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Efficacy and safety of finerenone in patients with an acute change in estimated glomerular filtration rate: FIDELITY analysis

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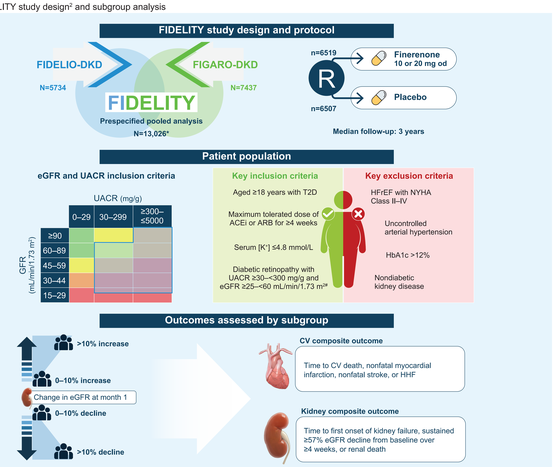
1. Background

- Reno-protective drugs are associated with a 5–30% initial decline in glomerular filtration rate (GFR). This includes renin–angiotensin–aldosterone blockers, sodium-glucose co-transporter-2 inhibitors (SGLT-2is), and mineralocorticoid receptor antagonists (MRAs) such as finerenone[1]
- Clinicians may be reluctant to prescribe or continue agents associated with acute estimated GFR (eGFR) decline and require reassurance of the efficacy and safety of these drugs
- Finerenone is a distinct, selective, nonsteroidal MRA that has been shown to slow the progression of chronic kidney disease (CKD) and reduce cardiovascular (CV) events in patients with CKD and type 2 diabetes (T2D)[2]
- This subgroup analysis assesses the efficacy and safety of finerenone in patients who experienced an acute change in eGFR following drug initiation and identifies predictors of acute eGFR decline specifically

2. Methods

- FIDELITY, a prespecified pooled analysis of two phase III trials (FIGARO-DKD and FIDELIO-DKD), included 13,026 patients with T2D and a wide spectrum of CKD, forming the largest program of an MRA in CKD associated with T2D to date (as previously published: **Figure 1**)[2]
- In this subgroup analysis, composite CV and kidney outcomes were analyzed by eGFR change (>10% decline, 0–10% decline, 0–10% increase, >10% increase) from baseline to month 1 (**Figure 1**)
- Non-linear modeling was used to assess the continuous relative change from baseline to month 1 of eGFR and subsequent cardiorenal outcomes. A Cox proportional hazards model was stratified by region, albuminuria at screening, and eGFR at screening, with treatment interaction as a covariate. Cubic B-splines were used with three equally spaced knots
- Logistic regression was used to identify baseline risk factors for experiencing eGFR decline >30% at month 1, and the significant variables were then used in an interaction model to check if the effect of finerenone varied across different levels of baseline risk factors
  - The >30% decline threshold was chosen for this analysis because a >30% change is accepted as a substantial and robust decline in eGFR
- Safety was assessed using investigator-reported adverse events (AEs)

Figure 1. FIDELITY study design[2] and subgroup analysis



*Prospective exclusion of 145 patients due to Good Clinical Practice violations; †in FIDELIO-DKD
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; [K+], potassium concentration; NYHA, New York Heart Association; od, once daily; R, randomization; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

3. Results

3.1. Baseline characteristics

- Among patients with available data (N=12,834), 25.1% and 34.3% experienced an acute eGFR decline of >10% and 0–<10%, respectively, whereas 23.8% and 16.8% had an acute eGFR increase of 0–<10% and >10%, respectively
- The baseline characteristics and medications were generally balanced between eGFR decline and eGFR increase subgroups (**Table 1**)
  - Baseline eGFR was lowest in patients with an acute eGFR increase of >10%, and those with other categories of eGFR change had similar baseline eGFR
  - Baseline median urine albumin-to-creatinine ratio (UACR) was lowest in the acute eGFR increase >10% subgroup
- Compared with the acute eGFR decline subgroups, patients with an acute eGFR increase were more likely to use glucose-lowering therapies such as insulin. Glucagon-like peptide-1 receptor agonists and SGLT-2i use at baseline was similar in the eGFR decrease and eGFR increase groups (**Table 1**)

Table 1. Baseline characteristics of the FIDELITY study sample by eGFR change category

	Acute eGFR change subgroup			
	eGFR decline		eGFR increase	
Characteristic*	>10% (n=3220)	0–10% (n=4398)	0–10% (n=3055)	>10% (n=2161)
Age, years	65.2 ± 9.4	64.5 ± 9.7	64.5 ± 9.6	64.9 ± 9.3
Male sex, n (%)	2214 (68.8)	3124 (71.0)	2157 (70.6)	1472 (68.1)
HbA1c, %	7.7 ± 1.4	7.6 ± 1.3	7.7 ± 1.4	7.7 ± 1.4
Systolic blood pressure, mmHg	138.4 ± 14.0	137.4 ± 14.1	135.9 ± 13.9	134.1 ± 14.8
History of CV disease, n (%)	1571 (48.8)	1922 (43.7)	1318 (43.1)	1032 (47.8)
Baseline medications, n (%)				
RAS inhibitors	3213 (99.8)	4390 (99.8)	3048 (99.8)	2160 (>99.9)
Statins	2344 (72.8)	3161 (71.9)	2224 (72.8)	1532 (70.9)
Diuretics	1769 (54.9)	2152 (48.9)	1488 (48.7)	1187 (54.9)
Insulin and analogues	1960 (60.9)	2523 (57.4)	2015 (66.0)	1479 (68.4)
GLP-1RAs	242 (7.5)	291 (6.6)	220 (7.2)	171 (7.9)
SGLT-2is	199 (6.2)	301 (6.8)	238 (7.8)	134 (6.2)
eGFR, mL/min/1.73 m²	57.5 ± 20.0	61.4 ± 23.2	58.5 ± 22.3	48.8 ± 16.8
eGFR, n (%)				
<25 mL/min/1.73 m²	23 (0.7)	27 (0.6)	32 (1.0)	78 (3.6)
25–<45 mL/min/1.73 m²	986 (30.6)	1257 (28.6)	985 (32.2)	939 (43.5)
45–<60 mL/min/1.73 m²	880 (27.3)	1105 (25.1)	785 (25.7)	613 (28.4)
≥60 mL/min/1.73 m²	1331 (41.3)	2009 (45.7)	1253 (41.0)	531 (24.6)
UACR, mg/g, median (IQR)	560 (208–1324)	540 (215–1173)	492 (194–1070)	440 (170–1007)
UACR, n (%)				
<30 mg/g	51 (1.6)	75 (1.7)	42 (1.4)	56 (2.6)
30–<300 mg/g	987 (30.7)	1310 (29.8)	987 (32.3)	747 (34.6)
≥300 mg/g	2182 (67.8)	3013 (68.5)	2024 (66.3)	1358 (62.8)

*Plus–minus values indicate mean ± SD
CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; IQR, interquartile range; RAS, renin–angiotensin system; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

3.2. CV and kidney outcomes by acute eGFR change subgroups

- The beneficial effect of finerenone on reducing the risk of both the CV and kidney composite outcome was consistent when eGFR change was modeled as a continuous variable ($p_{interaction}$=0.6007 and 0.3542, respectively) (**Figure 2**)
- Patients who experience a large decline in eGFR in the finerenone arm have a similar probability of a CV or kidney event as those with smaller eGFR decline in the placebo arm (**Figure 2**)
  - The probability of a CV composite event in the finerenone group with a 30% decline in eGFR is similar to the event probability in the placebo group without any eGFR change at month 1
  - The probability of a kidney composite event in the finerenone group experiencing a large eGFR decline (>10%) is similar to the event probability in the placebo group with a small decline (<10%) at month 1

3.3. Predictors of an acute eGFR decline

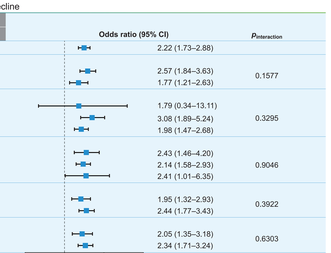
- Logistic regression analyses were used to identify the predictors of a >30% decline in eGFR from baseline to month 1. Risk factors for experiencing a >30% decline in eGFR were identified, as shown in **Table 2**
- The factors significantly associated with a >30% decline in eGFR were identified as: finerenone treatment, baseline UACR, baseline systolic blood pressure, and diuretic or beta blocker use at baseline. A >30% decline in eGFR occurred less frequently in male patients (**Table 2**)
  - Of these predicted significant risk factors, none had a significant interaction with finerenone (**Figure 3**)

Table 2. Logistic regression of baseline risk factors for a >30% eGFR decline

Risk factor	Odds ratio (95% CI)	*p*-value
Age	0.87 (0.75–1.00)	0.0572
Sex		
Male	0.63 (0.50–0.81)	0.0002
Female	1.00	
Race		
Black	1.04 (0.58–1.73)	0.8811
Non-black	1.00	
Baseline eGFR	1.04 (0.98–1.11)	0.1450
Baseline UACR	1.01 (1.00–1.03)	0.0112
Baseline SBP	1.14 (1.04–1.26)	0.0060
Baseline DBP	0.99 (0.86–1.15)	0.9210
Duration of diabetes	1.06 (0.98–1.13)	0.1284
History of cardiac failure		
No	1.00	0.3232
Yes	1.22 (0.81–1.77)	
Diuretic use at baseline		
No	1.00	0.0231
Yes	1.34 (1.04–1.73)	
Beta blocker use at baseline		
No	1.00	<0.0001
Yes	1.84 (1.42–2.38)	
SGLT-2i use at baseline		
No	1.00	0.1838
Yes	0.68 (0.37–1.15)	
Planned treatment		
Finerenone	2.25 (1.75–2.92)	<0.0001
Placebo	1.00	

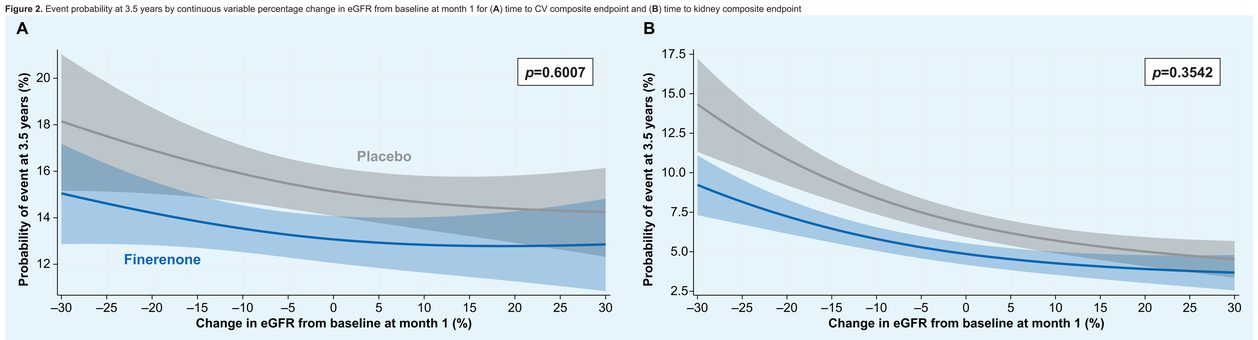
CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

Figure 3. Significant risk factors for developing an acute >30% eGFR decline



CI, confidence interval; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio

Figure 2. Event probability at 3.5 years by continuous variable percentage change in eGFR from baseline at month 1 for (**A**) time to CV composite endpoint and (**B**) time to kidney composite endpoint



The Cox proportional hazards model was stratified by region, albuminuria at screening, and eGFR at screening, and with treatment interaction as a covariate. Cubic B-splines were used for eGFR month 1 relative change from baseline with three equally spaced knots
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate

3.4. Safety outcomes by eGFR change subgroups

- Overall, incidence of investigator-reported serious AEs was consistent between treatment arms and acute eGFR change subgroups (**Table 3**)
  - Incidence of serious hyperkalemia was greater with finerenone compared with placebo in all acute eGFR change patient subgroups, but the clinical impact was low (**Table 3**)
  - Kidney-related serious AEs were also generally balanced between the eGFR change subgroups and occurred slightly less frequently in the finerenone group versus placebo group. Similar trends were observed for any serious acute kidney injury event (**Table 3**)

Table 3. Key safety outcomes by eGFR change subgroups

	Acute eGFR change subgroup							
	eGFR decline >10%		eGFR decline 0–10%		eGFR increase 0–10%		eGFR increase >10%	
Safety outcomes, %	Finerenone (n=1994)	Placebo (n=1224)	Finerenone (n=2223)	Placebo (n=2169)	Finerenone (n=1338)	Placebo (n=1715)	Finerenone (n=871)	Placebo (n=1290)
Any AE	86.6	85.3	86.8	86.3	86.4	88.2	84.8	87.2
Any study drug-related AE	21.4	14.6	17.7	11.8	17.5	13.5	16.4	14.1
Any AE leading to discontinuation of study drug	7.4	5.7	6.2	5.3	4.9	5.1	6.3	4.8
Any SAE	33.8	33.8	32.0	33.1	28.8	35.5	31.2	33.0
Any study drug-related SAE	1.7	1.5	1.2	0.7	0.8	1.0	1.3	0.7
Any SAE leading to discontinuation of study drug	2.8	2.9	2.2	2.4	1.3	2.3	2.8	1.9
Any hyperkalemia	15.9	8.0	13.4	5.6	13.8	6.9	12.6	8.3
Drug-related	10.0	4.4	8.5	3.1	8.2	3.7	8.4	4.8
Leading to permanent discontinuation of study drug	1.7	0.7	1.7	0.6	1.9	0.5	1.5	0.7
Serious hyperkalemia	1.6	0.2	1.0	0	0.7	0.5	0.6	0.4
Drug-related	1.1	0.2	0.6	0	0.4	0.2	0.3	0.2
Leading to hospitalization	1.4	<0.1	0.9	0	0.7	0.2	0.6	0.4
Leading to permanent discontinuation of study drug	0.3	<0.1	0.1	0	<0.1	<0.1	0	0
Leading to death	0	0	0	0	0	0	0	0
Any kidney-related event	18.5	17.5	14.8	17.3	13.4	16.0	15.2	17.4
Acute kidney injury (AE)	4.4	4.2	3.2	3.6	2.2	3.3	3.2	3.5
Any serious kidney-related event	4.3	4.8	3.4	4.2	3.4	3.9	3.1	4.0
Acute kidney injury (SAE)	2.0	2.0	1.3	1.7	0.8	1.2	1.5	1.2

AE, adverse event; eGFR, estimated glomerular filtration rate; SAE, serious adverse event

4. Conclusions

- Finerenone treatment, baseline UACR, baseline systolic blood pressure, and diuretic or beta blocker use at baseline were identified as predictive risk factors for an acute eGFR decline of >30% at month 1
- In general, the efficacy and safety of finerenone in reducing CV and kidney outcomes were not modified by eGFR change at month 1
- However, an acute decline in eGFR on finerenone may even be protective against CV and kidney composite events compared with placebo

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Disclosures

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