

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

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# 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.
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# 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

# MRAs in HF: Methods

- We identified the four randomised trials adequately powered to examine clinical outcomes

Key trial characteristics	RALES	EMPHASIS-HF	TOPCAT	FINEARTS-HF
<b>Investigational drug</b>	spironolactone	eplerenone	spironolactone	finerenone
<b>Number of patients, sites and countries</b>	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
<b>Key inclusion criteria</b>	Ejection fraction $\leq 35\%$	Ejection fraction $\leq 30\%$ (or, if $>30$ to $35\%$ , a QRS duration of $>130$ msec on electrocardiography)	Ejection fraction $\geq 45\%$	Ejection fraction $\geq 40\%$ including improved ejection fraction

# MRA in HF: Background

- 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 practice
- Due to concerns regarding the TOPCAT trial a sensitivity analysis was conducted using the patients enrolled in the Americas only in TOPCAT
- Sensitivity analyses including and excluding undetermined deaths from the definition of cardiovascular death were performed

# MRA 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  $\geq 2.5$  and  $\geq 3$  mg/dl (221 and 265  $\mu\text{mol/l}$ )
  - 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

# MRA in HF: Key baseline characteristics

	<b>RALES</b>	<b>EMPHASIS-HF</b>	<b>TOPCAT</b>	<b>FINEARTS-HF</b>	<b>Total</b>
	N=1,663	N=2,737	N=3,445	N=6,001	N=13,846
<b>Age (years)</b>	65±11	68±7	68±9	72±9	69±9
<b>Sex N (%)</b>					
Men	73%	78%	48%	54%	60%
Women	27%	22%	52%	46%	40%
<b>Race, N (%)</b>					
White	87%	83%	89%	79%	83%
Black	7%	2%	9%	1%	4%
Asian	2%	12%	1%	17%	10%
Other	4%	3%	2%	3%	3%
<b>Region, N (%)</b>					
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%



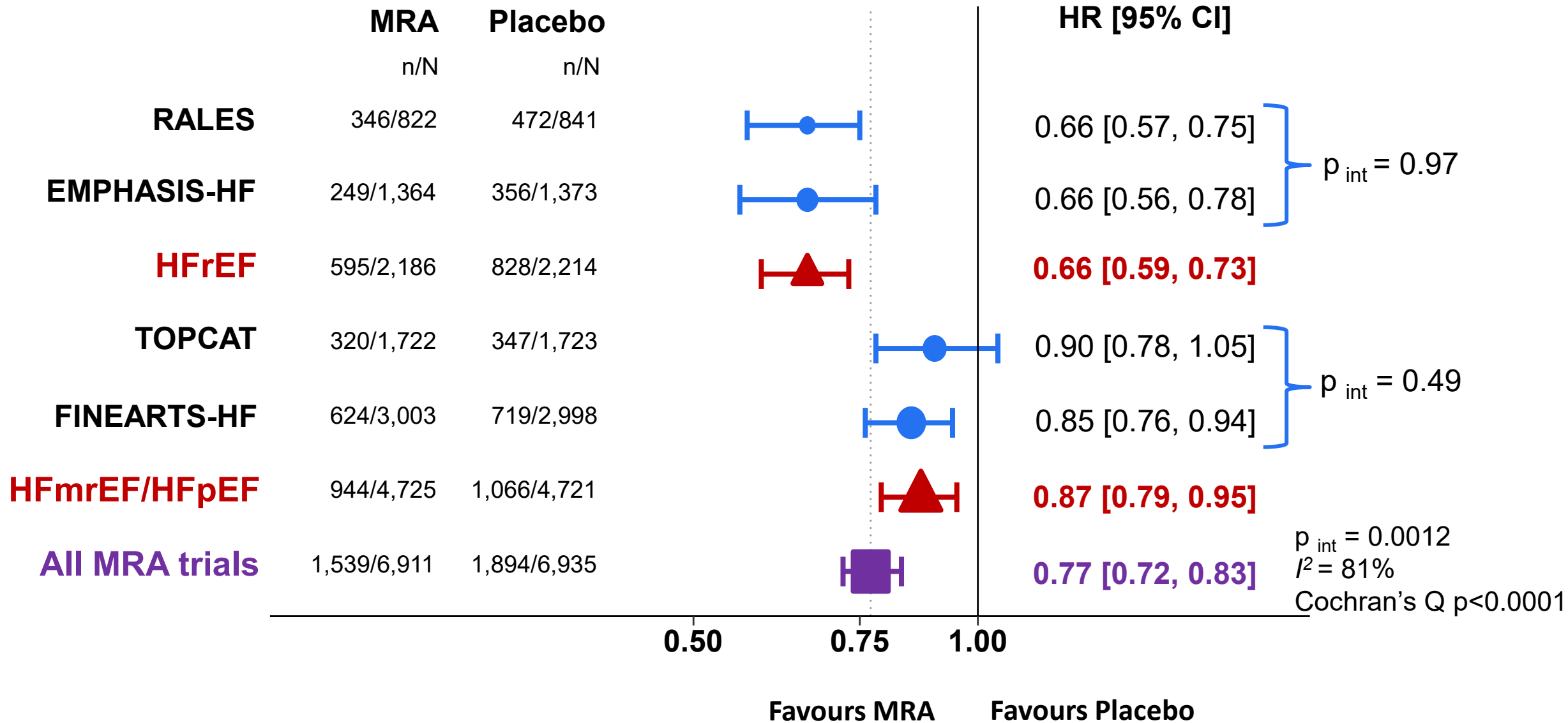
# MRA in HF: Key baseline characteristics

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

# MRA in HF: Key baseline characteristics

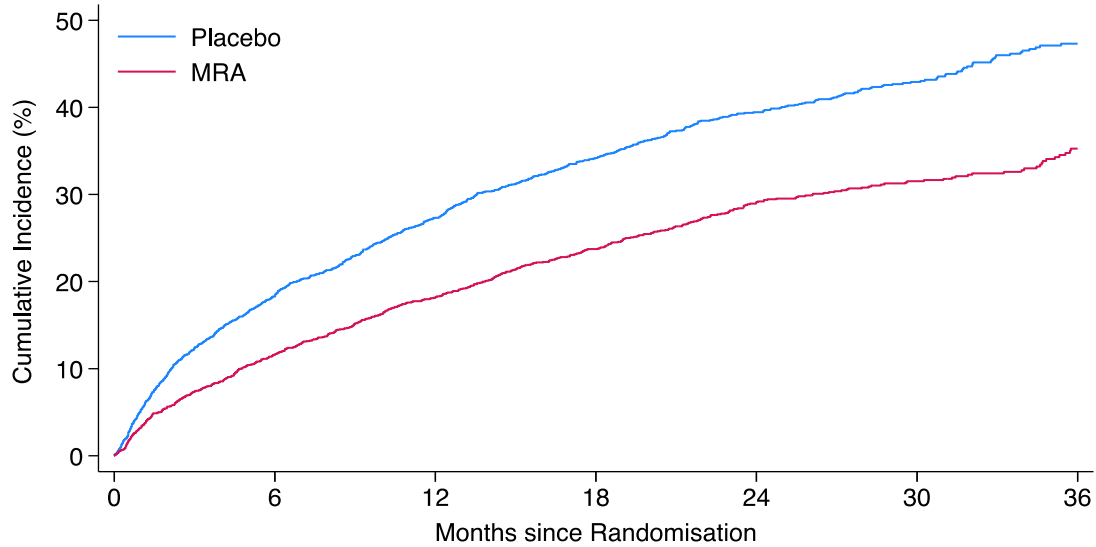
	<b>RALES</b>	<b>EMPHASIS-HF</b>	<b>TOPCAT</b>	<b>FINEARTS-HF</b>	<b>Total</b>
	N=1,663	N=2,737	N=3,445	N=6,001	N=13,846
<b>ACEI/ARB, N (%)</b>	96%	93%	84%	71%	82%
<b>ARNI, N(%)</b>	Not available	Not available	Not available	9%	4%
<b>SGLT2 inhibitor, N (%)</b>	Not available	Not available	Not available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

# MRAs in HF: CV Death/hospitalisation for HF



# MRA in HF: CV Death/hospitalisation for HF

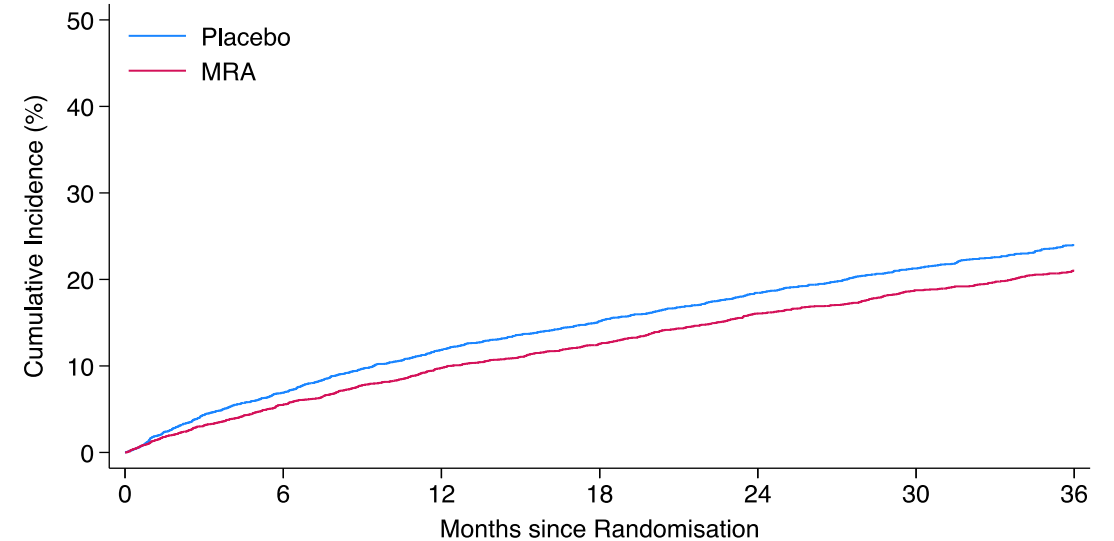
## HFrEF



Number at risk		0	6	12	18	24	30	36
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

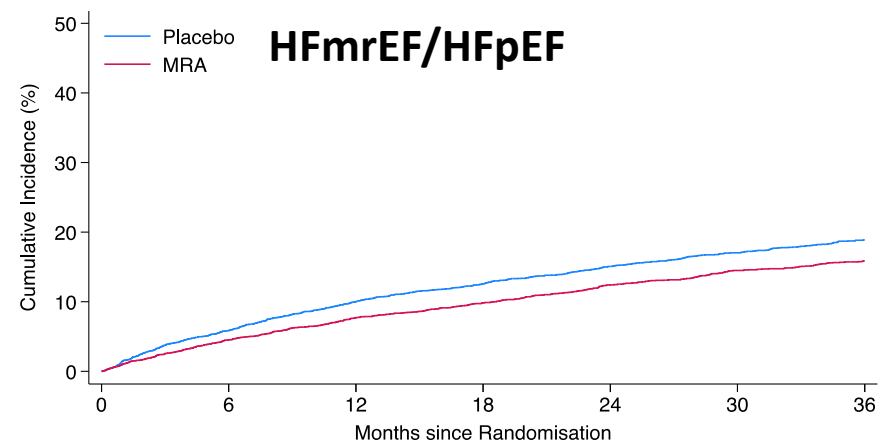
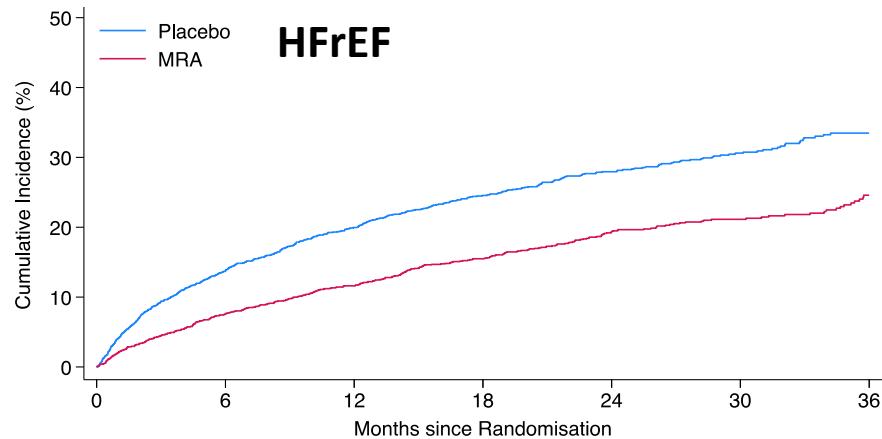
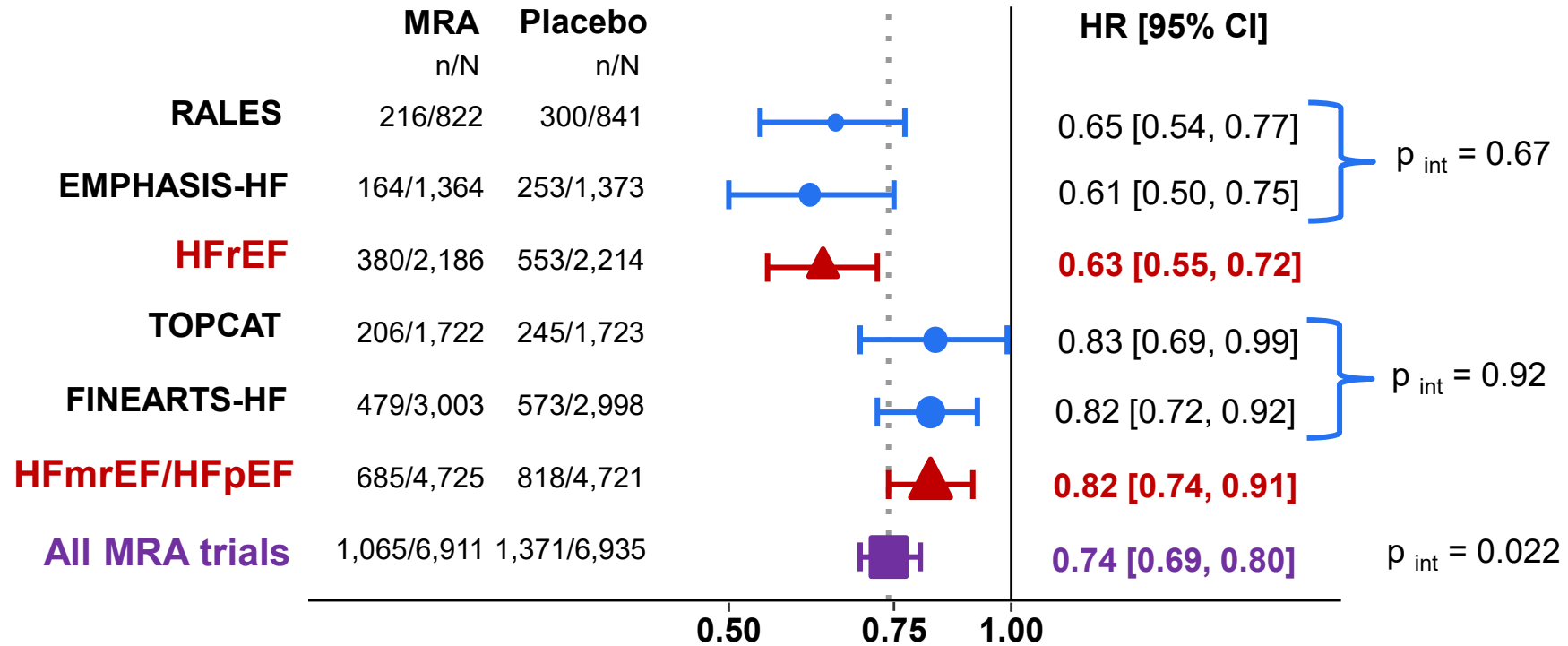


Number at risk		0	6	12	18	24	30	36
Placebo	4721	4317	4008	3567	3057	2449	1557	
MRA	4725	4400	4104	3675	3111	2507	1607	

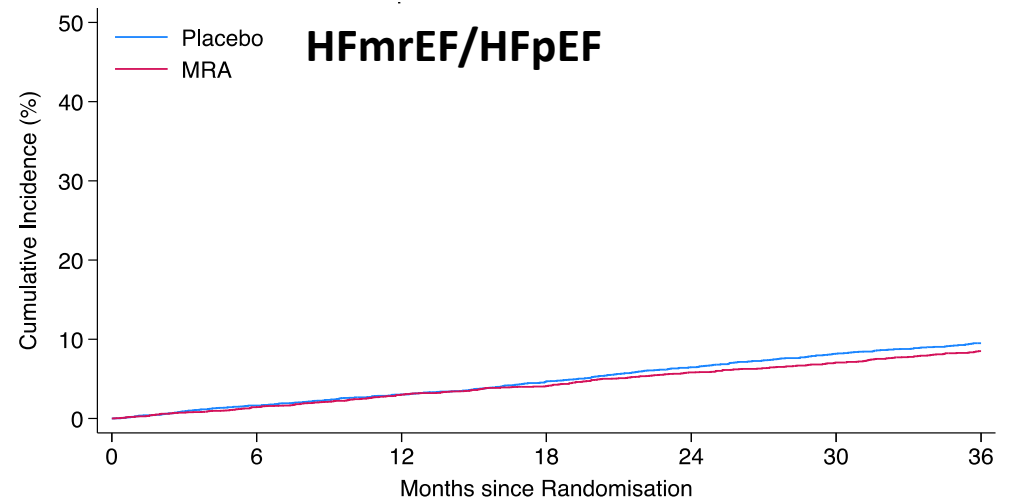
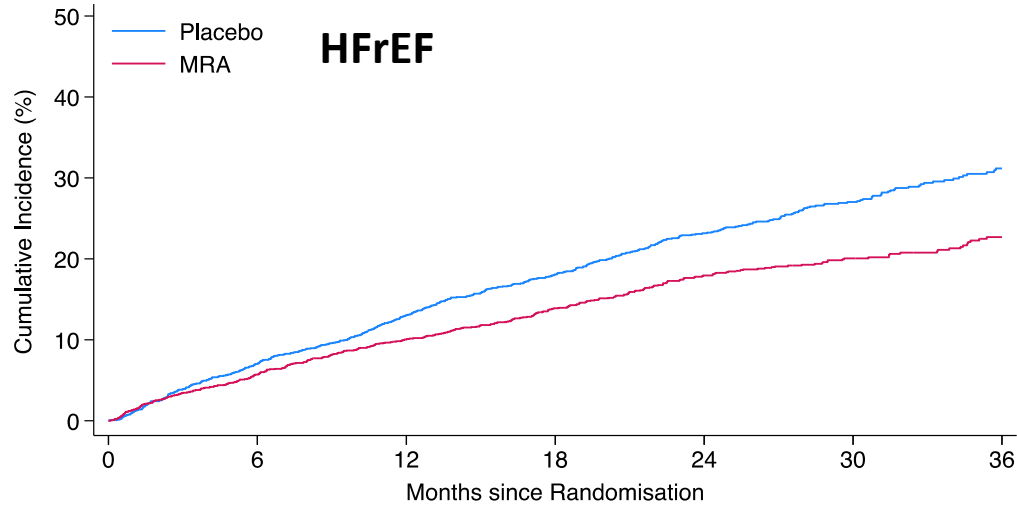
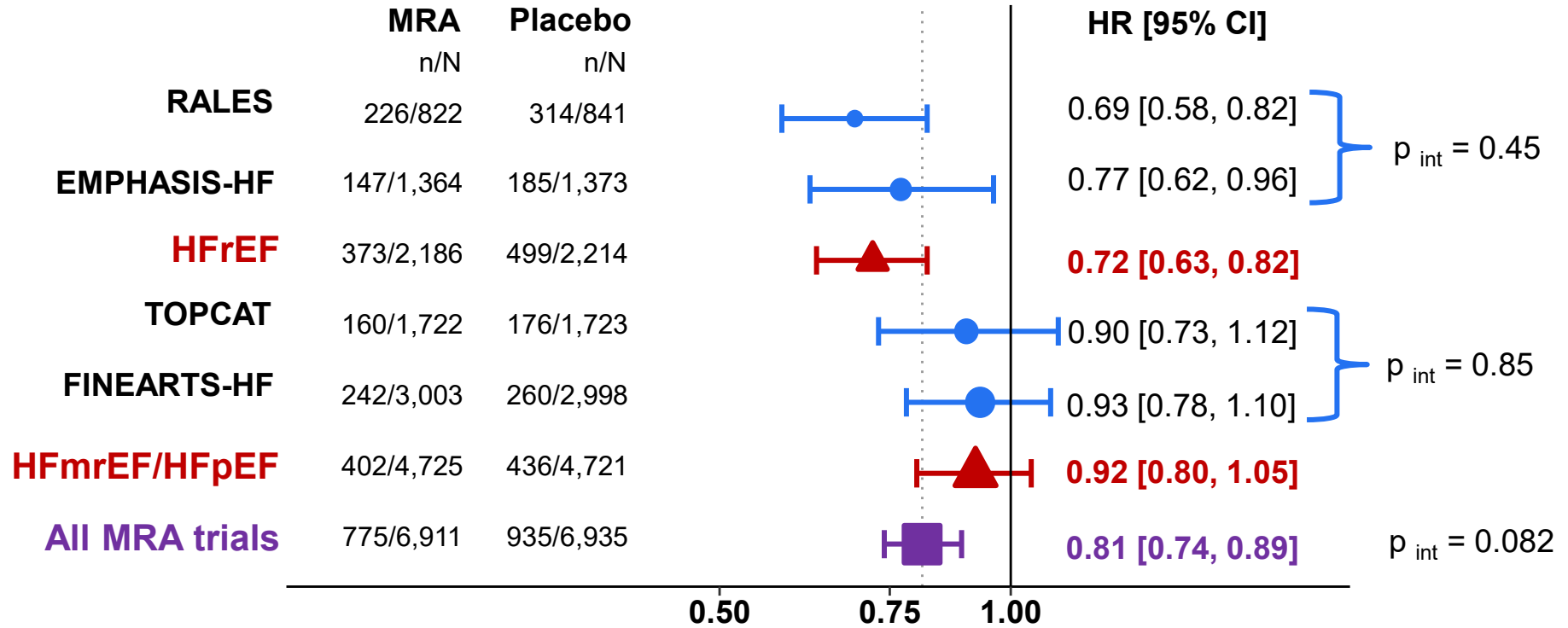
Placebo rate\* 9 (95%CI 8 - 10)  
MRA rate\* 8 (95%CI 7 - 8)

\* Per 100 patient years of follow up

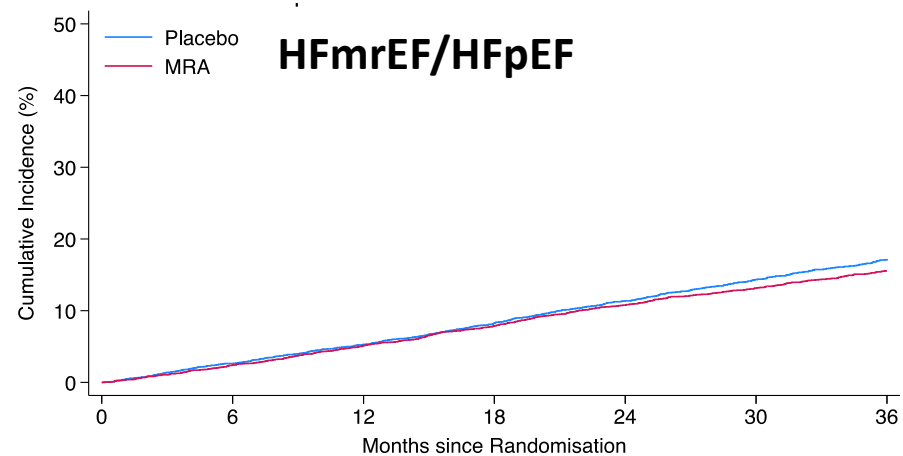
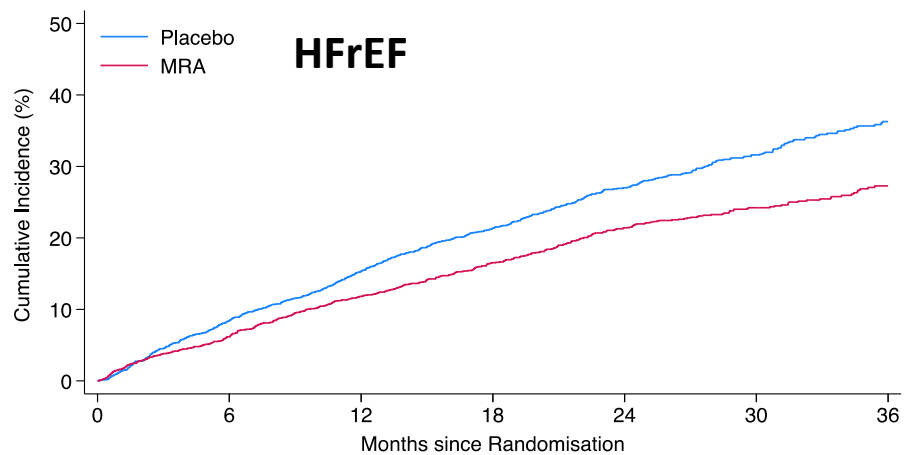
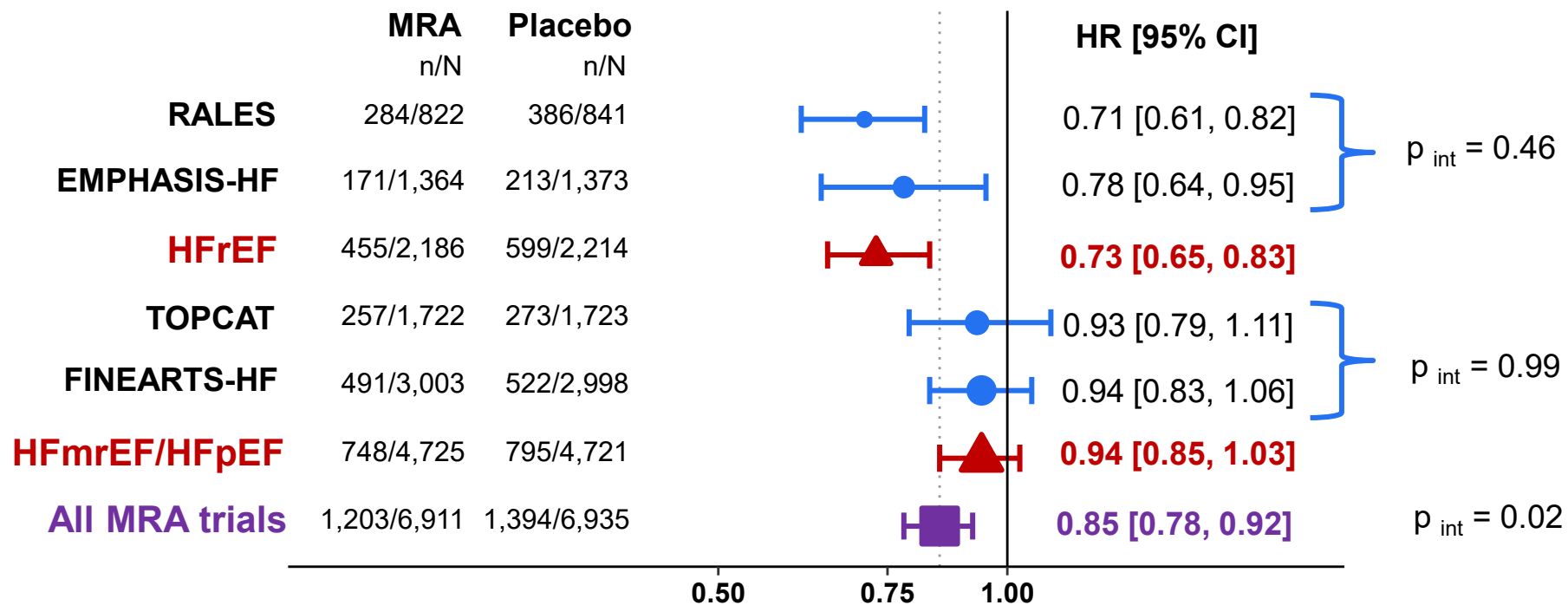
# MRA in HF: Hospitalisation for HF



# MRAs in HF: Cardiovascular death

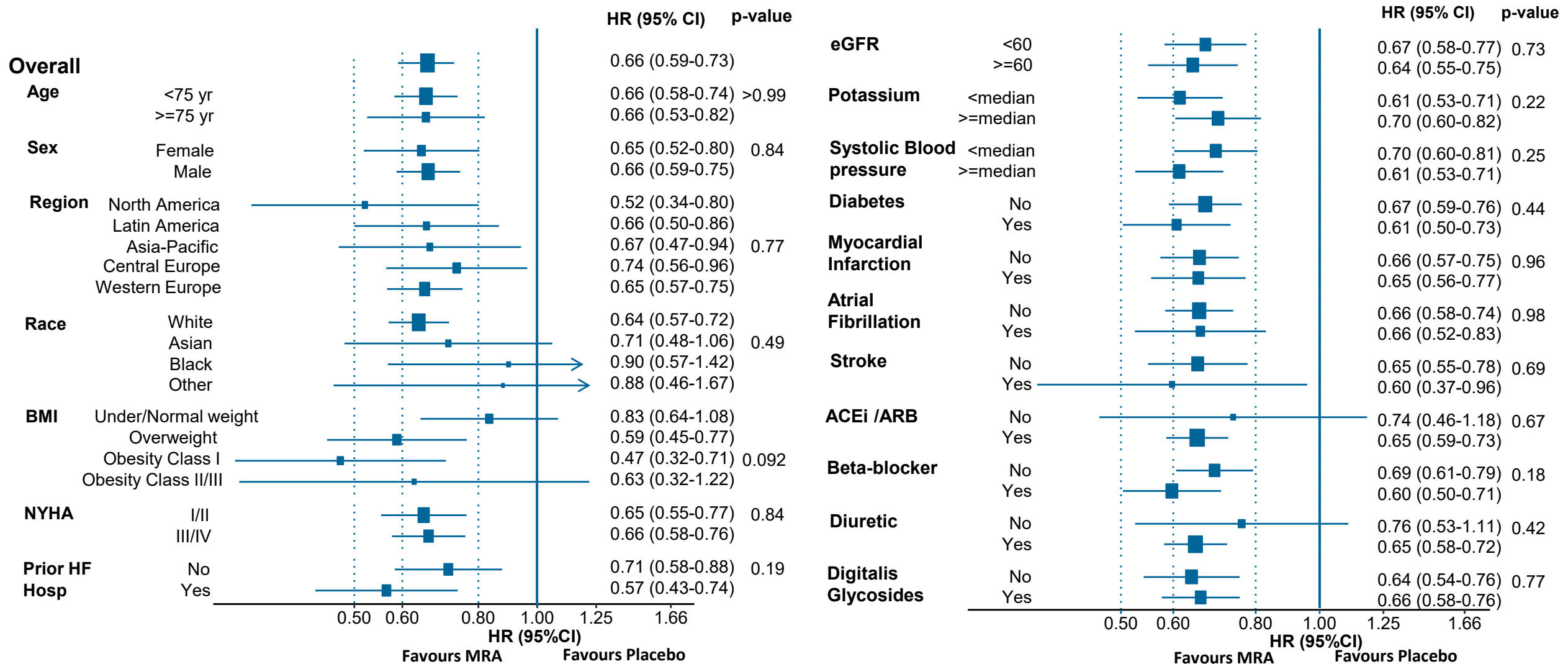


# MRA in HF: All-cause death



# MRA in HF: CV Death/hospitalisation for HF

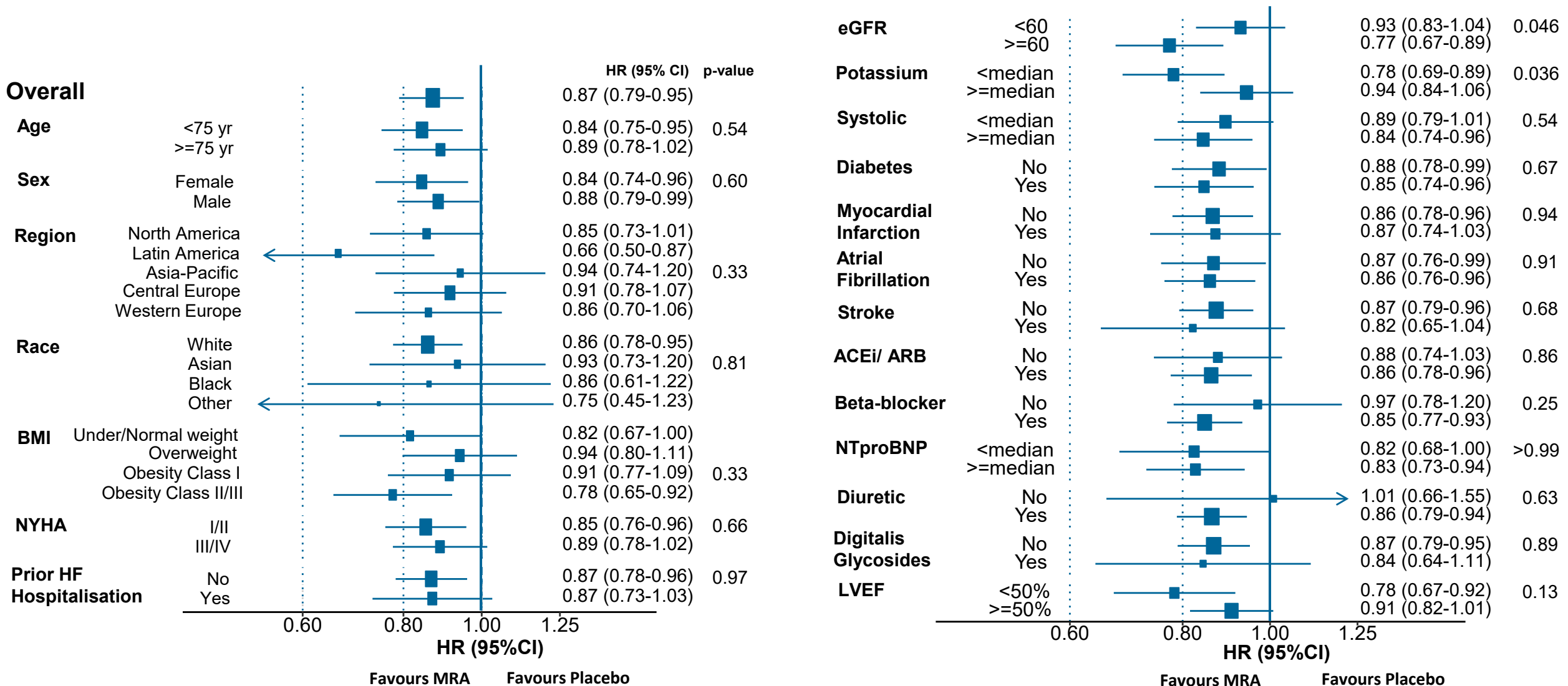
## Subgroups - HFrEF





# MRA in HF: CV Death/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)

# MRA in HF: Safety Outcomes – BP and creatinine

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

# MRA in HF: Safety Outcomes – Potassium

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

# MRAs in HF: Summary and conclusions

- This meta-analysis confirms the benefits of MRAs in HF: the risk of the composite of HF hospitalisation or CV death was reduced in both HFrEF (sMRAs eplerenone and spironolactone) and HFmrEF/HFpEF (nsMRA finerenone)
- The benefits of MRAs were observed in all subgroups examined
- MRAs increased the risk of hyperkalaemia but the risk of serious hyperkalaemia was low (~3%) and the risk of hypokalaemia was reduced by half or more
- An MRA should be considered in patients with HF without a contra-indication

# THE LANCET

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