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A FIDELITY Analysis on Finerenone With SGLT-2i and GLP-1RA in CKD

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Introduction: Finerenone demonstrated kidney and cardiovascular benefits in participants with chronic kidney disease (CKD) and type 2 diabetes (T2D) on optimized renin-angiotensin system (RAS) inhibition in FIDELITY, a pooled individual-level analysis of 2 clinical trials. Considering that treatment recommendations increasingly support combination therapies for CKD and T2D, this FIDELITY subanalysis assessed the efficacy and safety of finerenone versus placebo when taken with concomitant sodium-glucose cotransporter-2 inhibitor (SGLT-2i) and/or glucagon-like peptide-1 receptor agonist (GLP-1RA).

Methods: Change in urine albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR) and systolic blood pressure (SBP) over time, and treatment-emergent adverse events (TEAEs) were analyzed in subgroups by concomitant medication at baseline as follows: (i) combined SGLT-2i and GLP-1RA ($n = 167$), (ii) no SGLT-2i or GLP-1RA ($n = 11{,}341$), (iii) SGLT-2i only ($n = 706$), and (iv) GLP-1RA only ($n = 776$).

Results: Finerenone led to a greater reduction than with placebo in UACR and SBP from baseline to month 4 across all concomitant medication subgroups. At month 12, the greatest UACR reduction difference between the treatment arms was observed in the finerenone subgroup with combined SGLT-2i and GLP-1RA. Decline of eGFR from baseline was slower with finerenone than with placebo across all subgroups. The safety profile of finerenone was not modified by concomitant SGLT-2i and/or GLP-1RA use; hyperkalemia events leading to treatment discontinuation or hospitalization with finerenone were low.

Conclusion: The concomitant use of finerenone with SGLT-2i and/or GLP-1RA demonstrated potential synergistic effects on preserving kidney function and reducing blood pressure versus placebo in people with CKD and T2D.

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T2D is a leading cause of CKD, with approximately 40% of people with T2D having CKD.[1] People with CKD and T2D have higher risks of cardiovascular (CV) morbidity and mortality, and these risks increase with the severity and stage of CKD.[2,3] The treatment landscape for slowing CKD progression and reducing CV risk in people with T2D has evolved substantially

in recent years.[4,5] Previously, only lifestyle intervention and metabolic management were available; now, however, clinical practice guidelines recommend RAS inhibitors, SGLT-2is, and the nonsteroidal mineralocorticoid receptor antagonist, finerenone for CV and kidney protection.[6–10] GLP-1RAs with proven CV benefit are also recommended for people with a history of CV disease.[6,8,10]

RAS inhibition with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers has been the cornerstone of treatment for albuminuric CKD in people with T2D and hypertension.[6,7] The addition of SGLT-2i is recommended for all people with CKD (eGFR $\geq$ 20 ml/min per 1.73 m^2), including those with T2D, because of their proven kidney and CV benefits.[6–8] The nonsteroidal mineralocorticoid receptor antagonist, finerenone, which demonstrated significant reductions in the risk of CV and kidney outcomes in participants with CKD and T2D in FIDELITY (a prespecified pooled analysis of the phase 3 FIDELIO-DKD and FIGARO-DKD trials),[11–13] is recommended for people with T2D who are at risk of CKD progression and CV events with persistent albuminuria despite optimized RAS blockade.[6–8] More recently, GLP-1RAs have been added to recommendations for people with CKD (eGFR $>$ 15 ml/min per 1.73 m^2) and T2D who have not achieved glycemic control despite treatment with metformin and/or SGLT-2is.[6–8] Results from the FLOW study have subsequently demonstrated that the GLP-1RA, semaglutide, reduces the risk of adverse kidney outcomes in participants with CKD and T2D.[14]

Concomitant therapy with these 4 distinct classes of drugs is an attractive concept for the nephrology, cardiology, and diabetes communities, because each of these 4 drug classes use different mechanism of actions to address the perturbations in hemodynamics, metabolism, inflammation, and fibrosis that characterize CKD in people with T2D.[4] The benefits of finerenone versus placebo on CV and kidney outcomes in participants with CKD and T2D was shown in the FIDELITY analysis irrespective of concomitant use with SGLT-2i or GLP-1RA.[15,16] Furthermore, it was previously reported that participants in FIDELITY who were taking finerenone with concomitant SGLT-2i and GLP-1RA had a 40% reduction in UACR from baseline to month 4 with finerenone versus placebo plus both therapies.[15] The same study suggested that increasing the number of kidney and CV protective agents at baseline did not modify the treatment effect of finerenone. Therefore, the aim of this FIDELITY *post hoc* subanalysis was to explore the efficacy and safety of finerenone when used concomitantly with SGLT-2i and/or GLP-1RA.

METHODS

Study Design and Participants

This FIDELITY subanalysis combines individual participant-level data from the FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) phase 3 trials. The design of the FIDELIO-DKD and FIGARO-DKD trials, along with the results from the FIDELITY analysis, have been published previously.[11–13] Briefly, adults (aged $\geq$ 18 years) with CKD (UACR: 30 to $<$ 300 mg/g and eGFR: 25 to $\leq$ 90 ml/min per 1.73 m^2, or UACR: 300 to $\leq$ 5000 mg/g and eGFR $\geq$ 25 ml/min per 1.73 m^2) and T2D, on optimized RAS blockade were eligible to participate, if they had a serum potassium level $\leq$ 4.8 mmol/l at both screening and run-in, and were without a clinical diagnosis of symptomatic chronic heart failure with reduced ejection fraction.

SGLT-2i and/or GLP-1RA use was permitted at baseline and throughout the FIGARO-DKD and FIDELIO-DKD trials; initiation of these therapies was allowed during the trials.[11,12] Participants were not stratified according to SGLT-2i or GLP-1RA use at baseline. Medications taken on or before the day of randomization and ended after randomization were considered as baseline use, whereas those that began after the start of study drug were considered as new concomitant medications.

Randomization and Masking

Participants were randomly assigned (1:1) to receive once-daily oral treatment with finerenone or matching placebo. Participants with an eGFR of 25 to $<$ 60 ml/min per 1.73 m^2 at the screening visit received an initial dose of 10 mg once daily, whereas those with an eGFR $\geq$ 60 ml/min per 1.73 m^2 received an initial dose of 20 mg once daily. From month 1 onward, the target dose of finerenone or placebo was 20 mg once daily. Doses were increased from 10 mg to 20 mg once daily, provided that the serum potassium level was $\leq$ 4.8 mmol/l and the eGFR was stable. Study drug was withheld if potassium concentrations were $>$ 5.5 mmol/l and restarted when potassium levels dropped to $<$ 5.0 mmol/l. Randomizations for FIDELIO-DKD and FIGARO-DKD were stratified by region (North America, Europe, Asia, Latin America, and other), albuminuria at screening (moderately or severely increased), and eGFR at screening (25 to $<$ 45, 45 to $<$ 60, $\geq$ 60 ml/min per 1.73 m^2). History of CV disease was an additional stratification factor in FIGARO-DKD.

Outcomes

For this FIDELITY subanalysis, efficacy outcomes were change in the following: (i) UACR, (ii) eGFR slope, and

(iii) SBP from baseline over time; safety outcomes were TEAEs, including investigator-reported hyperkalemia, laboratory evaluations for hyperkalemia (serum potassium levels $>$ 5.5 and $>$ 6.0 mmol/l), and incidence of treatment discontinuation and hospitalization for hyperkalemia. Adverse events were considered treatment-emergent if they started or worsened during study drug intake or $\leq$ 3 days after any temporary or permanent interruption.[11,12] For the assessment of outcomes, participants were categorized into 4 subgroups based on concomitant medication use with finerenone or placebo at baseline as follows: (i) combined SGLT-2i and GLP-1RA, (ii) no SGLT-2i or GLP-1RA, (iii) SGLT-2i only, and (iv) GLP-1RA only.

Statistical Analysis

Demographics were reported according to concomitant medication subgroups, and efficacy outcomes were analyzed according to treatment arms in each concomitant medication subgroup using the full analysis set, which included all randomized participants who did not have critical Good Clinical Practice violations. Types of SGLT-2i and GLP-1RA, and changes in their usage were reported. Safety analyses were performed on the safety analysis set, which included randomized participants who took $\geq$ 1 dose of study drug and were without critical Good Clinical Practice violations.

Changes in UACR, eGFR, and SBP over time were analyzed using mixed effects models with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history, study (FIDELIO-DKD or FIGARO-DKD), time during the study, and the interactions of treatment by time, baseline value by time, and treatment by study as covariates. For UACR, the least-squares (LS)-mean ratio to baseline was reported for the finerenone and placebo arms in each concomitant medication subgroup. LS-mean changes from baseline were reported for eGFR and SBP. A 2-slope linear spline mixed effects model based on the methods described by Vonesh *et al.*[17] with a specified change point at month 4 was used to estimate the chronic eGFR slope (month 4 to the end-of-study visit) and the total eGFR slope (baseline to month 48). Differences between finerenone and placebo were reported using LS-mean differences. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

Participants

Participants were followed up for a median of 3.0 years (interquartile range: 2.3–3.8 years). Of 12,990 participants included in this analysis, 167 (1.3%) were taking combined SGLT-2i and GLP-1RA at baseline, 706 (5.4%) were taking SGLT-2i only, 776 (6.0%) were taking GLP-1RA only, and the remaining 11,341 (87.3%) were taking neither. A total of 86 of 6498 participants (1.3%) in the finerenone arm and 81 of 6492 (1.2%) in the placebo arm were taking the combined SGLT-2i and GLP-1RA at baseline (Supplementary Table S1). An additional 463 participants (3.6%) initiated combined SGLT-2i and GLP-1RA therapy during the trials (224/6498 [3.4%] in the finerenone arm and 239/6492 [3.7%] in the placebo arm). The most frequently used SGLT-2i and GLP-1RA combination was liraglutide and empagliflozin (53 [0.4%] at baseline and 208 [1.6%] on-treatment; Supplementary Table S2).

Baseline Characteristics

Overall, the baseline demographics of participants were generally balanced between the finerenone and placebo arms (Supplementary Table S3); however, there were some notable differences between the subgroups with concomitant SGLT-2i and/or GLP-1RA use (Table 1 and Supplementary Table S3). Compared with participants who did not receive SGLT-2i or GLP-1RA at baseline, participants who received combined treatment with these therapies tended to be younger ($\sim$ 4 years) and White, with the majority of participants being from western Europe and Asia (Table 1 and Supplementary Table S4). Participants on concomitant SGLT-2i and/or GLP-1RA had a higher mean body mass index, greater mean waist circumference ($\sim$ 10 cm) and a higher mean heart rate. In addition, participants who were taking combined SGLT-2i and GLP-1RA had lower median baseline UACR and higher mean eGFR than those on neither medication (UACR: 441.8 mg/g vs. 522.7 mg/g, respectively, and eGFR: 64.9 ml/min per 1.73 m^2 vs. 56.9 ml/min per 1.73 m^2, respectively). A higher proportion of participants in the combined SGLT-2i and GLP-1RA subgroup were taking metformin (132/167 [79.0%]) than those in the no SGLT-2i or GLP-1RA subgroup (6330/11,341 [55.8%]).

Efficacy

Ratio to Baseline of UACR Over Time

Finerenone led to a greater reduction in UACR from baseline to month 4 that was nominally significant versus placebo, irrespective of concomitant SGLT-2i and/or GLP-1RA use at baseline (Figure 1). Reductions in the finerenone arm relative to placebo at month 4 were 38%, 31%, 37%, and 38% in the combined SGLT-2i and GLP-1RA, no SGLT-2i/GLP-1RA, SGLT-2i–only, and GLP-1RA–only subgroups, respectively. Greater reductions in UACR with

Table 1. Baseline demographic and clinical characteristics by concomitant SGLT-2i and/or GLP-1RA use at baseline (FAS)

Characteristic	Combined SGLT-2i and GLP-1RA use (n = 167)	No SGLT-2i or GLP-1RA use (n = 11 341)	SGLT-2i use only (n = 706)	GLP-1RA use only (n = 776)
Age, yrs, mean (SD)	61.29 (9.75)	65.10 (9.51)	61.86 (9.62)	63.24 (8.76)
Sex, male, *n* (%)	125 (74.9)	7840 (69.1)	543 (76.9)	550 (70.9)
Race, *n* (%)				
White	133 (79.6)	7638 (67.3)	511 (72.4)	587 (75.6)
Black/African American	5 (3.0)	463 (4.1)	14 (2.0)	38 (4.9)
Asian	25 (15.0)	2553 (22.5)	157 (22.2)	125 (16.1)
Duration of diabetes, yrs, mean (SD)	16.30 (7.77)	15.29 (8.76)	15.41 (8.14)	16.95 (8.21)
HbA1c, %, mean (SD)	7.84 (1.17)	7.67 (1.37)	7.98 (1.23)	7.80 (1.23)
BMI, kg/m^2, mean (SD)	34.28 (6.34)	31.02 (5.94)	32.13 (5.88)	34.12 (5.98)
Waist circumference, cm, mean (SD)	116.14 (14.47)	106.24 (14.92)	110.02 (14.64)	114.37 (15.37)
Systolic blood pressure, mm Hg, mean (SD)	133.44 (14.36)	137.02 (14.15)	133.24 (14.40)	136.71 (14.31)
Serum potassium, mmol/l, mean (SD)	4.31 (0.39)	4.36 (0.44)	4.29 (0.42)	4.30 (0.43)
eGFR, ml/min per 1.73 m^2, mean (SD)	64.89 (21.03)	56.91 (21.59)	66.57 (21.11)	57.44 (21.49)
eGFR, ml/min per 1.73 m^2, *n* (%)				
< 25	0 (0)	155 (1.4)	0 (0)	7 (0.9)
25 to < 45	30 (18.0)	3818 (33.7)	112 (15.9)	264 (34.0)
45 to < 60	45 (26.9)	2982 (26.3)	194 (27.5)	205 (26.4)
≥ 60	92 (55.1)	4383 (38.6)	400 (56.7)	300 (38.7)
UACR, mg/g, median (Q1–Q3)	441.76 (186.65–903.59)	522.71 (202.01–1168.05)	449.14 (184.97–959.04)	492.79 (174.84–1085.13)
UACR, mg/g, *n* (%)				
< 30	2 (1.2)	199 (1.8)	14 (2.0)	15 (1.9)
30 to <300	58 (34.7)	3545 (31.3)	223 (31.6)	255 (32.9)
≥ 300	107 (64.1)	7592 (66.9)	469 (66.4)	506 (65.2)
Current smoker, *n* (%)	25 (15.0)	1815 (16.0)	137 (19.4)	105 (13.5)
Heart rate, bpm, mean (SD)	77.91 (10.86)	72.64 (11.35)	74.17 (11.69)	77.19 (11.45)
hs-CRP, mg/l, median (Q1–Q3)	2.20 (1.13–4.95)	2.21 (0.95–5.17)	2.25 (1.07–4.75)	2.31 (0.92–5.03)
History of hyperkalemia, *n* (%)	2 (1.2)	188 (1.7)	10 (1.4)	24 (3.1)
History of diabetic retinopathy, *n* (%)	66 (39.5)	4301 (37.9)	255 (36.1)	319 (41.1)
History of HF, *n* (%)	4 (2.4)	925 (8.2)	42 (5.9)	36 (4.6)
History of atrial fibrillation,[a] *n* (%)	9 (5.4)	957 (8.4)	63 (8.9)	75 (9.7)
History of CV disease, *n* (%)	72 (43.1)	5191 (45.8)	332 (47.0)	333 (42.9)
History of coronary artery disease, *n* (%)	59 (35.3)	3447 (30.4)	249 (35.3)	238 (30.7)
History of hypertension, *n* (%)	162 (97.0)	10 926 (96.3)	687 (97.3)	756 (97.4)
Medication use at baseline,[b] *n* (%)				
RAS inhibitors (ACEis or ARBs)	166 (99.4)	11 321 (99.8)	705 (99.9)	775 (99.9)
Beta blockers	88 (52.7)	5644 (49.8)	343 (48.6)	424 (54.6)
Diuretics	87 (52.1)	5787 (51.0)	350 (49.6)	477 (61.5)
Statins	148 (88.6)	8018 (70.7)	588 (83.3)	633 (81.6)
Potassium-lowering agents	0 (0)	166 (1.5)	7 (1.0)	9 (1.2)
Potassium supplements	7 (4.2)	317 (2.8)	17 (2.4)	44 (5.7)
Other glucose-lowering agents				
Insulin and analogues	114 (68.3)	6598 (58.2)	399 (56.5)	509 (65.6)
DPP-4 inhibitors	7 (4.2)	2961 (26.1)	248 (35.1)	39 (5.0)
Sulphonamides	29 (17.4)	2976 (26.2)	189 (26.8)	184 (23.7)
Metformin	132 (79.0)	6330 (55.8)	558 (79.0)	519 (66.9)
Alpha glucosidase inhibitors	3 (1.8)	591 (5.2)	32 (4.5)	26 (3.4)
Meglitinides	7 (4.2)	461 (4.1)	22 (3.1)	39 (5.0)
Thiazolidinediones	12 (7.2)	412 (3.6)	46 (6.5)	45 (5.8)

ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; bpm, beats per minute; CV, cardiovascular; DDP-4, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FAS, full analysis set; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; Q, quartile; RAS, renin-angiotensin system; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.
[a]Includes atrial flutter.
[b]Multiple drug groups per drug are possible. Therefore, the same drug may be counted in more than one category for the same subject. Medications taken on or before day of randomization and ended after randomization are included in this table.
Patient demographics were conducted on the FAS, which included all 12 990 randomized participants.

finerenone than with placebo persisted throughout the study in all 4 subgroups. At month 12, the greatest reduction in UACR was observed in the finerenone subgroup with combined SGLT-2i and GLP-1RA treatment (Figure 1). At month 24, LS-mean UACR ratios to baseline in the combined SGLT-2i and

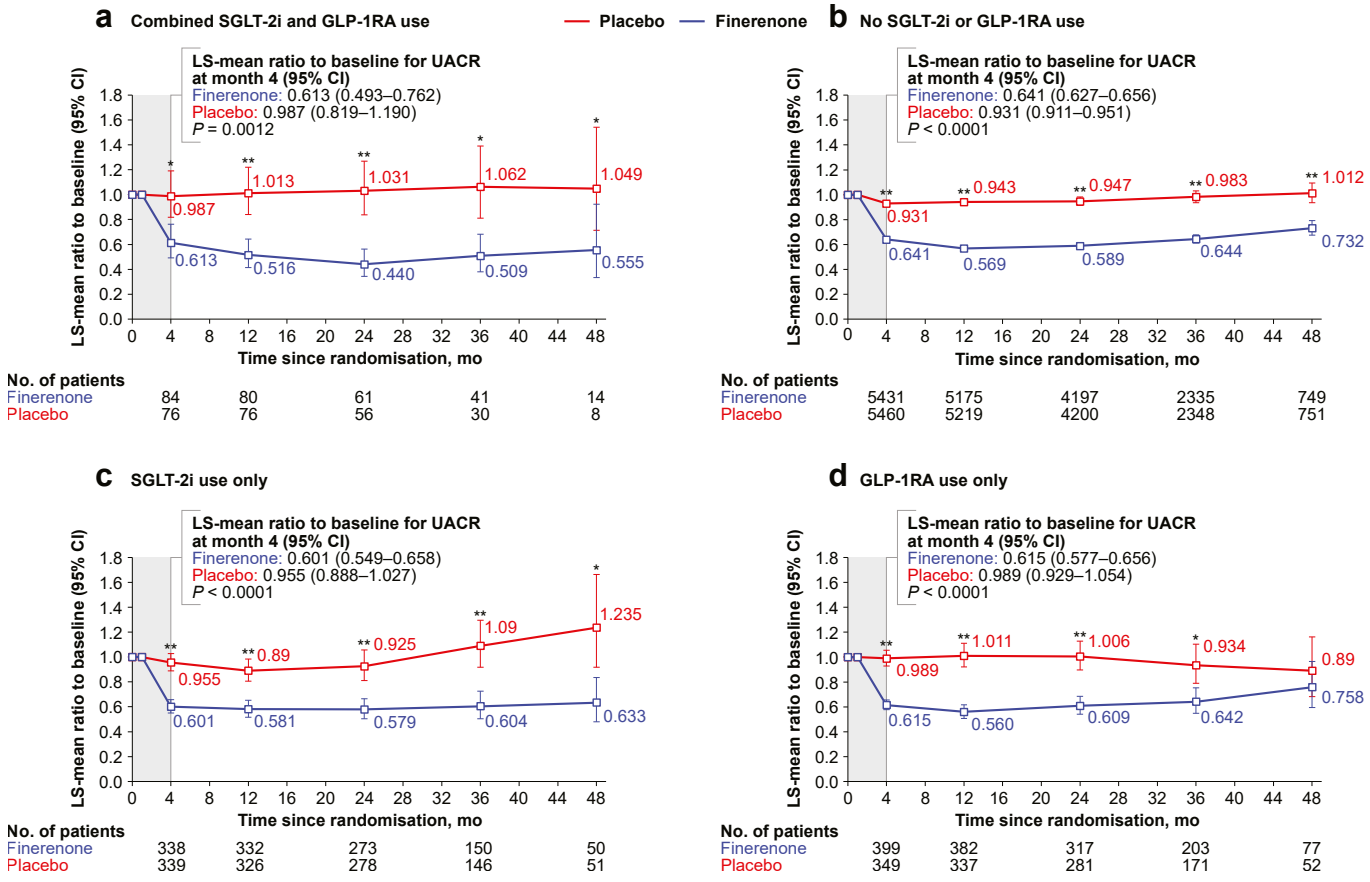

Figure 1. Least-squares–mean ratio to baseline for UACR over time by SGLT-2i and/or GLP-1RA use. For each subgroup category, a mixed model was applied with factors of treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history, time, treatment*time, study, study*treatment, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariates. Values after the onset of end-stage kidney disease were excluded from this analysis. Treatment ratio shows finerenone versus placebo. Treatment group comparisons *P* values: $*P < 0.05$; $**P < 0.0001$. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least-squares; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

GLP-1RA group were 0.44 for finerenone versus 1.03 for placebo (LS-mean treatment ratio: 0.43; 95% confidence interval [CI]: 0.31–0.59; $P < 0.0001$). Respective values in the other subgroups were 0.59 versus 0.95 (LS-mean treatment ratio: 0.62; 95% CI: 0.59–0.65; $P < 0.0001$) in the no SGLT-2i/GLP-1RA subgroup, 0.58 versus 0.93 (LS-mean treatment ratio, 0.63; 95% CI: 0.52–0.76; $P < 0.0001$) in the SGLT-2i–only subgroup, and 0.61 versus 1.01 (LS-mean treatment ratio, 0.61; 95% CI: 0.51–0.71; $P < 0.0001$) in the GLP-1RA–only subgroup. UACR remained lower with finerenone than with placebo thereafter irrespective of subgroup.

Change in eGFR From Baseline Over Time

Over time, eGFR decline was slower with finerenone than with placebo, irrespective of concomitant SGLT-2i and/or GLP-1RA use at baseline (Figure 2). Total eGFR slope from baseline to month 48 was lower with finerenone than with placebo in all subgroups, although the data were not significant in subgroups where participants were concomitantly treated with an SGLT-2i. There was an acute decline in eGFR in the finerenone arm at month 1 across all subgroups, with a greater acute decline observed in participants in the combined SGLT-2i and GLP-1RA subgroup (LS-mean treatment difference: −4.22 ml/min per 1.73 m^2; 95% CI: −7.28 to −1.15) than in the no SGLT-2i/GLP-1RA subgroup (LS-mean treatment difference: −2.19 ml/min per 1.73 m^2; 95% CI: −2.48 to −1.90), SGLT-2i–only subgroup (LS-mean treatment difference: −2.39 ml/min per 1.73 m^2; 95% CI: −3.59 to −1.20), and the GLP-1RA–only subgroup (LS-mean treatment difference −1.38 ml/min per 1.73 m^2; 95% CI: −2.52 to −0.24). Thereafter, the rate of eGFR decline in the finerenone arm attenuated compared with placebo, and less decline in eGFR was observed in the chronic eGFR slope from month 4 to the end-of-study visit with finerenone than with placebo in all subgroups. A difference in the chronic eGFR slope was observed with

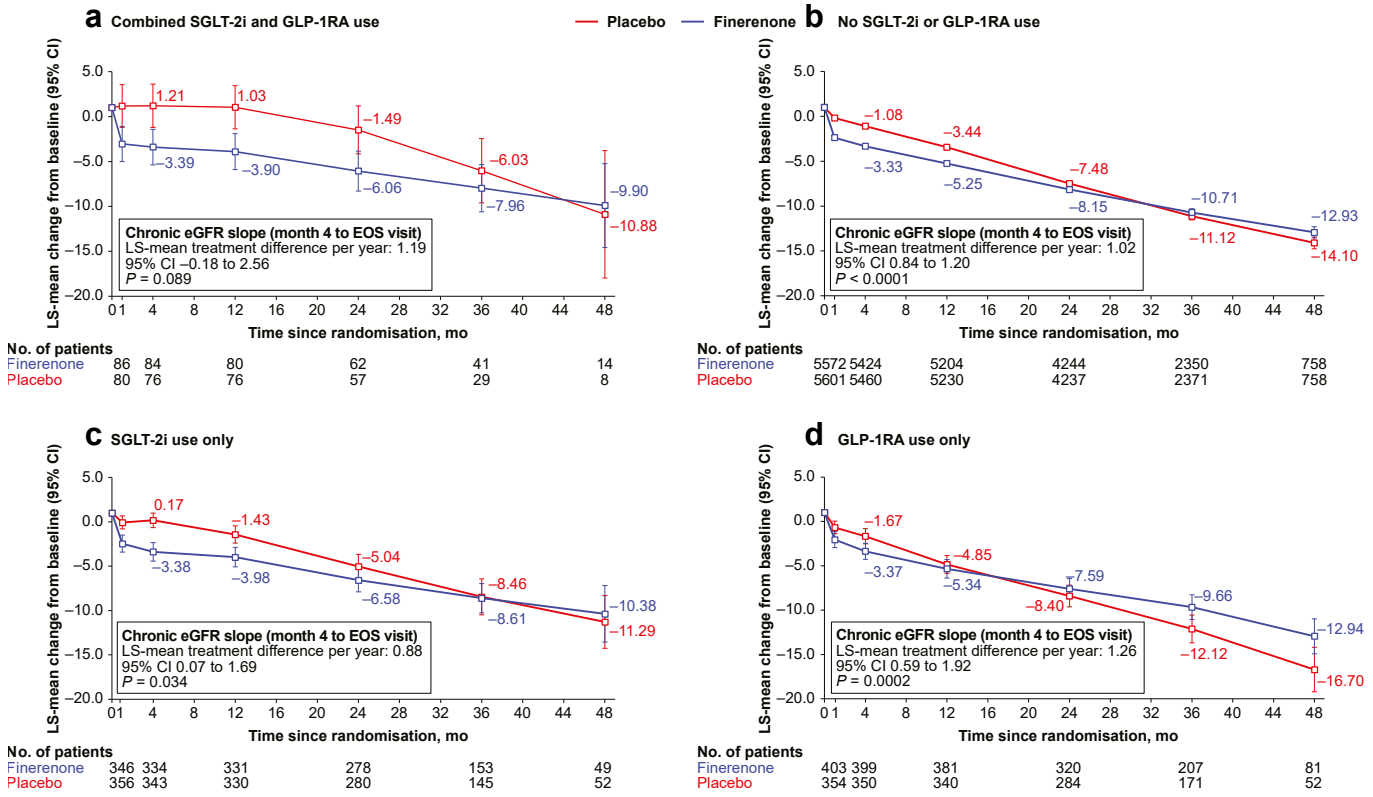

Figure 2. Least-squares–mean change in eGFR from baseline over time by SGLT-2i and/or GLP-1RA use. For each subgroup category, a mixed model was applied with factors of treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history, time, treatment*time, study, baseline value nested within eGFR category at screening, baseline value*time, and treatment*study interaction as covariates. Values after the onset of end-stage kidney disease were excluded from this analysis. Chronic eGFR slope was estimated using a 2-slope linear spline mixed model for repeated measures analysis. Treatment difference displays finerenone versus placebo. Least-squares–mean changes from baseline are presented as ml/min per 1.73 m^2. Chronic eGFR slope data are presented as ml/min per 1.73 m^2/yr. Treatment difference shows finerenone versus placebo. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOS, end of study; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least-squares; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

finerenone versus placebo irrespective of concomitant SGLT-2i and/or GLP-1RA use at baseline and was nominally significant in all subgroups apart from the combined SGLT-2i and GLP-1RA subgroup (LS-mean treatment difference: 1.19 ml/min per 1.73 m^2/yr, 95% CI: −0.18 to 2.56, $P = 0.089$ for the combined SGLT-2i and GLP-1RA subgroup compared with LS-mean treatment difference: 1.02 ml/min per 1.73 m^2/yr, 95% CI: 0.84–1.20, $P < 0.0001$ in the no SGLT-2i/GLP-1RA subgroup; LS-mean treatment difference: 0.88 ml/min per 1.73 m^2/yr, 95% CI: 0.07–1.69, $P = 0.034$ in the SGLT-2i–only subgroup; and LS-mean treatment difference: 1.26 ml/min per 1.73 m^2/yr; 95% CI: 0.59–1.92, $P = 0.0002$ in the GLP-1RA–only subgroup; Figure 2).

Change in Blood Pressure From Baseline Over Time

Finerenone led to a reduction in mean SBP from baseline to month 4 that was nominally significant versus placebo, irrespective of concomitant SGLT-2i and/or GLP-1RA use at baseline, with the change apparent at month 1 (Figure 3). At month 4, the greatest reduction in SBP was observed in participants taking finerenone with combined SGLT-2i and GLP-1RA treatment (LS-mean treatment difference: −5.77 mm Hg, 95% CI: −10.06 to −1.48, $P = 0.0085$); SBP reductions with finerenone versus placebo were observed in the no SGLT-2i/GLP-1RA (LS-mean treatment difference: −3.63 mm Hg, 95% CI: −4.13 to −3.13; $P < 0.0001$), SGLT-2i–only (LS-mean treatment difference: −2.69 mm Hg, 95% CI: −4.67 to −0.71, $P = 0.0078$) and GLP-1RA–only subgroups (LS-mean treatment difference: −3.76 mm Hg, 95% CI: −5.80 to −1.73, $P = 0.0003$). Mean SBP was generally lower with finerenone than placebo and this persisted throughout the trials, irrespective of concomitant SGLT-2i and/or GLP-1RA use (Figure 3).

Safety Outcomes

Overall

The overall safety profile of finerenone was not modified by concomitant use of SGLT-2i and/or GLP-1RA at baseline. The incidences of TEAEs and serious TEAEs

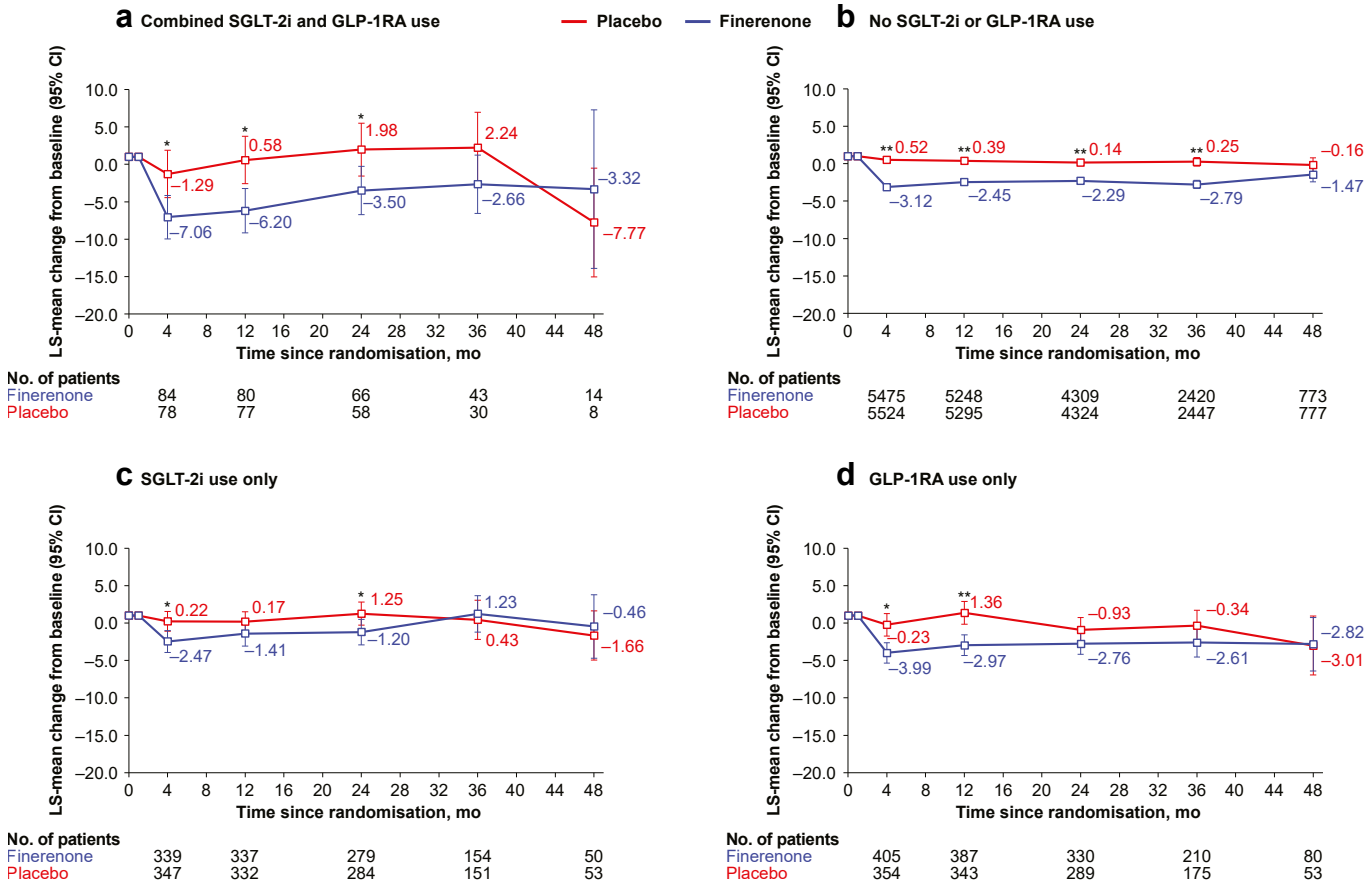

Figure 3. Least-squares–mean change in SBP from baseline over time by SGLT-2i and/or GLP-1RA use. For each subgroup category, a mixed model was applied with factors of treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history, time, treatment*time, study, baseline value and baseline value*time as covariates. Separate unstructured covariance patterns are estimated for each treatment group. Treatment difference shows finerenone versus placebo. Treatment group comparisons P values: *$P < 0.05$; **$P < 0.0001$. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; LS, least-squares; SBP, systolic blood pressure; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

were similar between treatment arms, irrespective of SGLT-2i and/or GLP-1RA use (Table 2). Adverse events leading to discontinuation of finerenone were low. TEAEs leading to discontinuation were lowest in the combined SGLT-2i and GLP-1RA subgroup with finerenone (3/86 [3.5%] vs. 7/81 [8.6%] with placebo) compared with the no SGLT-2i/GLP-1RA (364/5643 [6.5%] vs. 308/5676 [5.4%] with placebo), SGLT-2i–only (15/350 [4.3%] vs. 16/356 [4.5%] with placebo) and GLP-1RA–only subgroups (32/410 [7.8%] vs. 19/361 [5.3%] with placebo). TEAEs affecting ≥ 5% of participants are listed in Supplementary Table S5 and were generally balanced across the 4 subgroups.

Hyperkalemia

The overall incidence of investigator-reported hyperkalemia was higher with finerenone versus placebo (908/6489 participants [14.0%] vs. 448/6474 participants [6.9%], respectively) (Table 2). Hyperkalemia events observed with finerenone or placebo were 12 of 86 participants (14.0%) versus 5 of 81 participants (6.2%) in the combined SGLT-2i and GLP-1RA group, 801 of 5643 participants (14.2%) versus 405 of 5676 participants (7.1%) in the no SGLT-2i/GLP-1RA group, 33 of 350 participants (9.4%) versus 7 of 356 participants (2.0%) in the SGLT-2i–only group and 62 of 410 participants (15.1%) versus 31 of 361 participants (8.6%) in the GLP-1RA–only group, respectively. Hyperkalemia events with finerenone leading to treatment discontinuation or hospitalization were low across the subgroups, and none were reported in the combined SGLT-2i and GLP-1RA subgroup. Laboratory-confirmed serum potassium > 5.5 mmol/l was more common with finerenone than with placebo in all 4 subgroups, but less frequent in both the finerenone and placebo arms with combined SGLT-2i and GLP-1RA (7/86 participants [8.1%] vs. 3/80 participants [3.8%], respectively) and SGLT-2i only (27/343 participants

Table 2. Treatment-emergent adverse events, hyperkalemia and serum [K^+] by SGLT-2i and/or GLP-1RA use at baseline (SAS)

	Combined SGLT-2i and GLP-1RA use (n = 167)		No SGLT-2i or GLP-1RA use (n = 11 319)		SGLT-2i use only (n = 706)		GLP-1RA use only (n = 771)	
Characteristic, n (%)	Finerenone (n = 86)	Placebo (n = 81)	Finerenone (n = 5643)	Placebo (n = 5676)	Finerenone (n = 350)	Placebo (n = 356)	Finerenone (n = 410)	Placebo (n = 361)
Any treatment-emergent AE	77 (89.5)	76 (93.8)	4802 (85.1)	4876 (85.9)	320 (91.4)	306 (86.0)	383 (93.4)	334 (92.5)
Related to study drug	23 (26.7)	9 (11.1)	1041 (18.4)	755 (13.3)	44 (12.6)	37 (10.4)	96 (23.4)	58 (16.1)
Leading to discontinuation	3 (3.5)	7 (8.6)	364 (6.5)	308 (5.4)	15 (4.3)	16 (4.5)	32 (7.8)	19 (5.3)
Any treatment-emergent SAE	29 (33.7)	31 (38.3)	1750 (31.0)	1910 (33.7)	117 (33.4)	109 (30.6)	158 (38.5)	131 (36.3)
Related to study drug	0 (0)	1 (1.2)	74 (1.3)	56 (1.0)	2 (0.6)	1 (0.3)	7 (1.7)	3 (0.8)
Leading to discontinuation	1 (1.2)	1 (1.2)	129 (2.3)	140 (2.5)	6 (1.7)	7 (2.0)	9 (2.2)	6 (1.7)
Any treatment-emergent AE with outcome death	0 (0)	2 (2.5)	102 (1.8)	139 (2.4)	2 (0.6)	7 (2.0)	5 (1.2)	3 (0.8)
Hyperkalemia-related events								
Any treatment-emergent hyperkalemia	12 (14.0)	5 (6.2)	801 (14.2)	405 (7.1)	33 (9.4)	7 (2.0)	62 (15.1)	31 (8.6)
Related to study drug	8 (9.3)	3 (3.7)	505 (8.9)	225 (4.0)	18 (5.1)	4 (1.1)	40 (9.8)	17 (4.7)
Leading to permanent discontinuation	0 (0)	1 (1.2)	96 (1.7)	32 (0.6)	5 (1.4)	2 (0.6)	9 (2.2)	3 (0.8)
Any serious treatment-emergent hyperkalemia	0 (0)	1 (1.2)	65 (1.2)	14 (0.2)	1 (0.3)	0 (0)	3 (0.7)	1 (0.3)
Related to study drug	0 (0)	1 (1.2)	40 (0.7)	7 (0.1)	1 (0.3)	0 (0)	2 (0.5)	0 (0)
Leading to permanent discontinuation	0 (0)	0 (0)	9 (0.2)	2 (< 0.1)	1 (0.3)	0 (0)	0 (0)	0 (0)
Leading to hospitalization	0 (0)	1 (1.2)	58 (1.0)	8 (0.1)	1 (0.3)	0 (0)	2 (0.5)	1 (0.3)
Reported as life threatening	0 (0)	0 (0)	4 (< 0.1)	5 (< 0.1)	0 (0)	0 (0)	0 (0)	0 (0)
Central laboratory assessments, n/N (%)[a]								
Treatment-emergent serum [K^+] > 5.5 mmol/l	7/86 (8.1)	3/80 (3.8)	983/5547 (17.7)	439/5569 (7.9)	27/343 (7.9)	10/352 (2.8)	55/405 (13.6)	18/354 (5.1)
Treatment-emergent serum [K^+] > 6.0 mmol/l	1/86 (1.2)	0/80 (0.0)	202/5581 (3.6)	74/5607 (1.3)	3/345 (0.9)	3/355 (0.8)	5/406 (1.2)	3/356 (0.8)

AE, adverse event; GLP-1RA, glucagon-like peptide-1 receptor agonist; [K^+], potassium concentration; SAE, serious adverse event; SAS, safety analysis set; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.
Safety analysis set included 6489 and 6474 participants in the finerenone and placebo treatment groups, respectively, who received any combined SGLT-2i and/or GLP-1RA use at baseline.
[a]For laboratory evaluations, N represents all participants at risk of a treatment-emergent laboratory abnormality. Participants must have both a baseline and postbaseline treatment-emergent value and the baseline value must not exceed the displayed threshold. n represents the number of participants at risk with ≥ 1 treatment-emergent laboratory assessment meeting the criterion for treatment-emergent only assessments from start of treatment until 3 days after any temporary or permanent interruption of study drug were considered.

[7.9%] vs. 10/352 participants [2.8%], respectively) compared with no SGLT-2i/GLP-1RA (983/5547 participants [17.7%] vs. 439/5569 participants [7.9%], respectively) or GLP-1RA–only subgroups (55/405 participants [13.6%] vs. 18/354 participants [5.1%], respectively). Similarly, laboratory-confirmed serum potassium > 6 mmol/l was more common with finerenone than with placebo in all subgroups; however, the rates were much lower overall (211/6418 participants [3.3%] vs. 80/6398 participants [1.3%]).

DISCUSSION

This FIDELITY *post hoc* analysis suggests that concomitant use of finerenone with SGLT-2i and/or GLP-1RA may have a potential additive effect in reducing UACR from baseline, slowing eGFR decline, and lowering SBP, compared with placebo. These findings build on previous observations and recent results from the CONFIDENCE trial, which demonstrated that combination use of finerenone and SGLT-2i provides a synergistic reduction in UACR, a marker of adverse kidney outcomes, in people with CKD and T2D.[16,18]

In this analysis, finerenone reduced UACR from baseline to month 4, irrespective of concomitant SGLT-2i and/or GLP-1RA use. The importance of early reduction in UACR was demonstrated in a mediation analysis to be the key mechanistic pathway by which UACR reduction with finerenone explained ≤ 87% of the improved kidney composite outcome in the FIDELITY dataset.[19,20] There is some indication in the current analysis of a trend toward a greater reduction in UACR following concomitant use of finerenone with SGLT-2i and GLP-1RA, which raises the possibility that combining these 3 agents might further augment the UACR reduction. Change in UACR is a good surrogate marker in trials of CKD and T2D because it is associated with both CV and kidney outcomes, can be predictive of kidney function, and is easy to measure.[21] In terms of mechanism, whether the reduction in UACR observed with concomitant use of finerenone with SGLT-2i and GLP-1RA is driven by the combined activity of these agents or via discrete mechanisms remains to be elucidated.

CKD progression was found to be slower with finerenone than with placebo, irrespective of concomitant SGLT-2i and/or GLP-1RA use at baseline, despite an initial acute eGFR decrease with finerenone in all subgroups. This acute decline has been described not only with finerenone but also with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and SGLT-2i[22–27]; indeed, the greatest acute eGFR decline was observed when participants were

treated with finerenone, SGLT-2i, and GLP-1RA. A recent FIDELITY exploratory analysis demonstrated that an acute change in eGFR does not negatively impact the clinical benefits of finerenone on kidney and CV outcomes.[28] Similar observations were reported with angiotensin II receptor blocker and SGLT-2i, where an initial decline in eGFR was associated with long-term preservation of kidney function.[22-27] Despite these findings, acute declines in eGFR may lead clinicians to recommend early discontinuation, which could negatively impact CKD progression and CV events. The results of this analysis further demonstrate the importance of continuing treatment with finerenone despite an initial acute eGFR decline.

Finerenone was previously shown to reduce both office and 24-hour ambulatory SBP.[29,30] Although the reduction was modest, mediation analysis demonstrated that the effect of finerenone on SBP reduction accounted for 13% to 14% of the kidney and CV event reduction outcomes in a FIDELIO-DKD subanalysis.[30] SGLT-2is are also known to improve blood pressure via diuresis or natriuresis and a reduction in sympathetic tone.[31,32] Here, reduction in mean SBP from baseline to month 4 was greatest in the subgroup with finerenone and combined SGLT-2i and GLP-1RA use, but was unexpectedly lowest in the SGLT-2i–only subgroup (LS-mean treatment difference: −5.77 [95% CI: −10.06 to −1.48) vs. −2.69 [95% CI: −4.67 to −0.71], respectively).

Although currently little is known about the complementary effect of triple therapy with finerenone, SGLT-2i, and GLP-1RA, part of the data observed in this FIDELITY subanalysis is consistent with preclinical findings in a rat model of hypertension-induced end-organ damage in which finerenone with an SGLT-2i conferred greater kidney protection than either agent alone.[33] Further validation is now available from the CONFIDENCE trial that investigated the effect of simultaneous initiation of finerenone with SGLT-2i on UACR, eGFR, and SBP in patients with CKD and T2D. In support of the additive effect observed in this FIDELITY combination analysis, concomitant treatment with finerenone and SGLT-2i in CONFIDENCE resulted in a 29% and 32% greater reduction in UACR at day 180 than respective use of finerenone and SGLT-2i alone. Considering that an acute change in eGFR has previously been observed following initiation of treatment with finerenone or an SGLT-2i,[22-28] the incidence of $>$ 30% decline in eGFR from baseline to day 30 was the highest with combination therapy, as expected, compared with finerenone or SGLT-2i alone; however, stabilization occurred shortly after the initial decline. Reduction in SBP was found to be $\leq$ 2-fold higher with finerenone and SGLT-2i than with separate use.[18]

Present guidelines recommend a holistic approach to managing kidney and CV risk factors in people with CKD and T2D, beginning with lifestyle modification.[6,10,34] RAS inhibitors in the highest tolerated doses are recommended as first-line therapy for people with T2D who also have hypertension and albuminuria. However, residual risks for CKD and CV disease have been reported even with RAS blockade,[35-37] and the addition of nonsteroidal mineralocorticoid receptor antagonist and SGLT-2i with proven kidney and CV benefits is recommended to further mitigate kidney and CV risks.[6,10,34] Finerenone is currently the only nonsteroidal mineralocorticoid receptor antagonist that has demonstrated kidney and CV benefits in people with CKD and T2D.[11,12,38] Preclinical evidence shows that overactivation of the mineralocorticoid receptors is linked to high levels of inflammation and fibrosis that lead to end-organ damage in kidney and CV diseases such as CKD and T2D.[38] As for SGLT-2i, aside from its glucose-lowering effect, this class of drugs acts directly on the kidney to result in kidney and CV benefits independent of glycemia.[34] These effects include reduction of kidney tubular glucose reabsorption, as well as effects on weight, blood pressure, and albuminuria. In addition, the anti-inflammatory and antifibrotic effects contribute to the kidney and CV benefits with SGLT-2i.[39] GLP-1RAs are recommended for glucose management in people with T2D, a history of CV disease, and CKD based on their proven CV benefit.[6,10,34] The recently concluded kidney outcomes trial FLOW will likely strengthen this recommendation further in guidelines and cement GLP-1RA as the fourth pillar of combination care for reducing the risk of CV and kidney events in people with CKD and T2D.[14]

The best way to initiate treatment and the timing of delivery of these pillars in people with CKD and T2D is yet to be established. As outlined by Neuen *et al.*,[4] approaches could include rapid sequential treatment in which multiple therapies are initiated simultaneously or within a short period of time. Data from CONFIDENCE have provided insights on the efficacy and safety of simultaneous initiation with finerenone and an SGLT-2i.[18] An accelerated risk-based hybrid approach is another option, where treatment intensity is matched according to risk level. Risk levels could be assessed using the Kidney Disease: Improving Global Outcomes heatmap to help identify those who are at greatest risk of end-stage kidney disease progression; and rapid-sequence treatment could be initiated accordingly.[4]

As expected, this analysis found a higher incidence of investigator-reported treatment-emergent

hyperkalemia with finerenone than with placebo across all subgroups. Interestingly, there were fewer investigator-reported treatment-emergent hyperkalemia events among participants treated with finerenone in the SGLT-2i–only subgroup than in the no SGLT-2i/GLP-1RA subgroup. The data from this FIDELITY analysis expand on the trend toward a reduction in investigator-reported treatment-emergent hyperkalemia events, which was observed in participants treated with concomitant SGLT-2i and finerenone versus finerenone alone in FIDELIO-DKD and is supported by safety data from the CONFIDENCE trial.[18,40] Fewer reports of laboratory-confirmed serum potassium of $>$ 5.5 and $>$ 6 mmol/l were observed among participants treated with finerenone in the SGLT-2i and combined SGLT-2i and GLP-1RA subgroups compared with the no SGLT-2i/GLP-1RA subgroup. However, the interpretation of these results is limited by the relatively small number of finerenone recipients in the combined SGLT-2i and GLP-1RA subgroup who had a hyperkalemia event.

Findings from *post hoc* analyses such as the current analysis of FIDELITY must be interpreted with caution because of their exploratory nature. The small number of participants receiving SGLT-2i and/or GLP-1RA at baseline is a limitation of this analysis. Numbers were low because SGLT-2is (with the exception of dapagliflozin) and GLP-1RAs were not yet recommended for people with eGFR $<$ 45 ml/min per 1.73 m^2 at the time of FIDELIO-DKD and FIGARO-DKD trial initiation.[15,16,41] Consequently, participants who were taking combined SGLT-2i and GLP-1RA medication at baseline initially had a higher mean eGFR and a lower median UACR than those taking neither medication, indicative of a lower CKD stage. Sample size at time points after 12 months adds to this limitation, because the number of participants was too low to conduct formal comparisons between treatment arms. Furthermore, participants in the trials were not stratified based on SGLT-2i or GLP-1RA use at baseline. Other limitations include the duration of SGLT-2i and/or GLP-1RA therapy prior to study enrollment and the duration of SGLT-2i and/or GLP-1RA therapy throughout the follow-up period being unknown. The length of time on treatment required to demonstrate possible additive kidney benefits with finerenone and concomitant SGLT-2i and/or GLP-1RA use is undefined. As such, the findings in this analysis are hypothesis generating and randomized clinical trials with larger populations are required to prospectively assess the effect of concomitant therapy with finerenone, SGLT-2i, and GLP-1RA on top of optimized RAS blockade to help substantiate the data presented here.

In conclusion, this FIDELITY *post hoc* analysis has shown that finerenone preserved kidney function and reduced blood pressure than placebo did over time, irrespective of baseline SGLT-2i and/or GLP-1RA use. In addition, the safety profile of finerenone was not modified by concomitant use of these therapies.

DISCLOSURE

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ML is an external employee of Bayer AG. GF reports that he is a committee member of trials and registries sponsored by Amgen, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier, and Vifor Pharma; he is a Senior Consulting Editor for *JACC Heart Failure*; and he has received research support from the European Union.

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DATA AVAILABILITY STATEMENT

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

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

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

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

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Change in SGLT-2i and GLP-1RA use during the study (FAS).

Table S2. Type of combined SGLT-2i and GLP-1RA administered throughout the study (FAS).

Table S3. Baseline demographic and clinical characteristics by concomitant SGLT-2i and/or GLP-1RA use at baseline (FAS).

Table S4. SGLT-2i and/or GLP-1RA use at baseline according to region (FAS).

Table S5. Treatment-emergent adverse events affecting ≥5% of participants in any treatment group by concomitant SGLT-2i and/or GLP-1RA use at baseline (SAS).

CONSORT checklist

FIDELIO-DKD investigators

FIGARO-DKD investigators

REFERENCES

1. Wu B, Bell K, Stanford A, et al. Understanding CKD among patients with T2DM: prevalence, temporal trends, and treatment patterns—NHANES 2007–2012. *BMJ Open Diabetes Res Care*. 2016;4:e000154. https://doi.org/10.1136/bmjdrc-2015-000154
2. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet*. 2012;380:1662–1673. https://doi.org/10.1016/S0140-6736(12)61350-6
3. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet*. 2013;382:339–352. https://doi.org/10.1016/s0140-6736(13)60595-4
4. Neuen BL, Tuttle KR, Vaduganathan M. Accelerated risk-based implementation of guideline-directed medical therapy for type 2 diabetes and chronic kidney disease. *Circulation*. 2024;149:1238–1240. https://doi.org/10.1161/CIRCULATIONAHA.123.068524
5. Blazek O, Bakris GL. The evolution of "pillars of therapy" to reduce heart failure risk and slow diabetic kidney disease progression. *Am Heart J Plus*. 2022;19:100187. https://doi.org/10.1016/j.ahjo.2022.100187
6. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2022;102:S1–S127. https://doi.org/10.1016/j.kint.2022.06.008
7. Marx N, Federici M, Schütt K, et al. 2023 ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;44:4043–4140. https://doi.org/10.1093/eurheartj/ehad192
8. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45:2753–2786. https://doi.org/10.2337/dci22-0034
9. American Diabetes Association Professional Practice Committee. Chronic kidney disease and risk management: standards of medical care in diabetes–2022. *Diabetes Care*. 2022;45(Suppl 1):s175–s184. https://doi.org/10.2337/dc22-S011
10. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care*. 2022;45:3075–3090. https://doi.org/10.2337/dci22-0027
11. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J*

Med. 2020;383:2219–2229. https://doi.org/10.1056/NEJMoa2025845

12. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med*. 2021;385:2252–2263. https://doi.org/10.1056/NEJMoa2110956
13. Agarwal R, Filippatos G, Pitt B, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J*. 2022;43:474–484. https://doi.org/10.1093/eurheartj/ehab777
14. Perkovic V, Tuttle K, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N Engl J Med*. 2024;391:109–121. https://doi.org/10.1056/NEJMoa2403347
15. Rossing P, Agarwal R, Anker SD, et al. Finerenone in patients across the spectrum of chronic kidney disease and type 2 diabetes by glucagon-like peptide-1 receptor agonist use. *Diabetes Obes Metab*. 2023;25:407–416. https://doi.org/10.1111/dom.14883
16. Rossing P, Anker SD, Filippatos G, et al. Finerenone in patients with chronic kidney disease and type 2 diabetes by sodium-glucose cotransporter 2 inhibitor treatment: the FIDELITY analysis. *Diabetes Care*. 2022;45:2991–2998. https://doi.org/10.2337/dc22-0294
17. Vonesh E, Tighiouart H, Ying J, et al. Mixed-effects models for slope-based endpoints in clinical trials of chronic kidney disease. *Stat Med*. 2019;38:4218–4239. https://doi.org/10.1002/sim.8282
18. Agarwal R, Green JB, Heerspink HJL, et al. Finerenone with empagliflozin in chronic kidney disease and type 2 diabetes. *N Engl J Med*. 2025;393:533–543. https://doi.org/10.1056/NEJMoa2410659
19. Agarwal R, Tu W, Farjat AE, et al. Impact of finerenone-induced albuminuria reduction on chronic kidney disease outcomes in type 2 diabetes: a mediation analysis. *Ann Intern Med*. 2023;176:1606–1616. https://doi.org/10.7326/M23-1023
20. Heerspink HJL, Birkenfeld AL, Cherny DZI, et al. Rationale and design of a randomised phase III registration trial investigating finerenone in participants with type 1 diabetes and chronic kidney disease: the FINE-ONE trial. *Diabetes Res Clin Pract*. 2023;204:110908. https://doi.org/10.1016/j.diabres.2023.110908
21. Palmer BF. Change in albuminuria as a surrogate endpoint for cardiovascular and renal outcomes in patients with diabetes. *Diabetes Obes Metab*. 2023;25:1434–1443. https://doi.org/10.1111/dom.15030
22. Kraus BJ, Weir MR, Bakris GL, et al. Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. *Kidney Int*. 2021;99:750–762. https://doi.org/10.1016/j.kint.2020.10.031
23. Cherney DZI, Cosentino F, Dagogo-Jack S, et al. Ertugliflozin and slope of chronic eGFR: prespecified analyses from the randomized VERTIS CV trial. *Clin J Am Soc Nephrol*. 2021;16:1345–1354. https://doi.org/10.2215/CJN.01130121
24. Oshima M, Jardine MJ, Agarwal R, et al. Insights from CREDENCE trial indicate an acute drop in estimated glomerular filtration rate during treatment with canagliflozin with implications for clinical practice. *Kidney Int*. 2021;99:999–1009. https://doi.org/10.1016/j.kint.2020.10.042
25. Holtkamp FA, de Zeeuw D, Thomas MC, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int*. 2011;80:282–287. https://doi.org/10.1038/ki.2011.79
26. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375:323–334. https://doi.org/10.1056/NEJMoa1515920
27. Jongs N, Chertow GM, Greene T, et al. Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor dapagliflozin in patients with CKD. *J Am Soc Nephrol*. 2022;33:2094–2107. https://doi.org/10.1681/ASN.2022030306
28. Navaneethan SC, Anker SD, Filippatos G, et al. Efficacy and safety of finerenone in patients with an acute change in estimated glomerular filtration rate in the prespecified FIDELITY pool analysis. *Kidney Int*. 2025;108:136–144. https://doi.org/10.1016/j.kint.2025.03.018
29. Agarwal R, Ruilope LM, Ruiz-Hurtado G, et al. Effect of finerenone on ambulatory blood pressure in chronic kidney disease in type 2 diabetes. *J Hypertens*. 2023;41:295–302. https://doi.org/10.1097/hjh.0000000000003330
30. Ruilope LM, Agarwal R, Anker SD, et al. Blood pressure and cardiorenal outcomes with finerenone in chronic kidney disease in type 2 diabetes. *Hypertension*. 2022;79:2685–2695. https://doi.org/10.1161/HYPERTENSIONAHA.122.19744
31. Benham JL, Booth JE, Sigal RJ, Daskalopoulou SS, Leung AA, Rabi DM. Systematic review and meta-analysis: SGLT2 inhibitors, blood pressure and cardiovascular outcomes. *Int J Cardiol Heart Vasc*. 2021;33:100725. https://doi.org/10.1016/j.ijcha.2021.100725
32. Briasoulis A, Al Dhaybi O, Bakris GL, Bakris GL. SGLT2 inhibitors and mechanisms of hypertension. *Curr Cardiol Rep*. 2018;20:1. https://doi.org/10.1007/s11886-018-0943-5
33. Kolkhoff P, Hatmann E, Freyberger A, et al. Effects of finerenone combined with empagliflozin in a model of hypertension-induced end-organ damage. *Am J Nephrol*. 2021;52:642–652. https://doi.org/10.1159/000516213
34. American Diabetes Association Professional Practice Committee, El Sayed NA, Aleppo G, et al. 11. Chronic kidney disease and risk management: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S219–S230. https://doi.org/10.2337/dc24-S011
35. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol*. 2017;12:2032–2045. https://doi.org/10.2215/CJN.11491116
36. Sarafidis P, Papadopoulos CE, Kamperidis V, Giannakoulas G, Doumas M. Cardiovascular protection with sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists in chronic kidney disease: a milestone achieved. *Hypertension*. 2021;77:1442–1455. https://doi.org/10.1161/HYPERTENSIONAHA.121.17005
37. Sarafidis PA, Iatridi F, Ferro C, et al. Mineralocorticoid receptor antagonist use in chronic kidney disease with type 2 diabetes: a clinical practice document by the European Renal Best Practice (ERBP) board of the European Renal

Association (ERA). *Clin Kidney J*. 2023;16:1885–1907. https://doi.org/10.1093/ckj/sfad139

38. Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. *Eur Heart J*. 2021;42:152–161. https://doi.org/10.1093/eurheartj/ehaa736
39. Neumiller JJ, Lienhard FJ, Alicic RZ, Tuttle KR. Clinical evidence and proposed mechanisms for cardiovascular and kidney benefits from sodium-glucose co-transporter-2 inhibitors. *touchREV Endocrinol*. 2022;18:106–115. https://doi.org/10.17925/EE.2022.18.2.106
40. Rossing P, Filippatos G, Agarwal R, et al. Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose cotransporter-2 inhibitor therapy. *Kidney Int Rep*. 2021;7:36–45. https://doi.org/10.1016/j.ekir.2021.10.008
41. Neumiller JJ, Hirsch IB. Management of hyperglycemia in diabetic kidney disease. *Diabetes Spectr*. 2015;28:214–219. https://doi.org/10.2337/diaspect.28.3.214