Finerenone in patients with chronic kidney disease, type 2 diabetes, and anemia: A FIDELITY analysis

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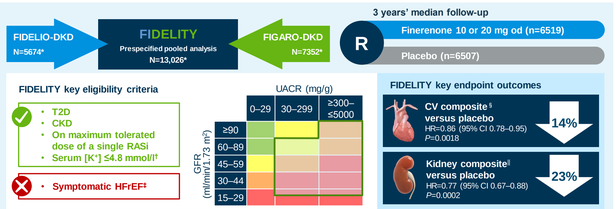
Introduction

- Anemia has been associated with a heightened risk of adverse heart and kidney outcomes and mortality in patients with chronic kidney disease (CKD)[1], and management of these patients remains suboptimal
  - The World Health Organization defines anemia as hemoglobin (Hb) <12 or <13 g/dl for females and males, respectively[2]
- Anemia is a common complication in patients with CKD and diabetes, and has increased prevalence with decreased estimated glomerular filtration rate (eGFR)[3,4]
- The etiology of anemia in CKD is multifactorial and includes erythropoietin deficiency, disordered iron homeostasis, and inflammation[5]
- Mineralocorticoid receptor (MR) overactivation is thought to contribute to cardiovascular (CV) and kidney disease progression[6,7]
- Finerenone is a nonsteroidal MR antagonist (MRA) that selectively blocks MR overactivation and has demonstrated CV and kidney benefits in patients with CKD and type 2 diabetes (T2D)
- The FIDELITY[4] pooled analysis of the FIDELIO-DKD[8] (NCT02540993) and FIGARO-DKD[9] (NCT02545049) studies showed that finerenone significantly reduced risk of CV outcomes and slowed CKD progression versus placebo in patients with CKD and T2D[6]
- The purpose of this post-hoc analysis was to investigate the effect of finerenone on patients with anemia versus patients without anemia with the hypothesis that baseline anemia status does not modify the effect of finerenone on CV and kidney protection, but may be a potential marker for more severe disease

Methods

- The patient population included in the FIDELITY pooled analysis is described in Figure 1
- Primary endpoints included a CV composite outcome (time to CV death, non-fatal myocardial infarction [MI], non-fatal stroke, or hospitalization for heart failure [HHF]), a kidney composite outcome (time to kidney failure, sustained ≥57% decrease in eGFR from baseline, or kidney death), and HHF
- Secondary endpoints were a kidney composite outcome (time to kidney failure, sustained ≥40% decrease in eGFR from baseline over ≥4 weeks, or kidney death) and safety outcomes (adverse events [AEs], including hyperkalemia)
- Key outcomes were stratified by baseline anemia status
- Analysis:
  - Time-to-event analyses of clinical outcomes were conducted using stratified Cox proportional hazards models; stratification factors included geographic region, eGFR and urine albumin-to-creatinine ratio (UACR) categories at screening, history of CV disease and study
  - In a sensitivity analysis, anemia status over time (from baseline to end of study) and the relationship to efficacy outcomes were investigated with time-dependent Cox proportional hazards models with additional stratification factors: treatment (finerenone or placebo), anemia status as a time-dependent covariate, and its interaction with treatment
  - To account for possible non-linear effects of Hb level on clinical outcomes, Hb was modelled using cubic splines with three knots in the stratified Cox proportional hazards models

Figure 1. FIDELITY pooled analysis study design



ªPatients analysed; †at run-in or screening visit; ‡run-in only; §time to CV death, non-fatal MI, non-fatal stroke, or HHF; ‖time to kidney failure, sustained ≥57% eGFR from baseline over ≥4 weeks decline, or kidney-related death
eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MI, myocardial infarction; od, once daily; R, randomization; RASi, renin–angiotensin system inhibitor; UACR, urine albumin-to-creatinine ratio

Results

- Of the 13,007 patients included in the full analysis set, approximately one-third had anemia (*n*=4293), defined as Hb <12 g/dl for females and <13 g/dl for males, and <10 g/dl as moderate–severe anemia. Baseline characteristics are shown in Table 1

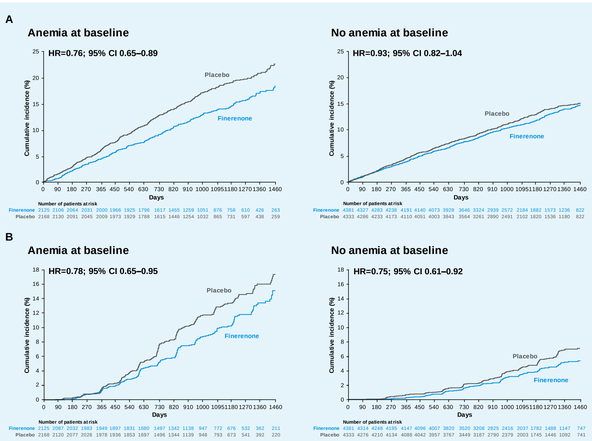
Table 1. Baseline characteristics by anemia status

Patient characteristics	Anemia (n=4293)	No anemia (n=8714)
Age, years, mean	65.5	64.4
Sex, female, %	33.6	28.6
Race and ethnicity, %		
Asian	26.6	20.1
Black/African American	7.0	2.5
White	59.9	72.1
SBP/DBP, mmHg, mean	137/73	137/78
Duration of diabetes, years, mean	17.0	14.6
HbA1c, %, mean	7.6	7.8
Laboratory parameters at baseline		
Serum potassium, mmol/l, mean	4.4	4.3
hs-CRP, mg/l, mean	5.5	4.4
eGFR, ml/min/1.73 m², mean	49.3	61.7
UACR, mg/g, median	582.4	487.3
Medical history, %		
CV disease	48.3	44.2
Heart failure	8.9	7.6
Atrial fibrillation or flutter	7.1	8.8
Medications, %		
CV medications		
RASi	99.8	99.9
Statins	75.0	70.8
Diuretics	56.0	49.4
Beta blockers	51.2	49.3
Calcium channel blockers	60.7	54.4
Erythropoietin stimulating agents	2.0	0
≥1 glucose-lowering therapy		
Insulin	62.1	56.8
GLP-1RA	6.4	7.7
SGLT-2i	3.0	8.6

CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

- Finerenone was associated with a lower risk of the CV composite outcome versus placebo in patients with anemia, but not in those without (Figure 2A)
- A reduced risk of the ≥57% eGFR kidney composite outcome was observed with finerenone versus placebo in all patients regardless of baseline anemia status with and without anemia (Figure 2B)

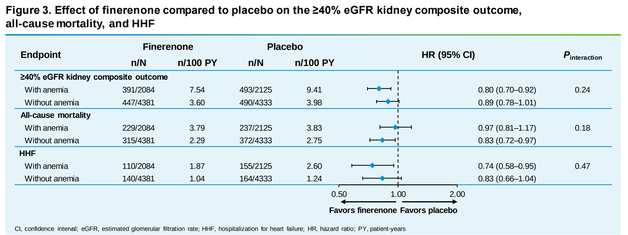
Figure 2. CV composite outcome* (A) and kidney composite outcome (≥57% eGFR)† (B) with finerenone versus placebo in patients with and without anemia



*Time to CV death, non-fatal MI, non-fatal stroke, or HHF; †time to kidney failure, sustained ≥57% decrease in eGFR from baseline, or kidney-related death
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction

- Finerenone also reduced the risk of the kidney composite outcome, all-cause mortality, and HHF versus placebo, with no heterogeneity between the treatment groups and across anemia subgroups (Figure 3)

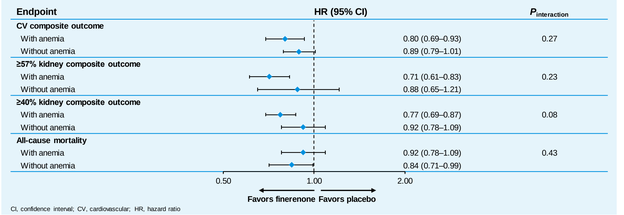
Figure 3. Effect of finerenone compared to placebo on the ≥40% eGFR kidney composite outcome, all-cause mortality, and HHF



CI, confidence interval; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; PY, patient-years

- The effect of finerenone on all outcomes was not modified by anemia status when assessed as a time-dependent variable (Figure 4)

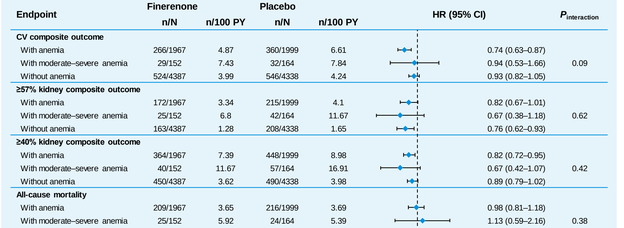
Figure 4. Impact of finerenone on all outcomes compared to placebo



CI, confidence interval; CV, cardiovascular; HR, hazard ratio

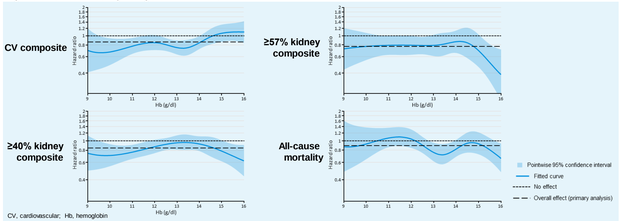
- The benefit of finerenone was observed irrespective of severity of anemia (Figure 5) and across a broad range of Hb levels (Figure 6)

Figure 5. Outcomes by severity of anemia



CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; PY, patient-years

Figure 6. Outcomes by range of Hb levels



CV, cardiovascular; Hb, hemoglobin

- Information on AEs is shown in Table 2
- Patients with anemia experienced a higher number of AEs, including hyperkalemia, versus patients without anemia for both the finerenone and placebo treatment arms
- The number of AEs was highest in patients with moderate–severe anemia compared to patients with mild–moderate anemia or no anemia

Table 2. AEs in patients with and without anemia

n (%)	Anemia		No anemia	
	Finerenone (n=2123)	Placebo (n=2156)	Finerenone (n=4375)	Placebo (n=4328)
Any AE (%)	1865 (87.8)	1916 (88.9)	3727 (85.2)	3687 (85.2)
Related to study drug	521 (24.5)	353 (16.4)	682 (15.6)	509 (11.8)
Leading to discontinuation	178 (8.4)	161 (7.5)	236 (5.4)	189 (4.4)
Any serious AE	764 (36.0)	824 (38.2)	1291 (29.5)	1360 (31.4)
Related to study drug	44 (2.1)	29 (1.3)	38 (0.9)	32 (0.7)
Leading to discontinuation	69 (3.3)	67 (3.1)	76 (1.7)	86 (2.0)
Any AE leading to death	52 (2.4)	49 (2.3)	58 (1.3)	102 (2.4)
Any investigator-reported hyperkalemia	501 (23.6)	306 (14.2)	496 (11.3)	245 (5.7)
Any treatment-emergent event	451 (21.2)	249 (11.5)	459 (10.5)	199 (4.6)
Leading to permanent discontinuation	55 (2.6)	25 (1.2)	55 (1.3)	13 (0.3)
Classified as a serious AE	42 (2.0)	13 (0.6)	26 (0.6)	3 (<0.1)
Leading to hospitalization	36 (1.7)	7 (0.3)	24 (0.5)	3 (<0.1)
Leading to death	0	0	0	0
Serum potassium >5.5 mmol/l, (Num/Den, %)*	512/2083 (24.6)	207/2113 (9.8)	557/4307 (12.9)	263/4254 (6.2)

AE, adverse event; Num/Den, number/denominator

Discussion

- Anemia could be a marker for high-risk patients who may gain greater heart and kidney benefit with finerenone

Summary

- This post-hoc analysis of FIDELITY demonstrated that finerenone had a greater impact on CV outcomes in patients with anemia than those without, and kidney composite outcomes were not impacted by anemia
- Patients with anemia were at a higher risk of AEs, likely due to having more severe disease at baseline

Conclusions

- In patients with CKD and T2D, finerenone's effect on the CV composite outcome was modified by anemia. The effect of finerenone on the kidney composite outcome, all-cause mortality, and HHF was similar irrespective of baseline anemia status
- Finerenone treatment was beneficial compared to placebo regardless of anemia severity or Hb levels
- Patients with anemia experienced a higher number of AEs (including hyperkalemia) than patients without anemia

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