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Effects of finerenone on kidney and cardiovascular outcomes in patients with chronic kidney disease and type 1 diabetes: An analysis from FINE-ONE and FIDELITY

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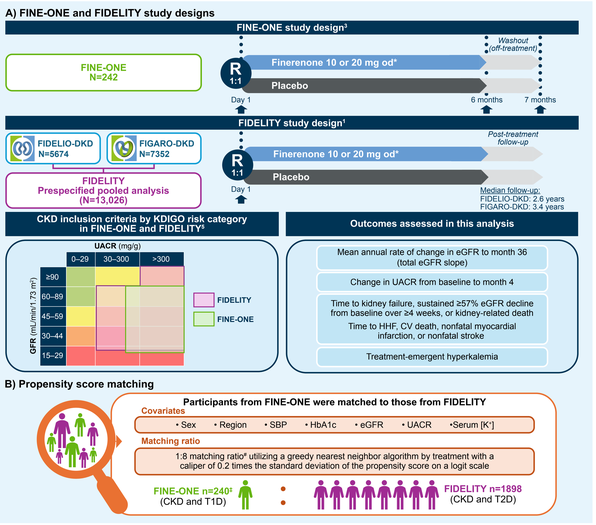
Background

- In FIDELITY, a prespecified pooled analysis of the phase III FIDELIO-DKD and FIGARO-DKD trials (NCT02540993 and NCT02545049, respectively), the nonsteroidal mineralocorticoid receptor antagonist finerenone reduced urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR) decline, and the risk of kidney and cardiovascular outcomes compared with placebo in people with chronic kidney disease (CKD) and type 2 diabetes (T2D)[1]
  - In this population, early UACR reduction with finerenone accounted for up to 84% of its benefit on reducing kidney outcome risk[2]
- In adults with type 1 diabetes (T1D) and CKD, large, long-term clinical outcome trials are more difficult to conduct than in those with T2D and CKD given the relatively low disease prevalence (~1.5% of diabetes cases)
- Finerenone significantly reduced UACR compared with placebo in people with T1D and CKD in the FINE-ONE trial (NCT05901831), but long-term clinical outcomes were not investigated[3]
  - UACR was used as a bridging biomarker to translate evidence of the efficacy of finerenone in people with T2D and CKD to those with T1D and CKD[4,5]
- This propensity score analysis aimed to estimate long-term outcomes with finerenone in people with T1D and CKD based on observed kidney and cardiovascular event rates and eGFR declines in FINE-ONE–like patients from the FIDELITY pooled dataset

Methods

- The FINE-ONE and FIDELITY study designs, CKD inclusion criteria, and outcomes assessed in this analysis are shown in **Figure 1A**
- Participants in FINE-ONE and FIDELITY on optimized renin–angiotensin system inhibition, randomized 1:1 to finerenone or placebo, were matched 1:8 via propensity score based on baseline characteristics (**Figure 1B**)

Figure 1. Study design



*10 mg od: eGFR ≥25 to <60 mL/min/1.73 m²; 20 mg od: eGFR ≥60 mL/min/1.73 m²; #the matching ratio was chosen by minimizing the maximum absolute standardized mean difference and precision of treatment effects; ‡propensity score could not be estimated for two participants from FINE-ONE as they had missing values for HbA1c. The median absolute value of the standardized mean difference for the matched population was 0.02

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HHF, hospitalization for heart failure; [K⁺], potassium concentration; KDIGO, Kidney Disease: Improving Global Outcomes; od, once daily; R, randomized; SBP, systolic blood pressure; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio

Results

Baseline characteristics

- Overall, baseline characteristics were similar between matched participants, except that insulin use was more frequent and diabetes duration was longer in FINE-ONE versus FIDELITY (**Table 1**)

Table 1. Baseline characteristics of FINE-ONE and FIDELITY after propensity score matching

Characteristic	FINE-ONE (n=240)*		FIDELITY (n=1898)	
	Finerenone (n=120)	Placebo (n=120)	Finerenone (n=948)	Placebo (n=950)
Sex, male, n (%)	79 (65.8)	77 (64.2)	602 (63.5)	597 (62.8)
Region, n (%)				
Europe	66 (55.0)	54 (45.0)	533 (56.2)	413 (43.5)
North America	38 (31.7)	43 (35.8)	296 (31.2)	360 (37.9)
Asia	16 (13.3)	23 (19.2)	119 (12.6)	177 (18.6)
Serum [K⁺], mmol/L, mean ± SD	4.6 ± 0.4	4.6 ± 0.4	4.6 ± 0.4	4.5 ± 0.4
HbA1c, %, mean ± SD	7.8 ± 1.1	7.5 ± 1.0	7.8 ± 1.4	7.5 ± 1.3
eGFR, mL/min/1.73 m², mean ± SD	59.0 ± 19.5	58.7 ± 19.1	59.1 ± 22.6	58.3 ± 22.2
UACR, mg/g, median (Q1–Q3)	574.6 (315.8–1224.9)	506.4 (290.0–1211.1)	553.5 (243.3–1244.4)	504.5 (176.7–1119.7)
SBP, mmHg, mean ± SD	136.5 ± 15.8	134.2 ± 17.9	136.9 ± 13.3	133.8 ± 14.4
Diabetes duration,# years, mean ± SD	32.0 ± 14.1	31.9 ± 14.5	15.6 ± 8.6	15.3 ± 8.8‡
Insulin use,# n (%)	120 (100.0)	120 (100.0)	567 (59.8)	507 (53.4)

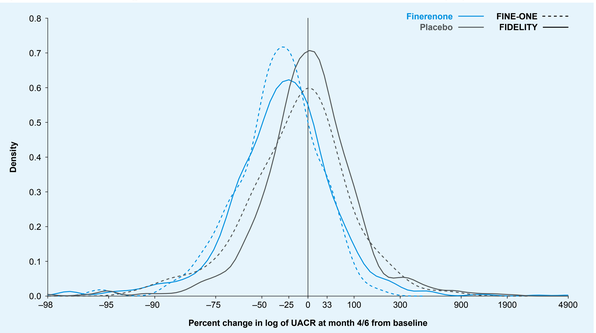
*Propensity score could not be estimated for two participants from FINE-ONE as they had missing values for HbA1c; #not used for matching; ‡one participant had missing data for diabetes duration

eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; [K⁺], potassium concentration; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; UACR, urinary albumin-to-creatinine ratio

Effect of finerenone on UACR over time

- In the FIDELITY-matched population, the distribution of change from baseline in UACR at month 4 was similar to that in the FINE-ONE population at month 6 (**Figure 2**)
- Finerenone reduced UACR by 31% at month 4 ($p<0.001$)

Figure 2. Logarithmic change in UACR from baseline to month 4 in the FIDELITY-matched population and change from baseline to month 6 in the FINE-ONE population

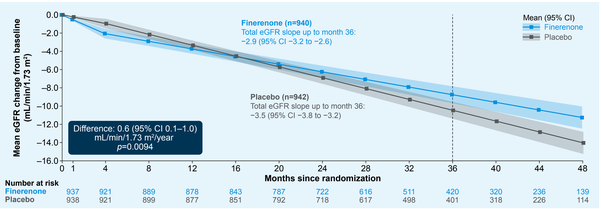


UACR, urinary albumin-to-creatinine ratio

Effect of finerenone on total eGFR slope

- In the FIDELITY-matched population, finerenone reduced total eGFR slope by 0.6 mL/min/1.73 m²/year versus placebo (95% confidence interval [CI] 0.1–1.0; **Figure 3**)

Figure 3. Total eGFR slope in the FIDELITY-matched population*



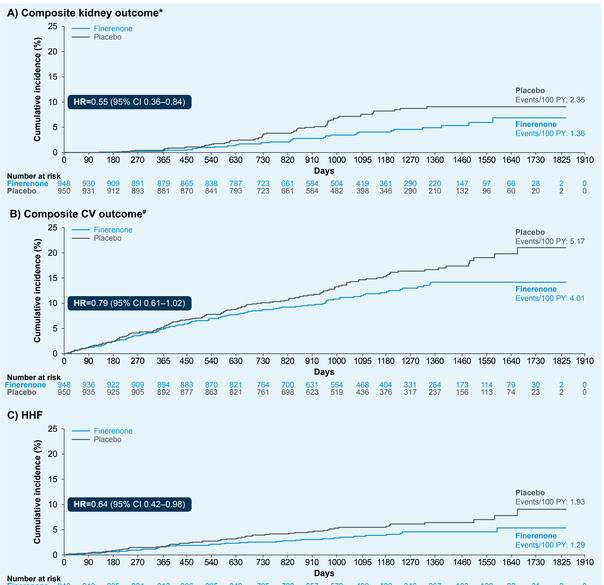
*Analyzed using a two-slope linear spline mixed-effects model. Fixed effects included study, region, type of albuminuria at screening, eGFR category at screening, and CV disease history. Only patients with one or more post-baseline eGFR measurements were considered for analysis. Values after the onset date of end-stage kidney disease were excluded from the analysis. The FIDELITY population reference values including unmatched patients for total slope (95% CI) were: finerenone −3.1 (−3.2 to −3.0), placebo −3.6 (−3.7 to −3.5). Total slope was defined as the mean annual rate of change in eGFR from baseline to month 36

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate

Effect of finerenone on kidney and CV outcomes

- Finerenone reduced composite kidney outcome risk by 45% (95% CI 16–64) and hospitalization for heart failure risk by 36% (95% CI 2–58) versus placebo (**Figure 4**)

Figure 4. Time-to-event outcomes by treatment



Events based on a sustained decrease in eGFR are considered from randomization up until 5 months after the last eGFR is recorded at a clinic visit. Stratified Cox models with the stratification factors study, history of CV disease, region, eGFR category at screening, and type of albuminuria at screening were fitted. Cumulative incidence was calculated using Aalen–Johansen estimates.

*Time to onset of kidney failure, sustained ≥57% decrease in eGFR from baseline over ≥4 weeks, or kidney-related death; #time to onset of HHF, CV death, nonfatal myocardial infarction, or nonfatal stroke

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; PY, patient-years

Treatment-emergent hyperkalemia in the FIDELITY-matched population

- Overall, the incidence of hyperkalemia was more frequent with finerenone (16.5%) versus placebo (7.8%), with related treatment discontinuation (1.7% vs 0.8%) and hospitalization rates (1.1% vs 0.3%) being low

Table 2. Treatment-emergent hyperkalemia

Events, n (%)	Finerenone (n=947)	Placebo (n=948)	Total (n=1895)
Any hyperkalemia	156 (16.5)	74 (7.8)	230 (12.1)
Drug-related	97 (10.2)	40 (4.2)	137 (7.2)
Leading to permanent discontinuation	16 (1.7)	8 (0.8)	24 (1.3)
Any serious hyperkalemia	13 (1.4)	5 (0.5)	18 (0.9)
Drug-related	9 (1.0)	3 (0.3)	12 (0.6)
Leading to death	0 (0)	0 (0)	0 (0)
Life-threatening	0 (0)	1 (0.1)	1 (<0.1)
Leading to hospitalization	10 (1.1)	3 (0.3)	13 (0.7)

The treatment-emergent period was defined as the time from study intervention start until the end of study intervention + 3 days. Hyperkalemia included adverse events with MedDRA codes 10020646 (Hyperkalemia) and 10005725 (Blood potassium increased). A serious adverse event could fulfil more than one reason for seriousness

MedDRA, Medical Dictionary for Regulatory Activities

Conclusions

- In the FIDELITY-matched population, finerenone slowed the rate of kidney disease progression and reduced kidney and CV outcome risk versus placebo
- These data suggest that UACR reduction with finerenone is likely to lead to long-term kidney and CV benefits in patients with T1D and CKD, as seen in matched patients with T2D and CKD

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Disclosures

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