Kidney Medicine

Finerenone in Black Patients With Type 2 Diabetes and CKD: A Post hoc Analysis of the Pooled FIDELIO-DKD and FIGARO-DKD Trials

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Rationale & Objective: In FIDELITY, finerenone improved cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). This analysis explored the efficacy and safety of finerenone in Black patients.

Study Design: Subanalysis of randomized controlled trials.

Setting & Participants: Patients with T2D and CKD.

Intervention: Finerenone or placebo.

Outcomes: Composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; composite of kidney failure, sustained ≥57% estimated glomerular filtration rate (eGFR) decline from baseline maintained for ≥4 weeks, or renal death.

Results: Of the 13,026 patients, 522 (4.0%) self-identified as Black. Finerenone demonstrated similar effects on the cardiovascular composite outcome in Black (HR, 0.79 [95% CI, 0.51-1.24]) and non-Black patients (HR, 0.87 [95% CI, 0.79-0.96; $P = 0.5$ for interaction]). Kidney composite outcomes were consistent in Black (HR, 0.71 [95% CI, 0.43-1.16]) and non-Black patients (HR, 0.76 [95% CI, 0.66-0.88; $P = 0.9$ for interaction]). Finerenone reduced urine albumin-to-creatinine ratio by 40% at month 4 (least-squares mean treatment ratio, 0.60 [95% CI, 0.52-0.69; $P < 0.001$]) in Black patients and 32% at month 4 (least-squares mean treatment ratio, 0.68 [95% CI, 0.66-0.70; $P < 0.001$]) in non-Black patients, versus placebo. Chronic eGFR decline (month 4 to end-of-study) was slowed in Black and non-Black patients treated with finerenone versus placebo (between-group difference, 1.4 mL/min/1.73 m^2 per year [95% CI, 0.33-2.44; $P = 0.01$] and 1.1 mL/min/1.73 m^2 per year [95% CI, 0.89-1.28; $P < 0.001$], respectively). Safety outcomes were similar between subgroups.

Limitations: Small number of Black patients; analysis was not originally powered to determine an interaction effect based on Black race.

Conclusions: The efficacy and safety of finerenone appears consistent in Black and non-Black patients with CKD and T2D.

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Visual Abstract included

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Diabetes is the leading cause of chronic kidney disease (CKD) and, despite current therapies, a large residual risk of kidney disease progression exists.[1] Self-identified Black or African American individuals (herein referred to as Black) are at increased risk of kidney failure.[2] They are almost 4 times more likely to develop kidney failure compared with non-Black people. Although Black people only constitute ≈13% of the US population, they account for >35% of all patients receiving dialysis for kidney failure.[3] Higher incidence of kidney failure among Black patients appears to be related to multiple factors, such as the number and control of CKD risk factors. Compared with non-Black people, Black people have a higher prevalence of obesity and are more likely to have elevated albuminuria.[4] Similarly, the prevalence of hypertension is higher in Black patients, and this population is more likely to have severe or resistant hypertension.[5] In addition, their increased risk of CKD may be partly explained by lack of access to health care and other socioeconomic factors.[6] Previous studies have shown the association of low socioeconomic status with greater odds of CKD in Black people but not in non-Black people.[7]

Despite guideline-directed therapy, patients with CKD and type 2 diabetes (T2D) remain at high risk of kidney disease progression and cardiovascular (CV) events.[8] Black patients with CKD experience faster progression to kidney failure compared with non-Black patients; therefore, there is an urgent need for new treatment strategies to reduce the burden of disease in this population.[9] Finerenone is a distinct, selective, nonsteroidal mineralocorticoid receptor antagonist designed to treat CKD in patients with T2D.[10] In the FIDELITY (Finerenone in chronic kidney disease and type 2 diabetes: combined FIDELIO-DKD and FIGARO-DKD trial program analysis) prespecified pooled analysis of the FIDELIO-DKD (Finerenone in reducing kidney failure and disease progression in Diabetic Kidney Disease; NCT02540993) and

PLAIN-LANGUAGE SUMMARY

Diabetes is a major cause of chronic kidney disease (CKD), affecting more Black adults than White adults. Most adults with CKD ultimately die from heart and vascular complications (eg, heart attack and stroke) rather than kidney failure. This analysis of 2 recent trials shows that the drug finerenone was beneficial for patients with diabetes and CKD. Along with reducing kidney function decline and protein in the urine, it also decreased heart and vascular issues and lowered blood pressure in both Black and non-Black adults with diabetes and CKD. These findings have promising implications for slowing the progression of CKD and protecting against cardiovascular problems in diverse populations.

FIGARO-DKD (Finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease; NCT02545049) trials, finerenone reduced the risk of kidney and CV outcomes versus placebo in patients with CKD and T2D.[11] This subgroup analysis aims to evaluate whether the kidney and CV benefits of finerenone are consistent in Black and non-Black patients with CKD and T2D.

METHODS

Study Design and Patients

This FIDELITY 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.[12-15] Written informed consent was provided by all participants. Eligible patients were adults aged ≥18 years with CKD and T2D who were receiving optimized renin–angiotensin system inhibitor therapy and had a serum potassium level of ≤4.8 mmol/L at screening. Patients had either a urine albumin-to-creatinine ratio (UACR) of ≥30-<300 mg/g and an estimated glomerular filtration rate (eGFR) of ≥25-≤90 mL/min/1.73 m^2, or UACR of ≥300-≤5,000 mg/g, and eGFR of ≥25 mL/min/1.73 m^2. Patients with nondiabetic kidney disease, uncontrolled hypertension, glycated hemoglobin > 12%, systolic blood pressure < 90 mm Hg, chronic symptomatic heart failure (HF) with reduced ejection fraction, a recent CV event, dialysis for acute kidney failure, or kidney transplant were excluded. Patients were asked to self-identify their race, including Asian, Black or African American, American Indian or Alaska Native, or Native Hawaiian, or other Pacific Islander. Patients were permitted to identify as multiple races, Patients who identified Black as 1 of multiple races were included in the non-Black subgroup.

Randomization and Masking

Patients were randomized in a 1:1 ratio to receive double-blind therapy with either oral finerenone (titrated doses of 10 or 20 mg) or matching placebo once daily. Randomization was stratified by region (North America, Europe, Asia, Latin America, and other), albuminuria at screening (moderately or severely increased), and eGFR at screening (25-<45, 45-<60, ≥60 mL/min/1.73 m^2). All patients and study personnel were masked to treatment allocation.

Outcomes

The efficacy outcomes of the current analysis included a CV composite end point of time to CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for HF, and a kidney composite end point of time to kidney failure, a sustained decrease of ≥57% in the eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for ≥4 weeks, or renal death. Additional efficacy outcomes included change in UACR over time and the eGFR slope. All clinical outcomes were prospectively adjudicated by an independent clinical event committee blinded to treatment assignment. Safety outcomes and vital signs were also evaluated and included assessments of adverse events and central laboratory testing. Adverse events that occurred during the treatment period were defined as those that started or worsened during study drug intake or up to 3 days after any temporary or permanent interruption. In this analysis, data for these outcomes and safety data are reported for Black and non-Black patients.

Statistical Analysis

Statistical analysis methods for the efficacy outcomes in the FIDELIO-DKD and FIGARO-DKD studies have been described previously.[14,15] In this analysis, efficacy outcomes were analyzed in the pooled full analysis set of both studies (FIDELITY) by planned treatment, comprising all patients randomized whose trial participation proceeded under the principles of Good Clinical Practice (Fig S1). Baseline characteristics were grouped by Black or non-Black. Continuous variables are reported as mean and standard deviation or median and interquartile range (IQR). Categorical variables are presented as frequency and percentage from total. Events were reported from randomization up to the end-of-study visits. Data on patients without an event were censored at the date of their last contact. The eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) 2009 equation, which incorporates an adjustment factor for Black or African American patients compared with patients of other races, thus resulting in higher eGFR estimates in Black patients.[16,17] Sensitivity analyses were undertaken without the race coefficient included in eGFR measures. Event rates and their associated confidence intervals (CIs) are expressed in 100 patient-years. Time-to-event analyses of outcomes were performed with stratified Cox proportional-hazards models. Stratification factors were geographic region, eGFR category at screening, albuminuria category at screening, history of CV disease, and study

(FIDELIO-DKD or FIGARO-DKD). Treatment effects for time-to-event outcomes are expressed as hazard ratios (HRs) with corresponding CIs and were derived from stratified Cox proportional-hazard models. Interaction between treatment and each subgroup was based on stratified Cox proportional-hazards models, including treatment and their interaction as fixed effects. The P values for the interaction term were based on the χ^2 tests. Changes of UACR and eGFR over time were analyzed with linear mixed effects models assuming an unstructured covariance matrix and adjusting for treatment, stratification factors, visit, interaction between treatment group and visit, baseline value, and interaction between baseline value and visit. Chronic slope of eGFR (defined as change in mean slope from 4 months to end-of-study) decrease over time was estimated using the 2-slope linear spline mixed model repeated measure.[18] Safety and vital signs analyses were performed in the safety analysis set, comprising all randomized patients without critical Good Clinical Practice violations who received ≥1 dose of study drug intake.

RESULTS

Patients

This analysis includes a total of 13,026 patients, of whom 522 (4.0%) self-identified as Black (253 in the finerenone arm and 269 in the placebo arm). A total of 72.2% of Black patients were from North America, 13.4% were from Latin America, and 7.5% were from Europe (Fig S2). In Black patients, the median follow-up was 2.8 years (IQR, 1.5 years) with finerenone and 2.8 years (IQR, 1.6 years) with placebo; the mean daily dose of study treatment was 16.4 and 16.9 mg for Black patients treated with finerenone and placebo, respectively. In non-Black patients, the median follow-up was comparable with Black patients at 3.0 years (IQR, 1.5 years) with finerenone and 3.0 years (IQR, 1.5 years) with placebo; the mean daily dose of study treatment was 16.5 and 17.5 mg for non-Black patients treated with finerenone and placebo, respectively. Mean adherence to study drug treatment was 95.9% for Black patients treated with finerenone and 85.2% with placebo, compared with 91.6% and 93.1% for non-Black patients treated with finerenone and placebo, respectively. Baseline clinical and demographic characteristics of Black patients were generally comparable with those of non-Black patients, with some key differences (Table 1 and Table S1). Overall, Black patients were younger, and a higher proportion were female. Black patients had a higher median UACR, higher mean body mass index, greater waist circumference, longer duration of diabetes, higher systolic blood pressure and diastolic blood pressure, and greater use of diuretics at baseline compared with non-Black patients. The baseline mean eGFR was lower in the Black subgroup compared with the non-Black subgroup. The baseline mean eGFR was further reduced in the Black subgroup after excluding adjustment for the race coefficient.

Efficacy

Cardiovascular Outcomes

Overall, the CV composite end point of time to CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF occurred in 825 of 6,519 (12.7%) patients randomized to finerenone and 939 of the6,507 (14.4%) of patients randomized to placebo (HR, 0.86 [95% CI, 0.78-0.95]; Fig 1). In Black patients, the CV composite end point occurred in 39 of the253 (15.4%) and 53 of the 269 (19.7%) of patients randomized to finerenone and placebo, respectively (HR, 0.79 [95% CI, 0.51-1.24; Fig 1 and S3). This effect for finerenone was not dissimilar with that observed in non-Black patients (HR, 0.87 [95% CI, 0.79-0.96]) with no significant interaction between the 2 subgroups and treatment (P = 0.5 for interaction). The effect of finerenone appeared to be consistent among non-Black patients, Black patients from the United States, and Black patients from other geographic regions (Black non-US) (non-Black: HR, 0.87 [95% CI, 0.79-0.96]; Black US: HR, 0.86 [95% CI, 0.53-1.40]; Black non-US: HR, 0.41 [95% CI, 0.10-1.60]; P = 0.3 for interaction).

Kidney Outcomes

Overall, the kidney composite end point of time to kidney failure, sustained ≥ 57% eGFR decline, or kidney-related death occurred in 360 of the 6,519 (5.5%) of patients randomized to finerenone and 465 of the 6,507 (7.1%) of patients randomized to placebo (HR, 0.77 [95% CI, 0.67-0.88]; Fig 1). In Black patients, the kidney composite end point occurred in 35 of the 253 (13.8%) and 39 of the 269 (14.5%) of patients randomized to finerenone and placebo, respectively (HR, 0.71 [95% CI, 0.43-1.16]; Fig 1 and S3). This effect for finerenone was consistent with that observed in non-Black patients (HR, 0.76 [95% CI, 0.66-0.88]), with no significant interaction between the 2 subgroups and treatment (P = 0.9 for interaction). Furthermore, the effect of finerenone appeared to be consistent among non-Black patients, Black patients from the United States, and Black non-US patients (non-Black: HR, 0.76 [95% CI, 0.66-0.88]; Black US: HR, 0.63 [95% CI, 0.36-1.12]; Black non-US: HR, 0.79 [95% CI, 0.26-2.41]; P = 0.3 for interaction).

In Black patients, finerenone reduced UACR by 40% at month 4 (least-squares [LS] mean treatment ratio, 0.60 [95% CI, 0.52-0.69]; P < 0.001) compared with placebo. In non-Black patients, finerenone reduced UACR by 32% at month 4 (LS mean treatment ratio, 0.68 [95% CI, 0.66-0.70]; P < 0.001) compared with placebo (Fig 2).

In Black patients, LS mean change in eGFR from baseline to month 1 was −2.55 mL/min/1.73 m^2 with finerenone (95% CI, −3.52 to −1.58) and 0.27 mL/min/1.73 m^2 with placebo (95% CI, −0.79 to 1.32); between-group difference of LS mean −2.82 (95% CI, −4.25 to −1.39; P < 0.001). In the Black subgroup, LS mean change in chronic eGFR slope from month 4 to end-of-study was −3.459 mL/min/1.73 m^2 per year (95% CI, −4.214 to −2.704) with finerenone and −4.843

Table 1. Baseline Demographic and Clinical Characteristics of Black and non-Black Patients

Characteristic	Black Patients (n=522)	Non-Black Patients (n=12,504)
Age, y, mean ± SD	61.8 ± 10.0	64.9 ± 9.5
Sex, male, n (%)	284 (54.4)	8,804 (70.4)
Systolic blood pressure, mm Hg, mean ± SD[a]	138.6 ± 15.7	136.7 ± 14.1
Diastolic blood pressure, mm Hg, mean ± SD[a]	77.6 ± 9.6	76.3 ± 9.6
BMI, kg/m^2, mean ± SD[b]	34.1 ± 7.4	31.2 ± 5.9
Waist-hip ratio, mean ± SD[a]	1.0 ± 0.1	1.0 ± 0.1
Waist circumference, cm, mean ± SD[a]	112.4 ± 19.0	106.8 ± 14.9
Duration of diabetes, y, mean ± SD	16.2 ± 8.8	15.4 ± 8.7
HbA1c, %, mean ± SD[a]	7.9 ± 1.4	7.7 ± 1.4
Serum potassium, mmol/L, mean ± SD[a]	4.25 ± 0.46	4.35 ± 0.44
eGFR, mL/min/1.73 m^2, mean ± SD[a]	53.8 ± 21.8	57.7 ± 21.7
eGFR, mL/min/1.73 m^2, mean ± SD (without race coefficient)[a]	46.4 ± 18.8	57.7 ± 21.7
eGFR, mL/min/1.73 m^2, n/N (%)		
<45	211 (40.4)	4,183 (33.5)
45-<60	138 (26.4)	3,296 (26.4)
≥60	173 (33.1)	5,022 (40.2)
UACR, mg/g, median (IQR)[a]	529 (229-1,175)	514 (196-1,146)
UACR, mg/g, n (%)		
<30	6 (1.1)	224 (1.8)
30-<300	153 (29.3)	3,946 (31.6)
≥300	363 (69.5)	8,329 (66.6)
Current smoker, n (%)	54 (10.3)	2,039 (16.3)
History of CVD, n (%)	233 (44.6)	5,702 (45.6)
Hypertension	507 (97.1)	12,059 (96.4)
Cardiac failure	54 (10.3)	953 (7.6)
Coronary artery disease	136 (26.1)	3,861 (30.9)
Medication use at baseline, n (%)		
Angiotensin-converting enzyme inhibitors	255 (48.9)	5,389 (43.1)
Angiotensin receptor blockers	302 (57.9)	8,135 (65.1)
Beta-blockers	356 (68.2)	7,394 (59.1)
Diuretics	393 (75.3)	8,268 (66.1)
Loop diuretics	235 (45.0)	4,762 (38.1)
Thiazide diuretics	172 (33.0)	3,781 (30.2)
Statins	443 (84.9)	9,905 (79.2)
Potassium supplements	69 (13.2)	1,167 (9.3)
Potassium-lowering agents (including binders)	23 (4.4)	849 (6.8)
Glucose-lowering therapies		
Insulin and analogs	394 (75.5)	8,347 (66.8)
Metformin	239 (45.8)	7,856 (62.8)
Sulfonylureas	167 (32.0)	3,729 (29.8)
DPP-4 inhibitors	112 (21.5)	4,338 (34.7)
GLP-1Ras	76 (14.6)	1,801 (14.4)
SGLT-2is	41 (7.9)	2,118 (16.9)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; IQR, interquartile range; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.
[a]Missing data for ≥3 patients.
[b]Missing data for 10 patients.

(95% CI, −5.573 to −4.112) with placebo; the between-group difference was 1.384 mL/min/1.73 m^2 per year (95% CI, 0.334-2.435; P = 0.01; Fig 3). In non-Black patients, LS mean change in chronic eGFR slope from month 4 to end of study was −2.816 mL/min/1.73 m^2 per year (95% CI, −2.956 to −2.677) with finerenone and −3.903 (95% CI, −4.0 43 to −3.763) with placebo; the between-group difference was 1.087 mL/min/1.73 m^2 per year (95% CI, 0.890-1.284; P < 0.001; Fig 3). In additional analyses without using the CKD-EPI 2009 equation race coefficient, LS mean change in chronic eGFR slope from month 4 to end of study was −3.0 mL/min/

	Finerenone	Placebo	Finerenone	Placebo	HR (95% CI)	*P* for interaction
	n/N (%)		n per 100 PY			
Cardiovascular composite[a]						
Overall	825/6,519 (12.7)	939/6,507 (14.4)	4.34	5.01	0.86 (0.78-0.95)	
Black	39/253 (15.4)	53/269 (19.7)	5.68	7.40	0.79 (0.51-1.24)	0.5
Non-Black	786/6,266 (12.5)	886/6,238 (14.2)	4.29	4.91	0.87 (0.79-0.96)	
Kidney composite[b]						
Overall	360/6,519 (5.5)	465/6,507 (7.1)	1.96	2.55	0.77 (0.67-0.88)	
Black	35/253 (13.8)	39/269 (14.5)	5.55	5.86	0.71 (0.43-1.16)	0.9
Non-Black	325/6,266 (5.2)	426/6,238 (6.8)	1.84	2.43	0.76 (0.66-0.88)	

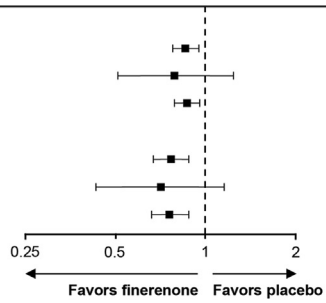

Figure 1. Analysis of cardiovascular and kidney composite outcomes in Black and non-Black patients. eGFR, estimated glomerular filtration rate; HR, hazard ratio; PY, patient-years. [a]The composite of time to first onset of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. [b]The composite of time to first onset of kidney failure, sustained ≥57% decrease in eGFR from baseline maintained for ≥4 weeks, or renal death.

1.73 m^2 per year (95% CI, −3.64 to −2.33) with finerenone and −4.2 mL/min/1.73 m^2 per year (95% CI, −4.81 to −3.55) with placebo in Black patients; the between-group difference was 1.19 (95% CI, 0.29-2.10; P = 0.01).

Safety and Vital Signs

Overall incidence of any adverse events was balanced between the finerenone and placebo groups and between Black and non-Black patients. The incidence of serious adverse events was numerically similar between the finerenone and placebo groups and between Black and non-Black patients (Table 2).

Overall, the incidence of investigator-reported, treatment-emergent hyperkalemia was higher in patients treated with finerenone versus placebo. The incidence of hyperkalemia leading to discontinuation of the study drug was low in both treatment groups and in Black and non-Black patients (Table 2). In the finerenone treatment arm, the incidence of treatment-emergent hyperkalemia was higher in Black versus non-Black patients. In the placebo treatment arm, incidence of treatment-emergent hyperkalemia was lower in Black versus non-Black patients. The incidence of hyperkalemia in Black and non-Black patients treated with and without potassium supplements at baseline is shown in Table 2.

Modest reductions in SBP were observed with finerenone versus placebo (Fig S4). In the finerenone treatment arm, the mean change in SBP from baseline to month 4 was −3.9 mm Hg in Black patients, and −3.2 mm Hg in non-Black patients.

DISCUSSION

In this analysis, the efficacy and safety of finerenone were similar in Black and non-Black patients with CKD

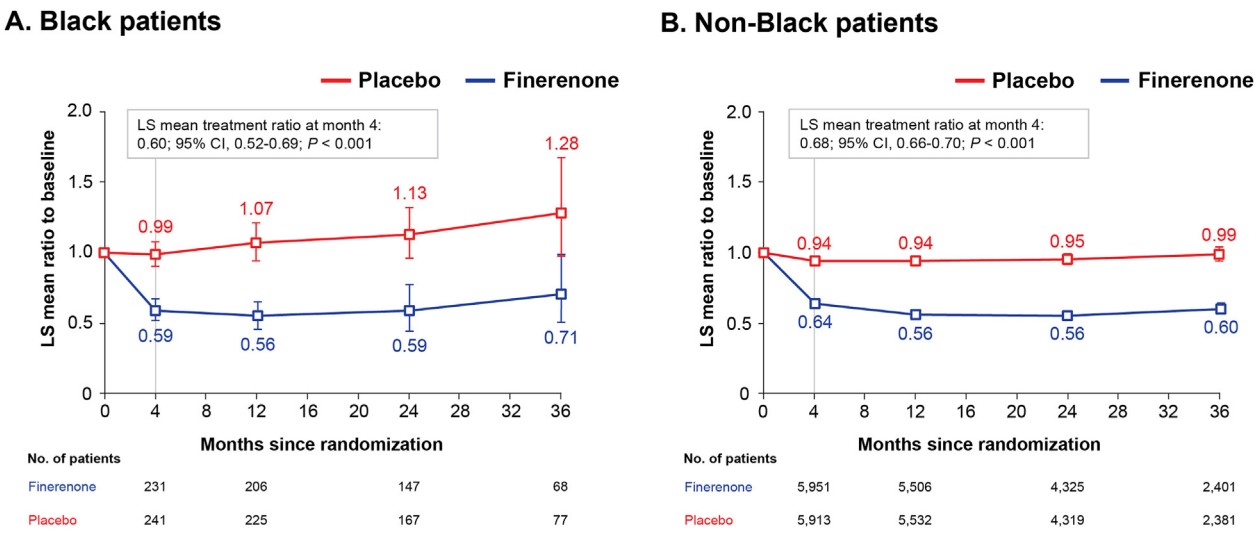

Figure 2. Change in UACR over time in Black and non-Black patients.[a] LS, least-squares; UACR, urine albumin-to-creatinine ratio. [a]Mixed model.

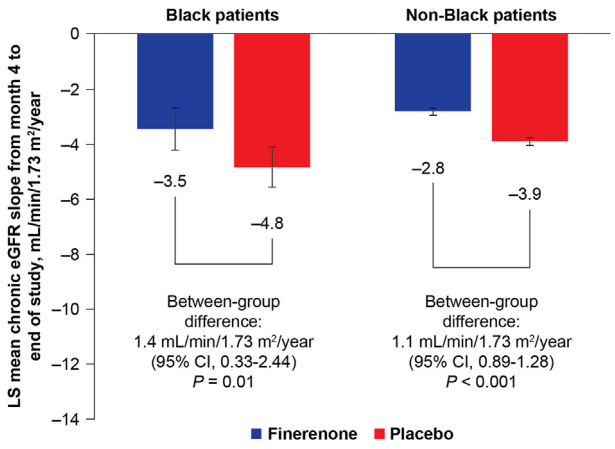

Figure 3. Chronic eGFR slope from month 4 to end-of-study in Black and non-Black patients. eGFR, estimated glomerular filtration rate; LS, least-squares.

and T2D. Consistent with previous findings that Black patients have a disproportionately higher burden of kidney and CV disease,[19] in this analysis, overall incidence for the kidney and CV outcomes, and the annual rate of eGFR decline were higher in Black versus non-Black patients. Despite this, the benefit of finerenone appeared to be preserved in these individuals. In Black patients, finerenone reduced UACR by 40% at month 4 and led to a smaller decline in chronic eGFR slope from month 4 to end of study compared with placebo. Overall safety outcomes were similar in the Black and non-Black subgroups, with low discontinuation rates due to hyperkalemia.

Overall, in the finerenone treatment arm, the clinical impact of serious hyperkalemia was low in Black patients, with permanent treatment discontinuation at 2.8% versus 0.7% in the placebo group and a total of 7 (2.8%) hyperkalemia-related hospitalization events versus 1 (0.4%) in the placebo group. In the finerenone treatment arm, the incidence of treatment-emergent hyperkalemia was higher in Black patients (18.3%) versus non-Black patients (15.2%). This may be explained by the fact that Black patients had a lower mean eGFR at baseline, particularly after excluding false elevation owing to the Black race coefficient (46.4 vs 57.7 mL/min/1/73 m^2, respectively), suggesting more severe kidney disease versus non-Black patients. In addition, Black patients had a longer duration of diabetes and greater use of insulin, beta-blockers, and potassium supplements at baseline, all of which plausibly heightened the risk for hyperkalemia. Given the limited number of patients in the analysis, it is difficult to draw firm conclusions on the effect of finerenone on hyperkalemia in Black patients. Further studies are warranted to explore potential differences between these subgroups.

Exclusion of the CKD-EPI 2009 equation[16] race-coefficient resulted in a lower mean eGFR at baseline in Black patients (with race-coefficient adjustment: 53.8 mL/min/1.73 m^2; without race-coefficient adjustment: 46.4 mL/min/1.73 m^2). The use of race-based calculations to guide clinical decisions has been widely criticized. For example, the CKD-EPI 2009 equation[16] results in higher eGFR among Black patients and has been suggested

Table 2. Overall Safety and Selected Treatment-Emergent Adverse Events of Interest in Black and Non-Black Patients

	Black Patients		Non-Black Patients	
Patients With Treatment-Emergent AEs, n (%)	**Finerenone (n=252)**	**Placebo (n=269)**	**Finerenone (n=6,258)**	**Placebo (n=6,220)**
Any AE	207 (82.1)	229 (85.1)	5,395 (86.2)	5,378 (86.5)
Related to study drug	50 (19.8)	35 (13.0)	1,156 (18.5)	827 (13.3)
Leading to discontinuation	17 (6.7)	15 (5.6)	397 (6.3)	336 (5.4)
Any SAE	80 (31.7)	88 (32.7)	1,980 (31.6)	2,098 (33.7)
Related to study drug	5 (2.0)	1 (0.4)	78 (1.2)	60 (1.0)
Leading to discontinuation	6 (2.4)	5 (1.9)	139 (2.2)	149 (2.4)
AE leading to death	5 (2.0)	4 (1.5)	105 (1.7)	147 (2.4)
Any hyperkalemia	46 (18.3)	17 (6.3)	954 (15.2)	534 (8.6)
Related to study drug	27 (10.7)	8 (3.0)	546 (8.7)	241 (3.9)
Leading to discontinuation	7 (2.8)	2 (0.7)	103 (1.6)	36 (0.6)
Any serious hyperkalemia	7 (2.8)	1 (0.4)	62 (1.0)	15 (0.2)
Leading to hospitalization	7 (2.8)	1 (0.4)	54 (0.9)	9 (0.1)
Reported as life-threatening	1 (0.4)	0	3 (<0.1)	5 (<0.1)
Any hyperkalemia by use of potassium supplements at baseline				
Yes, n/N (%)	5/15 (33.3)	0/19	20/181 (11.0)	3/170 (1.8)
No, n/N (%)	37/237 (15.6)	12/250 (4.8)	850/6,077 (14.0)	433/6,050 (7.2)
Central laboratory measurements				
Serum potassium >5.5 mmol/L	38/249 (15.3)	15/263 (5.7)	1,037/6,153 (16.9)	445/6,107 (7.5)
Serum potassium >6.0 mmol/L	9/249 (3.6)	2/264 (0.8)	202/6,190 (3.3)	78/6,149 (1.3)

Abbreviations: AE, adverse event; SAE, serious adverse event.

to cause later recognition of CKD and delayed referral for kidney transplantation or dialysis in this population.[17,20] The Chronic Renal Insufficiency Cohort study demonstrated the relationship between directly measured GFR based on iothalamate clearance and eGFR based on the CKD-EPI 2009 equation using intervals that included 95% of measured GFR values corresponding to each eGFR value.[21] At an eGFR of 30 mL/min/1.73 m^2, the directly measured GFR may range from 17 to 48 mL/min/1.73 m^2. At this level of kidney function, the effect of Black race on eGFR is 5 mL/min/1.73 m^2, which is much smaller than the width of the 95% prediction interval (31 mL/min/1.73 m^2).[21] In effect, eGFR may not be used to precisely categorize patients into GFR categories.[21] Many medical centers have recently removed the race coefficient for Black patients because of broad misuses of race as a biologic category.[20] Meanwhile, a recent analysis of the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial investigating the sodium-glucose co-transporter-2 inhibitor (SGLT-2i) canagliflozin reported that recalculation of eGFR without a race-specific coefficient would have excluded 10% of randomized Black patients for eGFR of <30 mL/min/1.73 m^2.[17] Despite this, the effect of canagliflozin on kidney and CV outcomes remained consistent across eGFR subgroups regardless of a coefficient for Black race.[17] The recently published CKD-EPI 2021 creatinine and creatinine-cystatin C equations were refitted without the race coefficient using development data sets from the CKD-EPI 2009 and 2012 equations, providing an opportunity to measure eGFR without the use of a race coefficient and to standardize the reporting of eGFR.[22]

Historically, there has been an underrepresentation of Black patients in clinical trials for various reasons, including challenges associated with socioeconomic status, insufficient transportation, poor health literacy, and historical fear of abuse and unethical treatment.[23] In the present analysis, 522 out of a total of 13,026 patients (4.0%) self-identified as Black. Although this low enrollment of Black patients may be partly attributed to the barriers mentioned above, clinical studies of patients with cancer have reported similar refusal rates of participation between Black and White people.[24] The selected participating study sites may have also contributed to the low enrollment of Black patients in the present analysis. For example, FIDELIO-DKD and FIGARO-DKD did not enroll patients from countries in Sub-Saharan Africa. A previous systematic review and meta-analysis of randomized trials of newer diabetes medications (SGLT-2is, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors) versus placebo included major adverse cardiovascular events (MACE) as the primary outcome.[25] With only 4.5% of the total meta-analysis population identifying as Black, these trials were not sufficiently powered to evaluate treatment differences in this population.[25] The analyses reported no significant difference in the incidence of MACE between diabetes treatments and placebo in Black patients; however, when considering the 95% CI around the point estimate (relative risk, 0.94 [95% CI, 0.77-1.16], which was also directionally consistent with an improvement), as much as a 23% risk reduction in Black patients could have been missed. This highlights the importance of including sufficient numbers of disproportionately affected populations to ensure adequate power to draw confident conclusions in subgroup analyses.[25] Contrary to this, another study showed that in Black patients with HF with reduced ejection fraction, treatment with an SGLT-2i was associated with greater reduction in the risk of hospitalization for HF or CV death versus placebo (and vs non-Black patients).[26] Given the underrepresentation of Black patients in clinical trials, there is a clear need for additional studies evaluating the benefits of cardiorenal therapies in this population.

Some limitations should be considered when interpreting the data presented in this analysis. In the FIDELIO-DKD and FIGARO-DKD trials, a small number of patients self-identified as Black; therefore, patient and event numbers in the Black subgroup are low (n=522). In addition, a small number of Black patients were receiving an SGLT-2i at baseline (n=41), which limits any potential conclusions that can be drawn regarding concomitant diabetes medication and disparities in event rates between Black and non-Black patients. Moreover, the analysis was not originally powered to determine an interaction effect of finerenone based on Black race. This study lacks power to fully determine an interaction between Black and non-Black patients, and we acknowledge that nonsignificant *P* values for interaction do not provide hard evidence for an absence of interaction. Furthermore, we did not determine the apolipoprotein L1 (*APOL1*) genotype in this study. The *APOL1* genotype (2 high-risk alleles) occurs in ~12 to 15% of Black people and has been linked to faster decline in kidney function.[27,28] In the African American Study of Kidney Diseases, no interaction was found between the blood pressure-lowering intervention (strict versus usual blood pressure control) and the *APOL1* genotype,[29] although another analysis of the same clinical trial found a greater reduction in mortality in the high- versus low-risk *APOL1* genotype subgroup.[30] These observations highlight important treatment benefits in Black patients with CKD carrying this high-risk genotype. In our study, the higher overall (residual) risk for the composite kidney endpoint after finerenone treatment in Black patients relative to non-Black patients may have been influenced by undetected carriers of the high-risk *APOL1* alleles in the former patient group.

Overall, in this FIDELITY subgroup analysis, finerenone appeared to have a similar effect in reducing albuminuria and eGFR slope in Black and non-Black patients with CKD and T2D. These data provide support for the use of finerenone in Black patients with CKD and T2D to address the high burden of disease in this patient population and reduce the risk of kidney disease progression and CV events.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Consort diagram. FIDELITY prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials.

Figure S2. Geographic distribution of randomized patients in the Black subgroup.

Figure S3. Cardiovascular and kidney outcomes in Black and non-Black patients.

Figure S4. Placebo-corrected change from baseline SBP with finerenone in Black and non-Black patients.

Item S1. List of FIDELIO-DKD Investigators and Committees

Item S2. List of FIGARO-DKD Investigators and Committees

Table S1. Baseline Characteristics in Black and Non-Black Patients.

ARTICLE INFORMATION

FIDELIO-DKD and FIGARO-DKD Investigators: A list of the investigators is provided in Items S1 and S2.

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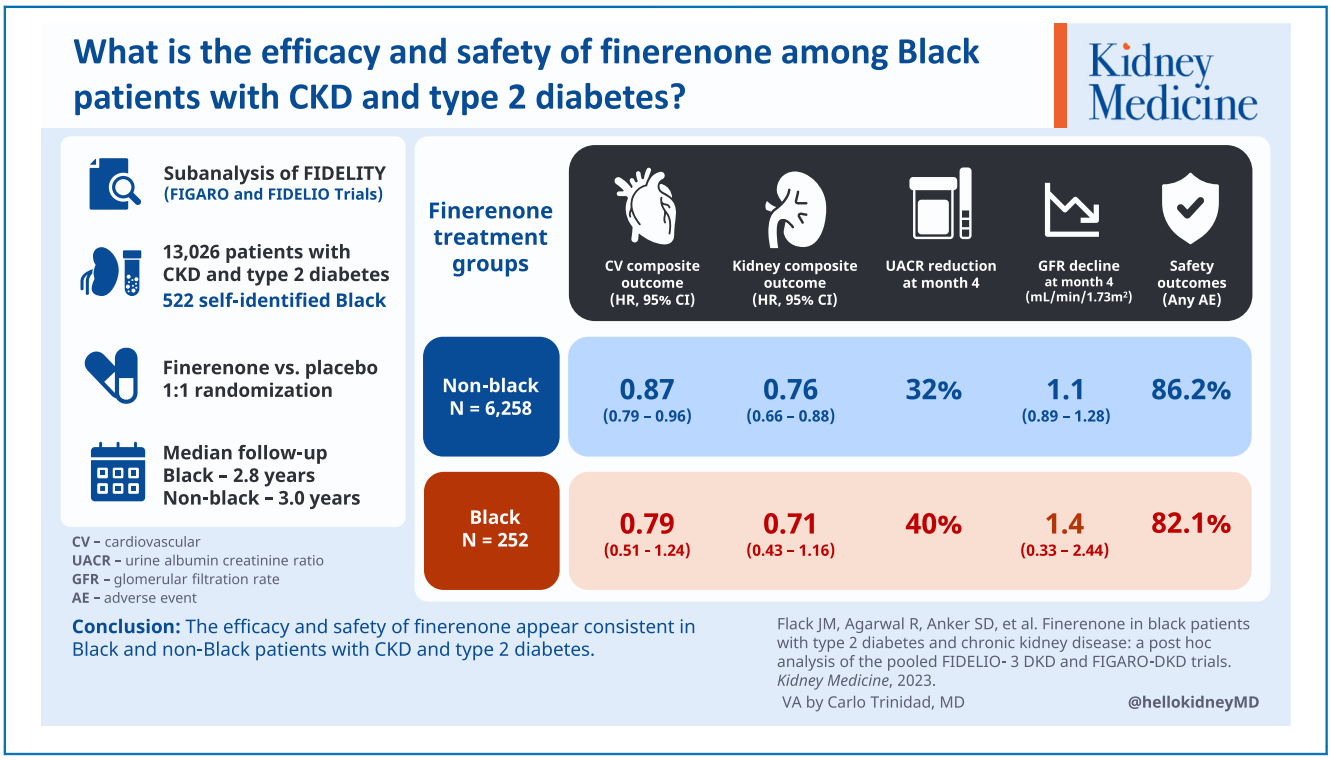
What is the efficacy and safety of finerenone among Black patients with CKD and type 2 diabetes?
Kidney Medicine
Subanalysis of FIDELITY
(FIGARO and FIDELIO Trials)
13,026 patients with CKD and type 2 diabetes
522 self-identified Black
Finerenone vs. placebo
1:1 randomization
Median follow-up
Black – 2.8 years
Non-black – 3.0 years
CV – cardiovascular
UACR – urine albumin creatinine ratio
GFR – glomerular filtration rate
AE – adverse event
Finerenone treatment groups
CV composite outcome (HR, 95% CI)
Kidney composite outcome (HR, 95% CI)
UACR reduction at month 4
GFR decline at month 4 (mL/min/1.73m²)
Safety outcomes (Any AE)
Non-black N = 6,258
0.87 (0.79 – 0.96)
0.76 (0.66 – 0.88)
32%
1.1 (0.89 – 1.28)
86.2%
Black N = 252
0.79 (0.51 - 1.24)
0.71 (0.43 – 1.16)
40%
1.4 (0.33 – 2.44)
82.1%
Conclusion: The efficacy and safety of finerenone appear consistent in Black and non-Black patients with CKD and type 2 diabetes.
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