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Cardiorenal Outcomes by Age and Sex in Patients Treated With Finerenone: FIDELITY Post Hoc Analysis

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Abstract

Objectives: To evaluate the effects of finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist, on cardiorenal outcomes by age and/or sex.

Design: Post hoc analysis of the FIDELITY study (prespecified pooled analysis of FIDELIO-DKD and FIGARO-DKD), with a median follow-up of 3 years.

Setting: FIDELITY was a prespecified analysis of two phase 3, multicenter, double-blind trials.

Participants: Adults with type 2 diabetes and chronic kidney disease receiving maximum tolerated renin–angiotensin system inhibitor; 13 171 patients randomized and 13 026 patients included in the analyses.

Interventions: Randomized 1:1 to finerenone or placebo.

Primary and secondary outcome measures: Primary outcomes were a cardiovascular composite outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) and a kidney composite outcome (kidney failure, sustained ≥57% estimated glomerular filtration rate decline, or renal death).

Results: The mean age of 13 026 participants was 64.8 years; 45.2%, 40.1%, and 14.7% were aged <65, 65–74, and ≥75 years, respectively; 69.8% were male. Cardiovascular benefits of finerenone versus placebo were consistent across age ($P_{interaction}$=.42) and sex categories ($P_{interaction}$=.99); effects of finerenone to reduce hospitalization for heart failure were not modified by age ($P_{interaction}$=.70) but were more pronounced in males ($P_{interaction}$=.02). Kidney events were lower with finerenone versus placebo in patients aged <65 and 65–74 but not ≥75; no heterogeneity in treatment effect was observed ($P_{interaction}$=.51). In sex subgroups, finerenone consistently reduced kidney events ($P_{interaction}$=.85). Finerenone reduced albuminuria and estimated glomerular filtration rate decline regardless of age and sex. Hyperkalemia increased with finerenone, but rates of subsequent discontinuation were <3% across subgroups. Gynecomastia in males was uncommon across age subgroups and identical between treatment groups.

Conclusions: Finerenone improved cardiorenal outcomes with no new safety concerns across ages and sexes.

Registration: FIDELIO-DKD (NCT02540993); FIGARO-DKD (NCT02545049)

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Strengths and limitations of this study

- An advantage of this study was the use of combined individual-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, resulting in a large number of patients included in the full analysis set
- This study did not use predefined age categories, as it was a post hoc analysis, which may have resulted in some of the tests performed being underpowered
- Limitations present in FIDELITY are present in this analysis, such as the small proportion of Black patients and exclusion of patients with nonalbuminuric CKD

Introduction

In patients with diabetes, the risk of cardiovascular (CV) disease and chronic kidney disease (CKD) increases with age.[1] Likewise, vascular complications are affected by sex and are increased in females more than males in patients with diabetes.[2]

Among individuals aged 50 to 75 years without baseline diabetes, CKD, or CV disease, males have a steeper decline in glomerular filtration rate (GFR) than females.[3] However, reported effects of sex on risk of incidental and progressive CKD in patients with type 2 diabetes (T2D) have been inconsistent.[4-6] In trials including patients with CKD, female representation varies (25-40%),[7-11] whereas in real-world studies, females make up over half of patients.[12,13]

Overactivation of the mineralocorticoid receptor (MR) is associated with CV and kidney diseases.[14,15] In epithelial cells, the 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme prevents inappropriate MR activation by cortisol.[16-18] The activity of 11β-HSD2 decreases with age, resulting in MR overactivation in the elderly despite low circulating aldosterone levels.[16-18] Sex also influences 11β-HSD2 activity, particularly in patients with hypertension, where 11β-HSD2 activity is reduced in males versus females.[16] The MR is also expressed in nonepithelial cells, including endothelial cells, vascular smooth muscle cells, adipocytes, and immune cells.[17] In many of these, the MR may be activated by cortisol because of a lack of protection by 11β-HSD2.[19,20]

Despite management with recommended treatments for CKD in T2D, patients experience CKD progression or kidney failure and are at high risk of CV events.[10,21-23] Finerenone, a selective, nonsteroidal MR antagonist (MRA), reduced the risk of CKD progression and CV outcomes compared with placebo in patients with CKD and T2D in FIDELITY (The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and

FIGARO-DKD Trial programme analYsis), a prespecified pooled analysis of the FIDELIO-DKD (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; NCT02540993) and FIGARO-DKD (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease; NCT02545049) phase 3 trials.[21] However, the influence of age and sex on outcomes with finerenone is unknown. This post hoc analysis evaluated whether the cardiorenal benefits and safety profile of finerenone observed in FIDELITY are consistent in patients with CKD and T2D across ages and in both sexes.

Methods

Study Design and Patients

FIDELITY combined individual patient-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials. The study design, procedures, and outcomes for the trials have been previously published.[24-26]

Eligible patients were aged ≥18 years with CKD and T2D, receiving maximum tolerated renin–angiotensin system inhibitor, and with serum potassium levels ≤4.8 mmol/L at screening. Patients had either a urine albumin-to-creatinine ratio (UACR) ≥30 to <300 mg/g and an estimated glomerular filtration rate (eGFR) ≥25 to ≤90 mL/min/1.73 m^2, or UACR ≥300 to ≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2. Patients with symptomatic heart failure (HF) with reduced ejection fraction were excluded because this implies an indication for a steroidal MRA.

Standard-of-care therapy with a renin–angiotensin system inhibitor was optimized during the run-in period. Patients were randomly assigned (1:1) to receive finerenone at titrated doses (10 or 20 mg) once-daily oral treatment or matching placebo.

Key Outcomes

Efficacy outcomes included a CV composite outcome (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF [HHF]), a kidney composite outcome (kidney failure, sustained ≥57% eGFR decline, or renal death), HHF, and change in UACR and eGFR over time.

Safety outcomes included incidence of investigator-reported adverse events (AEs), including those leading to treatment discontinuation, central laboratory assessment of serum potassium levels >5.5 and >6.0 mmol/L, and other safety events of interest, such as hypotension, hyperkalemia, and gynecomastia in males.

Outcomes were analyzed according to patient age at baseline (<65, 65 to 75, ≥75 years) and sex (females were categorized as either pre- or postmenopausal if they were aged <51.4 or ≥51.4 years at baseline, respectively).

Statistical Analysis

Statistical analyses were performed as described in FIDELITY.[24] The full analysis set comprised all randomized patients (except those with critical Good Clinical Practice violations, who were prospectively excluded). Safety analyses were performed in the safety analysis set (randomized patients without critical Good Clinical Practice violations who took >1 dose of study drug). The analyses were prespecified exploratory evaluations of outcomes according to age and sex, with events reported from randomization up to the end-of-study visit. Stratified Cox proportional hazards models were used for the analysis of time-to-event clinical outcomes with stratification factors: geographic region, eGFR and albuminuria category at screening, history of CV disease, and study. The *P*-values for interaction between the treatment group (finerenone or placebo) and each baseline subgroup were based on stratified Cox proportional hazards models, accounting for the treatment effect, the subgroup effect, and their interaction.

Changes in UACR and eGFR over time were assessed using a linear mixed-model analysis accounting for repeated measurements over time. The least-squares mean ratio and absolute change from baseline were estimated from the models for changes in UACR and eGFR, respectively. The 2-slope, linear spline, mixed-model, repeated measure method[27] was used to estimate the rate of change in eGFR across time, specifically total (annualized rate of change in eGFR from baseline to permanent discontinuation or end of study) and chronic (from month 4 to permanent discontinuation or end of study) eGFR slopes. To account for possible nonlinear effects of age on clinical outcomes, age was modeled with cubic splines with 3 knots in Cox proportional hazards models, to produce plots of the HRs and 95% CI as functions of age and sex.

Patients and public involvement

No patient or public involvement in the current study.

Results

Patients

FIDELITY included 13 026 patients.[24] Median follow-up was 3 years (interquartile range 2.3 to 3.8).[24] Mean age at baseline was 64.8 years (standard deviation 9.5), with 45.2%, 40.1%, and 14.7% of patients aged <65, 65 to 74, and ≥75 years at baseline, respectively. Most patients (69.8%; *n*=9088/13 026) were male; 2.5% (*n*=323/13 026) were premenopausal females, and 27.8% (*n*=3615/13 026) were postmenopausal females. Patients were distributed evenly between treatment arms within age and sex subgroups (**eTable 1**).

Baseline Characteristics

Baseline characteristics were similar across age subgroups except for some key differences (**Table 1**). The overall FIDELITY population was predominantly White (68.1%), the proportion of which increased with age. Mean eGFR and median UACR were higher in the <65 years

group. History of CV disease was more common in the ≥75 years group; this trend was also observed for atrial fibrillation/atrial flutter.

Baseline characteristics in sex subgroups are shown in **Table 1**.

Efficacy

CV composite outcome by age

CV composite event rates increased with patient age in both treatment arms (**Figure 1A**). However, CV composite event rates were lower with finerenone than placebo in all age groups (**Figure 1A**). The effect of finerenone on reducing the risk of the CV composite outcome was consistent across categorical age subgroups ($P_{interaction}$=.42). There was no evidence of treatment effect modification when age was modeled as a continuous variable ($P_{interaction}$=.10). The trend of HR as a function of age was modeled with cubic splines (**eFigure 1A**).

HHF event rates were lower with finerenone than placebo in all age subgroups (**Figure 1A**). The effect of finerenone on HHF risk reduction was consistent across age subgroups ($P_{interaction}$=.70).

CV composite outcome by sex

CV composite event rates were lower with finerenone than placebo for males, premenopausal females, and postmenopausal females (**Figure 1B**). The effect of finerenone on reducing the risk of the CV composite outcome was consistent across sex subgroups ($P_{interaction}$=.10). When age was modeled with cubic splines by sex, the effect of finerenone was consistent with advancing age in males; however, a trend toward a stronger effect in older versus younger females was noted (**eFigure 1B, 1C**). Age distribution by sex is demonstrated in **eFigure 1D**.

The reduction of HHF with finerenone versus placebo was more pronounced in males than premenopausal/postmenopausal females (**Figure 1B**). These results persisted after adjustment for differences in baseline age, body mass index, systolic blood pressure, hemoglobin, eGFR, UACR, smoking history, and history of atrial fibrillation between sex subgroups ($P_{interaction}$=.02).

Kidney composite outcome by age

Kidney composite event rates were lower with finerenone than placebo in the <65 years and the 65 to 74 years groups but were similar in the ≥75 years group (**Figure 2A**). The effect of finerenone on reducing the risk of the kidney composite outcome was consistent across age subgroups ($P_{interaction}$=.51), with no evidence of treatment effect modification when age was modeled as a continuous variable ($P_{interaction}$=.77). The trend of HR as function of age was modeled with cubic splines (**eFigure 2A**).

Kidney composite outcome by sex

Kidney composite event rates were lower with finerenone than placebo in males but were similar in premenopausal and postmenopausal females (**Figure 2B**). The effect of finerenone on reducing the risk of the kidney composite outcome was consistent across sex subgroups ($P_{interaction}$=.85). When age was modeled with cubic splines by sex subgroups, the effect of finerenone suggests trends similar to overall results in males and females across all age groups (**eFigure 2B, 2C**). Age distribution by sex is demonstrated in **eFigure 2D**.

Effect of finerenone on markers of kidney function and damage by age and sex

Finerenone significantly attenuated the least-squares mean change in eGFR from month 4 to end of treatment (chronic eGFR slope) compared with placebo across all age and sex subgroups (**Figure 3, eFigure 3**). Finerenone reduced UACR over time compared with placebo regardless of age and sex (**eFigure 4**).

Safety

The incidence of any AE was similar between treatment groups irrespective of age or sex (**Table 2**). There were more drug-related AEs with finerenone than placebo in age and sex subgroups except premenopausal females, where the incidence was similar. AEs leading to drug discontinuation were more frequent in patients given finerenone than placebo (6.4% and 5.4%, respectively), with higher incidences in the 65 to 74 and ≥75 years groups than the <65 years group; there were more AEs leading to drug discontinuation with finerenone than placebo in males and premenopausal females but not in postmenopausal females.

Although the incidences of any serious AEs (SAEs), study drug-related SAEs, or SAEs leading to drug discontinuation were similar between treatment arms across all age and sex subgroups, the overall incidences of SAEs increased with age and was highest in males, followed by postmenopausal females, then premenopausal females.

In all age and sex subgroups, the incidences of treatment-emergent hypotension AEs were higher with finerenone than placebo but did not have a substantial impact on related clinical outcomes, including falls, dizziness, and fatigue. The incidence of hypotension in patients treated with finerenone increased with age (**Table 2**).

In FIDELITY, finerenone increased the risk of any hyperkalemia event versus placebo; similar findings were observed in all age and sex subgroups, except premenopausal females (**Table 2**). The incidences of any hyperkalemia AEs leading to discontinuation of study drug and any serious hyperkalemia AEs leading to hospitalization were low across all age and sex subgroups (<3% and <2%, respectively). However, the relative risk of treatment discontinuation because of hyperkalemia with finerenone versus placebo increased with advancing age (relative risk [95% CI] for ages 45 to 64, 65 to 74, and ≥75 years: 2.2 [1.2 to 4.3], 2.8 [1.7 to 4.7], and 4.4 [1.8 to 10.8], respectively). Treatment-emergent serum

potassium levels >5.5 mmol/L and >6.0 mmol/L were more frequent with finerenone than placebo, being consistent across all age and sex subgroups. The incidence of gynecomastia in males was the same with finerenone (0.2%) and placebo (0.2%) across all ages.

Discussion

In this post hoc analysis, finerenone demonstrated reduced risk of CV and kidney composite outcomes versus placebo across all age and sex subcategories. In FIDELITY, HHF was the main driver of CV benefit with finerenone[24]; lower incidences of HHF with finerenone versus placebo were observed in this analysis across all age subgroups, with some differences noted between sex subgroups. Moreover, the incidences of any AEs or SAEs were similar between the treatment groups regardless of age and sex.

The results for the CV outcome in this analysis are consistent with findings from other studies of MRAs in HF. In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), age did not affect the efficacy of spironolactone in patients with HF, [28] and in analyses of HF studies (RALES [Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure], EMPHASIS-HF [Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms], and TOPCAT), MRAs reduced morbidity and mortality in elderly patients,[29] demonstrating a consistent benefit regardless of sex.[30] In contrast to our results, female sex was associated with poorer kidney outcomes versus male sex in patients receiving a steroidal MRA for bilateral primary aldosteronism.[31] The MR can be activated by different drivers in different diseases; MR activation in diabetes is driven by additional factors other than high aldosterone in comparison with primary aldosteronism, which may account for differences in outcomes observed across different indications.[32]

In this study, although the elderly population had higher risk of certain AEs (e.g., hypotension, AEs leading to discontinuation, and death), they occurred less frequently with finerenone than placebo. Hyperkalemia was more prevalent with finerenone but was

generally similar across age and sex. In a FIDELIO-DKD subanalysis, younger age and female sex were independent risk factors for hyperkalemia (>6.0 mmol/L).[33] Similar findings for age were observed in TOPCAT post hoc data for patients with HF.[28] Steroidal MRAs have been associated with gynecomastia in males,[34,35] which was not observed in this study, most likely because finerenone has no detectable affinity for androgen receptors.[35]

Preclinical data suggest that different molecular mechanisms drive endothelial dysfunction in male and female mice[36,37] and that increased age and male sex are associated with MR overactivation, which is linked to vascular stiffness and endothelial dysfunction.[38,39] In human aortic smooth muscle cells, MR expression increased with age, leading to epigenetic changes associated with increased vascular stiffness. These effects were reversed with MR inhibition.[40] In vitro, MR expression in the whole aortae and early passage aortic vascular smooth muscle cells was increased in aged (30 months) versus adult (8 months) rat cells.[38] In a preclinical mouse model, aortic stiffness occurred earlier in male than female mice and correlated with the timing of increased aortic MR expression; vascular stiffness was prevented in smooth muscle cell MR-deficient mice.[39] These data suggest that elderly males may derive the greatest benefit from finerenone; indeed, in this analysis, finerenone-treated males had lower risk of the CV composite outcome and HHF versus placebo across age groups, including >75 years. Moreover, statistical heterogeneity was observed for HHF by sex, persisting after adjustment for differences in baseline characteristics, with a more pronounced effect of finerenone to reduce HHF versus placebo in males than females.

In this study, markers of kidney damage (eGFR decline and UACR) were reduced with finerenone in age subgroups; however, no benefit on kidney outcomes was observed in the >75 years age group. The small sample size of this subgroup precluded definitive conclusions, which may be accounted for by the slowing rate of CKD progression with advancing age.[41,42]

Limitations include the study being a post hoc analysis and the chosen age categories not being predefined. In addition, patients may have initiated other treatments during the study. Sample size and number of events for premenopausal females were relatively small, resulting in uncertainty around the estimates for this subgroup. Results for premenopausal females versus postmenopausal females/males should be interpreted with caution because age may partly account for differences observed; the average age of premenopausal females was ~45 years old compared with postmenopausal females (~66 years old) and males (~65 years old) **(Table 1)**. As such, these groups had different baseline characteristics. Higher baseline mean eGFR and median UACR, and lower history of CV comorbidities and hypotension were observed in premenopausal females versus males and postmenopausal females. Additionally, the study design and tests performed may have been underpowered to address the research questions. Furthermore, FIDELITY limitations, mainly the small proportion of Black patients and exclusion of patients with nonalbuminuric CKD, were present in this analysis.

In conclusion, this post hoc FIDELITY analysis suggests that finerenone effectively lowers the risk of clinically important cardiorenal outcomes in patients with CKD and T2D across ages and sexes, with no new safety concerns in those aged >65 years or by sex. These data highlight the therapeutic potential of finerenone in older patients and both sexes in patients with CKD and T2D.

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Contributors:

SB prepared the initial analysis and interpretation of data, as well as the initial manuscript draft, which was then reviewed and edited by all authors. All authors vouch for the completeness and accuracy of the data and agreed to submit the manuscript for publication. The funder had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Data sharing statement

Data not currently available

Will data be available: Yes

Where: Electronic repository

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Tables

Table 1. Patient Baseline Characteristics According to Age and Sex

	Age			Sex		
	<65 Years (*n*=5889)	**65–74 Years (*n*=5221)**	**≥75 Years (*n*=1916)**	**Male (*n*=9088)**	**Premenopausal Female (*n*=323)**	**Postmenopausal Female (*n*=3615)**
Sex, *n* (%)				Age, y, mean ± SD		
Female	1839 (31.2)	1501 (28.7)	598 (31.2)	64.8 ± 9.5	45.1 ± 4.9	66.3 ± 8.0
Male	4050 (68.8)	3720 (71.3)	1318 (68.8)			
Race, *n* (%)						
Asian	1591 (27.0)	997 (19.1)	306 (16.0)	2136 (23.5)	87 (26.9)	671 (18.6)
Black/African American	309 (5.2)	160 (3.1)	53 (2.8)	284 (3.1)	37 (11.5)	201 (5.6)
White	3592 (61.0)	3817 (73.1)	1460 (76.2)	6231 (68.6)	167 (51.7)	2471 (68.4)
Other[a]	397 (6.7)	247 (4.7)	97 (5.1)	437 (4.8)	32 (9.9)	272 (7.5)
Systolic blood pressure, mm Hg, mean (SD)	135.6 ± 14.0	137.4 ± 14.2	138.4 ± 14.6	136.8 ± 14.2	133.0 ± 14.0	136.9 ± 14.3
Diastolic blood pressure, mm Hg, mean (SD)	78.8 ± 9.1	74.9 ± 9.4	72.8 ± 9.8	76.5 ± 9.7	80.1 ± 8.4	75.6 ± 9.5
Duration of diabetes, years, mean (SD)	13.5 ± 7.6	16.4 ± 8.6	18.6 ± 10.4	15.3 ± 8.5	10.6 ± 7.0	16.0 ± 9.1
HbA1c, %, mean (SD)	7.9 ± 1.5	7.6 ± 1.3	7.4 ± 1.2	7.6 ± 1.3	8.2 ± 1.7	7.9 ± 1.4
Serum potassium, mmol/L, mean (SD)	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.4 ± 0.4
eGFR, mL/min/1.73 m^2, mean (SD)	64.3 ± 24.0	53.5 ± 18.5	48.1 ± 15.1	57.7 ± 21.2	77.0 ± 28.9	55.6 ± 21.3
eGFR, mL/min/1.73 m^2, *n* (%)[b]						

	Age			Sex		
	<65 Years (*n*=5889)	**65–74 Years (*n*=5221)**	**≥75 Years (*n*=1916)**	**Male (*n*=9088)**	**Premenopausal Female (*n*=323)**	**Postmenopausal Female (*n*=3615)**
<25	53 (0.9)	72 (1.4)	37 (1.9)	98 (1.1)	2 (0.6)	62 (1.7)
25–<45	1448 (24.6)	1898 (36.4)	886 (46.2)	2871 (31.6)	57 (17.6)	1304 (36.1)
45–<60	1315 (22.3)	1514 (29.0)	605 (31.6)	2468 (27.2)	50 (15.5)	916 (25.3)
≥60	3071 (52.1)	1736 (33.3)	388 (20.3)	3651 (40.2)	214 (66.3)	1330 (36.8)
UACR, mg/g, median (IQR)	650.48 (315.2–1363.5)	438.63 (154.1–1030.7)	332.29 (107.8–830.5)	511.53 (200.9–1130.1)	793.52 (376.6–1547.3)	501.47 (173.6–1149.1)
UACR, mg/g, *n* (%)[c]						
<30	79 (1.3)	103 (2.0)	48 (2.5)	137 (1.5)	3 (0.9)	90 (2.5)
30–<300	1331 (22.6)	1907 (36.5)	861 (44.9)	2881 (31.7)	54 (16.7)	1164 (32.2)
≥300	4475 (76.0)	3210 (61.5)	1007 (52.6)	6068 (66.8)	266 (82.4)	2358 (65.2)
BMI, kg/m^2, mean (SD)	32.0 ± 6.4	31.1 ± 5.7	29.6 ± 5.0	31.0 ± 5.6	34.1 ± 7.9	32.0 ± 6.6
Current smoker, *n* (%)	1283 (21.8)	686 (13.1)	124 (6.5)	1730 (19.0)	35 (10.8)	328 (9.1)
History of CV disease, present, *n* (%)	2188 (37.2)	2667 (51.1)	1080 (56.4)	4374 (48.1)	56 (17.3)	1505 (41.6)
History of heart failure	413 (7.0)	432 (8.3)	162 (8.5)	630 (6.9)	22 (6.8)	355 (9.8)
History of atrial fibrillation/atrial flutter	266 (4.5)	547 (10.5)	293 (15.3)	867 (9.5)	0	239 (6.6)
Baseline medications, *n* (%)[d]						
RAS inhibitors (ACEis/ARBs)	5876 (99.8)	5213 (99.8)	1914 (99.9)	9069 (99.8)	323 (100.0)	3611 (99.9)
Beta-blockers	2619 (44.5)	2849 (54.6)	1036 (54.1)	4545 (50.0)	111 (34.4)	1848 (51.1)
Diuretics	2790 (47.4)	2813 (53.9)	1107 (57.8)	4706 (51.8)	137 (42.4)	1867 (51.6)
Statins	4033 (68.5)	3920 (75.1)	1446 (75.5)	6696 (73.7)	203 (62.8)	2500 (69.2)
Calcium channel blockers	3127 (53.1)	3052 (58.5)	1179 (61.5)	5208 (57.3)	149 (46.1)	2001 (55.4)

	Age			Sex		
	<65 Years (*n*=5889)	**65–74 Years (*n*=5221)**	**≥75 Years (*n*=1916)**	**Male (*n*=9088)**	**Premenopausal Female (*n*=323)**	**Postmenopausal Female (*n*=3615)**
≥1 glucose-lowering medication, *n* (%)[d]	5779 (98.1)	5111 (97.9)	1830 (95.5)	8860 (97.5)	317 (98.1)	3543 (98.0)
Insulin	3637 (61.8)	3020 (57.8)	973 (50.8)	5203 (57.3)	193 (59.8)	2234 (61.8)
GLP-1RA	492 (8.4)	378 (7.2)	74 (3.9)	676 (7.4)	30 (9.3)	238 (6.6)
SGLT-2i	517 (8.8)	289 (5.5)	71 (3.7)	671 (7.4)	36 (11.1)	170 (4.7)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; IQR = interquartile range; RAS = renin–angiotensin system; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; UACR = urine albumin-to-creatinine ratio.

[a] Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific, not reported, multiple.

[b] Missing (eGFR): <65 years, *n*=2; 65 to 74 years, *n*=1; postmenopausal female, *n*=3.

[c] Missing (UACR): <65 years, *n*=4; 65 to 74 years, *n* = 1; male, *n*=2; postmenopausal female, *n*=3.

[d] Analysis allowed multiple drug groups for the same drug.

Table 2. Treatment-Emergent AEs According to Age and Sex

n (%)	Age						Sex					
	<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	Finerenone (*n*=2953)	Placebo (*n*=2926)	Finerenone (*n*=2631)	Placebo (*n*=2578)	Finerenone (*n*=926)	Placebo (*n*=985)	Finerenone (*n*=4476)	Placebo (*n*=4595)	Finerenone (*n*=163)	Placebo (*n*=160)	Finerenone (*n*=1871)	Placebo (*n*=1734)
Any AE	2494 (84.5)	2523 (86.2)	2301 (87.5)	2225 (86.3)	807 (87.1)	859 (87.2)	3899 (87.1)	4011 (87.3)	137 (84.0)	138 (86.3)	1566 (83.7)	1458 (84.1)
Related to study drug	478 (16.2)	384 (13.1)	558 (21.2)	337 (13.1)	170 (18.4)	141 (14.3)	884 (19.7)	612 (13.3)	21 (12.9)	20 (12.5)	301 (16.1)	230 (13.3)
Leading to discontinuation	128 (4.3)	124 (4.2)	212 (8.1)	153 (5.9)	74 (8.0)	74 (7.5)	313 (7.0)	249 (5.4)	9 (5.5)	7 (4.4)	92 (4.9)	95 (5.5)
Any SAE	856 (29.0)	938 (32.1)	871 (33.1)	876 (34.0)	333 (36.0)	372 (37.8)	1487 (33.2)	1590 (34.6)	33 (20.2)	42 (26.3)	540 (28.9)	554 (31.9)
Related to study drug	29 (1.0)	27 (0.9)	39 (1.5)	17 (0.7)	15 (1.6)	17 (1.7)	56 (1.3)	46 (1.0)	0	1 (0.6)	27 (1.4)	14 (0.8)
Leading to discontinuation	41 (1.4)	48 (1.6)	75 (2.9)	71 (2.8)	29 (3.1)	35 (3.6)	115 (2.6)	112 (2.4)	1 (0.6)	2 (1.3)	29 (1.5)	40 (2.3)
Any AE leading to death	43 (1.5)	55 (1.9)	42 (1.6)	62 (2.4)	25 (2.7)	34 (3.5)	73 (1.6)	115 (2.5)	0	3 (1.9)	37 (2.0)	33 (1.9)
AEs of interest												
Hypotension	101 (3.4)	70 (2.4)	127 (4.8)	76 (2.9)	54 (5.8)	31 (3.1)	216 (4.8)	131 (2.9)	3 (1.8)	0	63 (3.4)	46 (2.7)
Orthostatic hypotension	18 (0.6)	15 (0.5)	23 (0.9)	15 (0.6)	5 (0.5)	9 (0.9)	34 (0.8)	30 (0.7)	0	2 (1.3)	12 (0.6)	7 (0.4)
Hyperkalemia	360 (12.2)	238 (8.1)	420 (16.0)	158 (6.1)	132 (14.3)	52 (5.3)	647 (14.5)	304 (6.6)	14 (8.6)	16 (10.0)	251 (13.4)	128 (7.4)
Leading to permanent discontinuation	31 (1.0)	13 (0.4)	54 (2.1)	19 (0.7)	25 (2.7)	6 (0.6)	83 (1.9)	28 (0.6)	4 (2.5)	1 (0.6)	23 (1.2)	9 (0.5)
Classified as a serious AE	28 (0.9)	8 (0.3)	29 (1.1)	5 (0.2)	12 (1.3)	3 (0.3)	45 (1.0)	9 (0.2)	1 (0.6)	0	23 (1.2)	7 (0.4)
Leading to hospitalization	26 (0.9)	6 (0.2)	25 (1.0)	2 (<0.1)	10 (1.1)	2 (0.2)	38 (0.8)	5 (0.1)	1 (0.6)	0	22 (1.2)	5 (0.3)
Gynecomastia	2 (<0.1)	4 (0.1)	5 (0.2)	3 (0.1)	1 (0.1)	4 (0.4)	8 (0.2)	11 (0.2)	NA	NA	NA	NA
Central laboratory assessments, n/N (%)[a]												

Serum potassium >5.5 mmol/L	444/2904 (15.3)	233/2871 (8.1)	460/2585 (17.8)	180/2529 (7.1)	171/913 (18.7)	57/970 (5.9)	720/4403 (16.4)	308/4523 (6.8)	16/159 (10.1)	8/154 (5.2)	339/1840 (18.4)	154/1693 (9.1)
Serum potassium >6.0 mmol/L	90/2926 (3.1)	44/2896 (1.5)	89/2598 (3.4)	31/2544 (1.2)	32/915 (3.5)	5/973 (0.5)	143/4428 (3.2)	48/4544 (1.1)	4/160 (2.5)	1/156 (0.6)	64/1851 (3.5)	31/1713 (1.8)

AE = adverse event; NA = not applicable; SAE = serious adverse event.

[a] The “n” numerator represents the number of patients at risk with ≥1 treatment-emergent laboratory assessment meeting the criterion. The “N” denominator represents all patients at risk for a treatment-emergent laboratory abnormality. Patients had both a baseline and postbaseline treatment-emergent value while the baseline value did not exceed the displayed threshold.

Figure Legends

Figure 1. Analysis of CV composite outcome and HHF according to (A) age and (B) sex.

CV composite outcome includes CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF.

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; PY = patient-years.

Figure 2. Analysis of kidney composite outcome according to (A) age and (B) sex.

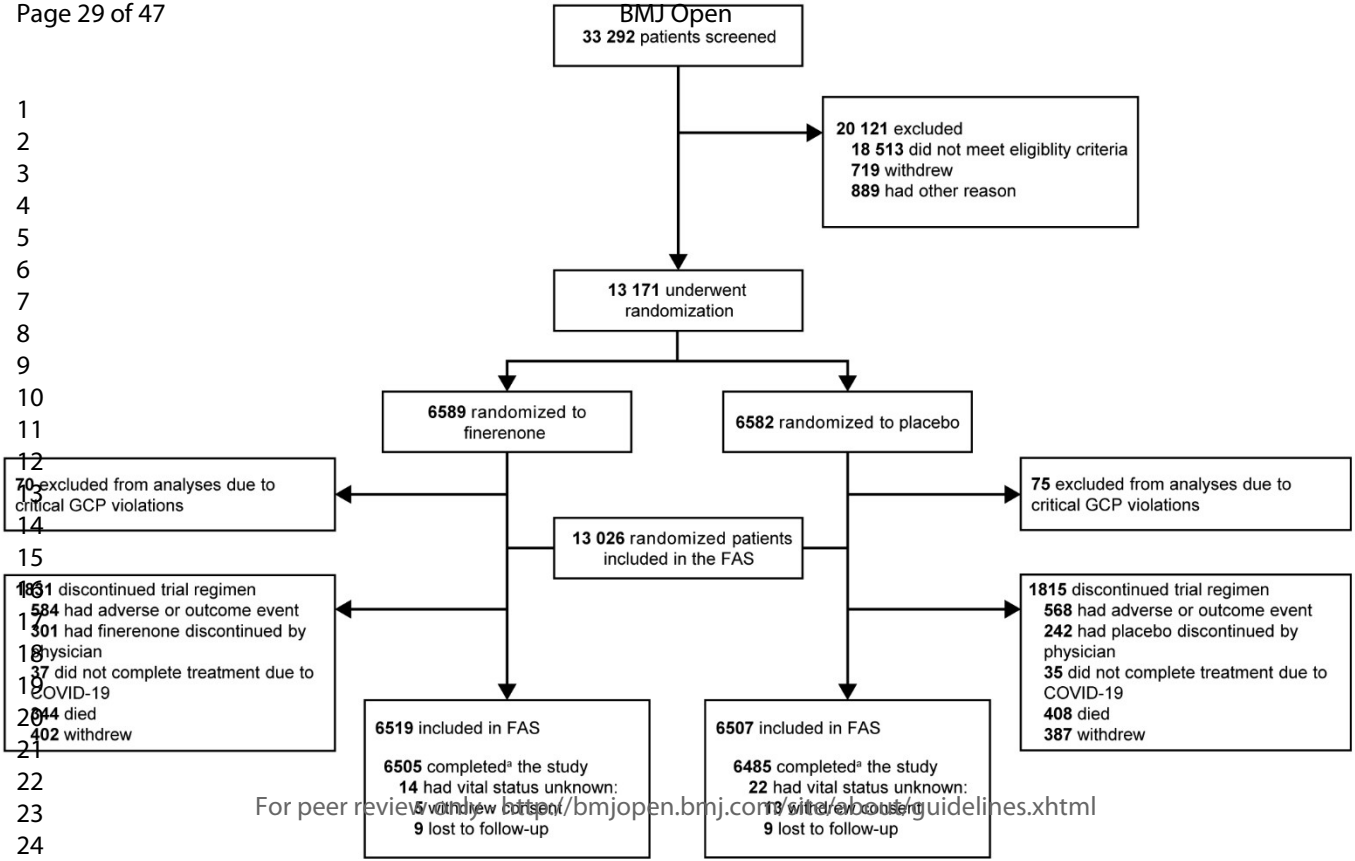
Kidney composite outcome includes kidney failure, sustained ≥57% eGFR decline, or renal death.

CI = confidence interval; eGFR = estimated glomerular filtration rate; PY = patient-years.

Figure 3. LS mean change in eGFR from baseline, chronic, and total slopes over time by age.

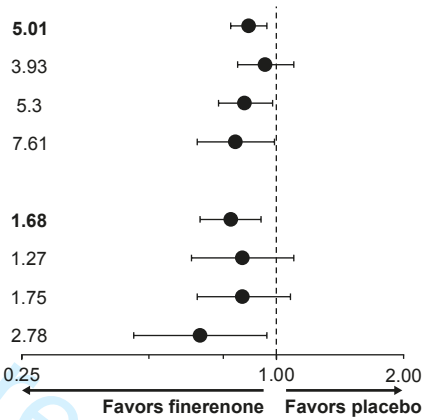
Chronic eGFR slope from month 4 to end-of-study visit.

CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares



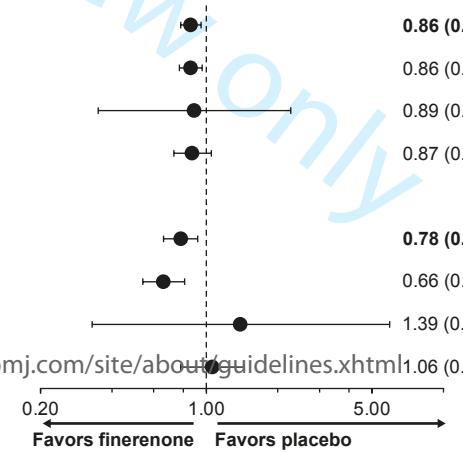
A

Endpoint	Finerenone n/N (%)	Finerenone n/100 PY	Placebo n/N (%)	Placebo n/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
CV composite, age (years)						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78-0.95)**	
Age <65	323/2958 (10.9)	3.74	337/2931 (11.5)	3.93	0.94 (0.81-1.10)	
Age 65-74	339/2635 (12.9)	4.36	396/2586 (15.3)	5.3	0.84 (0.73-0.98)	.4198
Age ≥75	163/926 (17.6)	6.25	206/990 (20.8)	7.61	0.80 (0.65-0.99)	
HHF, age (years)						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66-0.92)**	
Age <65	94/2958 (3.2)	1.06	112/2931 (3.8)	1.27	0.83 (0.63-1.10)	
Age 65-74	111/2653 (4.2)	1.38	135/2586 (5.2)	1.75	0.83 (0.65-1.08)	.6977
Age ≥75	51/926 (5.5)	1.91	78/990 (7.9)	2.78	0.66 (0.46-0.95)	



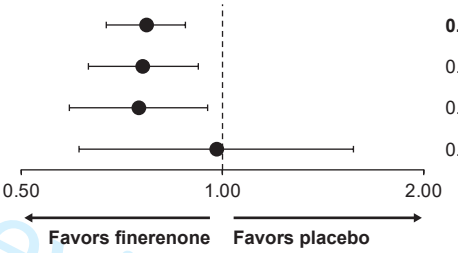
B

Endpoint	Finerenone n/N (%)	Finerenone n/100 PY	Placebo n/N (%)	Placebo n/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
CV composite, sex						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78-0.95)**	
Male	579/4481 (12.9)	4.39	675/4607 (14.7)	5.08	0.86 (0.77-0.96)	
Premenopausal female	11/163 (6.7)	2.29	12/160 (7.5)	2.62	0.89 (0.35-2.27)	.9942
Postmenopausal female	235/1875 (12.5)	4.38	252/1740 (14.5)	5.03	0.87 (0.73-1.05)	
HHF, sex						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66-0.92)**	
Male	163/4481 (3.6)	1.20	244/4607 (5.3)	1.78	0.66 (0.54-0.81)	
Premenopausal female	5/163 (3.1)	1.02	4/160 (2.5)	0.85	1.39 (0.33-5.93)	.0245
Postmenopausal female	88/1875 (4.7)	1.63	77/1740 (4.4)	1.50	1.06 (0.78-1.44)	



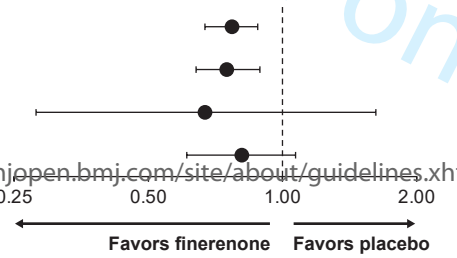
A

Endpoint	Finerenone n/N (%)	Finerenone n/100 PY	Placebo n/N (%)	Placebo n/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
Kidney composite, age (years)						
Overall	**360/6519 (5.5)**	**1.96**	**465/6507 (7.1)**	**2.55**	**0.77 (0.67-0.88)**	
Age <65	202/2958 (6.8)	2.44	266/2931 (9.1)	3.21	0.76 (0.63-0.92)	
Age 65-74	123/2635 (4.7)	1.63	162/2586 (6.3)	2.23	0.75 (0.59-0.95)	.5088
Age ≥75	35/926 (3.8)	1.41	37/990 (3.7)	1.40	0.98 (0.61-1.57)	

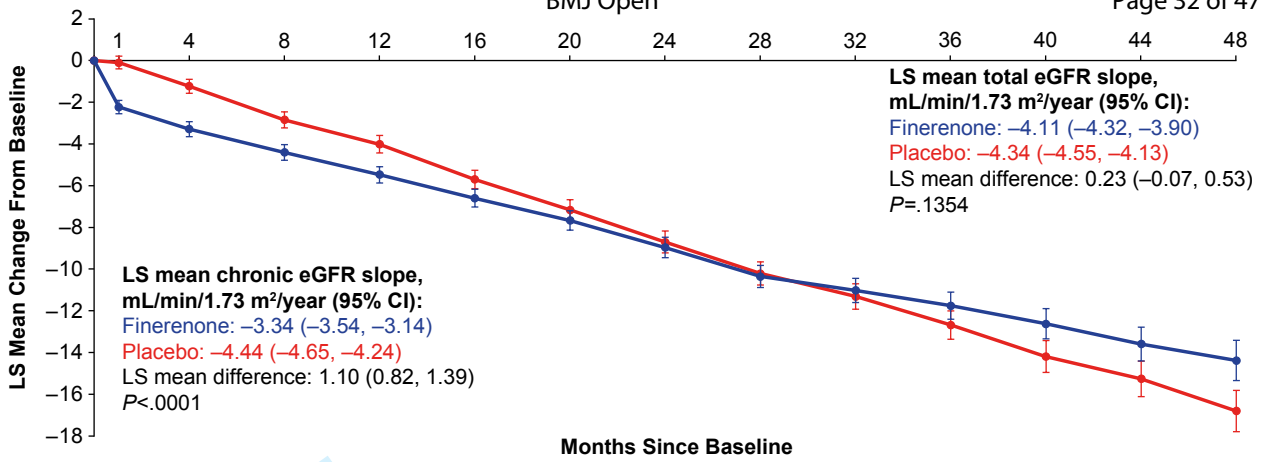


B

Endpoint	Finerenone n/N (%)	Finerenone n/100 PY	Placebo n/N (%)	Placebo n/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
Kidney composite, sex						
Overall	**360/6519 (5.5)**	**1.96**	**465/6507 (7.1)**	**2.55**	**0.77 (0.67-0.88)**	
Male	257/4481 (5.7)	2.02	341/4607 (7.4)	2.63	0.75 (0.64-0.89)	
Premenopausal female	11/163 (6.7)	2.48	13/160 (8.1)	3.16	0.67 (0.28-1.62)	.8524
Postmenopausal female	92/1875 (4.9)	1.79	111/1740 (6.4)	2.30	0.81 (0.61-1.07)	



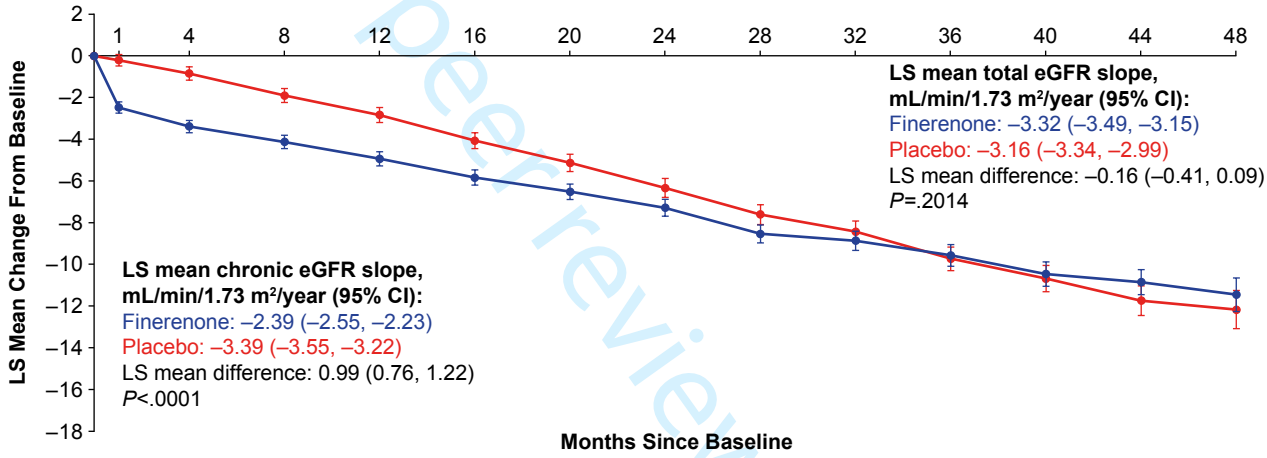
A <65 Years



Number of Subjects at Visit

Finerenone	2921	2849	2778	2730	2656	2505	2281	1918	1541	1246	962	716	409
Placebo	2892	2829	2779	2719	2649	2491	2226	1952	1566	1271	1006	731	417

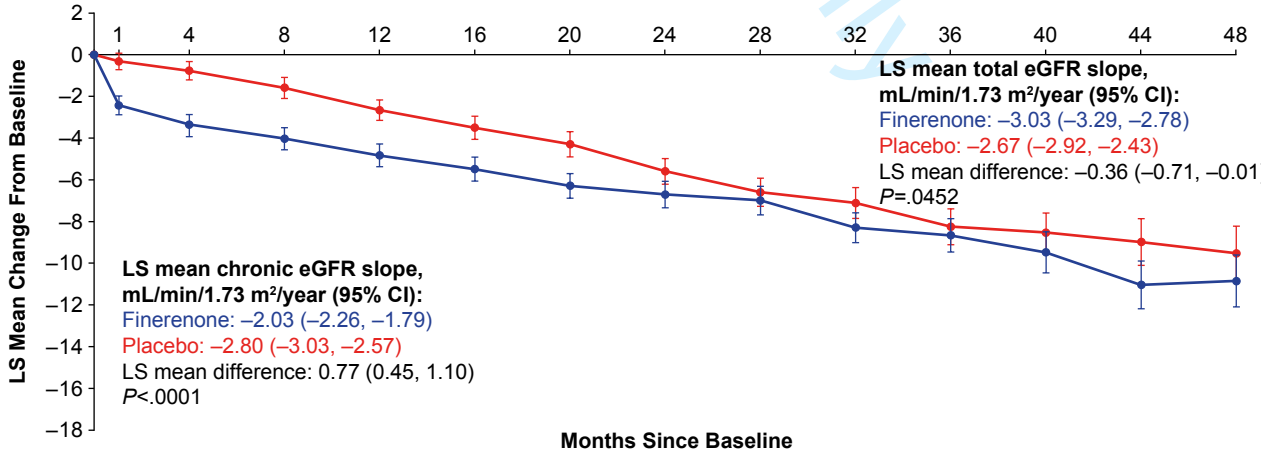
B 65 to 74 Years



Number of Subjects at Visit

Finerenone	2597	2536	2474	2460	2388	2220	1995	1732	1462	1158	935	663	387
Placebo	2539	2481	2429	2376	2326	2163	1951	1674	1360	1097	876	637	346

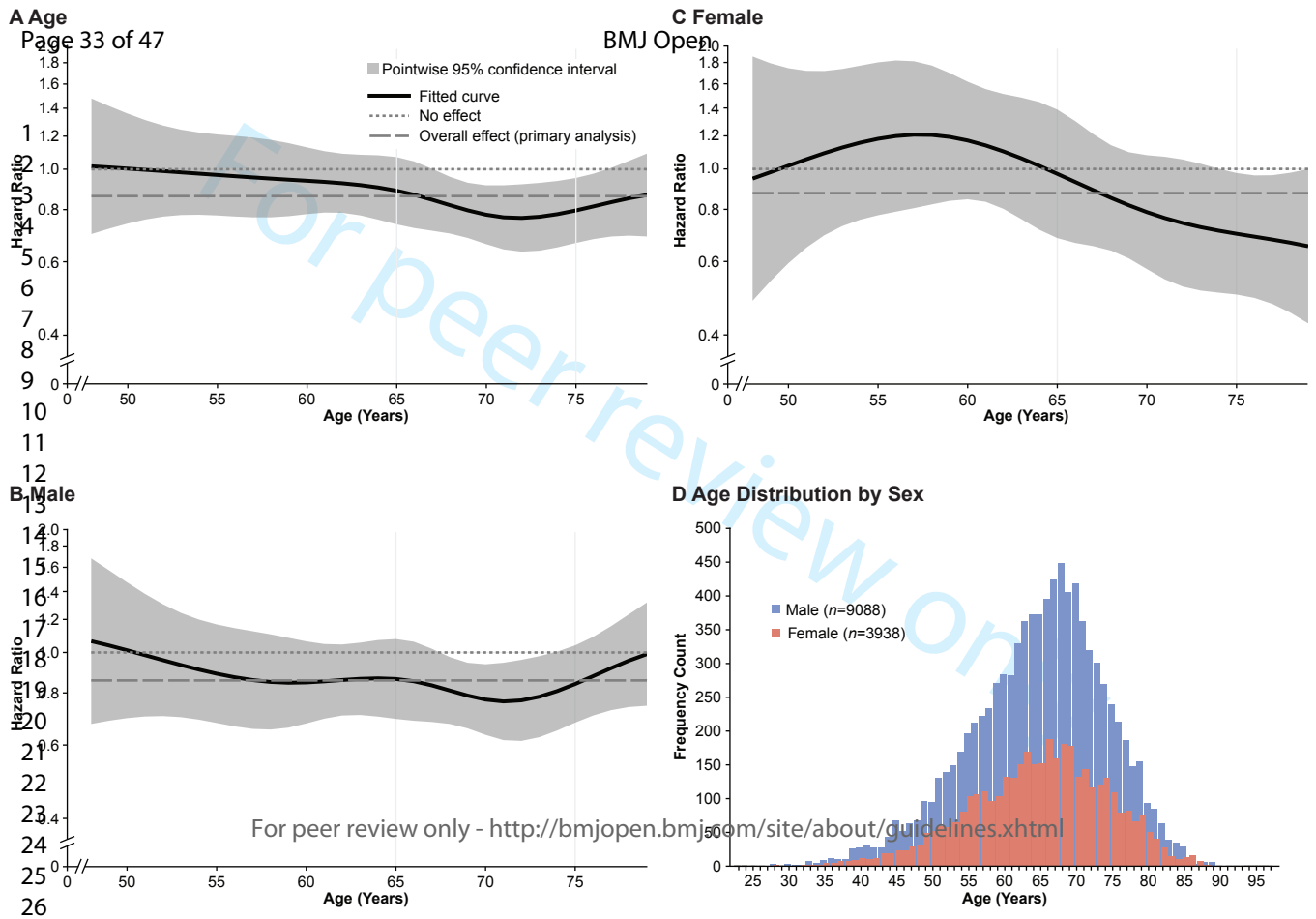
C ≥75 Years

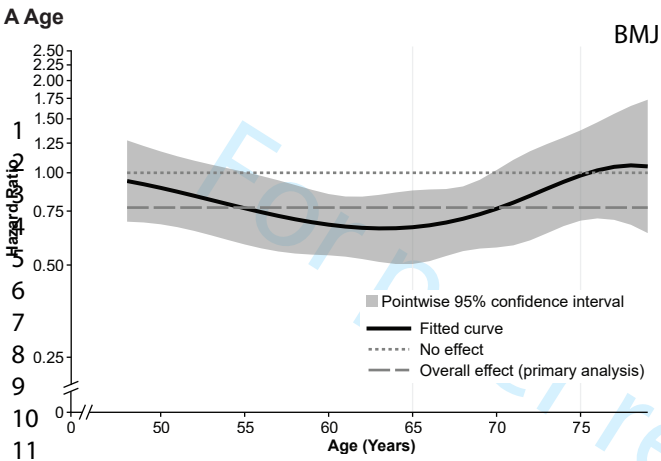


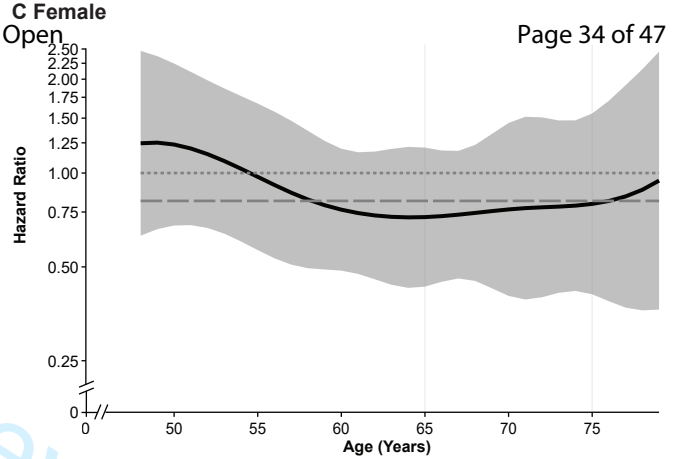
Number of Subjects at Visit

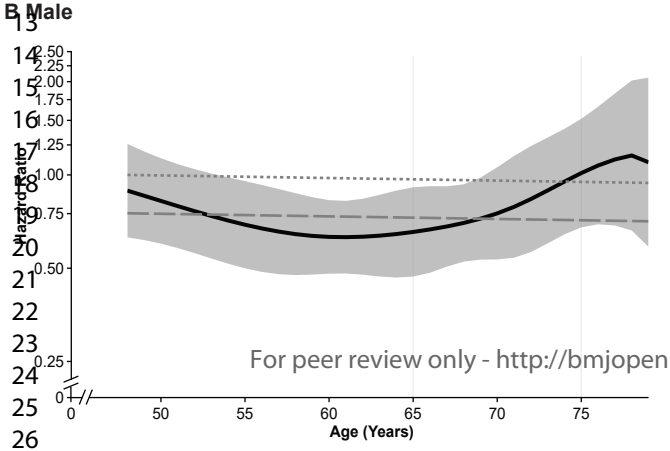
Finerenone	910	877	848	825	792	732	647	567	447	363	277	210	115
Placebo	975	934	919	896	850	780	695	578	481	359	281	204	117

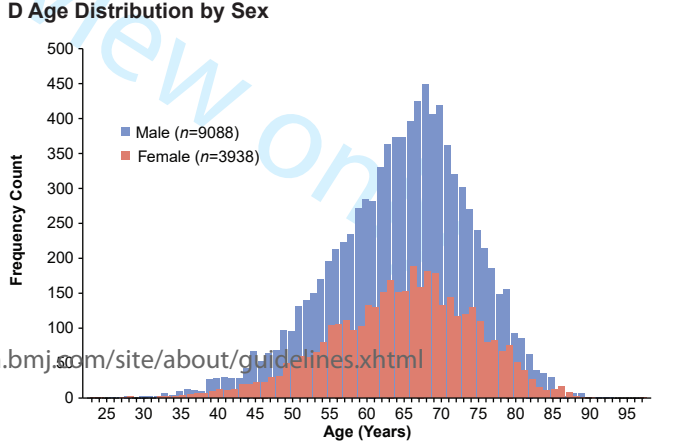
Finerenone Placebo



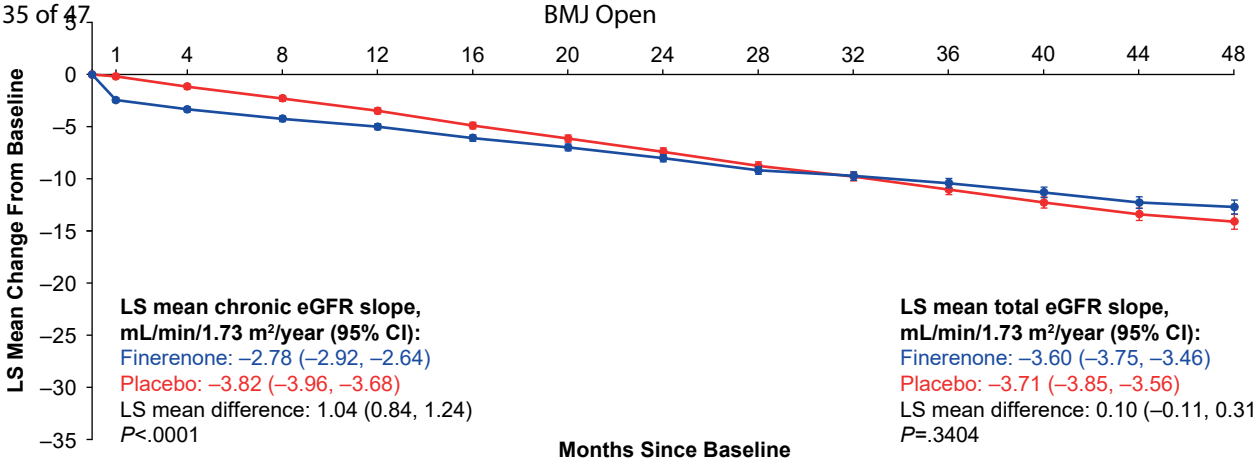








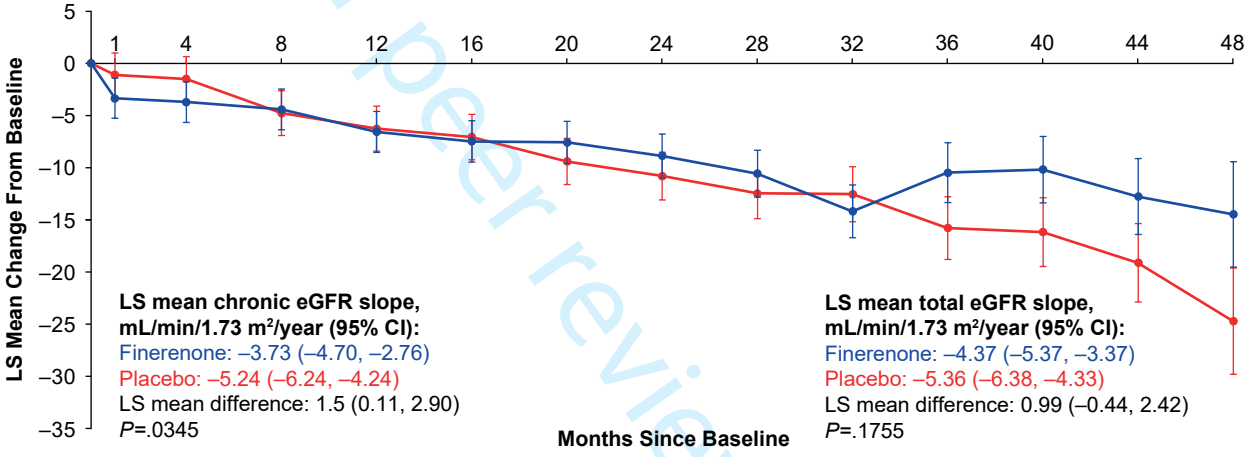
A Male



Number of Subjects at Visit

Finerenone	4423	4314	4215	4154	4016	3774	3409	2934	2410	1937	1550	1148	670
Placebo	4544	4423	4336	4243	4126	3847	3456	1985	2413	1955	1549	1158	652

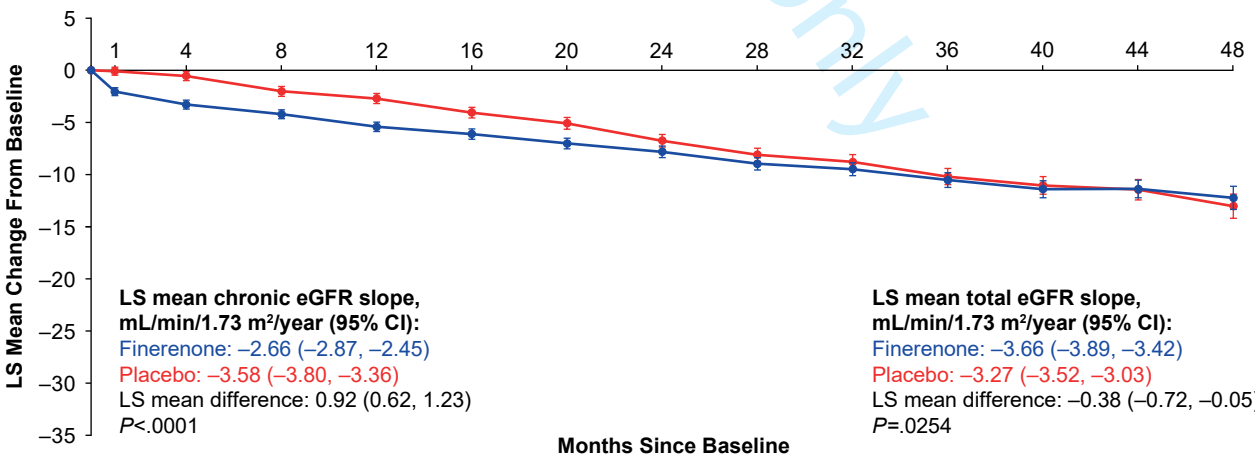
B Premenopausal Female



Number of Subjects at Visit

Finerenone	161	154	152	151	146	140	124	102	75	57	47	36	21
Placebo	156	148	143	141	137	131	118	99	77	57	46	33	15

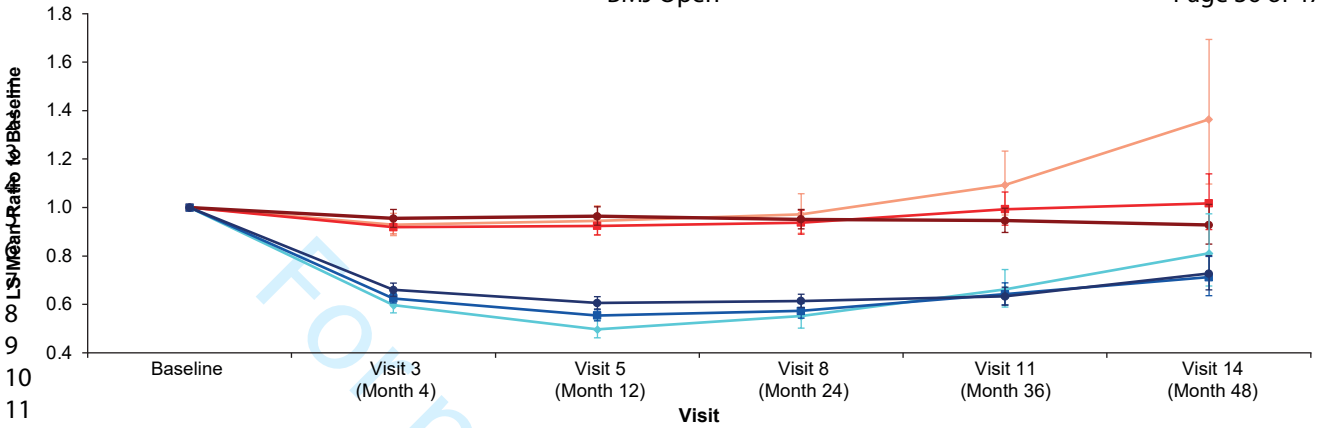
C Postmenopausal Female



Number of Subjects at Visit

Finerenone	1844	1794	1733	1710	1674	1543	1390	1181	965	773	577	405	220
Placebo	1706	1673	1647	1607	1562	1456	1298	1120	917	715	568	381	213

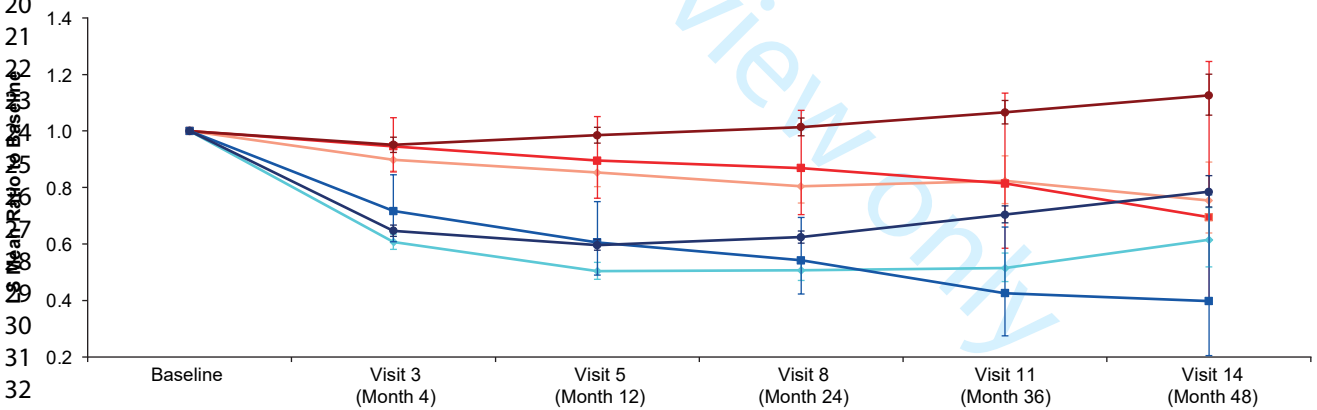
A



Number of Subjects at Visit

Finerenone	2860	2727	2250	1235	408
Placebo	2831	2721	2209	1255	411

B



Number of Subjects at Visit

Finerenone	2860	2727	2250	1235	408
Placebo	2831	2721	2209	1255	411

Cardiorenal Outcomes by Age and Sex in Patients Treated With Finerenone: FIDELITY Post Hoc Analysis

Contents

Supplementary Tables and Figures

eTable 1. Patient Baseline Characteristics According to Age and Sex Stratified by Treatment Group

n (%)	Age						Sex					
	<65 Years		65-74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	Finerenone (*n*=2958)	Placebo (*n*=2931)	Finerenone (*n*=2635)	Placebo (*n*=2586)	Finerenone (*n*=926)	Placebo (*n*=990)	Finerenone (*n*=4481)	Placebo (*n*=4607)	Finerenone (*n*=163)	Placebo (*n*=160)	Finerenone (*n*=1875)	Placebo (*n*=1740)
Sex, *n* (%)							Age, y, mean ± SD					
Female	959 (32.4)	880 (30.0)	772 (29.3)	729 (28.2)	307 (33.2)	291 (29.4)	64.8 ± 9.3	64.9 ± 9.6	45.3 ± 4.4	44.9 ± 5.4	66.2 ± 8.0	66.4 ± 8.0
Male	1999 (67.6)	2051 (70.0)	1863 (70.7)	1857 (71.8)	619 (66.8)	699 (70.6)						
Race, *n* (%)												
Asian	772 (26.1)	819 (27.9)	518 (19.7)	479 (18.5)	142 (15.3)	164 (16.6)	1032 (23.0)	1104 (24.0)	45 (27.6)	42 (26.3)	355 (18.9)	316 (18.2)
Black/African American	158 (5.3)	151 (5.2)	75 (2.8)	85 (3.3)	20 (2.2)	33 (3.3)	137 (3.1)	147 (3.2)	17 (10.4)	20 (12.5)	99 (5.3)	102 (5.9)
White	1827 (61.8)	1765 (60.2)	1908 (72.4)	1909 (73.8)	714 (77.1)	746 (75.4)	3099 (69.2)	3132 (68.0)	84 (51.5)	83 (51.9)	1266 (67.5)	1205 (69.3)
Other[a]	201 (6.8)	196 (6.7)	134 (5.1)	113 (4.4)	50 (5.4)	47 (4.7)	213 (4.8)	224 (4.9)	17 (10.4)	15 (9.4)	155 (8.3)	117 (6.7)
Systolic blood pressure, mm Hg, mean (SD)	135.7 ± 13.9	135.5 ± 14.1	137.4 ± 14.2	137.5 ± 14.2	138.4 ± 14.6	138.5 ± 14.6	136.9 ± 14.1	136.7 ± 14.3	131.6 ± 13.1	134.4 ± 14.7	136.8 ± 14.4	136.9 ± 14.0
Diastolic blood pressure, mm Hg, mean (SD)	78.7 ± 9.2	79.0 ± 8.9	74.8 ± 9.4	74.9 ± 9.4	73.2 ± 9.8	72.4 ± 9.8	76.6 ± 9.7	76.5 ± 9.7	78.7 ± 8.2	81.6 ± 8.4	75.6 ± 9.6	75.6 ± 9.4
Duration of diabetes, y, mean (SD)	13.6 ± 7.6	13.3 ± 7.7	16.4 ± 8.7	16.5 ± 8.5	18.7 ± 10.7	18.5 ± 10.2	15.4 ± 8.6	15.3 ± 8.4	11.0 ± 7.4	10.1 ± 6.5	15.9 ± 9.0	16.0 ± 9.2
HbA1c, %, mean (SD)	7.9 ± 1.5	7.9 ± 1.5	7.6 ± 1.3	7.6 ± 1.3	7.5 ± 1.2	7.4 ± 1.2	7.6 ± 1.3	7.6 ± 1.3	8.1 ± 1.7	8.3 ± 1.6	7.9 ± 1.4	7.9 ± 1.5
Serum potassium, mmol/L, mean (SD)	4.3 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	4.3 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4

n (%)	Age						Sex					
	<65 Years		65-74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	Finerenone (*n*=2958)	Placebo (*n*=2931)	Finerenone (*n*=2635)	Placebo (*n*=2586)	Finerenone (*n*=926)	Placebo (*n*=990)	Finerenone (*n*=4481)	Placebo (*n*=4607)	Finerenone (*n*=163)	Placebo (*n*=160)	Finerenone (*n*=1875)	Placebo (*n*=1740)
eGFR, mL/min/1.73 m^2, mean (SD)	63.9 ± 23.9	64.6 ± 24.0	53.7 ± 18.4	53.3 ± 18.6	48.0 ± 15.5	48.3 ± 14.8	57.8 ± 21.0	57.7 ± 21.4	76.3 ± 28.7	77.5 ± 29.1	55.3 ± 21.5	55.8 ± 21.1
eGFR, mL/min/1.73 m^2, *n* (%)[b]												
<25	24 (0.8)	29 (1.0)	35 (1.3)	37 (1.4)	22 (2.4)	15 (1.5)	44 (1.0)	54 (1.2)	0	2 (1.3)	37 (2.0)	25 (1.4)
25-<45	744 (25.2)	704 (24.0)	937 (35.6)	961 (37.2)	436 (47.1)	450 (45.5)	1392 (31.1)	1479 (32.1)	31 (19.0)	26 (16.3)	694 (37.0)	610 (35.1)
45-<60	666 (22.5)	649 (22.1)	775 (29.4)	739 (28.6)	276 (29.8)	329 (33.2)	1240 (27.7)	1228 (26.7)	26 (16.0)	24 (15.0)	451 (24.1)	465 (26.7)
6□	1523 (51.5)	1548 (52.8)	888 (33.7)	848 (32.8)	192 (20.7)	196 (19.8)	1805 (40.3)	1846 (40.1)	106 (65.0)	108 (67.5)	692 (36.9)	638 (36.7)
UACR, mg/g, median (IQR)	649.2 (308.0-1331.8)	651.4 (322.5-1382.2)	433.8 (150.7-1025.7)	441.3 (157.8-1032.8)	325.6 (107.00-802.7)	340.5 (109.8-871.7)	514.5 (205.3-1116.5)	509.2 (195.4-1143.0)	733.0 (336.3-1522.7)	868.4 (398.5-1604.2)	496.4 (169.9-1124.4)	509.1 (185.0-1174.5)
UACR, mg/g, *n* (%)[c]												
<30	39 (1.3)	40 (1.4)	53 (2.0)	50 (1.9)	28 (3.0)	20 (2.0)	69 (1.5)	68 (1.5)	2 (1.2)	1 (0.6)	49 (2.6)	41 (2.4)
30-<300	686 (23.2)	645 (22.0)	971 (36.9)	936 (36.2)	419 (45.2)	442 (44.6)	1422 (31.7)	1459 (31.7)	34 (20.9)	20 (12.5)	620 (33.1)	544 (31.3)
6□	2231 (75.4)	2244 (76.6)	1611 (61.1)	1599 (61.8)	479 (51.7)	528 (53.3)	2989 (66.7)	3079 (66.8)	127 (77.9)	139 (86.9)	1205 (64.3)	1153 (66.3)
BMI, kg/m^2, mean (SD)	32.1 ± 6.5	32.0 ± 6.3	31.1 ± 5.7	31.1 ± 5.7	29.5 ± 4.8	29.6 ± 5.1	30.9 ± 5.6	30.9 ± 5.6	34.0 ± 7.9	34.3 ± 7.9	32.0 ± 6.7	32.1 ± 6.5
Current smoker, *n* (%)	657 (22.2)	626 (21.4)	351 (13.3)	335 (13.0)	57 (6.2)	67 (6.8)	874 (19.5)	856 (18.6)	17 (10.4)	18 (11.3)	174 (9.3)	154 (8.9)
History of CV disease, present, *n* (%)	1127 (38.1)	1061 (36.2)	1330 (50.5)	1337 (51.7)	522 (56.4)	558 (56.4)	2152 (48.0)	2222 (48.2)	36 (22.1)	20 (12.5)	791 (42.2)	714 (41.0)
History of heart failure	211 (7.1)	202 (6.9)	192 (7.3)	240 (9.3)	82 (8.9)	80 (8.1)	302 (6.7)	328 (7.1)	11 (6.7)	11 (6.9)	172 (9.2)	183 (10.5)

n (%)	Age						Sex					
	<65 Years		65-74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	Finerenone (*n*=2958)	Placebo (*n*=2931)	Finerenone (*n*=2635)	Placebo (*n*=2586)	Finerenone (*n*=926)	Placebo (*n*=990)	Finerenone (*n*=4481)	Placebo (*n*=4607)	Finerenone (*n*=163)	Placebo (*n*=160)	Finerenone (*n*=1875)	Placebo (*n*=1740)
History of atrial fibrillation/atrial flutter	144 (4.9)	122 (4.2)	280 (10.6)	267 (10.3)	144 (15.6)	149 (15.1)	439 (9.8)	428 (9.3)	0	0	129 (6.9)	110 (6.3)
Baseline medications, *n* (%)[d]												
RAS inhibitors (ACEis/ARBs)	2951 (99.8)	2925 (99.8)	2631 (99.8)	2582 (99.8)	926 (100.0)	988 (99.8)	4473 (99.8)	4596 (99.8)	163 (100.0)	160 (100.0)	1872 (99.8)	1739 (>99.9)
Beta-blockers	1311 (44.3)	1308 (44.6)	1419 (53.9)	1430 (55.3)	506 (54.6)	530 (53.5)	2237 (49.9)	2308 (50.1)	57 (35.0)	54 (33.8)	942 (50.2)	906 (52.1)
Diuretics	1378 (46.6)	1412 (48.2)	1412 (53.6)	1401 (54.2)	535 (57.8)	572 (57.8)	2320 (51.8)	2386 (51.8)	67 (41.1)	70 (43.8)	938 (50.0)	929 (53.4)
Statins	1993 (67.4)	2040 (69.6)	1975 (75.0)	1945 (75.2)	689 (74.4)	757 (76.5)	3291 (73.4)	3405 (73.9)	93 (57.1)	110 (68.8)	1273 (67.9)	1227 (70.5)
Calcium channel blockers	1564 (52.9)	1563 (53.3)	1544 (58.6)	1508 (58.3)	556 (60.0)	623 (62.9)	2554 (57.0)	2654 (57.6)	74 (45.4%)	75 (46.9)	1036 (55.3)	965 (55.5)
6 glucose-lowering medication, *n* (%)[d]	2898 (98.0)	2881 (98.3)	2574 (97.7)	2537 (98.1)	882 (95.2)	948 (95.8)	4361 (97.3)	4499 (97.7)	161 (98.8)	156 (97.5)	1832 (97.7)	1711 (98.3)
Insulin	1848 (62.5)	1789 (61.0)	1539 (58.4)	1481 (57.3)	479 (51.7)	494 (49.9)	2598 (58.0)	2605 (56.5)	94 (57.7)	99 (61.9)	1174 (62.6)	1060 (60.9)
GLP-1RA	273 (9.2)	219 (7.5)	190 (7.2)	188 (7.3)	34 (3.7)	40 (4.0)	359 (8.0)	317 (6.9)	12 (7.4)	18 (11.3)	126 (6.7)	112 (6.4)
SGLT-2i	251 (8.5)	266 (9.1)	149 (5.7)	140 (5.4)	38 (4.1)	33 (3.3)	331 (7.4)	340 (7.4)	19 (11.7)	17 (10.6)	88 (4.7)	82 (4.7)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; IQR = interquartile range; RAS = renin–angiotensin system; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; UACR = urine albumin-to-creatinine ratio.

Values are based on available data.

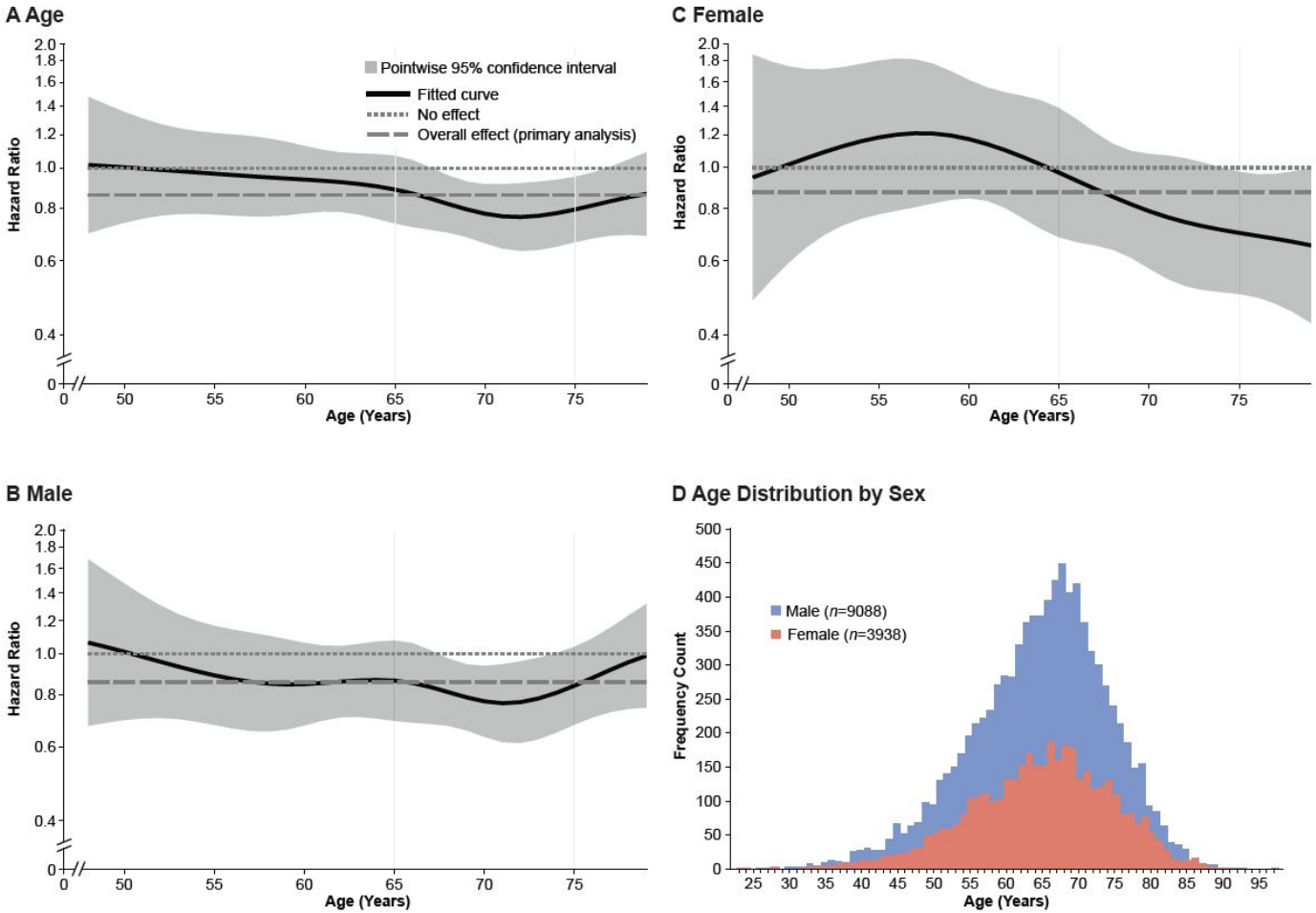
[a] Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific, not reported, multiple.

[b] Missing (eGFR): <65 years, *n*=2; 65 to 74 years, *n*=1; postmenopausal female, *n*=3.

[c] Missing (UACR): <65 years, *n*=4; 65 to 74 years, *n*=1; male, *n*=2; postmenopausal female, *n*=3.

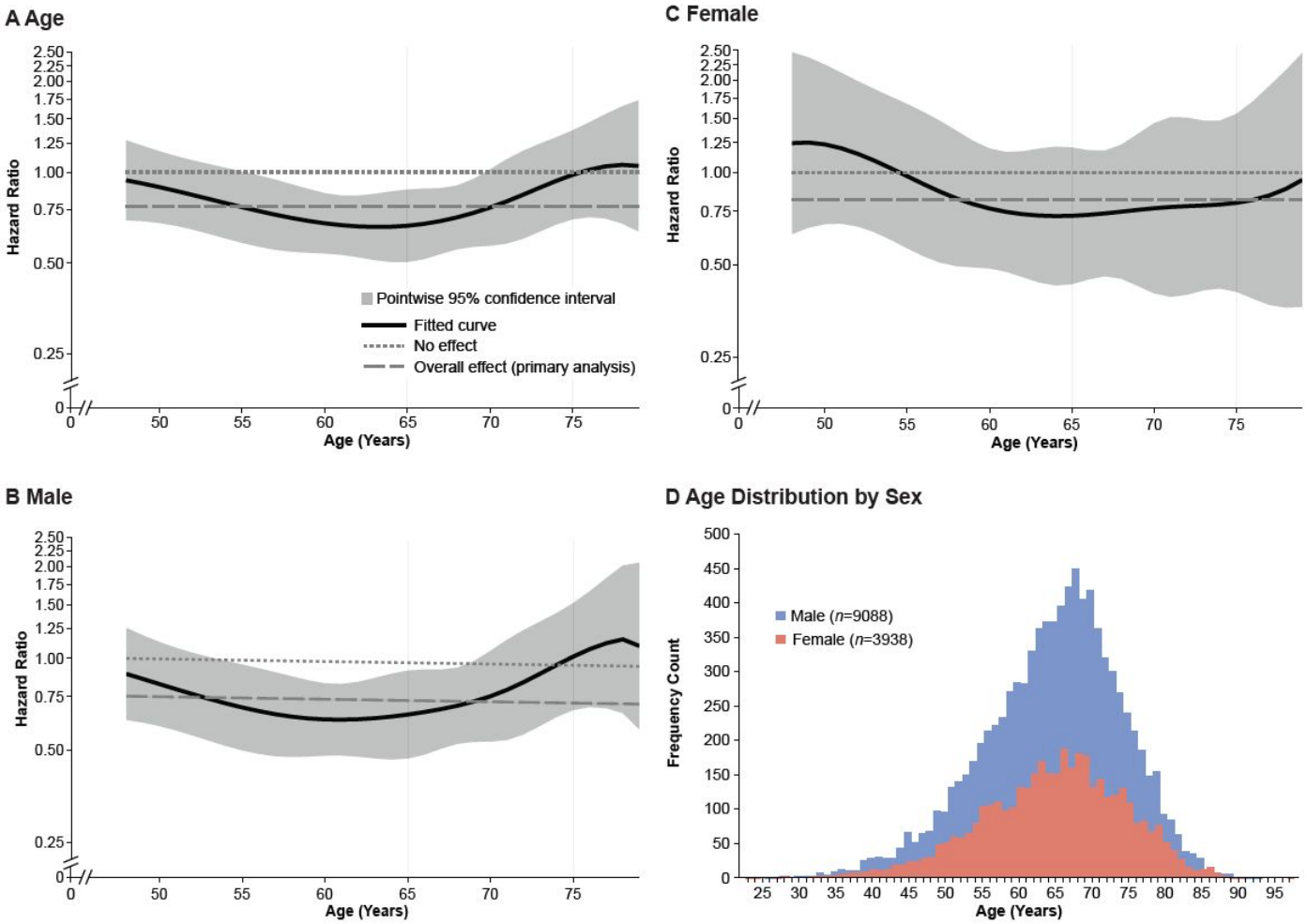
[d] Analysis allowed multiple drug groups for the same drug.

eFigure 1. Hazard ratio (finerenone vs. placebo) as a function of age modeled with cubic splines for CV composite outcome by age (A), spline for hazard ratio of CV composite outcomes by sex (B, C) and age distribution by sex (D).

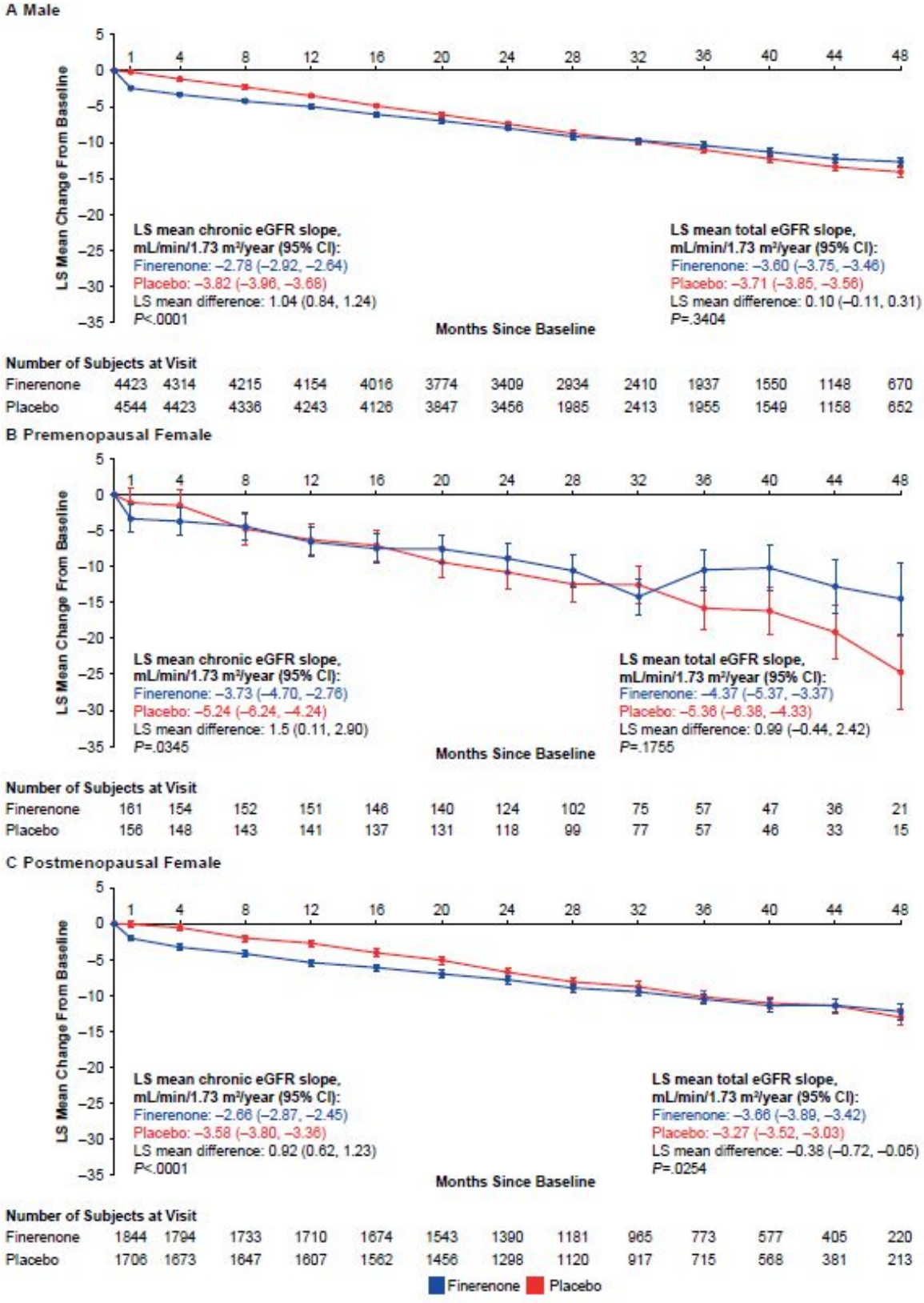


CV = cardiovascular.

eFigure 2. Hazard ratio (finerenone vs. placebo) as a function of age modeled with cubic splines for kidney composite outcome by age (A), spline for hazard ratio of kidney composite outcomes by sex (B, C) and age distribution by sex (D).

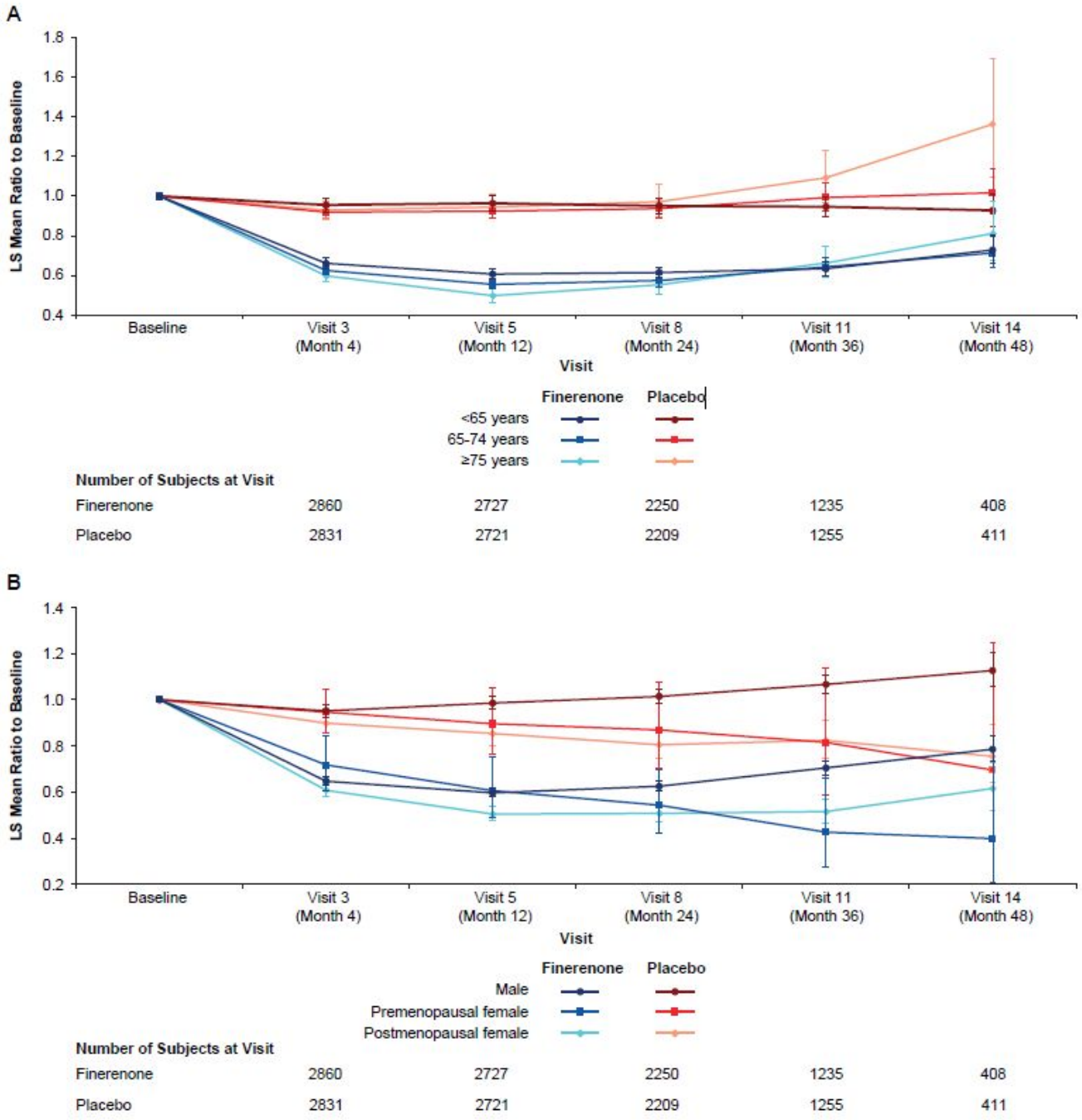


eFigure 3. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.



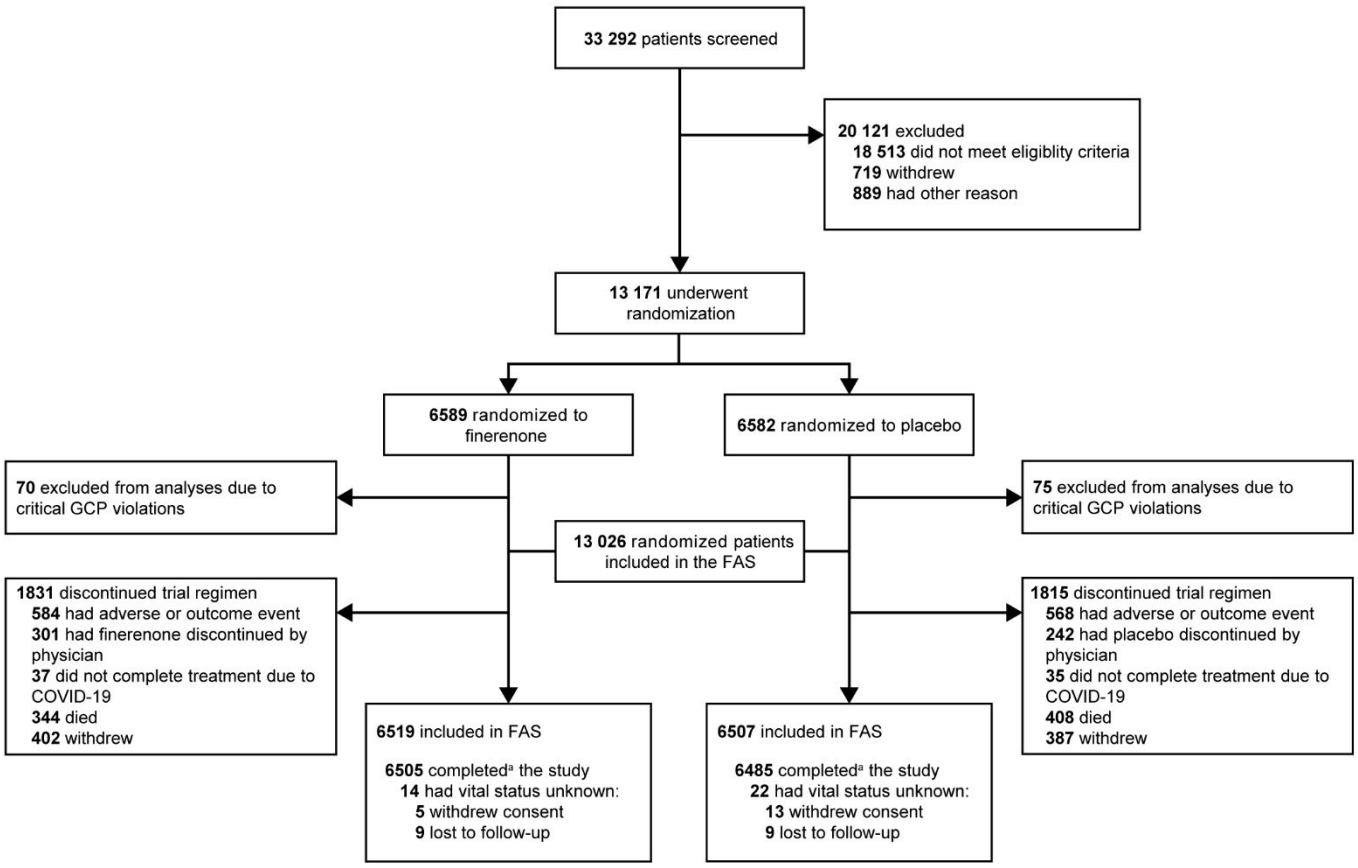
Chronic eGFR slope from month 4 to end-of-study visit.
CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

eFigure 4. LS mean ratio to baseline UACR over time by age and sex.



LS = least-squares; UACR = urine albumin-to-creatinine ratio.

eFigure 5. FIDELITY CONSORT diagram.



[a] The patient was considered as having completed the study if there was a contact with the patient after the end-of-study notification or if the patient died.
FAS, full analysis set; GCP, Good Clinical Practice.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1 – Secondary analysis of a previously reported RCT
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	Reported previously
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	Reported previously
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Reported previously
Randomisation:			
Sequence	8a	Method used to generate the random allocation sequence	Reported

generation			previously
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Reported previously
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Reported previously
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Reported previously
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Reported previously
	11b	If relevant, description of the similarity of interventions	Reported previously
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8-9; Table 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	eFigure 5
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Reported previously
	14b	Why the trial ended or was stopped	Reported previously
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8-9; Table 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-12 Figures 1-2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	eFigures 1-4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 2
Discussion			

Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Reported previously
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-15
Other information			
Registration	23	Registration number and name of trial registry	6
Protocol	24	Where the full trial protocol can be accessed, if available	Primary publications with full protocols are cited (6)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16-17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials

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Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials

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ABSTRACT

Objectives: To evaluate the efficacy and safety of finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist, on cardiovascular and kidney outcomes by age and/or sex.

Design: FIDELITY post hoc analysis; 3 years median follow-up.

Setting: FIDELITY, a prespecified analysis of the multicenter, double-blind FIDELIO-DKD and FIGARO-DKD trials.

Participants: Adults with type 2 diabetes and chronic kidney disease receiving optimized renin–angiotensin system inhibitor treatment (N=13 026 patients).

Interventions: Randomized 1:1 to finerenone or placebo.

Primary and secondary outcome measures: Cardiovascular (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure [HHF]) and kidney (kidney failure, sustained ≥57% estimated glomerular filtration rate decline, or renal death) composite outcomes.

Results: Mean age was 64.8 years; 45.2%, 40.1%, and 14.7% were aged <65, 65–74, and ≥75 years, respectively; 69.8% were male. Cardiovascular benefits of finerenone versus placebo were consistent across age (hazard ratio 0.94 [<65 years], 0.84 [65–74 years], 0.80 [≥75 years]; $P_{interaction}$=.42) and sex categories (hazard ratio 0.86 [male], 0.89 [premenopausal female], 0.87 [postmenopausal female]; $P_{interaction}$=.99); effects on HHF reduction were not modified by age ($P_{interaction}$=.70) but appeared more pronounced in males ($P_{interaction}$=.02). Kidney events were reduced with finerenone versus placebo in patients aged <65 and 65–74 but not ≥75; no heterogeneity in treatment effect was observed ($P_{interaction}$=.51). In sex subgroups, finerenone consistently reduced kidney events ($P_{interaction}$=.85). Finerenone reduced albuminuria and estimated glomerular filtration rate decline regardless of age and sex. Hyperkalemia increased with finerenone, but discontinuation rates were <3% across subgroups. Gynecomastia in males was uncommon across age subgroups and identical between treatment groups.

Conclusions: Finerenone improved cardiovascular and kidney composite outcomes with no significant heterogeneity between age and sex subgroups; however, the effect on HHF appeared more pronounced in males. Finerenone demonstrated a similar safety profile across age and sex subgroups.

Registration: FIDELIO-DKD (NCT02540993); FIGARO-DKD (NCT02545049)

Abstract word count: 300 of 300

STRENGTHS AND LIMITATIONS OF THIS STUDY

- An advantage of this study was the use of combined individual-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, resulting in a large number of patients included in the full analysis set
- This study did not use predefined age categories, as it was a post hoc analysis, which may have resulted in some of the tests performed being underpowered
- Limitations present in FIDELITY are present in this analysis, such as the small proportion of Black patients and exclusion of patients with nonalbuminuric CKD

INTRODUCTION

In patients with diabetes, the risk of cardiovascular (CV) disease and chronic kidney disease (CKD) increases with age.[1] Likewise, vascular complications are affected by sex and are increased in females more than males in patients with diabetes.[2]

Among individuals aged 50–75 years without baseline diabetes, CKD, or CV disease, males have a steeper decline in glomerular filtration rate (GFR) than females.[3] However, reported effects of sex on risk of incidental and progressive CKD in patients with type 2 diabetes (T2D) have been inconsistent.[4-6] In trials including patients with CKD, female representation varies (25–40%),[7-11] whereas in real-world studies, females make up over half of patients.[12,13]

Overactivation of the mineralocorticoid receptor (MR) is associated with CV and kidney diseases.[14,15] In epithelial cells, the 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme prevents inappropriate MR activation by cortisol.[16-18] The activity of 11β-HSD2 decreases with age, resulting in MR overactivation in the elderly despite low circulating aldosterone levels.[16-18] Sex also influences 11β-HSD2 activity, particularly in patients with hypertension, where 11β-HSD2 activity is reduced in males versus females.[16] The MR is also expressed in nonepithelial cells, including endothelial cells, vascular smooth muscle cells, adipocytes, and immune cells.[17] In many of these, the MR may be activated by cortisol because of a lack of protection by 11β-HSD2.[19,20]

Despite management with recommended treatments for CKD in T2D, 10–13% of patients experience CKD progression or kidney failure and are at high risk of CV events, including CV death within 2–3 years following treatment initiation.[10,21,22] Finerenone, a selective, nonsteroidal MR antagonist (MRA), reduced the risk of CKD progression and CV outcomes compared with placebo in patients with CKD and T2D in FIDELITY (The FInerenone in

chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis), a prespecified pooled analysis of the FIDELIO-DKD (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; NCT02540993) and FIGARO-DKD (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease; NCT02545049) phase 3 trials.[21] However, the influence of age and sex on outcomes with finerenone is unknown. This post hoc analysis evaluated whether the cardiovascular and kidney benefits and safety profile of finerenone observed in FIDELITY are consistent in patients with CKD and T2D across ages and in both sexes.

METHODS

Study design and patients

FIDELITY combined individual patient-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials. The study design, procedures, and outcomes for the trials have been previously published.[23-25] The FIDELIO-DKD and FIGARO-DKD trials were conducted in accordance with the principles of the Declaration of Helsinki. Protocol approvals were obtained from local regulatory authorities and ethics committees. Written informed consent was provided by all participants. These studies were reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Eligible patients were aged ≥18 years with CKD and T2D, receiving maximum tolerated renin–angiotensin system inhibitor, and with serum potassium levels ≤4.8 mmol/L at screening. Patients had either a urine albumin-to-creatinine ratio (UACR) ≥30–<300 mg/g and an estimated GFR (eGFR) ≥25–≤90 mL/min/1.73 m^2, or UACR ≥300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2. Patients with symptomatic heart failure (HF) with reduced ejection fraction were excluded because this implies an indication for a steroidal MRA.

Standard-of-care therapy with a renin–angiotensin system inhibitor was optimized during the run-in period. Patients were randomly assigned (1:1) to receive finerenone at titrated doses (10 or 20 mg) once-daily oral treatment or matching placebo.

Key outcomes

Efficacy outcomes included a CV composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF (HHF), and a kidney composite outcome of kidney failure, sustained ≥57% eGFR decline, or renal death. Additional outcomes included HHF and change in UACR and eGFR over time.

Safety outcomes included incidence of investigator-reported adverse events (AEs), including those leading to treatment discontinuation, central laboratory assessment of serum potassium levels >5.5 and >6.0 mmol/L, and other safety events of interest, such as hypotension, hyperkalemia, and gynecomastia in males.

Outcomes were analyzed according to patient age at baseline (<65, 65–75, ≥75 years) and sex. Females were categorized as either pre- or postmenopausal if they were aged <51.4 or ≥51.4 years at baseline, respectively (based on the median age of menopause onset from the Massachusetts Women's Health Study).[26]

Statistical analysis

Statistical analyses were performed as described in FIDELITY.[23] The full analysis set comprised all randomized patients (except those with critical Good Clinical Practice violations, who were prospectively excluded). Safety analyses were performed in the safety analysis set (randomized patients without critical Good Clinical Practice violations who took >1 dose of study drug). The analyses were prespecified exploratory evaluations of outcomes according to age and sex, with events reported from randomization up to the end-of-study visit. Stratified Cox proportional hazards models,[27,28] including stratification factors:

geographic region, eGFR and albuminuria category at screening, history of CV disease, and study, were used for the analysis of time-to-event clinical outcomes. The *P*-values for interaction between the treatment group (finerenone or placebo) and each baseline subgroup (age or sex) were based on stratified Cox proportional hazards models, accounting for the treatment effect, the subgroup effect, and their interaction.

Changes in UACR and eGFR over time were assessed using a linear mixed-model analysis accounting for repeated measurements over time. The least-squares mean ratio and absolute change from baseline were estimated from the models for changes in UACR and eGFR, respectively. The 2-slope, linear spline, mixed-model, repeated measure method[29] was used to estimate the rate of change in eGFR across time, specifically total (annualized rate of change in eGFR from baseline to permanent discontinuation or end of study) and chronic (from month 4 to permanent discontinuation or end of study) eGFR slopes. To account for possible nonlinear effects of age on clinical outcomes, age was modeled with cubic splines with 3 knots in Cox proportional hazards models, to produce plots of the hazard ratios (HRs) and 95% confidence interval as functions of age and sex.

Patients and public involvement

No patient or public involvement in the current study.

RESULTS

Patients

FIDELITY included 13 026 patients.[23] Median follow-up was 3 years (interquartile range 2.3–3.8).[23] Mean age at baseline was 64.8 years (standard deviation 9.5), with 45.2%, 40.1%, and 14.7% of patients aged <65, 65–74, and ≥75 years at baseline, respectively. Most patients (69.8%) were male; 2.5% were premenopausal females, and 27.8% were postmenopausal females. Patients were distributed evenly between treatment arms within age and sex subgroups (**eTable 1**).

Baseline characteristics

Baseline characteristics were similar across age subgroups except for some key differences (**Table 1**). The overall FIDELITY population was predominantly White (68.1%), the proportion of which increased with age. Mean eGFR was 64, 54, and 48 mL/min/1.73 m^2 in patients aged <65, 65–75, and ≥75 years, respectively. Median UACR was 650, 439, and 332 mg/g in patients aged <65, 65–75, and ≥75 years, respectively. History of CV disease was more common in the ≥75 years group; this trend was also observed for atrial fibrillation/atrial flutter. Baseline characteristics in sex subgroups are shown in **Table 1**.

Table 1. Patient Baseline Characteristics According to Age and Sex

Characteristic	All (*N*=13 026)	Age			Sex		
		<65 Years (*n*=5889)	65–74 Years (*n*=5221)	≥75 Years (*n*=1916)	Male (*n*=9088)	Premenopausal Female (*n*=323)	Postmenopausal Female (*n*=3615)
Age, y, mean ± SD	64.8 ± 9.5	56.4 ± 6.6	69.2 ± 2.8	78.4 ± 3.1	64.8 ± 9.5	45.1 ± 4.9	66.3 ± 8.0
Sex, *n* (%)							
Female	3938 (30.2)	1839 (31.2)	1501 (28.7)	598 (31.2)	9088 (100)	0 (0.0)	0 (0.0)
Male	9088 (69.8)	4050 (68.8)	3720 (71.3)	1318 (68.8)	0 (0.0)	323 (100)	3615 (100)
Race, *n* (%)							
Asian	2894 (22.2)	1591 (27.0)	997 (19.1)	306 (16.0)	2136 (23.5)	87 (26.9)	671 (18.6)
Black/African American	522 (4.0)	309 (5.2)	160 (3.1)	53 (2.8)	284 (3.1)	37 (11.5)	201 (5.6)
White	8869 (68.1)	3592 (61.0)	3817 (73.1)	1460 (76.2)	6231 (68.6)	167 (51.7)	2471 (68.4)
Other[a]	741 (5.7)	397 (6.7)	247 (4.7)	97 (5.1)	437 (4.8)	32 (9.9)	272 (7.5)
Systolic blood pressure, mm Hg, mean (SD)	136.7 ± 14.2	135.6 ± 14.0	137.4 ± 14.2	138.4 ± 14.6	136.8 ± 14.2	133.0 ± 14.0	136.9 ± 14.3
Diastolic blood pressure, mm Hg, mean (SD)	76.4 ± 9.6	78.8 ± 9.1	74.9 ± 9.4	72.8 ± 9.8	76.5 ± 9.7	80.1 ± 8.4	75.6 ± 9.5
Duration of diabetes, years, mean (SD)	15.4 ± 8.7	13.5 ± 7.6	16.4 ± 8.6	18.6 ± 10.4	15.3 ± 8.5	10.6 ± 7.0	16.0 ± 9.1
HbA1c, %, mean (SD)	7.7 ± 1.4	7.9 ± 1.5	7.6 ± 1.3	7.4 ± 1.2	7.6 ± 1.3	8.2 ± 1.7	7.9 ± 1.4
Serum potassium, mmol/L, mean (SD)	4.4 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.4 ± 0.4
eGFR, mL/min/1.73 m^2, mean (SD)	57.6 ± 21.7	64.3 ± 24.0	53.5 ± 18.5	48.1 ± 15.1	57.7 ± 21.2	77.0 ± 28.9	55.6 ± 21.3

UACR, mg/g, median (Q1–Q3)	514.68 (197.8–1147.1)	650.48 (315.2–1363.5)	438.63 (154.1–1030.7)	332.29 (107.8–830.5)	511.53 (200.9–1130.1)	793.52 (376.6–1547.3)	501.47 (173.6–1149.1)
BMI, kg/m^2, mean (SD)	31.3 ± 6.0	32.0 ± 6.4	31.1 ± 5.7	29.6 ± 5.0	31.0 ± 5.6	34.1 ± 7.9	32.0 ± 6.6
Current smoker, *n* (%)	2093 (16.1)	1283 (21.8)	686 (13.1)	124 (6.5)	1730 (19.0)	35 (10.8)	328 (9.1)
History of CV disease, present, *n* (%)	5935 (45.6)	2188 (37.2)	2667 (51.1)	1080 (56.4)	4374 (48.1)	56 (17.3)	1505 (41.6)
History of heart failure	1007 (7.7)	413 (7.0)	432 (8.3)	162 (8.5)	630 (6.9)	22 (6.8)	355 (9.8)
History of atrial fibrillation/atrial flutter	1106 (8.5)	266 (4.5)	547 (10.5)	293 (15.3)	867 (9.5)	0	239 (6.6)
Baseline medications, *n* (%)[b]							
RAS inhibitors (ACEis/ARBs)	13003 (99.8)	5876 (99.8)	5213 (99.8)	1914 (99.9)	9069 (99.8)	323 (100.0)	3611 (99.9)
Beta-blockers	6504 (49.9)	2619 (44.5)	2849 (54.6)	1036 (54.1)	4545 (50.0)	111 (34.4)	1848 (51.1)
Diuretics	6710 (51.5)	2790 (47.4)	2813 (53.9)	1107 (57.8)	4706 (51.8)	137 (42.4)	1867 (51.6)
Statins	9399 (72.2)	4033 (68.5)	3920 (75.1)	1446 (75.5)	6696 (73.7)	203 (62.8)	2500 (69.2)
Calcium channel blockers	7358 (56.5)	3127 (53.1)	3052 (58.5)	1179 (61.5)	5208 (57.3)	149 (46.1)	2001 (55.4)
Insulin	7630 (58.6)	3637 (61.8)	3020 (57.8)	973 (50.8)	5203 (57.3)	193 (59.8)	2234 (61.8)
GLP-1RA	944 (7.2)	492 (8.4)	378 (7.2)	74 (3.9)	676 (7.4)	30 (9.3)	238 (6.6)
SGLT-2i	877 (6.7)	517 (8.8)	289 (5.5)	71 (3.7)	671 (7.4)	36 (11.1)	170 (4.7)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; Q = quartile; RAS = renin–angiotensin system; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; UACR = urine albumin-to-creatinine ratio.

[a] Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, not reported, multiple.

[b] Analysis allowed multiple drug groups for the same drug.

Efficacy

CV composite outcome by age

CV composite event rates, including the components of the composite outcome, increased with patient age in both treatment arms (**Figure 1A** and **eFigure 1A**). Treatment with finerenone resulted in a numerical reduction in CV composite event rates versus placebo in all age groups (**Figure 1A**); however, no significant heterogeneity was observed for the effect of finerenone across categorical age subgroups ($P_{interaction}$=.42). There was also no evidence of treatment effect modification when age was modeled as a continuous variable ($P_{interaction}$=.10). The trend of HR as a function of age was modeled with cubic splines (**eFigure 2A**).

HHF event rates were numerically lower with finerenone than placebo in all age subgroups (**Figure 1A**). The effect of finerenone on HHF risk reduction was consistent across age subgroups, with no significant heterogeneity observed ($P_{interaction}$=.70).

CV composite outcome by sex

CV composite event rates were numerically lower with finerenone than placebo for males, premenopausal females, and postmenopausal females (**Figure 1B** and **eFigure 1B**). There was no significant heterogeneity in the effect of finerenone on reducing the risk of the CV composite outcome across sex subgroups ($P_{interaction}$=.99). When age was modeled with cubic splines by sex, the effect of finerenone was consistent with advancing age in males; however, a trend toward a stronger effect in older versus younger females was noted (**eFigure 2B, eFigure 2C**). Age distribution by sex is demonstrated in **eFigure 2D**.

No heterogeneity was observed in the effect of finerenone on reducing the risk of the CV death, nonfatal myocardial infarction, and nonfatal stroke components of the CV composite outcome (**eFigure 1B**). However, statistical heterogeneity was observed in the reduction of

HHF with finerenone versus placebo ($P_{interaction}$=.02), and the effect appeared to be more pronounced in males than premenopausal/postmenopausal females (**Figure 1B**). These results persisted after adjustment for differences in baseline age, body mass index, systolic blood pressure, hemoglobin, eGFR, UACR, smoking history, and history of atrial fibrillation between sex subgroups ($P_{interaction}$=.02).

Kidney composite outcome by age

Kidney composite event rates were lower with finerenone than placebo in the <65 years and the 65–74 years groups but were similar in the ≥75 years group (**Figure 2A**). The effect of finerenone on reducing the risk of the kidney composite outcome was consistent across age subgroups, with no significant heterogeneity detected ($P_{interaction}$=.51) and no evidence of treatment effect modification when age was modeled as a continuous variable ($P_{interaction}$=.77). The trend of HR as function of age was modeled with cubic splines (**eFigure 3A**).

Kidney composite outcome by sex

Kidney composite event rates were lower with finerenone than placebo in males but were similar in premenopausal and postmenopausal females (**Figure 2B**). There was no significant heterogeneity in the effect of finerenone on reducing the risk of the kidney composite outcome across sex subgroups ($P_{interaction}$=.85). When age was modeled with cubic splines by sex subgroups, the effect of finerenone suggests trends similar to overall results in males and females across all age groups (**eFigure 3B, eFigure 3C**). Age distribution by sex is demonstrated in **eFigure 3D**.

Effect of finerenone on markers of kidney function and damage by age and sex

Finerenone significantly attenuated the least-squares mean change in eGFR from month 4 to end of treatment (chronic eGFR slope) compared with placebo across all age (P<.0001 for all 3 subgroups) (**Figure 3**) and sex subgroups (**eFigure 4**). Finerenone reduced UACR over time compared with placebo regardless of age and sex (**eFigure 5**).

Safety

The incidence of any AE was similar between treatment groups irrespective of age or sex (**eTable 2**). There were more drug-related AEs with finerenone than placebo in age and sex subgroups except premenopausal females, where the incidence was similar. AEs leading to drug discontinuation were more frequent in patients given finerenone than placebo (6.4% and 5.4%, respectively), with higher incidences in the 65–74 and ≥75 years groups than the <65 years group; there were more AEs leading to drug discontinuation with finerenone than placebo in males and premenopausal females but not in postmenopausal females.

Although the incidences of any serious AEs (SAEs), study drug-related SAEs, or SAEs leading to drug discontinuation were similar between treatment arms across all age and sex subgroups, the overall incidences of SAEs increased with age and was highest in males, followed by postmenopausal females, then premenopausal females.

In all age and sex subgroups, the incidences of treatment-emergent hypotension AEs were higher with finerenone than placebo but did not have a substantial impact on related clinical outcomes, including falls, dizziness, and fatigue. A trend of increased incidence of hypotension with increasing age was observed in patients treated with finerenone; however, the incidence of hypotension was generally low across all age subgroups (<6%; **eTable 2**).

In FIDELITY, finerenone increased the risk of any hyperkalemia event versus placebo; similar findings were observed in all age and sex subgroups, except premenopausal females (e**Table 2**). The incidences of any hyperkalemia AEs leading to discontinuation of study drug and any serious hyperkalemia AEs leading to hospitalization were low across all age and sex subgroups (<3% and <2%, respectively). However, the relative risk of treatment discontinuation because of hyperkalemia with finerenone versus placebo increased with advancing age (relative risk [95% confidence interval] for ages 45–64, 65–74, and ≥75 years:

2.2 [1.2–4.3], 2.8 [1.7–4.7], and 4.4 [1.8–10.8], respectively; **eFigure 6**). Treatment-emergent serum potassium levels >5.5 mmol/L and >6.0 mmol/L were more frequent with finerenone than placebo, being consistent across all age and sex subgroups. The incidence of gynecomastia in males was the same with finerenone (0.2%) and placebo (0.2%) across all ages.

DISCUSSION

The findings of this post hoc analysis suggest that finerenone reduced the risk of CV and kidney composite outcomes versus placebo across all age and sex subcategories. In FIDELITY, HHF was the main driver of CV benefit with finerenone[23]; lower incidences of HHF with finerenone versus placebo were observed in this analysis across all age subgroups, with some differences noted between sex subgroups. Moreover, the incidences of any AEs or SAEs were similar between the treatment groups regardless of age and sex.

The current results are supported by findings from a pharmacokinetics (PK) analysis based on FIDELIO-DKD and FIGARO-DKD data, in which both age and sex were tested as covariates for a population PK model, and their effect on finerenone exposure was not significant, suggesting a lack of influence of these factors on the PK of the drug.[30] Additionally, the results for the CV outcome in this analysis are similar to findings from other studies of MRAs in HF. In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), age did not affect the efficacy of spironolactone in patients with HF with reduced ejection fraction (primary composite outcome: CV death, aborted cardiac arrest and HHF; secondary outcomes included CV death, all-cause death and HHF).[31] Moreover, in analyses of HF studies (RALES [Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure], EMPHASIS-HF [Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms], and TOPCAT), MRAs reduced morbidity and mortality in elderly patients,[32] demonstrating a consistent benefit regardless of sex.[33] In contrast to our results, female sex was associated with poorer kidney outcomes

versus male sex in patients receiving a steroidal MRA for bilateral primary aldosteronism.[34] The MR can be activated by different drivers in different diseases; MR activation in diabetes is driven by additional factors other than high aldosterone in comparison with primary aldosteronism, which may account for differences in outcomes observed across different indications.[35]

In this study, the elderly population had higher risk of certain AEs including hypotension, AEs leading to discontinuation, and death. Hypotension occurred more frequently in the finerenone group but did not seem to substantially affect related clinical outcomes. Hyperkalemia was more prevalent with finerenone but was generally similar across age and sex. In a FIDELIO-DKD subanalysis, younger age and female sex were independent risk factors for hyperkalemia (>6.0 mmol/L).[36] Similar findings for age were observed in TOPCAT post hoc data for patients with HF.[31] Steroidal MRAs have been associated with gynecomastia in males,[37,38] which was not observed in this study, most likely because finerenone has no detectable affinity for androgen receptors.[38]

Preclinical data suggest that different molecular mechanisms drive endothelial dysfunction in male and female mice[39,40] and that increased age and male sex are associated with MR overactivation, which is linked to vascular stiffness and endothelial dysfunction.[41,42] In human aortic smooth muscle cells, MR expression increased with age, leading to epigenetic changes associated with increased vascular stiffness. These effects were reversed with MR inhibition.[43] In vitro, MR expression in the whole aortae and early passage aortic vascular smooth muscle cells was increased in aged (30 months) versus adult (8 months) rat cells.[41] In a preclinical mouse model, aortic stiffness occurred earlier in male than female mice and correlated with the timing of increased aortic MR expression; vascular stiffness was prevented in smooth muscle cell MR-deficient mice.[42] These data suggest that elderly males may derive the greatest benefit from finerenone; indeed, in this analysis, finerenone-treated males had lower risk of the CV composite outcome and HHF versus placebo across

age groups, including >75 years. Moreover, statistical heterogeneity was observed for HHF by sex, persisting after adjustment for differences in baseline characteristics, which might suggest a more pronounced effect of finerenone on HHF reduction in the male subgroup compared with the 2 female subgroups. However, because of the small sample size of the sex subgroups (especially that of the premenopausal female subgroup), definitive conclusions cannot be reached based on this finding.

In this study, markers of kidney damage (eGFR decline and UACR) were reduced with finerenone in age subgroups; however, no benefit on kidney outcomes was observed in the >75 years age group. The small sample size of this subgroup precluded definitive conclusions, which may be accounted for by the slowing rate of CKD progression with advancing age.[44,45]

Limitations include the study being a post hoc analysis and the chosen age categories not being predefined. In addition, patients may have initiated other treatments during the study. Sample size and number of events for females, particularly premenopausal females, were small. Therefore, there is uncertainty around the estimates and the analysis was underpowered to draw meaningful conclusions in this subgroup. Results for premenopausal females versus postmenopausal females/males should be interpreted with caution because age may partly account for differences observed; the average age of premenopausal females was ~45 years old compared with postmenopausal females (~66 years old) and males (~65 years old) **(Table 1)**. As such, these groups had different baseline characteristics. Higher baseline mean eGFR and median UACR, and lower history of CV comorbidities and hypotension were observed in premenopausal females versus males and postmenopausal females. Additionally, the study design and tests performed may have been underpowered to address the research questions. Furthermore, FIDELITY limitations, mainly the small proportion of Black patients and exclusion of patients with nonalbuminuric CKD, were present in this analysis.

In conclusion, this post hoc FIDELITY analysis suggests that finerenone effectively lowers the risk of clinically important cardiovascular and kidney outcomes in patients with CKD and T2D across ages and sexes, with a potentially more pronounced effect on HHF in males than in females. No new safety concerns were identified in those aged >65 years or by sex.

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CONTRIBUTORS

SB prepared the initial analysis; SB, MEFC, RB, SDA, GLB, GF, PR, LMR, AEF, PK, AL, MB, and BP had access to and participated in the interpretation of the data. SB developed the initial manuscript draft, which was then reviewed and edited by MEFC, RB, SDA, GLB, GF, PR, LMR, AEF, PK, AL, MB, and BP. SB, MEFC, RB, SDA, GLB, GF, PR, LMR, AEF, PK, AL, MB, and BP vouch for the completeness and accuracy of the data and agreed to submit the manuscript for publication. The Executive Committee (including SDA, GLB, GF, PR, LMR and BP) in collaboration with the funder (including AEF, PK, AL, and MB) designed the trials and protocols and supervised trial conduct. The funder also had a role in the management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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DATA SHARING STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, timepoint, and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal.

Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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FIGURE LEGENDS

Figure 1. Analysis of CV composite outcome and HHF according to (A) age and (B) sex.

CV composite outcome includes CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF.

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; PY = patient-years.

Figure 2. Analysis of kidney composite outcome according to (A) age and (B) sex.

Kidney composite outcome includes kidney failure, sustained ≥57% eGFR decline, or renal death.

CI = confidence interval; eGFR = estimated glomerular filtration rate; PY = patient-years.

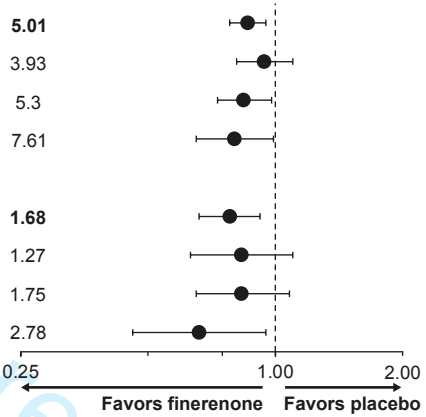
Figure 3. LS mean change in eGFR from baseline, chronic, and total slopes over time by age.

Chronic eGFR slope from month 4 to end-of-study visit.

CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

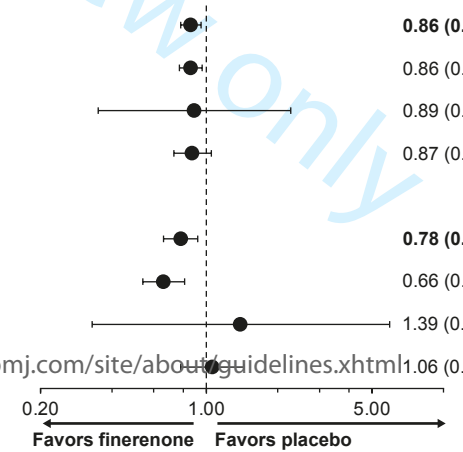
A

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/*N* (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
CV composite, age (years)						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	
Age <65	323/2958 (10.9)	3.74	337/2931 (11.5)	3.93	0.94 (0.81–1.10)	
Age 65–74	339/2635 (12.9)	4.36	396/2586 (15.3)	5.3	0.84 (0.73–0.98)	.4198
Age ≥75	163/926 (17.6)	6.25	206/990 (20.8)	7.61	0.80 (0.65–0.99)	
HHF, age (years)						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Age <65	94/2958 (3.2)	1.06	112/2931 (3.8)	1.27	0.83 (0.63–1.10)	
Age 65–74	111/2653 (4.2)	1.38	135/2586 (5.2)	1.75	0.83 (0.65–1.08)	.6977
Age ≥75	51/926 (5.5)	1.91	78/990 (7.9)	2.78	0.66 (0.46–0.95)	



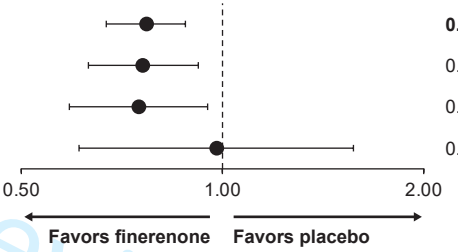
B

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/N (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
CV composite, sex						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	
Male	579/4481 (12.9)	4.39	675/4607 (14.7)	5.08	0.86 (0.77–0.96)	
Premenopausal female	11/163 (6.7)	2.29	12/160 (7.5)	2.62	0.89 (0.35–2.27)	.9942
Postmenopausal female	235/1875 (12.5)	4.38	252/1740 (14.5)	5.03	0.87 (0.73–1.05)	
HHF, sex						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Male	163/4481 (3.6)	1.20	244/4607 (5.3)	1.78	0.66 (0.54–0.81)	
Premenopausal female	5/163 (3.1)	1.02	4/160 (2.5)	0.85	1.39 (0.33–5.93)	.0245
Postmenopausal female	88/1875 (4.7)	1.63	77/1740 (4.4)	1.50	1.06 (0.78–1.44)	



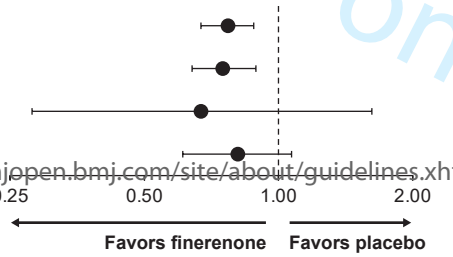
A

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/*N* (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
Kidney composite, age (years)						
Overall	**360/6519 (5.5)**	**1.96**	**465/6507 (7.1)**	**2.55**	**0.77 (0.67–0.88)**	
Age <65	202/2958 (6.8)	2.44	266/2931 (9.1)	3.21	0.76 (0.63–0.92)	
Age 65–74	123/2635 (4.7)	1.63	162/2586 (6.3)	2.23	0.75 (0.59–0.95)	.5088
Age ≥75	35/926 (3.8)	1.41	37/990 (3.7)	1.40	0.98 (0.61–1.57)	

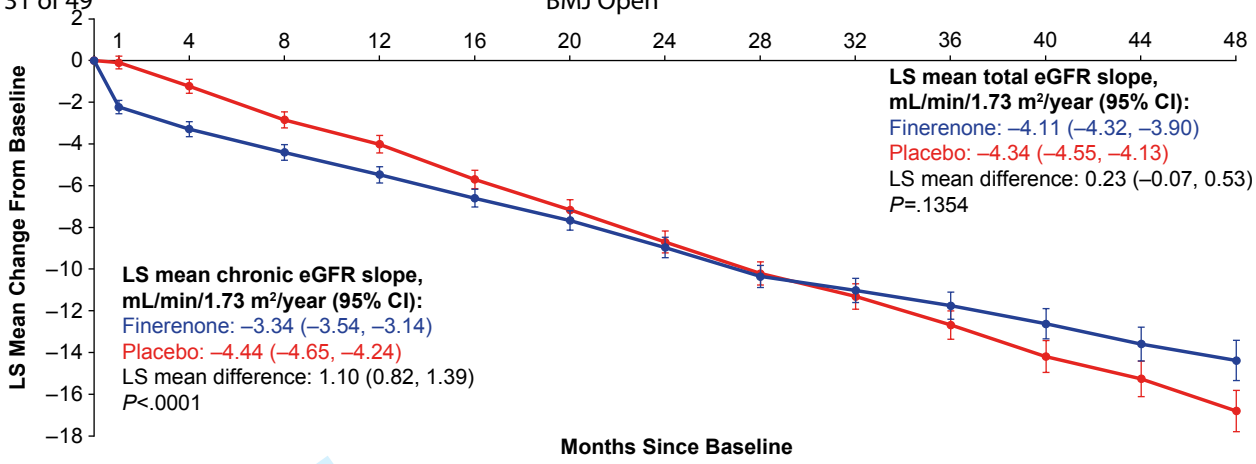


B

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/*N* (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
Kidney composite, sex						
Overall	**360/6519 (5.5)**	**1.96**	**465/6507 (7.1)**	**2.55**	**0.77 (0.67–0.88)**	
Male	257/4481 (5.7)	2.02	341/4607 (7.4)	2.63	0.75 (0.64–0.89)	
Premenopausal female	11/163 (6.7)	2.48	13/160 (8.1)	3.16	0.67 (0.28–1.62)	.8524
Postmenopausal female	92/1875 (4.9)	1.79	111/1740 (6.4)	2.30	0.81 (0.61–1.07)	



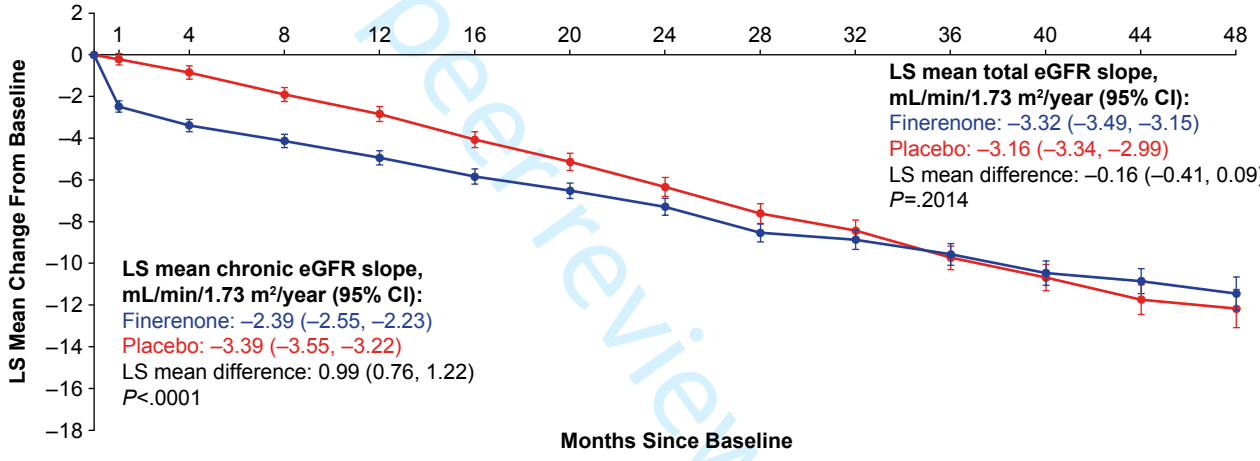
A <65 Years



Number of Subjects at Visit

Finerenone	2921	2849	2778	2730	2656	2505	2281	1918	1541	1246	962	716	409
Placebo	2892	2829	2779	2719	2649	2491	2226	1952	1566	1271	1006	731	417

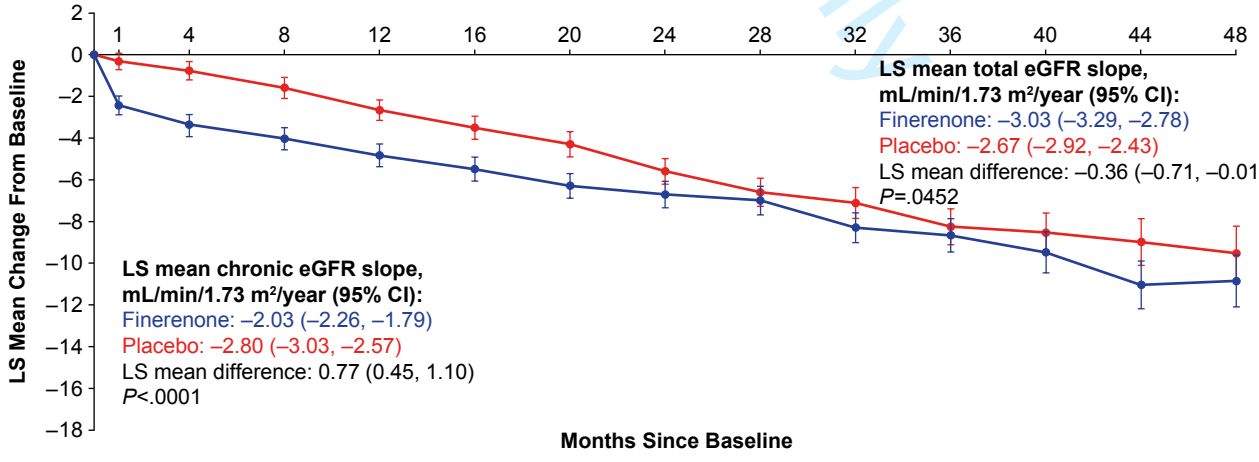
B 65 to 74 Years



Number of Subjects at Visit

Finerenone	2597	2536	2474	2460	2388	2220	1995	1732	1462	1158	935	663	387
Placebo	2539	2481	2429	2376	2326	2163	1951	1674	1360	1097	876	637	346

C ≥75 Years



Number of Subjects at Visit

Finerenone	910	877	848	825	792	732	647	567	447	363	277	210	115
Placebo	975	934	919	896	850	780	695	578	481	359	281	204	117

Finerenone Placebo

Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials

Contents

Supplementary Tables and Figures

eTable 1. Patient Baseline Characteristics According to Age and Sex Stratified by Treatment Group

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
Age, y, mean ± SD	64.7 ± 9.4	64.8 ± 9.7	56.5 ± 6.4	56.3 ± 6.7	69.1 ± 2.7	69.2 ± 2.8	78.4 ± 3.0	78.4 ± 3.1	64.8 ± 9.3	64.9 ± 9.6	45.3 ± 4.4	44.9 ± 5.4	66.2 ± 8.0	66.4 ± 8.0
Sex, *n* (%)														
Female	2038 (31.3)	1900 (29.2)	959 (32.4)	880 (30.0)	772 (29.3)	729 (28.2)	307 (33.2)	291 (29.4)	0 (0.0)	0 (0.0)	163 (100)	160 (100)	1875 (100)	1740 (100)
Male	4481 (68.7)	4607 (70.8)	1999 (67.6)	2051 (70.0)	1863 (70.7)	1857 (71.8)	619 (66.8)	699 (70.6)	4481 (100)	4607 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race, *n* (%)														
Asian	1432 (22.0)	1462 (22.5)	772 (26.1)	819 (27.9)	518 (19.7)	479 (18.5)	142 (15.3)	164 (16.6)	1032 (23.0)	1104 (24.0)	45 (27.6)	42 (26.3)	355 (18.9)	316 (18.2)
Black/African American	253 (3.9)	269 (4.1)	158 (5.3)	151 (5.2)	75 (2.8)	85 (3.3)	20 (2.2)	33 (3.3)	137 (3.1)	147 (3.2)	17 (10.4)	20 (12.5)	99 (5.3)	102 (5.9)
White	4449 (68.2)	4420 (67.9)	1827 (61.8)	1765 (60.2)	1908 (72.4)	1909 (73.8)	714 (77.1)	746 (75.4)	3099 (69.2)	3132 (68.0)	84 (51.5)	83 (51.9)	1266 (67.5)	1205 (69.3)
Other[a]	385 (5.9)	356 (5.5)	201 (6.8)	196 (6.7)	134 (5.1)	113 (4.4)	50 (5.4)	47 (4.7)	213 (4.8)	224 (4.9)	17 (10.4)	15 (9.4)	155 (8.3)	117 (6.7)
Systolic blood pressure, mm Hg, mean (SD)	136.8 ± 14.2	136.7 ± 14.3	135.7 ± 13.9	135.5 ± 14.1	137.4 ± 14.2	137.5 ± 14.2	138.4 ± 14.6	138.5 ± 14.6	136.9 ± 14.1	136.7 ± 14.3	131.6 ± 13.1	134.4 ± 14.7	136.8 ± 14.4	136.9 ± 14.0
Diastolic blood pressure,	76.3 ± 9.6	76.4 ± 9.6	78.7 ± 9.2	79.0 ± 8.9	74.8 ± 9.4	74.9 ± 9.4	73.2 ± 9.8	72.4 ± 9.8	76.6 ± 9.7	76.5 ± 9.7	78.7 ± 8.2	81.6 ± 8.4	75.6 ± 9.6	75.6 ± 9.4

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
mm Hg, mean (SD)														
Duration of diabetes, y, mean (SD)	15.4 ± 8.7	15.4 ± 8.7	13.6 ± 7.6	13.3 ± 7.7	16.4 ± 8.7	16.5 ± 8.5	18.7 ± 10.7	18.5 ±10.2	15.4 ± 8.6	15.3 ± 8.4	11.0 ± 7.4	10.1 ± 6.5	15.9 ± 9.0	16.0 ± 9.2
HbA1c, %, mean (SD)	7.7 ± 1.4	7.7 ± 1.4	7.9 ± 1.5	7.9 ± 1.5	7.6 ± 1.3	7.6 ± 1.3	7.5 ± 1.2	7.4 ± 1.2	7.6 ± 1.3	7.6 ± 1.3	8.1 ± 1.7	8.3 ± 1.6	7.9 ± 1.4	7.9 ± 1.5
Serum potassium, mmol/L, mean (SD)	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	4.3 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4
eGFR, mL/min/1.73 m^2, mean (SD)	57.5 ± 21.6	57.7 ± 21.8	63.9 ± 23.9	64.6 ± 24.0	53.7 ± 18.4	53.3 ± 18.6	48.0 ± 15.5	48.3 ± 14.8	57.8 ± 21.0	57.7 ± 21.4	76.3 ± 28.7	77.5 ± 29.1	55.3 ± 21.5	55.8 ± 21.1
eGFR, mL/min/1.73 m^2, *n* (%)[b]														
<25	81 (1.2)	81 (1.2)	24 (0.8)	29 (1.0)	35 (1.3)	37 (1.4)	22 (2.4)	15 (1.5)	44 (1.0)	54 (1.2)	0	2 (1.3)	37 (2.0)	25 (1.4)
25–<45	2117 (32.5)	2115 (32.5)	744 (25.2)	704 (24.0)	937 (35.6)	961 (37.2)	436 (47.1)	450 (45.5)	1392 (31.1)	1479 (32.1)	31 (19.0)	26 (16.3)	694 (37.0)	610 (35.1)
45–<60	1717 (26.3)	1717 (26.4)	666 (22.5)	649 (22.1)	775 (29.4)	739 (28.6)	276 (29.8)	329 (33.2)	1240 (27.7)	1228 (26.7)	26 (16.0)	24 (15.0)	451 (24.1)	465 (26.7)
≥60	2603 (39.9)	2592 (39.8)	1523 (51.5)	1548 (52.8)	888 (33.7)	848 (32.8)	192 (20.7)	196 (19.8)	1805 (40.3)	1846 (40.1)	106 (65.0)	108 (67.5)	692 (36.9)	638 (36.7)
UACR, mg/g, median (Q1–Q3)	514.2 (197.5–1129.4)	514.9 (198.2–1163.4)	649.2 (308.0-1331.8)	651.4 (322.5-1382.2)	433.8 (150.7-1025.7)	441.3 (157.8-1032.8)	325.6 (107.00-802.7)	340.5 (109.8-871.7)	514.5 (205.3-1116.5)	509.2 (195.4-1143.0)	733.0 (336.3-1522.7)	868.4 (398.5-1604.2)	496.4 (169.9-1124.4)	509.1 (185.0-1174.5)
UACR, mg/g, *n* (%)[c]														
<30	120 (1.8)	110 (1.7)	39 (1.3)	40 (1.4)	53 (2.0)	50 (1.9)	28 (3.0)	20 (2.0)	69 (1.5)	68 (1.5)	2 (1.2)	1 (0.6)	49 (2.6)	41 (2.4)
30–<300	2076 (31.8)	2023 (31.1)	686 (23.2)	645 (22.0)	971 (36.9)	936 (36.2)	419 (45.2)	442 (44.6)	1422 (31.7)	1459 (31.7)	34 (20.9)	20 (12.5)	620 (33.1)	544 (31.3)

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
≥300	4321 (66.3)	4371 (67.2)	2231 (75.4)	2244 (76.6)	1611 (61.1)	1599 (61.8)	479 (51.7)	528 (53.3)	2989 (66.7)	3079 (66.8)	127 (77.9)	139 (86.9)	1205 (64.3)	1153 (66.3)
BMI, kg/m^2, mean (SD)	31.3 ± 6.0	31.3 ± 6.0	32.1 ± 6.5	32.0 ± 6.3	31.1 ± 5.7	31.1 ± 5.7	29.5 ± 4.8	29.6 ± 5.1	30.9 ± 5.6	30.9 ± 5.6	34.0 ± 7.9	34.3 ± 7.9	32.0 ± 6.7	32.1 ± 6.5
Current smoker, *n* (%)	1065 (16.3)	1028 (15.8)	657 (22.2)	626 (21.4)	351 (13.3)	335 (13.0)	57 (6.2)	67 (6.8)	874 (19.5)	856 (18.6)	17 (10.4)	18 (11.3)	174 (9.3)	154 (8.9)
History of CV disease, present, *n* (%)	2979 (45.7)	2956 (45.4)	1127 (38.1)	1061 (36.2)	1330 (50.5)	1337 (51.7)	522 (56.4)	558 (56.4)	2152 (48.0)	2222 (48.2)	36 (22.1)	20 (12.5)	791 (42.2)	714 (41.0)
History of heart failure	485 (7.4)	522 (8.0)	211 (7.1)	202 (6.9)	192 (7.3)	240 (9.3)	82 (8.9)	80 (8.1)	302 (6.7)	328 (7.1)	11 (6.7)	11 (6.9)	172 (9.2)	183 (10.5)
History of atrial fibrillation/atrial flutter	568 (8.7)	538 (8.3)	144 (4.9)	122 (4.2)	280 (10.6)	267 (10.3)	144 (15.6)	149 (15.1)	439 (9.8)	428 (9.3)	0	0	129 (6.9)	110 (6.3)
Baseline medications, *n* (%)[d]														
RAS inhibitors (ACEis/ARBs)	6508 (99.8)	6495 (99.8)	2951 (99.8)	2925 (99.8)	2631 (99.8)	2582 (99.8)	926 (100.0)	988 (99.8)	4473 (99.8)	4596 (99.8)	163 (100.0)	160 (100.0)	1872 (99.8)	1739 (>99.9)
Beta-blockers	3236 (49.6)	3268 (50.2)	1311 (44.3)	1308 (44.6)	1419 (53.9)	1430 (55.3)	506 (54.6)	530 (53.5)	2237 (49.9)	2308 (50.1)	57 (35.0)	54 (33.8)	942 (50.2)	906 (52.1)
Diuretics	3325 (51.0)	3385 (52.0)	1378 (46.6)	1412 (48.2)	1412 (53.6)	1401 (54.2)	535 (57.8)	572 (57.8)	2320 (51.8)	2386 (51.8)	67 (41.1)	70 (43.8)	938 (50.0)	929 (53.4)
Statins	4657 (71.4)	4742 (72.9)	1993 (67.4)	2040 (69.6)	1975 (75.0)	1945 (75.2)	689 (74.4)	757 (76.5)	3291 (73.4)	3405 (73.9)	93 (57.1)	110 (68.8)	1273 (67.9)	1227 (70.5)
Calcium channel blockers	3664 (56.2)	3694 (56.8)	1564 (52.9)	1563 (53.3)	1544 (58.6)	1508 (58.3)	556 (60.0)	623 (62.9)	2554 (57.0)	2654 (57.6)	74 (45.4%)	75 (46.9)	1036 (55.3)	965 (55.5)
≥1 glucose-lowering medication	6354 (97.5)	6366 (97.8)	2898 (98.0)	2881 (98.3)	2574 (97.7)	2537 (98.1)	882 (95.2)	948 (95.8)	4361 (97.3)	4499 (97.7)	161 (98.8)	156 (97.5)	1832 (97.7)	1711 (98.3)

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
n (%)[d]														
Insulin	3866 (59.3)	3764 (57.8)	1848 (62.5)	1789 (61.0)	1539 (58.4)	1481 (57.3)	479 (51.7)	494 (49.9)	2598 (58.0)	2605 (56.5)	94 (57.7)	99 (61.9)	1174 (62.6)	1060 (60.9)
GLP-1RA	497 (7.6)	447 (6.9)	273 (9.2)	219 (7.5)	190 (7.2)	188 (7.3)	34 (3.7)	40 (4.0)	359 (8.0)	317 (6.9)	12 (7.4)	18 (11.3)	126 (6.7)	112 (6.4)
SGLT-2i	438 (6.7)	439 (6.7)	251 (8.5)	266 (9.1)	149 (5.7)	140 (5.4)	38 (4.1)	33 (3.3)	331 (7.4)	340 (7.4)	19 (11.7)	17 (10.6)	88 (4.7)	82 (4.7)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; FIN = finerenone; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; PBO = placebo; Q = quartile; RAS = renin–angiotensin system; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; UACR = urine albumin-to-creatinine ratio.

Values are based on available data.

[a] Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific, not reported, multiple.

[b] Missing (eGFR): <65 years, *n*=2; 65 to 74 years, *n*=1; postmenopausal female, *n*=3.

[c] Missing (UACR): <65 years, *n*=4; 65 to 74 years, *n*=1; male, *n*=2; postmenopausal female, *n*=3.

[d] Analysis allowed multiple drug groups for the same drug.

eTable 2. Treatment-Emergent AEs According to Age and Sex

n (%)	ALL		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6510)	PBO (*n*=6489)	FIN (*n*=2953)	PBO (*n*=2926)	FIN (*n*=2631)	PBO (*n*=2578)	FIN (*n*=926)	PBO (*n*=985)	FIN (*n*=4476)	PBO (*n*=4595)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1871)	PBO (*n*=1734)
Any AE	5602 (86.1)	5607 (86.4)	2494 (84.5)	2523 (86.2)	2301 (87.5)	2225 (86.3)	807 (87.1)	859 (87.2)	3899 (87.1)	4011 (87.3)	137 (84.0)	138 (86.3)	1566 (83.7)	1458 (84.1)
Related to study drug	1206 (18.5)	862 (13.3)	478 (16.2)	384 (13.1)	558 (21.2)	337 (13.1)	170 (18.4)	141 (14.3)	884 (19.7)	612 (13.3)	21 (12.9)	20 (12.5)	301 (16.1)	230 (13.3)
Leading to discontinuation	414 (6.4)	351 (5.4)	128 (4.3)	124 (4.2)	212 (8.1)	153 (5.9)	74 (8.0)	74 (7.5)	313 (7.0)	249 (5.4)	9 (5.5)	7 (4.4)	92 (4.9)	95 (5.5)
Any SAE	2060 (31.6)	2186 (33.7)	856 (29.0)	938 (32.1)	871 (33.1)	876 (34.0)	333 (36.0)	372 (37.8)	1487 (33.2)	1590 (34.6)	33 (20.2)	42 (26.3)	540 (28.9)	554 (31.9)
Related to study drug	83 (1.3)	61 (0.9)	29 (1.0)	27 (0.9)	39 (1.5)	17 (0.7)	15 (1.6)	17 (1.7)	56 (1.3)	46 (1.0)	0	1 (0.6)	27 (1.4)	14 (0.8)
Leading to discontinuation	145 (2.2)	154 (2.4)	41 (1.4)	48 (1.6)	75 (2.9)	71 (2.8)	29 (3.1)	35 (3.6)	115 (2.6)	112 (2.4)	1 (0.6)	2 (1.3)	29 (1.5)	40 (2.3)
Any AE leading to death	110 (1.7)	151 (2.3)	43 (1.5)	55 (1.9)	42 (1.6)	62 (2.4)	25 (2.7)	34 (3.5)	73 (1.6)	115 (2.5)	0	3 (1.9)	37 (2.0)	33 (1.9)
AEs of interest														
Hypotension	282(4.3)	177 (2.7)	101 (3.4)	70 (2.4)	127 (4.8)	76 (2.9)	54 (5.8)	31 (3.1)	216 (4.8)	131 (2.9)	3 (1.8)	0	63 (3.4)	46 (2.7)
Orthostatic hypotension	46 (0.7)	39 (0.6)	18 (0.6)	15 (0.5)	23 (0.9)	15 (0.6)	5 (0.5)	9 (0.9)	34 (0.8)	30 (0.7)	0	2 (1.3)	12 (0.6)	7 (0.4)
Hyperkalemia	912 (14.0)	448 (6.9)	360 (12.2)	238 (8.1)	420 (16.0)	158 (6.1)	132 (14.3)	52 (5.3)	647 (14.5)	304 (6.6)	14 (8.6)	16 (10.0)	251 (13.4)	128 (7.4)
Leading to permanent discontinuation	110 (1.7)	38 (0.6)	31 (1.0)	13 (0.4)	54 (2.1)	19 (0.7)	25 (2.7)	6 (0.6)	83 (1.9)	28 (0.6)	4 (2.5)	1 (0.6)	23 (1.2)	9 (0.5)
Classified as a serious AE	69 (1.1)	16 (0.2)	28 (0.9)	8 (0.3)	29 (1.1)	5 (0.2)	12 (1.3)	3 (0.3)	45 (1.0)	9 (0.2)	1 (0.6)	0	23 (1.2)	7 (0.4)
Leading to hospitalization	61 (0.9)	10 (0.2)	26 (0.9)	6 (0.2)	25 (1.0)	2 (<0.1)	10 (1.1)	2 (0.2)	38 (0.8)	5 (0.1)	1 (0.6)	0	22 (1.2)	5 (0.3)
Gynecomastia	8 (0.1)	11 (0.2)	2 (<0.1)	4 (0.1)	5 (0.2)	3 (0.1)	1 (0.1)	4 (0.4)	8 (0.2)	11 (0.2)	NA	NA	NA	NA
Central laboratory assessments, *n*/*N* (%)[a]														

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Serum potassium >5.5 mmol/L	1075/ 6402 (16.8)	470/ 6370 (7.4)	444/2904 (15.3)	233/2871 (8.1)	460/2585 (17.8)	180/2529 (7.1)	171/913 (18.7)	57/970 (5.9)	720/4403 (16.4)	308/4523 (6.8)	16/159 (10.1)	8/154 (5.2)	339/1840 (18.4)	154/1693 (9.1)
Serum potassium >6.0 mmol/L	211/ 6439 (3.3)	80/ 6413 (1.2)	90/2926 (3.1)	44/2896 (1.5)	89/2598 (3.4)	31/2544 (1.2)	32/915 (3.5)	5/973 (0.5)	143/4428 (3.2)	48/4544 (1.1)	4/160 (2.5)	1/156 (0.6)	64/1851 (3.5)	31/1713 (1.8)

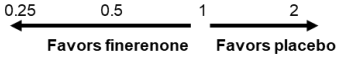
AE = adverse event; FIN = finerenone; NA = not applicable; PBO = placebo; SAE = serious adverse event.

[a] The "*n*" numerator represents the number of patients at risk with ≥1 treatment-emergent laboratory assessment meeting the criterion. The "*N*" denominator represents all patients at risk for a treatment-emergent laboratory abnormality. Patients had both a baseline and postbaseline treatment-emergent value while the baseline value did not exceed the displayed threshold.

eFigure 1. Analysis of CV composite outcome and subcomponents according to (A) age and (B) sex.

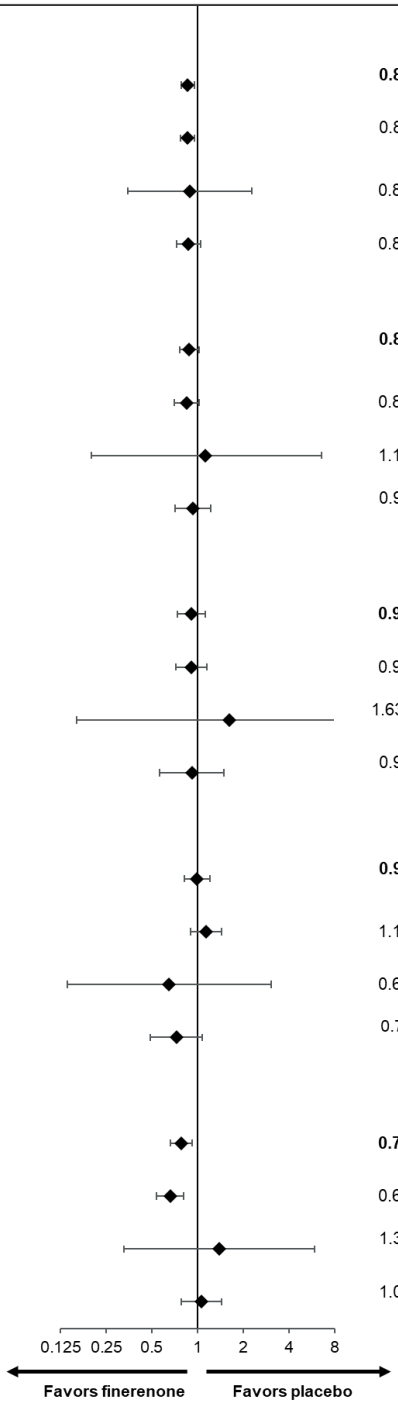
A.

	Finerenone		Placebo		Hazard ratio (95% CI)	*P*-interaction
	n/*N* (%)	*n*/100 PY	*n*/*N* (%)	*n*/100 PY		
CV composite, age (years)						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	
Age <65	323/2958 (10.9)	3.74	337/2931 (11.5)	3.93	0.94 (0.81–1.10)	0.4198
Age 65–74	339/2635 (12.9)	4.36	396/2586 (15.3)	5.30	0.84 (0.73–0.98)	
Age ≥75	163/926 (17.6)	6.25	206/990 (20.8)	7.61	0.80 (0.65–0.99)	
CV death						
Overall	**322/6519 (4.9)**	**1.61**	**364/6507 (5.6)**	**1.84**	**0.88 (0.76–1.02)**	
Age <65	120/2958 (4.1)	1.33	122/2931 (4.2)	1.36	0.97 (0.75–1.25)	0.2064
Age 65–74	117/2635 (4.4)	1.43	157/2586 (6.1)	1.98	0.76 (0.60–0.97)	
Age ≥75	85/926 (9.2)	3.08	85/990 (8.6)	2.91	1.05 (0.77–1.44)	
Nonfatal MI						
Overall	**173/6519 (2.7)**	**0.88**	**189/6507 (2.9)**	**0.97**	**0.91 (0.74–1.12)**	
Age <65	67/2958 (2.3)	0.75	70/2931 (2.4)	0.79	0.97 (0.69–1.36)	0.3250
Age 65–74	79/2635 (3.0)	0.98	76/2586 (2.9)	0.98	1.02 (0.74–1.40)	
Age ≥75	27/926 (2.9)	1.00	43/990 (4.3)	1.52	0.64 (0.39–1.04)	
Nonfatal stroke						
Overall	**198/6519 (3.0)**	**1.01**	**198/6507 (3.0)**	**1.02**	**0.99 (0.82–1.21)**	
Age <65	84/2958 (2.8)	0.95	78/2931 (2.7)	0.89	1.07 (0.78–1.46)	0.8515
Age 65–74	82/2635 (3.1)	1.02	87/2586 (3.4)	1.12	0.90 (0.66–1.22)	
Age ≥75	32/926 (3.5)	1.18	78/990 (7.9)	1.16	1.09 (0.66–1.80)	
HHF						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Age <65	94/2958 (3.2)	1.06	112/2931 (3.8)	1.27	0.83 (0.63–1.10)	.0245
Age 65–74	111/2653 (4.2)	1.38	135/2586 (5.2)	1.75	0.83 (0.65–1.08)	
Age ≥75	51/926 (5.5)	1.91	78/990 (7.9)	2.78	0.66 (0.46–0.95)	



B.

	Finerenone		Placebo		Hazard ratio (95% CI)	*P*-interaction
	n/*N* (%)	*n*/100 PY	*n*/*N* (%)	*n*/100 PY		
CV composite, sex						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	–
Male	579/4481 (12.9)	4.39	675/4607 (14.7)	5.08	0.86 (0.77–0.96)	.9942
Premenopausal female	11/163 (6.7)	2.29	12/160 (7.5)	2.62	0.89 (0.35–2.27)	
Postmenopausal female	235/1875 (12.5)	4.38	252/1740 (14.5)	5.03	0.87 (0.73–1.05)	
CV death						
Overall	**322/6519 (4.9)**	**1.61**	**364/6507 (5.6)**	**1.84**	**0.88 (0.76–1.02)**	
Male	207/4481 (4.6)	1.49	249/4607 (5.4)	1.77	0.85 (0.70–1.02)	.6925
Premenopausal female	4/163 (2.5)	0.80	3/160 (1.9)	0.63	1.13 (0.20–6.54)	
Postmenopausal female	111/1875 (5.9)	1.98	112/1740 (6.4)	2.12	0.93 (0.71–1.22)	
Nonfatal MI						
Overall	**173/6519 (2.7)**	**0.88**	**189/6507 (2.9)**	**0.97**	**0.91 (0.74–1.12)**	
Male	138/4481 (3.1)	1.02	152/4607 (3.3)	1.10	0.91 (0.72–1.15)	.8211
Premenopausal female	2/163 (1.2)	0.40	1/160 (0.6)	0.21	1.63 (0.16–16.87)[a]	
Postmenopausal female	33/1875 (1.8)	0.60	36/1740 (2.1)	0.69	0.92 (0.56–1.49)	
Nonfatal stroke						
Overall	**198/6519 (3.0)**	**1.01**	**198/6507 (3.0)**	**1.02**	**0.99 (0.82–1.21)**	
Male	150/4481 (3.3)	1.11	135/4607 (2.9)	0.98	1.14 (0.90–1.44)	.1103
Premenopausal female	3/163 (1.8)	0.61	4/160 (2.5)	0.86	0.65 (0.14–3.06)	
Postmenopausal female	45/1875 (2.4)	0.81	59/1740 (3.4)	1.14	0.73 (0.49–1.08)	
HHF						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Male	163/4481 (3.6)	1.20	244/4607 (5.3)	1.78	0.66 (0.54–0.81)	.0245
Premenopausal female	5/163 (3.1)	1.02	4/160 (2.5)	0.85	1.39 (0.33–5.93)	
Postmenopausal female	88/1875 (4.7)	1.61	77/1740 (4.4)	1.50	1.06 (0.78–1.44)	



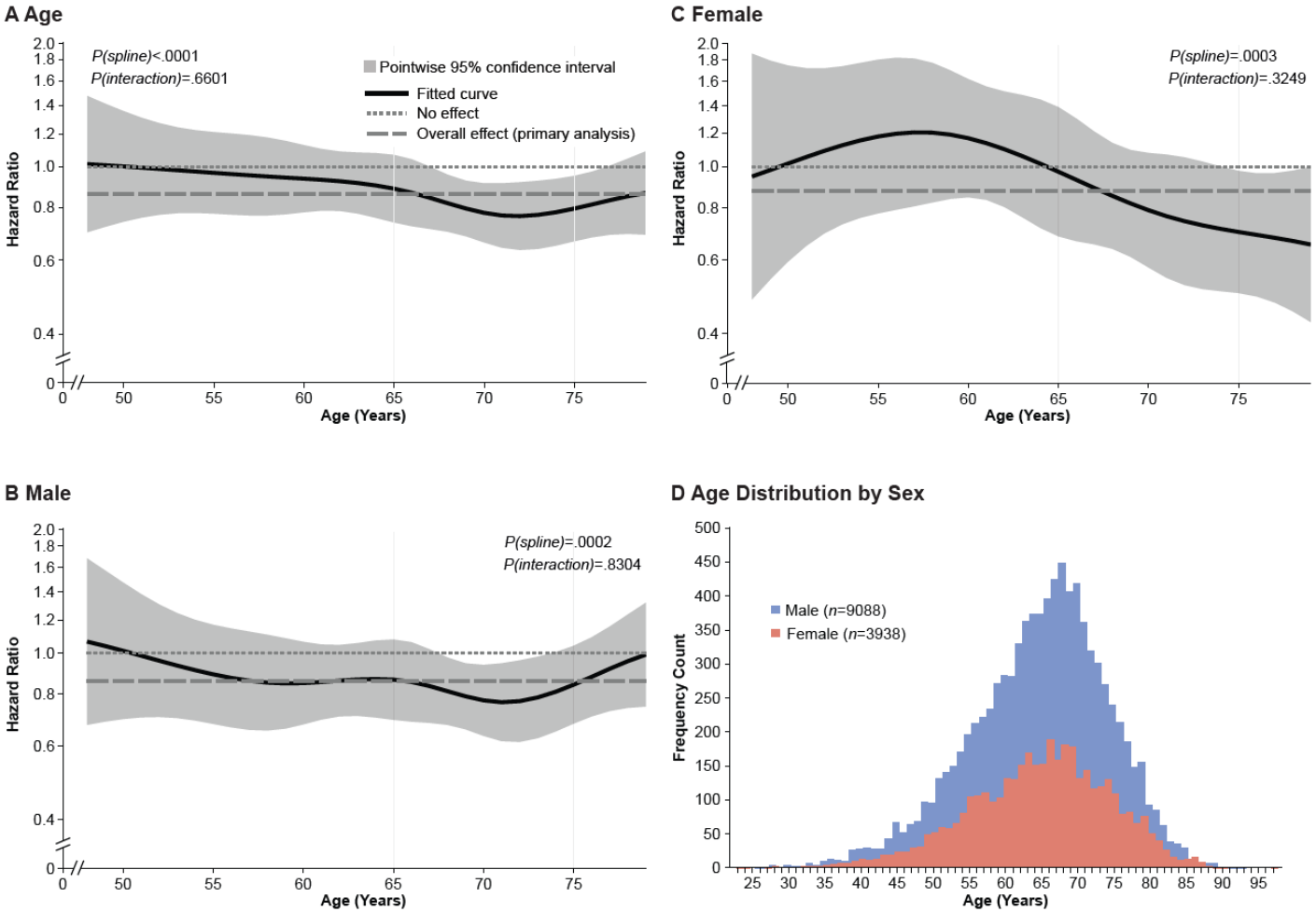
A stratified Cox proportional hazards model including treatment was calculated separately by subgroup category. The $P_{interaction}$ is based on a stratified Cox proportional hazards model including treatment, subgroup, and treatment by subgroup interaction.

CV composite outcome includes CV death, nonfatal MI, nonfatal stroke, or HHF.

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; MI = myocardial infarction; PY = patient-years.

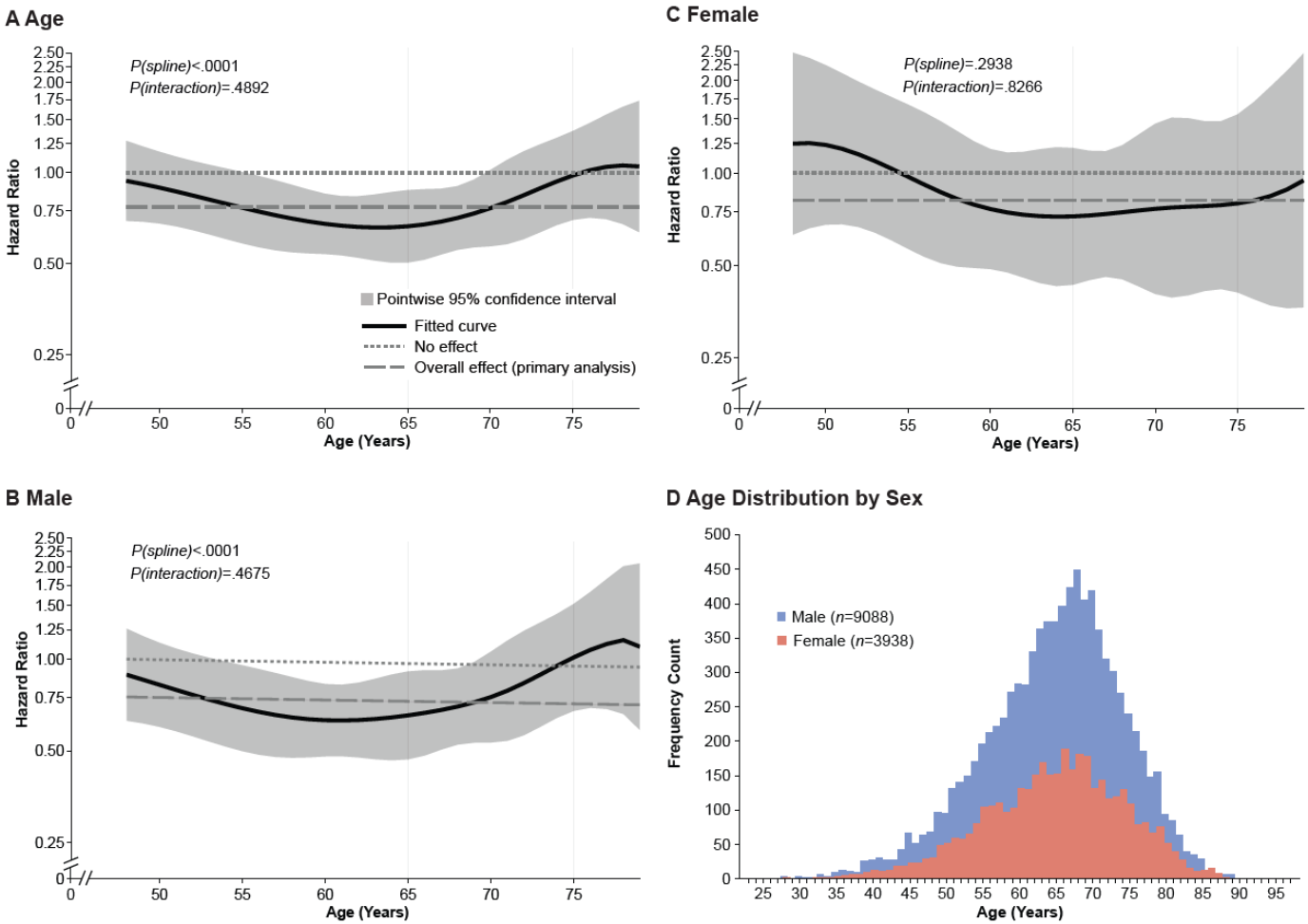
[a] An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts and/or convergence issues.

eFigure 2. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for CV composite outcome by age (A), spline for hazard ratio of CV composite outcomes by sex (B, C), and age distribution by sex (D).

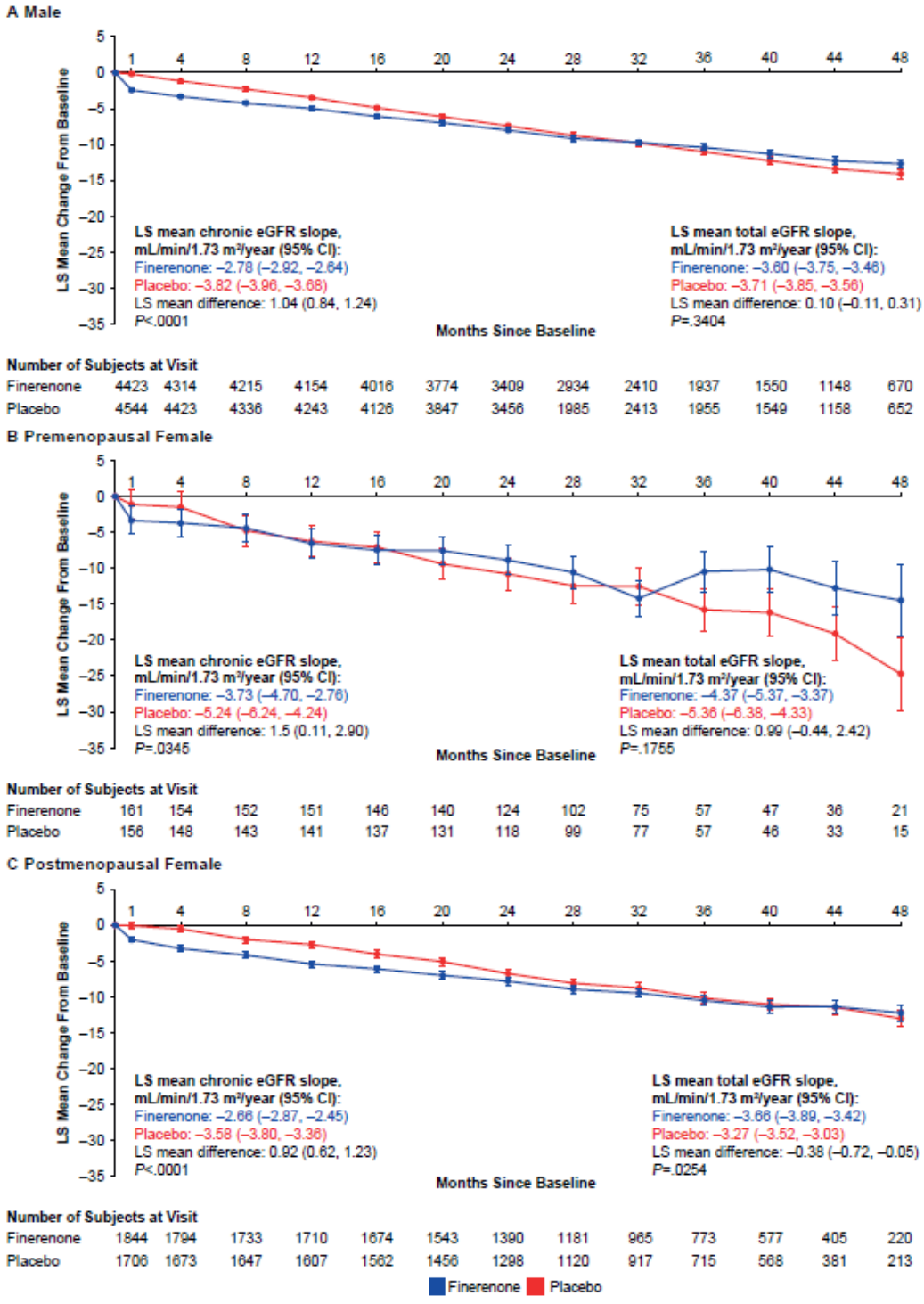


CV = cardiovascular.

eFigure 3. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for kidney composite outcome by age (A), spline for hazard ratio of kidney composite outcomes by sex (B, C), and age distribution by sex (D).



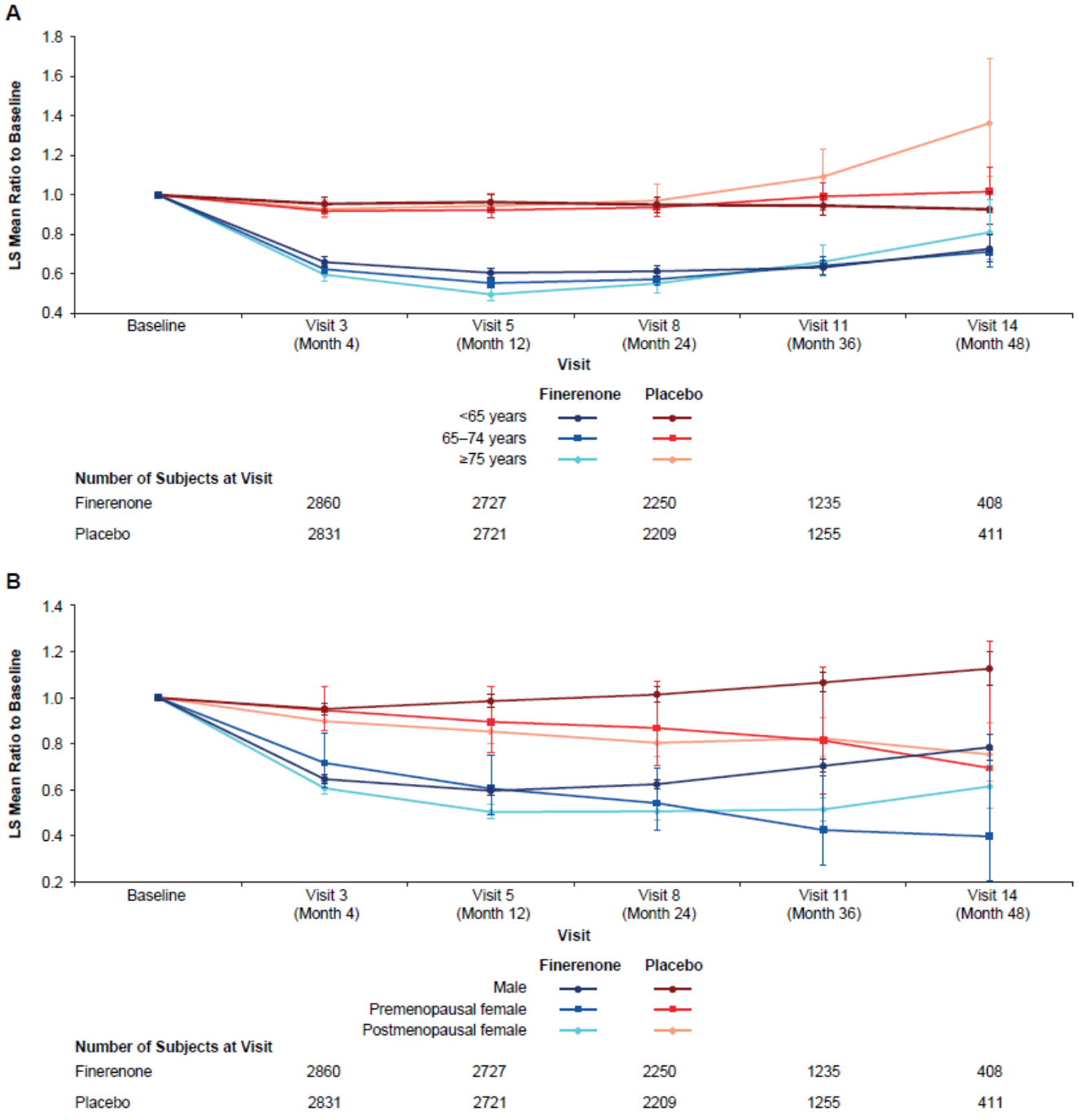
eFigure 4. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.



Chronic eGFR slope from month 4 to end-of-study visit.

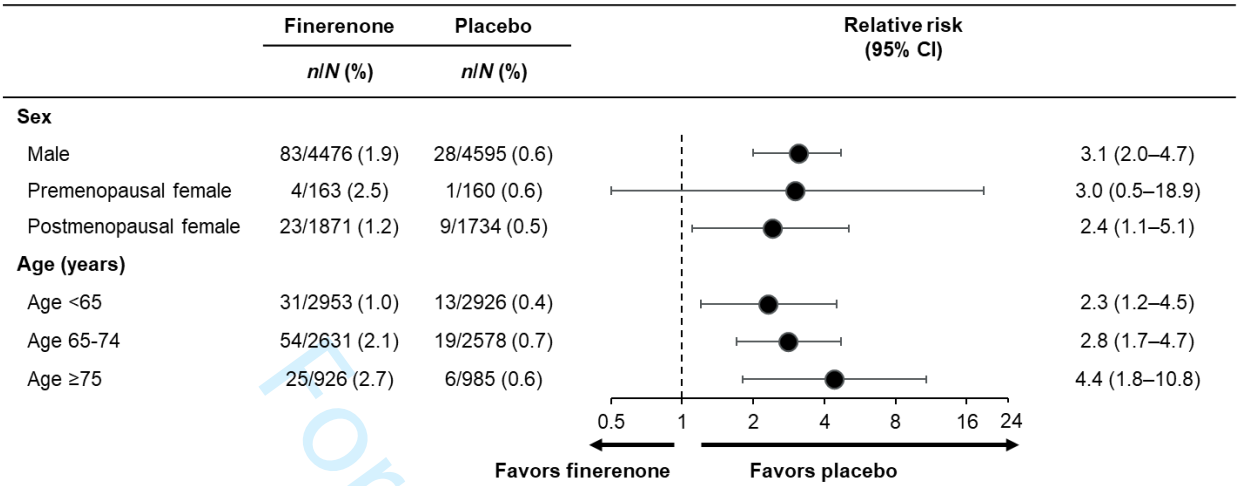
CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

eFigure 5. LS mean ratio to baseline UACR over time by age and sex



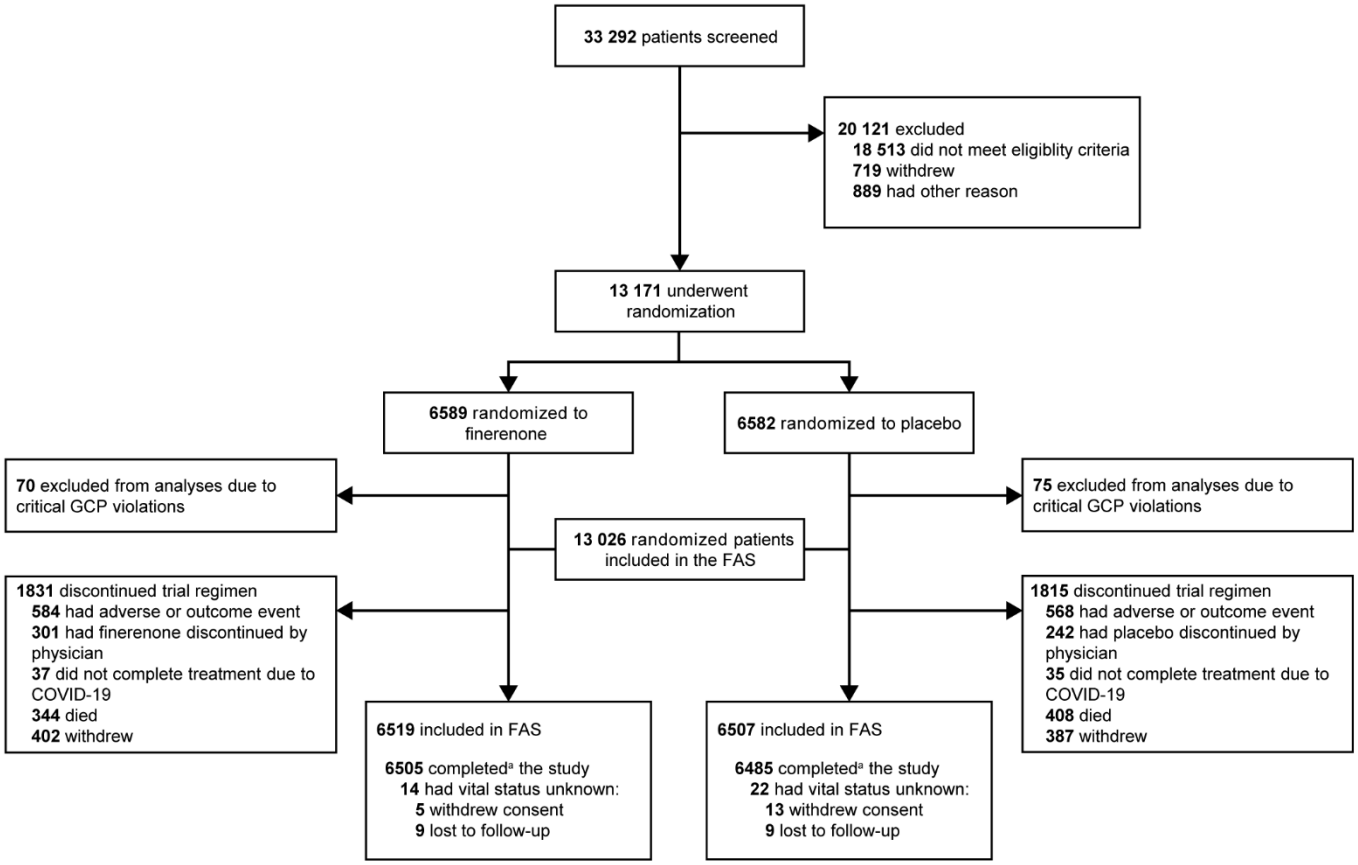
LS = least-squares; UACR = urine albumin-to-creatinine ratio.

eFigure 6. Relative risk of treatment-emergent hyperkalemia causing permanent discontinuation of study drug by age and sex



Relative risk values based on Mantel-Haenszel estimates (stratified by study). For the relative risk, a treatment-arm-size zero cell correction with zero term = 0.5 was applied.

eFigure 7. FIDELITY CONSORT diagram.



[a] The patient was considered as having completed the study if there was a contact with the patient after the end-of-study notification or if the patient died.

CONSORT = Consolidated Standards of Reporting Trials; COVID-19, coronavirus disease of 2019; FAS, full analysis set; FIDELITY = The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis; GCP, Good Clinical Practice.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1 – Post hoc analysis of a previously reported RCT
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6-7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	Reported previously
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6-7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	Reported previously
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Reported previously
Randomisation: Sequence generation	8a	Method used to generate the random allocation sequence	Reported previously

	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Reported previously
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Reported previously
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Reported previously
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Reported previously
	11b	If relevant, description of the similarity of interventions	Reported previously
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8-11; eTable 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	eFigure 7
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Reported previously
	14b	Why the trial ended or was stopped	Reported previously
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1; eTable 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8-11; eTable 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13 Figures 1-2 eFigure 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	eFigures 2-5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14-15

Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Reported previously
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-18
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	Primary publications with full protocols are cited (6)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19-20

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials

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Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials

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ABSTRACT

Objectives: To evaluate the efficacy and safety of finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist, on cardiovascular and kidney outcomes by age and/or sex.

Design: FIDELITY post-hoc analysis; 3-year median follow-up.

Setting: FIDELITY: a prespecified analysis of FIDELIO-DKD and FIGARO-DKD.

Participants: Adults with type 2 diabetes and chronic kidney disease receiving optimized renin–angiotensin system inhibitors (N=13 026).

Interventions: Randomized 1:1; finerenone or placebo.

Primary and secondary outcome measures: Cardiovascular (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure [HHF]) and kidney (kidney failure, sustained ≥57% estimated glomerular filtration rate [eGFR] decline, or renal death) composite outcomes.

Results: Mean age was 64.8 years; 45.2%, 40.1%, and 14.7% were aged <65, 65–74, and ≥75 years, respectively; 69.8% were male. Cardiovascular benefits of finerenone versus placebo were consistent across age (hazard ratio [95% confidence interval]: 0.94 [0.81–1.10] [<65 years], 0.84 [0.73–0.98] [65–74 years], 0.80 [0.65–0.99] [≥75 years]; $P_{interaction}$=.42) and sex (hazard ratio [95% confidence interval]: 0.86 [0.77–0.96] [male], 0.89 [0.35– 2.27] [premenopausal female], 0.87 [0.73– 1.05] [postmenopausal female]; $P_{interaction}$=.99). HHF risk reduction was not modified by age ($P_{interaction}$=.70) but appeared more pronounced in males ($P_{interaction}$=.02). Kidney events were reduced with finerenone versus placebo in ages <65 and 65–74 but not ≥75; no heterogeneity in treatment effect was observed ($P_{interaction}$=.51). In sex subgroups, finerenone consistently reduced kidney events ($P_{interaction}$=.85). Finerenone reduced albuminuria and eGFR decline regardless of age and sex. Hyperkalemia increased with finerenone, but discontinuation rates were <3% across subgroups. Gynecomastia in males was uncommon across age subgroups and identical between treatment groups.

Conclusions: Finerenone improved cardiovascular and kidney outcomes with no significant heterogeneity between age and sex subgroups; HHF risk reduction appeared more pronounced in males. Finerenone demonstrated a similar safety profile across age and sex.

Registration: FIDELIO-DKD (NCT02540993); FIGARO-DKD (NCT02545049)

Abstract word count: 300 of 300

STRENGTHS AND LIMITATIONS OF THIS STUDY

- An advantage of this study was the use of combined individual-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, resulting in a large number of patients included in the full analysis set
- This study did not use predefined age categories, as it was a post hoc analysis, which may have resulted in some of the tests performed being underpowered
- Limitations present in FIDELITY are present in this analysis, such as the small proportion of Black patients and exclusion of patients with nonalbuminuric CKD

INTRODUCTION

In patients with diabetes, the risk of cardiovascular (CV) disease and chronic kidney disease (CKD) increases with age.[1] Likewise, vascular complications are affected by sex and are increased in females more than males in patients with diabetes.[2]

Among individuals aged 50–75 years without baseline diabetes, CKD, or CV disease, males have a steeper decline in glomerular filtration rate (GFR) than females.[3] However, reported effects of sex on risk of incidental and progressive CKD in patients with type 2 diabetes (T2D) have been inconsistent.[4-6] In trials including patients with CKD, female representation varies (25–40%),[7-11] whereas in real-world studies, females make up over half of patients.[12,13]

Overactivation of the mineralocorticoid receptor (MR) is associated with CV and kidney diseases.[14,15] In epithelial cells, the 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme prevents inappropriate MR activation by cortisol.[16-18] The activity of 11β-HSD2 decreases with age, resulting in MR overactivation in the elderly despite low circulating aldosterone levels.[16-18] Sex also influences 11β-HSD2 activity, particularly in patients with hypertension, where 11β-HSD2 activity is reduced in males versus females.[16] The MR is also expressed in nonepithelial cells, including endothelial cells, vascular smooth muscle cells, adipocytes, and immune cells.[17] In many of these, the MR may be activated by cortisol because of a lack of protection by 11β-HSD2.[19,20]

Despite management with recommended treatments for CKD in T2D, 10–13% of patients experience CKD progression or kidney failure and are at high risk of CV events, including CV death within 2–3 years following treatment initiation.[10,21,22] Finerenone, a selective, nonsteroidal MR antagonist (MRA), reduced the risk of CKD progression and CV outcomes compared with placebo in patients with CKD and T2D in FIDELITY (The FInerenone in

chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis), a prespecified pooled analysis of the FIDELIO-DKD (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; NCT02540993) and FIGARO-DKD (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease; NCT02545049) phase 3 trials.[21] However, the influence of age and sex on outcomes with finerenone is unknown. This post hoc analysis evaluated whether the cardiovascular and kidney benefits and safety profile of finerenone observed in FIDELITY are consistent in patients with CKD and T2D across ages and in both sexes.

METHODS

Study design and patients

FIDELITY combined individual patient-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials. The study design, procedures, and outcomes for the trials have been previously published.[23-25] The FIDELIO-DKD and FIGARO-DKD trials were conducted in accordance with the principles of the Declaration of Helsinki. Protocol approvals were obtained from local regulatory authorities and ethics committees. Written informed consent was provided by all participants. These studies were reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Eligible patients were aged ≥18 years with CKD and T2D, receiving maximum tolerated renin–angiotensin system inhibitor, and with serum potassium levels ≤4.8 mmol/L at screening. Patients had either a urine albumin-to-creatinine ratio (UACR) ≥30–<300 mg/g and an estimated GFR (eGFR) ≥25–≤90 mL/min/1.73 m^2, or UACR ≥300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2. Patients with symptomatic heart failure (HF) with reduced ejection fraction were excluded because this implies an indication for a steroidal MRA.

Standard-of-care therapy with a renin–angiotensin system inhibitor was optimized during the run-in period. Patients were randomly assigned (1:1) to receive finerenone at titrated doses (10 or 20 mg) once-daily oral treatment or matching placebo.

Key outcomes

Efficacy outcomes included a CV composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF (HHF), and a kidney composite outcome of kidney failure, sustained ≥57% eGFR decline, or renal death. Additional outcomes included HHF and change in UACR and eGFR over time.

Safety outcomes included incidence of investigator-reported adverse events (AEs), including those leading to treatment discontinuation, central laboratory assessment of serum potassium levels >5.5 and >6.0 mmol/L, and other safety events of interest, such as hypotension, hyperkalemia, and gynecomastia in males.

Outcomes were analyzed according to patient age at baseline (<65, 65–75, ≥75 years) and sex. Females were categorized as either pre- or postmenopausal if they were aged <51.4 or ≥51.4 years at baseline, respectively (based on the median age of menopause onset from the Massachusetts Women's Health Study).[26]

Statistical analysis

Statistical analyses were performed as described in FIDELITY.[23] The full analysis set comprised all randomized patients (except those with critical Good Clinical Practice violations, who were prospectively excluded). Safety analyses were performed in the safety analysis set (randomized patients without critical Good Clinical Practice violations who took >1 dose of study drug). The analyses were prespecified exploratory evaluations of outcomes according to age and sex, with events reported from randomization up to the end-of-study visit. Stratified Cox proportional hazards models,[27,28] including stratification factors:

geographic region, eGFR and albuminuria category at screening, history of CV disease, and study, were used for the analysis of time-to-event clinical outcomes. The *P*-values for interaction between the treatment group (finerenone or placebo) and each baseline subgroup (age or sex) were based on stratified Cox proportional hazards models, accounting for the treatment effect, the subgroup effect, and their interaction.

Changes in UACR and eGFR over time were assessed using a linear mixed-model analysis accounting for repeated measurements over time. The least-squares mean ratio and absolute change from baseline were estimated from the models for changes in UACR and eGFR, respectively. The 2-slope, linear spline, mixed-model, repeated measure method[29] was used to estimate the rate of change in eGFR across time, specifically total (annualized rate of change in eGFR from baseline to permanent discontinuation or end of study) and chronic (from month 4 to permanent discontinuation or end of study) eGFR slopes. To account for possible nonlinear effects of age on clinical outcomes, age was modeled with cubic splines with 3 knots in Cox proportional hazards models, to produce plots of the hazard ratios (HRs) and 95% confidence interval as functions of age and sex.

Patients and public involvement

No patient or public involvement in the current study.

RESULTS

Patients

FIDELITY included 13 026 patients.[23] Median follow-up was 3 years (interquartile range 2.3–3.8).[23] Mean age at baseline was 64.8 years (standard deviation 9.5), with 45.2%, 40.1%, and 14.7% of patients aged <65, 65–74, and ≥75 years at baseline, respectively. Most patients (69.8%) were male; 2.5% were premenopausal females, and 27.8% were postmenopausal females. Patients were distributed evenly between treatment arms within age and sex subgroups (**eTable 1**).

Baseline characteristics

Baseline characteristics were similar across age subgroups except for some key differences (**Table 1**). The overall FIDELITY population was predominantly White (68.1%), the proportion of which increased with age. Mean eGFR was 64, 54, and 48 mL/min/1.73 m^2 in patients aged <65, 65–75, and ≥75 years, respectively. Median UACR was 650, 439, and 332 mg/g in patients aged <65, 65–75, and ≥75 years, respectively. History of CV disease was more common in the ≥75 years group; this trend was also observed for atrial fibrillation/atrial flutter. Baseline characteristics in sex subgroups are shown in **Table 1**.

Table 1. Patient Baseline Characteristics According to Age and Sex

Characteristic	All (*N*=13 026)	Age			Sex		
		<65 Years (*n*=5889)	65–74 Years (*n*=5221)	≥75 Years (*n*=1916)	Male (*n*=9088)	Premenopausal Female (*n*=323)	Postmenopausal Female (*n*=3615)
Age, y, mean ± SD	64.8 ± 9.5	56.4 ± 6.6	69.2 ± 2.8	78.4 ± 3.1	64.8 ± 9.5	45.1 ± 4.9	66.3 ± 8.0
Sex, *n* (%)							
Female	3938 (30.2)	1839 (31.2)	1501 (28.7)	598 (31.2)	9088 (100)	0 (0.0)	0 (0.0)
Male	9088 (69.8)	4050 (68.8)	3720 (71.3)	1318 (68.8)	0 (0.0)	323 (100)	3615 (100)
Race, *n* (%)							
Asian	2894 (22.2)	1591 (27.0)	997 (19.1)	306 (16.0)	2136 (23.5)	87 (26.9)	671 (18.6)
Black/African American	522 (4.0)	309 (5.2)	160 (3.1)	53 (2.8)	284 (3.1)	37 (11.5)	201 (5.6)
White	8869 (68.1)	3592 (61.0)	3817 (73.1)	1460 (76.2)	6231 (68.6)	167 (51.7)	2471 (68.4)
Other[a]	741 (5.7)	397 (6.7)	247 (4.7)	97 (5.1)	437 (4.8)	32 (9.9)	272 (7.5)
Systolic blood pressure, mm Hg, mean (SD)	136.7 ± 14.2	135.6 ± 14.0	137.4 ± 14.2	138.4 ± 14.6	136.8 ± 14.2	133.0 ± 14.0	136.9 ± 14.3
Diastolic blood pressure, mm Hg, mean (SD)	76.4 ± 9.6	78.8 ± 9.1	74.9 ± 9.4	72.8 ± 9.8	76.5 ± 9.7	80.1 ± 8.4	75.6 ± 9.5
Duration of diabetes, years, mean (SD)	15.4 ± 8.7	13.5 ± 7.6	16.4 ± 8.6	18.6 ± 10.4	15.3 ± 8.5	10.6 ± 7.0	16.0 ± 9.1
HbA1c, %, mean (SD)	7.7 ± 1.4	7.9 ± 1.5	7.6 ± 1.3	7.4 ± 1.2	7.6 ± 1.3	8.2 ± 1.7	7.9 ± 1.4
Serum potassium, mmol/L, mean (SD)	4.4 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.4 ± 0.4
eGFR, mL/min/1.73 m^2, mean (SD)	57.6 ± 21.7	64.3 ± 24.0	53.5 ± 18.5	48.1 ± 15.1	57.7 ± 21.2	77.0 ± 28.9	55.6 ± 21.3

UACR, mg/g, median (Q1–Q3)	514.68 (197.8–1147.1)	650.48 (315.2–1363.5)	438.63 (154.1–1030.7)	332.29 (107.8–830.5)	511.53 (200.9–1130.1)	793.52 (376.6–1547.3)	501.47 (173.6–1149.1)
BMI, kg/m^2, mean (SD)	31.3 ± 6.0	32.0 ± 6.4	31.1 ± 5.7	29.6 ± 5.0	31.0 ± 5.6	34.1 ± 7.9	32.0 ± 6.6
Current smoker, *n* (%)	2093 (16.1)	1283 (21.8)	686 (13.1)	124 (6.5)	1730 (19.0)	35 (10.8)	328 (9.1)
History of CV disease, present, *n* (%)	5935 (45.6)	2188 (37.2)	2667 (51.1)	1080 (56.4)	4374 (48.1)	56 (17.3)	1505 (41.6)
History of heart failure	1007 (7.7)	413 (7.0)	432 (8.3)	162 (8.5)	630 (6.9)	22 (6.8)	355 (9.8)
History of atrial fibrillation/atrial flutter	1106 (8.5)	266 (4.5)	547 (10.5)	293 (15.3)	867 (9.5)	0	239 (6.6)
Baseline medications, *n* (%)[b]							
RAS inhibitors (ACEis/ARBs)	13003 (99.8)	5876 (99.8)	5213 (99.8)	1914 (99.9)	9069 (99.8)	323 (100.0)	3611 (99.9)
Beta-blockers	6504 (49.9)	2619 (44.5)	2849 (54.6)	1036 (54.1)	4545 (50.0)	111 (34.4)	1848 (51.1)
Diuretics	6710 (51.5)	2790 (47.4)	2813 (53.9)	1107 (57.8)	4706 (51.8)	137 (42.4)	1867 (51.6)
Statins	9399 (72.2)	4033 (68.5)	3920 (75.1)	1446 (75.5)	6696 (73.7)	203 (62.8)	2500 (69.2)
Calcium channel blockers	7358 (56.5)	3127 (53.1)	3052 (58.5)	1179 (61.5)	5208 (57.3)	149 (46.1)	2001 (55.4)
Insulin	7630 (58.6)	3637 (61.8)	3020 (57.8)	973 (50.8)	5203 (57.3)	193 (59.8)	2234 (61.8)
GLP-1RA	944 (7.2)	492 (8.4)	378 (7.2)	74 (3.9)	676 (7.4)	30 (9.3)	238 (6.6)
SGLT-2i	877 (6.7)	517 (8.8)	289 (5.5)	71 (3.7)	671 (7.4)	36 (11.1)	170 (4.7)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; Q = quartile; RAS = renin–angiotensin system; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; UACR = urine albumin-to-creatinine ratio.

[a] Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, not reported, multiple.

[b] Analysis allowed multiple drug groups for the same drug.

Efficacy

CV composite outcome by age

CV composite event rates, including the components of the composite outcome, increased with patient age in both treatment arms (**Figure 1A** and **eFigure 1A**). Treatment with finerenone resulted in a numerical reduction in CV composite event rates versus placebo in all age groups (**Figure 1A**); however, no significant heterogeneity was observed for the effect of finerenone across categorical age subgroups ($P_{interaction}$=.42). There was also no evidence of treatment effect modification when age was modeled as a continuous variable ($P_{interaction}$=.10). The trend of HR as a function of age was modeled with cubic splines (**eFigure 2A**).

HHF event rates were numerically lower with finerenone than placebo in all age subgroups (**Figure 1A**). The effect of finerenone on HHF risk reduction was consistent across age subgroups, with no significant heterogeneity observed ($P_{interaction}$=.70).

CV composite outcome by sex

CV composite event rates were numerically lower with finerenone than placebo for males, premenopausal females, and postmenopausal females (**Figure 1B** and **eFigure 1B**). There was no significant heterogeneity in the effect of finerenone on reducing the risk of the CV composite outcome across sex subgroups ($P_{interaction}$=.99). When age was modeled with cubic splines by sex, the effect of finerenone was consistent with advancing age in males; however, a trend toward a stronger effect in older versus younger females was noted (**eFigure 2B, eFigure 2C**). Age distribution by sex is demonstrated in **eFigure 2D**.

No heterogeneity was observed in the effect of finerenone on reducing the risk of the CV death, nonfatal myocardial infarction, and nonfatal stroke components of the CV composite outcome (**eFigure 1B**). However, statistical heterogeneity was observed in the reduction of

HHF with finerenone versus placebo ($P_{interaction}$=.02), and the effect appeared to be more pronounced in males than premenopausal/postmenopausal females (**Figure 1B**). These results persisted after adjustment for differences in baseline age, body mass index, systolic blood pressure, hemoglobin, eGFR, UACR, smoking history, and history of atrial fibrillation between sex subgroups ($P_{interaction}$=.02).

Kidney composite outcome by age

Kidney composite event rates were lower with finerenone than placebo in the <65 years and the 65–74 years groups but were similar in the ≥75 years group (**Figure 2A**). The effect of finerenone on reducing the risk of the kidney composite outcome was consistent across age subgroups, with no significant heterogeneity detected ($P_{interaction}$=.51) and no evidence of treatment effect modification when age was modeled as a continuous variable ($P_{interaction}$=.77). The trend of HR as function of age was modeled with cubic splines (**eFigure 3A**).

Kidney composite outcome by sex

Kidney composite event rates were lower with finerenone than placebo in males but were similar in premenopausal and postmenopausal females (**Figure 2B**). There was no significant heterogeneity in the effect of finerenone on reducing the risk of the kidney composite outcome across sex subgroups ($P_{interaction}$=.85). When age was modeled with cubic splines by sex subgroups, the effect of finerenone suggests trends similar to overall results in males and females across all age groups (**eFigure 3B, eFigure 3C**). Age distribution by sex is demonstrated in **eFigure 3D**.

Effect of finerenone on markers of kidney function and damage by age and sex

Finerenone significantly attenuated the least-squares mean change in eGFR from month 4 to end of treatment (chronic eGFR slope) compared with placebo across all age (P<.0001 for all 3 subgroups) (**Figure 3**) and sex subgroups (**eFigure 4**). Finerenone reduced UACR over time compared with placebo regardless of age and sex (**eFigure 5**).

Safety

The incidence of any AE was similar between treatment groups irrespective of age or sex (**eTable 2**). There were more drug-related AEs with finerenone than placebo in age and sex subgroups except premenopausal females, where the incidence was similar. AEs leading to drug discontinuation were more frequent in patients given finerenone than placebo (6.4% and 5.4%, respectively), with higher incidences in the 65–74 and ≥75 years groups than the <65 years group; there were more AEs leading to drug discontinuation with finerenone than placebo in males and premenopausal females but not in postmenopausal females.

Although the incidences of any serious AEs (SAEs), study drug-related SAEs, or SAEs leading to drug discontinuation were similar between treatment arms across all age and sex subgroups, the overall incidences of SAEs increased with age and was highest in males, followed by postmenopausal females, then premenopausal females.

In all age and sex subgroups, the incidences of treatment-emergent hypotension AEs were higher with finerenone than placebo but did not have a substantial impact on related clinical outcomes, including falls, dizziness, and fatigue. A trend of increased incidence of hypotension with increasing age was observed in patients treated with finerenone; however, the incidence of hypotension was generally low across all age subgroups (<6%; **eTable 2**).

In FIDELITY, finerenone increased the risk of any hyperkalemia event versus placebo; similar findings were observed in all age and sex subgroups, except premenopausal females (e**Table 2**). The incidences of any hyperkalemia AEs leading to discontinuation of study drug and any serious hyperkalemia AEs leading to hospitalization were low across all age and sex subgroups (<3% and <2%, respectively). However, the relative risk of treatment discontinuation because of hyperkalemia with finerenone versus placebo increased with advancing age (relative risk [95% confidence interval] for ages 45–64, 65–74, and ≥75 years:

2.2 [1.2–4.3], 2.8 [1.7–4.7], and 4.4 [1.8–10.8], respectively; **eFigure 6**). Treatment-emergent serum potassium levels >5.5 mmol/L and >6.0 mmol/L were more frequent with finerenone than placebo, being consistent across all age and sex subgroups. The incidence of gynecomastia in males was the same with finerenone (0.2%) and placebo (0.2%) across all ages.

DISCUSSION

The findings of this post hoc analysis suggest that finerenone reduced the risk of CV and kidney composite outcomes versus placebo across all age and sex subcategories. In FIDELITY, HHF was the main driver of CV benefit with finerenone[23]; lower incidences of HHF with finerenone versus placebo were observed in this analysis across all age subgroups, with some differences noted between sex subgroups. Moreover, the incidences of any AEs or SAEs were similar between the treatment groups regardless of age and sex.

The current results are supported by findings from a pharmacokinetics (PK) analysis based on FIDELIO-DKD and FIGARO-DKD data, in which both age and sex were tested as covariates for a population PK model, and their effect on finerenone exposure was not significant, suggesting a lack of influence of these factors on the PK of the drug.[30] Additionally, the results for the CV outcome in this analysis are similar to findings from other studies of MRAs in HF. In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), age did not affect the efficacy of spironolactone in patients with HF with reduced ejection fraction (primary composite outcome: CV death, aborted cardiac arrest and HHF; secondary outcomes included CV death, all-cause death and HHF).[31] Moreover, in analyses of HF studies (RALES [Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure], EMPHASIS-HF [Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms], and TOPCAT), MRAs reduced morbidity and mortality in elderly patients,[32] demonstrating a consistent benefit regardless of sex.[33] In contrast to our results, female sex was associated with poorer kidney outcomes

versus male sex in patients receiving a steroidal MRA for bilateral primary aldosteronism.[34] The MR can be activated by different drivers in different diseases; MR activation in diabetes is driven by additional factors other than high aldosterone in comparison with primary aldosteronism, which may account for differences in outcomes observed across different indications.[35]

In this study, the elderly population had higher risk of certain AEs including hypotension, AEs leading to discontinuation, and death. Hypotension occurred more frequently in the finerenone group but did not seem to substantially affect related clinical outcomes. Hyperkalemia was more prevalent with finerenone but was generally similar across age and sex. In a FIDELIO-DKD subanalysis, younger age and female sex were independent risk factors for hyperkalemia (>6.0 mmol/L).[36] Similar findings for age were observed in TOPCAT post hoc data for patients with HF.[31] Steroidal MRAs have been associated with gynecomastia in males,[37,38] which was not observed in this study, most likely because finerenone has no detectable affinity for androgen receptors.[38]

Preclinical data suggest that different molecular mechanisms drive endothelial dysfunction in male and female mice[39,40] and that increased age and male sex are associated with MR overactivation, which is linked to vascular stiffness and endothelial dysfunction.[41,42] In human aortic smooth muscle cells, MR expression increased with age, leading to epigenetic changes associated with increased vascular stiffness. These effects were reversed with MR inhibition.[43] In vitro, MR expression in the whole aortae and early passage aortic vascular smooth muscle cells was increased in aged (30 months) versus adult (8 months) rat cells.[41] In a preclinical mouse model, aortic stiffness occurred earlier in male than female mice and correlated with the timing of increased aortic MR expression; vascular stiffness was prevented in smooth muscle cell MR-deficient mice.[42] These data suggest that elderly males may derive the greatest benefit from finerenone; indeed, in this analysis, finerenone-treated males had lower risk of the CV composite outcome and HHF versus placebo across

age groups, including >75 years. Moreover, statistical heterogeneity was observed for HHF by sex, persisting after adjustment for differences in baseline characteristics, which might suggest a more pronounced effect of finerenone on HHF reduction in the male subgroup compared with the 2 female subgroups. However, because of the small sample size of the sex subgroups (especially that of the premenopausal female subgroup), definitive conclusions cannot be reached based on this finding.

In this study, markers of kidney damage (eGFR decline and UACR) were reduced with finerenone in age subgroups; however, no benefit on kidney outcomes was observed in the >75 years age group. The small sample size of this subgroup precluded definitive conclusions, which may be accounted for by the slowing rate of CKD progression with advancing age.[44,45]

Limitations include the study being a post hoc analysis and the chosen age categories not being predefined. In addition, patients may have initiated other treatments during the study. Sample size and number of events for females, particularly premenopausal females, were small. Therefore, there is uncertainty around the estimates and the analysis was underpowered to draw meaningful conclusions in this subgroup. Results for premenopausal females versus postmenopausal females/males should be interpreted with caution because age may partly account for differences observed; the average age of premenopausal females was ~45 years old compared with postmenopausal females (~66 years old) and males (~65 years old) **(Table 1)**. As such, these groups had different baseline characteristics. Higher baseline mean eGFR and median UACR, and lower history of CV comorbidities and hypotension were observed in premenopausal females versus males and postmenopausal females. Additionally, the study design and tests performed may have been underpowered to address the research questions. Furthermore, FIDELITY limitations, mainly the small proportion of Black patients and exclusion of patients with nonalbuminuric CKD, were present in this analysis.

In conclusion, this post hoc FIDELITY analysis suggests that finerenone effectively lowers the risk of clinically important cardiovascular and kidney outcomes in patients with CKD and T2D across ages and sexes, with a potentially more pronounced effect on HHF in males than in females. No new safety concerns were identified in those aged >65 years or by sex.

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CONTRIBUTORS

SB prepared the initial analysis; SB, MEFC, RB, SDA, GLB, GF, PR, LMR, AEF, PK, AL, MB, and BP had access to and participated in the interpretation of the data. SB developed the initial manuscript draft, which was then reviewed and edited by MEFC, RB, SDA, GLB, GF, PR, LMR, AEF, PK, AL, MB, and BP. SB, MEFC, RB, SDA, GLB, GF, PR, LMR, AEF, PK, AL, MB, and BP vouch for the completeness and accuracy of the data and agreed to submit the manuscript for publication. The Executive Committee (including SDA, GLB, GF, PR, LMR and BP) in collaboration with the funder (including AEF, PK, AL, and MB) designed the trials and protocols and supervised trial conduct. The funder also had a role in the management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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DATA SHARING STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, timepoint, and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal.

Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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FIGURE LEGENDS

Figure 1. Analysis of CV composite outcome and HHF according to (A) age and (B) sex.

CV composite outcome includes CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF.

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; PY = patient-years.

Figure 2. Analysis of kidney composite outcome according to (A) age and (B) sex.

Kidney composite outcome includes kidney failure, sustained ≥57% eGFR decline, or renal death.

CI = confidence interval; eGFR = estimated glomerular filtration rate; PY = patient-years.

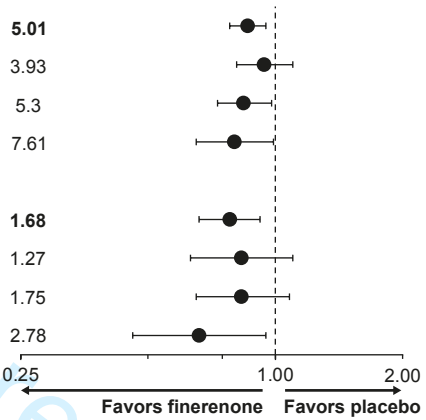
Figure 3. LS mean change in eGFR from baseline, chronic, and total slopes over time by age.

Chronic eGFR slope from month 4 to end-of-study visit.

CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

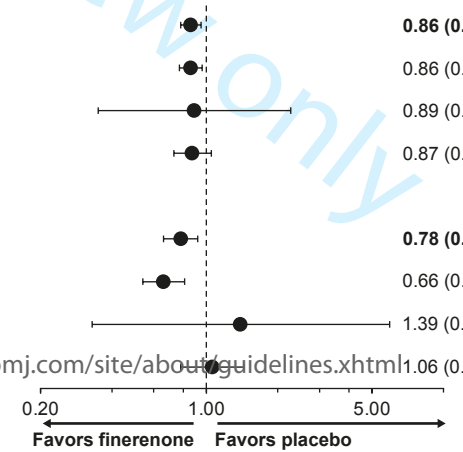
A

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/*N* (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
CV composite, age (years)						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	
Age <65	323/2958 (10.9)	3.74	337/2931 (11.5)	3.93	0.94 (0.81–1.10)	
Age 65–74	339/2635 (12.9)	4.36	396/2586 (15.3)	5.3	0.84 (0.73–0.98)	.4198
Age ≥75	163/926 (17.6)	6.25	206/990 (20.8)	7.61	0.80 (0.65–0.99)	
HHF, age (years)						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Age <65	94/2958 (3.2)	1.06	112/2931 (3.8)	1.27	0.83 (0.63–1.10)	
Age 65–74	111/2653 (4.2)	1.38	135/2586 (5.2)	1.75	0.83 (0.65–1.08)	.6977
Age ≥75	51/926 (5.5)	1.91	78/990 (7.9)	2.78	0.66 (0.46–0.95)	



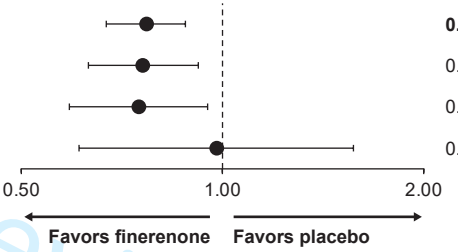
B

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/N (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
CV composite, sex						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	
Male	579/4481 (12.9)	4.39	675/4607 (14.7)	5.08	0.86 (0.77–0.96)	
Premenopausal female	11/163 (6.7)	2.29	12/160 (7.5)	2.62	0.89 (0.35–2.27)	.9942
Postmenopausal female	235/1875 (12.5)	4.38	252/1740 (14.5)	5.03	0.87 (0.73–1.05)	
HHF, sex						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Male	163/4481 (3.6)	1.20	244/4607 (5.3)	1.78	0.66 (0.54–0.81)	
Premenopausal female	5/163 (3.1)	1.02	4/160 (2.5)	0.85	1.39 (0.33–5.93)	.0245
Postmenopausal female	88/1875 (4.7)	1.63	77/1740 (4.4)	1.50	1.06 (0.78–1.44)	



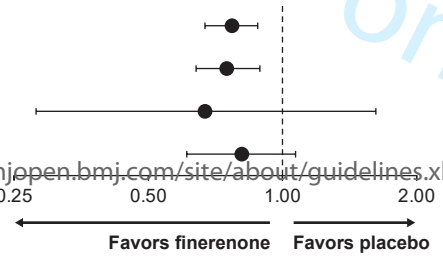
A

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/*N* (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
Kidney composite, age (years)						
Overall	**360/6519 (5.5)**	**1.96**	**465/6507 (7.1)**	**2.55**	**0.77 (0.67–0.88)**	
Age <65	202/2958 (6.8)	2.44	266/2931 (9.1)	3.21	0.76 (0.63–0.92)	
Age 65–74	123/2635 (4.7)	1.63	162/2586 (6.3)	2.23	0.75 (0.59–0.95)	.5088
Age ≥75	35/926 (3.8)	1.41	37/990 (3.7)	1.40	0.98 (0.61–1.57)	

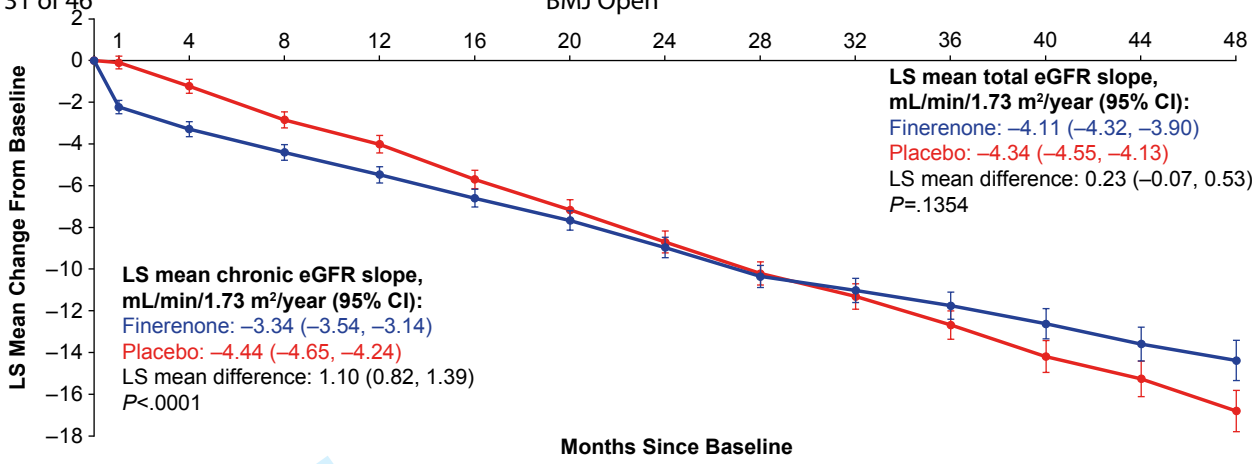


B

Endpoint	Finerenone *n*/*N* (%)	Finerenone *n*/100 PY	Placebo *n*/*N* (%)	Placebo *n*/100 PY	Hazard Ratio (95% CI)	*P*-Value for Interaction
Kidney composite, sex						
Overall	**360/6519 (5.5)**	**1.96**	**465/6507 (7.1)**	**2.55**	**0.77 (0.67–0.88)**	
Male	257/4481 (5.7)	2.02	341/4607 (7.4)	2.63	0.75 (0.64–0.89)	
Premenopausal female	11/163 (6.7)	2.48	13/160 (8.1)	3.16	0.67 (0.28–1.62)	.8524
Postmenopausal female	92/1875 (4.9)	1.79	111/1740 (6.4)	2.30	0.81 (0.61–1.07)	



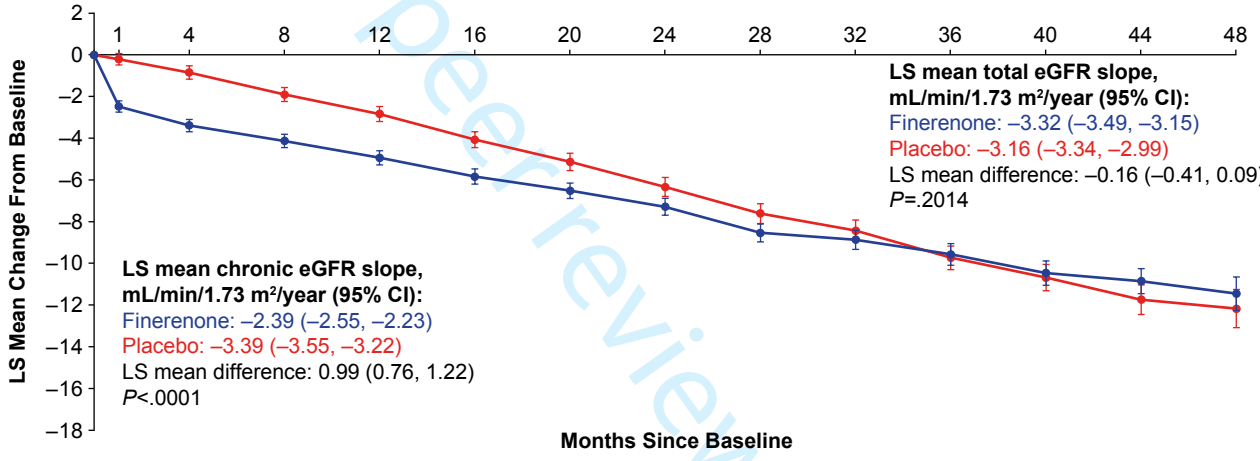
A <65 Years



Number of Subjects at Visit

Finerenone	2921	2849	2778	2730	2656	2505	2281	1918	1541	1246	962	716	409
Placebo	2892	2829	2779	2719	2649	2491	2226	1952	1566	1271	1006	731	417

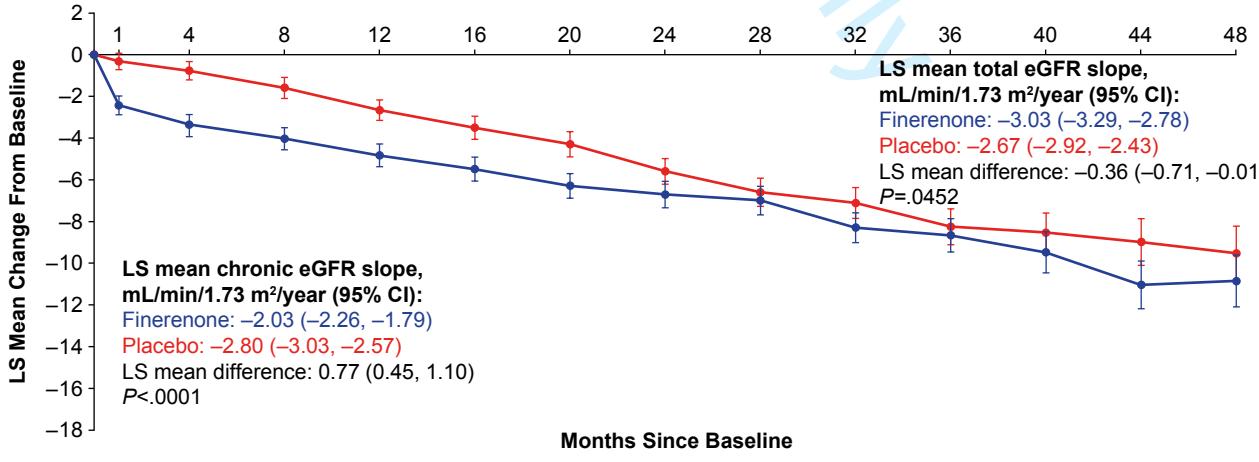
B 65 to 74 Years



Number of Subjects at Visit

Finerenone	2597	2536	2474	2460	2388	2220	1995	1732	1462	1158	935	663	387
Placebo	2539	2481	2429	2376	2326	2163	1951	1674	1360	1097	876	637	346

C ≥75 Years



Number of Subjects at Visit

Finerenone	910	877	848	825	792	732	647	567	447	363	277	210	115
Placebo	975	934	919	896	850	780	695	578	481	359	281	204	117

Finerenone Placebo

Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials

Contents

Supplementary Tables and Figures

eTable 1. Patient Baseline Characteristics According to Age and Sex Stratified by Treatment Group

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
Age, y, mean ± SD	64.7 ± 9.4	64.8 ± 9.7	56.5 ± 6.4	56.3 ± 6.7	69.1 ± 2.7	69.2 ± 2.8	78.4 ± 3.0	78.4 ± 3.1	64.8 ± 9.3	64.9 ± 9.6	45.3 ± 4.4	44.9 ± 5.4	66.2 ± 8.0	66.4 ± 8.0
Sex, *n* (%)														
Female	2038 (31.3)	1900 (29.2)	959 (32.4)	880 (30.0)	772 (29.3)	729 (28.2)	307 (33.2)	291 (29.4)	0 (0.0)	0 (0.0)	163 (100)	160 (100)	1875 (100)	1740 (100)
Male	4481 (68.7)	4607 (70.8)	1999 (67.6)	2051 (70.0)	1863 (70.7)	1857 (71.8)	619 (66.8)	699 (70.6)	4481 (100)	4607 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race, *n* (%)														
Asian	1432 (22.0)	1462 (22.5)	772 (26.1)	819 (27.9)	518 (19.7)	479 (18.5)	142 (15.3)	164 (16.6)	1032 (23.0)	1104 (24.0)	45 (27.6)	42 (26.3)	355 (18.9)	316 (18.2)
Black/African American	253 (3.9)	269 (4.1)	158 (5.3)	151 (5.2)	75 (2.8)	85 (3.3)	20 (2.2)	33 (3.3)	137 (3.1)	147 (3.2)	17 (10.4)	20 (12.5)	99 (5.3)	102 (5.9)
White	4449 (68.2)	4420 (67.9)	1827 (61.8)	1765 (60.2)	1908 (72.4)	1909 (73.8)	714 (77.1)	746 (75.4)	3099 (69.2)	3132 (68.0)	84 (51.5)	83 (51.9)	1266 (67.5)	1205 (69.3)
Other[a]	385 (5.9)	356 (5.5)	201 (6.8)	196 (6.7)	134 (5.1)	113 (4.4)	50 (5.4)	47 (4.7)	213 (4.8)	224 (4.9)	17 (10.4)	15 (9.4)	155 (8.3)	117 (6.7)
Systolic blood pressure, mm Hg, mean (SD)	136.8 ± 14.2	136.7 ± 14.3	135.7 ± 13.9	135.5 ± 14.1	137.4 ± 14.2	137.5 ± 14.2	138.4 ± 14.6	138.5 ± 14.6	136.9 ± 14.1	136.7 ± 14.3	131.6 ± 13.1	134.4 ± 14.7	136.8 ± 14.4	136.9 ± 14.0
Diastolic blood pressure,	76.3 ± 9.6	76.4 ± 9.6	78.7 ± 9.2	79.0 ± 8.9	74.8 ± 9.4	74.9 ± 9.4	73.2 ± 9.8	72.4 ± 9.8	76.6 ± 9.7	76.5 ± 9.7	78.7 ± 8.2	81.6 ± 8.4	75.6 ± 9.6	75.6 ± 9.4

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
mm Hg, mean (SD)														
Duration of diabetes, y, mean (SD)	15.4 ± 8.7	15.4 ± 8.7	13.6 ± 7.6	13.3 ± 7.7	16.4 ± 8.7	16.5 ± 8.5	18.7 ± 10.7	18.5 ±10.2	15.4 ± 8.6	15.3 ± 8.4	11.0 ± 7.4	10.1 ± 6.5	15.9 ± 9.0	16.0 ± 9.2
HbA1c, %, mean (SD)	7.7 ± 1.4	7.7 ± 1.4	7.9 ± 1.5	7.9 ± 1.5	7.6 ± 1.3	7.6 ± 1.3	7.5 ± 1.2	7.4 ± 1.2	7.6 ± 1.3	7.6 ± 1.3	8.1 ± 1.7	8.3 ± 1.6	7.9 ± 1.4	7.9 ± 1.5
Serum potassium, mmol/L, mean (SD)	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.5	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.5	4.3 ± 0.4	4.4 ± 0.4	4.4 ± 0.4	4.4 ± 0.4
eGFR, mL/min/1.73 m^2, mean (SD)	57.5 ± 21.6	57.7 ± 21.8	63.9 ± 23.9	64.6 ± 24.0	53.7 ± 18.4	53.3 ± 18.6	48.0 ± 15.5	48.3 ± 14.8	57.8 ± 21.0	57.7 ± 21.4	76.3 ± 28.7	77.5 ± 29.1	55.3 ± 21.5	55.8 ± 21.1
eGFR, mL/min/1.73 m^2, *n* (%)[b]														
<25	81 (1.2)	81 (1.2)	24 (0.8)	29 (1.0)	35 (1.3)	37 (1.4)	22 (2.4)	15 (1.5)	44 (1.0)	54 (1.2)	0	2 (1.3)	37 (2.0)	25 (1.4)
25–<45	2117 (32.5)	2115 (32.5)	744 (25.2)	704 (24.0)	937 (35.6)	961 (37.2)	436 (47.1)	450 (45.5)	1392 (31.1)	1479 (32.1)	31 (19.0)	26 (16.3)	694 (37.0)	610 (35.1)
45–<60	1717 (26.3)	1717 (26.4)	666 (22.5)	649 (22.1)	775 (29.4)	739 (28.6)	276 (29.8)	329 (33.2)	1240 (27.7)	1228 (26.7)	26 (16.0)	24 (15.0)	451 (24.1)	465 (26.7)
≥60	2603 (39.9)	2592 (39.8)	1523 (51.5)	1548 (52.8)	888 (33.7)	848 (32.8)	192 (20.7)	196 (19.8)	1805 (40.3)	1846 (40.1)	106 (65.0)	108 (67.5)	692 (36.9)	638 (36.7)
UACR, mg/g, median (Q1–Q3)	514.2 (197.5–1129.4)	514.9 (198.2–1163.4)	649.2 (308.0-1331.8)	651.4 (322.5-1382.2)	433.8 (150.7-1025.7)	441.3 (157.8-1032.8)	325.6 (107.00-802.7)	340.5 (109.8-871.7)	514.5 (205.3-1116.5)	509.2 (195.4-1143.0)	733.0 (336.3-1522.7)	868.4 (398.5-1604.2)	496.4 (169.9-1124.4)	509.1 (185.0-1174.5)
UACR, mg/g, *n* (%)[c]														
<30	120 (1.8)	110 (1.7)	39 (1.3)	40 (1.4)	53 (2.0)	50 (1.9)	28 (3.0)	20 (2.0)	69 (1.5)	68 (1.5)	2 (1.2)	1 (0.6)	49 (2.6)	41 (2.4)
30–<300	2076 (31.8)	2023 (31.1)	686 (23.2)	645 (22.0)	971 (36.9)	936 (36.2)	419 (45.2)	442 (44.6)	1422 (31.7)	1459 (31.7)	34 (20.9)	20 (12.5)	620 (33.1)	544 (31.3)

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
≥300	4321 (66.3)	4371 (67.2)	2231 (75.4)	2244 (76.6)	1611 (61.1)	1599 (61.8)	479 (51.7)	528 (53.3)	2989 (66.7)	3079 (66.8)	127 (77.9)	139 (86.9)	1205 (64.3)	1153 (66.3)
BMI, kg/m^2, mean (SD)	31.3 ± 6.0	31.3 ± 6.0	32.1 ± 6.5	32.0 ± 6.3	31.1 ± 5.7	31.1 ± 5.7	29.5 ± 4.8	29.6 ± 5.1	30.9 ± 5.6	30.9 ± 5.6	34.0 ± 7.9	34.3 ± 7.9	32.0 ± 6.7	32.1 ± 6.5
Current smoker, *n* (%)	1065 (16.3)	1028 (15.8)	657 (22.2)	626 (21.4)	351 (13.3)	335 (13.0)	57 (6.2)	67 (6.8)	874 (19.5)	856 (18.6)	17 (10.4)	18 (11.3)	174 (9.3)	154 (8.9)
History of CV disease, present, *n* (%)	2979 (45.7)	2956 (45.4)	1127 (38.1)	1061 (36.2)	1330 (50.5)	1337 (51.7)	522 (56.4)	558 (56.4)	2152 (48.0)	2222 (48.2)	36 (22.1)	20 (12.5)	791 (42.2)	714 (41.0)
History of heart failure	485 (7.4)	522 (8.0)	211 (7.1)	202 (6.9)	192 (7.3)	240 (9.3)	82 (8.9)	80 (8.1)	302 (6.7)	328 (7.1)	11 (6.7)	11 (6.9)	172 (9.2)	183 (10.5)
History of atrial fibrillation/atrial flutter	568 (8.7)	538 (8.3)	144 (4.9)	122 (4.2)	280 (10.6)	267 (10.3)	144 (15.6)	149 (15.1)	439 (9.8)	428 (9.3)	0	0	129 (6.9)	110 (6.3)
Baseline medications, *n* (%)[d]														
RAS inhibitors (ACEis/ARBs)	6508 (99.8)	6495 (99.8)	2951 (99.8)	2925 (99.8)	2631 (99.8)	2582 (99.8)	926 (100.0)	988 (99.8)	4473 (99.8)	4596 (99.8)	163 (100.0)	160 (100.0)	1872 (99.8)	1739 (>99.9)
Beta-blockers	3236 (49.6)	3268 (50.2)	1311 (44.3)	1308 (44.6)	1419 (53.9)	1430 (55.3)	506 (54.6)	530 (53.5)	2237 (49.9)	2308 (50.1)	57 (35.0)	54 (33.8)	942 (50.2)	906 (52.1)
Diuretics	3325 (51.0)	3385 (52.0)	1378 (46.6)	1412 (48.2)	1412 (53.6)	1401 (54.2)	535 (57.8)	572 (57.8)	2320 (51.8)	2386 (51.8)	67 (41.1)	70 (43.8)	938 (50.0)	929 (53.4)
Statins	4657 (71.4)	4742 (72.9)	1993 (67.4)	2040 (69.6)	1975 (75.0)	1945 (75.2)	689 (74.4)	757 (76.5)	3291 (73.4)	3405 (73.9)	93 (57.1)	110 (68.8)	1273 (67.9)	1227 (70.5)
Calcium channel blockers	3664 (56.2)	3694 (56.8)	1564 (52.9)	1563 (53.3)	1544 (58.6)	1508 (58.3)	556 (60.0)	623 (62.9)	2554 (57.0)	2654 (57.6)	74 (45.4%)	75 (46.9)	1036 (55.3)	965 (55.5)
≥1 glucose-lowering medication	6354 (97.5)	6366 (97.8)	2898 (98.0)	2881 (98.3)	2574 (97.7)	2537 (98.1)	882 (95.2)	948 (95.8)	4361 (97.3)	4499 (97.7)	161 (98.8)	156 (97.5)	1832 (97.7)	1711 (98.3)

n (%)	All		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6519)	PBO (*n*=6507)	FIN (*n*=2958)	PBO (*n*=2931)	FIN (*n*=2635)	PBO (*n*=2586)	FIN (*n*=926)	PBO (*n*=990)	FIN (*n*=4481)	PBO (*n*=4607)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1875)	PBO (*n*=1740)
n (%)[d]														
Insulin	3866 (59.3)	3764 (57.8)	1848 (62.5)	1789 (61.0)	1539 (58.4)	1481 (57.3)	479 (51.7)	494 (49.9)	2598 (58.0)	2605 (56.5)	94 (57.7)	99 (61.9)	1174 (62.6)	1060 (60.9)
GLP-1RA	497 (7.6)	447 (6.9)	273 (9.2)	219 (7.5)	190 (7.2)	188 (7.3)	34 (3.7)	40 (4.0)	359 (8.0)	317 (6.9)	12 (7.4)	18 (11.3)	126 (6.7)	112 (6.4)
SGLT-2i	438 (6.7)	439 (6.7)	251 (8.5)	266 (9.1)	149 (5.7)	140 (5.4)	38 (4.1)	33 (3.3)	331 (7.4)	340 (7.4)	19 (11.7)	17 (10.6)	88 (4.7)	82 (4.7)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CV = cardiovascular; eGFR = estimated glomerular filtration rate; FIN = finerenone; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; PBO = placebo; Q = quartile; RAS = renin–angiotensin system; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; UACR = urine albumin-to-creatinine ratio.

Values are based on available data.

[a] Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific, not reported, multiple.

[b] Missing (eGFR): <65 years, *n*=2; 65 to 74 years, *n*=1; postmenopausal female, *n*=3.

[c] Missing (UACR): <65 years, *n*=4; 65 to 74 years, *n*=1; male, *n*=2; postmenopausal female, *n*=3.

[d] Analysis allowed multiple drug groups for the same drug.

eTable 2. Treatment-Emergent AEs According to Age and Sex

n (%)	ALL		Age						Sex					
			<65 Years		65–74 Years		≥75 Years		Male		Female (Premenopausal)		Female (Postmenopausal)	
	FIN (*n*=6510)	PBO (*n*=6489)	FIN (*n*=2953)	PBO (*n*=2926)	FIN (*n*=2631)	PBO (*n*=2578)	FIN (*n*=926)	PBO (*n*=985)	FIN (*n*=4476)	PBO (*n*=4595)	FIN (*n*=163)	PBO (*n*=160)	FIN (*n*=1871)	PBO (*n*=1734)
Any AE	5602 (86.1)	5607 (86.4)	2494 (84.5)	2523 (86.2)	2301 (87.5)	2225 (86.3)	807 (87.1)	859 (87.2)	3899 (87.1)	4011 (87.3)	137 (84.0)	138 (86.3)	1566 (83.7)	1458 (84.1)
Related to study drug	1206 (18.5)	862 (13.3)	478 (16.2)	384 (13.1)	558 (21.2)	337 (13.1)	170 (18.4)	141 (14.3)	884 (19.7)	612 (13.3)	21 (12.9)	20 (12.5)	301 (16.1)	230 (13.3)
Leading to discontinuation	414 (6.4)	351 (5.4)	128 (4.3)	124 (4.2)	212 (8.1)	153 (5.9)	74 (8.0)	74 (7.5)	313 (7.0)	249 (5.4)	9 (5.5)	7 (4.4)	92 (4.9)	95 (5.5)
Any SAE	2060 (31.6)	2186 (33.7)	856 (29.0)	938 (32.1)	871 (33.1)	876 (34.0)	333 (36.0)	372 (37.8)	1487 (33.2)	1590 (34.6)	33 (20.2)	42 (26.3)	540 (28.9)	554 (31.9)
Related to study drug	83 (1.3)	61 (0.9)	29 (1.0)	27 (0.9)	39 (1.5)	17 (0.7)	15 (1.6)	17 (1.7)	56 (1.3)	46 (1.0)	0	1 (0.6)	27 (1.4)	14 (0.8)
Leading to discontinuation	145 (2.2)	154 (2.4)	41 (1.4)	48 (1.6)	75 (2.9)	71 (2.8)	29 (3.1)	35 (3.6)	115 (2.6)	112 (2.4)	1 (0.6)	2 (1.3)	29 (1.5)	40 (2.3)
Any AE leading to death	110 (1.7)	151 (2.3)	43 (1.5)	55 (1.9)	42 (1.6)	62 (2.4)	25 (2.7)	34 (3.5)	73 (1.6)	115 (2.5)	0	3 (1.9)	37 (2.0)	33 (1.9)
AEs of interest														
Hypotension	282(4.3)	177 (2.7)	101 (3.4)	70 (2.4)	127 (4.8)	76 (2.9)	54 (5.8)	31 (3.1)	216 (4.8)	131 (2.9)	3 (1.8)	0	63 (3.4)	46 (2.7)
Orthostatic hypotension	46 (0.7)	39 (0.6)	18 (0.6)	15 (0.5)	23 (0.9)	15 (0.6)	5 (0.5)	9 (0.9)	34 (0.8)	30 (0.7)	0	2 (1.3)	12 (0.6)	7 (0.4)
Hyperkalemia	912 (14.0)	448 (6.9)	360 (12.2)	238 (8.1)	420 (16.0)	158 (6.1)	132 (14.3)	52 (5.3)	647 (14.5)	304 (6.6)	14 (8.6)	16 (10.0)	251 (13.4)	128 (7.4)
Leading to permanent discontinuation	110 (1.7)	38 (0.6)	31 (1.0)	13 (0.4)	54 (2.1)	19 (0.7)	25 (2.7)	6 (0.6)	83 (1.9)	28 (0.6)	4 (2.5)	1 (0.6)	23 (1.2)	9 (0.5)
Classified as a serious AE	69 (1.1)	16 (0.2)	28 (0.9)	8 (0.3)	29 (1.1)	5 (0.2)	12 (1.3)	3 (0.3)	45 (1.0)	9 (0.2)	1 (0.6)	0	23 (1.2)	7 (0.4)
Leading to hospitalization	61 (0.9)	10 (0.2)	26 (0.9)	6 (0.2)	25 (1.0)	2 (<0.1)	10 (1.1)	2 (0.2)	38 (0.8)	5 (0.1)	1 (0.6)	0	22 (1.2)	5 (0.3)
Gynecomastia	8 (0.1)	11 (0.2)	2 (<0.1)	4 (0.1)	5 (0.2)	3 (0.1)	1 (0.1)	4 (0.4)	8 (0.2)	11 (0.2)	NA	NA	NA	NA
Central laboratory assessments, *n*/*N* (%)[a]														

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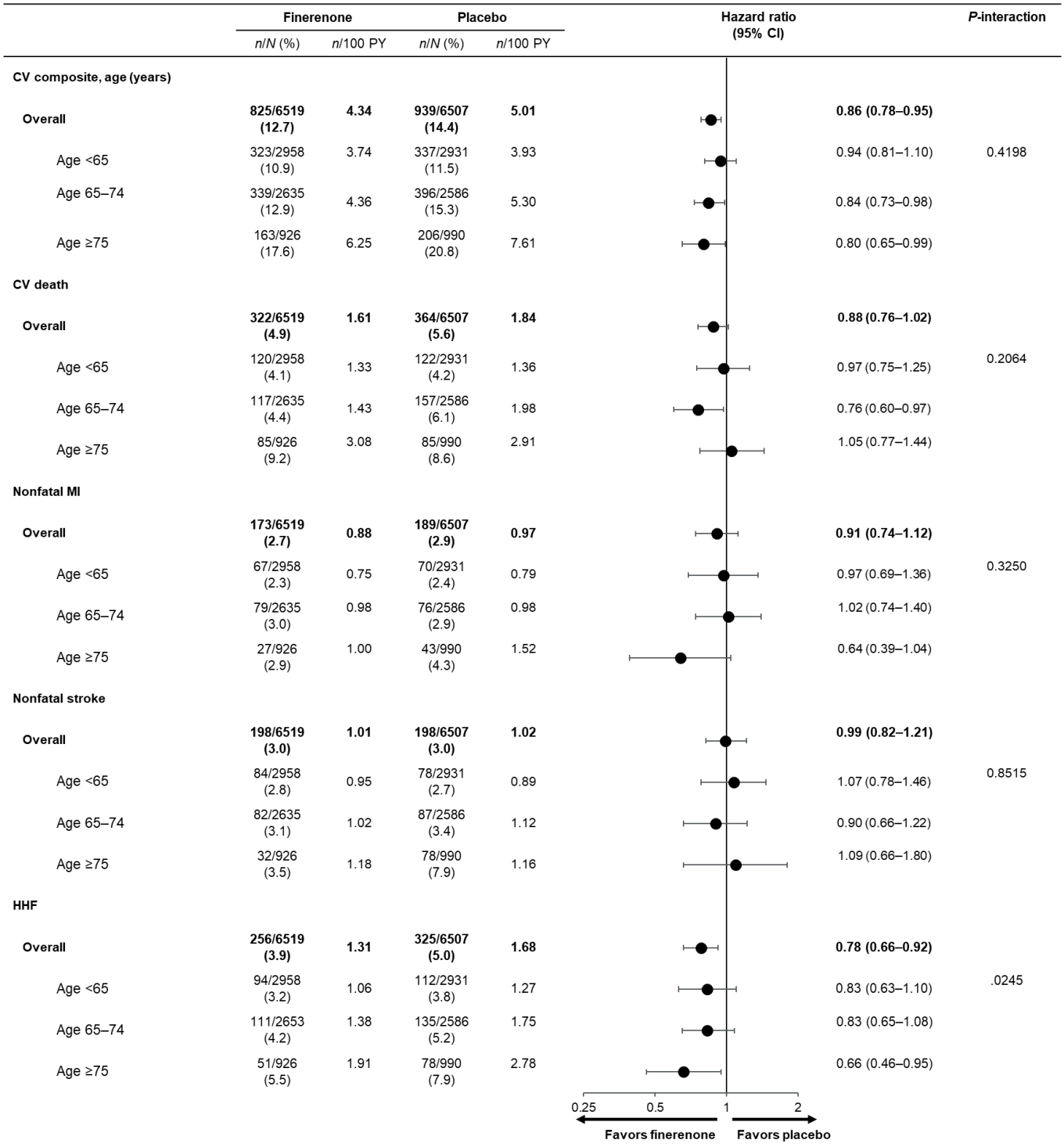
Serum potassium >5.5 mmol/L	1075/ 6402 (16.8)	470/ 6370 (7.4)	444/2904 (15.3)	233/2871 (8.1)	460/2585 (17.8)	180/2529 (7.1)	171/913 (18.7)	57/970 (5.9)	720/4403 (16.4)	308/4523 (6.8)	16/159 (10.1)	8/154 (5.2)	339/1840 (18.4)	154/1693 (9.1)
Serum potassium >6.0 mmol/L	211/ 6439 (3.3)	80/ 6413 (1.2)	90/2926 (3.1)	44/2896 (1.5)	89/2598 (3.4)	31/2544 (1.2)	32/915 (3.5)	5/973 (0.5)	143/4428 (3.2)	48/4544 (1.1)	4/160 (2.5)	1/156 (0.6)	64/1851 (3.5)	31/1713 (1.8)

AE = adverse event; FIN = finerenone; NA = not applicable; PBO = placebo; SAE = serious adverse event.

[a] The "*n*" numerator represents the number of patients at risk with ≥1 treatment-emergent laboratory assessment meeting the criterion. The "*N*" denominator represents all patients at risk for a treatment-emergent laboratory abnormality. Patients had both a baseline and postbaseline treatment-emergent value while the baseline value did not exceed the displayed threshold.

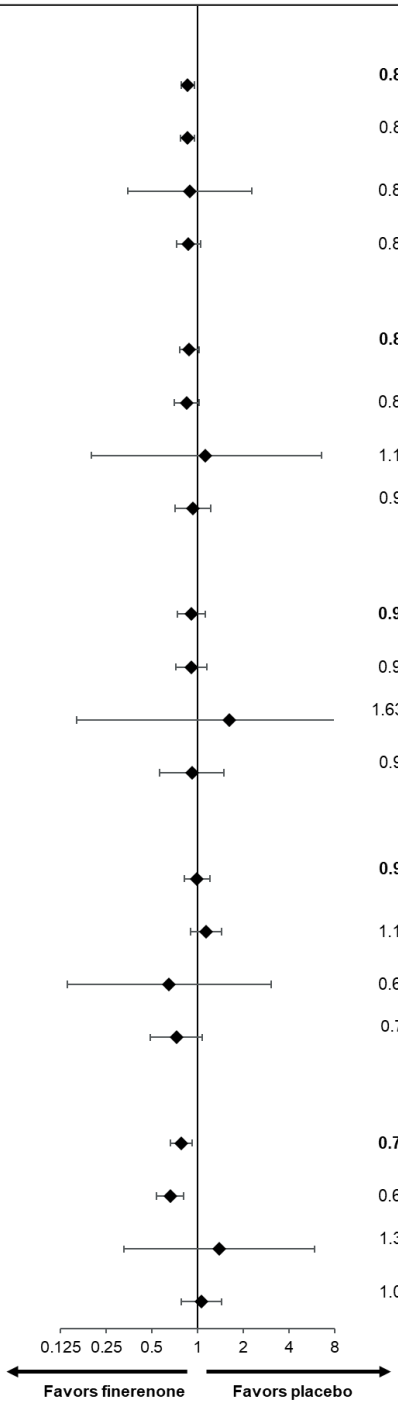
eFigure 1. Analysis of CV composite outcome and subcomponents according to (A) age and (B) sex.

A.



B.

	Finerenone		Placebo		Hazard ratio (95% CI)	*P*-interaction
	n/*N* (%)	*n*/100 PY	*n*/*N* (%)	*n*/100 PY		
CV composite, sex						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	–
Male	579/4481 (12.9)	4.39	675/4607 (14.7)	5.08	0.86 (0.77–0.96)	.9942
Premenopausal female	11/163 (6.7)	2.29	12/160 (7.5)	2.62	0.89 (0.35–2.27)	
Postmenopausal female	235/1875 (12.5)	4.38	252/1740 (14.5)	5.03	0.87 (0.73–1.05)	
CV death						
Overall	**322/6519 (4.9)**	**1.61**	**364/6507 (5.6)**	**1.84**	**0.88 (0.76–1.02)**	
Male	207/4481 (4.6)	1.49	249/4607 (5.4)	1.77	0.85 (0.70–1.02)	.6925
Premenopausal female	4/163 (2.5)	0.80	3/160 (1.9)	0.63	1.13 (0.20–6.54)	
Postmenopausal female	111/1875 (5.9)	1.98	112/1740 (6.4)	2.12	0.93 (0.71–1.22)	
Nonfatal MI						
Overall	**173/6519 (2.7)**	**0.88**	**189/6507 (2.9)**	**0.97**	**0.91 (0.74–1.12)**	
Male	138/4481 (3.1)	1.02	152/4607 (3.3)	1.10	0.91 (0.72–1.15)	.8211
Premenopausal female	2/163 (1.2)	0.40	1/160 (0.6)	0.21	1.63 (0.16–16.87)[a]	
Postmenopausal female	33/1875 (1.8)	0.60	36/1740 (2.1)	0.69	0.92 (0.56–1.49)	
Nonfatal stroke						
Overall	**198/6519 (3.0)**	**1.01**	**198/6507 (3.0)**	**1.02**	**0.99 (0.82–1.21)**	
Male	150/4481 (3.3)	1.11	135/4607 (2.9)	0.98	1.14 (0.90–1.44)	.1103
Premenopausal female	3/163 (1.8)	0.61	4/160 (2.5)	0.86	0.65 (0.14–3.06)	
Postmenopausal female	45/1875 (2.4)	0.81	59/1740 (3.4)	1.14	0.73 (0.49–1.08)	
HHF						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Male	163/4481 (3.6)	1.20	244/4607 (5.3)	1.78	0.66 (0.54–0.81)	.0245
Premenopausal female	5/163 (3.1)	1.02	4/160 (2.5)	0.85	1.39 (0.33–5.93)	
Postmenopausal female	88/1875 (4.7)	1.61	77/1740 (4.4)	1.50	1.06 (0.78–1.44)	



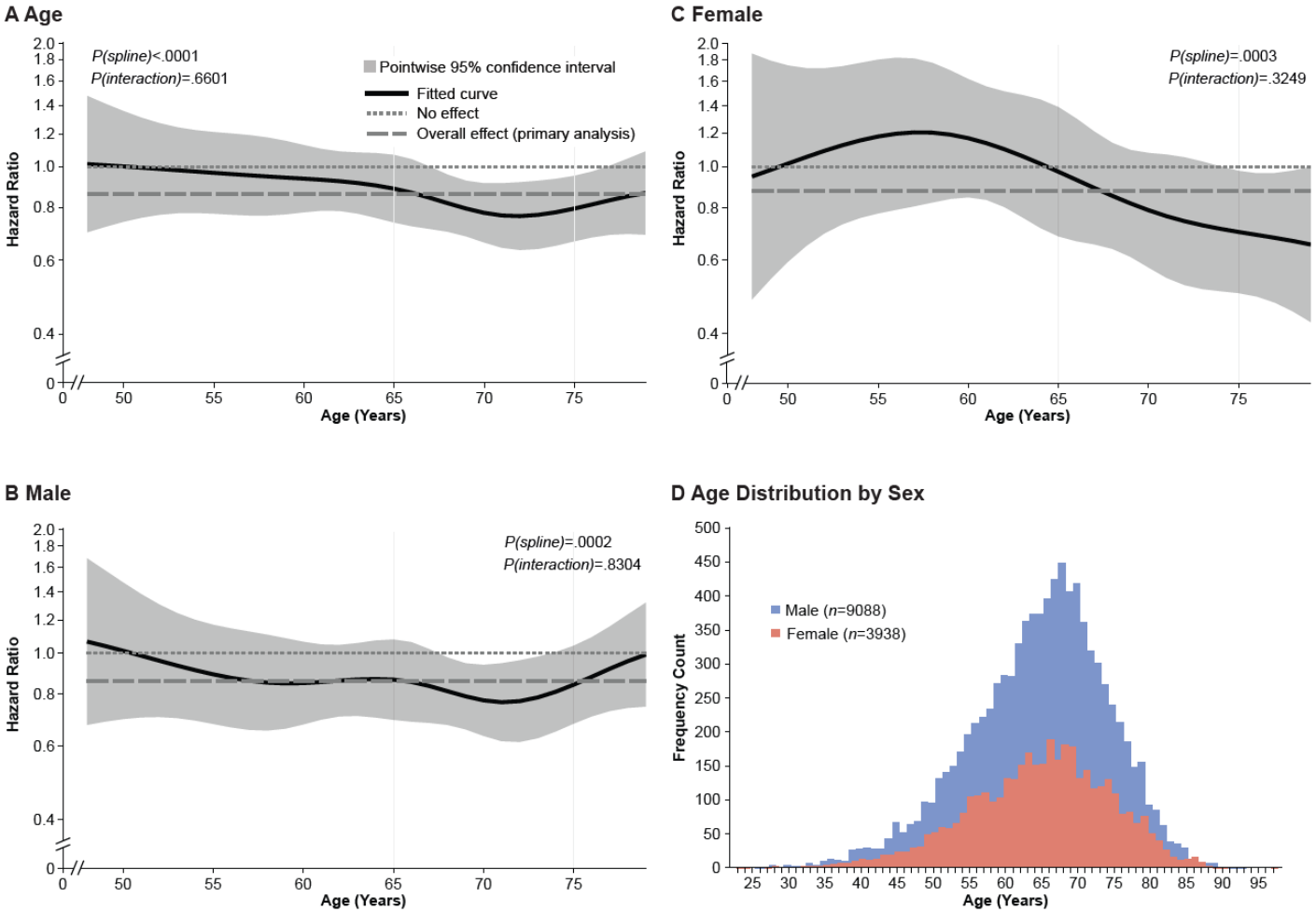
A stratified Cox proportional hazards model including treatment was calculated separately by subgroup category. The $P_{interaction}$ is based on a stratified Cox proportional hazards model including treatment, subgroup, and treatment by subgroup interaction.

CV composite outcome includes CV death, nonfatal MI, nonfatal stroke, or HHF.

CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; MI = myocardial infarction; PY = patient-years.

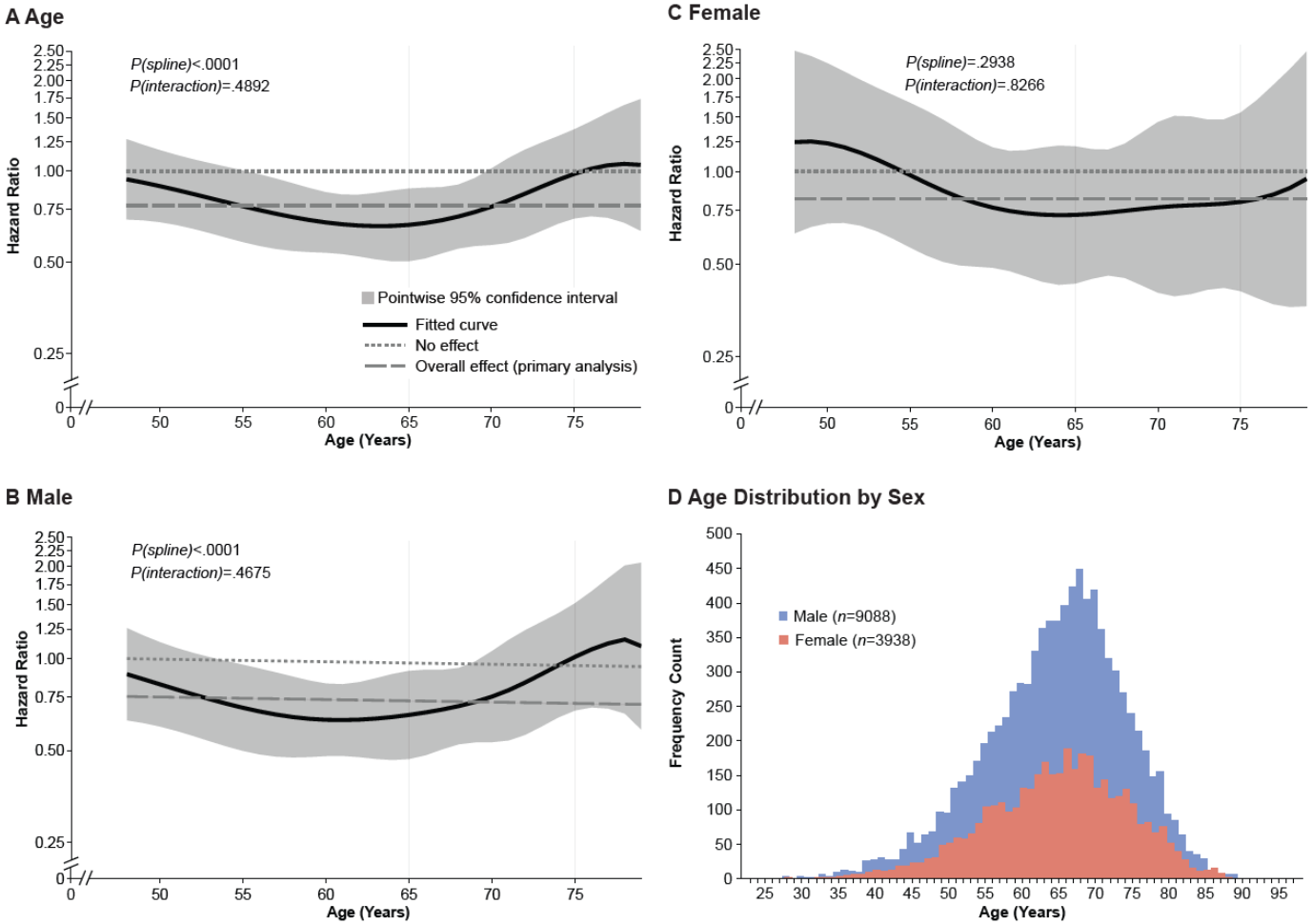
[a] An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts and/or convergence issues.

eFigure 2. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for CV composite outcome by age (A), spline for hazard ratio of CV composite outcomes by sex (B, C), and age distribution by sex (D).

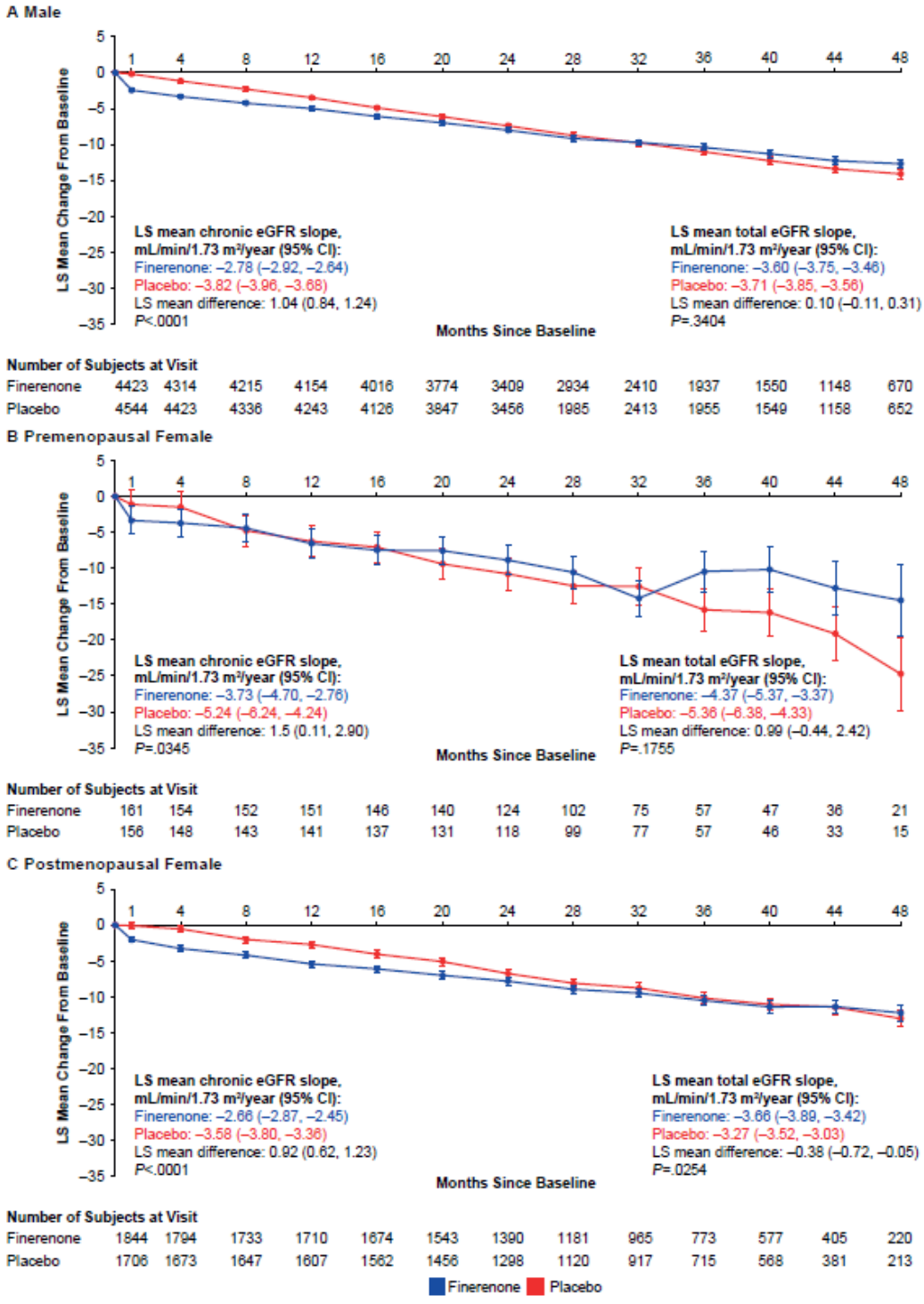


CV = cardiovascular.

eFigure 3. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for kidney composite outcome by age (A), spline for hazard ratio of kidney composite outcomes by sex (B, C), and age distribution by sex (D).



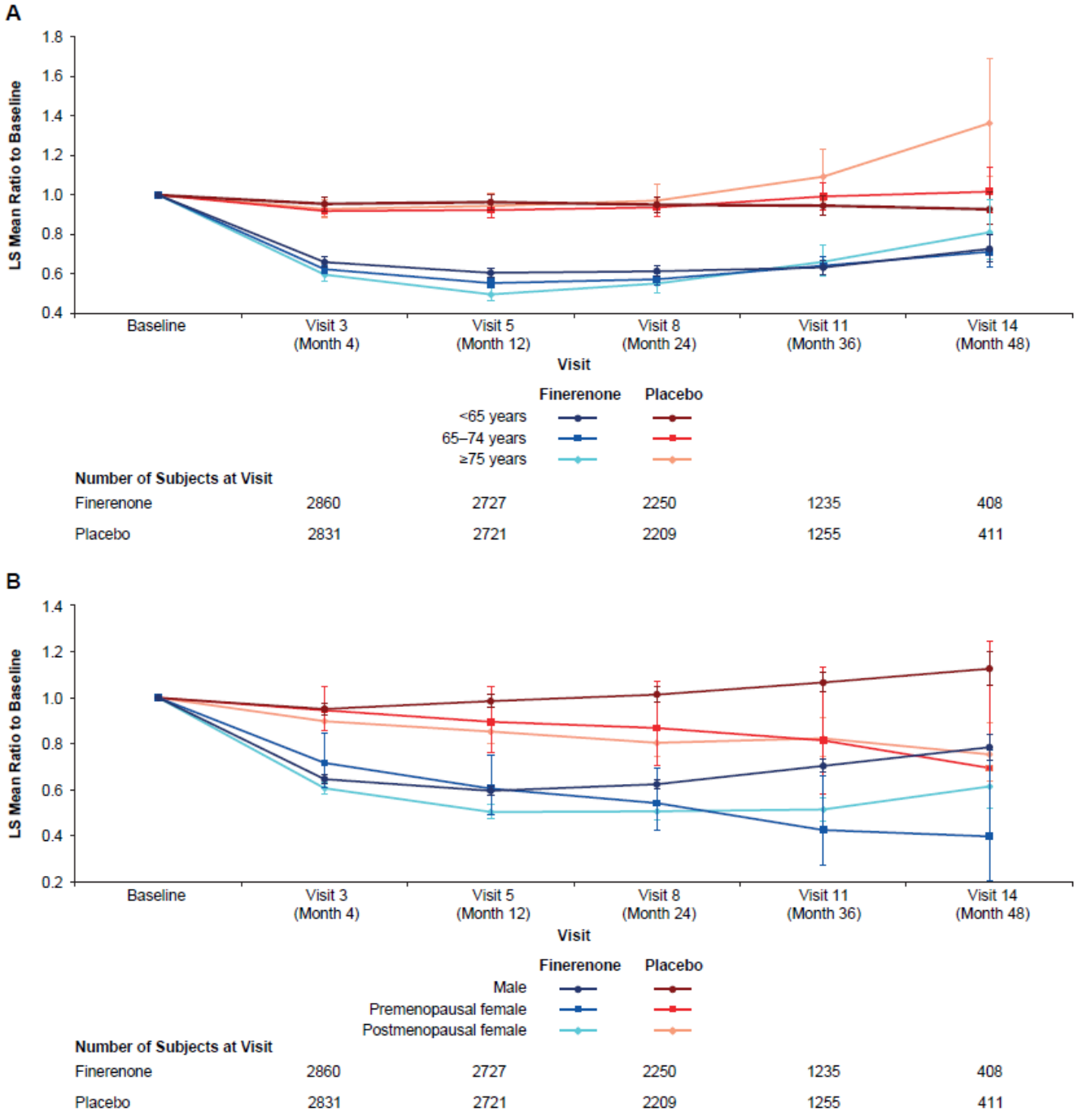
eFigure 4. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.



Chronic eGFR slope from month 4 to end-of-study visit.

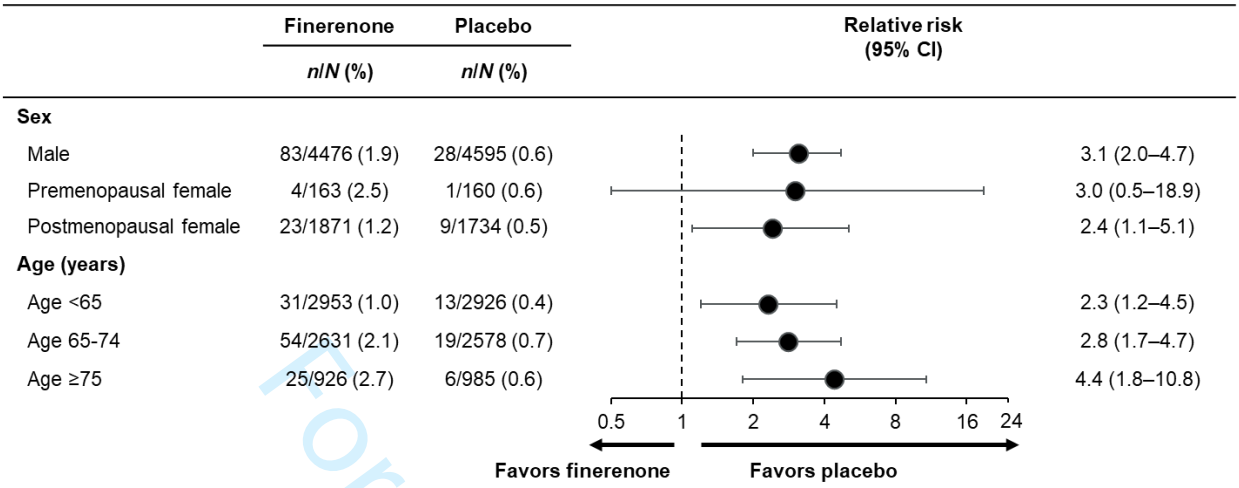
CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

eFigure 5. LS mean ratio to baseline UACR over time by age and sex



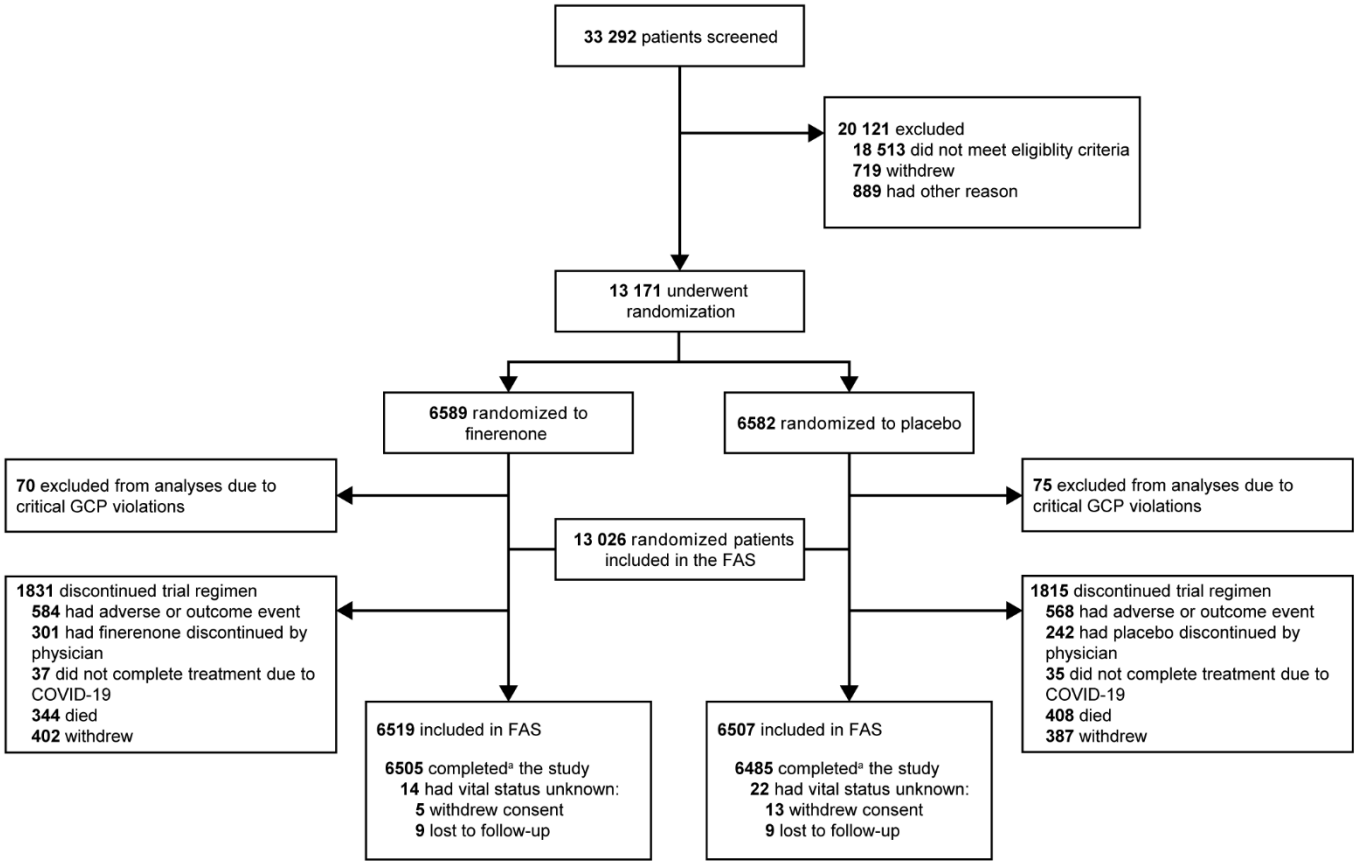
LS = least-squares; UACR = urine albumin-to-creatinine ratio.

eFigure 6. Relative risk of treatment-emergent hyperkalemia causing permanent discontinuation of study drug by age and sex



Relative risk values based on Mantel-Haenszel estimates (stratified by study). For the relative risk, a treatment-arm-size zero cell correction with zero term = 0.5 was applied.

eFigure 7. FIDELITY CONSORT diagram.



[a] The patient was considered as having completed the study if there was a contact with the patient after the end-of-study notification or if the patient died.

CONSORT = Consolidated Standards of Reporting Trials; COVID-19, coronavirus disease of 2019; FAS, full analysis set; FIDELITY = The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analysis; GCP, Good Clinical Practice.