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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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Abstract

Background: Finerenone improves outcomes in patients with HF and mildly reduced or preserved ejection fraction (HFmrEF/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), Q3 74-79 years (n=1,421), and Q4 \geq 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

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.



Circulation:
Heart Failure

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 globally¹⁻². 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 accelerate³. 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 patients⁷. 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 individuals⁸⁻¹⁰.

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 placebo¹¹. 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%

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 published¹¹⁻¹³. 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) $\geq 40\%$ 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 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 $\geq 40\%$ 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 m², 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 paper¹². 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. 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 $\geq 50\%$ 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 >5.5 mmol/L or >6.0 mmol/L), hypokalemia (defined as serum potassium <3.5 mmol/L), elevation of serum creatine (defined as serum creatinine ≥ 2.5 mg/dL or ≥ 3.0 mg/dL), and hypotension (defined as SBP <100 mmHg).

Statistical analysis

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



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 $\geq 60\%$) 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 models¹⁴, 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 (2.5th-97.5th 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.

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.

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 $\geq 50\%$ 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

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

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 trials¹⁵⁻¹⁹. 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 outcomes¹⁸⁻²¹. 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

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 treatments²²⁻²³.

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/HFpEF²⁴⁻²⁶.

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 ≥ 3.0 mg/dL was 1.8% in the finerenone group versus 0.7% in the placebo group.

Additionally, while hypotension and hyperkalemia occurred more frequently with

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 years²⁷⁻²⁹.

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 prescribing³⁰⁻⁴⁰. 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 findings⁴¹⁻⁴².

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

of age.

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Supplemental Material

Tables S1-S3

Figures S1-S7

References

1. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* 2017;14:591-602. doi: 10.1038/nrcardio.2017.65
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145:e895-e1032. doi: 10.1161/cir.0000000000001063
3. Yang M, Kondo T, Anand IS, de Boer RA, Campbell RT, Køber L, Lam CSP, Maggioni AP, Martinez FA, O'Meara E, et al. Clinical characteristics and outcomes of patients aged 80 years and over with heart failure: Need for better treatment. *Eur J Heart Fail.* 2024. doi: 10.1002/ejhf.3417
4. Miró Ò, Gil V, Martín-Sánchez FJ, Jacob J, Herrero P, Alquézar A, Llauger L, Aguiló S, Martínez G, Ríos J, et al. Short-term outcomes of heart failure patients with reduced and preserved ejection fraction after acute decompensation according to the final destination after emergency department care. *Clin Res Cardiol.* 2018;107:698-710. doi: 10.1007/s00392-018-1237-z
5. Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. *Curr Heart Fail Rep.* 2013;10:401-410. doi: 10.1007/s11897-013-0155-7
6. van Heerebeek L, Paulus WJ. Understanding heart failure with preserved ejection fraction: where are we today? *Neth Heart J.* 2016;24:227-236. doi: 10.1007/s12471-016-0810-1
7. Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. *Eur J Heart Fail.* 2013;15:717-723. doi: 10.1093/eurjhf/hft028
8. Stolfo D, Lund LH, Becher PM, Orsini N, Thorvaldsen T, Benson L, Hage C, Dahlström U, Sinagra G, Savarese G. Use of evidence-based therapy in heart failure with reduced ejection fraction across age strata. *Eur J Heart Fail.* 2022;24:1047-1062. doi: 10.1002/ejhf.2483
9. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. *J Am Coll Cardiol.* 2018;72:351-366. doi:

10.1016/j.jacc.2018.04.070

10. Mordi IR, Ouwerkerk W, Anker SD, Cleland JG, Dickstein K, Metra M, Ng LL, Samani NJ, van Veldhuisen DJ, Zannad F, et al. Heart failure treatment up-titration and outcome and age: an analysis of BIOSTAT-CHF. *Eur J Heart Fail*. 2021;23:436-444. doi: 10.1002/ejhf.1799
11. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Henderson AD, Lam CSP, Pitt B, Senni M, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2407107
12. Vaduganathan M, Claggett BL, Lam CSP, Pitt B, Senni M, Shah SJ, Voors AA, Zannad F, Desai AS, Jhund PS, et al. Finerenone in patients with heart failure with mildly reduced or preserved ejection fraction: Rationale and design of the FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26:1324-1333. doi: 10.1002/ejhf.3253
13. Solomon SD, Ostrominski JW, Vaduganathan M, Claggett B, Jhund PS, Desai AS, Lam CSP, Pitt B, Senni M, Shah SJ, et al. Baseline characteristics of patients with heart failure with mildly reduced or preserved ejection fraction: The FINEARTS-HF trial. *Eur J Heart Fail*. 2024;26:1334-1346. doi: 10.1002/ejhf.3266
14. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Ser B Stat Methodol*. 2000;62:711-730. doi:10.1111/1467-9868.00259.
15. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387:1089-1098. doi: 10.1056/NEJMoa2206286
16. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al. Angiotensin-Nepriylsin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med*. 2019;381:1609-1620. doi: 10.1056/NEJMoa1908655
17. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiure-Valenzuela E, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385:1451-1461. doi: 10.1056/NEJMoa2107038
18. Peikert A, Martinez FA, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, Jhund PS, de Boer RA, DeMets D, Hernandez AF, et al. Efficacy and Safety of Dapagliflozin in Heart Failure With Mildly Reduced or Preserved Ejection Fraction According to Age: The DELIVER Trial. *Circ Heart Fail*. 2022;15:e010080. doi: 10.1161/circheartfailure.122.010080
19. Böhm M, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Abidin A, Mahfoud F, Brueckmann M, Gollop ND, Iwata T, et al. Empagliflozin Improves Outcomes in Patients With Heart Failure and Preserved Ejection Fraction Irrespective of Age. *J Am Coll Cardiol*. 2022;80:1-18. doi: 10.1016/j.jacc.2022.04.040
20. Cunningham JW, Vaduganathan M, Claggett BL, Zile MR, Anand IS, Packer M, Zannad F, Lam CSP, Janssens S, Jhund PS, et al. Effects of Sacubitril/Valsartan on N-Terminal Pro-B-Type Natriuretic Peptide in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail*. 2020;8:372-381. doi: 10.1016/j.jchf.2020.03.002
21. Vardeny O, Claggett B, Vaduganathan M, Beldhuis I, Rouleau J, O'Meara E, Anand IS, Shah SJ, Sweitzer NK, Fang JC, et al. Influence of Age on Efficacy and Safety of Spironolactone in Heart Failure. *JACC Heart Fail*. 2019;7:1022-1028. doi: 10.1016/j.jchf.2019.08.019
22. Duong MH, Gnjidic D, McLachlan AJ, Sakiris MA, Goyal P, Hilmer SN. The Prevalence of Adverse Drug Reactions and Adverse Drug Events from Heart Failure

- Medications in Frail Older Adults: A Systematic Review. *Drugs Aging*. 2022;39:631-643. doi: 10.1007/s40266-022-00957-8
23. Van der Linden L, Hias J, Walgraeve K, Petrovic M, Tournoy J, Vandenbrielle C, Van Aelst L. Guideline-Directed Medical Therapies for Heart Failure with a Reduced Ejection Fraction in Older Adults: A Narrative Review on Efficacy, Safety and Timeliness. *Drugs Aging*. 2023;40:691-702. doi: 10.1007/s40266-023-01046-0
24. Butler J, Filippatos G, Jamal Siddiqi T, Brueckmann M, Böhm M, Chopra VK, Pedro Ferreira J, Januzzi JL, Kaul S, Piña IL, et al. Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. *Circulation*. 2022;145:184-193. doi: 10.1161/circulationaha.121.057812
25. Chandra A, Polanczyk CA, Claggett BL, Vaduganathan M, Packer M, Lefkowitz MP, Rouleau JL, Liu J, Shi VC, Schwende H, et al. Health-related quality of life outcomes in PARAGON-HF. *Eur J Heart Fail*. 2022;24:2264-2274. doi: 10.1002/ejhf.2738
26. Kosiborod MN, Bhatt AS, Claggett BL, Vaduganathan M, Kulac IJ, Lam CSP, Hernandez AF, Martinez FA, Inzucchi SE, Shah SJ, et al. Effect of Dapagliflozin on Health Status in Patients With Preserved or Mildly Reduced Ejection Fraction. *J Am Coll Cardiol*. 2023;81:460-473. doi: 10.1016/j.jacc.2022.11.006
27. Lam CSP, Piña IL, Zheng Y, Bonderman D, Pouleur AC, Saldarriaga C, Pieske B, Blaustein RO, Nkulikiyinka R, Westerhout CM, et al. Age, Sex, and Outcomes in Heart Failure With Reduced EF: Insights From the VICTORIA Trial. *JACC Heart Fail*. 2023;11:1246-1257. doi: 10.1016/j.jchf.2023.06.020
28. Filippatos G, Anker SD, Butler J, Farmakis D, Ferreira JP, Gollop ND, Brueckmann M, Iwata T, Pocock S, Zannad F, et al. Effects of empagliflozin on cardiovascular and renal outcomes in heart failure with reduced ejection fraction according to age: a secondary analysis of EMPEROR-Reduced. *Eur J Heart Fail*. 2022;24:2297-2304. doi: 10.1002/ejhf.2707
29. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, et al. Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to Age: Insights From DAPA-HF. *Circulation*. 2020;141:100-111. doi: 10.1161/circulationaha.119.044133
30. Hiura GT, Markossian TW, Probst BD, Tootooni MS, Wozniak G, Rakotz M, Kramer HJ. Age and Comorbidities Are Associated With Therapeutic Inertia Among Older Adults With Uncontrolled Blood Pressure. *Am J Hypertens*. 2024;37:280-289. doi: 10.1093/ajh/hpad108
31. Mancini D, Douglas PS, De Marco T, Constanzo MR, Walsh MN, Hunt S, Horn EM, Lindenfeld J, Jessup M. Hidden Bias: The Intersection of Ageism and Gender in Adult Cardiology. *JACC Heart Fail*. 2023;11:717-719. doi: 10.1016/j.jchf.2023.03.016
32. Ricardo AC, Yang W, Sha D, Appel LJ, Chen J, Krousel-Wood M, Manoharan A, Steigerwalt S, Wright J, Rahman M, et al. Sex-Related Disparities in CKD Progression. *J Am Soc Nephrol*. 2019;30:137-146. doi: 10.1681/asn.2018030296
33. Toth-Manikowski SM, Yang W, Appel L, Chen J, Deo R, Frydrych A, Krousel-Wood M, Rahman M, Rosas SE, Sha D, et al. Sex Differences in Cardiovascular Outcomes in CKD: Findings From the CRIC Study. *Am J Kidney Dis*. 2021;78:200-209.e201. doi: 10.1053/j.ajkd.2021.01.020
34. Tamargo J, Rosano G, Walther T, Duarte J, Niessner A, Kaski JC, Ceconi C, Drexel H, Kjeldsen K, Savarese G, et al. Gender differences in the effects of cardiovascular drugs. *Eur Heart J Cardiovasc Pharmacother*. 2017;3:163-182. doi: 10.1093/ehjcvp/pvw042
35. Zhao M, Woodward M, Vaartjes I, Millett ERC, Klipstein-Grobusch K, Hyun K, Carcel C, Peters SAE. Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2020;9:e014742. doi:

10.1161/jaha.119.014742

36. Blomkalns AL, Chen AY, Hochman JS, Peterson ED, Trynosky K, Diercks DB, Brogan GX, Jr., Boden WE, Roe MT, Ohman EM, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol*. 2005;45:832-837. doi: 10.1016/j.jacc.2004.11.055
37. Swartling O, Yang Y, Clase CM, Fu EL, Hecking M, Hödlmoser S, Trolle-Lagerros Y, Evans M, Carrero JJ. Sex Differences in the Recognition, Monitoring, and Management of CKD in Health Care: An Observational Cohort Study. *J Am Soc Nephrol*. 2022;33:1903-1914. doi: 10.1681/asn.2022030373
38. Masoudi FA, Rathore SS, Wang Y, Havranek EP, Curtis JP, Foody JM, Krumholz HM. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. *Circulation*. 2004;110:724-731. doi: 10.1161/01.Cir.0000138934.28340.Ed
39. Pecoits-Filho R, Fliser D, Tu C, Zee J, Bieber B, Wong MMY, Port F, Combe C, Lopes AA, Reichel H, et al. Prescription of renin-angiotensin-aldosterone system inhibitors (RAASi) and its determinants in patients with advanced CKD under nephrologist care. *J Clin Hypertens (Greenwich)*. 2019;21:991-1001. doi: 10.1111/jch.13563
40. Molnar MZ, Kalantar-Zadeh K, Lott EH, Lu JL, Malakauskas SM, Ma JZ, Quarles DL, Kovesdy CP. Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker use, and mortality in patients with chronic kidney disease. *J Am Coll Cardiol*. 2014;63:650-658. doi: 10.1016/j.jacc.2013.10.050
41. Lerman TT, Greenberg N, Fishman B, Goldman A, Talmor-Barkan Y, Bauer M, Goldberg I, Goldberg E, Kornowski R, Krause I, et al. The real-world safety of sacubitril / valsartan among older adults (≥ 75): A pharmacovigilance study from the FDA data. *Int J Cardiol*. 2024;397:131613. doi: 10.1016/j.ijcard.2023.131613
42. Maury E, Belmans A, Bogaerts K, Vancayzeele S, Jansen M. Real-life effectiveness of sacubitril/valsartan in older Belgians with heart failure, reduced ejection fraction and most severe symptoms. *Sci Rep*. 2024;14:13512. doi: 10.1038/s41598-024-6

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

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

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

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].

Circulation: Heart Failure

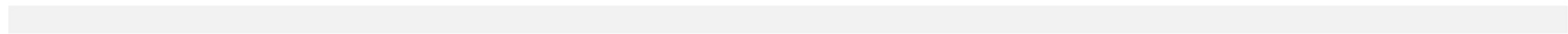


Table 2. Outcomes according to age category (quartiles) in FINEARTS-HF

	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)

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 per 100 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.

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

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 per 100 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.

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.

Figure Legends

Figure 1. 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).

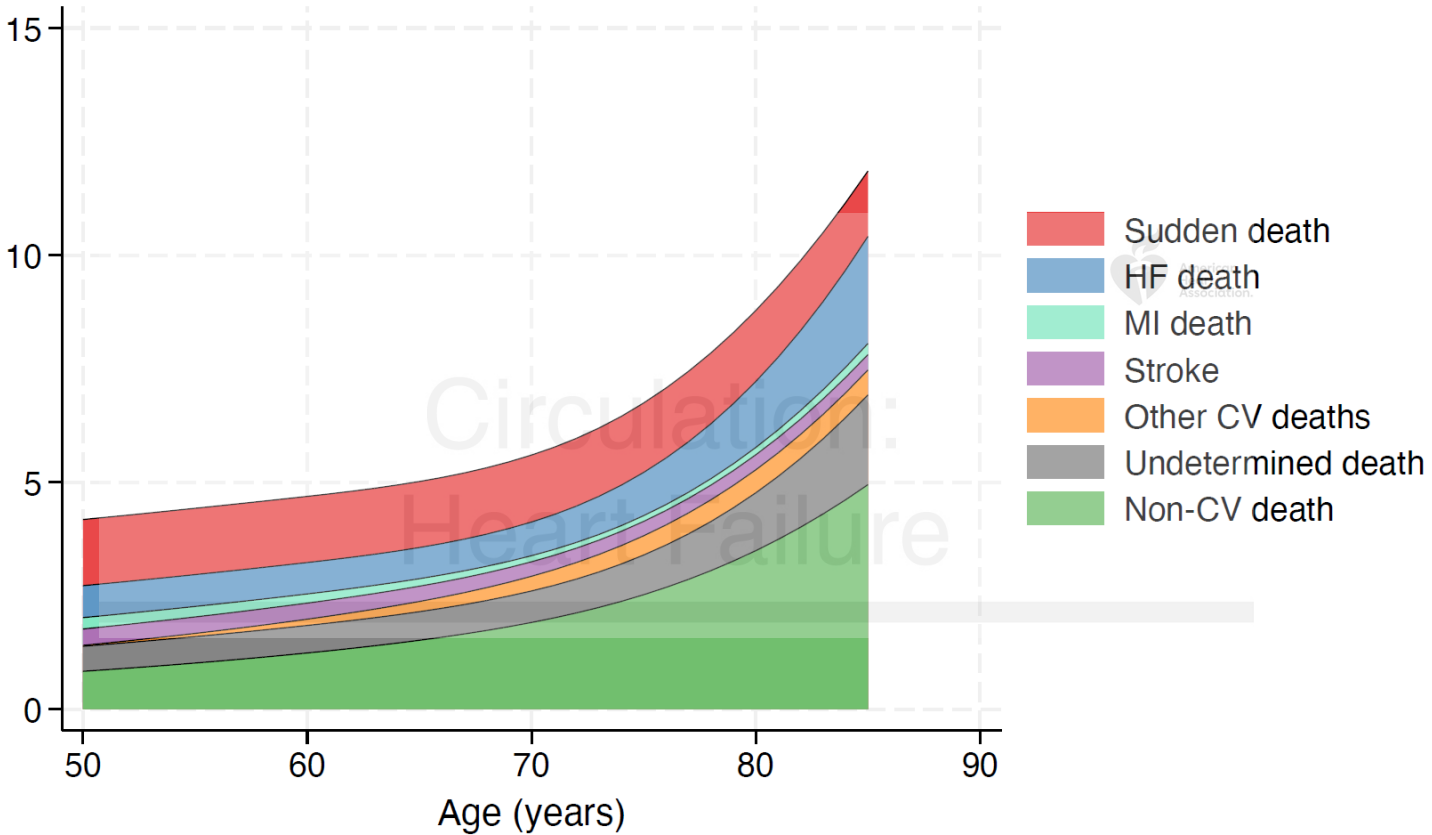
Figure 3. Effects of finerenone on key outcomes according to age categories (quartiles) in FINEARTS-HF. This figure shows the effect of finerenone, compared with placebo, on the primary composite point, total HF events, cardiovascular death or first HF event, cardiovascular death, first HF event, and 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 $\geq 60\%$) and adjusted for treatment assignment. P values are for interaction between age groups and treatment effect. Abbreviation: CI, confidence interval; HF, heart failure

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.

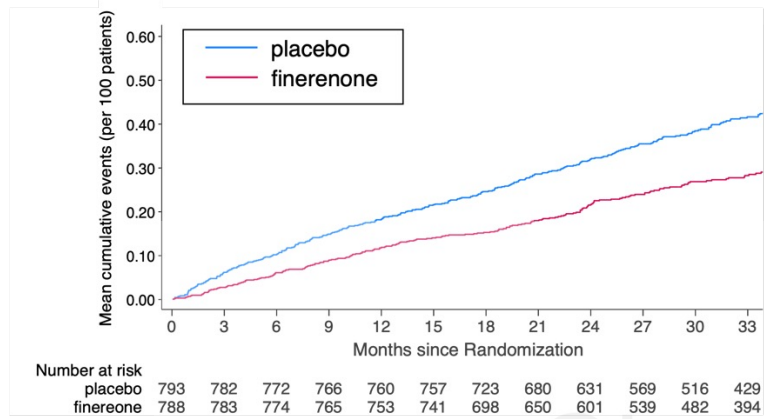
The upper panels show the associations between age and the incidence rate for the following outcomes. The lower panels show the absolute benefits of finerenone across the range of ages for the following outcomes. Panel (A) shows the primary composite outcome, and Panel (B) shows the total HF events. 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



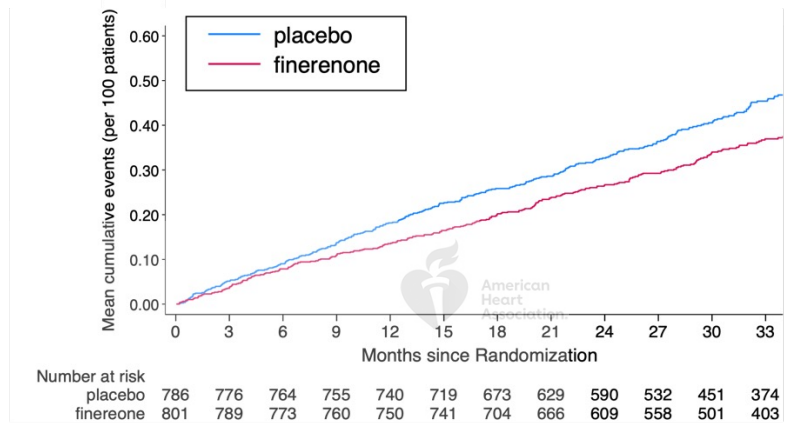
Circulation:
Heart Failure



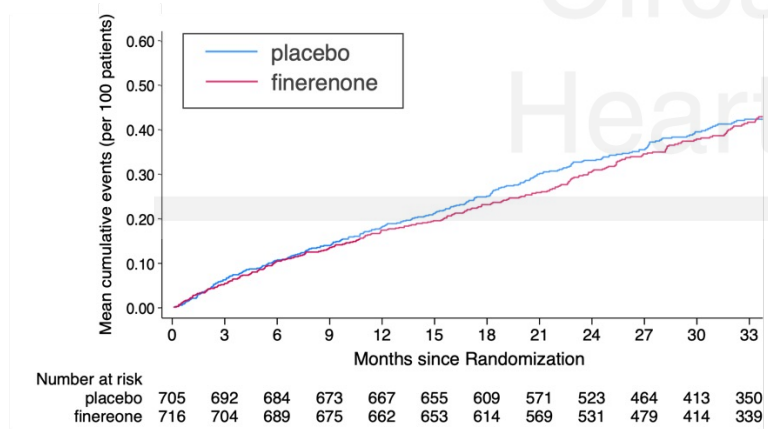
A 40-66 years



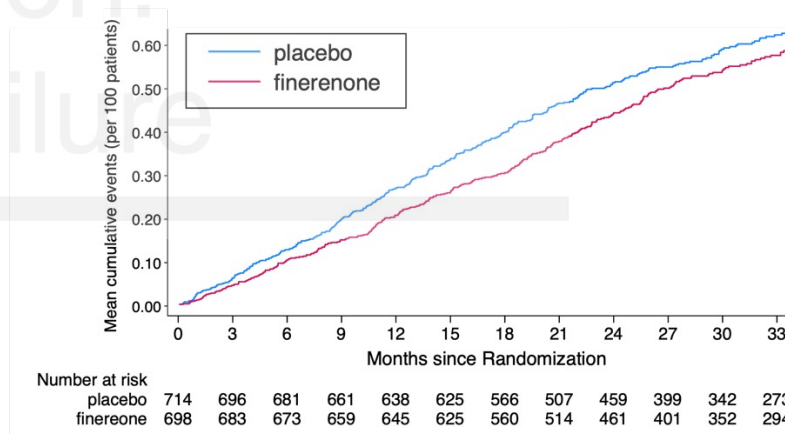
B 67-73 years



C 74-79 years

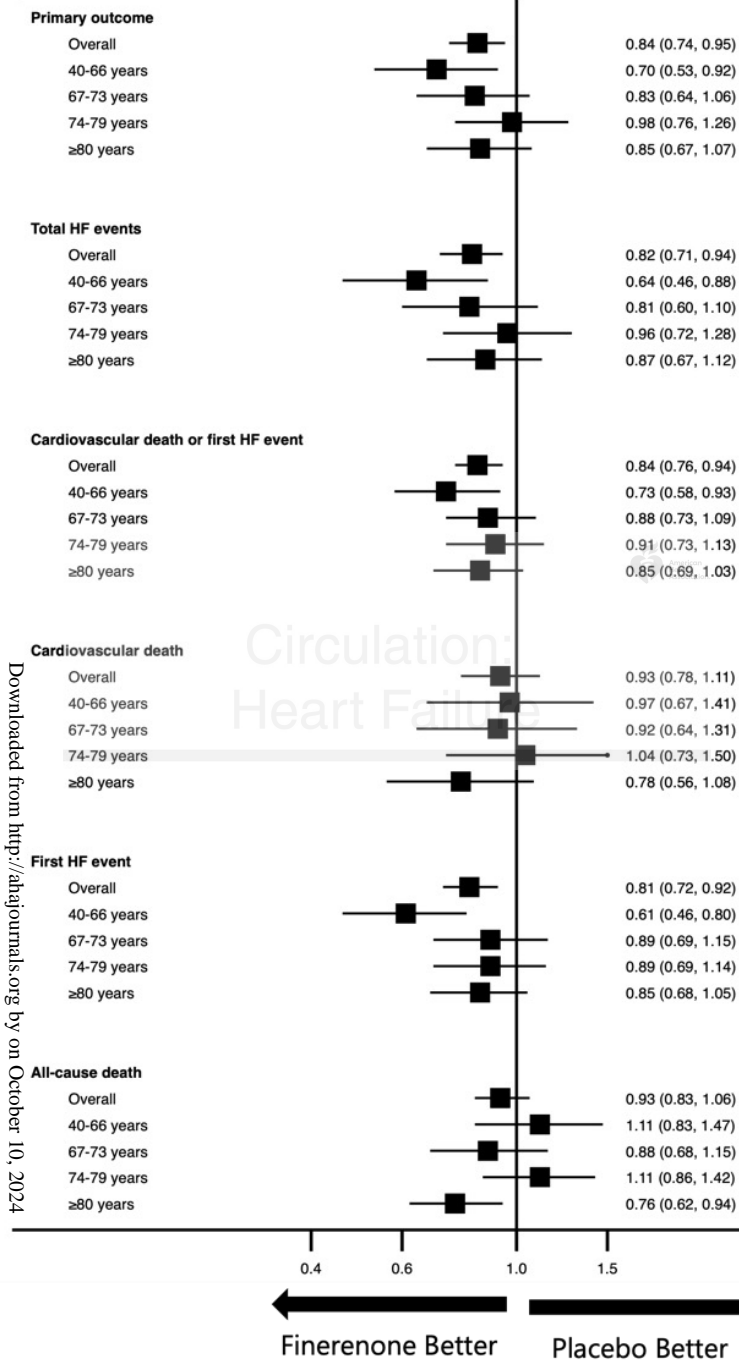


D ≥ 80 years

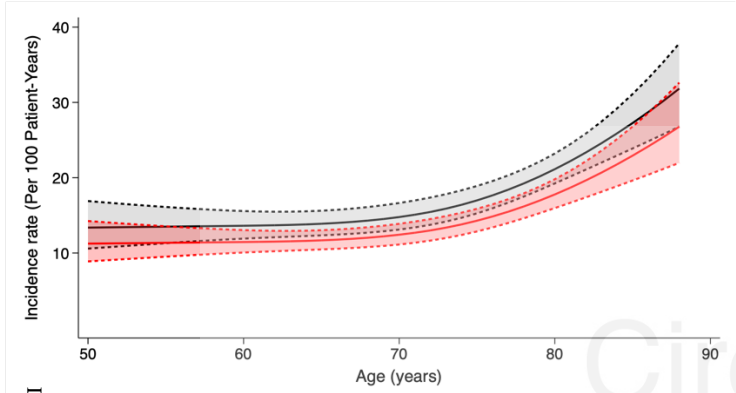


P value for interaction between age and treatment effect : 0.27

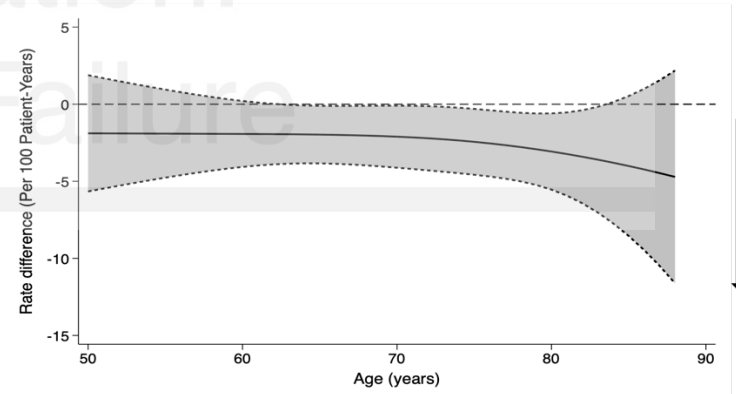
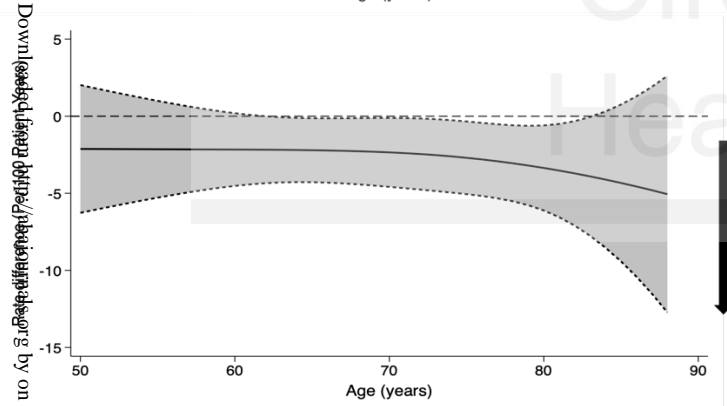
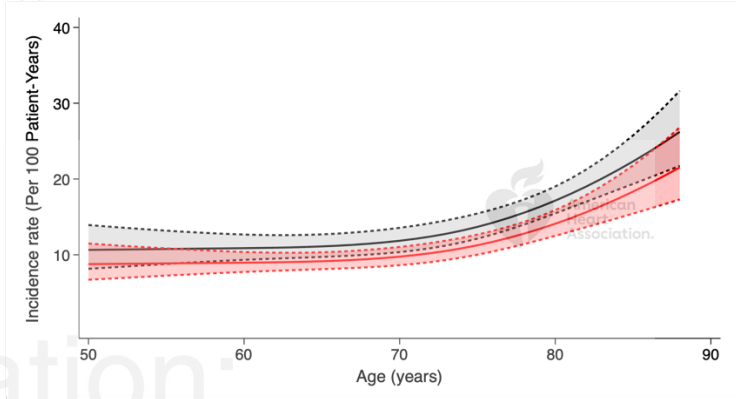
Circulation:
Heart Failure



(A) Primary composite endpoint



(B) Total HF events



Circulation:
Heart Failure

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