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Efficacy and Safety of Finerenone Across the Ejection Fraction Spectrum in Heart Failure With Mildly Reduced or Preserved Ejection Fraction: A Prespecified Analysis of the FINEARTS-HF Trial

Kieran F. Docherty, PhD; Alasdair D. Henderson, PhD; Pardeep S. Jhund, MBChB, MSc, PhD; Brian L. Claggett, PhD; Akshay S. Desai, MD, MPH; Katharina Mueller, MSc; Prabhakar Viswanathan, MBBS, PhD; Andrea Scalise, MD; Carolyn S.P. Lam, MD, PhD; Michele Senni, MD; Sanjiv J. Shah, MD; Adriaan A. Voors, MD; Faiez Zannad, MD; Bertram Pitt, MD; Muthiah Vaduganathan, MD, MPH; Scott D. Solomon, MD; John J.V. McMurray, MD

BACKGROUND: The effects of treatments for heart failure (HF) may vary among patients according to left ventricular ejection fraction (LVEF). In FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure), the nonsteroidal mineralocorticoid receptor antagonist finerenone reduced the risk of cardiovascular death and total worsening HF events in patients with HF with mildly reduced or preserved ejection fraction. We examined the effect of finerenone according to LVEF in FINEARTS-HF.

METHODS: FINEARTS-HF was a randomized, placebo-controlled trial examining the efficacy and safety of finerenone in patients with HF and LVEF ≥40%. The treatment effect of finerenone was examined in prespecified analyses according to LVEF categories (<50%, ≥50% to <60%, and ≥60%) and with LVEF as a continuous variable. The primary outcome was a composite of total (first and recurrent) worsening HF events and cardiovascular death.

RESULTS: Baseline LVEF data were available for 5993 of the 6001 participants in FINEARTS-HF. Mean and median LVEF were 53±8% and 53% (interquartile range, 46%–58%), respectively. LVEF was <50% in 2172 (36%), between 50% and <60% in 2674 (45%), and ≥60% in 1147 (19%). Patients with higher LVEF were older, were more commonly female, were less likely to have a history of coronary artery disease, and more frequently had a history of hypertension and chronic kidney disease compared with those with a lower LVEF. Finerenone reduced the risk of cardiovascular death and total HF events consistently across LVEF categories (LVEF <50% rate ratio, 0.84 [95% CI, 0.68–1.03]; LVEF ≥50% to <60% rate ratio, 0.80 [0.66–0.97]; and LVEF ≥60% rate ratio, 0.94 [0.70–1.25]; $P_{interaction}$=0.70). There was no modification of the benefit of finerenone across the range of LVEF when analyzed as a continuous variable ($P_{interaction}$=0.28). There was a similar consistent effect of finerenone on reducing the total number of worsening HF events (continuous $P_{interaction}$=0.26).

CONCLUSIONS: In patients with HF with mildly reduced or preserved ejection fraction, finerenone reduced the risk of cardiovascular death and worsening HF events, irrespective of LVEF.

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Correspondence to: John J.V. McMurray, MD, School of Cardiovascular & Metabolic Health, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, G12 8TA, UK. Email john.mcmurray@glasgow.ac.uk

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Clinical Perspective

What Is New?

- Previous post hoc analyses of randomized clinical trials in patients with heart failure with mildly reduced or preserved ejection fraction have suggested that the benefits of neurohumoral modulating therapies are attenuated or absent at higher left ventricular ejection fraction.
- In this prespecified analysis of FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure), the nonsteroidal mineralocorticoid receptor antagonist finerenone reduced the risk of cardiovascular death and worsening heart failure events consistently across the entire range of left ventricular ejection fraction in patients with heart failure with mildly reduced or preserved ejection fraction.

What Are the Clinical Implications?

- These data support that finerenone should be considered as a foundational treatment for heart failure with mildly reduced or preserved ejection fraction, regardless of left ventricular ejection fraction.

Nonstandard Abbreviations and Acronyms

BNP	B-type natriuretic peptide
eGFR	estimated glomerular filtration rate
FINEARTS-HF	Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure
HF	heart failure
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HR	hazard ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
RR	rate ratio
SGLT2i	sodium-glucose cotransporter-2 inhibitor

The clinical characteristics and the risk of outcomes vary substantially among patients with heart failure (HF) according to left ventricular ejection fraction (LVEF).[1,2] Furthermore, the efficacy of several treatments for heart failure differs across the range of LVEF. The benefits of some neurohumoral modulating therapies on reducing the risk of death and worsening HF in patients with HF with reduced ejection fraction were not replicated in trials of patients with HF with mildly reduced ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF).[3–7] However, a series of post hoc analyses from randomized, placebo-controlled trials pooling individual patient data from across the entire range of LVEF have shown that the benefits of some neurohumoral modulating treatments may extend to those with a LVEF reduced below the normal range (ie, <55%–60%), with attenuation or absence of benefit in those with a normal LVEF.[8–10] Conversely, the benefits of sodium-glucose cotransporter-2 inhibitors (SGLT2i) were consistent across the entire spectrum of LVEF.[11,12] Therefore, it is important to understand whether the efficacy of new treatments for patients with HFmrEF or HFpEF is modified by LVEF.

In FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure), the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone reduced the risk of cardiovascular death and worsening HF events in patients with HF and an LVEF ≥40%.[13–15] This analysis examined whether the benefits and safety of finerenone differed across the range of LVEF among patients with HFmrEF and HFpEF enrolled in FINEARTS-HF.

METHODS

FINEARTS-HF was a prospective, randomized, double-blind, placebo-controlled, event-driven trial that examined the efficacy and safety of finerenone compared with placebo in patients with HFmrEF or HFpEF. The design, baseline characteristics, and primary results have been published.[13–15] Ethics committees of the 653 participating institutions in 37 countries approved the protocol and all patients gave written consent.

Study Patients and Treatment

Key inclusion criteria were age ≥40 years, symptomatic HF in New York Heart Association (NYHA) functional class II through IV, treatment with a diuretic for ≥30 days before randomization, and LVEF ≥40% with evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy) measured within 12 months of screening. Patients were also required to have elevated natriuretic peptide levels (NT-proBNP [N-terminal pro–B-type natriuretic peptide] ≥300 pg/mL [or BNP (B-type natriuretic peptide) ≥100 pg/mL] for patients in sinus rhythm or NT-proBNP ≥900 pg/mL [or BNP ≥300 pg/mL] for patients in atrial fibrillation) measured within 90 days in those with a recent worsening HF event within 90 days of randomization or measured 30 days before randomization in those without a recent worsening HF event. Both ambulatory and hospitalized patients were eligible for enrollment. Patients

with previous LVEF <40% with subsequent improvement to ≥40% were also eligible for enrollment provided that ongoing HF symptoms were present and all other inclusion criteria were satisfied. Key exclusion criteria were estimated glomerular filtration rate (eGFR) <25 mL·min·1.73 m^2, serum/plasma potassium >5.0 mmol/L at screening or randomization, or symptomatic hypotension with mean systolic blood pressure <90 mm Hg at screening or randomization. A complete list of exclusion criteria is provided in the design article.[13]

Eligible participants were randomized in a 1:1 ratio to finerenone or matching placebo. The starting dose was 10 mg once daily in participants with an eGFR ≤60 mL·min·1.73 m^2 with a maximum maintenance dose of 20 mg once daily, whereas the starting dose was 20 mg once daily if the eGFR was >60 mL·min·1.73 m^2 with a maximum maintenance dose of 40 mg once daily.

Ejection Fraction

Investigators were asked to record a patient's LVEF on the electronic case report form using the most recent measurement recorded within 12 months of screening. An LVEF was available in 5993 of 6001 patients (>99%) at baseline. For the purposes of this analysis, LVEF was analyzed in groups (<50%, ≥50%–<60%, and ≥60%) and as a continuous variable. In a sensitivity analysis, LVEF was analyzed in groups according to LVEF <50%, ≥50% to <60%, ≥60% to <70%, and ≥70%.

Outcomes

The primary trial outcome was the composite of total (first and recurrent) HF events (ie, HF hospitalization or urgent HF visit) and cardiovascular death. Prespecified secondary outcomes were the total number of HF events; improvement in NYHA class from baseline to 12 months; change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score from baseline to 6, 9, and 12 months; a composite kidney end point (defined as a sustained decline in eGFR ≥50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 mL·min·1.73 m^2, or initiation of dialysis or renal transplantation); and all-cause death. All deaths and potential primary outcome nonfatal events were adjudicated by an independent blinded committee.

Prespecified safety analyses included adverse events leading to discontinuation of trial treatment and adverse events of interest (ie, elevations in serum creatinine, hyperkalemia, hypokalemia, and hypotension). Safety analyses were performed in patients who had undergone randomization and received at least one dose of finerenone or placebo (a total of 15 randomized patients were excluded from the safety analysis).

Statistical Analysis

Baseline characteristics are summarized according to LVEF groups as frequencies with percentages for categorical variables and means with standard deviations or medians with interquartile ranges for continuous variables. Differences across LVEF categories were compared by the Jonckheere-Terpstra trend test for continuous variables and the Cochran-Armitage trend test for categorical variables.

The crude incidence rates for each outcome of interest across the range of LVEF are presented per 100 patient-years of follow-up and are presented graphically using a Poisson regression model with LVEF included as a continuous variable using restricted cubic splines with 3 knots placed at the 10th, 50th, and 90th quantiles. The association between LVEF and clinical outcomes was evaluated using semiparametric proportional-rates models for total (first and recurrent) events and Cox proportional hazards models for time to first event data, stratified according to geographic region.[16] Further adjustment was performed for age, sex, eGFR, NYHA functional class, heart rate, systolic blood pressure, body mass index, (log)NT-proBNP, and history of type 2 diabetes, previous HF hospitalization, atrial fibrillation, and myocardial infarction.

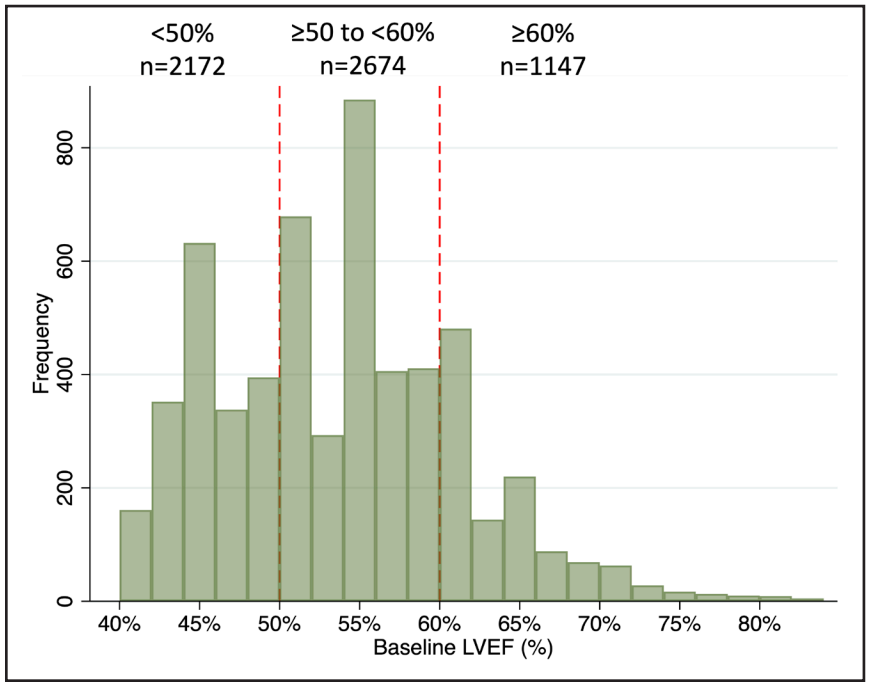

Figure 1. Distribution of baseline left ventricular ejection fraction.
LVEF indicates baseline left ventricular ejection fraction.

Table 1. Baseline Characteristics According to Baseline Left Ventricular Ejection Fraction Group

Characteristics	LVEF group			Trend *P* value
	<50% (n=2172)	≥50% to <60% (n=2674)	≥60% (n=1147)	
Age, y	69.6±10.1	73.3±9.1	73.5±9.2	<0.001
Women	679 (31.3)	1368 (51.2)	679 (59.2)	<0.001
Race and ethnicity				0.13
Asian	432 (19.9)	359 (13.4)	205 (17.9)	
Black	23 (1.1)	36 (1.3)	29 (2.5)	
Other	58 (2.7)	94 (3.5)	30 (2.6)	
White	1659 (76.4)	2185 (81.7)	883 (77.0)	
Geographic region				0.042
Asia	429 (19.8)	355 (13.3)	199 (17.3)	
Eastern Europe	1007 (46.4)	1140 (42.6)	503 (43.9)	
Latin America	255 (11.7)	281 (10.5)	105 (9.2)	
North America	125 (5.8)	218 (8.2)	123 (10.7)	
Western Europe, Oceania, others	356 (16.4)	680 (25.4)	217 (18.9)	
History of type 2 diabetes	866 (39.9)	1097 (41.0)	472 (41.2)	0.41
History of hypertension	1860 (85.6)	2411 (90.2)	1046 (91.2)	<0.001
History of myocardial infarction	806 (37.1)	569 (21.3)	163 (14.2)	<0.001
History of PCI	686 (31.6)	574 (21.5)	208 (18.1)	<0.001
History of CABG	446 (20.5)	350 (13.1)	119 (10.4)	<0.001
Any previous HF hospitalization	1450 (66.8)	1582 (59.2)	583 (50.8)	<0.001
Time since most recent HF event				<0.001
Randomized during HF event	295 (13.6)	335 (12.5)	119 (10.4)	
≤7 d from randomization	188 (8.7)	214 (8.0)	68 (5.9)	
>7 d to ≤3 mo	792 (36.5)	943 (35.3)	290 (25.3)	
>3 mo	357 (16.4)	400 (15.0)	179 (15.6)	
Baseline body mass index, kg/m^2	29.3±5.9	30.3±6.2	30.4±6.2	<0.001
Baseline LVEF, %	44.4±2.8	54.2±2.9	64.0±4.6	<0.001
History of LVEF <40%	196 (9.0)	68 (2.5)	9 (0.8)	<0.001
Baseline NT-proBNP, pg/mL	1139 (506–2205)	1008 (426–1880)	941 (406–1776)	<0.001
Sinus rhythm on baseline ECG	764 (368–1539)	532 (288–1119)	531 (300–1069)	<0.001
Atrial fibrillation on baseline ECG	1839 (1150–3304))	1676 (1140–2533)	1697 (1223–2537)	<0.001
KCCQ Total Symptom Score	69.3±23.9	65.9±23.8	65.5±23.9	<0.001
KCCQ Clinical Summary Score	67.9±22.6	64.0±22.3	63.7±22.4	<0.001
KCCQ Overall Summary Score	64.5±22.3	61.9±22.0	61.7±22.3	<0.001
NYHA functional class at baseline				0.33
II	1499 (69.0)	1828 (68.4)	815 (71.1)	
III/IV	673 (31.0)	846 (31.6)	331 (28.9)	
Atrial fibrillation on baseline ECG	771 (35.5)	1099 (41.1)	421 (36.7)	0.12
Baseline systolic blood pressure, mm Hg	127.5±14.9	130.2±15.5	131.2±15.3	<0.001
Baseline eGFR, mL·min·1.73 m^2	64.8±20.1	61.0±19.3	59.6±19.4	<0.001
Baseline eGFR <60 mL·min·1.73 m^2	929 (42.8)	1,345 (50.3)	610 (53.2)	<0.001
Baseline UACR, mg/g*	142±493	181±714	155±554	0.54
Baseline pharmacotherapy				
Beta-blocker	1919 (88.4)	2242 (83.8)	927 (80.8)	<0.001
ACEi	870 (40.1)	890 (33.3)	392 (34.2)	<0.001
ARB	616 (28.4)	1,016 (38.0)	465 (40.5)	<0.001
ARNI	341 (15.7)	145 (5.4)	27 (2.4)	<0.001
SGLT2i	336 (15.5)	366 (13.7)	113 (9.9)	<0.001

(*Continued*)

Table 1. Continued

Characteristics	LVEF group			Trend *P* value
	<50% (n=2172)	≥50% to <60% (n=2674)	≥60% (n=1147)	
Loop diuretic	1972 (90.8)	2318 (86.7)	943 (82.2)	<0.001
Mean furosemide equivalent dose, mg†	51.7±59.5	54.4±65.9	49.8±45.8	0.46
Thiazide diuretic	209 (9.6)	407 (15.2)	214 (18.7)	<0.001
CCB	515 (23.7)	945 (35.3)	504 (43.9)	<0.001

Values are n (%), mean±SD, or median (interquartile range). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

*Baseline urinary albumin to creatinine ratio (UACR) unavailable in 204 participants.

†Calculated as a mean daily furosemide equivalent dose with 80 mg of oral furosemide=40 mg of intravenous furosemide=1 mg of bumetanide=20 mg of torasemide=60 mg of azosemide.

The effect of finerenone compared with 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.[16] All models were stratified by geographic region as prespecified in the statistical analysis plan for the main trial.[15] These analyses were repeated with adjustment for the same variables described previously. The effect of finerenone on outcomes according to LVEF was examined with LVEF as a continuous variable modeled as a spline with 3 knots placed at the 10th, 50th, and 90th quantiles. The interaction between LVEF (as a spline with the same knots) and treatment was tested in the model. In the context of finding no treatment effect modification by baseline LVEF, the absolute benefit of finerenone on the primary outcome was calculated by modeling a consistent treatment effect across the range of baseline LVEF. The absolute rate difference was calculated using a Poisson regression model with LVEF included as a continuous variable using a restricted cubic spline with 3 knots placed at the 10th, 50th, and 90th quantiles. The proportion of patients with improvement in NYHA class from baseline to 12 months was analyzed using a logistic regression model, adjusted for geographic region. The change in KCCQ Total Symptom Score from baseline to 12 months was analyzed using a linear regression model, adjusted for baseline value and geographic region. Safety outcomes are reported as counts and percentages according to randomized treatment. Logistic regression was used with a treatment-by-LVEF category interaction term to examine the presence of any modification of treatment effect according to LVEF.

All analyses were performed using Stata version 18. $P<0.05$ was considered nominally statistically significant. Trial data will be made available by the sponsor, Bayer, in accordance with its data-sharing policy.

RESULTS

LVEF was recorded in 5993 of the 6001 participants in FINEARTS-HF. The mean±SD and median (interquartile range) LVEF at baseline were 53±8% and 53% (46%–58%), respectively, with a range of 34% to 84%. The distribution of LVEF is displayed in Figure 1. LVEF was <50% in 2172 (36%), between 50% and <60% in 2674 (45%), and ≥60% in 1147 (19%). Baseline characteristics according to LVEF group are detailed in Table 1 and Table S1. Compared with those with a lower LVEF, patients with a higher LVEF were older, were more commonly female, had lower (ie, worse) KCCQ Total Symptom Score values, had higher mean body mass index and systolic blood pressure, and had a greater prevalence of kidney dysfunction. Patients with a lower LVEF were more likely to have a history of myocardial infarction or a previous HF hospitalization, had higher NT-proBNP concentrations, and were more likely to be treated with a β-blocker, renin-angiotensin system inhibitor, angiotensin receptor-neprilysin inhibitor, SGLT2 inhibitor, or a loop diuretic than those with a higher LVEF. A history of previous LVEF <40% was most common in those with a baseline LVEF <50% compared with those with a higher LVEF.

Outcomes According to LVEF

The crude incidence of outcomes according to baseline LVEF are displayed as a continuous variable in Figure 2 and by LVEF category in Table 2. The rates of the primary composite outcome (cardiovascular death and the total number of worsening HF events), its individual components, and all-cause mortality were highest in patients with lower LVEF, with rates decreasing across the range of LVEF 40% to 60%, with a plateauing of event rates in patients with LVEF ≥60%.

After adjustment for baseline covariates, the rate of the primary composite outcome was similar across LVEF categories: RR, 1.07 (95% CI, 0.89–1.29) for LVEF <50% and 1.09 (95% CI, 0.91–1.31) for LVEF ≥50% to <60% (referent group=LVEF ≥60%; Table 2). Similar results were seen for the individual components of the primary composite outcome in both total and time to first event analyses, the composite kidney outcome, and all-cause mortality.

Treatment Effect of Finerenone According to LVEF

The treatment effect of finerenone compared with placebo on outcomes is detailed by LVEF groups in Table 3 and with LVEF analyzed as a continuous

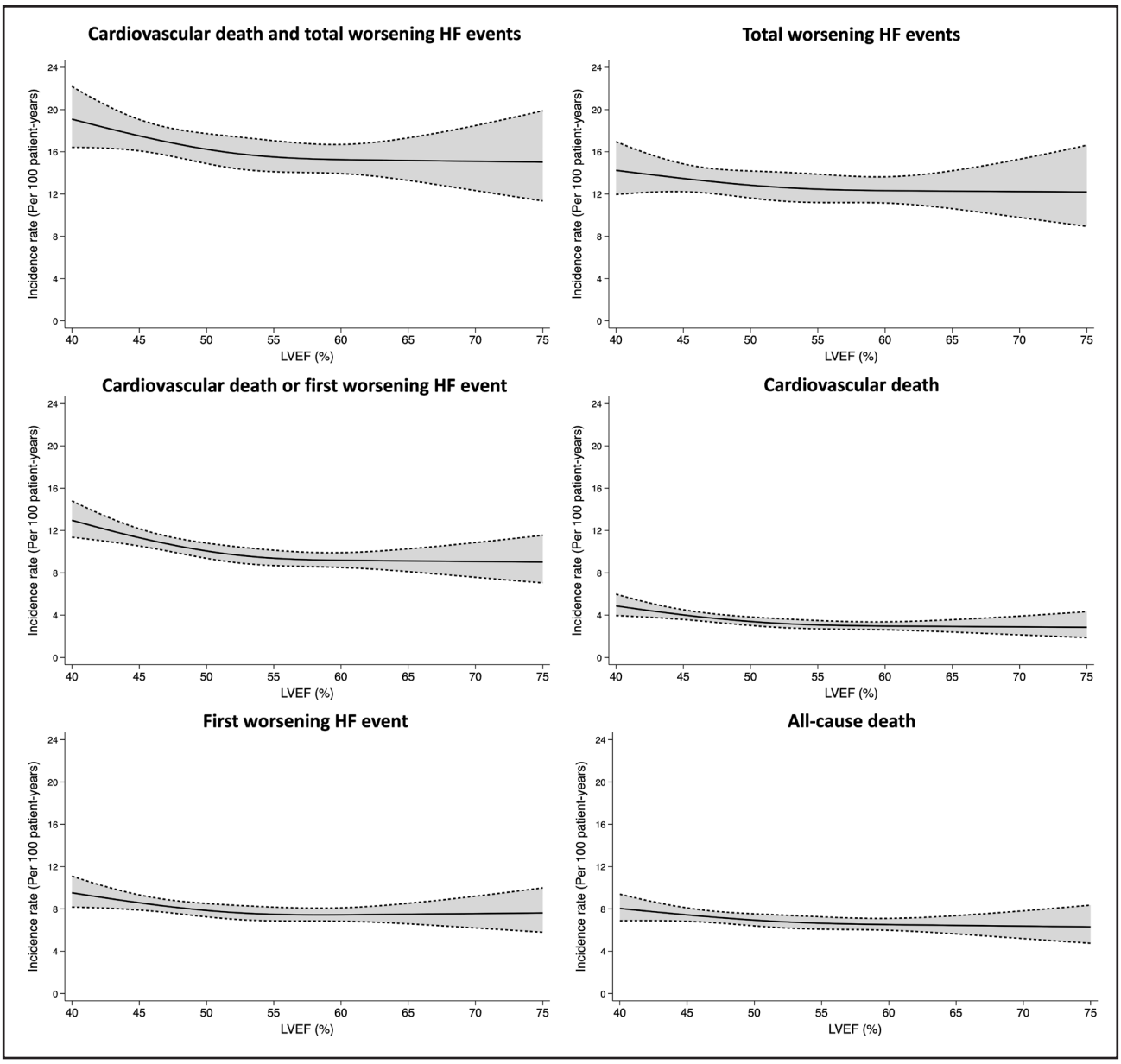

Figure 2. Incidence of outcomes across the spectrum of left ventricular ejection fraction.
The crude incidence rate of outcomes per 100 patient-years was calculated using a Poisson regression model with left ventricular ejection fraction (LVEF) included as a continuous variable using restricted cubic splines with 3 knots. HF indicates heart failure.

variable in Figure 3. The effect of finerenone on reducing the risk of the primary composite outcome of cardiovascular death and the total number of worsening HF events was not modified by LVEF when analyzed in categories ($P_{interaction}$=0.70) or as a continuous variable ($P_{interaction}$=0.28). In a continuous spline model (Figure 3), the RR estimate for the primary composite outcome was <1.0, indicating a benefit of finerenone, from an LVEF of 40% up to ≈70%, with a substantial widening of the 95% CI at higher LVEF values of >70%. The HR for finerenone compared with placebo for the time to first event outcome of cardiovascular death or first worsening HF event was <1.0 across the whole range of LVEFs studied ($P_{interaction}$=0.62). The absolute benefit of finerenone compared with placebo on the primary composite outcome was consistent when expressed as a rate difference across the range of LVEF, as displayed in Figure 4.

There was no statistically significant interaction between LVEF and the effect of finerenone on reducing the number of total worsening HF events (categorical $P_{interaction}$=0.67 and continuous $P_{interaction}$=0.26; Table 3). In the continuous spline analysis, a similar pattern to the primary outcome was observed for the total number of worsening HF events, with the RR estimate being <1.0 for the majority of the LVEF range ($P_{interaction}$=0.26; Figure 3).

Table 2. Risk of Outcomes According to Baseline Left Ventricular Ejection Fraction Group

Outcomes	LVEF group		
	<50% (n=2172)	≥50% to <60% (n=2674)	≥60% (n=1147)
Cardiovascular death and total No. of worsening HF events			
No. of events	910	1028	428
Event rate per 100 patient-years (95% CI)	17.4 (15.7–19.3)	16.4 (14.8–18.1)	14.3 (12.3–16.6)
Unadjusted RR (95% CI)	1.27 (1.06–1.52)	1.14 (0.95–1.36)	Ref.
Adjusted RR (95% CI)*	1.07 (0.89–1.29)	1.09 (0.91–1.31)	Ref.
Total no. of worsening HF events			
No. of events	688	840	338
Event rate per 100 patient-years (95% CI)	13.2 (11.7–14.8)	13.4 (11.9–15.0)	11.3 (9.5–13.3)
Unadjusted RR (95% CI)	1.23 (1.00–1.51)	1.17 (0.96–1.43)	Ref.
Adjusted RR (95% CI)*	1.06 (0.86–1.30)	1.13 (0.92–1.38)	Ref.
Cardiovascular death or first worsening HF event			
No. (%)	534 (24.6%)	572 (21.4%)	237 (20.7%)
Event rate per 100 patient-years (95% CI)	11.3 (10.4–12.3)	10.0 (9.2–10.8)	8.6 (7.6–9.8)
Unadjusted HR (95% CI)	1.34 (1.15–1.56)	1.13 (0.97–1.32)	Ref.
Adjusted HR (95% CI)*	1.11 (0.94–1.31)	1.07 (0.92–1.25)	Ref.
Cardiovascular death			
No. (%)	222 (10.2%)	189 (7.1%)	91 (7.9%)
Event rate per 100 patient-years (95% CI)	4.2 (3.7–4.8)	3.0 (2.6–3.5)	3.0 (2.5–3.7)
Unadjusted HR (95% CI)	1.39 (1.09–1.78)	1.00 (0.78–1.28)	Ref.
Adjusted HR (95% CI)*	1.10 (0.84–1.43)	0.95 (0.73–1.24)	Ref.
First worsening HF event			
No. (%)	394 (18.1%)	468 (17.5%)	190 (16.6%)
Event rate per 100 patient-years (95% CI)	8.3 (7.5–9.2)	8.1 (7.4–8.9)	6.9 (6.0–8.0)
Unadjusted HR (95% CI)	1.25 (1.05–1.49)	1.15 (0.97–1.36)	Ref.
Adjusted HR (95% CI)*	1.05 (0.87–1.26)	1.08 (0.91–1.29)	Ref.
Composite kidney outcome			
No. (%)	41 (1.9%)	62 (2.3%)	27 (2.4%)
Event rate per 100 patient-years (95% CI)	0.9 (0.7–1.2)	1.1 (0.9–1.4)	1.0 (0.7–1.5)
Unadjusted HR (95% CI)	0.96 (0.58–1.56)	1.19 (0.76–1.89)	Ref.
Adjusted HR (95% CI)*	0.79 (0.47–1.34)	1.20 (0.76–1.91)	Ref.
All-cause mortality			
No. (%)	393 (18.1%)	430 (16.1%)	189 (16.5%)
Event rate per 100 patient-years (95% CI)	7.5 (6.8–8.3)	6.8 (6.2–7.5)	6.3 (5.5–7.2)
Unadjusted HR (95% CI)	1.23 (1.03–1.47)	1.11 (0.93–1.31)	Ref.
Adjusted HR (95% CI)*	1.05 (0.87–1.26)	1.06 (0.89–1.27)	Ref.

HR indicates hazard ratio; LVEF, left ventricular ejection fraction; and RR, rate ratio.

*Adjusted for the following baseline variables: randomized treatment (finerenone or placebo), age, sex, estimated glomerular filtration rate, New York Heart Association functional class, heart rate, systolic blood pressure, body mass index, (log)NT-proBNP (N-terminal pro–B-type natriuretic peptide), and a history of type 2 diabetes, previous heart failure (HF) hospitalization, atrial fibrillation, or myocardial infarction. All models were stratified by geographic region.

Again similarly to the primary outcome, when considered as a time to first event outcome, the HR estimate was indicative of a benefit of finerenone (ie, remained <1.0) across the whole LVEF range studied ($P_{interaction}$=0.85).

The effect of finerenone was consistent across the range of LVEF on all other outcomes examined (Table 3; Figure 3) except for the kidney composite outcome. In those with an LVEF ≥60%, there was an apparent benefit of finerenone on the kidney outcome, whereas there were more kidney-related events in those randomized to finerenone as compared with placebo in the lower LVEF groups (categorical $P_{interaction}$=0.003 and continuous $P_{interaction}$=0.15). Finerenone had a consistent benefit on increasing the KCCQ Total

Table 3. Effect of Randomized Treatment on Outcomes According to Baseline Left Ventricular Ejection Fraction Group

Outcomes	LVEF group						*P* value for categorical LVEF group*treatment interaction	*P* value for continuous LVEF *treatment interaction
	<50% (n=2172)		≥50% to <60% (n=2674)		≥60% (n=1147)			
	Finerenone (n=1093)	Placebo (n=1079)	Finerenone (n=1329)	Placebo (n=1345)	Finerenone (n=575)	Placebo (n=572)		
Cardiovascular death and total number of worsening HF events								
No. 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	0.28
Adjusted RR (95% CI)†	0.83 (0.68–1.02)		0.76 (0.62–0.92)		0.82 (0.61–1.10)		0.75	0.30
Total number of worsening HF events								
No. 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	0.26
Adjusted RR (95% CI)†	0.83 (0.65–1.05)		0.73 (0.59–0.91)		0.79 (0.57–1.09)		0.65	0.19
Cardiovascular death or first worsening HF event								
No. (%)	243 (22.2)	291 (27.0)	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	0.62
Adjusted HR (95% CI)†	0.80 (0.67–0.95)		0.80 (0.68–0.95)		0.75 (0.58–0.98)		0.95	0.93
Cardiovascular death								
No. (%)	103 (9.4)	119 (11.0)	93 (7.0)	96 (7.1)	46 (8.0)	45 (7.9)		
Rate (95% CI)	3.9 (3.2–4.7)	4.6 (3.8–5.5)	3.0 (2.4–3.6)	3.0 (2.5–3.7)	3.1 (2.3–4.1)	3.0 (2.2–4.0)		
HR (95% CI)‡	0.85 (0.65–1.11)		0.96 (0.72–1.28)		1.04 (0.69–1.57)		0.70	0.70
Adjusted HR (95% CI)†	0.85 (0.65–1.11)		0.90 (0.67–1.20)		0.95 (0.61–1.46)		0.93	0.81
First worsening HF event								
No. (%)	175 (16.0)	219 (20.3)	219 (16.5)	249 (18.5)	85 (14.8)	105 (18.4)		
Rate (95% CI)	7.2 (6.2–8.4)	9.5 (8.3–10.9)	7.6 (6.6–8.7)	8.7 (7.7–9.9)	6.2 (4.9–7.6)	7.7 (6.3–9.3)		
HR (95% CI)‡	0.78 (0.64–0.95)		0.84 (0.70–1.00)		0.80 (0.60–1.07)		0.87	0.85
Adjusted HR (95% CI)†	0.77 (0.63–0.95)		0.78 (0.65–0.94)		0.69 (0.51–0.93)		0.80	0.98
Composite kidney outcome§								
No. (%)	25 (2.3)	16 (1.5)	42 (3.2)	20 (1.5)	8 (1.4)	19 (3.3)		
Rate (95% CI)	1.1 (0.7–1.6)	0.7 (0.4–1.1)	1.5 (1.1–2.0)	0.7 (0.5–1.1)	0.6 (0.3–1.2)	1.4 (0.9–2.2)		
HR (95% CI)‡	1.52 (0.81–2.86)		2.06 (1.21–3.52)		0.37 (0.15–0.87)		0.003	0.15
Adjusted HR (95% CI)†	1.45 (0.75–2.78)		1.91 (1.12–3.28)		0.44 (0.18–1.06)		0.007	0.13
All-cause mortality								
No. (%)	192 (17.6)	201 (18.6)	202 (15.2)	228 (17.0)	96 (16.7)	93 (16.3)		
Rate (95% CI)	7.3 (6.3–8.4)	7.7 (6.7–8.9)	6.4 (5.6–7.3)	7.2 (6.3–8.2)	6.4 (5.2–7.8)	6.2 (5.0–7.5)		
HR (95% CI)‡	0.94 (0.77–1.15)		0.87 (0.72–1.05)		1.03 (0.77–1.37)		0.62	0.91
Adjusted HR (95% CI)†	0.96 (0.78–1.17)		0.85 (0.70–1.04)		1.00 (0.74–1.34)		0.72	0.99
Improvement in NYHA class from baseline to month 12								
No. (%)	202 (18.5)	202 (18.7)	247 (18.6)	258 (19.2)	107 (18.6)	92 (16.1)		
OR (95% CI)	0.98 (0.79–1.22)		0.96 (0.79–1.17)		1.19 (0.87–1.62)		0.48	0.60

(*Continued*)

Table 3. Continued

Outcomes	LVEF group						*P* value for categorical LVEF group*treatment interaction	*P* value for continuous LVEF *treatment interaction
	<50% (n=2172)		≥50% to <60% (n=2674)		≥60% (n=1147)			
	Finerenone (n=1093)	Placebo (n=1079)	Finerenone (n=1329)	Placebo (n=1345)	Finerenone (n=575)	Placebo (n=572)		
Change in KCCQ-TSS from baseline to month 12								
LSM (95% CI)	8.17 (6.98–9.35)	6.78 (5.61–7.94)	9.33 (8.29–10.37)	7.95 (6.92–8.99)	8.83 (7.32–10.34)	5.81 (4.27–7.34)		
Difference (95% CI)	1.39 (−0.19, 2.97)		1.37 (−0.07, 2.82)		3.02 (0.91, 5.14)		0.44	0.47

Event rates are presented per 100 patient-years. KCCQ-TSS indicates Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LSM, least squares means; LVEF, left ventricular ejection fraction; and OR, odds ratio.

*For total (first and recurrent) event outcomes, rate ratios (RRs) and 95% CIs were estimated using the semiparametric proportional rates method of Lin et al[16] stratified according to geographic region.

†Adjusted for the following baseline variables: randomized treatment (finerenone or placebo), age, sex, estimated glomerular filtration rate, New York Heart Association (NYHA) functional class, heart rate, systolic blood pressure, body mass index, (log)NT-proBNP (N-terminal pro–B-type natriuretic peptide), and a history of type 2 diabetes, previous heart failure (HF) hospitalization, atrial fibrillation, or myocardial infarction. All models were stratified by geographic region.

‡For time to first event outcomes, hazard ratios (HRs) and 95% CIs were estimated using Cox regression models, stratified by geographic region.

§The composite kidney outcome was defined as a sustained decline in estimated glomerular filtration rate ≥50% relative to baseline over at least 4 weeks, or sustained estimated glomerular filtration rate decline <15 mL·min·1.73 m^2, or the initiation of dialysis or renal transplantation.

Symptom Score from baseline to month 12 across the range of LVEF.

In sensitivity analyses, results were consistent after adjustment for baseline covariates (Table 3) and when LVEF was categorized into <50%, ≥50% to <60%, ≥60% to <70%, and ≥70% (Table S2).

Safety Outcomes According to LVEF

The occurrence of safety outcomes of interest according to randomized treatment and LVEF category are detailed in Table 4. Patients randomized to finerenone had more frequent increases in serum creatinine and potassium than the placebo group, and this did not differ significantly across LVEF groups.

DISCUSSION

In FINEARTS-HF, the beneficial effect of finerenone on reducing the risk of cardiovascular death and the total number of HF hospitalizations was consistent across the range of LVEF in patients with HF and an LVEF ≥40%. These data support the use of finerenone as a foundational therapy for patients with HFmrEF or HFpEF, along with an SGLT2i.

Consistent with previous trials, we observed substantial heterogeneity according to LVEF in the clinical characteristics of patients with HFmrEF and HFpEF enrolled in FINEARTS-HF.[1,2] Patients with a lower LVEF in the HFmrEF range had several features resembling a "HF with reduced ejection fraction–like" phenotype; they were more likely to be men, had a greater prevalence of coronary artery disease, and were more frequently prescribed beta-blockers and renin-angiotensin receptor antagonists (either alone or in combination with a neprilysin inhibitor). Despite evidence of benefit in HF regardless of LVEF, the use of SGLT2i was more common in those with a lower ejection fraction, probably reflecting the later approval of the use of these drugs in HFmrEF or HFpEF, which occurred during follow-up of FINEARTS-HF. Patients with a higher LVEF were older, were more often women, and had less ischemic heart disease, but a greater prevalence of hypertension, higher body mass index, and lower eGFR. Natriuretic peptide concentrations were lower with increasing LVEF.

The crude rate of outcomes was highest in patients with the lowest LVEF in the HFmrEF range, with a plateauing of event rates for all outcomes above an LVEF of 50%. This is consistent with previous reports showing that patients with HFmrEF have intermediate event rates compared with patients with HF with reduced ejection fraction, in whom there is a linear inverse relationship between LVEF and a higher risk of adverse outcomes, and those with HFpEF.[1,2,8–11] In HFpEF, event rates were generally consistent across the range of LVEF ≥50%. After adjustment for baseline covariates, including NT-proBNP, we did not observe any significant between-LVEF category differences in the adjusted risk of outcomes.

FINEARTS-HF is the first trial to show that a drug targeting a neurohumoral pathway can reduce morbidity and mortality rates, as well as improve symptoms, in patients with HFmrEF or HFpEF. Previous trials in patients with HFmrEF or HFpEF did not show a clear benefit of renin-angiotensin system inhibition or the combined angiotensin receptor-neprilysin inhibitor sacubitril/valsartan.[3–5,7] In TOPCAT (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function; URL: https://www.clinicaltrials.gov; Unique identifier: NCT00094302), the steroidal MRA spironolactone did not reduce the risk of the primary end point of cardiovascular death, HF hospitalization, or resuscitated cardiac arrest in the overall trial population of patients with LVEF ≥45%.[6] However, in a post hoc analysis of TOPCAT according to LVEF, spironolactone improved outcomes in

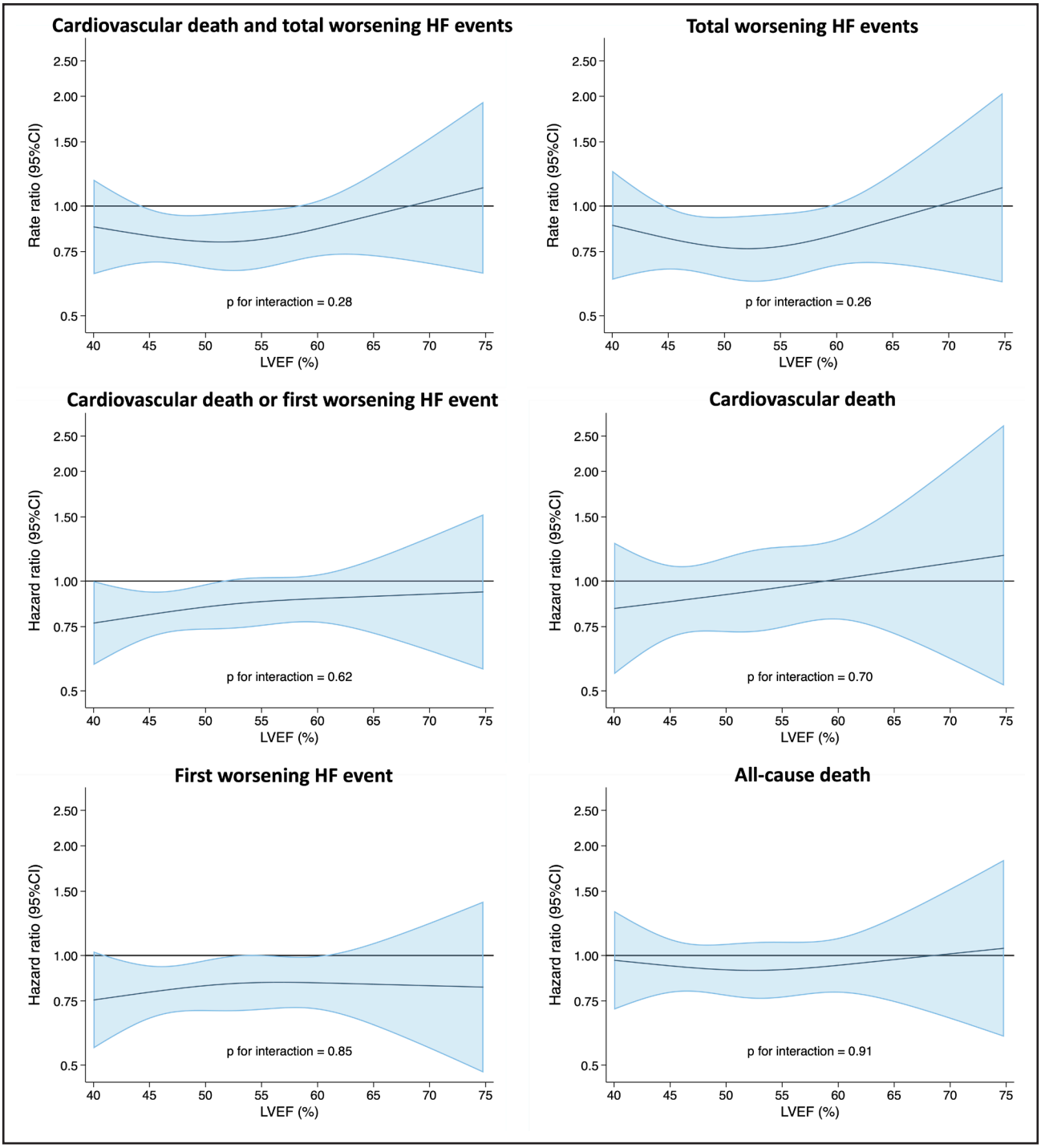

Figure 3. Treatment effect of finerenone compared with placebo across the spectrum of left ventricular ejection fraction.
The effect of finerenone on outcomes according to left ventricular ejection fraction (LVEF) analyzed as a continuous variable was examined with an LVEF by treatment interaction with LVEF modeled as a spline with 3 knots at the 10th, 50th, and 90th quantiles. For total (first and recurrent) event outcomes, rate ratios and 95% CIs were estimated using the semiparametric proportional rates method of Lin et al[16] stratified according to geographic region. For time to first event outcomes, hazard ratios and 95% CIs were estimated using Cox regression models, stratified by geographic region. An effect estimate of <1.0 indicates benefit of finerenone. Shaded areas represent 95% CIs. $P_{interaction}$ represents the interaction between LVEF as a continuous variable and treatment. HF indicates heart failure.

patients with a reduced LVEF in the mildly reduced range, but not in those with an LVEF in the normal range (ie, >55%–60%).[8] Similar findings of a varying treatment effect according to LVEF were seen with the angiotensin receptor blocker candesartan in the CHARM program (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity) and with sacubitril/valsartan in PARAGON-HF (Prospective Comparison

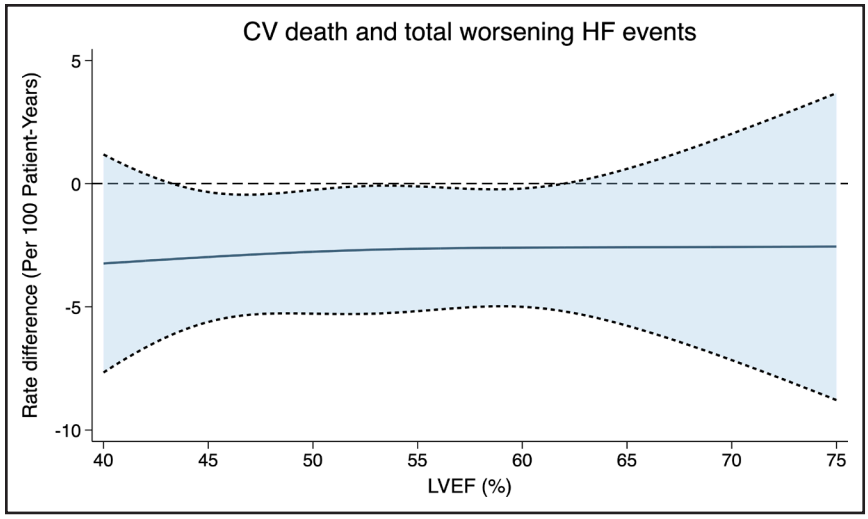

Figure 4. Absolute benefit of finerenone compared with placebo across the spectrum of left ventricular ejection fraction.
The absolute benefit of finerenone on the primary outcome was calculated by modeling a consistent treatment effect across the range of baseline left ventricular ejection fraction (LVEF). The absolute rate difference was calculated using a Poisson regression model with LVEF included as a continuous variable using a restricted cubic spline with 3 knots. HF indicates heart failure.

of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction; URL: https://www.clinicaltrials.gov; Unique identifier: NCT01920711), which enrolled patients with an LVEF ≥45%, although none of these findings was definitive, and all of these inferences were based on post hoc exploratory analyses.[9,10]

Although the benefits of finerenone on the primary composite outcome and the total number of worsening HF events appeared to be attenuated in patients with an LVEF >70% on visual assessment of the continuous spline analysis, the overall tests for heterogeneity of treatment effect were nonsignificant in both continuous and categorical analyses. The relatively small number of patients with an LVEF >70% and few events (41 primary outcome events in 23 of 108 patients with LVEF >70% [1.8% of patients and 2% of the total number of events in those with LVEF data]) may have limited the certainty in the treatment effect on recurrent event outcomes at higher LVEF values, as indicated by the relatively wide 95% CI. Ongoing trials with finerenone in similar patient populations will provide more data to help clarify this uncertainty (CONFIRMATION-HF [A Study to Determine the Efficacy and Safety of Finerenone and SGLT2i in Combination in Hospitalized Patients With Heart Failure]; URL: https://www.clinicaltrials.gov; Unique identifier: NCT06024746; and REDEFINE-HF [A Study to Determine the Efficacy and Safety of Finerenone on Morbidity and Mortality Among Hospitalized Heart Failure Patients]; URL: https://www.clinicaltrials.gov; Unique identifier: NCT06008197). Although there appeared to be an interaction between the effect of finerenone on the kidney outcome and baseline LVEF category, the improbably low hazard ratio in the LVEF ≥60% group probably reflects the play of chance due to the small number of kidney end points overall (n=130) and in this subgroup (n=27). Likewise, the apparent interaction between finerenone-related hyperkalemia and LVEF is likely to be spurious for similar reasons (with only 17 events in the LVEF >60% group).

Why might the consistency of the benefit of finerenone across the LVEF range in HFmrEF and HFpEF be different from the previously observed attenuation of the effect of other neurohumoral modulating treatments at higher LVEF values? The first potential explanation is that finerenone has a specific mechanism (or mechanisms) of action and properties that distinguish it from other treatments and underlie its clinical benefits across the spectrum of LVEF in HFmrEF and HFpEF. Finerenone is a nonsteroidal MRA that is thought to have greater selectivity and binding affinity for the mineralocorticoid receptor along with a more balanced tissue distribution between the heart and kidney than eplerenone or spironolactone.[17,18] There are few direct comparisons between finerenone and other MRAs in patients with HF. In ARTS-HF (Mineralocorticoid Receptor Antagonist Tolerability Study–Heart Failure; URL: https://www.clinicaltrials.gov; Unique identifier: NCT01807221), finerenone had a similar effect to eplerenone on the proportion of patients with a >30% decrease in NT-proBNP.[19] There was a suggestion of a greater benefit of finerenone on an exploratory clinical composite outcome; however, this trial was not powered for between-treatment comparisons on clinical outcomes.

The second potential explanation may be that patients with a higher LVEF enrolled in FINEARTS-HF were different from those in previous trials and may have had characteristics that made them more likely to benefit from an MRA. One notable difference in FINEARTS-HF was that NT-proBNP concentrations in patients with an LVEF ≥60% were higher than those in other comparative HFmrEF/HFpEF trials. In a pooled analysis of 4 large HFmrEF/HFpEF trials, the median NT-proBNP level in patients with an LVEF ≥60% was ≈375 pg/mL and 1470 pg/mL in patients with sinus rhythm and atrial fibrillation, respectively.[2] The corresponding values in FINEARTS-HF were 531 pg/mL and 1697 pg/mL. One of the reasons suggested for the apparent diminution of the effect of neurohumoral modulation with increasing LVEF is that the degree of neurohumoral activation is less in patients with higher LVEF compared with lower

Table 4. Safety Outcomes According to Randomized Treatment and Baseline Left Ventricular Ejection Fraction Group

Outcomes	LVEF group						$P_{interaction}$
	<50% (n=2170)		≥50% to <60% (n=2665)		≥60% (n=1143)		
	Finerenone (n=1092)	Placebo (n=1078)	Finerenone (n=1323)	Placebo (n=1342)	Finerenone (n=572)	Placebo (n=571)	
Any serious adverse event							
No. (%)	384/1092 (35.2)	397/1078 (36.8)	532/1323 (40.2)	557/1342 (41.5)	239/572 (41.8)	258/571 (45.2)	
OR (95% CI)	0.94 (0.79–1.13)		0.94 (0.81–1.10)		0.88 (0.69–1.11)		0.87
Adverse event leading to treatment discontinuation							
No. (%)	31/1092 (2.8)	30/1078 (2.8)	43/1323 (3.3)	38/1342 (2.8)	21/572 (3.7)	15/571 (2.6)	
OR (95% CI)	1.05 (0.63–1.75)		1.12 (0.72–1.75)		1.42 (0.72–2.80)		0.77
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 <100 mm Hg							
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

Data presented as the number of patients/total number (%). The safety population included all the patients who had undergone randomization and received at least one dose of finerenone or placebo (a total of 15 randomized patients were excluded from the safety analysis: 10 randomized to finerenone and 5 randomized to placebo). Safety events were considered treatment emergent if they occurred between the day of treatment initiation up to and including 3 days after treatment discontinuation. The data reported on creatinine, potassium, and systolic blood pressure levels were further restricted to patients with at least one assessment. Odds ratios (ORs) are presented for finerenone versus placebo from a logistic regression model with the outcome of interest as the dependent variable and randomized treatment and region as independent variables. LVEF indicates left ventricular ejection fraction.

values.[20] In FINEARTS-HF, the relatively higher NT-proBNP concentrations in patients with a higher LVEF may reflect a greater degree of neurohumoral activation. Patients therefore may have stood to gain more from antagonizing aldosterone's activation of the mineralocorticoid receptor. Against this hypothesis, however, is the absence of any treatment effect modification by baseline NT-proBNP level in the prespecified subgroup of less than or equal to, or greater than, the median baseline value.[15] Another potential contributing factor to the relatively higher NT-proBNP concentrations in patients with LVEF ≥60% may have been the high proportion of patients (42%) randomized during or within 3 months of a worsening HF event in this subgroup. In PARAGON-HF, patients with HFmrEF or HFpEF with a more recent episode of worsening HF appeared to benefit from sacubitril/valsartan, with no benefit in those without a history of HF hospitalization.[21] There was a similar suggestion of a trend to a greater benefit of finerenone in those with a more recent worsening HF event in FINEARTS-HF.[15]

Collagen deposition and myocardial fibrosis are key pathogenic processes in the development and progression of HFpEF and inhibition of aldosterone-mediated myocardial fibrosis is one of the key mechanisms of action of an MRA.[22–25] In a substudy of RALES (Randomized Aldactone Evaluation Study), the benefits of spironolactone on outcomes in patients with HF with reduced ejection fraction were more pronounced in patients with higher levels of circulating biomarkers reflective of collagen deposition.[24] The finding of a benefit of finerenone across the whole range of LVEF, and particularly in those with a higher LVEF (with a greater prevalence of hypertension, which is associated with myocardial fibrosis), may reflect the presence of

profibrotic activity that is modifiable by finerenone across the range of LVEF studied. The greater selectivity of finerenone for the mineralocorticoid receptor and better cardiac tissue distribution compared with spironolactone may explain, in part, the benefits of finerenone at higher LVEF values that were not seen in TOPCAT.[8,17] Future biomarker analyses may provide further mechanistic insight into the benefits of finerenone in patients with HFmrEF and HFpEF.

There is increasing awareness of the prevalence of amyloid cardiomyopathy among patients with HFpEF, particularly among those with a higher LVEF. This, along with a specific amyloid cardiomyopathy exclusion criterion, may have led to fewer patients being included in FINEARTS-HF with undiagnosed amyloid cardiomyopathy compared with previous trials.[13] The inclusion of these patients in previous trials may have contributed to the absence of benefit of neurohumoral modulating treatments at higher LVEF values. The relative absence of patients with undiagnosed amyloid cardiomyopathy in FINEARTS-HF may have resulted in more patients with a higher LVEF who were more likely to benefit from aldosterone antagonism.

There are limitations of this analysis. LVEF values were investigator-reported and were not verified by a core laboratory. Furthermore, an LVEF value could be used for eligibility if recorded within the 12 months before randomization, so was not necessarily contemporary to the time of randomization. Patients in FINEARTS-HF were required to have elevated levels of natriuretic peptides to be eligible for randomization; therefore, we are unable to comment on the efficacy of finerenone across the spectrum of LVEF in patients with HFmrEF or HFpEF with low or normal NT-proBNP levels.

Conclusions

In the randomized, placebo-controlled FINEARTS-HF trial, the nonsteroidal MRA finerenone reduced the risk of cardiovascular death and worsening HF events consistently across the range of LVEF in patients with HFmrEF or HFpEF.

ARTICLE INFORMATION

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Affiliations

British Heart Foundation Cardiovascular Research Centre, University of Glasgow, UK (K.F.D., A.D.H., P.S.J., J.J.V.M.). Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (B.L.C., A.S.D., M.V., S.D.S.). Research & Development, Pharmaceuticals, Bayer AG, Wuppertal, Germany (K.M.). Research & Development, Pharmaceuticals, Bayer, Berlin, Germany (P.V.). Cardiology and Nephrology Clinical Development, Bayer Hispania S.L., Barcelona, Spain (A.S.). National Heart Centre Singapore & Duke–National University of Singapore (C.S.P.L.). Papa Giovanni XXIII Hospital, University of Milano-Bicocca, Bergamo, Italy (M.S.). Northwestern University Feinberg School of Medicine, Chicago, IL (S.J.S.). University of Groningen, the Netherlands (A.A.V.). University of Lorraine, Nancy, France (F.Z.). University of Michigan, Ann Arbor (B.P.).

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Supplemental Material

Tables S1 and S2

REFERENCES

1. Solomon SD, Anavekar N, Skali H, McMurray JJV, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, et al; Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*. 2005;112:3738–3744. doi: 10.1161/CIRCULATIONAHA.105.561423
2. Kondo T, Dewan P, Anand IS, Desai AS, Packer M, Zile MR, Pfeffer MA, Solomon SD, Abraham WT, Shah SJ, et al. Clinical characteristics and outcomes in patients with heart failure: are there thresholds and inflection points in left ventricular ejection fraction and thresholds justifying a clinical classification? *Circulation*. 2023;148:732–749. doi: 10.1161/CIRCULATIONAHA.122.063642
3. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet*. 2003;362:777–781. doi: 10.1016/S0140-6736(03)14285-7
4. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*. 2006;27:2338–2345. doi: 10.1093/eurheartj/ehl250
5. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, et al; I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467. doi: 10.1056/NEJMoa0805450
6. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, et al; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392. doi: 10.1056/NEJMoa1313731
7. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620. doi: 10.1056/NEJMoa1908655
8. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, et al; TOPCAT Investigators. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37:455–462. doi: 10.1093/eurheartj/ehv464
9. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, Swedberg K, Yusuf S, Granger CB, Pfeffer MA, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail*. 2018;20:1230–1239. doi: 10.1002/ejhf.1149
10. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, Rouleau J, Pfeffer MA, Desai A, Lund LH, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;141:352–361. doi: 10.1161/CIRCULATIONAHA.119.044586
11. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, Vaduganathan M, Gasparyan SB, Bengtsson O, Lindholm D, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med*. 2022;28:1956–1964. doi: 10.1038/s41591-022-01971-4
12. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400:757–767. doi: 10.1016/S0140-6736(22)01429-5
13. Vaduganathan M, Claggett BL, Lam CSP, Pitt B, Senni M, Shah SJ, Voors AA, Zannad F, Desai AS, Jhund PS, et al. Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: rationale and design of the FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26:1324–1333. doi: 10.1002/ejhf.3253
14. Solomon SD, Ostrominski JW, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Lam CSP, Pitt B, Senni M, Shah SJ, et al. Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: the FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26:1334–1346. doi: 10.1002/ejhf.3266
15. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Henderson AD, Lam CSP, Pitt B, Senni M, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction [posted online September 1, 2024]. *N Engl J Med*. doi: 10.1056/NEJMoa2407107. https://www.nejm.org/doi/10.1056/NEJMoa2407107
16. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Ser B Stat Methodol*. 2000;62:711–730. doi: 10.1111/1467-9868.00259
17. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Bärfacker L, Eitner F, Albrecht-Küpper B, Schäfer S. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol*. 2014;64:69–78. doi: 10.1097/FJC.0000000000000091
18. Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, Zannad F. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J*. 2021;42:152–161. doi: 10.1093/eurheartj/ehaa736
19. Filippatos G, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, Maggioni AP, Ponikowski P, Voors AA, Zannad F, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J*. 2016;37:2105–2114. doi: 10.1093/eurheartj/ehw132
20. Vergaro G, Aimo A, Prontera C, Ghionzoli N, Arzilli C, Zyw L, Taddei C, Gabutti A, Poletti R, Giannoni A, et al. Sympathetic and renin-angiotensin-aldosterone system activation in heart failure with preserved, mid-range and reduced ejection fraction. *Int J Cardiol*. 2019;296:91–97. doi: 10.1016/j.ijcard.2019.08.040
21. Vaduganathan M, Claggett BL, Desai AS, Anker SD, Perrone SV, Janssens S, Milicic D, Arango JL, Packer M, Shi VC, et al. Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in HFpEF. *J Am Coll Cardiol*. 2020;75:245–254. doi: 10.1016/j.jacc.2019.11.003
22. Zile MR, DeSantis SM, Baicu CF, Stroud RE, Thompson SB, McClure CD, Mehurg SM, Spinale FG. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. *Circ Heart Fail*. 2011;4:246–256. doi: 10.1161/CIRCHEARTFAILURE.110.958199
23. Zile MR, Jhund PS, Baicu CF, Claggett BL, Pieske B, Voors AA, Prescott MF, Shi V, Lefkowitz M, McMurray JJV, et al; Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) Investigators. Plasma biomarkers reflecting profibrotic processes in heart failure with a preserved ejection fraction. *Circ Heart Fail*. 2016;9:e002551. doi: 10.1161/CIRCHEARTFAILURE.115.002551
24. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure. *Circulation*. 2000;102:2700–2706. doi: 10.1161/01.cir.102.22.2700
25. Iraqi W, Rossignol P, Angioi M, Fay R, Nuée J, Ketelslegers JM, Vincent J, Pitt B, Zannad F. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Circulation*. 2009;119:2471–2479. doi: 10.1161/CIRCULATIONAHA.108.809194