1.08) in women; $P_{\text{interaction}}$ = 0.210] or BB [HR 0.76 (0.64–0.90) in men; HR 0.72 (0.60–0.86) in women; $P_{\text{interaction}}$ = 0.650]. Results for mineralocorticoid receptor antagonists (MRA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) from previously published meta-analyses were included in the review. For the combined outcome of cardiovascular death or HF hospitalization, no significant interaction for sex was observed for MRA ($P_{\text{interaction}}$ = 0.78) or SGLT2i ($P_{\text{interaction}}$ = 0.37). Results for emerging pharmacological treatments, such as soluble guanylate cyclase stimulators and cardiac myosin activators, were included in the review and showed consistent treatment effects between men and women.

Conclusions Our meta-analysis showed no differences between sex in treatment effect for BB and RASi. Review on previously published trials for MRA, SGLT2i, and emerging therapies presented consistent treatment effects between men and women.

Keywords Heart failure with reduced ejection fraction; Sex differences; Pharmacology; Guideline-directed medical therapy

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Introduction

Foundational treatments recommended for heart failure (HF) with reduced ejection fraction (HFrEF) comprise of renin-angiotensin system inhibitors (RASi), which include angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB); angiotensin receptor-neprilysin inhibitors (ARNi); beta-blockers (BB); mineralocorticoid receptor antagonists (MRA); ivabradine; and sodium-glucose cotransporter-2 inhibitors (SGLT2i).[1,2] Emerging novel agents, such as soluble guanylate cyclase (sGC) stimulators and cardiac myosin activators, showed promising results in HFrEF.[3,4] There is a growing body of literature suggesting sex dimorphism in the pathophysiology and varying pharmacological response to cardiovascular drugs, including in the setting of HF.[5–7]

Aim

We performed a systematic review and meta-analysis comparing pharmacological therapy effects for mortality and hospitalization outcomes among men and women with HFrEF.

Methods

A systematic search was performed on PubMed, Embase, and Cochrane Library for randomized controlled trials published between 1990 and February 2021, with subject headings HFrEF, pharmacological therapy, and sex.[8] Treatments included RASi, BB, MRA, ARNi, ivabradine, SGLT2i, sGC stimulators, and cardiac myosin activators. Supporting information *Figure S1* shows the full search strategy. Inclusion criteria were (i) patients aged $\geq$ 18 years with HFrEF (EF $<$ 40%); (ii) $\geq$1 of the pharmacological therapies applied; (iii) comparison of treatment effect between sex with hazard ratio (HR), odds ratio or relative risk; and (iv) mortality and/or hospitalization outcome.

The abstracts extracted were screened by two investigators (C.D. & G.L.) independently. In case of disagreement, arbitration from a third independent reviewer (T.H.K.T. & W.O.) was sought. Full-text articles included by consensus were eligibility-reviewed by the third reviewer. The risk-of-bias analysis was performed according to Cochrane Consumers & Communication review group: Study quality guide.[9] Reporting bias was assessed with funnel plots and formally tested using the Egger test to assess funnel plot symmetry.[10] When this was found nonsignificant ($P > 0.05$), we considered the risk of reporting bias as 'low'.

Chosen outcomes were all-cause mortality or all-cause mortality and/or HF hospitalization (combined outcome). *Z* scores for outcomes in sex were analysed using combined fixed-and-random-effects meta-analysis with R software. The results were presented as HR comparing men to women with 95% confidence interval (CI) that the treatment is better than comparison. Heterogeneity was assessed using Higgins I^2 statistics.[11] Sensitivity analyses were performed for RASi and BB, excluding studies with unique methodological features that differ from the rest of the included trials. Excluded studies with reasoning and results for the sensitivity analyses are presented in the supporting information.

To assess the influence of background therapy on effect size, we performed a meta-regression using publication year as a predictor. Meta-regression model added studies in ascending order according to publication year, that is, increasing percentage of patients on background therapy in accordance with modern GDMT (*Table S7*). Ethics approval is not required for a systematic review and meta-analysis.

Results

Systematic search identified a total of 618 articles after exclusion of duplicates. After screening, 25 randomized controlled trials with 100 213 patients (mean age 62 ± 1.7 years, women 23.1%, mean LVEF 26.6 ± 1.3%) were included (*Table 1*). Trial outcomes, interventions, and sample sizes are presented in *Table 2*. All studies were assessed to have a low risk of bias (*Table S1*). Assessment of funnel plots is presented in *Figure S2*. There was no evidence of systematic reporting bias for the majority of outcomes, that is, RASi-mortality (Egger P = 0.621), RASi-combined (P = 0.586), or BB-combined (P = 0.487). Reporting bias was noted for BB-mortality outcome ($P < 0.001$, *Table S2*).

For all-cause mortality in patients using RASi, the overall HR was 0.86 (95% CI 0.73–1.01), with no significant interaction of sex ([HR 0.86 (0.75–0.99) in men; HR 0.97 (0.77–1.23) in women]; $P_{interaction}$ = 0.288, *Figure 1A*). Heterogeneity (I^2) among studies was 59.1%. Publication year accounted for up to 21.2% heterogeneity among effect sizes (*Table S4* and *Figure S4*). For the composite outcome of all-cause mortality and/or HF hospitalization, the overall HR was 0.84 (0.76–0.93), with no significant difference between sex ([HR 0.84 (0.77–0.93) in men; HR 0.94 (0.81–1.08) in women], $P_{interaction}$ = 0.210, *Figure 1B*). I^2 was 66.6%, with publication year explaining 7.6% of the difference in effect size (*Table S5* and *Figure S5*).

For BB, a consistent reduction in risk was observed in men [HR 0.71 (0.59–0.86)] and women [HR 0.87 (0.73–1.03)] for all-cause mortality, with overall HR 0.72 (0.60–0.85, $P_{interaction}$ = 0.345, *Figure 1C*). Heterogeneity (I^2) was 63.7%, with no heterogeneity accounted to publication year (*Table S6* and *Figure S6*). For the composite outcome, a significant risk reduction in both men [HR 0.76 (0.64–0.90)] and women [HR 0.72 (0.60–0.86)] treated with BB was observed, with

Table 1 Mean baseline characteristics of a pooled and averaged study population

	Number of studies (*n*)	Percentages (%)	Number of patients (*n*)	Mean (±SD)
Region				
Asia	0	0		
Europe	3	12		
North America	3	12		
South America	0	0		
Africa	0	0		
International	20	77		
Sample size	26		100 213	
Medication type				
Beta-blockers	5	22		
ACEi	5	22		
ARB	3	13		
MRA	3	13		
ARNi	1	4		
SGLT2 inhibitors	2	9		
Ivabradine	2	9		
Cardiac myosin activators	1	4		
sGC stimulators	1	4		
Characteristics				
Women		23.1	23 149	
Ischaemic heart disease		59.6	59 727	
LVEF				26.6 ± 1.3
Age				62.14 ± 1.7
Control variable				
Placebo	16	70		
Another drug	5	22		
Standard care	2	9		
Comorbidities				
Coronary artery disease		37.9	37 981	
Hypertension		54.3	54 416	
Chronic kidney disease		33.3	33 371	
Diabetes mellitus		30.8	30 866	
Anaemia		21.2	21 245	
Atrial fibrillation		29.4	29 463	
Risk factors				
Smoking		35.2	35 275	
Systolic blood pressure				122.3 ± 2.6
Diastolic blood pressure				75.5 ± 1.9
Heart rate				76.2 ± 1.9

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; sCG, soluble guanylate cyclase; SGLT2, sodium-glucose cotransporter 2.

overall HR 0.76 (0.64–0.90, $P_{interaction}$ = 0.650, I^2 = 0%, *Figure 1D*).

In sensitivity analyses considering BB and RASi with corresponding outcomes, results were comparable. Results remained similar for RASi outcomes, but excluding trials from BB outcomes resulted in numerically more beneficial results for men and women (*Table S3* and *Figure S3*).

Two studies analysing the effect of SGLT2i on cardiovascular death or HF hospitalization among patients with HFrEF were included.[12,13] DAPA-HF and EMPEROR-Reduced trials were previously meta-analysed, with a significant risk reduction in both men [HR 0.76 (0.68–0.85)] and women [HR 0.68 (0.56–0.84)], $P_{interaction}$ = 0.37.[14]

We found three trials examining MRA effect (RALES, EPHESUS, & EMPHASIS-HF).[15–17] RALES and EMPHASIS-HF were meta-analysed at individual patient-level previously, with a consistent treatment effect in men [HR 0.65 (0.58–0.74)] and women [HR 0.67 (0.54–0.83)] on the risk of cardiovascular death or HF hospitalization ($P_{interaction}$ = 0.78).[18]

The data collected for other included treatments was not sufficient for meta-analyses. ARNi, presented in PARADIGM-HF, was shown to be superior to ACEi in reducing cardiovascular mortality and HF hospitalization in both men and women ([HR 0.80 (0.72–0.90); HR 0.77 (0.62–0.95), respectively]; $P_{interaction}$ = 0.630).[19] Trials examining ivabradine presented no treatment interaction between sex in SHIFT ($P_{interaction}$ = 0.103) and BEAUTIFUL ($P_{interaction}$ = 0.226).[20,21] Recent studies VICTORIA-HF (on sGC stimulator) and GALACTIC-HF (on cardiac myosin activator) showed consistent favourable results in men and women for the composite outcome of cardiovascular mortality or HF hospitalization.[3,4]

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Table 2 Outcomes, interventions, and sample sizes for the corresponding trials included in the systematic review and meta-analysis

Trial name	Medication	Sample size	Percentage of women		HR (95% CI) men	HR (95% CI) women	Outcome	Background therapy (% of patients)[a]
			Intervention	Comparison				
AIRE	ACEi	2006	27.0%	26.0%	0.75 (0.58–0.98)	0.70 (0.50–0.98)	All-cause mortality	BB—22.0% RASi (intervention) MRA—NA
ATLAS	ACEi	3164	20.2%	20.7%	0.87 (0.78–1.00) 0.90 (0.83–0.97)	1.97 (0.83–1.35) 0.83 (0.70–0.98)	All-cause mortality Combined outcome	BB—11.0% RASi—88.0% (ACEi) MRA—NA
ATMOSPHERE	Aliskiren vs. ACEi	4676	21.2%	21.4%	0.95 (0.85–1.06) 1.00 (0.88–1.13)	1.21 (0.96–1.52) 1.27 (0.99–1.64)	Combined outcome All-cause mortality	BB—91.6% RASi (comparison) MRA—37.4%
BEAUTIFUL	Ivabradine	12 473	17.0%	17.0%	0.98 (0.75–1.15)	1.14 (0.80–1.50)	CV death, MI, or HF hospitalization	BB—87.0% RASi—90.0% MRA—NA
BEST	BB	2708	21.0%	23.0%	0.90 (0.70–1.03)	0.90 (0.60–1.20)	All-cause mortality	BB (tested) RASi—91.0% (ACEi), 6.5% (ARB) MRA—3.5%
CHARM	ARB	4576	25.9%	26.1%	0.82 (0.74–0.90)	0.80 (0.68–0.98)	CV death or HF hospitalization	BB—55.1% RASi—55.7% (ACEi) MRA—20.1%
CIBIS III	BB followed by ACEi	1010	34.1%	29.5%	0.80 (0.65–1.20)	0.85 (0.65–1.45)	Combined outcome	BB (intervention) RASi (intervention) MRA—13.3%
COMET	BB	3029	21.0%	20.0%	0.80 (0.70–0.91)	0.97 (0.73–1.27)	All-cause mortality	BB—4.0% RASi—91.5% (ACEi), 6.5% (ARB) MRA—11.0%
COPERNICUS	BB	2289	21.0%	20.0%	0.65 (0.52–0.80) 0.75 (0.65–0.90)	0.65 (0.40–1.10) 0.70 (0.50–0.85)	All-cause mortality Combined outcome	BB (intervention) RASi—97.0% MRA—19.5%
DAPA-HF	SGLT2i	4744	23.8%	23.0%	0.73 (0.63–0.85)	0.79 (0.59–1.06)	CV death or HF hospitalization	BB—96.1% RASi—56.1% (ACEi), 27.6% (ARB) MRA—71.1%
EMPEROR-Reduced	SGLT2i	3730	23.5%	24.4%	0.80 (0.68–0.93)	0.59 (0.44–0.80)	CV death or HF hospitalization	BB—94.7% RASi—69.7% MRA—71.4%
EMPHASIS-HF	MRA	2743	22.7%	21.9%	0.75 (0.65–0.85)	0.60 (0.40–0.85)	CV death or HF hospitalization	BB—86.8% RASi—77.6% on ACEi, 19.3% on ARB MRA (intervention)
EPHESUS	MRA	6632	28.0%	30.0%	0.85 (0.75–1.10)	0.80 (0.60–0.95)	All-cause mortality	BB—75.0% RASi—86.5% MRA (tested)
GALACTIC-HF	Cardiac myosin activator	8232	21.2%	21.3%	0.92 (0.85–0.99)	0.95 (0.81–1.12)	CV death or HF hospitalization	BB—94.3% RASi—87.0% (including ARNi) MRA—77.7%

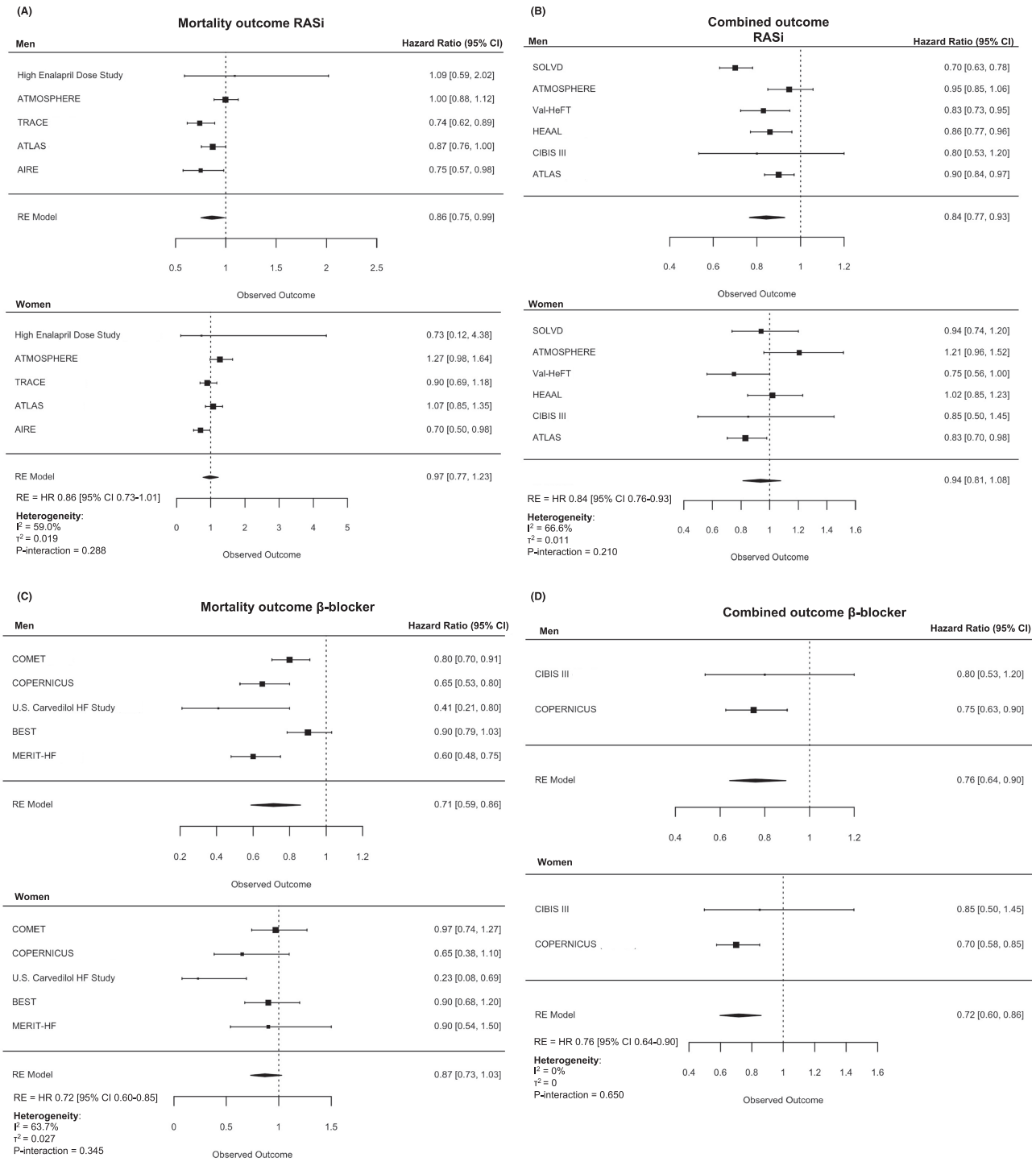
(*Continues*)

Table 2 (continued)

Trial name	Medication	Sample size	Percentage of women		HR (95% CI) men	HR (95% CI) women	Outcome	Background therapy (% of patients)[a]
			Intervention	Comparison				
HEAAL	ARB	3846	30.0%	29.0%	0.86 (0.77–0.96)	1.02 (0.85–1.23)	Combined outcome	BB—72% RASi (intervention) MRA—38.0%
High Enalapril Dose Study	ACEi	248	19.4%	10.4%	1.09 (0.58–2.02)	0.73 (0.12–4.38)	All-cause mortality	BB—NA RASi (tested) MRA—NA
MERIT-HF	BB	3991	23.0%	22.0%	0.60 (0.50–0.75)	0.90 (0.58–1.50)	All-cause mortality	BB (intervention) RASi—95.5% MRA—NA
PARADIGM-HF	ARNi vs. ACEi	8399	21.0%	22.6%	0.80 (0.72–0.90)	0.77 (0.62–0.95)	Combined outcome	BB—93.0% RASi (comparison) MRA—55.6%
RALES	MRA	1663	27.0%	27.0%	0.70 (0.60–0.85)	0.71 (0.52–0.98)	All-cause mortality	BB—10.5% RASi—94.5% (ACEi) MRA (intervention)
SHIFT	Ivabradine	6505	21.7%	28.0%	0.84 (0.76–0.94)	0.74 (0.60–0.91)	CV death or HF hospitalization	BB—89.5% RASi—78.5% (ACEi), 14.0% (ARB) MRA—60.0%
SOLVD	ACEi	2569	19.0%	20.0%	0.70 (0.62–0.78)	0.94 (0.74–1.20)	Combined outcome	BB—7.7% RASi (intervention) MRA—NA
TRACE	ACEi	1749	28.0%	29.0%	0.74 (0.62–0.89)	0.90 (0.69–1.18)	All-cause mortality	BB—16% RASi (intervention) MRA—NA
U.S. Carvedilol Heart Failure Study	BB	1094	23.0%	24.0%	0.41 (0.22–0.80)	0.23 (0.07–0.69)	All-cause mortality	BB (intervention) RASi—95.0% (ACEi) MRA—NA
Val-HeFT	ARB and ACEi	3034	19.6%	20.7%	0.83 (0.73–0.95)	0.75 (0.56–1.00)	Morbidity	BB—34.9% RASi—92.7% (ACEi) MRA—NA
VICTORIA	sGC stimulator	5050	24.0%	23.9%	0.90 (0.81–1.00)	0.88 (0.73–1.08)	CV death or HF hospitalization	BB—93.1% RASi—73.4% MRA—70.3%

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR – hazard ratio; MI, myocardial infarction; MRA, mineralcorticoid receptor antagonists; NA, non-assessed; sGC, soluble guanylate cyclase; SGLT2i, sodium-glucose cotransporter-2 inhibitors.
Combined outcome refers to all-cause mortality and/or hospitalization for heart failure.
[a]Background therapy measurements for each study were defined as mean values for intervention and comparison.

Figure 1 Meta-analysis of renin-angiotensin system inhibitors (RASi) and beta-blockers (BB) effects in heart failure with reduced ejection fraction treatment in men vs. women presented as hazard ratios with 95% confidence intervals. RASi effect was evaluated for the outcome of all-cause mortality (A) and combined outcome of all-cause mortality and HF hospitalization (B) in men and women. BB effect was respectively evaluated for all-cause mortality (C) and combined outcome of all-cause mortality and HF hospitalization (D). BB, beta-blockers; CI, confidence interval; HR, hazard ratio; RASi, renin-angiotensin system inhibitors; RE, random effects.



Discussion and conclusions

Our meta-analysis showed no sex differences in treatment effect of BB and RASi among patients with HFrEF. Previous systematic reviews on MRA, SGLT2i, and emerging pharmacological treatments presented consistent treatment effects between sex.

For this meta-analysis, ACEi and ARB treatments were analysed together as RASi. However, ARB is no longer recommended as first-option medication for patients with chronic HFrEF, partly because trials examining ARB could not demonstrate reduced all-cause mortality.[1] This, in turn, negatively affects the results for the combined analysis of ACEi and ARB in both sex, as illustrated by the differentiating results compared with an earlier meta-analysis on ACEi.[22]

Differences in pharmacodynamics and pharmacokinetics between men and women are a familiar phenomenon, but the exact mechanisms are still to be investigated for all HFrEF therapy.[23,24] These variations between sex could potentially influence the efficacy of HFrEF drugs, although its statistical relevance is unknown, likely due to a marginalised presentation of women in clinical trials.[25] Results in smaller trials are therefore likely to be affected by datasets for women not being large enough to give statistically powered information, which calls for bigger analyses or pooling of data for evaluation of therapy between sex. For example, GALACTIC-HF, a recent trial on a cardiac myosin activator, included a large population and therefore a considerable number of women for a statistically significant evaluation.[3] Moreover, a survival benefit in women is most likely to present if the treatment is clearly superior to the standard of care, as seen in PARADIGM-HF where a significant effect of ARNi was observed in women although they only constituted 21.8% of the population.[19]

This review underscores the under-representation of women in clinical trials of HF. While women represent approximately 40% of the HFrEF population, the total HF population is believed to consist >50% of women.[24,26] Yet only 23.1% of the patients included in this meta-analysis were women, a percentage consistent in trials involving patients with HFrEF.[27] Although this meta-analysis showed no sex differences in treatment effect, a trend of inconsistency between the HR estimates is noticeable, with women presenting neutral effects in response to BB and RASi as compared with consistently favourable outcomes in men. While reasons for this could be multifactorial, a prominent cause is selection bias due to low percentage of women included in HFrEF trials. Therefore, a more balanced recruitment of both sex into future trials on pharmacotherapy is warranted. One could expect that if the inclusion by sex was proportional, the estimate for women would regress around that of men, a trend seen in HFpEF trials.[28] A targeted approach directed at eligible women, coupled with an educational programme on the benefits of the study drug, might increase the participation of women in HFrEF trials.

This study includes several potential limitations. Included studies did not differentiate between symptomatic and asymptomatic patients with HFrEF, which is suggested to affect the long-term outcomes.[29] Dose-dependent effect differences between sex could not be assessed due to limited data in included trials, as dose-dependent differences between sex have been reported previously.[7] Finally, analysis was not performed at individual patient-level, which limited analyses to specific outcomes.

In conclusion, our meta-analysis showed no sex differences in response to BB and RASi in the management of chronic HFrEF. Previous systematic reviews on MRA, SGLT2i, and emerging pharmacological treatment presented consistent treatment effects between sex.

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Conflict of interest

The authors declared no conflict of interest relevant to the present work. C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, Cytokinetics, WebMD Global LLC, Radcliffe Group Ltd and Corpus; and serves as co-founder & non-executive director of eKo.ai.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. A) Flow chart for inclusion of articles. **B)** Search strategy for PubMed. Performed on 11th February 2021. Identical searches were performed on Embase and The Cochrane Library.

Figure S2. a) Forest and residual funnel plot with adjusted HRs with sex as a modifier showing the risk of bias for mortal-

ity outcome in patients using Renin Angtiotensin System inhibitors (RASi). **Analysed according to random-and-fixed-effects model using R package metaphor.**

Figure S2. b). Forest and residual funnel plot with adjusted HRs with sex as a modifier showing the risk of bias for combined outcome (all-cause mortality and/or HF-hospitalisation) in patients using Renin Angiotensin System inhibitors (RASi). **Analysed according to random-and-fixed-effects model using R package metaphor.**

Figure S2. c). Forest and residual funnel plot with adjusted HRs with sex as a modifier showing the risk of bias for mortality outcome in patients using beta-blockers (BB). **Analysed according to random-and-fixed-effects model using R package metaphor.**

Figure S2. d). Forest and residual funnel plot with adjusted HRs with sex as a modifier showing the risk of bias for combined outcome (all-cause mortality and/or HF-hospitalisation) in patients using beta-blockers (BB). **Analysed according to random-and-fixed-effects model using R package metaphor.**

Figure S3. Forest plots for sensitivity analysis in men and women. Performed using R-software, mixed-effect modelling.

Figure S4. Forest and funnel plots for RASi all-cause mortality according to publication year in ascending order. Analysed using meta-regression.

Figure S5. Forest and funnel plots for RASi combined outcome according to publication year in ascending order. Analysed using meta-regression.

Figure S6. Forest and funnel plots for BB all-cause mortality according to publication year in ascending order. Analysed using meta-regression.

Table S1. Risk of bias assessment and list of studies included in the systematic review and meta-analysis with references. Green circle symbolises 'yes,' yellow circle symbolises 'questionable,' and red circle symbolises 'no.' Questions for risk of bias and assessment to evaluate risk are presented under the table.

Table S2. Results of the Egger test. Corresponding values are presented as *p*-values, where a p-value >0.05 is considered nonsignificant.

Table S3. Summary of the results presented in sensitivity analyses performed for BB and RASi and for their corresponding outcomes.

Table S4. Meta-regression analysis for RASi all-cause mortality outcome. Studies were included in ascending order according to publication year.

Table S5. Meta-regression analysis for RASi combined outcome. Studies were included in ascending order according to publication year.

Table S6. Meta-regression analysis for BB all-cause mortality outcome. Studies were included in ascending order according to publication year.

Table S7. Percentage of patients on background medication in included trials in ascending order according to publication date.

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