

**Effects of canagliflozin versus finerenone on cardiorenal outcomes:
exploratory post-hoc analyses from FIDELIO-DKD compared to reported
CRENENCE results**

Running head: Analysis of a FIDELIO-DKD “CRENENCE-like” subgroup

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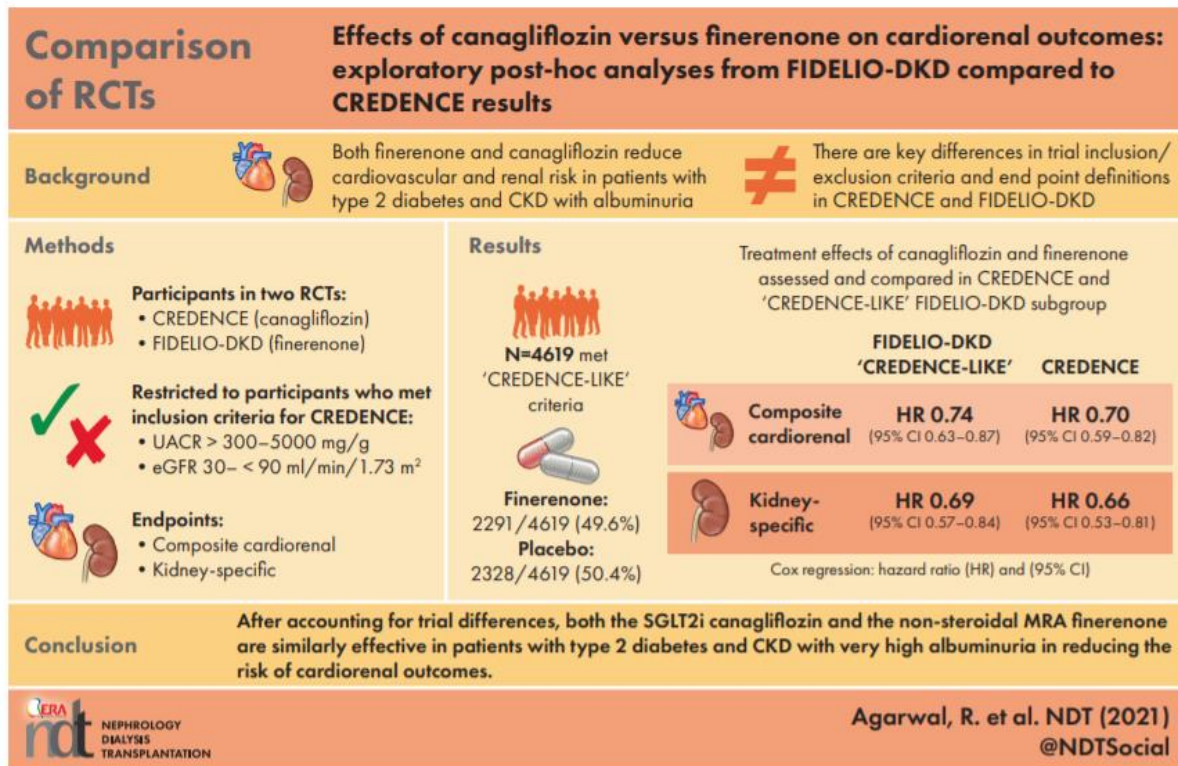
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GRAPHICAL ABSTRACT



ABSTRACT

Background. The nonsteroidal mineralocorticoid receptor antagonist finerenone and the sodium-glucose co-transporter-2 inhibitor canagliflozin reduce cardiorenal risk in albuminuric patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). At first glance, the results of FIDELIO-DKD (ClinicalTrials.gov, NCT02540993) and CREDENCE appear disparate. In FIDELIO-DKD, the primary end-point had a 18% (95% CI 7% to 27%) relative risk reduction; in CREDENCE the primary end-point had a 30% (95% CI 18% to 41%) relative risk reduction. Unlike CREDENCE, FIDELIO-DKD trial included patients with high albuminuria but excluded patients with symptomatic heart failure with reduced ejection fraction. The primary end-point in the FIDELIO-DKD trial was kidney specific and included a sustained decline in eGFR of $\geq 40\%$ from baseline. In contrast, the primary end-point in the CREDENCE trial was included a sustained decline in eGFR of $\geq 57\%$ from baseline and cardiovascular

death. This post-hoc exploratory analysis investigated how differences in trial design—inclusion/exclusion criteria and definition of primary outcomes— influenced observed treatment effects.

Methods. Patients from FIDELIO-DKD who met the CKD inclusion criteria of the CREDENCE study (urine albumin-to-creatinine ratio >300–5000 mg/g and an estimated glomerular filtration rate of 30–<90 ml/min/1.73 m² at screening) were included in this analysis. The primary end point was a cardiorenal composite (cardiovascular death, kidney failure, estimated glomerular filtration rate decrease of ≥57% sustained for ≥4 weeks or renal death). Patients with symptomatic heart failure with reduced ejection fraction were excluded from FIDELIO-DKD. Therefore, in a sensitivity analysis, we further adjusted for the baseline prevalence of heart failure.

Results. Of 4619/5674 (81.4%) patients who met the subgroup inclusion criteria, 49.6% were treated with finerenone and 50.4% received placebo. The rate of the cardiorenal composite end point was 43.9/1000 patient years with finerenone compared to 59.5/1000 patient years with placebo. The relative risk was significantly reduced by 26% with finerenone versus placebo (hazard ratio 0.74, 95% CI 0.63–0.87). In CREDENCE, the rate of the cardiorenal composite end point was 43.2/1000 patient years with canagliflozin compared to 61.2/1000 patient years with placebo; a 30% risk reduction was observed with canagliflozin (hazard ratio 0.70, 95% CI 0.59–0.82).

Conclusions. This analysis highlights the pitfalls of direct comparisons between trials. When key differences in trial design are considered, FIDELIO-DKD and CREDENCE demonstrate cardiorenal benefits of a similar magnitude.

Keywords: canagliflozin, cardiorenal, CREDENCE, FIDELIO-DKD, finerenone

KEY LEARNING POINTS

What is already known about this subject?

- Both the novel nonsteroidal mineralocorticoid receptor antagonist finerenone and the sodium-glucose co-transporter-2 inhibitor (SGLT-2i) canagliflozin have been shown to benefits for CV and kidney organ protection in albuminuric patients with type 2 diabetes and chronic kidney disease (CKD).
- At first glance the efficacy of finerenone in FIDELIO-DKD appears inferior to the efficacy with canagliflozin in CREDENCE.
- The primary end-point had a 18% (95% CI 7% to 27%) relative risk reduction in FIDELIO-DKD; in the primary end-point had a 30% (95% CI 18% to 41%) relative risk reduction in CREDENCE.

What this study adds?

- There are risks of directly comparing two trials even when conducted in the same disease state
- When key differences in trial inclusion/exclusion criteria and end point definitions are accounted for, both FIDELIO-DKD and CREDENCE demonstrate cardiorenal benefits of a similar magnitude.

What impact this may have on practice or policy?

- Both the SGLT2i canagliflozin and the non-steroidal MRA finerenone are similarly effective in patients with type 2 diabetes and CKD and very high albuminuria in reducing the risk of cardiorenal outcomes.

INTRODUCTION

Patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) are at increased risk of cardiovascular (CV) events and CKD progression.¹ Although there was a hiatus of treatment advances for CKD in T2D since the Reduction of Endpoints

in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT) published two decades ago,^{2, 3} in recent years, both finerenone and sodium-glucose co-transporter-2 inhibitors (SGLT-2is) have shown benefits for CV and kidney organ protection in this albuminuric patient population.^{1, 4-6}

Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) investigated the selective, nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone in patients with CKD and T2D and demonstrated a significant reduction in the risk of kidney and CV outcomes compared with placebo.¹ Two SGLT-2i kidney outcome trials (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation [CREDESCENCE] and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease [DAPA-CKD]) have reported positive cardiorenal outcomes for patients with CKD and T2D, and also in patients with CKD without T2D in DAPA-CKD.^{4, 6} In the CREDESCENCE, DAPA-CKD and FIDELIO-DKD trials, the relative risks of the primary outcomes were reduced by 30% (95% CI 18% to 41%), 39% (95% CI 28% to 49%) and 18% (95% CI 7% to 27%), respectively.^{1, 4, 5} At first glance, finerenone may be perceived to have a smaller benefit on kidney outcomes compared with the SGLT-2is canagliflozin and dapagliflozin.⁷ However, because of significant differences in the trial designs, primary end points (e.g. sustained change from baseline in eGFR of $\geq 40\%$, $\geq 50\%$, or $\geq 57\%$ in FIDELIO-DKD, DAPA-CKD, and CREDESCENCE, respectively) and patient populations, unadjusted comparisons among the trials are prone to biases.^{1, 4-6}

The objective of this analysis is to facilitate a more nuanced comparison of the treatment effect of finerenone with that of canagliflozin by adjusting for key differences in trial design. These include the use of a cardiorenal composite end point equivalent to that used in the CREDENCE trial, restricting the analysis to a subgroup of patients from FIDELIO-DKD who met the CKD inclusion criteria of CREDENCE, and lastly, an adjustment for differences in baseline heart failure (HF) incidence. We included the adjustment for HF incidence because prior studies have shown that HF in patients with CKD can affect cardiorenal outcomes and that these patients benefit from treatment with an SGLT-2i or an MRA.⁸⁻¹² Similar comparisons cannot be made between FIDELIO-DKD and DAPA-CKD because DAPA-CKD included patients without diabetes who were not included in the FIDELIO-DKD, and the primary end point in DAPA-CKD was a $\geq 50\%$ reduction in estimated glomerular filtration rate (eGFR), which was not an adjudicated event in FIDELIO-DKD.^{1,6}

MATERIALS AND METHODS

There were several important differences between the study designs of the FIDELIO-DKD and CREDENCE trials (Supplemental Figure S1). First, a kidney-specific composite end point (time to kidney failure, sustained $\geq 40\%$ decrease in eGFR from baseline or renal death) was the primary end point in FIDELIO-DKD, whereas a cardiorenal composite end point (end-stage kidney disease [ESKD], $\geq 57\%$ decrease in eGFR or death from renal and CV causes) was used in CREDENCE. Second, the inclusion criteria for eGFR in the FIDELIO-DKD trial was $25 < \text{eGFR} < 75 \text{ ml/min/1.73 m}^2$ versus $30 < \text{eGFR} < 90 \text{ ml/min/1.73 m}^2$ in CREDENCE.⁴ Third, the urine albumin-to-creatinine ratio (UACR) levels were $30\text{--}5000 \text{ mg/g}$ in FIDELIO-DKD compared with $>300\text{--}5000 \text{ mg/g}$ in CREDENCE. Fourth, FIDELIO-DKD excluded patients with symptomatic HF

with reduced ejection fraction, whereas CREDENCE excluded patients with HF only if they were treated with an MRA (in CREDENCE, MRA use was an exclusion criterion, although postbaseline use was permitted if deemed medically necessary).

The present analysis reports outcomes and safety data in a “CREDENCE-like” subgroup of patients from FIDELIO-DKD who had UACR >300–5000 mg/g and eGFR 30–<75 ml/min/1.73 m² at screening (patients with an eGFR >75 ml/min/1.73 m² were not eligible for FIDELIO-DKD), and accounts for differences in the baseline incidence of HF.

Study design and patient population

The design of the phase 3, randomised, double-blind, placebo-controlled, multicentre FIDELIO-DKD study and the results of the primary analysis (including the clinical study protocol) have been published previously.^{1, 13} 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. Briefly, adults (≥18 years of age) with CKD and T2D who were receiving optimised RAS inhibitor therapy, with serum potassium ≤4.8 mmol/l and without symptomatic HF with reduced ejection fraction (New York Heart Association class II–IV), were eligible. The FIDELIO-DKD study comprised a run-in period (during which RAS inhibitor therapy was optimised for 4–16 weeks), a screening period and a double-blind treatment period. Patients were randomised 1:1 to receive oral finerenone or matching placebo once daily. The starting dose of finerenone was 20 mg in participants with an eGFR ≥60 ml/min/1.73 m² and 10 mg in participants with an eGFR of 25–<60 ml/min/1.73 m², increasing to 20 mg after 1

month if serum potassium remained ≤ 4.8 mmol/l and eGFR was stable. Finerenone down-titration from 20 mg to 10 mg due to safety concerns was permitted at any time.

End points

The primary end point of interest for this FIDELIO-DKD “CREDENCE-like” subgroup analysis was a composite cardiorenal end point of time to first occurrence of CV death, kidney failure (defined as ESKD [the initiation of long-term dialysis for ≥ 90 days, or kidney transplantation] or an eGFR < 15 ml/min/1.73 m² sustained for ≥ 4 weeks), eGFR decrease of $\geq 57\%$ sustained for ≥ 4 weeks, or renal death. Other end points included a kidney-specific composite end point of time to onset of kidney failure, a sustained decrease of eGFR $\geq 57\%$ or renal death, a composite CV end point of CV death or hospitalisation for HF, CV death, death from any cause, and change in UACR from baseline over time. Urinalysis was performed centrally during run-in and screening visits as well as at baseline, month 4, month 12, and every 12 months thereafter. Central laboratory values, including serum potassium and serum creatinine, were obtained at all study visits.

Statistical analyses

A stratified log-rank test was used to analyse the time-to-event superiority of finerenone versus placebo. The individual components of the cardiorenal end points were analysed in post hoc exploratory analyses from patient-level data in the FIDELIO-DKD trial. Analysis included descriptive statistics and a statistical test for significance. Treatment effects for time-to-event end points are expressed as hazard

ratios (HRs) with corresponding 95% confidence intervals (CIs) from a stratified Cox regression model. Events were counted from randomisation to the end-of-study visit; participants without an event were censored at the time of their last contact when complete information on all components of the end point under investigation were available. Subgroup analyses for the primary and secondary efficacy variables included descriptive statistics and a statistical test for interaction. On-treatment analysis refers to analysis of events that occurred within 30 days of last study drug intake.

To investigate the effect of finerenone in a population with more patients with HF at baseline, in a sensitivity analysis we inflated the baseline HF population. The population of patients was constructed by drawing 100 random bootstrap samples with replacement containing the desired inflated number of patients with HF from the existing baseline HF population. The remaining population was randomly sampled in a similar fashion from the patients without HF at baseline. The 100 randomly bootstrapped sampled data sets were analysed using stratified Cox proportional hazards regression and estimates combined using standard bootstrap combination assumptions.

Change in UACR was analysed using a repeated measures mixed-model approach that incorporated additional variables to account for effects on UACR. Assuming an unstructured covariance matrix, the model was adjusted for treatment group, stratification factors (region, albuminuria category at screening and eGFR category at screening), visit, interaction between treatment group and visit, log-transformed baseline value and interaction between the log-transformed baseline value and visit.

RESULTS

Patients

Between September 2015 and June 2018, 13 911 patients from 48 countries were screened for eligibility to participate in FIDELIO-DKD; 5674 of whom were randomised and included in the full analysis set.¹ A total of 4619/5674 patients in FIDELIO-DKD met the “CREDESCENCE-like” criteria (with a UACR >300–5000 mg/g and an eGFR 30–<75 ml/min/1.73 m² at screening) and were included in this analysis. Comparison of the baseline demographics from the FIDELIO-DKD subgroup and the CREDESCENCE group were broadly similar with regard to the duration of diabetes, median UACR, percentage of patients who were Black/African American or White, and RAS inhibitor use (Table 1). Notable differences in the FIDELIO-DKD “CREDESCENCE-like” subgroup compared with the CREDESCENCE group included slightly older patients, lower systolic blood pressure, lower glycosylated haemoglobin, lower mean eGFR levels (including fewer patients with eGFR ≥60 ml/min/1.73 m²), fewer patients with a history of HF, more frequent use of CV medications and a greater proportion of Asian patients. Of the 4619 (81.4%) patients in the FIDELIO-DKD subgroup included in this analysis, 2291/4619 (49.6%) were treated with finerenone and 2328/4619 (50.4%) were treated with placebo, and baseline characteristics were balanced between treatment groups (Supplemental Table S1). The median follow-up was 2.6 years. A total of 1273 (27.6%) patients prematurely discontinued treatment in the study, and the number of discontinuations was similar between treatment arms. Of the 4608/4619 patients assessed, mean treatment adherence was high at 92.0%.

Efficacy

Cardiorenal composite end point

In the FIDELIO-DKD “CREDESCENCE-like” subgroup (with UACR >300–5000 mg/g and eGFR 30–<75 ml/min/1.73 m² at baseline), the risk of cardiorenal composite end point of time to first occurrence of CV death, kidney failure, eGFR decrease of ≥57% sustained for ≥4 weeks or renal death was significantly reduced by 26% with finerenone versus placebo (HR 0.74, 95% CI 0.63–0.87, *P* = 0.0003; Figures 1 and 2). In the overall FIDELIO-DKD population (*N* = 5674, i.e., before selecting patients that meet the “CREDESCENCE-like” inclusion criteria), the risk of the same cardiorenal composite end point was 22% lower with finerenone versus placebo (HR 0.78, 95% CI 0.67–0.90, *P* = 0.0005).

Among patients who did not meet the “CREDESCENCE-like” inclusion criteria, the composite cardiorenal “CREDESCENCE-like” outcome occurred in 99 of 542 patients who were assigned to finerenone and 104 of 513 patients who were assigned to placebo (hazard ratio 0.86 (95% CI 0.65 – 1.13)). In contrast, among patients who met the “CREDESCENCE-like” inclusion criteria, the composite cardiorenal outcome occurred in 241 of 2291 patients who were assigned to finerenone and 330 of 2328 patients who were assigned to placebo (hazard ratio 0.74 (95% CI 0.63 – 0.87)). The test of heterogeneity was not significant (*p*=0.37).

In the FIDELIO-DKD “CREDESCENCE-like” subgroup, adjustment of the baseline HF incidence from 7.6% to 14.8% of the overall population resulted in a 28% lower risk of the cardiorenal composite end point with finerenone versus placebo (HR 0.72, 95% CI 0.61–0.86, Figure 2). For comparison, in the CREDESCENCE study, canagliflozin reduced the risk of the cardiorenal composite end point by 30% compared with placebo (HR 0.70, 95% CI 0.59–0.82, *P* = 0.00001; Figure 2).⁴

The incidences of each of the components of the cardiorenal composite end point were lower with finerenone than placebo (Figure 3). Notably, the risk of ESKD was 28% lower with finerenone versus placebo (HR 0.72, 95% CI 0.53–0.98, $P=0.04$). Overall, the relative risk of the cardiorenal composite end point in the placebo groups of the FIDELIO-DKD subgroup and CREDENCE study were similar, with event rates of 59.5 and 61.2 per 1000 patient-years, as were incidences of eGFR <15 ml/min/1.73 m² (23.4 vs. 22.2 per 1000 patient-years) and ESKD (16.2 vs. 17.7 per 1000 patient-years) (Figure S3).⁴ However, whereas the incidence rate of sustained eGFR decline $\geq 57\%$ from baseline was larger in the placebo arm of the FIDELIO-DKD subgroup than the CREDENCE population (37.2 vs. 33.8 patients with event per 1000 patient-years), the CV death incidence rate was lower with placebo in FIDELIO-DKD than in CREDENCE (18.6 vs. 24.4 patients with event per 1000 patient-years).⁴

The efficacy of finerenone compared with placebo in the FIDELIO-DKD “CREDENCE-like” population was consistent for the cardiorenal composite end point for several key subgroups (Supplemental Figure S2) and in an “on-treatment” sensitivity analysis; details are included in the Supplemental Material.

Kidney-specific end points

A kidney-specific composite end point of kidney failure of time to onset of kidney failure, a sustained decrease of eGFR $\geq 57\%$ or renal death was significantly improved by 31% with finerenone versus placebo in the subgroup of “CREDENCE-like” patients (HR 0.69, 95% CI 0.57–0.84, $P=0.0002$) (Figure 3). In the CREDENCE

study, canagliflozin reduced the risk of kidney composite end point of ESKD, doubling of the creatinine level (equivalent to sustained decrease of eGFR $\geq 57\%$), or renal death by 34% compared with placebo (HR 0.66, 95% CI 0.53–0.81, $P < 0.001$; Figure 3).⁴

In the FIDELIO-DKD “CREDESCENCE-like” subgroup, the efficacy of finerenone compared with placebo was consistent for the kidney-specific composite end points for several subgroups (Figure 3) and in an “on-treatment” sensitivity analysis; details are included in the Supplemental Material. Improvements in albuminuria were similar between the 2 trials (see Supplemental Material).

Other efficacy end points

Other end points, including composite CV end point of time to first occurrence of CV death or hospitalisation for HF and death from any cause, trended toward favouring finerenone, but did not meet statistical significance (HR 0.86, 95% CI 0.71–1.05 and HR 0.88, 95% CI 0.72–1.08, respectively).

Safety

The overall numbers of adverse events and serious adverse events were similar with finerenone versus placebo (Supplemental Table S2). Consistent with the mechanism of action of finerenone, hyperkalaemia events were increased in patients treated with finerenone versus placebo (15.3% vs. 7.6%). In CREDESCENCE, hyperkalaemia events were less frequent in patients treated with canagliflozin versus placebo (6.9% vs. 8.2%).⁴

The incidence of acute kidney injury (AKI) in the two trials were similar and were not altered by finerenone or canagliflozin.

In the FIDELIO-DKD trial with “CREDESCENCE-like” inclusion criteria, those assigned to finerenone had 104 AKI events (4.5%) reported in 2288 patients, 21.4 events/1000 patient-years compared to those assigned to placebo who had 106 AKI events (4.6%) in 2320 patients, 21.2 events/1000 patient-years. By comparison, in the CREDESCENCE trial, those assigned to canagliflozin had 86 AKI events (3.9%) reported in 2200 patients, 16.9 events/1000 patient-years compared to those assigned to placebo who had 98 AKI events (4.5%) in 2197 patients, 20.0 events/1000 patient-years. ⁴

The incidences of amputation, fracture, and diabetic ketoacidosis were balanced and low in both the finerenone and placebo treatment groups (Supplemental Table 2).

DISCUSSION

Our study demonstrates the central importance of considering trial eligibility criteria and end point definitions on the effect size of therapies approved for the management of CKD in T2D. Three progressive adjustments—inclusion criteria, end-point, and a key exclusion criteria—provided effect size estimates that were strikingly similar between the trials. The joint consideration of the CREDESCENCE trial inclusion criteria (UACR >300–5000 mg/g and eGFR >30–<90 ml/min/1.73 m² at screening) and CREDESCENCE-like endpoint (the cardiorenal composite end point of time to first occurrence of CV death, kidney failure, eGFR decrease of ≥57% sustained for ≥4 weeks, or renal death) demonstrated that compared to placebo, finerenone demonstrated clinical efficacy. Furthermore, the relative risk reduction with

finerenone was larger in this subgroup population than in the overall patient population.

In the present FIDELIO-DKD “CREDESCENCE-like” subgroup, there was a 26% reduction in risk of the cardiorenal composite end point with finerenone compared with placebo. In CREDESCENCE, a 30% risk reduction in the same composite end point was observed with canagliflozin compared with placebo. Because FIDELIO-DKD excluded patients with symptomatic HF with reduced ejection fraction whereas CREDESCENCE excluded patients with HF treated with an MRA, the proportion of patients with HF was lower in the FIDELIO-DKD subgroup studied here than in CREDESCENCE (7.6% vs. 14.8%).^{1, 4} This imbalance is noteworthy because patients with HF are at much greater risk of experiencing CV death¹⁴; indeed, we saw a larger CV death event rate in the placebo arm of this FIDELIO-DKD “CREDESCENCE-like” subgroup than in CREDESCENCE (18.6 vs. 24.4 patients with event per 1000 patient-years, respectively). Therefore, we adjusted the proportion of patients with history of HF; after this modification, the risk of the cardiorenal composite end point was reduced by 28% with finerenone versus placebo in the FIDELIO-DKD subgroup studied here. The results of this analysis highlight the pitfalls of direct comparisons between trials with differing patient eligibility criteria, and how subtle differences in inclusion eligibility criteria, especially HF, can lead to meaningful variations in outcomes.

Comparisons between the FIDELIO-DKD “CREDESCENCE-like” subgroup studied here, and the CREDESCENCE population reveal differences in patient baseline characteristics (Supplemental Table S1), which are important to be aware of. Because FIDELIO-

DKD did not include patients with an eGFR ≥ 75 ml/min/1.73 m², patients in the FIDELIO-DKD subgroup had a lower mean eGFR (and fewer patients had a baseline eGFR ≥ 60 ml/min/1.73 m²) than in CREDENCE. Moreover, compared with CREDENCE, the FIDELIO-DKD “CREDENCE-like” subgroup included fewer patients with nephrotic-range severely elevated albuminuria. Together, these differences mean that the FIDELIO-DKD subgroup represents a more advanced CKD stage, with less albuminuria, so their kidney damage may potentially be more difficult to repair. The length of the period allowed for optimisation of medical therapy was different between the trials, which may, in part, account for lower systolic blood pressure (138 mm Hg vs. 140 mm Hg) and glycated haemoglobin levels (7.7% vs. 8.3%) between the FIDELIO-DKD subgroup and the CREDENCE population, as well as more frequent use of CV medications in the FIDELIO-DKD subgroup. Moreover, FIDELIO-DKD allowed combination therapy with finerenone and an SGLT-2i (with 4.6% of patients receiving an SGLT-2i at baseline), whereas combination therapy with an SGLT-2i and a steroidal MRA was limited in CREDENCE (as baseline MRA use was prohibited). Furthermore, in FIDELIO-DKD, the protocol allowed for treatment interruptions, and the discontinuation rate was greater than in CREDENCE. Therefore, on-treatment analysis is very important because the real comparison effect is somewhere between the intention-to-treat and on-treatment analyses. In future, matched indirect comparisons might be a suitable tool to further reduce the trial differences. However, such an analysis can also introduce bias.

In the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, which included patients with and without type 2 diabetes, a decline in eGFR of at least 50% from baseline was used in the primary cardiorenal

composite endpoint, in addition to end-stage kidney disease, renal or CV death. In the cohort of patients with type 2 diabetes, a 36% risk reduction in the primary outcome was observed with dapagliflozin compared to placebo (HR 0.64, 95% CI 0.52-0.79).⁶ We did not include DAPA-CKD as a comparator because a decline in eGFR of at least 50% from baseline was not a prespecified adjudicated outcome in the FIDELIO-DKD trial. Whereas the primary outcome points to a larger magnitude of risk reduction with dapagliflozin using a smaller threshold for eGFR decrease, the 95% confidence interval largely overlaps with that observed for the primary outcome in the CREDENCE study. This might suggest that a decline of at least 50% in eGFR could be as sensitive as a doubling of serum creatinine. On the other hand, it might suggest that there was a larger treatment effect with dapagliflozin in the trial population studied. Given the equipoise, future trials should use at least consistent definitions of clinical endpoints.

There are several limitations of our analyses. Despite attempts to match the CREDENCE and FIDELIO-DKD populations and endpoints, it is impossible to account for all differences. A true comparison of canagliflozin and finerenone would require a head-to-head trial. Furthermore, our analysis was not pre-specified, we did not have individual patient level data from CREDENCE, and we cannot account for differences in trial duration or adherence to study treatments between the two trials. Nonetheless, our paper highlights the risks of directly comparing two trials even when conducted in the same disease state; when key differences in trial design and end point definitions are accounted for, both FIDELIO-DKD and CREDENCE demonstrate cardiorenal benefits of a similar magnitude. With finerenone, canagliflozin, and dapagliflozin demonstrating clinically meaningful improvements in cardiorenal outcomes in patients with advanced CKD and T2D on top of RAS

blockade, the results from FIDELIO-DKD, CREDENCE and DAPA-CKD trials suggest a more optimistic future for patients with CKD and T2D.

CONFLICT OF INTEREST STATEMENT

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, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fresenius, Janssen, Relypsa, Sanofi, and Vifor Pharma; he has received personal fees from Ironwood Pharmaceuticals, Lexicon, Merck & Co, and Reata, and nonfinancial support from E. R. Squibb & Sons, Opko Pharmaceuticals, and Otsuka America Pharmaceutical; he is a member of data safety monitoring committees for AstraZeneca and Ironwood Pharmaceuticals; a member of steering committees of randomised trials for Akebia Therapeutics, Bayer, Janssen, and Relypsa; and 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 NIH and the U.S. Veterans Administration.

SDA has received research support from Abbott Vascular and Vifor Pharma, and personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, BRAHMS, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier, and Vifor Pharma.

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

BP reports consultant fees for Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, PhaseBio, Sanofi/Lexicon, Sarfez, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa; he has stock options for Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida, and Vifor/Relypsa; 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 Astellas, Boehringer Ingelheim, Eli Lilly, Gilead, Merck, Merck Sharp & Dohme, Mundipharma, Sanofi, and Vifor. All fees are given to Steno Diabetes Center Copenhagen.

LMR reports receipt of consultancy fees from Bayer.

JB reports that he has no disclosures.

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GEU reports that he is a principal investigator in clinical studies sponsored by AstraZeneca, Dexcom and Novo Nordisk.

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CS and **LR** full-time employee of Bayer PLC, United Kingdom.

AJ and **MFS** are full-time employees of Bayer AG, Division Pharmaceuticals, Germany. **MS** is also a shareholder in AstraZeneca, Bayer, Eli Lilly, and Novo Nordisk.

IO is a full-time employee of Bayer U.S. LLC, USA

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AUTHORS' CONTRIBUTIONS

The FIDELIO-DKD trial was conducted and funded by Bayer AG. The sponsor participated in study design, data collection, data analysis, data interpretation and approval of the manuscript. Analyses were conducted by the sponsor, and all authors had access to and participated in the interpretation of the data. RA wrote the first draft of the report. All authors were involved in drafting and critically revising the

report. All authors had access to study results and the first and corresponding author assumes responsibility for the integrity and accuracy of the data reported. All authors reviewed and approved the final submitted version of the report.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are not currently available in a public repository.

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Table 1. Baseline characteristics for the FIDELIO-DKD “CREDESCENCE-like” subgroup^a and CREDESCENCE

	FIDELIO-DKD “CREDESCENCE-like” subgroup total (N = 4619)	CREDESCENCE total (N = 4401)
Age, y	65.3 ± 9.2	63.2 ± 9.2
Female	1335 (28.9)	1494 (33.9)
Race		
White	2920 (63.2)	2931 (66.6)
Black/African American	208 (4.5)	224 (5.1)
Asian	1171 (25.4)	877 (19.9)
Systolic blood pressure, mm Hg	138.2 ± 14.1	140.0 ± 15.6
Diastolic blood pressure, mm Hg	76.2 ± 9.5	78.3 ± 9.4
BMI, kg/m ²	31.1 ± 6.0	31.3 ± 6.2
Duration of diabetes, y	16.1 ± 8.6	15.8 ± 8.6
HbA _{1c} , %	7.68 ± 1.36	8.3 ± 1.3
Serum potassium, mmol/l	4.36 ± 0.46	N/A
eGFR, ml/min/1.73 m ²	46.5 ± 12.0	56.2 ± 18.2

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<15	0 (0)	2 (<0.1)
≥15–<30	222 (4.8)	172 (3.9)
≥30–<45	2051 (44.4)	1191 (27.1)
≥45–<60	1715 (37.1)	1266 (28.8)
≥60–<90	621 (13.4)	1558 (35.4)
≥90	10 (0.2)	211 (4.8)
UACR, mg/g	917 (512–1696)	927 (463–1833)
<30	9 (0.2)	31 (0.7)
30–≤300	293 (6.3)	496 (11.3)
>300–≤3000	3951 (85.5)	3371 (76.6)
>3000	366 (7.9)	503 (11.4)
History of CV disease		
Coronary artery disease	1398 (30.3)	1313 (29.8)
Cerebrovascular disease	555 (12.0)	700 (15.9)
Peripheral artery disease	741 (16.0)	1046 (23.8)
Heart failure	350 (7.6)	652 (14.8)
Current smoker	695 (15.0)	639 (14.5)
Medication use at baseline		
RAAS inhibitor	4609 (99.8)	4395 (99.9)
Beta-blocker	2393 (51.8)	1770 (40.2)

Diuretic	2535 (54.9)	2057 (46.7)
Statin	3432 (74.3)	3036 (69.0)
Antithrombotic	2889 (62.4)	2624 (59.6)
Glucose-lowering therapies		
Insulin and analogues	2901 (62.8)	2884 (65.5)
Metformin	2211 (47.9)	2545 (57.8)
Sulphonylurea	1101 (23.8)	1268 (28.8)
DPP-4 inhibitor	1216 (26.3)	751 (17.1)
GLP-1RA	329 (7.1)	183 (4.2)
SGLT-2i	231 (5.0)	2202 (50.0)
Alpha glucosidase inhibitor	269 (5.8)	139 (3.2)
Thiazolidinedione	184 (4.0)	136 (3.1)

^aUACR >300 mg/g and eGFR >30 ml/min/1.73 m² at baseline.

Data are mean ± standard deviation, *n* (%), or median (interquartile range).

BMI, body mass index; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; RAAS, renin–angiotensin–aldosterone system; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

35 (0.8%) of the patients in the CREDENCE trial were on steroidal MRAs at baseline.

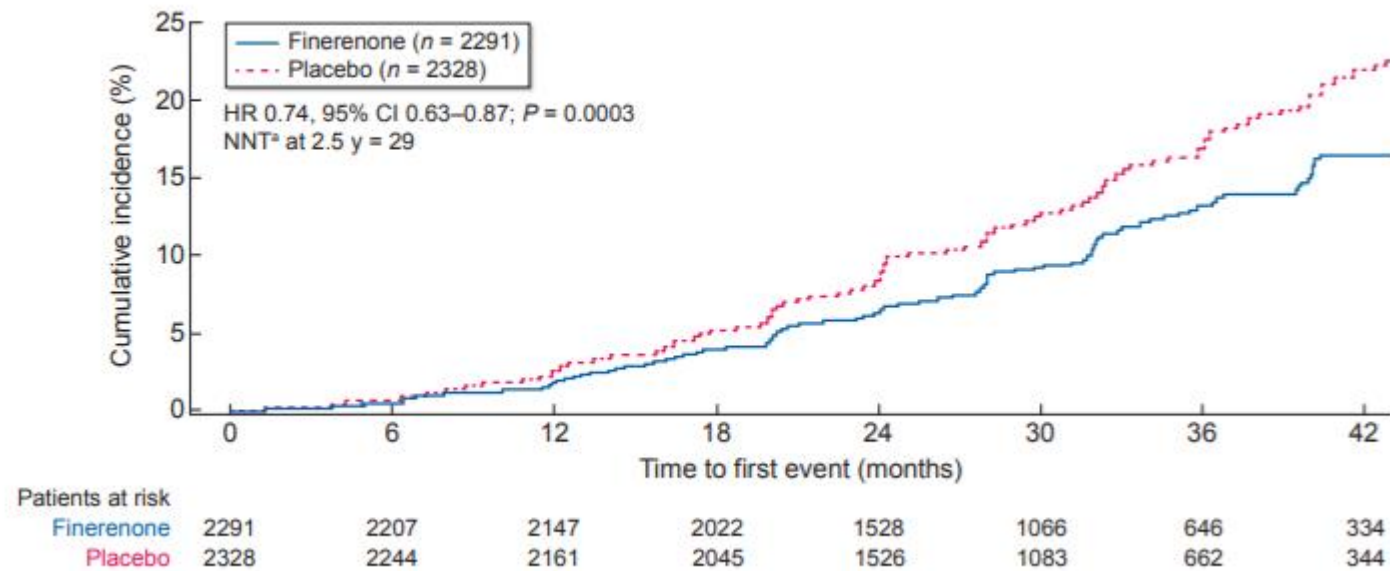


Figure 1: Analysis of the composite cardiorenal end point in the FIDELIO-DKD “CREDENCE-like” subgroup.^b

^aBased on an absolute risk reduction of 3.4%. ^bUACR >300 mg/g and eGFR >30 ml/min/1.73 m² at baseline.

CI, confidence interval; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; HR, hazard ratio; NNT, number needed to treat; UACR, urine albumin-to-creatinine ratio.

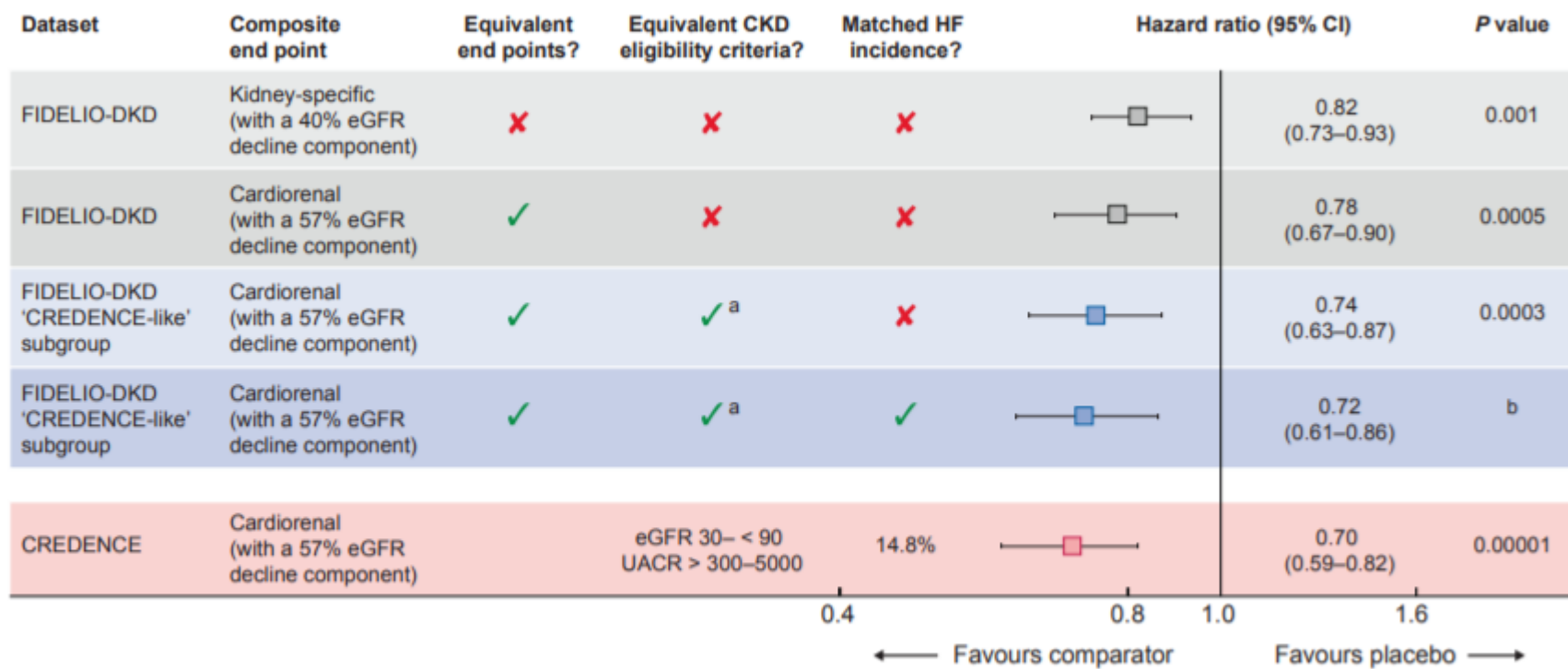


Figure 2: Importance of trial design when comparing cardiorenal outcomes – effects of different composite end points and patient characteristics. ^aPatients with an eGFR >75 ml/min/1.73 m² were ineligible for FIDELIO-DKD. ^bP value unavailable as inflation analysis.

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CI, confidence interval; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; HF, heart failure; UACR, urine albumin-to-creatinine ratio.

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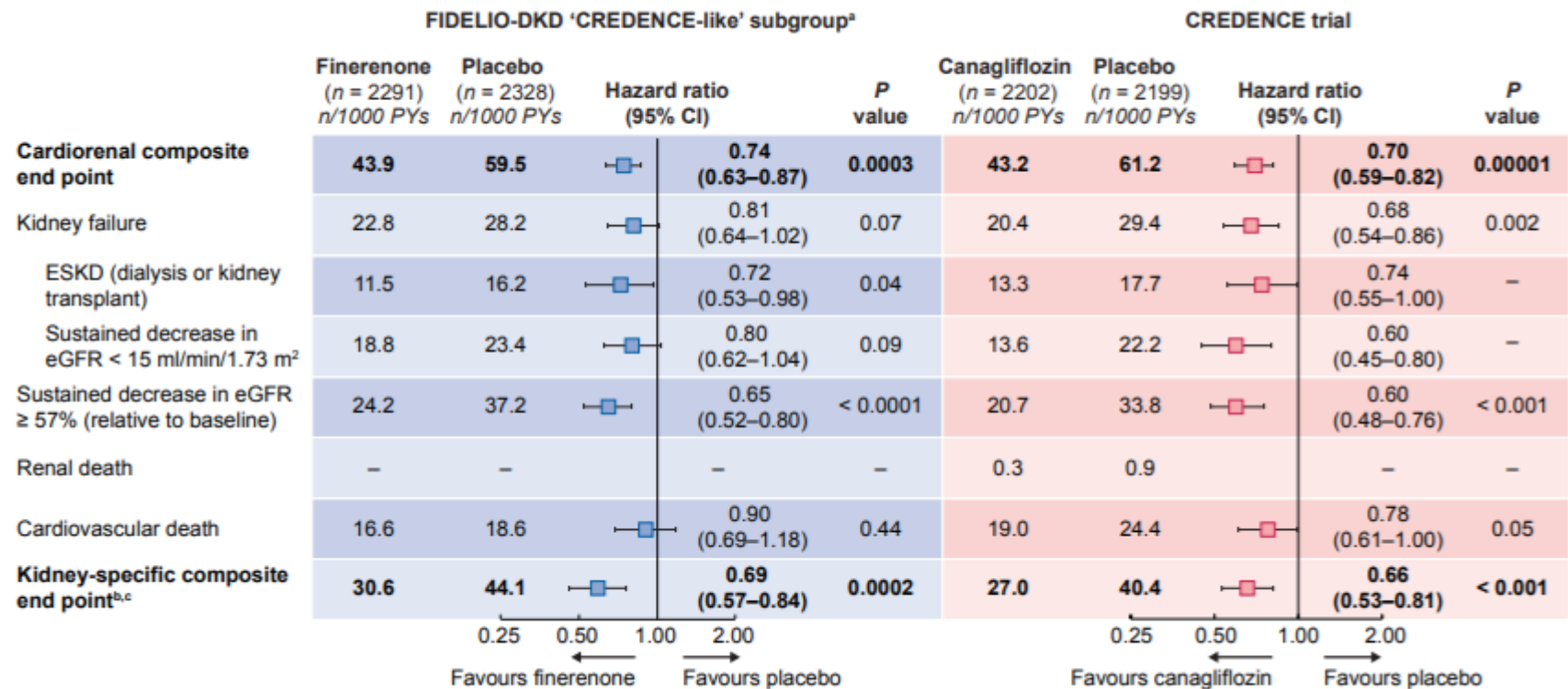


Figure 3: Analysis of key end points from the FIDELIO-DKD “CREDESCENCE-like subgroup (UACR >300 mg/g and eGFR >30 ml/min/1.73 m² at baseline) and the CREDESCENCE population. ^aFull analysis set restricted to patients with UACR >300 mg/g and eGFR >30 ml/min/1.73 m². ^bTime to onset of kidney failure, sustained decrease of eGFR ≥57%, or renal death for

FIDELIO-DKD. ^cESKD, doubling of serum creatinine, or renal death for CREDENCE. CI, confidence interval; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; PY, patient-years; UACR, urine albumin-to-creatinine ratio.

Figure 3: Event rates for the individual components of the cardiorenal composite end point in the FIDELIO-DKD “CREDENCE-like” subgroup.^b ^aTime to onset of kidney failure, a sustained decrease of eGFR $\geq 57\%$, or renal death. ^bUACR >300 mg/g and eGFR >30 ml/min/1.73 m² at baseline. Among patients who did not meet the “CREDENCE-like” inclusion criteria, the composite cardiorenal “CREDENCE-like” outcome had a hazard ratio of 0.86 (95% CI 0.65 – 1.13). In contrast, among patients who met the “CREDENCE-like” inclusion criteria, the composite cardiorenal outcome had a hazard ratio 0.74 (95% CI 0.63 – 0.87). The test of heterogeneity between the “CREDENCE-like” and the population that was not “CREDENCE-like” was not significant ($p=0.37$).

CI, confidence interval; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FIDELIO-DKD, Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease; PY, patient-years; UACR, urine albumin-to-creatinine ratio.