

Figures

Fig. 1

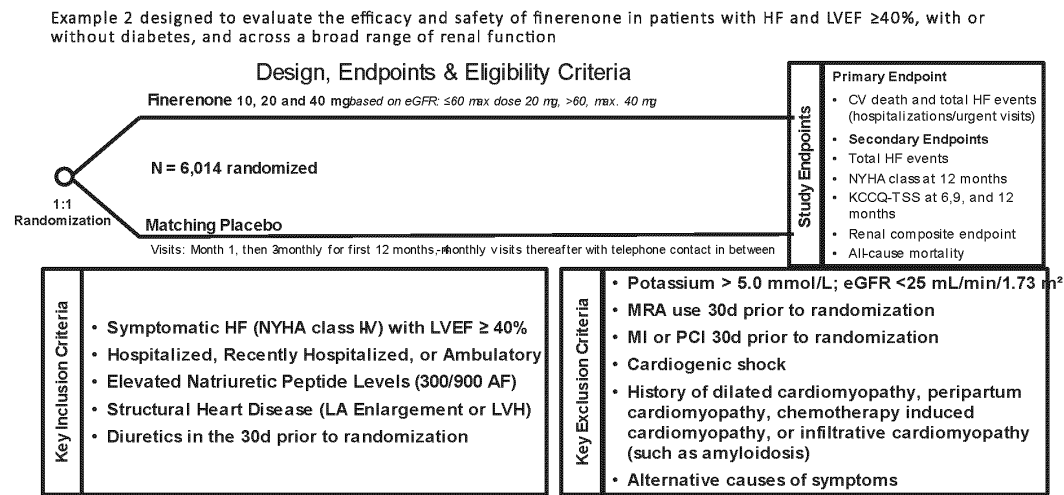


Fig. 2

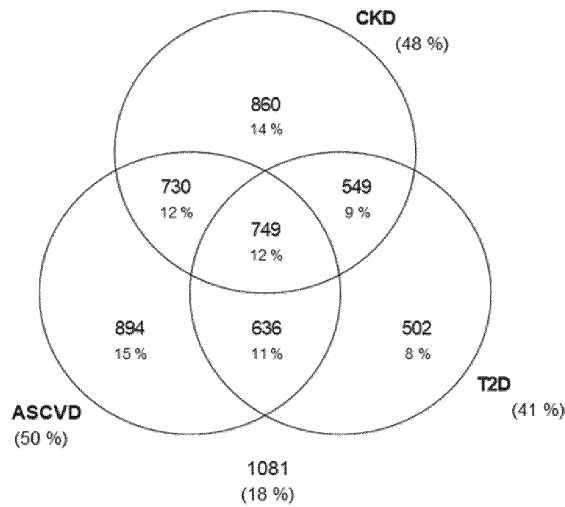


Fig. 3

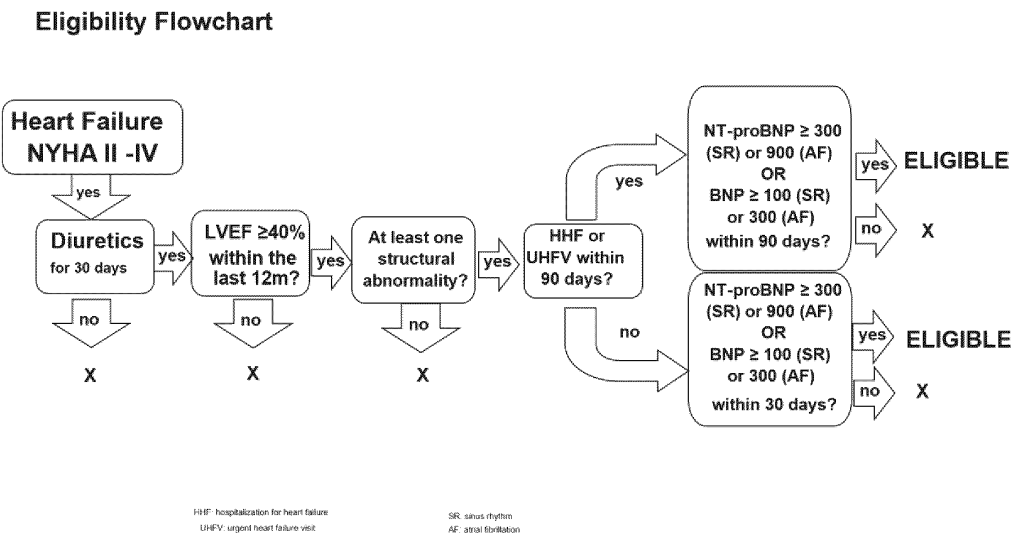


Fig. 4

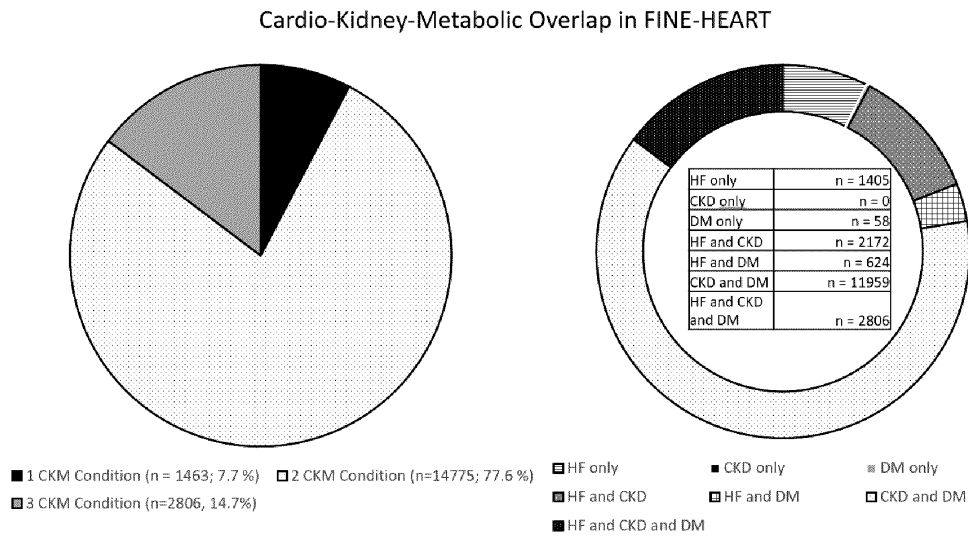


Fig. 5

Recency of Worsening HF Events Before Randomization in FINEARTS-HF

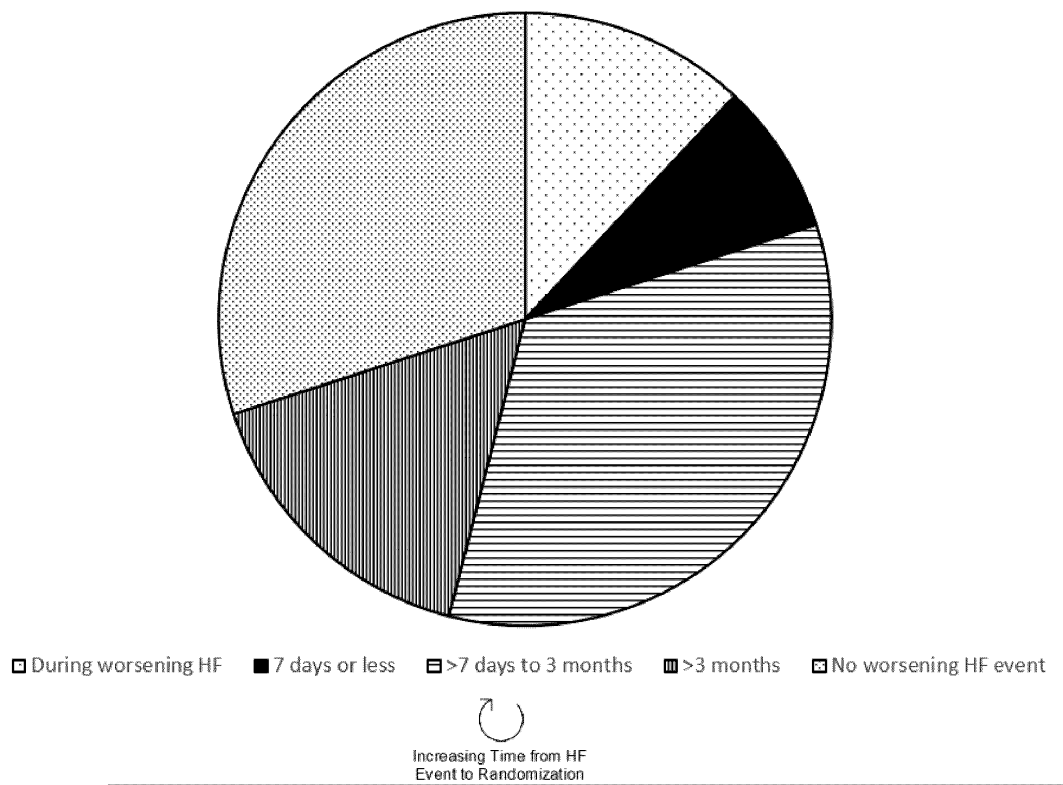


Fig. 6

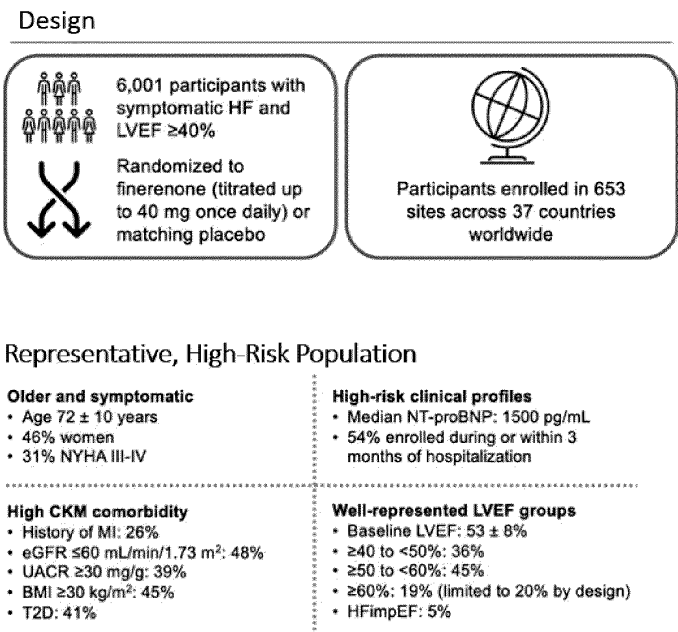
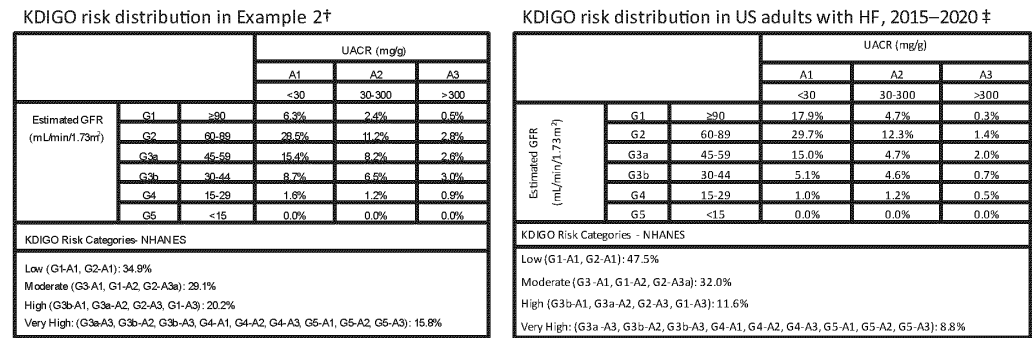


Fig. 7

Distribution of KDIGO kidney risk among Example 2 participants and US adults with heart failure



Kidney risk reclassification in Example 2 participants at baseline after UACR incorporation§

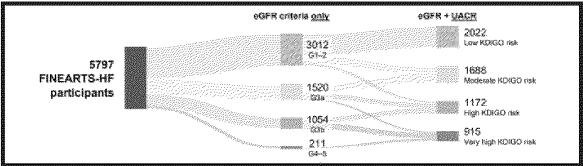


Fig. 8

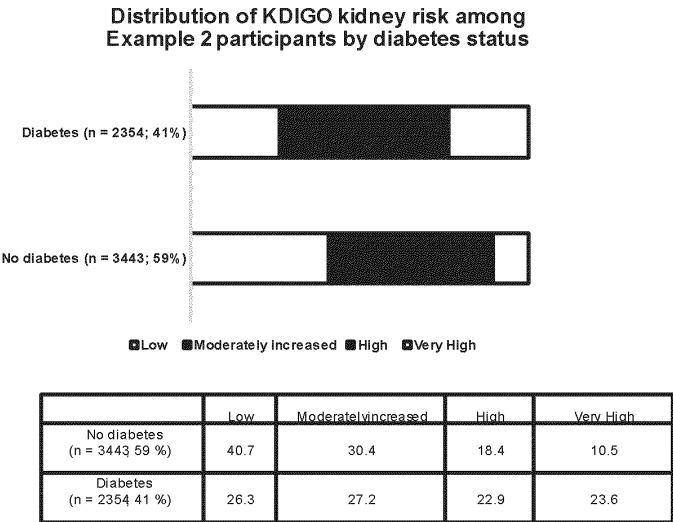


Fig. 9

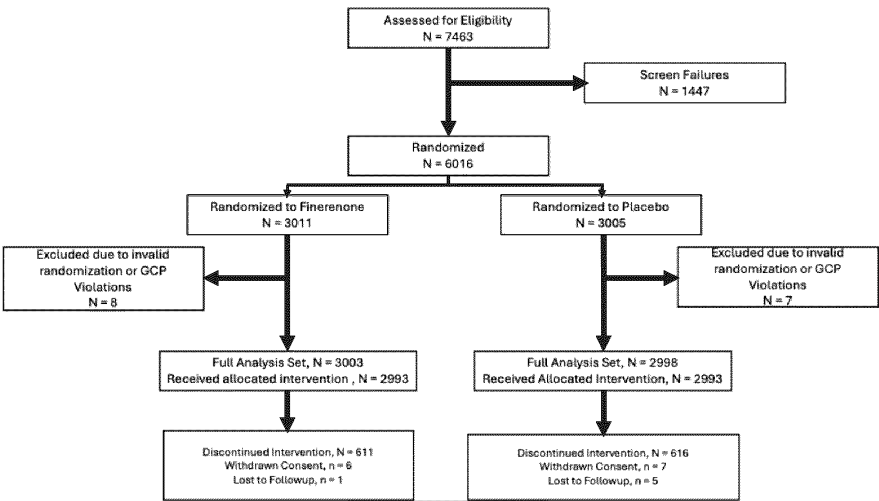


Fig. 10a)

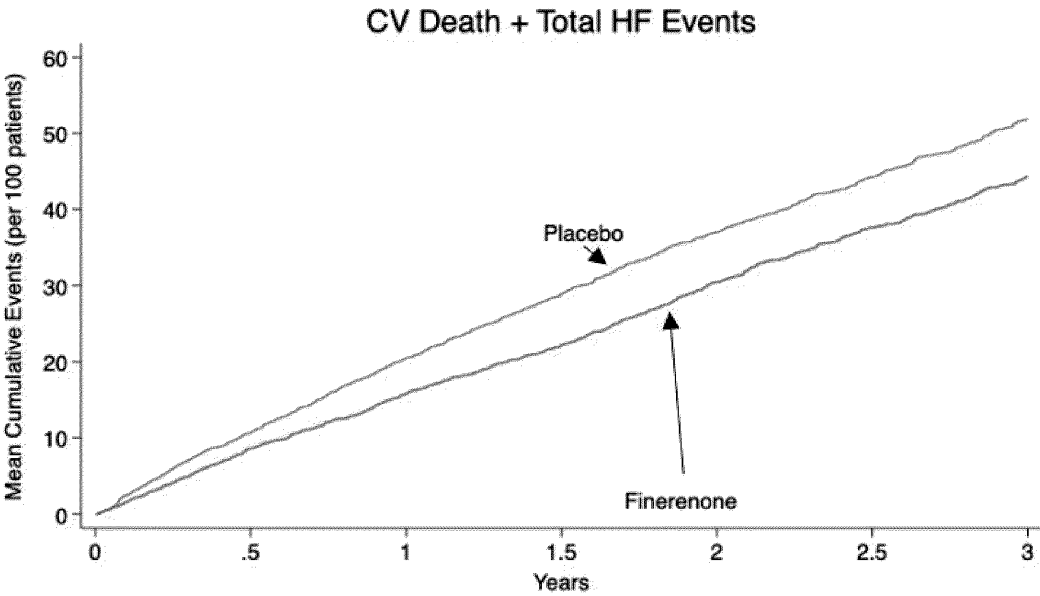


Fig. 10b)

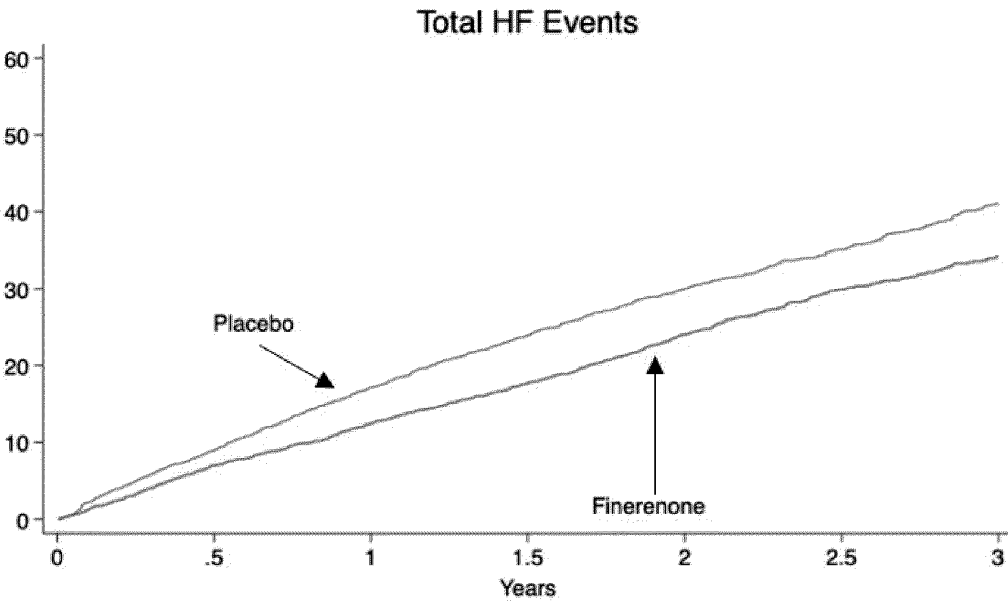


Fig. 10c)

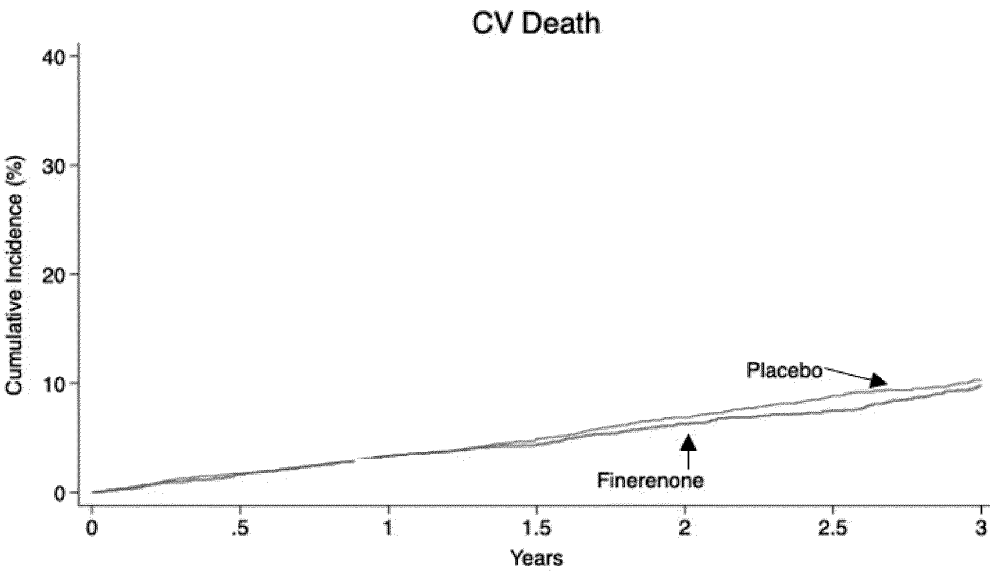


Fig. 10d)

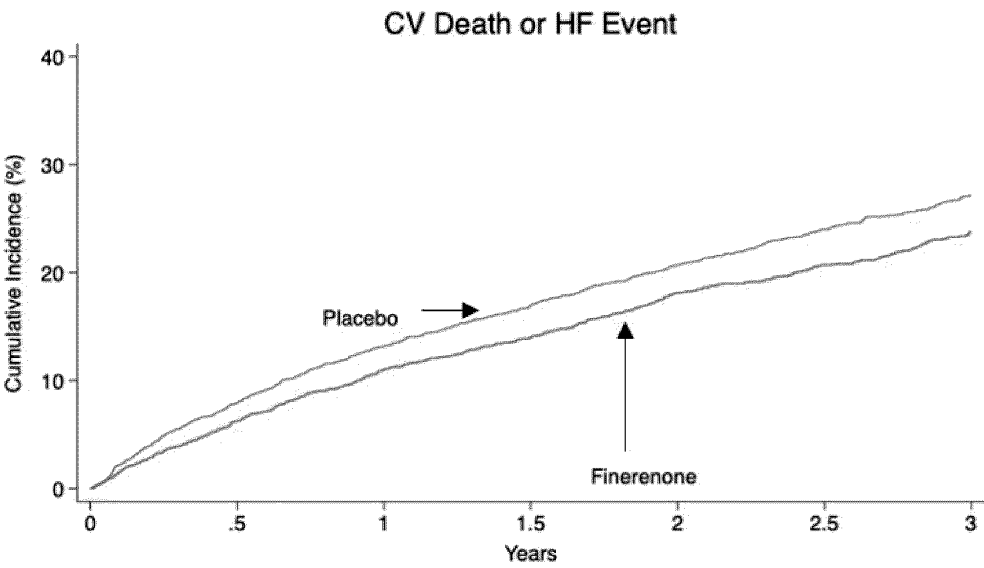


Fig.11

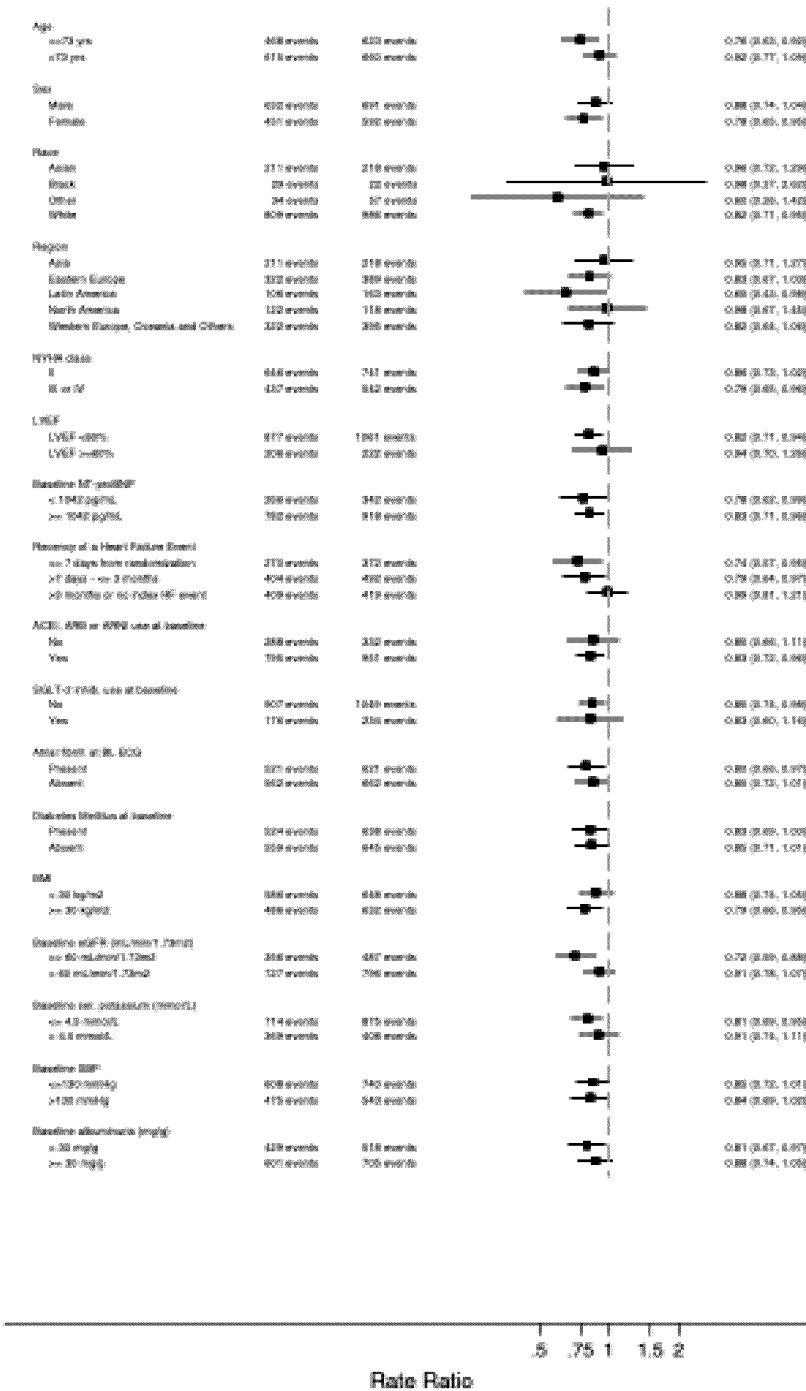


Fig. 12

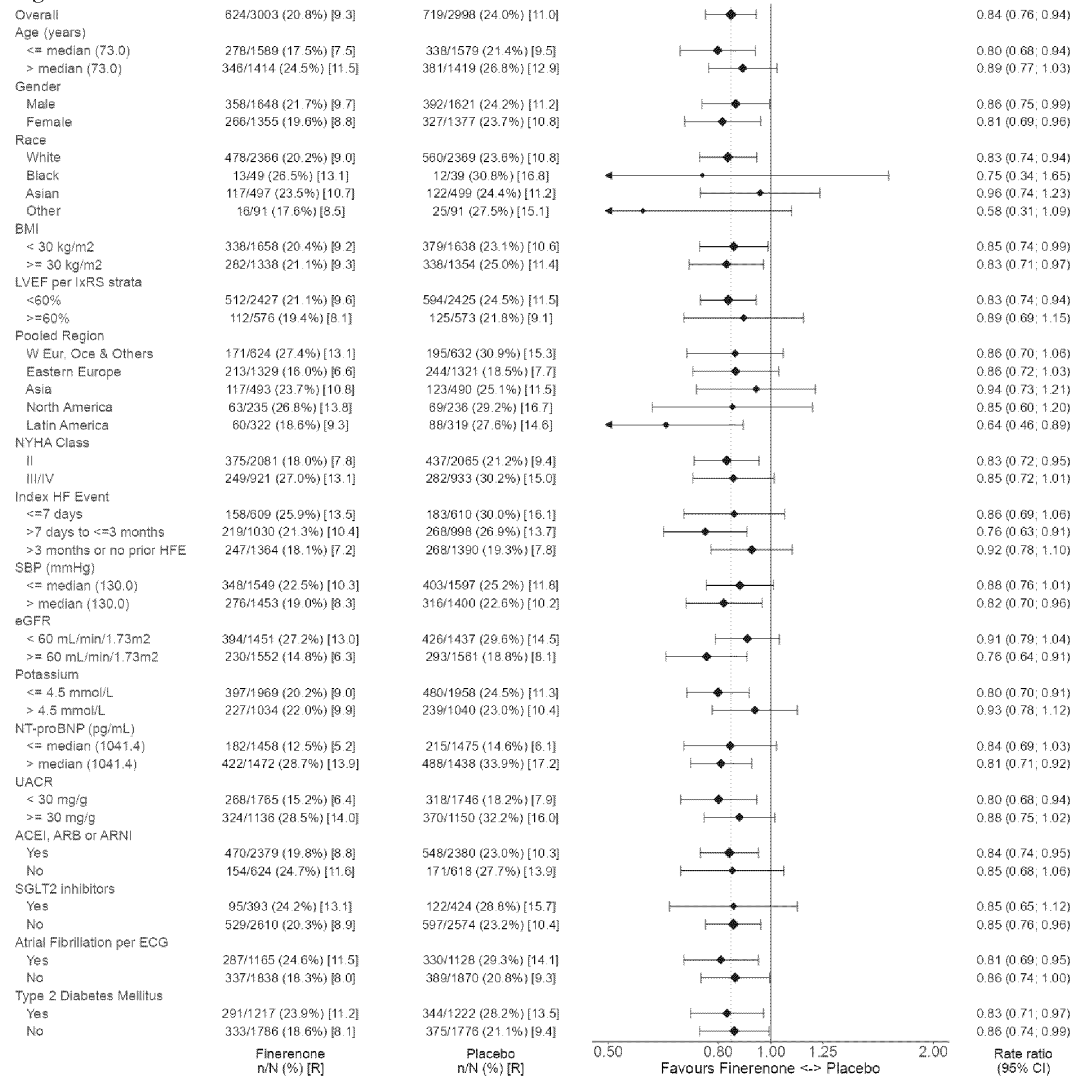


Fig. 13

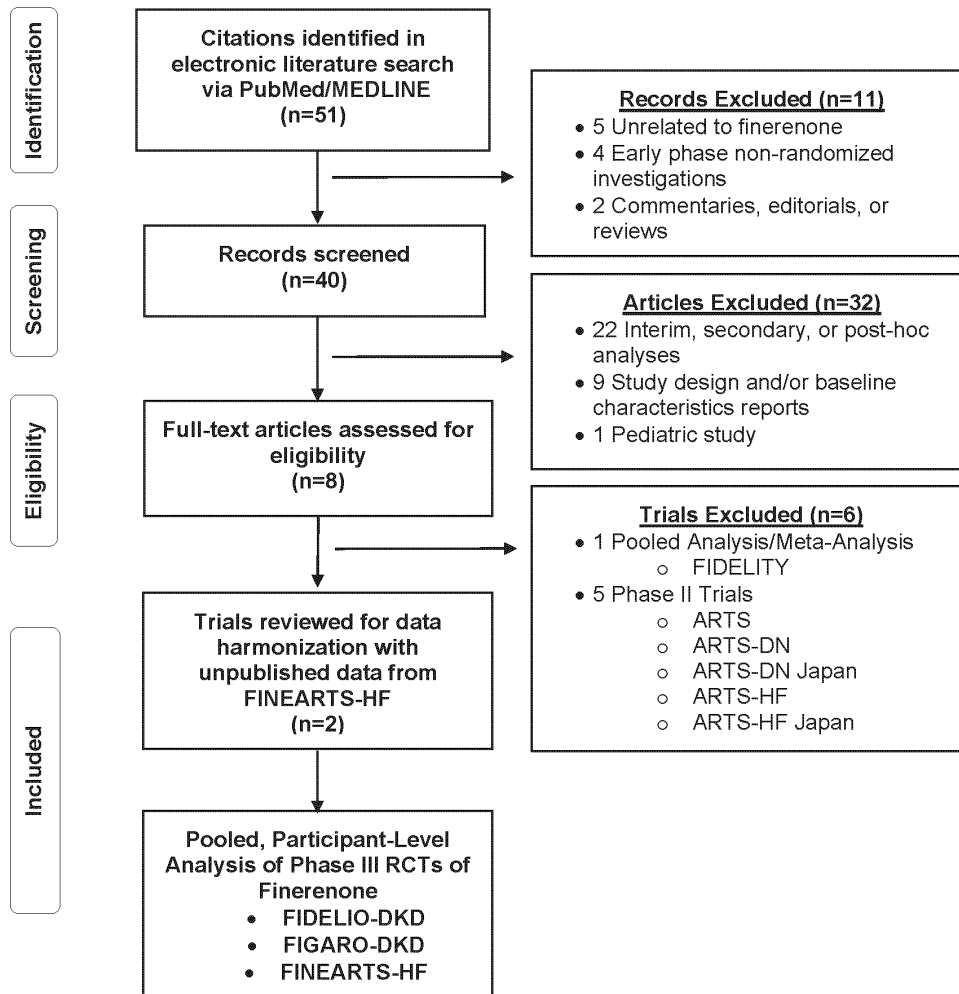


Fig. 14

FINE-HEART (n=18,781 with Available Data)

		UACR (mg/g)		
		A1	A2	A3
		Normal to Mildly Increased	Moderately Increased	Severely Increased
		<30	30 to <300	≥300
Normal or High	≥90	2.0%	1.8%	6.1%
Mildly Decreased	60-89	9.1%	9.0%	15.6%
Mildly or Moderately Decreased	45-59	5.2%	9.9%	11.3%
Moderately or Severely Decreased	30-44	3.0%	8.5%	12.7%
Severely Decreased	15-29	0.6%	1.6%	3.6%
Kidney Failure	<15	0.0%	0.0%	0.0%

KDIGO Risk Categories			
Low	Moderate	High	Very High
11.1%	16.0%	34.6%	38.3%

Fig. 15

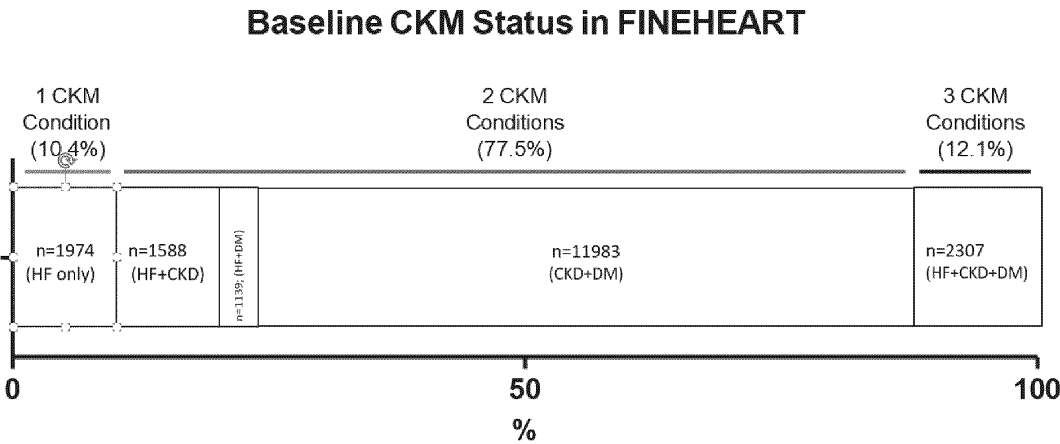


Fig. 16 a)

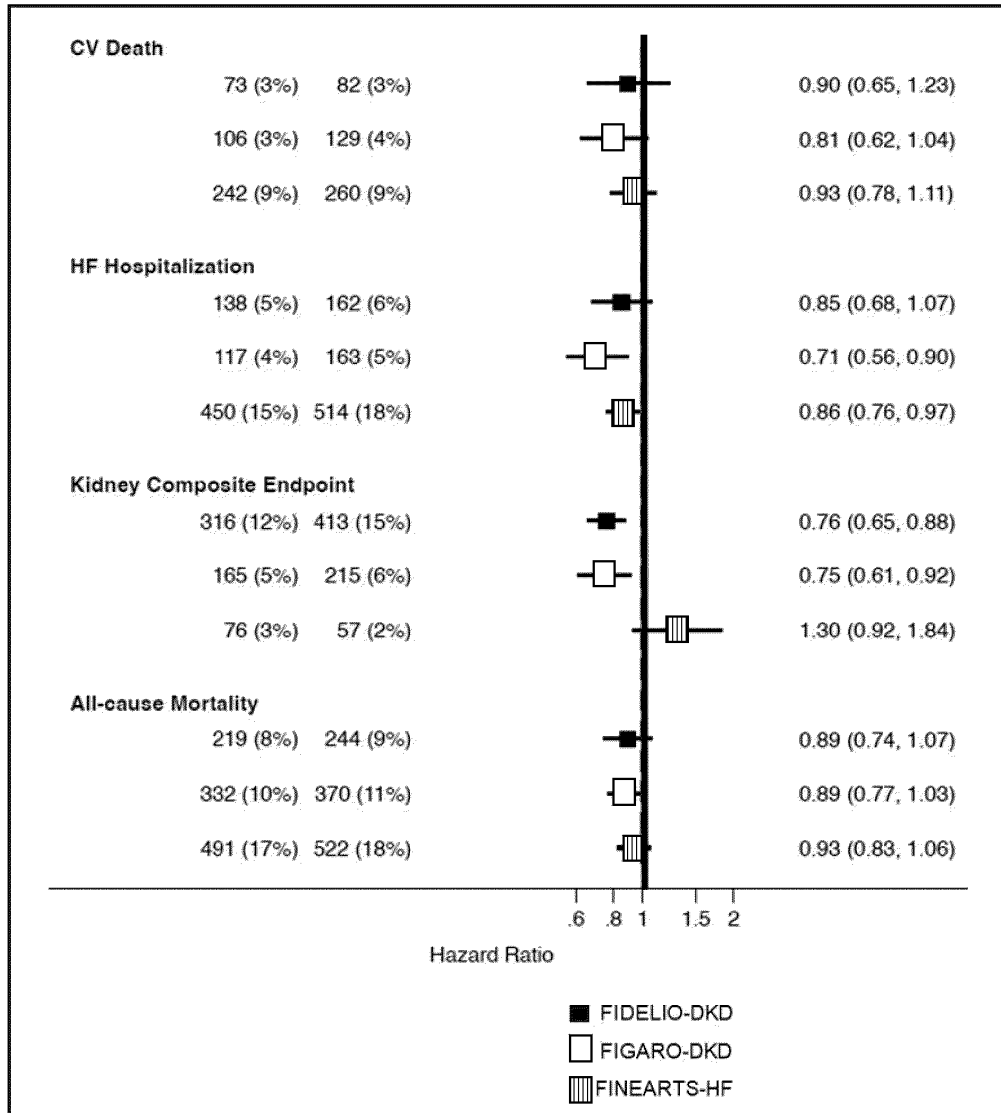
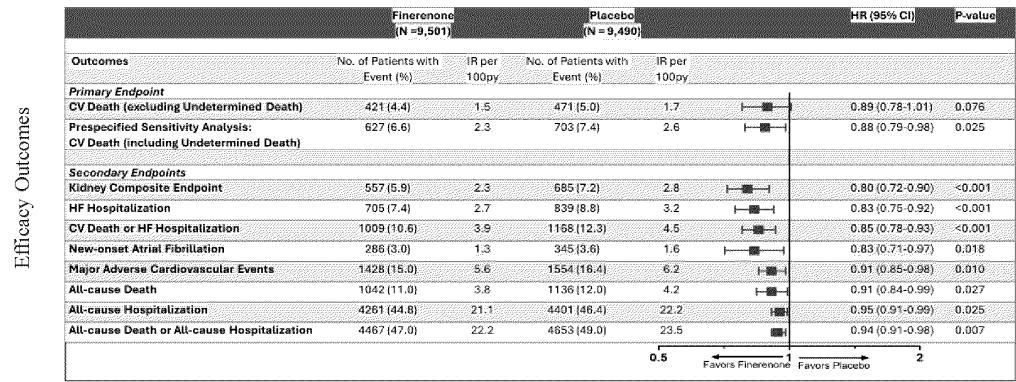


Fig. 16b)



Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; IR = incidence rate

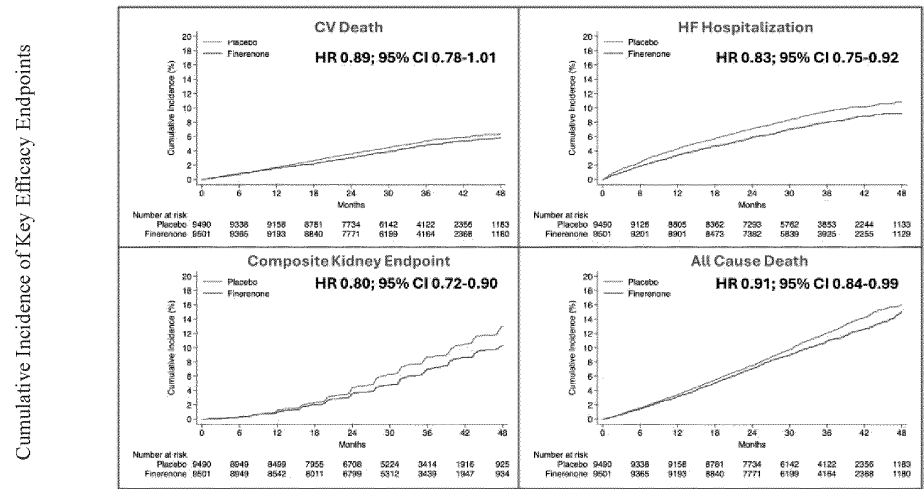
The primary efficacy endpoint was cardiovascular death (where deaths of undetermined causes were excluded). Pre-specified sensitivity analysis of the primary efficacy endpoint considered deaths of undetermined causes as cardiovascular cause.

The kidney composite endpoint was defined as a sustained decline in eGFR to $\geq 50\%$ from baseline, sustained decrease in eGFR to <15 mL/min/1.73m², end stage kidney disease, and death due to kidney causes.

Major adverse cardiovascular events included cardiovascular death or a non-fatal cardiovascular event (HF hospitalization, myocardial infarction, stroke)

The composite of all-cause mortality or all-cause hospitalization was defined *post hoc*.

Fig. 16c)

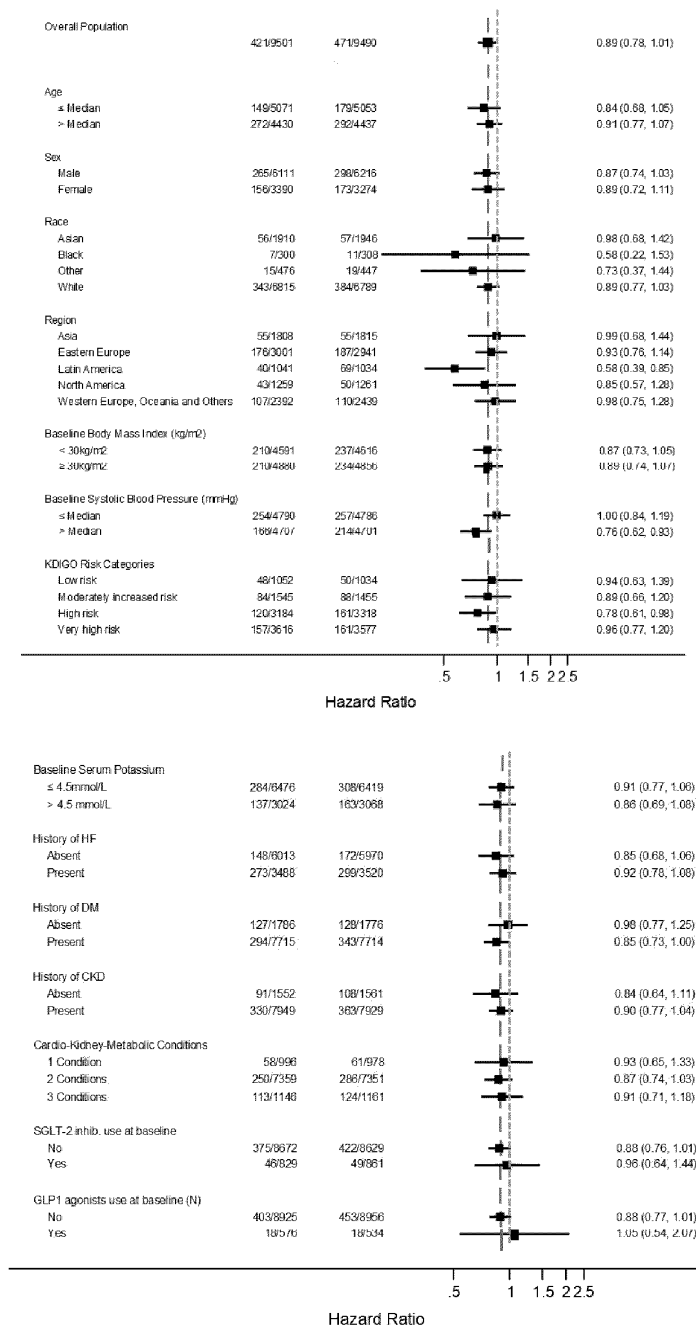


Panel A displays cardiovascular (CV) death (primary endpoint); **Panel B** displays heart failure (HF) hospitalization; **Panel C** displays the kidney composite outcome (sustained decline in eGFR to $\geq 50\%$ from baseline, sustained decrease in eGFR to <15 mL/min/1.73m², end stage kidney disease, and death due to kidney causes); and **Panel D** displays all-cause death. Abbreviations: CI = confidence interval; HR = hazard ratio

Fig. 16d)

Subgroup Forest Plot for Primary Endpoint (CV Death)

Subgroup Forest Plot for Primary Endpoint (CV Death)

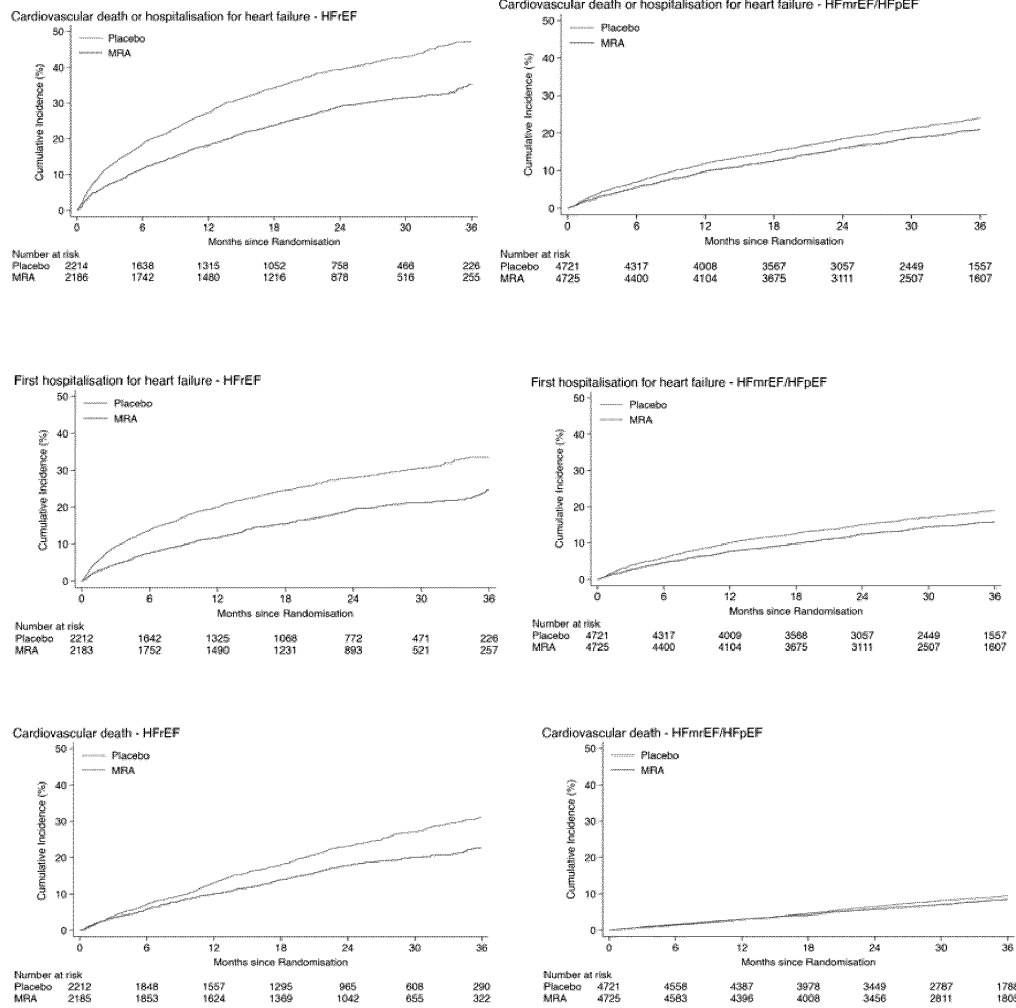


Abbreviations: CKD = chronic kidney disease; DM = diabetes mellitus; GLP-1 = glucagon-like peptide-1 receptor agonist; HF = heart failure; KDIGO = Kidney Disease: Improving Global Outcomes; SGLT-2 = sodium-glucose co-transporter-2

Median age was 68 years and median systolic blood pressure was 135mmHg.

Number of cardio-kidney-metabolic conditions (histories of CKD, HF, and/or DM) were summed as 1 condition, 2 conditions, or all 3 conditions.

Fig. 17



(Fig. 17 continued)

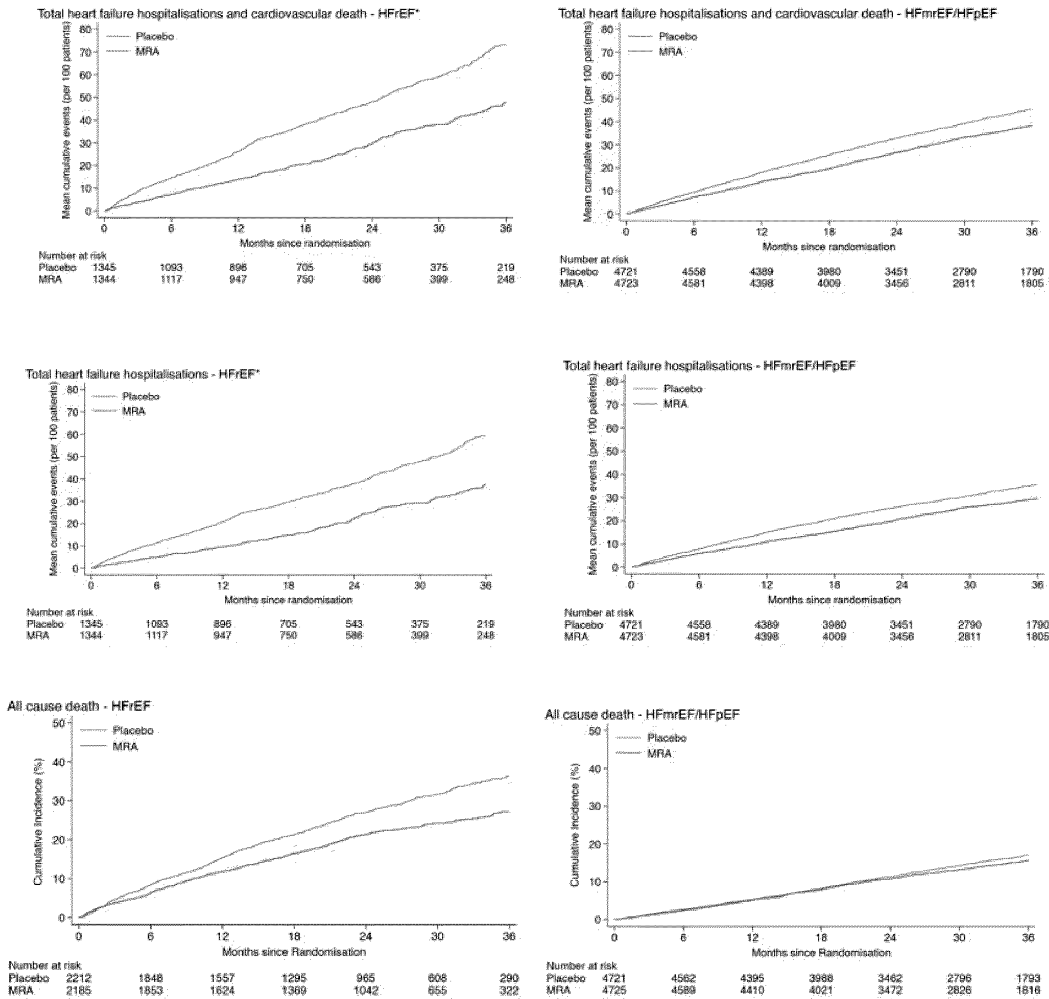


Fig. 18

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

Outcomes	RALES-Spiromolactone		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)	14.83 (13.01,16.89)	314 (36.20)	21.64 (19.37,24.17)	147 (10.71)	5.96 (5.07,7.00)	165 (13.56)	7.72 (6.69,8.92)
HF hospitalisation	216 (25.88)	16.64 (14.57,19.02)	300 (36.50)	26.96 (24.07,30.19)	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)	21.19 (17.21,26.09)	529 (238, 28.95)	36.39 (31.07,42.61)	313 (186, 13.55)	12.68 (10.66,15.08)	461 (277, 20.31)	20.08 (17.55,22.98)
CVD or HF hospitalisation (first and total)	503 (319, 37.93)	33.00 (28.54,38.15)	759 (442, 53.77)	52.24 (46.50,58.69)	411 (271, 19.74)	16.65 (14.42,19.23)	598 (379, 27.79)	24.96 (22.25,28.01)
All cause death	283 (33.65)	18.57 (16.52,20.86)	386 (46.96)	26.60 (24.08,29.39)	171 (12.45)	6.93 (5.96,8.05)	213 (15.62)	8.89 (7.77,10.17)

Outcomes	TOPCAT-Spiromolactone		TOPCAT-Placebo		FINEARTS-Finerenone		FINEARTS-Placebo	
	N = 1722		N = 1723		N = 3003		N = 2996	
	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 (3.19,4.05)
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)	744 (450, 15.01)	8.42 (7.19, 9.98)	11.57 (10.37,12.91)	1024 (573, 19.08)
CVD or HF hospitalisation (first and total)	550 (320, 16.57)	9.46 (8.24,10.85)	648 (347, 20.15)	11.22 (9.87,12.75)	986 (599, 19.98)	10.03 (8.64, 11.61)	14.08 (12.52, 15.68)	1283 (719, 23.94)
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)

Fig. 19

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 = 2186		N = 2214		N = 4725		N = 4721		N = 6911		N = 6935	
	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)	N (%)	Rate (95%CI)
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)	10.51 (9.50,11.62)	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	914 (590, 26.65)	22.89 (20.65,25.37)	1357 (821, 37.56)	35.25 (32.42,38.33)	1633 (944, 20.00)	12.47 (11.53,13.50)	1931 (1066, 22.56)	14.82 (13.78,15.94)	2547 (1534, 22.12)	14.91 (14.00,15.88)	3288 (1887, 27.30)	19.48 (18.43,20.59)
All cause death	454 (20.51)	11.37 (10.37,12.47)	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)	1202 (17.33)	7.02 (6.63,7.43)	1394 (20.17)	8.25 (7.83,8.69)

Fig. 20

Effect of mineralocorticoid receptor antagonist treatment on the pre-specified efficacy outcomes in each of the trials

Outcomes	RALES		EMPHASIS-HF		EMPHASIS-HF & RALES		TOPCAT		FINEARTS-HF		TOPCAT & FINEARTS-HF		All trials	
	N = 1663		N = 2737		N = 4400		N = 3445		N = 6001		N = 9446		N = 13846	
	HR/RR (95%CI)	P-value	HR/RR (95%CI)	P-value	HR/RR (95%CI)	Int P-value	HR/RR (95%CI)	P-value	HR/RR (95%CI)	P-value	HR/RR (95%CI)	Int P-value	HR/RR (95%CI)	Int P-value
CV death or HF hospitalisation*	0.66 (0.57,0.75)	<0.001	0.66 (0.56,0.78)	<0.001	0.66 (0.58,0.73)	0.965	0.90 (0.78,1.05)	0.195	0.85 (0.76,0.94)	0.003	0.87 (0.79,0.95)	0.494	0.77 (0.72,0.83)	<0.001
HF hospitalisation*	0.65 (0.55,0.77)	<0.001	0.61 (0.50,0.75)	<0.001	0.63 (0.58,0.72)	0.664	0.83 (0.69,0.99)	0.043	0.82 (0.72,0.92)	0.001	0.82 (0.74,0.91)	0.925	0.74 (0.69,0.80)	<0.001
CV death*	0.69 (0.58,0.82)	<0.001	0.77 (0.62,0.96)	0.018	0.72 (0.63,0.82)	0.445	0.90 (0.73,1.12)	0.347	0.93 (0.78,1.10)	0.399	0.92 (0.80,1.05)	0.845	0.81 (0.74,0.89)	<0.001
Total HF hospitalisations* *	0.65 (0.54,0.77)	<0.001	0.53 (0.42,0.67)	<0.001	0.60 (0.52,0.69)	0.606	0.79 (0.65,0.96)	0.018	0.83 (0.74,0.93)	0.001	0.82 (0.74,0.90)	0.784	0.74 (0.68,0.80)	0.004
CV death and total HF hospitalisations**	0.70 (0.61,0.80)	<0.001	0.57 (0.47,0.68)	<0.001	0.64 (0.57,0.72)	0.448	0.82 (0.69,0.98)	0.024	0.85 (0.76,0.95)	0.003	0.84 (0.77,0.92)	0.818	0.76 (0.71,0.82)	0.002
All-cause death	0.70 (0.60,0.82)	<0.001	0.78 (0.64,0.95)	0.014	0.73 (0.65,0.82)	0.440	0.93 (0.79,1.11)	0.434	0.94 (0.83,1.06)	0.269	0.94 (0.85,1.03)	0.980	0.85 (0.78,0.91)	<0.001

CV, cardiovascular HF, heart failure HR, hazard ratio RR, rate ratio CI, confidence interval

Int P-value = p-value for test of interaction between trial and treatment effect

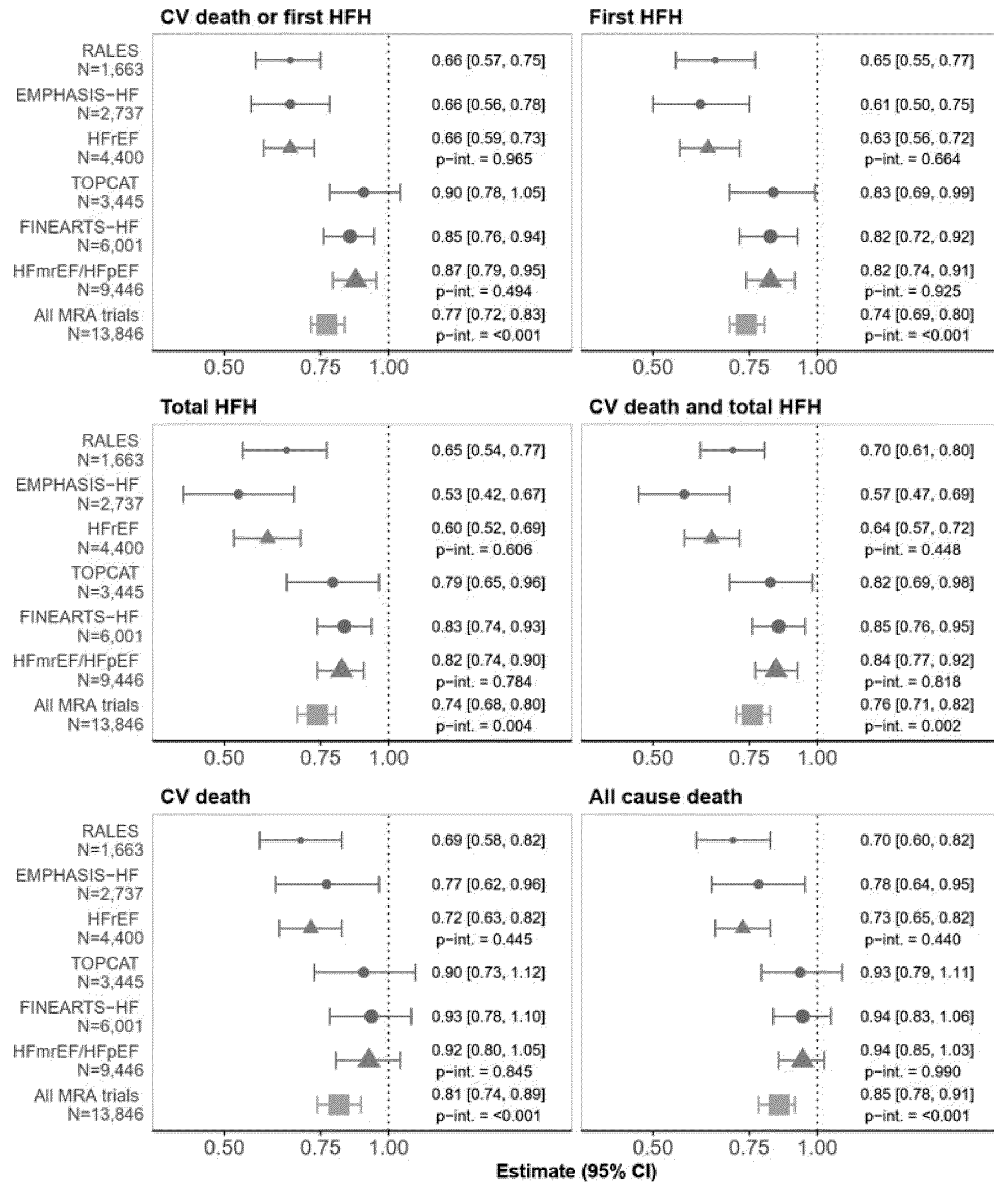
* includes urgent visits for worsening heart failure as a hospitalisation equivalent

** the definition of cardiovascular death was that used in the original trials

*rate ratio estimated using a negative binomial model due to missing data on time to recurrent hospitalisations in RALES

FIG. 20: EFFECT OF MINERALOCORTICOID RECEPTOR ANTAGONIST TREATMENT ON THE PRE-SPECIFIED EFFICACY OUTCOMES IN EACH OF THE TRIALS

Fig.21



CV, cardiovascular; HFH, hospitalisation for heart failure; p-int. values for interaction by trial and treatment

Fig. 22

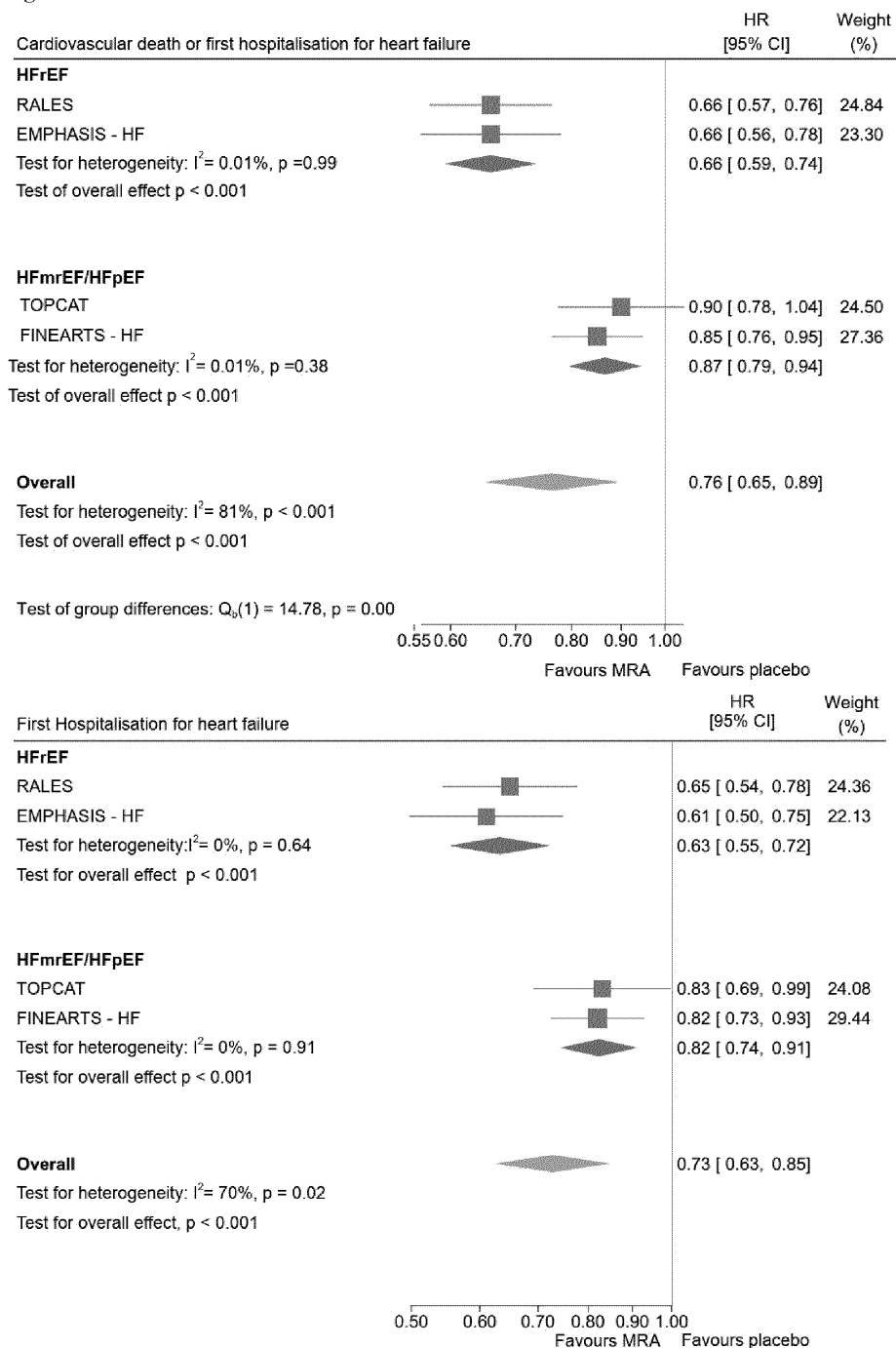


Fig. 22 (cont.)

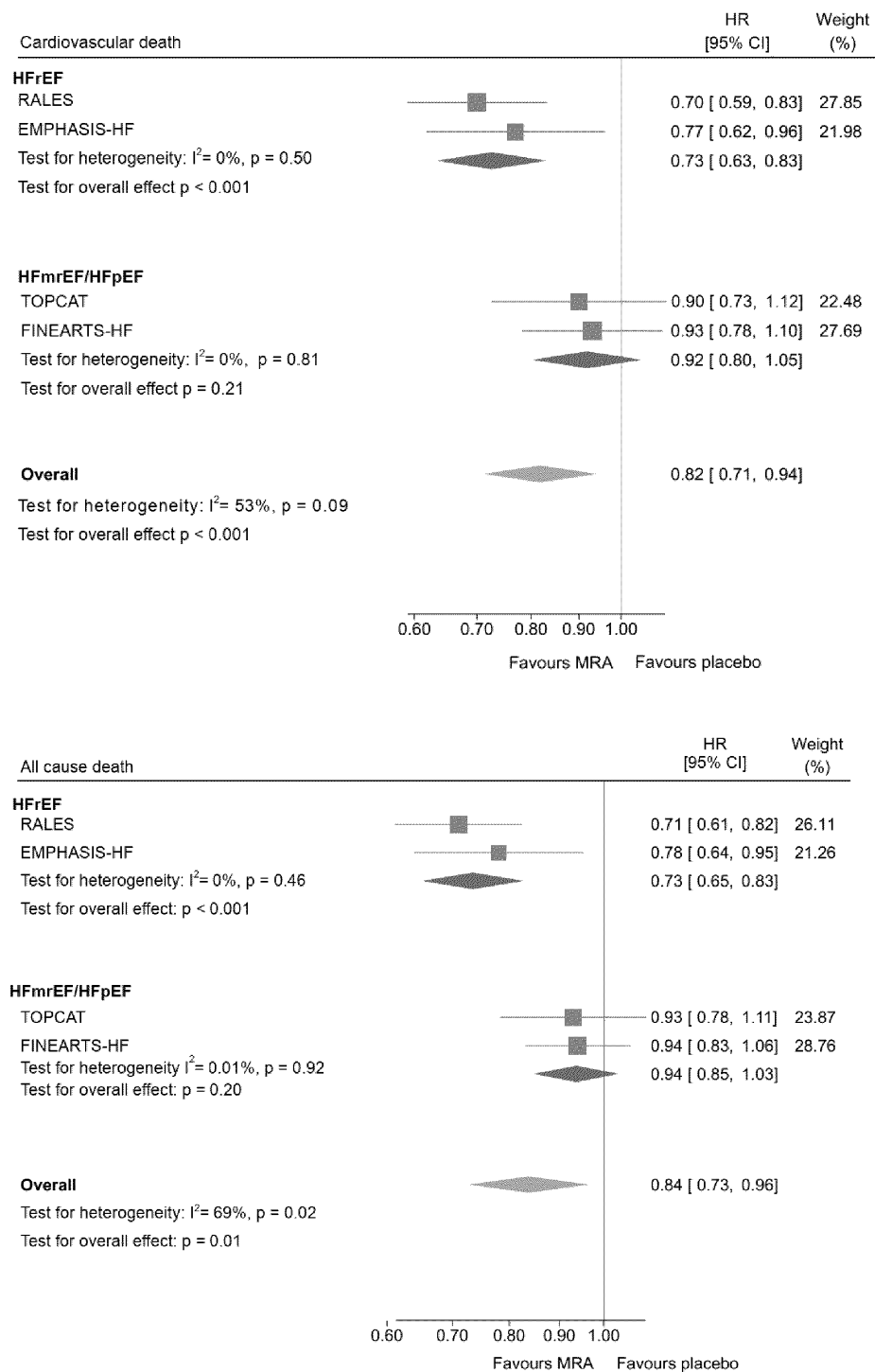


Fig. 23

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 (0.57,0.76)	<0.001	0.66 (0.56,0.78)	<0.001	0.66 (0.59,0.73)	0.967	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 (0.59,0.83)	<0.001	0.78 (0.62,0.96)	0.021	0.73 (0.64,0.83)	0.468	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)	<0.001
CV death including excluding 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)	0.266	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 (0.74,0.90)	<0.001

Fig. 24

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 = 13846	
	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)**	0.134
CV death and total HF hospitalisation	*	*	0.65 (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)**	0.134

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

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

Fig. 25

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)	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 / HF hospitalisation	0.66 (0.57,0.76)	<0.001	0.66 (0.56,0.78)	<0.001	0.66 (0.59,0.73)	0.988	0.84 (0.70,0.99)	0.043	0.85 (0.76,0.94)	0.003	0.84 (0.77,0.93)	0.898	0.76 (0.71,0.81)	<0.001
CV death	0.70 (0.59,0.83)	<0.001	0.77 (0.62,0.96)	0.018	0.72 (0.63,0.83)	0.472	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 (0.71,0.87)	<0.001
HF hospitalisation	0.65 (0.55,0.77)	<0.001	0.61 (0.50,0.75)	<0.001	0.63 (0.56,0.72)	0.664	0.81 (0.67,0.99)	0.041	0.82 (0.72,0.92)	0.001	0.82 (0.74,0.91)	0.984	0.74 (0.68,0.80)	<0.001
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)	0.001	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)	0.70 (0.61,0.81)	<0.001	0.58 (0.48,0.70)	<0.001	0.65 (0.57,0.73)	0.465	0.78 (0.66,0.92)	0.004	0.85 (0.76,0.95)	0.003	0.83 (0.75,0.91)	0.386	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)	0.069	0.82 (0.71,0.95)	0.008	0.81 (0.72,0.92)	0.886	0.77 (0.69,0.86)	0.146
CV death and total HF hospitalisation (semi parametric model)	*	*	0.58 (0.48,0.70)	<0.001	*	*	0.78 (0.66,0.92)	0.004	0.84 (0.74,0.96)	0.008	0.83 (0.74,0.92)	0.886	0.78 (0.71,0.86)	0.146
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)	0.466	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)	<0.001

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

Fig. 26
Panel A

HFrEF trials (RALES/EMPHASIS-HF)

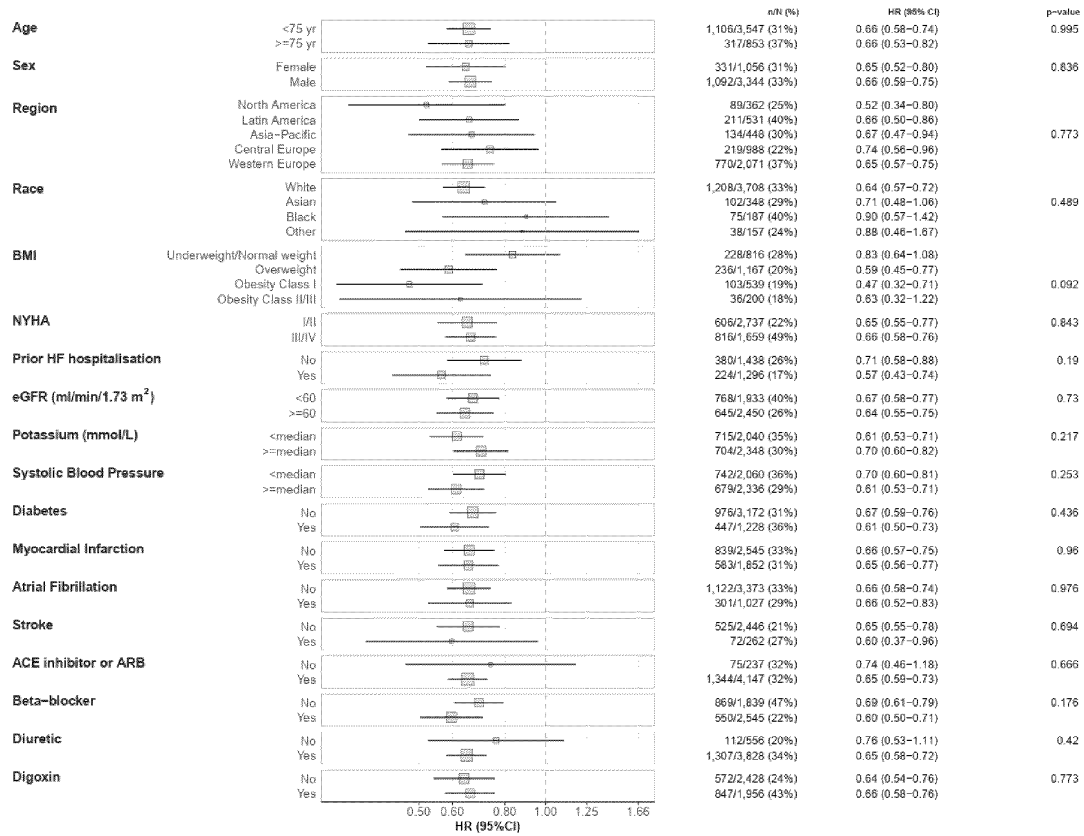


Fig. 26 (cont.)

Panel B

HFmrEF/HRpEF trials (TOPCAT/FINEARTS-HF)

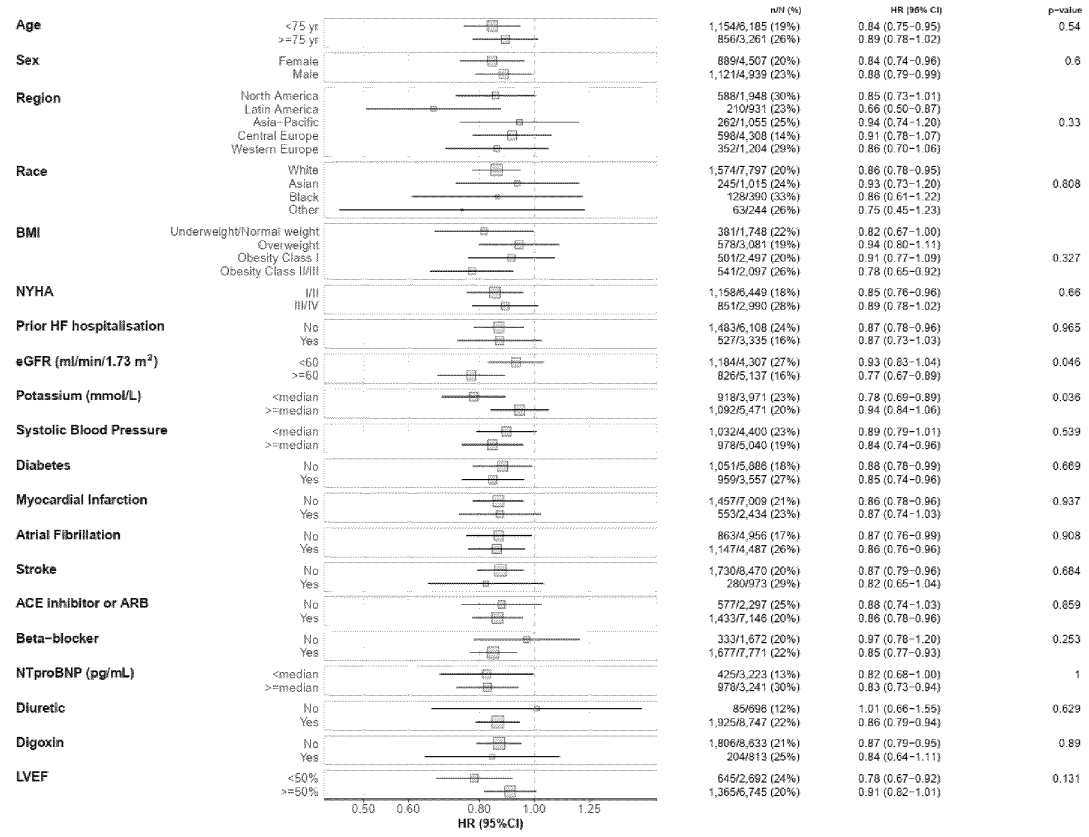


Fig. 27

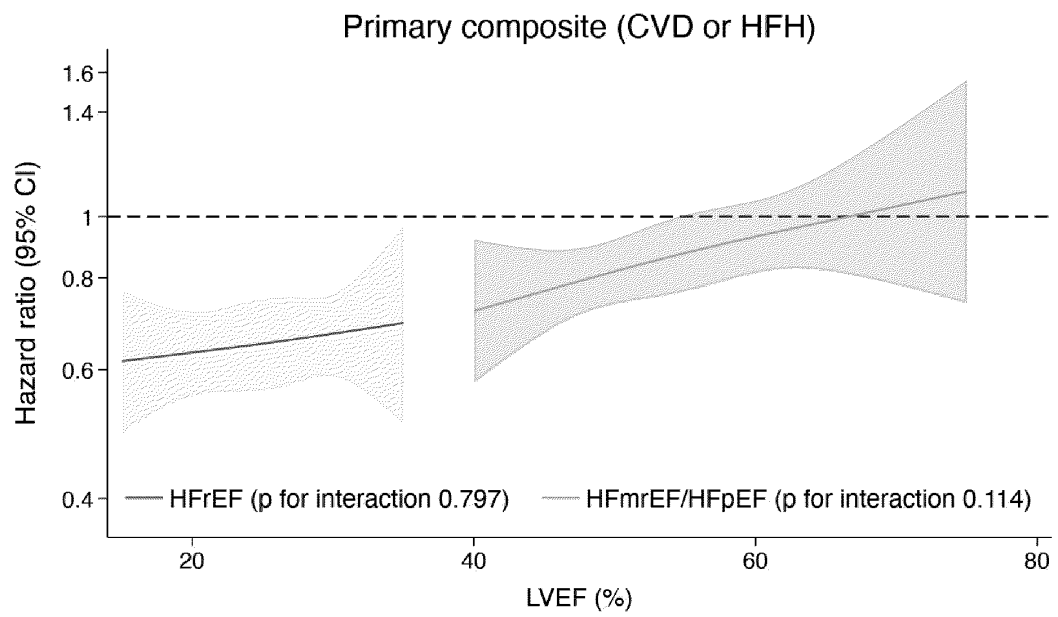


Fig. 28

Subgroup analysis of the outcome of cardiovascular death or first hospitalization for heart failure in all four trials

All MRA trials

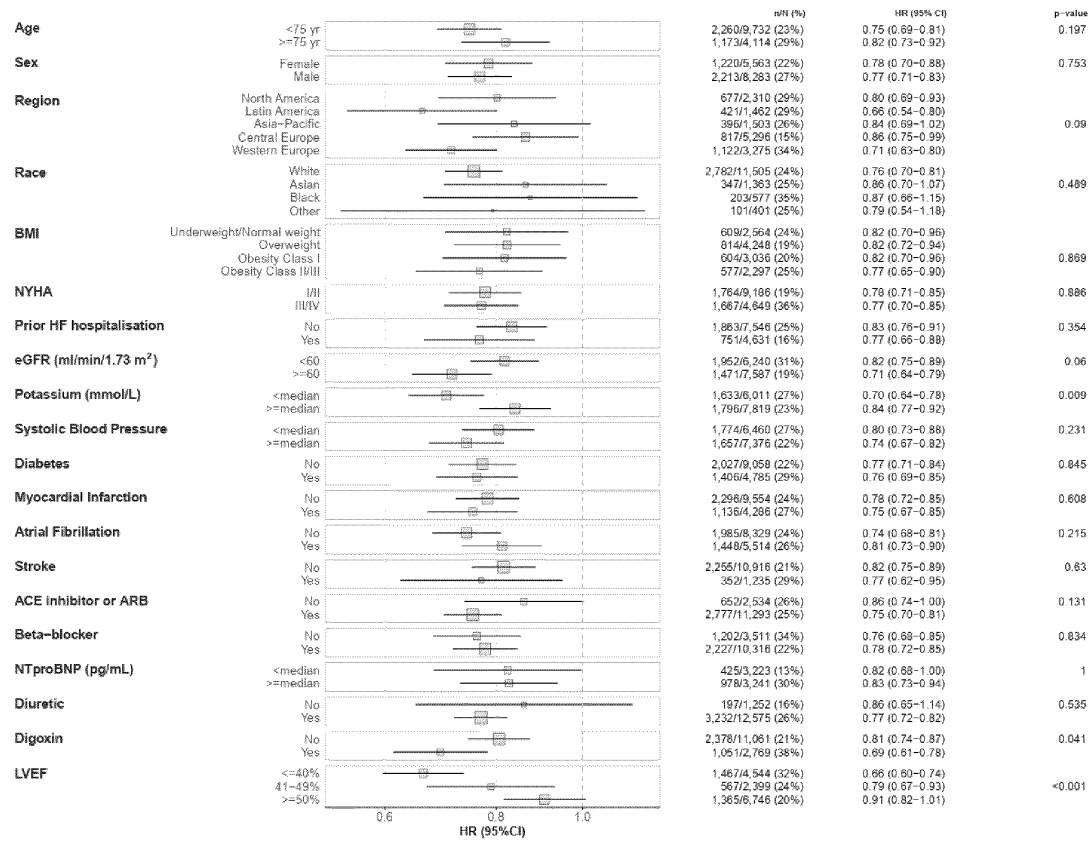


Fig. 29

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

Safety outcomes	RALES		EMPHASIS-HF		TOPCAT		FINELARIS-HF	
	spironolactone n=820 N (%)	placebo n=841 N (%)	epirenone n=1360 N (%)	placebo n=1369 N (%)	spironolactone n=1699 N (%)	placebo n=1691 N (%)	finerenone n=2993 N (%)	placebo n=2993 N (%)
Elevated serum creatinine	796/797 (100)	796/797 (100)	1171/1171 (100)	1170/1170 (100)	864/864 (100)	854/854 (100)	1265/2928 (43)	825/2921 (28)
≤0.3 mg/dl	796/797 (100)	796/797 (100)	1171/1171 (100)	1170/1170 (100)	864/864 (100)	854/854 (100)	1265/2928 (43)	825/2921 (28)
>0.3 mg/dl	796/797 (100)	796/797 (100)	1171/1171 (100)	1170/1170 (100)	864/864 (100)	854/854 (100)	677/2928 (23)	418/2921 (14)
Reduction in eGFR	564/820 (69)	506/840 (60)	431/899 (48)	367/922 (40)	664/837 (79)	607/832 (73)	2335/2928 (80)	1969/2921 (67)
>10%	564/820 (69)	506/840 (60)	431/899 (48)	367/922 (40)	664/837 (79)	607/832 (73)	2335/2928 (80)	1969/2921 (67)
Reduction in eGFR	585/820 (71)	530/840 (63)	462/899 (51)	412/922 (45)	670/837 (80)	625/832 (75)	2393/2930 (82)	2078/2924 (71)
≤5	585/820 (71)	530/840 (63)	462/899 (51)	412/922 (45)	670/837 (80)	625/832 (75)	2393/2930 (82)	2078/2924 (71)
≥10	478/820 (58)	390/840 (46)	337/899 (37)	278/922 (30)	533/837 (64)	456/832 (55)	1872/2930 (64)	1447/2924 (49)

Safety outcomes	HFpEF (EMPHASIS-RALES)				HFpEF (TOPCAT-FINEARTS)				All trial			
	MRA	Placebo			MRA	Placebo			MRA	Placebo		
	N = 2180	N = 2210			N = 4692	N = 4684			N = 6872	N = 6894		
	N (%)	N (%)	OR (95%CI)	interaction p-value	N (%)	N (%)	OR (95%CI)	interaction p-value	N (%)	N (%)	OR (95%CI)	interaction p-value
Hypotension												
<90 mm Hg	150/213 (7)	114/2138 (5)	1.27 (1.02,1.58)	0.679	211/3803 (6)	128/3795 (3)	1.68 (1.34,2.11)	0.316	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	811/3803 (21)	551/3795 (15)	1.60 (1.42,1.80)	0.994	1299/6746 (19)	981/6764 (15)	1.39 (1.27,1.52)	0.013
Elevated serum creatinine												
≥2.5 mg/dl	98/1948 (5)	63/1967 (3)	1.55 (1.13,2.13)	0.383	264/3792 (7)	164/3775 (4)	1.65 (1.35,2.01)	0.376	366/6567 (6)	230/6573 (3)	1.63 (1.38,1.93)	0.638
≥3 mg/dl	39/1948 (2)	28/1967 (1)	1.41 (0.87,2.31)	0.136	118/3792 (3)	69/3775 (2)	1.73 (1.28,2.33)	0.995	138/6567 (2)	97/6573 (1)	1.65 (1.28,2.12)	0.443
Elevated serum potassium												
>5.5 mmol/l	285/2113 (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	909/6725 (14)	433/6737 (6)	2.28 (2.02,2.57)	0.008
>6 mmol/l	66/2113 (3)	34/2137 (2)	1.99 (1.31,3.03)	0.030	123/3785 (3)	53/3769 (1)	2.35 (1.70,3.26)	0.165	196/6725 (3)	94/6737 (1)	2.12 (1.66,2.72)	0.153
Reduced serum potassium												
<3.5 mmol/l	154/2113 (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	504/6725 (7)	929/6737 (14)	0.51 (0.45,0.57)	0.006
Elevated serum creatinine												
≥0.3 mg/dl	1947/1948 (100)	1966/1967 (100)	0.99 (0.06,15.84)	-	2129/3792 (56)	1679/3775 (44)	1.60 (1.46,1.75)	-	4903/6567 (75)	4476/6573 (68)	1.38 (1.28,1.49)	0.629
≥0.5 mg/dl	1964/1948 (100)	1964/1967 (100)	1.49 (0.25,8.90)	0.700	1541/3792 (41)	1272/3775 (34)	1.35 (1.23,1.48)	-	4314/6567 (66)	4067/6573 (62)	1.18 (1.10,1.27)	0.907
Reduction in eGFR												
>10%	995/1719 (58)	873/1762 (50)	1.40 (1.22,1.60)	0.758	2999/3765 (80)	2576/3753 (69)	1.79 (1.61,1.99)	0.026	4522/6299 (72)	3955/6333 (62)	1.53 (1.42,1.65)	<0.001
>20%	690/1719 (40)	556/1762 (32)	1.45 (1.27,1.67)	0.060	2200/3765 (58)	1650/3753 (44)	1.79 (1.64,1.96)	0.118	3236/6299 (51)	2522/6333 (40)	1.60 (1.49,1.71)	<0.001
>30%	437/1719 (25)	288/1762 (16)	1.74 (1.48,2.06)	0.814	1371/3765 (36)	891/3753 (24)	1.84 (1.66,2.03)	0.095	1984/6299 (31)	1332/6333 (21)	1.71 (1.59,1.87)	0.012
Reduction in eGFR ml/min/1.73m²												
≥5	1047/1719 (61)	942/1762 (53)	1.36 (1.19,1.55)	0.450	306/3767 (81)	2703/3756 (72)	1.69 (1.52,1.88)	0.022	4687/6301 (66)	4203/6336 (67)	1.47 (1.36,1.59)	0.001
≥10	815/1719 (47)	668/1762 (38)	1.48 (1.29,1.69)	0.288	2405/3767 (64)	1903/3756 (51)	1.72 (1.57,1.89)	0.050	3660/6301 (58)	3003/6336 (47)	1.54 (1.43,1.65)	<0.001

Fig. 31

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	spiro.	placebo		epler.	placebo		spiro.	placebo		finer.	placebo	
	N = 178 N (%)	N = 188 N (%)	OR (95%CI)	N = 181 N (%)	N = 201 N (%)	OR (95%CI)	N = 249 N (%)	N = 249 N (%)	OR (95%CI)	N = 613 N (%)	N = 646 N (%)	OR (95%CI)
Hypotension												
<90 mm Hg			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 (0.43,3.98)	26/593 (4)	24/630 (4)	1.16 (0.66,2.04)
<100 mm Hg			0.86 (0.36,1.32)	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			1.77 (1.06,2.97)	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			1.90 (0.90,4.02)	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%			2.32 (1.51,3.57)	28/122 (23)	21/123 (17)	1.45 (0.77,2.72)	131/239 (55)	128/244 (52)	1.10 (0.77,1.57)	324/588 (55)	238/623 (38)	1.99 (1.58,2.50)
>30%			1.92 (1.19,3.10)	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			3.82 (2.03,7.20)	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			2.70 (0.93,7.85)	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			0.23 (0.10,0.52)	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)

Fig. 32

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT			FINEARTS-HF		
	spiro.	placebo		epler.	placebo		spiro.	placebo		finer.	placebo	
	N = 640	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												
≥2.5 mg/dl	25/612 (4)	12/619 (2)	2.15 (1.07,4.33)	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)
≥3 mg/dl	10/612 (2)	5/619 (1)	2.04 (0.69,6.00)	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%	345/640 (54)	280/650 (43)	1.55 (1.24,1.93)	231/777 (30)	201/799 (25)	1.26 (1.01,1.57)	739/1413 (52)	618/1406 (44)	1.40 (1.21,1.62)	1352/2340 (58)	982/2298 (43)	1.83 (1.63,2.06)
>30%	225/640 (35)	152/650 (23)	1.78 (1.39,2.27)	139/777 (18)	93/799 (12)	1.65 (1.25,2.20)	423/1413 (30)	331/1406 (24)	1.39 (1.17,1.64)	823/2340 (35)	511/2298 (22)	1.90 (1.67,2.16)
Elevated serum potassium												
>5.5 mmol/l	84/612 (14)	22/619 (4)	4.32 (2.66,7.00)	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	20/612 (3)	4/619 (1)	5.19 (1.76,15.29)	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	45/612 (7)	116/619 (19)	0.34 (0.24,0.50)	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)

Fig. 33

Safety outcomes	RALES			EMPHASIS-HF			TOPCAT- Americas			FINEARTS-HF		
	spiro.	placebo		epler.	placebo		spiro.	placebo		finer.	placebo	
	N = 820	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)
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	70/777 (9)	43/797 (5)	1.74 (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	30/777 (4)	17/797 (2)	1.84 (1.01,3.37)	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%	431/820 (53)	334/840 (40)	1.68 (1.38,2.04)	259/899 (29)	222/922 (24)	1.28 (1.04,1.57)	524/837 (63)	430/832 (52)	1.57 (1.29,1.90)	1676/2928 (57)	1220/2921 (42)	1.87 (1.68,2.07)
>30%	282/820 (34)	189/840 (22)	1.81 (1.45,2.24)	155/899 (17)	99/922 (11)	1.73 (1.32,2.27)	338/837 (40)	249/832 (30)	1.59 (1.29,1.94)	1033/2928 (35)	642/2921 (22)	1.94 (1.72,2.17)
Elevated serum potassium												
>5.5 mmol/l	127/777 (16)	38/797 (5)	3.90 (2.68,5.69)	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	32/777 (4)	9/797 (1)	3.76 (1.78,7.93)	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	54/777 (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)

Fig. 34

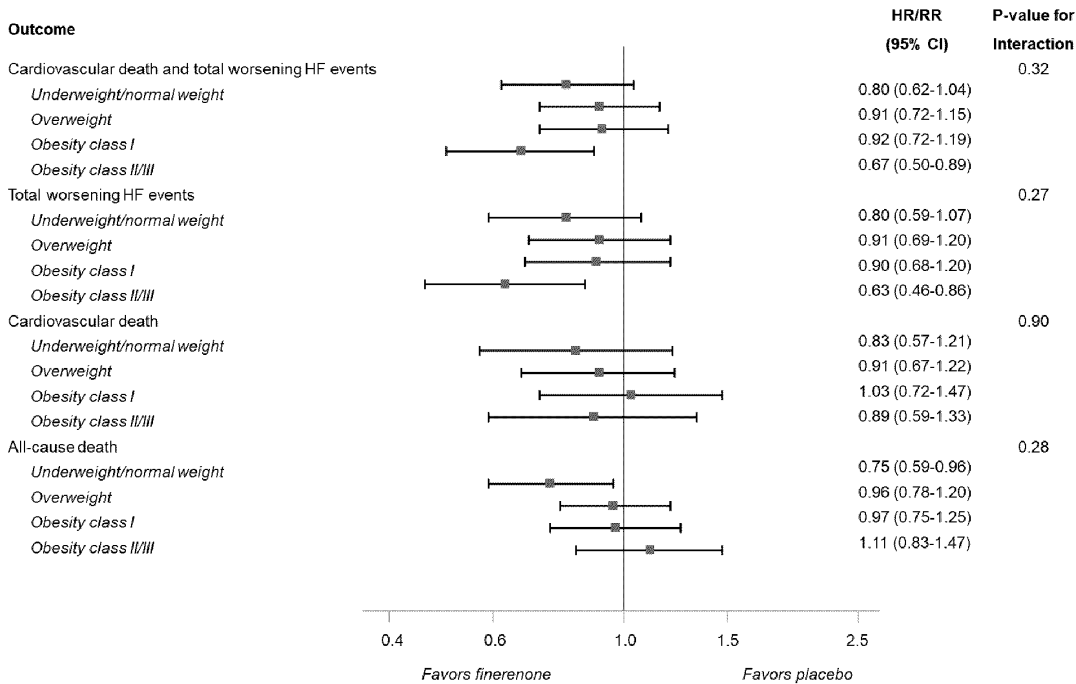


Fig. 35

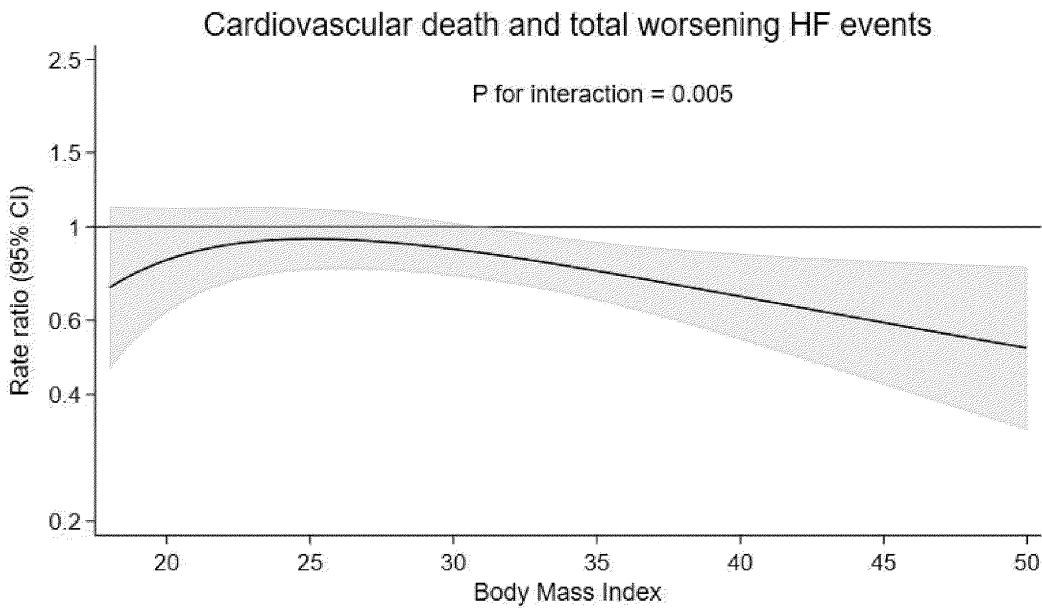
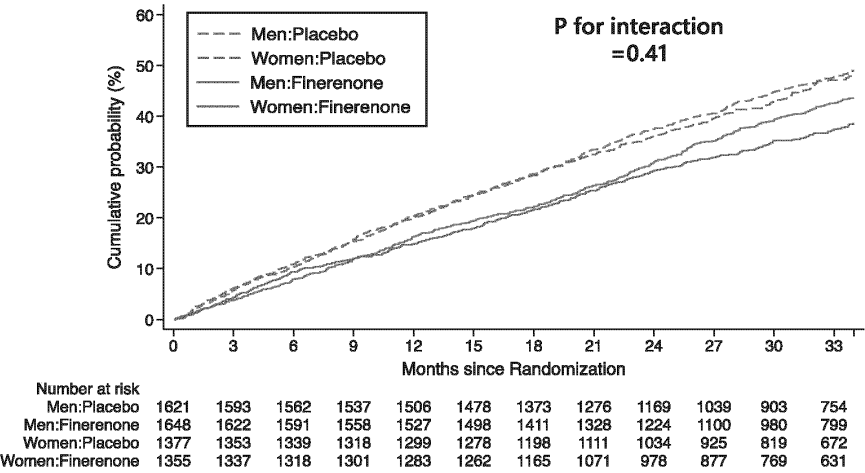


Fig. 36

A Primary End Point



B Total HF events

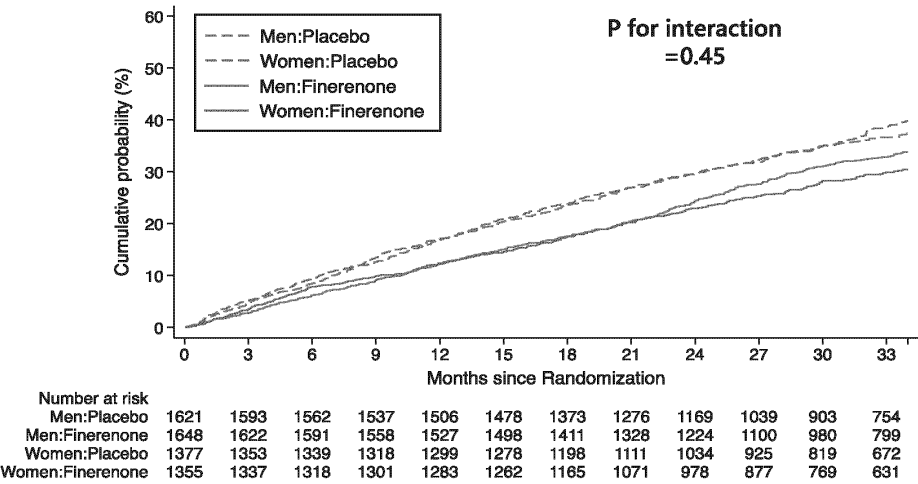


Fig. 37

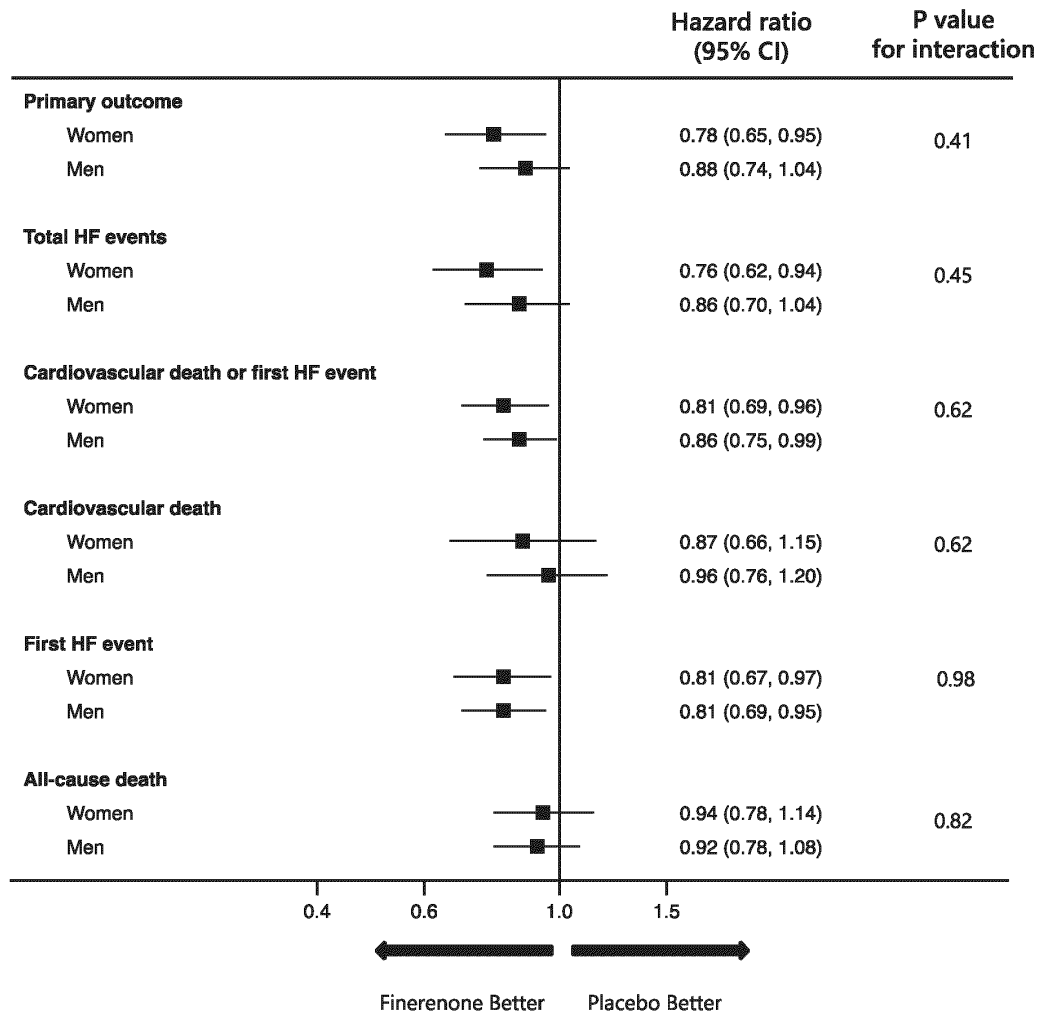


Fig. 38

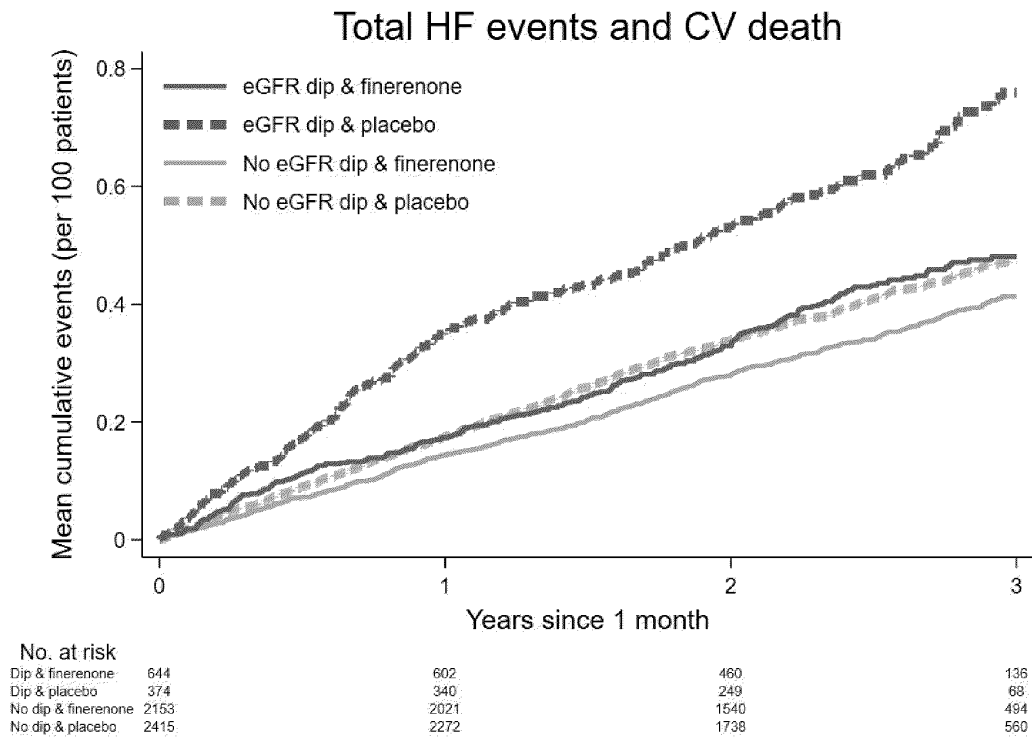


Fig. 39

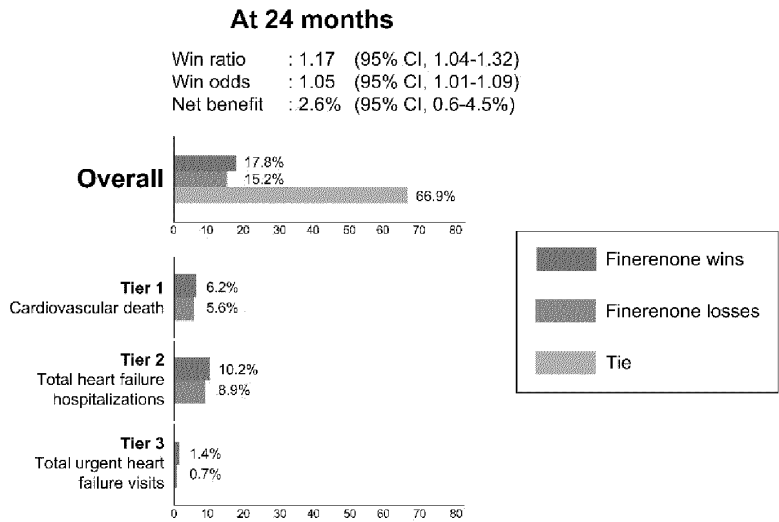


Fig. 40

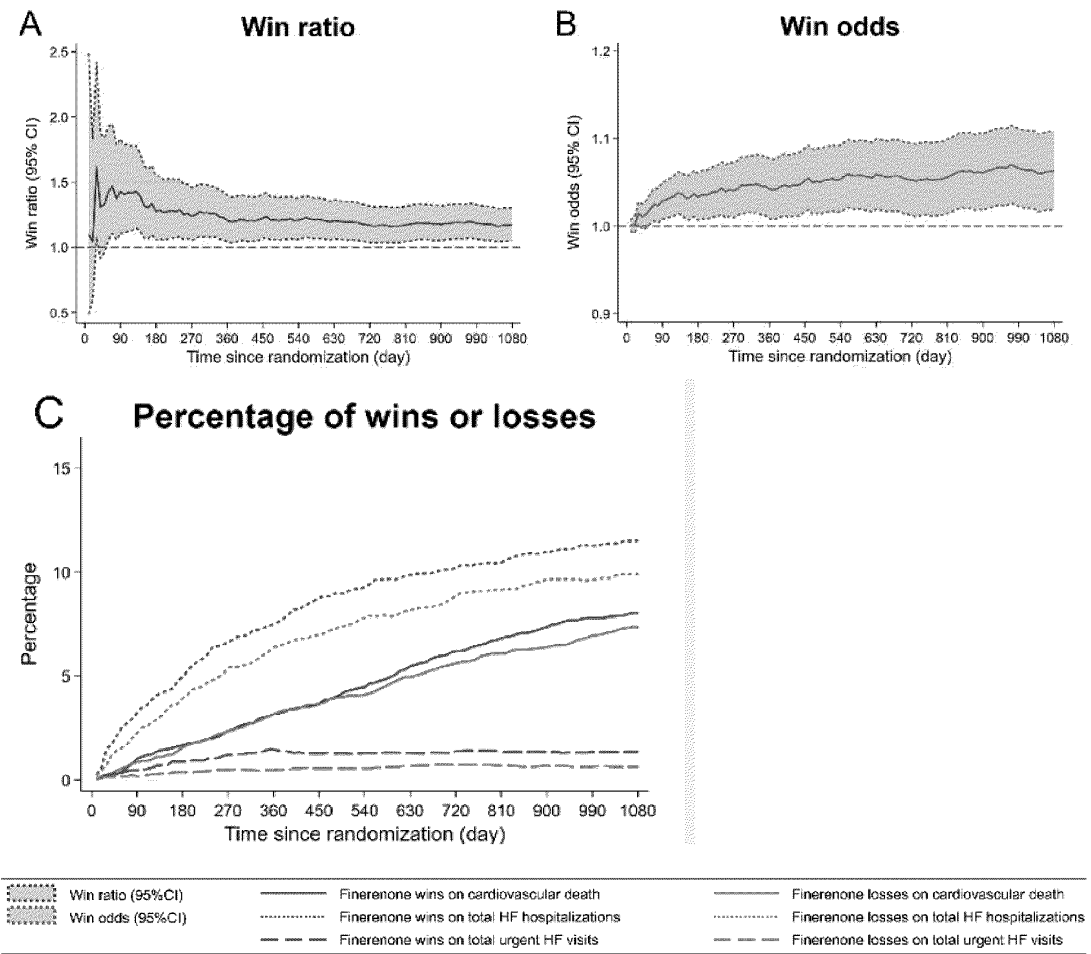


Fig. 41

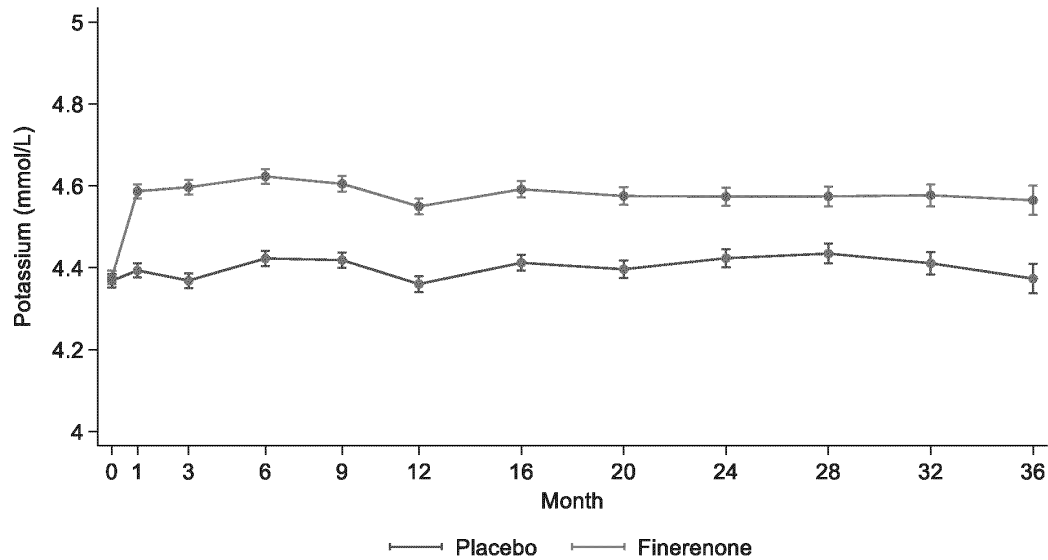
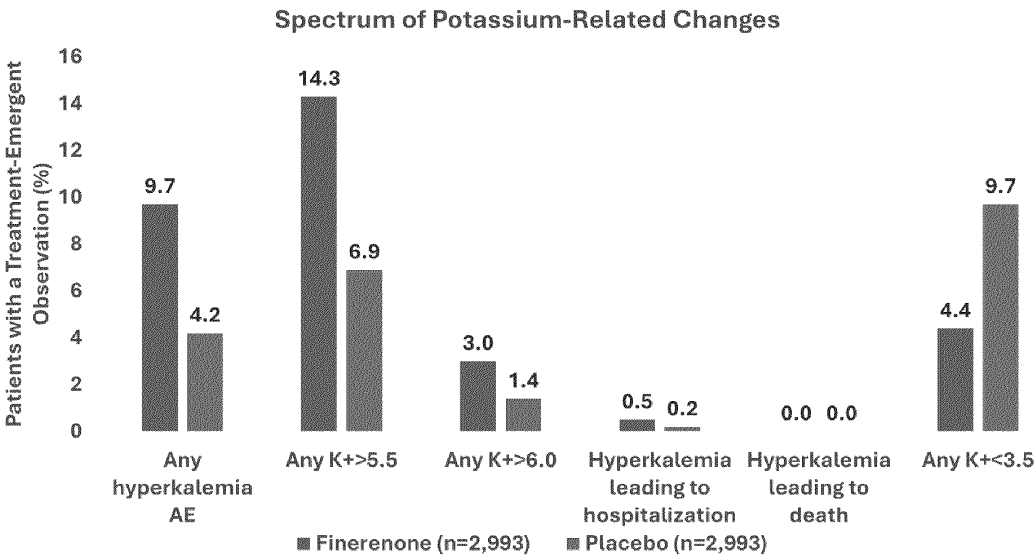


Fig. 42



All adverse events and safety markers of interest displayed in this table are treatment-emergent observations, defined as any observation occurring after first dose of study drug and up to 3 days after permanent discontinuation.

Fig. 43

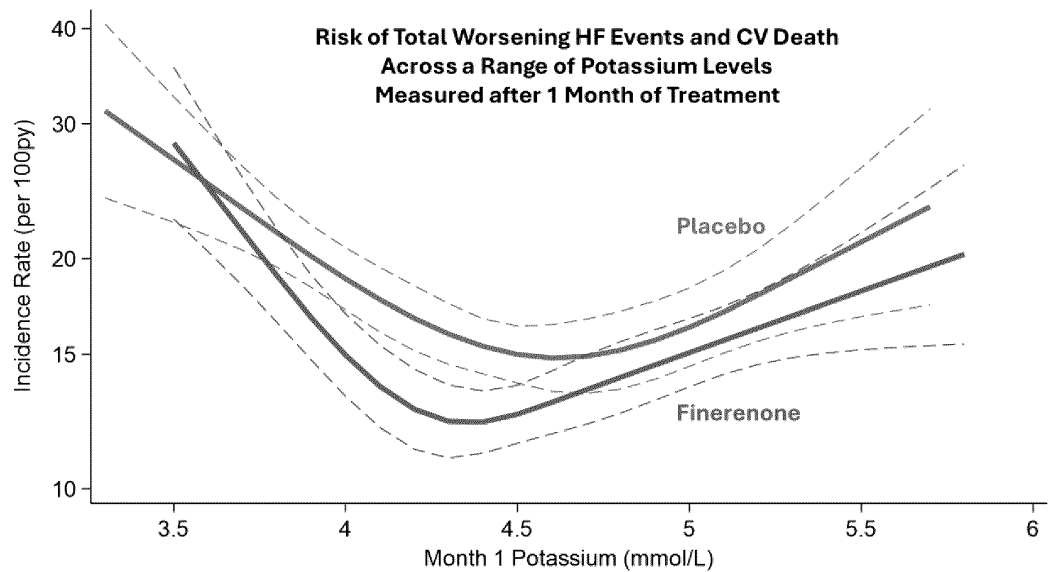
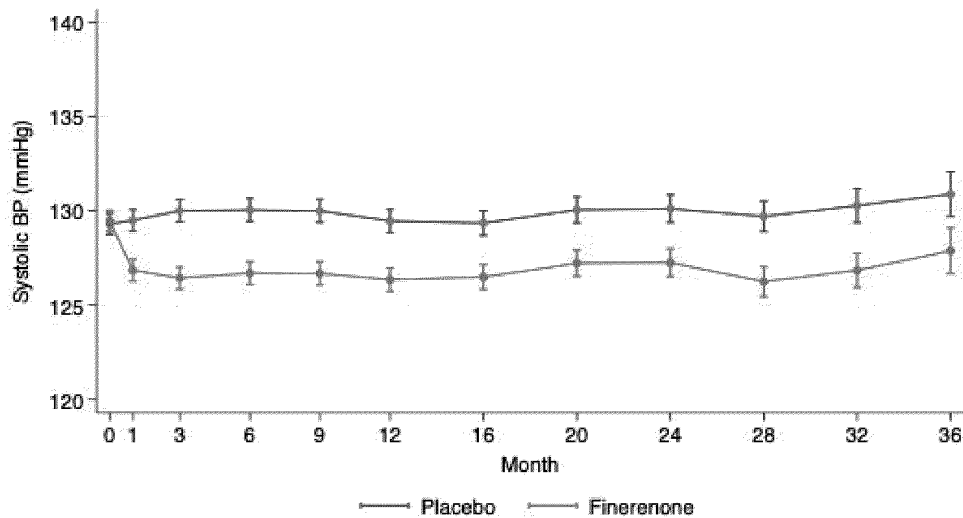


Fig. 44
A: Profiles of Systolic Blood Pressure in FINEARTS-HF, by Treatment Arm



B: Treatment Effects of Finerenone on Systolic Blood Pressure Between Baseline and Month 1, by Baseline BP Category

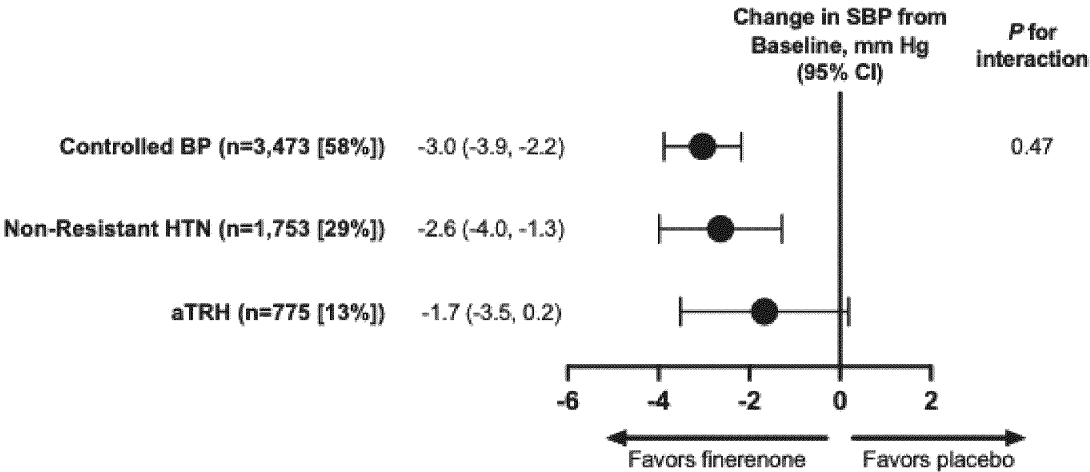
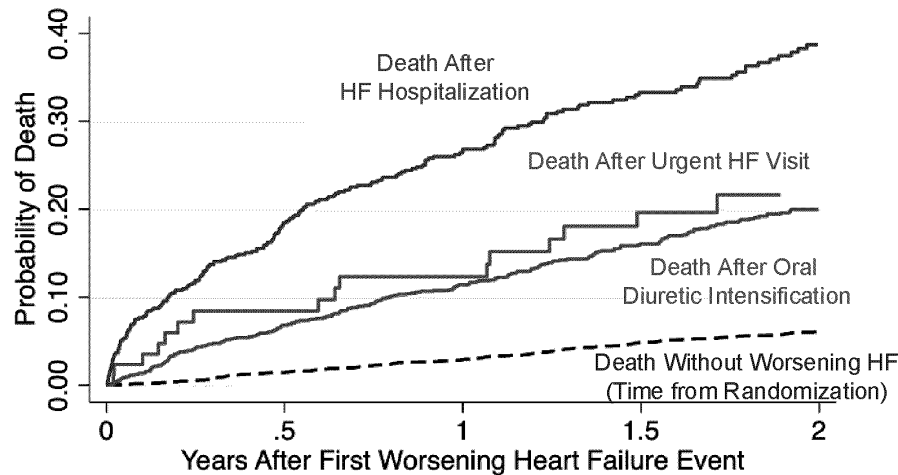


Figure displays mean values of systolic blood pressure by treatment arm at baseline and each post-baseline visit (A) and treatment effects of finerenone on systolic blood pressure at 1 month, according to blood pressure category at baseline (B).

Abbreviations: aTRH = apparent treatment-resistant hypertension; BP = blood pressure; HTN = hypertension; SBP = systolic BP

Fig. 45

A. Death Following First Worsening HF Event



B. Effect of Finerenone on Outpatient Oral Diuretic Intensification

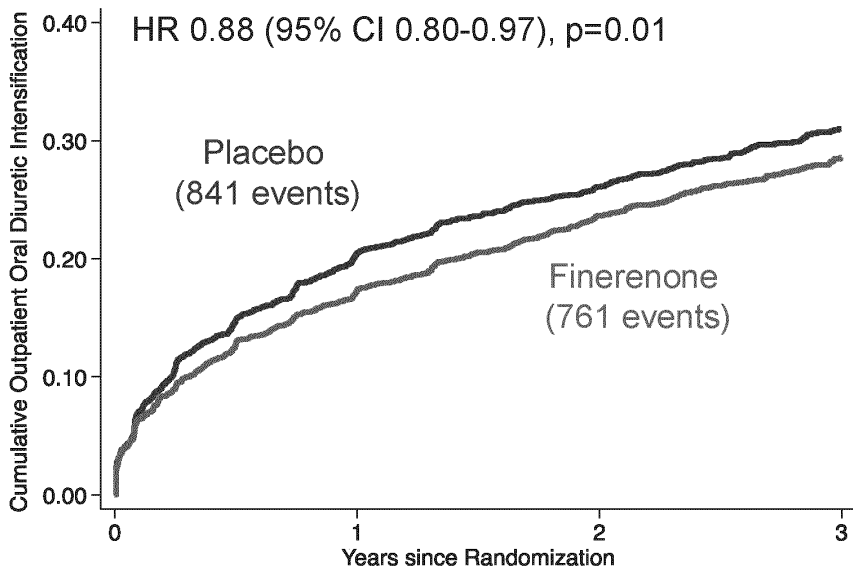


Fig. 46

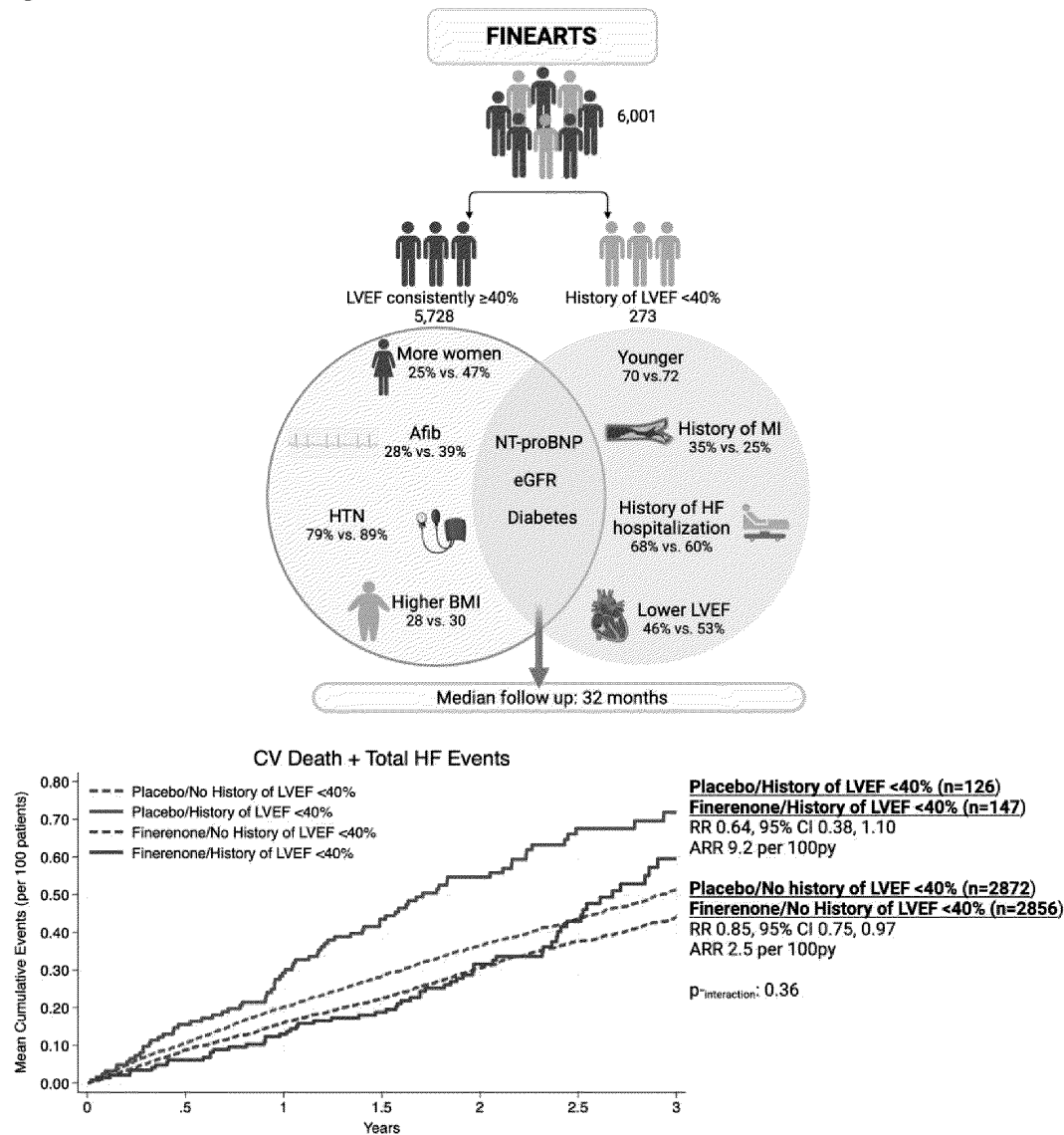


Fig. 47
Cononous bilirubin

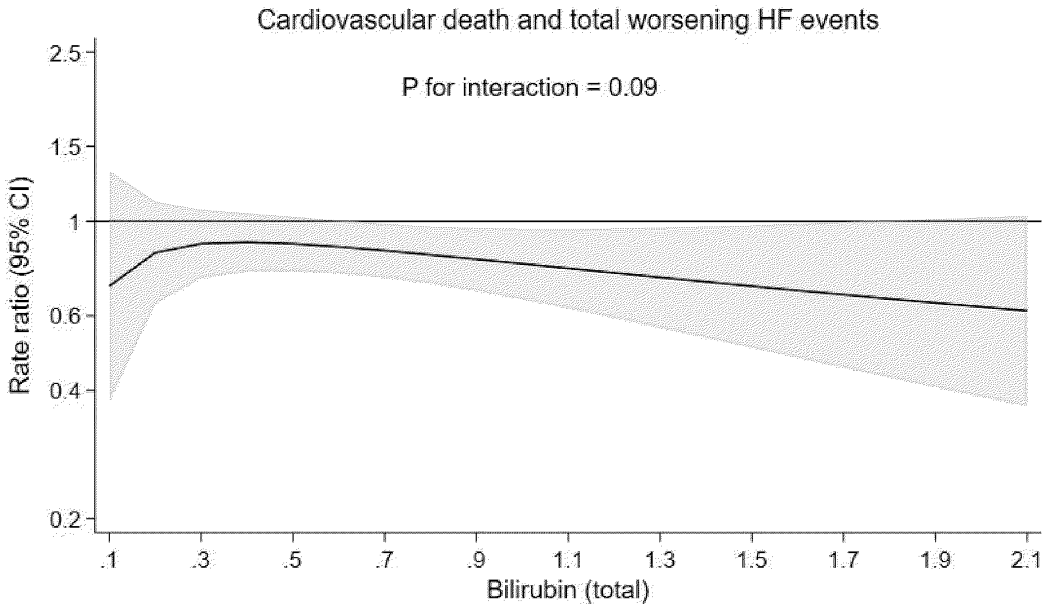


Fig. 48

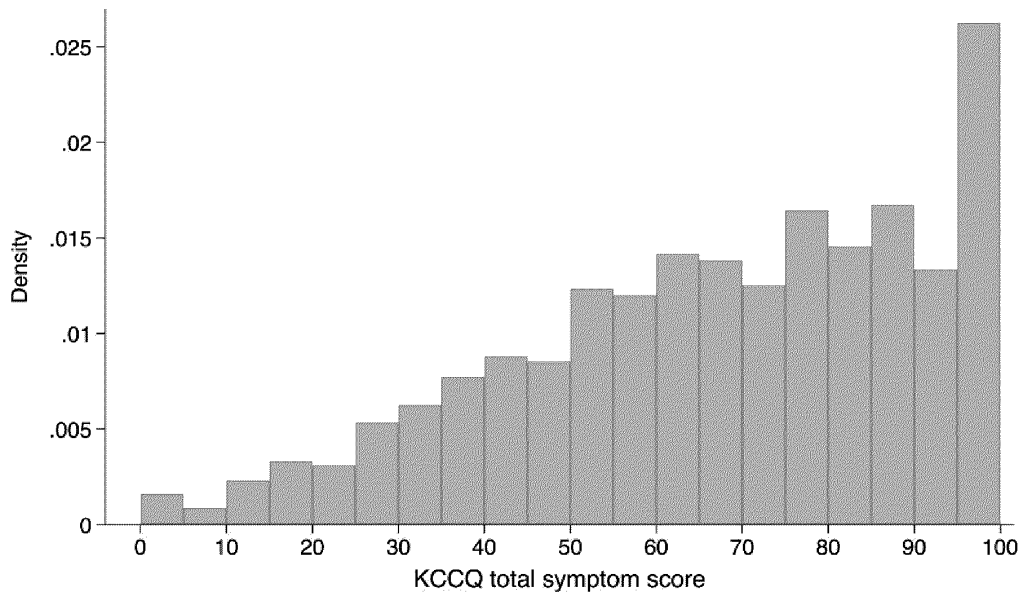


Fig. 49

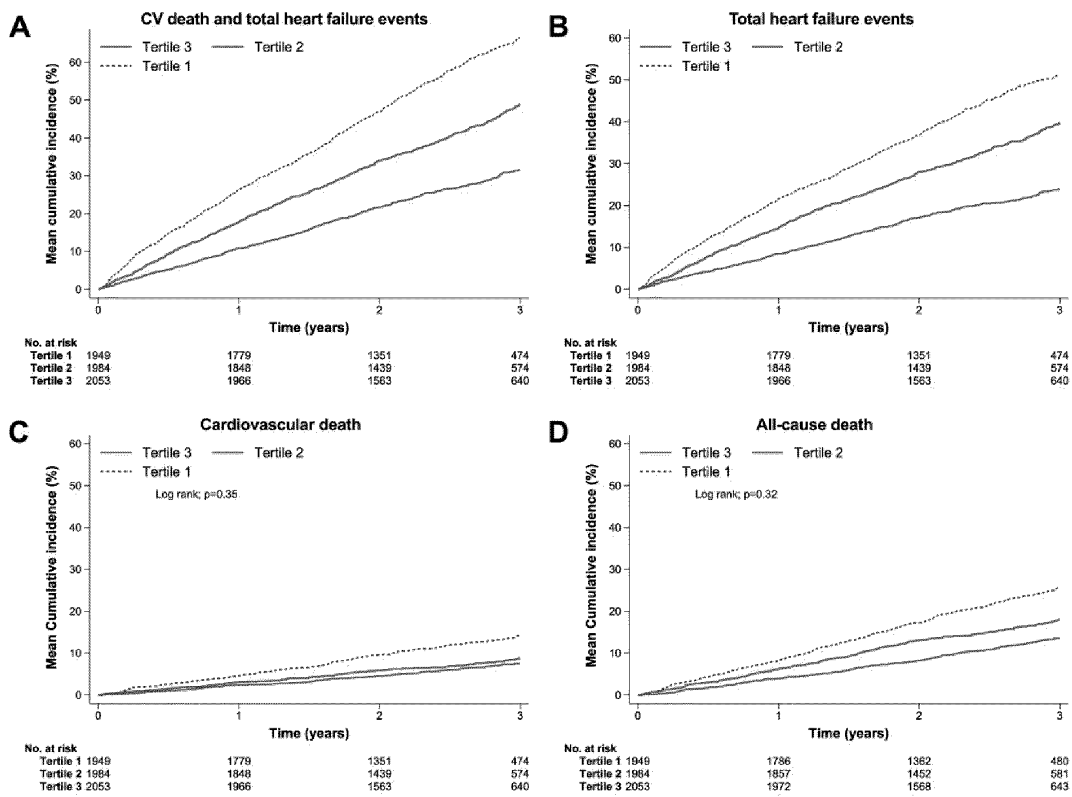


Fig. 50

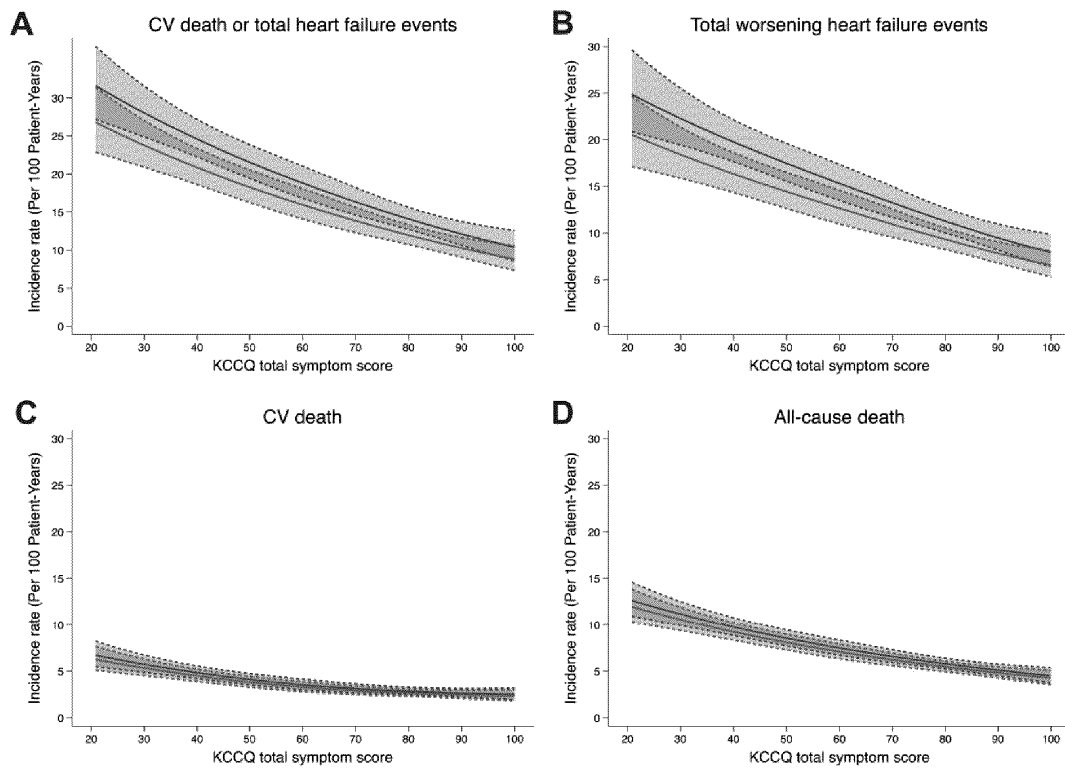


Fig. 51

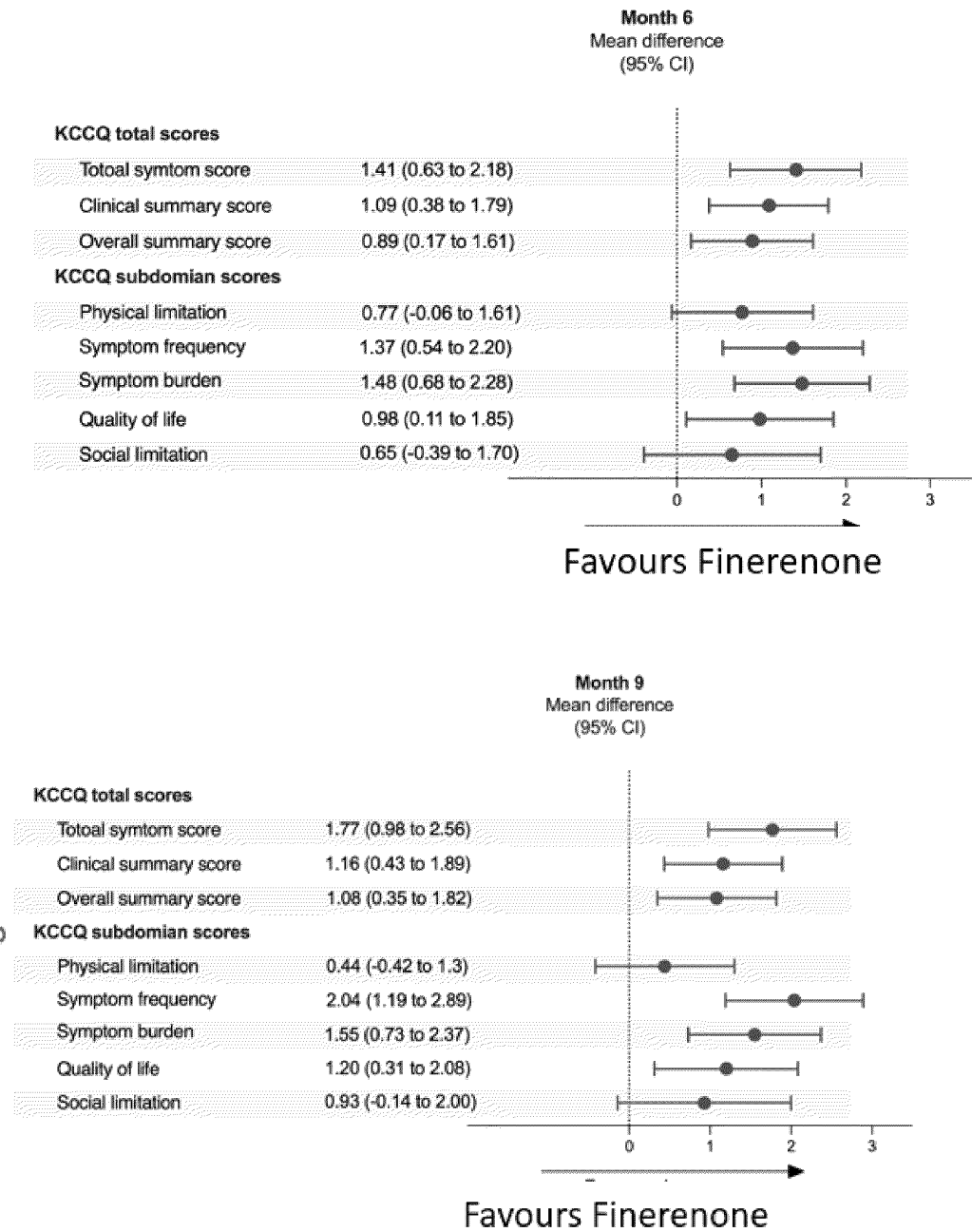


Fig. 51 (cont.)

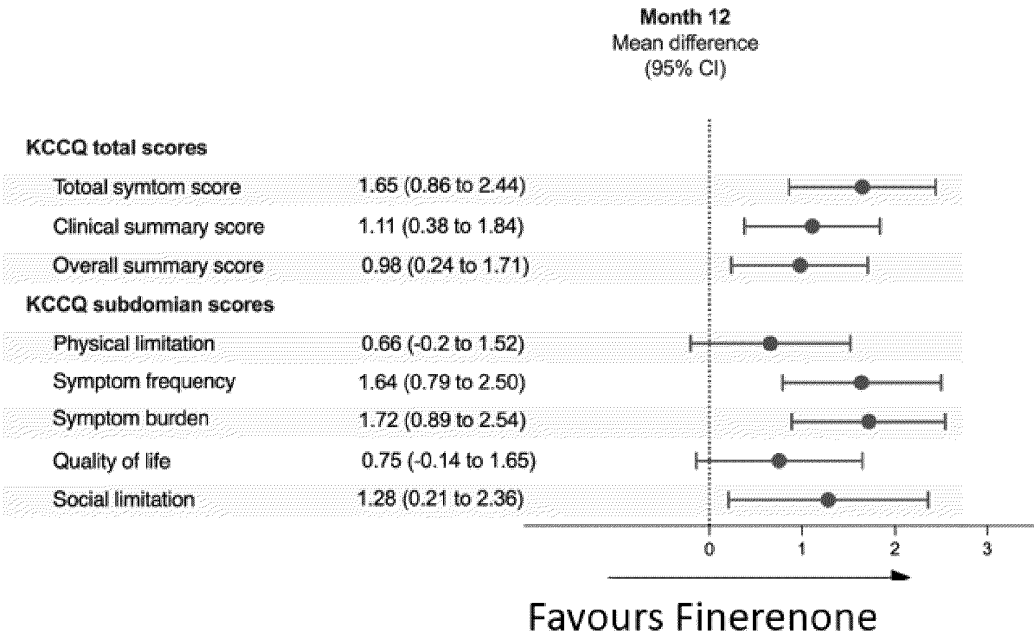


Fig. 52

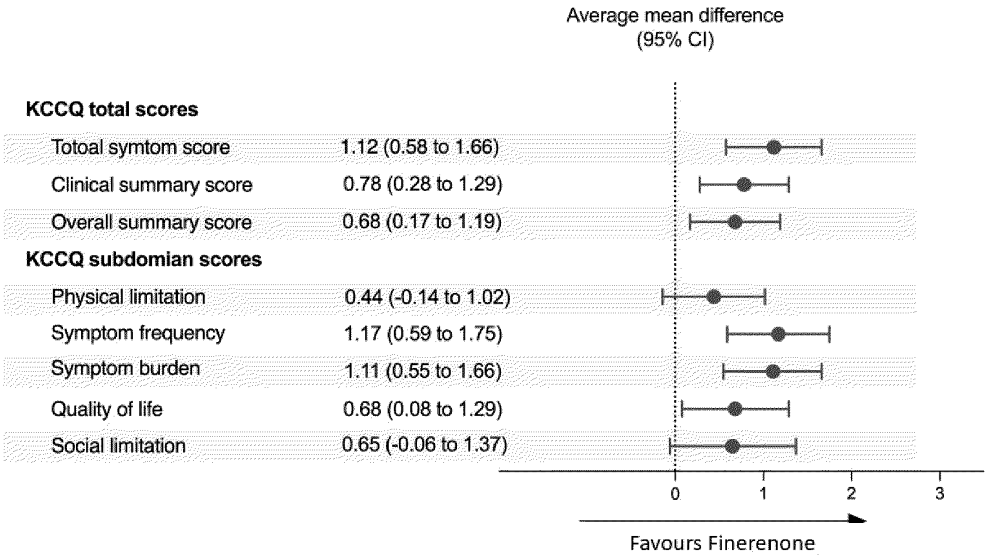


Fig. 53

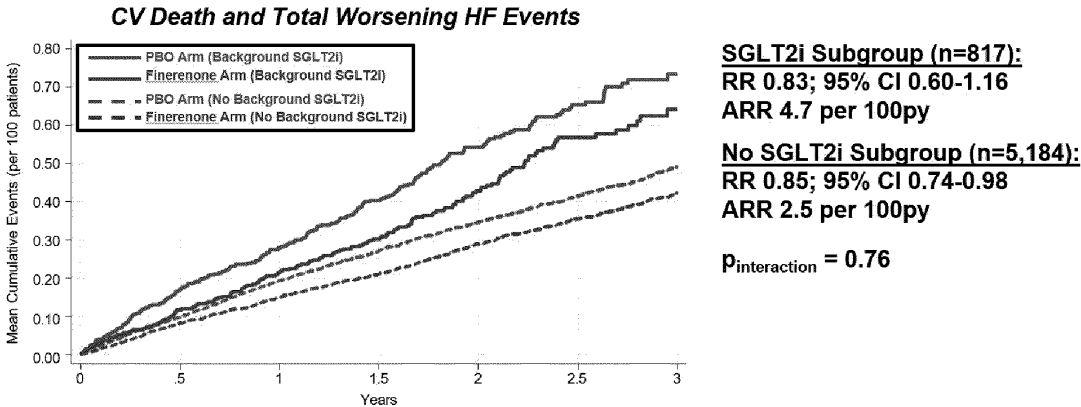


Fig. 54

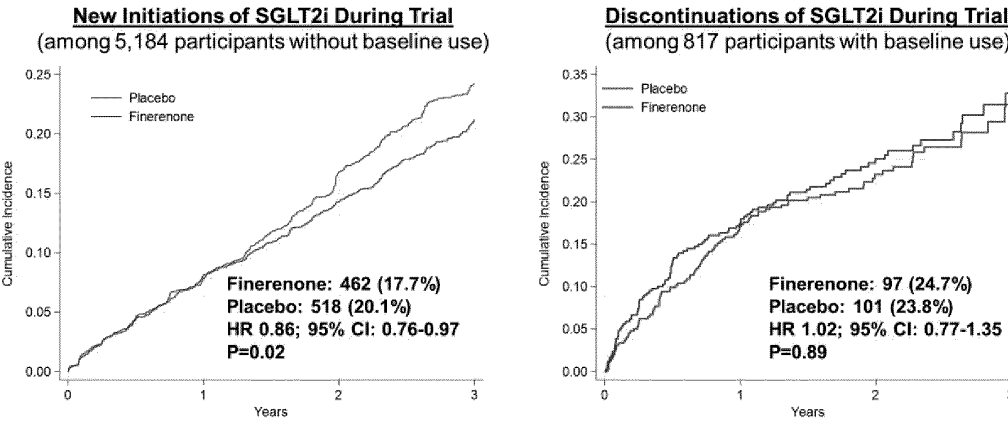


Fig. 55
CYP3A4 inhibitor updates

OPTUM EHR (US database)*	HF patients with >=40% LVEF		HF patients with >=40% LVEF with CKD and T2D	
	N	%	N	%
	644968	100	142117	100
With any strong CYP3A4 inhibitor	13530	2,10	3173	2,23
Itraconazole	1629	0,25	378	0,27
Ketoconazole	1374	0,21	408	0,29
Ritonavir	7316	1,13	1624	1,14
Nelfinavir	40	0,01	8	0,01
Cobicistat	724	0,11	162	0,11
Clarithromycin	2718	0,42	657	0,46
Telithromycin	45	0,01	13	0,01
Nefazodone	217	0,03	45	0,03

*OPTUM EHR (US database consists of de-identified patient-related information and data on more than 100 million patients provided by over 80 partners across all 50 states, covering more than 700 hospitals and 7,000 clinics.

Fig. 56

Subgroup analysis of FINEARTS-HF and FIDELITY (pooled data from FIDELIO-DKD and FIGARO-DKD): Strong CYP3A4 inhibitors were exclusion criteria in all 3 Phase III studies, however ~ 0.4-0.7 % of participants used strong CYP3A4 inhibitors at baseline. Moderate, weak and unclassified CYP3A4 inhibitor use was more prominent.

Drug Grouping WHO-DD Version 2024MAR	FINEARTS-HF		FIDELITY		FINEARTS-HF & FIDELITY		
	Finerenone N=2993 (100%)	Placebo N=2993 (100%)	Finerenone N=6489 (100%)	Placebo N=6474 (100%)	Finerenone N=9482 (100%)	Placebo N=9467 (100%)	Total N=18949 (100%)
CYP3A4 inhibitors	1839 (61.4%)	1837 (61.4%)	4127 (63.6%)	4133 (63.8%)	5966 (62.9%)	5970 (63.1%)	11936 (63.0%)
Strong CYP3A4 inhibitors	22 (0.7%)	23 (0.8%)	38 (0.6%)	28 (0.4%)	60 (0.6%)	51 (0.5%)	111 (0.6%)
Moderate CYP3A4 inhibitors	71 (2.4%)	65 (2.2%)	171 (2.6%)	174 (2.7%)	242 (2.6%)	239 (2.5%)	481 (2.5%)
Weak CYP3A4 inhibitors	1773 (59.2%)	1774 (59.3%)	4003 (61.7%)	4016 (62.0%)	5776 (60.9%)	5790 (61.2%)	11566 (61.0%)
Unclassified CYP3A4 inhibitors	48 (1.6%)	45 (1.5%)	88 (1.4%)	96 (1.5%)	136 (1.4%)	141 (1.5%)	277 (1.5%)

Fig. 57

Hyperkalemia and use of CYP3A4 inhibitors at baseline in FINEARTS-HF and FIDELITY

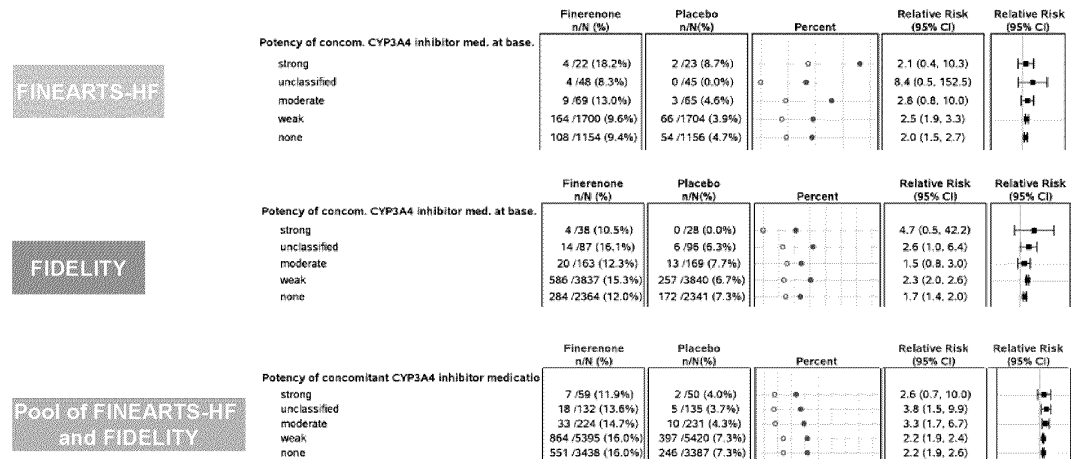


Fig. 58

Hyperkalemia by extent of co-medication use of CYP3A4 inhibitors

	FINEARTS-HF				FIDELITY				FINEARTS-HF & FIDELITY			
	Finerenone		Placebo		Finerenone		Placebo		Finerenone		Placebo	
Extent of co-medication use	n	No. of participants with event (%)	n	No. of participants with event (%)	n	No. of participants with event (%)	n	No. of participants with event (%)	n	No. of participants with event (%)	n	No. of participants with event (%)
Overall	2993	289 (9.7%)	2993	125 (4.2%)	6489	908 (14.0%)	6474	448 (6.9%)	9482	1197 (12.6%)	9467	573 (6.1%)
CYP3A4 inhibitors												
No use	815	89 (10.8%)	782	34 (4.3%)	1583	218 (13.8%)	1408	106 (7.5%)	2398	306 (12.8%)	2190	140 (6.4%)
Limited use (<50%)	322	17 (5.3%)	336	17 (5.1%)	662	65 (9.5%)	760	48 (6.3%)	1004	82 (8.2%)	1096	65 (5.9%)
Longer use (>=50%)	1856	184 (9.9%)	1875	74 (3.9%)	4224	625 (14.8%)	4306	294 (6.8%)	6080	809 (13.3%)	6181	368 (6.0%)
Strong CYP3A4 inhibitors												
Limited use (<50%)	86	6 (7.0%)	88	3 (3.4%)	221	20 (9.0%)	232	14 (6.0%)	307	26 (8.5%)	320	17 (5.3%)
Longer use (>=50%)	27	5 (18.5%)	30	2 (6.7%)	45	5 (11.1%)	38	2 (5.3%)	72	10 (13.9%)	68	4 (5.9%)
Moderate CYP3A4 inhibitors												
Limited use (<50%)	169	13 (7.7%)	184	5 (2.7%)	654	54 (8.3%)	678	35 (5.2%)	823	67 (8.1%)	862	40 (4.6%)
Longer use (>=50%)	73	7 (9.6%)	92	3 (4.8%)	156	23 (14.7%)	186	13 (7.9%)	229	30 (13.1%)	228	16 (7.0%)
Weak CYP3A4 inhibitors												
Limited use (<50%)	238	14 (5.9%)	237	15 (6.3%)	490	54 (11.0%)	573	37 (6.5%)	728	68 (9.3%)	810	52 (6.4%)
Longer use (>=50%)	1787	178 (10.0%)	1896	71 (3.9%)	4099	613 (15.0%)	4199	288 (6.9%)	5886	791 (13.4%)	6005	359 (6.0%)
Unclassified CYP3A4 inhibitors												
Limited use (<50%)	207	5 (2.4%)	272	3 (1.1%)	316	34 (10.8%)	389	29 (7.5%)	523	39 (7.5%)	661	32 (4.8%)
Longer use (>=50%)	54	4 (7.4%)	80	0 (0.0%)	96	14 (14.6%)	103	7 (6.8%)	150	18 (12.0%)	163	7 (4.3%)

Fig. 59

Potassium >5.5 mmol/l and use of CYP3A4 inhibitors at baseline in FINEARTS-HF and FIDELITY

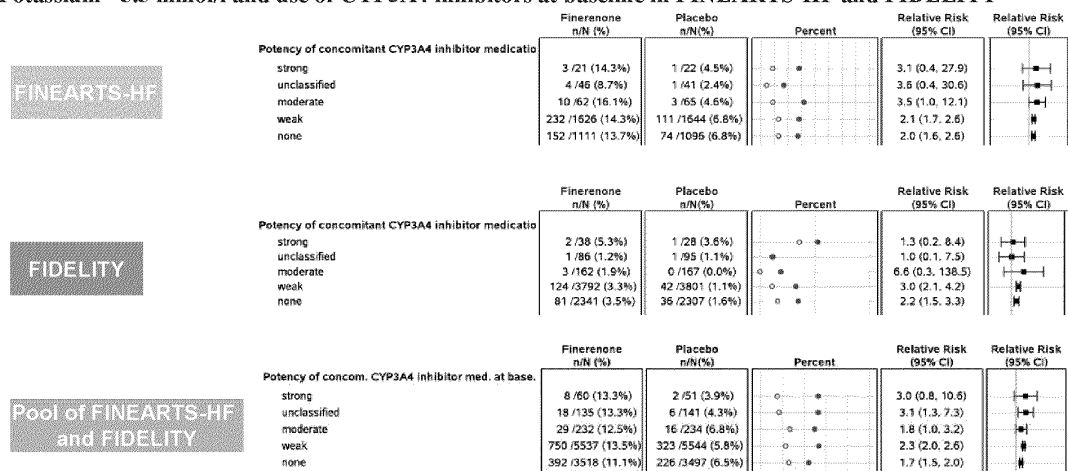


Fig. 60
MIDD “subgroup” analysis
Serum potassium levels

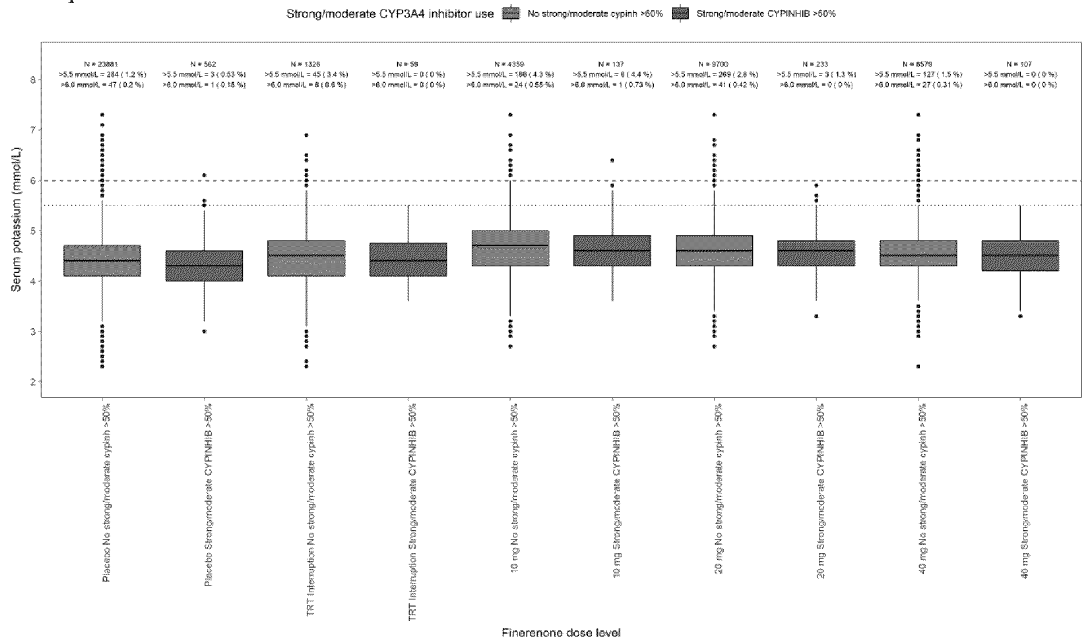


Fig. 61
MIDD cardiac safety assessment

Concentration-QTc analysis of TQT study data (upper panel) and estimated FINEARTS-HF maximal concentrations

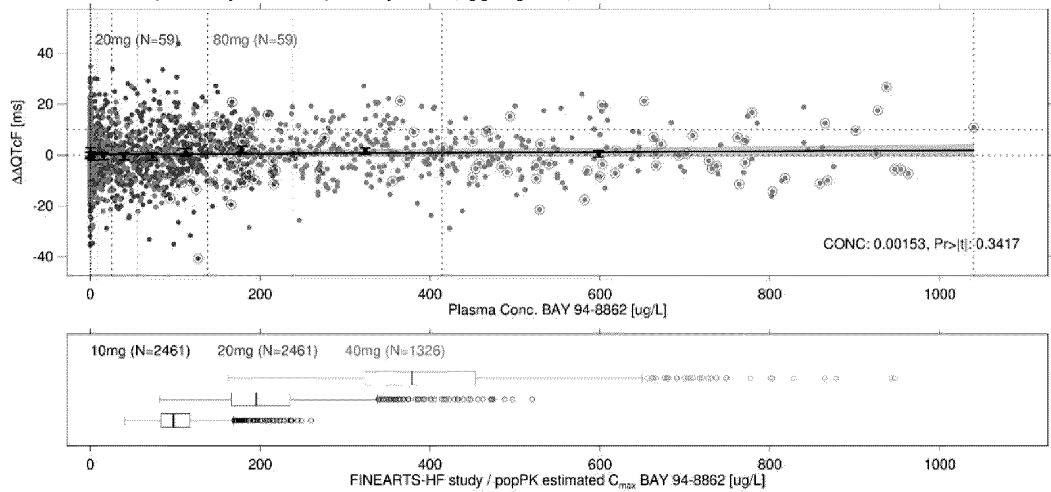


Fig. 62a

Finerenone plasma concentration-time profiles of PBPK population simulations of 20 mg finerenone concomitant with 200 mg BID itraconazole (red) and 40 mg finerenone concomitant with 500 mg TID erythromycin (blue); time corresponds to time after the finerenone dose.

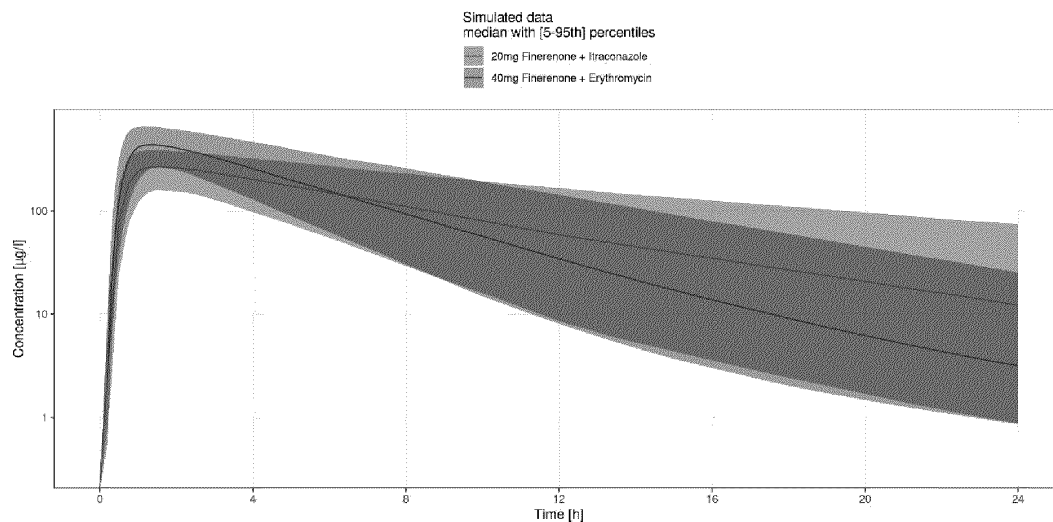


Fig. 62 b

Finerenone plasma concentration-time profiles of PBPK population simulations of 10 mg finerenone concomitant with 200 mg BID itraconazole (red) and 20 mg finerenone concomitant with 500 mg TID erythromycin (blue); time corresponds to time after the finerenone dose.

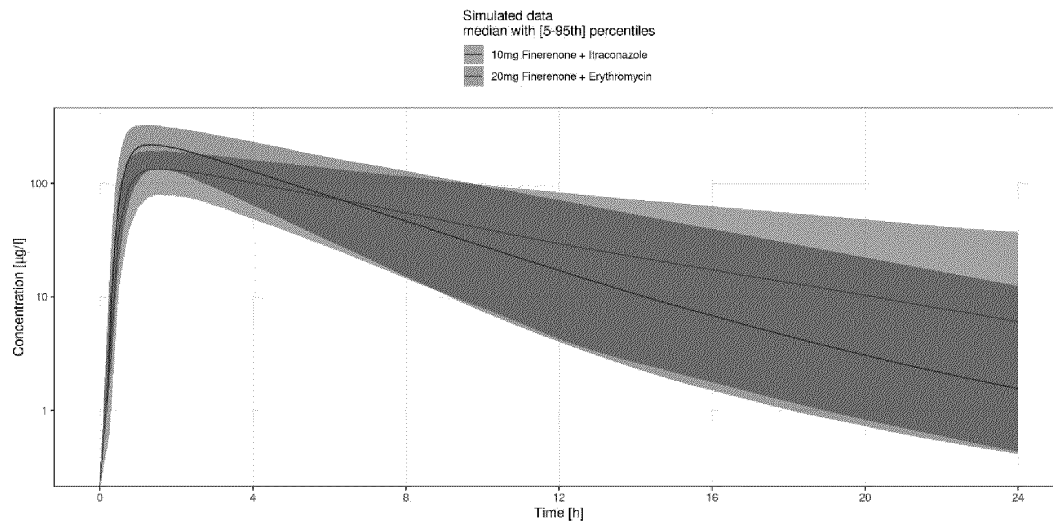


Fig. 62c

Finerenone plasma concentration-time profiles of PBPK population simulations of 10 mg finerenone concomitant with 200 mg BID itraconazole (red) and 40 mg finerenone concomitant with 500 mg TID erythromycin (blue); time corresponds to time after the finerenone dose.

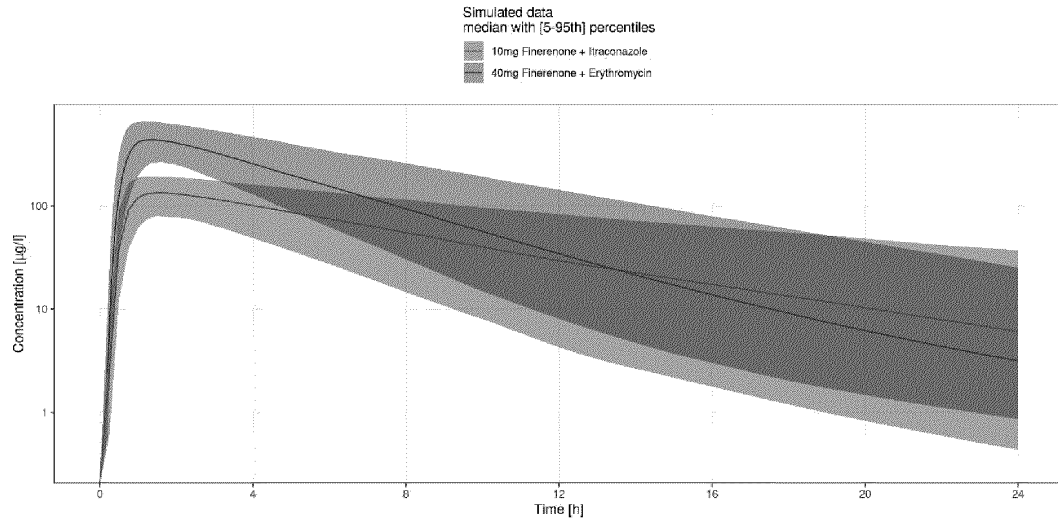


Fig. 63 a

Forest plot of PBPK population simulated AUC values of finerenone in doses of 10, 20 and 40 mg under concomitant administration of strong (itraconazole and clarithromycin), moderate (erythromycin and verapamil), moderate to weak (fluvoxamine, classified as weak CYP3A4 inhibitor until 2019, afterwards as moderate) and weak (cimetidine) CYP3A4 inhibitors, dots represent the median and the whiskers represent the 5th to 95th percentiles.

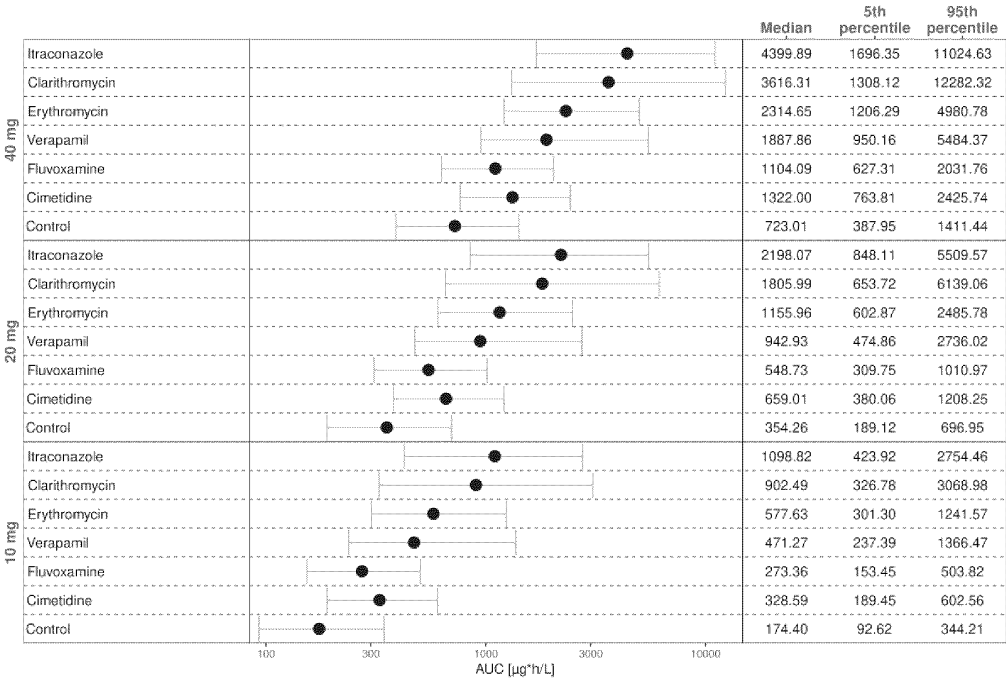


Fig. 63b

Forest plot of PBPK population simulated $C_{\max}$ values of finerenone in doses of 10, 20 and 40 mg under concomitant administration of strong (itraconazole and clarithromycin), moderate (erythromycin and verapamil), moderate to weak (fluvoxamine, classified as weak CYP3A4 inhibitor until 2019, afterwards as moderate) and weak (cimetidine) CYP3A4 inhibitors, dots represent the median and the whiskers represent the 5th to 95th percentiles.

