Importance of trial design when investigating cardiorenal outcomes in patients with CKD and T2D: Focus on CREDENCE and FIDELIO-DKD

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Abstract

Background: Recent trials investigating novel therapies in chronic kidney disease (CKD) and type 2 diabetes (T2D) include the randomized, placebo-controlled phase III 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) studies of finerenone (a selective, nonsteroidal mineralocorticoid receptor antagonist [MRA]) and canagliflozin (a sodium-glucose co-transporter-2 inhibitor [SGLT-2i]), respectively. This analysis investigated how differences in trial design between FIDELIO-DKD and CREDENCE influence the treatment effects of the two drugs. **Methods:** This was a post hoc analysis of FIDELIO-DKD that included patients meeting the CKD inclusion criteria of the CREDENCE study (urine albumin-to-creatinine ratio [UACR] >300–5000 mg/g and estimated glomerular filtration rate [eGFR] 30–<90 mL/min/1.73 m^2 at screening). The cardiorenal composite endpoint comprised kidney failure, eGFR decrease of ≥57% from baseline sustained for ≥4 weeks, or renal or cardiovascular (CV) death (equivalent to the CREDENCE primary endpoint). **Results:** Overall, 81.4% (4619/5674) of patients were eligible for this analysis; 2291 (49.6%) received finerenone and 2328 (50.4%) received placebo. The cardiorenal composite endpoint risk was significantly reduced by 26% with finerenone versus placebo (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.63–0.87; p=0.0003); after adjusting for history of heart failure [HF], the risk was reduced by 28%. In CREDENCE, the cardiorenal endpoint risk reduction was 30% with canagliflozin versus placebo. **Conclusion:** The results of this analysis highlight the pitfalls of direct comparisons between trials, and how subtle differences in patient eligibility criteria and endpoint definitions can lead to meaningful differences in outcomes. Both the FIDELIO-DKD and CREDENCE studies demonstrate cardiorenal benefits of a similar magnitude when these differences are considered.

Introduction

- FIDELIO-DKD was a phase III, randomized, double-blind, placebo-controlled clinical trial that evaluated the selective, nonsteroidal MRA finerenone in patients with CKD and T2D; finerenone significantly reduced the risk of kidney and CV outcomes compared with placebo[1]
- CREDENCE was a phase III, randomized, double-blind, placebo-controlled clinical trial that assessed the effects of the SGLT-2i canagliflozin in patients with CKD and T2D and reported positive cardiorenal outcomes[2]
- The aim of this analysis was to facilitate a more nuanced comparison of the treatment effect of finerenone in FIDELIO-DKD with that of canagliflozin in CREDENCE by adjusting for key differences in trial design

Study design and methods

- This post hoc analysis of FIDELIO-DKD included patients with T2D who met the CKD inclusion criteria of CREDENCE at screening (UACR >300–5000 mg/g and eGFR 30–<90 mL/min/1.73 m^2)
- The primary endpoint was a cardiorenal composite of kidney failure (defined as end-stage kidney disease [chronic dialysis or kidney transplantation] or an eGFR <15 mL/min/1.73 m^2 sustained for ≥4 weeks), eGFR decrease of ≥57% sustained for ≥4 weeks, or renal or CV death (equivalent to the CREDENCE primary endpoint)
- Other endpoints included a kidney-specific composite endpoint of time to onset of kidney failure, a sustained decrease of eGFR ≥57%, or renal death

Results

Patients

- Of 5674 patients included in the FIDELIO-DKD analyses, 4619 patients met the CKD inclusion criteria of CREDENCE and were included in this analysis; 2291 patients received finerenone and 2328 patients received placebo
- The key baseline patient characteristics of the FIDELIO-DKD “CREDENCE-like” subgroup and the CREDENCE group are shown in **Table 1**
  - There were fewer patients in the FIDELIO-DKD “CREDENCE-like” subgroup with a history of heart failure than in CREDENCE (7.6% versus 14.8%)[2]

Table 1. Key baseline patient demographic and disease characteristics

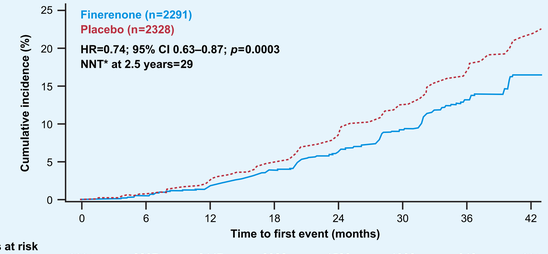
Baseline characteristics	FIDELIO-DKD “CREDENCE-like” subgroup (N=4619)	CREDENCE (N=4401)
Mean age, years	65.3	63.2
Male sex, n (%)	3284 (71.1)	2907 (66.1)
Race, n (%)		
White	2920 (63.2)	2931 (66.6)
Asian	1171 (25.4)	877 (19.9)
Black/African American	208 (4.5)	224 (5.1)
Median duration of T2D, years	16.1	15.8
Mean HbA1c, %	7.7	8.3
Mean SBP/DBP, mmHg	138.2/76.2	140/78.3
Mean eGFR, mL/min/1.73 m^2	46.5	56.2
Median UACR, mg/g	917	927
History of HF, n (%)	350 (7.6)	652 (14.8)
Medication use at baseline, n (%)		
RAS inhibitors	4609 (99.8)	4395 (99.9)
Statins	3432 (74.3)	3036 (69.0)
Antithrombotics	2889 (62.4)	2624 (59.6)
Diuretics	2535 (54.9)	2057 (46.7)
Beta-blockers	2393 (51.8)	1770 (40.2)
SGLT-2is	231 (5.0)	2202 (50.0)

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; RAS, renin–angiotensin system; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

Efficacy

- In the FIDELIO-DKD “CREDENCE-like” subgroup, the cardiorenal composite endpoint risk was significantly reduced by 26% with finerenone vs placebo (HR=0.74; 95% CI 0.63–0.87; p=0.0003) (**Figures 1–3**). After adjusting for differences in history of HF at baseline, the risk was reduced by 28% (**Figure 2**)
  - In CREDENCE, by comparison, the cardiorenal endpoint risk reduction was 30% with canagliflozin vs placebo[2] (**Figure 2**)
- In the FIDELIO-DKD “CREDENCE-like” subgroup, the kidney-specific composite endpoint was significantly improved by 31% with finerenone vs placebo (HR=0.69; 95% CI 0.57–0.84; p=0.0002) (**Figure 3**)
  - In the CREDENCE study, the kidney composite endpoint was reduced by 34% with canagliflozin vs placebo (HR=0.66; 95% CI 0.53–0.81; p<0.001)2 (**Figure 3**)

Figure 1. Analysis of the cardiorenal composite endpoint in the FIDELIO-DKD “CREDENCE-like” subgroup (UACR >300 mg/g and eGFR >30 mL/min/1.73 m^2 at baseline)



*Based on an absolute risk reduction of 3.4%
CI, confidence interval; eGFR, estimated glomerular filtration rate; 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 endpoints and patient characteristics

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)	☒	☒	☒	0.82 (0.73–0.93)	0.001
FIDELIO-DKD	Cardiorenal (with a 57% eGFR decline component)	☑	☒	☒	0.78 (0.67–0.90)	0.0005
FIDELIO-DKD “CREDENCE-like” subgroup	Cardiorenal (with a 57% eGFR decline component)	☑	☑*	☒	0.74 (0.63–0.87)	0.0003
FIDELIO-DKD “CREDENCE-like” subgroup	Cardiorenal (with a 57% eGFR decline component)	☑	☑*	☑	0.72 (0.61–0.86)	#
CREDENCE	Cardiorenal (with a 57% eGFR decline component)		eGFR 30–<90 UACR >300–5000	14.8%	0.70 (0.59–0.82)	0.00001

*Patients with an eGFR >75 mL/min/1.73 m^2 were ineligible for FIDELIO-DKD
#p-value unavailable as inflation analysis
CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; UACR, urine albumin-to-creatinine ratio

Figure 3. Analysis of key endpoints from the FIDELIO-DKD “CREDENCE-like” subgroup (UACR >300 mg/g and eGFR >30 mL/min/1.73 m^2 at baseline) and the CREDENCE population

	FIDELIO-DKD “CREDENCE-like” subgroup*				CREDENCE trial			
	Finerenone (n=2291)	Placebo (n=2328)	Hazard ratio (95% CI)	p-value	Canagliflozin (n=2202)	Placebo (n=2199)	Hazard ratio (95% CI)	p-value
	n/1000 PY	n/1000 PY			n/1000 PY	n/1000 PY		
Cardiorenal composite endpoint	**43.9**	**59.5**	**0.74 (0.63–0.87)**	**0.0003**	**43.2**	**61.2**	**0.70 (0.59–0.82)**	**0.00001**
Kidney failure	22.8	28.2	0.81 (0.64–1.02)	0.07	20.4	29.4	0.68 (0.54–0.86)	0.002
ESKD (dialysis or kidney transplant)	11.5	16.2	0.72 (0.53–0.98)	0.04	13.3	17.7	0.74 (0.55–1.00)	–
Sustained decrease in eGFR <15 ml/min/1.73 m^2	18.8	23.4	0.80 (0.62–1.04)	0.09	13.6	22.2	0.60 (0.45–0.80)	–
Sustained decrease in eGFR ≥57% (relative to baseline)	24.2	37.2	0.65 (0.52–0.80)	<0.0001	20.7	33.8	0.60 (0.48–0.76)	<0.001
Renal death	–	–	–	–	0.3	0.9	–	–
Cardiovascular death	16.6	18.6	0.90 (0.69–1.18)	0.4396	19.0	24.4	0.78 (0.61–1.00)	0.05
Kidney-specific composite endpoint	**30.6**	**44.1**	**0.69 (0.57–0.84)**	**0.0002**	**27.0**	**40.4**	**0.66 (0.53–0.81)**	**<0.001**

*Full analysis set restricted to patients with UACR >300 mg/g and eGFR >30 mL/min/1.73 m^2
CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; PY, patient-years; UACR, urine albumin-to-creatinine ratio

Safety

- Overall, the incidences of adverse events and serious adverse events were similar with finerenone vs placebo (**Table 2**), with increased hyperkalemia observed with finerenone (15.3% vs 7.6% with placebo)
  - In CREDENCE, the incidence of hyperkalemia was less frequent with canagliflozin vs placebo (6.9% vs 8.2%)[2]

Table 2. Overall safety and treatment-emergent adverse events of interest in the FIDELIO-DKD subgroup (UACR >300 mg/g and eGFR >30 mL/min/1.73 m^2 at baseline)

Events, n (%)	Finerenone (n=2288)	Placebo (n=2320)
Any adverse event	1989 (86.9)	2012 (86.7)
Any serious adverse event	715 (31.3)	773 (33.3)
Serious adverse event related to trial drug	33 (1.4)	23 (1.0)
Hyperkalemia*	349 (15.3)	176 (7.6)
Acute kidney injury	104 (4.5)	106 (4.6)

*Investigator-reported adverse events using the MedDRA preferred terms “hyperkalemia” and “blood potassium increased”
eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio

Conclusions

- This analysis underlines how slight differences in a clinical trial’s eligibility criteria, especially HF, and definitions in endpoints can affect the magnitude of treatment effects
- Caution is required when directly comparing two trials conducted in the same disease state. After accounting for key differences in trial design and endpoint definitions, similar cardiorenal benefits are observed with finerenone in FIDELIO-DKD and canagliflozin in CREDENCE

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