Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes by Sodium–Glucose Cotransporter 2 Inhibitor Treatment: The FIDELITY Analysis

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OBJECTIVE

Finerenone reduced the risk of kidney and cardiovascular events in people with chronic kidney disease (CKD) and type 2 diabetes in the FIDELIO-DKD and FIGARO-DKD phase 3 studies. Effects of finerenone on outcomes in patients taking sodium–glucose cotransporter 2 inhibitors (SGLT2is) were evaluated in a prespecified pooled analysis of these studies.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes and urine albumin-to-creatinine ratio (UACR) ≥30 to ≤5,000 mg/g and estimated glomerular filtration rate (eGFR) ≥25 mL/min/1.73 m^2 were randomly assigned to finerenone or placebo; SGLT2is were permitted at any time. Outcomes included cardiovascular composite (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) and kidney composite (kidney failure, sustained ≥57% eGFR decline, or renal death) end points, changes in UACR and eGFR, and safety outcomes.

RESULTS

Among 13,026 patients, 877 (6.7%) received an SGLT2i at baseline and 1,113 (8.5%) initiated one during the trial. For the cardiovascular composite, the hazard ratios (HRs) were 0.87 (95% CI 0.79–0.96) without SGLT2i and 0.67 (95% CI 0.42–1.07) with SGLT2i. For the kidney composite, the HRs were 0.80 (95% CI 0.69–0.92) without SGLT2i and 0.42 (95% CI 0.16–1.08) with SGLT2i. Baseline SGLT2i use did not affect risk reduction for the cardiovascular or kidney composites with finerenone ($P_{interaction}$ = 0.46 and 0.29, respectively); neither did SGLT2i use concomitant with study treatment.

CONCLUSIONS

Benefits of finerenone compared with placebo on cardiorenal outcomes in patients with CKD and type 2 diabetes were observed irrespective of SGLT2i use.

Diabetes is a leading cause of kidney failure, with >50% of end-stage kidney disease cases resulting from diabetes in many countries (1). Sodium–glucose cotransporter 2 inhibitors (SGLT2is) are recommended for patients with type 2 diabetes and chronic kidney disease (CKD) and/or with cardiovascular (CV) disease to reduce

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the risk of kidney disease progression or CV events (2–4). However, despite the use of guideline-recommended therapies, including SGLT2is and renin-angiotensin system (RAS) inhibitors, there remains a residual risk of patients with CKD and type 2 diabetes still progressing to kidney failure (5,6).

Finerenone is a novel, selective, nonsteroidal mineralocorticoid receptor antagonist (MRA) approved for use in adults with CKD associated with type 2 diabetes (7–10). Given the current recommendations for the use of an SGLT2i in patients with CKD and type 2 diabetes (2–4), their combined use with finerenone is of interest. A recent analysis of data from the phase 3 Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) study stratified by the use of an SGLT2i at baseline showed that finerenone reduced the urine albumin-to-creatinine ratio (UACR) in patients with CKD and type 2 diabetes already receiving an SGLT2i at baseline (11); however, the analysis had limited power with regard to important clinical cardiorenal outcomes.

In this Finerenone in Chronic Kidney Disease and type 2 diabetes combined with FIDELIO-DKD and FIGARO-DKD trial program analysis (FIDELITY), we expand upon the previous investigations by examining the effect of finerenone and the interaction with SGLT2i use on the prespecified CV and kidney composite outcomes in the pooled populations of the FIDELIO-DKD and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) studies, which included patients across the spectrum of CKD associated with type 2 diabetes. In addition, we evaluated the intermediate changes in UACR and estimated glomerular filtration rate (eGFR) slopes.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This analysis combines individual patient–level data from the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials. The designs and results of these studies have been published previously (7,8). Briefly, adults (≥18 years of age) with CKD and type 2 diabetes who were receiving a maximum tolerated labeled dose of a RAS inhibitor were eligible to participate if they had a serum potassium level ≤4.8 mmol/L at screening. Patients had either moderately increased albuminuria (i.e., UACR of 30 to <300 mg/g) with an eGFR of either 25 to <60 and diabetic retinopathy (FIDELIO-DKD) or 25 to ≤90 mL/min/1.73 m^2 (FIGARO-DKD) or severely increased albuminuria (i.e., UACR 300 to ≤5000 mg/g) with an eGFR of either 25 to <75 mL/min/1.73 m^2 (FIDELIO-DKD) or ≥60 mL/min/1.73 m^2 (FIGARO-DKD). Standard-of-care therapy, including treatment with a RAS inhibitor, was optimized during the run-in period. Use of SGLT2is was permitted at baseline, as was the initiation of SGLT2i treatment during the trial. Patients were recruited from September 2015 through October 2018, a period during which guidelines and recommendations for SGLT2i use in CKD and type 2 diabetes were being updated. The trial protocol was approved by the institutional review board at each study site, and all participants provided written informed consent.

Randomization and Masking

In both studies, patients were randomly assigned 1:1 to receive double-blind therapy with either oral finerenone (at titrated doses of 10 or 20 mg once daily) or matching placebo. Randomization was stratified by region (North America, Europe, Asia, Latin America, other), albuminuria at screening (30 to <300 mg/g, ≥300 mg/g), and eGFR at screening (25 to <45 mL/min/1.73 m^2, 45 to <60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2). In FIGARO-DKD, randomization was additionally stratified by history of CV disease. All participants and study personnel (except for the independent data monitoring committee) were masked to treatment allocation.

Outcomes

Efficacy outcomes of the current prespecified analysis included a CV composite end point of time to the first occurrence of CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure and a kidney composite end point of time to first occurrence of kidney failure, a sustained ≥57% decline in eGFR from baseline, or renal death. Potential end points were prospectively adjudicated by an independent clinical event committee blinded to treatment assignment. Sustained declines in eGFR were confirmed by two consecutive central laboratory measurements over a period of at least 4 weeks. Kidney failure was defined as end-stage kidney disease or sustained eGFR <15 mL/min/1.73 m^2. Change in UACR and eGFR slope were also reported. Data for these outcomes and safety data were based on SGLT2i use at baseline. The CV and kidney composite end points were also analyzed by postbaseline SGLT2i use. A post hoc analysis of hospitalization for heart failure as an individual end point was also performed by SGLT2i use at baseline.

Statistical Analysis

The overall statistical analysis methodology for FIDELITY has been published previously (12). Efficacy outcomes were analyzed in the pooled full analysis set (by planned treatment), comprising all patients randomly assigned who did not have critical Good Clinical Practice violations. Treatment effect for time-to-event first outcomes in patients were derived separately by SGLT2i use at baseline (yes/no), based on separate Cox regression models including

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treatment (finerenone vs. placebo), and stratified by prespecified stratification factors (albuminuria and eGFR at screening, CV disease history, region, and study). Data are expressed as hazard ratios (HRs) with corresponding 95% CIs. *P* values for the subgroup-by-treatment interaction were derived from a stratified Cox proportional hazards model that included terms for treatment, subgroup, and subgroup-by-treatment interaction. To consider on-treatment SGLT2i use, outcome HRs and associated 95% CIs were based on a stratified Cox model including treatment as a fixed covariate, co-medication use as a time-varying covariate, and the interaction of the fixed and time-varying terms. All Cox models were also adjusted for baseline levels of HbA_{1c}, systolic blood pressure (SBP), UACR (log-transformed), and eGFR.

Changes in UACR and eGFR were analyzed for short-term (baseline to the month 4 visit) and long-term (month 4 to the permanent discontinuation or end-of-study visit) changes by SGLT2i use at baseline. Separate mixed-model repeated-measures analyses were conducted for change in UACR, assuming an unstructured covariance matrix and adjusting for treatment group, stratification factors, visit, treatment-by-visit interaction, treatment-by-study interaction, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value-by-visit interaction. The annualized change in eGFR from month 4 to permanent discontinuation or the end-of-study visit was evaluated by means of an ANCOVA model, including treatment group, the stratification factors, baseline eGFR (nested within eGFR category), and the study-by-treatment interaction as covariates. All available eGFR measurements were included in the analyses, irrespective of discontinuation of study treatment.

A mediation analysis was performed by SGLT2i use at baseline using a Cox proportional hazards model to determine the proportion of the effect of finerenone on UACR regression from severely increased albuminuria to moderately increased albuminuria and from moderately increased albuminuria to normal albuminuria attributed to time-varying SBP. The model was stratified by region, albuminuria at screening, eGFR at screening, CV disease history, and study, including the covariates of treatment group and time-varying SBP, and compared with the model without SBP adjustment. Albuminuria category changes were considered as shifts if they were accompanied by a UACR change of ≥30% from baseline to each visit. Analysis of safety outcomes, including treatment-emergent hyperkalemia-related adverse events (AEs), were performed in all randomly assigned patients who received one or more doses of study drug (by treatment received) by SGLT2i use at baseline (yes/no).

RESULTS

Patients

Of 13,026 patients included in the analysis, 877 (6.7%) received an SGLT2i at baseline, comprising 438 (6.7%) of 6,519 in the finerenone group and 439 (6.7%) of 6,507 in the placebo group (Supplementary Table 1). Overall, 58% of patients who were taking an SGLT2i at baseline had initiated treatment >6 months before random assignment. The remaining 42% of patients initiated treatment gradually over the preceding 6 months, with <10% starting an SGLT2i within 1 month of random assignment (Supplementary Table 2). Overall, 958 patients (14.7%) in the finerenone group and 1,032 (15.9%) in the placebo group received an SGLT2i at any time concomitant with study treatment (Supplementary Table 1). For finerenone- and placebo-treated patients, 371 (38.7%) of 958 and 387 (37.5%) of 1,032, respectively, received co-medication with an SGLT2i for ≥90% of the treatment period; 203 (21.1%) of 958 and 214 (20.7%) of 1,032 received an SGLT2i 50–90% of the time; and 384 (40.1%) of 958 and 431 (41.8%) of 1,032 received an SGLT2i <50% of the time (Supplementary Fig. 1). The median follow-up period for the FIDELITY analysis was 3.0 years (interquartile range 2.3–3.8 years).

Baseline demographics and patient characteristics were similar between the finerenone and placebo groups (Supplementary Table 3). However, when considering SGLT2i subgroups, there were differences reflecting that use of SGLT2is was not randomly allocated (Table 1 and Supplementary Table 2). For example, a greater proportion of White patients and lower proportion of Black patients were receiving an SGLT2i at baseline compared with patients who were not receiving an SGLT2i at baseline. Additionally, patients receiving an SGLT2i were younger, had a higher HbA_{1c} and lower SBP, and used statins, metformin, and glucagon-like peptide 1 receptor agonists (GLP-1RAs) more frequently. In addition, baseline mean eGFR was higher and median UACR lower in patients who were receiving an SGLT2i at baseline than in those who were not; this observation is consistent with the initiation criteria according to the manufacturers' labels for SGLT2is at the time the studies were enrolling patients. Use of potassium-lowering agents was low at baseline and at any time throughout the trial (used in <5% of patients), with most patients taking calcium polystyrene sulfonate or sodium polystyrene sulfonate (Supplementary Table 4). Characteristics of patients who initiated an SGLT2i during the on-treatment period were similar to patients who received an SGLT2i at baseline (Supplementary Table 5).

Efficacy

The HR for the CV composite end point was 0.87 (95% CI 0.79–0.96) in patients not receiving an SGLT2i at baseline and 0.67 (95% CI 0.42–1.07) in those receiving an SGLT2i at baseline (Fig. 1). Similarly, the HR for the kidney composite end point was 0.80 (95% CI 0.69–0.92) in patients not receiving an SGLT2i at baseline and 0.42 (95% CI 0.16–1.08) in those receiving an SGLT2i at baseline (Fig. 1). Incidence of the composite CV and kidney end points suggested a trend toward a lower risk with the combination of finerenone and an SGLT2i at baseline; however, the corresponding tests for interaction were not significant ($P_{interaction}$ = 0.46 and 0.29, respectively). Additionally, the HR for all-cause death was 0.90 (95% CI 0.80–1.02) in patients not receiving an SGLT2i at baseline and 0.58 (95% CI 0.30–1.10) in those receiving an SGLT2i at baseline ($P_{interaction}$ = 0.24) (Fig. 1). Analyses considering SGLT2i use at any time during the on-treatment period also showed no clear differences in the response to finerenone in patients who received an SGLT2i at any time concomitant with study treatment versus those who did not (Fig. 1).

Post hoc analysis showed that finerenone reduced the risk of hospitalization for heart failure compared with placebo, irrespective of SGLT2i use at baseline (HR 0.80 [95% CI 0.68–0.95] vs. 0.44 [0.19–0.99] in patients not receiving an SGLT2i vs. those receiving an SGLT2i; $P_{interaction}$ = 0.16) (Fig. 1). These findings

Table 1—Baseline characteristics in patients receiving or not receiving an SGLT2i at baseline

	SGLT2i at baseline (*n* = 877)	No SGLT2i at baseline (*n* = 12,149)
Age, years	61.8 ± 9.7	65.0 ± 9.5
Sex		
Male	671 (76.5)	8,417 (69.3)
Female	206 (23.5)	3,732 (30.7)
Race		
White	644 (73.4)	8,225 (67.7)
Asian	185 (21.1)	2,709 (22.3)
Black/African American	20 (2.3)	502 (4.1)
SBP, mmHg	133.3 ± 14.4	137.0 ± 14.2
Duration of diabetes, years	15.6 ± 8.1	15.4 ± 8.7
HbA_{1c}		
%	8.0 ± 1.2	7.7 ± 1.4
mmol/mol	63.5 ± 13.4	60.4 ± 14.9
Serum potassium, mmol/L	4.3 ± 0.4	4.4 ± 0.4
eGFR, mL/min/1.73 m^2		
Mean	66.3 ± 21.1	57.0 ± 21.6
Distribution		
<25	0	162 (1.3)
25 to <45	142 (16.2)	4,090 (33.7)
45 to <60	241 (27.5)	3,193 (26.3)
≥60	494 (56.3)	4,701 (38.7)
UACR, mg/g		
Median	448 (185–945)	521 (199–1,161)
Distribution		
<30	16 (1.8)	214 (1.8)
30 to <300	283 (32.3)	3,816 (31.4)
≥300	578 (65.9)	8,114 (66.8)
Medication use at baseline		
RAS inhibitor	875 (99.8)	12,128 (99.8)
β-Blocker	432 (49.3)	6,072 (50.0)
Diuretic	439 (50.1)	6,271 (51.6)
Statin	737 (84.0)	8,662 (71.3)
Potassium supplement	24 (2.7)	361 (3.0)
Potassium-lowering agent	7 (0.8)	175 (1.4)
Glucose-lowering therapies		
Insulin and analogs	515 (58.7)	7,115 (58.6)
Metformin	692 (78.9)	6,865 (56.5)
Sulfonylurea	218 (24.9)	3,171 (26.1)
DPP-4 inhibitor	256 (29.2)	3,022 (24.9)
GLP-1RA	167 (19.0)	777 (6.4)
α-Glucosidase inhibitor	35 (4.0)	621 (5.1)
Thiazolidinedione	58 (6.6)	459 (3.8)

Data are mean ± SD, *n* (%), or median (interquartile range). DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; RAS, renin–angiotensin system; SBP, systolic blood pressure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

were consistent in analyses that considered SGLT2i use at any time during the on-treatment period versus no SGLT2i use (Fig. 1).

The effect of finerenone versus placebo on reducing UACR from baseline to month 4 also appeared to be independent of SGLT2i use at baseline, with a 37% reduction observed with finerenone in patients receiving an SGLT2i at baseline (ratio of geometric mean changes 0.63 [95% CI 0.57–0.70]) and a 31% reduction in patients without an SGLT2i at baseline (ratio of geometric mean changes 0.69 [95% CI 0.67–0.71]; $P_{interaction}$ = 0.17). The reduction in UACR with finerenone was persistent throughout the duration of the trial (Fig. 2).

The between-group difference in least squares mean change in eGFR from baseline to month 4 was −3.69 mL/min/1.73 m^2 in patients receiving an SGLT2i at baseline and −2.23 mL/min/1.73 m^2 in patients not receiving an SGLT2i at baseline. The difference in treatment effects between SGLT2i groups was −1.46 mL/min/1.73 m^2 (95% CI −1.89 to −1.04). Chronic eGFR decline was reduced with finerenone. The between-group difference (finerenone vs. placebo) in chronic eGFR slope from month 4 to the end of the study was greater in patients receiving an SGLT2i at baseline than in those not receiving an SGLT2i at baseline (−1.54 and −1.18 mL/min/1.73 m^2, respectively) (Supplementary Fig. 2). In patients receiving an SGLT2i at baseline, the least squares mean change in chronic eGFR slope from month 4 to the end of the study was −1.92 (95% CI −2.61 to −1.23) with finerenone and −3.45 (95% CI −4.15 to −2.76) with placebo. Corresponding changes in patients not receiving an SGLT2i at baseline were −2.54 (95% CI −2.81 to −2.27) with finerenone and −3.72 (95% CI −3.99 to −3.45) with placebo.

Modest reductions in SBP were observed with finerenone versus placebo, irrespective of whether patients were receiving an SGLT2i at baseline, with a maximum between-group difference (finerenone vs. placebo) in SBP at month 4 of −3.6 mmHg for patients receiving an SGLT2i at baseline and −3.7 mmHg for those not receiving an SGLT2i at baseline (Supplementary Fig. 3). Mediation analyses demonstrated that the effect of finerenone versus placebo on UACR regression from severely increased to moderately increased, and from moderately increased to normal, was not mediated by the change in SBP in patients with or without SGLT2i use at baseline; time-varying change in SBP accounted for 9.6% and 8.4% of the effect of finerenone in each subgroup category, respectively.

Safety

Overall safety by SGLT2i use at baseline is shown in Table 2; tolerability profiles were similar across all treatment groups. Patients receiving an SGLT2i at baseline exhibited a lower incidence of hyperkalemia than those not receiving an SGLT2i at baseline in both the finerenone and placebo treatment arms (patients receiving

	Finerenone	Placebo	Finerenone	Placebo	HR (95% CI)	$P_{interaction}$
	n/*N* (%)		*n* per 100 PY			
Analysis for outcomes in patients receiving/not receiving an SGLT2i at baseline						
Cardiovascular composite						
SGLT2i at baseline	39/438 (8.9)	52/439 (11.8)	2.95	4.08	0.67 (0.42–1.07)*	0.46†
No SGLT2i at baseline	786/6,081 (12.9)	887/6,068 (14.6)	4.44	5.08	0.87 (0.79–0.96)*	
Kidney composite						
SGLT2i at baseline	9/438 (2.1)	17/439 (3.9)	0.70	1.37	0.42 (0.16–1.08)*	0.29†
No SGLT2i at baseline	351/6,081 (5.8)	448/6,068 (7.4)	2.06	2.64	0.80 (0.69–0.92)*	
Hospitalization for heart failure						
SGLT2i at baseline	10/438 (2.3)	22/439 (5.0)	0.74	1.68	0.44 (0.19–0.99)*	0.18†
No SGLT2i at baseline	246/6,081 (4.0)	303/6,068 (5.0)	1.35	1.68	0.80 (0.68–0.95)*	
All-cause death						
SGLT2i at baseline	20/438 (4.6)	30/439 (6.8)	1.46	2.23	0.58 (0.30–1.10)*	0.24†
No SGLT2i at baseline	532/6,081 (8.7)	584/6,068 (9.6)	2.86	3.16	0.90 (0.80–1.02)*	
On-treatment period – Time-varying analyses for outcomes in patients receiving/not receiving an SGLT2i at any time‡						
	n		*n* per 100 PY			
Cardiovascular composite						
SGLT2i use	41	58	2.40	3.20	0.77 (0.51–1.15)§	0.77§
No SGLT2i use	579	700	3.83	4.69	0.82 (0.73–0.91)§	
Kidney composite						
SGLT2i use	11	13	0.63	0.70	0.92 (0.41–2.08)§	0.50§
No SGLT2i use	213	312	1.40	2.06	0.69 (0.58–0.83)§	
Hospitalization for heart failure						
SGLT2i use	4	23	0.23	1.24	0.18 (0.06–0.53)§	0.015§
No SGLT2i use	175	248	1.14	1.62	0.71 (0.58–0.86)§	
All-cause death						
SGLT2i use	14	15	0.79	0.80	0.98 (0.47–2.03)§	0.64§
No SGLT2i use	266	329	1.71	2.12	0.82 (0.70–0.96)§	

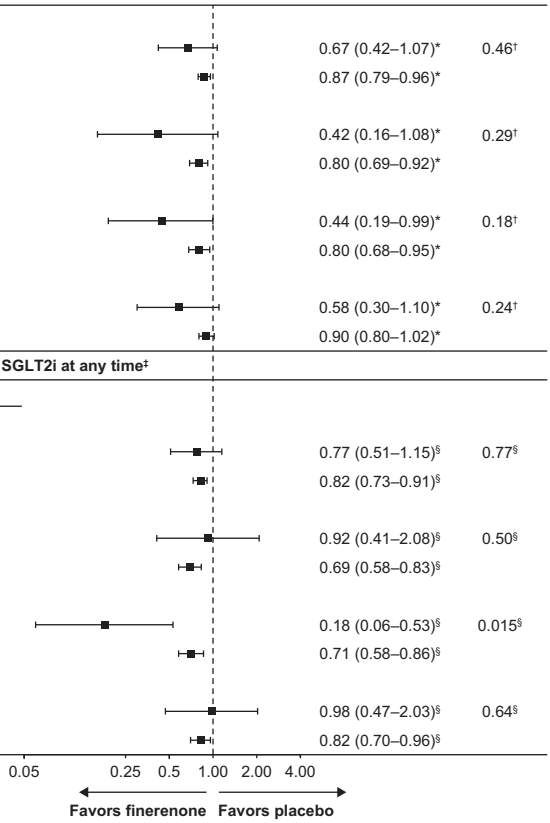


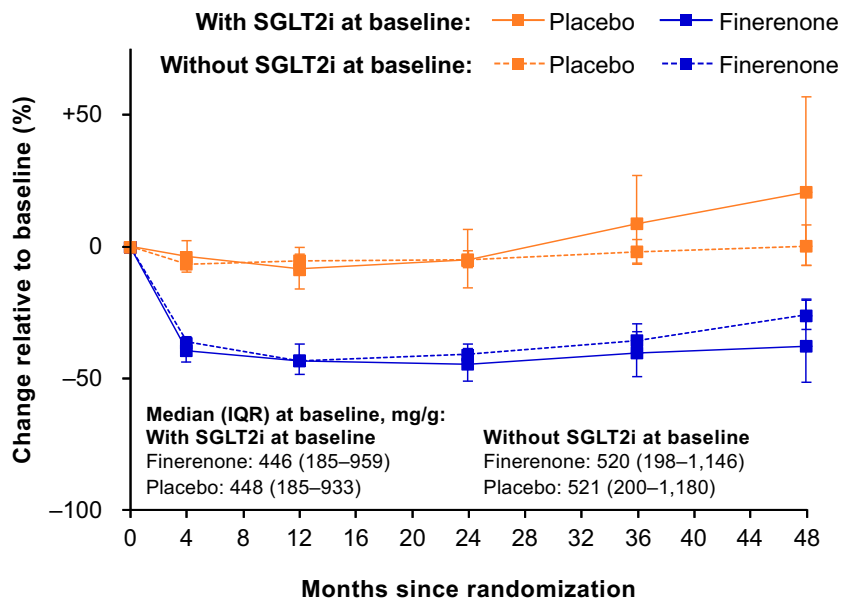
Figure 1—Analysis of kidney and cardiovascular composite outcomes in patients receiving or not receiving an SGLT2i at baseline and in patients receiving or not receiving an SGLT2i at any time during the on-treatment period. Shown are adjusted *HRs for HbA_{1c}, SBP, and UACR at baseline (log-transformed) and eGFR at baseline. †$P_{interaction}$ is based on a stratified Cox proportional hazards model including treatment, subgroup, the additional covariates, and treatment-by-subgroup interaction. ‡Comedication use is defined as exposure to comedication in the on-treatment period (i.e., a patient can contribute to the use and nonuse categories based on the actual exposure time with and without comedication). §HR and $P_{interaction}$ are based on a stratified Cox model including treatment as simple and comedication use as time-varying covariates as well as their interaction and the additional covariates. eGFR, estimated glomerular filtration rate; HR, hazard ratio; PY, patient-years; SBP, systolic blood pressure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

an SGLT2i at baseline 10.3% vs. 2.7%; patients not receiving an SGLT2i 14.3% vs. 7.2%). Among patients receiving an SGLT2i at baseline, elevations in laboratory serum potassium to >6.0 mmol/L occurred in 4 patients (0.9%) in the finerenone group vs. 3 (0.7%) in the placebo group, whereas in patients not receiving an SGLT2i at baseline, this occurred in 207 (3.4%) and 77 (1.3%) patients in the finerenone and placebo groups, respectively. Incidences of hyperkalemia events leading to permanent discontinuation were low with finerenone and placebo in both SGLT2i baseline groups (patients receiving an SGLT2i at baseline 1.1% vs. 0.7%; patients not receiving an SGLT2i 1.7% vs. 0.6%).

Renal AEs were similar with finerenone and placebo; there was no increase in renal AEs in patients receiving versus not receiving an SGLT2i at baseline. The incidence of acute kidney injury appeared to be lower with finerenone versus placebo in patients receiving an SGLT2i at baseline (5 [1.1%] vs. 15 [3.4%]), but similar between groups in those not receiving an SGLT2i at baseline (215 [3.5%] vs. 219 [3.6%]) (Table 2).

CONCLUSIONS

In the FIDELITY analysis of patients across a broad spectrum of CKD in type 2 diabetes, finerenone reduced the risk of CV and kidney outcomes compared with placebo, and concomitant treatment with an SGLT2i at baseline or at any time concomitant with study treatment did not modify the observed benefits. These results build on the observation from the FIDELIO-DKD trial that demonstrated a consistent reduction in UACR with finerenone irrespective of SGLT2i intake at baseline (11). The greater power from >13,000 participants provided in the present individual patient–level pooled analysis allows us to extend these findings into other, more important clinical outcomes with improved precision. In patients receiving an SGLT2i at baseline, the risk of cardiorenal events was lower than in those not receiving an SGLT2i on the basis of a comparison of the placebo groups. This may be explained by the differences in baseline characteristics of these groups, including higher mean eGFR and lower median UACR. However, the benefit of finerenone compared with placebo was also observed in those treated with an SGLT2i at baseline. A greater reduction in eGFR from baseline to month 4 was observed with finerenone treatment in patients who received



No. of patients

With SGLT2i at baseline					
Finerenone	424	413	336	191	64
Placebo	417	404	336	178	61
Without SGLT2i at baseline					
Finerenone	5,849	5,575	4,531	2,554	835
Placebo	5,822	5,569	4,493	2,528	811

Figure 2—Change in UACR over time in patients receiving or not receiving an SGLT2i at baseline. Mixed model with factors included treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment-by-time interaction, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value-by-time interaction as covariates. eGFR, estimated glomerular filtration rate; IQR, interquartile range; SGLT2i, sodium–glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

an SGLT2i at baseline than in those who did not; however, chronic eGFR slope was improved with concomitant treatment.

We did not detect any safety signals associated with concomitant use of finerenone and an SGLT2i. This would suggest that stopping rules in the FIGARO-DKD and FIDELIO-DKD trials based on serum potassium levels (7,8) were appropriate to limit the risk of hyperkalemia. A lower incidence of hyperkalemia was reported with concomitant treatment with SGLT2i and finerenone than with finerenone alone; however, an increased risk of any hyperkalemia event with finerenone compared with placebo was still observed. Notably, in patients receiving an SGLT2i at baseline, no difference between the finerenone and placebo groups was observed for serum potassium increases to >6.0 mmol/L. Hyperkalemia events with clinical implications remained infrequent, irrespective of SGLT2i treatment at baseline. Taken together, these data suggest that treatment with an SGLT2i may offer protection from hyperkalemia events when used in combination with finerenone; however, these data need to be interpreted with caution because of the low number of events observed. Despite the low number of hyperkalemia events in FIDELITY, data from the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial appear to support these findings; a subgroup analysis revealed that the incidence of hyperkalemia was reduced with dapagliflozin in patients who also received concomitant treatment with a steroidal MRA (13). Although the incidence of acute kidney injury appeared to be lower with finerenone compared with placebo in patients receiving an SGLT2i at baseline but comparable in those not receiving an SGLT2i at baseline, the low incidences in both groups make it difficult to provide clinical relevance to the results.

The mechanisms by which finerenone provides cardiorenal benefits have yet to be fully elucidated. As reported in this analysis, finerenone had a modest effect on SBP irrespective of SGLT2i treatment at baseline, and data from preclinical studies in rats have also revealed a reduction in SBP at higher doses of finerenone (14). However, the preclinical models suggested that the cardiorenal protective effects of finerenone are multifactorial, with CV and kidney benefits driven by inhibition of inflammation and fibrosis (14). Finerenone may therefore improve cardiorenal outcomes through a combination of hemodynamic and nonhemodynamic mechanisms. Preclinical data have suggested overadditive effects when combining finerenone and empagliflozin, with the strongest survival benefit (93%) observed with a combination of low-dose finerenone and empagliflozin compared with the individual monotherapy arms or placebo in a rat model of hypertension-induced organ damage (15). The largely independent and complementary mechanisms of action of finerenone and SGLT2is provide a basis for their efficacious and safe combined use. Indeed, kidney and CV benefits of SGLT2is on top of concomitant treatment with a steroidal MRA in patients with heart failure and reduced ejection fraction have been reported in the EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) and Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) (16,17). Recommended treatment for heart failure is based on combination therapy upon a foundation of RAS inhibitors or angiotensin receptor-neprilysin inhibitors, MRAs, and SGLT2is, with the addition of a β-blocker (18). As a parallel, the use of finerenone, SGLT2is, and GLP-1RAs on top of RAS inhibitors is likely to represent combined treatment options for patients with CKD and type 2 diabetes in the future.

There are limitations to the presented analyses that should be considered when interpreting these data. Patients in the FIDELIO-DKD and FIGARO-DKD studies were not stratified in their random assignments on the basis of SGLT2i use, and we also cannot exclude the possibility that patients

Table 2—Overall safety and selected treatment-emergent AEs of interest in patients receiving or not receiving an SGLT2i at baseline

	SGLT2i at baseline		No SGLT2i at baseline	
Investigator-reported, treatment-emergent AE	Finerenone (*n* = 438)	Placebo (*n* = 439)	Finerenone (*n* = 6,072)	Placebo (*n* = 6,050)
Any AE	398 (90.9)	384 (87.5)	5,204 (85.7)	5,223 (86.3)
Leading to discontinuation	18 (4.1)	23 (5.2)	396 (6.5)	328 (5.4)
Any serious AE	146 (33.3)	141 (32.1)	1,914 (31.5)	2,045 (33.8)
Leading to discontinuation	7 (1.6)	8 (1.8)	138 (2.3)	146 (2.4)
Any AE resulting in death	2 (0.5)	9 (2.1)	108 (1.8)	142 (2.3)
Hyperkalemia-related AEs				
Any AE	45 (10.3)	12 (2.7)	867 (14.3)	436 (7.2)
Leading to discontinuation	5 (1.1)	3 (0.7)	105 (1.7)	35 (0.6)
Leading to hospitalization	1 (0.8)	0	39 (1.4)	8 (0.3)
Renal AEs				
Acute kidney injury	5 (1.1)	15 (3.4)	215 (3.5)	219 (3.6)
Worsening renal function leading to discontinuation	2 (0.5)	2 (0.5)	50 (0.8)	40 (0.7)
Hypertension	15 (3.4)	30 (6.8)	404 (6.7)	551 (9.1)
Hypotension	21 (4.8)	14 (3.2)	261 (4.3)	163 (2.7)
Hypoglycemia	17 (3.9)	19 (4.3)	323 (5.3)	356 (5.9)
Central laboratory assessments				
Serum potassium >5.5 mmol/L	34 (7.9)	13 (3.0)	1,041 (17.4)	457 (7.7)
Serum potassium >6.0 mmol/L	4 (0.9)	3 (0.7)	207 (3.4)	77 (1.3)

Data are *n* (%). AE, adverse event; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

receiving an SGLT2i at baseline were recruited from centers with more aggressive approaches toward therapy. Indeed, GLP-1RA and statin use in patients receiving an SGLT2i at baseline was higher than in those not receiving an SGLT2i at baseline despite similar proportions of patients with a history of CV disease. While the present analysis was adjusted for HbA_{1c}, SBP, and baseline UACR and eGFR, other imbalances in baseline characteristics, for example, GLP-1RA use, may have confounded the results. However, these limitations are unlikely to impact the observed treatment effects for comparisons of finerenone versus placebo because of the randomized study design. Overall, the analysis lacked statistical power for the composite kidney and CV outcomes because of the relatively small number of patients receiving SGLT2i at baseline in the FIDELITY population and the small number of clinical events in these patients. Given the sample size, we were unable to evaluate whether dose or type of SGLT2i modified the reported outcomes.

Although the study is not powered to affirm a definitive conclusion, this FIDELITY subgroup analysis suggests that finerenone provides kidney and CV outcome benefits in adults with CKD and type 2 diabetes irrespective of treatment with an SGLT2i, with no concerning safety signals observed with the concomitant use of finerenone and an SGLT2i. The role of combination therapies for cardiorenal protection remains unknown. Randomized trials should assess prospectively whether the combination of a selective, nonsteroidal MRA with an SGLT2i on top of RAS inhibition would provide further protection from heart and kidney failure.

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and M.F.S. reported being full-time employees of Division of Pharmaceuticals, Bayer AG, Germany. M.F.S. is also a shareholder in AstraZeneca, Bayer AG, Eli Lilly, and Novo Nordisk. M.G. is also a shareholder in AstraZeneca, Bayer AG, and Gilead Sciences. A.J. reported having been a full-time employee of Division of Pharmaceuticals, Bayer AG, Germany, at the time of the studies and analysis; he is now a full-time employee of Chiesi S.p.A, Parma, Italy. G.L.B. reported receiving research funding, paid to the Department of Medicine, University of Chicago, from Bayer AG during the conduct of the study; receiving research funding, paid to the university from Novo Nordisk and Vascular Dynamics; acting as a consultant and receiving personal fees from Alnylam, Merck, and Relypsa; being an editor of the *American Journal of Nephrology, Nephrology,* and *Hypertension*; being a section editor of UpToDate; and being an associate editor of *Diabetes Care* and *Hypertension Research*. R.A. reported receiving personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc. during the conduct of the study as well as personal fees and nonfinancial support from Akebia Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fresenius, Janssen Pharmaceuticals, Relypsa, Sanofi, and Vifor Pharma; personal fees from Ironwood Pharmaceuticals, Lexicon, Merck & Co., and Reata; receiving nonfinancial support from ER Squibb & Sons, Opko Pharmaceuticals, and Otsuka America Pharmaceutical; being a member of data safety monitoring committees for Amgen, AstraZeneca, and Celgene; being a member of steering committees of randomized trials for Akebia Therapeutics, Bayer AG, Janssen Pharmaceuticals, and Relypsa; being a member of adjudication committees for AbbVie, Bayer AG, Boehringer Ingelheim, and Janssen Pharmaceuticals; serving as associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation*; having been an author for UpToDate; and receiving research grants from the U.S. Veterans Administration and the National Institutes of Health. No other potential conflicts of interest relevant to this article were reported.

The sponsor participated in the analysis design, data collection, data analysis, data interpretation, and approval of the manuscript. Analyses were conducted by the sponsor, and all authors had access to and participated in the interpretation of the data. The authors made the decision to submit for publication.

Author Contributions. The Executive Committee designed the study in conjunction with the sponsor. P.R. wrote the first draft of the report. P.R., S.D.A., G.F., B.P., L.M.R., A.L.B., J.B.M., S.E.R., A.J., M.G., L.R., M.F.S., G.L.B., and R.A. had access to the study results, were involved in data analysis and interpretation and drafting and critically revising the report, and reviewed and approved the final submitted version of the report. P.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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