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10.1161/CIRCHEARTFAILURE.124.012437

Finerenone Improves Outcomes in Patients with Heart Failure with Mildly Reduced or Preserved Ejection Fraction Irrespective of Age: A Prespecified Analysis of FINEARTS-HF

Running Title: *Chimura, et al; Age and Finerenone in HFmrEF/HFpEF*

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This article is published in its accepted form, it has not been copyedited and has not appeared in an issue of the journal. Preparation for inclusion in an issue of *Circulation: Heart Failure* involves copyediting, typesetting, proofreading, and author review, which may lead to differences between this accepted version of the manuscript and the final, published version.

This work was presented as an abstract at the HFSA Annual Scientific Meeting 2024, September 27 to September 30, 2024.

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Abstract

Background: Finerenone improves outcomes in patients with HF and mildly reduced or preserved ejection fraction (HFmrHF/HFpEF). It is important to understand the efficacy and safety of finerenone in these patients according to age.
Methods: The aim of this analysis was to evaluate the interaction between age and the efficacy and safety of finerenone in the FINEARTS-HF trial (Finerenone trial to investigate efficacy and safety compared to placebo in patients with heart failure). A total of 6,001 patients aged 40-97 years were stratified by quartile (Q 1-4) of baseline age: Q1 40-66 years (n=1,581), Q2 67-73 years (n=1,587), Q 3 74-79 years (n=1,421), and Q4 ≥ 80 years (n=1,412). FINEARTS-HF evaluated the impact of age on the efficacy of finerenone with respect to the primary composite outcome of cardiovascular death and total (first and recurrent) HF events, including HF hospitalization or urgent HF event, along with secondary efficacy and safety outcomes.
Results: The incidence of primary outcome increased with age. Finerenone reduced the risk of the primary outcome consistently across all age categories: RR (95% CI) Q1 0.70 (0.53-0.92), Q2 0.83 (0.64-1.07), Q3 0.98 (0.76-1.26), and Q4 0.85 (0.67-1.07); p for interaction =0.27. Similarly, a consistent effect was observed for the components of the primary outcome. The mean increase in Kansas City Cardiomyopathy Questionnaire-total symptom score from baseline to 12 months was greater with finerenone than placebo, with a consistent effect across all age categories: mean placebo-corrected change (95% CI) Q1 2.87 (1.09-4.66), Q2 1.24 (-0.59-3.07), Q3 0.94 (-0.98-2.86), and Q4 1.24 (-0.90-3.38); P-interaction=0.50. Adverse events were similar across all age categories. The odds of experiencing hypotension, elevated creatinine, or hyperkalemia (increased) or hypokalemia (decreased) related to finerenone did not differ by age.
Conclusions: In the FINEARTS-HF trial, finerenone reduced the primary outcome and components of the primary outcome, and improved symptoms across a wide age spectrum. In addition, finerenone was safe and well-tolerated, irrespective of age.
Trial Registration: URL: https://clinicaltrials.gov Unique Identifiers: NCT04435626 and EudraCT 2020-000306-29.

Key Words: age; heart failure with mildly reduced or preserved ejection fraction (HFmrEF/HFpEF); finerenone; heart failure hospitalization; prognosis; treatment effect

Nonstandard Abbreviations and Acronyms
BMI: Body mass index
CI: Confidence interval
eGFR: Estimated glomerular filtration rate
FINEARTS-HF trial: 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
LVEF: Left ventricular ejection fraction
NT-proBNP: N-terminal pro-B-type natriuretic peptide
NYHA: New York Heart Association

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What is New?

- In the FINEARTS-HF trial (Finerenone trial to investigate efficacy and safety superior to placebo in patients with heart failure), finerenone improved clinical outcomes and alleviated heart failure (HF) symptoms in 6,001 HF patients with mildly reduced and preserved ejection fraction.
- The efficacy and safety of finerenone were consistent across the age spectrum studied (40– 97 years).

What are the Clinical Implications?

- The benefits of finerenone are consistent across all age groups, including patients aged 80 years and older.
- Hypotension, elevated creatinine, and hyperkalemia were more common with finerenone and hypokalemia less common with finerenone, but these differences between finerenone and placebo did not vary according to age.
- Advanced age, in itself, should not be a reason to withhold finerenone in patients with mildly reduced and preserved ejection fraction.

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Introduction

The prevalence of heart failure with mildly reduced and preserved ejection fraction (HFmrEF/HFpEF) is increasing, and it is projected that HFmrEF/HFpEF will soon surpass heart failure with reduced ejection fraction (HFrEF) to become the predominant heart failure (HF) phenotype globally[1-2]. This trend is primarily driven by aging populations worldwide and in the United States alone, the population aged 80 years and over increased from 4.1 million in 1971 to 13.1 million in 2020 with this change expected to continue or accelerate[3]. Consequently, identifying effective treatments for HFmrEF/HFpEF, particularly in the elderly, to reduce worsening HF events and improve health status, has emerged as an important contemporary therapeutic challenge[1,4-6]. This challenge is amplified by concerns that older patients with HFmrEF/HFpEF are often frail and have multiple comorbidities leading to polypharmacy. These considerations, coupled with differing pharmacodynamics and pharmacokinetics in older compared to younger people, raise further concerns that treatments may be less well tolerated in older adults. Therefore, it is crucial to also evaluate the safety of incorporating new medications into the existing therapeutic regimens of these patients[7]. Without an in-depth understanding of the efficacy and tolerability of novel therapies there is a significant risk of their underuse as has been repeatedly observed for many valuable treatments in older individuals [8-10].

In the FINEARTS-HF trial (Finerenone trial to investigate efficacy and safety superior to placebo in patients with heart failure), the effects of the selective non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone were compared to those of placebo in patients with HFmrEF/HFpEF. Among the 6001 participants analyzed, finerenone added to background therapy reduced the risk of cardiovascular death and total (first and recurrent) HF events compared to placebo[11]. FINEARTS-HF enrolled patients with a wide range of ages (40 to 97 years) and, notably, 64% of trial participants were aged 70 years or above and 24%

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were 80 years of age or older. In this prespecified analysis, we examined the efficacy and safety of finerenone compared to placebo, stratified by age.

Methods

FINEARTS-HF trial design and objectives

FINEARTS-HF was a multicenter, prospective, randomized, double-blind, event-driven 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[11-13]. Key inclusion criteria were age ≥40 years, symptomatic HF in New York Heart Association (NYHA) functional class II-IV, treatment with a diuretic for ≥30 days before randomization, and a left ventricular ejection fraction (LVEF) ≥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 levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) >300 pg/mL or B-type natriuretic peptide (BNP) >100 pg/mL for those in sinus rhythm, or NT-proBNP >900 pg/mL or BNP >300 pg/mL for those in atrial fibrillation. These measurements were to be taken within 90 days for patients with a recent worsening HF event within 90 days prior to randomization, or within 30 days before randomization for those without a recent worsening HF 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 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 potassium >5.0 mmol/L at screening or randomization, or symptomatic hypotension with mean systolic blood pressure (SBP) <90 mmHg at screening or randomization. A complete list of exclusion criteria is provided in the design paper[12]. Eligible participants

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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. Ethics Committees for the 653 participating institutions in 37 countries approved the protocol and all patients gave written consent. The corresponding author had full access to all the trial data and takes responsibility for its integrity and the data analysis. Trial data will be made available by the sponsor, Bayer, in accordance with their data sharing policy.

Trial outcomes

The primary outcome was the composite of total (first and recurrent) HF events, including HF hospitalization or an urgent HF event, and cardiovascular death. The secondary outcomes included total HF events (we also examined cardiovascular death and cardiovascular death or a first HF event); improvement in NYHA functional class from baseline to 12 months; change from baseline to 6,9 and 12 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS); time to first occurrence of the composite renal endpoint (defined as a sustained decrease in eGFR ≥50% relative to baseline over at least 4 weeks, or a sustained eGFR decline <15 ml/min/1.73 m², or the initiation of dialysis or renal transplantation); and time to all-cause death. Due to the small number of events for the composite renal endpoint, this endpoint was not examined in this subgroup analysis. The prespecified safety outcomes included incidents of hyperkalemia (defined as serum potassium >5.5mmol/L or >6.0mmol/L), hypokalemia (defined as serum potassium <3.5mmol/L), elevation of serum creatine (defined as serum creatinine ≥2.5 mg/dL or ≥3.0 mg/dL), and hypotension (defined as SBP <100mmHg).

Statistical analysis

Between 2020 and 2023, a total of 7,463 patients from 37 countries were screened, with

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6,001 patients ultimately analyzed. Participants were stratified by quartile of baseline age: 40- 66, 67-73, 74-79, and ≥80 years. Baseline characteristics were summarized as frequencies with percentages for categorical variables, means with standard deviations for normally distributed continuous variables, and medians with interquartile ranges for non-normally distributed continuous variables. Differences in baseline characteristics were assessed using the Cochran-Armitage trend test for binary variables, the Cochran-Mantel-Haenszel test for categorical variables, and the Jonckheere-Terpstra test for continuous variables. The Poisson regression model with robust standard errors was used to calculate the incidence rate of events by age quartile, and the rate of specific causes of death across the age spectrum. To compare the effects of finerenone versus placebo according to age, time-to-event data were evaluated using Kaplan-Meier curves and Cox proportional-hazards models, with treatment assignment as a fixed effect and region and baseline LVEF (< 60% or ≥ 60%) as stratification factors, and hazard ratios (HR) with 95% confidence intervals (CIs) were reported. Total (first and recurrent) events were evaluated using Nelson-Aalen cumulative hazard curves and rate ratios (RRs) with 95% CIs semiparametric proportional rates models[14], with adjustments and stratification for the same covariates mentioned above. Additionally, HRs and RRs were adjusted for baseline variables (sex,heart rate, SBP, body mass index, NT-proBNP [log], eGFR, NYHA functional class III/IV, LVEF, myocardial infarction, diabetes mellitus, history of atrial fibrillation and history of HF hospitalization). The effect of finerenone versus placebo across the range of age as a continuous variable (2.5^{th}-97.5^{th} percentiles) was modeled using restricted cubic splines (RCS) with 3 knots. The difference in the incidence rate of the primary composite outcome and total HF events across the range of age was estimated using predictions from a Poisson model (that included an offset variable to account for the differential follow-up) with robust standard errors adjusted for treatment effect and an RCS of age with 3 knots.

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The change in KCCQ-TSS from baseline to 12 months was analyzed using a linear regression of change in month 12 KCCQ-TSS adjusted for baseline KCCQ-TSS, geographic region and baseline LVEF strata. We computed least squares estimates of the mean change by treatment group at 12 months, and the difference between treatment groups within each age quartile. In addition, the proportion of patients with improvement in NYHA functional class from baseline to 12 months was evaluated using logistic regression models, adjusted for treatment assignment and stratification levels and odds ratios (OR) with 95% CIs were reported. In addition, ORs adjusted for the variables mentioned above were also reported. The incidence of safety endpoints was estimated using similar logistic regression models and an interaction with age quartile was tested using a likelihood ratio test. Additional, *post-hoc,* exploratory analyses were conducted on elderly patients, specifically those aged 75-79, 80-84, and over 85 years. All statistical analyses were conducted using STATA version 18 (College Station, TX, USA), and a P value of <0.05 was considered nominally statistically significant.

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Results

Overall, 6,001 patients aged between 40 and 97 years were randomized, with a mean age of 72 years. The age distribution (by quartile) was as follows: 1,581 patients were aged 40-66 years, 1,587 patients were 67-73 years, 1,421 patients were 74-79 years, and 1,412 patients were ≥80 years (Figure S1).

Patient characteristics according to age category

Older patients were predominantly female (Table 1). Most comorbidities including atrial fibrillation, stroke, and anemia, were more prevalent among older patients, compared to younger patients (although coronary heart disease and diabetes were not, showing an opposite age-related gradient). Older patients also had higher NT-proBNP levels but lower body mass

index, eGFR, and hemoglobin levels. Patients aged ≥80 years had the highest mean LVEF, with a greater proportion of LVEF ≥50% compared to the 40-66 years category (73% versus 51%). Median baseline KCCQ-TSS, KCCQ-overall summary score, and KCCQ-clinical summary score decreased with age, indicating that older patients had worse health status (Table 1). Consistent with this, NYHA functional class distribution was also worse in older compared to younger patients. Regarding background HF medications, older patients were less frequently treated with renin-angiotensin system blockers and beta-blockers, compared to younger patients. The use of sodium-glucose cotransporter 2 inhibitors was low overall but similar across all age categories (Table 1).

Clinical outcomes according to age category

The incidence rate (per 100 patient-years) of the primary composite outcome increased with age: 40-66 years, 12.8 (95% CI, 11.1 to 14.7); 67-73 years, 14.9 (95% CI, 13.1 to 17.1); 74-79 years, 15.7 (95% CI, 13.9 to 17.8); and ≥ 80 years, 22.9 (95% CI, 20.3 to 25.8). Similar trends were observed for the components of the primary composite outcome, cardiovascular death or worsening HF analyzed as the time-to-first event, a first worsening HF event, and all-cause death (Table 2). The higher risk of worsening HF events associated with older age was largely eliminated when adjusted for other recognized prognostic variables. Further analysis of all-cause death showed that the causes of death varied across the spectrum of age, with a greatly increasing proportion of non-cardiovascular deaths (and deaths from uncertain/unknown cause) with advancing age (Figure 1).

Effects of finerenone according to age category

Finerenone consistently reduced the risk of the primary outcome across all age categories, P for interaction = 0.27 (**Table 3; Figures 2 and 3**). Adjustments for key baseline differences across age groups and important prognostic variables did not change this finding (**Table 3**). The effect of finerenone was similarly consistent across the age spectrum for the

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components of the primary outcome, i.e., the total HF events (P for interaction =0.22) (**Figure S2**) and for cardiovascular death (P for interaction=0.75) (**Figure S3**). A similar pattern was seen for the composite of cardiovascular death or first HF event (P for interaction = 0.49), first HF event (p for interaction = 0.10), and all-cause death (P for interaction = 0.11) (**Table 3, Figure 3, and Figure S4-S6**). An analysis conducted exclusively on patients aged ≥75 years demonstrated similar trends (**Table S1**).

Analysis using age as a continuous rather than categorical variable gave similar findings for total HF events and cardiovascular death and total HF events (**Figure 4**) as well as for the other outcomes of cardiovascular death or first HF event, cardiovascular death, first HF event and all-cause death (**Figure S7**). The absolute rate reduction with finerenone tended to be greater in older patients because of their higher event rates (**Figure 4, Figure S7**). Mean KCCQ-TSS increased (improved) more between baseline and 12 months with finerenone than placebo, with a consistent benefit across age groups (P for interaction = 0.50) (**Table 3**). We observed similar improvements, with no difference by age, in the other summary scores of KCCQ, the overall summary score and the clinical summary score (**Table S2**). The odds of having a point or more improvement in the KCCQ total summary score, clinical summary score, and overall summary score were greater in the patients randomized to finerenone. Although the odds of improving were generally higher in the younger age groups there was no evidence of interaction in the effect of finerenone i.e. we could find no difference in the effect on KCCQ scores by age. NYHA functional class did not improve significantly with finerenone, compared to placebo, between baseline and 12 months and this did not differ across the age categories (P for interaction = 0.75).

Tolerability and safety according to age category

The occurrence of prespecified laboratory safety measures and hypotension (defined as SBP <100 mmHg) according to age group are shown in Table 4. Older patients were more likely

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to have hypotension than younger patients but there was no notable age gradient in the predefined laboratory safety measures. Patients randomized to finerenone were more likely to experience hypotension and hyperkalemia than those assigned to placebo, but less likely to experience hypokalemia. These between-treatment differences did not vary across age categories. Further exploratory analyses of these safety outcomes in very elderly patients showed a similar pattern (Table S3).

Discussion

In FINEARTS-HF, the nonsteroidal MRA finerenone was similarly effective in reducing the primary outcome of total worsening HF events, including HF hospitalizations or urgent HF visits, and cardiovascular death, across all age categories. Notably, 64% of trial participants were septuagenarians and 24% were octogenarians and the efficacy of finerenone was consistent in these patients. Finerenone also improved health status, compared to placebo, as evidenced by an increase in KCCQ-TSS, with no statistically significant interaction observed with age. Finally, the safety and tolerability profile of finerenone was favorable across all age categories.

The mean age in FINEARTS-HF (72 years) was similar to that reported in other recent HFmrEF/HFpEF trials and the age-related trends in baseline characteristics observed were also consistent with those described in prior trials[15-19]. Additionally, the majority of patients, regardless of age, were treated with renin-angiotensin-aldosterone system inhibitors, beta- blockers, and diuretics. Notably, older patients had higher baseline prevalences of atrial fibrillation, stroke, and anemia, as well as higher baseline NT-proBNP levels and lower eGFR and hemoglobin, variables known to be associated with worse outcomes[18-21]. Consistent with this, the rates of all trial endpoints were highest in the oldest age groups although, interestingly, the excess risk for worsening HF events in older age

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groups was substantially attenuated or even eliminated by adjustment for recognized prognostic variables suggesting age alone makes only a small contribution to several of the worse outcomes in older patients with HFmrEF/HFpEF. This was not the case for mortality, especially all-cause mortality, possibly because of the larger contribution of non-cardiovascular death to overall mortality in older patients.

The benefit of finerenone on the primary outcome was driven by a reduction in worsening HF events with no significant benefit on cardiovascular mortality. More importantly, we found that the benefit of finerenone, expressed as a relative risk reduction, was consistent across all age categories, with a greater absolute risk reduction in older patients. This highlights the potential risk–treatment paradox commonly identified in older patients who often have more to gain from therapies because of their higher baseline risk yet a lower probability of being prescribed such treatments[22-23].

An additional therapeutic objective in HF is to alleviate symptom burden, enhance physical function, and improve health-related quality of life, thereby improving the patient's overall health status. In the FINEARTS-HF trial, the increase in KCCQ-TSS was greater with finerenone compared to placebo, with a consistent increase observed across all age groups, including in very elderly patients. The mean overall increase in KCCQ-TSS was relatively small but this may reflect patients' generally mild symptoms at baseline (69% NYHA functional class II) and the improvement in KCCQ-TSS was similar to that seen in other trials of pharmacotherapy for HFmrEF/HFpEF[24-26].

The analysis of tolerability and safety was also favorable in the context of the aforementioned benefits of finerenone. For example, the proportion of patients ≥80 years exceeding a serum creatinine threshold of ≥3.0mg/dL was 1.8% in the finerenone group versus 0.7% in the placebo group.

Additionally, while hypotension and hyperkalemia occurred more frequently with

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finerenone compared to placebo, across all age groups, there was no significant interaction between age and the effect of treatment on these measures. Kidney dysfunction, hyperkalemia, and hypotension are often particular concerns in elderly patients and lead to reluctance to initiate treatment (or discontinuation of treatment). Indeed, several recent trials have shown a markedly lower use of MRAs in older compared to younger patients e.g., in the VICTORIA trial MRAs were used in 81% of patients <65 years versus 56% of patients ≥75 years[27-29].

Many other studies have demonstrated lower usage of a range of guideline recommended therapies in older patients with cardiovascular disease, relative to younger patients, raising concerns about ageism in prescribing[30-40]. Hopefully, the present findings are reassuring for the management of a growing and particularly high-risk population which is often undertreated with effective therapies.

Limitations

The interpretation of the findings from this trial must be considered in the light of several limitations. Subdividing the patients by age resulted in smaller group sizes and fewer events, reducing the statistical power of these subgroup analyses. Despite these limitations, this trial represents one of the largest cohorts to date examining patients with HFmrEF or HFpEF across the age spectrum. There is always concern that patients in clinical trials are overly selected and that the efficacy and safety demonstrated in trials may not be representative of unselected "real world" populations. Interestingly, several recent studies have found that "real world evidence" has been largely consistent with trial findings[41-42].

Conclusions

Finerenone reduced the risk of HF events and cardiovascular death, while also improving health-related quality of life and HF symptoms in patients with HFmrEF or HFpEF across the age spectrum. Additionally, finerenone was found to be safe and well-tolerated, irrespective

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of age.

Acknowledgments

None.

Sources of Funding

The FINEARTS-HF trial was funded by Bayer.

Disclosures

Dr. Chimura received research grants and personal fees from Otsuka Pharma, Daiwa Foundation and the Japan Research Foundation for Clinical Pharmacology.

Dr. Petrie reports, outside of the submitted work, grants or contracts form Boehringer Ingelheim, Roche, SQ Innovations, AstraZeneca, Novartis, Novo Nordisk, Medtronic, Boston Scientific, Pharmacosmos; consulting fees from Akero, Applied Thera- peutics, Amgen, AnaCardio, Biosensors, Boehringer Ingelheim, Novar- tis, AstraZeneca, Novo Nordisk, Abbvie, Bayer, Horizon Therapeutics, Foundry, Takeda, Cardiorentis, Pharmacosmos, Siemens, Eli Lilly, Vifor, New Amsterdam, Moderna, Teikoku, LIB Therapeutics, 3R Lifesciences; and is Director of Global Clinical Trials Partners.

Dr. Schou reports other from Novo Nordisk, Novartis, AstraZeneca, Boehringer, outside the submitted work. K.S. reports personal fees from Bayer during the conduct of the study and personal fees from Alleviant, AstraZeneca, Boehringer Ingelheim, Edwards Lifesciences, Janssen, Novar- tis, Novo Nordisk, and Rivus outside the study.

Dr. Martinez reports personal fees from Bayer, during the conduct of the study.

Dr. Claggett has received personal consulting fees from Alnylam, Bristol Myers Squibb, Cardior, Cardurion, Corvia, CVRx, Eli Lilly, Intellia, Rocket, and has served on a data safety

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monitoring board for Novo Nordisk.

Dr. Desai has received institutional research grants (to Brigham and Women's Hospital) from Abbott, Alnylam, AstraZeneca, Bayer, Novartis, and Pfizer as well as personal consulting fees from Abbott, Alnylam, AstraZeneca, Bayer, Biofourmis, Boston Scientific, Medpace, Medtronic, Merck, Novartis, Parexel, Porter Health, Regeneron, River2Renal, Roche, Veristat, Verily, Zydus.

Lay-Flurrie is a full-time employee of Bayer AG and reports personal fees from Bayer plc, outside the submitted work.

Dr. Viswanathan is a full-time employee of Bayer Pharmaceuticals.

Dr. Lam has received research support from NovoNordisk and Roche Diagnostics; has received consulting fees from Alleviant Medical, Allysta Pharma, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Biopeutics, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, CardioRenal, CPC Clinical Research, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Quidel Corporation, Radcliffe Group Ltd., Recardio Inc, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and is a co-founder & non-executive director of Us2.ai.

Dr. Senni has served on Advisory Boards, Consultancy and Honoraria for Novartis, Abbott, Merck, MSD, Vifor, AstraZeneca, Cardurion, Novo Nordisk, Bayer, Boehringer Ingelheim.

Dr. Shah has received research grants from NIH (U54 HL160273, X01 HL169712, R01 HL140731, R01 HL149423), AHA (24SFRNPCN1291224), AstraZeneca, Corvia, and Pfizer and consulting fees from Abbott, Alleviant, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia,

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Ionis, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics.

Dr. Voors' employer received consultancy fees and/or research support from Adrenomed, Anacardio, AstraZeneca, Bayer AG, BMS, Boehringer Ingelheim, Corteria, EliLilly, Merck, Moderna, Novartis, Novo Nordisk, Roche diagnostics, SalubrisBio.

Dr. Zannad reports personal fees from 89Bio, Abbott, Acceleron, Applied Therapeutics, Bayer, Betagenon, Boehringer, BMS, CVRx, Cambrian, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, Inventiva, KBP, Merck, NovoNordisk, Owkin, Otsuka, Roche Diagnostics, Northsea, USa2, having stock options at G3Pharmaceutical and equities at Cereno, Cardiorenal, Eshmoun Clinical research and being the founder of Cardiovascular Clinical Trialists.

Dr. Pitt is a consultant for Bayer, Astra Zeneca, Boehringer Ingelheim, Lexicon, Bristol Meyers Squibb, KBP Biosciences*, Sarfez Pharmaceuticals*, Pharmaceuticals*, SQinnovations*, G3 Pharmaceuticals, Sea Star medical*, Vifor* Prointel*, Brainstorm Medical* (*=stock/stock options). US Patent 9931412-site specific delivery of eplerenone to the myocardium, US Patent pending 63/045,783 Histone modulating agents for the prevention and treatment of organ failure.

Dr. Vaduganathan has received research grant support, served on advisory boards, or had speaker engagements with American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone Pharmaceuticals, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health, and participates on clinical trial committees for studies sponsored by AstraZeneca, Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics.

Dr. Jhund reports speakers' fees from AstraZeneca, Novartis, Alkem Metabolics,

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ProAdWise Communications, Sun Pharmaceuticals; advisory board fees from AstraZeneca, Boehringer Ingelheim, Novartis; research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc, Roche Diagnostics. PSJ's employer the University of Glasgow has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis and Novo Nordisk. Director GCTP Ltd.

Dr. Solomon has received research grants from Alexion, Alnylam, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos, Gossamer, GSK, Ionis, Lilly, MyoKardia, NIH/NHLBI, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Valo.

Dr. McMurray reports payments through Glasgow University from work on clinical trials, consulting and grants from: Amgen, AstraZeneca, Bayer, Cardurion, Cytokinetics, GSK and Novartis, British Heart Foundation, National Institute for Health – National Heart Lung and Blood Institute (NIH-NHLBI), Boehringer Ingelheim, SQ Innovations, Catalyze Group. Personal consultancy fees from: Alynylam Pharmaceuticals, Amgen, AnaCardio, AstraZeneca, Bayer, Berlin Cures, BMS, Cardurion, Cytokinetics, Ionis Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, River 2 Renal Corp. Personal lecture fees: Abbott, Alkem Metabolics, Astra Zeneca, Blue Ocean Scientific Solutions Ltd., Boehringer Ingelheim, Canadian Medical and Surgical Knowledge, Emcure Pharmaceuticals Ltd., Eris Lifesciences, European Academy of CME, Hikma Pharmaceuticals, Imagica Health, Intas Pharmaceuticals, J.B. Chemicals & Pharmaceuticals Ltd., Lupin Pharmaceuticals,

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Medscape/Heart.Org., ProAdWise Communications, Radcliffe Cardiology, Sun Pharmaceuticals, The Corpus, Translation Research Group, Translational Medicine Academy. Data Safety Monitoring Board: WIRB-Copernicus Group Clinical Inc. He is a director of Global Clinical Trial Partners Ltd. All other authors have no relevant disclosures.

Supplemental Material

Tables S1-S3

Figures S1-S7

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Table 1. Baseline characteristics according to age category (quartile) in FINEARTS-HF

	40 - 66 years (n = 1581)	67 - 73 years (n = 1587)	74 - 79 years (n = 1421)	≥80 years (n = 1412)	P for trend
Age (years)	59.3 ± 5.9	70.3 ± 2.0	76.4 ± 1.7	83.6 ± 3.1	<0.001
Female – no (%)	543 (34.3)	704 (44.4)	728 (51.2)	757 (53.6)	<0.001
Region – no (%)					<0.001
Asia	320 (20.2)	229 (14.4)	201 (14.1)	233 (16.5)	
Eastern Europe	828 (52.4)	817 (51.5)	627 (44.1)	378 (26.8)	
Latin America	226 (14.3)	175 (11.0)	112 (7.9)	128 (9.1)	
North America	86 (5.4)	111 (7.0)	120 (8.4)	154 (10.9)	
Western Europe, Oceania, Other	121 (7.7)	255 (16.1)	361 (25.4)	519 (36.8)	
Race – no (%)					0.007
Asian	319 (20.3)	233 (14.7)	203 (14.3)	241 (17.1)	
Black	36 (2.3)	25 (1.6)	14 (1.0)	13 (0.9)	
White	1,172 (74.5)	1,285 (81.2)	1,166 (82.1)	1,112 (79.0)	
Other	54 (3.4)	44 (2.8)	38 (2.7)	46 (3.3)	
Heart failure characteristics					
NYHA functional class – no (%)					<0.001
II	1,154 (73.0)	1,093 (68.9)	988 (69.5)	911 (64.5)	
III	412 (26.1)	486 (30.6)	422 (29.7)	493 (34.9)	
IV	14 (0.9)	8 (0.5)	11 (0.8)	8 (0.6)	
Any prior hospitalization for HF – no (%)	999 (63.2)	964 (60.7)	807 (56.8)	849 (60.1)	0.02
LVEF (%)	50.7 ± 7.7	52.2 ± 7.5	53.5 ± 7.8	54.1 ± 7.9	<0.001
LVEF ≥ 50% – no (%)	811 (51.3)	996 (62.9)	980 (69.2)	1,034 (73.2)	<0.001
LVEF ≥ 60% – no (%)	239 (15.1)	273 (17.2)	326 (22.9)	311 (22.0)	<0.001
Prior LVEF < 40% – no (%)	100 (6.3)	55 (3.5)	61 (4.3)	57 (4.0)	<0.001
KCCQ total symptom score	69.5 ± 24.3	67.8 ± 24.0	65.8 ± 23.5	64.7 ± 23.5	<0.001

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KCCQ overall summary score	65.5 ± 22.1	64.1 ± 22.2	61.4 ± 22.2	59.7 ± 21.9	<0.001
KCCQ clinical summary score	69.4 ± 22.4	66.6 ± 22.3	63.2 ± 22.2	61.7 ± 22.2	<0.001
ECG findings					
AF – no (%)	413 (26.1)	558 (35.2)	615 (43.3)	707 (50.1)	<0.001
Heart rate (AF), bpm	78.9 ± 12.9	77.4 ± 13.0	75.8 ± 11.5	75.0 ± 12.2	<0.001
Heart rate (non-AF), bpm	69.6 ± 10.4	68.4 ± 10.0	67.5 ± 10.2	67.1 ± 10.3	<0.001
LBBB – no (%)	66 (4.2)	53 (3.4)	59 (4.2)	60 (4.3)	0.66
RBBB – no (%)	68 (4.3)	87 (5.5)	81 (5.7)	96 (6.8)	0.004
Physiological and laboratory measurements					
Systolic blood pressure (mmHg)	128.3 ± 15.1	129.7 ± 14.7	129.6 ± 15.4	130.0 ± 16.2	0.003
Diastolic Blood Pressure (mmHg)	78.4 ± 9.6	76.2 ± 9.9	74.4 ± 10.1	72.4 ± 10.8	<0.001
Heart rate (bpm)	72.0 ± 11.8	71.6 ± 11.9	71.1 ± 11.5	71.1 ± 12.0	0.01
Body mass index (kg/m^2)	31.3 ± 6.5	30.7 ± 6.1	29.7 ± 5.7	27.9 ± 5.4	<0.001
Body mass index groups (kg/m^2) – no (%)					<0.001
< 18.5 (underweight)	10 (0.6)	12 (0.8)	11 (0.8)	32 (2.3)	
18.5–< 25 (normal weight)	268 (17.0)	268 (16.9)	286 (20.2)	419 (29.7)	
25–< 30 (overweight)	460 (29.1)	521 (32.9)	494 (34.9)	515 (36.6)	
30– < 35 (class I obesity)	444 (28.1)	410 (25.9)	393 (27.7)	299 (21.2)	
≥ 35 (class II–III obesity)	397 (25.1)	372 (23.5)	233 (16.4)	144 (10.2)	
Waist circumference (cm)	106.1 ± 16.8	105.6 ± 16.5	103.5 ± 15.4	100.0 ± 15.4	<0.001
Waist/hip ratio	0.98 ± 0.10	0.97 ± 0.12	0.96 ± 0.10	0.96 ± 0.10	<0.001
NT-proBNP (pg/mL)	670 (298-1444)	901 (391-1682)	1086 (516-2017)	1592 (844-2675)	<0.001
In patients with AF(pg/mL)	474 (240-1041)	526 (270-1095)	619 (371-1266)	972 (501-1868)	<0.001
In patients without AF (pg/mL)	1412 (907-2410)	1539 (1080-2502)	1692 (1130-2758)	2103 (1440-3197)	<0.001
Blood urea nitrogen (mg/dL)	20.0 ± 8.4	21.6 ± 9.1	23.4 ± 9.5	26.3 ± 10.4	<0.001
eGFR (ml/min/1.73m^2)	74.7 ± 20.0	63.9 ± 17.8	57.1 ± 17.0	51.0 ± 15.4	<0.001
eGFR < 60 (ml/min/1.73m^2) – no (%)	385 (24.4)	657 (41.4)	827 (58.2)	1,019 (72.2)	<0.001

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eGFR < 45 (ml/min/1.73m^2) – no (%)	136 (8.6)	256 (16.1)	367 (25.8)	573 (40.6)	<0.001
eGFR < 30 (ml/min/1.73m^2) – no (%)	22 (1.4)	49 (3.1)	65 (4.6)	85 (6.0)	<0.001
UACR (mg/g)	226 ± 820	155 ± 615	139 ± 498	118 ± 380	<0.001
UACR category (mg/g) [#] – no (%)					<0.001
< 30	980 (62.0)	966 (60.9)	812 (57.1)	753 (53.3)	
30 to < 300	380 (24.0)	428 (27.0)	431 (30.3)	473 (33.5)	
≥ 300	185 (11.7)	155 (9.8)	124 (8.7)	110 (7.8)	
Hemoglobin (g/L)	13.9 ± 1.7	13.5 ± 1.6	13.2 ± 1.6	12.8 ± 1.5	<0.001
Potassium (mmol/L)	4.4 ± 0.5	4.4 ± 0.5	4.4 ± 0.5	4.3 ± 0.5	<0.001
HbA1c (%)	6.6 ± 1.5	6.5 ± 1.3	6.3 ± 1.0	6.2 ± 0.9	<0.001
Medical history – no (%)					
Hypertension	1,348 (85.3)	1,431 (90.2)	1,293 (91.0)	1,253 (88.7)	<0.001
Diabetes mellitus	661 (41.8)	716 (45.1)	578 (40.7)	484 (34.3)	<0.001
Myocardial infarction	503 (31.8)	442 (27.9)	344 (24.2)	252 (17.9)	<0.001
Coronary artery bypass graft	239 (15.1)	276 (17.4)	227 (16.0)	174 (12.3)	0.02
Percutaneous coronary intervention	439 (27.8)	418 (26.3)	334 (23.5)	280 (19.8)	<0.001
AF (history)	620 (39.2)	829 (52.2)	860 (60.5)	964 (68.3)	<0.001
Chronic obstructive pulmonary disease	150 (9.5)	215 (13.6)	213 (15.0)	195 (13.8)	<0.001
Smoking status					<0.001
Current	274 (17.3)	137 (8.6)	70 (4.9)	30 (2.1)	
Former	449 (28.4)	478 (30.1)	447 (31.5)	419 (29.7)	
Never	858 (54.3)	972 (61.3)	904 (63.6)	963 (68.2)	
Stroke	148 (9.4)	168 (10.6)	198 (13.9)	194 (13.7)	<0.001
Anemia	287 (19.2)	376 (25.1)	405 (30.2)	516 (38.7)	<0.001
Treatments – no (%)					
Beta-blocker	1,399 (88.5)	1,371 (86.4)	1,198 (84.3)	1,127 (79.8)	<0.001
ACE inhibitor	638 (40.4)	586 (36.9)	497 (35.0)	434 (30.7)	<0.001

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ARB	490 (31.0)	572 (36.0)	538 (37.9)	501 (35.5)	0.004
ARNI	206 (13.0)	135 (8.5)	96 (6.8)	76 (5.4)	<0.001
SGLT2i	241 (15.2)	211 (13.3)	159 (11.2)	206 (14.6)	0.27
Loop diuretics	1,377 (87.1)	1,356 (85.4)	1,241 (87.3)	1,265 (89.6)	0.02
CCB	484 (30.6)	528 (33.3)	489 (34.4)	467 (33.1)	0.11
Anticoagulant	565 (35.7)	715 (45.1)	746 (52.5)	851 (60.3)	<0.001
Device therapy (pacemaker or ICD or CRTD)	46 (2.9)	90 (5.7)	126 (8.9)	151 (10.7)	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CCB, calcium channel blocker; CRT, Cardiac resynchronization therapy; ICD, Implantable cardiac defibrillator; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; 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; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio. #Baseline UACR unavailable in 204 participants, hence percentages are expressed as the number of participants out of 5797. Also, BMI is unavailable for 13 patients, SBP is unavailable for 2 patients, KCCQ is unavailable for 15 patients, LVEF is unavailable for 8 patients, NT-proBNP is unavailable for 158 patients, and HbA1c is unavailable for 113 patients. Values are mean ± standard deviation, n(%), or median [interquartile range].

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Table 2. Outcomes according to age category (quartiles) in FINEARTS-HF

	40 - 66 years (n = 1581)	67 - 73 years (n = 1587)	74 - 79 years (n = 1421)	≥80 years (n = 1412)
Primary composite outcome				
Number of events	509	582	542	733
Event rate (95% CI)	12.8 (11.1-14.7)	14.9 (13.1-17.1)	15.7 (13.9-17.8)	22.9 (20.3-25.8)
RR (95% CI)*	reference	1.17 (0.96-1.41)	1.17 (0.97-1.42)	1.52 (1.25-1.85)
RR (95% CI)**	reference	1.02 (0.83-1.24)	0.89 (0.73-1.09)	1.02 (0.82-1.26)
Total HF events				
Number of events	398	462	421	585
Event rate (95% CI)	10.0 (8.5-11.8)	11.9 (10.1-13.9)	12.2 (10.6-14.1)	18.3 (16-20.8)
RR (95% CI)*	reference	1.17 (0.93-1.46)	1.11 (0.89-1.38)	1.44 (1.15-1.79)
RR (95% CI)**	reference	1.00 (0.80-1.27)	0.83 (0.66-1.05)	0.95 (0.75-1.21)
Cardiovascular death or first HF event				
Number of events	289	327	326	401
Event rate (95% CI)	7.9 (7.0-8.9)	9.1 (8.2-10.2)	10.4 (9.3-11.6)	14.1 (12.8-15.6)
HR (95% CI)*	reference	1.16 (0.99-1.36)	1.30 (1.11-1.53)	1.59 (1.36-1.87)
HR (95% CI)**	reference	1.02 (0.87-1.21)	1.04 (0.87-1.24)	1.11 (0.93-1.34)
First HF event				
Number of events	217	245	255	355
Event rate (95% CI)	5.9 (5.2-6.8)	6.8 (6.0-7.7)	8.1 (7.2-9.2)	11.8 (10.6-13.2)
RR (95% CI)*	reference	1.13 (0.94-1.36)	1.27 (1.06-1.53)	1.61 (1.34-1.92)
HR (95% CI)**	reference	0.98 (0.80-1.18)	0.99 (0.81-1.22)	1.09 (0.89-1.35)

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Cardiovascular death				
Number of events	111	121	121	149
Event rate (95% CI)	2.8 (2.3-3.4)	3.1 (2.6-3.7)	3.5 (2.9-4.2)	4.7 (4.0-5.5)
HR (95% CI)*	reference	1.17 (0.90-1.51)	1.41 (1.09-1.84)	1.89 (1.46-2.45)
HR (95% CI)**	reference	1.09 (0.83-1.43)	1.15 (0.86-1.54)	1.35 (1.00-1.83)
All-cause death				
Number of events	188	221	248	356
Event rate (95% CI)	4.7 (4.1-5.4)	5.6 (4.9-6.4)	7.2 (6.3-8.1)	11.1 (10.0-12.3)
HR (95% CI)*	reference	1.22 (1.01-1.49)	1.62 (1.33-1.96)	2.49 (2.07-3.00)
HR (95% CI)**	reference	1.07 (0.87-1.31)	1.27 (1.03-1.57)	1.71 (1.38-2.12)

Abbreviations: CI, confidence interval; HR, hazard ratio; HF, heart failure; and RR, rate ratio Event rate is the number of events per100 person-years.

* Models were stratified by region and baseline left ventricular ejection fraction (< 60% or ≥ 60%), and adjusted for treatment assignment.

**Models were stratified by region and baseline left ventricular ejection fraction (< 60% or ≥ 60%), and adjusted for treatment assignment, sex, heart rate, systolic blood pressure, body mass index, N-terminal pro-B- type natriuretic peptide [log], estimated glomerular filtration rate, NYHA functional class III/IV, left ventricular ejection fraction, myocardial infarction, diabetes mellitus, history of atrial fibrillation and history of HF hospitalization

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Table 3. Effect of randomized treatment on outcomes according to age category (quartile) in FINEARTS-HF

	40 - 66 years		67 - 73 years		74 - 79 years		≥ 80 years		Interaction P value
	Placebo (n = 793)	Finerenone (n = 788)	Placebo (n = 786)	Finerenone (n = 801)	Placebo (n = 705)	Finerenone (n = 716)	Placebo (n =714)	Finerenone (n =698)	
Primary composite outcome									
Number of events	308	201	315	267	273	269	387	346	
Event rate (95% CI)	15.2 (12.7-18.3)	10.3 (8.3-12.7)	16.5 (13.6-20.0)	13.5 (11.2-16.2)	15.9 (13.3-18.9)	15.6 (13.0-18.6)	24.2 (20.8-28.2)	21.6 (17.9-25.9)	
RR (95% CI)*	0.70 (0.53-0.92)		0.83 (0.64-1.07)		0.98 (0.76-1.26)		0.85 (0.67-1.07)		0.27
RR (95% CI)**	0.64 (0.48-0.85)		0.81 (0.63-1.04)		0.96 (0.75-1.23)		0.82 (0.65-1.03)		0.17
Total HF events									
Number of events	250	148	253	209	214	207	307	278	
Event rate (95% CI)	12.4 (10.1-15.2)	7.6 (5.8-9.8)	13.2 (10.5-16.6)	10.5 (8.5-13.0)	12.4 (10.2-15.2)	12.0 (9.8-14.7)	19.7 (16.3-22.7)	17.3 (14.1-21.3)	
RR (95% CI)*	0.64 (0.46-0.88)		0.81 (0.60-1.10)		0.96 (0.72-1.28)		0.87 (0.67-1.12)		0.22
RR (95% CI)**	0.59 (0.43-0.82)		0.79 (0.59-1.06)		0.94 (0.72-1.25)		0.83 (0.64-1.07)		0.17
Cardiovascular death or first HF event									
Number of events	168	121	170	157	170	156	211	190	
Event rate (95% CI)	9.2 (7.9-10.8)	6.5 (5.5-7.8)	9.7 (8.3-11.3)	8.5 (7.3-10.0)	11.0 (9.4-12.8)	9.9 (8.4-11.6)	14.9 (13.0-17.2)	13.3 (11.5-15.4)	
HR (95% CI)*	0.73 (0.58-0.93)		0.88 (0.70-1.09)		0.91 (0.73-1.13)		0.85 (0.69-1.03)		0.49
HR (95% CI)**	0.67 (0.52-0.85)		0.81 (0.65-1.01)		0.90 (0.72-1.13)		0.83 (0.67-1.02)		0.32
First HF event									
Number of events	136	81	126	119	134	121	177	158	
Event rate (95% CI)	7.5 (6.3-8.9)	4.4 (3.5-5.5)	7.2 (6.0-8.6)	6.5 (5.4-7.7)	8.6 (7.3-10.3)	7.7 (6.4-9.2)	12.5 (10.8-14.6)	11.1 (9.5-13.0)	
HR (95% CI)*	0.61 (0.46-0.80)		0.89 (0.69-1.15)		0.89 (0.69-1.14)		0.85 (0.68-1.05)		0.10
HR (95% CI)**	0.56 (0.42-0.75)		0.82 (0.63-1.06)		0.87 (0.67-1.12)		0.84 (0.67-1.05)		0.09

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Cardiovascular death									
Number of events	58	53	62	59	59	62	81	68	
Event rate (95% CI)	2.9 (2.2-3.7)	2.7 (2.1-3.5)	3.2 (2.5-4.2)	3.0 (2.3-3.8)	3.4 (2.7-4.4)	3.6 (2.8-4.6)	5.1 (4.1-6.3)	4.2 (3.3-5.4)	
HR (95% CI)*	0.97 (0.67-1.41)		0.92 (0.64-1.31)		1.04 (0.73-1.50)		0.78 (0.56-1.08)		0.75
HR (95% CI)**	0.83 (0.56-1.24)		0.87 (0.61-1.26)		1.02 (0.70-1.47)		0.78 (0.55-1.09)		0.77
All cause death									
Number of events	92	96	115	106	117	131	198	158	
Event rate (95% CI)	4.6 (3.7-5.6)	4.9 (4.0-6.0)	6.0 (5.0-7.2)	5.3 (4.4-6.4)	6.8 (5.7-8.1)	7.6 (6.4-9.0)	12.4 (10.8-14.2)	9.8 (8.4-11.4)	
HR (95% CI)*	1.11 (0.83-1.47)		0.88 (0.68-1.15)		1.11 (0.86-1.42)		0.76 (0.62-0.94)		0.11
HR (95% CI)**	1.03 (0.77-1.39)		0.85 (0.65-1.12)		1.08 (0.83-1.40)		0.80 (0.64-1.00)		0.35
Improvement in NYHA functional class from baseline to 12 months									
Number – no (%)	153 (19)	162 (20)	152 (19)	147 (18)	121 (17)	131 (18)	127 (17)	117 (16)	
Odds ratio (95% CI)*#	1.08 (0.84-1.39)		0.94 (0.73-1.21)		1.07 (0.82-1.41)		0.94 (0.71-1.24)		0.75
Odds ratio (95% CI)**#	1.16 (0.88-1.52)		0.93 (0.70-1.24)		1.05 (0.77-1.45)		0.92 (0.67-1.25)		0.67
Change in KCCQ total symptom score from baseline to 12 months									
Mean change	6.2 (4.5, 8.0)	9.1 (7.4, 10.8)	7.2 (5.7, 8.8)	8.4 (6.9, 10.0)	7.7 (6.2, 9.2)	8.7 (7.2, 10.1)	6.1 (4.4, 7.8)	7.3 (5.6, 9.1)	
Differences#	2.87 (1.09, 4.66)		1.24 (-0.59, 3.07)		0.94 (-0.98, 2.86)		1.24 (-0.9, 3.38)		0.50

Abbreviations: CI, confidence interval, KCCQ, Kansas City Cardiomyopathy Questionnaire; HR, hazard ratio; HF, heart failure; NYHA, New York Heart Association; and RR, rate ratio Event rate is the number of events per100 person-years.

*Models were stratified by region and baseline left ventricular ejection fraction (< 60% or ≥ 60%), and adjusted for treatment assignment.

**Models were stratified by region and baseline left ventricular ejection fraction (< 60% or ≥ 60%), and adjusted for treatment assignment, sex, heart rate, systolic blood pressure, body mass index, N-terminal pro-B-type natriuretic peptide [log], estimated glomerular filtration rate, NYHA functional class III/IV, left ventricular ejection fraction, myocardial infarction, diabetes mellitus, history of atrial fibrillation and history of HF hospitalization

Linear regression model for change in KCCQ-total symptom score at month 12 adjusted for treatment, age quartile, baseline KCCQ total symptom score value, geographic region, and baseline left ventricular ejection fraction strata.

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Table 4. Laboratory safety assessments and hypotension according to age category in FINEARTS-HF

	40 - 66 years (n = 1581)		67 - 73 years (n = 1587)		74 - 79 years (n = 1421)		≥80 years (n = 1412)		Interaction P value
	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	Placebo	Finerenone	
Hypotension – no (%)									
Systolic blood pressure < 100 mmHg	81 (10.5)	147 (19.1)	89 (11.7)	122 (15.6)	85 (12.5)	116 (16.7)	106 (15.4)	153 (23.0)	
Odds ratio (95% CI)*	2.33 (1.70-3.18)		1.39 (1.01-1.90)		1.41 (1.03-1.94)		1.67 (1.26-2.23)		0.09
Elevated serum creatinine – no (%)									
≥ 2.5 mg/dl	23 (3.0)	38 (4.9)	23 (3.0)	32 (4.1)	21 (3.1)	36 (5.2)	22 (3.2)	35 (5.3)	
Odds ratio (95% CI)*	1.73 (1.02-2.95)		1.38 (0.79-2.39)		1.67 (0.96-2.90)		1.69 (0.98-2.92)		0.93
≥ 3.0 mg/dl	9 (1.7)	21 (2.7)	11 (1.5)	12 (1.5)	9 (1.3)	12 (1.8)	5 (0.7)	12 (1.8)	
Odds ratio (95% CI)*	2.43 (1.10-5.36)		1.05 (0.46-2.41)		1.20 (0.50-2.90)		2.57 (0.90-7.38)		0.38
Elevated serum potassium – no (%)									
> 5.5 mmol/L	59 (7.7)	112 (14.6)	58 (7.6)	110 (14.1)	47 (6.9)	99 (14.4)	35 (5.2)	92 (13.9)	
Odds ratio (95% CI)*	2.04 (1.46-2.86)		2.06 (1.47-2.90)		2.37 (1.64-3.44)		2.99 (1.98-4.49)		0.47
> 6.0 mmol/L	12 (1.6)	24 (3.1)	12 (1.6)	28 (3.6)	9 (1.3)	22 (3.2)	8 (1.2)	12 (1.8)	
Odds ratio (95% CI)*	2.00 (0.99-4.04)		2.35 (1.18-4.67)		2.81 (1.27-6.21)		1.41 (0.57-3.51)		0.83
Decreased serum potassium – no (%)									
< 3.5 mmol/L	80 (10.4)	34 (4.4)	65 (8.6)	33 (4.2)	58 (8.5)	23 (3.3)	78 (11.5)	37 (5.6)	
Odds ratio (95% CI)*	0.40 (0.26-0.61)		0.45 (0.29-0.70)		0.38 (0.23-0.62)		0.45 (0.30-0.67)		0.91

Abbreviations: CI, confidence interval

*Models were adjusted for region and baseline left ventricular ejection fraction (< 60% or ≥ 60%), and treatment assignment.

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Figure Legends

Figure1. Causes of death according to age in FINEARTS-HF. The figure shows the variation in the incidence of different causes of death according to age. The incidence rate of each cause of death was assessed across the age range using a Poisson regression model, where age was analyzed with restricted cubic splines incorporating 3 knots. Abbreviation: CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

Figure 2. Effect of finerenone on the primary composite outcome according to age category (quartiles) in FINEARTS-HF. The figures show the Nelson-Aalen estimate of the cumulative hazard for the primary composite endpoint according to age categorized by quartile: 40-66 years (Panel A), 67-73 years (Panel B), 74-79 years (Panel C), and ≥ 80 years (Panel D) (The blue solid line: placebo group, and the red solid line: finerenone group).

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Figure 3. Effects of finerenone on key outcomes according to age categories (quartiles) in FINEARTS-HF. This figure shows the effect of finerenone, compared with placebo, on the primary composite point, total HF events, cardiovascular death or first HF event, cardiovascular death, first HF event, and all-cause death according to age category (defined by quartile of baseline age). The LWYY (recurrent events) and Cox (time to first event) models are stratified by region and baseline LVEF (< 60% or ≥ 60%) and adjusted for treatment assignment. P values are for interaction between age groups and treatment effect. Abbreviation: CI, confidence interval; HF, heart failure

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Figure 4. Incidence of the primary and key secondary outcome across the spectrum of age (analyzed as a continuous variable) in FINEARTS-HF and effect of finerenone compared to placebo.

The upper panels show the associations between age and the incidence rate for the following outcomes. The lower panels show the absolute benefits of finerenone across the range of ages for the following outcomes. Panel (A) shows the primary composite outcome, and Panel (B) shows the total HF events. The shaded area represents the 95% CI. A rate difference less than zero indicates a benefit of finerenone over placebo.Abbreviation: CI, confidence interval and HF, heart failure

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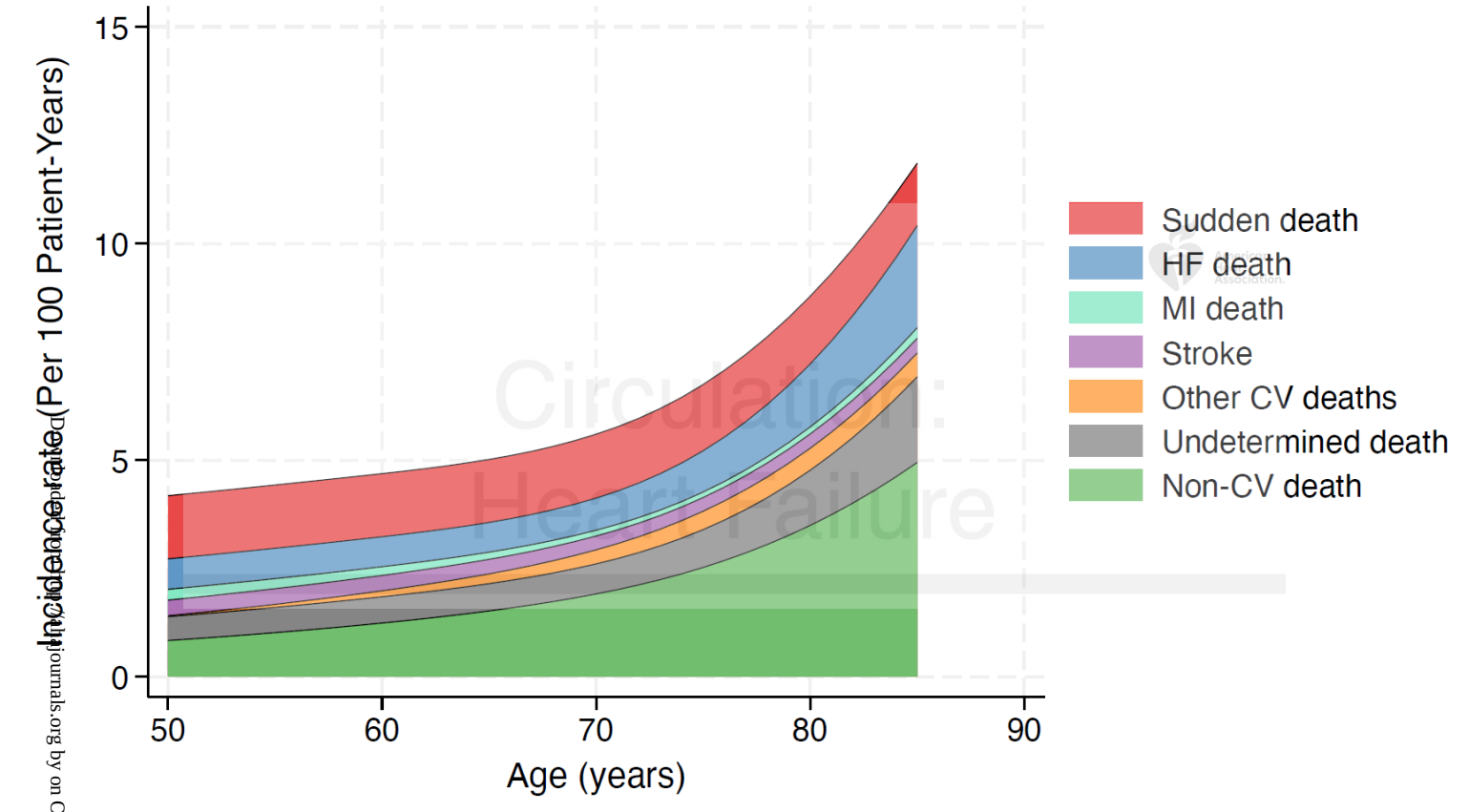

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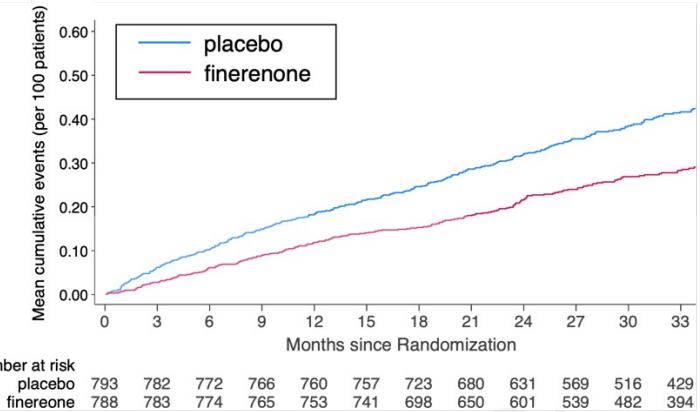
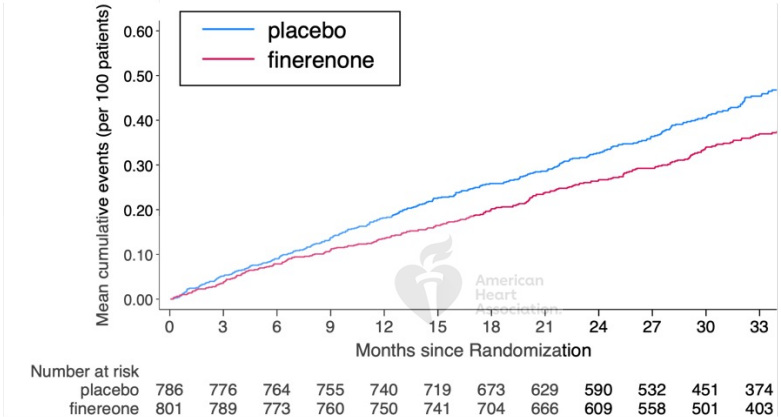
A 40-66 years



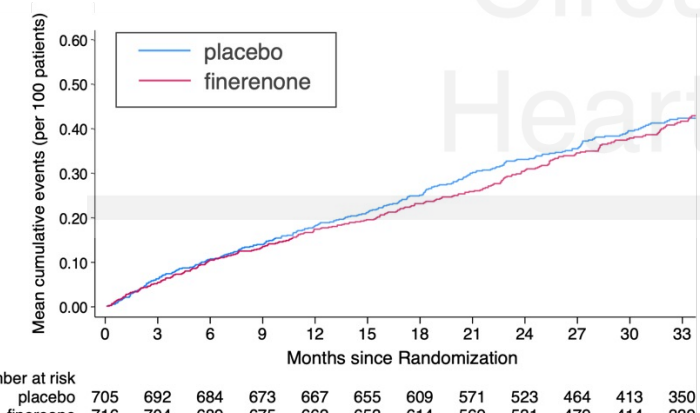
Number at risk												
placebo	793	782	772	766	760	757	723	680	631	569	516	429
finereone	788	783	774	765	753	741	698	650	601	539	482	394

B 67-73 years



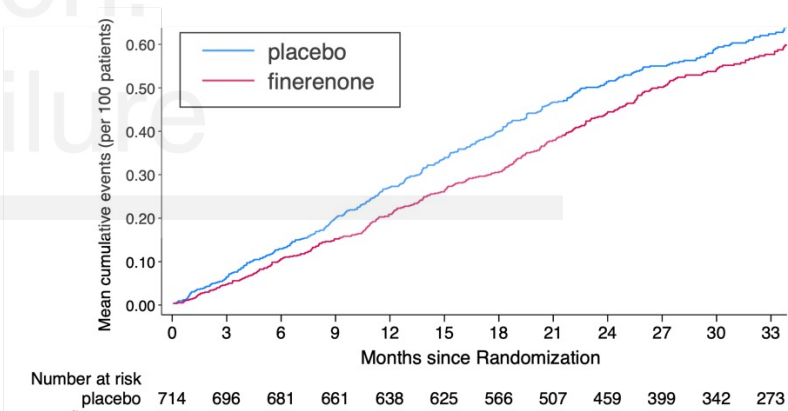
Number at risk												
placebo	786	776	764	755	740	719	673	629	590	532	451	374
finereone	801	789	773	760	750	741	704	666	609	558	501	403

C 74-79 years



Number at risk												
placebo	705	692	684	673	667	655	609	571	523	464	413	350
finereone	716	704	689	675	662	653	614	569	531	479	414	339

D ≥ 80 years



Number at risk												
placebo	714	696	681	661	638	625	566	507	459	399	342	273
finereone	698	683	673	659	645	625	560	514	461	401	352	294

P value for interaction between age and treatment effect : 0.27

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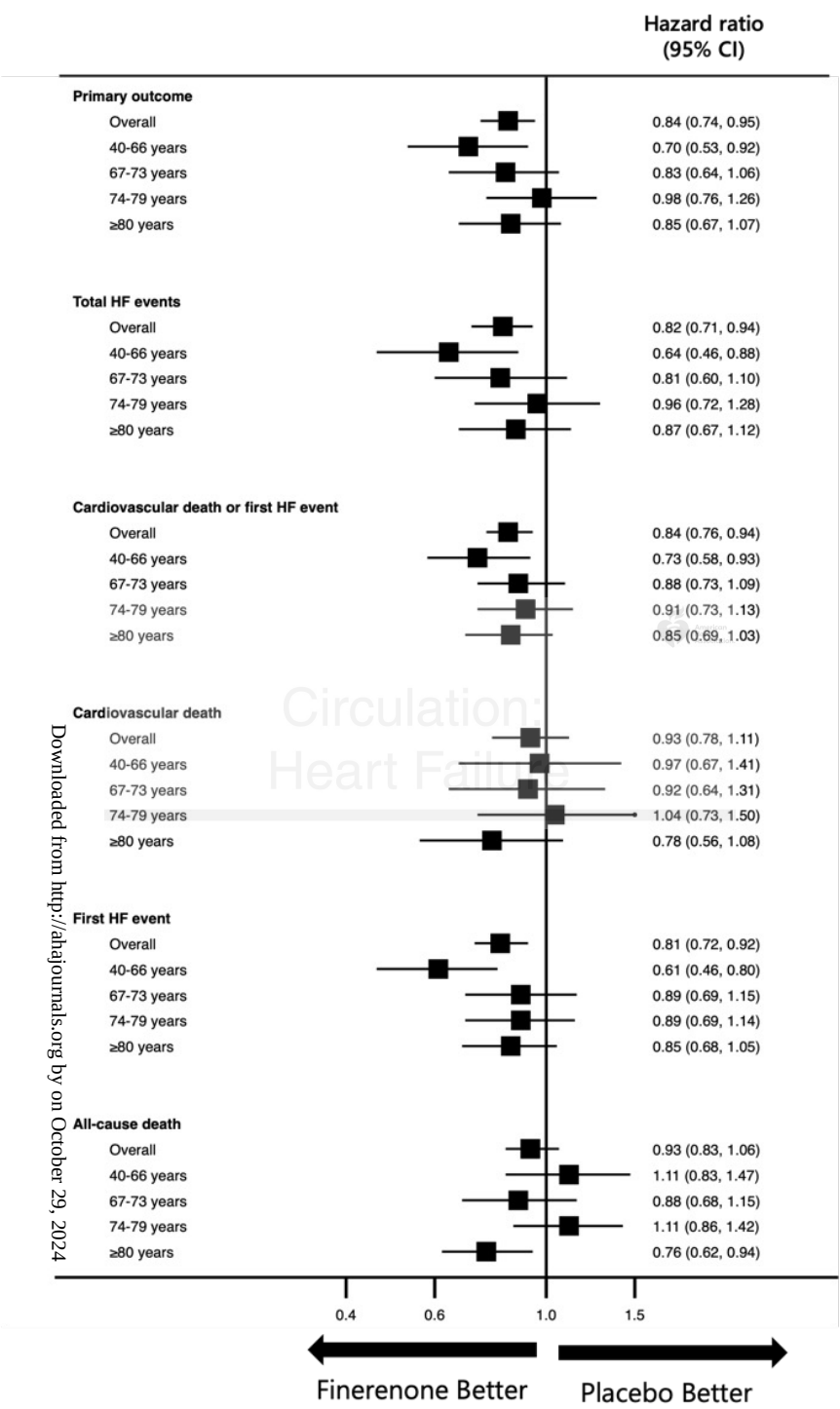

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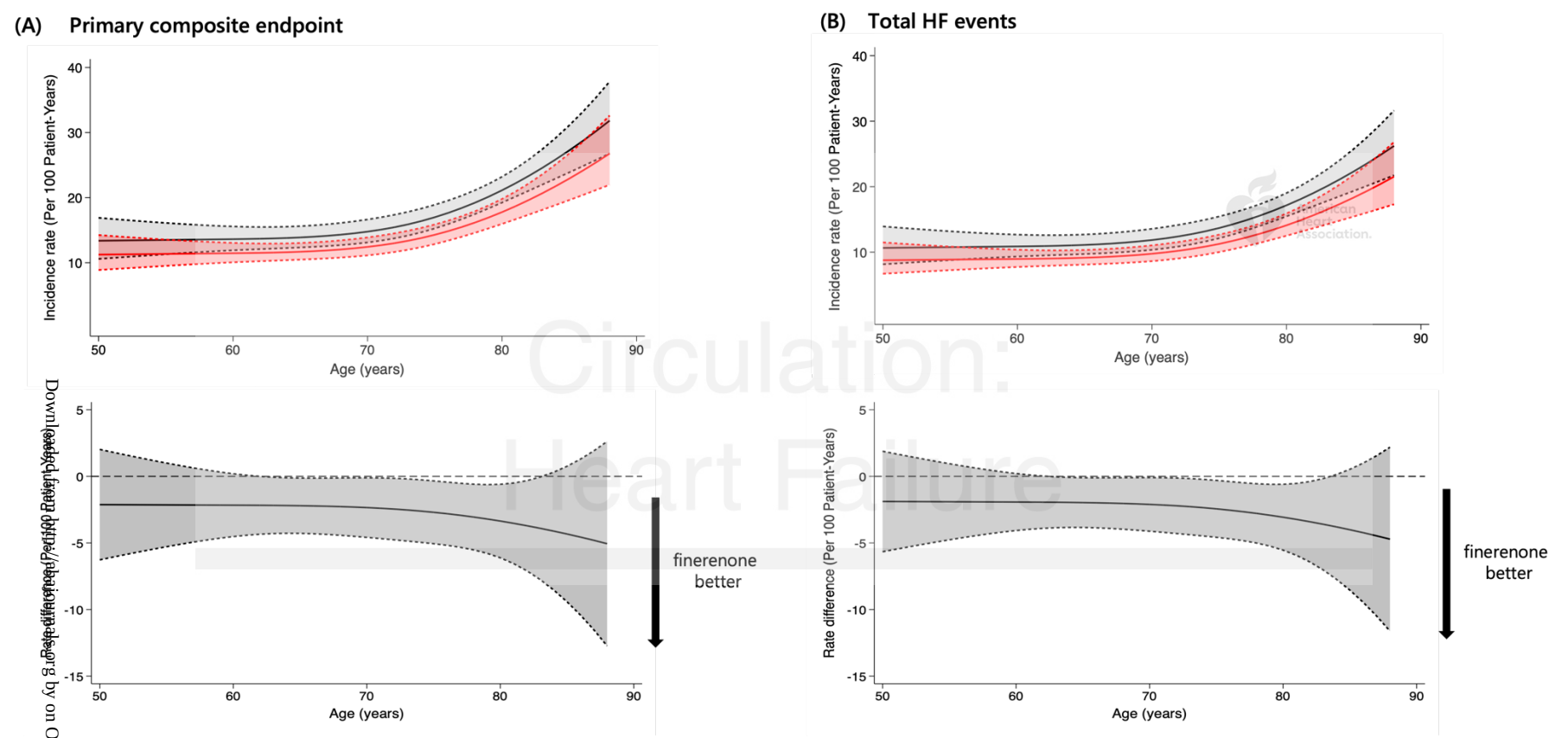

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