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

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ABSTRACT

Background. The nonsteroidal mineralocorticoid receptor antagonist finerenone and the sodium–glucose cotransporter-2 inhibitor (SGLT-2i) canagliflozin reduce cardiorenal risk in albuminuric patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). At first glance, the results of Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) appear disparate. In FIDELIO-DKD, the primary endpoint had an 18% [95% confidence interval (CI) 7–27] relative risk reduction; in CREDENCE, the primary endpoint had a 30% (95% CI 18–41) relative risk reduction. Unlike CREDENCE, the FIDELIO-DKD trial included a sustained decline in eGFR of ≥57% from baseline and cardiovascular (CV) 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: creatinine ratio > 300–5000 mg/g and an eGFR of 30–<90 mL/min/1.73 m² at screening) and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) appear disparate. In FIDELIO-DKD, the primary endpoint had an 18% [95% confidence interval (CI) 7–27] relative risk reduction; in CREDENCE, the primary endpoint had a 30% (95% CI 18–41) relative risk reduction. Unlike CREDENCE, the FIDELIO-DKD trial included patients with high albuminuria but excluded patients with symptomatic heart failure with reduced ejection fraction. The primary endpoint in the FIDELIO-DKD trial was kidney specific and included a sustained decline in the estimated glomerular filtration rate (eGFR) of ≥40% from baseline. In contrast, the primary endpoint in the CREDENCE trial included a sustained decline in eGFR of ≥57% from baseline and cardiovascular (CV) death. This post hoc exploratory analysis investigated how differences in trial design—inclusion/exclusion criteria and definition of primary outcomes—influenced observed treatment effects.

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 endpoint was 43.9/1000 patient-years with finerenone compared with 59.5/1000 patient-years with placebo. The
relative risk was significantly reduced by 26% with finerenone versus placebo [hazard ratio (HR) 0.74 (95% CI 0.63–0.87)]. In CREDENCE, the rate of the cardiorenal composite endpoint was 43.2/1000 patient-years with canagliflozin compared with 61.2/1000 patient-years with placebo; a 30% risk reduction was observed with canagliflozin [HR 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 (MRA) finerenone and the sodium–glucose cotransporter-2 inhibitor (SGLT-2i) canagliflozin have been shown to benefit cardiovascular and kidney organ protection in albuminuric patients with type 2 diabetes (T2D) and chronic kidney disease (CKD).
- At first glance, the efficacy of finerenone in FINERENONE in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) appears inferior to the efficacy of canagliflozin in Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE).
- The primary endpoint had an 18% [95% confidence interval (CI) 7–27] relative risk reduction in FIDELIO-DKD; the primary endpoint had a 30% (95% CI 18–41) relative risk reduction in CREDENCE.

**What this study adds?**
- There are risks in directly comparing two trials even when conducted in the same disease state.
- When key differences in trial inclusion/exclusion criteria and endpoint 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 SGLT-2i canagliflozin and the nonsteroidal MRA finerenone are similarly effective in patients with T2D 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 an increased risk of cardiovascular (CV) events and CKD progression [1]. Although there has been 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 cotransporter-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 (CREDENCE) 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 CREDENCE, DAPA-CKD and FIDELIO-DKD trials, the relative risks of the primary outcomes were reduced by 30% [95% confidence interval (CI) 18–41], 39% (95% CI 28–49) and 18% (95% CI 7–27), 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 endpoints [e.g. sustained change from baseline in estimated glomerular filtration rate (eGFR) of ≥40%, ≥50% and ≥57% in FIDELIO-DKD, DAPA-CKD and CREDENCE, respectively] and patient populations, unadjusted comparisons among the trials are prone to biases [1, 4–6].

The objective of this analysis was 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 endpoint 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 FIDELIO-DKD and the primary endpoint in DAPA-CKD was a ≥50% reduction in 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 (Supplementary data, Figure S1). First, a kidney-specific composite endpoint (time to kidney failure, sustained ≥40% decrease in eGFR from baseline or renal death) was the primary endpoint in FIDELIO-DKD, whereas a cardiorenal composite endpoint [end-stage kidney disease (ESKD), ≥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–<75 mL/min/1.73 m² versus 30–<90 mL/min/1.73 m² in CREDENCE [4]. Third, the urine albumin: creatinine ratio (UACR) levels were 30–5000 mg/g in FIDELIO-DKD compared with >300–5000 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 a 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, randomized, double-blind, placebo-controlled, multicenter 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 optimized renin-angiotensin system (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 optimized for 4–16 weeks), a screening period and a double-blind treatment period. Patients were randomized 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 downtitration from 20 mg to 10 mg due to safety concerns was permitted at any time.
Endpoints

The primary endpoint of interest for this FIDELIO-DKD ‘CREDENCE-like’ subgroup analysis was a composite cardiorenal endpoint of time to first occurrence of CV death, kidney failure (defined as ESKD (the initiation of long-term dialysis for \( \geq 90 \) days or kidney transplantation) or an eGFR \(< 15 \) mL/min/1.73 m\(^2\) sustained for \( \geq 4 \) weeks), an eGFR decrease of \( \geq 57\% \) sustained for \( \geq 4 \) weeks or renal death. Other endpoints included a kidney-specific composite endpoint of time to onset of kidney failure, a sustained decrease of eGFR \( \geq 57\% \) or renal death, a composite CV endpoint of CV death or hospitalization for HF, CV death, death from any cause and a change in UACR from baseline over time. Urinalysis was performed centrally during the 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 analyze the time-to-event superiority of finerenone versus placebo. The individual components of the cardiorenal endpoints were analyzed 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 endpoints are expressed as hazard ratios (HRs) with corresponding 95% CIs from a stratified Cox regression model. Events were counted from randomization 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 endpoint 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 an analysis of events that occurred within 30 days of the 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 replacements 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 analyzed using stratified Cox proportional hazards regression and estimates combined using standard bootstrap combination assumptions.

The change in UACR was analyzed 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 the 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 randomized and included in the full analysis set [1]. A total of 4619/5674 patients in FIDELIO-DKD met the ‘CREDENCE-like’ criteria (with a UACR >300–5000 mg/g and an eGFR of 30–<75 mL/min/1.73 m\(^2\) at screening) and were included in this analysis. Comparison of the baseline demographics from the FIDELIO-DKD subgroup and the CREDENCE group found they 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 ‘CREDENCE-like’ subgroup compared with the CREDENCE group included slightly older patients, with lower systolic blood pressure, lower glycated hemoglobin, lower mean eGFR levels (including fewer patients with eGFR \( \geq 60 \) mL/min/1.73 m\(^2\)), 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 (49.6%) were treated with finerenone and 2328 (50.4%) were treated with placebo, and baseline characteristics were balanced between treatment groups (Supplementary data, 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 patients assessed, mean treatment adherence was high at 92.0%.

Efficacy

Cardiorenal composite endpoint. In the FIDELIO-DKD ‘CREDENCE-like’ subgroup (with UACR >300–5000 mg/g and an eGFR of 30–<75 mL/min/1.73 m\(^2\) at baseline), the risk of the cardiorenal composite endpoint of time to first occurrence of CV death, kidney failure, eGFR decrease of \( \geq 57\% \) sustained for \( \geq 4 \) 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 ‘CREDENCE-like’ inclusion criteria), the risk of the same cardiorenal composite endpoint 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 ‘CREDENCE-like’ inclusion criteria, the composite cardiorenal ‘CREDENCE-like’ outcome occurred in 99 of 542 patients who were assigned to finerenone and 104 of 513 patients who were assigned to placebo [HR 0.86 (95% CI 0.65–1.13)]. In contrast, among patients who met the ‘CREDENCE-like’ inclusion criteria, the composite cardiorenal outcome occurred in 241 of 2291
Table 1. Baseline characteristics for the FIDELIO-DKD ‘CREDENCE-like’ subgroup* and CREDENCE

| Characteristics | FIDELIO-DKD ‘CREDENCE-like’ subgroup total (N = 4619) | CREDENCE total (N = 4401) |
|----------------|-----------------------------------------------------|--------------------------|
| Age (years), mean ± SD | 65.3 ± 9.2 | 63.2 ± 9.2 |
| Female, n (%) | 1335 (28.9) | 1494 (33.9) |
| Race, n (%) | | |
| 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 (mmHg), mean ± SD | 138.2 ± 14.1 | 140.0 ± 15.6 |
| Diastolic blood pressure (mmHg), mean ± SD | 76.2 ± 9.5 | 78.3 ± 9.4 |
| BMI (kg/m²), mean ± SD | 31.1 ± 6.0 | 31.3 ± 6.2 |
| Duration of diabetes (years), mean ± SD | 16.1 ± 8.6 | 15.8 ± 8.6 |
| HbA1c (%), mean ± SD | 7.68 ± 1.36 | 8.3 ± 1.3 |
| Serum potassium (mmol/L), mean ± SD | 4.36 ± 0.46 | N/A |
| eGFR (mL/min/1.73 m²), n (%) | 46.5 ± 12.0 | 56.2 ± 18.2 |
| < 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), median (IQR) | 917 (512–1696) | 927 (463–1833) |
| < 30, n (%) | 9 (0.2) | 31 (0.7) |
| ≥30–<300, n (%) | 293 (6.3) | 496 (11.3) |
| ≥300–<3000, n (%) | 3951 (85.5) | 3371 (76.6) |
| ≥3000, n (%) | 366 (7.9) | 503 (11.4) |
| History of CV disease, n (%) | | |
| 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, n (%) | 695 (15.0) | 639 (14.5) |
| 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, n (%) | | |
| Insulin and analogs | 2901 (62.8) | 2884 (65.5) |
| Metformin | 2211 (47.9) | 2545 (57.8) |
| Sulfonylurea | 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) |

*UACR > 300 mg/g and eGFR > 30 mL/min/1.73 m² at baseline.

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; RAAS, renin–angiotensin–aldosterone system.

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

patients who were assigned to finerenone and 330 of 2328 patients who were assigned to placebo [HR 0.74 (95% CI 0.63–0.87)]. The test of heterogeneity was not significant (P = 0.37).

In the FIDELIO-DKD ‘CREDENCE-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 endpoint with finerenone versus placebo [HR 0.72 (95% CI 0.61–0.86); Figure 2]. For comparison, in the CREDENCE study, canagliflozin reduced the risk of the cardiorenal composite endpoint 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 endpoint 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 endpoint 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 versus 22.2 per 1000 patient-years) and ESKD (16.2 versus 17.7 per 1000 patient-years) [4]. However, whereas the incidence rate of sustained eGFR decline ≥57% from baseline was larger in the placebo arm of the FIDELIO-DKD subgroup than the CREDENCE...
Patients at risk

**Finerenone**

- 2291

**Placebo**

- 2328

HR 0.74, 95% CI 0.63–0.87; \( P = 0.0003 \)

NNT\(^a\) at 2.5 y = 29

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**FIGURE 1:** Analysis of the composite cardiorenal endpoint in the FIDELIO-DKD ‘CREDENCE-like’ subgroup.\(^b\)

\(^{a}\)Based on an absolute risk reduction of 3.4%.\(^{b}\)UACR > 300 mg/g and eGFR > 30 mL/min/1.73 m\(^2\) at baseline. NNT, number needed to treat.

| Dataset           | Composite endpoint                                                                 | Equivalent endpoints? | Equivalent CKD eligibility criteria? | Matched HF incidence? | Hazard ratio (95% CI) | \( P \)-value |
|-------------------|------------------------------------------------------------------------------------|-----------------------|-------------------------------------|-----------------------|-----------------------|--------------|
| FIDELIO-DKD       | Kidney-specific (with a 40% eGFR decline component)                                | \xmark                 | \xmark                               | \xmark                 | 0.82 (0.73–0.93)      | 0.001        |
| FIDELIO-DKD       | Cardiorenal (with a 57% eGFR decline component)                                    | \checkmark            | \xmark                               | \xmark                 | 0.76 (0.67–0.90)      | 0.0005       |
| FIDELIO-DKD 'CREDENCE-like' subgroup | Cardiorenal (with a 57% eGFR decline component) | \checkmark            | \checkmark                            | \xmark                 | 0.74 (0.63–0.87)      | 0.0003       |
| FIDELIO-DKD 'CREDENCE-like' subgroup | Cardiorenal (with a 57% eGFR decline component) | \checkmark            | \checkmark                            | \checkmark             | 0.72 (0.61–0.86)      | \( \text{~b} \) |
| CREDENCE          | Cardiorenal (with a 57% eGFR decline component)                                    | \checkmark            | \checkmark                            | \checkmark             | 0.70 (0.59–0.82)      | 0.00001      |

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**FIGURE 2:** Importance of trial design when comparing cardiorenal outcomes—effects of different composite endpoints and patient characteristics. \(^{a}\)Patients with an eGFR > 75 mL/min/1.73 m\(^2\) were ineligible for FIDELIO-DKD. \(^{b}\)\( P \)-value unavailable as inflation analysis.

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population (37.2 versus 33.8 patients with event per 1000 patient-years), the CV death rate was lower with placebo in FIDELIO-DKD than in CREDENCE (18.6 versus 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 endpoint for several key subgroups (Supplementary data, Figure S2) and in an ‘on-treatment’ sensitivity analysis; details are included in the Supplementary data.

**Kidney-specific endpoints.** A kidney-specific composite endpoint 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 endpoint of ESKD, doubling of the creatinine level (equivalent to a 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 ‘CREDENCE-like’ subgroup, the efficacy of finerenone compared with placebo was consistent for the kidney-specific composite endpoints for several subgroups (Figure 3) and in an ‘on-treatment’ sensitivity analysis; details are included in the Supplementary data. Improvements in albuminuria were similar between the two trials (see the Supplementary data).

**Other efficacy endpoints.** Other endpoints, including composite CV endpoint of time to first occurrence of CV death or hospitalization for HF and death from any cause, trended toward favoring finerenone but did not meet statistical
significant [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 (Supplementary data, Table S2). Consistent with the mechanism of action of finerenone, hyperkalemia events were increased in patients treated with finerenone versus placebo (15.3% versus 7.6%). In CRESCENDO, hyperkalemia events were less frequent in patients treated with canagliflozin versus placebo (6.9% versus 8.2%) [4].

The incidences 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 ‘CRESCENDO-like’ inclusion criteria, those assigned to finerenone had 104 AKI events (4.5%) reported in 2288 patients (21.4 events per 1000 patient-years), compared with those assigned to placebo who had 106 AKI events (4.6%) in 2320 patients (21.2 events per 1000 patient-years). By comparison, in the CRESCENDO trial, those assigned to canagliflozin had 86 AKI events (3.9%) reported in 2200 patients (16.9 events per 1000 patient-years) compared with those assigned to placebo who had 98 AKI events (4.5%) in 2197 patients (20.0 events per 1000 patient-years) [4].

The incidences of amputation, fracture and diabetic ketoacidosis were balanced and low in both the finerenone and placebo treatment groups (Supplementary data, Table S2).

**DISCUSSION**

Our study demonstrates the central importance of considering trial eligibility criteria and endpoint definitions on the effect size of therapies approved for the management of CKD in T2D. Three progressive adjustments—inclusion criteria, endpoint and key exclusion criteria—provided effect size estimates that were strikingly similar between the trials. The joint consideration of the CRESCENDO trial inclusion criteria (UAER > 300–5000 mg/g and eGFR > 30–< 90 mL/min/1.73 m² at screening) and CRESCENDO-like endpoint (the cardiorenal composite endpoint of time to first occurrence of CV death, kidney failure, eGFR decrease of ≥57% or renal death for FIDELIO-DKD. *ESKD, doubling of serum creatinine or renal death for CRESCENDO. PY, patient-years.

![FIGURE 3: Analysis of key endpoints in the FIDELIO-DKD ‘CRESCENDO-like’ subgroup and the CRESCENDO trials.](image-url)

### Table 3: Analysis of key endpoints in the FIDELIO-DKD ‘CRESCENDO-like’ subgroup and the CRESCENDO trials.

| Cardiorenal composite end point | FIDELIO-DKD ‘CRESCENDO-like’ subgroup | CRESCENDO trial |
|-------------------------------|----------------------------------------|-----------------|
|                               | Hazard ratio (95% CI)                   | Hazard ratio (95% CI) |
| Kidney failure                | 0.74 (0.63–0.87)                       | 0.70 (0.59–0.82)   |
| ESKD (dialysis or kidney transplant) | 0.81 (0.64–1.02)                  | 0.68 (0.54–0.86)   |
| Sustained decrease in eGFR < 15 mL/min/1.73 m² | 0.72 (0.53–0.98)      | 0.74 (0.55–1.00)   |
| Sustained decrease in eGFR ≥ 57% (relative to baseline) | 0.80 (0.62–1.04)      | 0.60 (0.45–0.80)   |
| Renal death                   | 0.65 (0.52–0.80) < 0.0001              | 0.60 (0.48–0.76) < 0.001 |
| Cardiovascular death          | 0.90 (0.69–1.18) 0.44               | 0.78 (0.61–1.00) 0.05 |
| Kidney-specific composite end point | 0.69 (0.57–0.84) 0.0002 | 0.66 (0.53–0.81) < 0.001 |

| Placebo (n = 2202) | Favors canagliflozin | Placebo (n = 2199) |
|-------------------|---------------------|---------------------|
|                    | 0.25 0.50 1.00 2.00 | Favors placebo      |
|                    |                      |                     |
| 30mL/min/1.73 m² |                     |                     |
| In the present FIDELIO-DKD ‘CRESCENDO-like’ subgroup, there was a 26% reduction in the risk of the cardiorenal composite endpoint with finerenone compared with placebo. In CRESCENDO, a 30% risk reduction in the same composite endpoint was observed with canagliflozin compared with placebo. Because FIDELIO-DKD excluded patients with symptomatic HF with reduced ejection fraction, whereas CRESCENDO 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 CRESCENDO (7.6% versus 14.8%) [1, 4]. This imbalance is noteworthy because patients with HF are at much greater risk of experiencing CV death [14]; indeed, we saw a larger CV death event rate in the placebo arm of this FIDELIO-DKD ‘CRESCENDO-like’ subgroup than in CRESCENDO (18.6 versus 24.4 patients per 1000 patient-years, respectively). Therefore we adjusted the proportion of patients with a history of HF; after this modification, the risk of the cardiorenal composite endpoint 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 ‘CREDENCE-like’ subgroup studied here and the CREDENCE population reveal differences in patient baseline characteristics (Supplementary data, 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 optimization of medical therapy was different between the trials, which may, in part, account for lower systolic blood pressure (138 mmHg versus 140 mmHg) and glycated hemoglobin levels (7.7% versus 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 the 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 DAPA-CKD trial, which included patients with and without T2D, a decline in eGFR of at least 50% from baseline was used in the primary cardiorenal composite endpoint, in addition to ESKD and renal or CV death. In the cohort of patients with T2D, a 36% risk reduction in the primary outcome was observed with dapagliflozin compared with 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% CI 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 at least use 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 prespecified; 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 article highlights the risks of directly comparing two trials even when conducted in the same disease state; when key differences in trial design and endpoint 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 the FIDELIO-DKD, CREDENCE and DAPA-CKD trials suggest a more optimistic future for patients with CKD and T2D.

SUPPLEMENTARY DATA
Supplementary data are available at ndt online.

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

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