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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on behalf of the FIDELIO-DKD and FIGARO-DKD Investigators

FIDELITY

FInerenone in chronic ki**D**ney diseas**E** and type 2 diabetes:
Combined FIDE**L**IO-DKD and F**I**GARO-DKD **T**rial programme anal**Y**sis

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Disclosures

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- **Past President:** Heart Failure Association ESC
- **Past Dean:** University of Cyprus

Patients with T2D and CKD have an increased risk of ASCVD, 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[3]

Kidney impairment correlates with **a higher incidence of CV events**[4–6]

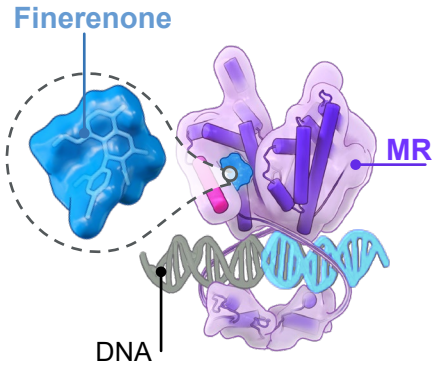
ASCVD is the **leading cause of morbidity and mortality** in patients with T2D[7]

Preventing CV complications is a key therapeutic focus for patients with T2D, CKD and ASCVD[7–9]

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; T2D, type 2 diabetes

1. Bramlage P, et al. *Cardiovasc Diabetol* 2019;18:33; 2. Afkarian M, et al. *J Am Soc Nephrol* 2013;24:302–308; 3. Rossing P et al. *Diabetes* 2021;70:39–50; 4. Jankowski J, et al. *Circulation* 2021;143:1157–1172; 5. van der Velde M, et al. *Kidney Int* 2011;79:1341–1352; 6. Currie CJ, et al. *PLoS One* 2019;14:e0221044; 7. American Diabetes Association. *Diabetes Care* 2022;45:S144–S174; 8. American Diabetes Association. *Diabetes Care* 2022;45:S125–S143; 10. American Diabetes Association. *Diabetes Care* 2022;45:S175–S184

Finerenone has demonstrated CV and kidney benefits in patients with CKD and T2D



FIDELIO-DKD[1]
N=5734

+

FIGARO-DKD[2]
N=7437

FIDELITY

Prespecified individual patient-data pooled analysis[3]
Total N=13,171

Finerenone is a **novel, selective, nonsteroidal MRA** that blocks MR overactivation.
MR overactivation is thought to contribute to kidney and CV damage[4,5]

In FIDELIO-DKD and FIGARO-DKD, **finerenone significantly improved CV outcomes and slowed CKD progression** in patients with CKD and T2D[1,2]

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[3,6]

FIDELIO-DKD, FInerenone in reducing kiDneEy faiLure and dIsease prOgression in Diabetic Kidney Disease; FIDELITY, The FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis; FIGARO-DKD, FInerenone in reducinG cArdiovascular moRtality and mOrbidity in Diabetic Kidney Disease; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist

1. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263; 3. Agarwal R, *et al. Eur Heart J* 2021:ehab886; 4. Agarwal R, *et al. Eur Heart J* 2021;42:152–161; 5. Agarwal R, *et al. Nephrol Dial Transplant* 2020:gfaa294; 6. Adamson C & Jhund P, *Eur Heart J* 2021:ehab827

FIDELITY is a large pooled trial dataset with pre-specified analyses of the FIDELIO-DKD and FIGARO-DKD trials

48 countries

13,171 patients randomized

3 years median follow-up

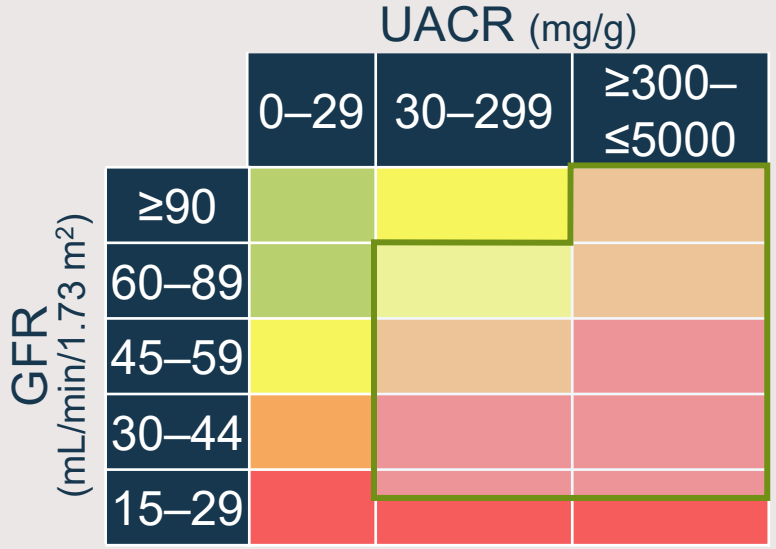
R

Finerenone 10 or 20 mg od*

Placebo

Key eligibility criteria

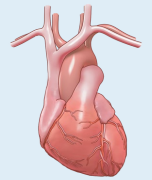
- ✓ T2D
- ✓ CKD
- ✓ On single RAASi
- ✓ Serum [K^+] ≤4.8 mmol/L
- ✗ Symptomatic HFrEF



Key outcomes

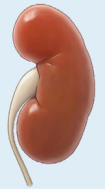
CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



≥57% eGFR kidney composite

Time to kidney failure#, sustained ≥57% decrease in eGFR from baseline, or kidney-related death



*10 mg if screening eGFR 25–<60 mL/min/1.73 m²; 20 mg if ≥60 mL/min/1.73 m², up-titration encouraged from month 1 if serum [K^+] ≤4.8 mEq/L and eGFR stable; #kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or sustained decrease in eGFR <15 mL/min/1.73 m²

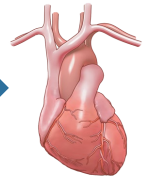
eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; [K^+], potassium concentration; MI, myocardial infarction; od, once daily; RAASi, renin–angiotensin-aldosterone system inhibitor; UACR, urine albumin-to-creatinine ratio

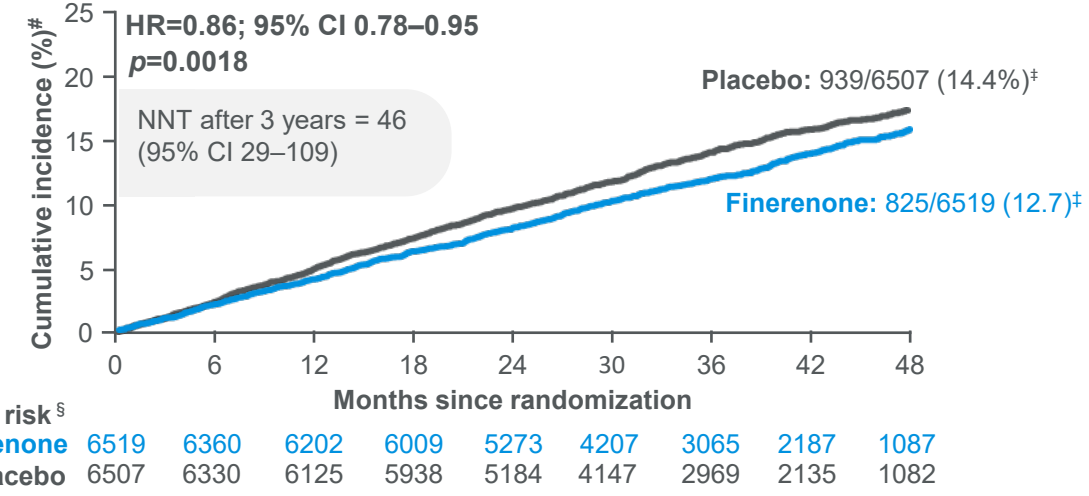
1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, *et al. N Engl J Med* 2021; doi: 10.1056/NEJMoa2110956

The FIDELITY primary analysis showed significant risk reductions in CV and kidney outcomes

CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



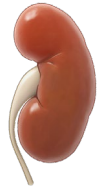


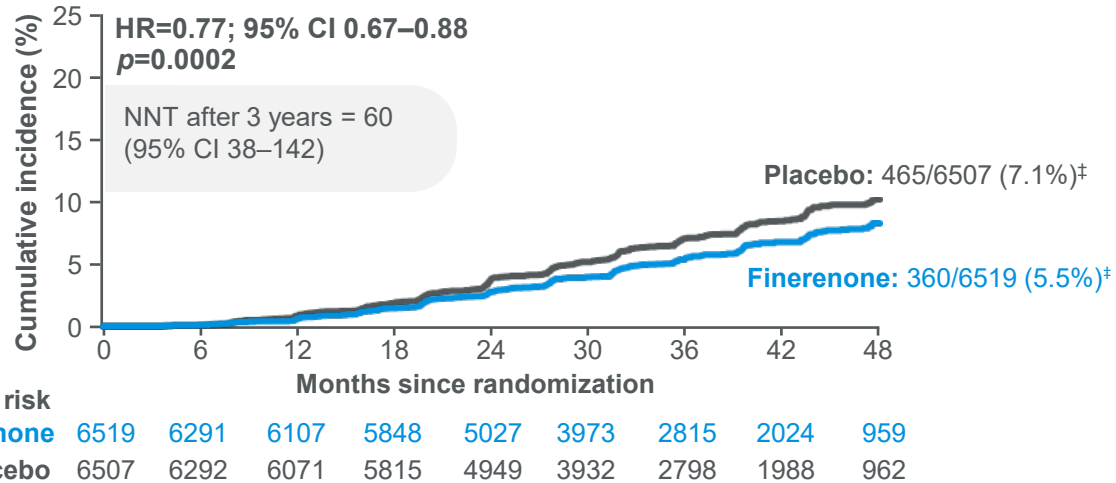
No. at risk §									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

14% reduced **risk of CV morbidity and mortality** vs placebo (HR=0.86; 95% CI 0.78–0.95)[1]

Kidney composite

Time to kidney failure*, sustained ≥57% decrease in eGFR from baseline, or kidney-related death





No. at risk									
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962

23% reduced **risk of CKD progression*** vs placebo (HR=0.77; 95% CI 0.67–0.88)[1]

*ESKD or an eGFR <15 mL/min/1.73 m^2; events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; #Cumulative incidence calculated by Aalen–Johansen estimator using deaths due to other causes as competing risk; ‡number of patients with an event over a median of 3.0 years of follow-up; § at-risk subjects were calculated at start of time point; CI, confidence interval; ESKD, end-stage kidney disease; HR hazard ratio; KRT, kidney replacement therapy; NNT, number needed to treat

1. Agarwal R, *et al. Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab777

Prespecified subgroup analyses of FIDELITY were performed according to medical history of ASCVD at baseline

ASCVD was defined as investigator-reported medical history of at least one the following:

- CAD
- Previous MI
- Coronary revascularization (PCI or CABG)
- Previous ischemic stroke
- Angiographically proven stenosis ≥50% in ≥1 major coronary artery
- PAD
- Carotid endarterectomy

A history of HF was not included in the definition of ASCVD

This substudy evaluated the efficacy and safety of finerenone on CV and kidney outcomes in primary and secondary prevention populations (by ASCVD history)

CABG, coronary artery bypass grafting; CAD, coronary artery disease; HF, heart failure; PAD, peripheral artery disease; PCI, percutaneous coronary intervention

Blood pressure and HbA1c were well-controlled in both groups, and patients with a history of ASCVD had lower eGFR and UACR than those without

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
BMI, kg/m^2 (mean)	31	31
Duration of diabetes, years (mean)	**17**	**15**
HbA1c, % (mean)	7.7	7.7

Characteristic	History of ASCVD	
	With (n=5935)	Without (n=7091)
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**
Current smoker (%)	15	17

AF, atrial fibrillation; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HTN, hypertension; SBP, systolic blood pressure

Patients with prevalent ASCVD were more likely to be prescribed beta blockers, statins and insulin

Medication use at baseline, %	History of ASCVD	
	With (n=5935)	Without (n=7091)
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**
Potassium supplements	3.6	2.4
Potassium-lowering agents	1.4	1.4

Medication use at baseline, %	History of ASCVD	
	With (n=5935)	Without (n=7091)
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

DPP-4i, dipeptidyl-peptidase 4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

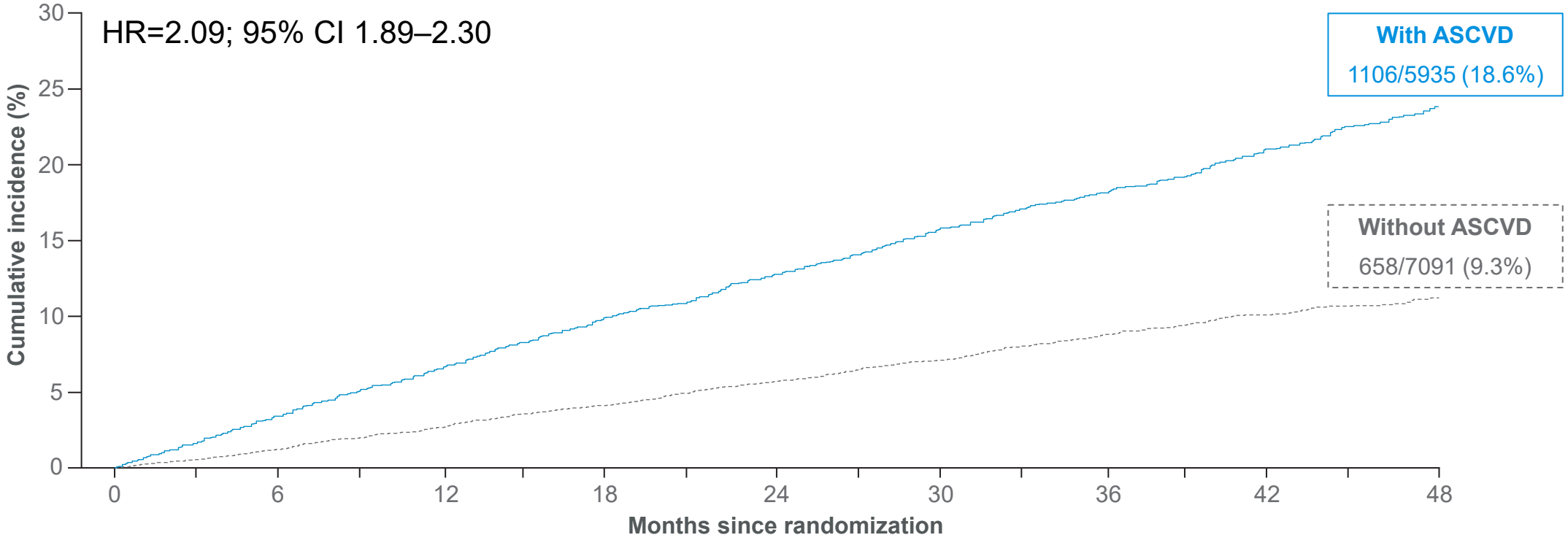
Incidence of the composite CV outcome, CV death or HHF, and all-cause mortality was higher in patients with vs without prevalent ASCVD

Outcome	History of ASCVD				HR (95% CI)
	With (n=5935)		Without (n=7091)		
	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
PY, patient years

Incidence of the composite CV outcome was higher in patients with vs without prevalent ASCVD

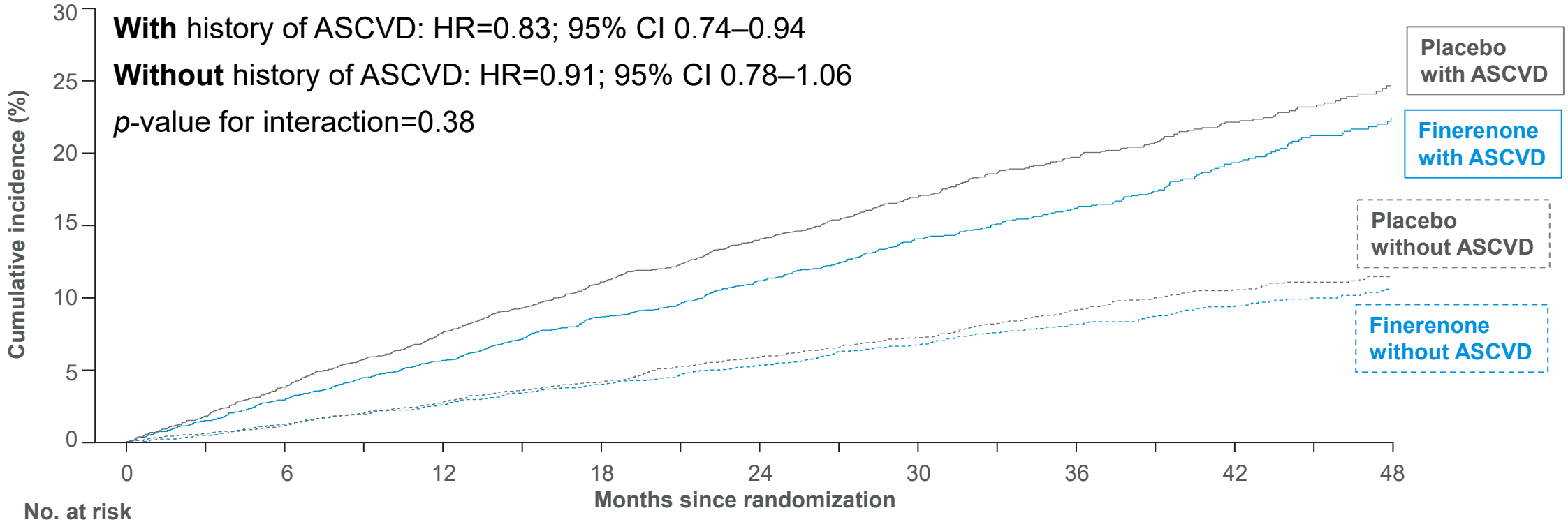
Time to CV death, non-fatal MI, non-fatal stroke or HHF



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

The CV benefit of finerenone was not modified by prevalent ASCVD status

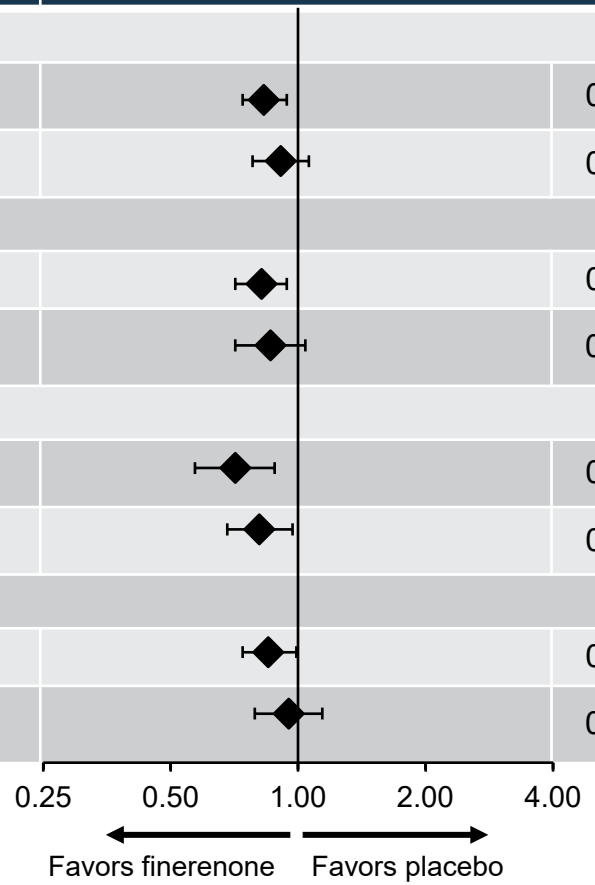
Time to CV death, non-fatal MI, non-fatal stroke or HHF



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

Finerenone reduced the risk of composite CV and kidney outcomes as well as CV death and HHF compared with placebo irrespective of history of 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
CI, confidence interval; HR, hazard ratio

The risk of hyperkalemia was higher with finerenone irrespective of ASCVD history, but discontinuation due to hyperkalemia was low

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**

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Summary

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 RAASi:

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**