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Supplementary appendix

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

Table of Contents

Supplemental Table 1: Key data and inclusion and exclusion criteria of the included trials and visit schedule	2
Search strategy used to search medline via Pubmed	4
Supplemental Figure 1: PRISMA flow chart of included studies	6
Supplemental Figure 2: Risk of bias assessment of included studies	7
Supplemental Table 2- Baseline characteristics in the included trials by randomised therapy	8
Supplemental Table 3- Event rates in RALES, EMPHASIS-HF, TOPCAT and FINEARTS-HF for each outcome by randomised therapy.....	11
Supplemental Table 4- Event rates in HF _r EF and HF _m rEF/HF _p EF trials combined and for all trials for each outcome by randomised therapy.....	12
Supplemental Figure 3- Nelson – Aalen curves showing the cumulative incidence of total heart failure hospitalisations and the composite of total (first and repeat) hospitalisations for heart failure and cardiovascular death (excluding RALES as time to events was not recorded). Kaplan Meier curve of all cause death in all trials.....	13
Supplemental Figure 4- Two stage meta-analysis of cardiovascular death or heart failure hospitalisations, heart failure hospitalisations, cardiovascular death and all cause deaths.....	14
Supplemental Table 5- Effect of MRAs in each of the trials on pre specified efficacy outcomes including and excluding undetermined deaths from the definition of cardiovascular death	16
Supplemental Table 6- Total heart failure hospitalisations and total heart failure hospitalisation and cardiovascular deaths analysed in semi-parametric proportional rates model excluding RALES and including EMPHASIS-HF, TOPCAT and FINEARTS-HF.....	17
Supplemental Table 7- Sensitivity analysis of the effect of MRAs in each of the trials on pre specified efficacy outcomes using all patients included in RALES, EMPHASIS-HF, FINEARTS-HF and only patients randomised in the Americas in TOPCAT	18
Supplemental Figure 5– Subgroup analysis of the outcome of cardiovascular death or first hospitalisation for heart failure in all four trials	19
Supplemental Figure 6 Interaction between left ventricular ejection fraction and the effect of randomised treatment on the composite of cardiovascular death or hospitalisation for heart failure (left ventricular ejection fraction modelled as a restricted cubic spline).	20
Supplemental Table 8 Effect of mineralocorticoid receptor antagonist treatment on additional pre-specified safety outcomes in each trial.....	21
Supplemental Table 9 Safety outcomes in HF _r EF and HF _m rEF/HF _p EF trials combined and all 4 trials combined	22
Supplemental Table 10 Effect of mineralocorticoid receptor antagonist treatment on the pre-specified safety outcomes in each trial eGFR<45	24
Supplemental Table 11 Effect of mineralocorticoid receptor antagonist treatment on the pre-specified safety outcomes in each trial eGFR≥45	25
Supplemental Table 12 Effect of mineralocorticoid receptor antagonist treatment on the pre-specified safety outcomes in each trial TOPCAT Americas.....	26

Supplemental Table 1: Key data and inclusion and exclusion criteria of the included trials and visit schedule

Key trial characteristics	RALES	EMPHASIS-HF	TOPCAT	FINEARTS-HF
Investigational drug	spironolactone	eplerenone	spironolactone	finerenone
Number of patients, sites and countries	1663 patients at 195 sites in 15 countries	2737 patients at 278 sites in 29 countries	3445 participants at 233 sites in 6 countries	6001 patients at 654 sites in 37 countries
Key inclusion criteria	<ul style="list-style-type: none"> • New York Heart Association (NYHA) class IV heart failure within the six months before enrolment and were in NYHA class III or IV at the time of enrolment • treated with an ACE inhibitor (if tolerated) and a loop diuretic • ejection fraction \leq 35% 	<ul style="list-style-type: none"> • NYHA class II • ejection fraction \leq 30% (or, if $>$30 to 35%, a QRS duration of $>$130 msec on electrocardiography) • treatment with an angiotensin-converting-enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or both and a beta-blocker (unless contraindicated) 	<ul style="list-style-type: none"> • Ejection fraction \geq45% • history of hospitalization within the previous 12 months, with management of heart failure a major component of the care provided or an elevated natriuretic peptide level within 60 days before randomization (BNP \geq100 pg/ml or an N-terminal pro-BNP \geq360 pg/ml) 	<ul style="list-style-type: none"> • Ejection fraction \geq40% including improved ejection fraction • Inpatients and outpatients • Structural heart abnormality on local imaging in the last 12 months • BNP \geq100 pg/ml or an N-terminal pro-BNP \geq300 pg/ml in sinus rhythm and BNP \geq300 pg/ml or an N-terminal pro-BNP \geq900 pg/ml in atrial fibrillation
Key exclusion criteria	<ul style="list-style-type: none"> • serum creatinine $>$ 2.5 mg/dl (221 μmol/l) • serum potassium $>$ 5.0 mmol/l 	<ul style="list-style-type: none"> • NYHA class III or IV heart failure • potassium $>$ 5.0 mmol/l • estimated glomerular filtration rate (GFR) of $<$30 ml /minute/1.73 m² 	<ul style="list-style-type: none"> • Estimated GFR of $<$30 ml /minute/1.73 m² • serum creatinine $>$ 2.5 mg/dl (221 μmol/l) • serum potassium \geq 5.0 mmol/l 	<ul style="list-style-type: none"> • Estimated GFR of $<$25 ml /minute/1.73 m² • serum potassium $>$ 5.0 mmol/l
Primary outcome	All cause death	Cardiovascular death or first hospitalisation for heart failure	Cardiovascular death, aborted cardiac arrest, or hospitalisation for heart failure	Total heart failure events (hospitalisations and urgent visits) and cardiovascular death
Visit Schedules	RALES	EMPHASIS-HF	TOPCAT	FINEARTS-HF

Baseline	x	x	x	x
Week 1		x		
Week 4	x	x	x	x
Week 8	x		x	
Month 3	x			x
Month 4			x	
Month 5		x		
Month 6	x			x
Month 7				
Month 8			x	
Month 9	x	x		x
Month 10				
Month 11				
Month 12	x*		x*	x*
Month 13		x*		

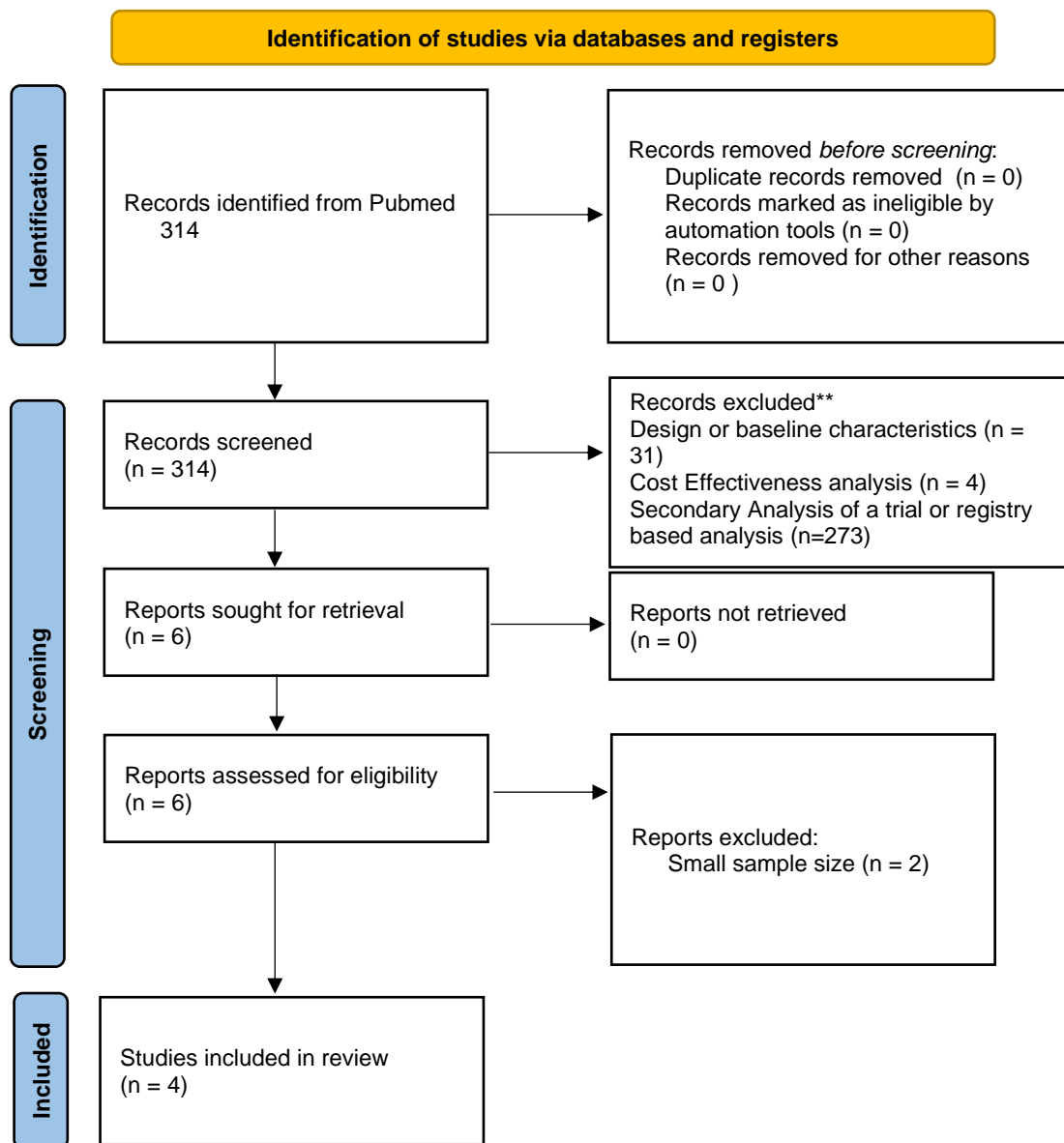
*following this visit, visits then took place every 4 months until the end of study visit

Search strategy used to search medline via Pubmed

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Supplemental Figure 1: PRISMA flow chart of included studies



Supplemental Figure 2: Risk of bias assessment of included studies

		Risk of bias domains					Overall
		D1	D2	D3	D4	D5	
Study	RALES						
	EMPHASIS-HF						
	TOPCAT						
	FINEARTS-HF						

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

Some concerns

Low

Supplemental Table 2- Baseline characteristics in the included trials by randomised therapy

	RALES spironolactone	RALES placebo	EMPHASIS- HF eplerenone	EMPHASIS- HF placebo	TOPCAT spironolactone	TOPCAT placebo	FINEARTS- HF finerenone	FINEARTS- HF placebo
	N=822	N=841	N=1,364	N=1,373	N=1,722	N=1,723	N=3,003	N=2,998
Age (years)	65±12	65±11	68±7	68±7	68±9	68±9	71±9	72±9
Sex, N(%)								
Male	603 (73)	614 (73)	1,055 (77)	1,072 (78)	834 (48)	836 (49)	1,648 (55)	1,621 (54)
Female	219 (27)	227 (27)	309 (23)	301 (22)	888 (52)	887 (51)	1,355 (45)	1,377 (46)
Race, N(%)								
White	712 (87)	728 (87)	1,127 (83)	1,141 (83)	1,525 (89)	1,537 (89)	2,366 (79)	2,369 (79)
Black	56 (7)	64 (8)	37 (3)	30 (2)	153 (9)	149 (9)	49 (2)	39 (1)
Asian	15 (2)	17 (2)	158 (12)	158 (12)	10 (1)	9 (1)	497 (17)	499 (17)
Other	39 (5)	32 (4)	42 (3)	44 (3)	34 (2)	28 (2)	91 (3)	91 (3)
Region, N(%)								
North America	56 (7)	58 (7)	126 (9)	122 (9)	738 (43)	739 (43)	235 (8)	236 (8)
Latin America	216 (26)	217 (26)	47 (3)	51 (4)	148 (9)	142 (8)	322 (11)	319 (11)
Western Europe	526 (64)	540 (64)	500 (37)	505 (37)	0 (0)	0 (0)	599 (20)	605 (20)
Central Europe	0 (0)	0 (0)	492 (36)	496 (36)	836 (49)	842 (49)	1,319 (44)	1,311 (44)
Asia-Pacific	24 (3)	26 (3)	199 (15)	199 (14)	0 (0)	0 (0)	528 (18)	527 (18)
BMI (kg/m ²)	*	*	27.5±4.9	27.5±4.9	32.1±7.1	32.1±7.1	29.9±6.1	30.0±6.1
< 30 kg/m ² , N (%)	*	*	975 (72)	1,008 (74)	764 (44)	769 (45)	1,658 (55)	1,638 (55)
≥ 30 kg/m ² , N (%)	*	*	383 (28)	356 (26)	956 (56)	946 (55)	1,338 (45)	1,354 (45)

Systolic blood pressure (mmHg)	123±21	122±20	124±17	124±17	129±14	129±14	130±15	129±15
Heart rate (beats/min)	81±14	81±15	72±12	72±13	69±11	69±10	72±12	71±12
LVEF (%)	26±7	25±7	26±5	26±5	57±7	57±8	53±7	53±8
NYHA, N (%)								
I, II	4 (0)	3 (0)	1,358 (100)	1,372 (100)	1,146 (67)	1,157 (67)	2,081 (69)	2,065 (69)
III, IV	818 (100)	838 (100)	2 (0)	1 (0)	575 (33)	561 (33)	921 (31)	933 (31)
Prior HF hospitalization, N (%)	*	*	714 (52)	724 (53)	1,246 (72)	1,243 (72)	1,797 (60)	1,822 (61)
NT-proBNP (pg/ml)	**	**	**	**	826.0 (460.0-1572.0)	879.5 (465.5-2033.0)	1052.5 (467.3-1937.0)	1028.0 (433.2-1963.1)
eGFR (ml per min per 1.73 m ²), N(%)	63±22	62±21	66±18	65±18	65±19	65±18	63±19	63±20
eGFR (ml/min/1.73 m ²), N (%)								
<60	419 (51)	422 (50)	531 (39)	561 (41)	747 (43)	716 (42)	1,432 (48)	1,412 (47)
≥60	401 (49)	416 (50)	829 (61)	804 (59)	975 (57)	1,005 (58)	1,571 (52)	1,586 (53)
Potassium (mmol/L)	4.2±0.5	4.2±0.4	4.3±0.4	4.3±0.4	4.2±0.4	4.3±0.4	4.4±0.5	4.4±0.5
Type 2 diabetes, N (%)	174 (21)	195 (23)	459 (34)	400 (29)	565 (33)	553 (32)	1,217 (41)	1,222 (41)
Hypertension, N (%)	193 (23)	198 (24)	910 (67)	909 (66)	1,567 (91)	1,580 (92)	2,640 (88)	2,685 (90)

Atrial fibrillation, N (%)	98 (12)	85 (10)	409 (30)	435 (32)	611 (35)	603 (35)	1,648 (55)	1,625 (54)
Myocardial infarction, N (%)	229 (28)	243 (29)	686 (50)	694 (51)	444 (26)	449 (26)	784 (26)	757 (25)
Stroke, N (%)			136 (10)	126 (9)	128 (7)	137 (8)	355 (12)	353 (12)
ACEI/ARB, N (%)	788 (96)	801 (95)	1,283 (95)	1,275 (93)	1,452 (84)	1,448 (84)	2,124 (71)	2,122 (71)
ARNI, N (%)	***	***	***	***	***	***	256 (9)	257 (9)
SGLT2 inhibitor, N (%)	***	***	***	***	***	***	393 (13)	424 (14)
β-Blocker, N (%)	85 (10)	86 (10)	1,181 (87)	1,193 (87)	1,346 (78)	1,330 (77)	2,541 (85)	2,554 (85)
Diuretic, N (%)	742 (90)	760 (90)	1,150 (85)	1,176 (86)	1,401 (81)	1,416 (82)	2,973 (99)	2,957 (99)
Digitalis glycosides, N (%)	611 (74)	605 (72)	363 (27)	377 (28)	178 (10)	164 (10)	241 (8)	230 (8)

NT-proBNP, N-terminal pro B type natriuretic peptide BMI, body mass index eGFR, estimated glomerular filtration rate ACEI, angiotensin-converting enzyme inhibitor ARB, angiotensin receptor blocker LVEF, left ventricular ejection fraction NYHA, New York Heart Association ARNI, angiotensin receptor neprilysin inhibitor SGLT2, Sodium-glucose co-transporter 2 inhibitors

*missing in RALES

** missing in RALES and EMPHASIS-HF

*** missing in RALES, EMPHASIS-HF and TOPCAT

Supplemental Table 3- Event rates in RALES, EMPHASIS-HF, TOPCAT and FINEARTS-HF for each outcome by randomised therapy

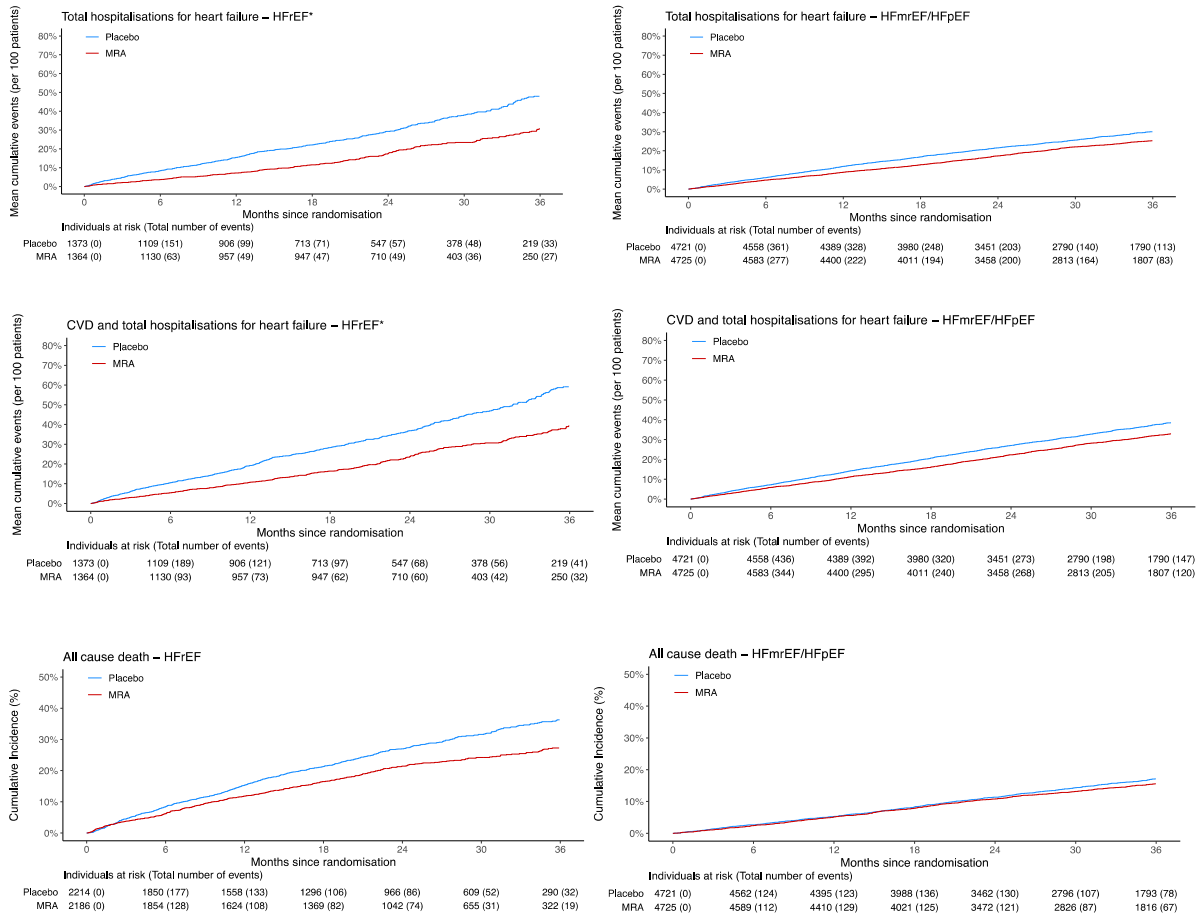
Outcomes	RALES-Spironolactone		RALES-Placebo		EMPHASIS-Eplerenone		EMPHASIS-Placebo	
	N = 822		N = 841		N = 1364		N = 1373	
	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)
CV death /HF hospitalisation	346 (41.14)	27.25 (24.52,30.28)	472 (57.42)	43.33 (39.59,47.42)	249 (18.14)	10.75 (9.49,12.17)	356 (26.10)	16.43 (14.81,18.23)
CV death	226 (26.87)	14.82 (13.01,16.88)	314 (38.20)	21.59 (19.33,24.11)	147 (10.71)	5.96 (5.07,7.00)	185 (13.56)	7.72 (6.69,8.92)
HF hospitalisation	216 (25.68)	16.60 (14.52,18.96)	300 (36.50)	26.91 (24.03,30.14)	164 (11.94)	7.08 (6.07,8.25)	253 (18.55)	11.67 (10.32,13.20)
HF hospitalisation (first and total)	323 (160, 19.02)	21.18 (17.20,26.08)	529 (238, 28.95)	36.37 (31.07,42.58)	313 (186, 13.55)	12.68 (10.66,15.09)	481 (277, 20.31)	20.08 (17.55,22.98)
CVD or HF hospitalisation (first and total)	503 (319, 37.93)	32.98 (28.50,38.17)	770 (442, 53.77)	52.94 (47.13,59.46)	408 (271, 19.74)	16.53 (14.31,19.09)	598 (379, 27.79)	24.96 (22.26,28.00)
All cause death	284 (33.77)	18.62 (16.58,20.92)	386 (46.96)	26.54 (24.02,29.32)	171 (12.45)	6.93 (5.96,8.05)	213 (15.62)	8.89 (7.77,10.17)

Outcomes	TOPCAT-Spironolactone		TOPCAT-Placebo		FINEARTS-Finerenone		FINEARTS-Placebo	
	N = 1722		N = 1723		N = 3003		N = 2998	
	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)
CV death / HF hospitalisation	320 (18.57)	5.87 (5.26,6.55)	347 (20.15)	6.50 (5.85,7.22)	624 (20.81)	9.31 (8.61,10.07)	719 (23.94)	11.01 (10.23,11.84)
CV death	160 (9.29)	2.75 (2.36,3.21)	176 (10.22)	3.05 (2.63,3.53)	242 (8.07)	3.33 (2.93,3.77)	260 (8.66)	3.59 (3.18,4.05)
HF hospitalisation	206 (11.96)	3.78 (3.30,4.33)	245 (14.23)	4.59 (4.05,5.20)	479 (15.98)	7.15 (6.54,7.82)	573 (19.08)	8.77 (8.08,9.52)
HF hospitalisation (first and total)	393 (206, 11.96)	6.76 (5.67,8.05)	476 (245, 14.23)	8.24 (7.07,9.60)	842 (479, 15.98)	11.57 (10.37,12.91)	1024 (573, 19.08)	14.12 (12.79,15.60)
CVD or HF hospitalisation (first and total)	550 (320, 18.57)	9.46 (8.24,10.85)	648 (347, 20.15)	11.22 (9.87,12.75)	1083 (624, 20.81)	14.88 (13.52,16.38)	1283 (719, 23.94)	17.70 (16.22,19.31)
All cause death	257 (14.92)	4.42 (3.91,4.99)	273 (15.85)	4.73 (4.20,5.32)	491 (16.38)	6.71 (6.14,7.33)	522 (17.38)	7.17 (6.58,7.82)

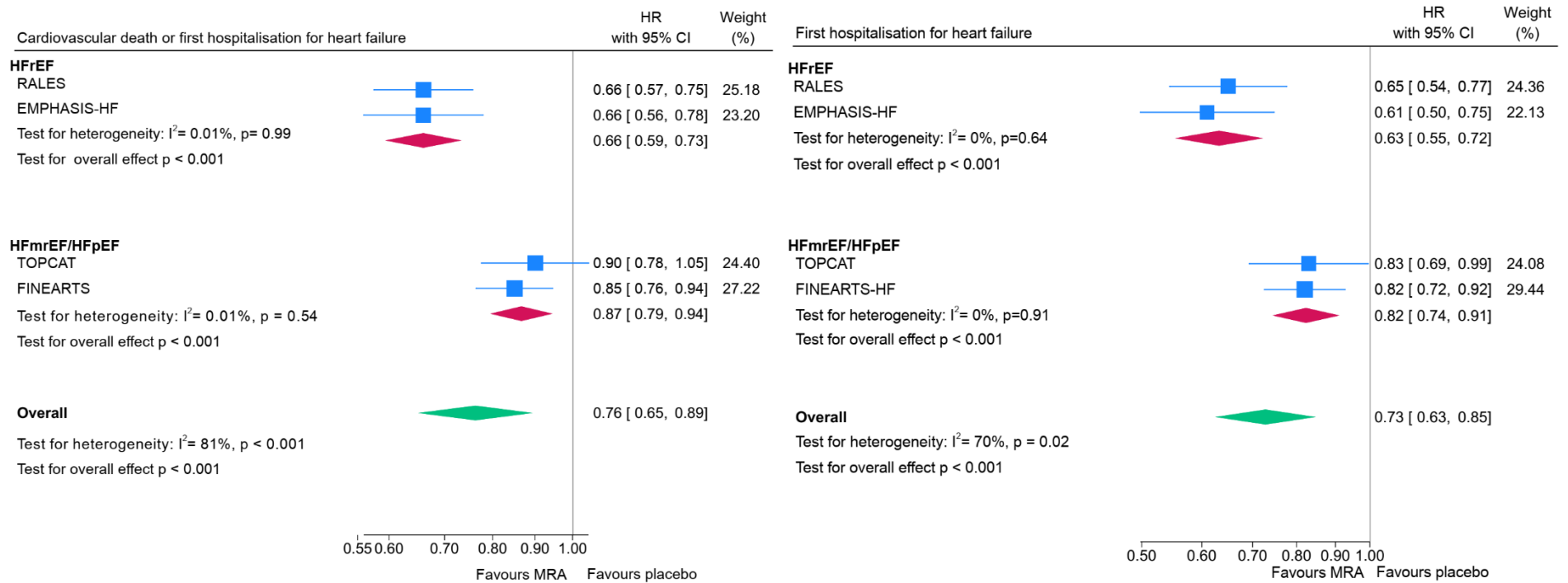
Supplemental Table 4- Event rates in HFref and HFmrEF/HFpEF trials combined and for all trials for each outcome by randomised therapy

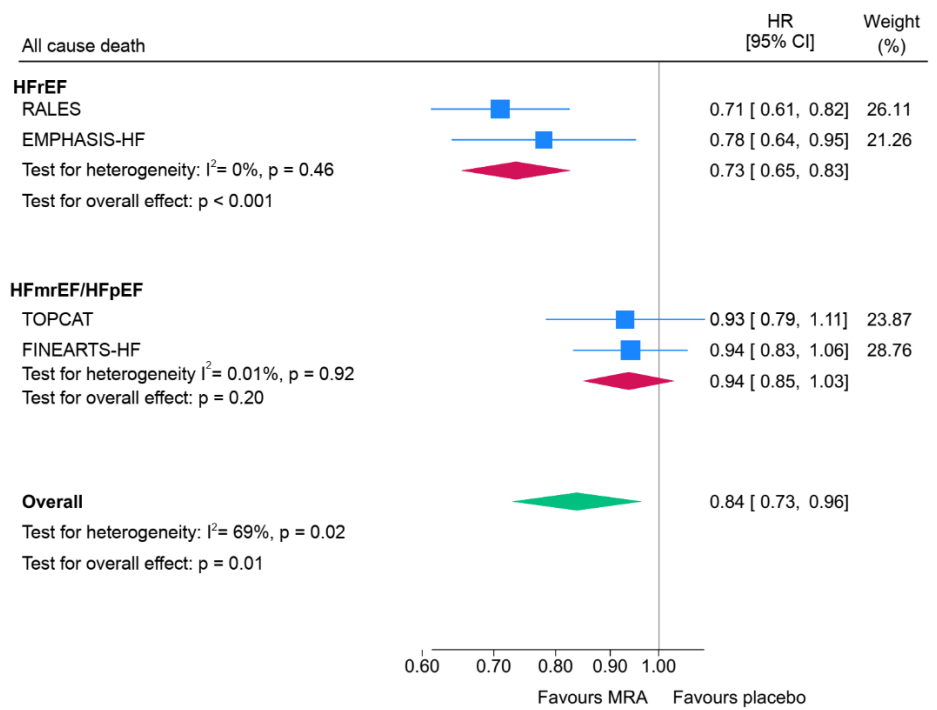
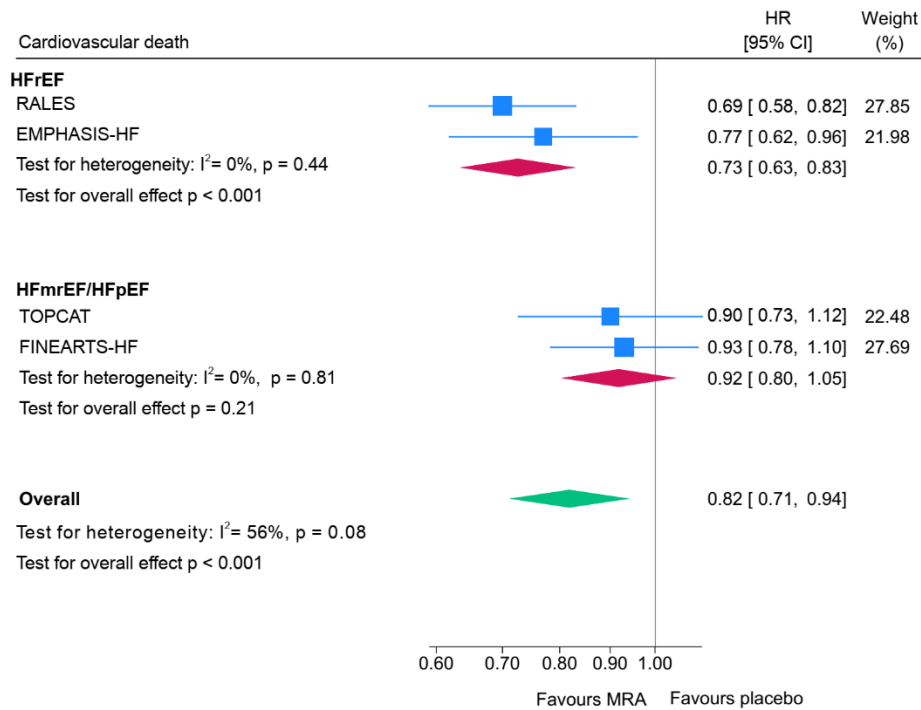
Outcomes	HFref-MRA		HFref-Placebo		HFpEF-MRA		HFpEF-Placebo		All trials-MRA		All trials-Placebo	
	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)
	N = 2186		N = 2214		N = 4725		N = 4721		N = 6911		N = 6935	
CV death / HF hospitalisation	595 (26.87)	16.59 (15.31,17.98)	828 (37.88)	25.43 (23.75,27.22)	944 (20.00)	7.77 (7.29,8.28)	1066 (22.56)	8.98 (8.46,9.54)	1539 (22.19)	9.78 (9.30,10.28)	1894 (27.41)	12.52 (11.97,13.10)
CV death	373 (16.85)	9.34 (8.44,10.34)	499 (22.83)	12.97 (11.88,14.16)	402 (8.52)	3.07 (2.78,3.39)	436 (9.23)	3.35 (3.05,3.68)	775 (11.18)	4.54 (4.23,4.87)	935 (13.53)	5.54 (5.20,5.91)
HF hospitalisation	380 (17.16)	10.50 (9.49,11.61)	553 (25.30)	16.86 (15.51,18.32)	685 (14.51)	5.64 (5.23,6.07)	818 (17.31)	6.89 (6.43,7.38)	1065 (15.36)	6.75 (6.36,7.17)	1371 (19.84)	9.05 (8.58,9.54)
Total HF hospitalisation	636 (346, 15.63)	15.93 (13.90,18.25)	1010 (515, 23.56)	26.23 (23.60,29.16)	1235 (685, 14.51)	9.43 (8.59,10.36)	1500 (818, 17.31)	11.52 (10.59,12.52)	1871 (1031, 14.87)	10.95 (10.13,11.83)	2510 (1333, 19.29)	14.87 (13.92,15.89)
CV death and total HF hospitalisation	911 (590, 26.65)	22.81 (20.57,25.30)	1368 (821, 37.56)	35.53 (32.68,38.63)	1633 (944, 20.00)	12.47 (11.53,13.50)	1931 (1066, 22.56)	14.82 (13.78,15.94)	2544 (1534, 22.12)	14.89 (13.98,15.86)	3299 (1887, 27.30)	19.55 (18.49,20.66)
All cause death	455 (20.55)	11.39 (10.39,12.49)	599 (27.40)	15.57 (14.37,16.87)	748 (15.84)	5.70 (5.30,6.12)	795 (16.83)	6.09 (5.68,6.53)	1203 (17.35)	7.03 (6.64,7.43)	1394 (20.17)	8.25 (7.83,8.69)

Supplemental Figure 3- Nelson – Aalen curves showing the cumulative incidence of total heart failure hospitalisations and the composite of total (first and repeat) hospitalisations for heart failure and cardiovascular death (*excluding RALES as time to events was not recorded). Kaplan Meier curve of all cause death in all trials.



Supplemental Figure 4- Two stage meta-analysis of cardiovascular death or heart failure hospitalisations, heart failure hospitalisations, cardiovascular death and all cause deaths





Supplemental Table 5- Effect of MRAs in each of the trials on pre specified efficacy outcomes including and excluding undetermined deaths from the definition of cardiovascular death

Outcomes	RALES		EMPHASIS		EMPHASIS-RALES		TOPCAT		FINEARTS		TOPCAT-FINEARTS		All trials	
	N = 1663		N = 2737		N = 4400		N = 3445		N = 6001		N = 9446		N = 13846	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	interaction p-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	interaction p-value	HR (95%CI)	interaction p-value
CV death including undetermined deaths														
CV death / HF hospitalisation	0.66 (0.58,0.76)	<0.001	0.66 (0.56,0.78)	<0.001	0.66 (0.60,0.74)	0.988	0.90 (0.77,1.04)	0.151	0.85 (0.77,0.95)	0.003	0.87 (0.80,0.94)	0.596	0.78 (0.73,0.83)	0.001
CV death	0.70 (0.60,0.83)	<0.001	0.78 (0.62,0.96)	0.021	0.73 (0.64,0.83)	0.494	0.90 (0.74,1.10)	0.298	0.90 (0.77,1.05)	0.179	0.90 (0.80,1.02)	0.998	0.82 (0.75,0.89)	0.134
CV death excluding undetermined deaths														
CV death / HF hospitalisation	0.66 (0.57,0.75)	<0.001	0.66 (0.56,0.78)	<0.001	0.66 (0.59,0.73)	0.915	0.90 (0.78,1.05)	0.195	0.85 (0.76,0.94)	0.003	0.87 (0.79,0.95)	0.494	0.78 (0.72,0.83)	0.001
CV death	0.69 (0.58,0.82)	<0.001	0.81 (0.65,1.02)	0.076	0.73 (0.64,0.84)	0.271	0.90 (0.73,1.12)	0.347	0.93 (0.78,1.10)	0.399	0.92 (0.80,1.05)	0.845	0.82 (0.75,0.90)	0.093

Supplemental Table 6- Total heart failure hospitalisations and total heart failure hospitalisation and cardiovascular deaths analysed in semi-parametric proportional rates model excluding RALES and including EMPHASIS-HF, TOPCAT and FINEARTS-HF

Outcomes	RALES		EMPHASIS-HF		HFref		TOPCAT		FINEARTS-HF		HFmrEF/HFpEF		All trials	
	N = 1663		N = 2737		N = 4400		N = 3445		N = 6001		N = 9446		N = 12,183	
	RR (95%CI)	P-value	RR (95%CI)	P-value	RR (95%CI)	interaction p-value	RR (95%CI)	P-value	RR (95%CI)	P-value	RR (95%CI)	interaction p-value	RR (95%CI)	interaction p-value
Total HF hospitalisation	*	*	0.63 (0.50,0.79)	<0.001	*	*	0.82 (0.65,1.03)	0.094	0.82 (0.71,0.95)	0.008	0.82 (0.72,0.93)	0.989	0.77 (0.69,0.86)**	0.132
CV death and total HF hospitalisation	*	*	0.66 (0.54,0.79)	<0.001	*	*	0.84 (0.70,1.02)	0.094	0.84 (0.74,0.96)	0.008	0.84 (0.76,0.94)	0.989	0.80 (0.73,0.88)**	0.132

* estimates not available due to missing data on time to recurrent hospitalisations in RALES

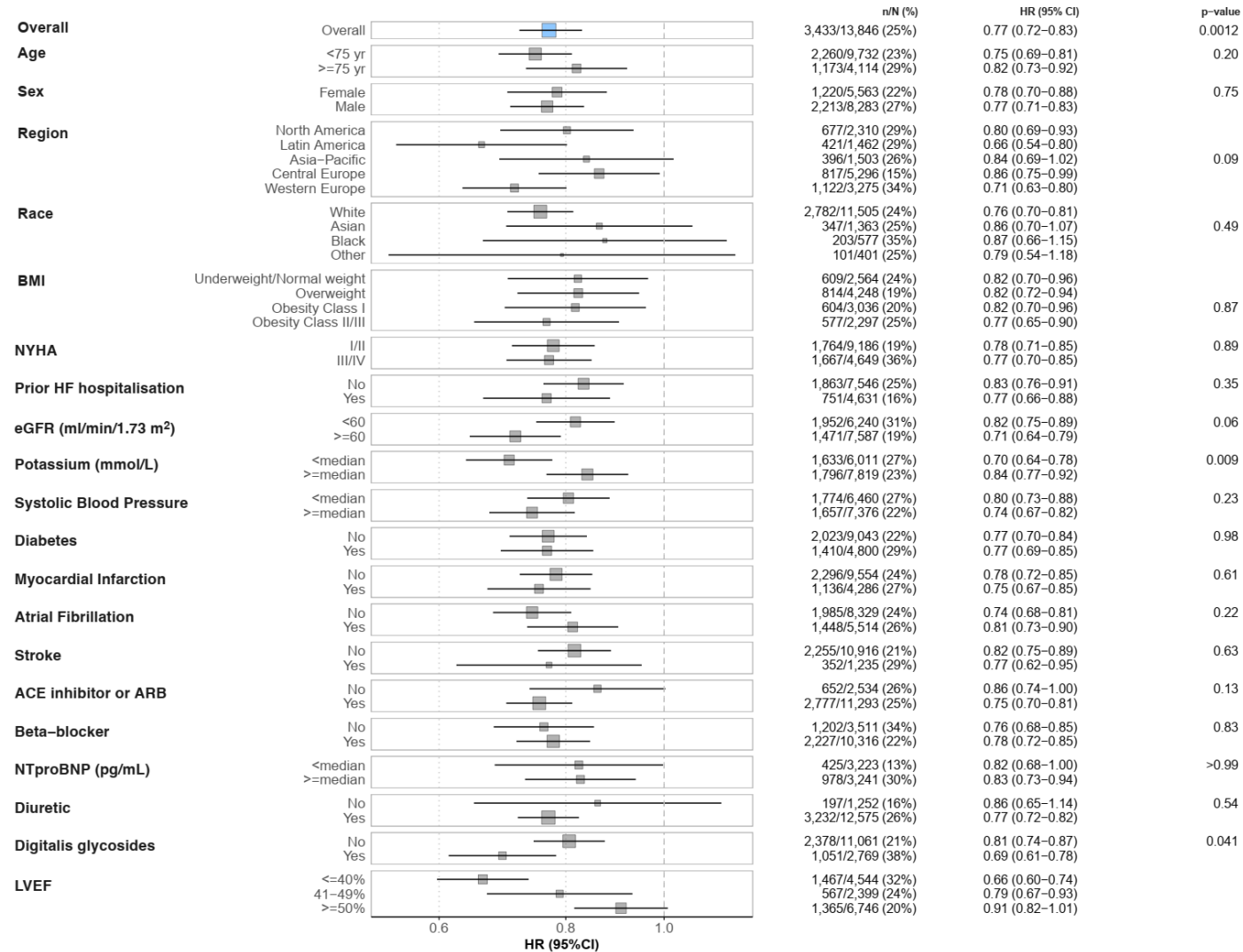
**includes EMPHASIS-HF-HF, TOPCAT and FINEARTS-HF only

Supplemental Table 7- Sensitivity analysis of the effect of MRAs in each of the trials on pre specified efficacy outcomes using all patients included in RALES, EMPHASIS-HF, FINEARTS-HF and only patients randomised in the Americas in TOPCAT

Outcomes	RALES		EMPHASIS-HF		EMPHASIS-HF - RALES		TOPCAT- Americas		FINEARTS-HF		TOPCAT Americas - FINEARTS-HF		All trials	
	N = 1663		N = 2737		N = 4400		N = 1767		N = 6001		N = 7768		N = 12168	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	int p-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	int p-value	HR (95%CI)	int p-value
CV death / HF hospitalisation	0.66 (0.57,0.75)	<0.001	0.66 (0.56,0.78)	<0.001	0.66 (0.59,0.73)	0.965	0.84 (0.70,0.99)	0.043	0.85 (0.76,0.94)	0.03	0.84 (0.77,0.93)	0.898	0.76 (0.71,0.81)	0.006
CV death	0.69 (0.58,0.82)	<0.001	0.77 (0.62,0.96)	0.018	0.72 (0.63,0.82)	0.453	0.74 (0.56,0.96)	0.023	0.93 (0.78,1.10)	0.399	0.86 (0.75,1.00)	0.154	0.78 (0.71,0.86)	0.122
HF hospitalisation	0.65 (0.54,0.77)	<0.001	0.61 (0.50,0.75)	<0.001	0.63 (0.55,0.72)	0.671	0.81 (0.67,0.99)	0.041	0.82 (0.72,0.92)	0.01	0.82 (0.74,0.91)	0.984	0.74 (0.68,0.80)	0.027
Total HF hospitalisation (negative binomial model)	0.65 (0.54,0.77)	<0.001	0.53 (0.42,0.67)	<0.001	0.60 (0.52,0.69)	0.605	0.80 (0.67,0.96)	0.017	0.83 (0.74,0.93)	0.01	0.82 (0.74,0.90)	0.738	0.74 (0.68,0.80)	0.005
CV death and total HF hospitalisation (negative binomial model)	0.68 (0.59,0.79)	<0.001	0.58 (0.48,0.70)	<0.001	0.64 (0.57,0.72)	0.617	0.78 (0.66,0.93)	0.004	0.85 (0.76,0.95)	0.003	0.83 (0.75,0.91)	0.393	0.75 (0.70,0.81)	0.003
Total HF hospitalisation (semi parametric model) *	*	*	0.63 (0.50,0.79)	<0.001	*	*	0.80 (0.63,1.02)	0.070	0.82 (0.71,0.95)	0.008	0.81 (0.72,0.92)	0.887	0.77 (0.69,0.86)	0.145
CV death and total HF hospitalisation (semi parametric model)	*	*	0.66 (0.54,0.79)	<0.001	*	*	0.79 (0.64,0.97)	0.070	0.84 (0.74,0.96)	0.008	0.83 (0.74,0.92)	0.887	0.79 (0.71,0.86)	0.145
All cause death	0.71 (0.61,0.82)	<0.001	0.78 (0.64,0.95)	0.014	0.73 (0.65,0.83)	0.465	0.86 (0.71,1.06)	0.153	0.94 (0.83,1.06)	0.289	0.92 (0.82,1.02)	0.509	0.83 (0.77,0.90)	0.039

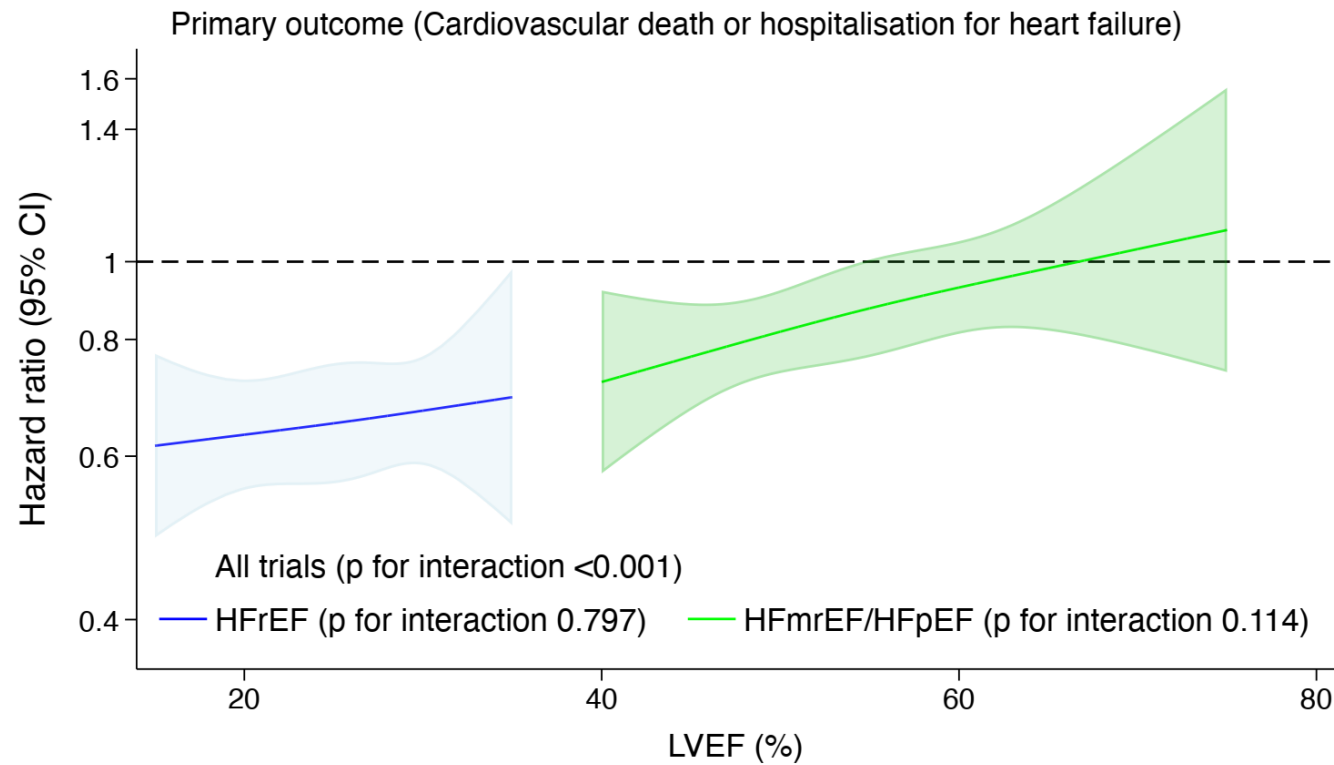
* estimates not available due to missing data on time to recurrent hospitalisations in RALES

Supplemental Figure 5– Subgroup analysis of the outcome of cardiovascular death or first hospitalisation for heart failure in all four trials



Supplemental Figure 6 Interaction between left ventricular ejection fraction and the effect of randomised treatment on the composite of cardiovascular death or hospitalisation for heart failure (left ventricular ejection fraction modelled as a restricted cubic spline).

The p-values are p-values for interaction between left ventricular ejection fraction and effect of mineralocorticoid receptor antagonist treatment in the trials including patients with heart failure and reduced ejection fraction (HFrEF) and in the trials including patients with heart failure and mildly reduced and preserved ejection fraction (HFmrEF/HFpEF). FINEARTS-HF includes urgent visits for worsening heart failure as a hospitalisation equivalent.



Supplemental Table 8 Effect of mineralocorticoid receptor antagonist treatment on additional pre-specified safety outcomes in each trial

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	spironolactone	placebo		eplerenone	placebo		spironolactone	placebo		finerenone	placebo	
	N = 822	N = 841		N = 1360	N = 1369		N = 1699	N = 1691		N = 2993	N = 2993	
	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)
Elevated serum creatinine												
≥0.3 mg/dl	778/779 (100)	796/797 (100)	0.98 (0.06,15.65)	1171/1171 (100)	1170/1170 (100)	-	864/864 (100)	854/854 (100)	-	1265/2928 (43)	825/2921 (28)	864/864 (100)
≥0.5 mg/dl	778/779 (100)	796/797 (100)	0.98 (0.06,15.65)	1170/1171 (100)	1168/1170 (100)	2.00 (0.18,22.12)	864/864 (100)	854/854 (100)	-	677/2928 (23)	418/2921 (14)	864/864 (100)
Reduction in eGFR												
>10%	567/821 (69)	505/840 (60)	1.48 (1.21,1.81)	431/899 (48)	367/922 (40)	1.39 (1.16,1.68)	664/837 (79)	607/832 (73)	1.42 (1.13,1.78)	2335/2928 (80)	1969/2921 (67)	1.90 (1.69,2.14)
Reduction in eGFR ml/min/1.73m²												
≥5	586/821 (71)	530/840 (63)	1.46 (1.19,1.79)	462/899 (51)	412/922 (45)	1.31 (1.09,1.57)	670/837 (80)	625/832 (75)	1.33 (1.05,1.67)	2391/2930 (82)	2078/2924 (71)	1.81 (1.60,2.04)
≥10	482/821 (59)	387/840 (46)	1.66 (1.37,2.02)	337/899 (37)	278/922 (30)	1.39 (1.14,1.69)	533/837 (64)	456/832 (55)	1.45 (1.19,1.76)	1872/2930 (64)	1447/2924 (49)	1.81 (1.63,2.01)

Supplemental Table 9 Safety outcomes in HFrEF and HFmrEF/HFpEF trials combined and all 4 trials combined

Safety outcomes	HFrEF (EMPHASIS-RALES)				HFpEF (TOPCAT-FINEARTS)				All trial			
	MRA	Placebo			MRA	Placebo			MRA	Placebo		
	N = 2182	N = 2210			N = 4692	N = 4684			N = 6874	N = 6894		
	N (%)	N (%)	OR (95%CI)	int p-value	N (%)	N (%)	OR (95%CI)	int p-value	N (%)	N (%)	OR (95%CI)	int p-value
Hypotension												
<90 mm Hg	150/2113 (7)	114/2138 (5)	1.27 (1.02,1.58)	0.679	211/4633 (5)	128/4626 (3)	1.68 (1.34,2.10)	0.338	361/6746 (5)	242/6764 (4)	1.45 (1.24,1.69)	0.278
<100 mm Hg	476/2113 (23)	419/2138 (20)	1.18 (1.02,1.36)	0.158	823/4633 (18)	562/4626 (12)	1.56 (1.39,1.75)	0.569	1299/6746 (19)	981/6764 (15)	1.39 (1.27,1.52)	0.013
Elevated serum creatinine												
≥2.5 mg/dl	98/1950 (5)	65/1967 (3)	1.55 (1.12,2.13)	0.388	264/3792 (7)	164/3775 (4)	1.65 (1.35,2.01)	0.376	366/6569 (6)	230/6573 (3)	1.63 (1.37,1.93)	0.639
≥3 mg/dl	39/1950 (2)	28/1967 (1)	1.41 (0.87,2.31)	0.137	118/3792 (3)	69/3775 (2)	1.73 (1.28,2.33)	0.995	158/6569 (2)	97/6573 (1)	1.65 (1.27,2.12)	0.444
Elevated serum potassium												
>5.5 mmol/l	285/2115 (13)	134/2137 (6)	2.33 (1.88,2.89)	0.001	554/3785 (15)	250/3769 (7)	2.41 (2.06,2.82)	0.060	909/6727 (14)	433/6737 (6)	2.27 (2.02,2.56)	0.008
>6 mmol/l	66/2115 (3)	34/2137 (2)	1.99 (1.31,3.03)	0.031	123/3785 (3)	53/3769 (1)	2.35 (1.70,3.26)	0.165	196/6727 (3)	94/6737 (1)	2.12 (1.65,2.72)	0.154
Reduced serum potassium												
<3.5 mmol/l	154/2115 (7)	299/2137 (14)	0.48 (0.39,0.59)	0.002	230/3785 (6)	491/3769 (13)	0.43 (0.37,0.51)	0.267	504/6727 (7)	929/6737 (14)	0.51 (0.45,0.57)	0.006
Elevated serum creatinine												
≥0.3 mg/dl	1949/1950 (100)	1966/1967 (100)	0.99 (0.06,15.86)	-	2129/3792 (56)	1679/3775 (44)	1.60 (1.46,1.75)	-	4905/6569 (75)	4476/6573 (68)	1.38 (1.28,1.49)	0.630
≥0.5 mg/dl	1948/1950 (100)	1964/1967 (100)	1.49 (0.25,8.91)	0.701	1541/3792 (41)	1272/3775 (34)	1.35 (1.23,1.48)	-	4316/6569 (66)	4067/6573 (62)	1.18 (1.10,1.27)	0.908
Reduction in eGFR												
>10%	998/1720 (58)	872/1762 (49)	1.41 (1.23,1.61)	0.662	2999/3765 (80)	2576/3753 (69)	1.79 (1.61,1.99)	0.026	4526/6300 (72)	3955/6333 (62)	1.53 (1.42,1.65)	4526/6300 (72)

>20%	692/1720 (40)	552/1762 (31)	1.48 (1.28,1.70)	0.039	2200/3765 (58)	1650/3753 (44)	1.79 (1.64,1.96)	0.118	3234/6300 (51)	2520/6333 (40)	1.60 (1.49,1.71)	3234/6300 (51)
>30%	443/1720 (26)	288/1762 (16)	1.78 (1.50,2.10)	0.684	1371/3765 (36)	891/3753 (24)	1.84 (1.66,2.03)	0.095	1989/6300 (32)	1332/6333 (21)	1.73 (1.60,1.88)	1989/6300 (32)
Reduction in eGFR ml/min/1.73m²												
≥5	1048/1720 (61)	942/1762 (53)	1.36 (1.19,1.55)	1048/1720 (61)	3061/3767 (81)	2703/3756 (72)	1.69 (1.52,1.88)	0.022	4689/6302 (74)	4202/6336 (66)	1.48 (1.37,1.59)	0.001
≥10	819/1720 (48)	665/1762 (38)	1.50 (1.31,1.72)	819/1720 (48)	2405/3767 (64)	1903/3756 (51)	1.72 (1.57,1.89)	0.050	3661/6302 (58)	3002/6336 (47)	1.54 (1.44,1.65)	<0.001

Supplemental Table 10 Effect of mineralocorticoid receptor antagonist treatment on the pre-specified safety outcomes in each trial eGFR<45

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	spiro.	placebo		epler.	placebo		spiro.	placebo		finer.	placebo	
	N = 179	N = 188		N = 181	N = 201		N = 249	N = 249		N = 613	N = 646	
	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)
Hypotension												
<90 mm Hg	17/162 (10)	17/175 (10)	1.20 (0.70,2.06)	14/175 (8)	16/197 (8)	0.98 (0.47,2.08)	9/249 (4)	8/249 (3)	1.13 (0.43,2.98)	26/593 (4)	24/630 (4)	1.16 (0.66,2.04)
<100 mm Hg	43/162 (27)	56/175 (32)	0.86 (0.56,1.32)	32/175 (18)	45/197 (23)	0.76 (0.46,1.26)	41/249 (16)	41/249 (16)	1.00 (0.62,1.61)	110/593 (19)	92/630 (15)	1.33 (0.98,1.80)
Elevated serum creatinine												
≥2.5 mg/dl	45/164 (27)	31/175 (18)	1.76 (1.05,2.95)	14/150 (9)	14/173 (8)	1.17 (0.54,2.54)	67/248 (27)	38/248 (15)	2.05 (1.31,3.19)	124/588 (21)	77/623 (12)	1.89 (1.39,2.58)
≥3 mg/dl	20/164 (12)	12/175 (7)	1.89 (0.89,3.99)	5/150 (3)	6/173 (3)	0.96 (0.29,3.21)	28/248 (11)	19/248 (8)	1.53 (0.83,2.83)	57/588 (10)	35/623 (6)	1.80 (1.17,2.79)
Reduction in eGFR												
>20%	86/179 (48)	54/188 (29)	2.29 (1.49,3.53)	28/122 (23)	21/123 (17)	1.45 (0.77,2.72)	132/239 (55)	130/244 (53)	1.08 (0.76,1.53)	324/588 (55)	238/623 (38)	1.99 (1.58,2.50)
>30%	58/179 (32)	37/188 (20)	1.96 (1.21,3.15)	16/122 (13)	6/123 (5)	2.94 (1.11,7.80)	91/239 (38)	71/244 (29)	1.50 (1.02,2.19)	210/588 (36)	131/623 (21)	2.09 (1.62,2.70)
Elevated serum potassium												
>5.5 mmol/l	43/164 (26)	15/175 (9)	3.79 (2.01,7.14)	29/175 (17)	14/196 (7)	2.58 (1.32,5.07)	51/248 (21)	18/248 (7)	3.31 (1.87,5.85)	125/588 (21)	60/624 (10)	2.54 (1.82,3.54)
>6 mmol/l	12/164 (7)	5/175 (3)	2.68 (0.92,7.79)	2/175 (1)	5/196 (3)	*	14/248 (6)	4/248 (2)	3.65 (1.18,11.25)	26/588 (4)	14/624 (2)	2.02 (1.04,3.90)
Reduced serum potassium												
<3.5 mmol/l	8/164 (5)	32/175 (18)	0.23 (0.10,0.51)	12/175 (7)	17/196 (9)	0.78 (0.36,1.67)	33/248 (13)	58/248 (23)	0.50 (0.31,0.80)	33/588 (6)	62/624 (10)	0.54 (0.35,0.84)

*not calculated due to <5 events in a cell

Supplemental Table 11 Effect of mineralocorticoid receptor antagonist treatment on the pre-specified safety outcomes in each trial eGFR \geq 45

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	spiro.	placebo		epi.	placebo		spiro.	placebo		finer.	placebo	
	N = 641	N = 650		N = 1175	N = 1160		N = 1450	N = 1442		N = 2380	N = 2347	
	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)
Hypotension												
<90 mm Hg	62/612 (10)	43/619 (7)	1.27 (0.92,1.77)	57/1159 (5)	37/1137 (3)	1.54 (1.01,2.35)	56/1450 (4)	25/1442 (2)	2.28 (1.41,3.67)	120/2341 (5)	71/2305 (3)	1.70 (1.26,2.29)
<100 mm Hg	171/612 (28)	153/619 (25)	1.14 (0.90,1.45)	229/1159 (20)	162/1137 (14)	1.48 (1.19,1.85)	226/1450 (16)	147/1442 (10)	1.63 (1.30,2.03)	446/2341 (19)	282/2305 (12)	1.69 (1.44,1.98)
Elevated serum creatinine												
\geq 2.5 mg/dl	25/613 (4)	12/619 (2)	2.15 (1.07,4.32)	14/1020 (1)	8/995 (1)	1.72 (0.72,4.11)	34/1443 (2)	17/1437 (1)	2.02 (1.12,3.62)	43/2340 (2)	33/2298 (1)	1.28 (0.81,2.03)
\geq 3 mg/dl	10/613 (2)	5/619 (1)	2.04 (0.69,5.99)	4/1020 (0)	5/995 (1)	0.78 (0.21,2.91)	14/1443 (1)	5/1437 (0)	2.81 (1.01,7.81)	20/2340 (1)	10/2298 (0)	1.97 (0.92,4.22)
Reduction in eGFR												
>20%	347/640 (54)	276/650 (42)	1.60 (1.29,2.00)	231/777 (30)	201/799 (25)	1.26 (1.01,1.57)	734/1413 (52)	618/1406 (44)	1.38 (1.19,1.60)	1352/2340 (58)	982/2298 (43)	1.83 (1.63,2.06)
>30%	230/640 (36)	152/650 (23)	1.84 (1.44,2.34)	139/777 (18)	93/799 (12)	1.65 (1.25,2.20)	422/1413 (30)	331/1406 (24)	1.38 (1.17,1.64)	823/2340 (35)	511/2298 (22)	1.90 (1.67,2.16)
Elevated serum potassium												
>5.5 mmol/l	84/613 (14)	22/619 (4)	4.31 (2.66,6.99)	129/1158 (11)	82/1137 (7)	1.61 (1.21,2.16)	147/1443 (10)	74/1437 (5)	2.09 (1.56,2.79)	301/2333 (13)	147/2291 (6)	2.16 (1.76,2.66)
>6 mmol/l	20/613 (3)	4/619 (1)	*	32/1158 (3)	20/1137 (2)	1.59 (0.90,2.79)	26/1443 (2)	12/1437 (1)	2.18 (1.10,4.34)	64/2333 (3)	30/2291 (1)	2.13 (1.37,3.29)
Reduced serum potassium												
<3.5 mmol/l	45/613 (7)	116/619 (19)	0.34 (0.24,0.49)	88/1158 (8)	133/1137 (12)	0.62 (0.47,0.82)	172/1443 (12)	273/1437 (19)	0.58 (0.47,0.71)	112/2333 (5)	237/2291 (10)	0.44 (0.35,0.55)

*not calculated due to <5 events in a cell

Supplemental Table 12 Effect of mineralocorticoid receptor antagonist treatment on the pre-specified safety outcomes in each trial TOPCAT Americas

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT- Americas			FINEARTS-HF		
	spiro.	placebo		epler.	placebo		spiro.	placebo		finer.	placebo	
	N = 822	N = 841		N = 1360	N = 1369		N = 869	N = 860		N = 2993	N = 2993	
	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)	N (%)	N (%)	OR (95%CI)
Hypotension												
<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)	65/869 (7)	33/860 (4)	2.03 (1.32,3.11)	146/2934 (5)	95/2935 (3)	1.57 (1.20,2.04)
<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)	255/869 (29)	177/860 (21)	1.60 (1.29,2.00)	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)	97/864 (11)	54/854 (6)	1.87 (1.32,2.65)	167/2928 (6)	110/2921 (4)	1.55 (1.21,1.98)
≥3 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)	41/864 (5)	24/854 (3)	1.72 (1.03,2.88)	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)	520/837 (62)	430/832 (52)	1.53 (1.26,1.86)	1676/2928 (57)	1220/2921 (42)	1.87 (1.68,2.07)
>30%	288/821 (35)	189/840 (22)	1.86 (1.50,2.31)	155/899 (17)	99/922 (11)	1.73 (1.32,2.27)	337/837 (40)	249/832 (30)	1.58 (1.29,1.93)	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)	128/864 (15)	43/854 (5)	3.28 (2.29,4.70)	426/2921 (15)	207/2915 (7)	2.23 (1.88,2.66)
>6 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)	33/864 (4)	9/854 (1)	3.73 (1.77,7.84)	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)	85/864 (10)	192/854 (22)	0.38 (0.29,0.50)	145/2921 (5)	299/2915 (10)	0.46 (0.37,0.56)