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

Pardeep S Jhund
BHF Glasgow Cardiovascular Research Centre, University of Glasgow
& Queen Elizabeth University Hospital, Glasgow

Disclosures

- **Presenter Disclosure**: Speakers Fees –AstraZeneca, Novartis, Alkem Metabolics, ProAdWise Communications, Sun Pharmaceuticals, Intas pharma; Advisory Board – AstraZeneca, Boehringer Ingelheim, Novartis; Research Funding – AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, Roche Diagnostics; My employer, the University of Glasgow, has been remunerated for my time working on clinical trials by AstraZeneca, Novartis, NovoNordisk and Bayer AG

- **Trial Sponsors:** The RALES trial was supported by a grant from Searle Pharmaceuticals, the EMPHASIS-HF trial was sponsored by Pfizer, the TOPCAT trial was supported by the National Heart Lung Blood Institute, USA, and the FINEARTS-HF trial was sponsored by Bayer AG.

- **Funding for the meta-analysis:** None

MRAs in HF: Background

- Mineralocorticoid receptor antagonists (MRAs) have a strong indication in guidelines for the treatment of HF with reduced ejection fraction (HFrEF)
- There is weaker evidence for the use of MRAs in heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) as prior trials were neutral
- In the ESC guidelines there is a weak recommendation for MRAs in HFmrEF, based on post-hoc analyses, and no recommendation for HFpEF
- With the completion of FINEARTS-HF we conducted an individual patient level meta-analysis of the large trials using MRAs in HF to assess their efficacy and safety in HFrEF and HFmrEF/HFpEF

PROSPERO: CRD42024541487

MRAs in HF: Methods

	HFrEF		HFmrEF/HFpEF	
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	Ejection fraction ≤35%	Ejection fraction ≤30% (or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography)	Ejection fraction ≥45%	Ejection fraction ≥40% including improved ejection fraction

PROSPERO: CRD42024541487

MRAs in HF: Methods

- Data were harmonised and combined into a single dataset
- We undertook a pre-specified individual patient-level meta-analysis of the four MRA trials
- A two stage meta-analysis was used to confirm the results
- The definition of HF hospitalisation in the FINEARTS-HF trial included urgent HF visits as the trial was conducted during the COVID-19 pandemic and reflecting current clinical practice
- Sensitivity analyses including and excluding undetermined deaths from the definition of cardiovascular death, and using the patients enrolled in the Americas in TOPCAT were performed

PROSPERO: CRD42024541487

MRAs in HF: Aims - Efficacy

- The following outcomes were studied :
  - Time to first hospitalisation for HF or cardiovascular death
  - Time to first hospitalisation for heart failure
  - Total (first and repeat) heart failure hospitalisations
  - Total heart failure hospitalisations and cardiovascular death
  - Cardiovascular death
  - All-cause death
- We used a Cox proportional hazards model stratified by trial
- An interaction term between randomised treatment and trial was tested

MRAs in HF: Aims - Safety

- The following safety outcomes were studied:
  - systolic blood pressure <90 and <100 mmHg
  - serum creatinine ≥2.5 and ≥3 mg/dl (221 and 265 µmol/l)
  - serum potassium >5.5 and >6 mmol/l
  - serum potassium <3.5 mmol/l

- Safety outcomes were defined based on laboratory measures or clinical examination during follow up recorded in the trial databases, independent of whether patients were on or off treatment

MRAs in HF: Key baseline characteristics

	RALES	EMPHASIS-HF	TOPCAT	FINEARTS-HF	Total
	N=1,663	N=2,737	N=3,445	N=6,001	N=13,846
Age (years)	65±11	68±7	68±9	72±9	69±9
Sex N (%)					
Men	73%	78%	48%	54%	60%
Women	27%	22%	52%	46%	40%
Race, N (%)					
White	87%	83%	89%	79%	83%
Black	7%	2%	9%	1%	4%
Asian	2%	12%	1%	17%	10%
Other	4%	3%	2%	3%	3%
Region, N (%)					
North America	7%	9%	43%	8%	17%
Latin America	26%	4%	8%	11%	11%
Western Europe	64%	37%	0%	20%	24%
Central and Eastern Europe	0%	36%	49%	44%	38%
Asia-Pacific	3%	15%	0%	18%	11%

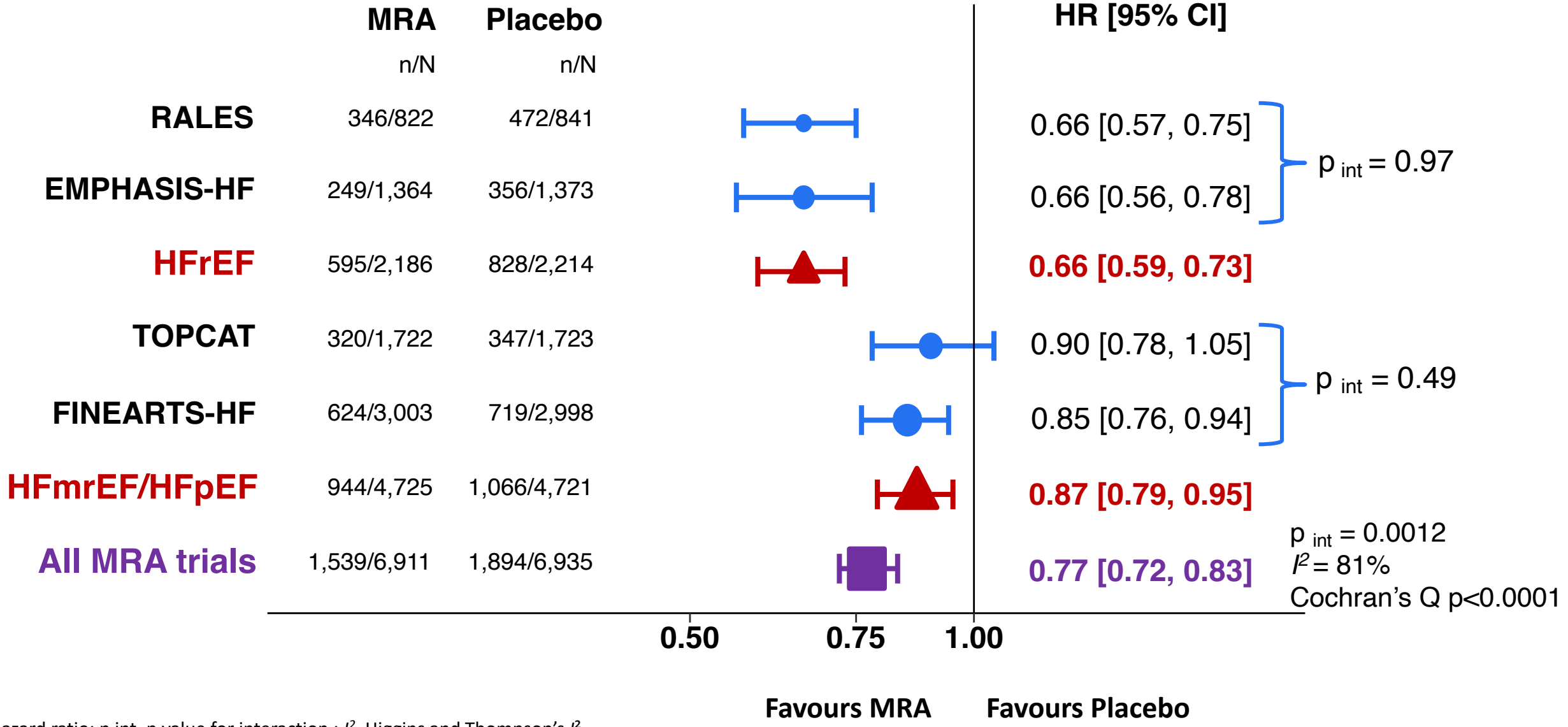
MRAs in HF: Key baseline characteristics

	RALES	EMPHASIS-HF	TOPCAT	FINEARTS-HF	Total
	N=1,663	N=2,737	N=3,445	N=6,001	N=13,846
Systolic BP (mmHg)	122±20	124±17	129±14	129±15	127±16
Heart rate (beats/min)	81±14	72±13	69±10	71±12	72±12
LVEF (%)	25±7	26±5	57±7	53±8	45±15
NYHA class, N (%)					
I, II	0%	100%	67%	69%	66%
III, IV	100%	0%	33%	31%	34%
NT-proBNP (pg/ml), median Q1-Q3	Not available	Not available	843.0 (463.0-1720.0)	1041.4 (448.5-1945.9)	1013.5 (449.6-1929.8)
eGFR (ml /min / 1.73 m^2)	63±22	65±18	65±19	63±20	64±19
Diabetes, N (%)	22%	31%	32%	41%	35%
Atrial fibrillation, N (%)	11%	31%	35%	55%	40%
Myocardial infarction, N (%)	28%	50%	26%	26%	31%

MRAs in HF: Key baseline characteristics

	RALES	EMPHASIS-HF	TOPCAT	FINEARTS-HF	Total
	N=1,663	N=2,737	N=3,445	N=6,001	N=13,846
ACEI/ARB, N (%)	96%	93%	84%	71%	82%
ARNI, N(%)	Not available	Not available	Not available	9%	4%
SGLT2 inhibitor, N (%)	Not available	Not available	Not available	14%	6%
β-Blocker, N (%)	10%	87%	78%	85%	75%
Diuretic, N (%)	90%	85%	82%	99%	91%
Digitalis glycosides, N(%)	73%	27%	10%	8%	20%

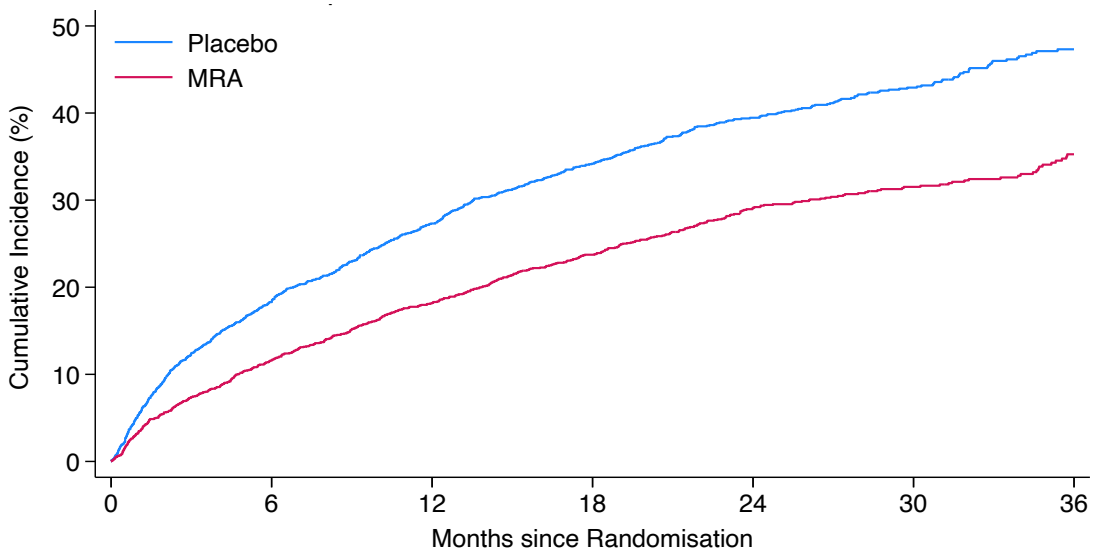
MRAs in HF: CV Death or hospitalisation for HF



HR, hazard ratio; p int, p value for interaction ; I^2, Higgins and Thompson's I^2

MRAs in HF: CV Death or hospitalisation for HF

HFrEF



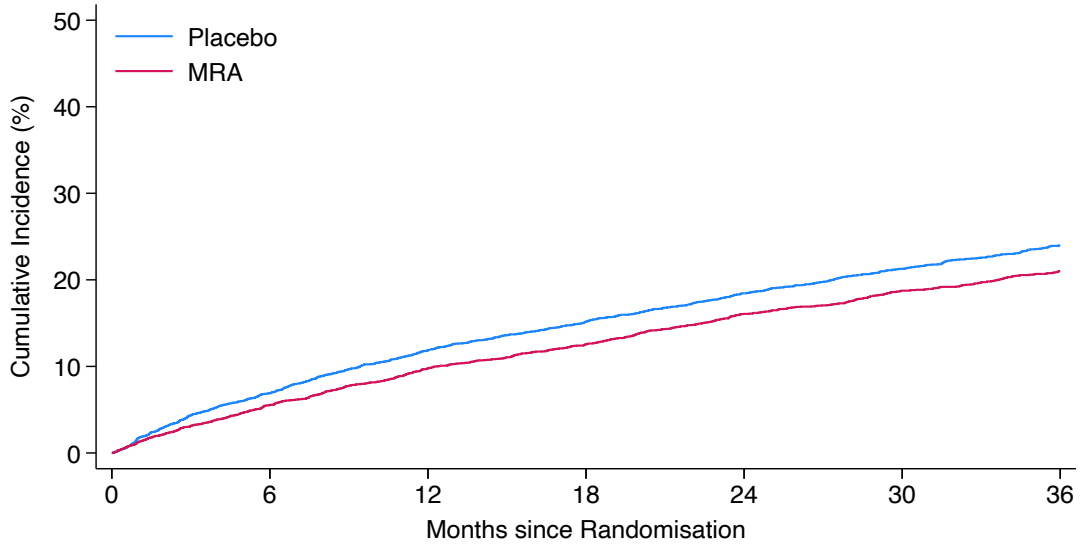
Number at risk

Placebo	2214	1638	1315	1052	758	466	226
MRA	2186	1742	1480	1216	878	516	255

Placebo rate* 25 (95%CI 24 - 27)

MRA rate* 17 (95%CI 15 - 18)

HFmrEF/HFpEF



Number at risk

Placebo	4721	4317	4008	3567	3057	2449	1557
MRA	4725	4400	4104	3675	3111	2507	1607

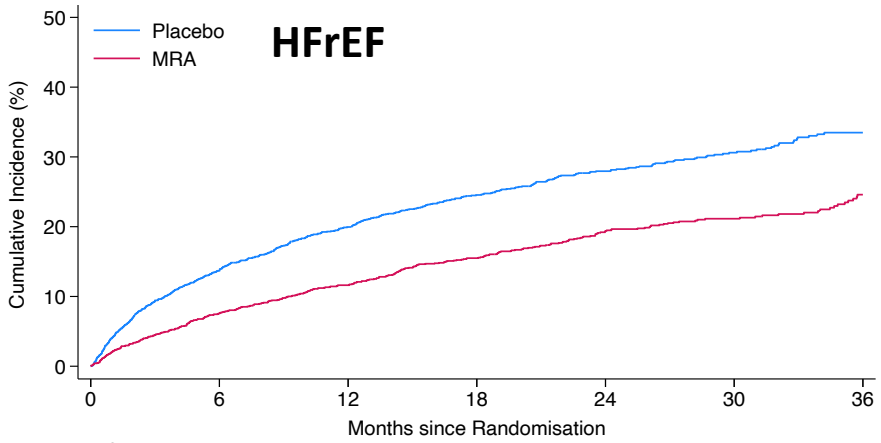
Placebo rate* 9 (95%CI 8 - 10)

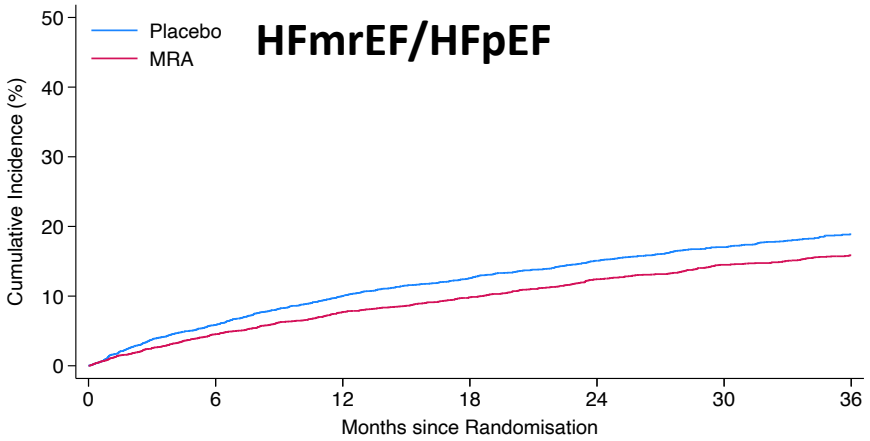
MRA rate* 8 (95%CI 7 - 8)

* Per 100 patient years of follow up

MRAs in HF: Hospitalisation for HF

	MRA n/N	Placebo n/N	HR [95% CI]	
RALES	216/822	300/841	0.65 [0.54, 0.77]	p_{int} = 0.67
EMPHASIS-HF	164/1,364	253/1,373	0.61 [0.50, 0.75]	
HFrEF	380/2,186	553/2,214	**0.63 [0.55, 0.72]**	
TOPCAT	206/1,722	245/1,723	0.83 [0.69, 0.99]	p_{int} = 0.92
FINEARTS-HF	479/3,003	573/2,998	0.82 [0.72, 0.92]	
HFmrEF/HFpEF	685/4,725	818/4,721	**0.82 [0.74, 0.91]**	
All MRA trials	1,065/6,911	1,371/6,935	**0.74 [0.69, 0.80]**	p_{int} = 0.022

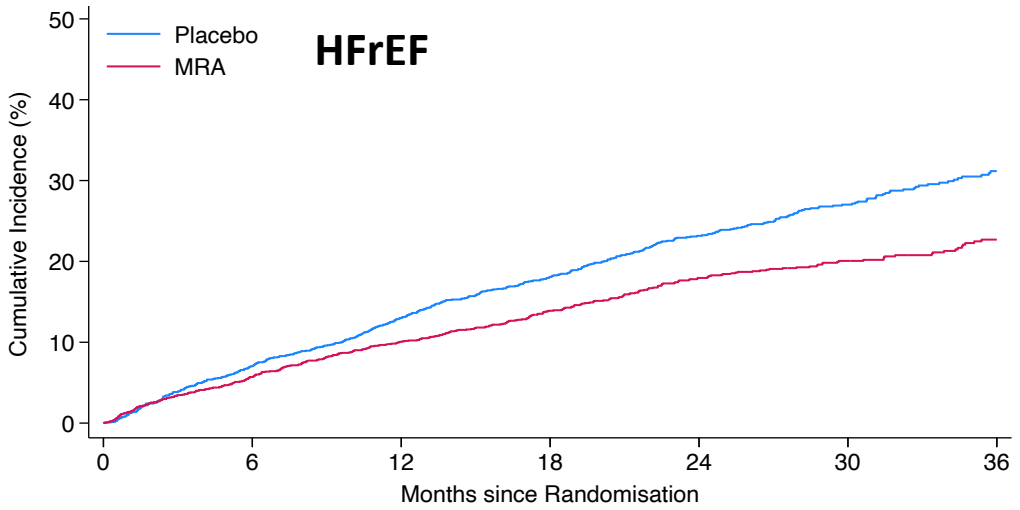


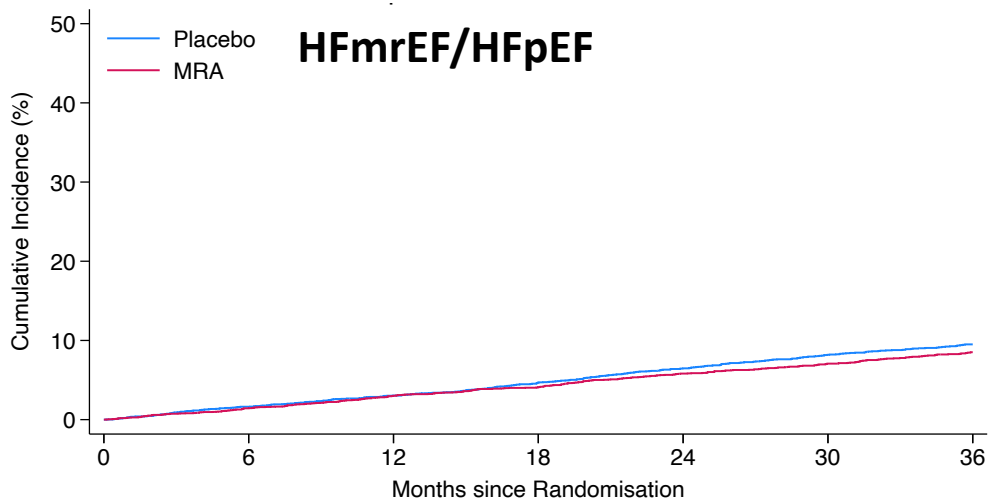


HR, hazard ratio; p int, p value for interaction

MRAs in HF: Cardiovascular death

	MRA n/N	Placebo n/N	HR [95% CI]	
RALES	226/822	314/841	0.69 [0.58, 0.82]	p_{int} = 0.45
EMPHASIS-HF	147/1,364	185/1,373	0.77 [0.62, 0.96]	
HFrEF	373/2,186	499/2,214	**0.72 [0.63, 0.82]**	
TOPCAT	160/1,722	176/1,723	0.90 [0.73, 1.12]	p_{int} = 0.85
FINEARTS-HF	242/3,003	260/2,998	0.93 [0.78, 1.10]	
HFmrEF/HFpEF	402/4,725	436/4,721	**0.92 [0.80, 1.05]**	
All MRA trials	775/6,911	935/6,935	**0.81 [0.74, 0.89]**	p_{int} = 0.082

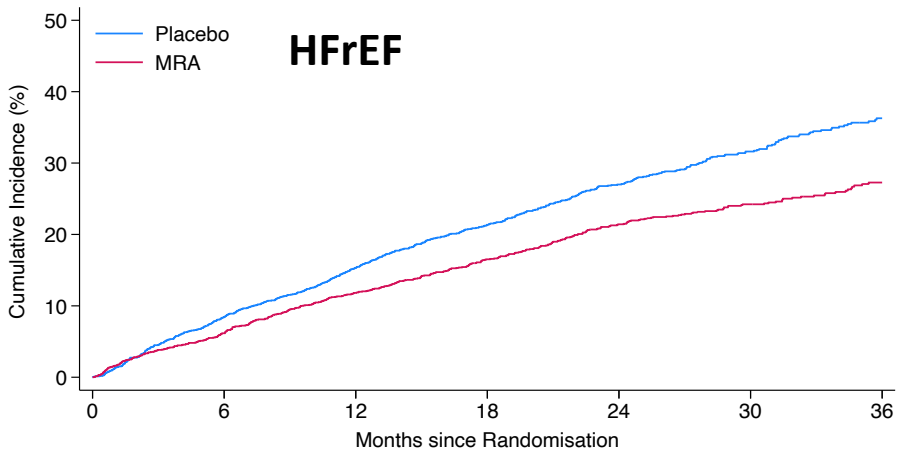


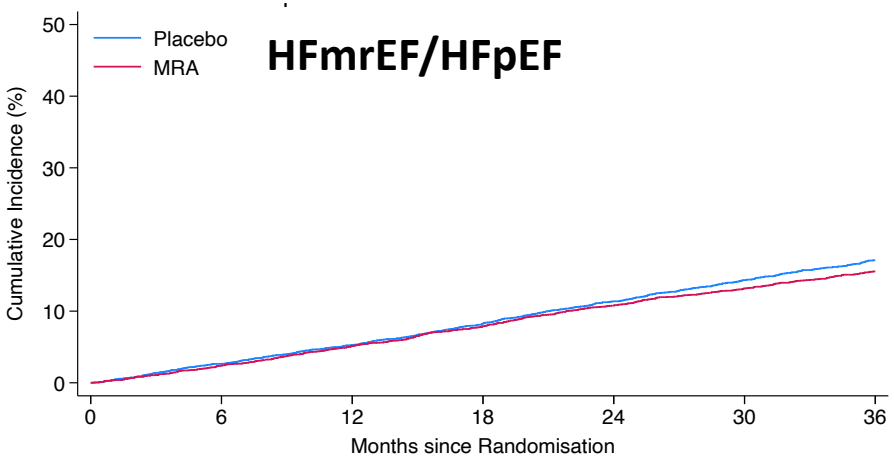


HR, hazard ratio; p int, p value for interaction

MRAs in HF: All-cause death

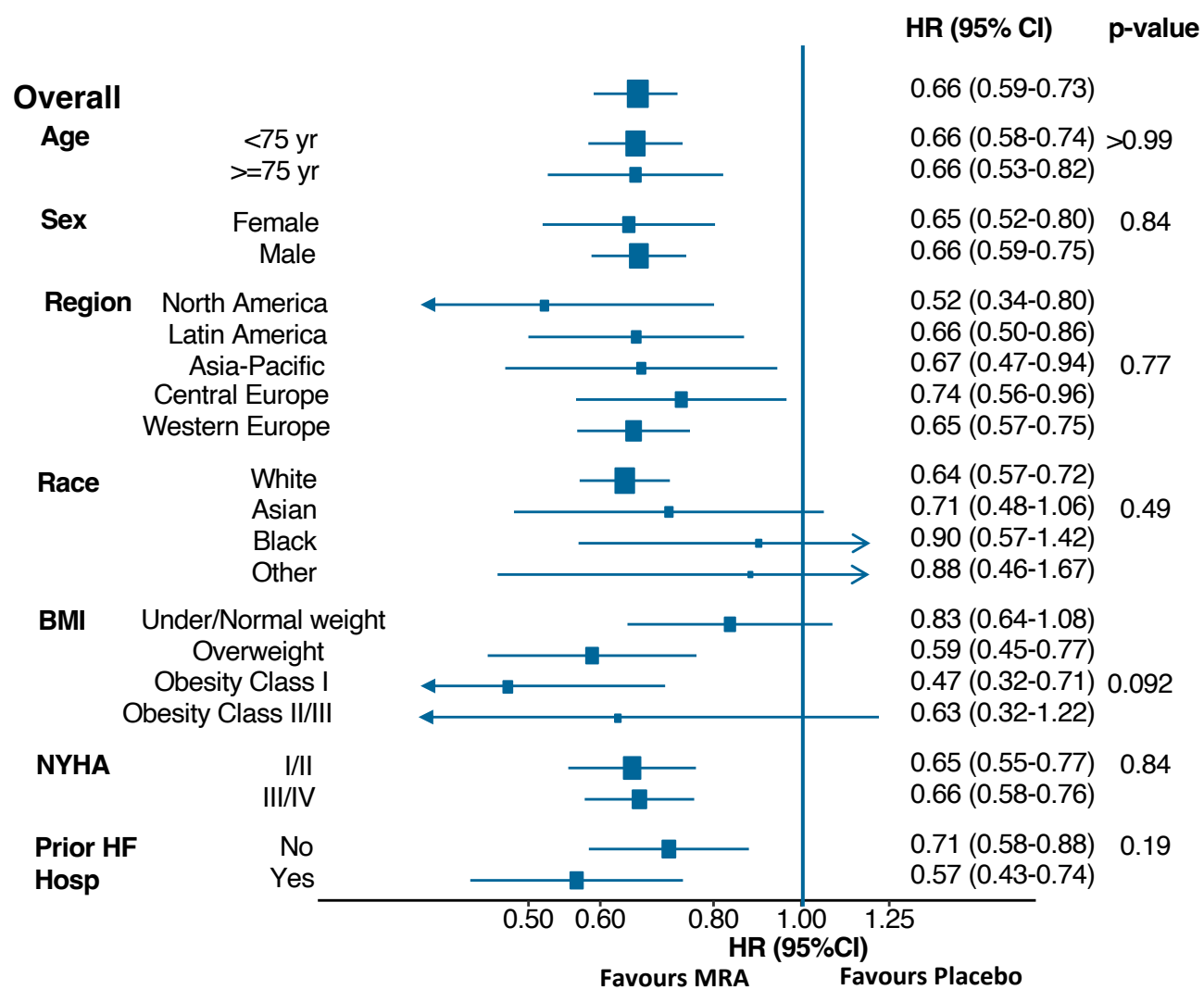
	MRA n/N	Placebo n/N	HR [95% CI]	
RALES	284/822	386/841	0.71 [0.61, 0.82]	p_{int} = 0.46
EMPHASIS-HF	171/1,364	213/1,373	0.78 [0.64, 0.95]	
HFrEF	455/2,186	599/2,214	**0.73 [0.65, 0.83]**	
TOPCAT	257/1,722	273/1,723	0.93 [0.79, 1.11]	p_{int} = 0.99
FINEARTS-HF	491/3,003	522/2,998	0.94 [0.83, 1.06]	
HFmrEF/HFpEF	748/4,725	795/4,721	**0.94 [0.85, 1.03]**	
All MRA trials	1,203/6,911	1,394/6,935	**0.85 [0.78, 0.92]**	p_{int} = 0.02

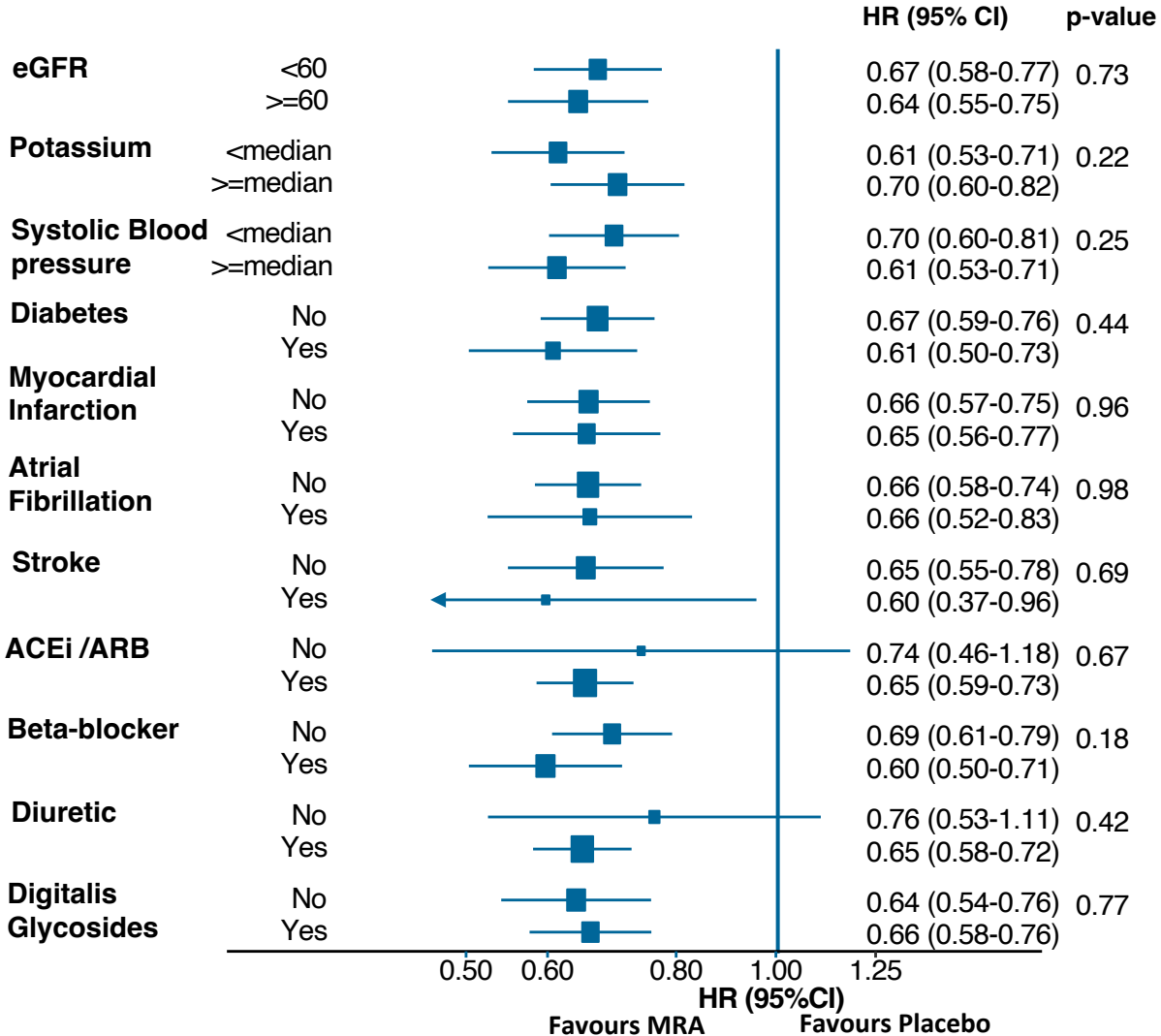




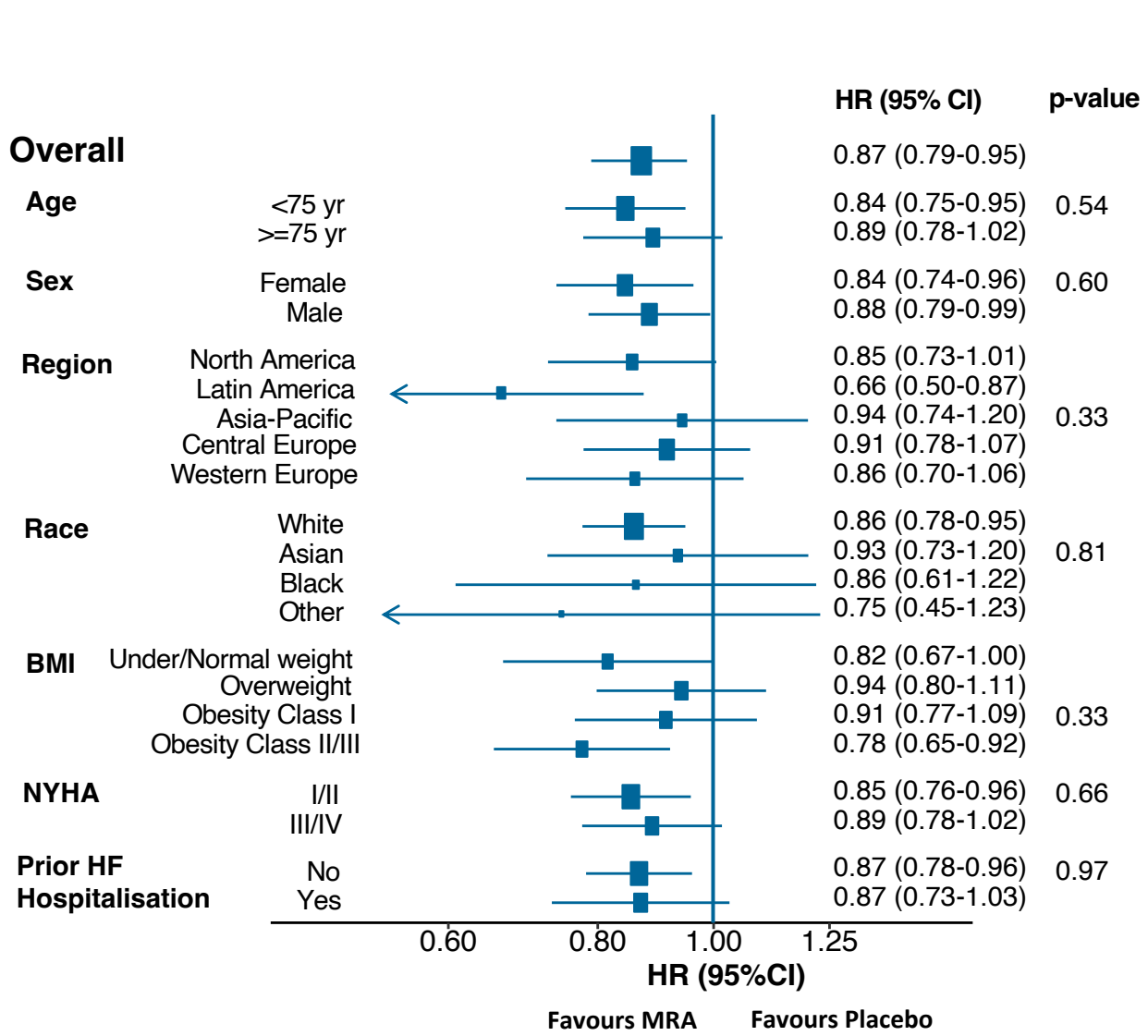
HR, hazard ratio; p int, p value for interaction ; I^2, Higgins and Thompson's I^2

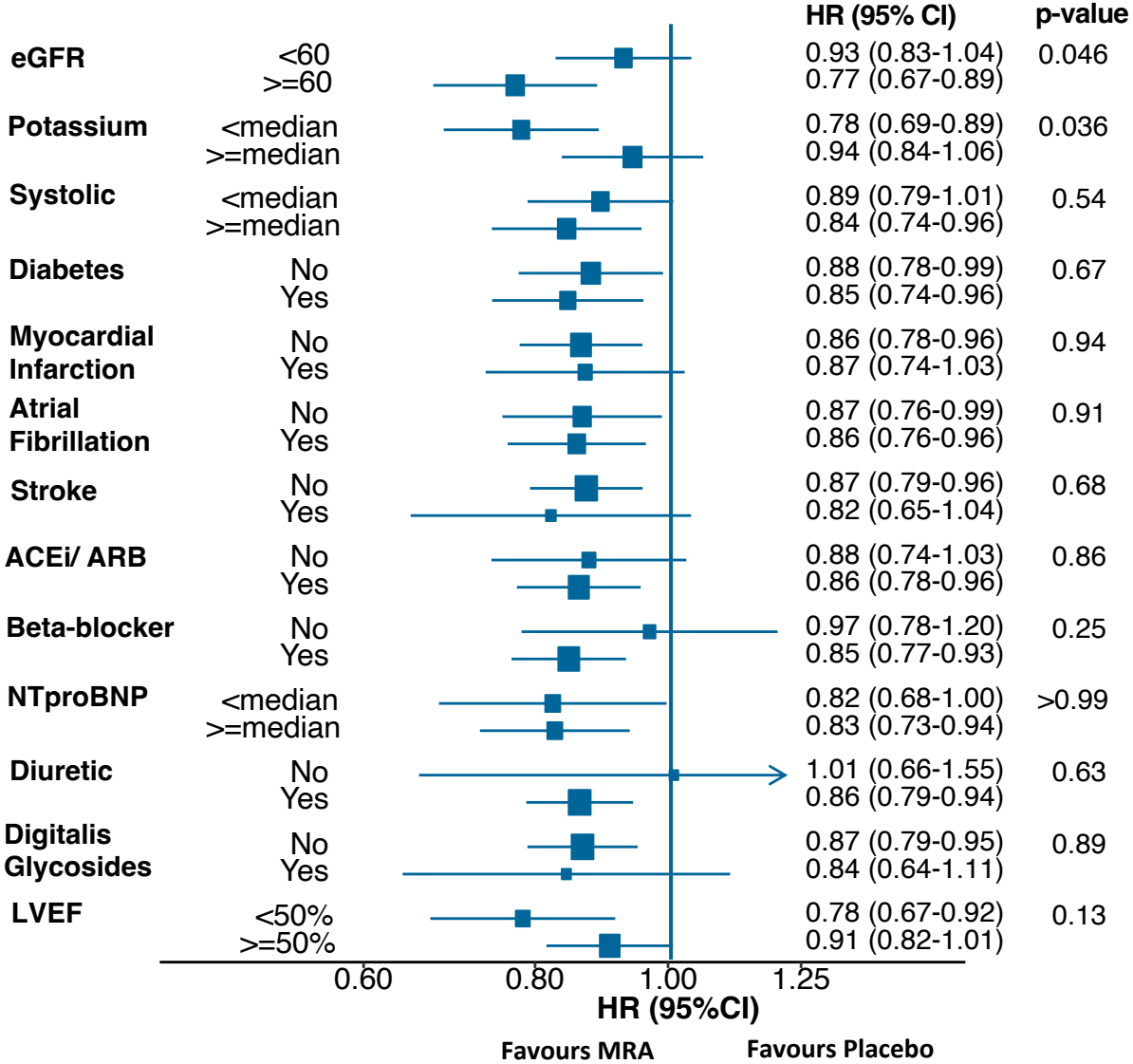
MRAs in HF: CV Death or hospitalisation for HF Subgroups - HFrEF





MRAs in HF: CV Death or hospitalisation for HF Subgroups – HFmrEF/ HFpEF





MRAs in HF: Sensitivity Analysis

- Results were unchanged including or excluding undetermined deaths from the definition of CV death
- Results were unchanged for HFmrEF/HFpEF when only the patients enrolled in the Americas in TOPCAT were used
  - HR for CV death or HF hospitalisation 0.84 (95%CI 0.77-0.93)
  - HF hospitalisation 0.82 (95%CI 0.74-0.91)
  - CV death 0.86 (95%CI 0.75-1.00)

MRAs in HF: Safety Outcomes – BP and creatinine

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	spiro.	placebo		epler.	placebo		spiro.	placebo		finer.	placebo	
	N = 822	N = 841	OR (95%CI)	N = 1360	N = 1369	OR (95%CI)	N = 1699	N = 1691	OR (95%CI)	N = 2993	N = 2993	OR (95%CI)
Hypotension												
<90 mmHg	10%	8%	**1.24 (0.93,1.64)**	5%	4%	**1.36 (0.95,1.96)**	4%	2%	**2.00 (1.31,3.06)**	5%	3%	**1.57 (1.20,2.04)**
<100 mmHg	28%	26%	**1.07 (0.87,1.31)**	20%	16%	**1.31 (1.08,1.60)**	16%	11%	**1.49 (1.22,1.82)**	19%	13%	**1.60 (1.39,1.85)**
Elevated serum creatinine												
≥2.5 mg/dl (221 µmol/l)	9%	5%	**1.73 (1.17,2.57)**	2%	2%	**1.28 (0.73,2.25)**	6%	3%	**1.88 (1.35,2.63)**	6%	4%	**1.55 (1.21,1.98)**
≥3 mg/dl (265 µmol/l)	4%	2%	**1.84 (1.01,3.36)**	1%	1%	**0.82 (0.34,1.98)**	2%	1%	**1.76 (1.06,2.92)**	3%	2%	**1.73 (1.19,2.50)**

MRAs in HF: Safety Outcomes – Potassium

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	spiro.	placebo		epler.	placebo		spiro.	placebo		finer.	placebo	
	N = 822	N = 841	**OR (95%CI)**	N = 1360	N = 1369	**OR (95%CI)**	N = 1699	N = 1691	**OR (95%CI)**	N = 2993	N = 2993	**OR (95%CI)**
Elevated serum potassium												
>5.5 mmol/l	16%	5%	**3.89 (2.67,5.67)**	12%	7%	**1.74 (1.33,2.27)**	12%	5%	**2.30 (1.78,2.97)**	15%	7%	**2.23 (1.88,2.66)**
>6 mmol/l	4%	1%	**3.75 (1.78,7.91)**	3%	2%	**1.37 (0.81,2.32)**	2%	1%	**2.53 (1.41,4.53)**	3%	2%	**2.07 (1.44,2.99)**
Reduced serum potassium												
<3.5 mmol/l	7%	19%	**0.32 (0.23,0.45)**	7%	11%	**0.64 (0.49,0.84)**	12%	20%	**0.56 (0.47,0.68)**	5%	10%	**0.46 (0.37,0.56)**

MRAs in HF: Summary and conclusions

- This meta-analysis in ~14,000 patients confirms the benefits of MRAs in HF
- Steroidal MRAs (eplerenone and spironolactone) reduce the risk of the composite of CV death or HF hospitalisation in HFrEF and a non-steroidal MRA (finerenone) reduced the risk HFmrEF/HFpEF
- The benefits of MRAs were observed in all subgroups examined
- MRAs increased the risk of hyperkalaemia but the risk of serious hyperkalaemia was low (2.9%) and the risk of hypokalaemia was reduced by half or more
- A MRA should be considered in patients with HF without a contra-indication

THE LANCET

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

Pardeep S Jhund, Atefeh Talebi, Alasdair D Henderson, Brian L Claggett, Muthiah Vaduganathan, Akshay S Desai, Carolyn S P Lam, Bertram Pitt, Michele Senni, Sanjiv J Shah, Adriaan A Voors, Faiez Zannad, Scott D Solomon, John J V McMurray

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.

Published **Online** September 1, 2024 https://doi.org/10.1016/ S0140-6736(24)01733-1

See **Online/Comment** https://doi.org/10.1016/ S0140-6736(24)01755-0

BHF Glasgow Cardiovascular Research Centre, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK (Prof P S Jhund MBChB PhD, A Talebi PhD, A D Henderson PhD, Prof J J V McMurray MD); **Cardiovascular Division, Brigham and Women's**

https://doi.org/10.1016/ S0140-6736(24)01733-1