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Efficacy and safety of finerenone in patients with CKD and T2D by GLP-1RA treatment

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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]
- This analysis aimed to report outcomes in FIDELIO-DKD by glucagon-like peptide-1 receptor agonist (GLP-1RA) use at baseline and during the trial

Key findings

- Finerenone reduced the relative risk of the primary kidney composite outcome by 18% and the key secondary cardiovascular (CV) composite outcome by 14%[1]
  - Results were consistent regardless of GLP-1RA use at baseline (*P*-interaction 0.15 and 0.51, respectively)
  - Cardiorenal benefit was also consistent considering GLP-1RA use during the trial
- Reduction in urine albumin-to-creatinine ratio (UACR) with finerenone was observed in patients with and without GLP-1RA use at baseline and during the trial
  - Results were independent of GLP-1RA use, with a potential benefit for UACR reduction on top of baseline GLP-1RA use

Background

- GLP-1RA treatment is recommended for some patients with T2D and CKD[2]
- CKD is a leading cause of morbidity and mortality in patients with T2D,[3–5] with the presence of CKD increasing the risk of CV disease, hypertension, and death[3–6]
- Several agents already approved for use in patients with T2D have demonstrated CV and renal benefits; these agents include GLP-1RAs[2]
- Finerenone is a novel, nonsteroidal, selective mineralocorticoid receptor agonist (MRA) that inhibits inflammation and fibrosis, and has been shown to reduce the risk of CV disease and CKD progression in patients with CKD and T2D[1,7,8]
- This analysis examines outcomes in FIDELIO-DKD by GLP-1RA use at baseline and during the trial, because patients with CKD and T2D may be treated with GLP-1RAs in clinical practice

Study design and methods

- FIDELIO-DKD included adults with CKD and T2D with and without GLP-1RA use at baseline[1,9]

Figure 1. FIDELIO-DKD: Study design

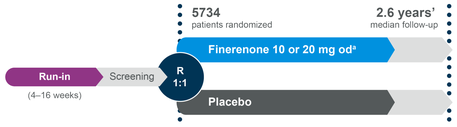


Figure 2. FIDELIO-DKD: Key eligibility

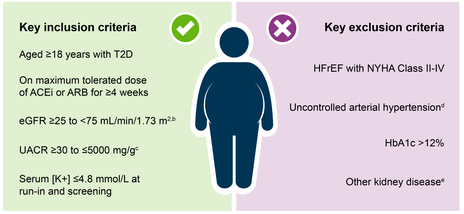
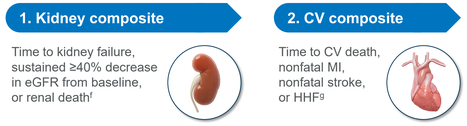


Figure 3. FIDELIO-DKD: Key endpoints



AIM OF THIS SUBGROUP ANALYSIS

To evaluate the impact of baseline GLP-1RA treatment on composite kidney and CV outcomes and safety in patients treated with finerenone or placebo

[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.[2] [g]Secondary composite CV outcome included the number of patients with CV death, nonfatal MI, nonfatal stroke, or HHF.[2]

Results

- Patients treated with GLP-1RAs at baseline had higher glycated hemoglobin (HbA1c), lower median UACR, and a longer duration of diabetes versus those without

Table 1. Baseline demographics and medications

Patient characteristic[a]	No GLP-1RA (n=5280)	GLP-1RA (n=394)
Age, years	66 ± 9	64 ± 8
Race, White	3304 (63)	288 (73)
Black/African American	238 (5)	26 (7)
Asian	1375 (26)	65 (17)
Sex, male	3713 (70)	270 (69)
SBP, mmHg	138 ± 14	139 ± 14
BMI, kg/m²	31 ± 6	34 ± 6
Duration of diabetes, years	16 ± 9	18 ± 8
HbA1c, %	7.7 ± 1.4	7.9 ± 1.2
eGFR, mL/min/1.73 m²	44 ± 13	45 ± 12
Serum potassium, mmol/L	4.4 ± 0.5	4.3 ± 0.4
UACR, mg/g, median (IQR)	860 (452–1635)	749 (409–1576)
History of CV disease	2439 (46)	166 (42)

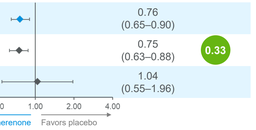
Medication use, n (%)	No GLP-1RA (n=5280)	GLP-1RA (n=394)
ACEi	1819 (35)	123 (31)
ARB	3455 (65)	270 (69)
Diuretics	2962 (56)	252 (64)
Statins	3888 (74)	327 (83)
Potassium-lowering agents	129 (2)	7 (2)
Glucose-lowering therapies	5130 (97)	394 (100)
Insulin and analogs	3354 (64)	283 (72)
SGLT-2 inhibitors	211 (4)	48 (12)
GLP-1RAs	5280 (100)	394 (100)
DPP-4 inhibitors	1502 (28)	20 (5)
Sulfonylureas	1250 (24)	48 (12)
Metformin	2277 (43)	213 (54)
Alpha-glucosidase inhibitors	308 (6)	16 (4)

[a]Values are n (%) or mean ± SD unless otherwise stated.

- At baseline, 394 (6.9%) of patients were receiving a GLP-1RA
- GLP-1RA was initiated as a new medication in 368 (6.5%) patients

Figure 4. Composite kidney outcomes

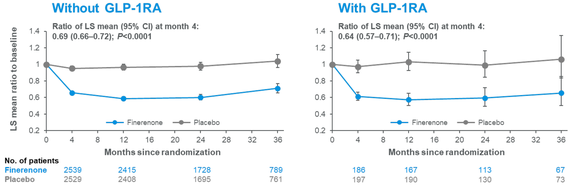
Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)[a]	*P*-interaction[b]
Primary composite kidney outcome[c]				
Overall FIDELIO-DKD population[1]	504/2833 (17.8)	600/2841 (21.1)	0.82 (0.73–0.93)	
No GLP-1RA at baseline	472/2644 (17.9)	568/2636 (21.5)	0.80 (0.71–0.91)	0.15
GLP-1RA at baseline	32/189 (16.9)	32/205 (15.6)	1.17 (0.71–1.90)	
Secondary composite kidney outcome[d]				
Overall FIDELIO-DKD population[1]	252/2833 (8.9)	326/2841 (11.5)	0.76 (0.65–0.90)	
No GLP-1RA at baseline	234/2644 (8.9)	306/2636 (11.6)	0.75 (0.63–0.88)	0.33
GLP-1RA at baseline	18/189 (9.5)	20/205 (9.8)	1.04 (0.55–1.96)	



- Kidney benefit was consistent irrespective of GLP-1RA use at baseline and during the trial[1]
- The benefit of finerenone on the primary kidney outcome was also consistent regardless of GLP-1RA use at any time (*P* value for interaction 0.31)[e]; however, the small sample size of patients taking a GLP-1RA makes it difficult to interpret the results

[a]Hazard ratios (95% CI) are based on the stratified Cox proportional hazards model estimated within each level of the subgroup variable. [b]Interaction *P* value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including the terms treatment group, baseline subgroup, and their interaction. [c]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] [d]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] [e]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 SBP, and duration of diabetes at baseline) was also used to determine the effect of GLP-1RA use at any time during the trial, including GLP-1RA use as a time-dependent covariate.

Figure 2. Change in UACR from baseline according to GLP-1RA use at baseline



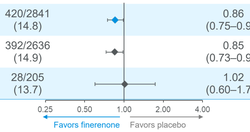
No. of patients								
Finerenone	2539	2415	1728	789	186	167	113	67
Placebo	2529	2408	1695	761	197	190	130	73

Full analysis set. Mixed model with factors 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 covariate.

- The change in UACR from baseline to month 4 was consistent irrespective of GLP-1RA use at baseline

Figure 6. Composite CV outcomes

Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)[a]	*P*-interaction[b]
Key secondary composite CV outcome[c]				
Overall FIDELIO-DKD population[1]	367/2833 (13.0)	420/2841 (14.8)	0.86 (0.75–0.99)	
No GLP-1RA at baseline	340/2644 (12.9)	392/2636 (14.9)	0.85 (0.73–0.98)	0.51
GLP-1RA at baseline	27/189 (14.3)	28/205 (13.7)	1.02 (0.60–1.74)	



- CV benefit was consistent irrespective of GLP-1RA use at baseline and during the trial[1]
- Finerenone benefit for the key secondary CV outcome was also consistent regardless of GLP-1RA use at any time (*P* value for interaction 0.86)[d]

[a]Hazard ratios (95% CI) are based on the stratified Cox proportional hazards model estimated within each level of the subgroup variable.[1] [b]Interaction *P* value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including the terms treatment group, baseline subgroup, and their interaction. [c]Secondary composite CV outcome included the number of patients with CV death, nonfatal MI, nonfatal stroke, or HHF. [d]Cox proportional hazards model after forward selection (including the following variables: history of CV disease, diuretics use at baseline, age at run-in, BMI at baseline, baseline HbA1c, baseline C-reactive protein, baseline serum creatinine, baseline serum albumin, and baseline SBP) was also used to determine the effect of GLP-1RA use at any time during the trial, including GLP-1RA use as a time-dependent covariate.

Safety

- Overall safety and incidence of investigator-reported hyperkalemia were similar between patients who received GLP-1RAs at baseline compared with those who did not (safety analysis set)

Table 2. Treatment-emergent adverse events

Treatment-emergent AE, n (%)	No GLP-1RA at baseline		GLP-1RA at baseline	
	Finerenone (n=2638)	Placebo (n=2628)	Finerenone (n=189)	Placebo (n=203)
Any AE	2292 (86.9)	2288 (87.1)	176 (93.1)	190 (93.6)
Related to study drug	594 (22.5)	414 (15.8)	52 (27.5)	35 (17.2)
Leading to permanent discontinuation	188 (7.1)	152 (5.8)	19 (10.1)	16 (7.9)
Any SAE	835 (31.7)	902 (34.3)	67 (35.4)	69 (34.0)
Related to study drug	44 (1.7)	32 (1.2)	4 (2.1)	2 (1.0)
Leading to permanent discontinuation	70 (2.7)	74 (2.8)	5 (2.6)	4 (2.0)
AE with outcome death	31 (1.2)	50 (1.9)	0 (0.0)	1 (0.5)
Treatment-emergent hyperkalemia AE, n (%)				
Any AE	480 (18.2)	235 (8.9)	36 (19.0)	20 (9.9)
Related to study drug	309 (11.7)	126 (4.8)	24 (12.7)	9 (4.4)
Leading to permanent discontinuation	58 (2.2)	22 (0.8)	6 (3.2)	3 (1.5)

- Of the patients who received a GLP-1RA at baseline, treatment-emergent AEs of interest (in >5% patients) included acute kidney injury (6.9% vs 9.5%) and hypoglycemia (5.9% vs 4.8%) in placebo and finerenone groups, respectively[a]

[a]Other treatment-emergent AEs of interest included the following: hypovolemia: no GLP-1RA, finerenone 4 (0.2%), placebo 1 (<0.1%); GLP-1RA, finerenone 0, placebo 0; pancreatitis: no GLP-1RA, finerenone 1 (<0.1%), placebo 3 (0.1%); GLP-1RA, finerenone 1 (0.5), placebo 0; acute pancreatitis: no GLP-1RA, finerenone 7 (0.3%), placebo 9 (0.1%); GLP-1RA, finerenone 0, placebo 0; chronic pancreatitis: no GLP-1RA, finerenone 5 (0.2%), placebo 6 (0.2%); GLP-1RA, finerenone 0, placebo 0; medullary thyroid carcinoma: none in any treatment groups.

Conclusions

Summary of treatment effects of finerenone with and without concomitant GLP-1RA use

- Consistent kidney and CV benefits of finerenone versus placebo, irrespective of GLP-1RA use[1]
- Reduction in UACR with finerenone observed in both groups
  - Results were independent of GLP-1RA use at baseline, with a potential benefit for UACR reduction on top of baseline GLP-1RA use
- Overall safety and hyperkalemia incidence were similar in patients with and without GLP-1RA use

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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; DPP-4i, dipeptidyl peptidase-4 inhibitor; 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-2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

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