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Efficacy and safety of finerenone in patients with CKD and T2D across the frailty spectrum: A FIDELITY post hoc analysis

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Introduction

- Frailty is often defined as a state of increased vulnerability associated with a decline in physiological system function and is associated with increased risk of adverse outcomes[1-4]
- Given the accumulation of risk factors and comorbidities in people with more severe frailty, inappropriate prescribing is prevalent in older people with frailty[5]
- An estimated 7–20% of adults with chronic kidney disease (CKD) are considered to have frailty, and this has been associated with a lower quality of life, an increased rate of disease progression, and an increased risk of death[6-8]
- Finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, reduced the risk of adverse cardiovascular (CV) and kidney outcomes vs placebo in FIDELITY, a prespecified pooled analysis of the phase III FIDELIO-DKD and FIGARO-DKD trials[9-11]

Aim

- This FIDELITY post hoc analysis explored the efficacy and safety of finerenone in patients with CKD and type 2 diabetes (T2D) according to baseline frailty index score

Methods

- Full eligibility criteria are outlined in the FIDELIO-DKD and FIGARO-DKD primary analyses[10,11], and included those who:
  - Were aged ≥18 years with CKD and T2D
  - Had a serum potassium level ≤4.8 mmol/l at screening
  - Had either a urine albumin-to-creatinine ratio (UACR) ≥30 to <300 mg/g and an estimated glomerular filtration rate (eGFR) ≥25 to ≤90 ml/min/1.73 m^2, or UACR ≥300 to ≤5000 mg/g and eGFR ≥25 ml/min/1.73 m^2
  - Were treated with standard-of-care therapy, including a maximum tolerated labelled dose of a renin−angiotensin system inhibitor
- Patients were randomly assigned to receive finerenone at titrated doses of 10 or 20 mg once daily as oral treatment or matching placebo (1:1)
- Frailty was defined using the Rockwood cumulative deficit approach
  - 30 baseline clinical characteristics, including laboratory measures, quality of life measures and medical history, were used to construct the frailty index and assign a normalised frailty index score between 0 (no frailty) and 1 (maximal frailty) to each patient
  - All enrolled participants were categorised into subgroups based on frailty index quartiles (≤Q1, >Q1 to ≤Q2, >Q2 to ≤Q3, and >Q3)
- Efficacy outcomes included a CV composite outcome (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for heart failure) and a kidney composite outcome (kidney failure, sustained ≥57% eGFR decline from baseline, or kidney-related death)
- Changes in eGFR compared with baseline values were measured at multiple visits across the study period

Results

- A total of 12,990 people were included in this analysis; the mean frailty index was 0.463 (standard deviation 0.105) and participants in both treatment arms were equally distributed across the frailty spectrum (**Table 1**)

Table 1. Baseline characteristics of enrolled participants stratified by baseline frailty index

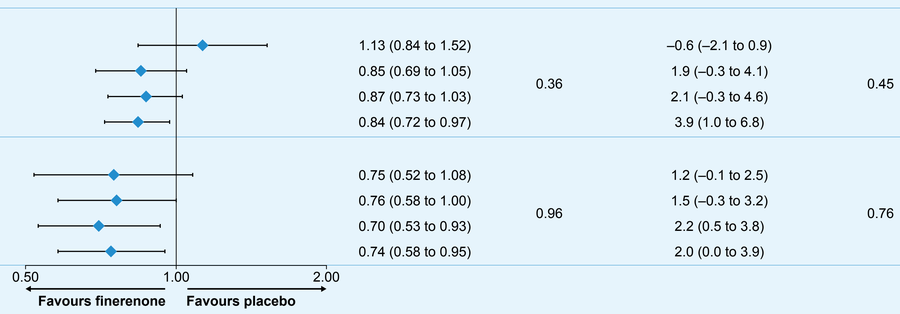
Baseline characteristic	≤Q1 (least frail)		>Q1 to ≤Q2		>Q2 to ≤Q3		>Q3 (most frail)	
	Finerenone (*n* = 1619)	Placebo (*n* = 1691)	Finerenone (*n* = 1643)	Placebo (*n* = 1549)	Finerenone (*n* = 1685)	Placebo (*n* = 1661)	Finerenone (*n* = 1551)	Placebo (*n* = 1591)
Sex, n (%)								
Female	467 (28.8)	413 (24.4)	480 (29.2)	422 (27.2)	523 (31.0)	504 (30.3)	565 (36.4)	558 (35.1)
Male	1152 (71.2)	1278 (75.6)	1163 (70.8)	1127 (72.8)	1162 (69.0)	1157 (69.7)	986 (63.6)	1033 (64.9)
Age, years, mean (SD)	61.0 (9.4)	61.4 (10.1)	64.5 (9.3)	64.3 (9.6)	66.2 (9.0)	66.1 (9.2)	67.3 (8.5)	67.7 (8.6)
Race, n (%)								
Asian	591 (36.5)	627 (37.1)	424 (25.8)	396 (25.6)	286 (17.0)	287 (17.3)	112 (7.2)	137 (8.6)
Black or African American	42 (2.6)	46 (2.7)	55 (3.3)	47 (3.0)	72 (4.3)	81 (4.9)	82 (5.3)	95 (6.0)
White	880 (54.4)	919 (54.3)	1063 (64.7)	1000 (64.6)	1229 (72.9)	1212 (73.0)	1277 (82.3)	1289 (81.0)
BMI, kg/m^2, mean (SD)	29.2 (5.5)	29.2 (5.5)	30.8 (5.8)	30.8 (5.6)	31.6 (5.8)	31.7 (5.7)	33.8 (6.2)	33.5 (6.2)
Current smoker, n (%)	370 (22.9)	365 (21.6)	284 (17.3)	268 (17.3)	235 (13.9)	216 (13.0)	170 (11.0)	174 (10.9)
UACR, mg/g, median (IQR)	450 (178–943)	431 (161–926)	497 (185–1168)	512 (208–1147)	490 (194–1099)	517 (196–1223)	642 (247–1380)	647 (254–1426)
eGFR, ml/min/1.73 m^2, mean (SD)	67.5 (21.4)	67.4 (21.8)	58.9 (21.4)	60.3 (21.8)	55.2 (20.5)	54.1 (20.4)	48.1 (18.4)	48.4 (18.1)
Serum potassium, mmol/l, mean (SD)	4.28 (0.39)	4.28 (0.38)	4.33 (0.42)	4.32 (0.43)	4.35 (0.45)	4.37 (0.45)	4.43 (0.49)	4.43 (0.49)
Systolic blood pressure, mmHg, mean (SD)	131.8 (12.7)	131.5 (13.0)	134.9 (13.4)	136.0 (13.6)	138.2 (14.2)	138.0 (14.3)	142.4 (14.2)	141.7 (14.2)
HbA1c, %, mean (SD)	7.22 (1.22)	7.21 (1.24)	7.60 (1.38)	7.53 (1.34)	7.83 (1.35)	7.85 (1.34)	8.20 (1.31)	8.17 (1.31)
Duration of diabetes, years, mean (SD)	12.6 (7.6)	12.9 (8.0)	15.0 (8.5)	14.4 (8.1)	16.4 (8.9)	16.4 (9.1)	17.8 (9.1)	17.9 (8.6)
History of CV disease, n (%)	361 (22.3)	326 (19.3)	648 (39.4)	593 (38.3)	935 (55.5)	911 (54.8)	1029 (66.3)	1125 (70.7)
History of hypertension, n (%)	1506 (93.0)	1574 (93.1)	1587 (96.6)	1511 (97.5)	1648 (97.8)	1621 (97.6)	1519 (97.9)	1565 (98.4)
History of MI, n (%)	96 (5.9)	88 (5.2)	217 (13.2)	192 (12.4)	299 (17.7)	316 (19.0)	404 (26.0)	408 (25.6)
History of atrial fibrillation and atrial flutter, n (%)	48 (3.0)	48 (2.8)	121 (7.4)	103 (6.6)	179 (10.6)	168 (10.1)	218 (14.1)	219 (13.8)
Baseline medications, n (%)								
Beta blocker	538 (33.2)	547 (32.3)	769 (46.8)	735 (47.4)	920 (54.6)	935 (56.3)	1005 (64.8)	1050 (66.0)
GLP-1RA	111 (6.9)	99 (5.9)	137 (8.3)	113 (7.3)	132 (7.8)	115 (6.9)	117 (7.5)	119 (7.5)
SGLT-2i	137 (8.5)	136 (8.0)	117 (7.1)	116 (7.5)	110 (6.5)	111 (6.7)	72 (4.6)	74 (4.7)

BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; IQR, interquartile range; MI, myocardial infarction; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

- Overall, incidence of CV and kidney events increased with increasing frailty in both treatment arms (**Figure 1**)
- Finerenone lowered the risk of CV and kidney outcomes irrespective of frailty status (**Figure 1**)
  - Absolute risk reduction of CV composite outcome with finerenone vs placebo was nominally higher in severely frail patients (*p*-value for interaction = 0.45)

Figure 1. Efficacy outcomes for finerenone and placebo across the frailty subgroups

Outcome	Finerenone n/N (IR per 100 PY)	Placebo n/N (IR per 100 PY)	HR (95% CI)	*p*-value for interaction	Absolute risk difference (95% CI)	*p*-value for interaction
CV composite outcome						
≤Q1	92/1619 (1.8)	86/1691 (1.6)	1.13 (0.84 to 1.52)	0.36	–0.6 (–2.1 to 0.9)	0.45
>Q1 to ≤Q2	174/1643 (3.5)	193/1549 (4.2)	0.85 (0.69 to 1.05)		1.9 (–0.3 to 4.1)	
>Q2 to ≤Q3	240/1685 (5.0)	272/1661 (5.9)	0.87 (0.73 to 1.03)		2.1 (–0.3 to 4.6)	
>Q3	317/1551 (7.9)	387/1591 (9.7)	0.84 (0.72 to 0.97)		3.9 (1.0 to 6.8)	
≥57% kidney composite outcome						
≤Q1	52/1619 (1.0)	75/1691 (1.4)	0.75 (0.52 to 1.08)	0.96	1.2 (–0.1 to 2.5)	0.76
>Q1 to ≤Q2	100/1643 (2.1)	117/1549 (2.7)	0.76 (0.58 to 1.00)		1.5 (–0.3 to 3.2)	
>Q2 to ≤Q3	89/1685 (1.9)	124/1661 (2.7)	0.70 (0.53 to 0.93)		2.2 (0.5 to 3.8)	
>Q3	115/1551 (3.0)	149/1591 (3.8)	0.74 (0.58 to 0.95)		2.0 (0.0 to 3.9)	



CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IR, incidence rate; PY, patient-years; Q, quartile.

- From baseline to month 48, finerenone was associated with a lower rate of eGFR decline compared with placebo for all frailty subgroups (**Table 2**)
  - The attenuation of total eGFR slope by finerenone compared with placebo was more pronounced with increasing severity of frailty

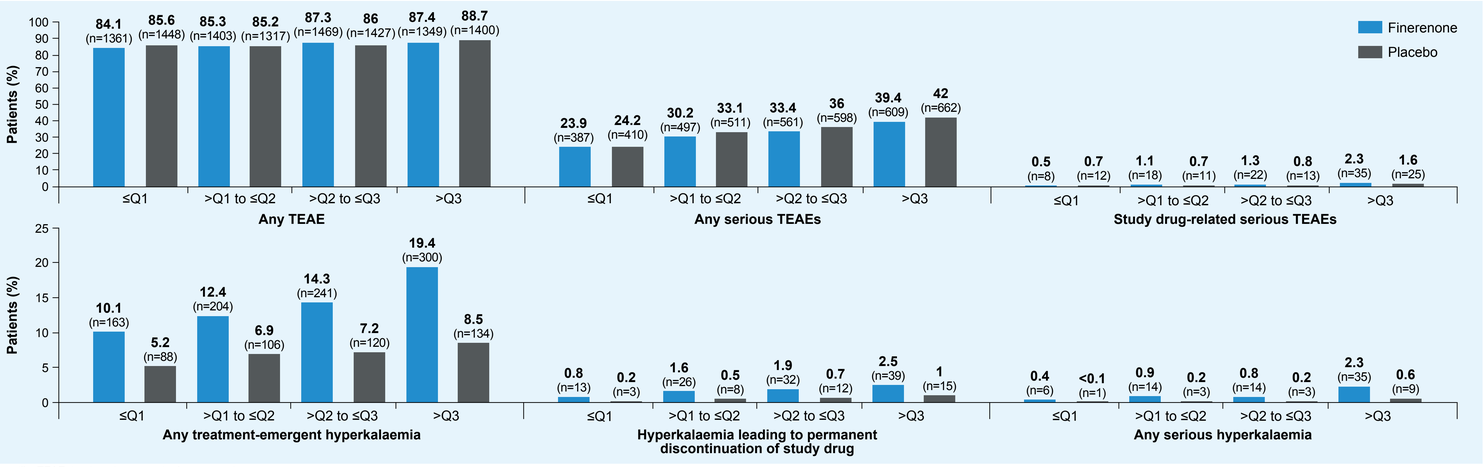
Table 2. Change in eGFR across the study period for finerenone and placebo according to frailty index score

ml/min/1.73 m^2 (95% CI)	≤Q1 (least frail)		>Q1 to ≤Q2		>Q2 to ≤Q3		>Q3 (most frail)	
	Difference of LS-means (finerenone vs placebo)	*p*-value	Difference of LS-means (finerenone vs placebo)	*p*-value	Difference of LS-means (finerenone vs placebo)	*p*-value	Difference of LS-means (finerenone vs placebo)	*p*-value
Acute eGFR slope from baseline to month 4	–5.55 (–7.13 to –3.96)	<0.0001	–5.62 (–7.34 to –3.89)	<0.0001	-6.41 (-8.04 to -4.78)	<0.0001	–2.85 (–4.48 to –1.23)	0.0006
Chronic eGFR slope from month 4 to end of study visit	0.75 (0.46 to 1.05)	<0.0001	1.12 (0.76 to 1.48)	<0.0001	1.23 (0.90 to 1.56)	<0.0001	1.03 (0.67 to 1.39)	<0.0001
Total slope from baseline to month 48	0.23 (–0.05 to 0.51)	0.1113	0.56 (0.23 to 0.89)	0.0010	0.59 (0.28 to 0.91)	0.0002	0.71 (0.37 to 1.04)	<0.0001

CI, confidence interval; eGFR, estimated glomerular filtration rate; LS, least-squares; Q, quartile.

- The safety profile of finerenone relative to placebo was not modified by frailty status (**Figure 2**)
  - Incidence of serious adverse events (SAEs) was slightly lower with finerenone vs placebo across all frailty subgroups; although incidence rates increased with increasing frailty, the incidence rates of study drug–related SAEs were low across all subgroups
  - Incidence of hyperkalaemia was higher with finerenone vs placebo and increased with increasing frailty; serious hyperkalaemia was low across frailty subgroups and treatment arms

Figure 2. Incidence of treatment-emergent adverse events and hyperkalaemia for finerenone and placebo across the frailty subgroups



Q, quartile; TEAE, treatment-emergent adverse event.

Conclusions

- Finerenone lowered the risk of CV and kidney outcomes in patients with CKD and T2D regardless of frailty status
- Incidence rates of SAEs and hyperkalaemia increased with frailty index score; however, the relative risk remained consistent between the treatment arms across the frailty subgroups
- Compared with placebo, finerenone slowed the rate of eGFR decline from baseline to month 48 for all frailty subgroups

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References: 1. Sciacchitano S, *et al. J Clin Med* 2024;13:721; **2.** Strain WD, *et al. Diabetes Ther* 2021;12:1227–1247; **3.** Vart P, *et al. J Gerontol A Biol Sci Med Sci* 2024;79; **4.** Walker SR, *et al. BMC Nephrology* 2013;14:228; **5.** Lavan AH, *et al. Age Ageing* 2017;46:600–607; **6.** Roshanravan B, *et al. Am J Kidney Dis* 2012;60:912–921; **7.** Mansur HN, *et al. Health Qual Life Outcomes* 2014;12:27; **8.** Hannan M, *et al. Am J Kidney Dis* 2024;83:208–215; **9.** Agarwal R, *et al. Eur Heart J* 2022;43:474–484; **10.** Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; **11.** Pitt B, *et al. N Engl J Med* 2021;385:2252–2263.

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