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Effects of finerenone on clinical outcomes by CKD severity: An INFINITY analysis

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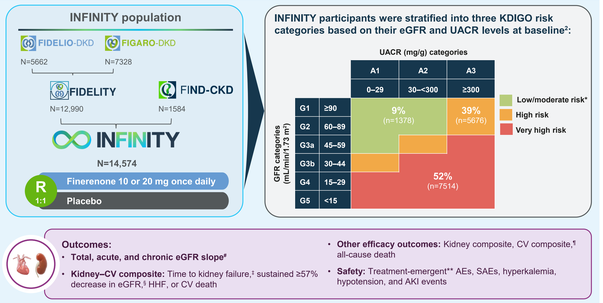
Background

- Kidney and cardiovascular (CV) risks increase with chronic kidney disease (CKD) severity as assessed by estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (UACR)[1]
- Kidney Disease: Improving Global Outcomes (KDIGO) risk categories by eGFR and UACR guide CKD monitoring and management[2]
- In the INFINITY pooled analysis, which included participant-level data from the phase III FIDELIO-DKD, FIGARO-DKD (CKD and type 2 diabetes; NCT02540993 and NCT02545049, respectively), and FIND-CKD (nondiabetic CKD; NCT05047263) trials, the nonsteroidal mineralocorticoid receptor antagonist finerenone reduced kidney and CV risks[3]
- In a broad CKD population, the effects of finerenone on clinical outcomes by CKD severity remain unknown
- This prespecified analysis of the INFINITY population aimed to examine the impact of baseline CKD severity on kidney and CV risk reduction with finerenone

Methods

- The INFINITY pooled analysis design is shown in **Figure 1**
- In all trials, patients were randomized 1:1 to finerenone (10 or 20 mg oral) or placebo[3]
  - Patients were also required to be receiving a stable, maximum tolerated dose of renin–angiotensin system inhibitor
- Inclusion criteria for eGFR and UACR varied by trial[3]
  - FIDELIO-DKD: either an eGFR ≥25 to <60 mL/min/1.73 m^2, UACR ≥30 to <300 mg/g and a history of diabetic retinopathy or an eGFR ≥25 to <75 mL/min/1.73 m^2 with a UACR of ≥300 to ≤5000 mg/g
  - FIGARO-DKD: either an eGFR ≥25 to <90 mL/min/1.73 m^2, UACR ≥30 to <300 mg/g, or an eGFR ≥60 mL/min/1.73 m^2 with a UACR of ≥300 to ≤5000 mg/g
  - FIND-CKD: either an eGFR of ≥25 to <60 mL/min/1.73 m^2, UACR of ≥200 to <500 mg/g, or an eGFR of ≥25 to <90 mL/min/1.73 m^2 with a UACR ≥500 to ≤3500 mg/g
- The INFINITY population was stratified into three KDIGO risk categories (low/moderate, high, very high) based on their eGFR and UACR levels at baseline[3]
- Outcomes measured included eGFR slope, kidney–CV composite, kidney composite, CV composite, death from any cause, and safety (treatment-emergent adverse events [AEs], serious AEs, and hyperkalemia events)

Figure 1. Study design and outcomes



*For the purpose of this analysis, low and moderate risk groups have been combined; †total slope: mean change from baseline to month 32, acute slope: mean change from baseline to month 3, chronic slope: mean change from month 3 to end of treatment; ‡defined as eGFR <15 mL/min/1.73 m^2, initiation of chronic dialysis or kidney transplantation; §from baseline for ≥4 weeks; ¶kidney composite: kidney failure or sustained ≥57% decrease in eGFR, CV composite: HHF or CV death; **AEs that started or worsened after the first dose of study intervention up to 3 days after any temporary or permanent interruption of study intervention were considered treatment-emergent

AE, adverse event; AKI, acute kidney injury; CV, cardiovascular; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HHF, hospitalization for heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; R, randomization; SAE, serious adverse event; UACR, urinary albumin-to-creatinine ratio

Results

Baseline characteristics

- Of 14,568 INFINITY participants with eGFR and UACR measurements at baseline who were included in this analysis, 1378 (9%) were classified as being in the low/moderate KDIGO risk category, with the majority being classified as high (5676; 39%) or very high risk (7514; 52%)
- Aside from eGFR and UACR, baseline demographics were broadly similar between KDIGO risk groups; however, a higher proportion of participants in the higher risk groups were female and a lower proportion of participants in the very high-risk groups were prescribed sodium-glucose co-transporter-2 inhibitors (**Table 1**)

Table 1. Baseline characteristics according to KDIGO risk category

KDIGO risk category	Low/moderate risk (n=1378)	High risk (n=5676)	Very high risk (n=7514)
Finerenone, n	720	2798	3771
Placebo, n	658	2878	3743
Age, years, mean ± SD	64.5 ± 9.0	62.1 ± 10.5	64.7 ± 10.8
Sex, female, n (%)	367 (26.6)	1762 (31.0)	2334 (31.1)
Race, n (%)			
White	1044 (75.8)	3840 (67.7)	4629 (61.6)
Asian	233 (16.9)	1322 (23.3)	2173 (28.9)
Black	43 (3.1)	194 (3.4)	320 (4.3)
Other*	58 (4.2)	320 (5.6)	392 (5.2)
BMI, kg/m^2, mean ± SD	31.6 ± 6.0	31.2 ± 6.0	30.6 ± 6.1
eGFR, mL/min/1.73 m^2, mean ± SD	75.1 ± 13.8	72.8 ± 17.9	40.5 ± 9.5
UACR, mg/g, median (Q1–Q3)	120.1 (58.4–217.7)	563.1 (276.0–1082.0)	720.7 (357.5–1407.6)
SBP, mmHg, mean ± SD	135.1 ± 13.8	136.1 ± 14.0	136.1 ± 14.7
Medication use, n (%)			
ACEi	610 (44.3)	2370 (41.8)	2529 (33.7)
ARB	768 (55.7)	3298 (58.1)	4979 (66.3)
SGLT-2i	125 (9.1)	523 (9.2)	494 (6.6)

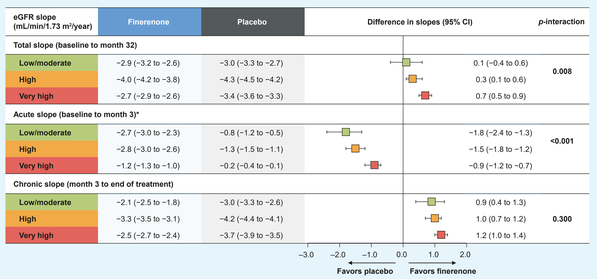
*Includes American Indian, Alaska native, native Hawaiian, Pacific Islander, participants who reported that they belong to more than one race, and participants whose race was not reported

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; Q, quartile; Q1, first quartile; Q3, third quartile; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urinary albumin-to-creatinine ratio

eGFR slopes by KDIGO risk category

- Overall, finerenone reduced total eGFR slope from baseline to month 32 versus placebo across disease severity groups, with differences of 0.1 (−0.4 to 0.6), 0.3 (0.1 to 0.6), and 0.7 (0.5 to 0.9) mL/min/1.73m^2/year across low/moderate, high, and very high-risk groups, respectively (*p*-interaction=0.008; **Figure 2**)
- While there was an acute dip in eGFR with finerenone from baseline to month 3, thereafter, the chronic slope (from month 3 to end of treatment) was reduced with finerenone versus placebo with no effect interaction for baseline disease severity (*p*-interaction=0.3; **Figure 2**)

Figure 2. eGFR slope stratified by KDIGO risk category

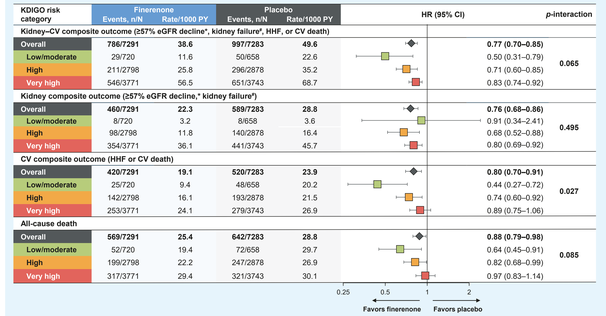


eGFR slopes were calculated using a two-slope spline mixed-effects model. Total slope: mean annual rate of change in eGFR from baseline to month 32; acute slope: mean rate of change in eGFR from baseline to month 3; chronic slope: mean annual rate of change in eGFR from month 3 to end of treatment
*Reported in mL/min/1.73 m^2/3 months
CI, confidence interval; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes

Time-to-event outcomes by baseline KDIGO risk category

- Finerenone reduced the risk of the kidney–CV and kidney composite outcomes compared with placebo, with hazard ratios (HRs) of 0.77 (95% CI 0.70–0.85) and 0.76 (95% CI 0.68–0.86), respectively (**Figure 3**)
  - This effect was consistent regardless of baseline KDIGO risk category (*p*-interaction=0.065 and 0.495 for the kidney–CV and kidney composites, respectively)
- Finerenone also lowered the risk of the CV composite outcome versus placebo (HR=0.80 [95% CI 0.70–0.91]) and all-cause death (HR=0.88 [95% CI 0.79–0.98]) across KIDGO risk categories (*p*-interaction=0.027 and 0.085, respectively; **Figure 3**)

Figure 3. Time-to-event outcomes across KDIGO risk categories



Time-to-event outcomes were analyzed using stratified log-rank tests and stratified Cox proportional hazards models to estimate HRs with two-sided 95% CIs
*From baseline, sustained for ≥4 weeks; †defined as an eGFR of <15 mL/min/1.73 m^2, initiation of chronic dialysis or kidney transplantation
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; PY, patient-years

Adverse events

- Overall, the rates of AEs were broadly similar across treatment groups and KDIGO risk categories (**Table 2**)
- The incidence of hyperkalemia was higher with finerenone versus placebo, with a higher incidence in the very high (19.7% vs 10.3%) and high (8.9% vs 5.0%) risk groups compared with the lower risk group (7.2% vs 3.4%)
- Incidence of serious hyperkalemia was low (≤1.5%) in both treatment groups across risk categories
- Hypotension was more common with finerenone versus placebo and occurred at similar rates across CKD risk groups

Table 2. Treatment-emergent AEs by KDIGO risk category

	Low/moderate risk (n=1377)		High risk (n=5668)		Very high risk (n=7498)	
Treatment-emergent AE, n (%)	**Finerenone (n=721)**	**Placebo (n=656)**	**Finerenone (n=2795)**	**Placebo (n=2873)**	**Finerenone (n=3765)**	**Placebo (n=3733)**
Any AE	609 (84.5)	562 (85.7)	2331 (83.4)	2400 (83.5)	3183 (84.5)	3146 (84.3)
Related to study drug	108 (15.0)	66 (10.1)	379 (13.6)	305 (10.6)	891 (23.7)	621 (16.6)
Leading to permanent discontinuation	30 (4.2)	34 (5.2)	133 (4.8)	127 (4.4)	268 (7.1)	212 (5.7)
Any serious AE	224 (31.1)	205 (31.2)	818 (29.3)	882 (30.7)	1177 (31.3)	1262 (33.8)
Leading to death	14 (1.9)	18 (2.7)	46 (1.6)	67 (2.3)	55 (1.5)	76 (2.0)
Any hyperkalemia	52 (7.2)	22 (3.4)	250 (8.9)	145 (5.0)	741 (19.7)	386 (10.3)
Serum [K$^+$] >6 mmol/L, n/N (%)	13/713 (1.8)	4/647 (0.6)	60/2763 (2.2)	31/2846 (1.1)	172/3724 (4.6)	63/3685 (1.7)
Any serious hyperkalemia	2 (0.3)	0	18 (0.6)	2 (0.1)	57 (1.5)	19 (0.5)
Hypotension	17.65 (5.5)	8.69 (2.7)	14.40 (3.9)	7.30 (2.0)	23.92 (5.3)	16.99 (4.0)
AKI	4.28 (1.4)	6.23 (2.0)	7.52 (2.1)	9.67 (2.7)	20.44 (4.6)	19.15 (4.5)

AEs that started or worsened after the first dose of study intervention up to 3 days after any temporary or permanent interruption of study intervention were considered treatment-emergent. All AEs were reported for the safety analysis set, which was defined as all randomly assigned patients without critical GCP violations, with eGFR and UACR measurements at baseline, who took one or more doses of the study drug
AE, adverse event; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; GCP, Good Clinical Practice; [K$^+$], potassium concentration; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urinary albumin-to-creatinine ratio

Conclusions

- Finerenone consistently slowed the progression of kidney function decline in a broad CKD population, and reduced the risk of kidney and CV events across different levels of baseline risk
  - The effect of finerenone on chronic eGFR slope was consistent irrespective of CKD severity
  - Heterogeneity was observed for total and acute eGFR slope with less eGFR decline in the very high-risk group
  - Heterogeneity was not observed between CKD subgroups for effects of finerenone on the kidney composite outcome
  - CV risk reduction may have been greater in the low/moderate KDIGO risk category
- Finerenone was well tolerated with similar overall treatment-emergent AE rates observed between treatment groups and KDIGO risk categories
  - Hyperkalemia was more frequent with finerenone versus placebo, with greater frequency in higher risk groups
    - Serious hyperkalemia events were rare overall
  - Hypotension was more frequent with finerenone irrespective of CKD severity
- The totality of data support the use of finerenone to reduce kidney and CV risks with an acceptable safety profile across a broad CKD population

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Disclosures

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