Efficacy and safety of finerenone across the ejection fraction spectrum in HFmrEF/HFpEF: The FINEARTS-HF Trial

John McMurray
BHF Cardiovascular Research Centre, University of Glasgow & Queen Elizabeth University Hospital, Glasgow, Scotland, UK on behalf of the FINEARTS-HF committees and investigators

FINEARTS-HF LVEF analysis: Background

- In FINEARTS-HF, the nonsteroidal MRA finerenone reduced the risk of the primary composite endpoint (cardiovascular death and total worsening heart failure events) in patients with HFmrEF/HFpEF (rate ratio 0.84, 95%CI 0.74-0.95; p = 0.007)
- However, the efficacy of neurohumoral modulating therapies may differ across the range of LVEF, with possible attenuation of benefit in patients with a LVEF >55-60%.
- Therefore, we prespecified analyses of the effect of finerenone according to LVEF in FINEARTS-HF.

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Solomon SD, McMurray JJV, Vaduganathan M, et al N Engl J Med. 2024 Sep 1. doi: 10.1056/NEJMoa2407107. Online ahead of print.

FINEARTS-HF LVEF analysis: Methods

- An analysis using investigator reported LVEF which was available in 5993 of 6001 (>99%) of patients at baseline.
- LVEF was analyzed in categories (<50%, ≥50 to <60%, and ≥60%) and as a continuous variable (modeled as a spline with 3 knots placed at the 10th, 50th, and 90th quantiles).
- The effect of finerenone compared to placebo was calculated as a rate ratio (RR) and 95% CI derived from semiparametric proportional-rates models for total (first and recurrent) events or as a hazard ratio (HR) and 95% CI from Cox proportional hazards models for time-to-first events.

FINEARTS-HF: Results

- **LVEF distribution at baseline**
- **Baseline characteristics by LVEF**
- **Baseline treatment by LVEF**
- **Effect of finerenone across LVEF (categorical variable)**
- **Effect of finerenone across LVEF (continuous variable)**
- **Treatment tolerability**

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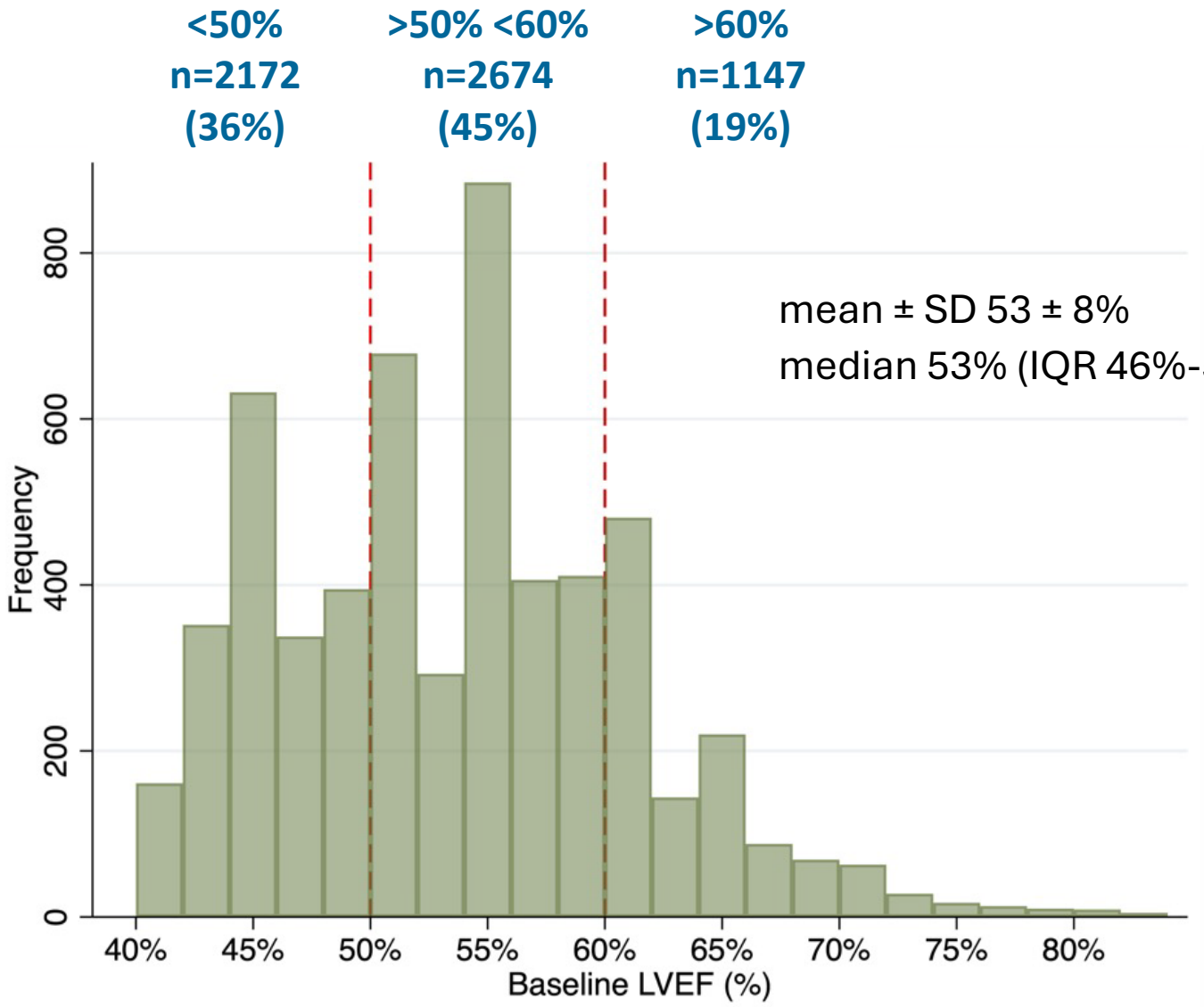
FINEARTS-HF LVEF analysis: Results

Distribution of LVEF at baseline



mean ± SD 53 ± 8%

median 53% (IQR 46%-58%; range 34%-84%)

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FINEARTS-HF: Baseline characteristics by LVEF

Characteristic		LVEF <50% (n=2172)	LVEF ≥50% to <60% (n=2674)	LVEF ≥60% (n=1147)	P value for trend
Age, years		70±10	73±9	**73.5±9**	<0.001
Women (%)		31	51	**59**	<0.001
Race (%)	White/Asian	76/20	82/13	77/18	0.13
	Black/other	1.1/2.7	1.3/3.5	2.5/2.6	
History (%)	Type 2 diabetes	40	41	41	0.41
	Hypertension	86	90	**91**	<0.001
	Myocardial infarction	**37**	21	14	<0.001
	HF hospitalization	**67**	59	51	<0.001
	LVEF <40%	**9.0**	2.5	0.8	<0.001
Atrial fibrillation on baseline ECG (%)		35.5	41	37	0.12
Body mass index, kg/m^2		29±6	30±6	30±6	<0.001
Systolic blood pressure, mmHg		127.5±15	130±15.5	**131±15**	<0.001
eGFR, mL/min/1.73 m^2		65±20	61±19	**60±19**	<0.001
LVEF, %		44±3	54±3	64±5	<0.001
NT-proBNP, pg/mL		1139 (506-2205)	1008 (426-1880)	**941 (406-1776)**	<0.001
KCCQ - Total Symptom Score		69±24	66±24	**65.5±24**	<0.001
NYHA class (%) II vs. III/IV		69/31	68/32	71/29	0.33

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FINEARTS-HF: Medication at baseline by LVEF

Treatment	LVEF <50% (n=2172)	LVEF ≥50% to <60% (n=2674)	LVEF ≥60% (n=1147)	P value for trend
β-blocker	88	84	**81**	<0.001
ACEi	40	33	**34**	<0.001
ARB	28	38	**40.5**	<0.001
ARNI	**15.7**	5.4	2.4	<0.001
SGLT2i	**15.5**	14	10	<0.001
Loop diuretic	91	87	82	<0.001
Mean furosemide equivalent dose, mg	52±59.5	54±66	50±46	0.46
Thiazide diuretic	10	15	**19**	<0.001
CCB	24	35	**44**	<0.001

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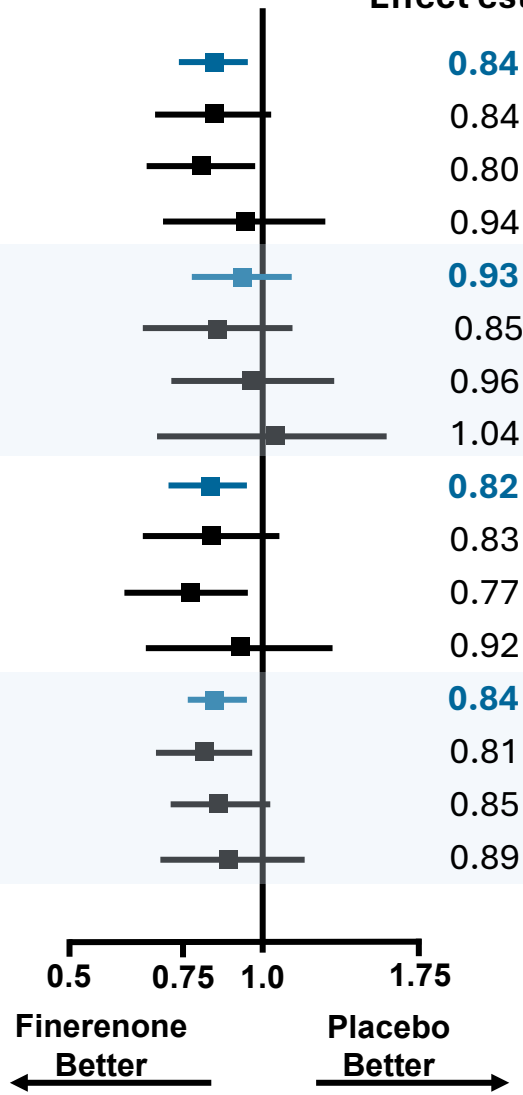
FINEARTS-HF: Treatment effects by LVEF category

	Event rate per 100 PY		Effect estimate (95% CI)*	Interaction p value
	Finerenone	Placebo		
Cardiovascular death and total worsening HF events	**14.9**	**17.7**	**0.84 (0.74, 0.95)**	**0.70**
<50%	15.7	19.2	0.84 (0.68, 1.03)	
≥50% to <60%	14.8	17.9	0.80 (0.66, 0.97)	
≥60%	13.8	14.8	0.94 (0.70, 1.25)	
Cardiovascular death	**3.3**	**3.6**	**0.93 (0.78, 1.11)**	**0.70**
<50%	3.9	4.6	0.85 (0.65,1.11)	
≥50% to <60%	3.0	3.0	0.96 (0.72, 1.28)	
≥60%	3.1	3.0	1.04 (0.69, 1.57)	
Total worsening HF events	**11.6**	**14.1**	**0.82 (0.71, 0.94)**	**0.67**
<50%	11.8	14.6	0.83 (0.65. 1.06)	
≥50% to <60%	11.8	14.9	0.77 (0.61. 0.95)	
≥60%	10.8	11.8	0.92 (0.66, 1.27)	
Cardiovascular death or first worsening HF event	**9.3**	**11.0**	**0.84 (0.76, 0.94)**	**0.81**
<50%	10.0	12.7	0.81 (0.68, 0.96)	
≥50% to <60%	9.3	10.6	0.85 (0.72, 1.01)	
≥60%	8.1	9.1	0.89 (0.69, 1.15)	



*The effect estimate for total (i.e. first and recurrent) event outcomes is a rate ratio and for time-to-first event outcomes is a hazard ratio.
The interaction p value is from a test for interaction between the treatment effect of finerenone versus placebo and LVEF analyzed as a categorical variable (<50%, ≥50% to <60%, and ≥60%).

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FINEARTS-HF: Treatment effect by LVEF

	LVEF <50% (n=2172)		LVEF ≥50% to <60% (n=2674)		LVEF ≥60% (n=1147)		
	Finerenone (n=1093)	Placebo (n=1079)	Finerenone (n=1329)	Placebo (n=1345)	Finerenone (n=575)	Placebo (n=572)	P value for interaction
Cardiovascular death and total number of worsening HF events							
Number of events	414	496	463	565	206	222	
Rate (95% CI)	15.7 (13.4, 18.4)	19.2 (16.8, 21.9)	14.8 (12.8, 17.1)	17.9 (15.6, 20.6)	13.8 (11.1, 17.2)	14.8 (12.1, 18.0)	
RR (95% CI)*	0.84 (0.68, 1.03)		0.80 (0.66, 0.97)		0.94 (0.70, 1.25)		0.70
Adjusted RR (95% CI)†	**0.83 (0.68, 1.02)**		**0.76 (0.62, 0.92)**		**0.82 (0.61, 1.10)**		0.75
Total number of worsening HF events							
Number of events	311	377	370	470	161	177	
Rate (95% CI)	11.8 (9.7, 14.2)	14.6 (12.5, 17.0)	11.8 (10.1, 13.8)	14.9 (12.7, 17.5)	10.8 (8.4, 13.8)	11.8 (9.4, 14.7)	
RR (95% CI)*	0.83 (0.65, 1.06)		0.77 (0.61, 0.95)		0.92 (0.66, 1.27)		0.67
Adjusted RR (95% CI)†	**0.83 (0.65, 1.05)**		**0.73 (0.59, 0.91)**		**0.79 (0.57, 1.09)**		0.65
Cardiovascular death or first worsening HF event							
No (%)	243 (22.2%)	291 (27%)	269 (20.2%)	303 (22.5%)	112 (19.5%)	125 (21.9%)	
Rate (95% CI)	10.0 (8.8, 11.4)	12.7 (11.3, 14.3)	9.3 (8.3, 10.5)	10.6 (9.4, 11.9)	8.1 (6.7, 9.8)	9.1 (7.6, 10.9)	
HR (95% CI)‡	0.81 (0.68, 0.96)		0.85 (0.72, 1.01)		0.89 (0.69, 1.15)		0.81
Adjusted HR (95% CI)†	**0.80 (0.67, 0.95)**		**0.80 (0.68, 0.95)**		**0.75 (0.58, 0.98)**		0.95

† Adjusted for the following baseline variables: randomized treatment (finerenone or placebo), age, sex, eGFR, NYHA functional class, heart rate, systolic blood pressure, BMI, (log)NT-proBNP, and a history of type 2 diabetes, prior heart failure hospitalization, atrial fibrillation, and myocardial infarction. All models were stratified by geographic region.

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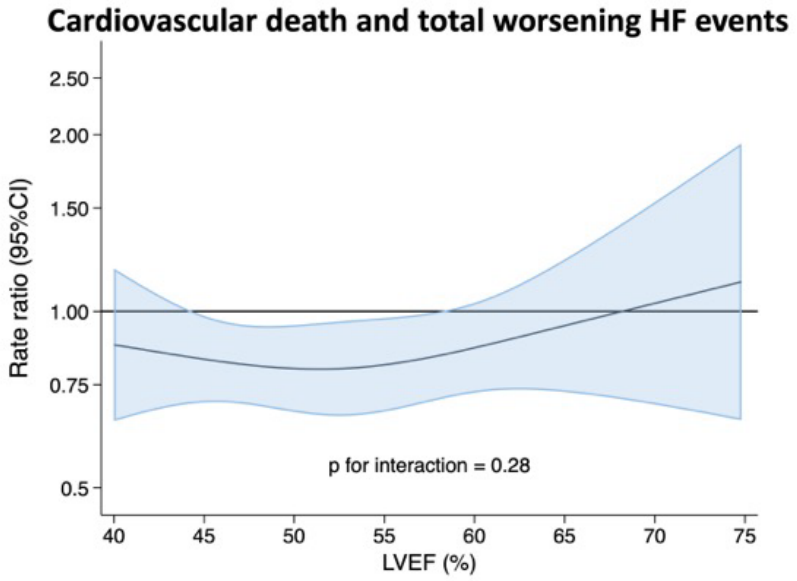

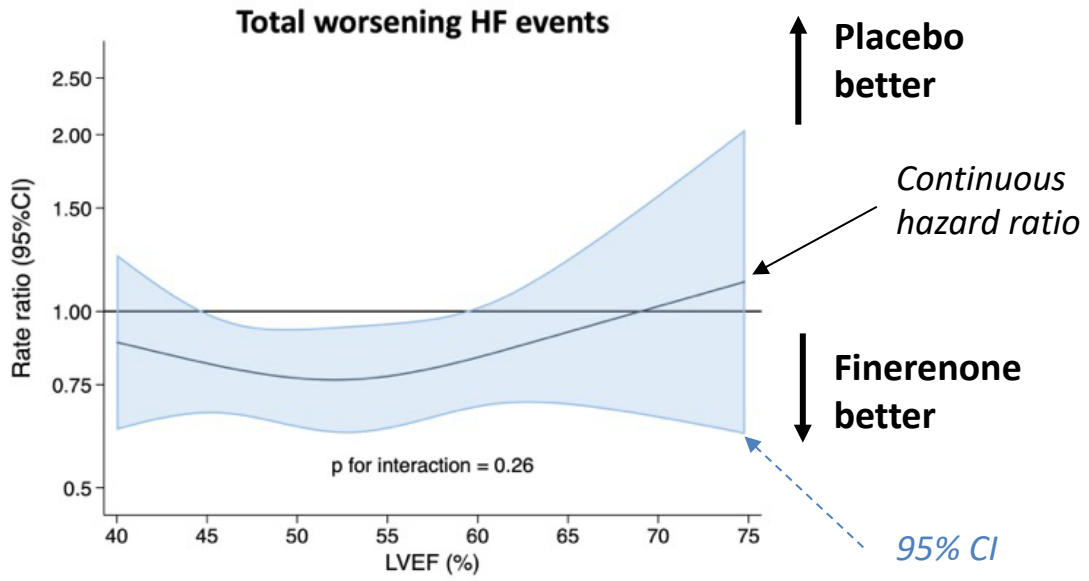

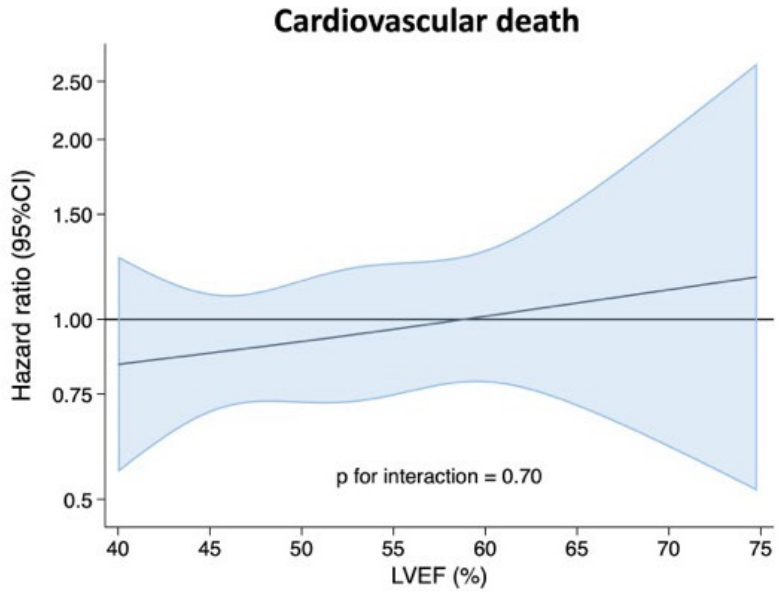

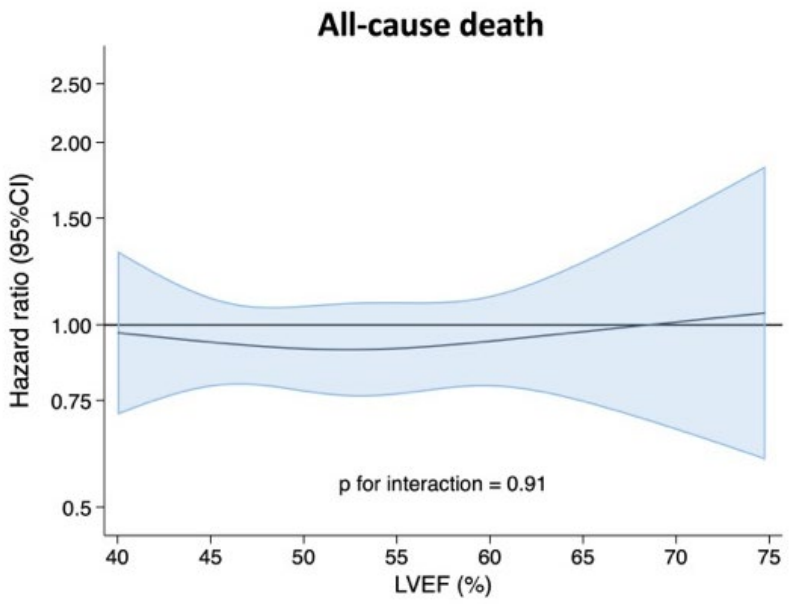

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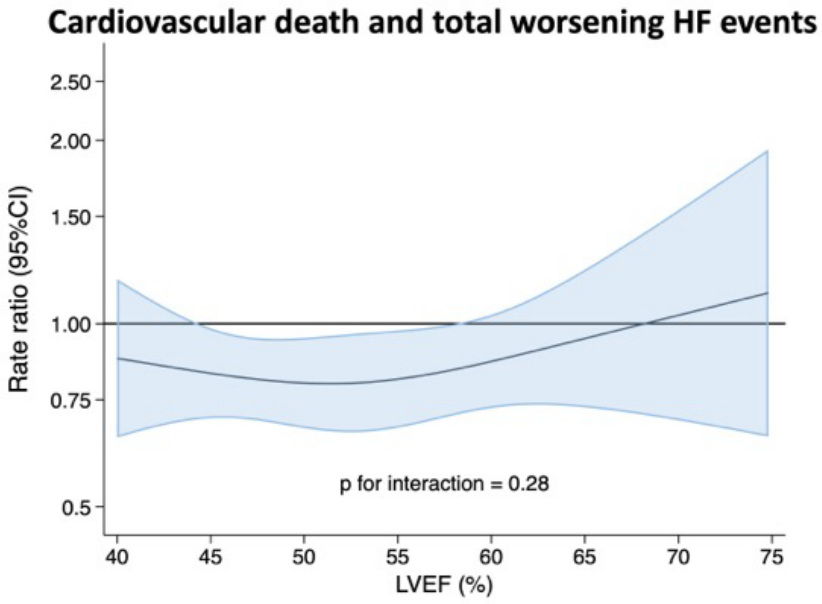

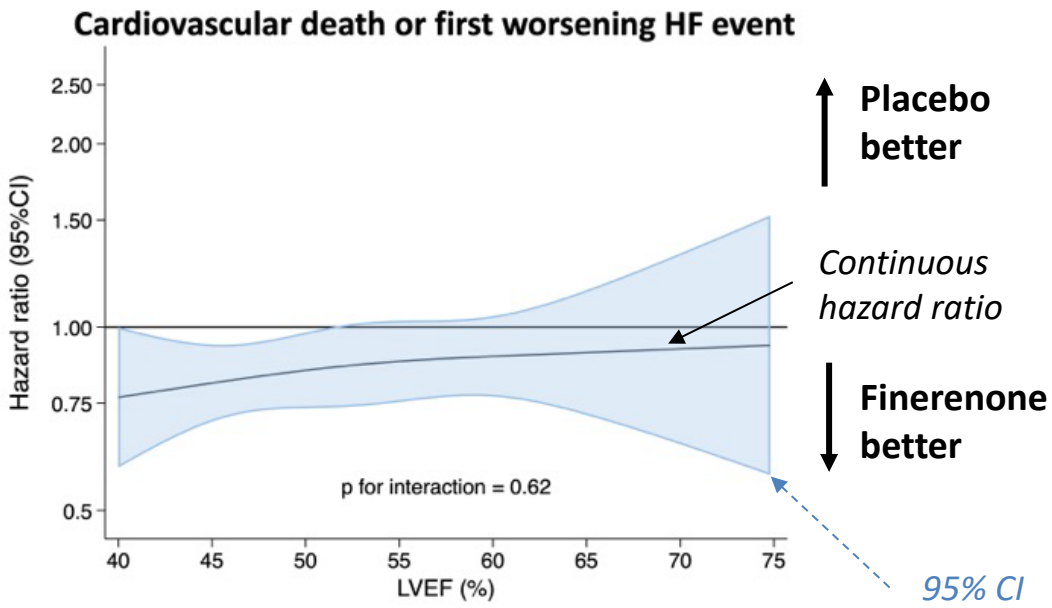

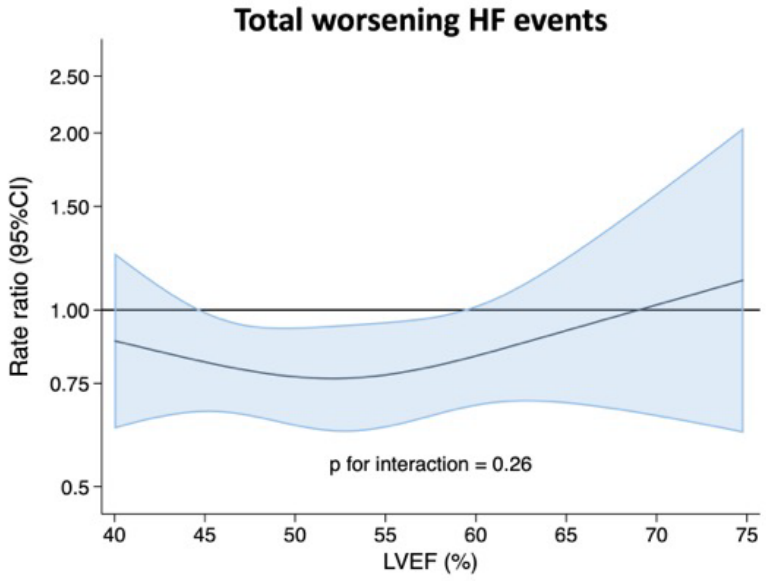

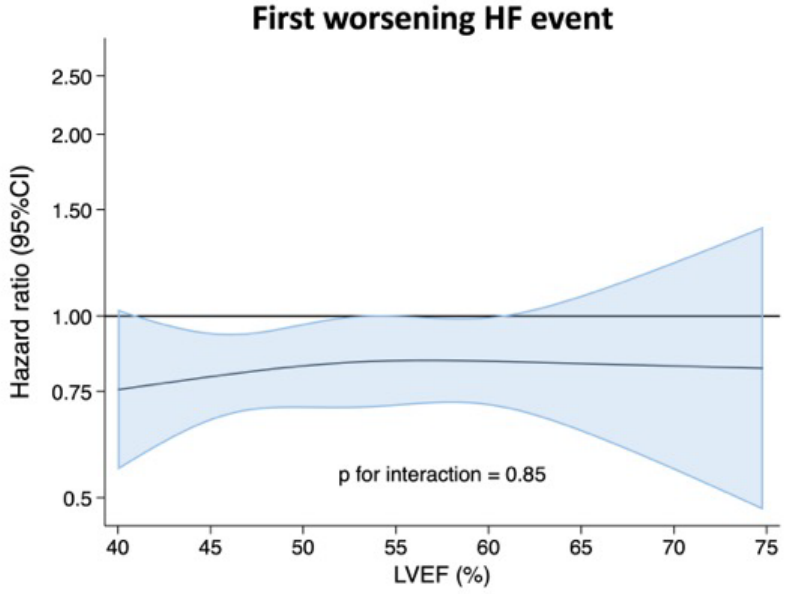

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FINEARTS-HF: Prespecified tolerability

	LVEF <50% (n=2170)		LVEF ≥50% to<60% (n=2665)		LVEF ≥60% (n=1143)		P value for interaction
	Finerenone (n=1092)	Placebo (n=1078)	Finerenone (n=1323)	Placebo (n=1342)	Finerenone (n=572)	Placebo (n=571)	
Creatinine ≥2.5 mg/dL							
No (%)	48/1059 (4.5)	28/1035 (2.7)	69/1275 (5.4)	46/1300 (3.5)	24/558 (4.3)	15/551 (2.7)	
OR (95% CI)	**1.75 (1.09, 2.81)**		**1.54 (1.05, 2.25)**		**1.62 (0.84, 3.14)**		0.92
Creatinine ≥3.0 mg/dL							
No (%)	21/1059 (2.0)	15/1035 (1.4)	27/1275 (2.1)	15/1300 (1.2)	9/558 (1.6)	4/551 (0.7)	
OR (95% CI)	**1.41 (0.72, 2.76)**		**1.84 (0.97, 3.48)**		**2.23 (0.68, 7.32)**		0.75
Potassium >5.5 mmol/L							
No (%)	161/1060 (15.2)	77 /1038 (7.4)	182/1275 (14.3)	87/1298 (6.7)	70/558 (12.5)	35/551 (6.4)	
OR (95% CI)	**2.22 (1.66, 2.96)**		**2.37 (1.81, 3.11)**		**2.16 (1.41, 3.32)**		0.88
Potassium >6.0 mmol/L							
No (%)	40/1060 (3.8)	25/1038 (2.4)	32/1275 (2.5)	13/1298 (1.0)	14/558 (2.5)	3/551 (0.5)	
OR (95% CI)	**1.53 (0.92, 2.55)**		**2.62 (1.37, 5.03)**		**4.85 (1.38, 17.05)**		0.15
Potassium <3.5 mmol/L							
No (%)	33/1060 (3.1)	95/1038 (9.2)	69/1275 (5.4)	122/1298 (9.4)	25/558 (4.5)	63/551 (11.4)	
OR (95% CI)	**0.32 (0.21, 0.48)**		**0.54 (0.40, 0.73)**		**0.36 (0.22, 0.58)**		0.09
Systolic blood pressure <100mmHg							
No (%)	213/1064 (20.0)	137/1042 (13.1)	228/1282 (17.8)	166/1305 (12.7)	96/560 (17.1)	58/555 (10.5)	
OR (95% CI)	**1.83 (1.43, 2.35)**		**1.50 (1.20, 1.89)**		**1.89 (1.31, 2.73)**		0.44

FINEARTS-HF LVEF analysis: Conclusions

- Among patients with HFmrEF/HFpEF, finerenone reduced the risk of the primary composite outcome of cardiovascular death and total heart failure events and there was no evidence of a LVEF by treatment interaction (whether LVEF was analyzed as a categorical or continuous variable).
- However, we had limited power to examine this interaction at the higher end of the LVEF range, with only 41 primary endpoints among 23 of 108 patients with a LVEF >70%. Ongoing trials with finerenone in similar patient populations should provide more data to help clarify any remaining uncertainty (REDEFINE-HF and CONFIRMATION-HF ClinicalTrials.gov identifiers NCT06024746 and NCT06008197).

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