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Effect of finerenone treatment discontinuation on kidney and CV outcomes in patients with CKD and T2D: A FIDELITY analysis

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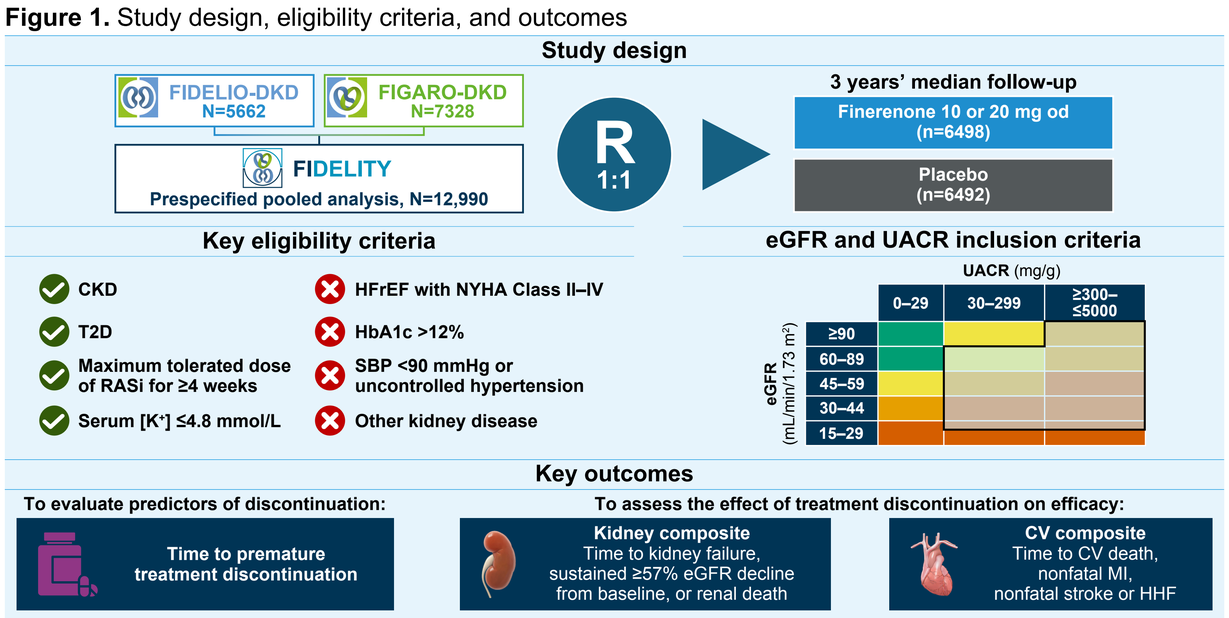
Background

- Diabetes is currently estimated to affect over 800 million people worldwide, with type 2 diabetes (T2D) accounting for over 90% of cases[1,2]
- T2D is a global leading cause of chronic kidney disease (CKD), and approximately 40% of people living with diabetes eventually develop CKD[3]
  - Both conditions left inadequately treated can lead to end-stage kidney disease and heart failure, since damage to the kidneys induces cardiovascular (CV) complications and vice versa through interlinked pathophysiological mechanisms[4,5]
- Current guidelines recommend multiple therapies for people with comorbid CKD and T2D, but the impact of discontinuing such treatments is currently not well-understood, especially for drugs approved in the last decade, such as finerenone[6,7]
- Finerenone is a distinct, selective, nonsteroidal mineralocorticoid receptor antagonist that inhibits mineralocorticoid receptor overactivation[8]
- In FIDELITY, a prespecified pooled analysis combining data from the phase III randomized, double-blind, placebo-controlled, multicenter clinical trials FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049), finerenone reduced the risk of kidney disease progression and CV events compared with placebo in participants with CKD and T2D[8]
- Over a median follow-up of 2.6 and 3.4 years, 24.1% and 21.4% of participants in FIDELIO-DKD and FIGARO-DKD, respectively, permanently discontinued finerenone treatment, excluding discontinuations due to death[9,10]
- This FIDELITY post hoc analysis aimed to explore predictors of premature finerenone treatment discontinuation and to assess the effect of treatment discontinuation on kidney and CV outcomes in participants with CKD and T2D

Study design and methods

- The study design, key eligibility criteria for FIDELIO-DKD and FIGARO-DKD, and key outcomes assessed in this FIDELITY post hoc analysis are described in **Figure 1**
  - Adults with CKD and T2D on optimized renin–angiotensin system blockade and with serum potassium levels ≤4.8 mmol/L at both run-in and screening were randomized 1:1 to receive once-daily oral treatment with finerenone or matching placebo[8]
  - CKD was defined as either: i) urine albumin-to-creatinine ratio (UACR) 30–<300 mg/g and estimated glomerular filtration rate (eGFR) 25−≤90 mL/min/1.73 m^2, or ii) UACR 300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2

Figure 1. Study design, eligibility criteria, and outcomes



CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; [K+], potassium concentration; MI, myocardial infarction; NYHA, New York Heart Association; od, once daily; R, randomization; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

Outcomes

- To evaluate predictors of treatment discontinuation, the main outcome assessed in this post hoc analysis was time to premature discontinuation
  - Treatment discontinuations due to death were excluded from the analysis
- To investigate the effect of finerenone treatment discontinuation on efficacy outcomes, the following outcomes were assessed:
  - A composite kidney outcome, defined as time to kidney failure, a sustained decrease in eGFR ≥57% from baseline over at least 4 weeks, or kidney-related death
  - A composite CV outcome, defined as time to CV death, nonfatal stroke, nonfatal myocardial infarction, or hospitalization for heart failure

Statistical analysis

- Baseline demographics, reasons for treatment discontinuation, and efficacy outcome analyses were based on the full analysis set, which included all randomized participants, excluding those with critical Good Clinical Practice violations
- Analyses to identify and assess predictors of treatment discontinuation were conducted in the safety analysis set, which included randomized participants who took ≥1 dose of study drug and without critical Good Clinical Practice violations
- Baseline characteristics were selected as potential predictors of treatment discontinuation based on clinically relevant factors and observed differences in univariate Cox models
  - The identified factors were analyzed in a multivariate Cox proportional hazards model using automatic variable selection based on Akaike information criterion
- The effect of treatment discontinuation on efficacy outcomes was assessed using stratified Cox models with treatment discontinuation as a time-varying covariate
- Treatment effects derived from the Cox proportional hazards models were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs)
- All analyses reported here were performed with the use of SAS software, version 9.4 (SAS Institute Inc.)

Results

Participants and baseline characteristics

- Of 12,990 participants included in the full analysis set, 2889 (22.2%) prematurely discontinued treatment for reasons other than death (finerenone arm: 22.8%; placebo arm: 21.6%) while 10,101 (77.8%) remained on treatment (finerenone arm: 77.2%; placebo arm: 78.4%)
- Baseline characteristics and medication use were generally balanced between treatment arms; however, a few key differences were observed between participants who prematurely discontinued treatment and those who did not

Reasons for premature discontinuation

- The primary reason for premature discontinuation of study drug in both treatment arms was the occurrence of adverse events (9.0%: finerenone; 8.7%: placebo) (**Table 1**)
  - The incidence of treatment-emergent adverse events leading to study drug discontinuation was slightly higher in participants treated with finerenone (6.4%) versus placebo (5.4%)
  - The rate of treatment discontinuation due to hyperkalemia was low in both the finerenone (1.7%) and placebo (0.6%) arms

Table 1. Primary reasons for premature discontinuation of study drug by treatment arm

n (%)	Finerenone (n=6498)	Placebo (n=6492)	Total (n=12,990)
Maintained study drug	4671 (71.9)	4679 (72.1)	9350 (72.0)
Prematurely discontinued study drug	1827 (28.1)	1813 (27.9)	3640 (28.0)
Primary reason: Death	343 (5.3)	408 (6.3)	751 (5.8)
Primary reasons (other than death)	1484 (22.8)	1405 (21.6)	2889 (22.2)
Adverse event	583 (9.0)	567 (8.7)	1150 (8.9)
Withdrawal by participant	402 (6.2)	386 (5.9)	788 (6.1)
Physician decision	300 (4.6)	242 (3.7)	542 (4.2)
Technical problems	74 (1.1)	91 (1.4)	165 (1.3)
Protocol deviation	21 (0.3)	30 (0.5)	51 (0.4)
Noncompliance with study drug	29 (0.4)	19 (0.3)	48 (0.4)
Participant decision: COVID-19 pandemic related	26 (0.4)	21 (0.3)	47 (0.4)
Other*	15 (0.2)	13 (0.2)	28 (0.2)
Logistical reason: COVID-19 pandemic related	4 (<0.1)	11 (0.2)	15 (0.1)
Site terminated by sponsor	9 (0.1)	5 (<0.1)	14 (0.1)
Lost to follow-up	6 (<0.1)	6 (<0.1)	12 (0.1)
Physician decision: COVID-19 pandemic related	7 (0.1)	3 (<0.1)	10 (0.1)
Participant decision	6 (<0.1)	4 (<0.1)	10 (0.1)
Deterioration of general conditions	1 (<0.1)	5 (<0.1)	6 (<0.1)
Pregnancy	0 (0)	1 (<0.1)	1 (<0.1)
Progressive disease	0 (0)	1 (<0.1)	1 (<0.1)
Logistical reason	1 (<0.1)	0 (0)	1 (<0.1)

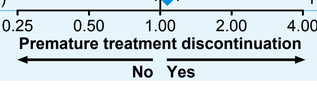
Primary reasons for premature drug discontinuation in FIDELITY are listed from most to least frequent and are shown for the full analysis set.
*'Other' reasons included 'protocol-driven decision point,' 'site closed by health authority,' 'recruitment stopped by sponsor,' and 'qualified but not needed'

Predictors of treatment discontinuation

- In the finerenone arm, the risk of treatment discontinuation was increased in participants with older age, Black and White race versus Asian race, with lower eGFR, higher UACR, and higher serum potassium (**Figure 2**)
  - An interaction analysis showed that no significant heterogeneity in the effect of baseline characteristics on discontinuation was detected between the finerenone and placebo arms for any of the variables assessed (data not shown)

Figure 2. Multivariate Cox model for time to premature treatment discontinuation in the finerenone arm

Covariate	Category	n/N (%)	HR (95% CI)	*p*-value (Wald)	Overall *p*-value
Sex	Male	1038/4458 (23.3)	1	–	–
	Female	437/2031 (21.5)	0.91 (0.81–1.02)	0.0900	
Age, years	<65	581/2942 (19.7)	1	–	<0.0001
	65–74	635/2623 (24.2)	1.18 (1.05–1.33)	0.0043	
	≥75	259/924 (28.0)	1.42 (1.21–1.65)	<0.0001	
Race	White	1061/4441 (23.9)	1.34 (1.16–1.54)	<0.0001	<0.0001
	Black	81/250 (32.4)	1.99 (1.55–2.56)	<0.0001	
	Asian	261/1414 (18.5)	1	–	
	Other	72/384 (18.8)	1.18 (0.91–1.54)	0.2113	
Baseline eGFR, mL/min/1.73 m²	<45	618/2188 (28.2)	1	–	<0.0001
	45–≤60	353/1717 (20.6)	0.71 (0.62–0.81)	<0.0001	
	>60	504/2584 (19.5)	0.62 (0.53–0.72)	<0.0001	
Baseline UACR, mg/g	<300	503/2183 (23.0)	1	–	<0.0001
	≥300–<1000	469/2430 (19.3)	1.06 (0.92–1.23)	0.4172	
	≥1000	503/1875 (26.8)	1.65 (1.42–1.92)	<0.0001	
Baseline serum [K+], mmol/L	<4.5	838/3952 (21.2)	1	–	0.0001
	4.5–≤4.8	433/1764 (24.5)	1.21 (1.07–1.36)	0.0016	
	>4.8	204/773 (26.4)	1.33 (1.14–1.55)	0.0003	
SGLT-2i use at baseline	No	1391/6053 (23.0)	1	–	–
	Yes	84/436 (19.3)	0.95 (0.76–1.18)	0.6212	
Beta blocker use at baseline	No	690/3261 (21.2)	1	–	–
	Yes	785/3228 (24.3)	1.07 (0.96–1.19)	0.2024	



The variable study was used as stratification factor. The Akaike information criterion optimal model was selected within models with (close to) optimal model size. The *p*-value for the (overall) effect was derived using a two-sided Wald test and only displayed for categorical variables with more than two categories. Discontinuations for deaths were censored
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

Effect of treatment discontinuation as a time-varying covariate on kidney and CV composite outcomes

- The effect of finerenone vs placebo on the composite kidney outcome was numerically reduced after treatment discontinuation (HR=0.82; 95% CI 0.66–1.02) compared with the treatment period (HR=0.65; 95% CI 0.54–0.78; *p*=0.0959) (**Figure 3**)
- For the composite CV outcome, a numerical decrease in the treatment effect of finerenone was also observed after discontinuation of treatment (HR=0.93; 95% CI 0.79–1.09) compared with the treatment period (HR=0.79; 95% CI 0.70–0.88; *p*=0.0960) (**Figure 3**)

Figure 3. Composite kidney and CV outcomes by treatment discontinuation status

Outcome	HR (95% CI)	*p*-value for interaction
Composite kidney outcome*		0.0959
Treatment discontinuation: No	0.65 (0.54–0.78)	
Treatment discontinuation: Yes	0.82 (0.66–1.02)	
Composite CV outcome#		0.0960
Treatment discontinuation: No	0.79 (0.70–0.88)	
Treatment discontinuation: Yes	0.93 (0.79–1.09)	

Composite kidney and CV outcomes are shown for the full analysis set. A person could contribute to the exposure time in both categories, before and after treatment discontinuation. A Cox proportional hazards model was fitted, stratified by study and included the covariates treatment group and time-varying discontinuation of study drug as well as the interaction of treatment discontinuation. The model was additionally adjusted for region, CV disease history, sex, race (White, Black, Asian, other), age, baseline eGFR, log(urine albumin-to-creatinine ratio), systolic blood pressure, and glycated hemoglobin
*Time to kidney failure, a sustained decrease in eGFR ≥57% from baseline over at least 4 weeks, or kidney-related death; #time to CV death, nonfatal stroke, nonfatal myocardial infarction, or hospitalization for heart failure
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio

Conclusions

- Overall, treatment discontinuation rates in FIDELITY were similar to those reported with placebo, with the occurence of adverse events as the most common reason for stopping treatment
  - Discontinuation due to hyperkalemia was low in both treatment arms
- The risk of discontinuation increased with older age, Black and White race, lower eGFR, higher UACR, and higher serum potassium
  - No differences were identified between finerenone and placebo with regard to these risk factors
- The treatment effect of finerenone was numerically higher during the treatment period compared with the time after treatment discontinuation

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