

Efficacy and Safety of Finerenone Across the Ejection Fraction Spectrum in Heart Failure with Mildly Reduced and Preserved Ejection Fraction: a Prespecified Analysis of The FINEARTS-HF Trial

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Efficacy and Safety of Finerenone Across the Ejection Fraction Spectrum in Heart Failure with Mildly Reduced and Preserved Ejection Fraction: a Prespecified Analysis of The FINEARTS-HF Trial

Runing title: Docherty et al.; Effect of finerenone according to LVEF

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Abstract

Background: The effect of treatments for heart failure may vary among patients according to left ventricular ejection fraction (LVEF). In the FINEARTS-HF, the nonsteroidal MRA finerenone reduced the risk of cardiovascular death and total worsening heart failure events in patients with heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF). 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 heart failure and LVEF \geq 40%. The treatment effect of finerenone was examined in prespecified analyses according to LVEF categories (<50%, \geq 50 to <60%, and \geq 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 $53 \pm 8\%$ and 53% (IOR 46%-58%), respectively. LVEF was <50% in 2172 (36%), between 50 to <60% in 2674 (45%), and \geq 60% in 1147 (19%). Patients with a higher LVEF were older, 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 to those with a lower LVEF. Finerenone reduced the risk of cardiovascular death and total heart failure events consistently across LVEF categories: LVEF <50% rate ratio (RR) = 0.84 (95% CI 0.68, 1.03), LVEF ≥50 to <60% RR = 0.80 (0.66, 0.97) and LVEF >60% RR = 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 heart failure events (continuous p interaction = 0.26).

Conclusions: In patients with HFmrEF/HFpEF, finerenone reduced the risk of cardiovascular death and worsening heart failure events, irrespective of LVEF.

Clinical Trial Registration: ClinicalTrials.go; NCT04435626 and EudraCT 2020-000306-29.

Keywords: Heart failure, ejection fraction, aldosterone, finerenone.

Nonstandard Acronyms and Abbreviations

FINEARTS-HF	FINerenone trial to investigate Efficacy and sAfety superioR to placebo
	in paTientS with Heart Failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association
SGLT2	Sodium-glucose co-transporter 2

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 (HFmrEF/HFpEF) have suggested that the benefits of neurohumoral modulating therapies are attenuated or even absent at higher left ventricular ejection fractions (LVEF).
- In this prespecified analysis of the FINEARTS-HF trial, the non-steroidal mineralocorticoid receptor antagonist finerenone reduced the risk of cardiovascular death and worsening heart failure events consistently across the entire range of LVEF in patients with HFmrEF/HFpEF.

What are the clinical implications?

These data support that finerenone should be considered as a foundational treatment for HFmrEF/HFpEF, regardless of LVEF.



Introduction

The clinical characteristics and the risk of outcomes vary substantially among patients with heart failure 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 mortality and worsening heart failure in patients with heart failure with reduced ejection fraction (HFrEF) were not replicated in trials of patients with a mildly reduced (HFmrEF) or 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 (i.e., <55-60%), with attenuation or absence of benefit in those with a normal LVEF.⁸⁻¹⁰ Conversely, the benefits of sodium-glucose co-transporter 2 (SGLT2) inhibitors 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 the FINEARTS-HF (FINerenone trial to investigate Efficacy and sAfety superioR to placebo in paTientS with Heart Failure) trial, the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone reduced the risk of cardiovascular death and worsening heart failure events in patients with heart failure and an LVEF \geq 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 the FINEARTS-HF trial.

Methods

FINEARTS-HF was a prospective, randomized, double-blind, placebo-controlled, eventdriven trial which examined the efficacy and safety of finerenone compared with placebo, in

patients with HFmrEF/HFpEF. The design, baseline characteristics, and primary results are published.^{13–15} Ethics Committees for 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 heart failure in New York Heart Association (NYHA) functional class II-IV, treatment with a diuretic for \geq 30 days before randomization, and a left ventricular ejection fraction (LVEF) \geq 40% with evidence of structural heart disease (either 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 >300 pg/mL [or BNP >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 heart failure event. Both ambulatory and hospitalized patients were eligible for enrolment. Patients with prior LVEF <40% with subsequent improvement to >40% were also eligible for enrolment provided that ongoing heart failure symptoms were present and all other inclusion criteria were satisfied. Key exclusion criteria were eGFR <25 ml/min/1.73 m², serum/plasma potassium >5.0 mmol/L at screening or randomization, or symptomatic hypotension with mean systolic blood pressure <90 mmHg at screening or randomization. A complete list of exclusion criteria is provided in the design paper.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 m² 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 m² 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 (>99%) of patients at baseline. For the purposes of this analysis, LVEF was analyzed in groups (<50%, \geq 50 to <60%, and \geq 60%) and as a continuous variable. In a sensitivity analysis, LVEF was analyzed in groups according to LVEF <50%, \geq 50 to <60%, \geq 60% to <70% and \geq 70%.

Outcomes

The primary trial outcome was the composite of total (first and recurrent) heart failure events (i.e., heart failure hospitalization or urgent heart failure visit) and cardiovascular death. Prespecified secondary outcomes were the total number of heart failure events; improvement in NYHA class from baseline to 12 months; change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (KCCQ-TSS) from baseline to 6, 9, and 12 months; a composite kidney endpoint (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 m², or initiation of dialysis or renal transplantation); and all-cause death. All deaths and potential primary outcome non-fatal 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 (i.e. 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 (IQR) 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 person-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, BMI, (log)NT-proBNP, and a history of type 2 diabetes, prior heart failure hospitalization, atrial fibrillation, and myocardial infarction.

The effect of finerenone compared to placebo was calculated as a rate ratio (RR) and 95% confidence interval (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-TSS 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 for the presence of any modification of treatment effect according to LVEF.

All analyses were performed using Stata version 18 (College Station, TX, USA) A pvalue of <0.05 was considered nominally statistically significant. Trial data will be made available by the sponsor, Bayer, in accordance with their data-sharing policy.

Results

LVEF was recorded in 5993 of the 6001 participants in FINEARTS-HF. The mean \pm SD and median (IQR) LVEF at baseline were 53 \pm 8% and 53% (46%-58%), respectively, with a range of 34%-84%. The distribution of LVEF is displayed in Figure 1. LVEF was <50% in 2172 (36%), between 50 to <60% in 2674 (45%) and \geq 60% in 1147 (19%). Baseline characteristics according to LVEF group are detailed in Table 1 and Supplementary Table 1. Compared to those with a lower LVEF, patients with a higher LVEF were older, more commonly a woman, had lower (i.e., worse) KCCQ-TSS values, had a higher mean BMI and systolic blood pressure, and a greater prevalence of kidney dysfunction. Conversely, patients with a lower LVEF were more likely to have a history of myocardial infarction or a prior heart failure hospitalization, had higher NT-proBNP concentrations, and were more likely to be treated with a beta-blocker, a renin-angiotensin system inhibitor, an angiotensin receptor-

neprilysin inhibitor, an SGLT2 inhibitor and a loop diuretic than those with a higher LVEF. A history of a previous LVEF <40% was most common in those with a baseline LVEF <50% compared to those with a higher LVEF.

Outcomes according to left ventricular ejection fraction

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 heart failure events), its individual components, and all-cause mortality were highest in patients with lower LVEF, with rates decreasing across the range of LVEF 40-60% with a plateauing of event rates in patients with an LVEF \geq 60%.

After adjustment for baseline covariates, the rate of the primary composite outcome was similar across LVEF categories; rate ratio (RR) = 1.07 (95% confidence interval (CI) 0.89, 1.29) for LVEF <50% and 1.09 (95%CI 0.91, 1.31) for LVEF \geq 50% to <60% (referent group = LVEF \geq 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 left ventricular ejection fraction

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 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 heart failure events was not modified by LVEF when analyzed in categories (p for interaction = 0.70) or as a continuous variable (p for interaction = 0.28). In a continuous spline model (**Figure 3**), the rate ratio estimate for the primary composite outcome was below 1.0, indicating a benefit of finerenone, from an LVEF of 40% up to approximately 70%, with a substantial widening of the 95% CI at higher LVEF values

of >70%. Notably, the hazard ratio for finerenone compared with placebo for the time-to-first event outcome of cardiovascular death or first worsening heart failure event was below 1.0 across the whole range of LVEF 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 heart failure events (categorical p for interaction = 0.67 and continuous p for 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 heart failure events, with the rate ratio estimate being below 1.0 for the majority of the LVEF range (p interaction = 0.26) (**Figure 3**). Again similarly to the primary outcome, when considered as a time-to-first event outcome, the hazard ratio estimate was indicative of a benefit of finerenone (i.e., remained below 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 and Figure 3**) except for the kidney composite outcome. In those with an LVEF \geq 60% there was an apparent benefit of finerenone on the kidney outcome whereas, contrastingly, there were numerically more kidney-related events in those randomized to finerenone as compared with placebo in the lower LVEF groups (categorical p for interaction = 0.003 and continuous p for interaction = 0.09). Finerenone had a consistent benefit on increasing the KCCQ-TSS 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%, $\ge60\%$ to <70%, and $\ge70\%$ (Supplementary Table 2).

Safety outcomes according to left ventricular ejection fraction

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 the FINEARTS-HF trial, the beneficial effect of finerenone on reducing the risk of cardiovascular death and the total number of heart failure hospitalizations was consistent across the range of LVEF in patients with heart failure and an LVEF \geq 40%. These data support the use of finerenone as a foundational therapy for patients with HFmrEF or HFpEF, along with sodium-glucose cotransporter 2 (SGLT2) inhibitors.

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 "HFrEF-like" phenotype; they were more likely to be male, 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 heart failure regardless of LVEF, the use of SGLT2 inhibitors was more common in those with a lower ejection fraction, probably reflecting the later approval of the use of these drugs in HFmrEF/HFpEF, which occurred during follow-up of FINEARTS-HF. Conversely, patients with a higher LVEF were older, more often females, and had less ischemic heart disease but a greater prevalence of hypertension, higher BMI, 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 to patients with HFrEF, 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 \geq 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, as well as improve symptoms, in patients with HFmrEF/HFpEF. Previous trials in patients with HFmrEF/HFpEF did not show a clear benefit of renin-angiotensin-system inhibition or the combined angiotensin receptorneprilysin inhibitor (ARNI) sacubitril/valsartan.^{3–5,7} In TOPCAT, the steroidal MRA spironolactone did not reduce the risk of the primary endpoint of cardiovascular death, heart failure hospitalization, or resuscitated cardiac arrest in the overall trial population of patients with an LVEF \geq 45%.⁶ However, in a *post hoc* analysis of TOPCAT according to LVEF, spironolactone improved outcomes in patients with a reduced LVEF in the mildly reduced range, but not in those with an LVEF in the normal range (i.e., >55-60%).⁸ Similar findings of a varying treatment effect according to LVEF were seen with the angiotensin receptor blocker candesartan in the CHARM programme and with sacubitril/valsartan in PARAGON-HF (which enrolled patients with an LVEF \geq 45%) although none of these were 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 heart failure events appeared to be attenuated in patients with an LVEF >70% on visual assessment of the continuous spline analysis, the overall tests for

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heterogeneity of treatment effect were non-significant 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 (ClinicalTrials.gov identifiers NCT06024746 and 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 \geq 60% group probably reflects the play of chance due to the small number of kidney endpoints 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/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/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 heart failure. In the MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF), 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 betweentreatment comparisons on clinical outcomes.

The second potential explanation may be that patients with a higher LVEF enrolled in FINEARTS-HF were different to 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 $\geq 60\%$ were higher than those in other comparative HFmrEF/HFpEF trials. In a pooled analysis of four large HFmrEF/HFpEF trials, the median NT-proBNP in patients with an LVEF $\geq 60\%$ was approximately 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 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 may therefore have potentially 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 in the prespecified subgroup of $\leq >$ the median baseline value.¹⁵ Another potential contributing factor to the relatively higher NT-proBNP concentrations in patients with LVEF $\geq 60\%$ may have been the high proportion of patients (42%) randomized during or within 3 months of a worsening HF event in this subgroup. Notably, in PARAGON-HF, patients with HFmrEF/HFpEF with a more recent episode of worsening HF appeared to benefit from sacubitril/valsartan, with no benefit in those without a history of heart failure hospitalization.²¹ There was a similar suggestion of a trend to a greater

benefit of finerenone in those with a more recent worsening heart failure 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, the benefits of spironolactone on outcomes in patients with HFrEF 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. Finerenone's greater selectivity 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 HFmEF and HFpEF.

Finally, 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 which should be noted. 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 prior to 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 FINEARTS-HF randomized, placebo-controlled trial, the nonsteroidal MRA finerenone reduced the risk of cardiovascular death and worsening heart failure events consistently across the range of LVEF in patients with HFmrEF or HFpEF.



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Disclosures

Dr Docherty reports that his employer, the University of Glasgow, has been remunerated by AstraZeneca for his work on clinical trials; he has received speaker fees from AstraZeneca, Boehringer Ingelheim, Pharmacosomos, and Translational Medicine Academy; has served on advisory boards or performed consultancy for FIRE-1, Us2.ai and Bayer AG; holds stock in Us2.ai; has served on a Clinical Endpoint Committee for Bayer AG; and has received research grant support (paid to his institution) from AstraZeneca, Roche, Novartis and Boehringer Ingelheim.

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Supplemental Materials

Supplemental Tables 1-2

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Characteristic	<50% (n=2172)	≥50% to <60% (n=2674)	≥60% (n=1147)	Trend P value
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		. ,		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 prior 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)	
\leq 7 days from randomization	188 (8.7)	214 (8.0)	68 (5.9)	
>7 days to \leq 3 months	792 (36.5)	943 (35.3)	290 (25.3)	
>3 months	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

Table 1. Baseline characteristics according to baseline left ventricular ejection fraction group.

			1		
Sinus rhythm on baseline ECG	764 (368-1539)	532 (288-1119)	531 (300-1069)	< 0.001	
Atrial fibrillation on baseline ECG	1820 (1150 2204)	1676 (1140-	1697 (1223-	<0.001	
	1839 (1130-3304)	2533)	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, mmHg	127.5±14.9	130.2±15.5	131.2±15.3	< 0.001	6
Baseline eGFR, mL/min/1.73 m ²	64.8±20.1	61.0±19.3	59.6±19.4	< 0.001	Amor
Baseline eGFR <60 mL/min/1.73 m ²	929 (42.8)	1,345 (50.3)	610 (53.2)	< 0.001	Amer Heart Assoc
Baseline UACR, mg/g [*]	142±493	181±714	155±554	0.54	ASSOC
Baseline pharmacotherapy					
β-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	
Loop diuretic	1,972 (90.8)	2,318 (86.7)	943 (82.2)	< 0.001	
Mean furosemide equivalent dose,	51 7 50 5	54 4+65 0	10 9 1 15 9	0.46	
mg [†]	31.7±39.3	34.4±03.9	49.8±43.8	0.40	
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	
	KCCQ - Total Symptom ScoreKCCQ - Clinical Summary ScoreKCCQ - Overall Summary ScoreNYHA functional class at baselineIIIII/IVAtrial fibrillation on baseline ECGBaseline systolic blood pressure, mmHgBaseline eGFR, mL/min/1.73 m²Baseline eGFR <60 mL/min/1.73 m²	Atrial fibrillation on baseline ECG1839 (1150-3304)KCCQ - Total Symptom Score 69.3 ± 23.9 KCCQ - Clinical Summary Score 67.9 ± 22.6 KCCQ - Overall Summary Score 64.5 ± 22.3 NYHA functional class at baseline1499 (69.0)III/IV 673 (31.0)Atrial fibrillation on baseline ECG 771 (35.5)Baseline systolic blood pressure, mmHg 127.5 ± 14.9 Baseline eGFR, mL/min/1.73 m² 64.8 ± 20.1 Baseline eGFR <60 mL/min/1.73 m²	Atrial fibrillation on baseline ECG $1839 (1150-3304)$ $1676 (1140-2533)$ KCCQ - Total Symptom Score 69.3 ± 23.9 65.9 ± 23.8 KCCQ - Clinical Summary Score 67.9 ± 22.6 64.0 ± 22.3 KCCQ - Overall Summary Score 64.5 ± 22.3 61.9 ± 22.0 NYHA functional class at baselineIII/IV $673 (31.0)$ $846 (31.6)$ Atrial fibrillation on baseline ECG $771 (35.5)$ $1099 (41.1)$ Baseline systolic blood pressure, mmHg 127.5 ± 14.9 130.2 ± 15.5 Baseline eGFR, mL/min/ $1.73 m^2$ 64.8 ± 20.1 61.0 ± 19.3 Baseline eGFR <60 mL/min/ $1.73 m^2$ $929 (42.8)$ $1,345 (50.3)$ Baseline pharmacotherapy $616 (28.4)$ $1,016 (38.0)$ ARB $616 (28.4)$ $1,016 (38.0)$ ARNI $341 (15.7)$ $145 (5.4)$ SGLT2i $336 (15.5)$ $366 (13.7)$ Loop diuretic $1,972 (90.8)$ $2,318 (86.7)$ Mean furosemide equivalent dose, mg ⁺ 51.7 ± 59.5 54.4 ± 65.9 Thiazide diuretic $209 (9.6)$ $407 (15.2)$	Atrial fibrillation on baseline ECG1839 (1150-3304)1676 (1140- 2533)1697 (1223- 2537)KCCQ - Total Symptom Score 69.3 ± 23.9 65.9 ± 23.8 65.5 ± 23.9 KCCQ - Clinical Summary Score 67.9 ± 22.6 64.0 ± 22.3 63.7 ± 22.4 KCCQ - Overall Summary Score 64.5 ± 22.3 61.9 ± 22.0 61.7 ± 22.3 NYHA functional class at baselineII1499 (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)Baseline systolic blood pressure, mmHg 127.5 ± 14.9 130.2 ± 15.5 131.2 ± 15.3 Baseline eGFR, mL/min/1.73 m ² 64.8 ± 20.1 61.0 ± 19.3 59.6 ± 19.4 Baseline UACR, mg/g* 142 ± 493 181 ± 714 155 ± 554 Baseline pharmacotherapyI 77 (40.1) 890 (33.3) 392 (34.2)ARB 616 (28.4) $1,016$ (38.0) 465 (40.5)ARB 616 (28.4) $1,016$ (38.0) 465 (40.5)ARNI 341 (15.7) 145 (5.4) 27 (2.4)SGLT2i 336 (15.5) 366 (13.7) 113 (9.9)Loop diuretic $1,972$ (90.8) $2,318$ (86.7) 943 (82.2)Mean furosemide equivalent dose, mg* 51.7 ± 59.5 54.4 ± 65.9 49.8 ± 45.8	Atrial fibrillation on baseline ECG1839 (1150-3304)1676 (1140- 2533)1697 (1223- 2537)<0.001KCCQ - Total Symptom Score69.3 \pm 23.965.9 \pm 23.865.5 \pm 23.9<0.001

Values are n (%), mean \pm SD, or median (IQR).

*: Baseline UACR unavailable in 204 participants

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CABG, coronary artery bypass grafting; CCB = calcium channel blocker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association; PCI, percutaneous coronary intervention; SGLT2i = sodium-glucose co-transporter 2 inhibitor; UACR = urinary albumin-to-creatinine ratio

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

Table 2. Risk of outcomes according to baseline left ventricular ejection fraction group.

		LVEF Group	
	<50% (n=2172)	≥50% to <60% (n=2674)	≥60% (n=1147)
Cardiovascular death and total number of v			(#=1147)
Number of events	910	1,028	428
Event rate per 100 person-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 number of worsening heart failure ev	ents		
Number of events (%)	688	840	338
Event rate per 100 person-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 he	art failure event		
No (%)	534 (24.6%)	572 (21.4%)	237 (20.7%)
Event rate per 100 person-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 person-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 heart failure event			
No (%)	394 (18.1%)	468 (17.5%)	190 (16.6%)
Event rate per 100 person-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			American
No (%)	41 (1.9%)	62 (2.3%)	27 (2.4%) Association.
Event rate per 100 person-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 person-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.

*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. Abbreviations: CI, confidence interval; HR=Hazard Ratio; RR, rate ratio.

			LVEF	Group				
		50% 2172)		to <60% 2674)	_	0% 147)		
	Finerenone (n=1093)	Placebo (n=1079)	Finerenone (n=1329)	Placebo (n=1345)	Finerenone (n=575)	Placebo (n=572)	P value for categorical LVEF group*treatme nt interaction	P value for continuous LVEF *treatment interaction
Cardiovascular death	and total number of	f worsening heart fa	ilure events				American	
Number of events	414	496	463	565	206	222	Heart Association.	
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 worse	ening heart failure e	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)		
R [‡] (95% CI) [*]	0.83 (0.65, 1.06)		0.77 (0.61, 0.95)		0.92 (0.66, 1.27)		0.67	0.26
Asijusted RR (95%	0.83 (0.65, 1.05)		0.73 (0.59, 0.91)		0.79 (0.57, 1.09)		0.65	0.19
Gardiovascular death	or first worsening h	eart failure 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)		
[₫] H₽ (95% CI) [‡]	0.81 (0.68, 0.96)	L	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

Table 3. Effect of randomized treatment on outcomes according to baseline left ventricular ejection fraction group.

Cardiovascular death	1							
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)	1	0.70	0.70
Adjusted HR (95% CI) [†]	0.85 (0.65, 1.11)	0.85 (0.65, 1.11))	0.95 (0.61, 1.46)		0.93	0.81
First worsening hear	t failure 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)	Amorican	
HR (95% CI) [‡]	0.78 (0.64, 0.95)		0.84 (0.70, 1.00)		0.80 (0.60, 1.07)		0.87 ^{leart}	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 ou	tcome ^{**}		-				-	
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	0.09
$\vec{\mathbf{A}}_{\mathbf{I}}^{\mathbf{I}}$ justed HR (95%	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)		
₩ (95% CI) [‡]	0.94 (0.77, 1.15))	0.87 (0.72, 1.05))	1.03 (0.77, 1.37)		0.62	0.91
Agdjusted HR (95% CH) [†]	0.96 (0.78, 1.17)		0.85 (0.70, 1.04)		1.00 (0.74, 1.34)		0.72	0.99
Improvement in NYI	HA class from base	line 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
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 person-years

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

[†]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.

[‡]For time-to-first event outcomes, hazard ratios and 95% confidence intervals were estimated using Cox regression models, stratified by geographic region.

**The composite kidney outcome was defined as a sustained decline in eGFR \geq 50% relative to baseline over at least 4 weeks, or sustained eGFR decline <15 ml/min/1.73 m², or the initiation of dialysis or renal transplantation.

Abbreviations: CI, confidence interval; HR, Hazard Ratio; RR, rate ratio.

		LVEF Group							
		<50% (n=2170)		≥50% to<60% (n=2665)		≥60% (n=1143)			
	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Finerenone Placebo			
	(n=1092)	(n=1078)	(n=1323)	(n=1342)	(n=572)	(n=571)			
Any serious adv	verse 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)	American		
OR (95% CI)	0.94 (0.79, 1.13)	1	0.94 (0.81, 1.10)	1	0.88 (0.69, 1.11)		0.87		
Adverse event le	eading to treatment d	liscontinuation	_		_				
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	1.84 (0.97, 3.48)		2.23 (0.68, 7.32)		0.75		
Potassium >5.5	mmol/L						1		
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)	1	2.37 (1.81, 3.11)	1	2.16 (1.41, 3.32)	1	0.88		
Potassium >6.0	mmol/L		1		1		1		
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)			

Table 4. Safety outcomes according to randomized treatment and baseline left ventricular ejection fraction group.

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 n	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)	0.32 (0.21, 0.48)		0.54 (0.40, 0.73)		0.36 (0.22, 0.58)	
Systolic blood p	ressure <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	1.50 (1.20, 1.89)		1.89 (1.31, 2.73)	1	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 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 an independent variables.

Abbreviations: OR, odds ratio; CI, confidence interval.

Figure Legends

Figure 1. Distribution of Baseline Left Ventricular Ejection Fraction

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 LVEF included as a continuous variable using restricted cubic splines with 3 knots.

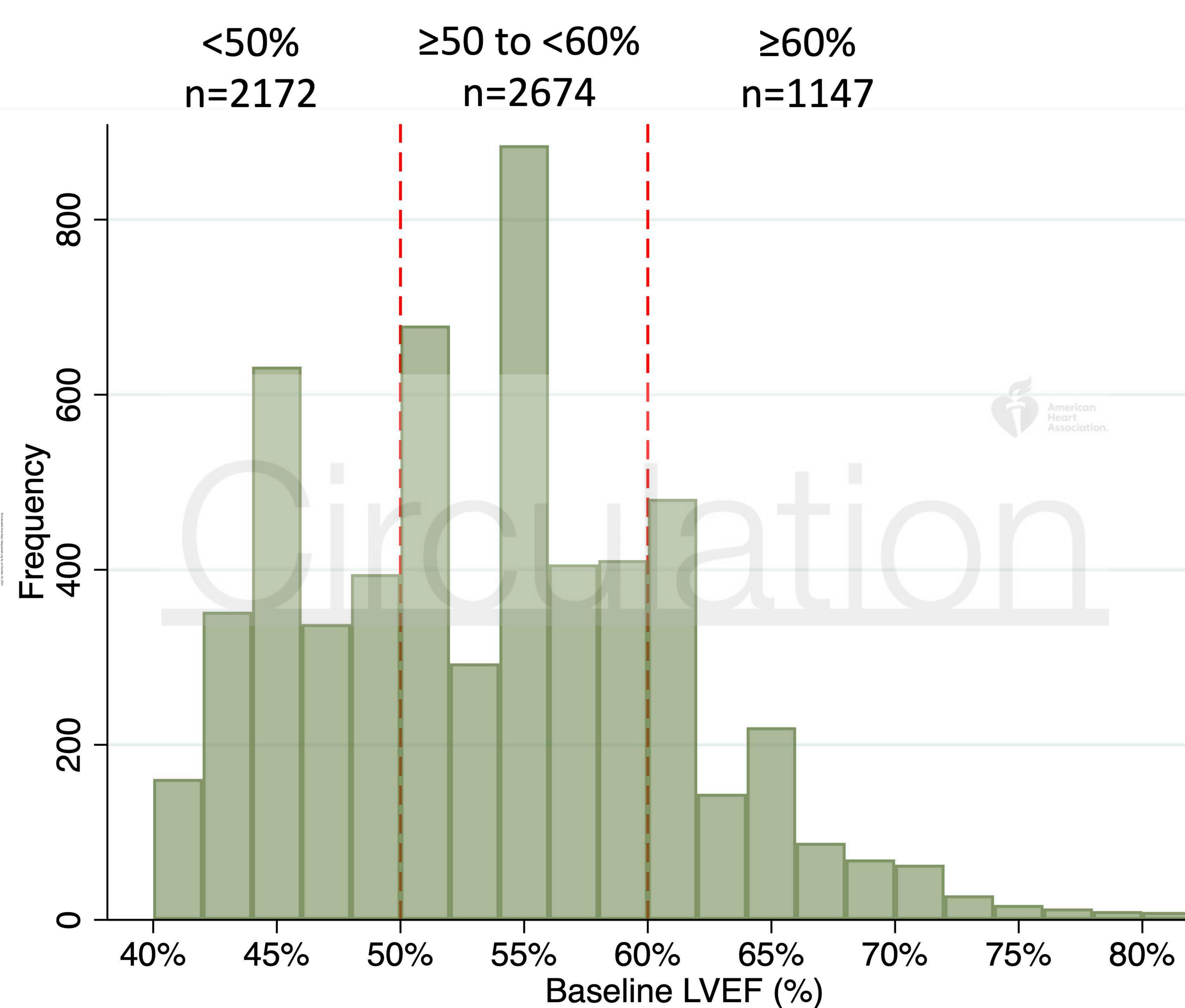
Figure 3. Treatment Effect of Finerenone Compared With Placebo Across the Spectrum of Left Ventricular Ejection Fraction

The effect of finerenone on outcomes according to 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% confidence intervals were estimated using the semiparametric proportional rates method of Lin et al. stratified according to geographic region. For time-to-first event outcomes, hazard ratios and 95% confidence intervals were estimated using Cox regression models, stratified by geographic region. An effect estimate of less than 1.0 indicates benefit of finerenone. Shaded areas represent 95% confidence intervals. P values for interaction represent the interaction between LVEF as a continuous variable and treatment.

Figure 4. Absolute Benefit of Finerenone Compared With Placebo Cross the Spectrum of Left Ventricular Ejection Fraction

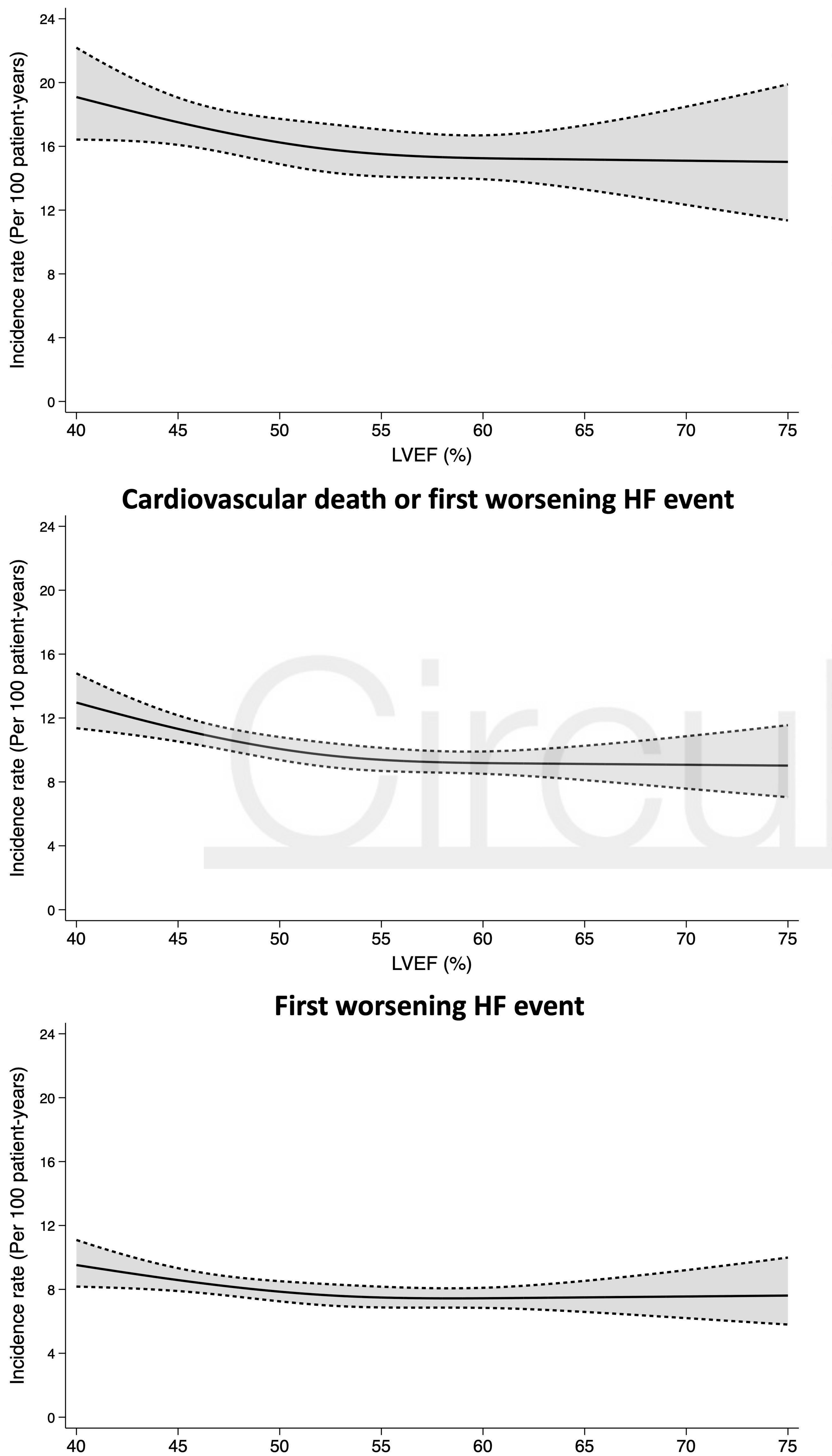
The absolute benefit of finerenone on the primary outcome was calculated by modeling a consistent treatment effect across the range of baseline LVEF. The absolute rate difference was calculated using a Poisson regression model with LVEF included as a continuous variable using a restricted cubic spline with 3 knots.











Cardiovascular death and total worsening HF events

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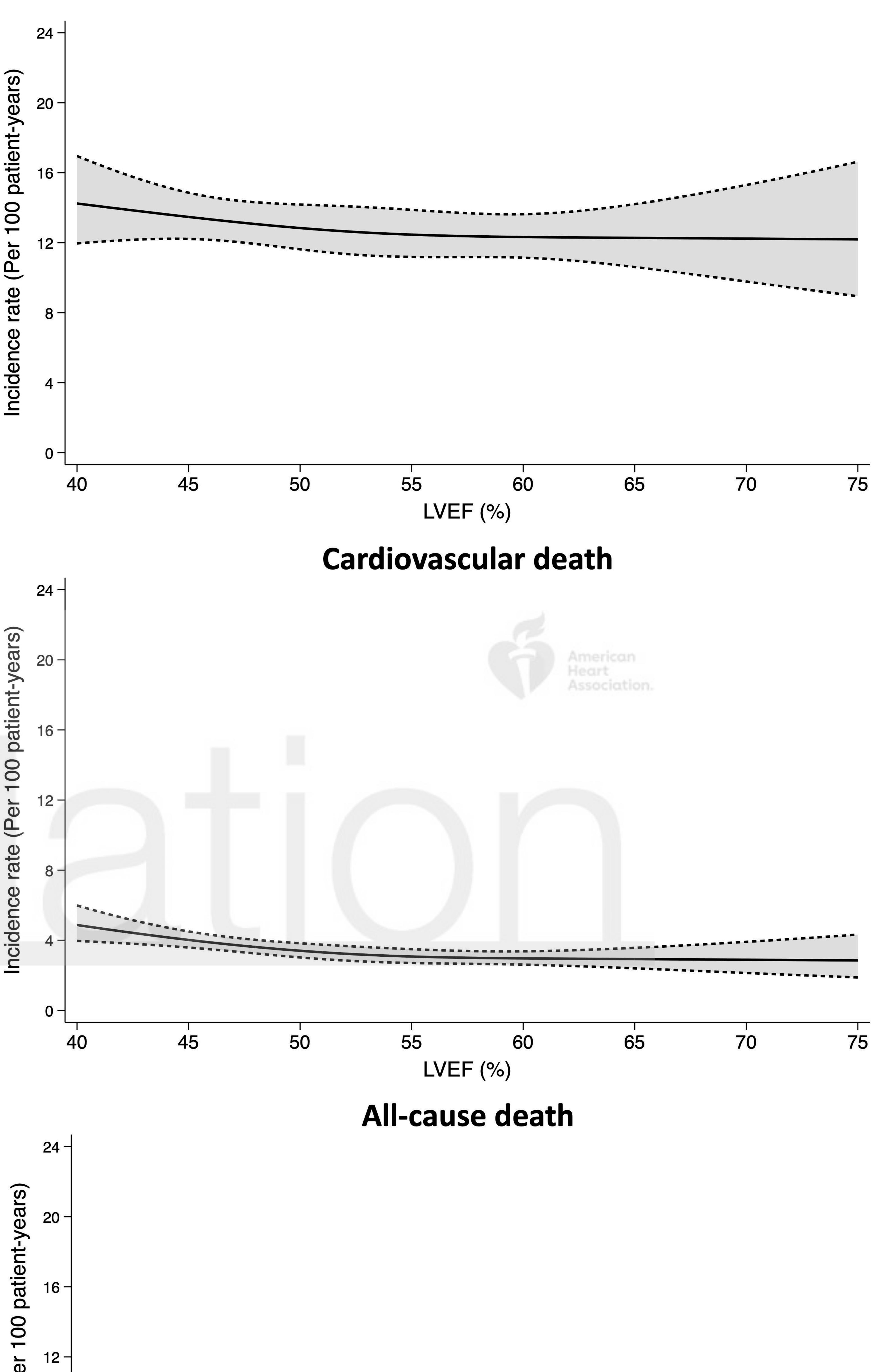
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


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Total worsening HF events

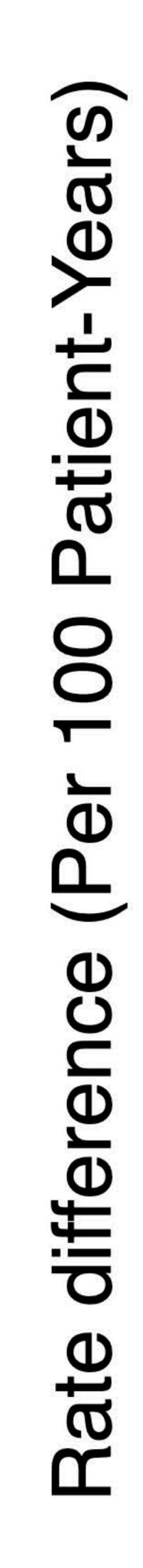
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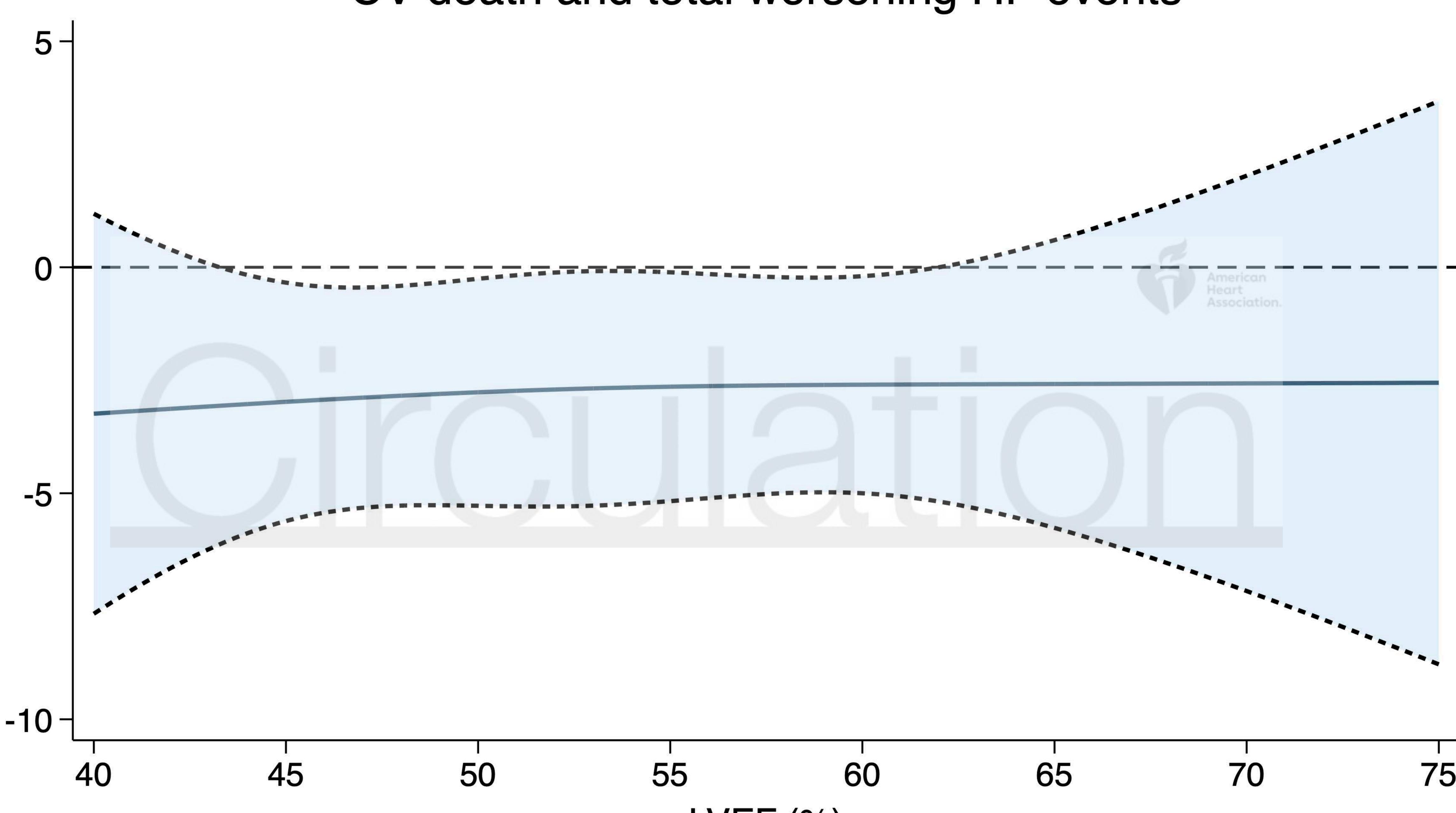




Cardiovascular death and total worsening HF events

Total worsening HF events





CV death and total worsening HF events