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Efficacy and safety of finerenone in patients with CKD and T2D by baseline insulin treatment

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Rationale and objective

- In FIDELIO-DKD (NCT02540993), finerenone reduced the incidence of cardiorenal events in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) without affecting glycated hemoglobin (HbA1c)[1]
- This subgroup analysis reports outcomes by insulin (and insulin analogs) use at baseline

Key findings

- Finerenone reduced the relative risk of a primary composite kidney outcome by 18% and a key secondary composite cardiovascular (CV) outcome by 14% versus placebo[1]
  - Results were consistent regardless of insulin use at baseline (*P*-interaction 0.56 and 0.33, respectively)
- Adverse events were similar between finerenone and placebo, independent of insulin use

Background

- 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[1,2]
- 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]
- This analysis examines outcomes in FIDELIO-DKD by insulin use at baseline and during the trial, because many patients with CKD and T2D are treated with insulin in clinical practice

Study design and methods

- This subgroup analysis from FIDELIO-DKD evaluated the impact of baseline insulin use in adults with CKD and T2D[1]

Figure 1. FIDELIO-DKD: Study design

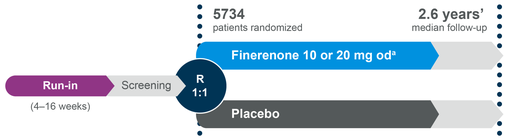


Figure 2. FIDELIO-DKD: Key eligibility

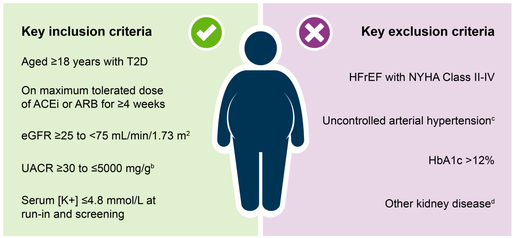
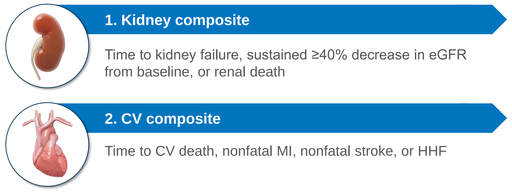


Figure 3. FIDELIO-DKD: Key endpoints



AIM OF THIS SUBGROUP ANALYSIS

To evaluate the impact of baseline insulin use
(including insulin analogs) 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 od was allowed any time after the initiation of finerenone or placebo. [b]Patients with moderately elevated albuminuria (UACR 30–300 mg/g) were required to also have diabetic retinopathy. [c]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. [d]Known significant nondiabetic kidney disease, including clinically relevant renal artery stenosis.

Results

- Patients using insulin at baseline had longer duration of diabetes, more cardiovascular disease (CVD), and higher body mass index (BMI), HbA1c, and urine albumin-to-creatinine ratio (UACR)

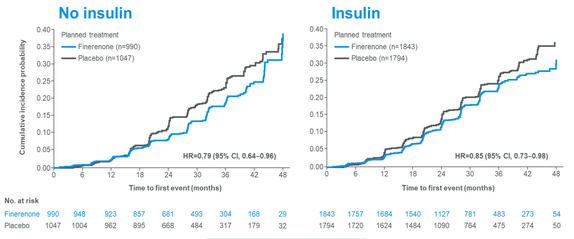
Table 1. Baseline demographics and medications

Patient characteristic[a]	No insulin (n=2037)	Insulin (n=3637)
Age, years	66.4 ± 9	65.1 ± 9
Sex, male	1469 (72)	2514 (69)
SBP, mmHg	137.2 ± 14.4	138.5 ± 14.3
BMI, kg/m²	30.1 ± 6	31.7 ± 6
Duration of diabetes, years	13.0 ± 8	18.6 ± 9
HbA1c, %	7.0 ± 1	8.0 ± 1
eGFR, mL/min/1.73 m²	45.1 ± 12.5	43.9 ± 12.6
UACR, mg/g, median (IQR)	785 (443–1482)	819 (448–1715)
History of CVD	836 (41)	1769 (49)
Medication use, n (%)		
ACEi	664 (33)	1278 (35)
ARB	1367 (67)	2358 (65)
Beta blockers	989 (49)	1979 (54)
Diuretics	1055 (52)	2159 (59)
Statins	1458 (72)	2757 (76)
Antidiabetic therapies	1887 (93)	3637 (100)
Metformin	1146 (56)	1344 (37)
Sulfonylureas	909 (45)	418 (11)
DPP-4 inhibitors	782 (38)	740 (20)
GLP-1RAs	111 (5)	283 (8)
SGLT-2 inhibitors	86 (4)	173 (5)
α-glucosidase inhibitors	137 (7)	187 (5)

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

- At baseline, 3637 (64.1%) patients were using insulin
- After the study start, insulin was initiated as a new medication in 469 (8.3%) patients

Figure 4. Kidney outcomes according to insulin use at baseline



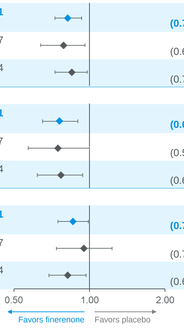
Full analysis set.

***P* value for interaction = 0.56**

- The effects of finerenone on the primary composite kidney outcome were consistent irrespective of baseline insulin use

Figure 5. Cardiorenal outcomes according to insulin use at baseline

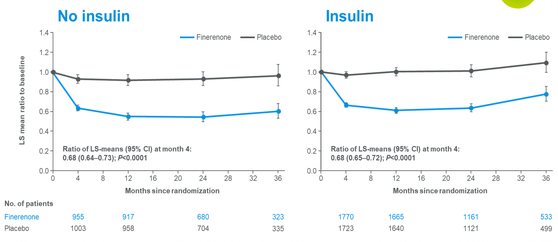
Outcome	Finerenone n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*P*-interaction
Primary composite kidney outcome[a]				
Overall FIDELIO-DKD population[1]	**504/2833 (17.8)**	**600/2841 (21.1)**	**0.82 (0.73–0.93)**	
No insulin at baseline	172/990 (17.4)	218/1047 (20.8)	0.79 (0.64–0.96)	0.56
Insulin at baseline	332/1843 (18.0)	382/1794 (21.3)	0.85 (0.73–0.98)	
Secondary composite kidney outcome[b]				
Overall FIDELIO-DKD population[1]	**252/2833 (8.9)**	**326/2841 (11.5)**	**0.76 (0.65–0.90)**	
No insulin at baseline	86/990 (8.7)	119/1047 (11.4)	0.75 (0.57–1.00)	0.93
Insulin at baseline	166/1843 (9.0)	207/1794 (11.5)	0.77 (0.62–0.94)	
Key secondary composite kidney outcome[c]				
Overall FIDELIO-DKD population[1]	**367/2833 (13.0)**	**420/2841 (14.8)**	**0.86 (0.75–0.99)**	
No insulin at baseline	112/990 (11.3)	121/1047 (11.6)	0.95 (0.74–1.23)	0.33
Insulin at baseline	255/1843 (13.8)	299/1794 (16.7)	0.82 (0.69–0.97)	



Full analysis set. [a]Kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death. [b]Kidney failure, sustained ≥57% decrease in eGFR from baseline, or renal death. [c]A composite of time to first onset of death from CV causes, nonfatal MI, nonfatal stroke, or HHF.

- Cardiorenal benefits of finerenone were consistent independent of insulin use at baseline

Figure 6. Change in UACR from baseline according to insulin use at baseline



Full analysis set. Mixed model including covariates: treatment group, stratification factors (region, eGFR category, and type of albuminuria at screening), time, treatment over time, log-transformed baseline value nested within type of albuminuria at screening, and log-transformed baseline value over time.

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

Safety

- The safety profile of finerenone was consistent regardless of insulin use at baseline

Table 2. Safety: Treatment-emergent adverse events

	No insulin		Insulin	
	Finerenone (n=989)	Placebo (n=1041)	Finerenone (n=1838)	Placebo (n=1790)
Any AE	854 (86.3)	903 (86.7)	1614 (87.8)	1575 (88.0)
AE related to study drug	205 (20.7)	148 (14.2)	441 (24.0)	301 (16.8)
AE leading to permanent discontinuation	76 (7.7)	69 (6.6)	131 (7.1)	99 (5.5)
Any serious AE	282 (28.5)	318 (30.5)	620 (33.7)	653 (36.5)
Serious AE related to study drug	12 (1.2)	11 (1.1)	36 (2.0)	23 (1.3)
Serious AE leading to permanent discontinuation	26 (2.6)	33 (3.2)	49 (2.7)	45 (2.5)
Most common AEs by organ class (>8% of patients)				
Hyperkalemia	133 (13.4)	67 (6.4)	313 (17.0)	154 (8.6)
Peripheral edema	47 (4.8)	87 (8.4)	139 (7.6)	217 (12.1)
Nasopharyngitis	106 (10.7)	119 (11.4)	135 (7.3)	131 (7.3)
Hypertension	67 (6.8)	97 (9.3)	145 (7.9)	176 (9.8)
Hypoglycemia	30 (3.0)	29 (2.8)	121 (6.6)	165 (9.2)

Safety analysis set.

Conclusions

This subgroup analysis suggests finerenone may be an important advance in treatment for patients with CKD and T2D, independent of insulin use

Consistent kidney and CV benefits of finerenone versus placebo were observed irrespective of insulin use

Overall, AEs were similar with finerenone and placebo, independent of insulin use. *Hyperkalemia was increased with finerenone, but its clinical impact was minimal*

Limitations: Secondary subgroup analysis—patients not recruited according to baseline insulin use

Affiliations

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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; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; 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; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; IQR, interquartile range; [K+], potassium concentration; LS, least squares; MI, myocardial infarction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; od, once daily; R, randomization; RAS, renin–angiotensin system; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.

References:

1. Bakris GL, et al. *N Engl J Med*. 2020;383(23):2219–2229.
2. Agarwal R, et al. *Eur Heart J*. 2021;42(2):152–161.