



Finerenone in Patients With Chronic Kidney Disease and Type 2 Diabetes According to Baseline HbA_{1c} and Insulin Use: An Analysis From the FIDELIO-DKD Study

Diabetes Care 2022;45:888–897 | <https://doi.org/10.2337/dc21-1944>

Peter Rossing,^{1,2} Ellen Burgess,³ Rajiv Agarwal,⁴ Stefan D. Anker,⁵ Gerasimos Filippatos,⁶ Bertram Pitt,⁷ Luis M. Ruilope,^{8–10} Pieter Gillard,¹¹ Richard J. MacIsaac,¹² Julio Wainstein,^{13,14} Amer Joseph,¹⁵ Meike Brinker,¹⁵ Lothar Roessig,¹⁵ Charlie Scott,¹⁶ and George L. Bakris,¹⁷ on behalf of the FIDELIO-DKD Investigators*

OBJECTIVE

Finerenone significantly improved cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease trial. We explored whether baseline HbA_{1c} level and insulin treatment influenced outcomes.

RESEARCH DESIGN AND METHODS

Patients with T2D, urine albumin-to-creatinine ratio (UACR) of 30–5,000 mg/g, estimated glomerular filtration rate (eGFR) of 25 to <75 mL/min/1.73 m², and treated with optimized renin–angiotensin system blockade were randomly assigned to receive finerenone or placebo. Efficacy outcomes included kidney (kidney failure, sustained decrease ≥40% in eGFR from baseline, or renal death) and cardiovascular (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) composite endpoints. Patients were analyzed by baseline insulin use and by baseline HbA_{1c} <7.5% (58 mmol/mol) or ≥7.5%.

RESULTS

Of 5,674 patients, 3,637 (64.1%) received insulin at baseline. Overall, 5,663 patients were included in the analysis for HbA_{1c}; 2,794 (49.3%) had baseline HbA_{1c} <7.5% (58 mmol/mol). Finerenone significantly reduced risk of the kidney composite outcome independent of baseline HbA_{1c} level and insulin use ($P_{\text{interaction}} = 0.41$ and 0.56, respectively). Cardiovascular composite outcome incidence was reduced with finerenone irrespective of baseline HbA_{1c} level and insulin use ($P_{\text{interaction}} = 0.70$ and 0.33, respectively). Although baseline HbA_{1c} level did not affect kidney event risk, cardiovascular risk increased with higher HbA_{1c} level. UACR reduction was consistent across subgroups. Adverse events were similar between groups regardless of baseline HbA_{1c} level and insulin use; few finerenone-treated patients discontinued treatment because of hyperkalemia.

CONCLUSIONS

Finerenone reduces kidney and cardiovascular outcome risk in patients with CKD and T2D, and risks appear consistent irrespective of HbA_{1c} levels or insulin use.

¹Steno Diabetes Center Copenhagen, Herlev, Denmark

²Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

³Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

⁴Richard L. Roudebush VA Medical Center and Indiana University, Indianapolis, IN

⁵Department of Cardiology, and Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany

⁶National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece

⁷Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI

⁸Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain

⁹Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares, Hospital Universitario 12 de Octubre, Madrid, Spain

¹⁰Faculty of Sport Sciences, European University of Madrid, Madrid, Spain

¹¹Department of Endocrinology, University Hospital Leuven – Katholieke Universiteit Leuven, Leuven, Belgium

¹²Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne and

Chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) is a major global health challenge, affecting an estimated 160 million people aged 20–79 years worldwide (1–3). Clinical guidelines for the management of CKD in patients with T2D recommend control of hypertension and hyperglycemia, with individualized targets for the level of HbA_{1c} of <6.5% (48 mmol/mol) to <8% (64 mmol/mol), as well as the use of a renin–angiotensin system blocker (an ACE inhibitor or angiotensin receptor blocker [ARB]) and, more recently, a sodium–glucose cotransporter 2 inhibitor (SGLT-2i) (4–7).

Insulin is often used as a glucose-lowering agent in patients with CKD and T2D, especially in patients with moderate to severe CKD in whom many other glucose-lowering agents cannot be used (8). It has been suggested that insulin treatment may increase sodium retention and hypertension (9), and hyperinsulinemia has been associated with inflammation in patients with T2D (10). Insulin is often used when β -cell failure is apparent and oral agents have failed; thus, insulin use at baseline may be suggestive of patients with complicated diabetes (11).

Available evidence suggests that glycemic control influences kidney risk in patients with T2D. Observational data suggest that poor glycemic control increases the risk for progression of CKD in patients with T2D with moderately elevated albuminuria (12), and data from clinical trials have shown that intensive blood glucose control improves kidney outcomes in patient groups with T2D and T2D with mild CKD (13–15). However, evidence from large phase 3 trials regarding the relationship between glycemic control and disease outcomes in patients with moderate to severe CKD and T2D is lacking.

The prognostic implication and response to treatment with a mineralocorticoid receptor antagonist (MRA) relative to glycemic control as reflected by HbA_{1c} levels is not well understood (16). Limited available data suggest that the nonselective steroidal MRA spironolactone may increase HbA_{1c} levels in patients with and without diabetes, whereas the more selective steroidal MRA eplerenone has no effect on HbA_{1c} levels (17,18). Finerenone is a novel, selective, nonsteroidal MRA that significantly reduced the risk of adverse kidney and cardiovascular (CV) outcomes in patients with CKD and T2D in the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) phase 3 trial, without influencing HbA_{1c} levels (19,20). The main aim of this analysis was to evaluate kidney, CV, and safety outcomes from the FIDELIO-DKD trial according to baseline HbA_{1c} level, and to determine whether baseline glycemic control affects the previously reported benefits of treatment with finerenone. Furthermore, the effects of insulin treatment at baseline on efficacy and safety outcomes were investigated because of the interdependency of insulin treatment and glycemic control (serum HbA_{1c} levels) in patients with CKD and T2D. As such, we hypothesized that finerenone would not influence HbA_{1c} levels and that the treatment effect of finerenone would not be modified by HbA_{1c} or by insulin use at baseline.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The study design of FIDELIO-DKD, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven phase 3 trial, has been described

previously (19,21). The trial was conducted in accordance with the principles of the Declaration of Helsinki; the protocol was approved by relevant regulatory authorities and ethics committees at each trial site, and written informed consent was obtained from all participants. Eligible patients were aged ≥ 18 years and had clinically diagnosed T2D as defined by the American Diabetes Association, with either moderately elevated albuminuria (defined as urine albumin-to-creatinine ratio [UACR] of 30 to <300 mg/g), an estimated glomerular filtration rate [eGFR] of 25 to <60 mL/min/1.73 m², and a history of diabetic retinopathy, or severely elevated albuminuria (defined as UACR ≥ 300 to $\leq 5,000$ mg/g) and an eGFR of 25 to <75 mL/min/1.73 m². Patients with HbA_{1c} >12% at screening were excluded. Furthermore, patients were required to have been treated with a maximum tolerated dose of an ACE inhibitor or ARB in accordance with the manufacturer's label for ≥ 4 weeks prior to the screening visit and to have a serum potassium level ≤ 4.8 mmol/L at the run-in and screening visits. Patients with known nondiabetic kidney disease, chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association class II–IV), a recent history of dialysis for acute kidney failure or a kidney transplant, or uncontrolled hypertension were excluded. The primary and secondary efficacy and safety outcomes have been reported previously (19). The study is registered with the EU Clinical Trials Register (EudraCT 2015-000990-11) and ClinicalTrials.gov (NCT02540993).

Procedures and Outcomes

Patients were randomly assigned (1:1) to receive once-daily oral treatment with finerenone (10 or 20 mg) or matched placebo; patients with an eGFR of 25 to

University of Melbourne, Melbourne, Victoria, Australia

¹³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

¹⁴Diabetes Unit, Edith Wolfson Medical Center, Holon, Israel

¹⁵Cardiology and Nephrology Clinical Development, Bayer AG, Berlin, Germany

¹⁶Data Science and Analytics, Bayer PLC, Reading, U.K.

¹⁷Department of Medicine, University of Chicago Medicine, Chicago, IL

Corresponding author: Peter Rossing, peter.rossing@regionh.dk

Received 17 September 2021 and accepted 28 December 2021

ClinicalTrials.gov reg. no. NCT02540993, clinicaltrials.gov, and EU Clinical Trials Register no. 2015-000990-11, <https://www.clinicaltrialsregister.eu/>

This article contains supplementary material online at <https://doi.org/10.2337/figshare.17701001>.

This article is featured in a podcast available at diabetesjournals.org/journals/pages/diabetes-core-update-podcasts.

*A complete list of the FIDELIO-DKD Investigators can be found in the supplementary material online.

© 2022 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://www.diabetesjournals.org/journals/pages/license>.

<60 mL/min/1.73 m² at the screening visit received a starting dose of 10 mg once daily, and those with an eGFR ≥60 mL/min/1.73 m² received a starting dose of 20 mg once daily. An increase in the dose of study medication from 10 mg to the target dose of 20 mg once daily was encouraged after 1 month, provided the serum potassium level was ≤4.8 mmol/L and the eGFR was stable; a decrease in the dose from 20 to 10 mg once daily was allowed any time after the initiation of finerenone or placebo for safety reasons. During the study, healthcare providers were advised to follow local guidelines for the management of T2D, including recommendations for glycemic control; concomitant antidiabetic drugs were recorded by the investigators. Oral antidiabetics included dipeptidyl peptidase 4 inhibitors, SGLT-2is, biguanides, sulfonylureas, α-glucosidase inhibitors, meglitinides, and thiazolidinediones.

The primary kidney outcome was a composite of time to kidney failure, defined as chronic dialysis for >90 days, kidney transplantation, or a sustained eGFR of <15 mL/min/1.73 m² confirmed after at least 4 weeks; a sustained ≥40% decrease in eGFR from baseline over at least 4 weeks; or renal death. The key secondary CV outcome was a composite of time to first onset of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The secondary kidney outcome was a composite of kidney failure, a sustained ≥57% decrease in eGFR from baseline (for ≥4 weeks), or renal death. Other secondary outcomes, such as change in UACR from baseline to month 4, were explored. An independent clinical event committee blinded to treatment assignment adjudicated all reported outcome events, using definitions published previously (19). Safety outcomes included investigator-reported adverse events (AEs) and central laboratory assessment; events were considered as treatment emergent if they started or worsened during intake of study drug or up to 3 days after treatment interruption or discontinuation.

For this analysis, the impact of baseline HbA_{1c} and insulin use (yes/no) on composite kidney and CV outcomes and safety in patients treated with finerenone or placebo was evaluated.

Statistical Analysis

Efficacy analyses were performed in the full analysis set (FAS), that is, all randomized patients without critical Good Clinical Practice violations. These prespecified subgroup analyses were exploratory and not designed to confirm or reject any predefined hypotheses. Analyses were performed according to each defined subgroup, that is, baseline HbA_{1c} <7.5% (58 mmol/mol) versus baseline HbA_{1c} ≥7.5% (58 mmol/mol), and baseline insulin use versus no baseline insulin use. The threshold value of 7.5% was used to define HbA_{1c} subgroups at baseline, because the median HbA_{1c} value in the study overall, as well as in each of the treatment arms, was 7.50%. All analyses were performed with SAS software, version 9.4 (SAS Institute).

Stratified log-rank testing was used to analyze the time-to-event superiority of finerenone versus placebo, and a stratified Cox proportional hazards regression model was used for hazard ratios (HRs). Stratification was according to geographic region and eGFR and UACR at screening (described previously) (19). A weighted Bonferroni–Holm procedure was used to test primary composite kidney and key secondary composite CV outcomes. Events were reported from randomization up to the end of study visit. Patients without an event were censored at the date of their last contact, with complete information on all components of their respective outcomes. The secondary efficacy outcome of change in UACR was analyzed with a linear mixed model, with all covariates entered as fixed effects and the subject effect entered as a random effect. Covariates in this analysis were treatment group (i.e., the treatment to which the patient was randomized to), visit, treatment-by-visit interaction, factors for the stratification levels, log-transformed baseline UACR value as a covariate nested within type of albuminuria, and log-transformed baseline value-by-visit interaction. To adjust the model for the within-subject variability of the repeated measures, we used an unstructured covariance pattern.

The relationship of the primary composite kidney and key secondary composite CV outcomes with baseline HbA_{1c} as a continuous variable was investigated post hoc using a Cox proportional hazards model with cubic B-splines of

HbA_{1c} with three equally spaced knots, stratified by region, albuminuria at screening, and eGFR at screening, and with treatment interaction as covariates. To investigate further the relationship between HbA_{1c} and outcomes, additional spline models with the same covariates were fitted separately in each treatment group (i.e., finerenone and placebo). Safety analyses were performed in the safety analysis set, which consisted of all eligible, randomized patients who took at least one dose of study drug.

RESULTS

Patients

A total of 5,734 patients were randomly assigned to an arm in the FIDELIO-DKD trial. After the prospective exclusion of 60 patients from all analyses because of critical Good Clinical Practice violations, 5,674 patients were assessed in the FAS. As baseline HbA_{1c} data were missing for 11 patients, 5,663 patients were included in the analysis for HbA_{1c}. The trial concluded after a median follow-up of 2.6 (interquartile range, 2.0–3.4) years, with vital status available for 99.7% of patients (19). In the FAS (*n* = 5,674), the mean duration of T2D was 16.6 years. Mean HbA_{1c} at baseline was 7.7% (61 mmol/mol) and remained stable in the finerenone and placebo treatment groups over the duration of the study (19). The distribution of HbA_{1c} at baseline in both treatment groups is shown in Supplementary Fig. 1. At baseline, the median HbA_{1c} was 7.5% (58 mmol/mol). In a mixed-model analysis, the least-squares (LS) mean change from baseline in HbA_{1c} over the trial period among patients with HbA_{1c} <7.5% (58 mmol/mol) was 0.03% (95% CI –0.04% to 0.09%), and 0.07% (95% CI –0.02% to 0.16%) in patients with baseline HbA_{1c} value ≥7.5% (58 mmol/mol) (Supplementary Fig. 2).

Of the 5,663 patients who were included in the HbA_{1c} analysis, 2,794 (49.3%) had an HbA_{1c} <7.5% (58 mmol/mol) (Table 1) at baseline. Of 5,674 patients in the FAS, 3,637 (64.1%) were treated with insulin at baseline and 469 (8.3% patients: *n* = 209 [7.4%] receiving finerenone; *n* = 260 [9.2%] receiving placebo) started treatment with insulin after the start of the study (Supplementary Table 1). Patients who were started on insulin after baseline were included in the subgroup without insulin at baseline.

Table 1—Patient baseline characteristics stratified according to median HbA_{1c} and insulin use at baseline

	Baseline HbA _{1c} ^a		Baseline insulin use	
	<7.5% (n = 2,794)	≥7.5% (n = 2,869) ^b	No (n = 2,037)	Yes (n = 3,637)
Age, years, mean ± SD	66.2 ± 9.3	65.0 ± 8.8	66.4 ± 9.4	65.1 ± 8.9
Sex, male, n (%)	2,073 (74.2)	1,904 (66.4)	1,469 (72.1)	2,514 (69.1)
Race, n (%)				
White	1,732 (62.0)	1,855 (64.7)	1,244 (61.1)	2,348 (64.6)
Black/African American	110 (3.9)	153 (5.3)	79 (3.9)	185 (5.1)
Asian	801 (28.7)	636 (22.2)	613 (30.1)	827 (22.7)
Other ^c	151 (5.4)	225 (7.8)	101 (5.0)	277 (7.6)
Systolic blood pressure, mmHg, mean ± SD	137.6 ± 14.5	138.5 ± 14.3	137.2 ± 14.4	138.5 ± 14.3 ^d
Diastolic blood pressure, mmHg, mean ± SD	75.5 ± 9.8	76.2 ± 9.5	76.4 ± 9.7	75.5 ± 9.6 ^d
Duration of diabetes, years, mean ± SD	15.0 ± 8.8	18.1 ± 8.4	13.0 ± 8.0	18.6 ± 8.6
HbA _{1c} , %, mean ± SD (mmol/mol)	6.6 ± 0.6 (48.6)	8.7 ± 1.0 (71.6)	7.0 ± 1.1 ^e (53.0)	8.0 ± 1.3 ^d (63.9)
eGFR, mL/min/1.73 m ² , mean ± SD	44.0 ± 12.5	44.7 ± 12.6	45.1 ± 12.5	43.9 ± 12.6
eGFR, mL/min/1.73 m ² , n (%)				
<25	66 (2.4)	69 (2.4)	41 (2.0)	94 (2.6)
25 to <45	1,506 (53.9)	1,469 (51.2)	1,035 (50.8)	1,946 (53.5)
45 to <60	923 (33.0)	974 (33.9)	716 (35.1)	1,184 (32.6)
≥60	299 (10.7)	357 (12.4)	245 (12.0)	411 (11.3)
UACR, mg/g, median (IQR)	835 (445–1,567)	864 (447–1,693)	784 (443–1,482) ^f	884 (448–1,715)
UACR, mg/g, n (%)				
<30	7 (0.3)	16 (0.6)	4 (0.2)	19 (0.5)
30 to <300	342 (12.2)	343 (12.0)	233 (11.4)	452 (12.4)
≥300	2,445 (87.5)	2,509 (87.5)	1,799 (88.3)	3,164 (87.0)
Missing data	1 (<0.1)	2 (<0.1)		
Serum potassium, mmol/L, mean ± SD	4.35 ± 0.46	4.39 ± 0.46	4.35 ± 0.45	4.38 ± 0.46
BMI, kg/m ² , mean ± SD	30.4 ± 5.9	31.8 ± 6.0	30.1 ± 5.7 ^e	31.7 ± 6.1
History of CVD, n (%)	1,233 (44.1)	1,368 (47.7)	836 (41.0)	1,769 (48.6)
History of diabetic retinopathy	1,156 (41.4)	1,501 (52.3)	697 (34.2)	1,966 (54.1)
History of diabetic neuropathy	591 (21.2)	861 (30.0)	349 (17.1)	1,105 (30.4)
Current smoker, n (%)	436 (15.6)	368 (12.8)	324 (15.9)	482 (13.3)
Baseline medications, n (%)				
ACE inhibitors	914 (32.7)	1,022 (35.6)	664 (32.6)	1,278 (35.1)
ARBs	1,875 (67.1)	1,845 (64.3)	1,367 (67.1)	2,358 (64.8)
β-Blockers	1,428 (51.1)	1,535 (53.5)	989 (48.6)	1,979 (54.4)
Diuretics	1,529 (54.7)	1,681 (58.6)	1,055 (51.8)	2,159 (59.4)
Statins	2,023 (72.4)	2,182 (76.1)	1,458 (71.6)	2,757 (75.8)
Glucose-lowering therapies	2,672 (95.6)	2,842 (99.1)	1,887 (92.6)	3,637 (100)
Insulin and analogs	1,353 (48.4)	2,279 (79.4)	0	3,637 (100)
Metformin	1,264 (45.2)	1,219 (42.5)	1,146 (56.3)	1,344 (37.0)
Sulfonylureas	687 (24.6)	639 (22.3)	909 (44.6)	418 (11.5)
DPP-4 inhibitors	833 (29.8)	686 (23.9)	782 (38.4)	740 (20.3)
GLP-1RAs	158 (5.7)	235 (8.2)	11 (5.4)	283 (7.8)
SGLT-2is	100 (3.6)	159 (5.5)	86 (4.2)	173 (4.8)
α-Glucosidase inhibitors	173 (6.2)	151 (5.3)	137 (6.7)	187 (5.1)
Meglitinides	189 (6.8)	133 (4.6)	167 (8.2)	156 (4.3)
TZDs	124 (4.4)	105 (3.7)	135 (6.6)	94 (2.6)

CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide 1 receptor agonist; IQR, interquartile range; TZD, thiazolidinedione. ^aMissing data for 11 patients (finerenone, n = 7; placebo, n = 4). ^bMissing data for 1 patient with HbA_{1c} ≥7.5% at baseline. ^cIncludes patients reporting multiple races. ^dMissing data for 5 patients. ^eMissing data for 6 patients. ^fMissing data for 1 patient.

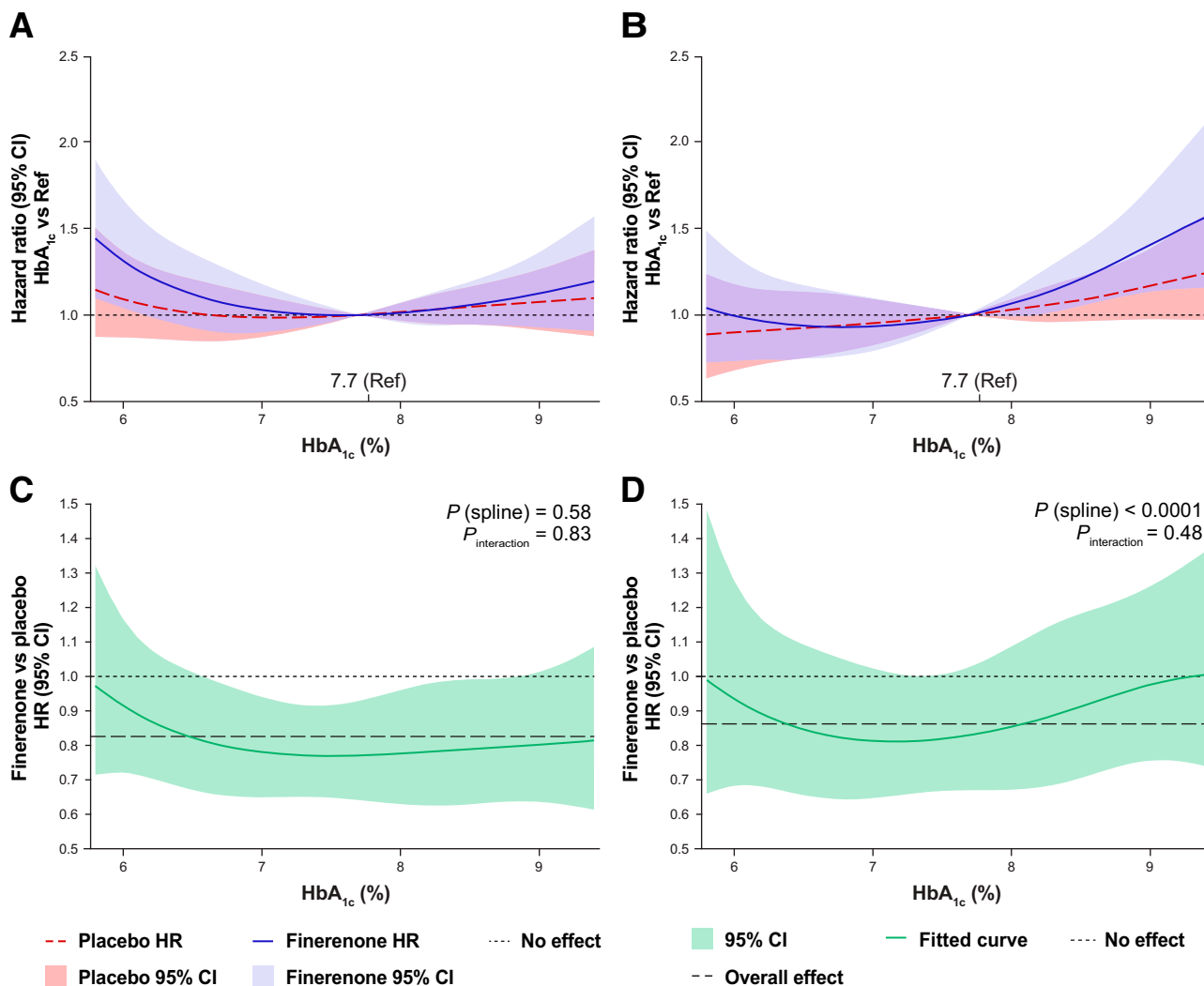


Figure 1—Cox proportional hazards model for the primary kidney outcomes and key secondary CV outcome in the FAS, with cubic B-splines of HbA_{1c} with three equally spaced knots stratified by region, and albuminuria and eGFR at screening. The model was fitted separately by treatment group for the primary kidney composite outcome (A) and the key secondary CV outcome (B), and with treatment interaction as a covariate for the primary kidney composite outcome (C) and the key secondary CV composite outcome (D). The reference (Ref) is mean HbA_{1c} (%) at baseline.

Baseline Characteristics

By HbA_{1c} Level

Patients with HbA_{1c} $\geq 7.5\%$ at baseline had a longer duration of T2D and a higher proportion had a history of CV disease compared with patients whose HbA_{1c} was $< 7.5\%$. However, median UACR, mean eGFR, and mean serum potassium levels were similar in patients regardless of HbA_{1c} (i.e., $\geq 7.5\%$ or $< 7.5\%$) (Table 1). Overall, 48.4% and 79.4% of patients with HbA_{1c} $< 7.5\%$ and $\geq 7.5\%$, respectively, were being treated with insulin at baseline. Greater use of glucagon-like peptide 1 receptor agonists and SGLT-2is was observed in patients with baseline HbA_{1c} $\geq 7.5\%$ vs. $< 7.5\%$ (Table 1).

By Insulin Use

Patients treated with insulin had a higher BMI, a longer duration of diabetes, and a higher UACR than did patients who did not receive insulin at baseline. Serum potassium and baseline eGFR values were similar between groups (Table 1).

Kidney Outcomes According to HbA_{1c} Level and Insulin Use at Baseline

By HbA_{1c} Level

No clear relationship was observed between baseline HbA_{1c} level and the risk of experiencing a primary kidney outcome event, after adjusting for confounding baseline variables, irrespective of treatment assignment. Thus, as an example, patients with a baseline HbA_{1c}

of 6.5% (48 mmol/mol) or 9.0% (75 mmol/mol) had a similar risk of experiencing an event as those with a baseline HbA_{1c} of 7.7% (61 mmol/mol) (Fig. 1A).

As previously reported, the incidence of the primary composite kidney outcome was significantly lower with finerenone versus placebo in the overall population of FIDELIO-DKD (HR 0.82; 95% CI 0.73–0.93; $P = 0.001$) (19). In this analysis, the primary kidney outcome occurred in fewer patients treated with finerenone compared with those who received placebo in both the HbA_{1c} $< 7.5\%$ and $\geq 7.5\%$ groups (18.8% vs. 21.6% of patients with HbA_{1c} $< 7.5\%$ [HR 0.86; 95% CI 0.73–1.02]; 16.9% vs. 20.7% of patients with HbA_{1c} $\geq 7.5\%$ [HR 0.78;

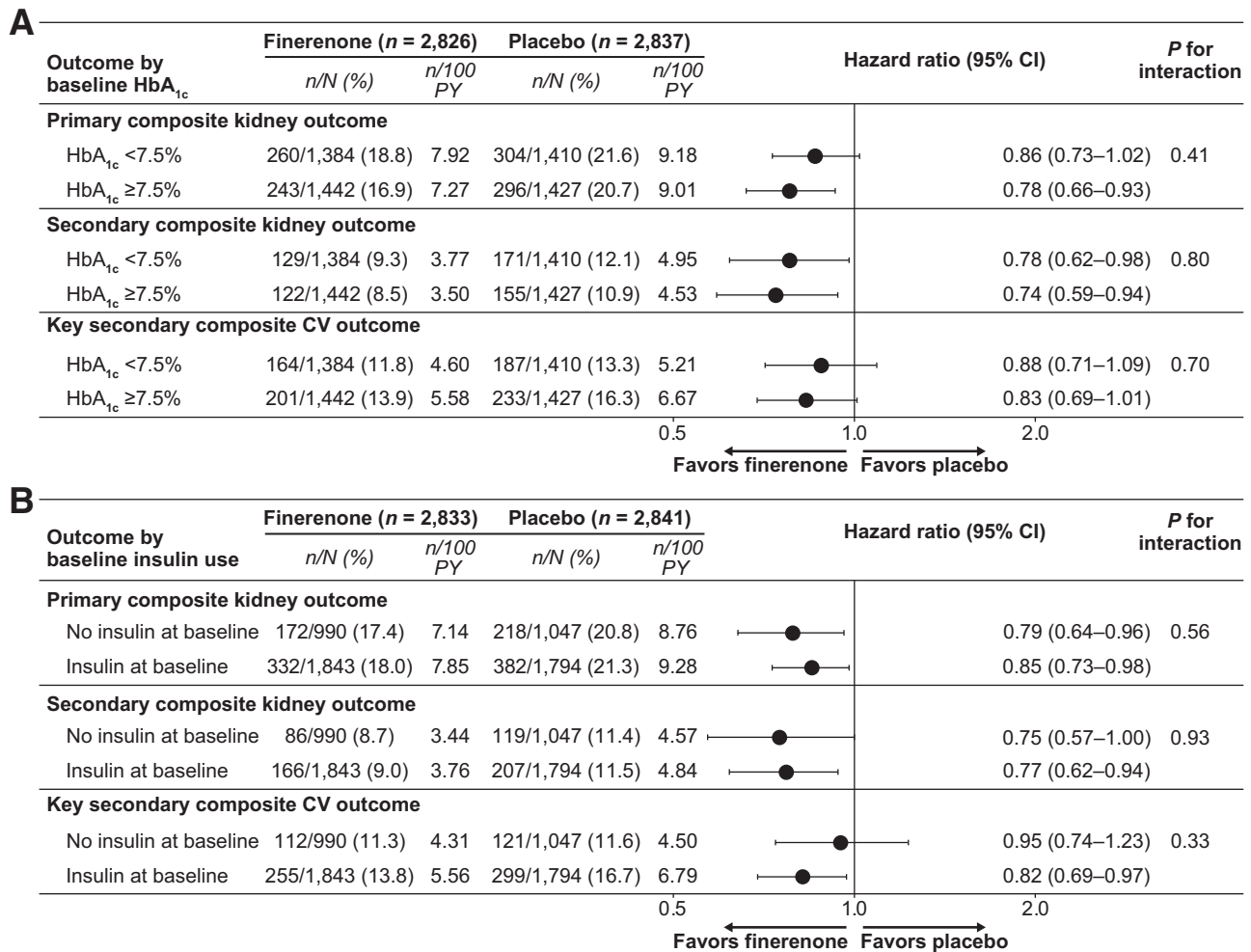


Figure 2—Composite kidney outcome (time to kidney failure, a sustained $\geq 40\%$ decrease in eGFR from baseline over at least 4 weeks; or death from renal causes), secondary composite kidney outcome (time to kidney failure, a sustained $\geq 57\%$ decrease in eGFR from baseline over at least 4 weeks; or death from renal causes), and CV outcomes (time to first onset of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) according to HbA_{1c} level at baseline (A) and insulin use at baseline (B). PY, patient-year.

95% CI 0.66–0.93]; $P_{\text{interaction}} = 0.41$) (Fig. 2 and Supplementary Fig. 3). The treatment effect of finerenone was consistent when HbA_{1c} was modeled as a continuous variable ($P_{\text{interaction}}$ for finerenone vs. placebo = 0.8334) (Fig. 1B). Incidence of the secondary composite kidney outcome followed a similar pattern, with fewer events in patients treated with finerenone compared with those who received placebo in both groups (9.3% vs. 12.1% of patients with HbA_{1c} <7.5% [HR 0.78; 95% CI 0.62–0.98]; 8.5% vs. 10.9% of patients with baseline HbA_{1c} $\geq 7.5\%$ [HR 0.74; 95% CI 0.59–0.94]; $P_{\text{interaction}} = 0.80$) (Fig. 2).

In the overall population, finerenone was associated with a 31% greater reduction in UACR from baseline to month 4 versus placebo (HR 0.69; 95% CI 0.66–0.71) (19). A mixed-model

analysis (accounting for differences in baseline characteristics) indicated a similar reduction in UACR at month 4 with finerenone versus placebo regardless of baseline HbA_{1c} value (ratio of LS means 0.67 [95% CI 0.64–0.71; $P < 0.0001$] with HbA_{1c} <7.5%; and 0.70 [95% CI 0.66–0.74; $P < 0.0001$] with HbA_{1c} $\geq 7.5\%$) (Supplementary Fig. 4).

By Insulin Use

The primary composite kidney outcome occurred in fewer patients treated with finerenone than in those who received placebo in patients with or without insulin use at baseline (18.0% vs. 21.3% of patients with insulin at baseline [HR 0.85; 95% CI 0.73–0.98]; 17.4% vs. 20.8% of patients without insulin at baseline [HR 0.79; 95% CI 0.64–0.96]; $P_{\text{interaction}} = 0.56$) (Fig. 2 and Supplementary Fig. 5). Incidence of the

secondary composite kidney outcome followed a similar pattern (Fig. 2).

The mixed-model analysis showed a similar reduction in UACR at month 4 with finerenone versus placebo regardless of baseline insulin use (ratio of LS means 0.68 [95% CI 0.64–0.73], $P < 0.0001$ without insulin use at baseline; 0.68 [95% CI 0.65–0.72], $P < 0.0001$ with baseline insulin use) (Supplementary Fig. 6).

CV Outcomes According to HbA_{1c} Level and Insulin Use at Baseline

By HbA_{1c} Level

After adjusting for confounding baseline variables, a relationship was observed between baseline HbA_{1c} level and the risk of experiencing a CV event. Patients with a baseline HbA_{1c} of 6.5% had a similar risk of experiencing an event as those with a baseline HbA_{1c} of 7.7%, whereas

those with a baseline HbA_{1c} of 9.0% had an ~30% higher risk of experiencing an event than did the reference population (Fig. 1C).

In the overall population, the key secondary composite CV outcome was lower with finerenone compared with placebo in the overall population (HR 0.86; 95% CI 0.75–0.99; $P = 0.03$) (19,20). In this analysis, the incidence of the key secondary CV outcome followed a similar pattern, with finerenone treatment resulting in a lower incidence of the secondary CV outcome compared with placebo (HR 0.88 [95% CI 0.71–1.09] for HbA_{1c} <7.5%; HR 0.83 [95% CI 0.69–1.01] for HbA_{1c} ≥7.5%; $P_{\text{interaction}} = 0.70$) (Fig. 2 and Supplementary Fig. 3). Results were consistent when HbA_{1c} was modeled as a continuous variable ($P_{\text{interaction}}$ for finerenone vs. placebo = 0.4802) (Fig. 1D).

By Insulin Use

The incidence of the key secondary CV outcome also was lower in patients treated with finerenone compared with those who received placebo, with a nonsignificant trend showing greater risk reduction with baseline insulin use (HR 0.82 [95% CI 0.69–0.97] with insulin use at baseline vs. HR 0.95 [95% CI 0.74–1.23] without insulin at baseline; $P_{\text{interaction}} = 0.33$) (Fig. 2 and Supplementary Fig. 5).

The rates of events for the primary composite kidney outcome and the key secondary CV outcome were lower with finerenone versus placebo irrespective of baseline treatment with any oral antidiabetic, any oral antidiabetic but not insulin, or insulin only (P values for the interaction were not significant for any groups) (Supplementary Fig. 7A and B).

Safety

In the overall population, 151 finerenone-treated patients (5.3%) versus 194 placebo-treated patients (6.9%) experienced hypoglycemia, and hyperglycemia occurred in 75 (2.7%) versus 78 (2.8%) patients, respectively. Diabetes-related AEs occurred in 52 finerenone-treated (1.8%) patients versus 77 placebo-treated patients (2.7%); and diabetes control was inadequate in 57 finerenone-treated patients (2.0%) versus 77 placebo-treated patients (2.7%). No difference in diabetic ketoacidosis was

observed between treatment groups ($n = 7$ [0.2%] patients in both arms).

The incidence of any treatment-emergent AE was similar with finerenone and placebo, irrespective of baseline HbA_{1c} level or insulin use (Table 2 and Supplementary Table 2). The incidence of hypoglycemia tended to be lower with finerenone than with placebo, particularly in patients with higher HbA_{1c} levels and in those receiving insulin at baseline (Supplementary Tables 3 and 4). A similar trend was observed for hypoglycemia and hyperglycemia as serious AEs, with lower incidence reported for finerenone versus placebo with higher HbA_{1c} levels and baseline insulin use (Supplementary Tables 5 and 6). There was also no increase in the incidence of urinary tract infections with finerenone versus placebo in either HbA_{1c} subgroup, irrespective of baseline HbA_{1c} level and insulin use. The incidence of any treatment-emergent, hyperkalemia-related AE was greater in patients treated with finerenone than in those who received placebo, with an approximately twofold increase with finerenone in both subgroups; however, no patients died and few patients discontinued the study drug due to hyperkalemia in either treatment arm in both subgroups (Table 2 and Supplementary Table 2).

Baseline systolic blood pressure was marginally higher in the group receiving insulin at baseline group than in those who were not receiving insulin at baseline (138.5 vs. 137.2 mmHg, respectively) (Table 1). There was an ~3 mmHg decrease in systolic blood pressure with finerenone compared with placebo at month 1 relative to baseline, and this was observed in patients with or without insulin use at baseline (Supplementary Fig. 8). No change in body weight was observed with finerenone compared with placebo in patients with or without insulin use at baseline (Supplementary Fig. 9).

CONCLUSIONS

In the FIDELIO-DKD study, finerenone significantly reduced the primary composite kidney outcome and the key secondary CV composite outcome compared with placebo in patients with CKD and T2D, without affecting HbA_{1c} levels. These subgroup analyses demonstrated that the benefits of finerenone in patients with CKD and T2D were

consistent irrespective of HbA_{1c} level or insulin use at baseline. These results expand on previous analyses from FIDELIO-DKD that demonstrated benefits of finerenone on kidney and CV outcomes are also independent of SGLT-2i or glucagon-like peptide 1 receptor agonist use at baseline (22,23).

Results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) trial indicated significant heterogeneity in the primary composite CV outcome between patients with T2D at high risk of CV events with HbA_{1c} <8.5% (69.4 mmol/mol) compared with HbA_{1c} ≥8.5%, suggesting empagliflozin has no CV benefits in patients with HbA_{1c} ≥8.5%, although the effects of empagliflozin to limit incident or worsening nephropathy were consistent irrespective of HbA_{1c} level (24,25). These data suggest that HbA_{1c} levels may contribute to differences in CV efficacy results. Therefore, it was of interest to evaluate whether poor glycemic control or increased HbA_{1c} levels in patients with CKD and T2D would alter the beneficial kidney and CV outcomes observed with finerenone treatment. Reassuringly, the results of the present analysis suggest that, unlike other approved therapies aiming to reduce kidney and CV risk, finerenone delays CKD progression and reduces CV events in patients with CKD and T2D regardless of baseline HbA_{1c} levels. Similar findings were observed in patients receiving or not receiving insulin at baseline. This strengthens our results because of the considerable overlap between both patient subgroups, with almost 80% of patients with HbA_{1c} ≥7.5% receiving insulin at baseline. For all outcomes, fewer events occurred with finerenone than with placebo, with no significant interactions according to HbA_{1c} level or insulin use at baseline. Although the P value for interaction for the secondary CV outcomes was not significant, there was a trend toward a larger risk reduction with baseline insulin use. A similar finding was noted in the Comparison of Outcomes in Patients in New York Heart Association Class II Heart Failure When Treated With Eplerenone or Placebo in Addition to Standard Heart Failure Medicines trial, in which greater CV benefits of the steroidal MRA

Table 2—Overall safety and treatment-emergent, hyperkalemia-related events in patients according to median HbA_{1c} level at baseline

	Baseline HbA _{1c}			
	<7.5%		≥7.5%	
	Finerenone (n = 1,382)	Placebo (n = 1,407)	Finerenone (n = 1,439)	Placebo (n = 1,421)
Any investigator-reported AE	1,206 (87.3)	1,229 (87.3)	1,258 (87.4)	1,246 (87.7)
Related to study drug	312 (22.6)	221 (15.7)	333 (23.1)	228 (16.0)
Leading to discontinuation	98 (7.1)	92 (6.5)	108 (7.5)	75 (5.3)
Any SAE	415 (30.0)	448 (31.8)	485 (33.7)	523 (36.8)
Related to study drug	23 (1.7)	16 (1.1)	24 (1.7)	18 (1.3)
Leading to discontinuation	36 (2.6)	39 (2.8)	38 (2.6)	39 (2.7)
AE with outcome death	15 (1.1)	23 (1.6)	16 (1.1)	28 (2.0)
Investigator-reported hyperkalemia-related AEs ^a				
Any AE	253 (18.3)	124 (8.8)	262 (18.2)	131 (9.2)
Related to study drug	157 (11.4)	60 (4.3)	175 (12.2)	75 (5.3)
Leading to discontinuation	28 (2.0)	13 (0.9)	36 (2.5)	12 (0.8)
Any SAE	22 (1.6)	2 (0.1)	21 (1.5)	10 (0.7)
Related to study drug	12 (0.9)	1 (<0.1)	13 (0.9)	4 (0.3)
Leading to hospitalization	19 (1.4)	2 (0.1)	20 (1.4)	6 (0.4)
Central laboratory assessment of serum potassium levels, mmol/L, n/N (%)				
>5.5	292/1,369 (21.3)	119/1,383 (8.6)	302/1,410 (21.4)	137/1,389 (9.9)
>6.0	61/1,374 (4.4)	18/1,389 (1.3)	65/1,422 (4.6)	20/1,404 (1.4)

Data reported as n (%) unless otherwise indicated. MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

^aReported using the MedDRA-preferred terms “hyperkalemia” and “blood potassium increased.”

eplerenone were observed in patients with insulin-treated diabetes than in patients with diabetes not treated with insulin (26). Because finerenone has a modest effect of lowering blood pressure, promoting natriuresis, and, perhaps, inhibiting inflammation, it may counteract the sodium retention, hypertension, and inflammation associated with insulin use or hyperinsulinemia (9,10). However, more analyses are required to determine whether the benefits of finerenone are greater when a patient is receiving insulin.

Modeling of serum HbA_{1c} levels as a continuous variable suggests that a higher baseline HbA_{1c} level is associated with an increased risk of experiencing CV events, a finding that was observed in both the finerenone and placebo treatment groups in the present study; in contrast, HbA_{1c} levels did not influence the risk of CKD progression in either group, which is an interesting dichotomous observation. These results contrast with what is known about intensive glycemic control and kidney and CV events in patients with T2D without CKD or with

mild CKD. The UK Prospective Diabetes Study (UKPDS) demonstrated that intensive glucose-lowering therapy in patients with newly diagnosed T2D significantly reduced microvascular complications, including a decrease in the progression of albuminuria, when compared with standard therapy, whereas no beneficial effect on CV events was observed (13). In the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, intensive glucose control significantly reduced the risk of end-stage kidney disease, microalbuminuria, and macroalbuminuria in patients with T2D without CKD or with mild CKD, with greater long-term benefits in patients with more preserved kidney function (14,15). And last, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, researchers showed that the use of intensive therapy to target normal HbA_{1c} levels did not significantly reduce CV events when compared with standard therapy and had limited benefits on kidney-specific outcomes in patients

with T2D and high CV risk (27,28). The main reason for the disparities between our results and these studies could be because the data analyses carried out in the present study used a single point-in-time assessment of HbA_{1c} levels at baseline and HbA_{1c} was well controlled, whereas in UKPDS, ADVANCE, and ACCORD, researchers evaluated intensive HbA_{1c} lowering over time. Another reason could be the different medication used (e.g., previous studies did not include patients receiving SGLT-2is or glucagon-like peptide 1 receptor agonists). Patients with a later stage of CKD were observed in this study, compared with patients in the UKPDS, ADVANCE, and ACCORD trials (13–15,27,28).

In the FIDELIO-DKD trial, finerenone was associated with a higher overall risk of hyperkalemia than was placebo, but discontinuation due to hyperkalemia was infrequent in patients receiving finerenone (19). These findings were reflected in this analysis, with no notable differences observed on the basis of baseline HbA_{1c} level or baseline insulin use. An interesting observation was that fewer hypoglycemia AEs and serious AEs

tended to be observed with finerenone than with placebo, particularly in the patient subgroups with HbA_{1c} \geq 7.5% (58 mmol/mol) and those treated with insulin at baseline. The reason for this is unclear because finerenone has no effect on HbA_{1c} levels. One hypothesis is that higher incidence of insulin use in the placebo arm may increase risk of hypoglycemic events, but the possibility that this may be a chance finding cannot be ruled out and more data are needed. Additionally, there was no imbalance in hyperglycemia events between treatment arms and no increase in the incidence of diabetic ketoacidosis or urinary tract infections with finerenone across subgroups. These findings distinguish finerenone from the SGLT-2is, which have been associated with an increased risk of diabetic ketoacidosis and serious urinary tract infections (29,30). Further insight may be provided by the results of the recently completed Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) study. FIGARO-DKD will offer the opportunity for the relationship between baseline HbA_{1c} levels and baseline insulin use to be further investigated in a larger population, including patients with mild CKD and with lower insulin use at baseline (31).

As a secondary analysis of a phase 3 trial, this analysis has some limitations. Namely, patients were not stratified according to baseline insulin use or HbA_{1c} level. Moreover, changes in treatment for diabetes were permitted during the study; although approximately two-thirds of the population was receiving insulin at baseline, insulin was also initiated as a new medication during the study, but this occurred in less than 10% of all patients in the FAS.

Conclusion

The results of this secondary analysis of the FIDELIO-DKD study suggest that finerenone protects the kidneys and CV system of patients with advanced CKD and T2D independent of HbA_{1c} level or insulin use and without reducing HbA_{1c}, and thus offers an important advance in treatment for patients with CKD and T2D.

Acknowledgments. The authors are indebted to the patients who have participated in this trial, the FIDELIO-DKD study investigators, the

study centers that supported the trial, and the study teams. Medical writing assistance was provided by Dr. Oyinkan Adesakin of Chameleon Communications International, and was funded by Bayer AG.

Funding. The FIDELIO-DKD trial was conducted and funded by Bayer AG.

Duality of Interest. P.R. reports receiving personal fees from Bayer during the conduct of the study, research support and personal fees from AstraZeneca and Novo Nordisk, and personal fees from Astellas, Boehringer Ingelheim, Eli Lilly and Company, Gilead, Merck, Merck Sharp & Dohme, Mundipharma, Sanofi, and Vifor Pharma. All fees are given to Steno Diabetes Center Copenhagen. E.B. is a member of the FIDELIO-DKD steering committee. R.A. has received personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals during the conduct of the study; personal fees and nonfinancial support from Akebia Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Fresenius Medical Care AG and Company, Janssen Pharmaceuticals, Relypsa, Sanofi, and Vifor Pharma; personal fees from Ironwood Pharmaceuticals, Lexicon Pharmaceuticals, Merck & Company, and Reata Pharmaceuticals; and nonfinancial support from E.R. Squibb & Sons, Opko Pharmaceuticals, and Otsuka America Pharmaceutical. R.A. is a member of data safety monitoring committees for AstraZeneca and Ironwood Pharmaceuticals, a member of steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen Pharmaceuticals, and Relypsa; a member of adjudication committees for AbbVie, Bayer, Boehringer Ingelheim, and Janssen Pharmaceuticals; has served as associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate; and has received research grants from the National Institutes of Health and the U.S. Veterans Administration. S.D.A. has received research support from Abbott Vascular and Vifor International, and personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, B.R.A.H.M.S., Cardiac Dimensions, Impulse Dynamics, Novartis, Servier Pharmaceuticals, and Vifor International. G.F. reports receiving lecture fees and/or that he is a committee member of trials and registries sponsored by Amgen, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier Pharmaceuticals, and Vifor Pharma; has received research support from the European Union; and is a senior consulting editor for *JACC Heart Failure*. B.P. has received consultant fees from Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Phasebio Pharmaceuticals, Sanofi/Lexicon, Sarfez Pharmaceuticals, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa; has stock options for Ardelyx, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa (Galencia Group); and holds a patent for site-specific delivery of eplerenone to the myocardium (U.S. patent 9931412) and a provisional patent for histone-acetylation-modulating agents for the treatment and prevention of organ injury (U.S. provisional patent 63/

045,784). L.M.R. reports receipt of consultancy fees from Bayer. P.G. serves or has served on the speakers' bureau for Abbott, Bayer, Boehringer Ingelheim, Insulet Corporation, Medtronic, Merck Sharp & Dohme, Novo Nordisk, and F. Hoffmann-La Roche AG. Financial compensation for these activities has been received by Katholieke Universiteit Leuven. Katholieke Universiteit Leuven received, for P.G., nonfinancial support for travel from A. Menarini Diagnostics, Medtronic, Roche, and Sanofi. All disclosures were unrelated to the present work. R.J.M. has received research grants from Grey Innovations, Medtronic, Novo Nordisk, Servier Pharmaceuticals, St. Vincent's Research Foundation, The Diabetes Australia Research Program, The Juvenile Diabetes Research Foundation, The National Health and Medical Research Council of Australia, and The Rebecca L. Cooper Medical Research Foundation; honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi Aventis; is on advisory boards for AstraZeneca, the Boehringer Ingelheim–Eli Lilly Diabetes Alliance, Merck Sharp & Dohme, and Novo Nordisk; has received travel support from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Sanofi; and has been a principal investigator for industry-sponsored clinical trials run by AbbVie, Bayer, Janssen-Cilag, Novo Nordisk, and Sanofi. J.W. has received research support from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, and Sanofi; honoraria for lectures from AstraZeneca, Eli Lilly and Company, Merck Sharp & Dohme, and Novo Nordisk. A.J., M.B., and L.R. are full-time employees of Bayer AG, Division Pharmaceuticals, Germany. C.S. is a full-time employee of Bayer PLC, United Kingdom. G.L.B. has received research funding, paid to the University of Chicago Medicine, from Bayer during the conduct of the study. He also reports research funding, paid to the University of Chicago Medicine, from Novo Nordisk and Vascular Dynamics; he consulted for and received personal fees from Alnylam Pharmaceuticals, Merck and Company, and Relypsa; is an editor of the *American Journal of Nephrology*, *Nephrology*, and *Hypertension*, a section editor of UpToDate, and an associate editor of *Diabetes Care* and *Hypertension Research*. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. The Executive Committee designed the study in conjunction with the sponsor, Bayer AG. PR researched the data and wrote manuscript. E.B., R.A., S.D.A., G.F., B.P., L.M.R., P.G., R.J.M., J.W., A.J., and G.L.B. researched the data, reviewed and edited the manuscript and contributed to the discussion. M.B. and L.R. reviewed and edited the manuscript and contributed to the discussion. C.S. analyzed the data, reviewed and edited the manuscript, and contributed to the discussion. P.R. and A.J. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. The data included in this manuscript were presented in part at the

American Diabetes Association 81st Scientific Sessions (virtual), 25–29 June 2021.

References

- Nelson RG, Grams ME, Ballew SH, et al.; CKD Prognosis Consortium. Development of risk prediction equations for incident chronic kidney disease. *JAMA* 2019;322:2104–2114
- 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
- International Diabetes Federation. *IDF Diabetes Atlas*. 9th ed. Brussels, Belgium, International Diabetes Federation, 2019
- Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int* 2020;98:S1–S115
- American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes –2021. *Diabetes Care* 2021;44(Suppl. 1):S73–S84
- Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020;63:221–228
- American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes-2021. *Diabetes Care* 2021;44(Suppl. 1):S151–S167
- Gor D, Gerber BS, Walton SM, Lee TA, Nutescu EA, Touchette DR. Antidiabetic drug use trends in patients with type 2 diabetes mellitus and chronic kidney disease: a cross-sectional analysis of the National Health and Nutrition Examination Survey. *J Diabetes* 2020;12:385–395
- Rutherford PA, Thomas TH, Wilkinson R. Insulin resistance and hypertension—implications for treatment. *Postgrad Med J* 1991;67:869–875
- Zhou MS, Wang A, Yu H. Link between insulin resistance and hypertension: what is the evidence from evolutionary biology? *Diabetol Metab Syndr* 2014;6:12
- Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord* 2002;26(Suppl. 3):S18–S24
- Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH. Progression of nephropathy in type 2 diabetic patients. *Kidney Int* 2004;66:1596–1605
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
- Perkovic V, Heerspink HL, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int* 2013;83:517–523
- Wong MG, Perkovic V, Chalmers J, et al.; ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care* 2016;39:694–700
- Korol S, Mottet F, Perreault S, Baker WL, White M, de Denuis S. A systematic review and meta-analysis of the impact of mineralocorticoid receptor antagonists on glucose homeostasis. *Medicine (Baltimore)* 2017;96:e8719
- Yamaji M, Tsutamoto T, Kawahara C, et al. Effect of eplerenone versus spironolactone on cortisol and hemoglobin A_{1c} levels in patients with chronic heart failure. *Am Heart J* 2010;160:915–921
- Zhao JY, Xu L, Lin SL, Schooling CM. Spironolactone and glucose metabolism, a systematic review and meta-analysis of randomized controlled trials. *J Am Soc Hypertens* 2016;10:671–682
- Bakris GL, Agarwal R, Anker SD, et al.; FIDELIO-DKD Investigators. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;383:2219–2229
- Filippatos G, Anker SD, Agarwal R, et al.; FIDELIO-DKD Investigators. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. *Circulation* 2021;143:540–552
- Bakris GL, Agarwal R, Anker SD, et al.; on behalf of the FIDELIO-DKD study investigators; FIDELIO-DKD study investigators. Design and baseline characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease Trial. *Am J Nephrol* 2019;50:333–344
- Rossing P, Filippatos G, Agarwal R, et al. Finerenone in predominantly advanced CKD and T2D with or without SGLT-2i therapy. *Kidney Int Rep* 2022;7:36–45. DOI: <https://doi.org/10.1016/j.ekir.2021.10.008>
- Rossing P, Agarwal R, Anker SD, et al. Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by GLP-1RA treatment: a subgroup analysis from the FIDELIO-DKD trial. *Diabetes Obes Metab* 2022;24:125–134. DOI: <https://doi.org/10.1111/dom.14558>
- Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128
- Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–334
- Ferreira JP, Lamiral Z, McMurray JJV, et al. Impact of insulin treatment on the effect of eplerenone: insights from the EMPHASIS-HF Trial. *Circ Heart Fail* 2021;14:e008075
- Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
- Ismail-Beigi F, Craven T, Banerji MA, et al.; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;376:419–430
- Douros A, Lix LM, Fralick M, et al.; Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Sodium-glucose cotransporter-2 inhibitors and the risk for diabetic ketoacidosis: a multicenter cohort study. *Ann Intern Med* 2020;173:417–425
- U.S. Food and Drug Administration, FDA Drug Safety Commission. FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. Accessed 21 July 2021. Available from <https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-labels-sglt2-inhibitors-diabetes-include-warnings-about-too-much-acid-blood-and-serious#:~:text=FDA%20has%20added%20warnings%20about,and%20serious%20urinary%20tract%20infections>
- Ruilope LM, Agarwal R, Anker SD, et al.; FIGARO-DKD study investigators. Design and baseline characteristics of the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease Trial. *Am J Nephrol* 2019;50:345–356