Efficacy and safety of finerenone in patients with chronic kidney disease and type 2 diabetes by diuretic use: A FIDELITY analysis

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Introduction

- Approximately 85% of patients with chronic kidney disease (CKD) suffer from hypertension,[1] significantly increasing their risk of cardiovascular (CV) disease morbidity and mortality as both CKD and hypertension represent independent risk factors for CV disease[2]
- Thiazide and loop diuretics are commonly used to treat hypertension and volume overload in patients with CKD[2,3] However, diuretic use may alter potassium levels increasing the risk of adverse CV outcomes.[4] As a result of this, despite blood pressure control with diuretics, patients with CKD and type 2 diabetes (T2D) remain at risk of adverse CV events[1,5]
- Finerenone is a selective, non-steroidal mineralocorticoid receptor antagonist which significantly improved CV outcomes and slowed CKD progression in patients with CKD and T2D in the phase 3 trials FIDELIO-DKD and FIGARO-DKD[6–10]
- FIDELITY is a prespecified pooled individual patient data analysis of the FIDELIO-DKD and FIGARO-DKD trials that provides more robust estimates of safety and efficacy of finerenone compared with placebo across a broad spectrum of patients with CKD[6–8]
- In this post-hoc analysis of the FIDELITY dataset, the effect of finerenone on CV and safety outcomes was assessed by baseline diuretic use

Methods

- FIDELITY uses data from patients enrolled in FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) trials randomized to receive finerenone (10 mg or 20 mg) or placebo
- Eligible patients were required to have been diagnosed with both CKD and T2D and be optimally treated with renin–angiotensin system inhibitors (RASi)
- Patients were categorized by baseline diuretic use
- The primary endpoint was a CV composite outcome of time to CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or hospitalization for heart failure (HHF) assessed using a stratified Cox proportional hazards model
- CV outcomes were analyzed in the following subgroups of interest:
  - Diuretic use (all, loop, and thiazide diuretics)
  - Diuretic doses (low versus high)
  - Estimated glomerular filtration rate (eGFR; <60 versus ≥60 ml/min/1.73 m^2)
  - Race (Asian versus non-Asian)
- Secondary endpoints included safety outcomes assessed by treatment-emergent adverse events (TEAEs), particularly hyperkalemia
- On-treatment sensitivity analysis was conducted to assess any fluctuations in diuretic use during the trial

Results

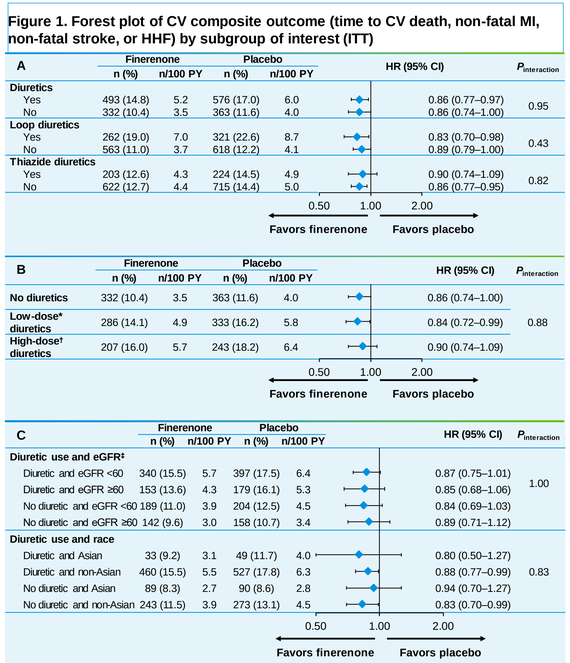
- Across 13,026 randomized patients, 51.5% were treated with diuretics at baseline (21.5% on loop and 24.2% on thiazide diuretics)
- Baseline disease characteristics, including eGFR, urine albumin-to-creatinine ratio (UACR), and prior/concomitant therapies are shown in Table 1
- Concomitant diuretic use with study treatment was mainly constant throughout the study (on-study treatment analysis)
- Finerenone reduced the risk of the CV composite outcome in patients treated with (hazard ratio [HR]: 0.86; 95% confidence interval [CI]: 0.77–0.97) and without diuretics (HR: 0.86; 95% CI: 0 .74–1.00; $P_{interaction}$=0.95)
- Among patients with diuretic use at baseline, finerenone reduced the risk of the CV composite outcome irrespective of diuretic dose (Figure 1)
- Similar trends were observed when the analyzed patient cohort was split into loop diuretic and thiazide diuretic use subgroups
- The incidence rate of the CV composite outcome was generally lower with finerenone versus placebo with or without concomitant diuretic use (on-treatment sensitivity analysis; Table 2)
- Overall TEAEs were similar between treatment arms and between patients treated with and without diuretics (Table 3)
- Incidence of hyperkalemia was higher with finerenone versus placebo, irrespective of diuretic use; however, the incidence of hyperkalemia leading to hospitalization or permanent discontinuation was low
- Finerenone reduced the risk of treatment-emergent hypokalemia in patients treated with and without diuretics (Figure 2)

Table 1.
Baseline demographics and disease characteristics

Baseline characteristics	With diuretics (n=6710; 51.5%)	Without diuretics (n=6316; 48.5%)
Age, years, mean	65.71	63.73
Sex, male, %	70.1	69.4
SBP, mmHg, mean	137.80	135.63
DBP, mmHg, mean	75.83	76.92
BMI, kg/m^2, mean	32.55	29.96
Duration of diabetes, years, mean	16.09	14.66
eGFR, ml/min/1.73 m^2, mean	54.01	61.38
UACR, mg/g, median	493	547
Medical history, %		
CV disease	49.2	41.7
Heart failure	10.1	5.3
Atrial fibrillation or flutter	11.1	5.7
Medications, %		
CV medications		
ACEi	38.3	39.8
ARB	61.8	60.0
Statins	76.5	67.5
Potassium supplements	5.0	0.8
Diuretics		
Loop diuretics	41.8	0
Thiazide diuretics	47.0	0
Glucose-lowering therapy		
Insulin and analogues	62.8	54.1
DPP-4i	23.6	26.8
GLP-1RA	8.4	6.0
SGLT-2i	6.5	6.9
Alpha glucosidase inhibitors	3.0	7.2

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

Figure 1. Forest plot of CV composite outcome (time to CV death, non-fatal MI, non-fatal stroke, or HHF) by subgroup of interest (ITT)



*Low dose: hydrochlorothiazide ≤12.5 mg , furosemide ≤40 mg, indapamide <2.5 mg, torasemide ≤10 mg, bendroflumethiazide ≤2.5 mg, chlortalidone ≤25 mg, metolazone ≤2.5 mg, trichlormethiazide ≤1 mg, azosemide ≤30 mg, bumetanide ≤1 mg. Diuretics not listed were considered low dose, irrespective of actual dosage; †high dose: hydrochlorothiazide >12.5 mg, furosemide >40 mg, indapamide ≥2.5 mg, torasemide >10 mg, bendroflumethiazide >2.5 mg, chlortalidone >25 mg, metolazone >2.5 mg, trichlormethiazide >1 mg, azosemide >30 mg, bumetanide >1 mg; ‡expressed in ml/min/1.73 m^2
CI, confidence interval; CV, cardiovascular disease; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; ITT, intention-to-treat population; MI, myocardial infarction; PY, patient-years

Table 2. On-treatment sensitivity analysis of the CV composite outcome (time to CV death, non-fatal MI, non-fatal stroke, or HHF)

Diuretic type	Planned treatment group	Concomitant diuretic use	n	Number of events	PY at risk	Estimated event rate per 100 PY (95% CI)
All diuretics	**Finerenone**	With	4128	432	8415.3	5.13 (4.66–5.64)
		Without	3766	188	8403.5	2.24 (1.93–2.58)
	Placebo	With	4264	553	8981.7	6.16 (5.65–6.69)
		Without	3577	205	7773.0	2.64 (2.29–3.02)

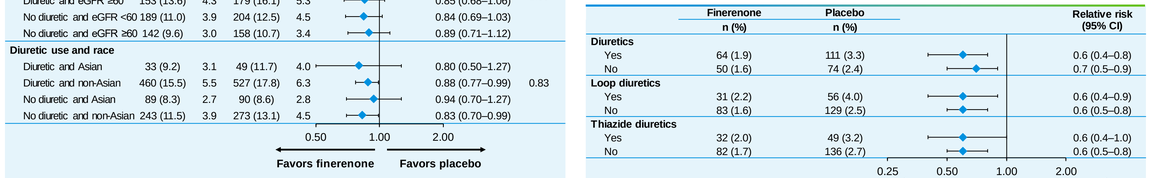
CI, confidence interval; CV, cardiovascular disease; HHF, hospitalization for heart failure; MI, myocardial infarction; PY, patient-years

Table 3. Summary of AEs in patients treated with or without diuretics (SAF)

AEs, n (%)	With diuretics		Without diuretics	
	Finerenone (n=3320)	Placebo (n=3375)	Finerenone (n=3190)	Placebo (n=3114)
Any AE	2882 (86.8)	2939 (87.1)	2720 (85.3)	2668 (85.7)
Any study drug-related AE	653 (19.7)	460 (13.6)	553 (17.3)	402 (12.9)
Any AE leading to discontinuation	225 (6.8)	185 (5.5)	189 (5.9)	166 (5.3)
Any SAE	1082 (32.6)	1203 (35.6)	978 (30.7)	983 (31.6)
Any study drug-related SAE	49 (1.5)	33 (1.0)	34 (1.1)	28 (0.9)
Any SAE leading to discontinuation	82 (2.5)	75 (2.2)	63 (2.0)	79 (2.5)
Any hyperkalemia	457 (13.8)	191 (5.7)	455 (14.3)	257 (8.3)
Any hyperkalemia leading to hospitalization	36 (1.1)	6 (0.2)	25 (0.8)	4 (0.1)
Any hyperkalemia leading to permanent discontinuation	54 (1.6)	20 (0.6)	56 (1.8)	18 (0.6)

AE, adverse event; SAE, serious adverse event; SAF, safety population

Figure 2. Forest plot of the risk of treatment-emergent hypokalemia* in patients treated with and without diuretics



*AEs were classified as hypokalemia based on the following SMQ terms: alkalosis hypokalemic, blood potassium abnormal, blood potassium decreased, electrocardiogram U-wave prominent, hypokalemia, hypokalaemic syndrome, and hypomagnesemia
AE, adverse event; CI, confidence interval; SAF, safety population; SMQ, standardized medical dictionary for regulatory activities queries

Discussion

- Baseline diuretic dose, eGFR, and race generally did not modify the CV composite outcome
- The incidence of hyperkalemia was higher with finerenone versus placebo, irrespective of diuretic use. However, the incidence of associated hospitalization or permanent discontinuation was low, and finerenone consistently reduced the risk of treatment-emergent hypokalemia versus placebo in patients treated with and without diuretics
- Due to the post-hoc nature of this analysis, all reported findings are exploratory and require further investigation

Summary

- Finerenone was associated with a decreased risk of the CV composite outcome versus placebo, irrespective of diuretic use

Conclusions

- Finerenone was associated with a reduced risk of CV outcomes and a low incidence of hyperkalemia leading to hospitalization in patients with CKD and T2D on optimized RAS blockade, irrespective of baseline diuretic use
- The incidence of TEAEs was consistent, regardless of diuretic use

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