Insight into A review of cardiovascular events with finerenone in ckd and diabetes Occlusions: Existing Findings

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Bachelor of Science

In

CARDIOVASCULAR TECHNOLOGY

Submitted by

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Admission No. :- 19smas1040042

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BONAFIDE CERTIFICATE

This is to certify that project report entitled "**Insight into a review of cardiovascular events with finerenone in ckd and diabetes Occlusions: Existing Findings**" is the bonafide work of "rosemary Richard kimaro" who carried out the project work under my supervision.

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APPROVAL SHEET

This project report entitled "**Insight into a review of cardiovascular events with finerenone in ckd and diabetes Occlusions: Existing Findings**" **by Rosemary Richard Kimaro** is approved for the degree of B.Sc. Cardiovascular Technology.

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Statement of Project Report Preparation

1. Project title: Insight into **a review of cardiovascular events with finerenone in ckd and diabetes** Occlusions: Existing Findings
2. Degree for which the report is submitted: B.Sc. Cardiovascular Technology
3. Project Supervisor: Dr. Saurav Gurjar was referred to for preparing the report.
4. Specifications regarding project format have been closely followed.
5. The content of the project has been organised based on the guidelines.
6. The report has been prepared without resorting to plagiarism.
7. All sources used have been cited appropriately.
8. The report has not been submitted elsewhere for a degree.

(Signature of student)

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ABBREVIATIONS AND ACRONYMS.

CKD = Chronic kidney disease

DKD=DIABETIC KIDNEY DISEASES

A review of cardiovascular events with finerenone in CKD and diabetes:

Abstract

A selective non-steroidal mineralocorticoid receptor antagonist that has favourable results on cardiorenal outcomes in victims with predominantly stage 3 or 4 chronic kidney disease (CKD) with extremely extended albuminuria and type 2 diabetes is known as Finerenone. It is unclear why finerenone is used in patients with type 2 diabetes and a broader range of CKD when it comes to treating them.

Chronic kidney disease and diabetes are common comorbidities that can lead to an increased risk for cardiovascular events, resulting in significant morbidity and mortality. The identification of effective therapeutic interventions to mitigate these risks is of utmost importance.

finerenone is a novel non-steroidal mineralocorticoid receptor antagonist that has been shown to be a promising therapeutic option for individuals with chronic kidney disease (CKD) and diabetes. The purpose of this review is to assess the influence of finerenone on cardiovascular events in victims who have these conditions, with a particular emphasis on its potential as a game-changer in cardiovascular care.

Introduction

Cardiovascular risk related with type 2 diabetes is extended by CKD.1Cardiovascular events risks and new-onset heart failure extend as the urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) transcends 10 and the approximate glomerular filtration rate (eGFR) decreases below 75 ml per minute per 1.73 m2 of body-surface area.1-4 Most victims with CKD are more likely for cardiovascular events than for kidney failure5; therefore it is important to identify and treat CKD so as to decrease the high cardiovascular and heart failure burden of CKD in victims with type 2 diabetes.1,6

Mineralocorticoid receptor over-activation is related with kidney and cardiovascular diseases, which often coexist as cardiorenal disease.7-9 Finerenone enhanced markers of kidney and cardiovascular damage in preclinical models and in victims with CKD in phase 2 studies.9-13 The planned phase 3 program for finerenone comprised 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 Decreasing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial, finerenone enhanced kidney outcomes in victims with predominantly stage 3 or 4 CKD with extremely extended albuminuria and type 2 diabetes, a population with high kidney risk.14,15 In the Finerenone in Decreasing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial, reported here, it was evaluatedwhether treatment with finerenone would lead to lor risks of cardiovascular events and death from cardiovascular causes among victims with either stage 2 to 4 CKD and moderately extended albuminuria or stage 1 or 2 CKD and extremely extended albuminuria — a patient population at high cardiovascular risk that was eliminated from or understudied in the FIDELIO-DKD trial.6

Methods

Traditional design and optical illusion

1. It was conducted a phase three, multi-centre, randomised, double-blind, placebo-controlled, event-based clinical trial. This trial design has been previously published6 and can be found in the trial protocol, which can be found at NEJM.org. The test was designed and supervised by the Executive Committee in collaboration with Bayer (the promoter). A committee that was independent and responsible for patient safety and a planned interim analysis on effectiveness was responsible for overseeing patient safety and conducting one planned efficacy interim analysis. The principles of the Declaration of Helsinkre adhered to during the trial, which follod the principles of the Declaration of Helsinki. All authors re able to access and participate in the interpretation of the analysed data, despite the sponsor conducting the analyses, and all authors having access to and participating in the interpreting of the analysed data. Both the first and second authors wrote the initial manuscript draft, which was revied and edited by all authors. The authors all confirm that the data is complete and accurate; the sponsor and investigators both confirm that the trial adheres to the protocol.

VICTIMS

Eligible victims re 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 results. The trial defined CKD by using one of two criteria. The first set comprised persistent, moderately extended 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 m2 (i.e., stage 2 to 4 CKD). The second set of criteria comprised persistent, extremely extended albuminuria (urinary albumin-to-creatinine ratio, 300 to 5000) and an eGFR of at least 60 ml per minute per 1.73 m2 (i.e., stage 1 or 2 CKD). Patients had to have a serum potassium level of 4.8 mmol per litre or less at the time of testing.

Victims who re 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 m2; 4367 of 5674 victims [77.0%]) re eliminated from the current trial.14 Other key exclusion criteria re symptomatic chronic heart failure with a decreased ejection fraction (i.e., a class 1A recommendation for mineralocorticoid receptor antagonist treatment). A complete list of inclusion and exclusion criteria can be found in the Additional Schedule.

TRIAL PROCEDURES

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.

Fig. In Table 1, there are details about the set-up, screening, and double-blind treatment periods of the S2 trial. To prevent any unpleasant reactions during the period of transition, but still provide enough protection to the patient, the maximum labeled dose of RAS inhibitor therapy was modified. Victims who met the eligibility criteria at the end of the run-in period re randomly assigned in a 1:1 ratio to receive oral finerenone or placebo; victims with an eGFR at the screening visit of 25 to less than 60 ml per minute per 1.73 m2 received an initial dose of 10 mg once daily, and those with an eGFR of at least 60 ml per minute per 1.73 m2 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 litre 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.
Randomisation was conducted and trials re held every month for months 1, 2, and 4, and every 4 months until trial completion. Finerenone or placebo was stopped if the serum potassium level reached 5.5 mmol per liter and resumed when the serum potassium levels decreased to 5.0 mmol per litre or less. Details are contained in the Supplementary Annex and Protocol.

OUTCOMES

The main outcome, analysed using a time-to-event analysis, was a composite of mortality from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation 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 eks, 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 m2 for a period of at least 4 eks. End-stage renal disease has been defined as the beginning of chronic dialysis (over 90 days) or renal transplantation.
Other secondary outcomes (in order of sequential hierarchical testing) re hospitalisation 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 eks (equivalent to a doubling of the serum creatinine level), or death from renal causes. A clinical event committee whose members re unaware of the trial-group assignments independently revied and adjudicated all reported outcome events (see the Supplementary Appendix and the protocol).
Safety analyses required the evaluation of adverse events and conducting central laboratory testing. Adverse events that occurred during the treatment period re 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% por to detect a 20% lor risk of a primary outcome event with finerenone than with placebo, on the basis of 976 victims with an event. Efficacy analyses re done on the entire analysis set (all victims who received randomisation and did not meet the criteria for 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 re geographic region, eGFR category at screening, albuminuria category at screening, and history of cardiovascular disease (see the Supplementary Appendix). Treatment outcomes are expressed in the form of hazard ratios with corresponding confidence intervals based on stratified proportional Cox risk models. Events re counted from randomisation to the end-of-trial visit, and victims 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 take into account the multiplicity of tests, a hierarchical test procedure was carried out. An adjustment was made to the significance level for the final analysis from 5% to 4.9674%, which is the final analysis's new value after the formal interim analysis. Stratified Fine–Gray models re used to calculate the sub distribution hazard ratios, with accounting for the competing risk of death for reasons that re not part of the respective outcomes.5 Safety analyses re performed in the safety analysis set, which comprised all the victims who had undergone randomisation, re without critical Good Clinical Practice violations, and had received at least one dose of finerenone or placebo. Further information on statistical analyses is provided in the supplemental annex and protocol, which includes the statistical analysis plan. The analysis was performed with the use of SAS software version 9.4 (SAS Institute) for analysis.

Results

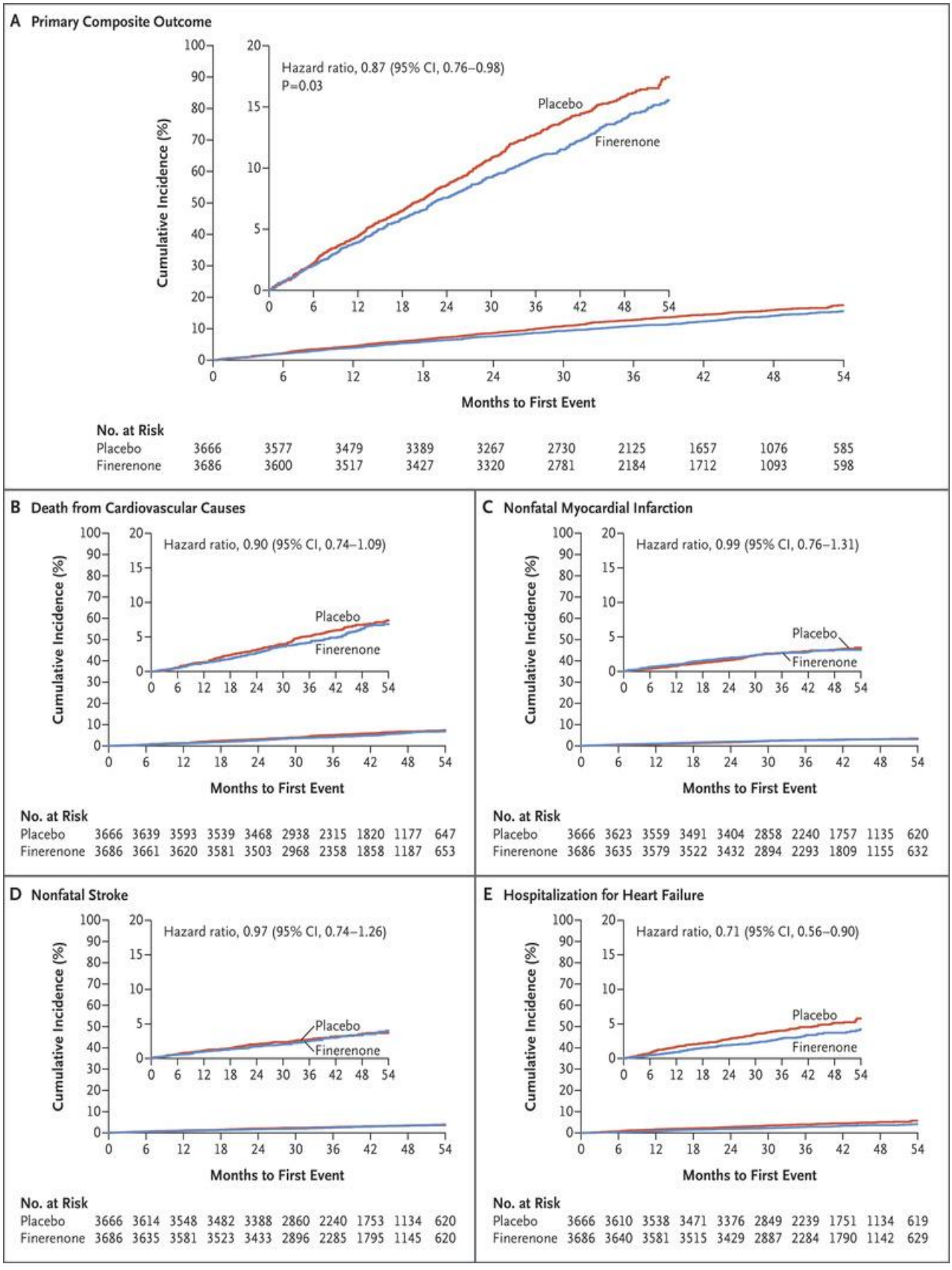
Victims

Table 1.

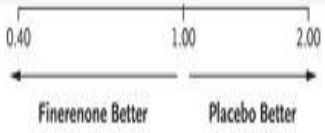
From September 2015 to October 2018, a total of 19,381 victims from 48 countries re screened, while 7437 victims re randomised (Fig. S3). A total of 85 victims re prospectively eliminated from all the analyses because of critical Good Clinical Practice violations (including violations that led to the closure of one site and other violations related to patient misconduct) (see the Supplementary Appendix). Among the 7352 victims comprised in the analyses, the baseline characteristics and medications, including the dose of RAS inhibitor, re balanced between the two groups (Table 1, S1, and S2 and Fig. S4). At baseline, 8.4% of the victims re 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 victims, respectively, started treatment during the trial. Table S3 presents the details of the drugs that re administered following the start of the trial.

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

RESULTS ON PRIMARY COMPOSITE OUTCOME AND COMPONENTS



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)	—



2.Efficacy Outcomes.

The incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for heart failure (the primary composite outcome) was significantly low in the finerenone group than in the placebo group (458 of 3686 victims [12.4%] vs. 519 of 3666 victims [14.2%]; hazard ratio, 0.87; 95% confidence interval [CI], 0.76 to 0.98; P=0.03) (Figures 1A and Figure 2). Each component has its own incidence, and each outcome is depicted in Figures 1B through 1E and Figure 2, with each component representing its own primary outcomes. The incidence of hospitalisation for heart failure was low in the finerenone group than in the placebo group (117 victims [3.2%] vs. 163 [4.4%]; hazard ratio, 0.71; 95% CI, 0.56 to 0.90) (Figures 1E and Figure 2). The number of victims 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.

This is a table with the effect of finerenone therapy on the primary outcome consistent across pre-specified subgroups. S5). Despite the competing risk of non-cardiovascular death, Table S4 shows consistent results after adjusting for it. Similar results re observed in a "in-process" analysis, which included all randomisation events up to 30 days after the final finerenone or placebo dose (Table S5). The number of victims who did not have the primary composite outcome's missing data was low, and a tipping-point analysis supported the robustness of the results (Fig. S6 and Table S6 are two tables in Table S6.

Results from secondary and exploratory investigations

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 eGFR, or death from renal causes (350 victims [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) (Figures 2 and S7A); analyses of the subsequent outcomes are, therefore, exploratory. An analysis which was adjusted according to the concurrent risk of death from non-fatal causes yielded consistent results, as did the analysis "under treatment".

Table 2 displays the occurrences of the components of the first secondary outcome. Terminal nephropathy occurred in 32 patients (0.9%) in the renone fin group and 49 patients (1.3%) in the placebo group (risk ratio 0.64; 95% C0.41-0.995). Figures 2, S7B and S7C illustrate the implications of hospitalisation for all causes and death for all causes. The decreastion 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 re 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 victims (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) (Figures 2 and S7D).

Final signs are fatal in safety scenarios, but safety outcomes are often the result

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.

Safety Outcomes.

An investigator-reported adverse events during the treatment period, resulting in safety issues, re reported as a result. The incidence of adverse reactions was similar across both groups (Table 2, S8 and S9). In the overall population, 31.4% of the victims treated with finerenone experienced a major adverse event, compared to 33.2% of those who received placebo. The impact of acute renal failure was balanced across 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 victims, respectively) or hospitalization (in 0.6% and 0.1%). The group with low incidence of hypokalemia had a higher prevalence of finerenone than the placebo group (1.1% vs. 2.4%), and the incidence of gynecomastia was equal across

Adverse events and serious adverse events of pneumonia re less common with finerenone than with placebo (in 3.9% vs. 5.6% of the victims and in 2.0% vs. 3.1%, respectively), as re adverse events related to Covid-19 (in 2.3% vs. 3.2%). Table S10 presents the results of additional after-the-fact analyses of the differences among groups with respect to the incidence of adverse events of interest.

Finerenone treatment was linked to a greater extent of potassium serum concentration relative to baseline than that observed with placebo. A difference in the groups of 0.16 mmol per litre was observed from the first month and remained largely unchanged thereafter. Finerenone treatment had modest results on blood pressure; the mean difference betweenfinerenone 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 experiment involved two groups of individuals, each with a similar average glycated haemoglobin levels over the period (Fig. S10 and S11).

Conclusion

The current trial found that patients with type 2 diabetes and CKD had a higher risk of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure compared to those in the placebo group. The finerenone group experienced a higher incidence of hospitalization for heart failure, which was the primary reason for this difference. The cardiovascular benefits of finerenone therapy were clinically meaningful and obtained on a background of guideline-directed therapy, including RAS blockade, frequent use of cardiovascular medications, and controlled glycated hemoglobin and blood-pressure levels. The recommended care for victims with CKD and type 2 diabetes evolved, with contemporary guidelines recommending the use of SGLT2 inhibitors or GLP-1 receptor agonists to decrease cardiorenal risk. The study suggested that finerenone therapy may represent an advance in the prevention and management of heart failure, minimizing the considerable health care costs associated with heart failure.

References

1. *Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013;382:339-352.*

2. Fox CS, Matsushita K, Woodward M, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662-1673.

3. Blecker S, Matsushita K, Köttgen A, et al. High-normal albuminuria and risk of heart failure in the community. Am J Kidney Dis 2011;58:47-55.

4. Kottgen A, Russell SD, Loehr LR, et al. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. J Am Soc Nephrol 2007;18:1307-1315.

5. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int 2006;69:375-382.

6. 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;50:345-356.

7. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. Kidney Int 2019;96:302-319.

8. Lother A, Moser M, Bode C, Feldman RD, Hein L. Mineralocorticoids in the heart and vasculature: new insights for old hormones. Annu Rev Pharmacol Toxicol 2015;55:289-312.

9. Agarwal R, Kolkhof P, Bakris G, et al. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. Eur Heart J 2021;42:152-161.

10. Agarwal R, Anker SD, Bakris G, et al. Investigating new treatment opportunities for patients with chronic kidney disease in type 2 diabetes: the role of finerenone. Nephrol Dial Transplant 2020 December 6(Epub ahead of print).

11. Filippatos G, Anker SD, Böhm M, et al. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 2016;37:2105-2114.

12. Pitt B, Kober L, PonikowskP, et al. Safety and tolerability of the novel non-steroidal 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;34:2453-2463.

13. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA 2015;314:884-894.

14. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med 2020;383:2219-2229.

15. Filippatos G, Anker SD, Agarwal R, et al. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes. Circulation 2021;143:540-552.

16. Palmer SC, Mavridis D, Navarese E, et al. Comparative efficacy and safety of blood pressure-loring agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet 2015;385:2047-2056.

17. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436-1446.

18. Wheeler DC, Stefánsson BV, Jongs N, et al. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol 2021;9:22-31.

19. McMurray JJV, Solomon SD, InzucchSE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.

20. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413-1424.

21. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2021;384:129-139.

22. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148-158.

23. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review

and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol 2019;7:776-785.

24. American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44:Suppl 1:S125-S150.

25. American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes-2021. Diabetes Care 2021;44:Suppl 1:S73-S84.

26. Kolkhof P, Hartmann E, Freyberger A, et al. Effects of finerenone combined with empagliflozin in a model of hypertension-induced end-organ damage. Am J Nephrol 2021 June 10 (Epub ahead of print).

27. ZareinB, Blanche P, D'Souza M, et al. Type 2 diabetes mellitus and impact of heart failure on prognosis compared to other cardiovascular diseases: a nationwide study. Circ Cardiovasc Qual Outcomes 2020;13(7):e006260-e006260.

28. Lawson CA, Seidu S, ZaccardF, et al. Outcome trends in people with heart failure, type 2 diabetes mellitus and chronic kidney disease in the UK over tnty years. EClinicalMedicine 2021;32:100739-100739.

29. Cardiovascular disease in patients with CKD. In: United States Renal Data System. USRDS Annual data report. Vol. 1. Chronic kidney disease. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, 2020

30. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 2014;311:2518-2531.

31. Patel RB, Fonarow GC, Greene SJ, et al. Kidney function and outcomes in patients hospitalized with heart failure. J Am Coll Cardiol 2021;78:330-343.

32. Ortiz A, Ferro CJ, Balafa O, et al. Mineralocorticoid receptor antagonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. Nephrol Dial Transplant 2021May 4 (Epub ahead of print).

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