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Finerenone and Cardiorenal Outcomes by History of Atherosclerotic Cardiovascular Disease in Patients With Type 2 Diabetes and Chronic Kidney Disease: FIDELITY Analyses

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Introduction

- Patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) have an increased risk of atherosclerotic cardiovascular disease (ASCVD), cardiovascular (CV) death and all-cause mortality.[1,2]
- The risk of ASCVD is up to 4-fold higher in patients with T2D compared with the general population. Kidney impairment correlates with a higher incidence of CV events.[3–6]
- ASCVD is the leading cause of morbidity and mortality in patients with T2D. Preventing CV complications is a key therapeutic focus for patients with T2D, CKD, and ASCVD.[7–9]
- Finerenone is a novel, selective, nonsteroidal mineralocorticoid receptor antagonist (MRA) that blocks mineralocorticoid receptor (MR) overactivation. MR overactivation is thought to contribute to kidney and CV damage. In FIDELIO-DKD (NCT02540993, N=5674) and FIGARO-DKD (NCT02545049, N=7352), finerenone significantly improved CV outcomes and slowed CKD progression in patients with CKD and T2D.[10,11]
- FIDELITY includes a broad spectrum of patients with T2D and CKD reflecting real-world practice and offers higher analytic precision than FIDELIO-DKD or FIGARO-DKD alone.[12,13]
- This sub-study compared CV and kidney outcomes in primary and secondary prevention populations (by ASCVD history).

Objectives

- To evaluate the efficacy and safety of finerenone on CV and kidney outcomes in primary and secondary prevention populations.

Methods

Study Design

- Patients with T2D, and either urine albumin-to-creatinine ratio (UACR) ≥30–<300 mg/g and estimated glomerular filtration rate (eGFR) ≥25–≤90 mL/min/1.73 m^2, or UACR ≥300–≤5,000 mg/g and eGFR ≥25 mL/min/1.73 m^2, treated with optimized renin–angiotensin system blockade, were randomized 1:1 to finerenone or placebo. Key exclusion criteria included symptomatic chronic HF with reduced ejection fraction.
- The key outcomes consisted of:
  - Composite CV outcome of time to the first onset of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for heart failure.
  - Composite kidney outcome of kidney failure, sustained ≥57% decrease in eGFR from baseline, or kidney-related death.
- Prespecified subgroup analyses of FIDELITY were performed according to medical history of ASCVD at baseline, defined as investigator-reported medical history of at least one of the following: coronary artery disease, previous MI, coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), angiographically proven stenosis ≥50% in ≥1 major coronary artery, peripheral artery disease, or carotid endarterectomy. A history of heart failure was not included in the definition of ASCVD.

Results

Patients

- Of 13,026 patients eligible for analysis, 5,935 (45.6%) had a history of CVD at baseline.
- Blood pressure and glycated hemoglobin (HbA1c) were well-controlled in both groups and patients with a history of ASCVD had lower eGFR and UACR than those without (**Table 1**).
- Patients with a history of ASCVD were more likely to be older, white, and male, as well as having had a slightly longer duration of diabetes on record, and less likely to have had a history of hypertension (**Table 1**).

Table 1. Baseline characteristics and medication use by ASCVD status

Characteristic	History of ASCVD	
	With (n=5935)	Without (n=7091)
Age, years (mean)	**67**	**63**
Sex, male (%)	**74**	**67**
Race (%)		
White	**74**	**63**
Black/African American	4	4
Asian	17	27
SBP/DBP, mmHg (mean)	137/75	137/77
Duration of diabetes, years (mean)	**17**	**15**
HbA1c, % (mean)	7.7	7.7
Serum potassium, mEq/l (mean)	4.4	4.3
eGFR, mL/min/1.73 m^2 (mean)	**54**	**61**
UACR, mg/g (median)	**456**	**564**
History of AF (%)	**12**	**7**
History of HTN (%)	**88**	**96**
Medication use		
RAASi	99.9	>99.9
Beta blockers	**64.9**	**37.4**
Diuretics	55.6	48.1
Loop diuretics	**26.7**	**17.2**
Thiazide diuretics	23.3	25.0
Statins	**81.0**	**64.7**
Antihyperglycemic therapies	97.8	97.6
Insulin and analogues	**62.9**	**54.9**
Metformin	53.8	61.5
Sulfonylureas	24.0	27.7
DPP-4i	23.3	26.8
GLP-1RA	**6.8**	**7.6**
SGLT-2i	**6.8**	**6.7**
Alpha-glucosidase inhibitors	4.8	5.2

AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; DPP-4i, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HTN, hypertension; RAASi, Renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

Efficacy outcomes

- In the overall FIDELITY population, ASCVD prevalence was associated with a higher incidence of composite CV outcome (hazard ratio [HR]=2.09; 95% confidence interval [CI] 1.89–2.30), CV death or hospitalization for heart failure (HR=2.12; 95% CI 1.88–2.40), and all-cause mortality (HR=1.72; 95% CI 1.52–1.94; **Table 2, Figure 1A**).
- The risk of composite kidney outcome did not differ between patients with and without a history of ASCVD (**Table 2**).
- Incidence of composite CV outcomes was reduced significantly with finerenone vs placebo in both ASCVD subgroups; 17% (HR=0.83; 95% CI 0.74–0.94) risk reduction in patients with history of ASCVD vs 9% (HR=0.91; 95% CI 0.78–1.06) in those without (**Figure 1B**).
- Risk of CV death or hospitalization for HF and composite kidney outcomes were also reduced with finerenone vs placebo, irrespective of ASCVD status (**Figure 2**).
- Overall, adverse events did not differ between ASCVD subgroups, with a low incidence of hyperkalemia-related treatment discontinuation that was more frequent in the finerenone group but similar between patients with and without ASCVD history (**Table 3**).

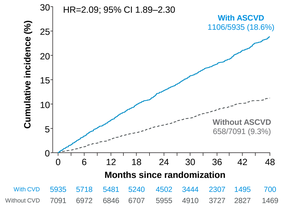
Table 2. Incidence of composite CV outcome, CV death or HHF, composite kidney outcome and all cause mortality events

Outcome	History of ASCVD				
	With (n=5935)		Without (n=7091)		HR (95% CI)
	n (%)	N per 100 PY	n (%)	N per 100 PY	
Composite CV outcome*	1106 (18.6)	**6.9**	658 (9.3)	**3.0**	2.09 (1.89–2.30)
CV death or HHF	753 (12.7)	**4.5**	426 (6.0)	**1.9**	2.12 (1.88–2.40)
Composite kidney outcome#	328 (5.5)	**2.1**	497 (7.0)	**2.4**	0.96 (0.83–1.10)
All-cause mortality	695 (11.7)	**4.0**	471 (6.6)	**2.1**	1.72 (1.52–1.94)

*Time to CV death, non-fatal MI, non-fatal stroke or HHF; #Time to kidney failure (ESKD or an eGFR <15 ml/min/1.73 m^2), sustained ≥57% decrease in eGFR from baseline, or renal death. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; PY, patient years.

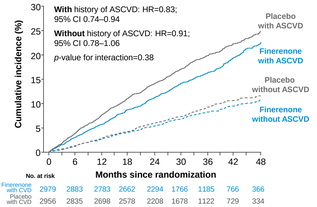
Figure 1. Time to CV death, non-fatal MI, non-fatal stroke or HHF by prevalent ASCVD status (A) and time to CV death, non-fatal MI, non-fatal stroke or HHF by prevalent ASCVD status by treatment (B)

A. Time to CV death, non-fatal MI, non-fatal stroke or HHF by prevalent ASCVD status



With CVD	5935	5718	5481	5240	4502	3444	2307	1495	700	
Without CVD	7091	6972	6846	6707	5955	4910	3727	2827	1469	

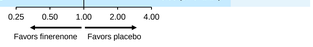
B. Time to CV death, non-fatal MI, non-fatal stroke or HHF by prevalent ASCVD status by treatment



No. at risk										
Finerenone with CVD	2979	2883	2783	2662	2294	1766	1185	766	366	
Placebo with CVD	2956	2835	2698	2578	2208	1678	1122	729	334	
Finerenone without CVD	3540	3477	3419	3347	2979	2441	1880	1421	721	
Placebo without CVD	3551	3495	3427	3360	2976	2469	1847	1406	748	

Figure 2. Forest plot of CV outcomes, kidney outcomes, and all-cause mortality by ASCVD status

Outcome	Finerenone		Placebo		HR (95% CI)	*p*-value for interaction
	n (%)	N per 100 PY	n (%)	N per 100 PY		
Composite CV outcome*						
With a history of ASCVD	511 (17.2)	6.3	595 (20.1)	7.6	0.83 (0.74–0.94)	0.38
Without a history of ASCVD	314 (8.9)	2.9	344 (9.7)	3.2	0.91 (0.78–1.06)	
CV death or HHF						
With a history of ASCVD	342 (11.5)	4.1	411 (13.9)	5.0	0.82 (0.71–0.94)	0.68
Without a history of ASCVD	197 (5.6)	1.8	229 (6.4)	2.1	0.86 (0.71–1.04)	
Composite kidney outcome#						
With a history of ASCVD	139 (4.7)	1.7	189 (6.4)	2.4	0.71 (0.57–0.88)	0.33
Without a history of ASCVD	221 (6.2)	2.1	276 (7.8)	2.7	0.81 (0.68–0.97)	
All-cause mortality						
With a history of ASCVD	323 (10.8)	3.7	372 (12.6)	4.4	0.85 (0.74–0.99)	0.38
Without a history of ASCVD	229 (6.5)	2.0	242 (6.8)	2.2	0.95 (0.79–1.14)	



*Time to CV death, non-fatal MI, non-fatal stroke or HHF; #Time to kidney failure (ESKD or an eGFR <15 ml/min/1.73 m^2), sustained ≥57% decrease in eGFR from baseline, or kidney-related death.

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HHF, hospitalization for heart failure; HR, hazard ratio; MI, myocardial infarction; PY, patient years.

Table 3. Adverse events by ASCVD status

TEAE, %	With history of ASCVD		Without history of ASCVD	
	Finerenone (n=2974)	Placebo (n=2950)	Finerenone (n=3536)	Placebo (n=3539)
Any SAE	34.4	36.8	29.4	31.1
Treatment related	1.5	1.1	1.0	0.8
Leading to treatment discontinuation	2.4	2.3	2.1	2.5
Serious hyperkalemia	1.4	0.3	0.8	0.2
Treatment related	1.0	0.1	0.4	0.1
Leading to hospitalization	**1.2**	**0.1**	**0.7**	**0.2**
Leading to treatment discontinuation	**0.2**	**<0.1**	**0.1**	**0**

ASCVD, atherosclerosis cardiovascular disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusion

- In a patient population with CKD (stage 1–4 with moderate-to-severely elevated albuminuria) and T2D, well-controlled blood pressure and HbA1c, and treated with a maximum tolerated dose of a renin-angiotensin-aldosterone system inhibitor:
  - The risk of adverse CV outcomes was higher in patients with ASCVD compared with those without; however, the risk of adverse kidney outcomes was similar between groups
  - The CV and kidney benefits of finerenone compared with placebo were consistent irrespective of ASCVD history
  - The safety profile of finerenone was similar between patients with and without a history of ASCVD
    - Although hyperkalemia was increased with finerenone, the clinical impact was minimal
- Finerenone has shown benefit in primary and secondary prevention across the spectrum of patients with CKD and T2D, with a good safety profile

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