Mineralocorticoid receptor antagonists in heart failure: an individual patient level meta-analysis

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Summary

Background Mineralocorticoid receptor antagonists (MRAs) reduce hospitalisations and death in patients with heart failure and reduced ejection fraction (HFrEF), but the benefit in patients with heart failure and mildly reduced ejection fraction (HFmrEF) or heart failure and preserved ejection fraction (HFpEF) is unclear. We evaluated the effect of MRAs in four trials that enrolled patients with heart failure across the range of ejection fraction.

Methods This is a prespecified, individual patient level meta-analysis of the RALES (spironolactone) and EMPHASIS-HF (eplerenone) trials, which enrolled patients with HFrEF, and of the TOPCAT (spironolactone) and FINEARTS-HF (finerenone) trials, which enrolled patients with HFmrEF or HFpEF. The primary outcome of this meta-analysis was a composite of time to first hospitalisation for heart failure or cardiovascular death. We also estimated the effect of MRAs on components of this composite, total (first or repeat) heart failure hospitalisations (with and without cardiovascular deaths), and all-cause death. Safety outcomes were also assessed, including serum creatinine, estimated glomerular filtration rate, serum potassium, and systolic blood pressure. An interaction between trials and treatment was tested to examine the heterogeneity of effect in these populations. This study is registered with PROSPERO, CRD42024541487.

Findings 13 846 patients were included in the four trials. MRAs reduced the risk of cardiovascular death or heart failure hospitalisation (hazard ratio 0·77 [95% CI 0·72–0·83]). There was a statistically significant interaction by trials and treatment (p for interaction=0·0012) due to the greater efficacy in HFrEF (0·66 [0·59–0·73]) compared with HFmrEF or HFpEF (0·87 [0·79–0·95]). We observed significant reductions in heart failure hospitalisation in the HFrEF trials (0·63 [0·55–0·72]) and the HFmrEF or HFpEF trials (0·82 [0·74–0·91]). The same pattern was observed for total heart failure hospitalisations with or without cardiovascular death. Cardiovascular death was reduced in the HFrEF trials (0·72 [0·63–0·82]) but not in the HFmrEF or HFpEF trials (0·92 [0·80–1·05]). All-cause death was also reduced in the HFrEF trials (0·73 [0·65–0·83]) but not in the HFmrEF or HFpEF trials (0·94 [0·85–1·03]). With an MRA, the risk of hyperkalaemia was doubled compared with placebo (odds ratio 2·27 [95% CI 2·02–2·56]), but the incidence of serious hyperkalaemia (serum potassium >6·0 mmol/L) was low (2·9% *vs* 1·4%); the risk of hypokalaemia (potassium <3·5 mmol/L) was halved (0·51 [0·45–0·57]; 7% *vs* 14%).

Interpretation Steroidal MRAs reduce the risk of cardiovascular death or heart failure hospitalisation in patients with HFrEF and non-steroidal MRAs reduce this risk in patients with HFmrEF or HFpEF.

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Introduction

The steroidal mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone have been shown to decrease the risk of death and hospitalisation in patients with heart failure and reduced ejection fraction (HFrEF) in two pivotal clinical trials: RALES (Randomized Aldactone Evaluation Study)[1] and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure).[2] As a result, international guidelines make consistent and strong recommendations for spironolactone and eplerenone in patients with HFrEF.[3] By contrast, the efficacy of these agents in heart failure and mildly reduced ejection fraction (HFmrEF) or heart failure and preserved ejection fraction (HFpEF) is uncertain. Specifically, spironolactone did not improve the primary outcome of first heart failure hospitalisation, resuscitated cardiac arrest, or cardiovascular death in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial.[4] However, a substantial proportion of participants in that trial might not have had heart failure because their event rates were much lower than expected, or might not have taken the randomly assigned treatment (many randomly assigned to spironolactone had no detectable metabolite in their urine), and post hoc analyses suggested possible benefit in those who did.[5,6] Consequently, guideline recommendations for MRAs in HFmrEF or HFpEF are weak or absent.[3,7] The question of whether the

Research in context

Evidence before this study

Clinical practice guidelines give a strong recommendation (class I) for the use of mineralocorticoid receptor antagonists (MRAs) in heart failure and reduced ejection fraction (HFrEF) based on two large randomised trials. By contrast, guidelines give either a weak recommendation or no recommendation for MRAs in heart failure and mildly reduced ejection fraction (HFmrEF) or heart failure and preserved ejection fraction (HFpEF) because the steroidal MRA spironolactone did not show significant benefit in this population.

Added value of this study

We performed an individual patient level meta-analysis of four large, prospective placebo-controlled trials of MRAs in heart failure. This analysis included almost 14 000 patients and confirms the large benefit in patients with HFrEF. It also shows that MRAs reduce the risk of the composite of cardiovascular death or hospitalisation for heart failure in patients with heart failure and an ejection fraction of 40% or greater. The benefits were consistent across a broad range of subgroups.

Implications of all the available evidence

This individual patient level meta-analysis shows that steroidal MRAs reduce the risk of cardiovascular death or heart failure hospitalisation in patients with HFrEF and non-steroidal MRAs reduce this risk in HFmrEF or HFpEF, and it supports their use in patients without a contraindication to treatment.

See Online for appendix

non-steroidal MRA finerenone is efficacious in patients with HFmrEF or HFpEF was evaluated in the FINEARTS-HF trial (the finerenone trial to investigate efficacy and safety superior to placebo in patients with heart failure).[8] Unlike spironolactone and eplerenone, finerenone is a non-steroidal MRA, a class with different physiochemical properties, and in FINEARTS-HF, finerenone significantly reduced the risk of the primary composite outcome of total worsening heart failure events and cardiovascular death in patients with heart failure and an ejection fraction of 40% or higher. We undertook a prespecified individual patient level meta-analysis of the four MRA trials to test the consistency of the effects of mineralocorticoid receptor antagonism across important clinical outcomes, including endpoints that no single trial was designed or powered to examine, such as cardiovascular mortality, and across both MRA classes. Furthermore, we examined key safety outcomes and the efficacy and safety of treatment over a range of clinically important subpopulations, including those at the highest end of the ejection fraction range and with kidney dysfunction.

Methods

Search strategy and selection criteria

For the **protocol for this meta-analysis** see https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024541487

Our prespecified aim was to study the efficacy and safety of MRAs across the full range of ejection fraction in patients with heart failure and according to MRA class. We analysed the RALES trial of spironolactone in patients with heart failure and left ventricular ejection fraction (LVEF) of 35% or less;[1] the EMPHASIS-HF trial of eplerenone in patients with heart failure and LVEF of 35% or less (if LVEF >30% to 35%, a QRS duration of >130 msec on electrocardiography was required);[2] the TOPCAT trial of spironolactone in patients with heart failure and LVEF of 45% or greater;[4] and the FINEARTS-HF trial of finerenone in patients with heart failure and LVEF of 40% or greater.[8] Key information on the included trials and their inclusion and exclusion criteria, along with the primary outcomes of each of the trials, is given in the appendix (p 2). BP and FZ were members of the steering committee for the RALES trial; FZ, BP, and JJVM were members of the steering committee for the EMPHASIS-HF trial; BP, SDS, and ASD were members of the executive committee, SJS was on the publication committee, and BLC was an independent statistician for the TOPCAT trial; and SDS, JJVM, MV, MS, SJS, AAV, CSPL, BP, and FZ were on the steering committee, PSJ and ASD were on the endpoint adjudication committee, and ADH, AT, and BLC were independent statisticians for the FINEARTS-HF trial. To ensure that we did not exclude any other important trials we conducted a systematic review of MEDLINE via PubMed of randomised trials of MRAs in patients with heart failure, published from database inception to June 1, 2024. The search strategy is detailed in the appendix (pp 4–5). Trials were included if they enrolled at least 1000 patients with heart failure with an appropriately powered morbidity or mortality outcome. No further trials were identified from the search (appendix p 6). Data from the FINEARTS-HF trial were unpublished at the time of analysis and were included with permission from the steering committee and trial sponsor.

The protocol and statistical analysis plan for this meta-analysis were prespecified before the FINEARTS-HF trial database was locked and were pre-registered on PROSPERO, CRD42024541487. All participants provided written consent, and the study protocols were approved by the ethics committees at all participating sites.

Data analysis

Data were extracted, harmonised, and analysed by two authors (AT and ADH), with discrepancies resolved by two authors (PSJ and JJVM).

The primary outcome of interest in this meta-analysis was a composite of time to first hospitalisation for heart failure or cardiovascular death. Secondary outcomes examined were time to first hospitalisation for heart

failure, total (first and repeat) heart failure hospitalisations, total heart failure hospitalisations and cardiovascular death, cardiovascular death, and all-cause death. In each trial, outcomes were adjudicated by a masked clinical endpoints committee. Cardiovascular death was analysed according to the original definition reported in each of the trials. Because the definition of cardiovascular death included undetermined deaths (deaths to which the adjudication committee could not assign a cardiovascular or non-cardiovascular cause) in RALES, EMPHASIS-HF, and TOPCAT but not in FINEARTS-HF, we conducted a sensitivity analysis with and without undetermined deaths counted as cardiovascular deaths. Unlike the older trials, FINEARTS-HF included urgent visits for worsening heart failure in the primary composite outcome as an equivalent to heart failure hospitalisation, reflecting changing clinical practice aimed at reducing admissions (and a practice which might have been more common during the COVID-19 pandemic). These events were defined as urgent, unscheduled ambulatory, or emergency room visits for the primary diagnosis of heart failure requiring intravenous diuretic or a vasoactive agent or mechanical or surgical intervention for heart failure. Intensification of an oral diuretic alone was not sufficient to meet this definition.

The effect of MRAs on the primary outcome was examined in key subgroups of interest, including age, sex, race, geographical region, BMI, New York Heart Association class, LVEF, history of previous hospitalisation for heart failure, N-terminal pro B-type natriuretic peptide, estimated glomerular filtration rate (eGFR), potassium, systolic blood pressure, history of diabetes, myocardial infarction, atrial fibrillation, stroke, and treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β blocker, diuretic, or a digitalis glycoside. A further subgroup of interest was the efficacy of steroidal MRAs (spironolactone and eplerenone) versus non-steroidal MRAs (finerenone).

Safety outcomes were examined in patients who received at least one dose of randomly assigned treatment. The outcomes of interest included serum creatinine of 2·5 mg/dL or higher and 3·0 mg/dL or higher, a more than 20% and more than 30% decline in eGFR, serum potassium of less than 3·5 mmol/L, greater than 5·5 mmol/L, and greater than 6 mmol/L, and systolic blood pressure of less than 90 mm Hg and less than 100 mm Hg.

For all time-to-first-event outcomes, point estimates from Cox proportional hazards models are presented as hazard ratios (HRs) with 95% CIs on an intention-to-treat basis. These models included a term for randomised treatment and were stratified by trial. Event rates for time to first events were calculated per 100 person-years and estimated using the normal approximation to the Poisson log-likelihood. For analysis of total events, rate ratios (RRs) with 95% CIs are presented from a negative binomial model because the time to subsequent hospitalisations was not available in RALES. The results were confirmed in a semi-parametric proportional rates model with a factor for randomised treatment and stratified by trial, excluding RALES but including the other trials.[9] Recurrent event rates were estimated from a Poisson model with robust standard errors. Between-trial heterogeneity of treatment effect was examined in the models described, with an interaction term between trial and randomly assigned therapy (p value for treatment-by-trial interaction, p_{int}). Rate differences per 100 patient-years were estimated using counterfactual predictions from Poisson models for each treatment group, adjusted for trial if more than one trial was included in the model. For recurrent events, we used robust standard errors. Additionally, we tested treatment-by-trial heterogeneity of effect using Cochran's Q test and Higgins and Thompson's I^2 from a two-stage meta-analysis using a random-effects model. The two-stage meta-analysis used the treatment estimates derived from our individual patient level analysis (the one-stage analysis) in the meta-analysis model. Subgroup analysis was performed in time-to-event Cox models with an interaction term between the subgroup of interest and randomised therapy in the model stratified by trial. For continuous variables, a restricted cubic spline was used with knots placed at points that resulted in the model with the lowest Akaike's information criterion value. An interaction term between the spline and randomised therapy was tested in the model and the interaction was represented graphically. The effect of randomly assigned therapy on safety outcomes was assessed by calculating an odds ratio (OR) in a logistic regression model with a factor for treatment and trial and the interaction tested with a treatment-by-trial interaction term. A p value of less than 0·05 was considered statistically significant. All analyses were performed using Stata (version 18.0).

All trials were assessed as high quality but the risk of bias for TOPCAT with regard to the assessment of deviation from the intended intervention was high (appendix p 7). A sensitivity analysis only including the participants from the Americas (North America and South America) was therefore undertaken to examine the impact of this potential bias (due to concerns about enrolment of patients without heart failure and non-adherence to trial treatment in the other participating countries).

Role of the funding source

There was no funding source for this study.

Results

Overall, 13 846 patients were included in the four trials. Patients enrolled in the two HFrEF trials (RALES and EMPHASIS-HF) were more often male and were less likely to have a history of hypertension than those enrolled

	RALES (n=1663)	EMPHASIS-HF (n=2737)	TOPCAT (n=3445)	FINEARTS-HF (n=6001)	Total (n=13 846)
Age, years	65 (11)	68 (7)	68 (9)	72 (9)	69 (9)
Sex					
Female	446 (27%)	610 (22%)	1775 (52%)	2732 (46%)	5563 (40%)
Male	1217 (73%)	2127 (78%)	1670 (48%)	3269 (54%)	8283 (60%)
Race or ethnicity					
White	1440 (87%)	2268 (83%)	3062 (89%)	4735 (79%)	11 505 (83%)
Black	120 (7%)	67 (2%)	302 (9%)	88 (1%)	577 (4%)
Asian	32 (2%)	316 (12%)	19 (1%)	996 (17%)	1363 (10%)
Other	71 (4%)	86 (3%)	62 (2%)	182 (3%)	401 (3%)
Region					
North America	114 (7%)	248 (9%)	1477 (43%)	471 (8%)	2310 (17%)
Latin America	433 (26%)	98 (4%)	290 (8%)	641 (11%)	1462 (11%)
Western Europe	1066 (64%)	1005 (37%)	0	1204 (20%)	3275 (24%)
Central and eastern Europe	0	988 (36%)	1678 (49%)	2630 (44%)	5296 (38%)
Asia-Pacific	50 (3%)	398 (15%)	0	1055 (18%)	1503 (11%)
BMI, kg/m²	NR	27·5 (4·9)	32·1 (7·1)	29·9 (6·1)	30·0 (6·4)
BMI category, kg/m²					
<30	NR	1983 (72%)	1533 (44%)	3296 (55%)	6812/12 145 (56%)
≥30	NR	739 (27%)	1902 (55%)	2692 (45%)	5333/12 145 (44%)
Missing	1663	15	10	13	1701
Systolic blood pressure, mm Hg	122 (20)	124 (17)	129 (14)	129 (15)	127 (16)
Heart rate, beats per min	81 (14)	72 (13)	69 (10)	71 (11)	72 (12)
LVEF, %	25% (7)	26% (5)	57% (7)	53% (8)	45% (15)
NYHA class					
I or II	7 (<1%)	2730 (100%)	2303 (67%)	4146 (69%)	9186/13 835 (66%)
III or IV	1656 (100%)	3 (<1%)	1136 (33%)	1854 (31%)	4649/13 835 (34%)
Missing	0	4	6	1	11
Previous heart failure hospitalisation	NR	1438 (53%)	2489 (72%)	3619 (60%)	7546/12 177 (62%)
Missing	1663	3	3	0	1669
NT-proBNP, pg/mL	NR	NR	843·0 (463·0–1720·0)	1041·4 (448·5–1945·9)	1013·5 (449·6–1929·8)
eGFR, mL/min per 1·73 m²	63 (22)	65 (18)	65 (19)	63 (20)	64 (19)
eGFR category, mL/min per 1·73 m²					
<60	841 (51%)	1092 (40%)	1463 (42%)	2844 (47%)	6240/13 827 (45%)
≥60	817 (49%)	1633 (60%)	1980 (57%)	3157 (53%)	7587/13 827 (55%)
Missing	5	12	2	0	19
Potassium, mmol/L	4·2 (0·4)	4·3 (0·4)	4·3 (0·4)	4·4 (0·5)	4·3 (0·5)
Diabetes	369 (22%)	859 (31%)	1118 (32%)	2454 (41%)	4800 (35%)
Hypertension	391 (24%)	1819 (66%)	3147 (91%)	5325 (89%)	10 682 (77%)
Atrial fibrillation	183 (11%)	844 (31%)	1214 (35%)	3273 (55%)	5514 (40%)
Myocardial infarction	472 (28%)	1380 (50%)	893 (26%)	1541 (26%)	4286 (31%)
Stroke	NR	262 (10%)	265 (8%)	708 (12%)	1235/12 183 (10%)
ACE inhibitor or ARB	1589 (96%)	2558 (93%)	2900 (84%)	4246 (71%)	11 293 (82%)
ARN inhibitor	NR	NR	NR	513 (9%)	513 (4%)
SGLT2 inhibitor	NR	NR	NR	817 (14%)	817 (6%)
β blocker	171 (10%)	2374 (87%)	2676 (78%)	5095 (85%)	10 316 (75%)
Diuretic	1502 (90%)	2326 (85%)	2817 (82%)	5930 (99%)	12 575 (91%)
Digitalis glycosides	1216 (73%)	740 (27%)	342 (10%)	471 (8%)	2769 (20%)

Data are reported as mean (SD), n (%), or median (IQR). NR=not reported. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association. NT-proBNP=N-terminal pro B-type natriuretic peptide. eGFR=estimated glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. ARN=angiotensin receptor neprilysin.

Table 1: **Baseline characteristics of patients in each mineralocorticoid receptor antagonist trial and in the total population studied**

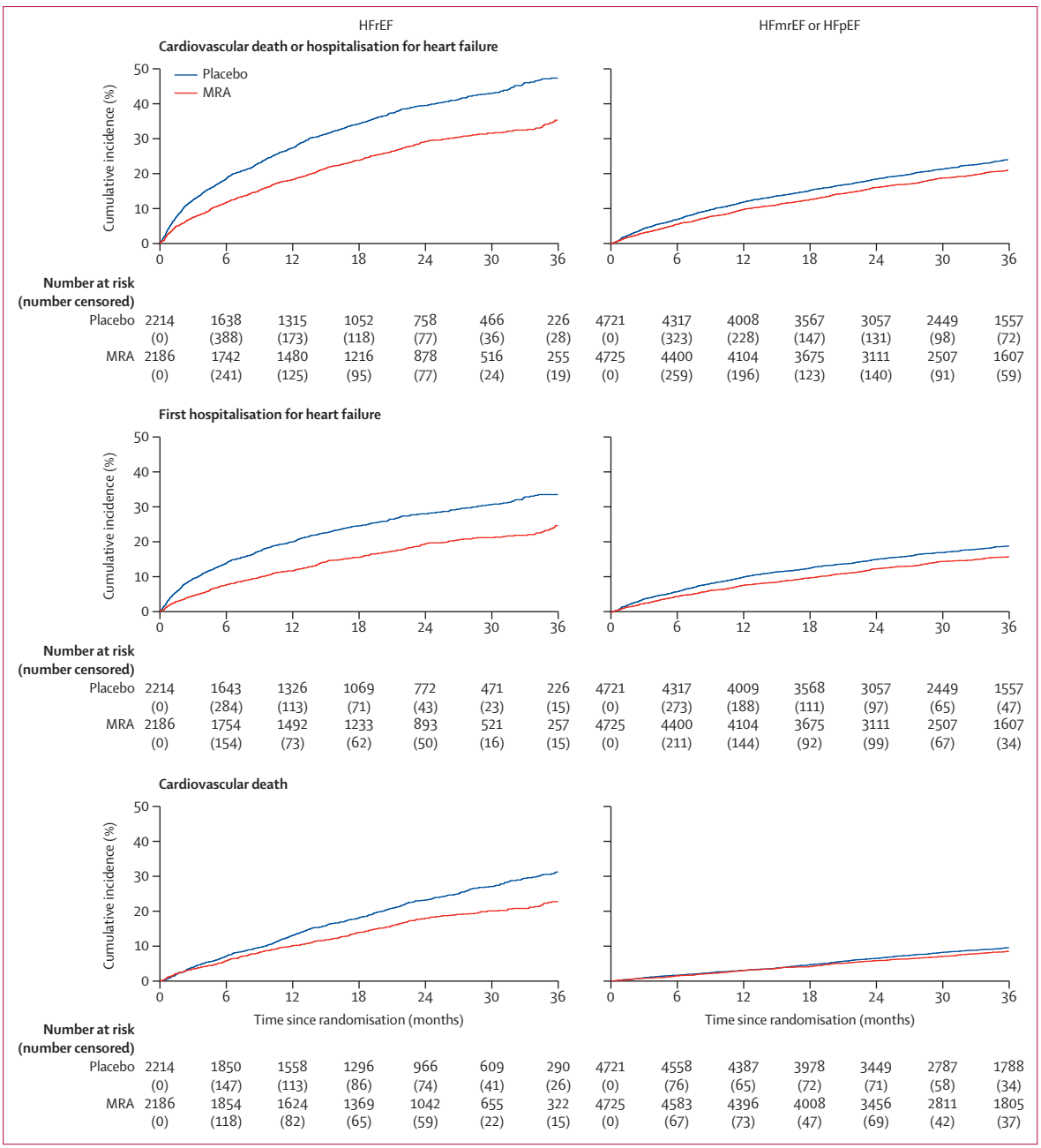


Figure 1: **Kaplan–Meier curves illustrating the cumulative incidence of prespecified efficacy outcomes**
The outcomes shown are cardiovascular death or hospitalisation for heart failure, hospitalisation for heart failure, and cardiovascular death. Panels on the left show patients with HFrEF and panels on the right show patients with HFmrEF or HFpEF. HFmrEF=heart failure and mildly reduced ejection fraction. HFpEF=heart failure and preserved ejection fraction. HFrEF=heart failure and reduced ejection fraction. MRA=mineralocorticoid receptor antagonist.

in the two HFmrEF and HFpEF trials (TOPCAT and FINEARTS-HF; table 1). The eGFR at baseline was lowest in RALES and FINEARTS-HF. Baseline characteristics by randomly assigned therapy are provided in the appendix (pp 8–10) and were balanced between treatment groups.

The rates of events in the placebo groups were higher in the trials including patients with HFrEF compared with those including patients with HFmrEF or HFpEF (figure 1, appendix pp 11–13). In the analysis of the time to first occurrence of cardiovascular death or heart failure hospitalisation, including all four trials, the HR for an MRA compared with placebo was 0·77 (95% CI 0·72–0·83; table 2, figure 2). However, there was a statistically significant interaction between trials and the effect of treatment (p_{int}=0·0012, table 2) which was also observed in the two-stage meta-analysis (Cochrane's Q p<0·0001,

	RALES (n=1663)		EMPHASIS-HF (n=2737)		EMPHASIS-HF and RALES (n=4400)		TOPCAT (n=3445)		FINEARTS-HF (n=6001)		TOPCAT and FINEARTS-HF (n=9446)		All trials (n=13 846)	
	HR or RR (95% CI)	p value	HR or RR (95% CI)	p value	HR or RR (95% CI)	Interaction p value	HR or RR (95% CI)	p value	HR or RR (95% CI)	p value	HR or RR (95% CI)	Interaction p value	HR or RR (95% CI)	Interaction p value
Cardiovascular death or heart failure hospitalisation*	0·66 (0·57 to 0·75)	<0·0001	0·66 (0·56 to 0·78)	<0·0001	0·66 (0·59 to 0·73)	0·97	0·90 (0·78 to 1·05)	0·20	0·85 (0·76 to 0·94)	0·0025	0·87 (0·79 to 0·95)	0·49	0·77 (0·72 to 0·83)	0·0012
ARR	16·1 (11·2 to 20·9)	..	5·7 (3·5 to 7·8)	..	6·0 (4·5 to 7·4)	..	0·6 (–0·3 to 1·6)	..	1·7 (0·6 to 2·8)	..	1·5 (0·6 to 2·4)	..	2·7 (2 to 3·4)	..
Heart failure hospitalisation*	0·65 (0·54 to 0·77)	<0·0001	0·61 (0·50 to 0·75)	<0·0001	0·63 (0·55 to 0·72)	0·67	0·83 (0·69 to 0·99)	0·043	0·82 (0·72 to 0·92)	0·0011	0·82 (0·74 to 0·91)	0·92	0·74 (0·69 to 0·80)	0·022
ARR	10·3 (6·6 to 14·1)	..	4·6 (2·8 to 6·4)	..	4·5 (3·3 to 5·8)	..	0·8 (0 to 1·6)	..	1·6 (0·7 to 2·6)	..	1·6 (0·8 to 2·4)	..	2·5 (1·8 to 3·1)	..
Cardiovascular death†	0·69 (0·58 to 0·82)	<0·0001	0·77 (0·62 to 0·96)	0·018	0·72 (0·63 to 0·82)	0·45	0·90 (0·73 to 1·12)	0·35	0·93 (0·78 to 1·10)	0·40	0·92 (0·80 to 1·05)	0·85	0·81 (0·74 to 0·89)	0·082
ARR	6·8 (3·7 to 9·8)	..	1·8 (0·3 to 3·2)	..	2·2 (1·3 to 3·2)	..	0·3 (–0·3 to 0·9)	..	0·3 (–0·3 to 0·9)	..	0·3 (–0·2 to 0·8)	..	0·7 (0·4 to 1·1)	..
Total heart failure hospitalisations*‡	0·65 (0·54 to 0·78)	<0·0001	0·53 (0·42 to 0·67)	<0·0001	0·60 (0·52 to 0·69)	0·58	0·79 (0·66 to 0·96)	0·019	0·83 (0·74 to 0·93)	0·0015	0·82 (0·74 to 0·90)	0·79	0·74 (0·68 to 0·80)	0·0044
ARR	15·2 (8 to 22·4)	..	7·4 (3·9 to 10·9)	..	8·0 (5·3 to 10·8)	..	1·5 (–0·2 to 3·2)	..	2·6 (0·7 to 4·4)	..	2·5 (0·9 to 4·2)	..	4·0 (2·7 to 5·3)	..
Cardiovascular death and total heart failure hospitalisations*‡	0·68 (0·59 to 0·79)	<0·0001	0·58 (0·48 to 0·70)	<0·0001	0·64 (0·57 to 0·72)	0·62	0·82 (0·70 to 0·98)	0·025	0·85 (0·76 to 0·95)	0·0032	0·84 (0·77 to 0·92)	0·82	0·76 (0·71 to 0·82)	0·0015
ARR	20·0 (12·1 to 27·8)	..	8·4 (4·7 to 12·2)	..	9·1 (6·4 to 11·8)	..	1·8 (–0·2 to 3·7)	..	2·8 (0·7 to 4·9)	..	2·8 (1·1 to 4·5)	..	4·5 (3·2 to 5·9)	..
All-cause death	0·71 (0·61 to 0·82)	<0·0001	0·78 (0·64 to 0·95)	0·014	0·73 (0·65 to 0·83)	0·46	0·93 (0·79 to 1·11)	0·43	0·94 (0·83 to 1·06)	0·29	0·94 (0·85 to 1·03)	0·99	0·85 (0·78 to 0·92)	0·021
ARR	7·9 (4·5 to 11·3)	..	2 (0·4 to 3·5)	..	2·5 (1·5 to 3·5)	..	0·3 (–0·5 to 1·1)	..	0·5 (–0·4 to 1·3)	..	0·5 (–0·2 to 1·2)	..	1·2 (0·6 to 1·7)	..

Interaction p value is the p value for test of interaction between trial and treatment effect. HR=hazard ratio. RR=rate ratio. ARR=absolute rate reduction per 100 patient-years. *Includes urgent visits for worsening heart failure as a hospitalisation equivalent. †The definition of cardiovascular death was that used in the original trials. ‡RR estimated using a negative binomial model due to missing data on time to recurrent hospitalisations in RALES.

Table 2: **Effect of mineralocorticoid receptor antagonist treatment on the prespecified efficacy outcomes in each of the trials**

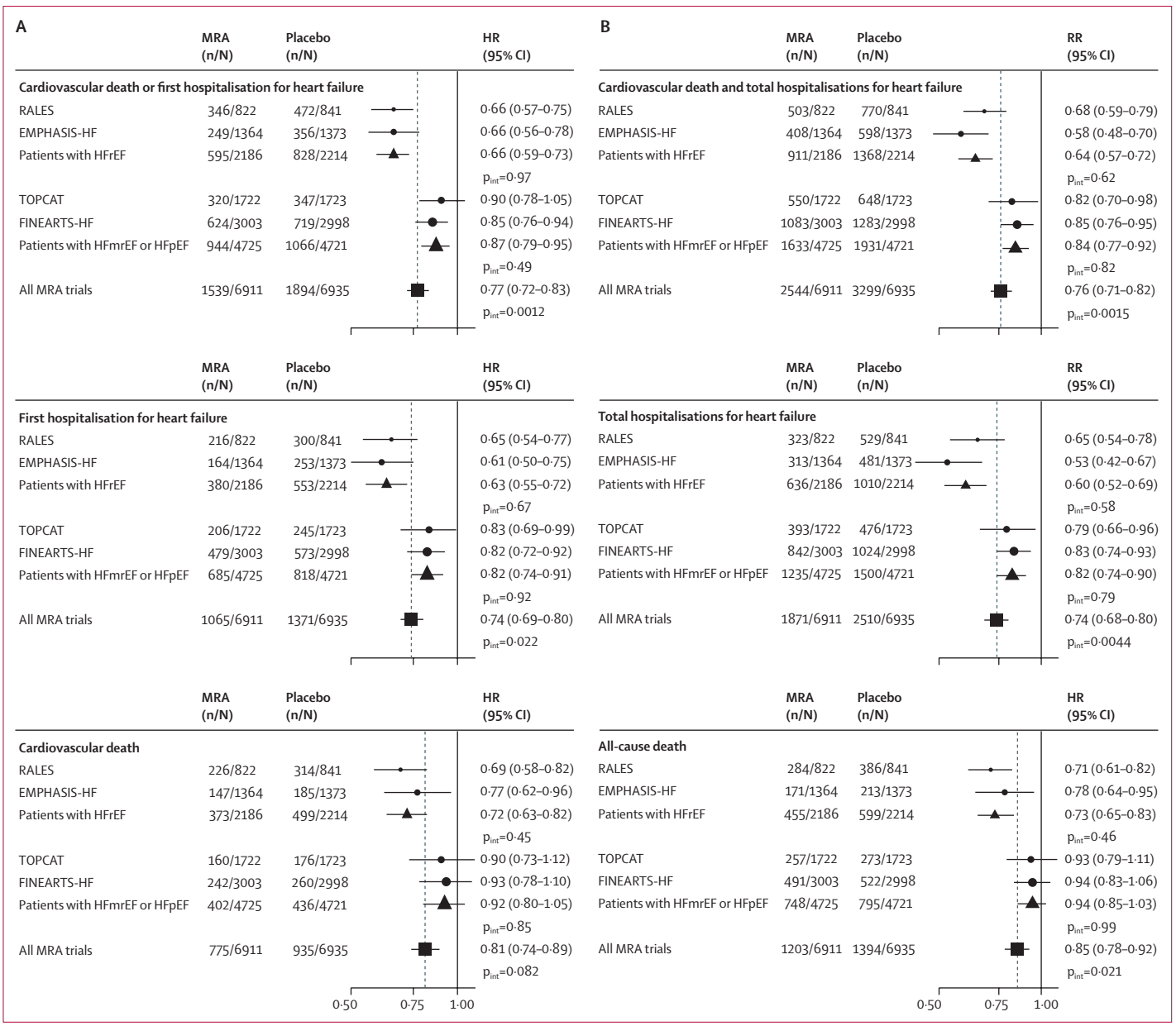
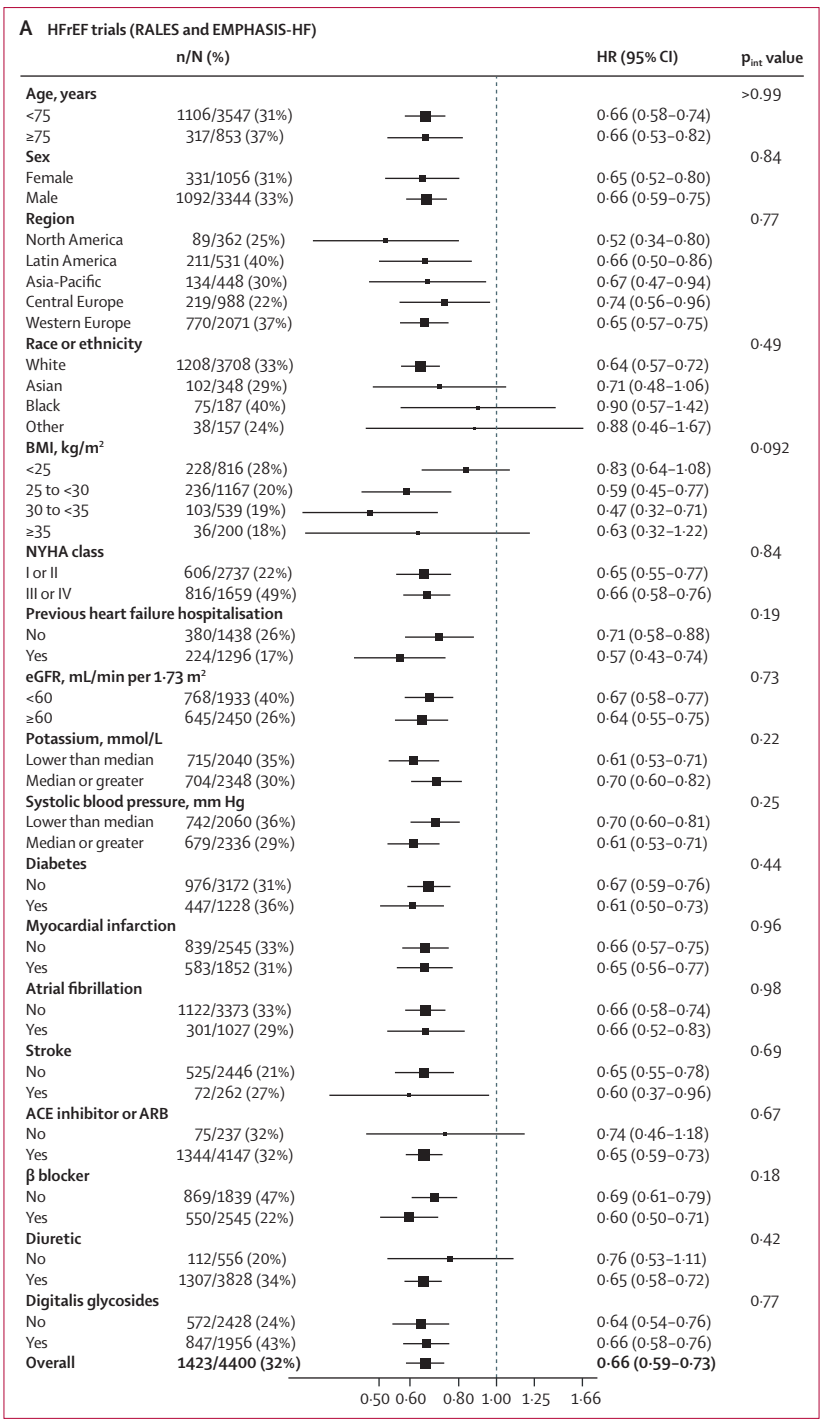


Figure 2: **Effect estimates from the individual patient level meta-analysis of MRAs and prespecified efficacy outcomes**
(A) Forest plots show cardiovascular death or hospitalisation for heart failure, heart failure hospitalisation, and cardiovascular death. (B) Forest plots show a composite of total heart failure hospitalisations and cardiovascular death, total (first and repeat) heart failure hospitalisations, and all-cause death. FINEARTS-HF included urgent visits for worsening heart failure as a hospitalisation equivalent. Estimates from the models in all four trials and split by HFrEF and HFmrEF or HFpEF trials, with p_{int} displayed. HFmrEF=heart failure and mildly reduced ejection fraction. HFpEF=heart failure and preserved ejection fraction. HFrEF=heart failure and reduced ejection fraction. HR=hazard ratio. MRA=mineralocorticoid receptor antagonist. p_{int}=p value for treatment-by-trial interaction. RR=rate ratio.

I^2=81%; appendix p 14). Inspection of the treatment estimates showed that the source of the interaction was the greater treatment efficacy in the HFrEF trials (pooled HR 0·66 [95% CI 0·59–0·73]) compared with the HFmrEF and HFpEF trials (0·87 [0·79–0·95]; table 2, figure 2). Among the HFrEF trials and the HFmrEF and HFpEF trials, as separate treatment groups, there was no further heterogeneity (HFrEF trials p_{int}=0·97; HFmrEF and HFpEF trials p_{int}=0·49).

The same heterogeneity of treatment effect by trials was present for cardiovascular death, heart failure hospitalisation, and all-cause death (table 2, figure 2). The HR for the effect of an MRA on cardiovascular death in the two HFrEF trials was 0·72 (95% CI 0·63–0·82) and in the two HFmrEF and HFpEF trials was 0·92 (0·80–1·05). Over all trials, the p value for interaction was 0·082, in the HFrEF trials it was 0·45, and in the HFmrEF and HFpEF trials, it was 0·85



(Figure 3 continues on next page)

(table 2, figure 2). For outcomes incorporating cardiovascular death, in sensitivity analyses including or excluding undetermined causes of death, the findings were similar (appendix p 16).

The HR for the effect of an MRA on a first heart failure hospitalisation was 0·63 (95% CI 0·55–0·72) in the HFrEF trials and 0·82 (95% CI 0·74–0·91) in the HFmrEF and HFpEF trials (p_{int}=0·022; table 2, figure 2). There was no further heterogeneity in these two sets of trials (HFrEF trials p_{int}=0·67; HFmrEF and HFpEF trials p_{int}=0·92).

The RR for the effect of an MRA on total heart failure hospitalisations was 0·60 (95% CI 0·52–0·69) in the HFrEF trials and 0·82 (0·74–0·90) in the HFmrEF and HFpEF trials (p_{int}=0·0044), with no interaction within the groups of trials (HFrEF trials p_{int}=0·58; HFmrEF and HFpEF trials p_{int}=0·79; table 2). We observed similar results for total heart failure hospitalisations and cardiovascular deaths: the RR was 0·64 (0·57–0·72) in the HFrEF trials and 0·84 (0·77–0·92) in the HFmrEF and HFpEF trials (p_{int}=0·0015), with no further heterogeneity within the groups of trials (HFrEF trials p_{int}=0·62; HFmrEF or HFpEF trials p_{int}=0·82; table 2). Results were similar using a semi-parametric proportional rates model (appendix p 17).

The HR for the effect of an MRA on all-cause death was 0·73 (95% CI 0·65–0·83) in the HFrEF trials and 0·94 (0·85–1·03) in the HFmrEF and HFpEF trials (p_{int}=0·021), with no further heterogeneity between the two groups of trials (HFrEF trials p_{int}=0·46; HFmrEF and HFpEF trials p_{int}=0·99; table 2, figure 2).

Given the interaction of the treatment effects by trial, the analyses of steroidal versus non-steroidal MRAs were not conducted. A sensitivity analysis with a two-stage meta-analysis confirmed the results from the one-stage individual patient level analysis (appendix p 14). The results of the individual patient level meta-analysis were unchanged in a sensitivity analysis that included only the patients randomly assigned in the Americas in TOPCAT (appendix p 18), with an HR estimate for cardiovascular death or heart failure hospitalisation of 0·84 (95% CI 0·77–0·93), for heart failure hospitalisation of 0·82 (0·74–0·91), and for cardiovascular death of 0·86 (0·75–1·00) in patients with HFmrEF or HFpEF.

The effect of MRA therapy was consistent across all subgroups in the HFrEF and HFmrEF or HFpEF trials (figure 3). In a subgroup analysis of all four trials, there was an interaction between baseline potassium and treatment efficacy with greater efficacy in those with lower potassium (appendix p 19). The interaction with LVEF as a categorical variable was similar to the interaction between the trials. When the interaction between therapy and ejection fraction was modelled as a continuous variable within the HFrEF and HFmrEF or HFpEF trials separately, there was no treatment heterogeneity for the primary outcome, confirming that the majority of the heterogeneity was between HFrEF and HFmrEF or HFpEF (appendix p 20).

Safety outcomes in each trial and treatment group in patients receiving trial treatment are shown in table 3 and the appendix (p 21). The risk of hyperkalaemia, defined as serum potassium >5·5 mmol/L (moderate) or

>6·0 mmol/L (severe) was twice as high in the MRA groups than in the placebo groups across all trials (OR 2·27 [95% CI 2·02–2·56]; appendix pp 22–23). However, the absolute risk of severe hyperkalaemia was low, at approximately 2·9% in the MRA group and 1·4% in the placebo group. There was little heterogeneity in the risk of any hyperkalaemia when rates were examined by trials defined by ejection fraction (appendix pp 22–23) or by type of MRA (table 3); however, this analysis did not differentiate between on-treatment and off-treatment hyperkalaemia. Conversely, the risk of hypokalaemia (potassium <3·5 mmol/L) was halved in patients assigned to MRAs compared with patients assigned to placebo (7% *vs* 14%) across all trials (0·51 [0·45–0·57]; appendix pp 22–23).

Although hypotension was more common in the HFrEF trials (table 3), we found no statistical heterogeneity for the effect of treatment on systolic blood pressure of less than 90 mm Hg by trial group (7% *vs* 5% in the HFrEF trials and 5% *vs* 3% in the HFmrEF or HFpEF trials). Additional safety outcomes, including by baseline eGFR and using only patients randomly assigned in the Americas for the TOPCAT trial, are presented in the appendix (pp 24–26).

Discussion

Before this meta-analysis, there was strong evidence of the benefits of the steroidal MRAs spironolactone and eplerenone in patients with heart failure and a substantially reduced LVEF, but uncertainty remained about the efficacy of MRAs in patients with mildly reduced or preserved ejection fraction,[3,7] especially because spironolactone had not shown a significant benefit in the TOPCAT trial. With completion of the FINEARTS-HF trial using finerenone, there is now evidence that blocking the mineralocorticoid receptor with a non-steroidal MRA is beneficial in people with an ejection fraction of 40 percent or higher.[8] In this meta-analysis, our findings demonstrate the value of steroidal MRAs in HFrEF and non-steroidal MRAs in HFmrEF or HFpEF.

However, this meta-analysis also shows significant heterogeneity in the treatment effect on efficacy outcomes in the trials that included patients with reduced LVEF compared with the trials in people with mildly reduced or preserved ejection fraction, with smaller relative risk reductions in the latter participants. This

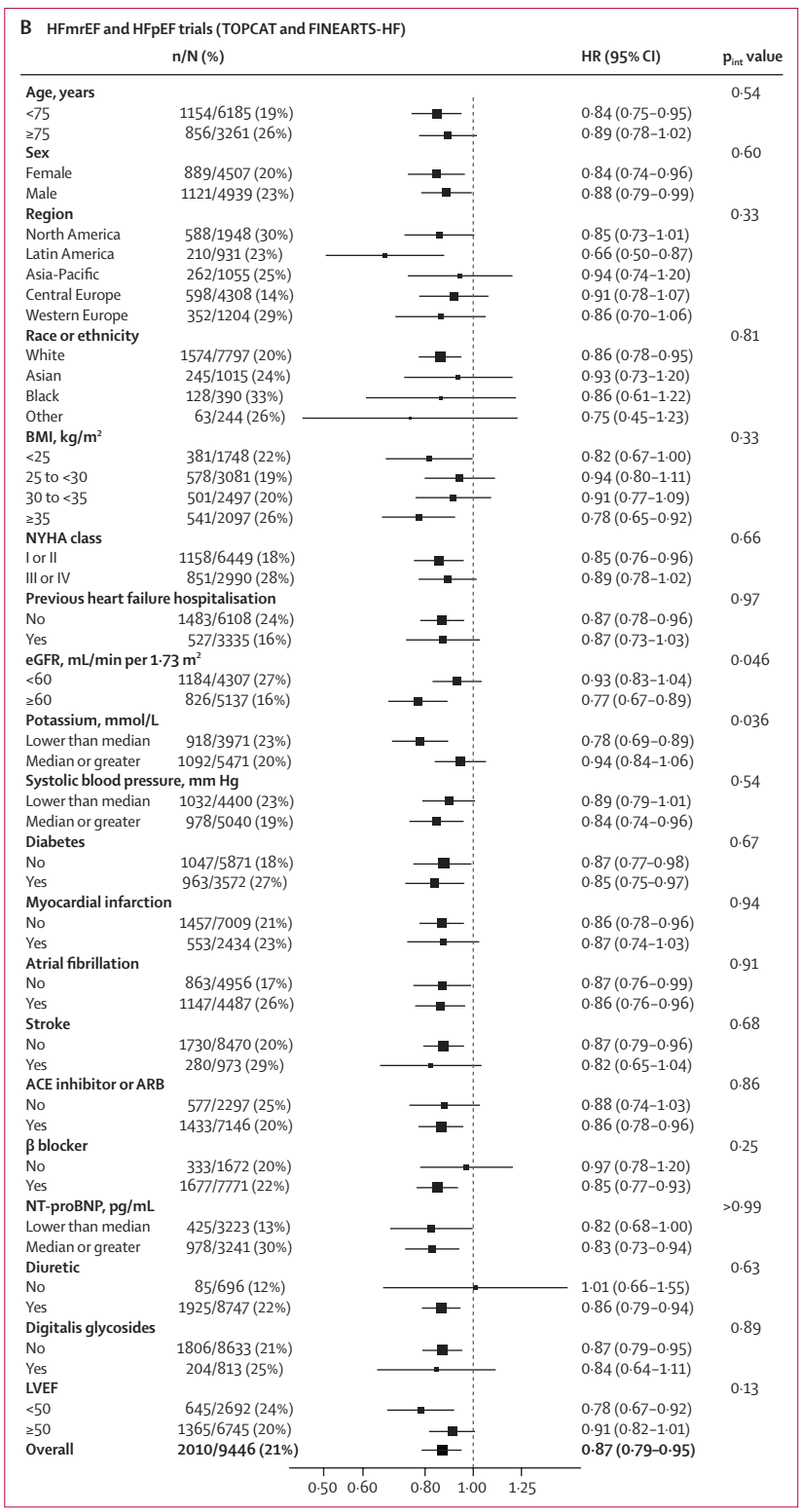


Figure 3: **Effect of mineralocorticoid receptor antagonist treatment on the composite of cardiovascular death or hospitalisation for heart failure (time-to-first-event analysis) in key subgroups**

(A) Combined RALES and EMPHASIS-HF trials. (B) Combined TOPCAT and FINEARTS-HF trials. FINEARTS-HF included urgent visits for worsening heart failure as a hospitalisation equivalent. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. eGFR=estimated glomerular filtration rate. HFmrEF=heart failure and mildly reduced ejection fraction. HFpEF=heart failure and preserved ejection fraction. HFrEF=heart failure and reduced ejection fraction. HR=hazard ratio. LVEF=left ventricular ejection fraction. NT-proBNP=N-terminal pro B-type natriuretic peptide. NYHA=New York Heart Association. p_{int}=p value for treatment-by-trial interaction.

	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	Spirono-lactone group (n=822)	Placebo group (n=841)	OR (95% CI)	Eplerenone group (n=1360)	Placebo group (n=1369)	OR (95% CI)	Spirono-lactone group (n=1699)	Placebo group (n=1691)	OR (95% CI)	Finerenone group (n=2993)	Placebo group (n=2993)	OR (95% CI)
Hypotension												
Systolic blood pressure <90 mm Hg	79/776 (10%)	61/797 (8%)	1·24 (0·93–1·64)	71/1337 (5%)	53/1341 (4%)	1·36 (0·95–1·96)	65/1699 (4%)	33/1691 (2%)	2·00 (1·31–3·06)	146/2934 (5%)	95/2935 (3%)	1·57 (1·20–2·04)
Systolic blood pressure <100 mm Hg	215/776 (28%)	210/797 (26%)	1·07 (0·87–1·31)	261/1337 (20%)	209/1341 (16%)	1·31 (1·08–1·60)	267/1699 (16%)	188/1691 (11%)	1·49 (1·22–1·82)	556/2934 (19%)	374/2935 (13%)	1·60 (1·39–1·85)
Elevated serum creatinine												
≥2·5 mg/dL	70/779 (9%)	43/797 (5%)	1·73 (1·17–2·57)	28/1171 (2%)	22/1170 (2%)	1·28 (0·73–2·25)	101/1691 (6%)	55/1685 (3%)	1·88 (1·35–2·63)	167/2928 (6%)	110/2921 (4%)	1·55 (1·21–1·98)
≥3·0 mg/dL	30/779 (4%)	17/797 (2%)	1·84 (1·01–3·36)	9/1171 (1%)	11/1170 (1%)	0·82 (0·34–1·98)	42/1691 (2%)	24/1685 (1%)	1·76 (1·06–2·92)	77/2928 (3%)	45/2921 (2%)	1·73 (1·19–2·50)
Reduction in eGFR												
>20%	433/821 (53%)	330/840 (39%)	1·72 (1·42–2·10)	259/899 (29%)	222/922 (24%)	1·28 (1·04–1·57)	869/1652 (53%)	750/1650 (45%)	1·33 (1·16–1·53)	1676/2928 (57%)	1220/2921 (42%)	1·87 (1·68–2·07)
>30%	288/821 (35%)	189/840 (23%)	1·86 (1·50–2·31)	155/899 (17%)	99/922 (11%)	1·73 (1·32–2·27)	516/1652 (31%)	402/1650 (24%)	1·41 (1·21–1·64)	1033/2928 (35%)	642/2921 (22%)	1·94 (1·72–2·17)
Elevated serum potassium												
>5·5 mmol/L	127/779 (16%)	38/797 (5%)	3·89 (2·67–5·67)	158/1336 (12%)	96/1340 (7%)	1·74 (1·33–2·27)	198/1691 (12%)	92/1685 (5%)	2·30 (1·78–2·97)	426/2921 (15%)	207/2915 (7%)	2·23 (1·88–2·66)
>6·0 mmol/L	32/779 (4%)	9/797 (1%)	3·75 (1·78–7·91)	34/1336 (3%)	25/1340 (2%)	1·37 (0·81–2·32)	40/1691 (2%)	16/1685 (1%)	2·53 (1·41–4·53)	90/2921 (3%)	44/2915 (2%)	2·07 (1·44–2·99)
Reduced serum potassium												
<3·5 mmol/L	54/779 (7%)	149/797 (19%)	0·32 (0·23–0·45)	100/1336 (7%)	150/1340 (11%)	0·64 (0·49–0·84)	205/1691 (12%)	331/1685 (20%)	0·56 (0·47–0·68)	145/2921 (5%)	299/2915 (10%)	0·46 (0·37–0·56)

Data are n/N (%) unless otherwise specified. OR=odds ratio. eGFR=estimated glomerular filtration rate.

Table 3: **Effect of mineralocorticoid receptor antagonist treatment on the prespecified safety outcomes in each trial**

variation in efficacy according to ejection fraction phenotype was evident for both heart failure hospitalisation and mortality, although there was a significant reduction in heart failure hospitalisation with MRAs across all ejection fraction phenotypes. By contrast, cardiovascular death was not reduced significantly in patients with mildly reduced or preserved ejection fraction and this conclusion was not altered by using different definitions of cardiovascular death (ie, whether deaths of unknown cause were included or excluded) or including only TOPCAT patients enrolled in the Americas, although in the latter sensitivity analysis, the HR was 0·86 (95% CI 0·75–1·00). This differential effect on fatal and non-fatal outcomes was also observed in the SGLT2 trials[10] and with sacubitril–valsartan.[11] The lack of effect of all of these treatments on all-cause death in patients with a higher ejection fraction could be due to the much larger proportion of non-cardiovascular deaths in this group compared with people with lower ejection fraction,[12] with non-cardiovascular deaths unlikely to be reduced by treatments such as an MRA.

Among patients with mildly reduced or preserved ejection fraction, other treatments acting through neurohumoral mechanisms show attenuated efficacy in patients with a normal ejection fraction.[13,14] Although our analyses by ejection fraction category or using ejection fraction as a continuous variable might suggest this visually, formal interaction testing did not show that ejection fraction modified the effects of MRAs in patients with mildly reduced or preserved ejection fraction. Similarly, we did not find an interaction between treatment and trials within the HFrEF and HFmrEF or HFpEF groups. However, we cannot conclude that the trial effects are the same, only that we found no evidence to say that they were different, and our analysis might have been underpowered to detect a difference. Although previous meta-analyses of MRAs have used summary level estimates (mainly weighted by RALES, EMPHASIS-HF, or TOPCAT), they have reached similar results for HFrEF but have been limited by scarce data on HFmrEF or HFpEF and have been unable to examine the interaction with ejection fraction.[15,16]

Examination of other subgroups, including by age, comorbidity, and laboratory and other physiological variables, showed mainly consistent results for the effect of an MRA on the primary outcome in the reduced ejection fraction trials and, separately, in the mildly reduced or preserved ejection fraction trials (and,

therefore, across all four trials). Of note, the meta-analysis included a substantial number of patients with significantly impaired kidney function and the benefit of MRA treatment was consistent in these patients as well as those with better baseline kidney function.

Hyperkalaemia is a safety concern with MRAs, and the risk of both modest and severe hyperkalaemia was approximately doubled with MRA treatment in the reduced ejection fraction trials and this risk was elevated to a similar extent in the mildly reduced or preserved ejection fraction trials. However, the absolute risk of serious hyperkalaemia (potassium >6·0 mmol/L) was low (around 3% in the MRA treatment group compared with 1–1·5% in the placebo group). We did not find heterogeneity between trials or between MRAs for hyperkalaemia. Hypokalaemia is a more common problem than hyperkalaemia in heart failure because of the use of diuretics and it is at least as important a safety concern.[17,18] The overall risk of hypokalaemia (potassium <3·5 mmol/L) was halved by MRA treatment (7% in the MRA group *vs* 14% in the placebo group).

Initiation of an MRA might also lead to a decline in eGFR, although decreases in eGFR are extremely common in patients with heart failure, as evidenced by the rate of these changes in the placebo group in all four trials. The risk of a 20–30% decrease in eGFR was between 1·5 and two times as common with MRA treatment compared with placebo.

Despite possible concerns about hypotension, a systolic blood pressure of less than 90 mmHg was uncommon overall and the difference in episodes of low systolic blood pressure between MRA treatment and placebo was small.

The results of these analyses should be interpreted with some limitations in mind. Certain variables were not available in individual trials, such as BMI in RALES. In RALES, the time to hospitalisation was only available for the first event and therefore a negative binomial model had to be used to analyse repeat events. The FINEARTS-HF trial included episodes of worsening heart failure requiring urgent treatment as an equivalent to hospitalisation. These episodes were not collected in the older trials but have been validated endpoints in more recent trials because thresholds for hospital admission have changed (although they constituted a minority of events). Our analysis was restricted to randomised controlled trials with more than 1000 participants and the exclusion of smaller trials might affect the generalisability of this meta-analysis, because the included trials had relatively homogenous exclusion criteria. Two further placebo-controlled trials testing spironolactone in patients with HFmrEF or HFpEF are currently under way (NCT04727073 and NCT02901184) and, in due course, these will add important additional information about spironolactone. Although we tried to control for the difference in baseline risk by stratifying by trial in our models, the level of heterogeneity was high, as demonstrated both in the individual patient level analysis and our two-stage meta-analysis. However, this meant that we were not able to perform a direct comparison between steroidal MRAs of spironolactone and eplerenone with the non-steroidal MRA finerenone. Our study was not designed to determine whether there is a class effect of MRAs in heart failure, and this would require appropriately designed and powered prospective trials. Although we did not find an interaction between ejection fraction and randomised treatment, and despite our large sample size, we might not have had enough power to examine the interaction. The meta-analysis includes trials conducted over several decades with changes in background care in that period. SGLT2 inhibitors are now considered a foundational treatment for heart failure but they were not developed or indicated at the time of the older trials. They were introduced as a treatment for heart failure during the conduct of the FINEARTS-HF trial and were prescribed to 14% of patients at baseline. In a subgroup analysis, the benefit of finerenone was consistent regardless of background SGLT2 inhibitor use[8] and this is consistent with similar findings in trials of finerenone in patients with diabetes and chronic kidney disease.[19] Our trial cohorts might not be representative of real-world patients, who tend to be older, and we had a small proportion of Black and Asian patients.[20,21] Finally, the availability of therapy depends on other considerations, including cost-effectiveness, and regulatory approval depends on an acceptable benefit-to-risk assessment.

In conclusion, this meta-analysis of almost 14000 patients across four large clinical trials provides comprehensive evidence that steroidal MRAs reduce the risk of cardiovascular death or heart failure hospitalisation in patients with HFrEF and non-steroidal MRAs reduce this risk in HFmrEF or HFpEF. These benefits were consistent across patient subgroups. Treatment with an MRA should be considered in all patients with heart failure who do not have a contraindication to this treatment.

Contributors

PSJ, JJVM, and SDS conceived of and designed the study. AT, ADH, PSJ, and JJVM did the analysis. PSJ and JJVM drafted the manuscript. All authors contributed to data interpretation and writing of the final version of the manuscript, and all authors were responsible for the decision to submit the manuscript for publication. PSJ, AT, ADH, and JJVM accessed and verified the data and all authors had full access to the study data.

Declaration of interests

PSJ reports speakers fees from AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, and Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, and Novartis; and research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices, and Roche Diagnostics; and is a director of Global Clinical Trial Partners. PSJ's employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer, Novartis, and Novo Nordisk. BLC has received personal consulting fees from Alnylam, Bristol Myers Squibb (BMS), Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, and Rocket, and has served on a data safety

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BP is a consultant for Bayer, AstraZeneca, Boehringer Ingelheim, Lexicon, BMS, KBP Biosciences, Sarfez Pharmaceuticals, Pharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Sea Star Medical, Vifor, Prointel, and Brainstorm Medical; and holds stock or stock options in KBP Biosciences, Sarfez Pharmaceuticals, SQ Innovation, Sea Star Medical, Vifor, Prointel, and Brainstorm Medical. He holds US Patent 9931412 on site specific delivery of eplerenone to the myocardium, and US Patent pending 63/045,783 on histone modulating agents for the prevention and treatment of organ failure. MS has served on advisory boards for and has received consultancy fees and honoraria from Novartis, Abbott, Merck, MSD, Vifor, AstraZeneca, Cardurion, Novo Nordisk, Bayer, and Boehringer Ingelheim. 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All other authors declare no competing interests.

Data sharing

Data from the RALES and TOPCAT trials are available on request at the NIH BioLINCC repository available at https://biolincc.nhlbi.nih.gov/home. The EMPASIS-HF trial is available on request from the corresponding author. The FINEARTS-HF trial is made available to qualified scientific and medical researchers through vivli.org. All requests will be reviewed by an independent scientific review panel and data provided according to the conditions described at: https://vivli.org/ourmember/bayer.

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