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Finerenone and Clinical Outcomes in CKD and Type 2 Diabetes by Frailty Index
FIDELITY *Post Hoc* Analysis

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Key Points
- Frailty is associated with a higher risk of adverse outcomes in people with CKD and type 2 diabetes.
- Finerenone reduced the risk of kidney and cardiovascular outcomes irrespective of baseline frailty.
- Finerenone was well tolerated; the relative risk of adverse events remained consistent between treatment arms across the frailty subgroups.

Abstract
Background Frailty is associated with a higher risk of adverse outcomes. It is believed that people with a higher frailty index (FI) may be less tolerant to new treatments, often leading to inappropriate prescribing. This *post hoc* analysis of FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD) and FIGARO-DKD Trial program analysis, a prespecified, pooled analysis of the FIDELIO-DKD and FIGARO-DKD phase 3 clinical trials, investigated the efficacy and safety of finerenone versus placebo according to baseline FI.

Methods Between September 2015 and October 2018, 12,990 people with CKD and type 2 diabetes receiving the maximum tolerated dose of a renin-angiotensin system inhibitor were randomized to receive finerenone 10 or 20 mg once daily or placebo. Baseline FI was calculated using the Rockwood cumulative deficit approach including 30 clinical characteristics. Primary efficacy outcomes included a kidney (kidney failure, sustained decrease of ≥57% in eGFR, or kidney-related death) and a cardiovascular (CV) composite outcome (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). Changes in urine albumin-to-creatinine ratio and eGFR were measured across the study period.

Results Overall, kidney and CV event rates increased with increasing frailty. Finerenone reduced the risk of primary kidney and CV composite outcomes irrespective of baseline frailty (P interaction = 0.93 and 0.35, respectively). Compared with placebo, finerenone also demonstrated significant reductions in urine albumin-to-creatinine ratio across all frailty subgroups ($P < 0.01$ for all visits) and significant attenuation of eGFR decline from baseline to month 48 in the three most frail quartiles (>Q1 to ≤Q2, $P = 0.001$; >Q2 to ≤Q3, $P < 0.001$; >Q3, $P < 0.001$, respectively). The incidence of serious adverse events and hyperkalemia increased with increasing frailty in both treatment arms.

Conclusions Finerenone reduced the risk of CV and kidney events in people with CKD and type 2 diabetes versus placebo irrespective of baseline frailty status.

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Introduction

Frailty is a clinical condition with implications across multiple aspects of life, including physical, social, and cognitive domains.[1–4] It is often defined as a state of increased vulnerability associated with a decline in physiologic system function.[1–4] However, there is no universal clinical definition for frailty, and identification of specific risk factors is challenging.[1] Despite this, frailty is an important global health burden and is expected to become more prevalent with an aging population.[5]

Incidence of frailty is often associated with increased age and presence of comorbidities and is believed to be more prevalent in women than in men, as women are more likely to live longer and develop chronic disease.[1,3,6,7] Globally, an estimated 35% of adults with CKD are considered to have physical frailty, and this has been associated with a lower quality of life, an increased rate of disease progression, and an increased risk of death.[8–11] In addition, the incidence of frailty has been shown to increase with reduced kidney function,[12] and fast decline in eGFR has been associated with incident frailty in people 70 years or older.[13] Type 2 diabetes (T2D) and associated complications are also linked to an increase in frailty.[14] Evidence suggests that people with frailty may experience worse clinical outcomes than those without frailty and therefore should be treated appropriately to reduce this risk.[8–10,13,14]

Given the accumulation of risk factors and comorbidities in people with more severe frailty, inappropriate prescribing is prevalent in older people with frailty.[15] Inappropriate prescribing includes misprescribing (described as prescribing medications at an incorrect dose or duration, or medications that are likely to cause significant drug-drug interactions[16]), overprescribing, and underprescribing medications, all of which may have negative consequences on clinical outcomes.[15] Underprescription of novel medications in people with frailty is a concern; clinicians are often less likely to initiate new treatments in this population, mostly because of concerns around tolerance of the therapy and a perceived lack of benefit.[2] However, there is limited evidence to support this, and the focus should be on appropriate and optimal prescribing.

In the FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease and FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease Trial program analysis (FIDELITY) pooled analysis, the selective nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone was associated with a reduced risk of cardiovascular (CV) and kidney outcomes compared with placebo in people with CKD and T2D.[17] This *post hoc* analysis of the FIDELITY cohort investigated the efficacy and safety of finerenone versus placebo in people with CKD and T2D according to baseline frailty index (FI) score as assessed by the Rockwood cumulative deficit approach.

Methods

Study Design and Participants

The FIDELITY analysis was a prespecified, pooled analysis of the FInerenone in reducing kiDnEy faiLure and dIsease prOgression in Diabetic Kidney Disease (FIDELIO-DKD; NCT02540993) and FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease (FIGARO-DKD; NCT02545049) phase 3 clinical trials.[17–19] The study design, procedures, and outcomes of the FIDELIO-DKD and FIGARO-DKD trials, along with the results from the primary FIDELITY analysis, have been published previously.[17–19]

Eligible participants were 18 years or older with CKD and T2D, with a serum potassium level ≤4.8 mmol/L at screening.[17–19] Participants had either a urine albumin-to-creatinine ratio (UACR) ≥30 to <300 mg/g and an eGFR ≥25 to ≤90 ml/min per 1.73 m^2 or UACR ≥300 to ≤5000 mg/g and eGFR ≥25 ml/min per 1.73 m^2 and were treated with standard-of-care therapy, including a maximum tolerated labeled dose of a renin-angiotensin system inhibitor.[17–19]

Those with symptomatic heart failure with reduced ejection fraction were excluded from the trials, as this implies an indication for a steroidal MRA.[17–19] All participants were randomly assigned to receive finerenone at titrated doses of 10 or 20 mg once daily as oral treatment (from month 1, 20 mg once daily was the target dose) or matching placebo (1:1).[17–19] Full inclusion and exclusion criteria can be found in the primary analyses.[18,19] The FIDELIO-DKD and FIGARO-DKD study protocols were approved by International Review Boards, independent Ethics Committees, and competent authorities according to national and international regulations. All participants provided written informed consent.[20,21]

Procedures and Outcomes

Efficacy outcomes mirrored the primary outcomes of the FIDELITY analysis, and included a kidney composite outcome (kidney failure, sustained ≥57% eGFR decline, or kidney-related death) and a CV composite outcome (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure [HHF]). A second kidney composite outcome (kidney failure, sustained ≥40% eGFR decline, or kidney-related death), all-cause mortality, all-cause hospitalization, and HHF were also analyzed. The event probability of efficacy outcomes at 3.5 years was calculated using baseline FI as a continuous variable. Changes in UACR, eGFR, and systolic and diastolic BP were measured at multiple visits across the study period.

Safety outcomes included the incidence of treatment-emergent adverse events (AEs). All efficacy and safety outcomes were analyzed by baseline frailty subgroup.

Statistical Analysis

Baseline FI was calculated using the Rockwood cumulative deficit approach.[22] The FI was defined as the sum of the presence or severity of 30 clinical characteristics at baseline, including laboratory measures, the EuroQol-5 Dimension (EQ-5D) questionnaire, and medical history (Supplemental Table 1). For each characteristic, participants were assigned a score between 0 and 1. Each participant's score was normalized by dividing the total score by the number of nonmissing characteristics to give a FI score between 0 (no frailty) and 1 (maximal frailty). All enrolled participants were categorized into subgroups

based on FI quartiles (≤Q1, >Q1 to ≤Q2, >Q2 to ≤Q3, and >Q3).

For all efficacy analyses, incidence rates (IRs) were estimated as the number of participants with incident events divided by the cumulative at-risk time in the reference population and expressed per 100 person-years (PY). Treatment effects for time to event efficacy analyses within the subgroup levels were expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for finerenone versus placebo treatment groups. Absolute risk differences between the event rates of finerenone and placebo were calculated using Mantel-Haenszel estimates.

Event probabilities at 3.5 years were calculated across the FI range using Cox proportional hazards models for each treatment group. The models were adjusted for age, sex, race, body mass index, and systolic BP, as well as the FIDELITY stratification factors. Cubic splines were plotted with knots at the first, 50th, and 99th percentiles of FI.

Changes in UACR were analyzed using a mixed model for repeated measures. Reductions in eGFR were analyzed using a two-slope linear spline mixed model for repeated measures that included all scheduled eGFR measurements per person where ≥1 postbaseline eGFR measurements were available.[23] These models included the FIDELITY stratification factors as fixed effects. When calculating changes in UACR and eGFR, values after the onset of ESKD were excluded from both analyses.

For all safety analyses, treatment interruptions were excluded from the person-time at risk. Three measurements of systolic and diastolic BP were taken per person at each study visit, and the mean value was calculated.

All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC). Further information on the statistical methods used in this analysis is available in the Supplementary Appendix.

Results

Study Population and Baseline Characteristics

A total of 12,990 people were included in this analysis. Overall, the mean FI was 0.463 (SD 0.105) and participants in both treatment arms were equally distributed across the frailty spectrum. Baseline characteristics of people treated with finerenone and placebo stratified by baseline FI are presented in Table 1. Overall, higher baseline FI was characterized by a higher proportion of females and those 75 years or older, as well as higher likelihood of White race. In addition, higher FI was characterized by lower mean eGFR, lower median UACR, and lower mean age, body mass index, duration of diabetes, and systolic BP. The proportion of people with medical history events, such as CV disease, myocardial infarction, and cardiac failure, was greater with higher baseline FI, whereas the proportion of current smokers was lower with greater FI.

The use of concomitant diuretics and antihypertensives was higher with higher baseline FI; however, the use of concomitant sodium-glucose cotransporter 2 inhibitors (SGLT2is) was low across all frailty subgroups, reflecting the lack of an indication for use in people with CKD and T2D at the index date of the FIDELIO-DKD and FIGARO-DKD clinical trials.

Efficacy

In general, IRs of the ≥57% and ≥40% kidney composite outcomes were higher with greater FI. The IR per 100 PY for the ≥57% kidney composite outcome ranged from 1.04 in the least frail participants (≤Q1) to 2.95 in those with the most severe frailty (>Q3) in the finerenone treatment arm and from 1.43 (≤Q1) to 3.75 (>Q3) in the placebo treatment arm. Finerenone demonstrated consistent reductions in the ≥57% and ≥40% kidney composite outcomes compared with placebo, with no heterogeneity between the frailty subgroups (*P* values for interaction = 0.93 and 0.76, respectively; Figure 1). There was no statistically significant difference in absolute risk reduction across the subgroups (*P* values for interaction = 0.76 and 0.66 for the ≥57% and ≥40% kidney composite outcomes, respectively); however, owing to the higher IR and similar relative risk reduction across all subgroups, absolute risk reduction was numerically higher with greater frailty.

Overall, the incidence of CV events was higher with greater frailty in both treatment arms, and this observation was more pronounced than for the kidney composite outcomes (Figure 1). The IR per 100 PY of the CV composite outcome ranged from 1.76 (≤Q1) to 7.90 (>Q3) in the finerenone treatment arm and from 1.57 to 9.65, respectively, in the placebo arm. The effect of finerenone on the CV composite outcome by baseline FI showed no statistically significant interaction compared with placebo across all frailty subgroups (*P* value for interaction = 0.35; Figure 1). Across the three most frail quartiles, >Q1 to ≤Q2, >Q2 to ≤Q3, and >Q3, there was a consistent lower relative risk of the CV composite outcome in people treated with finerenone versus placebo (HR, 0.84; 95% CI, 0.68 to 1.03; HR, 0.87; 95% CI, 0.73 to 1.04; and HR, 0.84; 95% CI, 0.72 to 0.97; respectively). Those in the lowest frailty quartile showed a nominally greater risk of CV outcomes with finerenone versus placebo; however, this was not statistically significant (HR, 1.14; 95% CI, 0.84 to 1.54). The absolute risk reduction of the CV composite outcome with finerenone versus placebo was nominally higher in people with the most severe frailty compared with the other subgroups (*P* value for interaction = 0.45).

Comparison of the ≤Q1 and >Q3 subgroups showed that the IR of all-cause mortality ranged from 1.18 to 4.92 per 100 PY, respectively, in the finerenone treatment arm and from 1.34 to 5.50 per 100 PY, respectively, in the placebo arm. Moreover, all-cause hospitalization IRs ranged from 11.47 to 30.83 per 100 PY and from 11.56 to 31.15 PY for the finerenone and placebo arms, respectively. Furthermore, IRs of HHF ranged from 0.30 to 3.10 per 100 PY and from 0.31 to 3.71 per 100 PY in the finerenone and placebo treatment arms, respectively. No heterogeneity in the treatment effect of finerenone versus placebo across frailty subgroups was observed for all-cause mortality (*P* value for interaction = 0.46), all-cause hospitalization (*P* value for interaction = 0.40), or HHF (*P* value for interaction = 0.35; Figure 1).

Using baseline FI as a continuous variable, calculations of event probabilities at 3.5 years illustrated the wide range of risk across the FI and showed consistent benefits with finerenone compared with placebo for all outcomes, particularly in people with a higher FI at baseline (Figure 2).

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

Baseline Characteristic	≤Q1[a] (Least Frail)		>Q1 to ≤Q2[b]		>Q2 to ≤Q3[c]		>Q3[d] (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, No. (%)								
Female	467 (29)	413 (24)	480 (29)	422 (27)	523 (31)	504 (30)	565 (36)	558 (35)
Male	1152 (71)	1278 (76)	1163 (71)	1127 (73)	1162 (69)	1157 (70)	986 (64)	1033 (65)
Age, yr, mean (SD)	61 (9)	61 (10)	64 (9)	64 (10)	66 (9)	66 (9)	67 (9)	68 (9)
Age group, yr, No. (%)								
<65	1064 (66)	1096 (65)	776 (47)	735 (47)	632 (38)	649 (39)	475 (31)	439 (28)
≥65–<75	428 (26)	429 (25)	649 (40)	609 (39)	771 (46)	718 (43)	779 (50)	829 (52)
≥75	127 (8)	166 (10)	218 (13)	205 (13)	282 (17)	294 (18)	297 (19)	323 (20)
Race, No. (%)								
Asian	591 (37)	627 (37)	424 (26)	396 (26)	286 (17)	287 (17)	112 (7)	137 (9)
Black or African American	42 (3)	46 (3)	55 (3)	47 (3)	72 (4)	81 (5)	82 (5)	95 (6)
White	880 (54)	919 (54)	1063 (65)	1000 (65)	1229 (73)	1212 (73)	1277 (82)	1289 (81)
Weight, kg, mean (SD)	82 (19)[e]	83 (19)[f]	87 (20)[g]	87 (19)[h]	89 (20)[i]	90 (20)[j]	94 (20)[k]	94 (20)[l]
BMI, kg/m^2, mean (SD)	29.2 (5.5)[m]	29.2 (5.5)[n]	30.8 (5.8)[o]	30.8 (5.6)[h]	31.6 (5.8)[p]	31.7 (5.7)[j]	33.8 (6.2)[q]	33.5 (6.2)[r]
Current smoker, No. (%)	370 (23)	365 (22)	284 (17)	268 (17)	235 (14)	216 (13)	170 (11)	174 (11)
UACR, mg/g, median (IQR)	450 (178–943)	431 (161–926)[s]	497 (185–1168)[t]	512 (208–1147)	490 (194–1099)	517 (196–1223)[u]	642 (247–1380)[v]	647 (254–1426)[w]
eGFR, ml/min per 1.73 m^2, mean (SD)	68 (21)	67 (22)	59 (21)	60 (22)	55 (21)	54 (20)	48 (18)[v]	48 (18)[x]
Serum potassium, mmol/L, mean (SD)	4.3 (0.4)	4.3 (0.4)[s]	4.3 (0.4)	4.3 (0.4)	4.4 (0.5)	4.4 (0.5)	4.4 (0.5)[v]	4.4 (0.5)[x]
Systolic BP, mm Hg, mean (SD)	132 (13)	132 (13)	135 (13)	136 (14)	138 (14)[y]	138 (14)	142 (14)[z]	142 (14)[x]
Diastolic BP, mm Hg, mean (SD)	76 (9)	77 (9)	76 (10)	77 (9)	76 (10)[y]	76 (10)	77 (10)[z]	77 (10)[x]
HbA_{1c}, %, mean (SD)	7.2 (1.2)[aa]	7.2 (1.2)[ab]	7.6 (1.4)[o]	7.5 (1.3)	7.8 (1.4)[ac]	7.9 (1.3)[u]	8.2 (1.3)[z]	8.2 (1.3)[r]
Duration of diabetes, yr, mean (SD)	13 (8)[ad]	13 (8)[s]	15 (9)[g]	14 (8)[h]	16 (9)[ae]	16 (9)[j]	18 (9)[v]	18 (9)[af]
History of CV disease, No. (%)	361 (22)	326 (19)	648 (39)	593 (38)	935 (56)	911 (55)	1029 (66)	1125 (71)
History of hypertension, No. (%)	1506 (93)	1574 (93)	1587 (97)	1511 (98)	1648 (98)	1621 (98)	1519 (98)	1565 (98)
History of MI, No. (%)	96 (6)	88 (5)	217 (13)	192 (12)	299 (18)	316 (19)	404 (26)	408 (26)
History of atrial fibrillation and atrial flutter, No. (%)	48 (3)	48 (3)	121 (7)	103 (7)	179 (11)	168 (10)	218 (14)	219 (14)
Baseline medications, No. (%)								
ACEi	601 (37)	627 (37)	609 (37)	581 (38)	680 (40)	683 (41)	633 (41)	662 (42)
ARB	1017 (63)	1064 (63)	1034 (63)	967 (62)	1001 (59)	977 (59)	917 (59)	927 (58)
β blocker	538 (33)	547 (32)	769 (47)	735 (47)	920 (55)	935 (56)	1005 (65)	1050 (66)
Diuretics	579 (36)	632 (37)	794 (48)	763 (49)	930 (55)	926 (56)	1015 (65)	1062 (67)
Potassium supplements	21 (1)	35 (2)	43 (3)	37 (2)	64 (4)	54 (3)	68 (4)	63 (4)
Potassium-lowering agents (including binders)	15 (1)	19 (1)	29 (2)	16 (1)	21 (1)	24 (1)	29 (2)	29 (2)
α blocking agents	235 (15)	266 (16)	336 (21)	319 (21)	376 (22)	396 (24)	417 (27)	425 (27)
Calcium channel blockers	830 (51)	885 (52)	950 (58)	929 (60)	983 (58)	966 (58)	888 (57)	905 (57)
DPP-4i	481 (30)	489 (29)	437 (27)	383 (25)	403 (24)	402 (24)	325 (21)	335 (21)
GLP-1RA	111 (7)	99 (6)	137 (8)	113 (7)	132 (8)	115 (7)	117 (8)	119 (8)
SGLT2i	137 (9)	136 (8)	117 (7)	116 (8)	110 (7)	111 (7)	72 (5)	74 (5)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; FI, frailty index; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; IQR, interquartile range; MI, myocardial infarction; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urine albumin-to-creatinine ratio.

[a]Frailty index ≤0.389; [b]frailty index >0.389 to ≤0.461; [c]frailty index >0.461 to ≤0.536; [d]frailty index >0.536; [e]*n*=1617; [f]*n*=1689; [g]*n*=1641; [h]*n*=1547; [i]*n*=1683; [j]*n*=1659; [k]*n*=1543; [l]*n*=1587; [m]*n*=1616; [n]*n*=1688; [o]*n*=1639; [p]*n*=1681; [q]*n*=1539; [r]*n*=1586; [s]*n*=1690; [t]*n*=1642; [u]*n*=1660; [v]*n*=1550; [w]*n*=1590; [x]*n*=1589; [y]*n*=1684; [z]*n*=1549; [aa]*n*=1618; [ab]*n*=1687; [ac]*n*=1680; [ad]*n*=1615; [ae]*n*=1682; [af]*n*=1588.

Outcome	Finerenone n/N	Finerenone IR/100 PY	Placebo n/N	Placebo IR/100 PY	HR (95% CI)	*P* Value for Interaction	Absolute Risk Difference (95% CI)	*P* Value for Interaction
CV composite outcome*								
≤Q1	92/1619	1.76	86/1691	1.57	1.14 (0.84 to 1.54)		–0.6 (–2.1 to 0.9)	
>Q1 to ≤Q2	174/1643	3.54	193/1549	4.22	0.84 (0.68 to 1.03)	0.35	1.9 (–0.3 to 4.1)	0.45
>Q2 to ≤Q3	240/1685	5.01	272/1661	5.89	0.87 (0.73 to 1.04)		2.1 (–0.3 to 4.6)	
>Q3	317/1551	7.90	387/1591	9.65	0.84 (0.72 to 0.97)		3.9 (1.0 to 6.8)	
≥57% kidney composite outcome†								
≤Q1	52/1619	1.04	75/1691	1.43	0.73 (0.50 to 1.06)		1.2 (–0.1 to 2.5)	
>Q1 to ≤Q2	100/1643	2.13	117/1549	2.66	0.78 (0.59 to 1.02)	0.93	1.5 (–0.3 to 3.2)	0.76
>Q2 to ≤Q3	89/1685	1.91	124/1661	2.73	0.71 (0.53 to 0.95)		2.2 (0.5 to 3.8)	
>Q3	115/1551	2.95	149/1591	3.75	0.70 (0.54 to 0.90)		2.0 (0.0 to 3.9)	
≥40% kidney composite outcome†								
≤Q1	152/1619	3.10	182/1691	3.56	0.84 (0.67 to 1.05)		1.4 (–0.7 to 3.4)	
>Q1 to ≤Q2	231/1643	5.09	247/1549	5.79	0.87 (0.72 to 1.04)	0.76	1.9 (–0.6 to 4.4)	0.66
>Q2 to ≤Q3	217/1685	4.84	272/1661	6.20	0.79 (0.66 to 0.95)		3.5 (1.1 to 5.9)	
>Q3	248/1551	6.60	294/1591	7.68	0.84 (0.71 to 1.00)		2.5 (–0.1 to 5.1)	
All-cause mortality								
≤Q1	63/1619	1.18	75/1691	1.34	0.92 (0.65 to 1.30)		0.5 (–0.8 to 1.9)	
>Q1 to ≤Q2	114/1643	2.22	139/1549	2.91	0.75 (0.58 to 0.96)	0.46	2.0 (0.2 to 3.9)	0.55
>Q2 to ≤Q3	160/1685	3.17	156/1661	3.15	1.05 (0.83 to 1.31)		–0.1 (–2.1 to 1.9)	
>Q3	214/1551	4.92	244/1591	5.50	0.91 (0.76 to 1.10)		1.5 (–0.9 to 4.0)	
All-cause hospitalization								
≤Q1	508/1619	11.47	538/1691	11.56	0.99 (0.88 to 1.13)		0.4 (–2.7 to 3.6)	
>Q1 to ≤Q2	670/1643	17.09	667/1549	18.70	0.91 (0.81 to 1.01)	0.40	2.3 (–1.1 to 5.7)	0.88
>Q2 to ≤Q3	780/1685	21.31	814/1661	23.08	0.94 (0.85 to 1.04)		2.7 (–0.7 to 6.1)	
>Q3	870/1551	30.83	901/1591	31.15	1.01 (0.92 to 1.11)		0.5 (–2.9 to 4.0)	
Hospitalization for heart failure								
≤Q1	16/1619	0.30	17/1691	0.31	0.93 (0.45 to 1.95)		0.0 (–0.7 to 0.7)	
>Q1 to ≤Q2	46/1643	0.91	50/1549	1.07	0.73 (0.46 to 1.17)	0.35	0.4 (–0.8 to 1.6)	0.38
>Q2 to ≤Q3	64/1685	1.30	102/1661	2.12	0.51 (0.35 to 0.74)		2.3 (0.9 to 3.8)	
>Q3	129/1551	3.10	156/1591	3.71	0.68 (0.52 to 0.89)		1.5 (–0.5 to 3.5)	

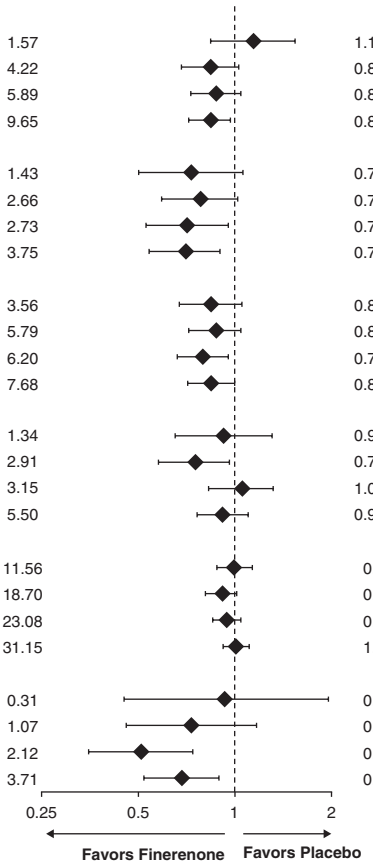

Figure 1. Efficacy outcomes for finerenone and placebo across the frailty subgroups. *Defined as a composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF. †Defined as kidney failure, sustained ≥57%/≥40% eGFR decline, or kidney-related death. CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; IR, incidence rate; PY, person-years.

Baseline UACR was higher with greater frailty (Table 1), but at month 4, finerenone was associated with an approximate 40% lower in albuminuria across all subgroups, which was significant compared with placebo ($P < 0.001$ for all subgroups). These significant reductions in UACR were maintained in people treated with finerenone compared with placebo for all frailty subgroups throughout the study period ($P < 0.01$ for all visits).

Across the study period, people treated with finerenone displayed consistent eGFR profiles irrespective of frailty subgroup. Consistent with the primary FIDELITY analysis, an acute decline in eGFR from baseline to month 4, followed by stabilization to month 48, was observed across all frailty subgroups.[17] Those treated with placebo showed greater declines in eGFR at month 48 compared with finerenone, and this difference was more pronounced as frailty increased (difference of least squares means: ≤Q1, 0.23; >Q1 to ≤Q2, 0.56; >Q2 to ≤Q3, 0.59; >Q3, 0.71, respectively). For the three most frail quartiles, differences between treatment groups in eGFR slope from baseline to month 48 were statistically significant (>Q1 to ≤Q2, $P = 0.001$; >Q2 to ≤Q3, $P < 0.001$; >Q3, $P < 0.001$, respectively).

Safety

The incidence of AEs was generally consistent across treatment arms and across frailty subgroups, as presented in Table 2. The incidence of serious AEs (SAEs) was lower with finerenone compared with placebo across all frailty subgroups. Although IRs increased with increasing frailty, the IRs of study drug-related SAEs were low across all subgroups (Table 2).

IRs of hyperkalemia were higher with greater frailty; however, the relative risk between the treatment arms remained consistent across all subgroups (Table 2). The incidence of hyperkalemia was approximately twice as high in the finerenone treatment arm compared with placebo for all frailty subgroups, which is consistent with previous analyses.[17] Event rates of hyperkalemia leading to permanent discontinuation or serious hyperkalemia were generally low across treatment arms and frailty subgroups, and no cases of death due to hyperkalemia were reported in the overall study population.

The IR of hypoglycemia was consistent between the finerenone and placebo treatment arms across all subgroups (Table 2). Modestly higher IRs of hypoglycemia were observed with greater frailty for both treatment arms.

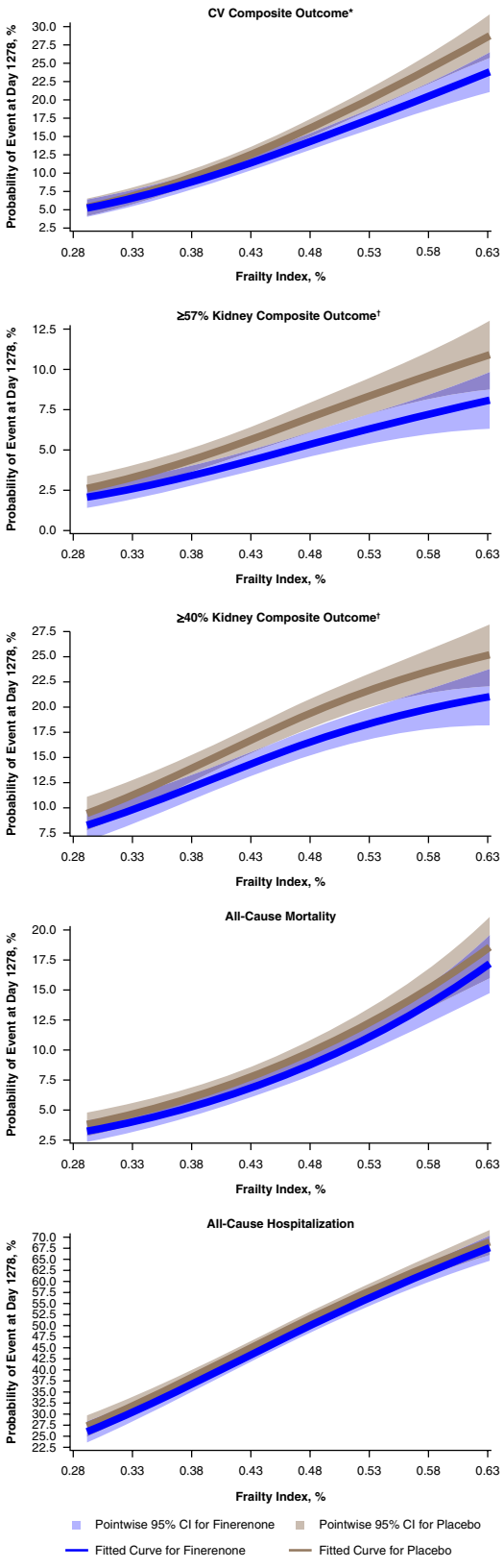

Figure 2. Event probabilities at 3.5 years for finerenone and placebo by baseline FI. *Defined as a composite of CV death, nonfatal myocardial infarction, nonfatal stroke, or HHF. †Defined as kidney failure, sustained ≥57%/≥40% eGFR decline, or kidney-related death. FI, frailty index.

Systolic and diastolic BP were well controlled across the entire study period for both treatment arms and all frailty subgroups.

Discussion

In this *post hoc* analysis of FIDELITY, greater severity of frailty was found to be associated with greater IRs of clinical events and AEs, suggesting a clinically important difference in risk across the spectrum of frailty. The current analysis demonstrated that finerenone provided consistent reductions in relative risk for all measured efficacy outcomes irrespective of baseline FI; there were no statistically significant differences between frailty subgroups for any of the efficacy outcomes analyzed. Nominal differences in the observed efficacy for individual subgroups may have been due to random heterogeneity or the low number of events. In addition, the absolute risk reduction was nominally higher with greater frailty. These findings were supported by the analyses using FI as a continuous variable, and UACR and eGFR analyses, which all demonstrated consistent benefits of finerenone versus placebo across the spectrum of frailty.

The baseline characteristics data showed that participants in the most frail subgroup were more likely to be older, have experienced previous medical events, and have more advanced CKD. The observed trends in baseline characteristics were expected since these characteristics were included in the FI, and therefore, increased incidence correlates with increased frailty. Interestingly, there was a lower proportion of current smokers with greater frailty. This may have been due to changes in lifestyle, as recommended by physicians and the Kidney Disease Improving Global Outcomes guidelines, to manage CKD disease progression.[24] Alternatively, this may reflect higher rates of death in people who smoke with greater frailty, lowering their representation in this analysis.

Because frailty is associated with a decline in physiologic function and increased vulnerability, it is expected that people with greater levels of frailty would experience greater IRs of AEs from treatment.[2,3,25] Indeed, in this analysis, the IRs of SAEs, hyperkalemia, and serious hyperkalemia increased with greater frailty across both treatment arms; however, the relative risk remained consistent between the treatment arms across the frailty subgroups. Greater IRs of SAEs and hyperkalemia were not associated with treatment with finerenone, suggesting finerenone was well tolerated in people with CKD and T2D across the spectrum of frailty. However, owing to their higher risk of AEs, all patients with greater frailty, regardless of treatment, should be monitored closely to minimize the risk of adverse outcomes.

Concerns from clinicians around tolerance of new treatments in people with more severe frailty may negatively affect the prescription of these treatments and clinical outcomes since these people are at the highest risk of kidney and CV events. This has been previously demonstrated in initiation rates of SGLT2is and glucagon-like peptide-1 receptor agonists in people with T2D and CV disease in Denmark, whereby people identified as moderately or severely frail were significantly less likely than people classified as nonfrail to be prescribed these

Table 2. Incidence of treatment-emergent adverse events stratified by baseline frailty index subgroup

Outcome	≤Q1 (Least Frail)		>Q1 to ≤Q2		>Q2 to ≤Q3		>Q3 (Most Frail)	
	Finerenone (*n*=1619)	Placebo (*n*=1691)	Finerenone (*n*=1644)	Placebo (*n*=1545)	Finerenone (*n*=1682)	Placebo (*n*=1660)	Finerenone (*n*=1544)	Placebo (*n*=1578)
Any AE	1361 (84)	1448 (86)	1403 (85)	1317 (85)	1469 (87)	1427 (86)	1349 (87)	1400 (89)
Any study drug-related AE	246 (15)	174 (10)	268 (16)	205 (13)	329 (20)	232 (14)	361 (23)	248 (16)
Any AE leading to discontinuation	62 (4)	71 (4)	106 (6)	71 (5)	99 (6)	108 (7)	147 (10)	100 (6)
AE leading to death	16 (1)	31 (2)	32 (2)	30 (2)	32 (2)	42 (3)	29 (2)	48 (3)
Any SAE	387 (24)	410 (24)	497 (30)	511 (33)	561 (33)	598 (36)	609 (39)	662 (42)
Any study drug-related SAE	8 (0.5)	12 (0.7)	18 (1)	11 (0.7)	22 (1)	13 (0.8)	35 (2)	25 (2)
Any SAE leading to discontinuation	21 (1)	31 (2)	33 (2)	29 (2)	41 (2)	50 (3)	50 (3)	44 (3)
Any hyperkalemia	163 (10)	88 (5)	204 (12)	106 (7)	241 (14)	120 (7)	300 (19)	134 (9)
Any hyperkalemia leading to permanent discontinuation	13 (0.8)	3 (0.2)	26 (2)	8 (0.5)	32 (2)	12 (0.7)	39 (3)	15 (1)
Any serious hyperkalemia	6 (0.4)	1 (<0.1)	14 (0.9)	3 (0.2)	14 (0.8)	3 (0.2)	35 (2)	9 (0.6)
Any hypoglycemia	77 (5)	78 (5)	83 (5)	90 (6)	95 (6)	105 (6)	85 (6)	102 (7)
Any serious hypoglycemia	4 (0.2)	5 (0.3)	6 (0.4)	13 (0.8)	14 (0.8)	20 (1)	14 (0.9)	21 (1)

All values are No. (%). AE, adverse event; SAE, serious adverse event.

cardioprotective therapies.[26] The results presented here clearly demonstrate that the efficacy of finerenone was retained in people with more severe frailty. Moreover, absolute risk reductions of the primary kidney and CV composite outcomes with finerenone versus placebo were higher in the two most frail subgroups compared with the two least frail. Compared with placebo, finerenone also demonstrated significant reductions in UACR and attenuation of eGFR decline across the study period consistently across all frailty subgroups. Acute decline in eGFR on initiation of treatment with finerenone is expected; this effect has been demonstrated in previous studies after initiation of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or SGLT2is in people with CKD and T2D.[27–31]

Optimal management of people with frailty should be carefully considered by clinicians; this is becoming increasingly important with an aging population. Elderly people are often underrepresented in clinical trials, limiting the data available to support treatment decisions. In the current analysis, people 75 years or older were well represented, making up 20% of the most frail subgroup compared with 9% of the least frail subgroup. However, clinical guidance is limited, and an evidence gap remains in the treatment decision-making process for people with CKD, T2D, and frailty. Recommendations 13.15 and 13.16 days of the 2024 American Diabetes Association guidelines state that "Overtreatment of diabetes is common in older adults and should be avoided" (level of recommendation: B), and "In older adults with T2D and established or high risk of atherosclerotic CV disease, heart failure, and/or CKD, the treatment plan should include agents that reduce cardiorenal risk, irrespective of glycemia" (level of recommendation: A), respectively.[32] Some evidence suggests that glucagon-like peptide-1 receptor agonists and SGLT2is may be beneficial in healthy older people, but further studies are required to support their use in people with frailty.[2] The current analysis may support a future recommendation for the use of finerenone as a preferred treatment option for people with CKD, T2D, and frailty, including older people; however, additional analyses would be required.

The results from this analysis were consistent with those from a prespecified analysis of the Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure trial, in people with heart failure with mildly reduced or preserved ejection fraction across the spectrum of frailty, and analysis of the Dapagliflozin and Prevention of Adverse Outcomes in CKD trial in people with CKD.[3,6] Similar to the current analysis, dapagliflozin showed beneficial effects on study outcomes across frailty subgroups.[3,6] AEs were more frequent with greater severity of frailty across both treatment arms, but the relative risk reduction of clinical outcomes with dapagliflozin versus placebo was consistent across frailty subgroups.[3,6] In these analyses, the FI was also defined using the Rockwood cumulative deficit approach, with different clinical characteristics included in the FI compared with the current analysis, and participants were grouped according to severity of frailty.[3,6]

This analysis has some limitations that should be considered. First, this was a *post hoc* analysis of a pooled dataset; the findings are hypothesis-generating only, and no causal relationship can be inferred since control for multiple comparisons was not conducted. Moreover, people with the most severe frailty were not included in this analysis due to not participating in the phase 3 FIDELIO-DKD and FIGARO-DKD trials. This is often the case for people with more severe frailty, whose higher levels of physical impairment and greater presence of comorbidities may make them ineligible or unable to participate in clinical trials. Therefore, the conclusions may not be generalizable to the broader population. The lack of a standard clinical definition for frailty makes comparison with other studies difficult, although similar FIs have been used previously.[3,6] Some characteristics of the FI (*e.g.*, EQ-5D questionnaire results) are subjective and may not have been consistently reported; therefore, comparison between participants may be difficult. In addition, the FI focuses on multimorbidity and may not capture all aspects of social, mental, and physical frailty; most notably, activities of daily living were only partially captured in the EQ-5D component of the index.

Overall, this analysis demonstrated that more severe frailty was associated with greater incidence of adverse outcomes. Finerenone was shown to be an effective and well-tolerated treatment option for people with CKD and T2D across the spectrum of frailty. The safety profile of finerenone was consistent relative to placebo across all frailty subgroups. This is the first study analyzing the effects of a nonsteroidal MRA in people with CKD and T2D by FI. It is important to keep in mind that frailty is not only a concern in older people; therefore, this efficacy and safety analysis is clinically relevant across the spectrum of people with CKD and T2D, and finerenone should be considered in this population regardless of the severity of frailty.[33]

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/CJN/C273.

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Data Sharing Statement

Anonymized data created for the study are or will be available in a persistent repository upon publication. Partial restrictions to the data and/or materials apply. Clinical Trial Data. Research Protocols. Other. Vivli. Go to www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance science or improve patient care. Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Association/Pharmaceutical Research and Manufacturers of America "Principles for responsible clinical trial data sharing." This pertains to scope, timepoint and process of data access. As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the European Union and US as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the European Union and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/C274.

Plain-Language Summary

FIDELIO-DKD Investigators

FIGARO-DKD Investigators

Statistical Analysis

Supplemental Table 1. Variables included in the FI.

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