ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

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ABSTRACT

BACKGROUND

Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, has favorable effects on cardiorenal outcomes in patients with predominantly stage 3 or 4 chronic kidney disease (CKD) with severely elevated albuminuria and type 2 diabetes. The use of finerenone in patients with type 2 diabetes and a wider range of CKD is unclear.

METHODS

In this double-blind trial, we randomly assigned patients with CKD and type 2 diabetes 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 and an estimated glomerular filtration rate (eGFR) of 25 to 90 ml per minute per 1.73 m^2 of body-surface area (stage 2 to 4 CKD) or a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of at least 60 ml per minute per 1.73 m^2 (stage 1 or 2 CKD). 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 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. The first secondary outcome was a composite of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR, or death from renal causes. Safety was assessed as investigator-reported adverse events.

RESULTS

A total of 7437 patients underwent randomization. Among the patients included in the analysis, during a median follow-up of 3.4 years, a primary outcome event occurred in 458 of 3686 patients (12.4%) in the finerenone group and in 519 of 3666 (14.2%) in the placebo group (hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P=0.03), with the benefit driven primarily by a lower incidence of hospitalization for heart failure (hazard ratio, 0.71; 95% CI, 0.56 to 0.90). The secondary composite outcome occurred in 350 patients (9.5%) in the finerenone group and in 395 (10.8%) in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 1.01). The overall frequency of adverse events did not differ substantially between groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone (1.2%) than with placebo (0.4%).

CONCLUSIONS

Among patients with type 2 diabetes and stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria, finerenone therapy improved cardiovascular outcomes as compared with placebo. (Funded by Bayer; FIGARO-DKD ClinicalTrials.gov number, NCT02545049.)

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

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Chronic kidney disease (CKD) exacerbates the cardiovascular risk associated with type 2 diabetes.[1] The risks of cardiovascular events and new-onset heart failure increase as the urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) exceeds 10 and the estimated glomerular filtration rate (eGFR) decreases below 75 ml per minute per 1.73 m^2 of body-surface area.[1-4] Most patients with CKD are at higher risk for cardiovascular events than for kidney failure[5]; thus, it is important to identify and treat CKD in order to reduce the high cardiovascular and heart failure burden of CKD in patients with type 2 diabetes.[1,6]

Mineralocorticoid receptor overactivation is associated with kidney and cardiovascular diseases, which often coexist as cardiorenal disease.[7-9] Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, improved markers of kidney and cardiovascular damage in preclinical models and in patients with CKD in phase 2 studies.[9-13] The planned phase 3 program for finerenone included two complementary trials, which together cover the spectrum of CKD in type 2 diabetes (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[10] In the Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, finerenone improved kidney outcomes in patients with predominantly stage 3 or 4 CKD with severely elevated albuminuria and type 2 diabetes, a population with high kidney risk.[14,15] In the Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial, reported here, we evaluated whether treatment with finerenone would lead to lower risks of cardiovascular events and death from cardiovascular causes among patients with either stage 2 to 4 CKD and moderately elevated albuminuria or stage 1 or 2 CKD and severely increased albuminuria — a patient population at high cardiovascular risk that was excluded from or understudied in the FIDELIO-DKD trial.[6]

Methods

Trial Design and Oversight

We conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven clinical trial. Details of the trial design have been published previously[6] and are included in the trial protocol, available at NEJM.org. The trial was designed and supervised by the executive committee in conjunction with Bayer (the sponsor). An independent data and safety monitoring committee oversaw patient safety and conducted one planned efficacy interim analysis. The trial was performed in accordance with the principles of the Declaration of Helsinki. The sponsor conducted the analyses, and all authors had access to and participated in the interpretation of the analyzed data. The first and second authors prepared the initial draft of the manuscript, which was reviewed and edited by all authors. All the authors vouch for the completeness and accuracy of the data; the sponsor and the investigators vouch for the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

Patients

Eligible patients were adults (≥18 years old) with type 2 diabetes and CKD treated with a renin–angiotensin system (RAS) inhibitor (angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker) 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) and an eGFR (calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration formula) of 25 to 90 ml per minute per 1.73 m^2 (i.e., stage 2 to 4 CKD). The second set of criteria included persistent, severely elevated albuminuria (urinary albumin-to-creatinine ratio, 300 to 5000) and an eGFR of at least 60 ml per minute per 1.73 m^2 (i.e., stage 1 or 2 CKD). Patients were required to have a serum potassium level of 4.8 mmol per liter or less at the time of screening.

Patients who were highly represented in the FIDELIO-DKD trial (i.e., those with a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to <60 ml per minute per 1.73 m^2; 4367 of 5674 patients [77.0%]) were excluded from the current trial.[14] Other key exclusion criteria were symptomatic chronic heart failure with a reduced ejection fraction (i.e., a class 1A recommendation for mineralocorticoid receptor antagonist treatment). A full list of the inclusion

and exclusion criteria is provided in the Supplementary Appendix.

TRIAL PROCEDURES

The current trial consisted of run-in, screening, and double-blind treatment periods (Fig. S2). During the run-in period, RAS inhibitor therapy was adjusted upward to a maximum labeled dose that did not cause unacceptable side effects. Patients who met the eligibility criteria at the end of the run-in period were randomly assigned in a 1:1 ratio to receive oral finerenone or placebo; patients with an eGFR at the screening visit of 25 to less than 60 ml per minute per 1.73 m^2 received an initial dose of 10 mg once daily, and those with an eGFR of at least 60 ml per minute per 1.73 m^2 received an initial dose of 20 mg once daily. From month 1 onward, the target dose of finerenone or placebo was 20 mg once daily; adjustment of the dose from 10 mg up to 20 mg once daily was encouraged, provided that the serum potassium level was no more than 4.8 mmol per liter and that the eGFR was stable; adjustment of the dose down from 20 mg to 10 mg once daily was allowed for any safety reason after the initiation of finerenone or placebo.

After randomization, trial visits were conducted at month 1, month 4, and then every 4 months until trial completion. Finerenone or placebo was withheld if the serum potassium level exceeded 5.5 mmol per liter and was restarted when serum potassium levels decreased to 5.0 mmol per liter or less. Further details are provided in the Supplementary Appendix and the protocol.

OUTCOMES

The primary 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. The first secondary outcome, assessed in a time-to-event analysis, was a composite of the first occurrence of kidney failure, a sustained decrease from baseline of at least 40% in the eGFR for a period of at least 4 weeks, or death from renal causes. Kidney failure was defined as end-stage kidney disease or as a sustained eGFR of less than 15 ml per minute per 1.73 m^2 for a period of at least 4 weeks. End-stage kidney disease was defined as the initiation of chronic dialysis (for ≥90 days) or kidney transplantation.

Other secondary outcomes (in order of sequential hierarchical testing) were hospitalization for any cause, assessed in a time-to-event analysis; death from any cause, assessed in a time-to-event analysis; the change in the urinary albumin-to-creatinine ratio from baseline to month 4; and a kidney composite outcome, assessed in a time-to-event analysis, of the first onset of kidney failure, a sustained decrease from baseline of at least 57% in the eGFR for a period of at least 4 weeks (equivalent to a doubling of the serum creatinine level), or death from renal causes. A clinical event committee whose members were unaware of the trial-group assignments independently reviewed and adjudicated all reported outcome events (see the Supplementary Appendix and the protocol).

Safety analyses included assessment of adverse events and central laboratory testing. Adverse events that occurred during the treatment period were designated 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 976 patients with an event. Efficacy analyses were performed in the full analysis set (all the patients who had undergone randomization and were without critical Good Clinical Practice violations). In time-to-event analyses, the superiority of finerenone over placebo was tested by means of stratified log-rank tests; stratification factors were geographic region, eGFR category at screening, albuminuria category at screening, and history of cardiovascular disease (see the Supplementary Appendix). 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 patients without an event had their data censored at the date of last contact with complete information on all the components of the respective outcome.

To account for multiplicity of testing, a hierarchical testing procedure was applied. Because of the formal interim analysis, the significance level for the final analysis was adjusted from 5% to

4.9674%. Stratified Fine–Gray models were used to calculate the subdistribution hazard ratios, with accounting for the competing risk of death for reasons that were not part of the respective outcomes.[5] Safety analyses were performed in the safety analysis set, which included all the patients who had undergone randomization, were without critical Good Clinical Practice violations, and had received at least one dose of finerenone or placebo. Additional details on the statistical analyses are provided in the Supplementary Appendix and the protocol, which includes the statistical analysis plan. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From September 2015 through October 2018, a total of 19,381 patients from 48 countries underwent screening, and 7437 patients underwent randomization (Fig. S3). A total of 85 patients were prospectively excluded from all the analyses because of critical Good Clinical Practice violations (including violations that led to the closure of one site and other violations related to patient misconduct) (see the Supplementary Appendix). Among the 7352 patients included in the analyses, the baseline characteristics and medications, including the dose of RAS inhibitor, were balanced between the two groups (Tables 1, S1, and S2 and Fig. S4). At baseline, 8.4% of the patients were being treated with a sodium–glucose cotransporter 2 (SGLT2) inhibitor and 7.5% with a glucagon-like peptide-1 (GLP-1) receptor agonist; an additional 15.8% and 11.3% of patients, respectively, started treatment during the trial. Table S3 lists details of the medications that were initiated after the start of the trial regimen.

At the trial conclusion, at a median follow-up of 3.4 years, vital status was ascertained for 7334 of the 7352 patients (99.8%) included in the primary analysis. The trial was ongoing during the coronavirus disease 2019 (Covid-19) pandemic, which caused trial disruption for 2096 patients (28.5%; mostly because of missed trial visits) and caused temporary interruption of the trial regimen for 696 patients (9.5%). The incidence of premature discontinuation of the trial regimen (including because of death) was balanced between the two groups (27.4% in the finerenone group and 27.7% in the placebo group). The mean daily dose of finerenone was 17.5 mg, and the mean daily dose of placebo was 18.2 mg. The mean adherence to the trial regimen (the percentage of administered doses relative to the number of planned doses) from randomization until receipt of the last dose was 91.5% in the finerenone group and 92.9% in the placebo group.

EFFECTS ON PRIMARY COMPOSITE OUTCOME AND COMPONENTS

The incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (the primary composite outcome) was significantly lower in the finerenone group than in the placebo group (458 of 3686 patients [12.4%] vs. 519 of 3666 patients [14.2%]; hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P=0.03) (Figs. 1A and 2). The incidences of the primary-outcome components are shown in Figures 1B through 1E and 2. The incidence of hospitalization for heart failure was lower in the finerenone group than in the placebo group (117 patients [3.2%] vs. 163 [4.4%]; hazard ratio, 0.71; 95% CI, 0.56 to 0.90) (Figs. 1E and 2). The number of patients who needed to be treated with finerenone to prevent one primary outcome event was 47 (95% CI, 26 to 226), on the basis of an absolute between-group difference of 2.1 percentage points (95% CI, 0.4 to 3.8) after 3.5 years.

The effect of finerenone therapy on the primary outcome was consistent across prespecified subgroups (Fig. S5). An analysis that was adjusted for the competing risk of noncardiovascular death showed consistent results (Table S4). Similar findings were observed in an "on-treatment" analysis, which included all the events from randomization up to 30 days after the last dose of finerenone or placebo (Table S5). The number of patients with missing data for the primary composite outcome was low, and a tipping-point analysis supported the robustness of the results (Fig. S6 and Table S6).

SECONDARY AND EXPLORATORY OUTCOMES

There was no significant between-group difference in the incidence of the first secondary composite outcome of kidney failure, a sustained decrease from baseline of at least 40% in the

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

Characteristic	Finerenone (N=3686)	Placebo (N=3666)	Total (N=7352)
Age — yr	64.1±9.7	64.1±10.0	64.1±9.8
Male sex — no. (%)	2528 (68.6)	2577 (70.3)	5105 (69.4)
Race or ethnic group — no. (%)†			
White	2672 (72.5)	2605 (71.1)	5277 (71.8)
Black	113 (3.1)	145 (4.0)	258 (3.5)
Asian	715 (19.4)	739 (20.2)	1454 (19.8)
Other	177 (4.8)	170 (4.6)	347 (4.7)
Missing data	9 (0.2)	7 (0.2)	16 (0.2)
Glycated hemoglobin — %	7.7±1.4	7.7±1.4	7.7±1.4
Systolic blood pressure — mm Hg	135.8±14.0	135.7±14.1	135.8±14.0
History of cardiovascular disease — no. (%)	1676 (45.5)	1654 (45.1)	3330 (45.3)
Estimated glomerular filtration rate			
Mean — ml/min/1.73 m^2	67.6±21.7	68.0±21.7	67.8±21.7
Distribution — no. (%)			
≥60 ml/min/1.73 m^2	2285 (62.0)	2254 (61.5)	4539 (61.7)
45 to <60 ml/min/1.73 m^2	745 (20.2)	789 (21.5)	1534 (20.9)
25 to <45 ml/min/1.73 m^2	641 (17.4)	610 (16.6)	1251 (17.0)
<25 ml/min/1.73 m^2	15 (0.4)	12 (0.3)	27 (0.4)
Missing data	0	1 (<0.1)	1 (<0.1)
Urinary albumin-to-creatinine ratio‡			
Median (interquartile range)	302 (105–749)	315 (111–731)	308 (108–740)
Distribution — no. (%)			
<30	109 (3.0)	98 (2.7)	207 (2.8)
30 to <300	1726 (46.8)	1688 (46.0)	3414 (46.4)
≥300	1851 (50.2)	1878 (51.2)	3729 (50.7)
Missing data	0	2 (0.1)	2 (<0.1)
Serum potassium — mmol/liter	4.33±0.43	4.33±0.43	4.33±0.43
Baseline medications — no. (%)			
Renin–angiotensin system inhibitor	3681 (99.9)	3662 (99.9)	7343 (99.9)
Diuretic	1748 (47.4)	1748 (47.7)	3496 (47.6)
Statin	2552 (69.2)	2632 (71.8)	5184 (70.5)
Glucose-lowering therapy	3607 (97.9)	3589 (97.9)	7196 (97.9)
Insulin	2023 (54.9)	1970 (53.7)	3993 (54.3)
GLP-1 receptor agonist	308 (8.4)	242 (6.6)	550 (7.5)
SGLT2 inhibitor	314 (8.5)	304 (8.3)	618 (8.4)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. GLP-1 denotes glucagon-like peptide-1, and SGLT2 sodium–glucose cotransporter 2.
† Race and ethnic group were reported by the patients. Other included American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, or multiple.
‡ The ratio was calculated with albumin measured in milligrams and creatinine measured in grams.

eGFR, or death from renal causes (350 patients [9.5%] in the finerenone group and 395 [10.8%] in the placebo group; hazard ratio, 0.87; 95% CI, 0.76 to 1.01) (Figs. 2 and S7A); analyses of the subsequent outcomes are, therefore, exploratory. An analysis that was adjusted for the competing risk of death from nonrenal causes showed consistent results, as did the "on-treatment" analysis.

The incidences of the components of the first secondary outcome are shown in Figure 2. End-stage kidney disease occurred in 32 patients (0.9%) in the finerenone group and in 49 (1.3%) in the placebo group (hazard ratio, 0.64; 95% CI, 0.41 to 0.995). The incidences of hospitalization for any cause and of death from any cause are shown in Figures 2, S7B, and S7C. The reduction in the urinary albumin-to-creatinine ratio from baseline to month 4 was 32% greater with finerenone than with placebo (ratio of the least-squares mean change from baseline, 0.68; 95% CI, 0.65 to 0.70), and similar results were seen in an analysis that accounted for death as a competing risk (Table S7). The kidney composite outcome of kidney failure, a sustained decrease from baseline of at least 57% in the eGFR, or death from renal causes occurred in 108 patients (2.9%) in the finerenone group and in 139 (3.8%) in the placebo group (hazard ratio, 0.77; 95% CI, 0.60 to 0.99) (Figs. 2 and S7D).

SAFETY OUTCOMES AND VITAL SIGNS

Safety issues during the treatment period were recorded as investigator-reported adverse events. The incidence of adverse events was similar in the two groups (Tables 2, S8, and S9). Overall, 31.4% of the patients treated with finerenone had a serious adverse event, as compared with 33.2% of those who received placebo. The incidence of acute kidney injury was balanced between the groups. The incidence of hyperkalemia was higher with finerenone than with placebo (10.8% vs. 5.3%), but none of these adverse events resulted in death, and few events led to permanent discontinuation of the regimen (in 1.2% and 0.4% of the patients, respectively) or hospitalization (in 0.6% and 0.1%). The incidence of hypokalemia was lower with finerenone than with placebo (1.1% vs. 2.4%), and gynecomastia was rare, with the incidence balanced between the groups (0.1% and 0.1%, respectively).

Adverse events and serious adverse events of pneumonia were less common with finerenone than with placebo (in 3.9% vs. 5.6% of the patients and in 2.0% vs. 3.1%, respectively), as were adverse events related to Covid-19 (in 2.3% vs. 3.2%). The results of additional post hoc analyses of the between-group differences in the incidence of adverse events of interest are provided in Table S10.

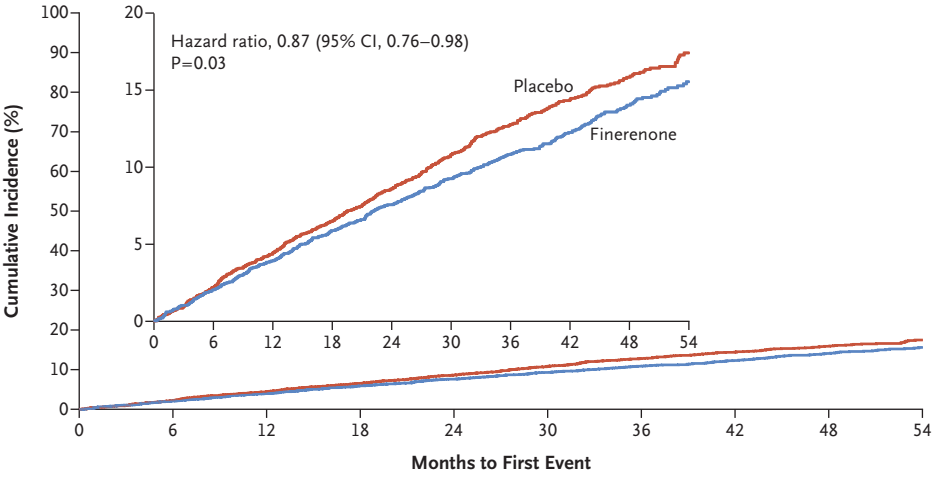
Finerenone treatment was associated with a greater increase in the serum potassium level from baseline than that observed with placebo. A between-group difference of 0.16 mmol per liter was seen from month 1 and remained largely stable thereafter (Fig. S8). Finerenone treatment had modest effects on blood pressure; the mean difference between finerenone and placebo in the change from baseline in the systolic blood pressure was –3.5 mm Hg at month 4 and –2.6 mm Hg at month 24 (Fig. S9). The mean glycated hemoglobin levels and body weight were similar in the two groups throughout the trial (Figs. S10 and S11).

DISCUSSION

The results of the current trial showed that, among patients with type 2 diabetes and CKD (stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria), those assigned to the finerenone group had a lower risk of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure than those assigned to the placebo group. This difference was driven predominantly by a lower incidence of hospitalization for heart failure in the finerenone group.

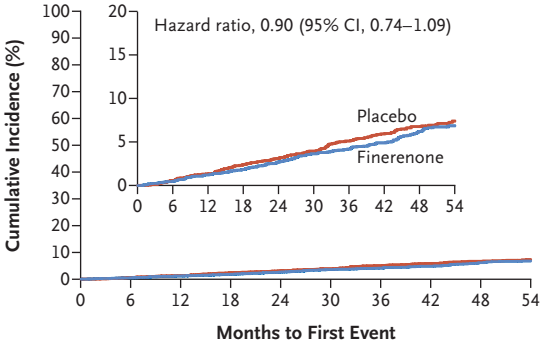
Although previous trials have examined cardiovascular outcomes in patients with type 2 diabetes and varying degrees of CKD, there remains scant evidence from dedicated clinical trials to support the use of therapies to improve cardiorenal outcomes in patients with less-advanced CKD.[16-23] This trial addressed that gap by enrolling patients with type 2 diabetes without heart failure with a reduced ejection fraction and with either stage 2 to 4 CKD with moderately elevated albuminuria

A Primary Composite Outcome



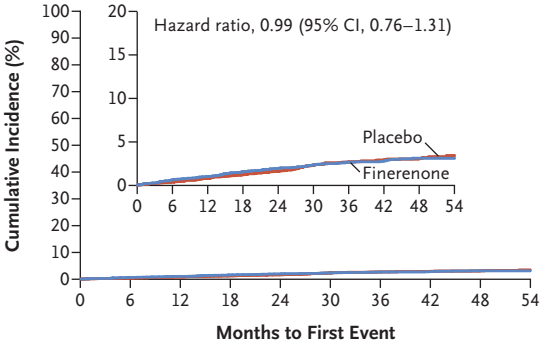
No. at Risk										
Placebo	3666	3577	3479	3389	3267	2730	2125	1657	1076	585
Finerenone	3686	3600	3517	3427	3320	2781	2184	1712	1093	598

B Death from Cardiovascular Causes



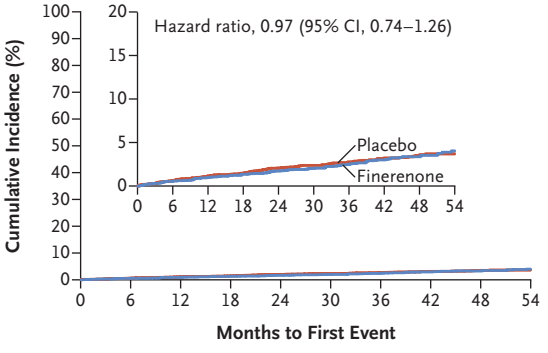
No. at Risk										
Placebo	3666	3639	3593	3539	3468	2938	2315	1820	1177	647
Finerenone	3686	3661	3620	3581	3503	2968	2358	1858	1187	653

C Nonfatal Myocardial Infarction



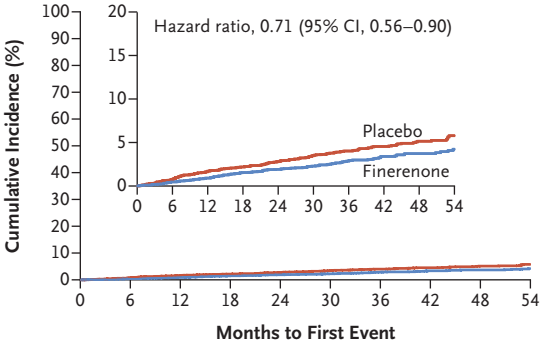
No. at Risk										
Placebo	3666	3623	3559	3491	3404	2858	2240	1757	1135	620
Finerenone	3686	3635	3579	3522	3432	2894	2293	1809	1155	632

D Nonfatal Stroke



No. at Risk										
Placebo	3666	3614	3548	3482	3388	2860	2240	1753	1134	620
Finerenone	3686	3635	3581	3523	3433	2896	2285	1795	1145	620

E Hospitalization for Heart Failure



No. at Risk										
Placebo	3666	3610	3538	3471	3376	2849	2239	1751	1134	619
Finerenone	3686	3640	3581	3515	3429	2887	2284	1790	1142	629

Figure 1 (facing page). Cardiovascular Outcomes.
Outcomes were assessed in time-to-event analyses. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Insets show the same data on an enlarged y axis.

or stage 1 or 2 CKD with severely elevated albuminuria. The present trial extends the findings of the FIDELIO-DKD trial.[10,14] Together, these two trials included a spectrum of CKD in type 2 diabetes — patients with stage 2 to 4 CKD with moderately elevated albuminuria or with stage 1 to 4 CKD with severely elevated albuminuria (Fig. S1).

In both trials, the observed cardiovascular benefits of finerenone therapy were clinically meaningful 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, as well as frequent use of cardiovascular medications (e.g., statins) and well-controlled glycated hemoglobin and blood-pressure levels.[14,15] In the present trial, the cardiovascular benefits of finerenone therapy were consistent across categories according to the baseline urinary albumin-to-creatinine ratio and eGFR. More than 60% of the patients had albuminuric CKD with an eGFR of at least 60 ml per minute per 1.73 m^2 at baseline, which highlights the need for early CKD diagnosis with the use of urinary albumin-to-creatinine ratio screening and for treatment to improve outcomes in this underrecognized population of patients with a high cardiovascular risk.

During the course of this trial, the recommended care for patients with CKD and type 2 diabetes evolved, with contemporary guidelines recommending the use of SGLT2 inhibitors or GLP-1 receptor agonists to reduce cardiorenal risk.[24,25] Consistent cardiovascular benefits of finerenone therapy were observed independent of and in combination with the use of either an SGLT2 inhibitor or a GLP-1 receptor agonist, with the point estimates suggesting benefits with combination use (as assessed in subgroups defined according to SGLT2 inhibitor use and GLP-1 receptor agonist use at baseline). Preclinical data suggest additive cardiorenal and survival benefits of coadministration of finerenone and empagliflozin.[26] More data are needed to establish whether combination therapy with finerenone and an SGLT2 inhibitor would result in greater cardiorenal protection than these therapies alone in patients with CKD. Together, these findings suggest a more positive future for patients with CKD and type 2 diabetes, with three effective drug classes now available.[14,22,23]

In this trial, despite the exclusion of patients who had symptomatic heart failure with a reduced ejection fraction, hospitalization for heart failure was a key driver of the primary outcome. Because patients with CKD and type 2 diabetes who have new-onset or preexisting heart failure are at very high risk for hospitalization and death,[27-29] treatment with finerenone may represent an advance in the prevention and management of heart failure, thus minimizing the considerable health care burdens in patients with CKD and type 2 diabetes. Although the effects of finerenone treatment on the kidney composite outcome that included a decrease from baseline of at least 40% in the eGFR were similar in the current trial and the FIDELIO-DKD trial, significance was not achieved here.[14] In this trial, the incidence of end-stage kidney disease was lower in the finerenone group than in the placebo group. In both trials, the incidence of the kidney composite outcome that included a decrease from baseline of at least 57% in the eGFR (a more sensitive surrogate outcome for kidney failure than a decrease of ≥40% in the eGFR[30]) was lower in the finerenone group than in the placebo group.[14]

In a finding that is consistent with mineralocorticoid receptor blockade,[9] treatment with finerenone led to a greater increase in the serum potassium level than placebo.[12-14] Given the higher mean eGFR in this trial than in the FIDELIO-DKD trial (68 vs. 44 ml per minute per 1.73 m^2), the incidence of hyperkalemia with finerenone treatment was lower (10.8% vs. 18.3%), despite the longer median follow-up (3.4 vs. 2.6 years).[14] Results from the Mineralocorticoid Receptor Antagonist Tolerability Study (ARTS) showed a lower incidence of hyperkalemia with finerenone therapy at a dose of 10 mg once daily than with spironolactone therapy at a dose of 25 to 50 mg once daily (4.5% vs. 11.1%).[12] Because concerns about hyperkalemia contribute to the underuse

Outcome	Finerenone (N=3686)	Placebo (N=3666)	Finerenone (N=3686)	Placebo (N=3666)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	458 (12.4)	519 (14.2)	3.87	4.45	0.87 (0.76–0.98)	0.03
Death from cardiovascular causes	194 (5.3)	214 (5.8)	1.56	1.74	0.90 (0.74–1.09)	—
Nonfatal myocardial infarction	103 (2.8)	102 (2.8)	0.85	0.85	0.99 (0.76–1.31)	—
Nonfatal stroke	108 (2.9)	111 (3.0)	0.89	0.92	0.97 (0.74–1.26)	—
Hospitalization for heart failure	117 (3.2)	163 (4.4)	0.96	1.36	0.71 (0.56–0.90)	—
Kidney composite outcome with ≥40% decrease in eGFR	350 (9.5)	395 (10.8)	3.15	3.58	0.87 (0.76–1.01)	—
Kidney failure	46 (1.2)	62 (1.7)	0.40	0.54	0.72 (0.49–1.05)	—
End-stage kidney disease	32 (0.9)	49 (1.3)	0.26	0.40	0.64 (0.41–0.995)	—
Sustained decrease in eGFR of <15 ml/min/1.73 m^2	28 (0.8)	38 (1.0)	0.24	0.33	0.71 (0.43–1.16)	—
Sustained ≥40% decrease in eGFR from baseline	338 (9.2)	385 (10.5)	3.04	3.49	0.87 (0.75–1.00)	—
Death from renal causes	0	2 (0.1)	—	—	—	—
Hospitalization for any cause	1573 (42.7)	1605 (43.8)	16.9	17.5	0.97 (0.90–1.04)	—
Death from any cause	333 (9.0)	370 (10.1)	2.68	3.01	0.89 (0.77–1.04)	—
Kidney composite outcome with ≥57% decrease in eGFR	108 (2.9)	139 (3.8)	0.95	1.23	0.77 (0.60–0.99)	—
Sustained ≥57% decrease in eGFR from baseline	90 (2.4)	116 (3.2)	0.79	1.02	0.76 (0.58–1.00)	—

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 primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The first secondary outcome was a composite of kidney failure, a sustained decrease from baseline of at least 40% in the estimated glomerular filtration rate (eGFR) for a period of at least 4 weeks, or death from renal causes. The additional prespecified kidney outcome was a composite of kidney failure, a sustained decrease from baseline of at least 57% in the eGFR for a period of at least 4 weeks, or death from renal causes.

Table 2. Safety Outcomes.*

Event	Finerenone (N=3683)	Placebo (N=3658)
Investigator-reported adverse events — no. (%)		
Any adverse event	3134 (85.1)	3129 (85.5)
Adverse event related to finerenone or placebo	560 (15.2)	413 (11.3)
Adverse event leading to discontinuation of trial regimen	207 (5.6)	183 (5.0)
Any serious adverse event	1158 (31.4)	1215 (33.2)
Serious adverse event related to finerenone or placebo	35 (1.0)	27 (0.7)
Serious adverse event leading to discontinuation of trial regimen	70 (1.9)	76 (2.1)
Adverse event with outcome of death	79 (2.1)	100 (2.7)
Hyperkalemia†	396 (10.8)	193 (5.3)
Hyperkalemia related to finerenone or placebo	240 (6.5)	114 (3.1)
Serious hyperkalemia	25 (0.7)	4 (0.1)
Hospitalization due to hyperkalemia	21 (0.6)	2 (0.1)
Permanent discontinuation of trial regimen due to hyperkalemia	46 (1.2)	13 (0.4)
Hypokalemia	42 (1.1)	88 (2.4)
Renal-related adverse events		
Acute kidney injury‡	91 (2.5)	98 (2.7)
Hospitalization due to acute kidney injury‡	32 (0.9)	39 (1.1)
Discontinuation of trial regimen due to acute kidney injury‡	9 (0.2)	3 (0.1)
Hospitalization due to acute renal failure§	45 (1.2)	49 (1.3)
Discontinuation of trial regimen due to acute renal failure§	26 (0.7)	12 (0.3)
Covid-19–related adverse event¶		
Any adverse event	84 (2.3)	116 (3.2)
Serious adverse event	38 (1.0)	63 (1.7)
Central laboratory assessments — no./total no. (%)‖		
Serum potassium level		
>5.5 mmol/liter	495/3677 (13.5)	233/3655 (6.4)
>6.0 mmol/liter	86/3677 (2.3)	43/3655 (1.2)

* 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. An adverse event was considered to be serious if it resulted in death, was life-threatening, led to 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. The safety analysis set included all the patients who had undergone randomization, were without critical Good Clinical Practice violations, and had received at least one dose of finerenone or placebo.

† 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.

¶ Shown are any adverse events related to coronavirus disease 2019 (Covid-19), including adverse events that occurred during the treatment period (as defined above) as well as those that occurred after randomization.

‖ Central laboratory assessments after the initiation of the trial regimen were missing for six patients who received finerenone and for three who received placebo.

of steroidal mineralocorticoid receptor antagonists in patients with heart failure and CKD,[31] finerenone may be an attractive therapeutic option in these patients, with the recommended monitoring of serum potassium levels and eGFR (as mandated in both the current trial and the FIDELIO-DKD trial).[32]

The Covid-19 pandemic caused disruption in the latter part of our trial. Despite this situation, only 10 patients were lost to follow-up. However, 85 patients were prospectively excluded from all the analyses because of critical Good Clinical Practice violations. Although our trial included a large population of patients with CKD and type 2 diabetes, the generalizability of the findings may be restricted because few Black patients underwent randomization.

In the FIGARO-DKD trial, finerenone therapy improved cardiovascular outcomes, as compared with placebo, in patients with type 2 diabetes who had stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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