ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with chronic kidney disease (CKD) and type 2 diabetes. However, its long-term effects on kidney and cardiovascular outcomes are unknown.

METHODS

In this double-blind trial, we randomly assigned 5734 patients with CKD and type 2 diabetes in a 1:1 ratio to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml per minute per 1.73 m^2 of body-surface area, and diabetic retinopathy, or they had a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml per minute per 1.73 m^2. All the patients were treated with renin–angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome, also assessed in a time-to-event analysis, was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

RESULTS

During a median follow-up of 2.6 years, a primary outcome event occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P=0.001). A key secondary outcome event occurred in 367 patients (13.0%) and 420 patients (14.8%) in the respective groups (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.03). Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively).

CONCLUSIONS

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. (Funded by Bayer; FIDELIO-DKD ClinicalTrials.gov number, NCT02540993.)

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*A complete list of the FIDELIO-DKD investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Type 2 diabetes is the leading cause of chronic kidney disease (CKD) worldwide.[1] International guidelines for the management of CKD in patients with type 2 diabetes recommend control of hypertension and hyperglycemia, as well as the use of a renin–angiotensin system (RAS) blocker (an angiotensin-converting–enzyme [ACE] inhibitor or angiotensin-receptor blocker [ARB]) and, more recently, a sodium–glucose cotransporter 2 (SGLT2) inhibitor.[2,3] Nonetheless, despite recommended treatment, a risk of CKD progression remains,[4] and newer therapies are needed.

Evidence supports a pathophysiological role for overactivation of the mineralocorticoid receptor in cardiorenal diseases, including CKD and diabetes, through inflammation and fibrosis that lead to progressive kidney and cardiovascular dysfunction.[5-8] Although a meta-analysis showed a 31% reduction in urinary protein or albumin excretion after treatment with a steroidal mineralocorticoid receptor antagonist in patients with CKD, data on hard clinical outcomes are lacking.[9] Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, had more potent antiinflammatory and antifibrotic effects than steroidal mineralocorticoid receptor antagonists in preclinical models.[10-13] Finerenone has been shown to reduce the urinary albumin-to-creatinine ratio in patients with CKD treated with an RAS blocker, while having smaller effects on serum potassium levels than spironolactone.[14,15] The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial was designed to test the hypothesis that finerenone slows CKD progression and reduces cardiovascular morbidity and mortality among patients with advanced CKD and type 2 diabetes.

Methods

Trial Design and Oversight

Our trial was a phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial. Details of the trial design have been published previously,[16] and the protocol is available with the full text of this article at NEJM.org. The executive committee in collaboration with the sponsor, Bayer, designed and amended the trial protocol and supervised the conduct of the trial; an independent data monitoring committee conducted one planned interim efficacy analysis and oversaw patient safety. The trial was performed in accordance with the principles of the Declaration of Helsinki. The sponsor conducted the analyses, and all the authors had access to the data and participated in the interpretation of the data. The first draft of the manuscript was prepared by the first author and was reviewed and edited by all the authors. Medical writing assistance was funded by Bayer. All the authors made the decision to submit the manuscript for publication and vouch for the completeness and accuracy of the data; the sponsor and the investigators vouch for the fidelity of the trial to the protocol.

Patients

Eligible patients were adults (≥18 years of age) with type 2 diabetes and CKD treated with an ACE inhibitor or ARB at the maximum dose on the manufacturer's label that did not cause unacceptable side effects. For the purposes of the trial, CKD was defined according to one of two sets of criteria. The first set included persistent, moderately elevated albuminuria (urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams], 30 to <300), an estimated glomerular filtration rate (eGFR, calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula, with adjustment for race in Black patients[17]) of 25 to less than 60 ml per minute per 1.73 m^2 of body-surface area, and a history of diabetic retinopathy. The second set of criteria included persistent, severely elevated albuminuria (urinary albumin-to-creatinine ratio, 300 to 5000) and an eGFR of 25 to less than 75 ml per minute per 1.73 m^2. Patients were required to have a serum potassium level of 4.8 mmol per liter or less at the time of screening. Full inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

Trial Procedures

The trial consisted of run-in, screening, and double-blind treatment periods (Fig. S1 in the Supplementary Appendix). The run-in period allowed background medical therapies to be adjusted, including adjustment of ACE inhibitor or ARB therapy to a maximum labeled dose that did not cause unacceptable side effects. At the end of the run-in period, patients were reassessed

for eligibility. Eligible patients were then randomly assigned in a 1:1 ratio to receive oral finerenone or placebo; patients with an eGFR of 25 to less than 60 ml per minute per 1.73 m^2 at the screening visit received an initial dose of 10 mg once daily, and those with an eGFR of 60 ml per minute per 1.73 m^2 or more at the screening visit received an initial dose of 20 mg once daily. An increase in the dose from 10 to 20 mg once daily was encouraged after 1 month, provided the serum potassium level was 4.8 mmol per liter or less 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. Patients in the placebo group underwent sham adjustment of the dose. After randomization, trial visits were conducted at month 1, month 4, then every 4 months until trial completion. Finerenone or placebo was withheld if potassium concentrations exceeded 5.5 mmol per liter and restarted when potassium levels fell to 5.0 mmol per liter or less. Further details are provided in the Supplementary Appendix and the trial protocol.

OUTCOMES

The primary outcome, assessed in a time-to-event analysis, was a composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over a period of at least 4 weeks, or death from renal causes. Kidney failure was defined as end-stage kidney disease or an eGFR of less than 15 ml per minute per 1.73 m^2; end-stage kidney disease was defined as the initiation of long-term dialysis (for ≥90 days) or kidney transplantation. All eGFR outcome events required confirmation with a second consecutive central laboratory measurement at least 4 weeks after the initial measurement.

The key secondary outcome, assessed in a time-to-event analysis, was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Other secondary outcomes (in order of sequential hierarchical testing) were death from any cause, hospitalization for any cause, the change in the urinary albumin-to-creatinine ratio from baseline to month 4, and a composite of kidney failure, a sustained decrease of at least 57% in the eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for at least 4 weeks, or death from renal causes (secondary composite kidney outcome). A clinical event committee whose members were unaware of the trial-group assignments independently reviewed and adjudicated all reported outcome events. Additional information, including outcome definitions, is provided in the Supplementary Appendix and the trial protocol.

Safety analyses included assessment of adverse events and central laboratory testing; serum potassium and creatinine levels were also measured at local laboratories at all trial visits. Adverse events that occurred during the treatment period were defined as those that started or worsened during finerenone or placebo intake or up to 3 days after any temporary or permanent interruption.

STATISTICAL ANALYSIS

This event-driven trial was designed to have 90% power to detect a 20% lower risk of a primary outcome event with finerenone than with placebo, on the basis of 1068 patients with a primary outcome event. Efficacy analyses were performed in the full analysis set (all randomly assigned patients without critical Good Clinical Practice violations). In time-to-event analyses, the superiority of finerenone over placebo was tested by means of a stratified log-rank test; stratification factors were geographic region (North America, Latin America, Europe, Asia, or other), eGFR category (25 to <45, 45 to <60, or ≥60 ml per minute per 1.73 m^2) at screening, and albuminuria category (moderately or severely elevated) at screening. Treatment effects are expressed as hazard ratios with corresponding confidence intervals from stratified Cox proportional-hazards models. Events were counted from randomization to the end-of-trial visit, and data on patients without an event were censored at the date of their last contact with complete information on all components of the respective outcome.

To account for multiple testing, the weighted Bonferroni–Holm procedure was used for the primary outcome and the key secondary outcome, followed by a hierarchical testing procedure of additional secondary outcomes, as described previously.[16] Because of the formal interim analysis, significance levels for the multiple-testing procedure in the final analysis were adjusted from 1.6667%, 3.3333%, and 5% to 1.5762%, 3.2827%, and 4.9674%, respectively. Additional statistical methods are described in

the Supplementary Appendix. Safety analyses were performed in the safety analysis set (all randomly assigned patients without critical Good Clinical Practice violations who received at least one dose of finerenone or placebo). Additional details on efficacy and safety analyses are provided in the trial protocol and the statistical analysis plan. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From September 2015 through June 2018, a total of 13,911 patients in 48 countries underwent screening, and 5734 patients underwent randomization (Fig. S2). Owing to critical Good Clinical Practice violations (including violations that led to the closure of one site and other violations related to patient misconduct), 60 patients were prospectively excluded from all analyses (further details are provided in the Supplementary Appendix), leaving 5674 patients who were included in the statistical analyses.

Baseline characteristics and concomitant medications were balanced between the two groups (Table 1 and Table S1). A total of 98.1% and 98.8% of the patients were treated with an ACE inhibitor or ARB, respectively, at a maximum labeled dose that did not cause unacceptable side effects (Table S2). Table S3 lists details of concomitant medications initiated after the start of finerenone or placebo administration.

At the trial conclusion, after a median follow-up of 2.6 years, 822 patients (29.0%) in the finerenone group and 801 patients (28.2%) in the placebo group had discontinued the trial regimen; vital status was ascertained for all but 18 patients (5656 patients [99.7%]) (Fig. S2). The mean adherence to the trial regimen (the percentage of administered doses relative to the number of planned doses) was 92.1% in the finerenone group and 92.6% in the placebo group, and the mean daily dose was 15.1 mg and 16.5 mg in the respective groups.

PRIMARY AND KEY SECONDARY OUTCOMES

The incidence of the primary composite outcome of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes was significantly lower in the finerenone group than in the placebo group, occurring in 504 patients (17.8%) and 600 patients (21.1%), respectively (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P=0.001) (Fig. 1A and Fig. 2). The incidences of the primary outcome components were consistently lower with finerenone than with placebo (Fig. 1B, Fig. 1C, and Fig. 2). On the basis of an absolute between-group difference of 3.4 percentage points (95% CI, 0.6 to 6.2) after 3 years, the number of patients who needed to be treated with finerenone to prevent one primary outcome event was 29 (95% CI, 16 to 166). The effects of finerenone on the primary outcome were generally consistent across prespecified subgroups (Fig. S3).

Patients in the finerenone group also had a significantly lower risk of a key secondary outcome event (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure), which occurred in 367 patients (13.0%) in the finerenone group and 420 patients (14.8%) in the placebo group (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.03) (Fig. 2 and Fig. S4A). The incidences of the components were lower with finerenone than with placebo except for nonfatal stroke, which had a similar incidence in the two groups (Fig. 2). On the basis of an absolute between-group difference of 2.4 percentage points (95% CI, 0.3 to 4.5) after 3 years, the number of patients who needed to be treated with finerenone to prevent one key secondary outcome event was 42 (95% CI, 22 to 397).

In prespecified "on-treatment" sensitivity analyses that included all events from randomization to 30 days after the last dose of finerenone or placebo, the risk of a primary outcome event and the risk of a key secondary outcome event were both lower by 22% with finerenone than with placebo (Table S4). The number of patients with missing data was low, and a prespecified tipping-point analysis of the primary outcome supported the robustness of the results (Table S5 and Fig. S5).

OTHER SECONDARY AND EXPLORATORY OUTCOMES

There was no significant between-group difference in the risk of death from any cause (Fig. 2 and Fig. S4B); analyses of subsequent prespecified outcomes are, therefore, exploratory. The incidence of hospitalization for any cause is shown in Figure 2 and Figure S4C. Finerenone was associated with a 31% greater reduction in the urinary albumin-to-creatinine ratio from baseline to month 4 than placebo (ratio of least-squares

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Finerenone (N=2833)	Placebo (N=2841)	Total (N=5674)
Age — yr	65.4±8.9	65.7±9.2	65.6±9.1
Male sex — no. (%)	1953 (68.9)	2030 (71.5)	3983 (70.2)
Race — no. (%)†			
White	1777 (62.7)	1815 (63.9)	3592 (63.3)
Black	140 (4.9)	124 (4.4)	264 (4.7)
Asian	717 (25.3)	723 (25.4)	1440 (25.4)
Other	199 (7.0)	179 (6.3)	378 (6.7)
Duration of diabetes — yr	16.6±8.8	16.6±8.8	16.6±8.8
Glycated hemoglobin — %	7.7±1.3	7.7±1.4	7.7±1.3
Systolic blood pressure — mm Hg	138.1±14.3	138.0±14.4	138.0±14.4
Estimated glomerular filtration rate			
Mean	44.4±12.5	44.3±12.6	44.3±12.6
Distribution — no. (%)			
≥60 ml/min/1.73 m^2	318 (11.2)	338 (11.9)	656 (11.6)
45 to <60 ml/min/1.73 m^2	972 (34.3)	928 (32.7)	1900 (33.5)
25 to <45 ml/min/1.73 m^2	1476 (52.1)	1505 (53.0)	2981 (52.5)
<25 ml/min/1.73 m^2	66 (2.3)	69 (2.4)	135 (2.4)
Missing data	1 (<0.1)	1 (<0.1)	2 (<0.1)
Urinary albumin-to-creatinine ratio‡			
Median (IQR)	833 (441–1628)	867 (453–1645)	852 (446–1634)
Distribution — no. (%)			
<30	11 (0.4)	12 (0.4)	23 (0.4)
30 to <300	350 (12.4)	335 (11.8)	685 (12.1)
≥300	2470 (87.2)	2493 (87.8)	4963 (87.5)
Missing data	2 (<0.1)	1 (<0.1)	3 (<0.1)
Serum potassium — mmol/liter	4.37±0.46	4.38±0.46	4.37±0.46
Baseline medications — no. (%)			
ACE inhibitor§	950 (33.5)	992 (34.9)	1942 (34.2)
Angiotensin-receptor blocker§	1879 (66.3)	1846 (65.0)	3725 (65.7)
Diuretic	1577 (55.7)	1637 (57.6)	3214 (56.6)
Statin	2105 (74.3)	2110 (74.3)	4215 (74.3)
Potassium-lowering agent¶	70 (2.5)	66 (2.3)	136 (2.4)
Glucose-lowering therapy	2747 (97.0)	2777 (97.7)	5524 (97.4)
Insulin	1843 (65.1)	1794 (63.1)	3637 (64.1)
GLP-1 receptor agonist	189 (6.7)	205 (7.2)	394 (6.9)
SGLT2 inhibitor	124 (4.4)	135 (4.8)	259 (4.6)

* Plus–minus values indicate means ±SD. Patients in the finerenone group received 10 or 20 mg once daily. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, GLP-1 glucagon-like peptide 1, IQR interquartile range, and SGLT2 sodium–glucose cotransporter 2.
† Race was reported by the patients.
‡ The ratio was calculated with albumin measured in milligrams and creatinine measured in grams.
§ A total of 14 patients were not treated with either an ACE inhibitor or an angiotensin-receptor blocker at baseline; 7 patients received treatment with both an ACE inhibitor and an angiotensin-receptor blocker
¶ These agents included sodium polystyrene sulfonate, calcium polystyrene sulfonate, and potassium-binding agents.

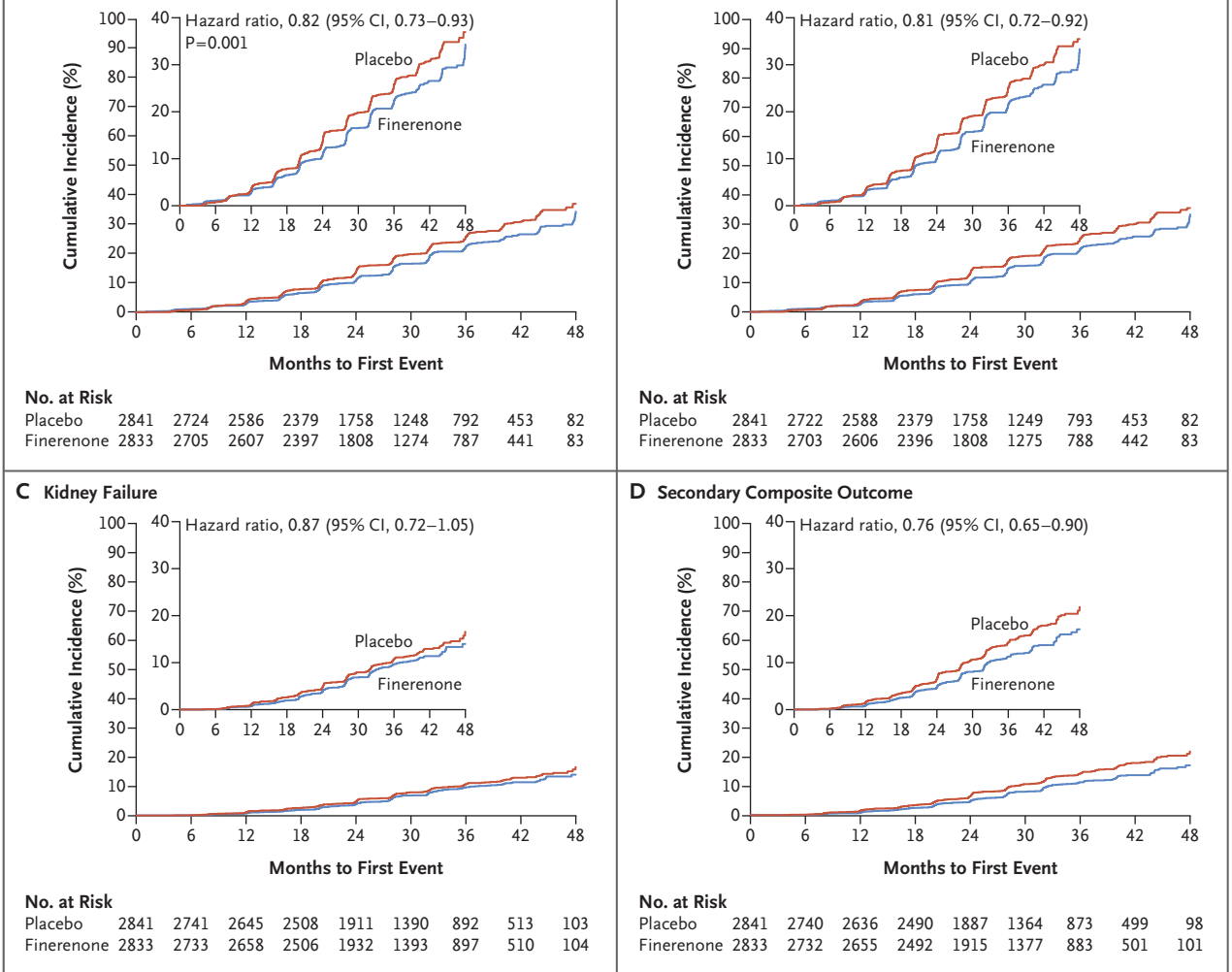


Figure 1. Kidney Outcomes.

Outcomes were assessed in time-to-event analyses. Panel A shows the primary composite outcome of kidney failure, a sustained decrease of at least 40% in the estimated glomerular filtration rate (eGFR) from baseline, or death from renal causes in the finerenone and placebo groups. Panel B shows a sustained decrease of at least 40% in the eGFR from baseline maintained for at least 4 weeks (a component of the primary composite outcome). Panel C shows kidney failure (defined as end-stage kidney disease or a sustained eGFR of <15 ml per minute per 1.73 m^2 of body-surface area, confirmed by a second measurement ≥4 weeks after the initial measurement); end-stage kidney disease was defined as the initiation of long-term dialysis or kidney transplantation. Panel D shows the secondary composite kidney outcome of kidney failure, a sustained decrease of at least 57% in the eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for at least 4 weeks, or death from renal causes. Insets show the same data on an enlarged y axis. CI denotes confidence interval.

mean change from baseline [finerenone vs. placebo], 0.69; 95% CI, 0.66 to 0.71), and a lower mean urinary albumin-to-creatinine ratio with finerenone than with placebo was maintained thereafter (Fig. 3A). A total of 252 patients (8.9%) who received finerenone and 326 patients (11.5%) who received placebo had a secondary composite kidney outcome event (kidney failure, a sustained decrease of ≥57% in the eGFR from baseline, or death from renal causes) (hazard ratio, 0.76; 95% CI, 0.65 to 0.90) (Fig. 1D, Fig. 2, and Fig. S4D). The effects on finerenone and placebo on the least-squares mean change from baseline in the eGFR slope are shown in Figure S6.

Outcome	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—

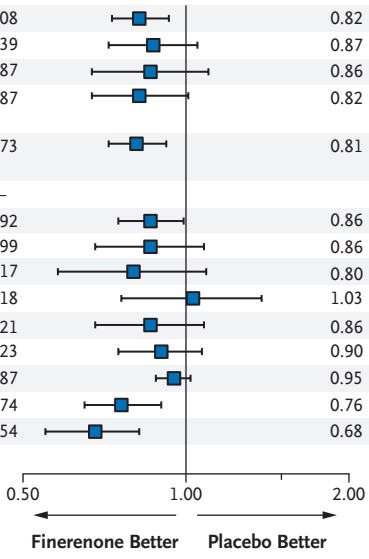


Figure 2. Efficacy Outcomes.

Shown are the hierarchical prespecified efficacy outcomes of the trial, including the components of the composite outcomes. Outcomes were assessed in time-to-event analyses. The key secondary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

SAFETY OUTCOMES AND VITAL SIGNS

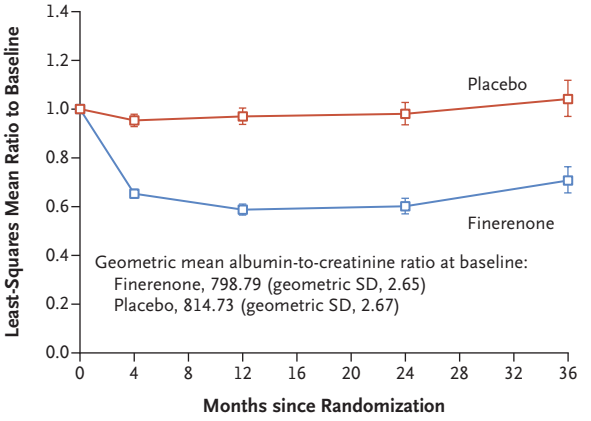
The incidence of adverse events that occurred during the treatment period was similar in the finerenone and placebo groups; serious adverse events occurred in 31.9% of the patients in the finerenone group and 34.3% of those in the placebo group (Table 2 and Table S6). Acute kidney injury–related adverse events and serious adverse events were balanced between the two groups (Table 2). Overall hyperkalemia-related adverse events were twice as frequent with finerenone as with placebo (18.3% and 9.0%, respectively), and the frequency of hyperkalemia leading to discontinuation of the trial regimen was also higher with finerenone (2.3% and 0.9% in the respective groups) (Table 2). No fatal hyperkalemia adverse events were reported. Patients who received finerenone had a higher mean serum potassium level than those who received placebo; a maximal difference of 0.23 mmol per liter was observed at month 4, and the difference remained largely stable thereafter (Fig. 3B). The incidences of serum potassium levels of more than 5.5 mmol per liter and more than 6.0 mmol per liter were 21.7% and 4.5%, respectively, in the finerenone group and 9.8% and 1.4%, respectively, in the placebo group. Hypokalemia was less common among patients who received finerenone than among those who received placebo (1.0% and 2.2%, respectively).

Finerenone had modest effects on blood pressure: the changes in mean systolic blood pressure from baseline to month 1 and to month 12 were −3.0 and −2.1 mm Hg, respectively, with finerenone and −0.1 and 0.9 mm Hg, respectively, with placebo (Fig. S7). Glycated hemoglobin levels (Fig. S8) and body weight (Fig. S9) were similar in the two groups.

DISCUSSION

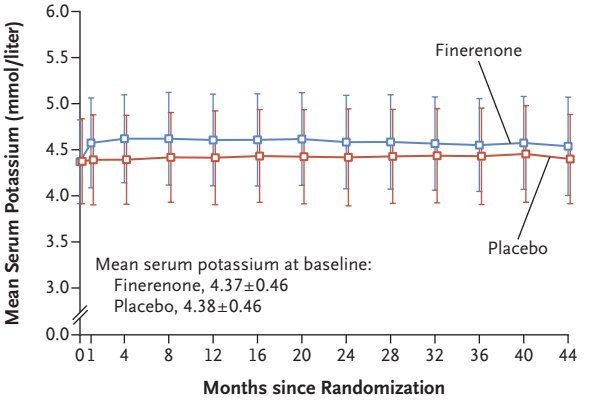
In the present trial, patients with CKD and type 2 diabetes who received finerenone had a lower risk of a primary outcome event (kidney failure, a sustained decrease of ≥40% in the eGFR from baseline, or death from renal causes) than those

A Urinary Albumin-to-Creatinine Ratio



No. of Patients						
Finerenone	2831	2725	2582	1841		856
Placebo	2840	2726	2598	1825		834
Mean Change from Baseline (percent)						
Finerenone	Ref.	−34.7	−41.3	−39.9		−29.3
Placebo	Ref.	−4.7	−3.0	−2.0		4.1

B Mean Serum Potassium



No. of Patients						
Finerenone	2827	2708	2600	1872	882	344
Placebo	2831	2709	2596	1865	862	348
Mean Change from Baseline (mmol/liter)						
Finerenone	Ref.	0.25	0.24	0.21	0.21	0.20
Placebo	Ref.	0.02	0.04	0.05	0.07	0.07

Figure 3. Effects on Albuminuria and Serum Potassium over Time.

Panel A shows the effects of finerenone and placebo on the urinary albumin-to-creatinine ratio in the full analysis set. The urinary albumin-to-creatinine ratio was calculated with albumin measured in milligrams and creatinine measured in grams. Shown is the ratio of the urinary albumin-to-creatinine ratio at specific time points to the urinary albumin-to-creatinine ratio at baseline. Panel B shows the effects of finerenone and placebo on serum potassium levels in the safety analysis set. Plus–minus values are means ±SD. The I bars indicate 95% confidence intervals.

who received placebo. Patients in the finerenone group also had a lower risk of a key secondary outcome event (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). These results suggest that in patients with CKD and type 2 diabetes, finerenone may be an effective treatment for kidney and cardiovascular protection.

The observed benefits of finerenone were clinically significant and were obtained on a background of guideline-directed therapy, including RAS blockade at a maximum labeled dose that did not cause unacceptable side effects plus well-controlled glycated hemoglobin and blood-pressure levels. The present long-term phase 3 trial examined the effects of the nonsteroidal mineralocorticoid receptor antagonist finerenone on major kidney and cardiovascular outcomes in patients with CKD and type 2 diabetes. In a patient population with multiple coexisting conditions and advanced CKD (almost 55% of the patients had a baseline eGFR of <45 ml per minute per 1.73 m^2) who were at high risk for kidney and cardiovascular events, the benefits of finerenone were observed after 12 months for the kidney outcome and as early as 1 month for the cardiovascular outcome, and these benefits persisted throughout the trial.

The magnitude of the between-group difference in the risk of a primary outcome event was smaller than that shown for the SGLT2 inhibitor canagliflozin in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.[4] The reasons for this difference are unknown and may relate to several factors. First, the patient populations differed in the two trials, since we included patients with an eGFR of less than 30 ml per minute per 1.73 m^2 and patients with a urinary albumin-to-creatinine ratio of 30 to less than 300 and excluded patients with heart failure with a reduced ejection fraction. Second, the trial designs differed: our trial allowed SGLT2 inhibitor treatment, whereas the CREDENCE trial excluded patients treated with mineralocorticoid receptor antagonists; our trial had a run-in period that allowed background medical therapies to be adjusted, including adjustment of ACE inhibitor or ARB therapy to a maximum labeled dose that did not cause unacceptable side effects. Third, the primary outcomes differed: there was

Table 2. Safety Outcomes.*

Event	Finerenone (N=2827)	Placebo (N=2831)
	no. of patients (%)	
Any adverse event	2468 (87.3)	2478 (87.5)
Adverse event related to trial regimen	646 (22.9)	449 (15.9)
Adverse event leading to discontinuation of trial regimen	207 (7.3)	168 (5.9)
Any serious adverse event†	902 (31.9)	971 (34.3)
Serious adverse event related to trial regimen†	48 (1.7)	34 (1.2)
Serious adverse event leading to discontinuation of trial regimen†	75 (2.7)	78 (2.8)
Investigator-reported hyperkalemia‡	516 (18.3)	255 (9.0)
Hyperkalemia related to trial regimen	333 (11.8)	135 (4.8)
Serious hyperkalemia†	44 (1.6)	12 (0.4)
Hospitalization due to hyperkalemia	40 (1.4)	8 (0.3)
Permanent discontinuation of trial regimen due to hyperkalemia	64 (2.3)	25 (0.9)
Investigator-reported hypokalemia	28 (1.0)	61 (2.2)
Investigator-reported renal-related adverse events		
Acute kidney injury§	129 (4.6)	136 (4.8)
Hospitalization due to acute kidney injury§	53 (1.9)	47 (1.7)
Discontinuation of trial regimen due to acute kidney injury§	5 (0.2)	7 (0.2)
Hospitalization due to acute renal failure¶	70 (2.5)	71 (2.5)
Discontinuation of trial regimen due to acute renal failure¶	31 (1.1)	36 (1.3)
Adverse events affecting ≥5% of patients in either group§		
Hyperkalemia	446 (15.8)	221 (7.8)
Nasopharyngitis	241 (8.5)	250 (8.8)
Hypertension	212 (7.5)	273 (9.6)
Anemia	209 (7.4)	191 (6.7)
Peripheral edema	186 (6.6)	304 (10.7)
Diarrhea	184 (6.5)	189 (6.7)
Upper respiratory tract infection	181 (6.4)	189 (6.7)
Glomerular filtration rate decreased	179 (6.3)	133 (4.7)
Urinary tract infection	179 (6.3)	192 (6.8)
Back pain	175 (6.2)	175 (6.2)
Hypoglycemia	151 (5.3)	194 (6.9)
Dizziness	146 (5.2)	153 (5.4)
Arthralgia	142 (5.0)	149 (5.3)
Bronchitis	134 (4.7)	151 (5.3)
Constipation	131 (4.6)	163 (5.8)
Pneumonia	128 (4.5)	181 (6.4)

* Shown are adverse events that occurred during the treatment period, defined as those that started or worsened during finerenone or placebo intake or up to 3 days after any temporary or permanent interruption. A causal relationship between any adverse event and administration of finerenone or placebo was based on the opinion of the reporting investigator.

† An adverse event was considered to be a serious adverse event if it resulted in death, was life-threatening, resulted in inpatient hospitalization (or prolongation of existing hospitalization), caused persistent or clinically significant disability or incapacity, was a congenital abnormality or birth defect, or was judged by the investigator to be a serious or important medical event.

‡ Shown are adverse events that were reported by investigators with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA) preferred terms "hyperkalemia" and "blood potassium increased."

§ These events were classified according to the MedDRA preferred term.

¶ These events were classified according to the standardized MedDRA Query term.

a kidney-specific composite in our trial and a cardiorenal composite in the CREDENCE trial. Fourth, the mechanisms of action differ between drug classes, including different effects on metabolic, hemodynamic, and diuretic factors and on inflammation and fibrosis.[4,13,18,19]

Previous kidney-outcome trials that involved patients with CKD and type 2 diabetes targeting dual RAS blockade have shown a lack of efficacy and increased risk (including increased incidences of acute kidney injury, hypotension, and hyperkalemia)[20-22]; such adverse events may be due to the inhibition of two proximal targets in the RAS cascade. In our trial, which combined a single RAS blocker with a drug, finerenone, targeting the mineralocorticoid receptor, patients in the finerenone and placebo groups had a similar risk of acute kidney injury–related adverse events. Furthermore, although finerenone was associated with a higher overall risk of hyperkalemia than placebo, discontinuation of the trial regimen due to hyperkalemia was infrequent in patients who received finerenone (2.3%) and markedly lower than in trials of dual RAS blockade (4.8% with combination therapy with a direct renin inhibitor and an ACE inhibitor or ARB[20] and 9.2% with dual ACE inhibitor and ARB therapy[22]). Such differences occurred despite the fact that the present trial had no protocol recommendations to restrict dietary potassium or potassium supplements, including in patients with hyperkalemia (in contrast to studies of dual RAS blockade[20,21]).

In this trial, the early reduction in albuminuria, early separation of the Kaplan–Meier curves for the key secondary outcome, and modest blood-pressure reduction (in the absence of effects on glycated hemoglobin levels and body weight) suggest that some benefits of finerenone may partly be mediated by natriuretic mechanisms. However, hemodynamic effects were also seen in trials of dual RAS blockade that did not show efficacy,[20-22] which implicates other mechanisms. Preclinical data showed that the kidney and cardiovascular benefits of finerenone were associated with potent antiinflammatory and antifibrotic effects through inhibition of overactivation of the mineralocorticoid receptor.[6,10-13,23] The delayed separation of the Kaplan–Meier curves for the primary outcome and persistent benefit over the trial duration provide evidence to support the hypothesis that finerenone may slow CKD progression by influencing tissue remodeling.

Our trial had certain limitations. Most patients had advanced CKD, we excluded patients with nonalbuminuric CKD and CKD not due to type 2 diabetes, and only 4.7% of the participating patients identified themselves as Black. These factors may restrict the generalizability of the findings. Further insight into the cardiorenal efficacy and safety of finerenone in patients with type 2 diabetes and less advanced CKD will be provided by the ongoing Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial.[24]

In our trial involving patients with type 2 diabetes and advanced CKD, finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. Overall, adverse events that occurred during the treatment period were balanced between the two groups.

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APPENDIX

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REFERENCES

1. Li H, Lu W, Wang A, Jiang H, Lyu J. Changing epidemiology of chronic kidney disease as a result of type 2 diabetes mellitus from 1990 to 2017: estimates from Global Burden of Disease 2017. J Diabetes Investig 2020 July 11 (Epub ahead of print).

2. American Diabetes Association. 11. Microvascular complications and foot care: *Standards of Medical Care in Diabetes — 2020*. Diabetes Care 2020;43:Suppl 1:S135-S151.

3. 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;63:221-8.

4. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.

5. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. Kidney Int 2019;96:302-19.

6. Barrera-Chimal J, Estrela GR, Lechner SM, et al. The myeloid mineralocorticoid receptor controls inflammatory and fibrotic responses after renal injury via macrophage interleukin-4 receptor signaling. Kidney Int 2018;93:1344-55.

7. Guo C, Martinez-Vasquez D, Mendez GP, et al. Mineralocorticoid receptor antagonist reduces renal injury in rodent models of types 1 and 2 diabetes mellitus. Endocrinology 2006;147:5363-73.

8. Buonafine M, Bonnard B, Jaisser F. Mineralocorticoid receptor and cardiovascular disease. Am J Hypertens 2018;31:1165-74.

9. Currie G, Taylor AHM, Fujita T, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol 2016;17:127.

10. Grune J, Beyhoff N, Smeir E, et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. Hypertension 2018;71:599-608.

11. Kolkhof P, Delbeck M, Kretschmer A, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. J Cardiovasc Pharmacol 2014;64:69-78.

12. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside. Handb Exp Pharmacol 2017;243:271-305.

13. Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J (in press).

14. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA 2015;314:884-94.

15. Pitt B, Kober L, Ponikowski P, et al. Safety and tolerability of the novel nonsteroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. Eur Heart J 2013;34:2453-63.

16. Bakris GL, Agarwal R, Anker SD, et al. Design and baseline characteristics of the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease trial. Am J Nephrol 2019;50:333-44.

17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.

18. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752-72.

19. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:422-34.

20. Parving H-H, Brenner BM, McMurray JJV, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204-13.

21. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med 2013;369:1892-903.

22. Imai E, Chan JCN, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Diabetologia 2011;54:2978-86.

23. Lattenist L, Lechner SM, Messaoudi S, et al. Nonsteroidal mineralocorticoid receptor antagonist finerenone protects against acute kidney injury-mediated chronic kidney disease: role of oxidative stress. Hypertension 2017;69:870-8.

24. Ruilope LM, Agarwal R, Anker SD, et al. Design and baseline characteristics of the finerenone in reducing cardiovascular mortality and morbidity in diabetic kidney disease trial. Am J Nephrol 2019;50:345-56.