RC8.2

Efficacy and safety of finerenone in people with chronic kidney disease and type 2 diabetes by treatment goal attainment: A FIDELITY analysis

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Background

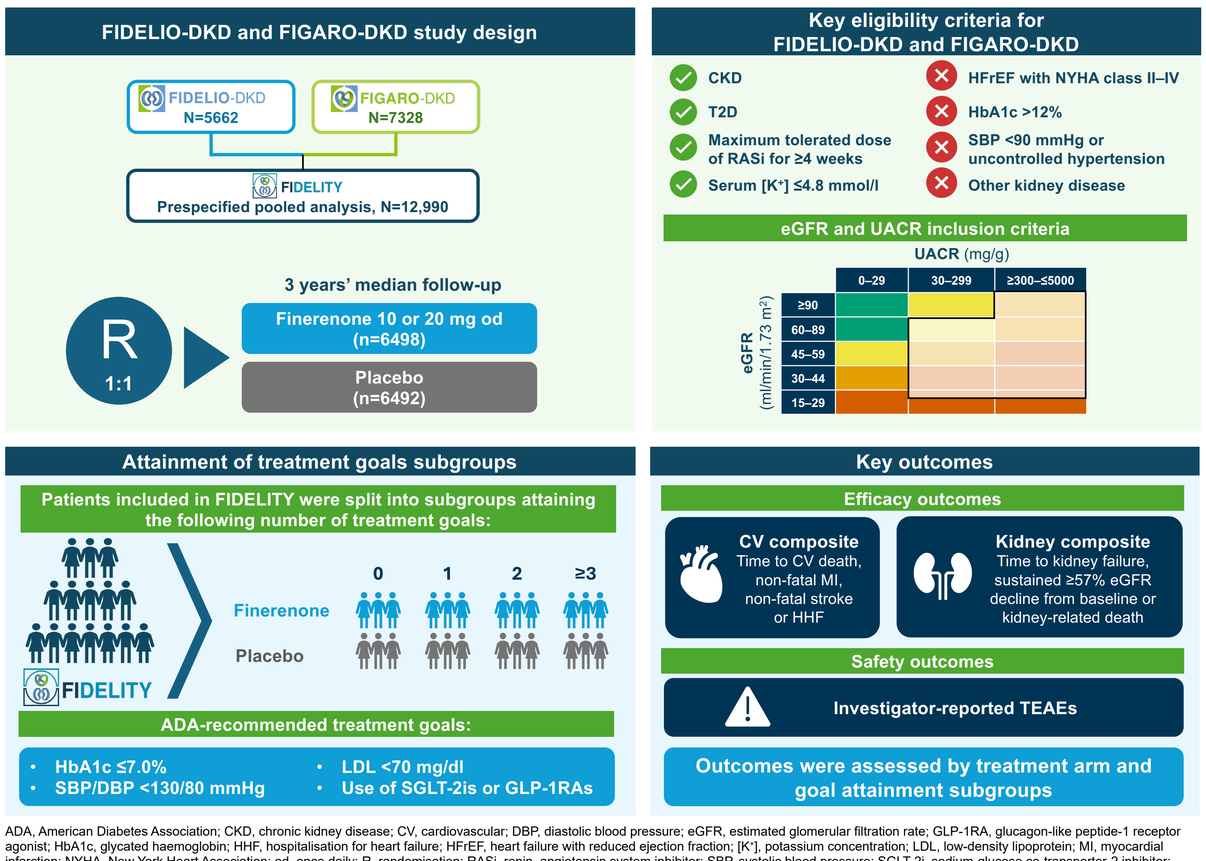
- Over one-third of patients with type 2 diabetes (T2D) develop chronic kidney disease (CKD)[1]
  - Compared with each of the two conditions alone, comorbid CKD and T2D are associated with increased cardiovascular (CV) and kidney risk[1,2]
- The American Diabetes Association (ADA) outlines a multifactorial approach to reduce complications associated with T2D[3]
  - In addition to lifestyle modifications and diabetes education, this approach includes the following treatment goals
    - Glycated haemoglobin (HbA1c): ≤7.0%
    - Systolic and diastolic blood pressure: <130 mmHg and <80 mmHg, respectively
    - Low-density lipoprotein (LDL) cholesterol: <70 mg/dl
    - Use of sodium-glucose co-transporter-2 inhibitors (SGLT-2is) or glucagon-like peptide-1 receptor agonists (GLP-1RAs)
- Finerenone is a selective nonsteroidal mineralocorticoid receptor antagonist that has been shown to significantly reduce CV and kidney risk versus placebo in patients with CKD and T2D in FIDELITY[4]
  - FIDELITY was a prespecified pooled analysis that combined data from two phase III randomised, double-blind, placebo-controlled, multicentre clinical trials: FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049)[4-6]
- This FIDELITY subanalysis aimed to evaluate the effects of finerenone versus placebo according to the attainment of ADA-recommended treatment goals at baseline in patients with CKD and T2D

Methods

Study design

- The study design, key eligibility criteria for FIDELIO-DKD and FIGARO-DKD and key outcomes assessed in this FIDELITY subanalysis are described in **Figure 1**
  - Adults with T2D and CKD included in FIDELITY were on optimised renin–angiotensin system (RAS) blockade, had serum potassium levels ≤4.8 mmol/l at both run-in and screening and were randomised 1:1 to oral finerenone (10 mg or 20 mg once daily) or placebo[4]
    - CKD was defined as either: i) estimated glomerular filtration rate (eGFR) 25−≤90 ml/min/1.73 m² and urine albumin-to-creatinine ratio (UACR) 30–<300 mg/g, or ii) eGFR ≥25 ml/min/1.73 m² and UACR 300–≤5000 mg/g[4]
  - In this subanalysis, efficacy (kidney and CV composites) and safety outcomes (**Figure 1**) were assessed by subgroups attaining 0, 1, 2, and ≥3 treatment goals at baseline and by treatment arm

Figure 1. Study design, eligibility criteria and outcomes



ADA, American Diabetes Association; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure; HFrEF, heart failure with reduced ejection fraction; [K+], potassium concentration; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association; od, once daily; R, randomisation; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio

Statistical analysis

- Efficacy outcome analyses were conducted in the full analysis set, which included all randomised patients without critical Good Clinical Practice (GCP) violations
- The association between attainment of treatment goals and efficacy outcomes was assessed using stratified Cox proportional hazards models for time-to-first event analyses with randomised treatment group and baseline attainment of treatment goals subgroup included as the explanatory variables, with a treatment-by-subgroup interaction term also included in the model
- Investigator-reported treatment-emergent adverse events (TEAEs) were analysed in the safety analysis set, which included all randomised patients without GCP violations who received ≥1 dose of the study drug
- All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC)

Results

Participants and baseline characteristics

- Out of the 12,990 patients included in the analysis, 29%, 40%, 24% and 7% achieved 0, 1, 2 and ≥3 goals at baseline, respectively
- Key baseline characteristics are shown in **Table 1**
  - Mean age increased with the number of treatment goals achieved across subgroups achieving 0–2 goals
  - The proportion of male patients increased with the number of goals achieved
  - In Asia and Western Europe, a larger proportion of patients achieved a higher number of goals compared with other regions
  - As the number of treatment goals achieved at baseline increased, a history of CV disease was more common and both median UACR and mean eGFR decreased

Table 1. Key baseline characteristics by the number of treatment goals attained

Characteristic	Number of treatment goals attained at baseline (N=12,990)			
	0 (n=3732)	1 (n=5208)	2 (n=3091)	≥3 (n=959)
Age, years, mean ± SD	63.9 ± 9.6	64.8 ± 9.6	65.6 ± 9.3	65.5 ± 9.6
Sex, male, n (%)	2330 (62.4)	3691 (70.9)	2288 (74.0)	749 (78.1)
Race, n (%)				
White	2608 (69.9)	3529 (67.8)	2051 (66.4)	681 (71.0)
Black/African American	168 (4.5)	219 (4.2)	113 (3.7)	20 (2.1)
Asian	684 (18.3)	1166 (22.4)	782 (25.3)	228 (23.8)
Others*	272 (7.3)	294 (5.6)	145 (4.7)	30 (3.1)
Region, n (%)				
Western Europe	629 (16.9)	1107 (21.3)	748 (24.2)	252 (26.3)
Eastern Europe	1250 (33.5)	1254 (24.1)	515 (6.7)	107 (11.2)
North America	453 (12.1)	803 (15.4)	584 (18.9)	209 (21.8)
Asia	742 (19.9)	1277 (24.5)	867 (28.0)	284 (29.6)
Latin America	550 (14.7)	582 (11.2)	234 (7.6)	68 (7.1)
Others#	108 (2.9)	185 (3.6)	143 (4.6)	39 (4.1)
Duration of diabetes, years, mean ± SD‡	16.1 ± 8.4	15.0 ± 8.8	15.2 ± 8.8	15.6 ± 8.7
HbA1c, %, mean ± SD‡	8.5 ± 1.2	7.6 ± 1.4	7.1 ± 1.2	6.7 ± 0.9
Systolic blood pressure, mmHg, mean ± SD‡	142.7 ± 10.9	138.3 ± 13.6	131.6 ± 14.6	122.1 ± 11.4
History of CV disease, n (%)‡	1595 (42.7)	2330 (44.7)	1511 (48.9)	492 (51.3)
History of HF, n (%)	356 (9.5)	392 (7.5)	200 (6.5)	59 (6.2)
eGFR, ml/min/1.73 m², mean ± SD‡	59.5 ± 22.6	57.2 ± 21.7	56.5 ± 20.7	55.8 ± 20.6
UACR, mg/g, median (Q1–Q3)‡	640.5 (272.3–1399.2)	540.0 (210.0–1215.2)	424.4 (152.7–932.8)	336.3 (109.9–728.4)
LDL cholesterol, mg/dl, mean ± SD‡	108.5 ± 32.0	86.4 ± 35.9	65.7 ± 29.6	52.0 ± 18.3
Serum potassium, mmol/l, mean ± SD‡	4.4 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4
Baseline medication use, n (%)				
ACEis	1559 (41.8)	2056 (39.5)	1123 (36.3)	338 (35.2)
ARBs	2172 (58.2)	3150 (60.5)	1960 (63.4)	622 (64.9)
Diuretics	1932 (51.8)	2665 (51.2)	1593 (51.5)	511 (53.3)
Statins	2341 (62.7)	3684 (70.7)	2511 (81.2)	851 (88.7)
Potassium-lowering agents§	44 (1.2)	72 (1.4)	51 (1.6)	15 (1.6)
Glucose-lowering therapies	3690 (98.9)	5077 (97.5)	2991 (96.8)	927 (96.7)
Insulin and analogues	2642 (70.8)	3009 (57.8)	1530 (49.5)	439 (45.8)
GLP-1RAs	0	281 (5.4)	411 (13.3)	251 (26.2)
SGLT-2is	0	256 (4.9)	376 (12.2)	241 (25.1)

*Includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, not reported and multiple (patients who reported belonging to >1 race); #New Zealand, South Africa and Australia; ‡data were not available for all patients for the indicated categories: duration of diabetes (missing: n=18); HbA1c (missing: n=22); systolic blood pressure (missing: n=5), history of CV disease (missing: n=1); mean eGFR (missing: n=3); median UACR (missing: n=5); LDL cholesterol (missing: n=692); serum potassium (missing: n=4); §including potassium binders
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; LDL, low-density lipoprotein; Q, quartile; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

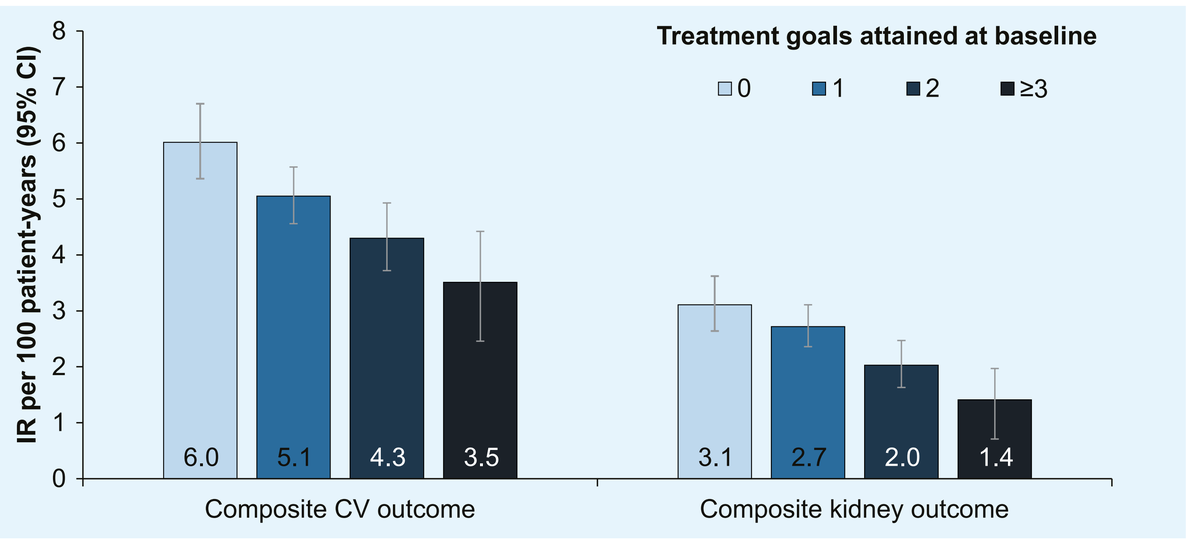
CV and kidney outcome incidence rates by treatment goal subgroups

- In both the finerenone and placebo arms, patients attaining a higher number of treatment goals had a lower incidence of composite CV outcome events (**Figures 2** and **3**)
  - Similar trends were observed for the composite kidney outcome in both treatment arms

Effect of finerenone on CV and kidney outcomes by treatment goal subgroups

- The risk of a composite CV outcome event was reduced among patients treated with finerenone compared with placebo irrespective of the number of treatment goals attained at baseline, with no significant heterogeneity observed between groups ($p_{interaction}$=0.75) (**Figure 3**)
- Similarly, the risk of a composite kidney outcome event was lower with finerenone regardless of the number of goals attained ($p_{interaction}$=0.61) (**Figure 3**)

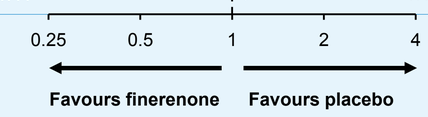
Figure 2. CV and kidney outcome incidence rate (95% CI) according to the number of treatment goals attained at baseline (placebo arm)



CI, confidence interval; CV, cardiovascular; IR, incidence rate

Figure 3. Cox proportional hazards model for CV and kidney outcomes by the number of treatment goals attained at baseline

	Finerenone n/N	Finerenone n/100 PY	Placebo n/N	Placebo n/100 PY	Hazard ratio (95% CI)	$p_{interaction}$
Composite CV outcome*						
Overall	823/6498	4.34	938/6492	5.02	0.86 (0.78–0.95)	
Number of goals achieved						
0	295/1905	5.52	307/1827	6.01	0.90 (0.76–1.05)	0.7481
1	299/2534	4.04	388/2674	5.05	0.79 (0.68–0.92)	
2	182/1568	3.85	194/1523	4.30	0.88 (0.72–1.08)	
≥3	47/491	3.19	49/468	3.51	0.89 (0.59–1.37)	
Composite kidney outcome#						
Overall	356/6498	1.95	465/6492	2.56	0.76 (0.66–0.88)	
Number of goals achieved						
0	128/1905	2.47	155/1827	3.11	0.77 (0.60–0.97)	0.6095
1	144/2534	2.03	202/2674	2.72	0.71 (0.57–0.88)	
2	63/1568	1.38	89/1523	2.03	0.70 (0.50–0.97)	
≥3	21/491	1.47	19/468	1.41	1.11 (0.56–2.18)	



Data are shown for the full analysis set. Events were adjudicated by an independent adjudication committee and considered from randomisation up until the end of study visit. A stratified Cox proportional hazards model including treatment was calculated separately by subgroup category. The interaction *p*-value was based on a stratified Cox proportional hazards model including treatment, subgroup and treatment by subgroup interaction. Events based on a sustained decrease in eGFR were considered from randomisation up until 5 months after the last eGFR was recorded at a clinic visit
*Time to CV death, non-fatal myocardial infarction, non-fatal stroke or HHF; #time to onset of kidney failure, a sustained ≥57% decrease in eGFR from baseline over ≥4 weeks or kidney-related death
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF; hospitalisation for heart failure; PY, patient-years

Safety outcomes

- The safety profile of finerenone versus placebo was generally similar across groups according to the number of treatment goals attained at baseline, although patients who achieved a higher number of treatment goals tended to have slightly higher TEAE rates (**Table 2**)
  - Investigator-reported hyperkalaemia was more common in the finerenone arm versus placebo in all treatment goal-attainment subgroups
  - Serious hyperkalaemia leading to hospitalisation or permanent discontinuation was rare across all subgroups (≤1.3% in the finerenone arm and ≤0.3% in the placebo arm across all four subgroups)

Table 2. TEAEs by the number of treatment goals attained at baseline

n (%)	Number of treatment goals attained at baseline: 0 Finerenone (n=1899)	0 Placebo (n=1824)	1 Finerenone (n=2535)	1 Placebo (n=2666)	2 Finerenone (n=1564)	2 Placebo (n=1517)	≥3 Finerenone (n=491)	≥3 Placebo (n=467)
Any TEAE	1579 (83.1)	1543 (84.6)	2173 (85.7)	2307 (86.5)	1387 (88.7)	1334 (87.9)	443 (90.2)	408 (87.4)
Study drug-related	296 (15.6)	218 (12.0)	473 (18.7)	351 (13.2)	334 (21.4)	213 (14.0)	101 (20.6)	77 (16.5)
Leading to discontinuation	118 (6.2)	86 (4.7)	151 (6.0)	132 (5.0)	110 (7.0)	99 (6.5)	35 (7.1)	33 (7.1)
Any serious TEAE	571 (30.1)	589 (32.3)	806 (31.8)	921 (34.5)	502 (32.1)	508 (33.5)	175 (35.6)	163 (34.9)
Death	40 (2.1)	47 (2.6)	36 (1.4)	62 (2.3)	27 (1.7)	29 (1.9)	6 (1.2)	13 (2.8)
Any hyperkalaemia-related TEAE	234 (12.3)	118 (6.5)	364 (14.4)	190 (7.1)	238 (15.2)	98 (6.5)	72 (14.7)	42 (9.0)
Any serious hyperkalaemia-related TEAE	15 (0.8)	6 (0.3)	30 (1.2)	8 (0.3)	21 (1.3)	1 (<0.1)	3 (0.6)	1 (0.2)
Leading to discontinuation	1 (<0.1)	1 (<0.1)	7 (0.3)	0	1 (<0.1)	1 (<0.1)	1 (0.2)	0
Leading to hospitalisation	14 (0.7)	3 (0.2)	25 (1.0)	6 (0.2)	19 (1.2)	0	3 (0.6)	1 (0.2)

TEAE, treatment-emergent adverse event

Conclusions

- Overall, a beneficial effect of finerenone on the composite CV and kidney outcomes was observed regardless of the number of treatment goals achieved by patients at baseline
- The risk of adverse events with finerenone was not impacted by the number of treatment goals achieved
- These findings suggest that finerenone treatment is suitable for the management of T2D and CKD in patients across the range of treatment goal attainment

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