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Finerenone and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Type 2 Diabetes

Running Title: *Filippatos et al.; CV Events with Finerenone in the FIDELIO-DKD Trial*

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Abstract

Background: The FIDELIO-DKD trial evaluated the effect of the nonsteroidal, selective mineralocorticoid receptor antagonist finerenone on kidney and cardiovascular (CV) outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) with optimized renin–angiotensin system blockade. Compared with placebo, finerenone reduced the composite kidney and CV outcomes. We report the effect of finerenone on individual CV outcomes and in patients with and without history of atherosclerotic CV disease (CVD).

Methods: This randomized, double-blind, placebo-controlled trial included patients with T2D and urine albumin-to-creatinine ratio 30–5000 mg/g and an estimated glomerular filtration rate (eGFR) ≥25–<75 mL/min/1.73 m^2, treated with optimized renin–angiotensin system blockade. Patients with a history of heart failure with reduced ejection fraction were excluded. Patients were randomized 1:1 to receive finerenone or placebo. The composite CV outcome included time to CV death, myocardial infarction, stroke, or hospitalization for heart failure. Prespecified CV analyses included analyses of the components of this composite and outcomes according to CVD history at baseline.

Results: Between September 2015 and June 2018, 13,911 patients were screened and 5674 were randomized; 45.9% of patients had CVD at baseline. Over a median follow-up of 2.6 years (interquartile range, 2.0–3.4 years), finerenone reduced the risk of the composite CV outcome compared with placebo (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.75–0.99; P=0.034), with no significant interaction between patients with and without CVD (HR, 0.85; 95% CI, 0.71–1.02 in patients with a history of CVD; HR, 0.86; 95% CI, 0.68–1.08 in patients without a history of CVD; P-value for interaction, 0.85). The incidence of treatment-emergent adverse events was similar between treatment arms, with a low incidence of hyperkalemia-related permanent treatment discontinuation (2.3% with finerenone vs 0.8% with placebo in patients with CVD and 2.2% with finerenone vs 1.0% with placebo in patients without CVD).

Conclusions: Among patients with CKD and T2D, finerenone reduced incidence of the composite CV outcome, with no evidence of differences in treatment effect based on pre-existing CVD status.

Clinical Trial Registration: URL: https://clinicaltrials.gov Unique Identifier: NCT02540993 (Funded by Bayer AG)

Key Words: Chronic kidney disease; type 2 diabetes; mineralocorticoid receptor; cardiovascular disease; finerenone; clinical trial; primary prevention; secondary prevention

Non-standard Abbreviations and Acronyms

AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
Bpm	beats per minute
CAD	coronary artery disease
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CV	cardiovascular
CVD	cardiovascular disease

DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practice
GLP-1RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin
HHF	hospitalization for heart failure
HR	hazard ratio
Hs-CRP	high-sensitivity C-reactive protein
IQR	interquartile range
LS	least-squares
MI	myocardial infarction
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
od	once daily
PAD	peripheral artery disease
PY	patient-year
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SGLT-2	sodium-glucose co-transporter-2
T2D	type 2 diabetes
UACR	urine albumin-to-creatinine ratio

Clinical Perspective

What is new?

- Patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) are an understudied patient population at high risk of cardiovascular (CV) morbidity and mortality. The FIDELIO-DKD trial investigated the effects of finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, on CV and kidney outcomes in this population.
- This prespecified subgroup analysis of the FIDELIO-DKD trial demonstrated that finerenone lowered the risk of CV events in patients with CKD and T2D, with or without a history of CV disease.
- The overall incidence of treatment-emergent adverse events was similar between the finerenone and placebo arms, irrespective of history of CV disease.

What are the clinical implications?

- This study demonstrated the benefit of finerenone for both primary and secondary prevention of CV events in patients with CKD and T2D on top of a background of optimized renin–angiotensin system inhibitor therapy with well-controlled blood pressure and blood glucose levels.
- These data suggest that finerenone has the potential to provide a new treatment option for patients with CKD and T2D to reduce their risk of CV events.
- Overall, finerenone was shown to be well-tolerated by patients in the FIDELIO-DKD trial, with a low incidence of hyperkalemia-related treatment discontinuation.

Introduction

The risk of cardiovascular (CV) disease (CVD), morbidity and mortality increases with type 2 diabetes (T2D), and is further exacerbated by the presence of chronic kidney disease (CKD).[1] Approximately 40% of patients with diabetes have CKD,[2] which exposes them to a three-fold higher risk of CV death versus those with T2D alone.[1] Both albuminuria and a reduced estimated glomerular filtration rate (eGFR) are independent predictors of CV mortality.[3,4] Even with mildly increased albuminuria, CV risk is increased, and as eGFR decreases to below 60 mL/min/1.73 m^2, the risk of heart failure doubles[5] and the probability of developing atherosclerotic CVD increases linearly.[6] Atherosclerotic CVD in patients with CKD and T2D is driven by a combination of traditional CV risk factors (e.g., metabolic factors, hypertension, and history of prior CV events) and nontraditional CV risk factors (e.g., endothelial dysfunction, inflammation, and oxidative stress), with the latter having a greater role as eGFR declines.[7,8] Strategies to protect the kidneys of patients with CKD and T2D may mitigate their risk of CV events.

In preclinical models, overactivation of the mineralocorticoid receptor (MR) is associated with elevated CV risk by driving inflammation and fibrosis, leading to damage to the heart, kidney, and peripheral vasculature.[9-13] Elevated aldosterone can contribute to a variety of conditions including CKD, heart failure, coronary artery disease (CAD), and stroke, and primary aldosteronism is prevalent in patients with resistant hypertension.[14] Increased aldosterone levels can lead to MR overactivation in patients at risk of CKD progression or CVD; other possible mechanisms in this population include increased MR expression, cortisol-mediated MR activation, and ligand-independent MR activation (e.g., due to oxidative stress).[15-18] Finerenone is a novel, nonsteroidal, selective MR antagonist (MRA), which, in an exploratory analysis of a phase IIb trial of patients with worsening chronic heart failure with reduced ejection fraction and

T2D and/or CKD, was associated with a reduction in the incidence of a composite endpoint of all-cause mortality and heart failure outcomes in comparison to the steroidal MRA eplerenone.[19] In the phase III FIDELIO-DKD study, finerenone significantly reduced the risk of kidney and CV events in patients with CKD and T2D.[20] The aim of this study was to further elucidate the effect of finerenone on CV and kidney failure outcomes in patients with CKD and T2D, including in those with and without a history of CVD.

Methods

FIDELIO-DKD was a phase III randomized, double-blind, placebo-controlled, parallel-group, event-driven trial performed in 48 countries and territories in Africa, Asia, Australia, Europe, Latin America, and North America. The trial was performed in accordance with the principles of the Declaration of Helsinki and was approved by the competent authorities and ethics committees at each trial site. All participants provided written informed consent. Anonymized data and materials will be made publicly available in the future.

Study design and participants

The study design has previously been described in detail,[21] and the main results have been reported.[20] Patients aged ≥18 years with a clinical diagnosis of T2D and moderately elevated albuminuria (defined as urine albumin-to-creatinine ratio [UACR] ≥30–<300 mg/g) and an eGFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) ≥25–<60 mL/min/1.73 m^2, and a history of diabetic retinopathy, or severely elevated albuminuria (defined as UACR ≥300–≤5000 mg/g) and an eGFR ≥25–<75 mL/min/1.73 m^2, were included. Patients were required to have been on stable treatment with a maximum tolerated labelled dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor

blocker for at least 4 weeks before the screening visit, and with a serum potassium ≤4.8 mEq/L. Patients were excluded if they had known nondiabetic kidney disease, chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association Class II–IV), a recent history of dialysis for acute kidney failure or a kidney transplant, or uncontrolled hypertension. For the purpose of this analysis, history of CVD was defined as investigator-reported medical history of coronary artery disease (CAD; myocardial infarction [MI], coronary revascularization, or angiography proven stenosis ≥50% in at least one major coronary artery), ischemic stroke, or peripheral artery disease (PAD). The study protocol and full inclusion and exclusion criteria are listed in the Supplemental Material.

Randomization and masking

Patients were randomized based on a computer-generated randomizations schedule stratified by geographical region (North America, Latin America, Europe, Asia, and other), eGFR (25–<45, 45–<60, or ≥60 mL/min/1.73 m^2) and albuminuria categories (UACR 30–<300 or ≥300 mg/g) at screening. All patients and study personnel were masked to treatment allocations (except the independent data monitoring committee). The study drug (finerenone) and placebo tablets were identical in appearance with uniform administration schedule, with packaging and labelling designed to maintain blinding.

Procedures and outcomes

Patients were randomly assigned (1:1) to receive oral finerenone or matching placebo (initial dose of study drug was either 10 or 20 mg once daily [od] based on an eGFR at the screening visit of 25–<60 or ≥60 mL/min/1.73 m^2, respectively). Study drug uptitration from 10 to 20 mg od was encouraged from month 1 onwards, provided the serum potassium was ≤4.8 mEq/L and eGFR was stable; downtitration from 20 to 10 mg od was allowed any time after treatment

initiation. The composite CV outcome included time to first onset of CV death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure (HHF). The composite kidney outcome included time to first onset of kidney failure (defined as chronic dialysis for >90 days, kidney transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed after at least 4 weeks), a sustained ≥40% decrease in eGFR from baseline over at least 4 weeks, or renal death. A clinical event committee blinded to treatment assignment independently reviewed and adjudicated all reported outcome events. The definitions used for clinical outcome events have been published previously.[20] For this analysis, focus will be placed on CV outcomes in the overall population and effects of finerenone in patients with and without a history of CVD, to assess the primary and secondary cardioprotective effects of finerenone, respectively.

Statistical analysis

Efficacy analyses were performed in the full analysis set, i.e. all randomized subjects without critical Good Clinical Practice (GCP) violations. In time-to-event analyses, the superiority of finerenone versus placebo was tested via a stratified log-rank test; stratification factors were region (North America, Latin America, Europe, Asia, and other), eGFR category at screening (25–<45, 45–<60, and ≥60 mL/min/1.73 m^2) and albuminuria category (moderately and severely elevated) at screening. The weighted Bonferroni–Holm procedure was used for the kidney composite and CV composite outcomes in combination with hierarchical testing for the remaining secondary outcomes to account for multiple testing. For the individual components of the composite kidney and CV outcomes, pre-specified exploratory analyses were performed. Treatment effect for time-to-event outcomes is expressed as a HR with corresponding CIs from a stratified Cox regression model. Events were counted from randomization up to the end of study visit, and patients without an event were censored at the date of their last contact with complete

information on all components of the respective outcome. The secondary efficacy outcome of change in UACR from baseline to month 4 was tested with an analysis of covariance (ANCOVA) model adjusting for treatment group, stratification factors, and baseline value. The above-mentioned methods were used to assess outcomes in patients with and without a history of CVD. For further subgroup analyses, HRs and P-values for the subgroup by treatment interaction were derived with stratified Cox proportional hazards models, including treatment, subgroup and a subgroup by treatment interaction term as fixed effects. Safety analyses were performed in the safety analysis set, consisting of all randomized patients without critical GCP violations who took ≥1 dose of study drug. The study is registered with the EU Clinical Trials Register (EudraCT 2015-000990-11) and ClinicalTrials.gov (NCT02540993). Additional details are provided in the Statistical Analysis Plan.

Results

Patients

In the FIDELIO-DKD study, 5734 patients were randomized, 60 patients were prospectively excluded from all analyses due to critical GCP violations at one site or due to patient misconduct (further details are included in the **Supplemental Materials**), and 5674 were included in the full analysis set (**Supplemental Figure I**). The median follow-up was 2.6 years (interquartile range, 2.0–3.4 years). Vital status was known for all but 18 (0.3%) participants at the end of the study. Of the patients included in the analyses, 2605 had a history of CVD at baseline (1303 [46.0%] and 1302 [45.8%] patients treated with finerenone and placebo, respectively).

Baseline characteristics and concomitant medications for patients with and without CVD were balanced between treatment arms (**Table 1**). Compared with patients without a history of

CVD, those with a history of CVD were more likely to be men, white, older, and with a longer duration of diabetes. Mean glycated hemoglobin, body mass index, blood pressure, and eGFR at baseline were similar between all groups; median UACR was slightly higher in patients receiving placebo. As expected, patients with a history of CVD were more likely to be receiving concomitant CV medications including beta blockers, statins, and platelet aggregation inhibitors than those without a history of CVD. The mean daily dose of finerenone or placebo administered was similar, irrespective of CVD history (patients with CVD: finerenone, 15.1 mg/day; placebo, 16.2 mg/day; patients without CVD: finerenone, 15.2 mg/day; placebo, 16.7 mg/day); median follow-up was broadly comparable between patients with or without a history of CVD at baseline (patients with CVD, 2.57 years; patients without CVD, 2.66 years).

Effects on cardiovascular outcomes

The incidence of the composite CV outcome was significantly lower in the finerenone group than in the placebo group (367 [13.0%] and 420 [14.8%] patients, respectively; incidence rates per 100 patient-years, 5.11 and 5.92, respectively; HR, 0.86; 95% CI, 0.75–0.99; P=0.034) (**Figure 1**).[20] In pre-specified exploratory analyses, incidences of death due to CV-related causes were 128 (4.5%) and 150 (5.3%) patients in the finerenone and placebo groups, respectively (HR, 0.86; 95% CI, 0.68–1.08). A total of 70 (2.5%) and 87 (3.1%) patients in the finerenone and placebo groups, respectively, experienced a nonfatal MI (HR, 0.80; 95% CI, 0.58–1.09). Nonfatal stroke occurred in 90 (3.2%) and 87 (3.1%) patients receiving finerenone or placebo, respectively (HR, 1.03; 95% CI, 0.76–1.38). HHF occurred in 139 (4.9%) and 162 (5.7%) patients receiving finerenone or placebo, respectively (HR, 0.86; 95% CI, 0.68–1.08) (**Figure 2**).

The effect of finerenone on the incidence of the composite CV outcome was not modified by a history of prior CVD (P-value for interaction, 0.85) (**Figure 3**). Of the patients with a history of CVD, the composite CV outcome occurred in 231 (17.7%) patients in the finerenone group and 263 (20.2%) patients in the placebo group (incidence rate per 100 patient-years, 7.18 and 8.5, respectively; HR, 0.85; 95% CI, 0.71–1.02). Of the patients without a history of CVD, the composite CV outcome occurred in 136 (8.9%) patients in the finerenone group and 157 (10.2%) patients in the placebo group (incidence rate per 100 patient-years, 3.43 and 3.92, respectively; HR, 0.86; 95% CI, 0.68–1.08). Results were consistent across subgroups of history of MI, ischemic stroke, MI and/or ischemic stroke, CAD, and PAD (**Figure 4**), and across prespecified subgroups including region, baseline eGFR, baseline UACR, baseline systolic blood pressure (SBP; above and below median), sex, age (above and below 65 years) and glycated hemoglobin (above and below median) (**Supplemental Figure II**). The effect of finerenone on the composite CV outcome was also consistent between patients with and without a history of heart failure (P-value for interaction, 0.33). The effects of finerenone on the individual components of the composite CV outcomes were consistent in patients with a history of CVD. In patients without a history of CVD, the effects of finerenone on the individual components were generally consistent, although the point estimates for nonfatal MI and nonfatal stroke diverged (both 95% CIs crossed 1) (**Supplemental Figure III**). In a prespecified 'on-treatment' sensitivity analyses, which included all events from randomization up to 30 days after last dose of study drug, finerenone reduced the risk of the composite CV outcome by 24% (HR, 0.76; 95% CI, 0.62–0.93) in patients with a history of CVD and 21% (HR, 0.79; 95% CI, 0.60–1.03) in those without a history of CVD, versus placebo.

Effect on kidney outcomes in patients with and without prior cardiovascular disease

The composite kidney outcome (kidney failure, a sustained ≥40% decrease in eGFR from baseline, or renal death) was lower with finerenone vs placebo; however, the effects were more pronounced in patients with a history of CVD than those without it (P-value for interaction, 0.016) (**Figure 5**). In patients with a history of CVD, the composite kidney outcome occurred in 200 (15.3%) patients in the finerenone group and 267 (20.5%) patients in the placebo group (incidence rate per 100 patient-years, 6.6 and 9.06, respectively; HR, 0.70; 95% CI, 0.58–0.84). In patients without a history of CVD, the composite kidney outcome occurred in 304 (19.9%) patients in the finerenone group and 333 (21.6%) patients in the placebo group (incidence rate per 100 patient-years, 8.42 and 9.1, respectively; HR, 0.94; 95% CI, 0.81–1.10). No indication of heterogeneity was observed across prespecified subgroups of patients with a history of ischemic stroke, CAD, and PAD (**Supplemental Figure IV**), and in patients with a history of heart failure (P-value for interaction, 0.83). In a prespecified 'on-treatment' sensitivity analyses, finerenone reduced the risk of the composite kidney outcome by 34% (HR, 0.66; 95% CI, 0.54–0.81) in patients with a history of CVD and 11% (HR, 0.89; 95% CI, 0.75–1.06) in those without a history of CVD, versus placebo. The effects of finerenone on another pre-specified composite kidney outcome of time to first onset of kidney failure, sustained ≥57% decrease in eGFR from baseline, or renal death, were consistent in patients with and without a history of CVD (HR, 0.64; 95% CI 0.49–0.83; and HR, 0.87; 95% CI 0.70–1.07, respectively; P-value for interaction, 0.07).

The reduction in UACR from baseline was similar at month 4, irrespective of history of CVD at baseline (patients with CVD: finerenone, –36.1%; placebo, –5.3%; placebo-corrected ratio of least squares [LS]-means under finerenone, 0.675 [95% CI, 0.635–0.717]; patients

without CVD: finerenone, –33.1%; placebo, –4.3%; placebo-corrected ratio of LS-means under finerenone, 0.699 [95% CI, 0.666–0.734]) (**Supplemental Figure V**), and a lower geometric mean for UACR was maintained throughout the duration of the trial with finerenone in both groups (**Figure 6**). The LS-mean change (95% CI) in chronic eGFR slope (from month 4 to the end of study) was smaller in the finerenone group than in the placebo group, with a similar between-group difference in both patients with or without a history of CVD; in patients with a history of CVD the change in eGFR slope was –2.44 (–2.90 to –1.99) with finerenone and –3.91 (–4.38 to –3.44) mL/min/1.73 m^2 with placebo, for a between-group difference of 1.47 (0.82–2.12) mL/min/1.73 m^2 over the duration of the trial; in patients without a history of CVD the change in eGFR slope was –2.84 (–3.24 to –2.44) with finerenone and –4.01 (–4.40 to –3.62) mL/min/1.73 m^2 with placebo, for a between-group difference of 1.17 (0.61–1.73) mL/min/1.73 m^2 over the duration of the trial **(Supplemental Figure VI**).

Safety outcomes and vital signs in patients with and without prior cardiovascular disease

Incidence of any treatment-emergent adverse event (AE) was similar across the finerenone and placebo groups both in patients with and without a history of CVD (**Table 2 and Supplemental Table I**). Study drug-related AEs were more common in patients treated with finerenone in both patients with and without a history of CVD. Serious AEs were less common in patients with a history of CVD treated with finerenone vs placebo (441 [33.9%] and 500 [38.5%] patients, respectively), but similar in patients without a history of CVD (461 [30.2%] and 471 [30.7%] patients, respectively). Incidence of any investigator-reported treatment-emergent hyperkalemia was higher in patients treated with finerenone, irrespective of history of CVD (finerenone, 238 [18.3%] patients with CVD; placebo, 110 [8.5%] patients with CVD; finerenone, 278 [18.2%] patients without CVD; placebo, 145 [9.5%] patients without CVD) (**Supplemental Table II**).

Few patients were hospitalized or discontinued treatment due to hyperkalemia, although these events were more frequent in patients treated with finerenone vs placebo, irrespective of history of CVD (hospitalization due to hyperkalemia: finerenone, 19 [1.5%] patients with CVD; placebo, 3 [0.2%] patients with CVD; finerenone, 21 [1.4%] patients without CVD; placebo, 5 [0.3%] patients without CVD; discontinuation due to hyperkalemia: finerenone, 30 [2.3%] patients with CVD; placebo, 10 [0.8%] patients with CVD; finerenone, 34 [2.2%] patients without CVD; placebo, 15 [1.0%] patients without CVD). Changes in mean serum potassium were higher with finerenone, with a maximal mean difference between the finerenone and placebo treatment groups of approximately 0.2 mEq/L in the first 4 months of treatment, with similar increases irrespective of CVD history (**Supplemental Figure VII**).

A modest reduction in blood pressure was observed with finerenone in both patients with and without a history of CVD. The change in SBP from baseline to month 4 was –3.31 mmHg and +0.85 mmHg in patients with a history of CVD and –3.11 mmHg and +0.53 mmHg in those without a history of CVD with finerenone and placebo, respectively. The corresponding values at month 12 were –1.93 mmHg and +1.17 mmHg in patients with a history of CVD and –2.29 mmHg and +0.63 mmHg in those without a history of CVD with finerenone and placebo, respectively (**Supplemental Figure VIII**). Change in bodyweight was similar between patients in the finerenone and placebo groups throughout the trial. At month 24, there was a mean change in bodyweight of –0.37 kg with finerenone and –0.38 kg with placebo in patients with a history of CVD; whilst in patients without a history of CVD, the corresponding mean change in bodyweight was –0.29 kg with finerenone and –0.28 kg with placebo.

Discussion

In the FIDELIO-DKD study, finerenone had a beneficial effect on the overall risk of CV events, as demonstrated by the reduction in incidence of the CV composite outcome. This benefit was consistent in patients with or without a history of CVD at baseline (including subgroups with prior MI, ischemic stroke, MI and/or ischemic stroke, CAD, and PAD) indicating that finerenone can be used for both primary and secondary CV prevention in patients with CKD and T2D. Patients with CKD and T2D who were treated with finerenone had a lower incidence of the individual components of CV death, nonfatal MI, and HHF compared with placebo; however, incidence of nonfatal stroke was similar. Previous studies have indicated that reductions in stroke outcomes are related to reductions in blood pressure[22]; therefore, the neutral effect of finerenone on nonfatal stroke outcomes may reflect the modest effects of finerenone on systolic blood pressure. Effects on the components of the CV composite outcome were generally consistent across CVD history subgroups; however, the point estimates for nonfatal MI and nonfatal stroke diverged for patients without a history of CVD; due to small number of events for these components in patients without a history of CVD, these could likely be chance findings. The safety profile for finerenone was consistent across both primary and secondary CV prevention groups, with a numerically lower incidence of treatment-emergent serious AEs in patients with a history of CVD treated with finerenone compared with placebo. The incidence of any investigator-reported treatment-emergent hyperkalemia was elevated to a similar degree in both patients with and without a history of CVD, and, therefore, appropriate potassium monitoring with finerenone would be recommended for both patient groups.

Previous evidence for the role of MRAs in nonheart failure populations is limited. This is the first study to demonstrate that finerenone, a novel, nonsteroidal, selective MRA can reduce risk of CV disease in a CKD population where patients with symptomatic heart failure with reduced ejection fraction were excluded, with only a minority of patients having a history of heart failure at baseline (7.7% of all patients). Meta-analysis of patient-level data from two trials with the steroidal MRAs spironolactone and eplerenone demonstrated a trend for a reduction in the risk of CV death in a secondary prevention setting, in a predominantly nonheart failure patient population with low-risk ST-segment elevation MI.[23] Preclinical data indicate greater CV protection with finerenone than the steroidal MRA eplerenone, associated with more potent anti-inflammatory and antifibrotic effects;[24,25] data from our study expand on this evidence to include clinical data demonstrating primary and secondary CV prevention with finerenone.

A similar reduction in UACR at month 4 from baseline and effect on chronic eGFR slope was observed in patients with or without a history of CVD, suggesting a consistent effect of finerenone to improve albuminuria and preserve kidney function in both patient cohorts, compared with placebo. The reasons for observing of a greater magnitude of composite kidney outcome benefit for finerenone in patients with prior CVD are not clear. It should be noted that the treatment benefit with finerenone for the composite kidney outcome was generally consistent across subgroups of patients with or without a history of individual CV conditions including stroke, CAD, and PAD, but not in those with prior MI, where a greater magnitude of effect was seen in patients without a history of MI; and that no significant heterogeneity of response was observed for a second pre-specified composite kidney outcome (**Supplemental Figure IV**). One hypothesis for the greater effect in patients with prior CVD may be a higher proportion of patients with hyperaldosteronism or primary aldosteronism. Patients with primary aldosteronism

have a higher risk of CVD and are at increased risk of CV complications compared with patients with essential hypertension.[26,27] Another reason for the improved outcomes in patients with prior CVD could be that the detrimental impact of MR overactivation might be of particular relevance when the vasculature has been previously damaged by classical CV risk factors including hypertension, obesity, or diabetes. There are substantial preclinical data demonstrating that vascular MRs contribute to the development of CVD either via the endothelial MR, the smooth muscle MR, or both.[13,28-30] In addition, the expression of MR in myeloid cells may play an important role for both inflammation and fibrosis in the kidney and the heart, and knockout of the myeloid MR has been shown to suppress macrophage activity and protect the kidney in animal models.[31] However, to counter these hypotheses, the effect on CV outcomes and UACR change was consistent in both subgroups with and without prior CVD, and moreover the treatment benefit with finerenone for both kidney and CV composite outcomes was consistent across different subgroups of baseline SBP (**Supplemental Figure III**).[20] The ongoing FIGARO-DKD study (NCT02540993), which is investigating the effect on finerenone on reducing CV mortality and morbidity in 7437 patients, a large proportion of whom have less advanced stages of CKD and T2D, will provide greater insights into the mechanisms of kidney and CV benefits observed with finerenone. In the FIGARO-DKD study, 3260 (44.3%) patients have a history of CVD, and furthermore randomization in this trial was stratified by history of CVD.[32]

In FIDELIO-DKD, changes in blood pressure were modest and similar between groups, suggesting a largely nonhemodynamic mechanism of action of finerenone, possibly due to an effect of finerenone improving myocardial, vascular, and kidney inflammation and fibrosis.[15,24,25,31,33,34] However, early separation of the Kaplan–Meier curves for the CV outcomes

suggests that some of the benefits of finerenone may be mediated in part by a natriuretic mechanism counteracting sodium and subsequent volume retention, as well as improvement in endothelial dysfunction and, with more prolonged treatment, vascular stiffness.[25,28,35-37]

FIDELIO-DKD was a large trial investigating the effect of finerenone on heart and kidney outcomes in a broad but predominantly advanced CKD and T2D patient population. However, one limitation of this report is that the history of CVD was determined by review of medical records and was not formally assessed at baseline; therefore, some patients recorded without a history of CVD may have had subclinical CVD (e.g. echocardiographic abnormalities, coronary calcification, and carotid artery stenosis).[38]

In conclusion, finerenone reduced the risk of CV and kidney failure outcomes in patients both with and without a history of CVD. The results suggest that finerenone may represent an important treatment advance to reduce CV morbidity and mortality in patients with CKD and T2D.

Contributors

The Executive Committee designed the study in conjunction with the sponsor. Gerasimos Filippatos wrote the first draft of the report. All authors were involved in data analysis and interpretation, and in drafting and critically revising the report. All authors had access to study results and the first and corresponding author assume responsibility for the integrity and accuracy of the data reported. All authors reviewed and approved the final submitted version of the report. Additional statistical review and assistance was provided by Nicole Mentenich of Bayer AG. Medical writing assistance was provided by Kate Weatherall, PhD, of Chameleon Communications International, and was funded by Bayer AG.

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Disclosures

RA reports personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc., during the conduct of the study; he also reports personal fees and nonfinancial support from Akebia Therapeutics, Janssen, Relypsa, Vifor Pharma, Boehringer Ingelheim, Sanofi, Eli Lilly, AstraZeneca, and Fresenius; he has received personal fees from Ironwood Pharmaceuticals, Merck & Co., Lexicon, and Reata, and nonfinancial support from Otsuka America Pharmaceutical, Opko Pharmaceuticals, and E. R. Squibb & Sons; he is a member of data safety monitoring committees for Amgen, AstraZeneca, and Celgene; a member of steering committees of randomized trials for Akebia Therapeutics, Bayer, Janssen, and Relypsa; a member of adjudication committees for AbbVie, Bayer, Boehringer Ingelheim, and Janssen; he has served as associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate; and he has received research grants from the U.S. Veterans Administration and the National Institutes of Health.

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GF reports lectures fees and /or that he is a committee member of trials and registries sponsored by Bayer, Novartis, Vifor, Medtronic, Servier, Amgen, and Boehringer Ingelheim. He is a Senior Consulting Editor for *JACC Heart Failure,* and he has received research support from the European Union.

BP reports consultant fees for Bayer, AstraZeneca, Sanofi/Lexicon, scPharmaceuticals, SQ Innovation, G3 Pharmaceuticals, Sarfez, Phasebio, Vifor/Relypsa, Cereno Scientific, Ardelyx, KBP Biosciences, Boehringer Ingelheim, Brainstorm Medical, and Tricida; he has stock options for Ardelyx, KBP Biosciences, SQ Innovation, Sarfez, scPharmaceuticals, Cereno Scientific G3 Pharmaceuticals, Vifor/Relypsa, Brainstorm Medical, and Tricida; he also holds a patent for site-specific delivery of eplerenone to the myocardium (US patent #9931412) and a provisional patent for histone-acetylation-modulating agents for the treatment and prevention of organ injury (provisional patent US 63/045,784).

PR reports personal fees from Bayer, during the conduct of the study; he has received research support and personal fees from AstraZeneca and Novo Nordisk, and personal fees from Eli Lilly,

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LMR has no disclosures.

PK is a full-time employee of Bayer AG, Division Pharmaceuticals, Germany. He is the co-inventor of finerenone and holds US and European patents relating to finerenone (US8436180B2 and EP2132206B1)

AJ, PS, and IT are full-time employees of Bayer AG, Division Pharmaceuticals, Germany.

Supplemental Materials

FIDELIO-DKD committees

Inclusion and exclusion criteria

Estimated glomerular filtration rate slope analyses

Critical Good Clinical Practice violations

Supplemental Tables I, II

Supplemental Figures I–VIII

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Table 1. Patient baseline characteristics in patients with and without history of CVD

Characteristic	With history of CVD		Without history of CVD	
	Finerenone (n=1303)	Placebo (n=1302)	Finerenone (n=1530)	Placebo (n=1539)
Age, years, mean (SD)	66.6 (8.2)	67.1 (8.4)	64.4 (9.4)	64.5 (9.6)
Gender, male, n (%)	943 (72.4)	982 (75.4)	1010 (66.0)	1048 (68.1)
Race, n (%)				
White	895 (68.7)	934 (71.7)	882 (57.6)	881 (57.2)
Black/African American	65 (5.0)	54 (4.1)	75 (4.9)	70 (4.5)
Asian	268 (20.6)	247 (19.0)	449 (29.3)	476 (30.9)
Systolic blood pressure, mmHg, mean (SD)	137.6 (14.1)	138.1 (14.2)	138.5 (14.5)	138.0 (14.6)
Diastolic blood pressure, mmHg, mean (SD)	75.4 (9.9)	75.2 (9.6)	76.2 (9.5)	76.4 (9.6)
BMI, kg/m^2, mean (SD),	31.2 (5.8)	31.3 (5.8)	31.1 (6.2)	30.9 (6.2)
Duration of diabetes, years, mean (SD),	17.5 (9.1)	17.3 (8.7)	15.8 (8.4)	15.9 (8.8)
HbA1c, %, mean (SD)	7.73 (1.4)	7.74 (1.4)	7.68 (1.3)	7.69 (1.4)
Serum potassium, mEq/L, mean (SD)	4.36 (0.46)	4.38 (0.47)	4.38 (0.44)	4.37 (0.45)
eGFR, mL/min/1.73 m^2, mean (SD)	44.1 (12.2)	43.8 (12.5)	44.6 (12.8)	44.8 (12.6)
eGFR, mL/min/1.73 m^2, n (%)				
<25	26 (2.0)	36 (2.8)	40 (2.6)	33 (2.1)
25 to <45	702 (53.9)	723 (55.5)	774 (50.6)	782 (50.8)
45 to <60	440 (33.8)	402 (30.9)	532 (34.8)	526 (34.2)
≥60	134 (10.3)	141 (10.8)	184 (12.0)	197 (12.8)
UACR, mg/g, median (± IQR)	820 (443–1578)	872 (459–1696)	842 (438–842)	863 (448–1606)
UACR, mg/g, n (%)				
<30*	4 (0.3)	6 (0.5)	7 (0.5)	6 (0.4)
30–300	171 (13.1)	135 (10.4)	179 (11.7)	200 (13.0)
≥300	1127 (86.5)	1161 (89.2)	1343 (87.8)	1332 (86.5)
Mean waist–hip ratio (SD)	1.00 (0.10)	1.01 (0.13)	0.99 (0.13)	0.99 (0.12)
Waist circumference, cm (SD)	107.4 (14.7)	1085 (15.0)	105.7 (15.2)	105.8 (15.7)
Hs-CRP (mg/L), mean (SD)	4.6 (9.1)	4.7 (7.9)	4.5 (8.7)	4.5 (10.0)
Heart rate, bpm, mean (SD)	70.8 (11.2)	70.7 (11.1)	73.6 (11.6)	73.5 (11.4)
Medical history				
Diabetic retinopathy	606 (46.5)	629 (48.3)	706 (46.1)	722 (46.9)
Diabetic neuropathy	388 (29.8)	386 (29.6)	354 (23.1)	336 (21.8)
Coronary artery bypass graft	112 (8.6)	114 (8.8)	0	0
Percutaneous coronary intervention	151 (11.6)	135 (10.4)	0	0
Hyperlipidemia	605 (46.4)	604 (46.4)	676 (44.2)	676 (43.9)
Atrial fibrillation	148 (11.4)	138 (10.6)	92 (6.0)	83 (5.4)
Heart failure	147 (11.3)	181 (13.9)	48 (3.1)	60 (3.9)
Hypertension	1255 (96.3)	1271 (97.6)	1482 (96.9)	1497 (97.3)

Current smoker, n (%)	167 (12.8)	182 (14.0)	247 (16.1)	210 (13.6)
Medication use at baseline, n (%)				
Angiotensin-converting enzyme inhibitors	464 (35.6)	515 (39.6)	486 (31.8)	477 (31.0)
Angiotensin receptor blockers	838 (64.3)	787 (60.4)	1041 (68.0)	1059 (68.8)
Alpha-blocking agents	357 (27.4)	362 (27.8)	336 (22.0)	353 (22.9)
Beta blockers	848 (65.1)	868 (66.7)	1162 (51.4)	1354 (53.9)
Calcium channel blockers	794 (60.9)	812 (62.4)	979 (64.0)	1000 (65.0)
Diuretics	758 (58.2)	796 (61.1)	819 (53.5)	841 (54.6)
Loop diuretics	400 (30.7)	445 (34.2)	386 (25.2)	388 (25.2)
Thiazide diuretics	291 (22.3)	281 (21.6)	409 (26.7)	374 (24.3)
Statins	1049 (80.5)	1057 (81.2)	1056 (69.0)	1053 (68.4)
Potassium supplements	43 (3.3)	49 (3.8)	71 (3.1)	80 (3.2)
Potassium-lowering agents	33 (2.5)	29 (2.2)	47 (2.1)	53 (2.1)
Platelet aggregation inhibitors	983 (75.4)	988 (75.9)	650 (42.5)	607 (39.4)
Glucose-lowering therapies	1267 (97.2)	1276 (98.0)	1480 (96.7)	1501 (97.5)
Insulin and analogues	885 (67.9)	884 (67.9)	958 (62.6)	910 (59.1)
Metformin	550 (42.2)	542 (41.6)	701 (45.8)	697 (45.3)
Sulfonylureas	279 (21.4)	294 (22.6)	375 (24.5)	379 (24.6)
DPP-4 inhibitors	314 (24.1)	304 (23.3)	450 (29.4)	454 (29.5)
GLP-1RA	77 (5.9)	89 (6.8)	112 (7.3)	116 (7.5)
SGLT-2 inhibitors	50 (3.8)	67 (5.1)	74 (4.8)	68 (4.4)

*23 patients had UACR ≥30 mg/g at screening that fell to <30 mg/g by the baseline UACR measurement
BMI=body mass index. bpm=beats per minute. CV=cardiovascular. CVD=cardiovascular disease. DPP-4=dipeptidyl peptidase-4. eGFR=estimated glomerular filtration rate. GLP-1RA=glucagon-like peptide-1 receptor agonist. HbA1c=glycated hemoglobin. Hs-CRP=high-sensitivity C-reactive protein. IQR=interquartile range. SD=standard deviation. SGLT-2=sodium-glucose co-transporter-2. UACR=urine albumin-to-creatinine ratio.

Table 2. Safety outcomes in patients with and without history of CVD

Treatment-emergent adverse events n patients (%)	With history of CVD		Without history of CVD	
	Finerenone (n=1301)	Placebo (n=1299)	Finerenone (n=1526)	Placebo (n=1532)
Any adverse event	1123 (86.3)	1133 (87.2)	1345 (88.1)	1345 (87.8)
Mild	349 (26.8)	308 (23.7)	473 (31.0)	456 (29.8)
Moderate	536 (41.2)	512 (39.4)	609 (39.9)	645 (42.1)
Severe	238 (18.3)	313 (24.1)	263 (17.2)	244 (15.9)
Any study drug-related AE	287 (22.1)	217 (16.7)	359 (23.5)	232 (15.1)
Any AE leading to discontinuation of study drug	89 (6.8)	69 (5.3)	118 (7.7)	99 (6.5)
Any SAE	441 (33.9)	500 (38.5)	461 (30.2)	471 (30.7)
Any study drug-related SAE	25 (1.9)	17 (1.3)	23 (1.5)	17 (1.1)
Any SAE leading to discontinuation of study drug	29 (2.2)	35 (2.7)	46 (3.0)	43 (2.8)

AE=adverse event. CVD=cardiovascular disease. SAE=serious adverse event.

Figure Legends

Figure 1. Composite cardiovascular outcome.

Reproduced with permission from Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope L, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020. doi: 10.1056/NEJMoa2025845.[20] Copyright Massachusetts Medical Society. Time to first onset of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure. CI=confidence interval. MI=myocardial infarction.

Figure 2. Components of the composite cardiovascular outcome

Panel A shows time to first onset of cardiovascular death. Panel B shows time to first onset of nonfatal MI. Panel C shows time to first onset of nonfatal stroke. Panel D shows time to first onset of hospitalization for heart failure.

CI=confidence interval.

Figure 3. Composite CV outcome in patients with and without history of CVD

Panel A shows the composite CV outcome of time to first onset of CV death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure in patients with a history of CVD at baseline. Panel B shows the composite CV outcome in patients without a history of CVD at baseline. CI=confidence interval. CV=cardiovascular. CVD=cardiovascular disease. MI=myocardial infarction.

Figure 4. Composite CV outcome in subgroups of history of CVD

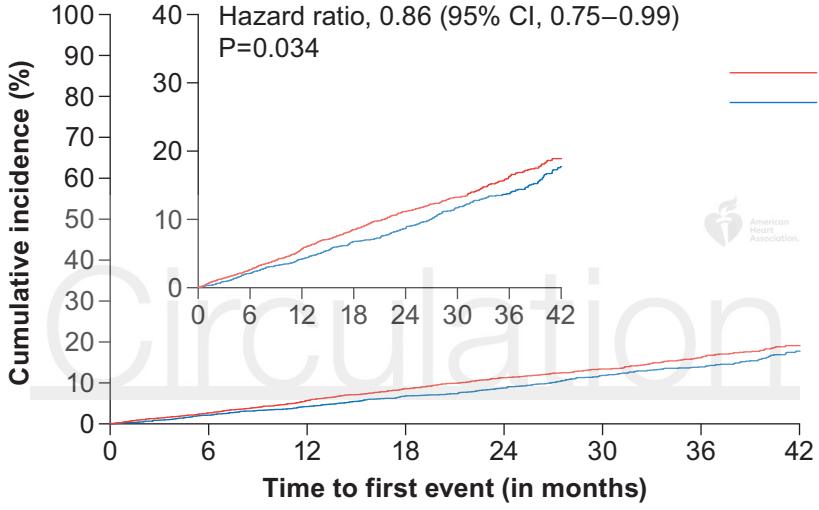
CI=confidence interval. CV= cardiovascular. CVD=cardiovascular disease. MI=myocardial infarction. PY=patient-year.

Figure 5. Composite kidney outcome according to history of CVD

Panel A shows the composite kidney outcome of time to first onset of kidney failure, a sustained ≥40% decrease in eGFR from baseline over at least 4 weeks, or renal death, in patients with a history of CVD at baseline. Panel B shows the primary outcome in patients without a history of CVD at baseline. CI=confidence interval. CVD=cardiovascular disease. eGFR=estimated glomerular filtration rate.

Figure 6. Effects on urine albumin-to-creatinine ratio over time in patients with and without history of CVD

Panel A shows the effects of finerenone and placebo on the UACR in patients with a history of CVD at baseline. Panel B shows effects on UACR in patients without a history of CVD at baseline. Data are least squares mean and 95% confidence interval presented on a logarithmic scale. CVD=cardiovascular disease. UACR=urine albumin-to-creatinine ratio.

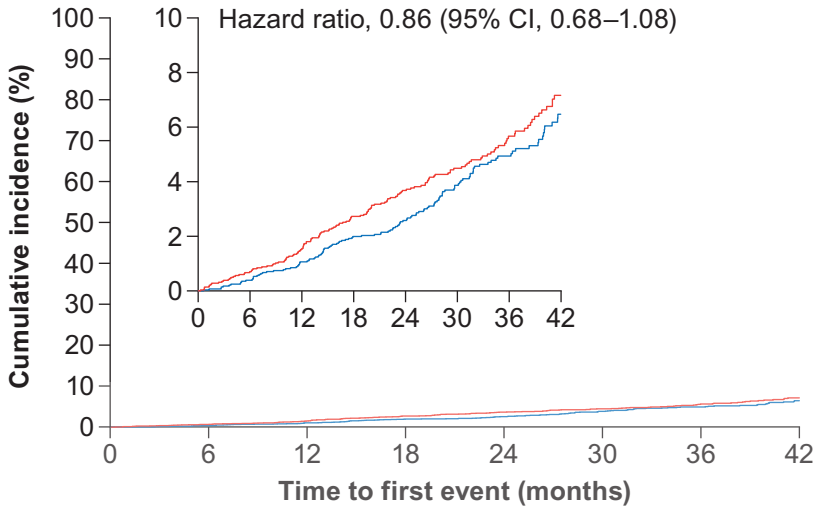


No. at risk

Finerenone	2833	2760	2688	2582	2017	1488	984	537
Placebo	2841	2753	2653	2549	1969	1475	951	536

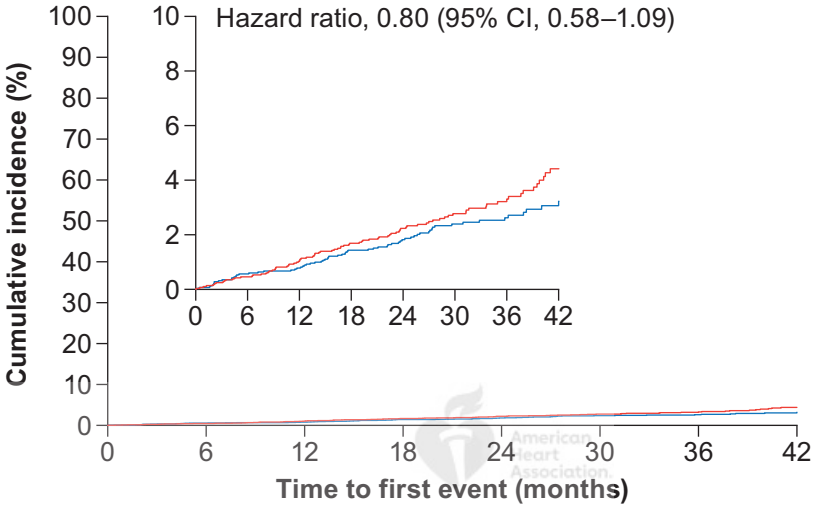
Placebo Finerenone

A CV death



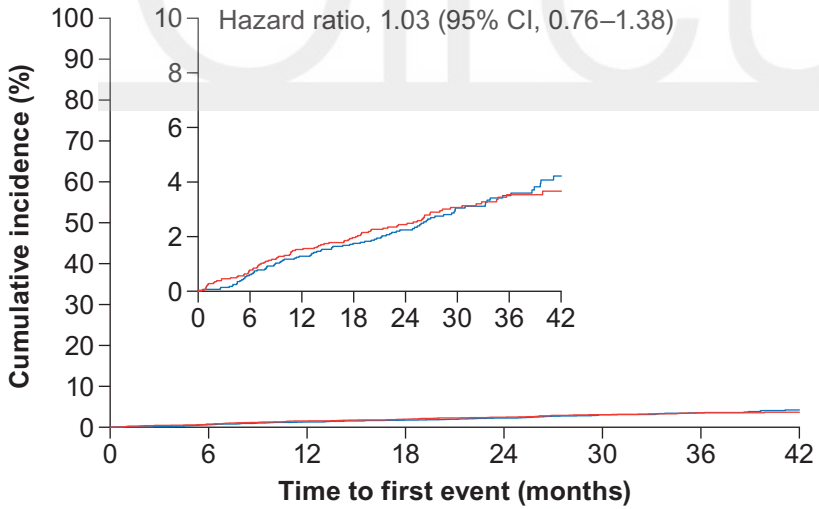
No. at risk								
Finerenone	2833	2811	2777	2717	2152	1624	1089	622
Placebo	2841	2810	2772	2714	2148	1637	1076	627

B Nonfatal myocardial infarction



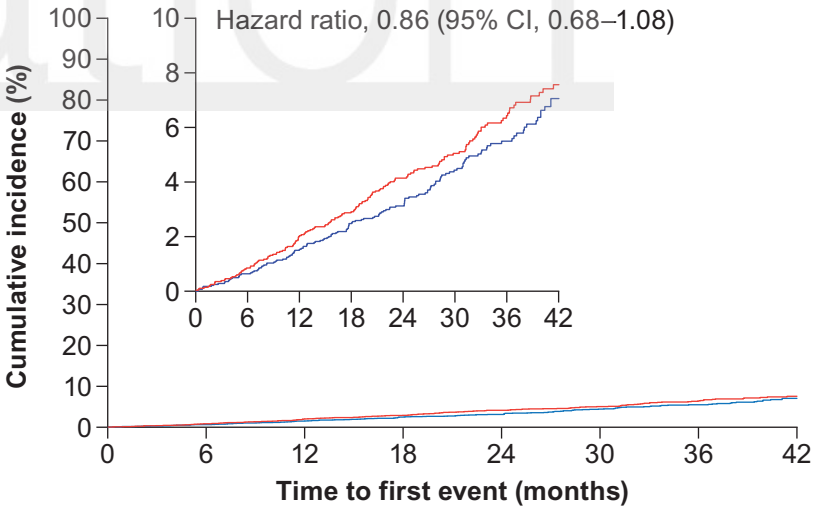
No. at risk								
Finerenone	2833	2792	2755	2675	2110	1578	1057	600
Placebo	2841	2795	2740	2664	2092	1587	1037	593

C Nonfatal stroke

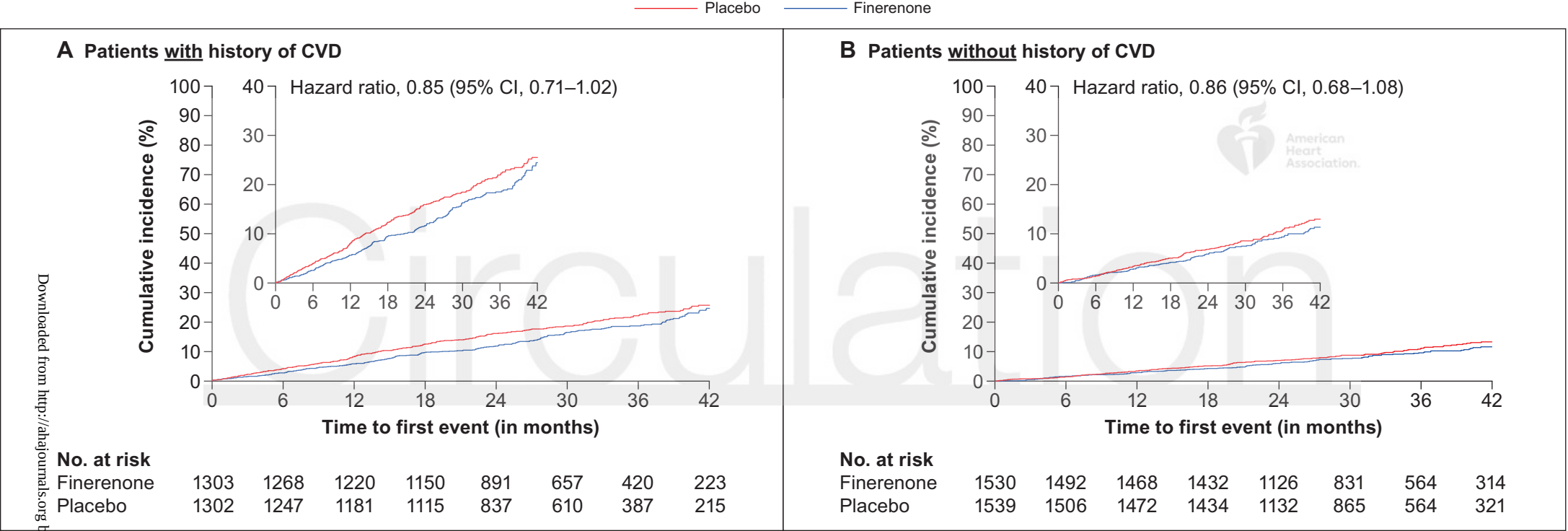


No. at risk								
Finerenone	2833	2791	2742	2671	2107	1577	1051	593
Placebo	2841	2788	2728	2659	2086	1578	1022	591

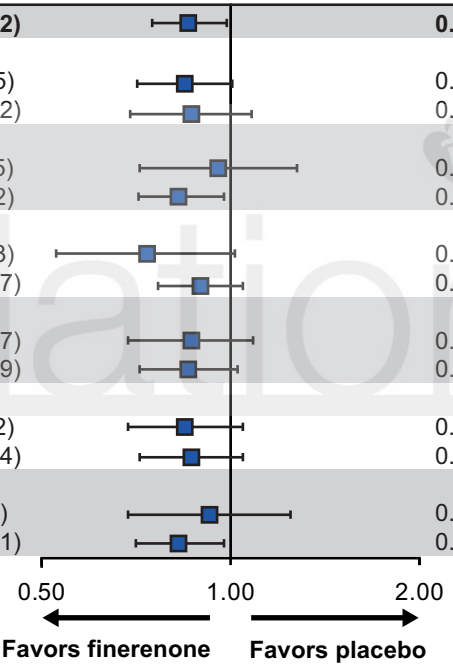
D Hospitalization for heart failure



No. at risk								
Finerenone	2833	2791	2735	2653	2086	1553	1028	570
Placebo	2841	2784	2713	2632	2057	1550	1009	580

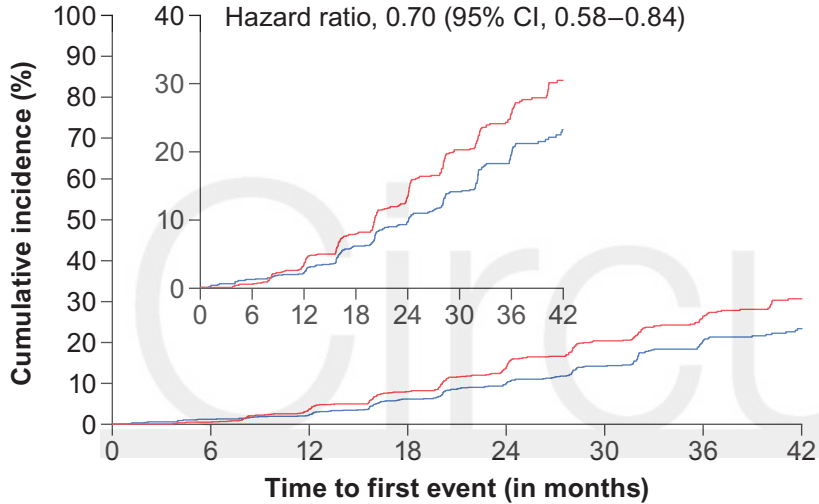


Subgroup	Finerenone n/N (n/100 PYs)	Placebo n/N (n/100 PYs)	Hazard ratio (95% CI)	p value for interaction
All patients	**367/2833 (5.11)**	**420/2841 (5.92)**	**0.86 (0.75–0.99)**	
History of CVD				0.85
Present	231/1303 (7.18)	263/1302 (8.5)	0.85 (0.71–1.02)	
Absent	136/1530 (3.43)	157/1539 (3.92)	0.86 (0.68–1.08)	
History of MI				0.38
Yes	93/378 (10.59)	97/388 (11.05)	0.96 (0.72–1.28)	
No	274/2455 (4.34)	323/2453 (5.2)	0.83 (0.71–0.98)	
History of ischemic stroke				0.28
Yes	65/329 (8.06)	90/360 (10.83)	0.74 (0.53–1.01)	
No	302/2504 (4.73)	330/2481 (5.27)	0.90 (0.77–1.05)	
History of MI and/or ischemic stroke				0.95
Yes	139/653 (8.89)	161/679 (10.27)	0.87 (0.69–1.09)	
No	228/2180 (4.05)	259/2162 (4.69)	0.86 (0.72–1.03)	
History of coronary artery disease				0.87
Yes	159/842 (7.73)	185/860 (9.12)	0.85 (0.69–1.05)	
No	208/1991 (4.05)	235/1981 (4.64)	0.87 (0.72–1.05)	
History of peripheral artery disease				0.53
Yes	90/470 (7.76)	89/453 (8.19)	0.93 (0.69–1.25)	
No	277/2363 (4.6)	331/2388 (5.51)	0.83 (0.71–0.98)	



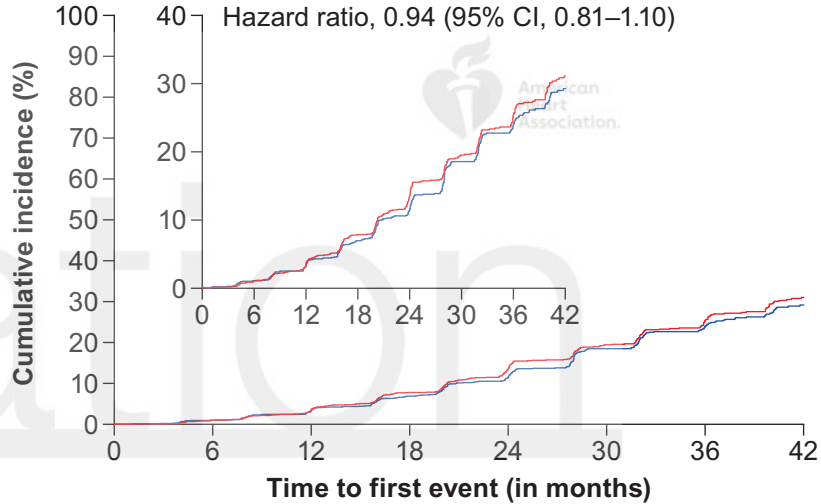
Placebo Finerenone

A **Patients with history of CVD**



No. at risk								
Finerenone	1303	1245	1200	1089	816	589	347	193
Placebo	1302	1242	1166	1072	776	538	331	186

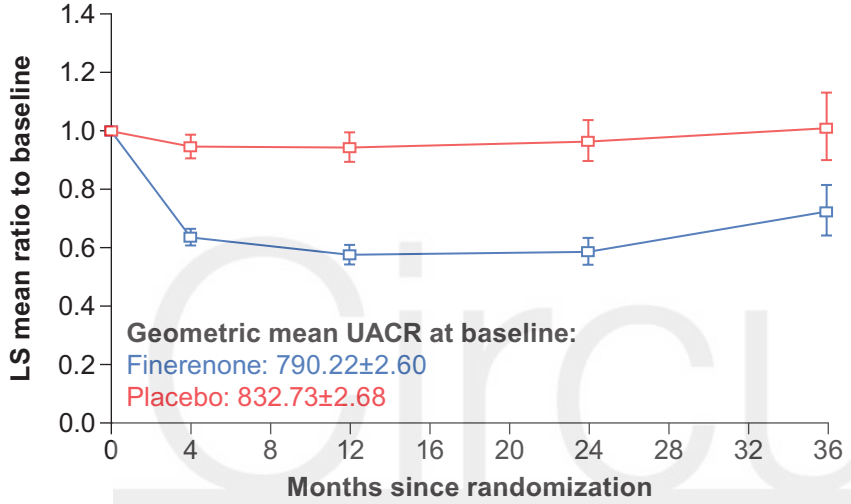
B **Patients without history of CVD**



No. at risk								
Finerenone	1530	1460	1407	1308	992	685	440	248
Placebo	1539	1482	1420	1307	982	710	461	267

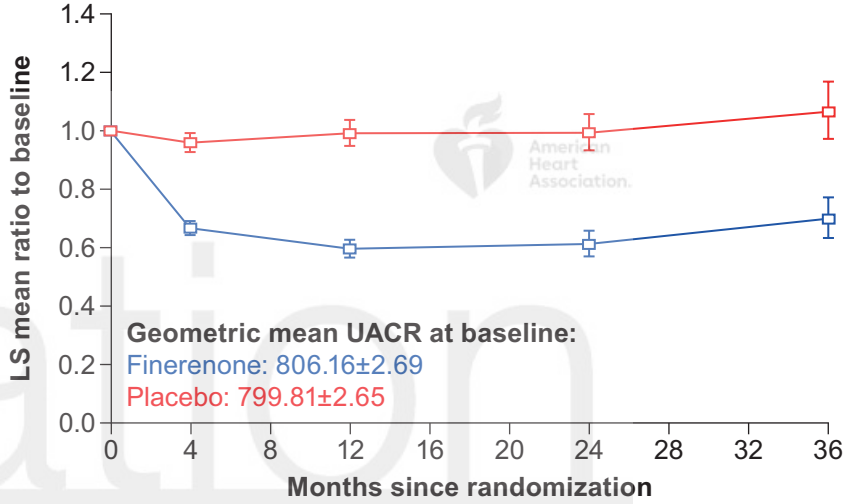
Placebo Finerenone

A **Patients with history of CVD**



No. of patients				
Finerenone	1253	1182	820	371
Placebo	1239	1169	803	350
Mean change in UACR from baseline (%)				
Finerenone	−36.3	−42.3	−41.3	−27.6
Placebo	−5.3	−5.6	−3.5	1.0

B **Patients without history of CVD**



No. of patients				
Finerenone	1472	1400	1021	485
Placebo	1487	1429	1022	484
Mean change in UACR from baseline (%)				
Finerenone	−33.3	−40.4	−38.8	−30.1
Placebo	−4.1	−0.9	−0.7	6.5