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Finerenone cardiovascular and kidney outcomes by age and sex: FIDELITY post hoc analysis of two phase 3, multicentre, double-blind trials

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ABSTRACT

Objectives This study aimed to evaluate the efficacy and safety of finerenone, a selective, non-steroidal mineralocorticoid receptor antagonist, on cardiovascular and kidney outcomes by age and/or sex.

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

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

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

Interventions Randomised 1:1; finerenone or placebo.

Primary and secondary outcome measures Cardiovascular (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure (HHF)) and kidney (kidney failure, sustained ≥57% estimated glomerular filtration rate (eGFR) decline or renal death) composite outcomes.

Results Mean age was 64.8 years; 45.2%, 40.1% and 14.7% were aged <65, 65–74 and ≥75 years, respectively; 69.8% were male. Cardiovascular benefits of finerenone versus placebo were consistent across age (HR 0.94 (95% CI 0.81 to 1.10) (<65 years), HR 0.84 (95% CI 0.73 to 0.98) (65–74 years), HR 0.80 (95% CI 0.65 to 0.99) (≥75 years); $P_{interaction}$=0.42) and sex categories (HR 0.86 (95% CI 0.77 to 0.96) (male), HR 0.89 (95% CI 0.35 to 2.27) (premenopausal female), HR 0.87 (95% CI 0.73 to 1.05) (postmenopausal female); $P_{interaction}$=0.99). Effects on HHF reduction were not modified by age ($P_{interaction}$=0.70) but appeared more pronounced in males ($P_{interaction}$=0.02). Kidney events were reduced with finerenone versus placebo in age groups <65 and 65–74 but not ≥75; no heterogeneity in treatment effect was observed ($P_{interaction}$=0.51). In sex subgroups, finerenone consistently reduced kidney events ($P_{interaction}$=0.85). Finerenone reduced albuminuria and eGFR decline regardless of age and sex. Hyperkalaemia increased with finerenone, but discontinuation rates were <3% across subgroups. Gynaecomastia in males was uncommon across age subgroups and identical between treatment groups.

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

Trial registration numbers NCT02540993, NCT02545049.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ An advantage of this study was the use of combined individual-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, resulting in a large number of patients included in the full analysis set.

⇒ This study did not use predefined age categories, as it was a post hoc analysis, which may have resulted in some of the tests performed being underpowered.

⇒ Limitations present in FIDELITY are present in this analysis, such as the small proportion of Black patients and exclusion of patients with non-albuminuric chronic kidney disease.

INTRODUCTION

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

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

Overactivation of the mineralocorticoid receptor (MR) is associated with CV and kidney diseases.[14 15] In epithelial cells,

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

Despite management with recommended treatments for CKD in T2D, 10%–13% of patients experience CKD progression or kidney failure and are at high risk of CV events, including CV death, within 2–3 years following treatment initiation.[10 21 22] Finerenone, a selective, non-steroidal MR antagonist (MRA), reduced the risk of CKD progression and CV outcomes compared with placebo in patients with CKD and T2D in FIDELITY (The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis), a prespecified pooled analysis of the FIDELIO-DKD (FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease; NCT02540993) and FIGARO-DKD (FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease; NCT02545049) phase 3 trials.[21] However, the influence of age and sex on outcomes with finerenone is unknown. This post hoc analysis evaluated whether the CV and kidney benefits and safety profile of finerenone observed in FIDELITY are consistent in patients with CKD and T2D across ages and in both sexes.

METHODS

Study design and patients

FIDELITY combined individual patient-level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials. The study design, procedures and outcomes for the trials have been previously published.[23–25] These studies were reported following the Consolidated Standards of Reporting Trials reporting guideline.

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

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

Key outcomes

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

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

Outcomes were analysed according to patient age at baseline (<65, 65–74 and ≥75 years) and sex. Females were categorised as either premenopausal or postmenopausal if they were aged <51.4 or ≥51.4 years at baseline, respectively (based on the median age of menopause onset from the Massachusetts Women's Health Study).[26]

Statistical analysis

Statistical analyses were performed as described in FIDELITY.[23] The full analysis set comprised all randomised patients (except those with critical Good Clinical Practice violations, who were prospectively excluded). Safety analyses were performed in the safety analysis set (randomised 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 randomisation up to the end-of-study visit. Stratified Cox proportional hazards models,[27 28] including stratification factors: geographical region, eGFR and albuminuria category at screening, history of CV disease and study, were used for the analysis of time-to-event clinical outcomes. The p values for interaction between the treatment group (finerenone or placebo) and each baseline subgroup (age or sex) were based on stratified Cox proportional hazards models, accounting for the treatment effect, the subgroup effect and their interaction.

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

Patients and public involvement

No patient or public involvement in the current study.

RESULTS

Patients

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

Baseline characteristics

Baseline characteristics were similar across age subgroups except for some key differences (table 1). The overall FIDELITY population was predominantly White (68.1%), the proportion of which increased with age. Mean eGFR was 64, 54 and 48 mL/min/1.73 m^2 in patients aged <65, 65–74 and ≥75 years, respectively. Median UACR was 650, 439 and 332 mg/g in patients aged <65, 65–74 and ≥75 years, respectively. History of CV disease was more common in the ≥75 years group; this trend was also observed for atrial fibrillation/atrial flutter.

Baseline characteristics in sex subgroups are shown in table 1.

Efficacy

CV composite outcome by age

CV composite event rates, including the components of the composite outcome, increased with patient age in both treatment arms (figure 1A and online supplemental efigure 1A). Treatment with finerenone resulted in a numerical reduction in CV composite event rates versus placebo in all age groups (figure 1A); however, no significant heterogeneity was observed for the effect of finerenone across categorical age subgroups ($P_{interaction}$=0.42). There was also no evidence of treatment effect modification when age was modelled as a continuous variable ($P_{interaction}$=0.10). The trend of HR as a function of age was modelled with cubic splines (online supplemental efigure 2A).

HHF event rates were numerically lower with finerenone than placebo in all age subgroups (figure 1A). The effect of finerenone on HHF risk reduction was consistent across age subgroups, with no significant heterogeneity observed ($P_{interaction}$=0.70).

CV composite outcome by sex

CV composite event rates were numerically lower with finerenone than placebo for males, premenopausal females and postmenopausal females (figure 1B and online supplemental efigure 1B). There was no significant heterogeneity in the effect of finerenone on reducing the risk of the CV composite outcome across sex subgroups ($P_{interaction}$=0.99). When age was modelled with cubic splines by sex, the effect of finerenone was consistent with advancing age in males; however, a trend towards a stronger effect in older versus younger females was noted (online supplemental efigure 2B and C). Age distribution by sex is demonstrated in online supplemental efigure 2D.

No heterogeneity was observed in the effect of finerenone on reducing the risk of the CV death, non-fatal myocardial infarction and non-fatal stroke components of the CV composite outcome (online supplemental efigure 1B). However, statistical heterogeneity was observed in the reduction of HHF with finerenone versus placebo ($P_{interaction}$=0.02) and the effect appeared to be more pronounced in males than premenopausal/postmenopausal females (figure 1B). These results persisted after adjustment for differences in baseline age, body mass index, systolic blood pressure, haemoglobin, eGFR, UACR, smoking history and history of atrial fibrillation between sex subgroups ($P_{interaction}$=0.02).

Kidney composite outcome by age

Kidney composite event rates were lower with finerenone than placebo in the <65 years and the 65–74 years groups but were similar in the ≥75 years group (figure 2A). The effect of finerenone on reducing the risk of the kidney composite outcome was consistent across age subgroups, with no significant heterogeneity detected ($P_{interaction}$=0.51) and no evidence of treatment effect modification when age was modelled as a continuous variable ($P_{interaction}$=0.77). The trend of HR as a function of age was modelled with cubic splines (online supplemental efigure 3A).

Kidney composite outcome by sex

Kidney composite event rates were lower with finerenone than placebo in males but were similar in premenopausal and postmenopausal females (figure 2B). There was no significant heterogeneity in the effect of finerenone on reducing the risk of the kidney composite outcome across sex subgroups ($P_{interaction}$=0.85). When age was modelled with cubic splines by sex subgroups, the effect of finerenone suggests trends similar to overall results in males and females across all age groups (online supplemental efigure 3B and C). Age distribution by sex is demonstrated in online supplemental efigure 3D.

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

Finerenone significantly attenuated the least-squares mean change in eGFR from month four to end of treatment (chronic eGFR slope) compared with placebo across all age (p<0.0001 for all three subgroups) (figure 3) and sex subgroups (online supplemental efigure 4). Finerenone reduced UACR

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, years, 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)	0	323 (100)	3615 (100)
Male	9088 (69.8)	4050 (68.8)	3720 (71.3)	1318 (68.8)	9088 (100)	0	0
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*	741 (5.7)	397 (6.7)	247 (4.7)	97 (5.1)	437 (4.8)	32 (9.9)	272 (7.5)
Systolic blood pressure, mm Hg, mean (SD)	136.7±14.2	135.6±14.0	137.4±14.2	138.4±14.6	136.8±14.2	133.0±14.0	136.9±14.3
Diastolic blood pressure, mm Hg, mean (SD)	76.4±9.6	78.8±9.1	74.9±9.4	72.8±9.8	76.5±9.7	80.1±8.4	75.6±9.5
Duration of diabetes, years, mean (SD)	15.4±8.7	13.5±7.6	16.4±8.6	18.6±10.4	15.3±8.5	10.6±7.0	16.0±9.1
HbA1c, %, mean (SD)	7.7±1.4	7.9±1.5	7.6±1.3	7.4±1.2	7.6±1.3	8.2±1.7	7.9±1.4
Serum potassium, mmol/L, mean (SD)	4.4±0.4	4.4±0.5	4.4±0.4	4.4±0.4	4.3±0.4	4.3±0.4	4.4±0.4
eGFR, mL/min/1.73 m^2, mean (SD)	57.6±21.7	64.3±24.0	53.5±18.5	48.1±15.1	57.7±21.2	77.0±28.9	55.6±21.3
UACR, mg/g, median (Q1–Q3)	514.68 (197.8–1147.1)	650.48 (315.2–1363.5)	438.63 (154.1–1030.7)	332.29 (107.8–830.5)	511.53 (200.9–1130.1)	793.52 (376.6–1547.3)	501.47 (173.6–1149.1)
BMI, kg/m^2, mean (SD)	31.3±6.0	32.0±6.4	31.1±5.7	29.6±5.0	31.0±5.6	34.1±7.9	32.0±6.6
Current smoker, n (%)	2093 (16.1)	1283 (21.8)	686 (13.1)	124 (6.5)	1730 (19.0)	35 (10.8)	328 (9.1)

Continued

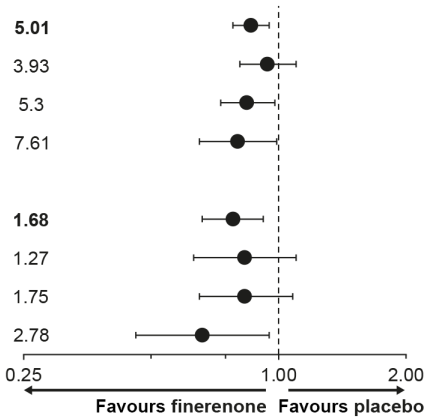
Table 1 Continued

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)
History of CV disease, present, n (%)	5935 (45.6)	2188 (37.2)	2667 (51.1)	1080 (56.4)	4374 (48.1)	56 (17.3)	1505 (41.6)
History of heart failure	1007 (7.7)	413 (7.0)	432 (8.3)	162 (8.5)	630 (6.9)	22 (6.8)	355 (9.8)
History of atrial fibrillation/atrial flutter	1106 (8.5)	266 (4.5)	547 (10.5)	293 (15.3)	867 (9.5)	0	239 (6.6)
Baseline medications, n (%)†							
RAS inhibitors (ACEis/ARBs)	13 003 (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)

*Other: included American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, not reported, multiple.
†Analysis allowed multiple drug groups for the same drug.
ACEi, ACE 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 haemoglobin; Q, quartile; RAS, renin–angiotensin system; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

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



B

Endpoint	Finerenone		Placebo		Hazard Ratio (95% CI)	*P*-Value for Interaction
	n/*N* (%)	*n*/100 PY	*n*/N (%)	*n*/100 PY		
CV composite, sex						
Overall	**825/6519 (12.7)**	**4.34**	**939/6507 (14.4)**	**5.01**	**0.86 (0.78–0.95)**	
Male	579/4481 (12.9)	4.39	675/4607 (14.7)	5.08	0.86 (0.77–0.96)	
Premenopausal female	11/163 (6.7)	2.29	12/160 (7.5)	2.62	0.89 (0.35–2.27)	.9942
Postmenopausal female	235/1875 (12.5)	4.38	252/1740 (14.5)	5.03	0.87 (0.73–1.05)	
HHF, sex						
Overall	**256/6519 (3.9)**	**1.31**	**325/6507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
Male	163/4481 (3.6)	1.20	244/4607 (5.3)	1.78	0.66 (0.54–0.81)	
Premenopausal female	5/163 (3.1)	1.02	4/160 (2.5)	0.85	1.39 (0.33–5.93)	.0245
Postmenopausal female	88/1875 (4.7)	1.61	77/1740 (4.4)	1.50	1.06 (0.78–1.44)	

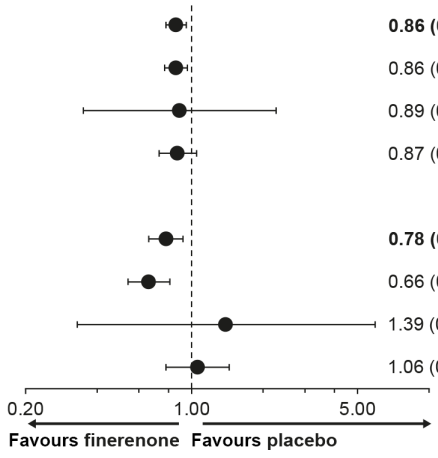


Figure 1 Analysis of CV composite outcome and HHF according to (A) age and (B) sex. CV composite outcome includes CV death, non-fatal myocardial infarction, non-fatal stroke or HHF. CV, cardiovascular; HHF, hospitalisation for heart failure; PY, patient-years.

over time compared with placebo regardless of age and sex (online supplemental efigure 5).

Safety

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

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

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

In FIDELITY, finerenone increased the risk of any hyperkalaemia event versus placebo; similar findings were observed in all age and sex subgroups, except

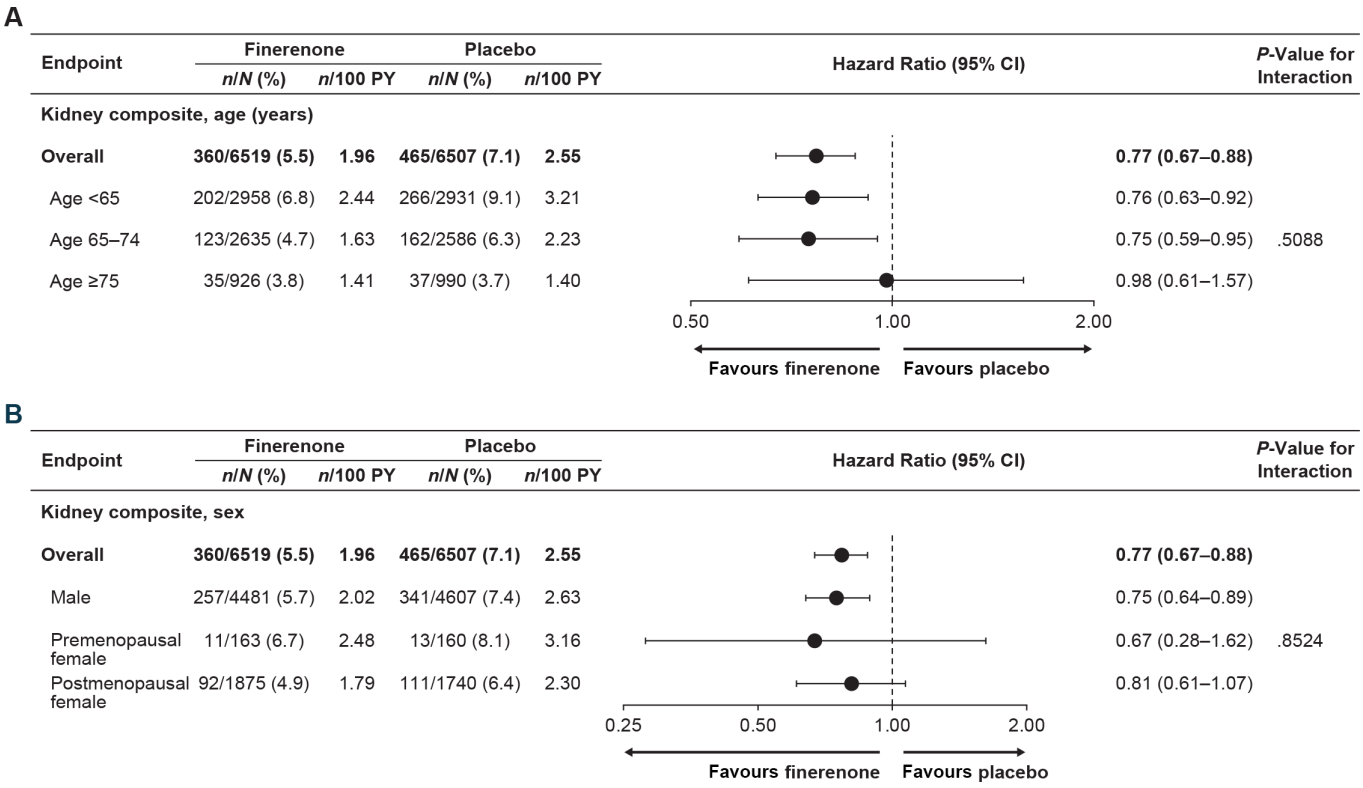


Figure 2 Analysis of kidney composite outcome according to (A) age and (B) sex. Kidney composite outcome includes kidney failure, sustained ≥57% eGFR decline or renal death. eGFR, estimated glomerular filtration rate; PY, patient-years.

premenopausal females (online supplemental etable 2). The incidences of any hyperkalaemia AEs leading to discontinuation of study drug and any serious hyperkalaemia AEs leading to hospitalisation were low across all age and sex subgroups (<3% and <2%, respectively). However, the relative risk of treatment discontinuation because of hyperkalaemia with finerenone versus placebo increased with advancing age (relative risk (95% CI) for ages 45–64, 65–74 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; online supplemental efigure 6). Treatment-emergent serum potassium levels >5.5 mmol/L and >6.0 mmol/L were more frequent with finerenone than placebo, being consistent across all age and sex subgroups. The incidence of gynaecomastia in males was the same with finerenone (0.2%) and placebo (0.2%) across all ages.

DISCUSSION

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

The current results are supported by findings from a pharmacokinetics (PK) analysis based on FIDELIO-DKD and FIGARO-DKD data, in which both age and sex were tested as covariates for a population PK model, and their effect on finerenone exposure was not significant, suggesting a lack of influence of these factors on the PK of the drug.[30] Additionally, the results for the CV outcome in this analysis are similar to findings from other studies of MRAs in HF. In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), age did not affect the efficacy of spironolactone in patients with HF with reduced ejection fraction (primary composite outcome: CV death, aborted cardiac arrest and HHF; secondary outcomes included CV death, all-cause death and HHF).[31] Moreover, in analyses of HF studies (RALES (Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure), EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms), and TOPCAT), MRAs reduced morbidity and mortality in elderly patients,[32] demonstrating a consistent benefit regardless of sex.[33] In contrast to our results, female sex was associated with poorer kidney outcomes versus male sex in patients receiving a steroidal MRA for bilateral primary aldosteronism.[34] The MR can be activated by different drivers in different diseases; MR activation in diabetes is driven by additional factors other than high aldosterone in comparison with primary aldosteronism, which may account for differences in outcomes observed across different indications.[35]

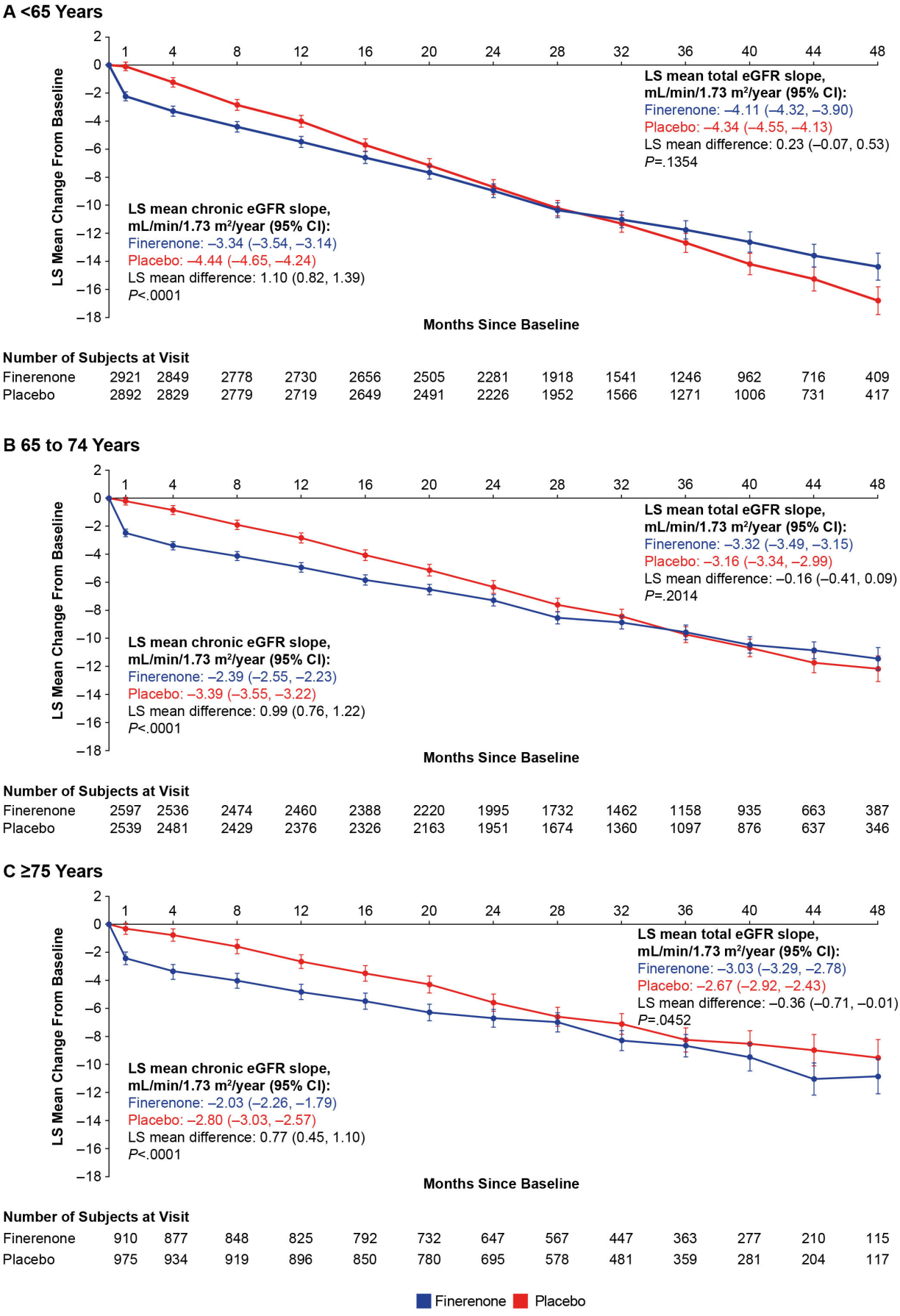


Figure 3 LS mean change in eGFR from baseline, chronic and total slopes over time by age. Chronic eGFR slope from month four to end-of-study visit. eGFR, estimated glomerular filtration rate; LS, least squares.

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

Preclinical data suggest that different molecular mechanisms drive endothelial dysfunction in male and female mice[39 40] and that increased age and male sex are associated with MR overactivation, which is linked to vascular stiffness and endothelial dysfunction.[41 42] In human aortic smooth muscle cells, MR expression increased with age, leading to epigenetic changes associated with increased vascular stiffness. These effects were reversed with MR inhibition.[43] In vitro, MR expression in the whole aortae and early passage aortic vascular smooth muscle cells was increased in aged (30 months) versus adult (8 months) rat cells.[41] In a preclinical mouse model, aortic stiffness occurred earlier in male than female mice and correlated with the timing of increased aortic MR expression; vascular stiffness was prevented in smooth muscle cell MR-deficient mice.[42] These data suggest that elderly males may derive the greatest benefit from finerenone; indeed, in this analysis, finerenone-treated males had lower risk of the CV composite outcome and HHF versus placebo across age groups, including ≥75 years. Moreover, statistical heterogeneity was observed for HHF by sex, persisting after adjustment for differences in baseline characteristics, which might suggest a more pronounced effect of finerenone on HHF reduction in the male subgroup compared with the two female subgroups. However, because of the small sample size of the sex subgroups (especially that of the premenopausal female subgroup), definitive conclusions cannot be reached based on this finding.

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

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

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

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and these trials were performed in accordance with the principles of the Declaration of Helsinki and were approved by the competent authorities and ethic committees at each site. All participants provided written informed consent. Participants gave informed consent to participate in the study before taking part.

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