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FIDELIO-DKD study: Analysis of effects of finerenone by baseline HbA1c

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Background and aim

- Mineralocorticoid receptor (MR) overactivation causes kidney and cardiovascular (CV) damage through inflammation and fibrosis
- Finerenone is a novel, nonsteroidal, selective MR antagonist (MRA) that inhibits inflammation and fibrosis in preclinical models[1]
- In FIDELIO-DKD, finerenone significantly reduced the risk of[2]:
  - Chronic kidney disease (CKD) progression by 18% (number needed to treat [NNT]=29)
  - CV morbidity and mortality by 14% (NNT=42)
  - NNT to prevent one event based on absolute risk reductions at 36 months
- Evidence regarding the relationship between glycemic control and disease outcomes in patients with advanced CKD and type 2 diabetes (T2D) from large phase 3 trials is lacking

Aim of this subgroup analysis of FIDELIO-DKD

- To evaluate the impact of baseline glycated hemoglobin (HbA1c) level (< or ≥ median at baseline) on the composite kidney and CV outcomes and safety in patients treated with finerenone or placebo

Figure 1. MR overactivation through multiple mechanisms[3,4]

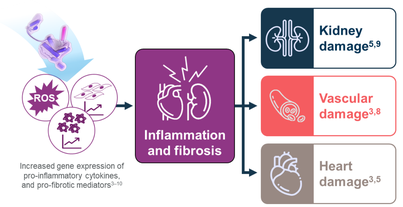
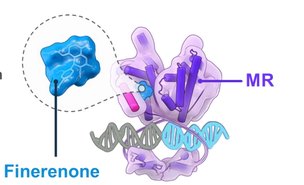


Figure 2. Finerenone binds to the MR with high selectivity



Study design and methods

Figure 3. FIDELIO-DKD: Study design

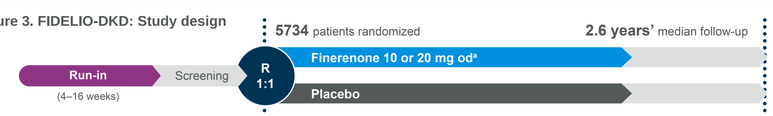
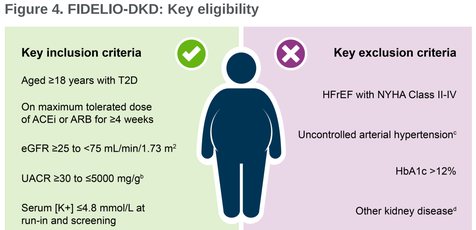
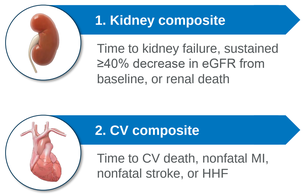


Figure 4. FIDELIO-DKD: Key eligibility



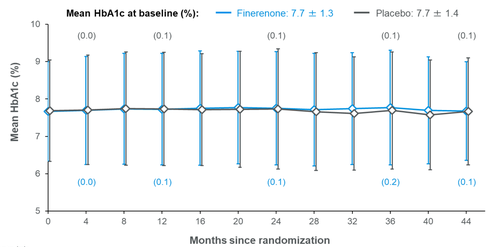
[a]10 mg if screening eGFR <60 mL/min/1.73 m²; 20 mg if ≥60 mL/min/1.73 m². Up-titration encouraged from month 1 if serum potassium ≤4.8 mmol/L and eGFR stable. A decrease in the dose from 20 to 10 mg od was allowed any time after the initiation of finerenone or placebo. [b]Patients with moderately elevated 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.

Figure 5. FIDELIO-DKD: Key endpoints



Results

Figure 6. In FIDELIO-DKD,[2] finerenone had no effect on HbA1c



Patients (n):						
Finerenone	2821	2697	2605	1889	893	346
Placebo	2828	2694	2610	1871	870	349

Data are mean ± SD. Numbers in parentheses show mean change from baseline; error bars show SD.

- Patients in both baseline HbA1c groups had advanced CKD

Table 1. Baseline demographics and disease characteristics

	HbA1c <7.5% (n=2794)	HbA1c ≥7.5% (n=2869)
Age, years	66 ± 9	65 ± 9
Gender, male	2073 (74)	1904 (66)
Duration of T2D, years	15 ± 9	18 ± 8
BMI, kg/m²	30 ± 6	32 ± 6
SBP, mmHg	138 ± 15	139 ± 14
Serum [K+], mmol/L	4.4 ± 0.5	4.4 ± 0.5
eGFR, mL/min/1.73 m²	44 ± 13	45 ± 13
UACR, mg/g, median (IQR)	798 (445–1567)	815 (447–1693)

Values are n (%) or mean ± SD unless otherwise stated. Full analysis set. Missing data for n=7 patients (finerenone) and n=4 patients (placebo).

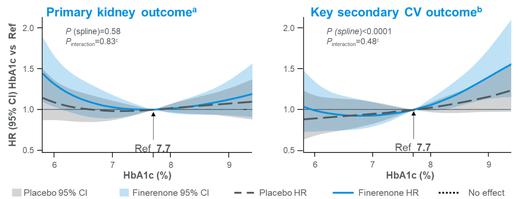
- A higher proportion of patients with HbA1c ≥7.5% were receiving insulin at baseline

Table 2. Baseline concomitant medications

	HbA1c <7.5% (n=2794)	HbA1c ≥7.5% (n=2869)
ACEi	914 (33)	1022 (36)
ARB	1875 (67)	1845 (64)
Diuretics	1529 (55)	1681 (59)
Glucose-lowering therapies	2672 (96)	2842 (99)
Insulin and analogs	1353 (48)	2279 (79)
Metformin	1264 (45)	1219 (43)
Sulfonylureas	687 (25)	639 (22)
DPP-4 inhibitors	833 (30)	686 (24)
GLP-1RAs	158 (6)	235 (8)
SGLT-2is	100 (4)	159 (6)

Full analysis set. Missing data for n=7 patients (finerenone) and n=4 patients (placebo).

Figure 7. Relationship between baseline HbA1c and primary composite kidney and key secondary composite CV outcomes



Full analysis set. Cox proportional hazards models fitted separately, by treatment group and stratified by region, albuminuria at screening, and eGFR at screening, and including a cubic B-spline of HbA1c with 3 equally spaced knots.
[a]Kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death. [b]A composite of time to first onset of death from CV causes, nonfatal MI, nonfatal stroke, or HHF. [c]Finerenone vs placebo.

- Cardiorenal benefits of finerenone were consistent independent of HbA1c category at baseline

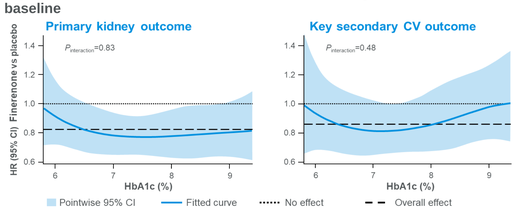
Figure 8. Primary and secondary composite outcomes

Outcome	Finerenone (n=2826) n/N (%)	Placebo (n=2837) n/N (%)	Hazard ratio (95% CI)	P-interaction
Primary composite kidney outcome[a]				
HbA1c <7.5%	260/1384 (19)	304/1410 (22)	0.86 (0.73–1.02)	0.41
HbA1c ≥7.5%	243/1442 (17)	296/1427 (21)	0.78 (0.66–0.93)	
Secondary composite kidney outcome[b]				
HbA1c <7.5%	129/1384 (9)	171/1410 (12)	0.78 (0.62–0.98)	0.80
HbA1c ≥7.5%	122/1442 (9)	155/1427 (11)	0.74 (0.59–0.94)	
Key secondary composite kidney outcome[c]				
HbA1c <7.5%	164/1384 (12)	187/1410 (13)	0.88 (0.71–1.09)	0.70
HbA1c ≥7.5%	201/1442 (14)	233/1427 (16)	0.83 (0.69–1.01)	

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 HbA1c category at baseline modeled as a continuous variable

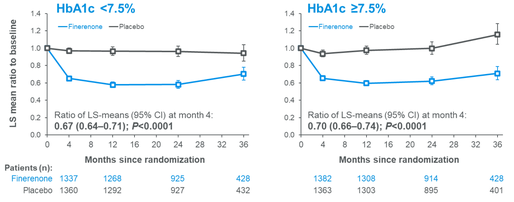
Figure 9. Cardiorenal benefits of finerenone according to HbA1c levels at baseline



Full analysis set. A Cox proportional hazards model is fitted stratified by region, albuminuria at screening, and eGFR at screening, including treatment, a cubic B-spline of HbA1c with 3 equally spaced knots and its interaction with treatment as covariates.

- The change in UACR from baseline to month 4 was consistent irrespective of HbA1c at baseline

Figure 10. Change in UACR from baseline according to HbA1c levels



Patients (n):								
Finerenone	1337	1268	925	428	1382	1308	914	428
Placebo	1360	1292	927	432	1363	1303	895	401

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 safety profile of finerenone was consistent regardless of HbA1c at baseline

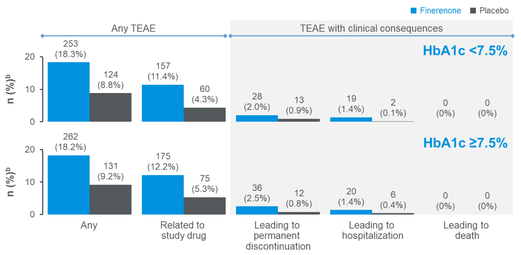
Table 3. General safety outcomes

	HbA1c <7.5%		HbA1c ≥7.5%	
	Finerenone (n=1382)	Placebo (n=1407)	Finerenone (n=1439)	Placebo (n=1421)
Any AE	1206 (87)	1229 (87)	1258 (87)	1246 (88)
AE related to study drug	312 (23)	221 (16)	333 (23)	228 (16)
AE leading to permanent discontinuation	98 (7)	92 (7)	108 (8)	75 (5)
Any serious AE	415 (30)	448 (32)	485 (34)	523 (37)
Serious AE related to study drug	23 (2)	16 (1)	24 (2)	18 (1)
Serious AE leading to permanent discontinuation	36 (3)	39 (3)	38 (3)	39 (3)

Safety analysis set. Missing data for n=6 patients (finerenone) and n=3 patients (placebo).

- Independent of HbA1c at baseline, finerenone increased the incidence of hyperkalemia, but the clinical impact was minimal

Figure 11. Investigator-reported hyperkalemia[a]



[a]Using the MedDRA preferred terms "hyperkalemia" and "blood potassium increased." [b]Patients with TEAE.

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Abbreviations

ACEi, angiotensin-converting enzyme inhibitor; AE, adverse event; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; 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; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; NYHA, New York Heart Association; od, once daily; R, randomization; RASi, renin–angiotensin system inhibitor; ROS, reactive oxygen species; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio.

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Summary

The kidney and CV benefits of finerenone vs placebo were consistent, irrespective of HbA1c at baseline

Overall, adverse events were similar with finerenone and placebo, independent of HbA1c at baseline

Risk of hyperkalemia was increased with finerenone, but its clinical impact was minimal

Limitations:

- Secondary subgroup analysis—patients not recruited according to baseline HbA1c
- Post-baseline changes in HbA1c were not considered

Conclusions

Finerenone is a novel, nonsteroidal, selective MRA that inhibits inflammation and fibrosis associated with MR overactivation in preclinical models

In FIDELIO-DKD:

- Finerenone reduced the incidence of kidney and CV outcomes in patients with CKD and T2D, despite differences in baseline glycemic control
- Treatment with finerenone was well-tolerated