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

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On behalf of Andreas L. Birkenfeld, Paola Fioretto, Janet B. McGill, Stefan D. Anker, Bertram Pitt, Andrea Scalise, Charlie Scott, Gerasimos Filippatos, and the FIDELIO-DKD and FIGARO-DKD Investigators

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FIDELITY
FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis

Disclosures

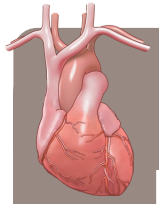
- **Peter Rossing** reports personal fees from Bayer during the conduct of the study; he has received research support and personal fees from AstraZeneca and Novo Nordisk, and personal fees from Astellas, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Sanofi and Vifor; all fees are given to Steno Diabetes Center Copenhagen

Frailty is associated with increased risk of adverse outcomes[1–3]

Finerenone, a selective nonsteroidal MRA, **reduced the risk of adverse CV and kidney outcomes vs placebo in FIDELITY**, a prespecified pooled analysis of the phase III FIDELIO-DKD and FIGARO-DKD trials[4–6]

FIDELITY

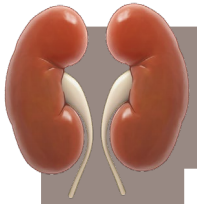
12,990 patients with CKD and T2D on optimised RAS inhibitor and randomised 1:1 to finerenone or placebo[4–6]



CV composite outcome

Time to first occurrence of:

- CV death
- Non-fatal MI
- Non-fatal stroke
- Hospitalisation for HF



Kidney composite outcome

Time to first occurrence of:

- Kidney failure
- Sustained ≥57% decrease in eGFR from baseline*
- Kidney-related death

Other outcomes

Safety outcomes assessed treatment-emergent AEs

Objective: This **FIDELITY post hoc analysis** explored the **efficacy and safety of finerenone** in patients with CKD and T2D according to baseline frailty index

*Events based on a sustained decrease in eGFR are considered from randomisation up until 5 months after the last eGFR is recorded at a clinic visit

AE, adverse event; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; RAS, renin−angiotensin system; T2D, type 2 diabetes

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Frailty was defined using the Rockwood cumulative deficit approach

30 characteristics

were used to construct the frailty index and assign a normalised frailty index score to each patient*

0
(no frailty)

1
(maximal frailty)

Laboratory parameters
UACR
eGFR
$[K]^+$
Systolic blood pressure
Diastolic blood pressure
Pulse pressure
HbA1c
Haemoglobin
C-reactive protein

Demographics
Diabetes duration
BMI
Age
Gender

EQ-5D questionnaire
EQ-5D-5L (usual)
EQ-5D-5L (mobility)
EQ-5D-5L (pain)
EQ-5D-5L (anxiety)
EQ-5D-5L (selfcare)

Medical history
HF
MI
Stroke
CAD
Atrial fibrillation/flutter
Peripheral arterial occlusive disease
PCI or CABG
Hypertension
Hyperlipidaemia
Diabetic neuropathy
COPD
Retinopathy

*For each characteristic, patients were assigned a score between 0 and 1. The frailty index score was normalised by dividing the total score by the number of non-missing characteristics. Patients were categorised by frailty index quartiles (≤Q1 [least frail], >Q1 to ≤Q2, >Q2 to ≤Q3, >Q3 [most frail])

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EQ-5D, EuroQol-5 Dimension; HbA1c, glycated haemoglobin; HF, heart failure; $[K]^+$, serum potassium concentration; MI, myocardial infarction; PCI, percutaneous coronary intervention; UACR, urine albumin-to-creatinine ratio

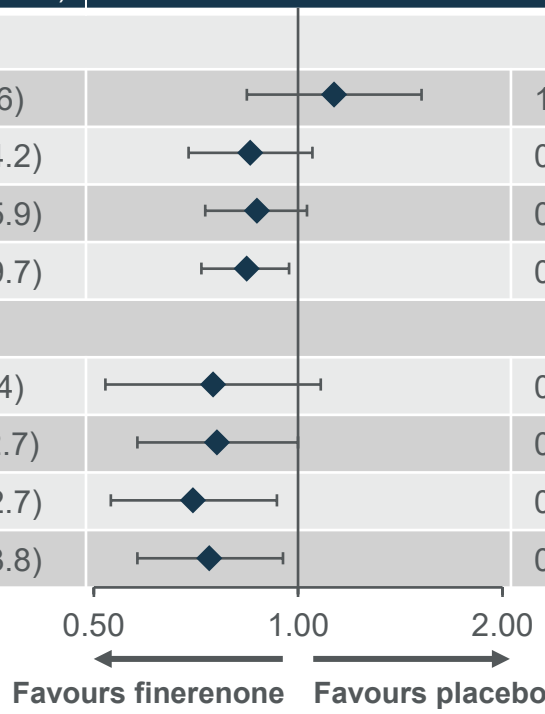
As severity of frailty increased, patients had older age, higher UACR and longer duration of diabetes, and lower eGFR at baseline

Frailty subgroup:	≤Q1 N=3310	>Q1 to ≤Q2 N=3192	>Q2 to ≤Q3 N=3346	>Q3 N=3142
Sex, Female	880 (26.6%)	902 (28.3%)	1027 (30.7%)	1123 (35.7%)
Race, White	1799 (54.4%)	2063 (64.6%)	2441 (73.0%)	2566 (81.7%)
UACR, mg/g	442 (167–936)	505 (196–1156)	504 (196–1151)	644 (249–1409)
Current smoker	735 (22.2%)	552 (17.3%)	451 (13.5%)	344 (10.9%)
Mean age, years	61.2 ± 9.7	64.4 ± 9.5	66.1 ± 9.1	67.5 ± 8.6
BMI, kg/m^2	29.2 ± 5.5	30.8 ± 5.7	31.7 ± 5.7	33.7 ± 6.2
eGFR, ml/min/1.73 m^2	67.4 ± 21.6	59.6 ± 21.6	54.7 ± 20.4	48.3 ± 18.2
Systolic blood pressure, mmHg	131.7 ± 12.8	135.4 ± 13.5	138.1 ± 14.2	142.1 ± 14.2
Medical History				
Duration of diabetes, years	12.8 ± 7.8	14.7 ± 8.3	16.4 ± 9.0	17.8 ± 8.8
History of CV disease	687 (20.8%)	1241 (38.9%)	1846 (55.2%)	2154 (68.6%)
History of MI	184 (5.6%)	409 (12.8%)	615 (18.4%)	812 (25.8%)
History of hypertension	3080 (93.1%)	3098 (97.1%)	3269 (97.7%)	3084 (98.2%)

Values are n (%), mean ± SD or median (IQR).
BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IQR, interquartile range, MI, myocardial infarction; Q, quartile; SD, standard deviation; UACR, urine albumin-to-creatinine ratio

Finerenone lowered the risk of CV and kidney outcomes irrespective of frailty status

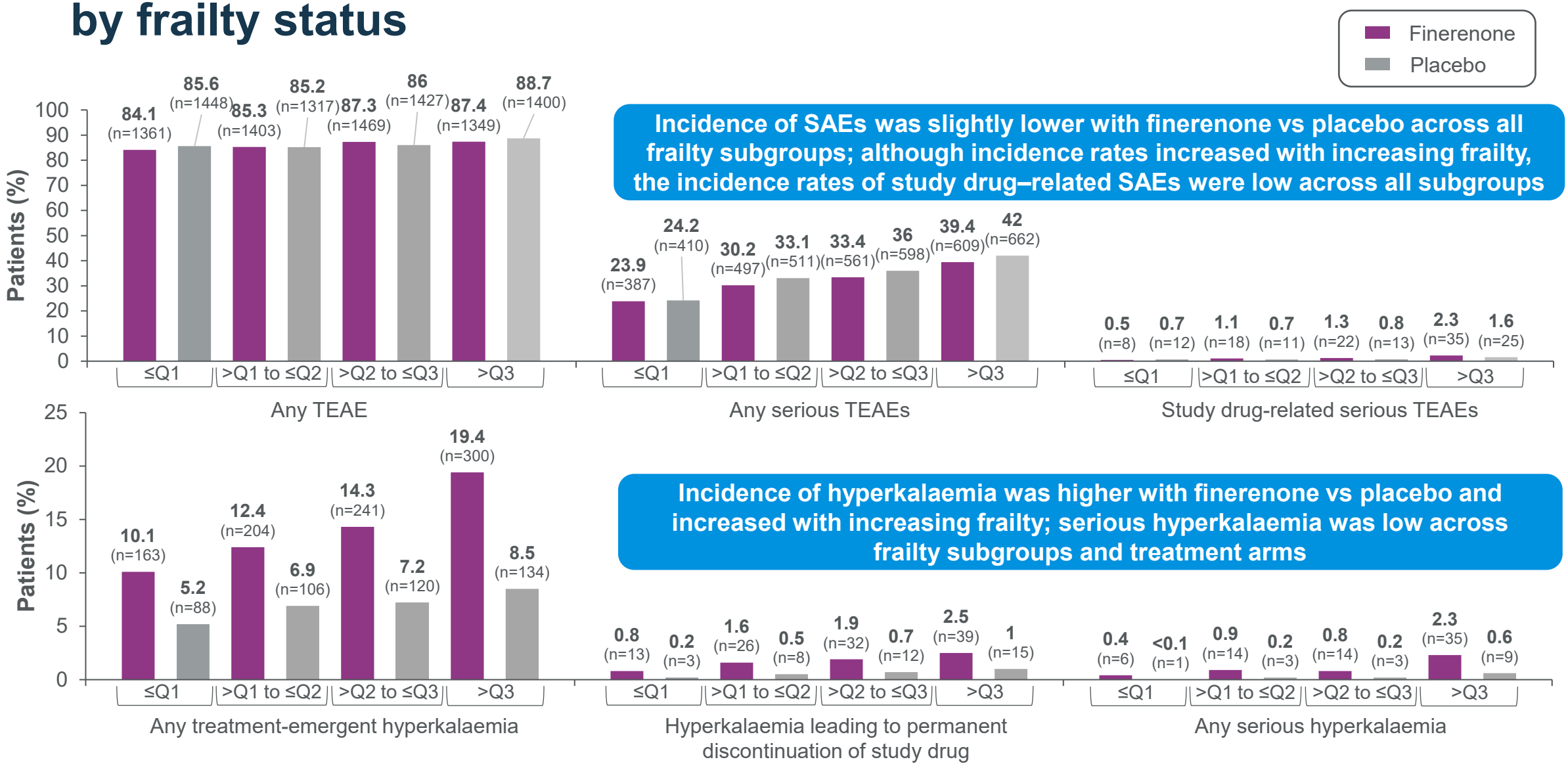
Outcome	Finerenone n/N (IR per 100 PY)	Placebo n/N (IR per 100 PY)	HR (95% CI)	*p*-value for interaction	Absolute risk difference (95% CI)	*p*-value for interaction
CV composite outcome*						
≤Q1	92/1619 (1.8)	86/1691 (1.6)	1.13 (0.84 to 1.52)	0.36	–0.6 (–2.1 to 0.9)	0.45
>Q1 to ≤Q2	174/1643 (3.5)	193/1549 (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)	



Absolute risk reduction of CV composite outcome with finerenone vs placebo was nominally higher in severely frail patients (*p*-value for interaction = 0.45)

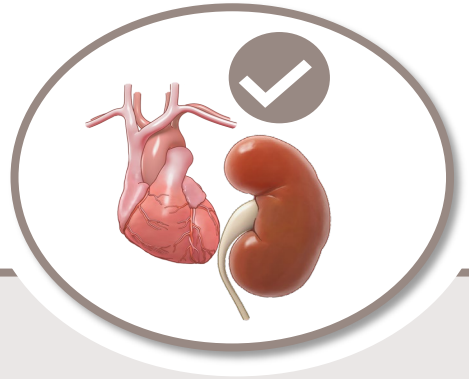
*Defined as a composite of CV death, non-fatal myocardial infarction, non-fatal stroke, or HHF; #defined as kidney failure, sustained ≥57% eGFR decline, or kidney-related death
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; HR, hazard ratio; IR, incidence rate; PY, person-years; Q, quartile

The safety profile of finerenone relative to placebo was not modified by frailty status



AE, adverse event; Q, quartile; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Summary



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**

These data suggest finerenone is an effective and well-tolerated treatment option for people with CKD and T2D across the spectrum of frailty

CKD, chronic kidney disease; CV, cardiovascular; SAE, serious adverse event; T2D, type 2 diabetes

Thank you

Executive committee

George L. Bakris* (co-chair); Gerasimos Filippatos (co-chair); Rajiv Agarwal; Stefan D. Anker; Bertram Pitt; Luis M. Ruilope

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***Our esteemed steering committee member, George Bakris, passed away in June 2024 and will be remembered for his passion for science and patient care.**

FIDELITY

FInerenone in chronic ki**D**ney diseas**E** and type 2 diabetes: Combined FIDE**L**IO-DKD and **FI**GARO-DKD **T**rial programme anal**Y**sis

The FIDELIO-DKD and FIGARO-DKD teams would also like to thank all participating investigators, the centres, and the participants and their families

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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 m², or UACR ≥300 to ≤5000 mg/g and eGFR ≥25 ml/min/1.73 m²
  - 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

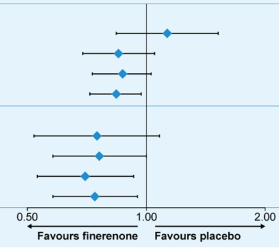
Baseline characteristic	≤Q1 (least frail)		>Q1 to ≤Q2		>Q2 to ≤Q3		>Q3 (most frail)	
	Finerenone (*n* = 1619)	Placebo (*n* = 1691)	Finerenone (*n* = 1643)	Placebo (*n* = 1549)	Finerenone (*n* = 1685)	Placebo (*n* = 1661)	Finerenone (*n* = 1551)	Placebo (*n* = 1591)
Sex, n (%)								
Female	467 (28.8)	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/m², 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 m², 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

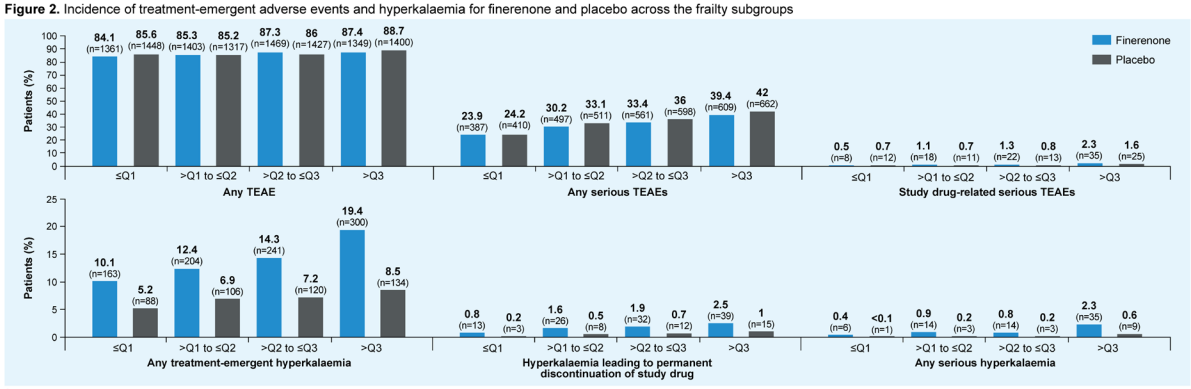
Table 2. Change in eGFR across the study period for finerenone and placebo according to frailty index score

ml/min/1.73 m² (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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