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RESEARCH ARTICLE

Sex differences in mineralocorticoid receptor antagonist trials: a pooled analysis of three large clinical trials

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Aims Women with heart failure (HF) are under-represented in individual randomized clinical trials (RCTs). Little is known about sex-specific treatment effects in HF medications. We evaluated sex differences in the response to mineralocorticoid receptor antagonists (MRAs) in major HF MRA trials, including a broad spectrum of left ventricular ejection fraction (LVEF).

Methods and results Individual patient data fixed-effect meta-analysis was performed using 6167 patients (31.4% were women) recruited in three placebo-controlled RCTs: Randomized Aldactone Evaluation Study (RALES), Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) and Spironolactone for Heart Failure with Preserved Ejection Fraction (TOPCAT)-Americas. Compared to men, women were older, had higher body mass index and lower glomerular filtration rate. They also had higher LVEF and poorer New York Heart Association functional class and were less likely to be taking angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers. Placebo-arm event rates were lower for women compared with men (15.4 vs. 22.1 per 100 person-year; $P = 0.002$). MRAs reduced consistently, in men and women, the relative risk for cardiovascular death or HF hospitalization (P for interaction = 0.83), cardiovascular death (P for interaction = 0.44) and all-cause death (P for interaction = 0.19). These findings remained consistent after adjustment for potential confounders, regardless of LVEF. There was no sex-specific impact of MRA on the rate of hyperkalaemia and worsening renal function during the median 22 months of follow-up.

Conclusion In three large MRA RCTs, women were substantially different from men with regard to their clinical features and event rates. Nonetheless, this meta-analysis supports a consistent and beneficial MRA effect regardless of sex.

Keywords Heart failure • Mineralocorticoid receptor antagonists • Meta-analysis • Women

Introduction

Current guidelines recommend the use of mineralocorticoid receptor antagonists (MRAs) in patients with symptomatic heart failure (HF), left ventricular ejection fraction (LVEF) ≤35% and New York Heart Association (NYHA) class II–IV, based on the results of the Randomized Aldactone Evaluation Study (RALES)[1] and the Eplerenone in Mild Patients Hospitalization and Survival

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Study in Heart Failure (EMPHASIS-HF) trial,[2] supported by the findings of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial.[3] Treatment with spironolactone did not show a reduction in the incidence of the time-to-first composite of cardiovascular death, aborted cardiac arrest or HF hospitalizations in patients with LVEF ≥45% in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial[4]; however, important regional differences in patient characteristics, event rates, drug adherence, and treatment effect were identified. Patients in two countries (Georgia and Russia) had low event rates, inconsistent with HF with preserved ejection fraction (HFpEF), and adherence in those countries was poorer than elsewhere.[5–7]

Some controversy has arisen in HF pharmacotherapy in light of the recent findings provided by the Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ARB [Angiotensin-Receptor Blockers] Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial, where a subgroup analysis suggested an heterogeneity of treatment effect with possible benefit of ARNI in women compared to men.[8] These findings should be considered in the context of the Prospective Comparison of ARNI with ACEI [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, which had nearly identical entry criteria apart from a lower LVEF and showed no interaction in treatment effect between women and men.[9]

There are many differences between men and women with HF.[10] Women with HF with reduced ejection fraction (HFrEF) have a better survival than men with the same condition and the same is true for HFpEF.[11,12] Moreover, women are, on average, older than men, have less coronary heart disease but more hypertension.[11,12] They have also worse symptoms and worse renal function and receive less evidence-based therapy than men.[13] These differences raise the possibility of a difference between men and women in relation to the efficacy or tolerability of HF treatments, such as ARNI or MRAs. This possibility has been difficult to evaluate as subgroups in individual trials are, by definition, underpowered, especially as women represent the minority of patients.[14,15] A meta-analytical approach helps mitigate this limitation.

We performed a meta-analysis, using individual patient data from three large randomized clinical trials (RALES, EMPHASIS-HF and TOPCAT), to assess the sex-specific responses to MRA treatment in individuals with HF across a broad spectrum of ejection fraction.

Methods

Study design, setting and participants

We pooled data from three placebo-controlled randomized clinical trials (RCTs): RALES (NYHA class III–IV with LVEF ≤35%)[1], EMPHASIS-HF (NYHA class II with LVEF ≤35%)[2] and TOPCAT (HF signs and symptoms with LVEF ≥45%)[4]. Online supplementary *Table S1* shows the main features of each trial, including inclusion/exclusion criteria, medication (spironolactone or eplerenone), primary endpoint and duration of follow-up. Given regional disparities described in TOPCAT, subsequent *post hoc* analyses of TOPCAT have been restricted to the patients randomized in other countries (all in Latin and North America),[6,7] where patients had characteristics compatible with HFpEF and high proportion of detectable circulating levels of spironolactone metabolites. Therefore, we used only data from the 'Americas' (United States, Canada, Brazil, and Argentina), excluding those from Russia and Georgia.

Each individual RCT was conducted in accordance with the Declaration of Helsinki[16] and approved by site ethics committees. All participants gave written informed consent to participate in the RCTs.

Study outcomes

The primary outcome used in the present analysis was the composite of cardiovascular death or HF hospitalization. Secondary outcomes included cardiovascular death and all-cause mortality. These clinical outcomes were centrally adjudicated by endpoint committees with broadly consistent definitions across the trials.[1,2,4]

Hyperkalaemia was defined as any laboratory value of serum potassium >5.5 mmol/L during follow-up, and worsening renal function was defined as a decline of >30% in estimated glomerular filtration rate (eGFR) during follow-up.

Statistical analysis

Baseline clinical features between men and women were described as frequency (%) and compared using chi-square tests for categorical data, whereas baseline continuous data were expressed as mean and standard deviation (SD) and compared using *t*-tests. The normal distribution of continuous data subset was evaluated using graphical methods.

Incidence rates for men and women (in each of the two treatment groups), as well as incidence rate ratios (for estimating relative risk reduction) and difference in rates (for estimating absolute risk reduction) were estimated for each HF phenotype and for the overall pooled sample. The number needed to treat (NNT) at 3 years was estimated using the inverse of the absolute risk reduction and their 95% confidence interval (CI).

Baseline time was defined by the timing of randomization (online supplementary *Table S1*), which was (i) within 6 months of meeting the inclusion criteria for RALES; (ii) within 6 months after hospitalization for a cardiovascular reason for EMPHASIS-HF; and (iii) within 12 months after hospitalization for HF or with an elevated natriuretic peptide level within 60 days before randomization (B-type natriuretic peptide ≥100 pg/mL or N-terminal pro-B-type natriuretic peptide ≥360 pg/mL). Kaplan–Meier curves for the composite endpoint of cardiovascular death or HF hospitalization were obtained for each subgroup (male-placebo, male-MRA, female-placebo and female-MRA) within each HF phenotype using the Kaplan–Meier method. Cox proportional hazards modelling was used to assess the treatment effect in the overall pooled sample as well as to explore whether this effect was consistent between men and women (adding the interaction *MRA x gender*) into the model and reporting the *P*-value for interaction. Hazard ratios (HRs) with their 95% CI were used for treatment effect estimates. The model was stratified by study, which assumes equal effects across strata but with a baseline hazard unique to each study.[17,18]

A fixed-effect model for a one-stage individual patient data meta-analysis was conducted based on the assumption that the underlying relative treatment effect was similar across trials.[19] In order to obtain an adjusted estimate of the effect of MRA for men and women separately, a set of covariates were chosen according to their clinical relevance or historical association with the outcome in

Table 1 Baseline clinical features by sex (pooled data across the three trials)

	Male (n = 4229)	Female (n = 1938)	P-value
Study, *n* (%)			
EMPHASIS-HF	2127 (50.3)	610 (31.5)	<0.001
RALES	1217 (28.8)	446 (23.0)	
TOPCAT-Americas	885 (20.9)	882 (45.5)	
Demographic data			
Age (years), mean (SD)	67.8 (9.6)	70.1 (10.1)	<0.001
Age > 75 years, *n* (%)	1070 (25.3)	686 (35.4)	<0.001
White race, *n* (%)	3612 (85.4)	1479 (76.3)	<0.001
Body mass index (kg/m^2), mean (SD)	29.2 (6.1)	31.7 (8.4)	<0.001
Current smoker, *n* (%)	1168 (38.8)	170 (11.4)	<0.001
Vital signs, mean (SD)			
Heart rate (bpm)	73.5 (13.9)	73.6 (13.1)	0.730
Systolic blood pressure (mmHg)	123.5 (17.2)	126.9 (18.5)	<0.001
Diastolic blood pressure (mmHg)	73.7 (10.8)	73.6 (11.5)	0.730
Medical history, *n* (%)			
Hypertension	2441 (57.8)	1359 (70.1)	<0.001
Diabetes	1354 (32.0)	661 (34.1)	0.110
Previous MI	1866 (44.2)	557 (28.7)	<0.001
Atrial fibrillation/flutter	1114 (26.5)	390 (20.2)	<0.001
COPD	675 (16.0)	234 (12.1)	<0.001
Heart failure history			
Left ventricular ejection fraction (%), mean (SD)	32.3 (14.0)	41.7 (18.1)	<0.001
≤35%, *n* (%)	3218 (78.3)	1024 (53.7)	<0.001
>45%, *n* (%)	886 (21.6)	882 (46.3)	
NYHA class, *n* (%)			
II	2726 (64.6)	1153 (59.6)	<0.001
III–IV	1497 (35.5)	782 (40.4)	
Previous HF hospitalization, *n* (%)	1653 (54.9)	826 (55.4)	0.790
Laboratory tests			
Haemoglobin (g/dL), mean (SD)	13.7 (2.0)	12.6 (2.2)	<0.001
Potassium (mmol/L), mean (SD)	4.3 (0.4)	4.2 (0.5)	<0.001
Sodium (mmol/L), mean (SD)	139.5 (4.4)	139.7 (3.6)	0.190
MDRD eGFR (mL/min/1.73 m^2), mean (SD)	68.4 (22.9)	62.7 (21.4)	<0.001
MDRD eGFR <60 mL/min/1.73 m^2, *n* (%)	1608 (38.3)	988 (51.8)	<0.001
Medications, *n* (%)			
ACEI or ARB	3830 (90.6)	1666 (86.0)	<0.001
Beta-blocker	2698 (63.8)	1224 (63.2)	0.620
Diuretic	3779 (89.4)	1745 (90.0)	0.430
Digoxin	1292 (38.6)	442 (41.9)	0.062
Lipid-lowering drug	2064 (48.8)	894 (46.1)	0.050
Anti-thrombotics	2892 (68.4)	1136 (58.6)	<0.001

ACEI, angiotensin-converting enzyme-inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; MRA; mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.

previous studies[18,20]: MRA, gender, age, race, systolic blood pressure, diabetes, hypertension, atrial fibrillation, ischaemic cause, NYHA class III–IV, LVEF, potassium, eGFR, diuretics, ACEI or ARB, beta-blockers and the interaction (*MRA x gender*). Further subgroup evaluations for the primary outcome were performed with a Cox model stratified by study, using the adjusted model and adding a three-way interaction for three clinically relevant patient subsets (age > 75 years, diabetes and eGFR <60mL/min/1.73 m^2).

Visual inspection of individual effect sizes and overall effect size estimations and their 95% CI were used to identify substantial variation in treatment effect estimates across trials beyond the variation expected by chance alone (statistical heterogeneity). Heterogeneity was formally tested using a 2 degree of freedom Wald test of the overall interaction *study x treatment x gender*.

Logistic regression models were used to assess whether the number of adverse events (hyperkalaemia and worsening renal function) were consistent between men and women at the end of follow-up. An interaction term (*MRA x gender*) was used to report whether adverse events differed by gender and the statistical significance was determined by the relevant *P*-value for interaction.

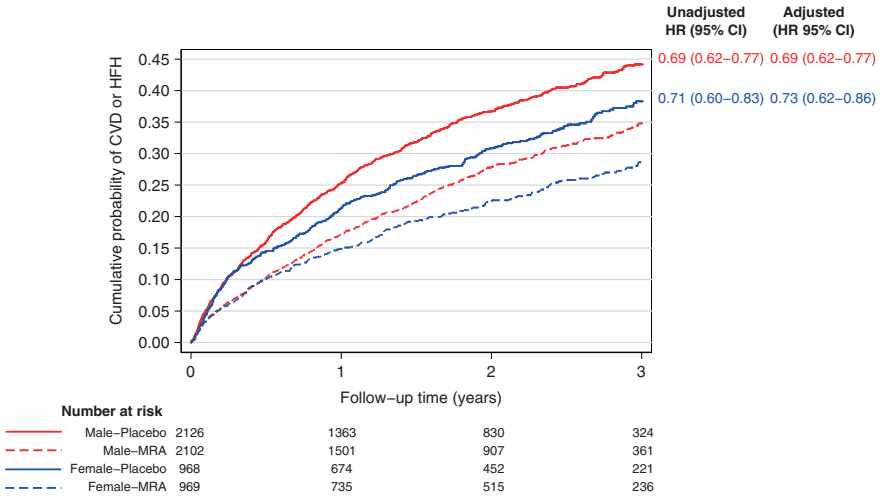

Figure 1 Kaplan–Meier survival curve for cardiovascular death (CVD) or heart failure hospitalization (HFH) by gender and treatment arm. Cumulative time-to-first-event curves for patients randomly assigned to mineralocorticoid receptor antagonist (MRA) vs. placebo by gender. Estimates for men and women are displayed in red and blue, respectively. CI, confidence interval; HR, hazard ratio.

The two-tailed significance level was set at 5%. STATA software version 15.1 (Stata Corp, College Station, TX, USA) was used to perform the analyses and produce most graphs. XR had full access to all the data in the study and takes responsibility for its integrity and data analysis.

Results

Sex differences in baseline variables

Individual patient data from the three randomised trials (RALES, EMPHASIS-HF and TOPCAT-Americas) were available for 6167 patients. Of these, 4229 (68.6%) were men (2127 and 2102 randomly allocated to placebo and MRA, respectively) and 1938 (31.4%) were women (968 and 970 randomly assigned to placebo and MRA, respectively). The median follow-up was 22 months (interquartile range 9–33 months) (the individual follow-up times of each RCT are given in online supplementary *Table S1*).

Baseline clinical features, medical history, laboratory findings and background treatment at randomization, according to sex, are shown in *Table 1*. Generally, women were older (35.4% vs. 25.3% were > 75 years) and had higher body mass index and poorer renal function (51.8% vs. 38.3% had eGFR <60 mL/min/1.73 m^2). Women more frequently had a history of hypertension, but less often a history of myocardial infarction, atrial fibrillation and chronic obstructive pulmonary disease. Women also had a significantly higher mean LVEF (32.3% vs. 41.7%) and poorer overall NHYA functional class. They were also less likely to be treated with an ACEI or ARB (86.0% vs. 90.6%), but there were no significant differences between men and women regarding beta-blocker and diuretic use. These data stratified by HF type (HFrEF vs. HFpEF) are presented in online supplementary *Table S2*.

Unadjusted treatment effect

Overall and by HF phenotype Kaplan–Meier curves for cardiovascular death or HF requiring hospitalization are described in *Figures 1* and *2*, respectively. The unadjusted incidence rate ratios and incidence rate differences are shown in *Table 2*. The effect of MRA therapy on the primary outcome was consistent between men and women overall and within each HF phenotype, though the relative risk reduction was greater in HFrEF compared with HFpEF. Consequently, the absolute reduction in number of events was greater in the subset of patients from RALES (NYHA class III–IV; LVEF ≤35%) and EMPHASIS-HF (NYHA class II, LVEF ≤35%) in comparison to those in TOPCAT-Americas (LVEF ≥45%), although the effect did not differ between men and women within each trial cohort (online supplementary *Table S2*).

After pooling the data, the primary outcome of cardiovascular death or HF hospitalization occurred in 798 men (37.5%) and 330 women (34.1%) taking placebo ($P = 0.002$), and in 602 men (28.6%) and 251 women (25.9%) taking an MRA. The overall unadjusted HR was 0.70 (95% CI 0.64–0.76), and was consistent between men (HR 0.69; 95% CI 0.62–0.77) and women (HR 0.71; 95% CI 0.60–0.83), as shown in *Figure 3* (P for interaction = 0.83). The overall absolute risk reduction of the primary composite outcome at 3 years was 10%, which provides an NNT of 10 (95% CI 8–14) patients at 3 years to avoid one event, and was consistent between men (NNT 10; 95% CI 8–15) and women (NNT 10; 95% CI 7–19).

The risk reductions in secondary outcomes were also relatively consistent between men and women (*Table 3*). For cardiovascular death, the unadjusted HR was 0.75 (95% CI 0.65–0.86) for men and 0.67 (95% CI 0.54–0.85) for women (P for interaction = 0.44), whereas for all-cause mortality the unadjusted HR was 0.80 (95% CI 0.71–0.90) for men and 0.69 (95% CI 0.56–0.84) for women (P for interaction = 0.19).

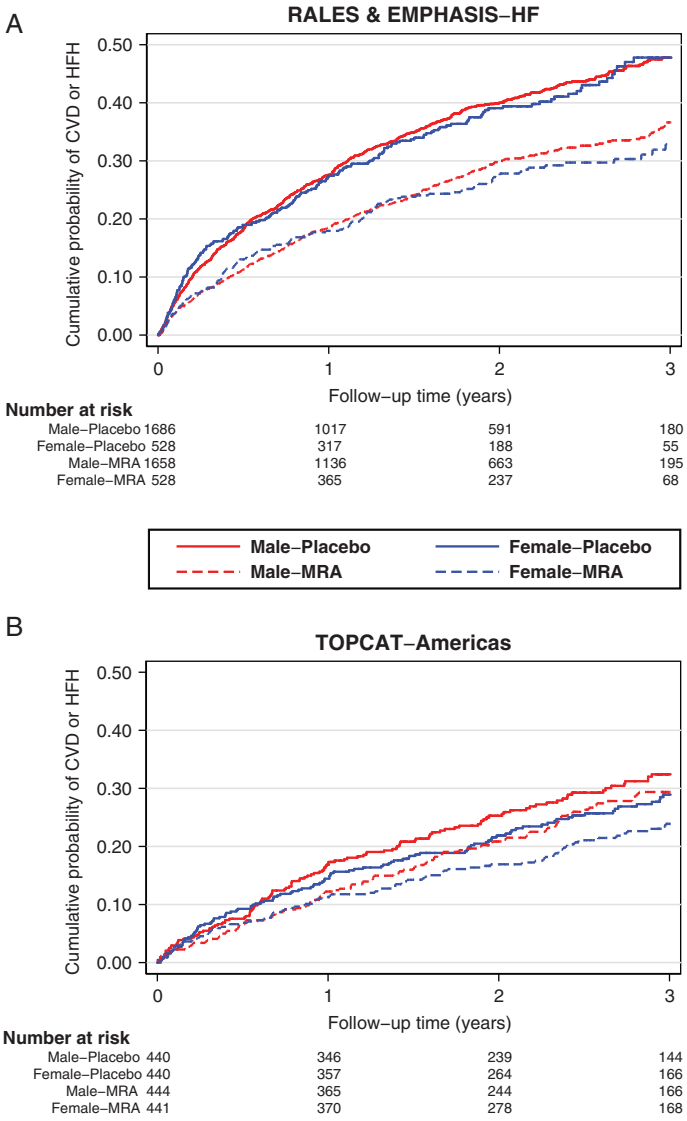

Figure 2 Kaplan–Meier survival curves for cardiovascular death (CVD) or heart failure hospitalization (HFH) by gender and treatment arm. Cumulative time-to-first-event curves for patients randomly assigned to mineralocorticoid receptor antagonist (MRA) vs. placebo by gender in heart failure patients with left ventricular ejection fraction ≤35% (*A*) and in heart failure patients with left ventricular ejection fraction ≥45% (*B*).

Adjusted treatment effect

After adjustment for baseline covariates (gender, age, race, systolic blood pressure, diabetes, hypertension, atrial fibrillation, non-ischaemic cause, NYHA class III–IV, LVEF, potassium, eGFR, diuretics, ACEI or ARB treatment, beta-blocker treatment), the treatment effect remained relatively consistent between men and women and within the HFrEF and HFpEF phenotypes (*Figure 3*): the MRA vs. placebo HR was 0.65 (95% CI 0.58–0.74) for men and 0.67 (95% CI 0.54–0.83) for women with HFrEF and 0.85 (95% CI 0.67–1.08) for men and 0.83 (95% CI 0.64–1.07) for women with HFpEF. In the adjusted analysis of all patients, irrespective of LVEF, MRA treatment reduced the risk of cardiovascular death or HF hospitalization by 31% in men (HR 0.69; 95% CI 0.62–0.77) and by 27% in women (HR 0.73; 95% CI 0.62–0.86).

Statistical heterogeneity

The individual effect size for each trial and overall effect size estimations and their 95% CI depicted in online supplementary *Figure S1* already suggest the lack of substantial statistical heterogeneity between RALES and EMPHASIS-HF cohorts. Similarly, the individual effect size for HFrEF and HFpEF subjects depicted in *Table 2* and *Figure 3* also suggest the lack of statistical heterogeneity. The hypothesis of little heterogeneity is also supported

Table 2 Time at risk, number of events and estimated incidence rates for the primary endpoint (cardiovascular mortality or heart failure hospitalization)

	Total person-time at risk	No. of events	Incidence rate (95% CI)	Incidence rate ratio (95% CI)	Absolute difference in rates (95% CI)
HFrEF (RALES + EMPHASIS-HF)					
Male-placebo	2528.7	648	25.6 (23.7–27.7)	0.67 (0.59–0.75)	8.5 (6.0–11.0)
Male-MRA	2755.1	471	17.1 (15.6–18.7)		
Female-placebo	788.3	200	25.4 (22.1–29.1)	0.61 (0.49–0.77)	9.8 (5.4–14.1)
Female-MRA	897.5	140	15.6 (13.2–18.4)		
HFpEF (TOPCAT-Americas)					
Male-placebo	1081.9	150	13.9 (11.8–16.3)	0.82 (0.65–1.05)	2.5 (−0.5–5.4)
Male-MRA	1149.6	131	11.3 (9.5–13.5)		
Female-placebo	1146.9	130	11.4 (9.6–13.5)	0.81 (0.63–1.06)	2.1 (−0.5–4.7)
Female-MRA	1204.4	111	9.2 (7.7–11.1)		
Overall					
Male-placebo	3610.5	798	22.1 (20.6–23.7)	0.70 (0.63–0.78)	6.7 (4.7–8.7)
Male-MRA	3904.7	602	15.4 (14.2–16.7)		
Female-placebo	1935.2	330	17.1 (15.3–19.0)	0.70 (0.59–0.83)	5.1 (2.8–7.5)
Female-MRA	2101.9	251	11.9 (10.6–13.5)		

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist. By trial and overall estimated incidence rates and absolute differences in rates for the primary endpoint. Total person-time at risk is expressed in 100 person-year.

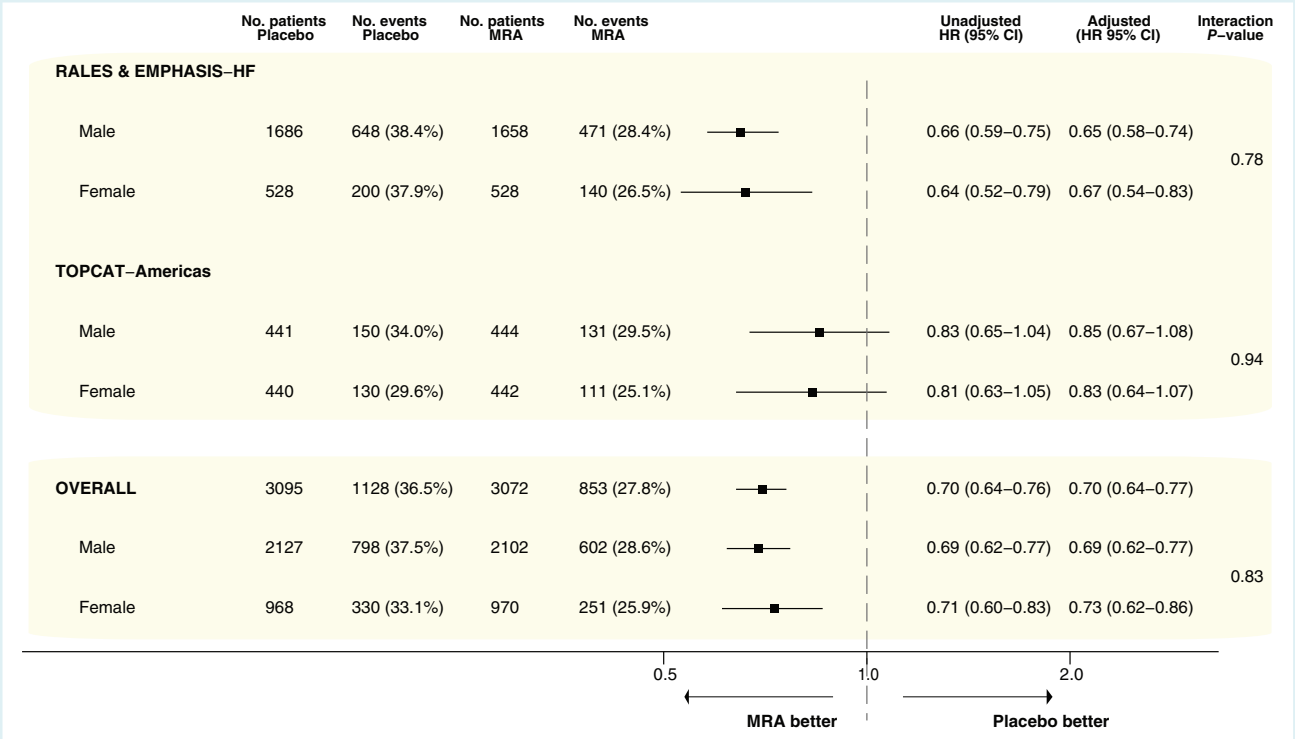

Figure 3 Forest plot with crude and adjusted hazard ratio (HRs) for cardiovascular death or heart failure hospitalization by gender. Adjusted HRs are plotted in this figure, although both unadjusted and adjusted HRs are reported in the right side. Model adjusted for mineralocorticoid receptor antagonist (MRA), gender, age, systolic blood pressure, diabetes, hypertension, atrial fibrillation, non-ischaemic cause, New York Heart Association class III–IV, left ventricular ejection fraction, potassium, estimated glomerular filtration rate, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers and the interaction (MRA x gender). CI, confidence interval.

Table 3 Time at risk, number of events and estimated incidence rates for the secondary endpoints (cardiovascular death and all-cause death)

	Total person-time at risk	No. of events	Incidence rate (95% CI)	Incidence rate ratio (95% CI)	Absolute difference in rates (95% CI)
Cardiovascular death					
HFrEF (RALES + EMPHASIS-HF)					
Male-placebo	2958.7	402	13.6 (12.3–15.0)	0.75 (0.65–0.87)	3.4 (1.6–5.1)
Male-MRA	3046.7	311	10.2 (9.1–11.4)		
Female-placebo	939.1	121	12.9 (10.8–15.4)	0.66 (0.49–0.87)	4.4 (1.5–7.4)
Female-MRA	994.1	84	8.5 (6.8–10.5)		
HFpEF (TOPCAT-Americas)					
Male-placebo	1271.1	69	5.4 (4.3–6.9)	0.79 (0.55–1.14)	1.1 (–0.01–2.8)
Male-MRA	1302.7	56	4.3 (3.3–5.6)		
Female-placebo	1331.8	58	4.4 (3.4–5.6)	0.68 (0.44–1.03)	1.4 (0.0–2.9)
Female-MRA	1360.5	40	2.9 (2.2–4.0)		
Overall					
Male-placebo	4229.8	471	11.1 (10.2–12.2)	0.76 (0.66–0.87)	2.7 (1.3–4.0)
Male-MRA	4349.4	367	8.4 (7.6–9.3)		
Female-placebo	2270.9	179	7.9 (6.8–9.1)	0.67 (0.53–0.84)	2.6 (1.1–4.1)
Female-MRA	2354.5	124	5.3 (4.4–6.3)		
All-cause death					
HFrEF (RALES + EMPHASIS-HF)					
Male-placebo	2958.7	460	15.5 (14.2–17.0)	0.76 (0.66–0.87)	3.7 (1.9–5.6)
Male-MRA	3046.7	360	11.8 (10.7–13.1)		
Female-placebo	939.1	139	14.8 (12.5–17.5)	0.66 (0.50–0.86)	5.0 (1.9–8.2)
Female-MRA	994.1	97	9.8 (8.0–11.9)		
HFpEF (TOPCAT-Americas)					
Male-placebo	1271.1	107	8.4 (7.0–10.2)	1.02 (0.78–1.34)	–0.2 (–2.4–2.1)
Male-MRA	1302.7	112	8.6 (7.1–10-3)		
Female-placebo	1331.8	98	7.4 (6.0–9.0)	0.70 (0.51–0.96)	2.2 (0.3–4.1)
Female-MRA	1360.5	70	5.1 (4.1–6.5)		
Overall					
Male-placebo	4229.8	567	13.4 (12.3–14.6)	0.81 (0.71–0.92)	2.5 (1.14.0)
Male-MRA	4349.4	472	10.9 (9.9–11.9)		
Female-placebo	2270.9	237	10.4 (9.2–11.9)	0.68 (0.55–0.83)	3.3 (1.6–5.1)
Female-MRA	2354.5	167	7.1 (6.1–8.3)		

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist. By-trial and overall estimated incidence rates and absolute differences in rates for cardiovascular and all-cause mortality. Total person-time at risk is expressed in 100 person-year.

by the Wald test for overall interaction *study x treatment x gender* ($P = 0.61$).

Subgroup analyses

Treatment effect was consistent between men and women across the three pre-specified subgroups examined, i.e. age > 75 vs. age ≤ 75 years, diabetes vs. no diabetes, and eGFR <60 vs. ≥60 mL/min/1.73 m^2 after adjustment for baseline covariates (*Figure 4*).

Adverse event effects

Differences in adverse events between men and women were consistent across treatment arms (*Table 4*). There were no significant sex-related differences in the rate of hyperkalaemia either in the placebo arm or the MRA arm (P for interaction = 0.94). By contrast, women more often had worsening renal function over follow-up in the placebo arm, though the between treatment group differences were similar by sex (P for interaction = 0.81).

Discussion

In this meta-analysis using individual patient-level data, including 6167 subjects, representing the full spectrum of LVEF, we found that: (i) women differed substantially from men with respect to baseline characteristics (they were older, had a higher body mass index, poorer renal function and fewer co-morbidities,

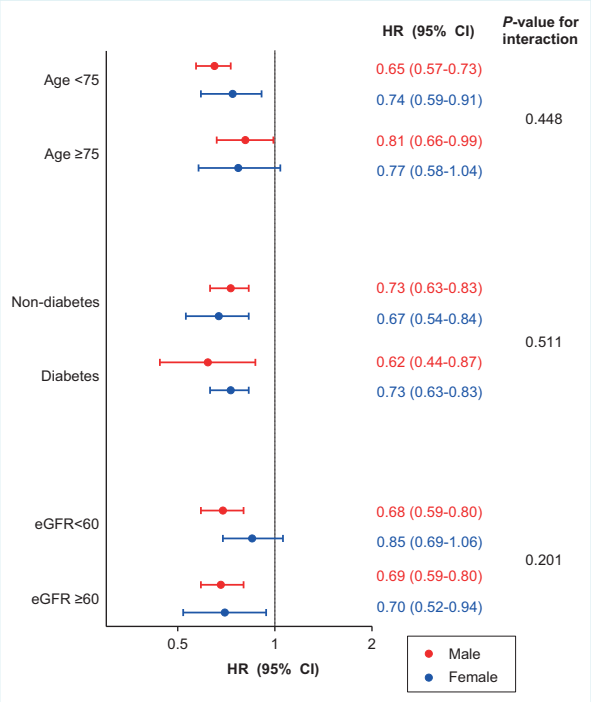

Figure 4 Adjusted hazard ratios (HRs) for cardiovascular death or heart failure hospitalization by gender and other relevant groups. *P*-values correspond to three-way interactions using the adjusted model – i.e. mineralocorticoid receptor antagonist x gender x diabetes. CI, confidence interval; eGFR, estimated glomerular filtration rate.

except for hypertension), had a higher mean LVEF, poorer NHYA functional class and were less likely to be treated with an ACEI or ARB; (ii) men were at higher risk of events than women; (iii) MRA consistently reduced the risk for cardiovascular death and HF hospitalization after a mean follow-up of 22 months; (iv) by sex treatment effect remained consistent after adjustment for potential confounders, confirming the lack of interaction between treatment effect and sex; (v) treatment effect was consistent between men and women across the three subgroups of patients studied (age > 75 years, diabetes and eGFR <60 mL/min/1.73 m^2) after adjustment for baseline covariates; and (vi) there was no sex-specific impact of MRA on hyperkalaemia and worsening renal function.

Men and women differ in relation to the physiology of their cardiovascular system (i.e. body composition and role of hormonal changes[21]), in risk factors for cardiovascular disease, presentation with cardiovascular disease and outcomes from cardiovascular disease. Moreover, there are also sex-related differences in the pharmacokinetics and pharmacodynamics among some of widely used cardiovascular drugs.[10,22] Thus, it is important to understand the sex-specific efficacy and tolerability of any therapy for cardiovascular disease. However, this type of analysis requires a dataset large enough to give statistically powered information. This issue is illustrated by the results of early trials with ACEI suggesting a benefit only in men,[22] when subsequent meta-analyses with greater statistical power showed no sex-related difference in treatment effect.[23] In contrast, we have incipient but apparently contradictory information from a younger drug (ARNI) in HFpEF: the PARAGON-HF trial reported a subgroup analysis suggesting a heterogeneity of treatment effect with possible benefit of ARNI

Table 4 Side effects within treatment arm by sex (pooled data across the three trials)

	MRA			Placebo			*P* for interaction
HFrEF (RALES+EMPHASIS-HF)	**Male (*n* = 1658)**	**Female (*n* = 528)**	***P*-value**	**Male (*n* = 1686)**	**Female (*n* = 528)**	***P*-value**	
Hyperkalaemia, *n* (%)	241 (14.9)	71 (1.0)	0.617	115 (7.0)	37 (7.2)	0.891	0.683
Worsening renal function, *n* (%)	446 (28.9)	165 (33.7)	0.040	311 (20.0)	123 (25.3)	0.012	0.630
HFpEF (TOPCAT-Americas)	**Male (*n* = 444)**	**Female (*n* = 442)**	***P*-value**	**Male (*n* = 441)**	**Female (*n* = 440)**	***P*-value**	
Hyperkalaemia, *n* (%)	73 (16.5)	68 (15.4)	0.657	22 (5.0)	24 (5.5)	0.762	0.625
Worsening renal function, *n* (%)	175 (39.4)	214 (48.5)	0.006	129 (29.3)	160 (36.4)	0.025	0.811
Overall	**Male (*n* = 2102)**	**Female (*n* = 970)**	***P*-value**	**Male (*n* = 2127)**	**Female (*n* = 968)**	***P*-value**	
Hyperkalaemia, *n* (%)	314 (15.2)	139 (14.7)	0.679	137 (6.6)	61 (6.4)	0.840	0.944
Worsening renal function, *n* (%)	621 (31.2)	379 (40.8)	<0.001	440 (22.0)	283 (30.6)	<0.001	0.813

HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.
Hyperkalaemia was defined as any laboratory value of serum potassium >5.5 mmol/L during follow-up. Worsening renal function was defined as an estimated glomerular filtration rate drop >30% during follow-up. Within gender comparison were made using the chi-square test, whereas differences in adverse event effects were tested using the interaction (MRA x gender) in a logistic regression. The hypothesis of little heterogeneity is also supported by the Wald test for overall interaction study x treatment x gender for both hyperkalaemia ($P = 0.85$) and worsening renal function ($P = 0.84$).

in women with respect to men (rates ratios of 0.73 and 1.03 for the composite outcome of total hospitalizations for HF and cardiovascular death, respectively),[8] whereas the PARADIGM-HF trial, which had nearly identical entry criteria apart from a lower LVEF, showed no interaction in treatment effect between women and men.[9] Notably, women (who represent a high proportion of HFpEF patients) were far more represented in the PARAGON-HF trial (51.7%) in comparison to the PARADIGM-HF trial (21.8%), though absolute numbers were more similar between trials. Importantly, we found that the benefit of MRA therapy was consistent between men and women across three large RCTs.

In line with the previous reports,[11–13,24] and as described above, there were many differences in the baseline characteristics of men and women. Our baseline characteristics data match those reported in the 'real-world' by the Swedish Heart Failure Registry[15]: women were older, and more symptomatic and more likely to have hypertension and poor renal function than men. Despite they show that women had a higher crude risk of mortality and morbidity in HFpEF,[15] their results after adjustment are in line with our findings showing that women have a lower crude risk for poor outcomes regardless of LVEF, though less differences between men and women are observed in our HFrEF subset of patients. Importantly, the treatment benefit of MRA therapy did not change substantially after adjusting for these and other potential confounders, which have an impact on clinical outcomes and are unevenly distributed between men and women.

At first sight, our results appear to contradict a recent secondary analysis from the TOPCAT-Americas suggesting a potential reduction in all-cause mortality associated with spironolactone in women that was not observed in men after adjustment for potential confounding (HR were 0.66 and 1.06 for women and men, respectively; P for interaction = 0.024).[25] Of note, this analysis did not find a significant interaction for the primary endpoint or other outcomes, including cardiovascular mortality, which seems much more appropriate to study the treatment effect provided by MRA, as we should expect little gain on non-cardiovascular causes of death by administering MRAs. It is likely that this reflects a spurious, chance finding reflecting the small numbers of events in the TOPCAT-Americas analysis, a conclusion supported by the finding of a mortality benefit from MRA therapy in our much larger and statistically more robust study. A different pathophysiology in women[10–12] or a simple regression to the mean might less likely explain the disagreement between our findings and those reported by Merrill and colleagues.[25] Some ongoing studies, such as the Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRRIT, NCT02901184) and the SPIRonolactone In the Treatment of Heart Failure (SPIRIT-HF, EudraCT 2017–000697-11) may shed some light on the issue of whether MRA has a different treatment effect between men and women in HFpEF.

We examined three clinically important subgroups of patients at particularly high risk of events in which there is often concern about using MRA therapy, i.e. the elderly, patients with diabetes and those with a low eGFR. We found that there was no evidence of a sex-related difference in either the efficacy or safety of MRA therapy in these subgroups.

In line with previous reports,[26] our findings on adverse event effects underscore the need to measure serum potassium and creatinine levels serially and to adjust accordingly the dose of MRA regardless of the gender of the patient. Other factors, such as eGFR, have a greater impact on the rate of side effects and drug discontinuation and should be taken into account to adjust for the dose of MRAs, and more broadly renin–angiotensin–aldosterone system inhibitors.[27,28]

Study limitations

We did not include a number of small trials which studied MRA treatment in patients with HF, because these had few events and are unlikely to alter our conclusions. We also combined two HFrEF trials with a HFpEF trial when these two HF phenotypes are distinct and do not respond to all therapies in a similar manner. Finally, our results are based on the assumption that MRAs represent a 'class effect',[29] although spironolactone and eplerenone differ in their molecular structure, pharmacokinetics and pharmacodynamics.

Conclusions

In this large meta-analysis using individual patient data, women were substantially different from men with regard to their clinical features and events. Nevertheless, MRA treatment led to consistent reductions in the risk for cardiovascular death and HF hospitalization, cardiovascular death alone and all-cause death, in both men and women, regardless of their NYHA class, LVEF and other confounding factors. Treatment-related hyperkalaemia and worsening renal function did not vary by sex. Both men and women can benefit from optimizing the use of an MRA treatment, which is commonly underused in routine practice. These findings are particularly important in the light of recent findings suggesting a different treatment effect between men and women with some HF drugs, such as ARNI.

Supplementary Information

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

Table S1. Major characteristics of the three randomized clinical trials

Table S2. Baseline clinical features by sex and type of heart failure.

Figure S1. Forest plot with crude and adjusted hazard ratios for cardiovascular death or heart failure hospitalization by gender in RALES and EMPHASIS-HF.

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