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Finerenone in patients with CKD and T2D by SGLT-2i treatment: an analysis of the FIDELIO-DKD study

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Rationale and objective

- In FIDELIO-DKD, finerenone reduced the incidence of cardiorenal events in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), without an effect on blood glucose[1]
- The objective of this analysis was to explore the treatment effect of finerenone in patients with concomitant sodium-glucose co-transporter-2 inhibitor (SGLT-2i) use, either at baseline or during the trial

Key findings

- The benefits of finerenone on kidney and cardiovascular (CV) outcomes in patients with CKD and T2D appeared consistent in the absence or presence of SGLT-2i use at baseline (interaction *P* value 0.21 and 0.46, respectively), or at any time during the trial
- This analysis also demonstrated a reduction in urine albumin-to-creatinine ratio (UACR) with finerenone compared with placebo, even in patients using SGLT-2i at baseline. The magnitude of reduction in UACR is consistent for patients with and without SGLT-2i use at baseline

Background

- Despite SGLT-2i treatment being recommended for patients with CKD and diabetes,[2] further treatment options are needed
- Finerenone is a novel, nonsteroidal, selective mineralocorticoid receptor antagonist (MRA) that inhibits mineralocorticoid receptor (MR) overactivation leading to inflammation and fibrosis in preclinical models, and was investigated in the phase 3 FIDELIO-DKD trial in patients with CKD and T2D[1,3–5]
- Findings from FIDELIO-DKD, which included patients receiving optimized renin–angiotensin system (RAS) therapy, demonstrated that finerenone lowers the risk of CKD progression and CV events in patients with CKD and T2D[1]
- Results from CREDENCE and DAPA-CKD have shown that SGLT-2is offer kidney protection and lower the risk of CV events; however, in these studies, CKD progression or kidney failure still occurred in ~10% of patients and CV events in ~8% of patients after a median follow-up of ~2.5 years[6,7,a]

[a]Based on the mean of primary composite kidney outcomes (decline in estimated glomerular filtration rate [eGFR] of ≥50%, end-stage kidney disease, or death from renal or CV causes), and CV outcomes (cardiovascular death, myocardial infarction [MI], stroke, or hospitalization for heart failure [HHF]) in both studies.

Study design and methods

- FIDELIO-DKD included adults with CKD and T2D with and without SGLT-2i use at baseline[1,4]

Figure 1. FIDELIO-DKD: Study design

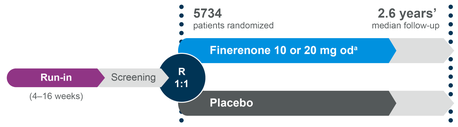


Figure 2. FIDELIO-DKD: Key eligibility

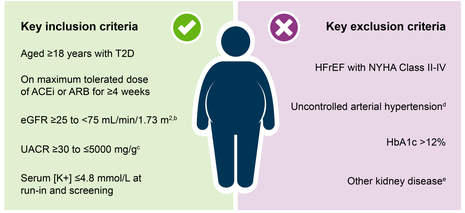
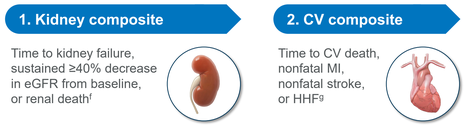


Figure 3. FIDELIO-DKD: Key endpoints



AIM OF THIS SUBGROUP ANALYSIS

To explore the treatment effect of finerenone in patients with and without concomitant SGLT-2i use

SGLT-2i use was permitted at any time during the trial but was not mandated

[a]10 mg if screening eGFR <60 mL/min/1.73 m²; 20 mg if ≥60 mL/min/1.73 m²; up-titration encouraged from month 1 if serum potassium ≤4.8 mmol/L and eGFR stable; a decrease in the dose from 20 to 10 mg once daily was allowed any time after the initiation of finerenone or placebo. [b]Patients either had an eGFR of ≥25 to <60 and with UACR ≥30 to <300 mg/g and diabetic retinopathy, or eGFR ≥25 to <75 with UACR ≥300 mg/g. [c]Patients with moderately elevated albuminuria (UACR 30 to 300 mg/g) were required to also have an eGFR ≥25 to <60 mL/min/1.73 m² and diabetic retinopathy. [d]Mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit. [e]Known significant nondiabetic kidney disease, including clinically relevant renal artery stenosis. [f]Primary composite kidney outcome defined as end-stage kidney disease (initiation of dialysis for ≥90 days or kidney transplantation) or eGFR <15 mL/min/1.73 m², a sustained decrease of ≥40% in eGFR from baseline maintained for ≥4 weeks, and death from renal causes.[1] [g]Secondary composite CV outcome included the number of patients with CV death, nonfatal MI, nonfatal stroke, or HHF.[1]

Results

- Patients treated with SGLT-2i at baseline had higher eGFR and glycated hemoglobin (HbA1c), and lower median UACR and systolic blood pressure (SBP) than those without

Table 1. Baseline demographics and medications

Patient characteristic[a]	No SGLT-2i (n=5415)	SGLT-2i (n=259)
Age, years	66 ± 9	63 ± 10
Race, White	3412 (63)	180 (70)
Black/African American	255 (5)	9 (4)
Asian	1382 (26)	58 (22)
Sex, male	3795 (70)	188 (73)
SBP, mmHg	138 ± 14[b]	135 ± 14
BMI, kg/m²	31 ± 6[c]	32 ± 6
Duration of diabetes, years	17 ± 9[d]	17 ± 9
HbA1c, %	7.7 ± 1.5[d]	8.0 ± 1.2
eGFR, mL/min/1.73 m²	44 ± 13[e]	51 ± 12
Serum potassium, mmol/L	4.4 ± 0.5[e]	4.3 ± 0.4
UACR, mg/g, median (IQR)	866 (456–1653)[f]	619 (370–1258)
History of CV disease	2488 (46)	117 (45)

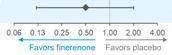
Medication use, n (%)	No SGLT-2i (n=5415)	SGLT-2i (n=259)
ACEi	1865 (34)	77 (30)
ARB	3543 (65)	182 (70)
Diuretics	3069 (57)	145 (56)
Statins	3992 (74)	223 (86)
Potassium-lowering agents	131 (2)	5 (2)
Glucose-lowering therapies	5265 (97)	259 (100)
Insulin and analogs	3464 (64)	173 (67)
GLP-1RA	346 (6)	48 (19)

[a]Values are n (%) or mean ± SD unless otherwise stated. Superscripted letters indicate data missing for the stated number of patients: [b]n=5, [c]n=17, [d]n=11, [e]n=2, and [f]n=3.

- At baseline, 259 (4.6%) patients were receiving SGLT-2i
- After the study start, SGLT-2i was initiated as a new medication in 328 (5.8%) patients

Figure 4. Composite kidney outcomes

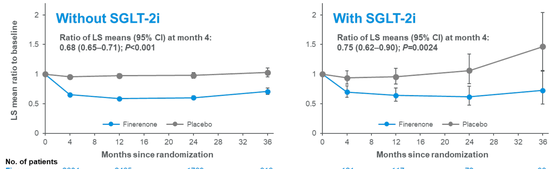
Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)[a]	*P*-interaction[a]
Primary composite kidney outcome[b]				
Overall FIDELIO-DKD population[1]	504/2833 (17.8)	600/2841 (21.1)	0.82 (0.73–0.93)	
No SGLT-2i at baseline	490/2709 (18.1)	590/2706 (21.8)	0.82 (0.72–0.92)	0.21
SGLT-2i at baseline	14/124 (11.3)	10/135 (7.4)	1.38 (0.61–3.10)	
Secondary composite kidney outcome[c]				
Overall FIDELIO-DKD population[1]	252/2833 (8.9)	326/2841 (11.5)	0.76 (0.65–0.90)	
No SGLT-2i at baseline	249/2709 (9.2)	320/2706 (11.8)	0.77 (0.65–0.91)	0.54
SGLT-2i at baseline	3/124 (2.4)	6/135 (4.4)	0.50 (0.12–1.99)	



- Kidney benefit was consistent irrespective of SGLT-2i use at baseline and during the trial
- Finerenone benefit for the primary kidney outcome was also consistent regardless of SGLT-2i use at any time (*P* value for interaction 0.83)[d]

[a]Hazard ratios (95% CI) and interaction *P* values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup, and a subgroup by treatment interaction term as fixed effects. [b]Primary composite kidney outcome defined as end-stage kidney disease (initiation of dialysis for ≥90 days or kidney transplantation) or eGFR <15 mL/min/1.73 m², a sustained decrease of ≥40% in eGFR from baseline maintained for ≥4 weeks, and death from renal causes.[1] [c]Secondary composite kidney outcome of kidney failure, a sustained decrease of at least 57% in the eGFR from baseline (equivalent to a doubling of the serum creatinine level) maintained for ≥4 weeks, or death from renal causes.[1] [d]Cox proportional hazards model after forward selection (including the following variables: age at run-in, BMI at baseline, baseline C-reactive protein, baseline hemoglobin in blood, baseline serum creatinine, baseline serum albumin, baseline systolic blood pressure, and duration of diabetes at baseline) was also used to determine the effect of SGLT-2i use at any time during the trial, including SGLT-2i use as a time-dependent covariate.

Figure 5. Change in UACR from baseline according to SGLT-2i use at baseline



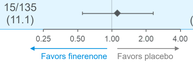
No. of patients							
Finerenone	2604	2465	1769	818	121	117	72	38
Placebo	2597	2471	1742	798	129	127	83	36

Full analysis set. Mixed model with factors for treatment group, region, eGFR category at screening, type of albuminuria at screening, time, treatment*time, log transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value*time as covariates.

- The change in UACR from baseline to month 4 was consistent irrespective of SGLT-2i use at baseline

Figure 6. Composite CV outcomes

Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)[a]	*P*-interaction[a]
Key secondary composite CV outcome[b]				
Overall FIDELIO-DKD population[1]	367/2833 (13.0)	420/2841 (14.8)	0.86 (0.75–0.99)	
No SGLT-2i at baseline	352/2709 (13.0)	405/2706 (15.0)	0.85 (0.74–0.98)	0.46
SGLT-2i at baseline	15/124 (12.1)	15/135 (11.1)	1.12 (0.55–2.30)	



- CV benefit was consistent irrespective of SGLT-2i use at baseline and during the trial
- Finerenone benefit for the key secondary CV outcome was also consistent regardless of SGLT-2i use at any time (*P* value for interaction 0.26)[c]

[a]Hazard ratios (95% CI) and interaction *P* values (two-sided) are based on stratified Cox proportional hazards models including treatment, subgroup, and a subgroup by treatment interaction term as fixed effects. [b]Secondary composite CV outcome included the number of patients with CV death, nonfatal MI, nonfatal stroke, or HHF.[1] [c]Cox proportional hazards model after forward selection (including the following variables: history of CV disease, diuretics use at baseline, age at run-in, baseline HbA1c, baseline C-reactive protein, baseline serum creatinine, baseline serum albumin, and baseline SBP) was also used to determine the effect of SGLT-2i use at any time during the trial, including SGLT-2i use as a time-dependent covariate.

Safety

- Overall safety outcomes were consistent, with treatment-emergent hyperkalemia-related events lower in patients with SGLT-2i use at baseline compared to those without

Table 2. Safety: Treatment-emergent adverse events

	No SGLT-2i at baseline		SGLT-2i at baseline	
	Finerenone (n=2703)	Placebo (n=2696)	Finerenone (n=124)	Placebo (n=135)
Any AE	2355 (87.1)	2361 (87.6)	113 (91.1)	117 (86.7)
Related to study drug	621 (23.0)	434 (16.1)	25 (20.2)	15 (11.1)
Leading to permanent discontinuation	202 (7.5)	161 (6.0)	5 (4.0)	7 (5.2)
Any SAE	863 (31.9)	931 (34.5)	39 (31.5)	40 (29.6)
Related to study drug	47 (1.7)	34 (1.3)	1 (0.8)	0
Leading to permanent discontinuation	71 (2.6)	77 (2.9)	4 (3.2)	1 (0.7)
AE with outcome death	30 (1.1)	49 (1.8)	1 (0.8)	2 (1.5)
Treatment-emergent hyperkalemia AE, n (%)				
Any AE	506 (18.7)	251 (9.3)	10 (8.1)	4 (3.0)
Related to study drug	328 (12.1)	132 (4.9)	5 (4.0)	3 (2.2)
Leading to permanent discontinuation	63 (2.3)	24 (0.9)	1 (0.8)	1 (0.7)
Treatment-emergent AEs of interest by system organ class (>5% patients)				
Hypertension	205 (7.6)	262 (9.7)	7 (5.6)	11 (8.1)
Hypoglycemia	147 (5.4)	187 (6.9)	4 (3.2)	7 (5.2)

Conclusions

Summary of treatment effects of finerenone with and without concomitant SGLT-2i use

- Consistent kidney and CV benefits of finerenone vs placebo, irrespective of SGLT-2i use at baseline or at any time during the trial
- Patients treated with SGLT-2is at baseline had higher mean eGFR, lower median UACR, and lower SBP
- Reduction in UACR with finerenone observed in both groups
  - Results were independent of SGLT-2i use at baseline; a consistent magnitude of UACR reduction was demonstrated in patients with and without SGLT-2i use at baseline
- Overall safety was similar, with a lower number of hyperkalemia events in those treated with SGLT-2i at baseline

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Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; IQR, interquartile range; [K+], potassium concentration; LS, least squares; MI, myocardial infarction; NYHA, New York Heart Association; od, once daily; R, randomization; SAE, serious adverse event; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine.

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