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

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Complete List of Authors:	Bansal, Shweta ; The University of Texas Health Science Center at San Antonio Department of Medicine Canziani, M. E. F.; Univ Fed Sao Paulo Birne, Rita; Centro Hospitalar Lisboa Ocidental, Department of Nephrology; University of Lisbon, Nova Medical School Anker, Stefan; Charité Universitätsmedizin, Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center for Regenerative Therapies (BCRT) Bakris, George; University of Chicago, Hypertension Center Filippatos, Gerasimos; National and Kapodistrian University of Athens Rossing, Peter; Steno Diabetes Center AS; University of Copenhagen, Department of Clinical Medicine Ruilope, Luis M ; Institute of Research imas12, Cardiorenal Translational Laboratory and Hypertension Unit; Hospital Universitario 12 de Octubre, CIBER-CV Farjat, Alfredo; Bayer plc Kolkhof, Peter; Cardiovascular Precision Medicines Bayer AG Lage, Andrea; Bayer SA Brinker, Meike; Cardiology and Nephrology Clinical Development Pitt, B; University of Michigan
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Cardiorenal Outcomes by Age and Sex in Patients Treated With Finerenone: FIDELITY Post Hoc Analysis

Author(s)

Shweta Bansal, MD,¹ Maria E.F. Canziani, MD,² Rita Birne, MD,^{3,4} Stefan D. Anker, MD, PhD,⁵ George L. Bakris, MD,⁶ Gerasimos Filippatos, MD,⁷ Peter Rossing, MD, DMSc,^{8,9} Luis M. Ruilope, MD,¹⁰⁻¹² Alfredo E. Farjat, PhD,¹³ Peter Kolkhof, PhD,¹⁴ Andrea Lage, MD,¹⁵ Meike Brinker, MD,¹⁶ Bertram Pitt, MD,¹⁷ on behalf of the FIDELIO-DKD and FIGARO-DKD investigators

Institution(s)

¹Division of Nephrology, Department of Medicine, University of Texas Health San Antonio, San Antonio, Texas, USA

²Nephrology Division, Federal University of São Paulo, São Paulo, Brazil

³Department of Nephrology, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

⁴Nova Medical School, University of Lisbon, Lisbon, Portugal

⁵Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany

⁶Department of Medicine, University of Chicago Medicine, Chicago, Illinois, USA

⁷National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece

⁸Steno Diabetes Center Copenhagen, Gentofte, Denmark

⁹Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

¹⁰Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain

¹¹CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain

1
2
3 ¹²Faculty of Sport Sciences, European University of Madrid, Madrid, Spain
4

5 ¹³Research and Development, Clinical Data Sciences and Analytics, Bayer PLC, Reading,
6
7 UK
8

9 ¹⁴Research and Early Development, Cardiovascular Precision Medicines, Bayer AG,
10
11 Wuppertal, Germany
12

13 ¹⁵Cardiology and Nephrology Clinical Development, Bayer SA, São Paulo, Brazil
14

15 ¹⁶Cardiology and Nephrology Clinical Development, Bayer AG, Wuppertal, Germany
16

17 ¹⁷Department of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan,
18
19 USA
20
21
22

23
24 **Contact information for corresponding author:**
25

26 Name: Shweta Bansal, MD, FASN
27

28 Address: Department of Medicine, Division of Nephrology, Joe R. & Teresa Lozano Long
29

30 School of Medicine, UT Health, San Antonio, TX, USA
31

32 7703 Floyd Curl Drive, MSC 7882
33

34 San Antonio, TX-78229, USA
35

36 Phone no: 210-422-0438
37

38 Fax no: 210-567-4712
39

40 Email: bansals3@uthscsa.edu
41
42
43
44

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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 $\geq 57\%$ 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 ($P_{\text{interaction}}=.42$) and sex categories ($P_{\text{interaction}}=.99$); effects of finerenone to reduce hospitalization for heart failure were not modified by age ($P_{\text{interaction}}=.70$) but were more pronounced in males ($P_{\text{interaction}}=.02$). 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 ($P_{\text{interaction}}=.51$). In sex subgroups, finerenone consistently reduced kidney events ($P_{\text{interaction}}=.85$). 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.

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3 **Conclusions:** Finerenone improved cardiorenal outcomes with no new safety concerns
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5 across ages and sexes.
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7 **Registration:** FIDELIO-DKD (NCT02540993); FIGARO-DKD (NCT02545049)
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11 **Abstract word count:** 290 of 300 allowed by the journal (no abbreviations)
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14 **Strengths and limitations of this study**

- 15 • An advantage of this study was the use of combined individual-level data from the
16 FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, resulting in a large number of
17 patients included in the full analysis set
- 18 • This study did not use predefined age categories, as it was a post hoc analysis, which
19 may have resulted in some of the tests performed being underpowered
- 20 • Limitations present in FIDELITY are present in this analysis, such as the small proportion
21 of Black patients and exclusion of patients with nonalbuminuric CKD
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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 (11 β -HSD2) enzyme prevents inappropriate MR activation by cortisol.¹⁶⁻¹⁸ The activity of 11 β -HSD2 decreases with age, resulting in MR overactivation in the elderly despite low circulating aldosterone levels.¹⁶⁻¹⁸ Sex also influences 11 β -HSD2 activity, particularly in patients with hypertension, where 11 β -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 11 β -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

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3 FIGARO-DKD Trial programme analysis), a prespecified pooled analysis of the
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5 FIDELIO-DKD (Finerenone in reducing kidney failure and disease progression in Diabetic
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7 Kidney Disease; NCT02540993) and FIGARO-DKD (Finerenone in reducing cardiovascular
8
9 mortality and morbidity in Diabetic Kidney Disease; NCT02545049) phase 3 trials.²¹
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11 However, the influence of age and sex on outcomes with finerenone is unknown. This post
12
13 hoc analysis evaluated whether the cardiorenal benefits and safety profile of finerenone
14
15 observed in FIDELITY are consistent in patients with CKD and T2D across ages and in both
16
17 sexes.
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20 21 **Methods**

22 23 **Study Design and Patients**

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25 FIDELITY combined individual patient-level data from the FIDELIO-DKD and FIGARO-DKD
26
27 phase 3 clinical trials. The study design, procedures, and outcomes for the trials have been
28
29 previously published.²⁴⁻²⁶
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35 Eligible patients were aged ≥ 18 years with CKD and T2D, receiving maximum tolerated
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37 renin–angiotensin system inhibitor, and with serum potassium levels ≤ 4.8 mmol/L at
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39 screening. Patients had either a urine albumin-to-creatinine ratio (UACR) ≥ 30 to < 300 mg/g
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41 and an estimated glomerular filtration rate (eGFR) ≥ 25 to ≤ 90 mL/min/1.73 m², or UACR
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43 ≥ 300 to ≤ 5000 mg/g and eGFR ≥ 25 mL/min/1.73 m². Patients with symptomatic heart failure
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45 (HF) with reduced ejection fraction were excluded because this implies an indication for a
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47 steroidal MRA.
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52 Standard-of-care therapy with a renin–angiotensin system inhibitor was optimized during the
53
54 run-in period. Patients were randomly assigned (1:1) to receive finerenone at titrated doses
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56 (10 or 20 mg) once-daily oral treatment or matching placebo.
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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 $\geq 57\%$ 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.

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5 Changes in UACR and eGFR over time were assessed using a linear mixed-model analysis
6 accounting for repeated measurements over time. The least-squares mean ratio and
7 absolute change from baseline were estimated from the models for changes in UACR and
8 eGFR, respectively. The 2-slope, linear spline, mixed-model, repeated measure method²⁷
9 was used to estimate the rate of change in eGFR across time, specifically total (annualized
10 rate of change in eGFR from baseline to permanent discontinuation or end of study) and
11 chronic (from month 4 to permanent discontinuation or end of study) eGFR slopes. To
12 account for possible nonlinear effects of age on clinical outcomes, age was modeled with
13 cubic splines with 3 knots in Cox proportional hazards models, to produce plots of the HRs
14 and 95% CI as functions of age and sex.
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27 **Patients and public involvement**

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29 No patient or public involvement in the current study.
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33 **Results**

34 **Patients**

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

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55 Baseline characteristics were similar across age subgroups except for some key differences
56 (**Table 1**). The overall FIDELITY population was predominantly White (68.1%), the proportion
57 of which increased with age. Mean eGFR and median UACR were higher in the <65 years
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3 group. History of CV disease was more common in the ≥ 75 years group; this trend was also
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5 observed for atrial fibrillation/atrial flutter.

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

8 9 10 **Efficacy**

11 12 13 *CV composite outcome by age*

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16 CV composite event rates increased with patient age in both treatment arms (**Figure 1A**).
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18 However, CV composite event rates were lower with finerenone than placebo in all age
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20 groups (**Figure 1A**). The effect of finerenone on reducing the risk of the CV composite
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22 outcome was consistent across categorical age subgroups ($P_{\text{interaction}}=.42$). There was no
23
24 evidence of treatment effect modification when age was modeled as a continuous variable
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26 ($P_{\text{interaction}}=.10$). The trend of HR as a function of age was modeled with cubic splines
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28 (**eFigure 1A**).

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

38 39 40 *CV composite outcome by sex*

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43 CV composite event rates were lower with finerenone than placebo for males,
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45 premenopausal females, and postmenopausal females (**Figure 1B**). The effect of finerenone
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47 on reducing the risk of the CV composite outcome was consistent across sex subgroups
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49 ($P_{\text{interaction}}=.10$). When age was modeled with cubic splines by sex, the effect of finerenone
50
51 was consistent with advancing age in males; however, a trend toward a stronger effect in
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53 older versus younger females was noted (**eFigure 1B, 1C**). Age distribution by sex is
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55 demonstrated in **eFigure 1D**.

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

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

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

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

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

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13 In this post hoc analysis, finerenone demonstrated reduced risk of CV and kidney composite
14 outcomes versus placebo across all age and sex subcategories. In FIDELITY, HHF was the
15 main driver of CV benefit with finerenone²⁴; lower incidences of HHF with finerenone versus
16 placebo were observed in this analysis across all age subgroups, with some differences
17 noted between sex subgroups. Moreover, the incidences of any AEs or SAEs were similar
18 between the treatment groups regardless of age and sex.
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28 The results for the CV outcome in this analysis are consistent with findings from other studies
29 of MRAs in HF. In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an
30 Aldosterone Antagonist), age did not affect the efficacy of spironolactone in patients with HF,
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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

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

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3 generally similar across age and sex. In a FIDELIO-DKD subanalysis, younger age and
4 female sex were independent risk factors for hyperkalemia (>6.0 mmol/L).³³ Similar findings
5 for age were observed in TOPCAT post hoc data for patients with HF.²⁸ Steroidal MRAs have
6 been associated with gynecomastia in males,^{34,35} which was not observed in this study, most
7 likely because finerenone has no detectable affinity for androgen receptors.³⁵
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15 Preclinical data suggest that different molecular mechanisms drive endothelial dysfunction in
16 male and female mice^{36,37} and that increased age and male sex are associated with MR
17 overactivation, which is linked to vascular stiffness and endothelial dysfunction.^{38,39} In human
18 aortic smooth muscle cells, MR expression increased with age, leading to epigenetic
19 changes associated with increased vascular stiffness. These effects were reversed with MR
20 inhibition.⁴⁰ In vitro, MR expression in the whole aortae and early passage aortic vascular
21 smooth muscle cells was increased in aged (30 months) versus adult (8 months) rat cells.³⁸
22 In a preclinical mouse model, aortic stiffness occurred earlier in male than female mice and
23 correlated with the timing of increased aortic MR expression; vascular stiffness was
24 prevented in smooth muscle cell MR-deficient mice.³⁹ These data suggest that elderly males
25 may derive the greatest benefit from finerenone; indeed, in this analysis, finerenone-treated
26 males had lower risk of the CV composite outcome and HHF versus placebo across age
27 groups, including >75 years. Moreover, statistical heterogeneity was observed for HHF by
28 sex, persisting after adjustment for differences in baseline characteristics, with a more
29 pronounced effect of finerenone to reduce HHF versus placebo in males than females.
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49 In this study, markers of kidney damage (eGFR decline and UACR) were reduced with
50 finerenone in age subgroups; however, no benefit on kidney outcomes was observed in the
51 >75 years age group. The small sample size of this subgroup precluded definitive
52 conclusions, which may be accounted for by the slowing rate of CKD progression with
53 advancing age.^{41,42}
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3 Limitations include the study being a post hoc analysis and the chosen age categories not
4 being predefined. In addition, patients may have initiated other treatments during the study.
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6 Sample size and number of events for premenopausal females were relatively small,
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8 resulting in uncertainty around the estimates for this subgroup. Results for premenopausal
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10 females versus postmenopausal females/males should be interpreted with caution because
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12 age may partly account for differences observed; the average age of premenopausal females
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14 was ~45 years old compared with postmenopausal females (~66 years old) and males (~65
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16 years old) (**Table 1**). As such, these groups had different baseline characteristics. Higher
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18 baseline mean eGFR and median UACR, and lower history of CV comorbidities and
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20 hypotension were observed in premenopausal females versus males and postmenopausal
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22 females. Additionally, the study design and tests performed may have been underpowered to
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24 address the research questions. Furthermore, FIDELITY limitations, mainly the small
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26 proportion of Black patients and exclusion of patients with nonalbuminuric CKD, were
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28 present in this analysis.
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35 In conclusion, this post hoc FIDELITY analysis suggests that finerenone effectively lowers
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37 the risk of clinically important cardiorenal outcomes in patients with CKD and T2D across
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39 ages and sexes, with no new safety concerns in those aged >65 years or by sex. These data
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41 highlight the therapeutic potential of finerenone in older patients and both sexes in patients
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43 with CKD and T2D.
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41 **Data sharing statement**

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45 Data not currently available

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47 Will data be available: Yes

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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, <i>n</i> (%) ^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, <i>n</i> (%)	1283 (21.8)	686 (13.1)	124 (6.5)	1730 (19.0)	35 (10.8)	328 (9.1)
History of CV disease, present, <i>n</i> (%)	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, <i>n</i> (%) ^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												

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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.

For peer review only

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 $\geq 57\%$ 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

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BMJ Open
33 292 patients screened

20 121 excluded
18 513 did not meet eligibility criteria
719 withdrew
889 had other reason

13 171 underwent randomization

6589 randomized to finerenone

6582 randomized to placebo

70 excluded from analyses due to critical GCP violations

75 excluded from analyses due to critical GCP violations

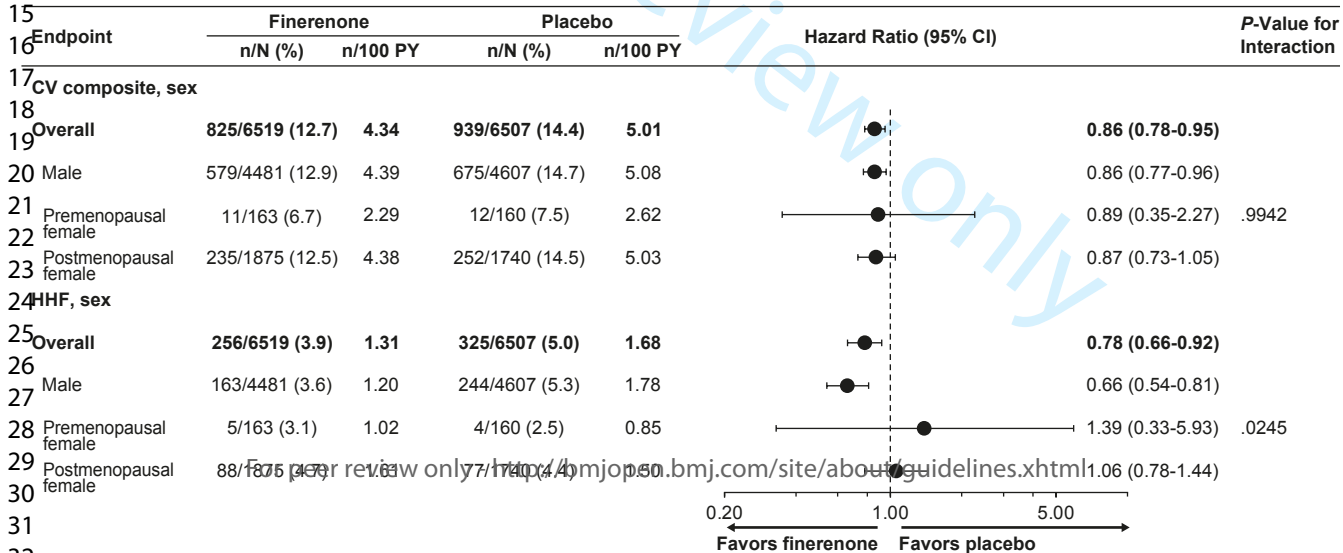
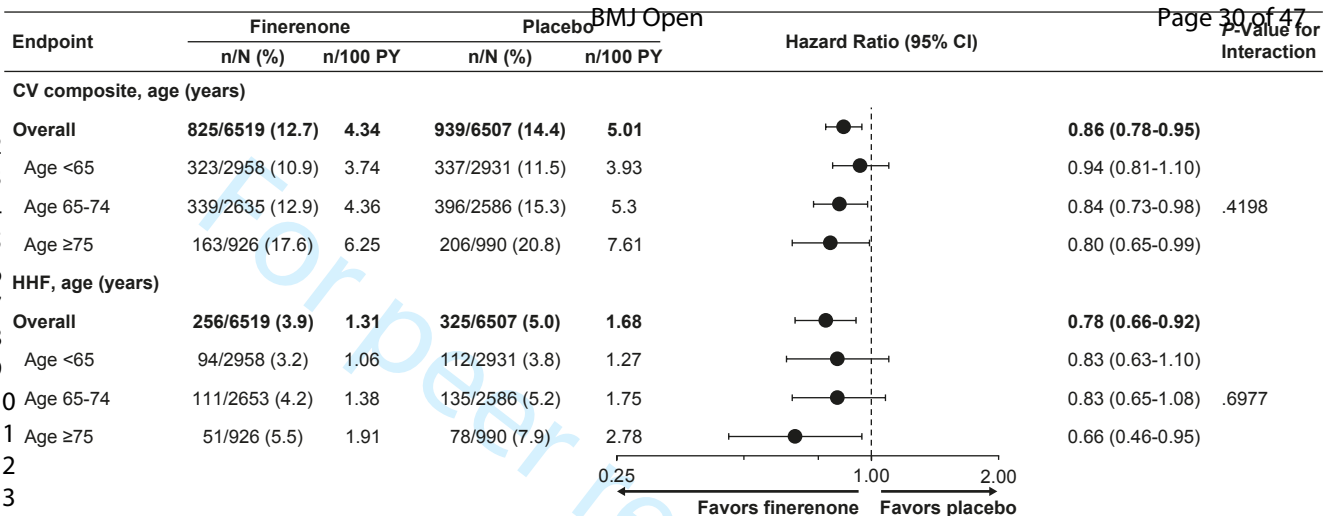
13 026 randomized patients included in the FAS

1831 discontinued trial regimen
584 had adverse or outcome event
301 had finerenone discontinued by physician
37 did not complete treatment due to COVID-19
2044 died
402 withdrew

1815 discontinued trial regimen
568 had adverse or outcome event
242 had placebo discontinued by physician
35 did not complete treatment due to COVID-19
408 died
387 withdrew

6519 included in FAS
6505 completed^a the study
14 had vital status unknown:
5 withdrew consent
9 lost to follow-up

6507 included in FAS
6485 completed^a the study
22 had vital status unknown:
10 withdrew consent
9 lost to follow-up

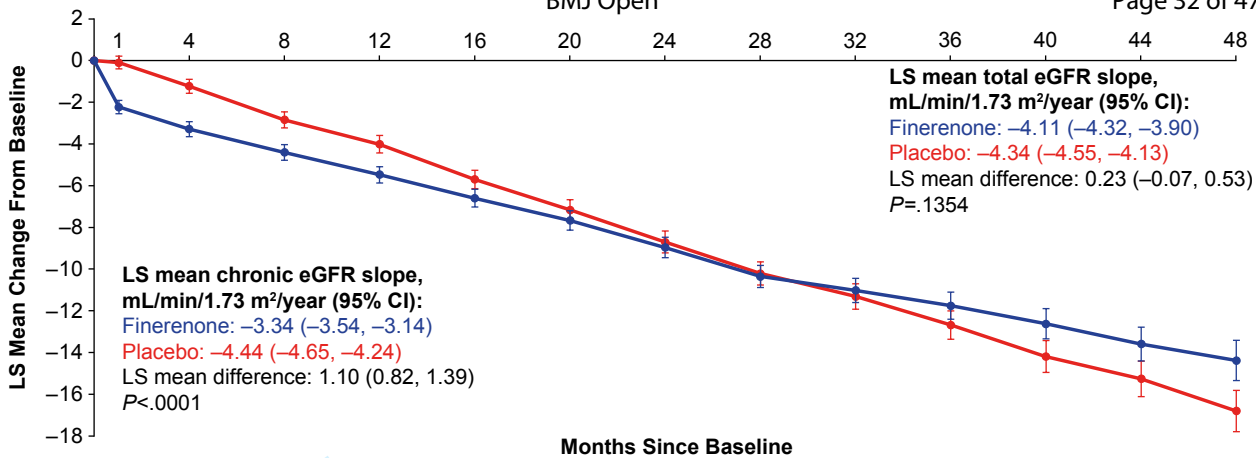


A

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

B

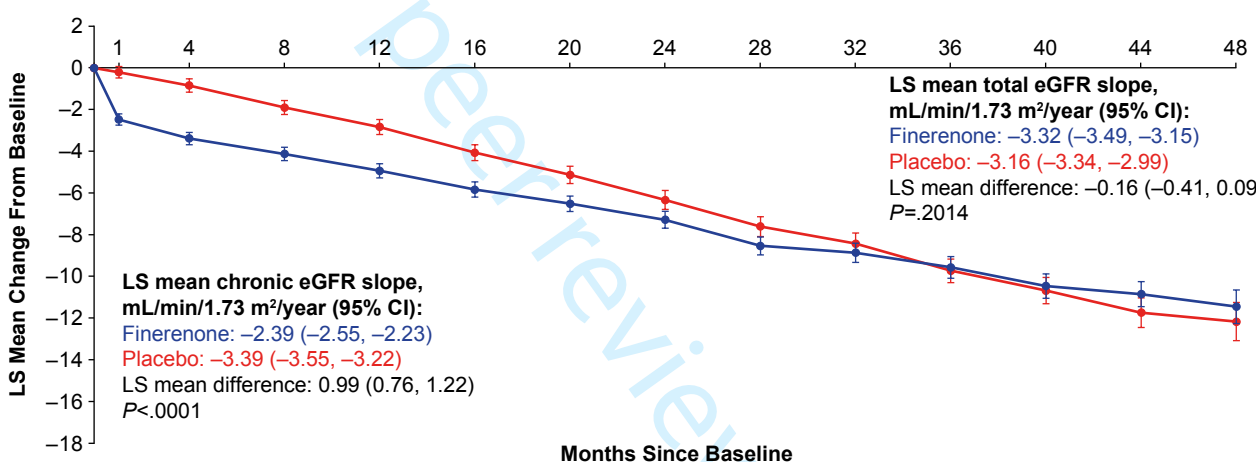
Endpoint	Finerenone		Placebo		Hazard Ratio (95% CI)	P-Value for Interaction
	n/N (%)	n/100 PY	n/N (%)	n/100 PY		
Kidney composite, sex						
1 Overall	360/6519 (5.5)	1.96	465/6507 (7.1)	2.55	0.77 (0.67-0.88)	
2 Male	257/4481 (5.7)	2.02	341/4607 (7.4)	2.63	0.75 (0.64-0.89)	
3 Premenopausal female	11/163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



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

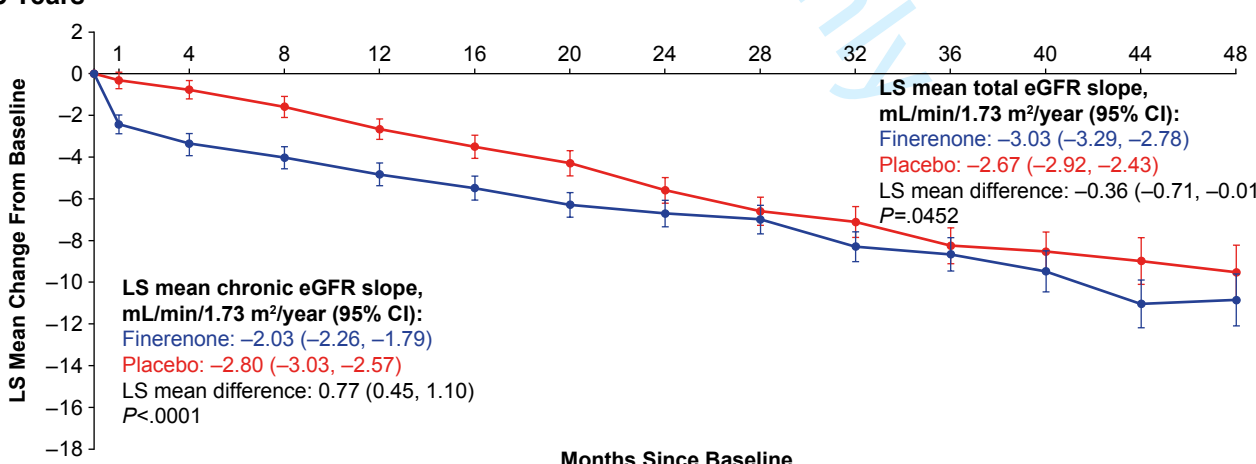
B 65 to 74 Years



Number of Subjects at Visit

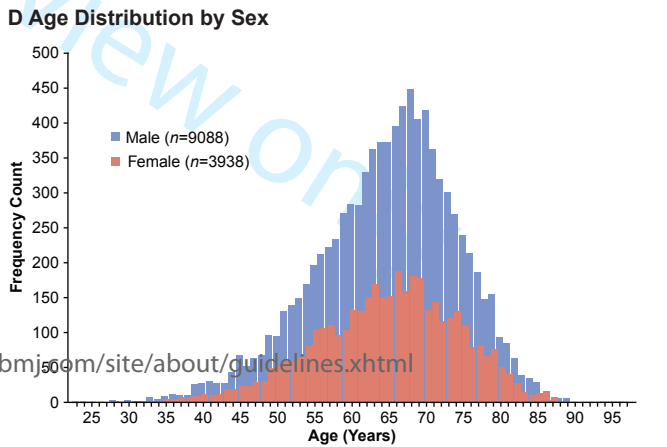
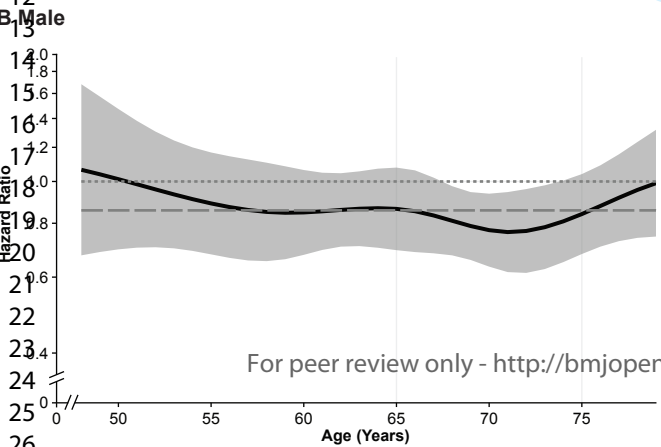
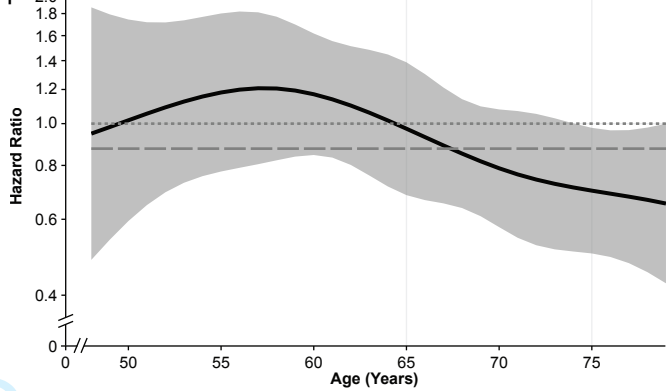
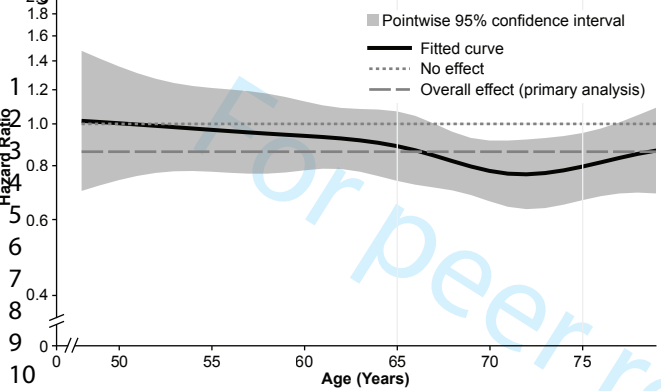
Finerenone	2597	2536	2474	2460	2388	2220	1995	1732	1462	1158	935	663	387
Placebo	2539	2481	2429	2376	2326	2163	1951	1674	1360	1097	876	637	346

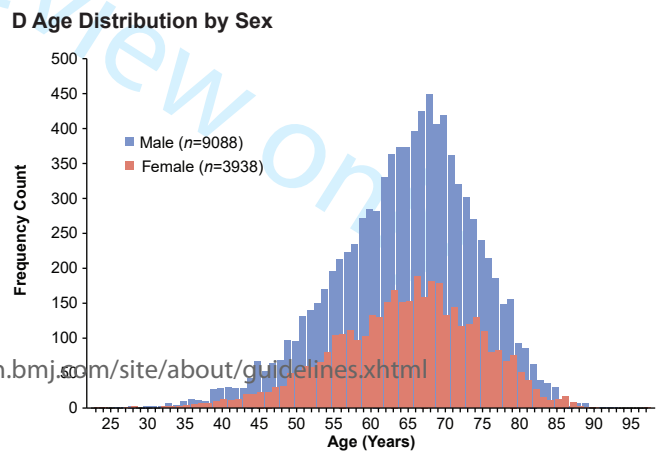
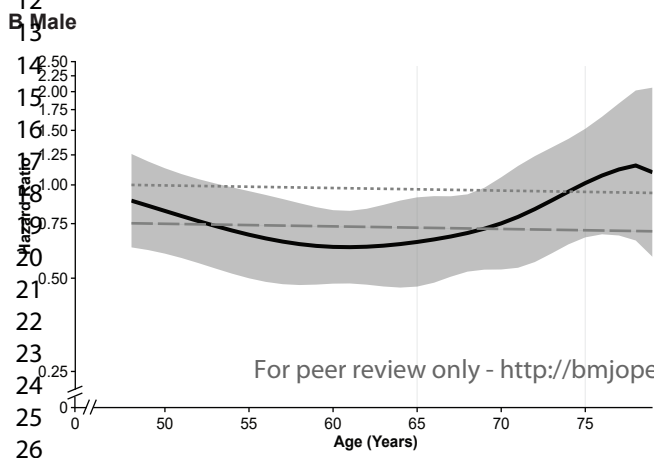
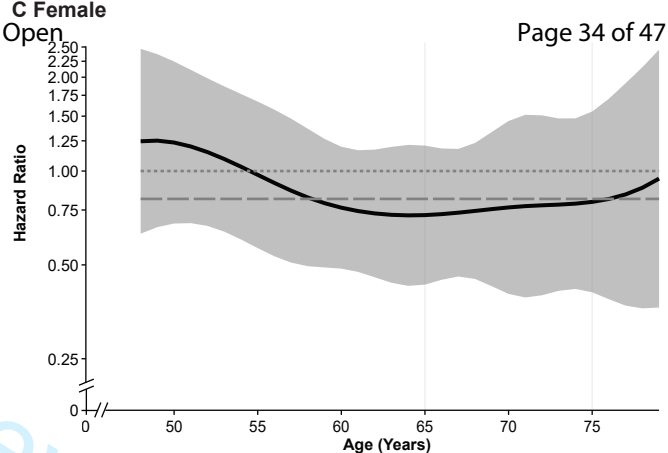
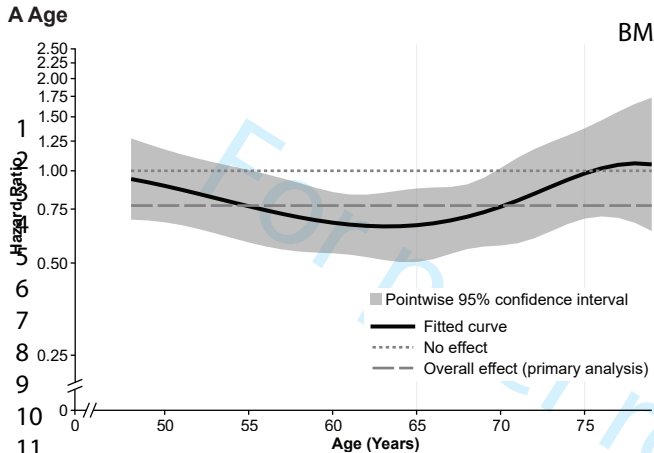
C ≥75 Years

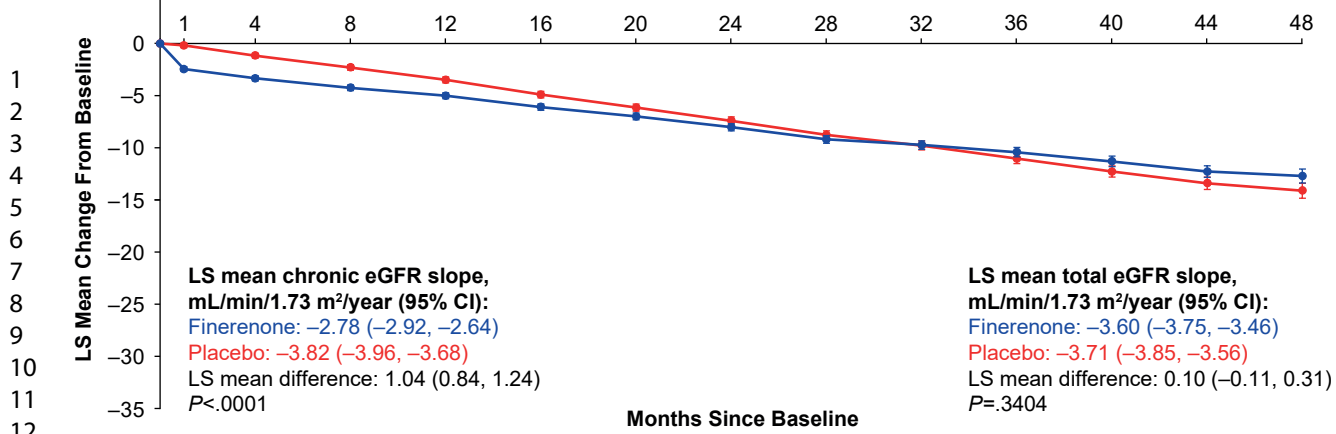


Number of Subjects at Visit

Finerenone	910	877	848	825	792	732	647	567	447	363	277	210	115
Placebo	975	934	896	850	780	696	606	511	401	359	281	204	117



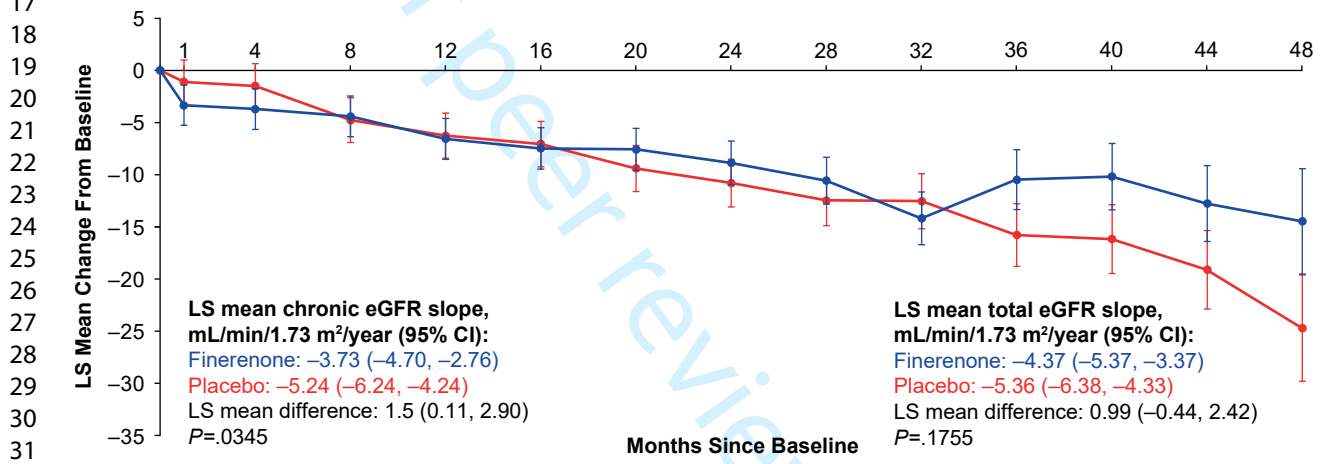




Number of Subjects at Visit

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

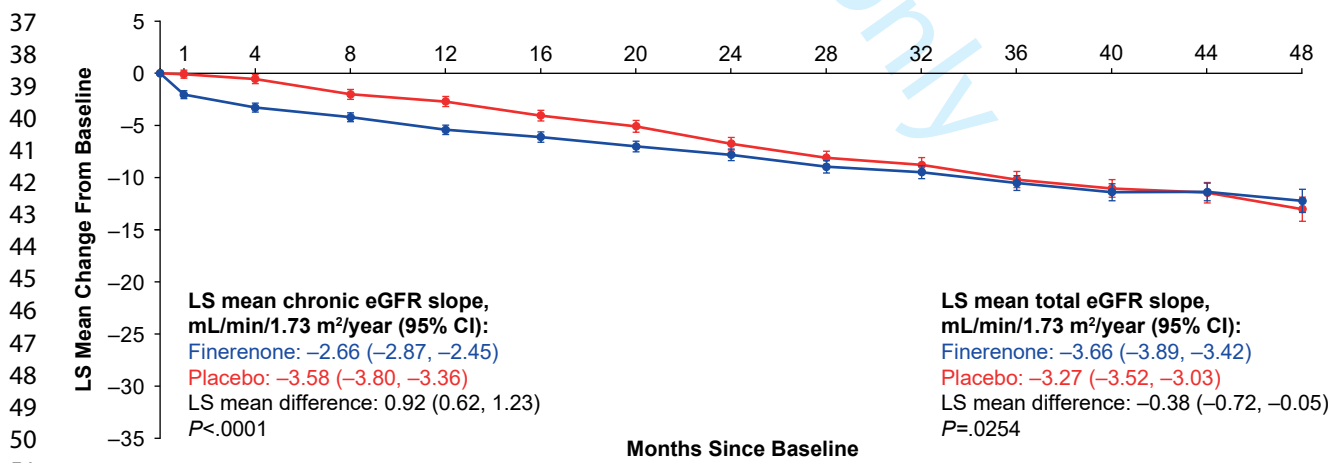
B Premenopausal Female



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

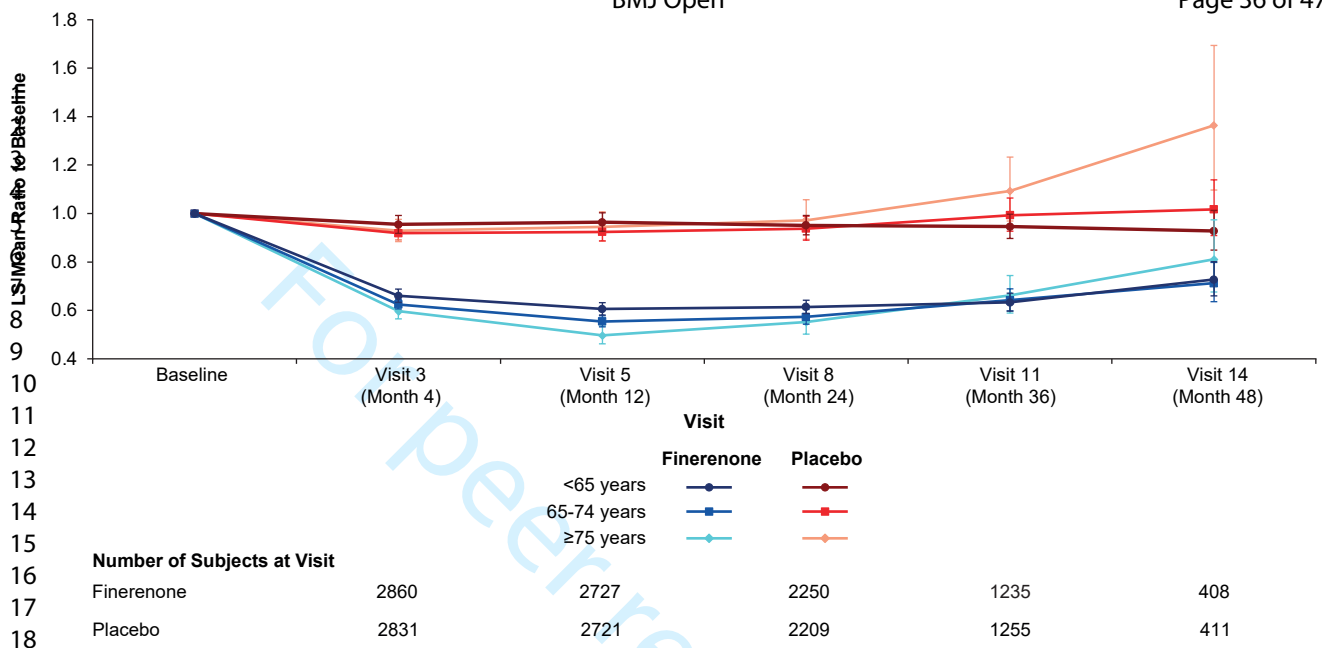
C Postmenopausal Female



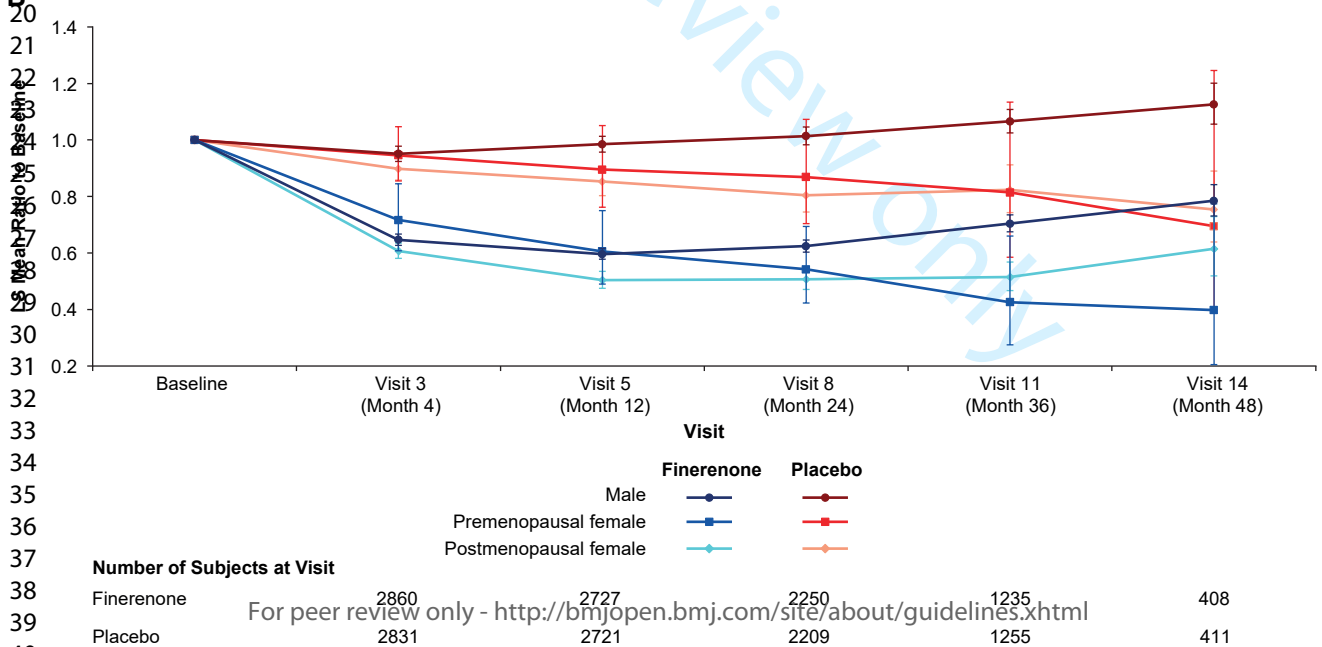
Number of Subjects at Visit

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



B



Cardiorenal Outcomes by Age and Sex in Patients Treated With Finerenone:

FIDELITY Post Hoc Analysis

Contents

Cardiorenal Outcomes by Age and Sex in Patients Treated With Finerenone: FIDELITY Post Hoc Analysis	1
Supplementary Tables and Figures	2
eTable 1. Patient Baseline Characteristics According to Age and Sex Stratified by Treatment Group	2
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).....	5
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).	6
eFigure 3. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.	7
eFigure 4. LS mean ratio to baseline UACR over time by age and sex.	8
eFigure 5. FIDELITY CONSORT diagram.	9

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)
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.

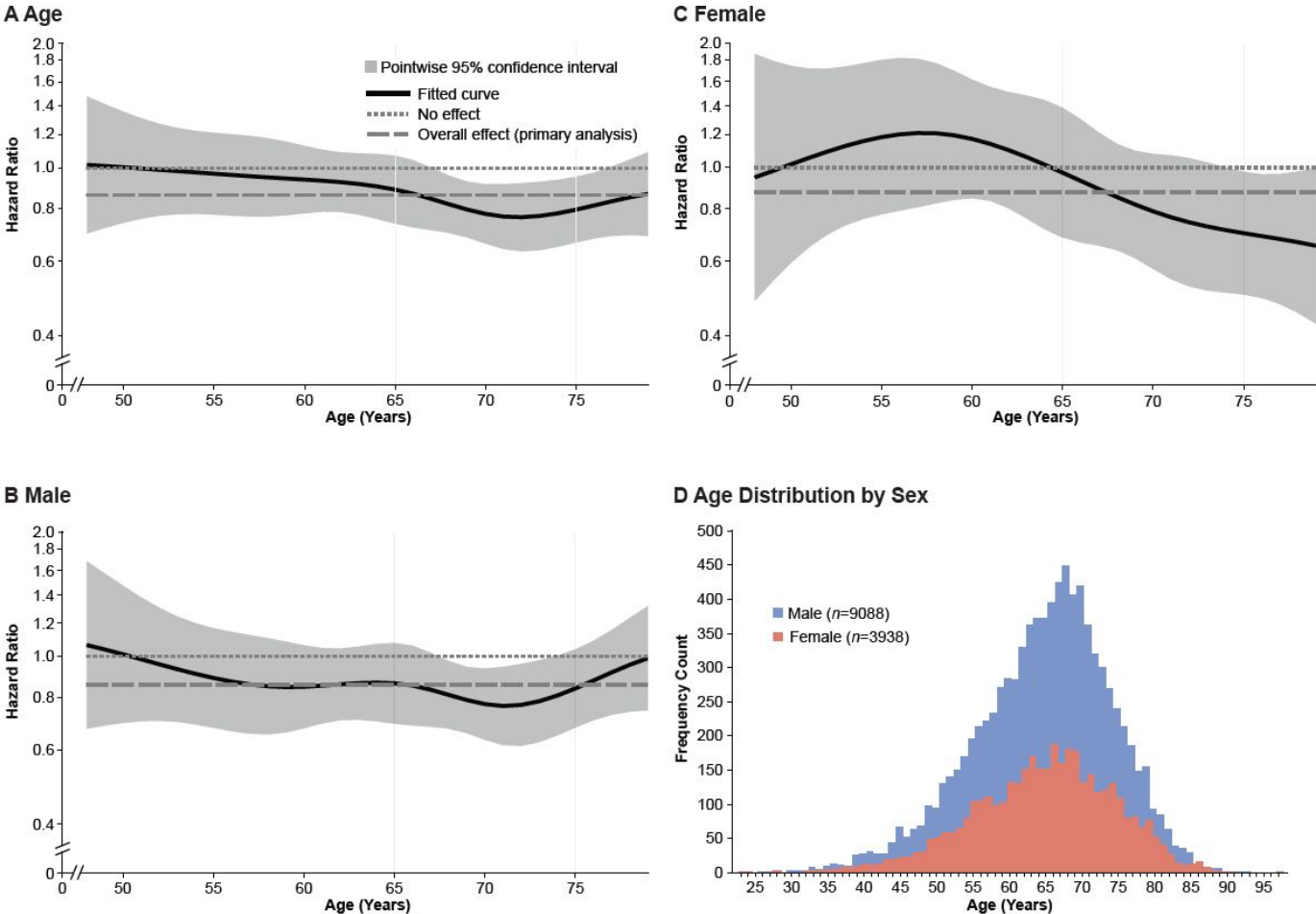
^b Missing (eGFR): <65 years, n=2; 65 to 74 years, n=1; postmenopausal female, n=3.

^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.

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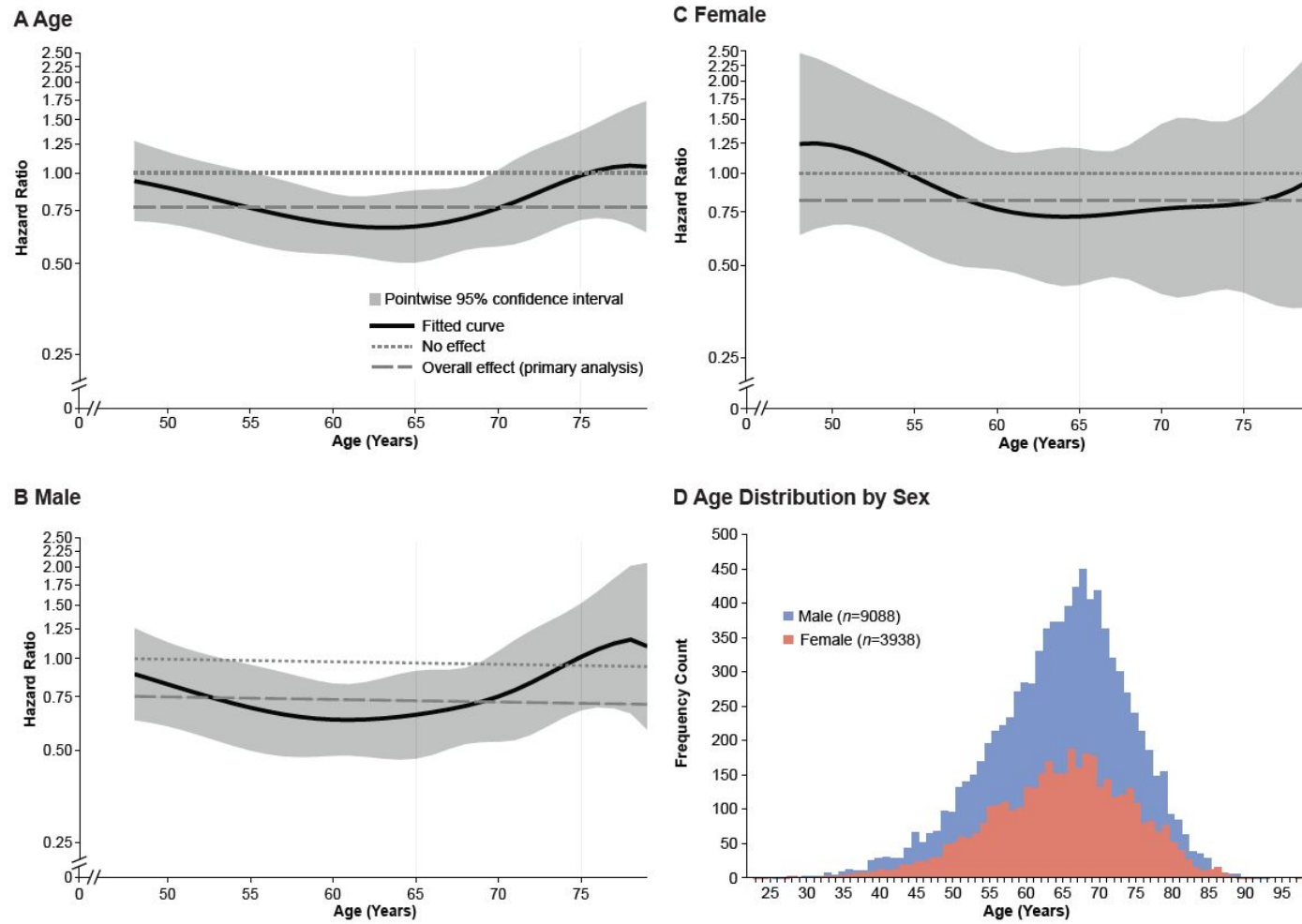
eFigure 1. Hazard ratio (finerenone vs. placebo) as a function of age modeled with cubic splines for CV composite outcome by age (A), spline for hazard ratio of CV composite outcomes by sex (B, C) and age distribution by sex (D).



CV = cardiovascular.

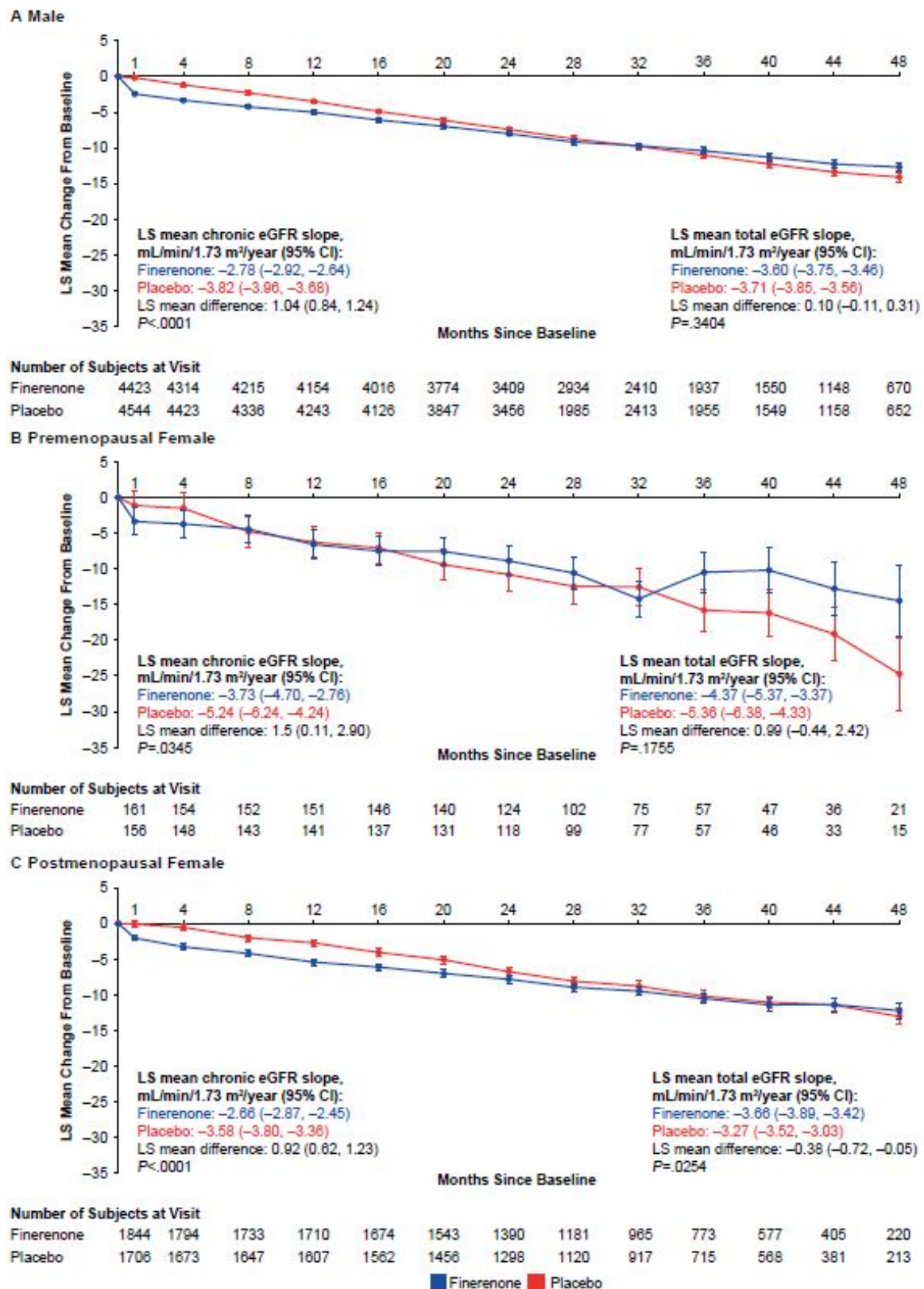
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eFigure 2. Hazard ratio (finerenone vs. placebo) as a function of age modeled with cubic splines for kidney composite outcome by age (A), spline for hazard ratio of kidney composite outcomes by sex (B, C) and age distribution by sex (D).



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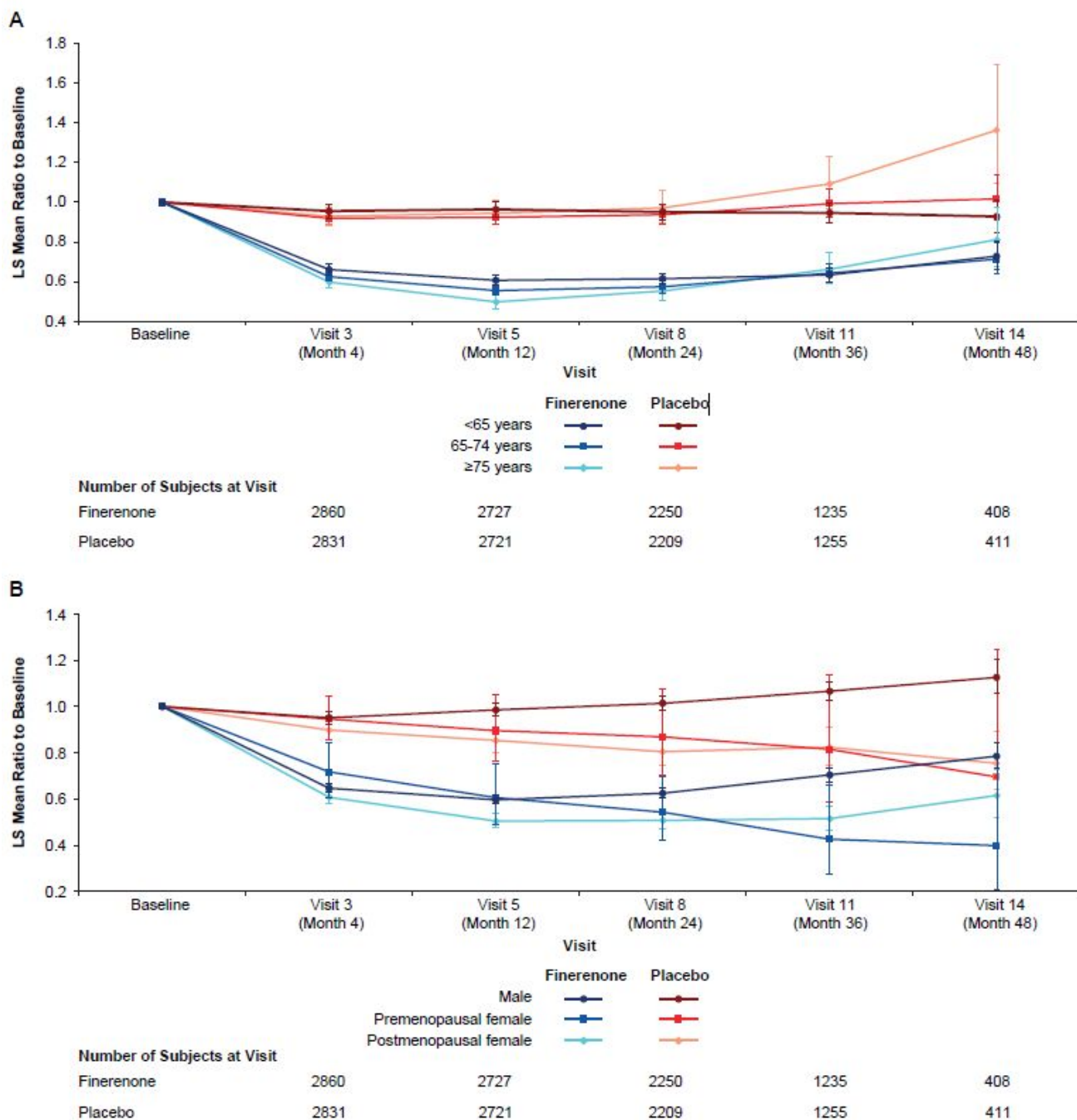
eFigure 3. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.



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

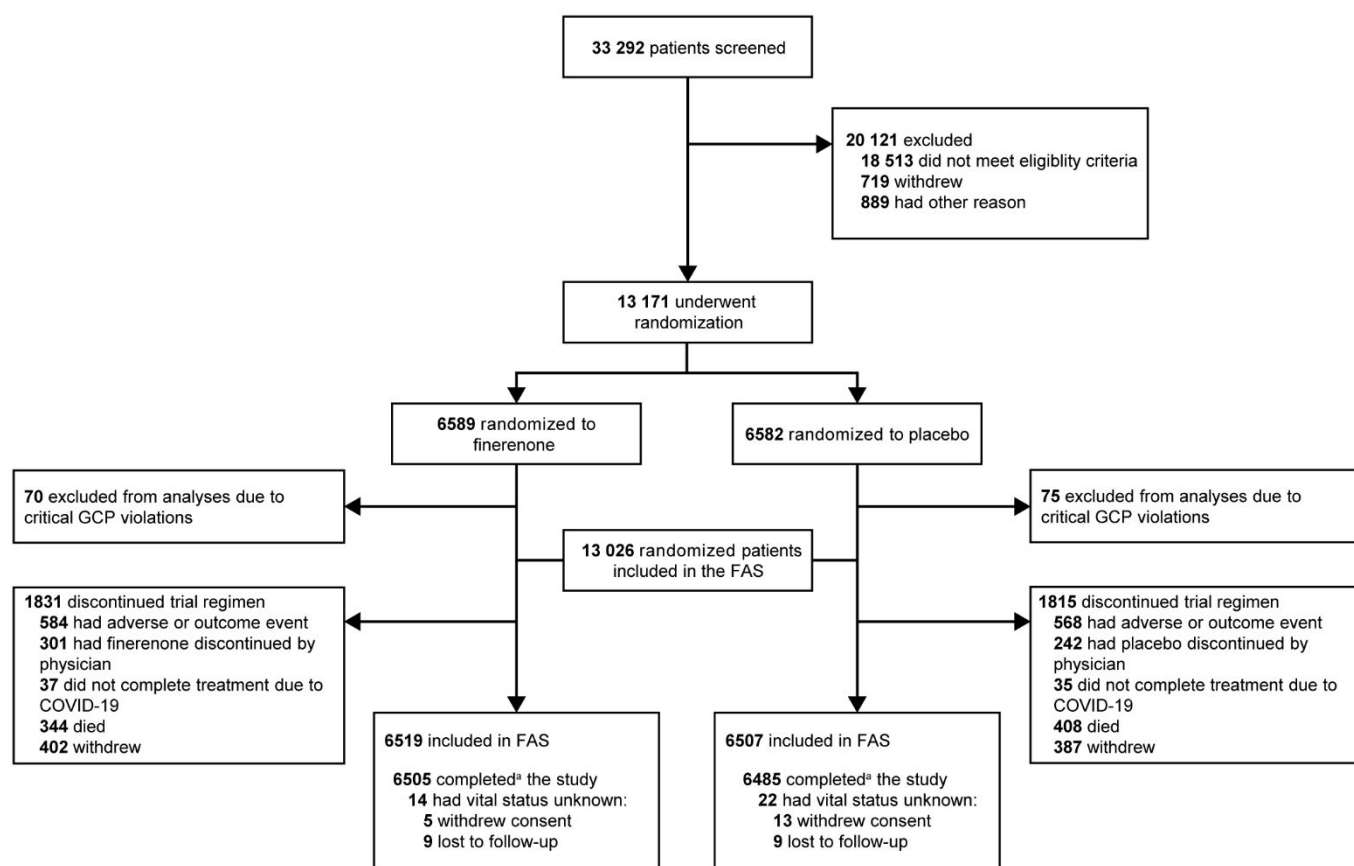
CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

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

1	generation			previously
2		8b	Type of randomisation; details of any restriction (such as blocking and block size)	Reported
3				previously
4	Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	Reported
5	concealment		describing any steps taken to conceal the sequence until interventions were assigned	previously
6	mechanism			
7	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Reported
8				previously
9				
10	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	Reported
11			assessing outcomes) and how	previously
12		11b	If relevant, description of the similarity of interventions	Reported
13				previously
14				
15	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
16		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
17				
18	Results			
19	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	8-9; Table 1
20	diagram is strongly		were analysed for the primary outcome	
21	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	eFigure 5
22	Recruitment	14a	Dates defining the periods of recruitment and follow-up	Reported
23				previously
24		14b	Why the trial ended or was stopped	Reported
25				previously
26				
27	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
28	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was	8-9; Table 1
29			by original assigned groups	
30	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	9-12
31	estimation		precision (such as 95% confidence interval)	Figures 1-2
32		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
33	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	eFigures 1-4
34			pre-specified from exploratory	
35	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Table 2
36				
37				
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40				
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42	Discussion			

1	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
2	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Reported
3				previously
4	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-15
5				
6	Other information			
7	Registration	23	Registration number and name of trial registry	6
8	Protocol	24	Where the full trial protocol can be accessed, if available	Primary
9				publications
10				with full
11				protocols are
12				cited (6)
13				
14	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16-17
15				

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
 18 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
 19 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

Author(s)

Shweta Bansal, MD,¹ Maria E.F. Canziani, MD,² Rita Birne, MD,^{3,4} Stefan D. Anker, MD, PhD,⁵ George L. Bakris, MD,⁶ Gerasimos Filippatos, MD,⁷ Peter Rossing, MD, DMSc,^{8,9} Luis M. Ruilope, MD,¹⁰⁻¹² Alfredo E. Farjat, PhD,¹³ Peter Kolkhof, PhD,¹⁴ Andrea Lage, MD,¹⁵ Meike Brinker, MD,¹⁶ Bertram Pitt, MD¹⁷

Institution(s)

¹Division of Nephrology, Department of Medicine, University of Texas Health San Antonio, San Antonio, Texas, USA

²Nephrology Division, Federal University of São Paulo, São Paulo, Brazil

³Department of Nephrology, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

⁴Nova Medical School, University of Lisbon, Lisbon, Portugal

⁵Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany

⁶Department of Medicine, University of Chicago Medicine, Chicago, Illinois, USA

⁷National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece

⁸Steno Diabetes Center Copenhagen, Gentofte, Denmark

⁹Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

¹⁰Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain

¹¹CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain

1
2
3 27 ¹²Faculty of Sport Sciences, European University of Madrid, Madrid, Spain
4
5 28 ¹³Research and Development, Clinical Data Sciences and Analytics, Bayer PLC, Reading,
6
7 29 UK
8
9 30 ¹⁴Research and Early Development, Cardiovascular Precision Medicines, Bayer AG,
10
11 31 Wuppertal, Germany
12
13 32 ¹⁵Cardiology and Nephrology Clinical Development, Bayer SA, São Paulo, Brazil
14
15 33 ¹⁶Cardiology and Nephrology Clinical Development, Bayer AG, Wuppertal, Germany
16
17 34 ¹⁷Department of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan,
18
19 35 USA
20
21
22
23

24 37 **Contact information for corresponding author:**

25
26 38 Name: Shweta Bansal, MD, FASN
27
28 39 Address: Department of Medicine, Division of Nephrology, Joe R. & Teresa Lozano Long
29
30 40 School of Medicine, UT Health, San Antonio, TX, USA
31
32 41 7703 Floyd Curl Drive, MSC 7882
33
34 42 San Antonio, TX-78229, USA
35
36 43 Phone no: 210-422-0438
37
38 44 Fax no: 210-567-4712
39
40 45 Email: bansals3@uthscsa.edu
41
42
43
44

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53 ABSTRACT

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

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

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

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

62 **Interventions:** Randomized 1:1 to finerenone or placebo.

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

67 **Results:** Mean age was 64.8 years; 45.2%, 40.1%, and 14.7% were aged <65 , 65–74, and
68 ≥ 75 years, respectively; 69.8% were male. Cardiovascular benefits of finerenone versus
69 placebo were consistent across age (hazard ratio 0.94 [<65 years], 0.84 [65–74 years], 0.80
70 [≥ 75 years]; $P_{\text{interaction}}=.42$) and sex categories (hazard ratio 0.86 [male], 0.89 [premenopausal
71 female], 0.87 [postmenopausal female]; $P_{\text{interaction}}=.99$); effects on HHF reduction were not
72 modified by age ($P_{\text{interaction}}=.70$) but appeared more pronounced in males ($P_{\text{interaction}}=.02$).
73 Kidney events were reduced with finerenone versus placebo in patients aged <65 and 65–74
74 but not ≥ 75 ; no heterogeneity in treatment effect was observed ($P_{\text{interaction}}=.51$). In sex
75 subgroups, finerenone consistently reduced kidney events ($P_{\text{interaction}}=.85$). Finerenone
76 reduced albuminuria and estimated glomerular filtration rate decline regardless of age and
77 sex. Hyperkalemia increased with finerenone, but discontinuation rates were $<3\%$ across
78 subgroups. Gynecomastia in males was uncommon across age subgroups and identical
79 between treatment groups.

1
2
3 80 **Conclusions:** Finerenone improved cardiovascular and kidney composite outcomes with no
4
5 81 significant heterogeneity between age and sex subgroups; however, the effect on HHF
6
7 82 appeared more pronounced in males. Finerenone demonstrated a similar safety profile
8
9 83 across age and sex subgroups.
10

11 84 **Registration:** FIDELIO-DKD (NCT02540993); FIGARO-DKD (NCT02545049)
12
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14 85

15 86 **Abstract word count:** 300 of 300
16
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18 19 87 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 20
21 88 • An advantage of this study was the use of combined individual-level data from the
22
23 89 FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, resulting in a large number of
24
25 90 patients included in the full analysis set
26
27 91 • This study did not use predefined age categories, as it was a post hoc analysis, which
28
29 92 may have resulted in some of the tests performed being underpowered
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31 93 • Limitations present in FIDELITY are present in this analysis, such as the small proportion
32
33 94 of Black patients and exclusion of patients with nonalbuminuric CKD
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35
36 95

96 INTRODUCTION

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

100
101 Among individuals aged 50–75 years without baseline diabetes, CKD, or CV disease, males
102 have a steeper decline in glomerular filtration rate (GFR) than females.[3] However, reported
103 effects of sex on risk of incidental and progressive CKD in patients with type 2 diabetes
104 (T2D) have been inconsistent.[4-6] In trials including patients with CKD, female
105 representation varies (25–40%),[7-11] whereas in real-world studies, females make up over
106 half of patients.[12,13]

107
108 Overactivation of the mineralocorticoid receptor (MR) is associated with CV and kidney
109 diseases.[14,15] In epithelial cells, the 11 β -hydroxysteroid dehydrogenase type 2 (11 β -
110 HSD2) enzyme prevents inappropriate MR activation by cortisol.[16-18] The activity of 11 β -
111 HSD2 decreases with age, resulting in MR overactivation in the elderly despite low
112 circulating aldosterone levels.[16-18] Sex also influences 11 β -HSD2 activity, particularly in
113 patients with hypertension, where 11 β -HSD2 activity is reduced in males versus females.[16]
114 The MR is also expressed in nonepithelial cells, including endothelial cells, vascular smooth
115 muscle cells, adipocytes, and immune cells.[17] In many of these, the MR may be activated
116 by cortisol because of a lack of protection by 11 β -HSD2.[19,20]

117
118 Despite management with recommended treatments for CKD in T2D, 10–13% of patients
119 experience CKD progression or kidney failure and are at high risk of CV events, including CV
120 death within 2–3 years following treatment initiation.[10,21,22] Finerenone, a selective,
121 nonsteroidal MR antagonist (MRA), reduced the risk of CKD progression and CV outcomes
122 compared with placebo in patients with CKD and T2D in FIDELITY (The Finerenone in

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3 123 chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD
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5 124 Trial programme analysis), a prespecified pooled analysis of the FIDELIO-DKD (Finerenone
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7 125 in reducing kidney failure and disease progression in Diabetic Kidney Disease;
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9 126 NCT02540993) and FIGARO-DKD (Finerenone in reducing cardiovascular mortality and
10
11 127 morbidity in Diabetic Kidney Disease; NCT02545049) phase 3 trials.[21] However, the
12
13 128 influence of age and sex on outcomes with finerenone is unknown. This post hoc analysis
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15 129 evaluated whether the cardiovascular and kidney benefits and safety profile of finerenone
16
17 130 observed in FIDELITY are consistent in patients with CKD and T2D across ages and in both
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19 131 sexes.
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23 132 **METHODS**

27 133 **Study design and patients**

29 134 FIDELITY combined individual patient-level data from the FIDELIO-DKD and FIGARO-DKD
30
31 135 phase 3 clinical trials. The study design, procedures, and outcomes for the trials have been
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33 136 previously published.[23-25] The FIDELIO-DKD and FIGARO-DKD trials were conducted in
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35 137 accordance with the principles of the Declaration of Helsinki. Protocol approvals were
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37 138 obtained from local regulatory authorities and ethics committees. Written informed consent
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39 139 was provided by all participants. These studies were reported following the Consolidated
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41 140 Standards of Reporting Trials (CONSORT) reporting guideline.
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46 142 Eligible patients were aged ≥ 18 years with CKD and T2D, receiving maximum tolerated
47
48 143 renin-angiotensin system inhibitor, and with serum potassium levels ≤ 4.8 mmol/L at
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50 144 screening. Patients had either a urine albumin-to-creatinine ratio (UACR) ≥ 30 – < 300 mg/g
51
52 145 and an estimated GFR (eGFR) ≥ 25 – ≤ 90 mL/min/1.73 m², or UACR ≥ 300 – ≤ 5000 mg/g and
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54 146 eGFR ≥ 25 mL/min/1.73 m². Patients with symptomatic heart failure (HF) with reduced
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56 147 ejection fraction were excluded because this implies an indication for a steroidal MRA.
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3 149 Standard-of-care therapy with a renin–angiotensin system inhibitor was optimized during the
4
5 150 run-in period. Patients were randomly assigned (1:1) to receive finerenone at titrated doses
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7 151 (10 or 20 mg) once-daily oral treatment or matching placebo.
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9

10 152 **Key outcomes**

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12
13 153 Efficacy outcomes included a CV composite outcome of CV death, nonfatal myocardial
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15 154 infarction, nonfatal stroke, or hospitalization for HF (HHF), and a kidney composite outcome
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17 155 of kidney failure, sustained $\geq 57\%$ eGFR decline, or renal death. Additional outcomes
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19 156 included HHF and change in UACR and eGFR over time.
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23 158 Safety outcomes included incidence of investigator-reported adverse events (AEs), including
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25 159 those leading to treatment discontinuation, central laboratory assessment of serum
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27 160 potassium levels >5.5 and >6.0 mmol/L, and other safety events of interest, such as
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29 161 hypotension, hyperkalemia, and gynecomastia in males.
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34 163 Outcomes were analyzed according to patient age at baseline (<65 , 65 – 75 , ≥ 75 years) and
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36 164 sex. Females were categorized as either pre- or postmenopausal if they were aged <51.4 or
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38 165 ≥ 51.4 years at baseline, respectively (based on the median age of menopause onset from
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40 166 the Massachusetts Women's Health Study).[26]
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42 43 167 **Statistical analysis**

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45
46 168 Statistical analyses were performed as described in FIDELITY.[23] The full analysis set
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48 169 comprised all randomized patients (except those with critical Good Clinical Practice
49
50 170 violations, who were prospectively excluded). Safety analyses were performed in the safety
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52 171 analysis set (randomized patients without critical Good Clinical Practice violations who took
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54 172 >1 dose of study drug). The analyses were prespecified exploratory evaluations of outcomes
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56 173 according to age and sex, with events reported from randomization up to the end-of-study
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58 174 visit. Stratified Cox proportional hazards models,[27,28] including stratification factors:
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3 175 geographic region, eGFR and albuminuria category at screening, history of CV disease, and
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5 176 study, were used for the analysis of time-to-event clinical outcomes. The *P*-values for
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7 177 interaction between the treatment group (finerenone or placebo) and each baseline subgroup
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9 178 (age or sex) were based on stratified Cox proportional hazards models, accounting for the
10
11 179 treatment effect, the subgroup effect, and their interaction.
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14 180

15 181 Changes in UACR and eGFR over time were assessed using a linear mixed-model analysis
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17 182 accounting for repeated measurements over time. The least-squares mean ratio and
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19 183 absolute change from baseline were estimated from the models for changes in UACR and
20
21 184 eGFR, respectively. The 2-slope, linear spline, mixed-model, repeated measure method[29]
22
23 185 was used to estimate the rate of change in eGFR across time, specifically total (annualized
24
25 186 rate of change in eGFR from baseline to permanent discontinuation or end of study) and
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27 187 chronic (from month 4 to permanent discontinuation or end of study) eGFR slopes. To
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29 188 account for possible nonlinear effects of age on clinical outcomes, age was modeled with
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31 189 cubic splines with 3 knots in Cox proportional hazards models, to produce plots of the hazard
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33 190 ratios (HRs) and 95% confidence interval as functions of age and sex.
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38 191 **Patients and public involvement**

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40 192 No patient or public involvement in the current study.
41
42

43 193 **RESULTS**

44 45 46 47 194 **Patients**

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49 195 FIDELITY included 13 026 patients.[23] Median follow-up was 3 years (interquartile range
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51 196 2.3–3.8).[23] Mean age at baseline was 64.8 years (standard deviation 9.5), with 45.2%,
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53 197 40.1%, and 14.7% of patients aged <65, 65–74, and ≥75 years at baseline, respectively.
54
55 198 Most patients (69.8%) were male; 2.5% were premenopausal females, and 27.8% were
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57 199 postmenopausal females. Patients were distributed evenly between treatment arms within
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59 200 age and sex subgroups (**eTable 1**).
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3 201 **Baseline characteristics**
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5 202 Baseline characteristics were similar across age subgroups except for some key differences
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7 203 (**Table 1**). The overall FIDELITY population was predominantly White (68.1%), the proportion
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9 204 of which increased with age. Mean eGFR was 64, 54, and 48 mL/min/1.73 m² in patients
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11 205 aged <65, 65–75, and ≥75 years, respectively. Median UACR was 650, 439, and 332 mg/g in
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13 206 patients aged <65, 65–75, and ≥75 years, respectively. History of CV disease was more
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15 207 common in the ≥75 years group; this trend was also observed for atrial fibrillation/atrial flutter.
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17 208 Baseline characteristics in sex subgroups are shown in **Table 1**.
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209 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, <i>n</i> (%)	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, <i>n</i> (%)	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, <i>n</i> (%) ^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.

215 Efficacy

216 CV composite outcome by age

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

225
226 HHF event rates were numerically lower with finerenone than placebo in all age subgroups
227 (**Figure 1A**). The effect of finerenone on HHF risk reduction was consistent across age
228 subgroups, with no significant heterogeneity observed ($P_{\text{interaction}}=.70$).

229 CV composite outcome by sex

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

237

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

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3 241 HHF with finerenone versus placebo ($P_{\text{interaction}}=.02$), and the effect appeared to be more
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5 242 pronounced in males than premenopausal/postmenopausal females (**Figure 1B**). These
6
7 243 results persisted after adjustment for differences in baseline age, body mass index, systolic
8
9 244 blood pressure, hemoglobin, eGFR, UACR, smoking history, and history of atrial fibrillation
10
11 245 between sex subgroups ($P_{\text{interaction}}=.02$).

14 246 Kidney composite outcome by age

16
17 247 Kidney composite event rates were lower with finerenone than placebo in the <65 years and
18
19 248 the 65–74 years groups but were similar in the ≥ 75 years group (**Figure 2A**). The effect of
20
21 249 finerenone on reducing the risk of the kidney composite outcome was consistent across age
22
23 250 subgroups, with no significant heterogeneity detected ($P_{\text{interaction}}=.51$) and no evidence of
24
25 251 treatment effect modification when age was modeled as a continuous variable ($P_{\text{interaction}}=.77$).
26
27 252 The trend of HR as function of age was modeled with cubic splines (**eFigure 3A**).

30 253 Kidney composite outcome by sex

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32
33 254 Kidney composite event rates were lower with finerenone than placebo in males but were
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35 255 similar in premenopausal and postmenopausal females (**Figure 2B**). There was no
36
37 256 significant heterogeneity in the effect of finerenone on reducing the risk of the kidney
38
39 257 composite outcome across sex subgroups ($P_{\text{interaction}}=.85$). When age was modeled with cubic
40
41 258 splines by sex subgroups, the effect of finerenone suggests trends similar to overall results in
42
43 259 males and females across all age groups (**eFigure 3B**, **eFigure 3C**). Age distribution by sex
44
45 260 is demonstrated in **eFigure 3D**.

48 261 Effect of finerenone on markers of kidney function and damage by age and sex

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50
51 262 Finerenone significantly attenuated the least-squares mean change in eGFR from month 4 to
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53 263 end of treatment (chronic eGFR slope) compared with placebo across all age ($P<.0001$ for all
54
55 264 3 subgroups) (**Figure 3**) and sex subgroups (**eFigure 4**). Finerenone reduced UACR over
56
57 265 time compared with placebo regardless of age and sex (**eFigure 5**).

266 **Safety**

267 The incidence of any AE was similar between treatment groups irrespective of age or sex
268 (**eTable 2**). There were more drug-related AEs with finerenone than placebo in age and sex
269 subgroups except premenopausal females, where the incidence was similar. AEs leading to
270 drug discontinuation were more frequent in patients given finerenone than placebo (6.4%
271 and 5.4%, respectively), with higher incidences in the 65–74 and ≥75 years groups than the
272 <65 years group; there were more AEs leading to drug discontinuation with finerenone than
273 placebo in males and premenopausal females but not in postmenopausal females.

274

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

279

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

285

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

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3 293 2.2 [1.2–4.3], 2.8 [1.7–4.7], and 4.4 [1.8–10.8], respectively; **eFigure 6**). Treatment-emergent
4
5 294 serum potassium levels >5.5 mmol/L and >6.0 mmol/L were more frequent with finerenone
6
7 295 than placebo, being consistent across all age and sex subgroups. The incidence of
8
9 296 gynecomastia in males was the same with finerenone (0.2%) and placebo (0.2%) across all
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11 297 ages.

14 298 **DISCUSSION**

17 299 The findings of this post hoc analysis suggest that finerenone reduced the risk of CV and
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19 300 kidney composite outcomes versus placebo across all age and sex subcategories. In
20
21 301 FIDELITY, HHF was the main driver of CV benefit with finerenone[23]; lower incidences of
22
23 302 HHF with finerenone versus placebo were observed in this analysis across all age
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25 303 subgroups, with some differences noted between sex subgroups. Moreover, the incidences
26
27 304 of any AEs or SAEs were similar between the treatment groups regardless of age and sex.

30 305
31
32 306 The current results are supported by findings from a pharmacokinetics (PK) analysis based
33
34 307 on FIDELIO-DKD and FIGARO-DKD data, in which both age and sex were tested as
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36 308 covariates for a population PK model, and their effect on finerenone exposure was not
37
38 309 significant, suggesting a lack of influence of these factors on the PK of the drug.[30]

40 310 Additionally, the results for the CV outcome in this analysis are similar to findings from other
41
42 311 studies of MRAs in HF. In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure
43
44 312 with an Aldosterone Antagonist), age did not affect the efficacy of spironolactone in patients
45
46 313 with HF with reduced ejection fraction (primary composite outcome: CV death, aborted
47
48 314 cardiac arrest and HHF; secondary outcomes included CV death, all-cause death and
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50 315 HHF).[31] Moreover, in analyses of HF studies (RALES [Effect of Spironolactone on
51
52 316 Morbidity and Mortality in Patients with Severe Heart Failure], EMPHASIS-HF [Eplerenone in
53
54 317 Patients with Systolic Heart Failure and Mild Symptoms], and TOPCAT), MRAs reduced
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56 318 morbidity and mortality in elderly patients,[32] demonstrating a consistent benefit regardless
57
58 319 of sex.[33] In contrast to our results, female sex was associated with poorer kidney outcomes

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3 320 versus male sex in patients receiving a steroidal MRA for bilateral primary aldosteronism.[34]
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5 321 The MR can be activated by different drivers in different diseases; MR activation in diabetes
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7 322 is driven by additional factors other than high aldosterone in comparison with primary
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9 323 aldosteronism, which may account for differences in outcomes observed across different
10

11 324 indications.[35]
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13 325
14

15 326 In this study, the elderly population had higher risk of certain AEs including hypotension, AEs
16

17 327 leading to discontinuation, and death. Hypotension occurred more frequently in the
18

19 328 finerenone group but did not seem to substantially affect related clinical outcomes.
20

21 329 Hyperkalemia was more prevalent with finerenone but was generally similar across age and
22

23 330 sex. In a FIDELIO-DKD subanalysis, younger age and female sex were independent risk
24

25 331 factors for hyperkalemia (>6.0 mmol/L).[36] Similar findings for age were observed in
26

27 332 TOPCAT post hoc data for patients with HF.[31] Steroidal MRAs have been associated with
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29 333 gynecomastia in males,[37,38] which was not observed in this study, most likely because
30

31 334 finerenone has no detectable affinity for androgen receptors.[38]
32

33 335
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35 336 Preclinical data suggest that different molecular mechanisms drive endothelial dysfunction in
36

37 337 male and female mice[39,40] and that increased age and male sex are associated with MR
38

39 338 overactivation, which is linked to vascular stiffness and endothelial dysfunction.[41,42] In
40

41 339 human aortic smooth muscle cells, MR expression increased with age, leading to epigenetic
42

43 340 changes associated with increased vascular stiffness. These effects were reversed with MR
44

45 341 inhibition.[43] In vitro, MR expression in the whole aortae and early passage aortic vascular
46

47 342 smooth muscle cells was increased in aged (30 months) versus adult (8 months) rat
48

49 343 cells.[41] In a preclinical mouse model, aortic stiffness occurred earlier in male than female
50

51 344 mice and correlated with the timing of increased aortic MR expression; vascular stiffness was
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53 345 prevented in smooth muscle cell MR-deficient mice.[42] These data suggest that elderly
54

55 346 males may derive the greatest benefit from finerenone; indeed, in this analysis, finerenone-
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57 347 treated males had lower risk of the CV composite outcome and HHF versus placebo across
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3 348 age groups, including >75 years. Moreover, statistical heterogeneity was observed for HHF
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5 349 by sex, persisting after adjustment for differences in baseline characteristics, which might
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7 350 suggest a more pronounced effect of finerenone on HHF reduction in the male subgroup
8
9 351 compared with the 2 female subgroups. However, because of the small sample size of the
10
11 352 sex subgroups (especially that of the premenopausal female subgroup), definitive
12
13 353 conclusions cannot be reached based on this finding.
14

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16 354

17
18 355 In this study, markers of kidney damage (eGFR decline and UACR) were reduced with
19
20 356 finerenone in age subgroups; however, no benefit on kidney outcomes was observed in the
21
22 357 >75 years age group. The small sample size of this subgroup precluded definitive
23
24 358 conclusions, which may be accounted for by the slowing rate of CKD progression with
25
26 359 advancing age.[44,45]
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30 361 Limitations include the study being a post hoc analysis and the chosen age categories not
31
32 362 being predefined. In addition, patients may have initiated other treatments during the study.
33
34 363 Sample size and number of events for females, particularly premenopausal females, were
35
36 364 small. Therefore, there is uncertainty around the estimates and the analysis was
37
38 365 underpowered to draw meaningful conclusions in this subgroup. Results for premenopausal
39
40 366 females versus postmenopausal females/males should be interpreted with caution because
41
42 367 age may partly account for differences observed; the average age of premenopausal females
43
44 368 was ~45 years old compared with postmenopausal females (~66 years old) and males
45
46 369 (~65 years old) (**Table 1**). As such, these groups had different baseline characteristics.
47
48 370 Higher baseline mean eGFR and median UACR, and lower history of CV comorbidities and
49
50 371 hypotension were observed in premenopausal females versus males and postmenopausal
51
52 372 females. Additionally, the study design and tests performed may have been underpowered to
53
54 373 address the research questions. Furthermore, FIDELITY limitations, mainly the small
55
56 374 proportion of Black patients and exclusion of patients with nonalbuminuric CKD, were
57
58 375 present in this analysis.
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377 In conclusion, this post hoc FIDELITY analysis suggests that finerenone effectively lowers
378 the risk of clinically important cardiovascular and kidney outcomes in patients with CKD and
379 T2D across ages and sexes, with a potentially more pronounced effect on HHF in males than
380 in females. No new safety concerns were identified in those aged >65 years or by sex.

381

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391 SB prepared the initial analysis; SB, MEFC, RB, SDA, GLB, GF, PR, LMR, AEF, PK, AL, MB,
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38
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42
43 427 Vifor/Relypsa; he also holds a patent for site-specific delivery of eplerenone to the
44
45 428 myocardium (US patent #9931412) and a provisional patent for histone-acetylation-
46
47 429 modulating agents for the treatment and prevention of organ injury (provisional patent US
48
49 430 63/045,784).

431 DATA SHARING STATEMENT

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

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

441 Interested researchers can use www.vivli.org to request access to anonymized patient-level
442 data and supporting documents from clinical studies to conduct further research that can
443 help advance medical science or improve patient care. Information on the Bayer criteria for
444 listing studies and other relevant information is provided in the member section of the portal.
445 Data access will be granted to anonymized patient-level data, protocols, and clinical study
446 reports after approval by an independent scientific review panel. Bayer is not involved in the
447 decisions made by the independent review panel. Bayer will take all necessary measures to
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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 $\geq 57\%$ 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.

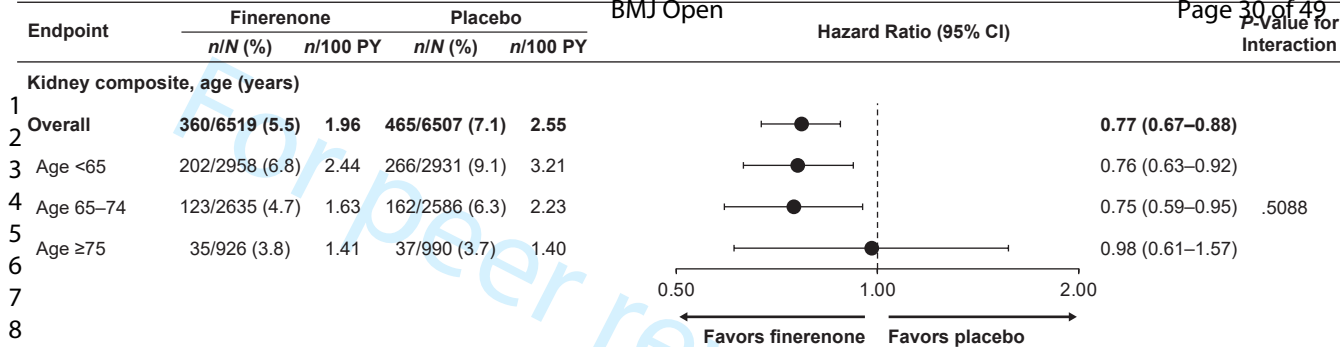
A

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

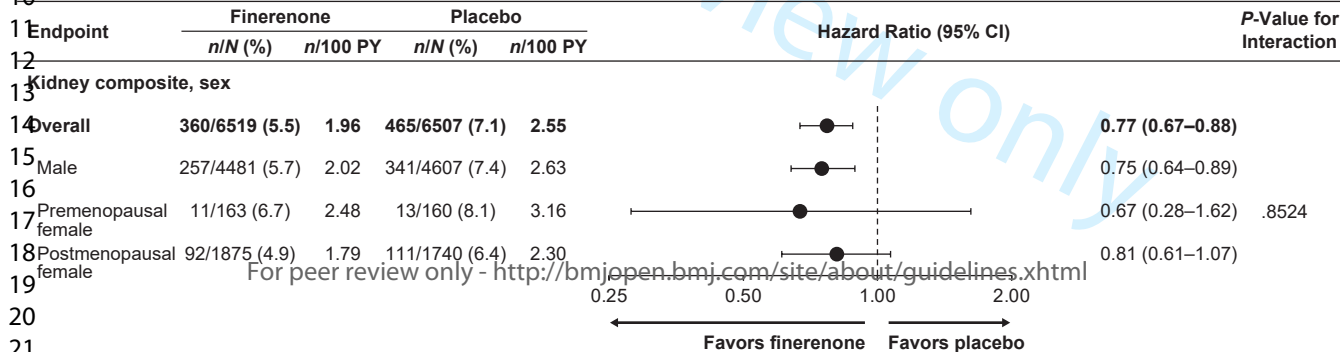
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Endpoint	Finerenone		Placebo		Hazard Ratio (95% CI)	P-Value for Interaction
	n/N (%)	n/100 PY	n/N (%)	n/100 PY		
CV composite, sex						
19 Overall	825/6519 (12.7)	4.34	939/6507 (14.4)	5.01	0.86 (0.78–0.95)	
20 Male	579/4481 (12.9)	4.39	675/4607 (14.7)	5.08	0.86 (0.77–0.96)	
21 Premenopausal female	11/163 (6.7)	2.29	12/160 (7.5)	2.62	0.89 (0.35–2.27)	.9942
22 Postmenopausal female	235/1875 (12.5)	4.38	252/1740 (14.5)	5.03	0.87 (0.73–1.05)	
HHF, sex						
25 Overall	256/6519 (3.9)	1.31	325/6507 (5.0)	1.68	0.78 (0.66–0.92)	
26 Male	163/4481 (3.6)	1.20	244/4607 (5.3)	1.78	0.66 (0.54–0.81)	
28 Premenopausal female	5/163 (3.1)	1.02	4/160 (2.5)	0.85	1.39 (0.33–5.93)	.0245
29 Postmenopausal female	88/1875 (4.7)	1.63	117/1740 (6.7)	2.14	1.06 (0.78–1.44)	

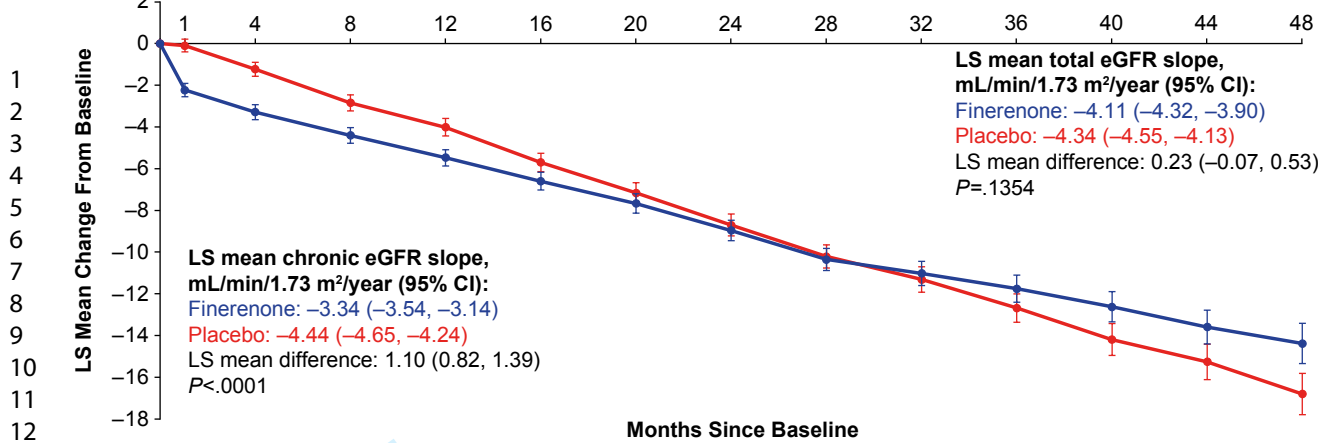
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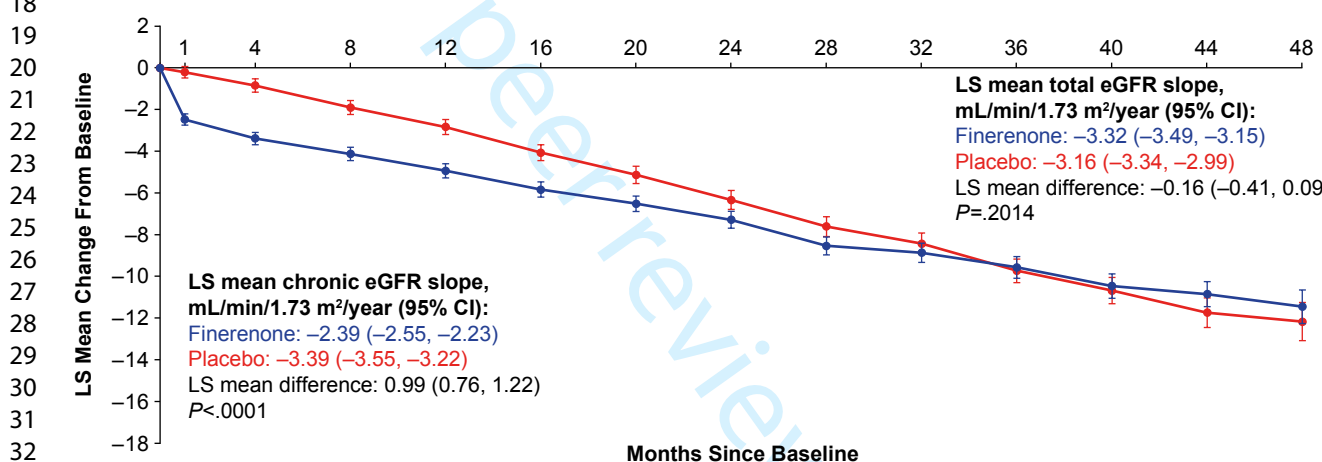
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Number of Subjects at Visit

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

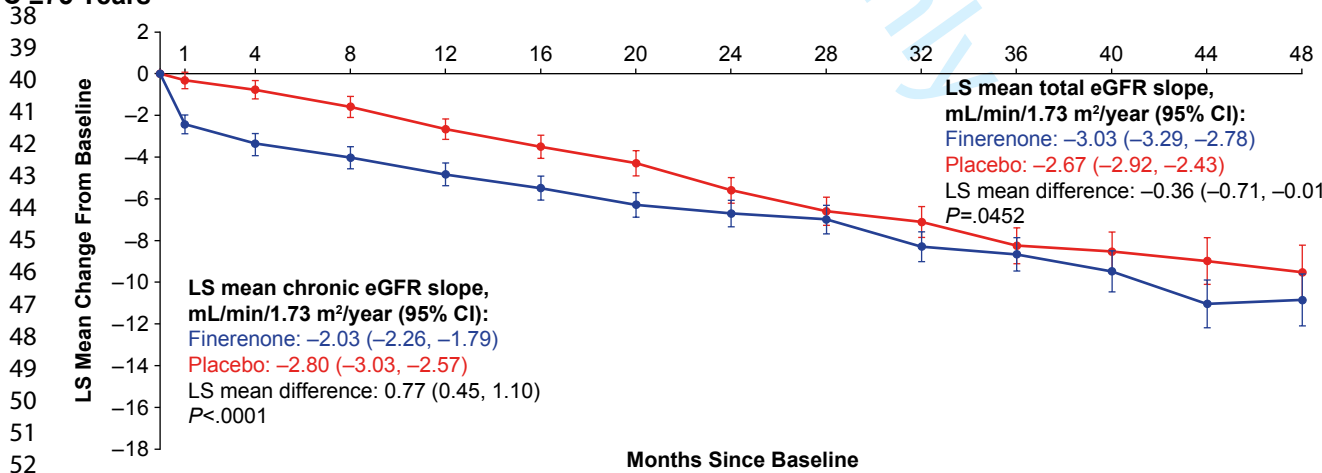
B 65 to 74 Years



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	696	618	491	359	281	204	117

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

Contents

Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials 1

Supplementary Tables and Figures 2

eTable 1. Patient Baseline Characteristics According to Age and Sex Stratified by Treatment Group 2

eTable 2. Treatment-Emergent AEs According to Age and Sex 6

eFigure 1. Analysis of CV composite outcome and subcomponents according to (A) age and (B) sex 8

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). 11

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). 12

eFigure 4. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex 13

eFigure 5. LS mean ratio to baseline UACR over time by age and sex 14

eFigure 6. Relative risk of treatment-emergent hyperkalemia causing permanent discontinuation of study drug by age and sex 15

eFigure 7. FIDELITY CONSORT diagram. 16

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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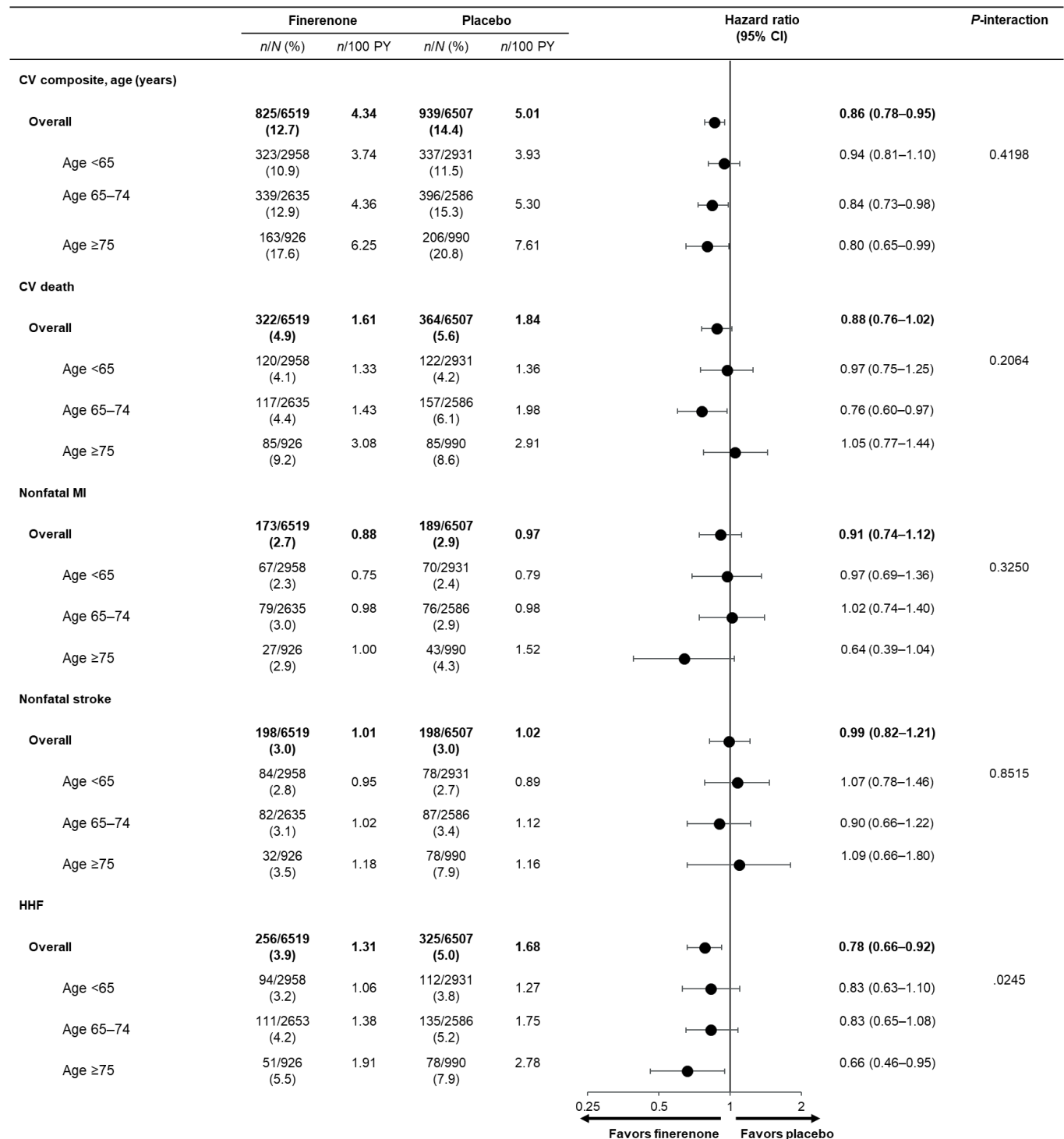
Serum potassium >5.5 mmol/L	1075/6402 (16.8)	470/6370 (7.4)	444/2904 (15.3)	233/2871 (8.1)	460/2585 (17.8)	180/2529 (7.1)	171/913 (18.7)	57/970 (5.9)	720/4403 (16.4)	308/4523 (6.8)	16/159 (10.1)	8/154 (5.2)	339/1840 (18.4)	154/1693 (9.1)
Serum potassium >6.0 mmol/L	211/6439 (3.3)	80/6413 (1.2)	90/2926 (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.

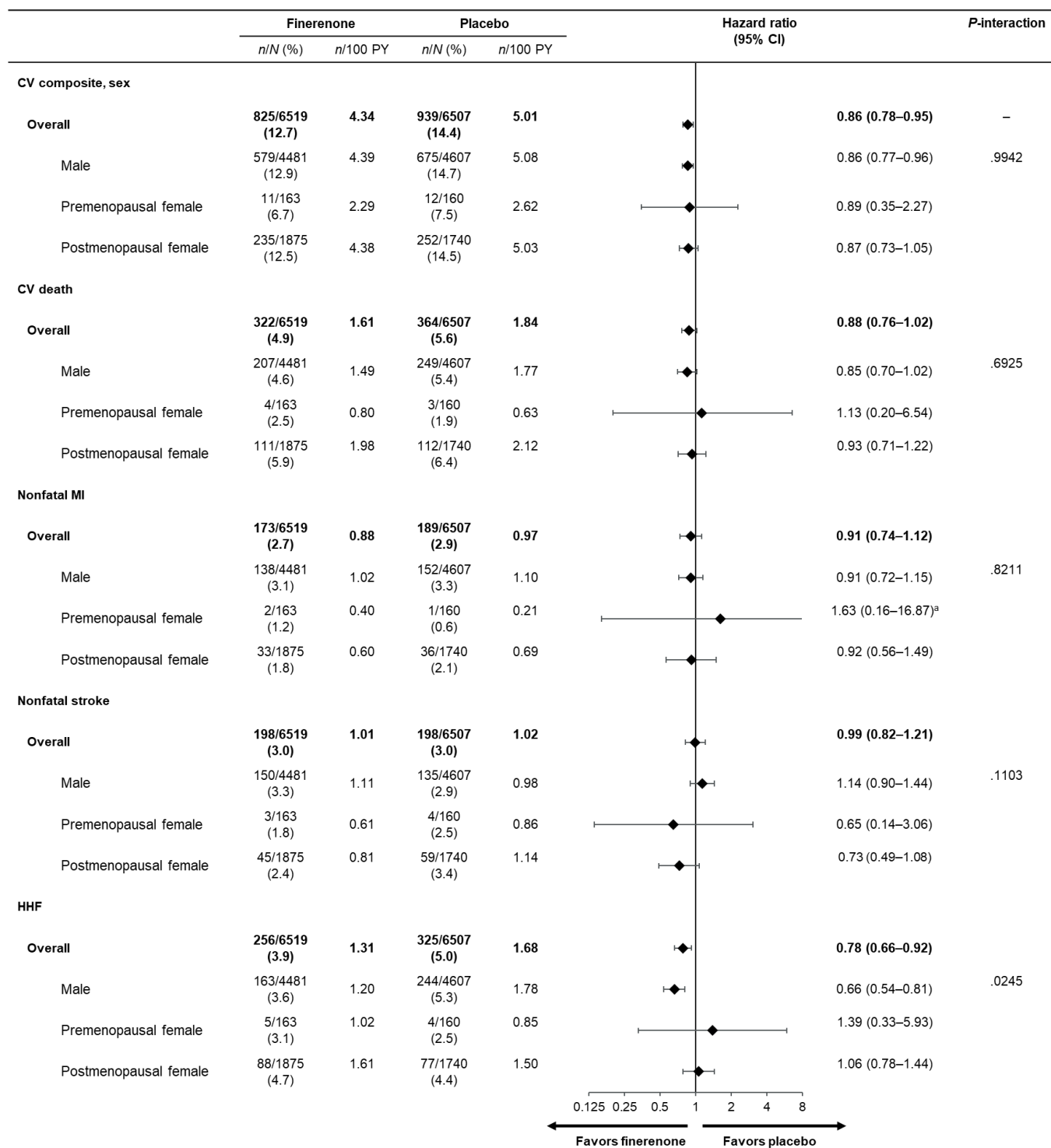
^a The “*n*” numerator represents the number of patients at risk with ≥ 1 treatment-emergent laboratory assessment meeting the criterion. The “*N*” denominator represents all patients at risk for a treatment-emergent laboratory abnormality. Patients had both a baseline and postbaseline treatment-emergent 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.



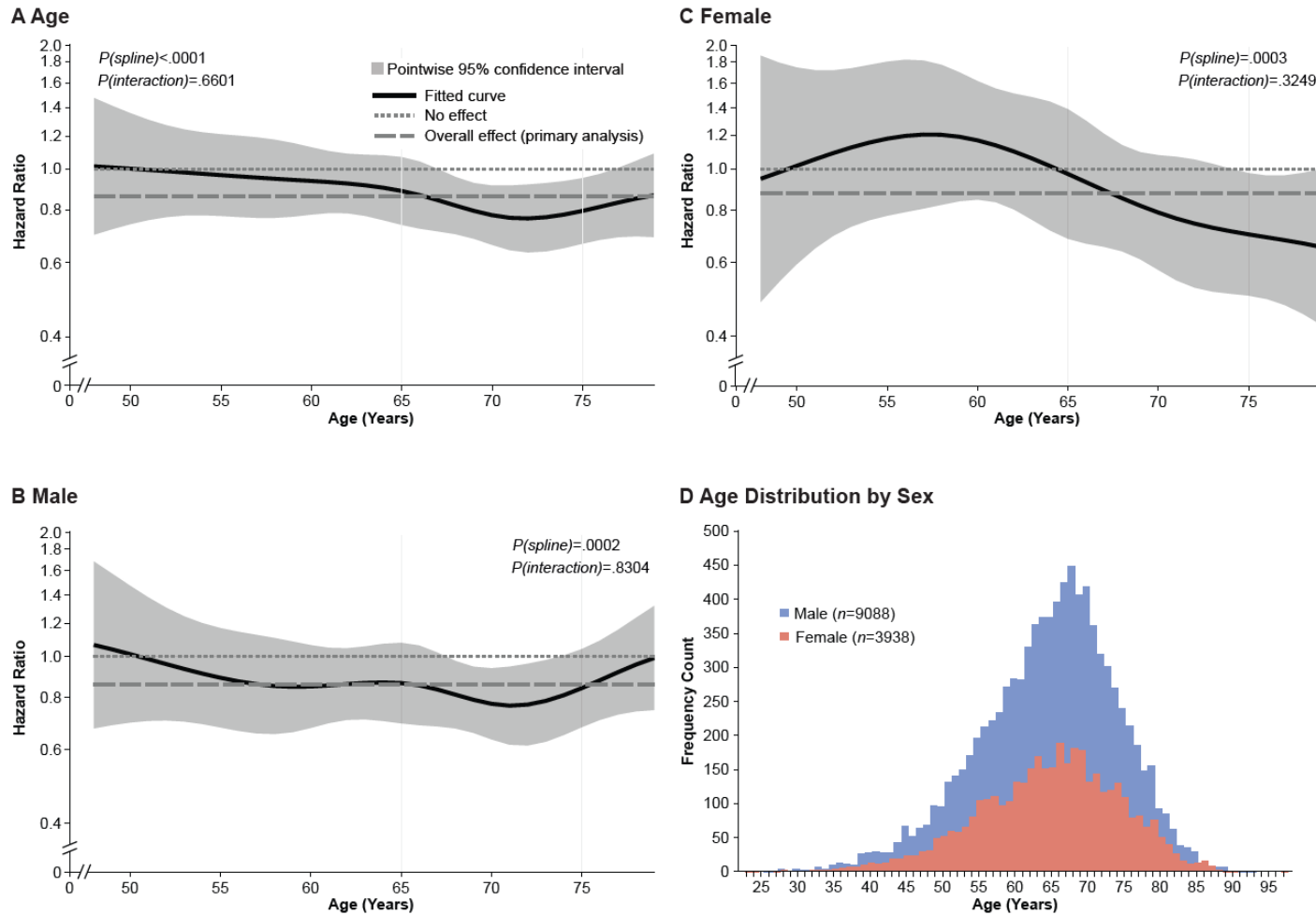
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3 A stratified Cox proportional hazards model including treatment was calculated separately by
4 subgroup category. The $P_{\text{interaction}}$ is based on a stratified Cox proportional hazards model including
5 treatment, subgroup, and treatment by subgroup interaction.
6
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8 CV composite outcome includes CV death, nonfatal MI, nonfatal stroke, or HHF.

9
10 CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; MI = myocardial
11 infarction; PY = patient-years.
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16 ^a An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts
17 and/or convergence issues.
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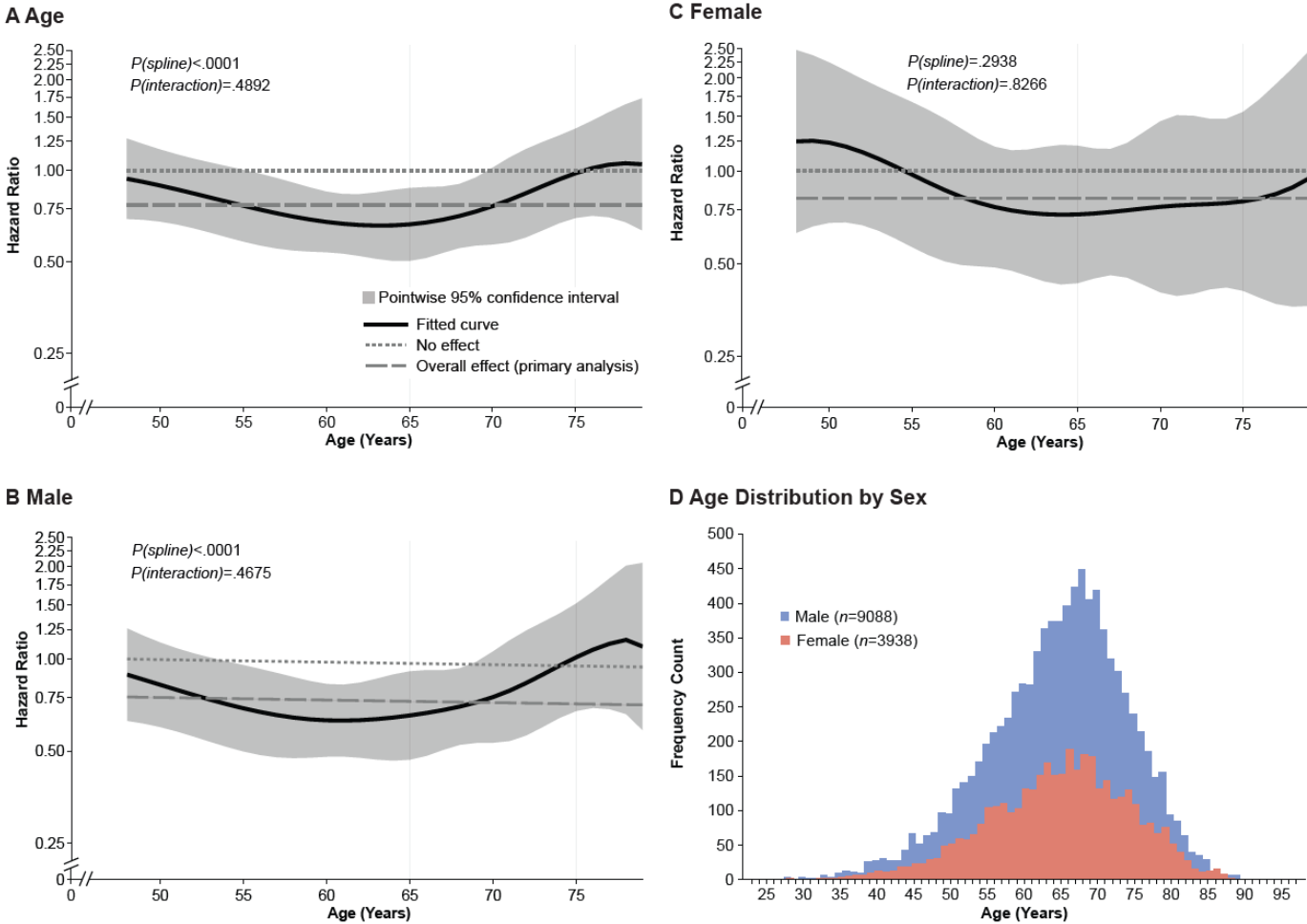
eFigure 2. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for CV composite outcome by age (A), spline for hazard ratio of CV composite outcomes by sex (B, C), and age distribution by sex (D).



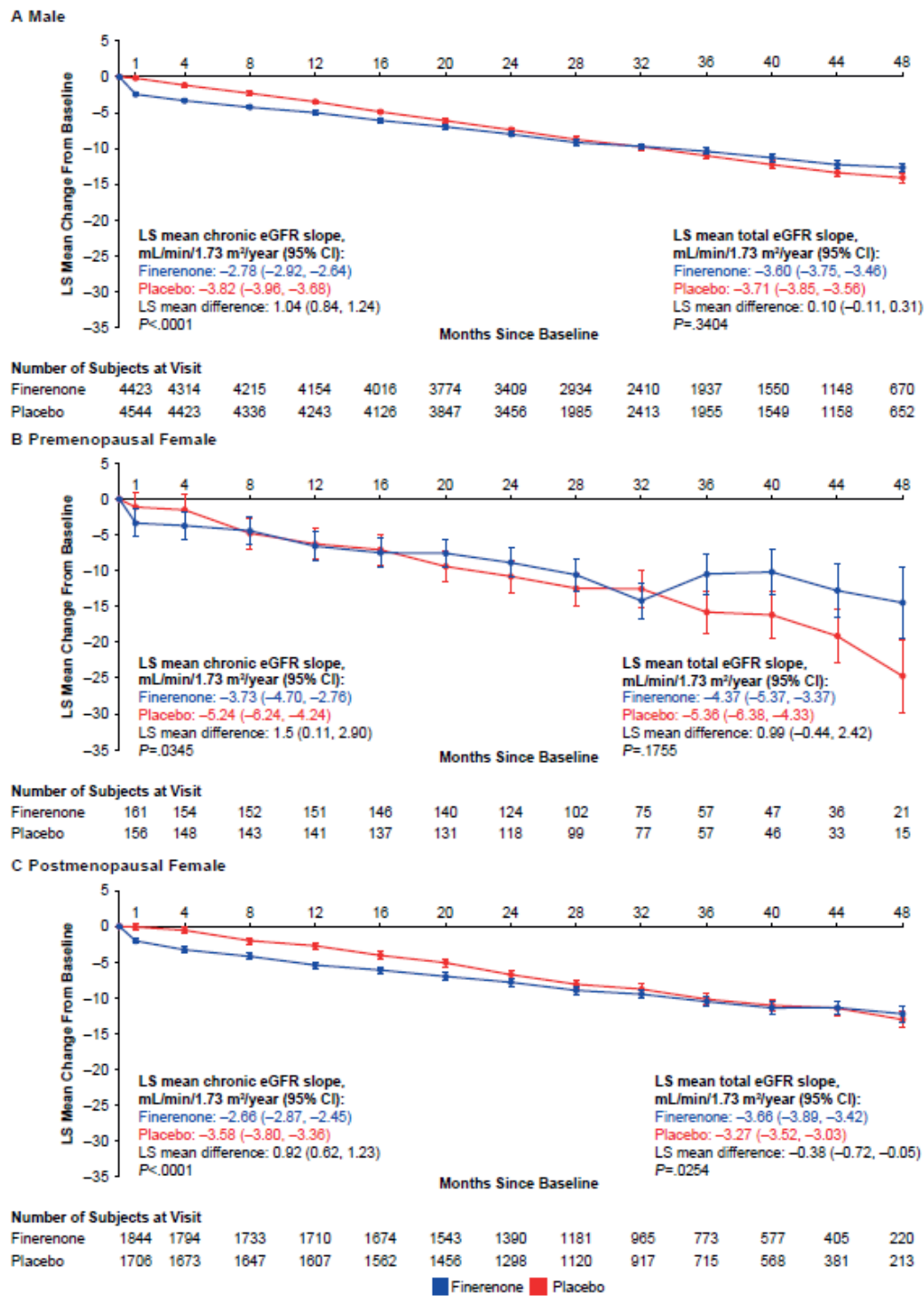
CV = cardiovascular.

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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).



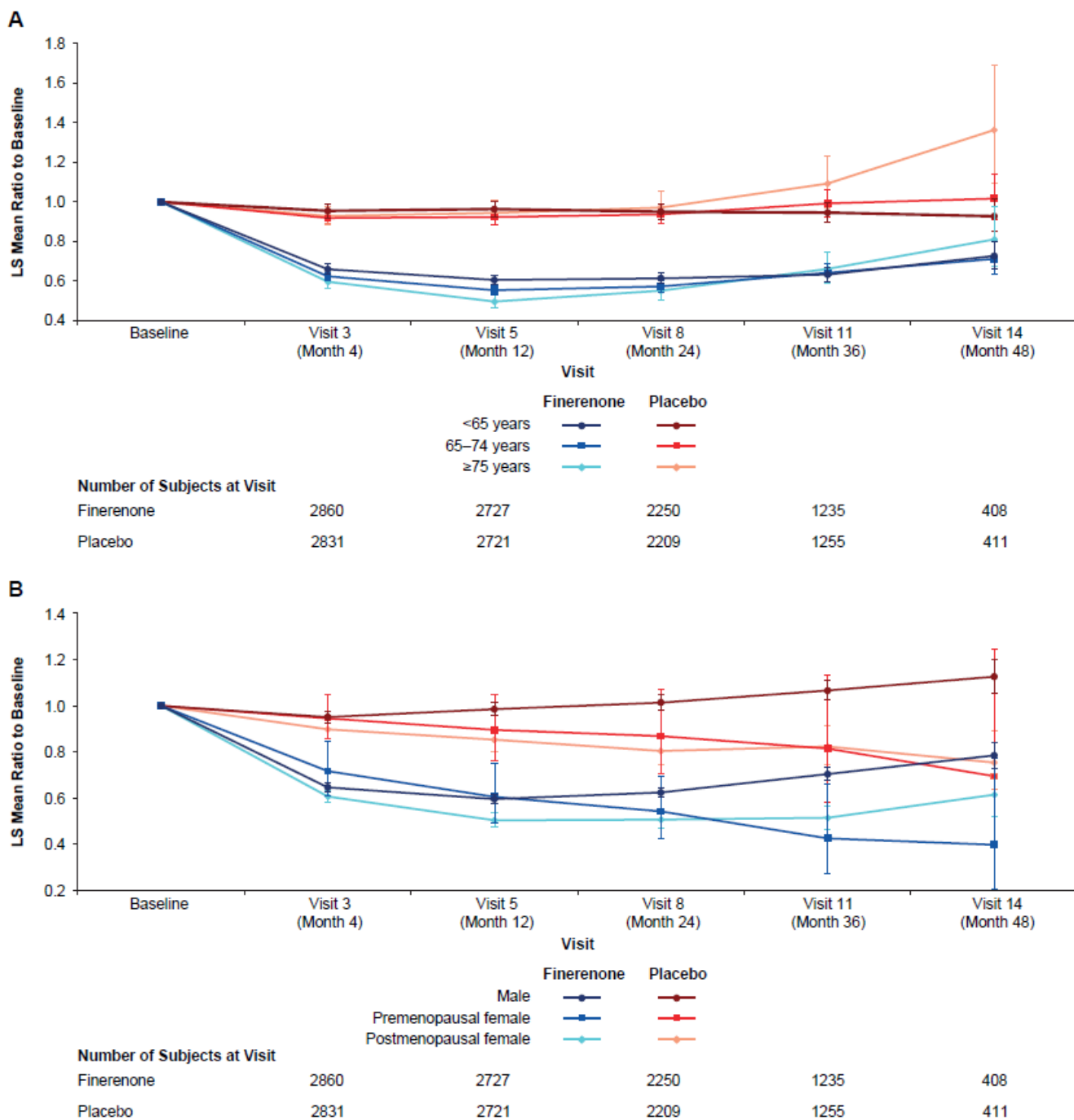
eFigure 4. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.



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

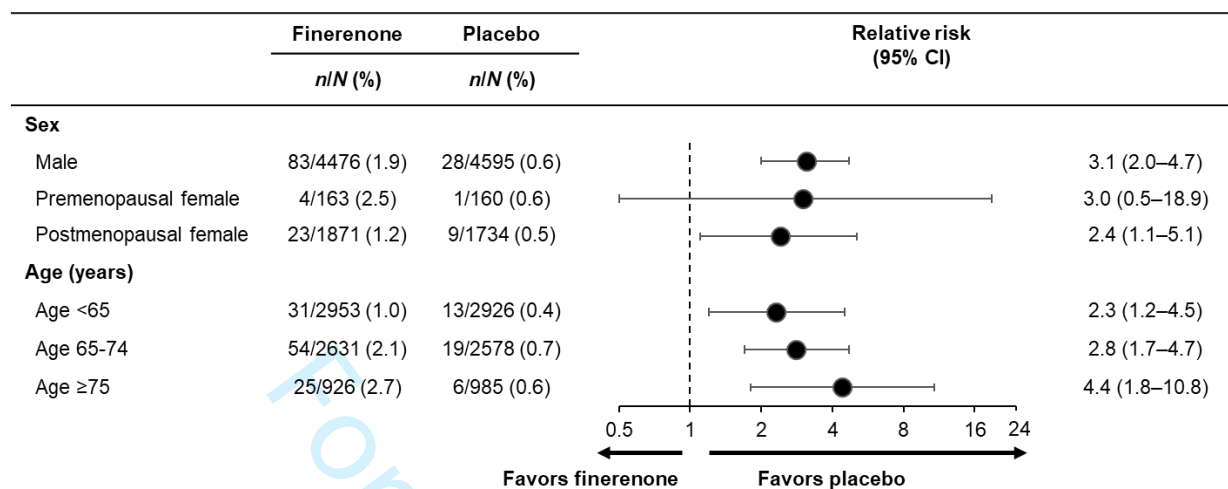
CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

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

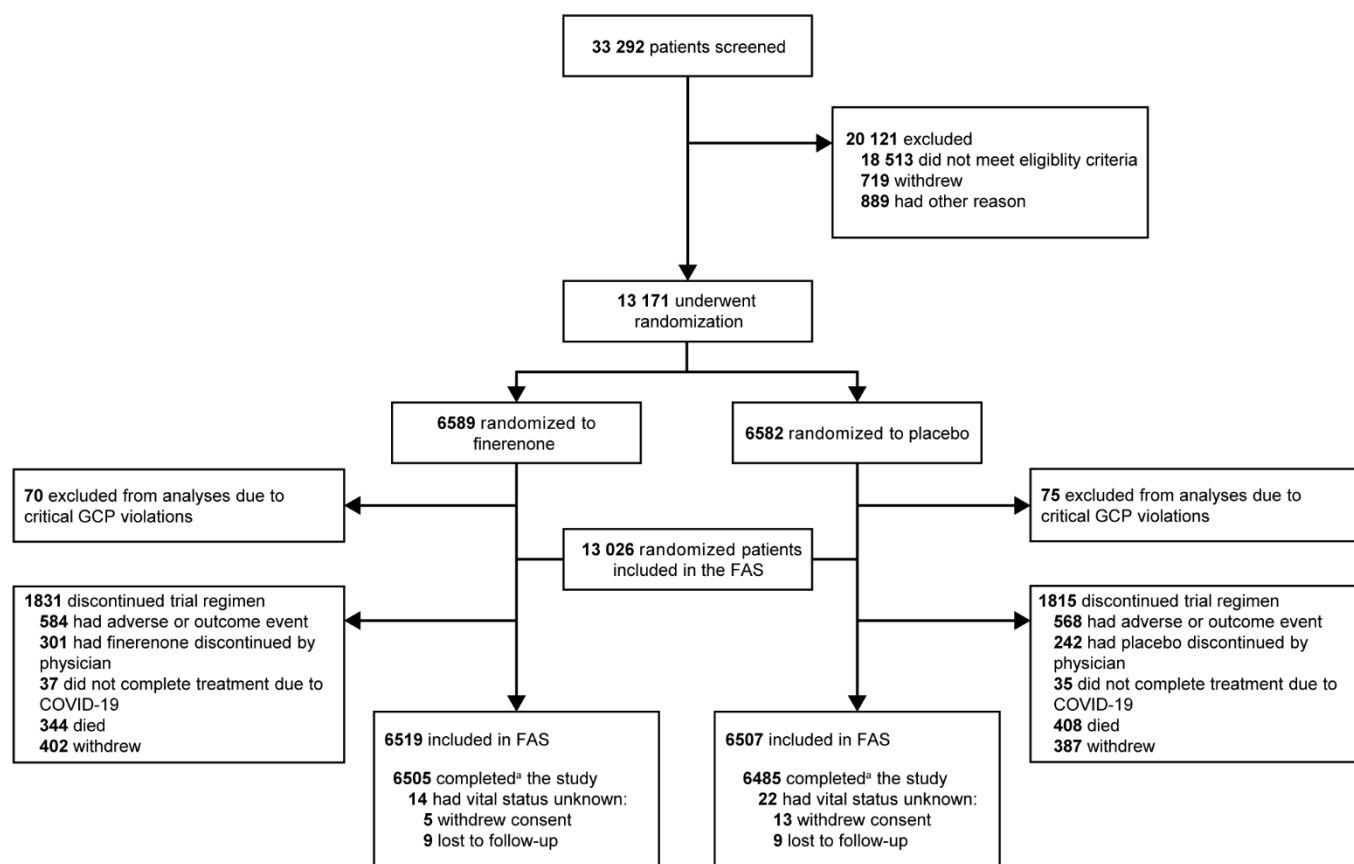


LS = least-squares; UACR = urine albumin-to-creatinine ratio.

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

1		8b	Type of randomisation; details of any restriction (such as blocking and block size)	Reported previously
2				
3	Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),	Reported previously
4	concealment		describing any steps taken to conceal the sequence until interventions were assigned	Reported previously
5	mechanism			
6				
7	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Reported previously
8				
9	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	Reported previously
10				
11		11b	If relevant, description of the similarity of interventions	Reported previously
12				
13				
14	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
15		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
16				
17	Results			
18	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	8-11; eTable 1
19	diagram is strongly		were analysed for the primary outcome	
20	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	eFigure 7
21	Recruitment	14a	Dates defining the periods of recruitment and follow-up	Reported previously
22				
23		14b	Why the trial ended or was stopped	Reported previously
24				
25				
26				
27	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1; eTable 1
28				
29				
30	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
31				
32	Outcomes and	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
33	estimation			Figures 1-2
34				eFigure 1
35				
36		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
37	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	eFigures 2-5
38				
39				
40	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14-15
41				
42				

Discussion

1				
2	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	17
3	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Reported
4				previously
5				15-18
6	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
7	Other information			
8	Registration	23	Registration number and name of trial registry	4
9	Protocol	24	Where the full trial protocol can be accessed, if available	Primary
10				publications
11				with full
12				protocols are
13				cited (6)
14				19-20
15				
16	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	
17				

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19 *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

20 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.

21 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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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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Complete List of Authors:	Bansal, Shweta ; The University of Texas Health Science Center at San Antonio, Department of Medicine Canziani, M. E. F.; Univ Fed Sao Paulo Birne, Rita; Centro Hospitalar Lisboa Ocidental, Department of Nephrology; University of Lisbon, Nova Medical School Anker, Stefan; Charité Universitätsmedizin, Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center for Regenerative Therapies (BCRT) Bakris, George; University of Chicago, Hypertension Center Filippatos, Gerasimos; National and Kapodistrian University of Athens Rossing, Peter; Steno Diabetes Center AS; University of Copenhagen, Department of Clinical Medicine Ruilope, Luis M ; Institute of Research imas12, Cardiorenal Translational Laboratory and Hypertension Unit; Hospital Universitario 12 de Octubre, CIBER-CV Farjat, Alfredo; Bayer plc Kolkhof, Peter; Cardiovascular Precision Medicines Bayer AG Lage, Andrea; Bayer SA Brinker, Meike; Cardiology and Nephrology Clinical Development Pitt, B; University of Michigan
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Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Risk Factors, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, DIABETES & ENDOCRINOLOGY, Cardiovascular Disease

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4 1 **Finerenone Cardiovascular and Kidney Outcomes by Age**
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7 2 **and Sex: FIDELITY Post Hoc Analysis of Two Phase 3,**
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10 3 **Multicenter, Double-Blind Trials**

13 4 **Author(s)**

15 5 Shweta Bansal, MD,¹ Maria E.F. Canziani, MD,² Rita Birne, MD,^{3,4} Stefan D. Anker, MD,
16 6 PhD,⁵ George L. Bakris, MD,⁶ Gerasimos Filippatos, MD,⁷ Peter Rossing, MD, DMSc,^{8,9} Luis
17 7 M. Ruilope, MD,¹⁰⁻¹² Alfredo E. Farjat, PhD,¹³ Peter Kolkhof, PhD,¹⁴ Andrea Lage, MD,¹⁵
18 8 Meike Brinker, MD,¹⁶ Bertram Pitt, MD¹⁷

23 9
24
25
26 10 **Institution(s)**

27 11 ¹Division of Nephrology, Department of Medicine, University of Texas Health San Antonio,
28 12 San Antonio, Texas, USA

29 13 ²Nephrology Division, Federal University of São Paulo, São Paulo, Brazil

30 14 ³Department of Nephrology, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal

31 15 ⁴Nova Medical School, University of Lisbon, Lisbon, Portugal

32 16 ⁵Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center
33 17 for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK)
34 18 partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany

35 19 ⁶Department of Medicine, University of Chicago Medicine, Chicago, Illinois, USA

36 20 ⁷National and Kapodistrian University of Athens, School of Medicine, Department of
37 21 Cardiology, Attikon University Hospital, Athens, Greece

38 22 ⁸Steno Diabetes Center Copenhagen, Gentofte, Denmark

39 23 ⁹Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

40 24 ¹⁰Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12,
41 25 Madrid, Spain

42 26 ¹¹CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain

43 1

1
2
3 27 ¹²Faculty of Sport Sciences, European University of Madrid, Madrid, Spain
4
5 28 ¹³Research and Development, Clinical Data Sciences and Analytics, Bayer PLC, Reading,
6
7 29 UK
8
9 30 ¹⁴Research and Early Development, Cardiovascular Precision Medicines, Bayer AG,
10
11 31 Wuppertal, Germany
12
13 32 ¹⁵Cardiology and Nephrology Clinical Development, Bayer SA, São Paulo, Brazil
14
15 33 ¹⁶Cardiology and Nephrology Clinical Development, Bayer AG, Wuppertal, Germany
16
17 34 ¹⁷Department of Medicine, University of Michigan School of Medicine, Ann Arbor, Michigan,
18
19 35 USA
20
21
22
23

24 37 **Contact information for corresponding author:**

25
26 38 Name: Shweta Bansal, MD, FASN
27
28 39 Address: Department of Medicine, Division of Nephrology, Joe R. & Teresa Lozano Long
29
30 40 School of Medicine, UT Health, San Antonio, TX, USA
31
32 41 7703 Floyd Curl Drive, MSC 7882
33
34 42 San Antonio, TX-78229, USA
35
36 43 Phone no: 210-422-0438
37
38 44 Fax no: 210-567-4712
39
40 45 Email: bansals3@uthscsa.edu
41
42
43
44

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52
53 51 **No. of figures and tables:** 4 of 5 tables/figures

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55 52 **No. of references:** 45
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53 ABSTRACT

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

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

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

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

61 **Interventions:** Randomized 1:1; finerenone or placebo.

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

66 **Results:** Mean age was 64.8 years; 45.2%, 40.1%, and 14.7% were aged <65 , 65–74, and
67 ≥ 75 years, respectively; 69.8% were male. Cardiovascular benefits of finerenone versus
68 placebo were consistent across age (hazard ratio [95% confidence interval]: 0.94 [0.81–1.10]
69 [<65 years], 0.84 [0.73–0.98] [65–74 years], 0.80 [0.65–0.99] [≥ 75 years]; $P_{\text{interaction}}=.42$) and
70 sex (hazard ratio [95% confidence interval]: 0.86 [0.77–0.96] [male], 0.89 [0.35–2.27]
71 [premenopausal female], 0.87 [0.73–1.05] [postmenopausal female]; $P_{\text{interaction}}=.99$). HHF
72 risk reduction was not modified by age ($P_{\text{interaction}}=.70$) but appeared more pronounced in
73 males ($P_{\text{interaction}}=.02$). Kidney events were reduced with finerenone versus placebo in ages
74 <65 and 65–74 but not ≥ 75 ; no heterogeneity in treatment effect was observed
75 ($P_{\text{interaction}}=.51$). In sex subgroups, finerenone consistently reduced kidney events
76 ($P_{\text{interaction}}=.85$). Finerenone reduced albuminuria and eGFR decline regardless of age and
77 sex. Hyperkalemia increased with finerenone, but discontinuation rates were $<3\%$ across
78 subgroups. Gynecomastia in males was uncommon across age subgroups and identical
79 between treatment groups.

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3 80 **Conclusions:** Finerenone improved cardiovascular and kidney outcomes with no significant
4
5 81 heterogeneity between age and sex subgroups; HHF risk reduction appeared more
6
7 82 pronounced in males. Finerenone demonstrated a similar safety profile across age and sex.

8
9 83 **Registration:** FIDELIO-DKD (NCT02540993); FIGARO-DKD (NCT02545049)
10
11 84

12
13 85 **Abstract word count:** 300 of 300
14
15

16 86 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 17 87 • An advantage of this study was the use of combined individual-level data from the
18
19 88 FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, resulting in a large number of
20
21 89 patients included in the full analysis set
22
23 90 • This study did not use predefined age categories, as it was a post hoc analysis, which
24
25 91 may have resulted in some of the tests performed being underpowered
26
27 92 • Limitations present in FIDELITY are present in this analysis, such as the small proportion
28
29 93 of Black patients and exclusion of patients with nonalbuminuric CKD
30
31 94

95 INTRODUCTION

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

99
100 Among individuals aged 50–75 years without baseline diabetes, CKD, or CV disease, males
101 have a steeper decline in glomerular filtration rate (GFR) than females.[3] However, reported
102 effects of sex on risk of incidental and progressive CKD in patients with type 2 diabetes
103 (T2D) have been inconsistent.[4-6] In trials including patients with CKD, female
104 representation varies (25–40%),[7-11] whereas in real-world studies, females make up over
105 half of patients.[12,13]

106
107 Overactivation of the mineralocorticoid receptor (MR) is associated with CV and kidney
108 diseases.[14,15] In epithelial cells, the 11 β -hydroxysteroid dehydrogenase type 2 (11 β -
109 HSD2) enzyme prevents inappropriate MR activation by cortisol.[16-18] The activity of 11 β -
110 HSD2 decreases with age, resulting in MR overactivation in the elderly despite low
111 circulating aldosterone levels.[16-18] Sex also influences 11 β -HSD2 activity, particularly in
112 patients with hypertension, where 11 β -HSD2 activity is reduced in males versus females.[16]
113 The MR is also expressed in nonepithelial cells, including endothelial cells, vascular smooth
114 muscle cells, adipocytes, and immune cells.[17] In many of these, the MR may be activated
115 by cortisol because of a lack of protection by 11 β -HSD2.[19,20]

116
117 Despite management with recommended treatments for CKD in T2D, 10–13% of patients
118 experience CKD progression or kidney failure and are at high risk of CV events, including CV
119 death within 2–3 years following treatment initiation.[10,21,22] Finerenone, a selective,
120 nonsteroidal MR antagonist (MRA), reduced the risk of CKD progression and CV outcomes
121 compared with placebo in patients with CKD and T2D in FIDELITY (The Finerenone in

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3 122 chronic kidney disease and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD
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5 123 Trial programme analysis), a prespecified pooled analysis of the FIDELIO-DKD (Finerenone
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7 124 in reducing kidney failure and disease progression in Diabetic Kidney Disease;
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9 125 NCT02540993) and FIGARO-DKD (Finerenone in reducing cardiovascular mortality and
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11 126 morbidity in Diabetic Kidney Disease; NCT02545049) phase 3 trials.[21] However, the
12
13 127 influence of age and sex on outcomes with finerenone is unknown. This post hoc analysis
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15 128 evaluated whether the cardiovascular and kidney benefits and safety profile of finerenone
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17 129 observed in FIDELITY are consistent in patients with CKD and T2D across ages and in both
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19 130 sexes.
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23 131 **METHODS**

24 25 26 132 **Study design and patients**

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29 133 FIDELITY combined individual patient-level data from the FIDELIO-DKD and FIGARO-DKD
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31 134 phase 3 clinical trials. The study design, procedures, and outcomes for the trials have been
32
33 135 previously published.[23-25] The FIDELIO-DKD and FIGARO-DKD trials were conducted in
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35 136 accordance with the principles of the Declaration of Helsinki. Protocol approvals were
36
37 137 obtained from local regulatory authorities and ethics committees. Written informed consent
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39 138 was provided by all participants. These studies were reported following the Consolidated
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41 139 Standards of Reporting Trials (CONSORT) reporting guideline.
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46 141 Eligible patients were aged ≥ 18 years with CKD and T2D, receiving maximum tolerated
47
48 142 renin-angiotensin system inhibitor, and with serum potassium levels ≤ 4.8 mmol/L at
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50 143 screening. Patients had either a urine albumin-to-creatinine ratio (UACR) ≥ 30 – < 300 mg/g
51
52 144 and an estimated GFR (eGFR) ≥ 25 – ≤ 90 mL/min/1.73 m², or UACR ≥ 300 – ≤ 5000 mg/g and
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54 145 eGFR ≥ 25 mL/min/1.73 m². Patients with symptomatic heart failure (HF) with reduced
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56 146 ejection fraction were excluded because this implies an indication for a steroidal MRA.
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3 148 Standard-of-care therapy with a renin–angiotensin system inhibitor was optimized during the
4
5 149 run-in period. Patients were randomly assigned (1:1) to receive finerenone at titrated doses
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7 150 (10 or 20 mg) once-daily oral treatment or matching placebo.
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10 151 **Key outcomes**

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13 152 Efficacy outcomes included a CV composite outcome of CV death, nonfatal myocardial
14
15 153 infarction, nonfatal stroke, or hospitalization for HF (HHF), and a kidney composite outcome
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17 154 of kidney failure, sustained $\geq 57\%$ eGFR decline, or renal death. Additional outcomes
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19 155 included HHF and change in UACR and eGFR over time.
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23 157 Safety outcomes included incidence of investigator-reported adverse events (AEs), including
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25 158 those leading to treatment discontinuation, central laboratory assessment of serum
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27 159 potassium levels >5.5 and >6.0 mmol/L, and other safety events of interest, such as
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29 160 hypotension, hyperkalemia, and gynecomastia in males.
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31 161
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33 162 Outcomes were analyzed according to patient age at baseline (<65 , 65 – 75 , ≥ 75 years) and
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35 163 sex. Females were categorized as either pre- or postmenopausal if they were aged <51.4 or
36
37 164 ≥ 51.4 years at baseline, respectively (based on the median age of menopause onset from
38
39 165 the Massachusetts Women's Health Study).[26]
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42 166 **Statistical analysis**

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45 167 Statistical analyses were performed as described in FIDELITY.[23] The full analysis set
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47 168 comprised all randomized patients (except those with critical Good Clinical Practice
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49 169 violations, who were prospectively excluded). Safety analyses were performed in the safety
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51 170 analysis set (randomized patients without critical Good Clinical Practice violations who took
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53 171 >1 dose of study drug). The analyses were prespecified exploratory evaluations of outcomes
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55 172 according to age and sex, with events reported from randomization up to the end-of-study
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57 173 visit. Stratified Cox proportional hazards models,[27,28] including stratification factors:
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3 174 geographic region, eGFR and albuminuria category at screening, history of CV disease, and
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5 175 study, were used for the analysis of time-to-event clinical outcomes. The *P*-values for
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7 176 interaction between the treatment group (finerenone or placebo) and each baseline subgroup
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9 177 (age or sex) were based on stratified Cox proportional hazards models, accounting for the
10
11 178 treatment effect, the subgroup effect, and their interaction.

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16 180 Changes in UACR and eGFR over time were assessed using a linear mixed-model analysis
17
18 181 accounting for repeated measurements over time. The least-squares mean ratio and
19
20 182 absolute change from baseline were estimated from the models for changes in UACR and
21
22 183 eGFR, respectively. The 2-slope, linear spline, mixed-model, repeated measure method[29]
23
24 184 was used to estimate the rate of change in eGFR across time, specifically total (annualized
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26 185 rate of change in eGFR from baseline to permanent discontinuation or end of study) and
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28 186 chronic (from month 4 to permanent discontinuation or end of study) eGFR slopes. To
29
30 187 account for possible nonlinear effects of age on clinical outcomes, age was modeled with
31
32 188 cubic splines with 3 knots in Cox proportional hazards models, to produce plots of the hazard
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34 189 ratios (HRs) and 95% confidence interval as functions of age and sex.

37 38 190 **Patients and public involvement**

39
40 191 No patient or public involvement in the current study.

42 43 192 **RESULTS**

46 47 193 **Patients**

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49 194 FIDELITY included 13 026 patients.[23] Median follow-up was 3 years (interquartile range
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51 195 2.3–3.8).[23] Mean age at baseline was 64.8 years (standard deviation 9.5), with 45.2%,
52
53 196 40.1%, and 14.7% of patients aged <65, 65–74, and ≥75 years at baseline, respectively.
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55 197 Most patients (69.8%) were male; 2.5% were premenopausal females, and 27.8% were
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57 198 postmenopausal females. Patients were distributed evenly between treatment arms within
58
59 199 age and sex subgroups (**eTable 1**).

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3 200 **Baseline characteristics**
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5 201 Baseline characteristics were similar across age subgroups except for some key differences
6
7 202 (**Table 1**). The overall FIDELITY population was predominantly White (68.1%), the proportion
8
9 203 of which increased with age. Mean eGFR was 64, 54, and 48 mL/min/1.73 m² in patients
10
11 204 aged <65, 65–75, and ≥75 years, respectively. Median UACR was 650, 439, and 332 mg/g in
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13 205 patients aged <65, 65–75, and ≥75 years, respectively. History of CV disease was more
14
15 206 common in the ≥75 years group; this trend was also observed for atrial fibrillation/atrial flutter.
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17 207 Baseline characteristics in sex subgroups are shown in **Table 1**.
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208 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, <i>n</i> (%)	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, <i>n</i> (%)	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, <i>n</i> (%) ^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.

214 Efficacy

215 CV composite outcome by age

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

224
225 HHF event rates were numerically lower with finerenone than placebo in all age subgroups
226 (**Figure 1A**). The effect of finerenone on HHF risk reduction was consistent across age
227 subgroups, with no significant heterogeneity observed ($P_{\text{interaction}}=.70$).

228 CV composite outcome by sex

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

236

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

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3 240 HHF with finerenone versus placebo ($P_{\text{interaction}}=.02$), and the effect appeared to be more
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5 241 pronounced in males than premenopausal/postmenopausal females (**Figure 1B**). These
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7 242 results persisted after adjustment for differences in baseline age, body mass index, systolic
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9 243 blood pressure, hemoglobin, eGFR, UACR, smoking history, and history of atrial fibrillation
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11 244 between sex subgroups ($P_{\text{interaction}}=.02$).

14 245 Kidney composite outcome by age

16
17 246 Kidney composite event rates were lower with finerenone than placebo in the <65 years and
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19 247 the 65–74 years groups but were similar in the ≥ 75 years group (**Figure 2A**). The effect of
20
21 248 finerenone on reducing the risk of the kidney composite outcome was consistent across age
22
23 249 subgroups, with no significant heterogeneity detected ($P_{\text{interaction}}=.51$) and no evidence of
24
25 250 treatment effect modification when age was modeled as a continuous variable ($P_{\text{interaction}}=.77$).
26
27 251 The trend of HR as function of age was modeled with cubic splines (**eFigure 3A**).

30 252 Kidney composite outcome by sex

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32
33 253 Kidney composite event rates were lower with finerenone than placebo in males but were
34
35 254 similar in premenopausal and postmenopausal females (**Figure 2B**). There was no
36
37 255 significant heterogeneity in the effect of finerenone on reducing the risk of the kidney
38
39 256 composite outcome across sex subgroups ($P_{\text{interaction}}=.85$). When age was modeled with cubic
40
41 257 splines by sex subgroups, the effect of finerenone suggests trends similar to overall results in
42
43 258 males and females across all age groups (**eFigure 3B**, **eFigure 3C**). Age distribution by sex
44
45 259 is demonstrated in **eFigure 3D**.

48 260 Effect of finerenone on markers of kidney function and damage by age and sex

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50
51 261 Finerenone significantly attenuated the least-squares mean change in eGFR from month 4 to
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53 262 end of treatment (chronic eGFR slope) compared with placebo across all age ($P<.0001$ for all
54
55 263 3 subgroups) (**Figure 3**) and sex subgroups (**eFigure 4**). Finerenone reduced UACR over
56
57 264 time compared with placebo regardless of age and sex (**eFigure 5**).

265 **Safety**

266 The incidence of any AE was similar between treatment groups irrespective of age or sex
267 (**eTable 2**). There were more drug-related AEs with finerenone than placebo in age and sex
268 subgroups except premenopausal females, where the incidence was similar. AEs leading to
269 drug discontinuation were more frequent in patients given finerenone than placebo (6.4%
270 and 5.4%, respectively), with higher incidences in the 65–74 and ≥75 years groups than the
271 <65 years group; there were more AEs leading to drug discontinuation with finerenone than
272 placebo in males and premenopausal females but not in postmenopausal females.

273
274 Although the incidences of any serious AEs (SAEs), study drug-related SAEs, or SAEs
275 leading to drug discontinuation were similar between treatment arms across all age and sex
276 subgroups, the overall incidences of SAEs increased with age and was highest in males,
277 followed by postmenopausal females, then premenopausal females.

278
279 In all age and sex subgroups, the incidences of treatment-emergent hypotension AEs were
280 higher with finerenone than placebo but did not have a substantial impact on related clinical
281 outcomes, including falls, dizziness, and fatigue. A trend of increased incidence of
282 hypotension with increasing age was observed in patients treated with finerenone; however,
283 the incidence of hypotension was generally low across all age subgroups (<6%; **eTable 2**).

284
285 In FIDELITY, finerenone increased the risk of any hyperkalemia event versus placebo;
286 similar findings were observed in all age and sex subgroups, except premenopausal females
287 (**eTable 2**). The incidences of any hyperkalemia AEs leading to discontinuation of study drug
288 and any serious hyperkalemia AEs leading to hospitalization were low across all age and sex
289 subgroups (<3% and <2%, respectively). However, the relative risk of treatment
290 discontinuation because of hyperkalemia with finerenone versus placebo increased with
291 advancing age (relative risk [95% confidence interval] for ages 45–64, 65–74, and ≥75 years:

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3 292 2.2 [1.2–4.3], 2.8 [1.7–4.7], and 4.4 [1.8–10.8], respectively; **eFigure 6**). Treatment-emergent
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5 293 serum potassium levels >5.5 mmol/L and >6.0 mmol/L were more frequent with finerenone
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7 294 than placebo, being consistent across all age and sex subgroups. The incidence of
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9 295 gynecomastia in males was the same with finerenone (0.2%) and placebo (0.2%) across all
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11 296 ages.

15 297 **DISCUSSION**

17 298 The findings of this post hoc analysis suggest that finerenone reduced the risk of CV and
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19 299 kidney composite outcomes versus placebo across all age and sex subcategories. In
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21 300 FIDELITY, HHF was the main driver of CV benefit with finerenone[23]; lower incidences of
22
23 301 HHF with finerenone versus placebo were observed in this analysis across all age
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25 302 subgroups, with some differences noted between sex subgroups. Moreover, the incidences
26
27 303 of any AEs or SAEs were similar between the treatment groups regardless of age and sex.
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31
32 305 The current results are supported by findings from a pharmacokinetics (PK) analysis based
33
34 306 on FIDELIO-DKD and FIGARO-DKD data, in which both age and sex were tested as
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36 307 covariates for a population PK model, and their effect on finerenone exposure was not
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38 308 significant, suggesting a lack of influence of these factors on the PK of the drug.[30]
39
40 309 Additionally, the results for the CV outcome in this analysis are similar to findings from other
41
42 310 studies of MRAs in HF. In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure
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44 311 with an Aldosterone Antagonist), age did not affect the efficacy of spironolactone in patients
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46 312 with HF with reduced ejection fraction (primary composite outcome: CV death, aborted
47
48 313 cardiac arrest and HHF; secondary outcomes included CV death, all-cause death and
49
50 314 HHF).[31] Moreover, in analyses of HF studies (RALES [Effect of Spironolactone on
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52 315 Morbidity and Mortality in Patients with Severe Heart Failure], EMPHASIS-HF [Eplerenone in
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54 316 Patients with Systolic Heart Failure and Mild Symptoms], and TOPCAT), MRAs reduced
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56 317 morbidity and mortality in elderly patients,[32] demonstrating a consistent benefit regardless
57
58 318 of sex.[33] In contrast to our results, female sex was associated with poorer kidney outcomes
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3 319 versus male sex in patients receiving a steroidal MRA for bilateral primary aldosteronism.[34]
4
5 320 The MR can be activated by different drivers in different diseases; MR activation in diabetes
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7 321 is driven by additional factors other than high aldosterone in comparison with primary
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9 322 aldosteronism, which may account for differences in outcomes observed across different
10
11 323 indications.[35]
12
13 324
14
15 325 In this study, the elderly population had higher risk of certain AEs including hypotension, AEs
16
17 326 leading to discontinuation, and death. Hypotension occurred more frequently in the
18
19 327 finerenone group but did not seem to substantially affect related clinical outcomes.
20
21 328 Hyperkalemia was more prevalent with finerenone but was generally similar across age and
22
23 329 sex. In a FIDELIO-DKD subanalysis, younger age and female sex were independent risk
24
25 330 factors for hyperkalemia (>6.0 mmol/L).[36] Similar findings for age were observed in
26
27 331 TOPCAT post hoc data for patients with HF.[31] Steroidal MRAs have been associated with
28
29 332 gynecomastia in males,[37,38] which was not observed in this study, most likely because
30
31 333 finerenone has no detectable affinity for androgen receptors.[38]
32
33 334
34
35 335 Preclinical data suggest that different molecular mechanisms drive endothelial dysfunction in
36
37 336 male and female mice[39,40] and that increased age and male sex are associated with MR
38
39 337 overactivation, which is linked to vascular stiffness and endothelial dysfunction.[41,42] In
40
41 338 human aortic smooth muscle cells, MR expression increased with age, leading to epigenetic
42
43 339 changes associated with increased vascular stiffness. These effects were reversed with MR
44
45 340 inhibition.[43] In vitro, MR expression in the whole aortae and early passage aortic vascular
46
47 341 smooth muscle cells was increased in aged (30 months) versus adult (8 months) rat
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49 342 cells.[41] In a preclinical mouse model, aortic stiffness occurred earlier in male than female
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51 343 mice and correlated with the timing of increased aortic MR expression; vascular stiffness was
52
53 344 prevented in smooth muscle cell MR-deficient mice.[42] These data suggest that elderly
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55 345 males may derive the greatest benefit from finerenone; indeed, in this analysis, finerenone-
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57 346 treated males had lower risk of the CV composite outcome and HHF versus placebo across
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3 347 age groups, including >75 years. Moreover, statistical heterogeneity was observed for HHF
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5 348 by sex, persisting after adjustment for differences in baseline characteristics, which might
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7 349 suggest a more pronounced effect of finerenone on HHF reduction in the male subgroup
8
9 350 compared with the 2 female subgroups. However, because of the small sample size of the
10
11 351 sex subgroups (especially that of the premenopausal female subgroup), definitive
12
13 352 conclusions cannot be reached based on this finding.
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17
18 354 In this study, markers of kidney damage (eGFR decline and UACR) were reduced with
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20 355 finerenone in age subgroups; however, no benefit on kidney outcomes was observed in the
21
22 356 >75 years age group. The small sample size of this subgroup precluded definitive
23
24 357 conclusions, which may be accounted for by the slowing rate of CKD progression with
25
26 358 advancing age.[44,45]
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30 360 Limitations include the study being a post hoc analysis and the chosen age categories not
31
32 361 being predefined. In addition, patients may have initiated other treatments during the study.
33
34 362 Sample size and number of events for females, particularly premenopausal females, were
35
36 363 small. Therefore, there is uncertainty around the estimates and the analysis was
37
38 364 underpowered to draw meaningful conclusions in this subgroup. Results for premenopausal
39
40 365 females versus postmenopausal females/males should be interpreted with caution because
41
42 366 age may partly account for differences observed; the average age of premenopausal females
43
44 367 was ~45 years old compared with postmenopausal females (~66 years old) and males
45
46 368 (~65 years old) (**Table 1**). As such, these groups had different baseline characteristics.
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48 369 Higher baseline mean eGFR and median UACR, and lower history of CV comorbidities and
49
50 370 hypotension were observed in premenopausal females versus males and postmenopausal
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52 371 females. Additionally, the study design and tests performed may have been underpowered to
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54 372 address the research questions. Furthermore, FIDELITY limitations, mainly the small
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56 373 proportion of Black patients and exclusion of patients with nonalbuminuric CKD, were
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58 374 present in this analysis.
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5 376 In conclusion, this post hoc FIDELITY analysis suggests that finerenone effectively lowers
6
7 377 the risk of clinically important cardiovascular and kidney outcomes in patients with CKD and
8
9 378 T2D across ages and sexes, with a potentially more pronounced effect on HHF in males than
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11 379 in females. No new safety concerns were identified in those aged >65 years or by sex.
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44
45 427 myocardium (US patent #9931412) and a provisional patent for histone-acetylation-
46
47 428 modulating agents for the treatment and prevention of organ injury (provisional patent US
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49 429 63/045,784).

430 DATA SHARING STATEMENT

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

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

440 Interested researchers can use www.vivli.org to request access to anonymized patient-level
441 data and supporting documents from clinical studies to conduct further research that can
442 help advance medical science or improve patient care. Information on the Bayer criteria for
443 listing studies and other relevant information is provided in the member section of the portal.
444 Data access will be granted to anonymized patient-level data, protocols, and clinical study
445 reports after approval by an independent scientific review panel. Bayer is not involved in the
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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.

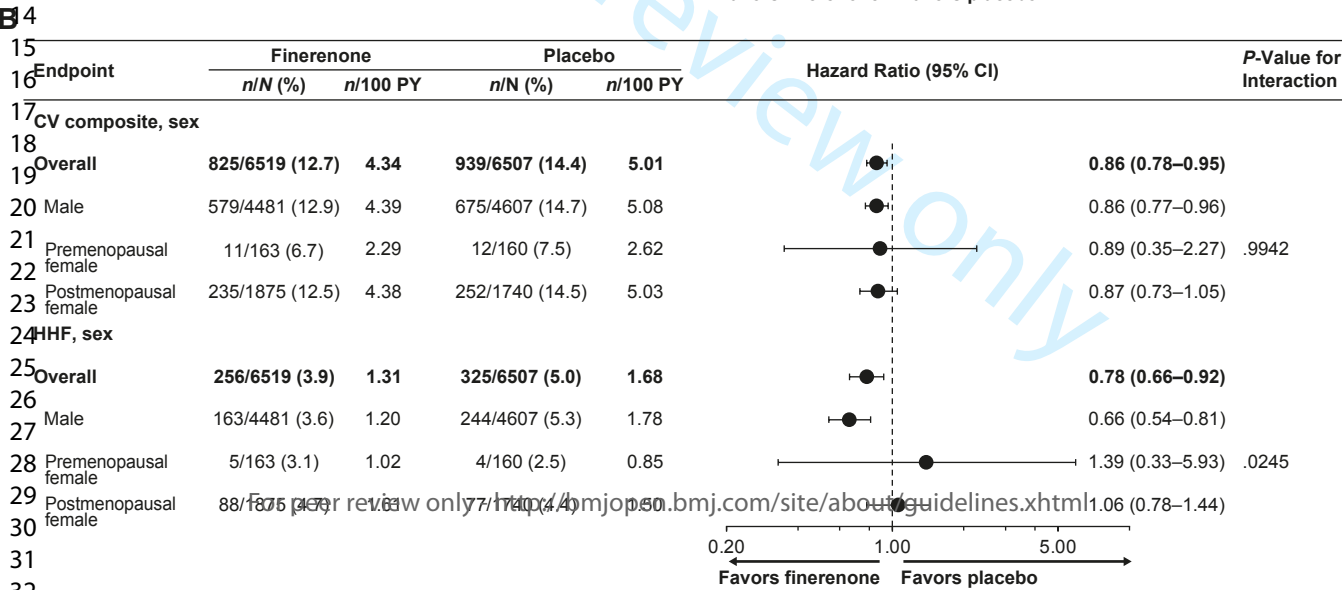
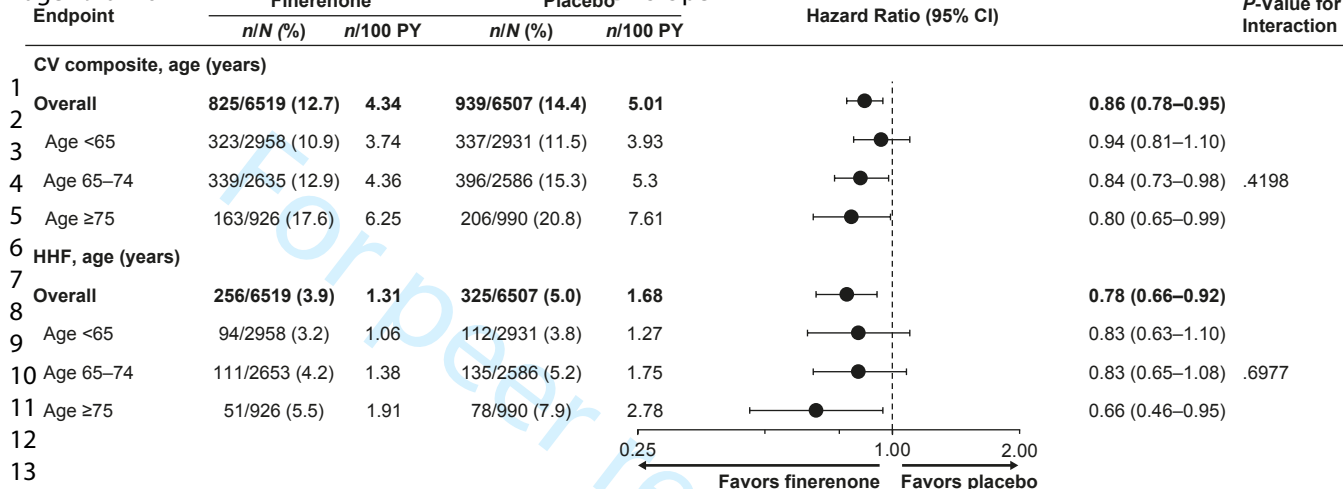
Kidney composite outcome includes kidney failure, sustained $\geq 57\%$ eGFR decline, or renal death.

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

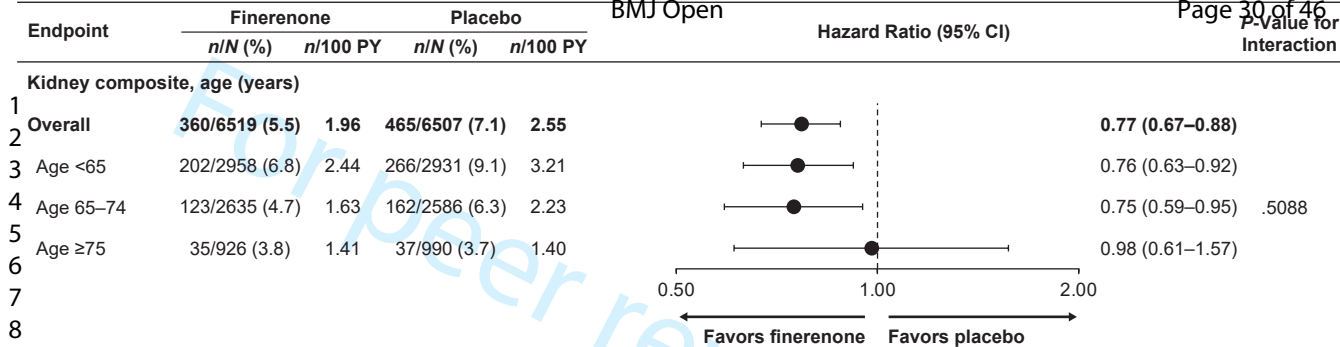
Figure 3. LS mean change in eGFR from baseline, chronic, and total slopes over time by age.

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

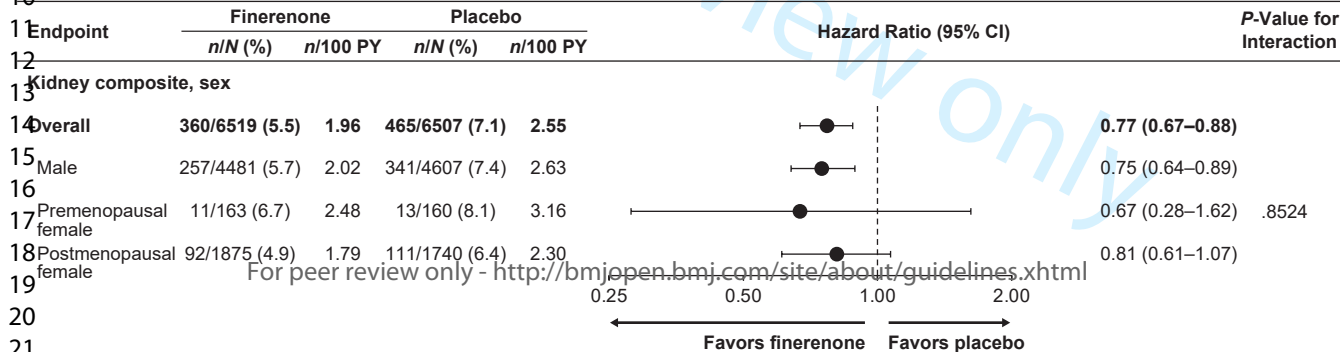
CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.



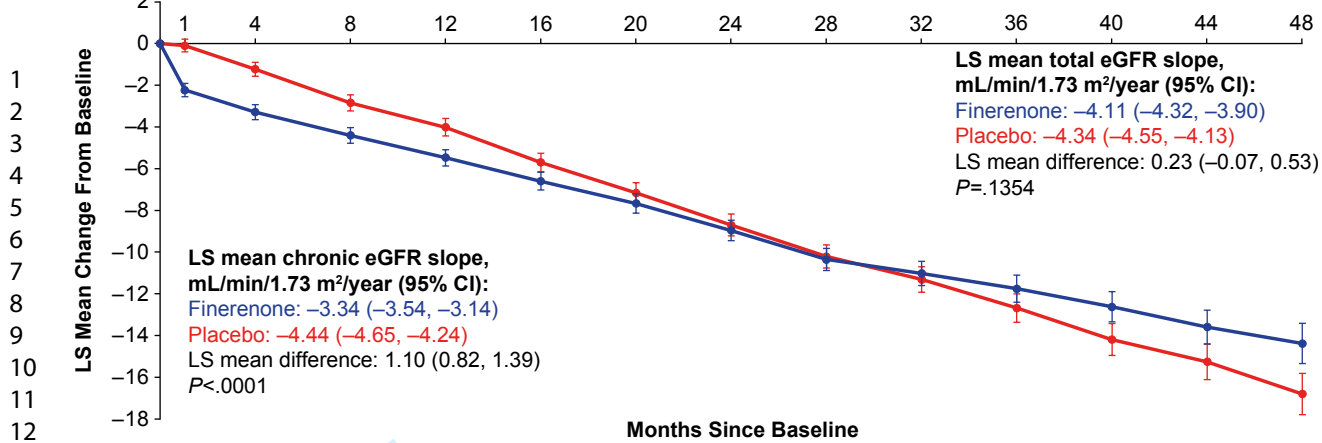
A



B



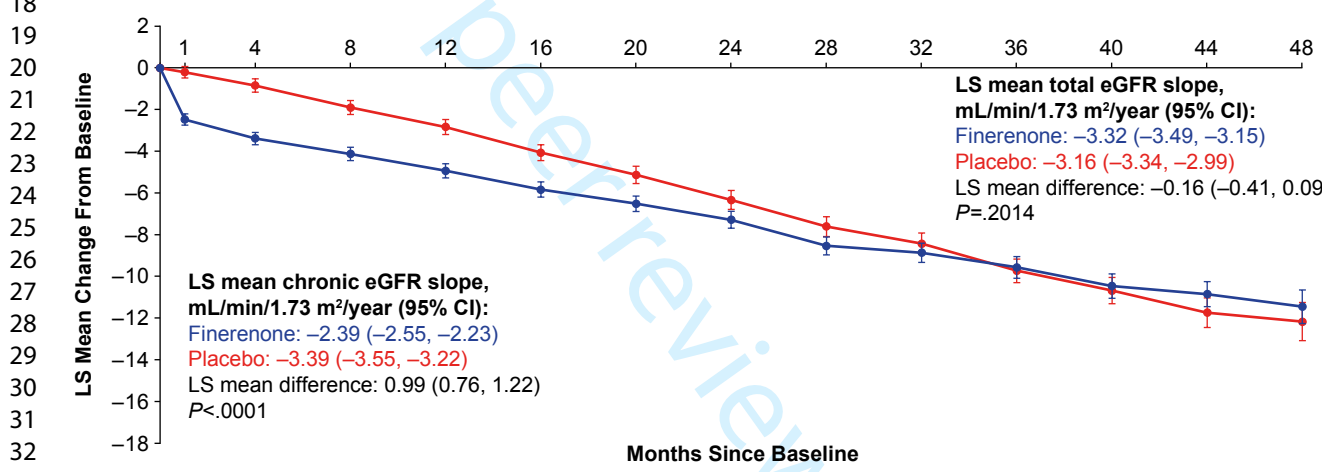
BMJ Open



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

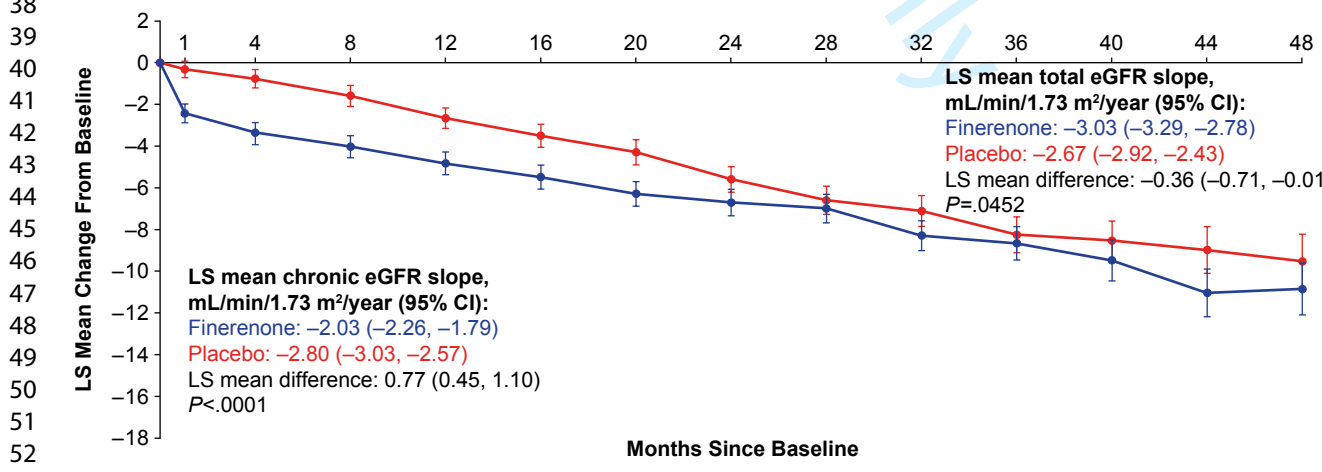
B 65 to 74 Years



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	696	578	461	359	281	204	117

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

Contents

Finerenone Cardiovascular and Kidney Outcomes by Age and Sex: FIDELITY Post Hoc Analysis of Two Phase 3, Multicenter, Double-Blind Trials	1
Supplementary Tables and Figures	2
eTable 1. Patient Baseline Characteristics According to Age and Sex Stratified by Treatment Group	2
eTable 2. Treatment-Emergent AEs According to Age and Sex	6
eFigure 1. Analysis of CV composite outcome and subcomponents according to (A) age and (B) sex	8
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).	11
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).	12
eFigure 4. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex	13
eFigure 5. LS mean ratio to baseline UACR over time by age and sex	14
eFigure 6. Relative risk of treatment-emergent hyperkalemia causing permanent discontinuation of study drug by age and sex	15
eFigure 7. FIDELITY CONSORT diagram.	16

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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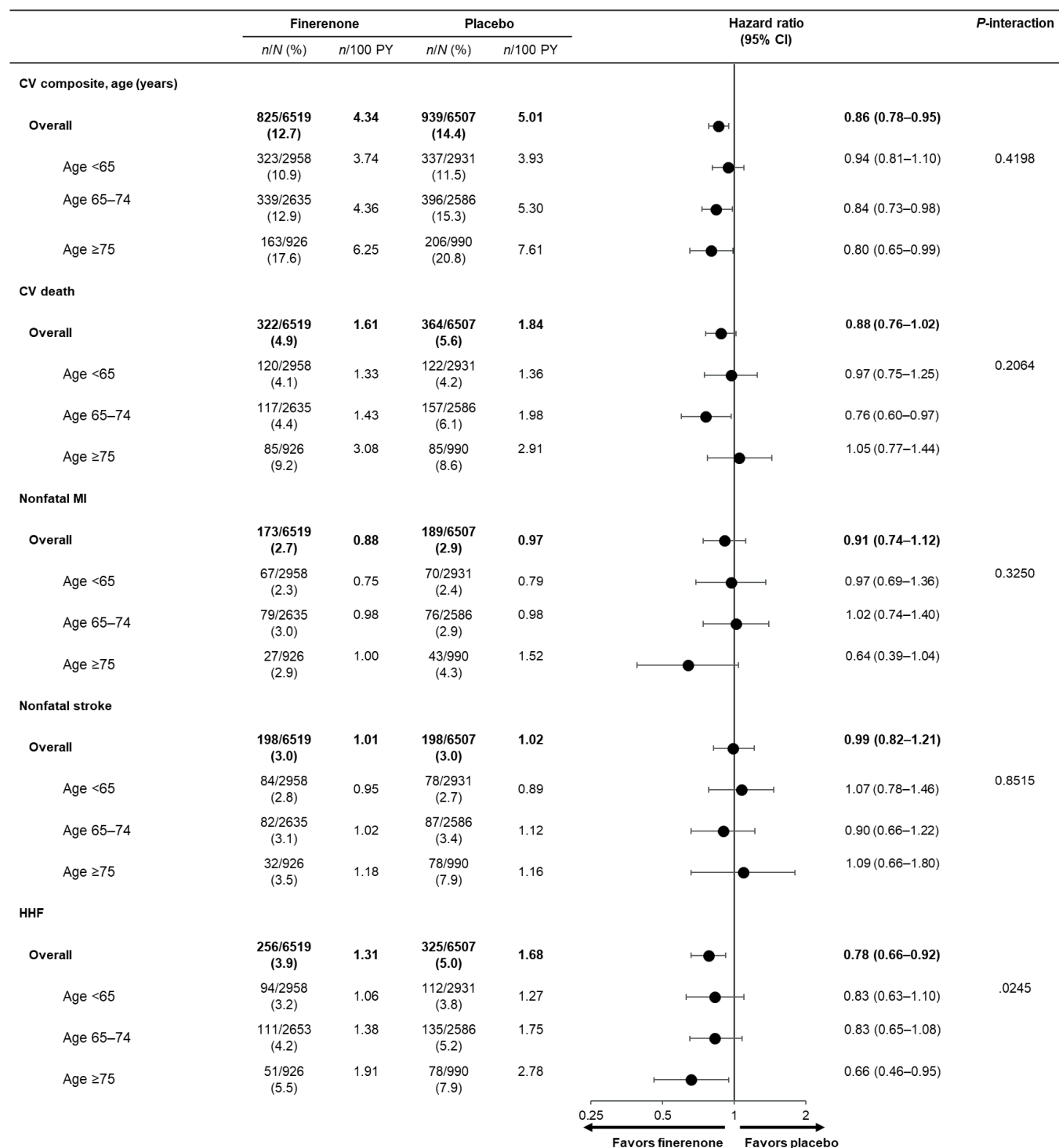
Serum potassium >5.5 mmol/L	1075/6402 (16.8)	470/6370 (7.4)	444/2904 (15.3)	233/2871 (8.1)	460/2585 (17.8)	180/2529 (7.1)	171/913 (18.7)	57/970 (5.9)	720/4403 (16.4)	308/4523 (6.8)	16/159 (10.1)	8/154 (5.2)	339/1840 (18.4)	154/1693 (9.1)
Serum potassium >6.0 mmol/L	211/6439 (3.3)	80/6413 (1.2)	90/2926 (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.

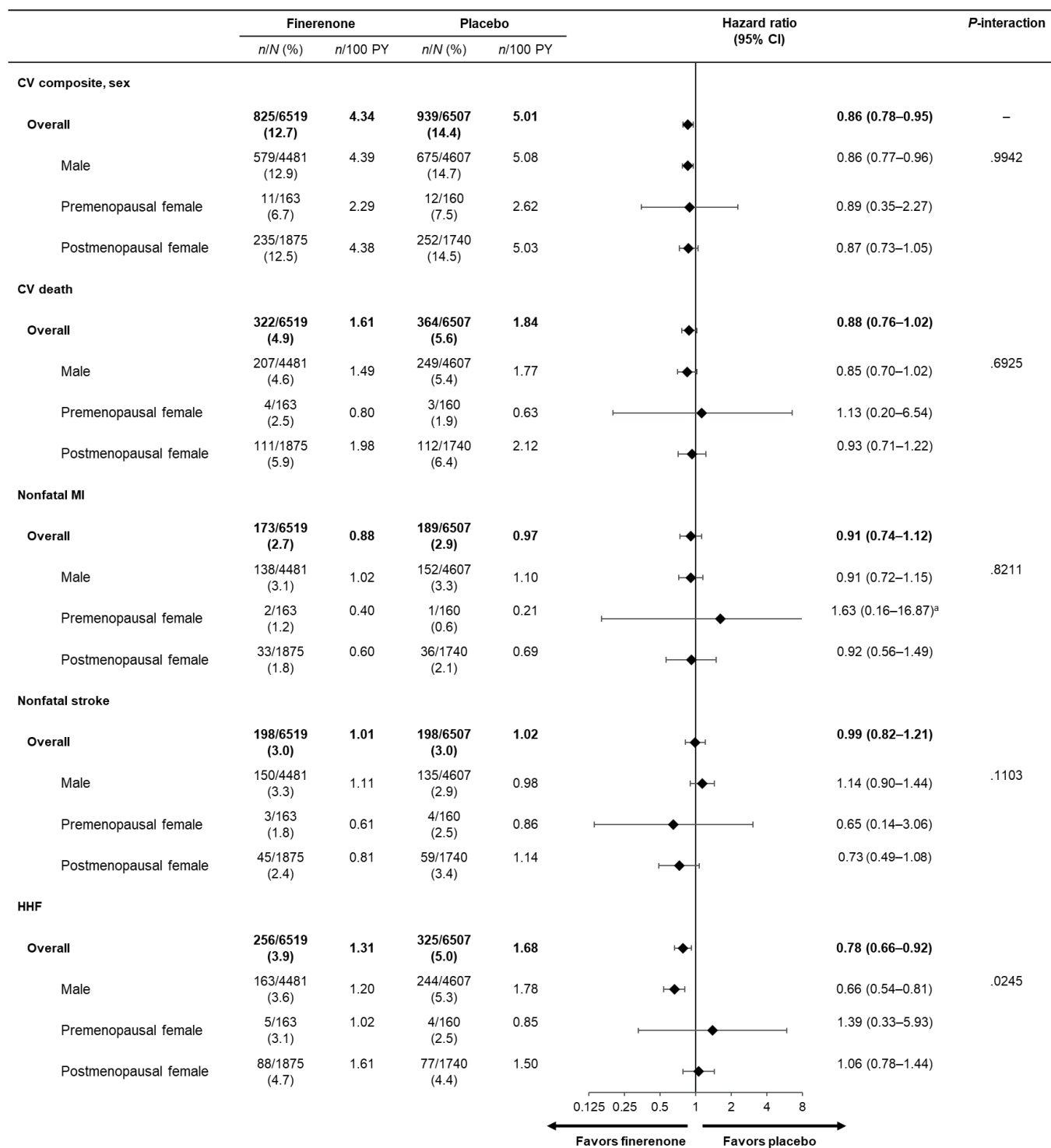
^a The “*n*” numerator represents the number of patients at risk with ≥ 1 treatment-emergent laboratory assessment meeting the criterion. The “*N*” denominator represents all patients at risk for a treatment-emergent laboratory abnormality. Patients had both a baseline and postbaseline treatment-emergent 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.



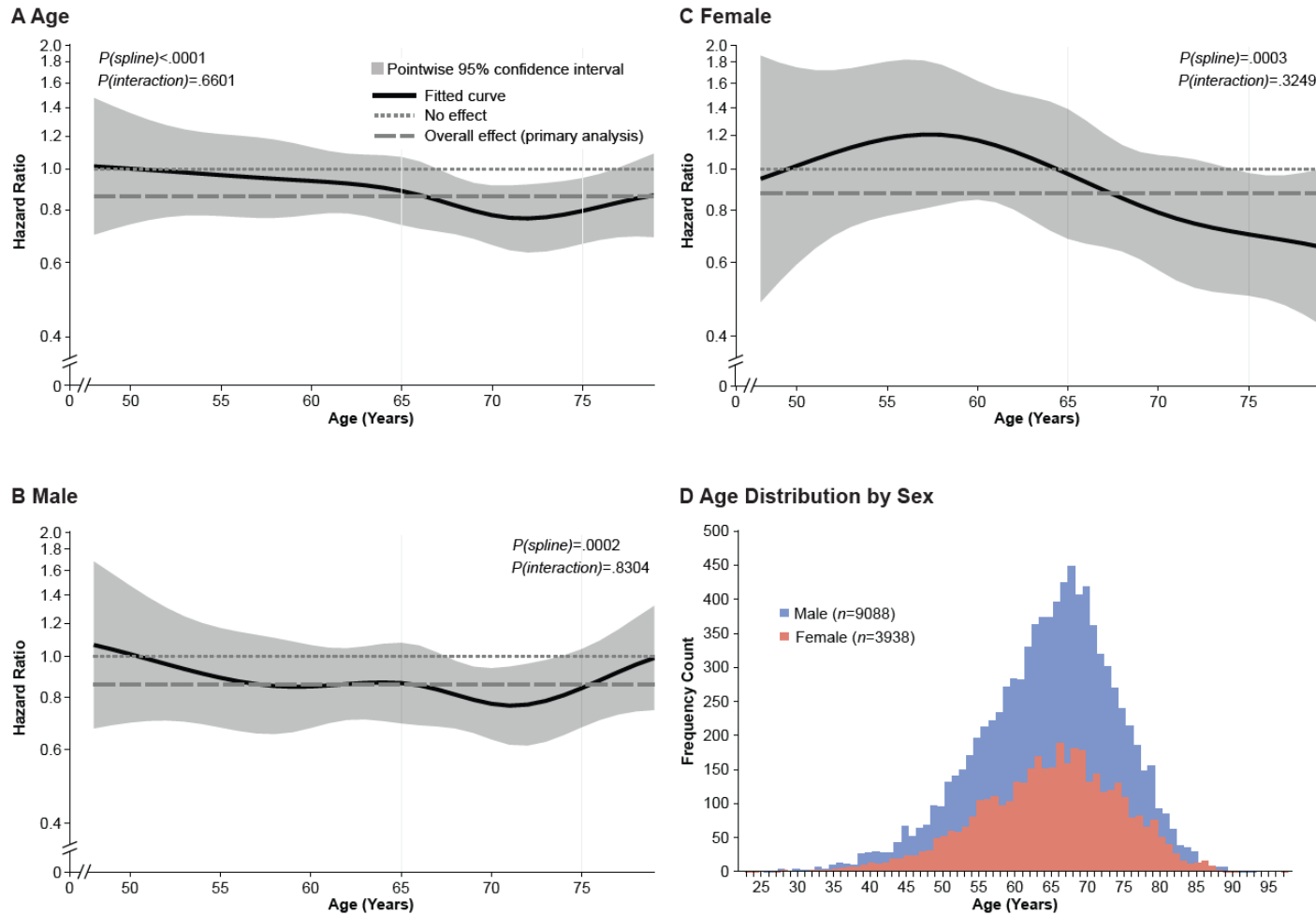
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3 A stratified Cox proportional hazards model including treatment was calculated separately by
4 subgroup category. The $P_{\text{interaction}}$ is based on a stratified Cox proportional hazards model including
5 treatment, subgroup, and treatment by subgroup interaction.
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8 CV composite outcome includes CV death, nonfatal MI, nonfatal stroke, or HHF.

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10 CI = confidence interval; CV = cardiovascular; HHF = hospitalization for heart failure; MI = myocardial
11 infarction; PY = patient-years.
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16 ^a An unstratified model using Firth's penalized likelihood approach was applied due to zero cell counts
17 and/or convergence issues.
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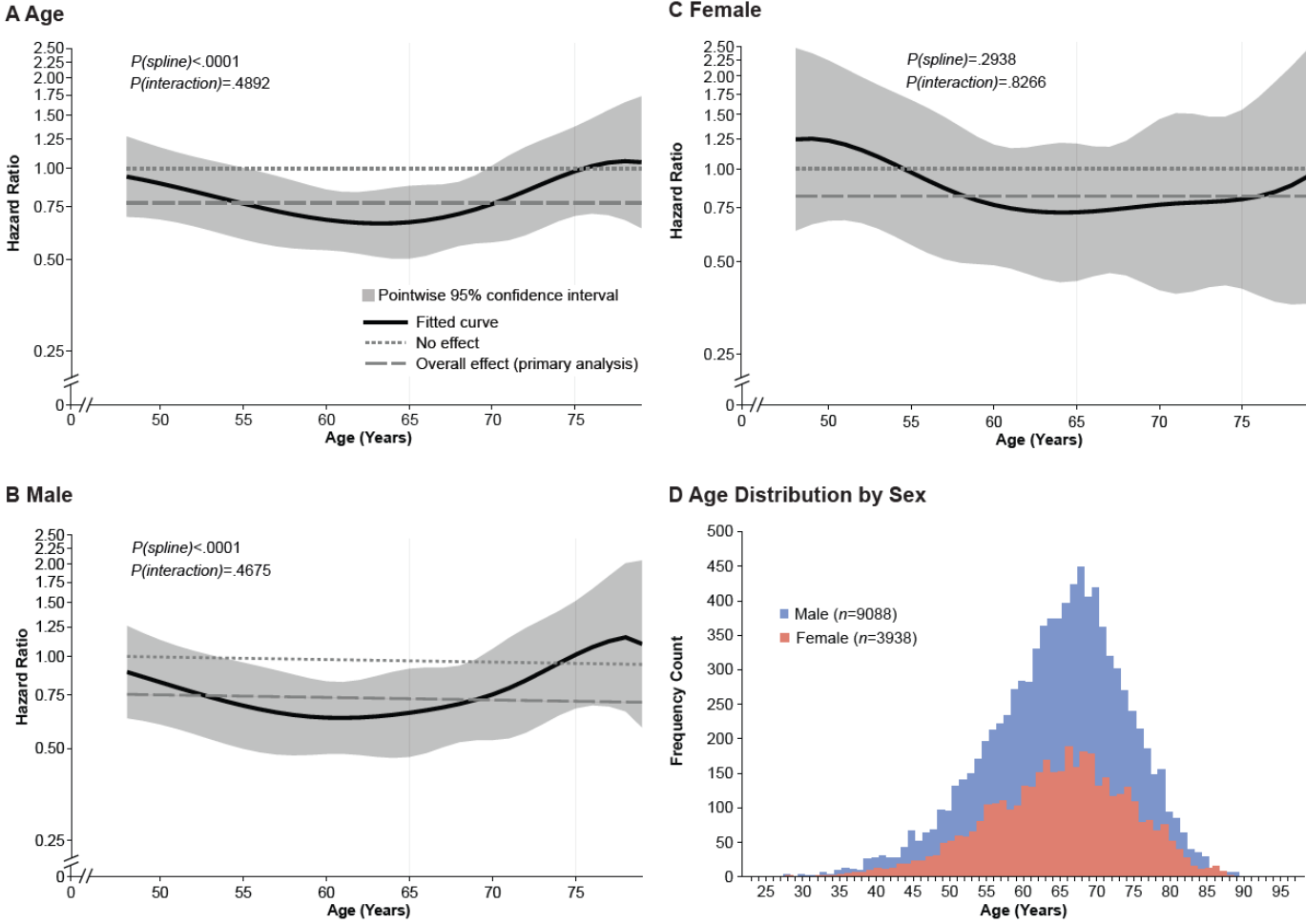
eFigure 2. Hazard ratio (finerenone vs placebo) as a function of age modeled with cubic splines for CV composite outcome by age (A), spline for hazard ratio of CV composite outcomes by sex (B, C), and age distribution by sex (D).



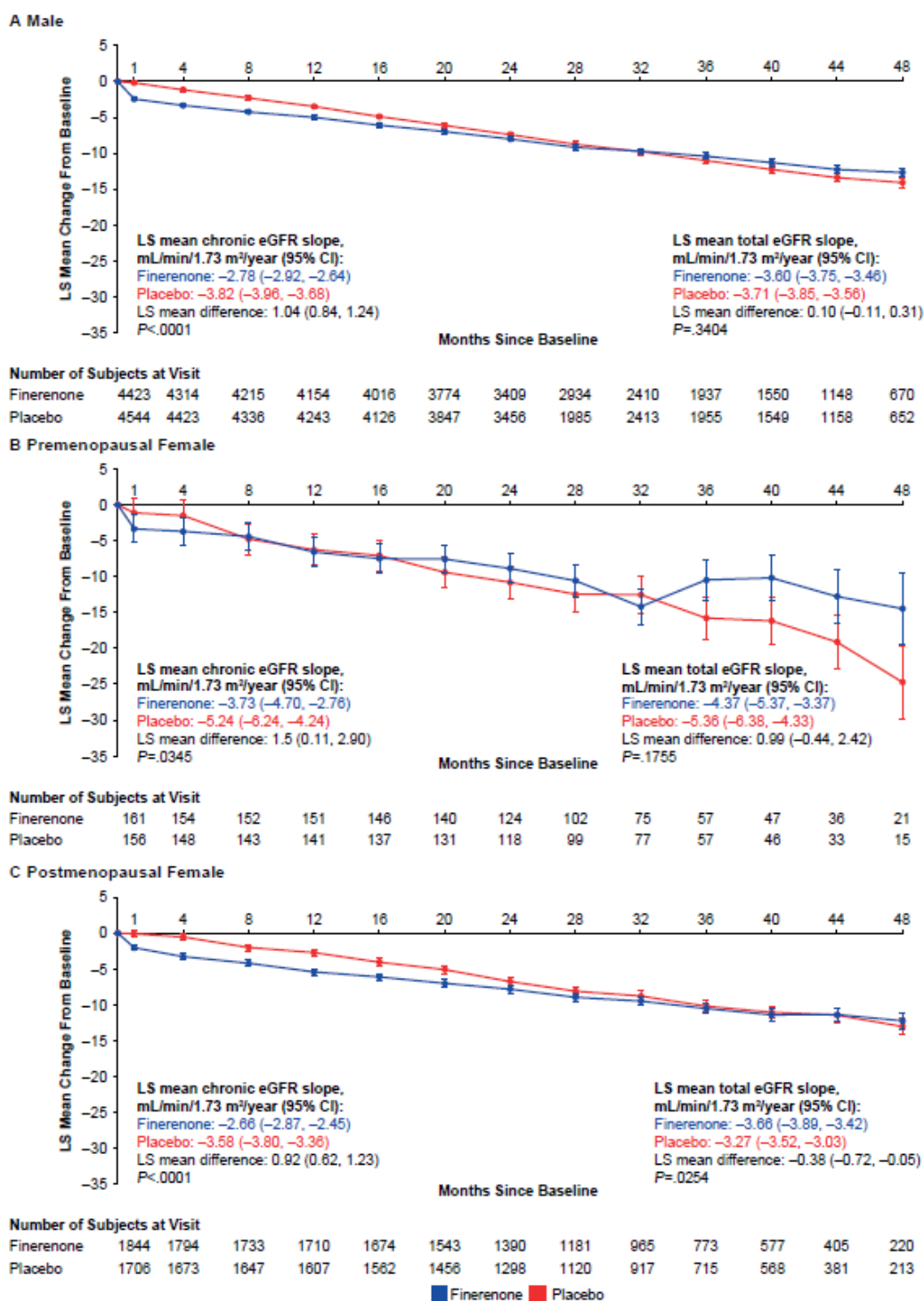
CV = cardiovascular.

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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).



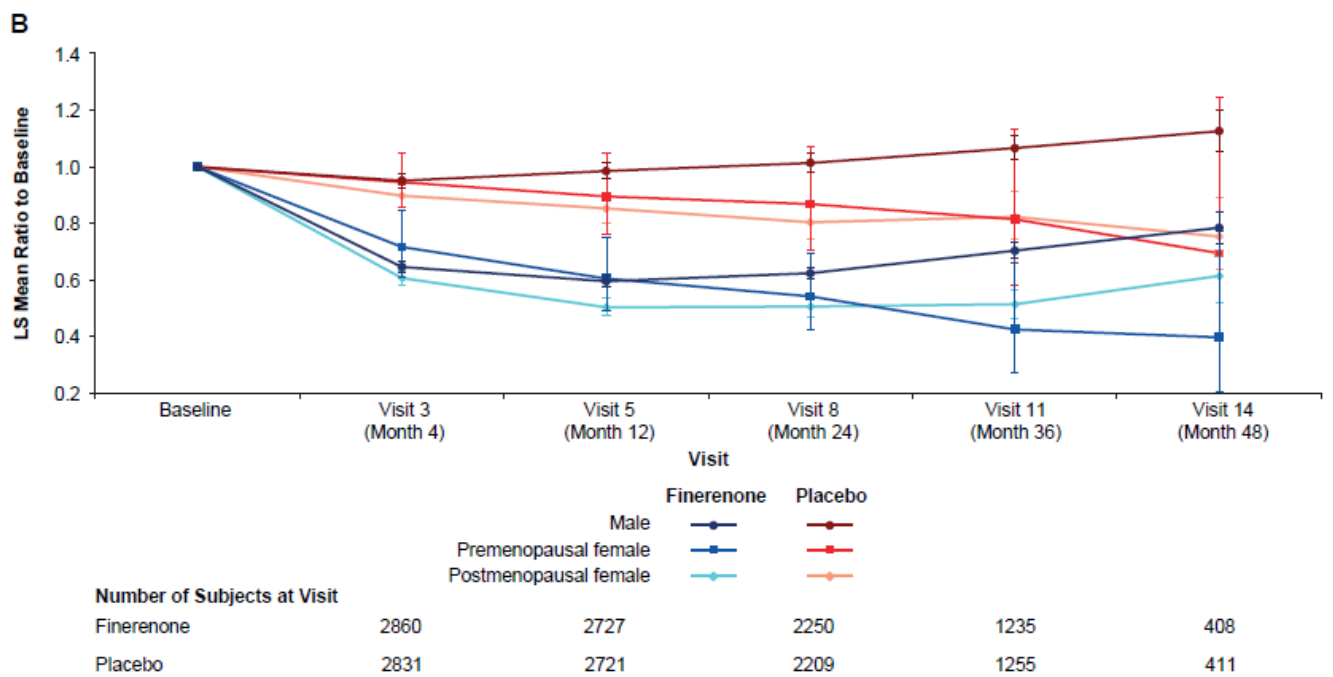
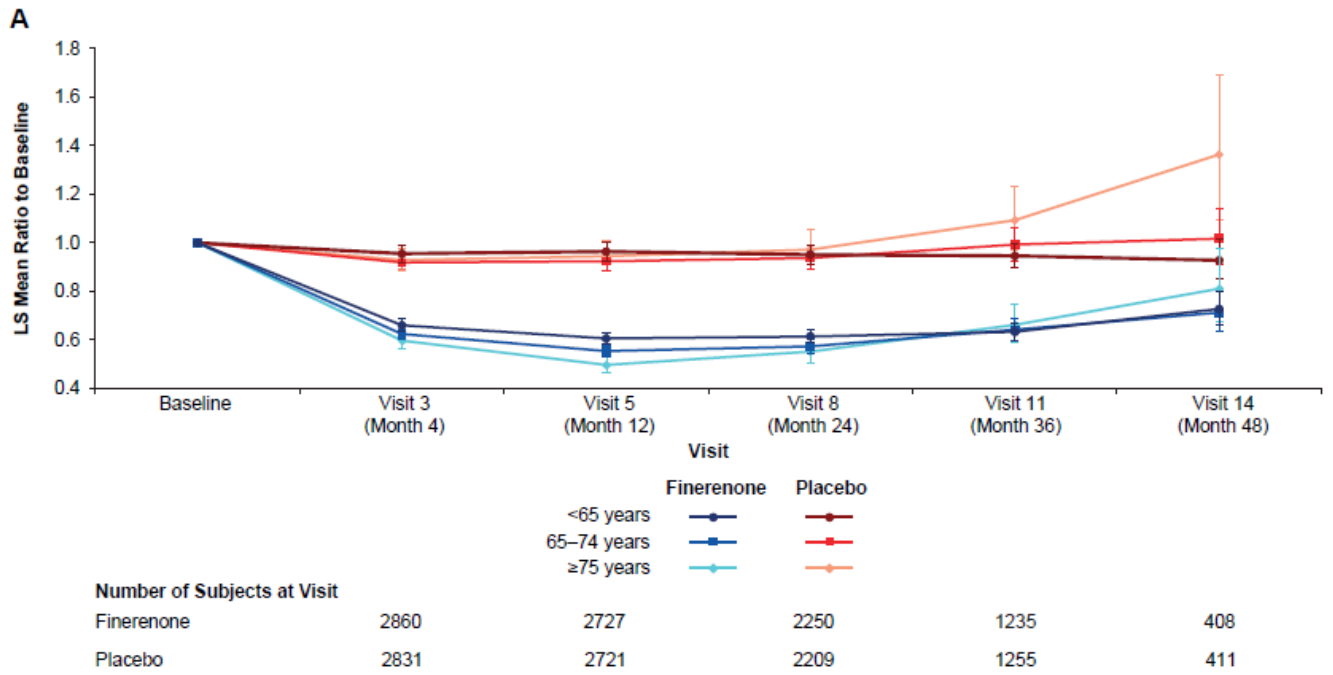
eFigure 4. LS mean change in eGFR from baseline, chronic, and total slopes over time by sex.



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

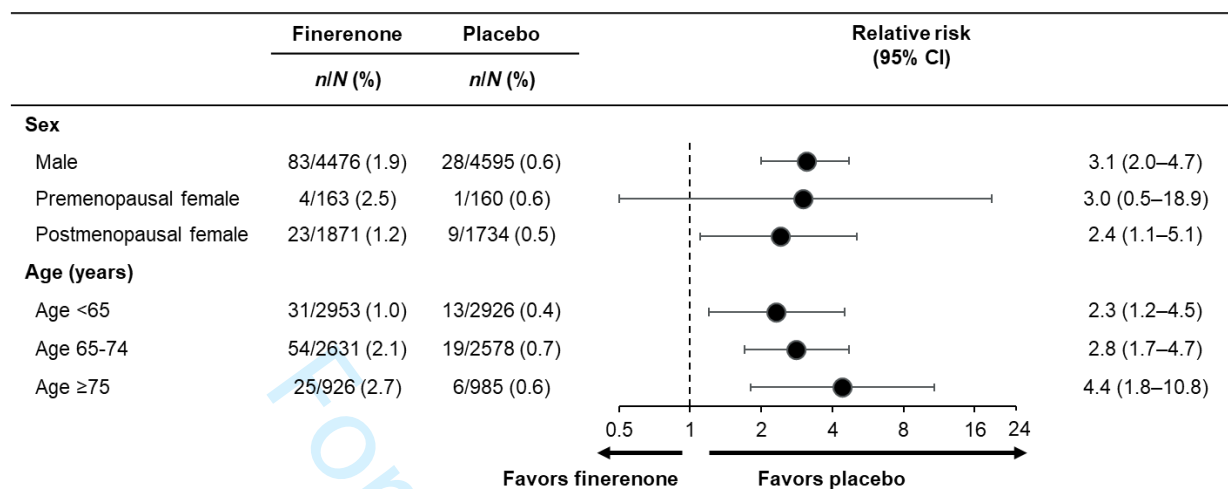
CI = confidence interval; eGFR = estimated glomerular filtration rate; LS = least-squares.

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

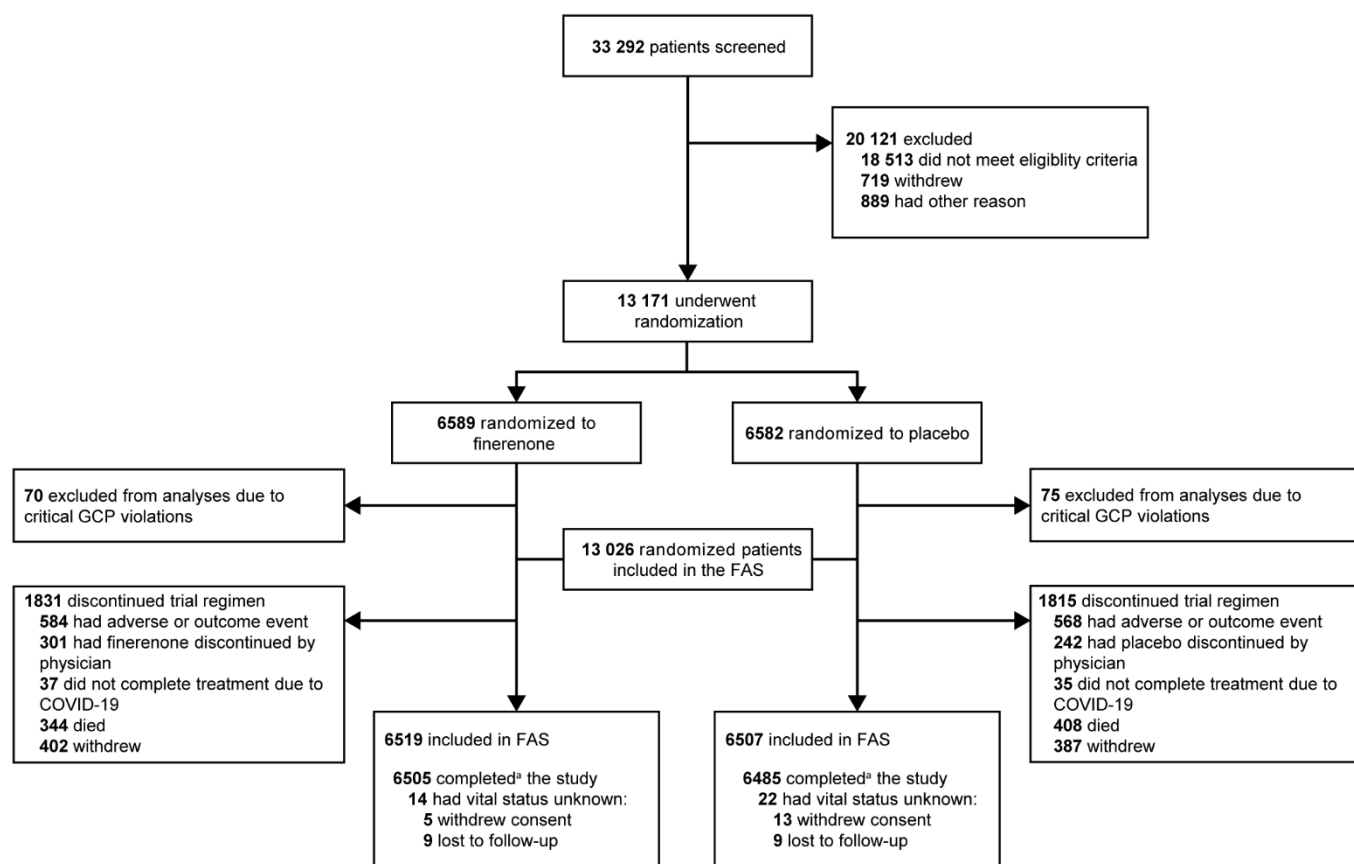


LS = least-squares; UACR = urine albumin-to-creatinine ratio.

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.