Finerenone in chronic kidney disease and type 2 diabetes: A FIDELITY analysis of left ventricle hypertrophy

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FIDELITY

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

Disclosures

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- Senior Consulting Editor: *JACC – Heart Failure*
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MR antagonism may reduce LVH and associated CV risks in patients with T2D and CKD

- **LVH is a predictor of CV disease,** associated morbidity and mortality,[1–4] and **frequently occurs** in patients with **CKD, T2D and hypertension**[5]

- **Increased RAAS activity** is correlated with **LVH** and **CV risk**[6]
- In adults with T2D, **LVH is associated** with susceptibility to atherothrombosis, **increased albuminuria** and **heart failure**[7,8]

- **MR antagonism** has been shown to **reduce LV mass** in patients with hypertension, and **in combination with ACEi**, had **greater reductions on LV mass** than either drug alone[9]

ACEi, angiotensin-converting enzyme inhibitors; CKD, chronic kidney disease; CV, cardiovascular; LV, left ventricle; LVH, left ventricular hypertrophy; MR, mineralocorticoid receptor; RAAS, renin–angiotensin–aldosterone system; T2D, type 2 diabetes

1. Kannel WB, *et al*. *J Am Coll Cardiol* 1985;5:141B–149B; 2. Mathew J, *et al*. *Circulation* 2001;104:1615–1621; 3. Okin PM, *et al*. *JAMA* 2004;292:2343−2349;
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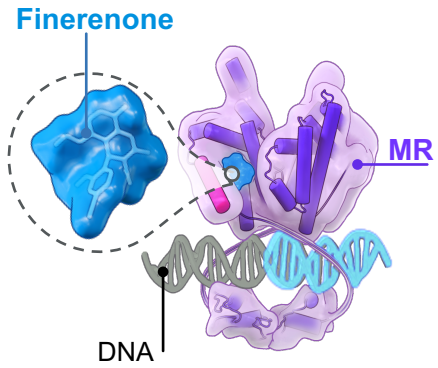
Finerenone has demonstrated CV and kidney benefits in patients with CKD and T2D



FIDELIO-DKD[1]
N=5,734

+

FIGARO-DKD[2]
N=7,437

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 CKD and T2D[3]

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. *et al. Eur Heart J* 2022;43:474–484; 4. Agarwal R, *et al. Eur Heart J* 2021;42:152–161;
5. Agarwal R, *et al. Nephrol Dial Transplant* 2020;gfaa294

FIDELITY is a large pooled trial dataset with prespecified analyses of the FIDELIO-DKD and FIGARO-DKD trials[1–3]

33,292 patients screened from 48 countries
(September 2015 to October 2018)

13,171 patients randomised

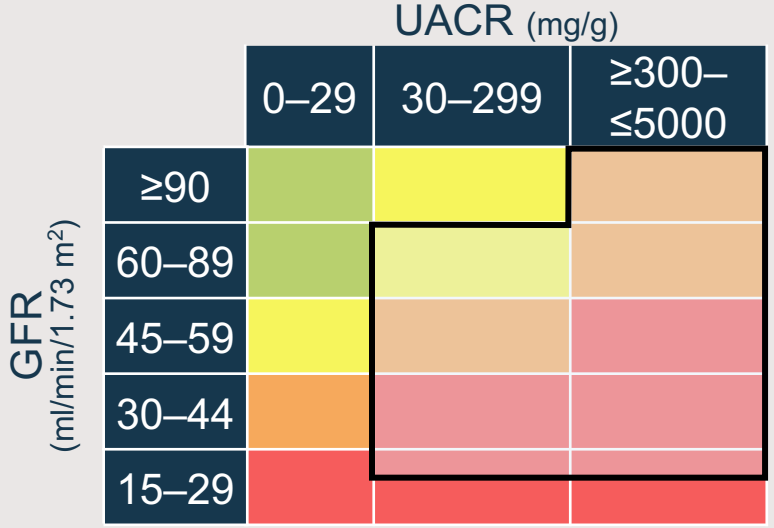
R

- **Finerenone 10 or 20 mg od***
- **Placebo**

3 years' median follow-up

Key eligibility criteria

- ✓ **T2D**
- ✓ **CKD**
- ✓ On single RASi
- ✓ Serum [K^+] ≤4.8 mmol/l
- ✗ Symptomatic HFrEF



Key outcomes

CV composite

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

≥57% eGFR kidney composite

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

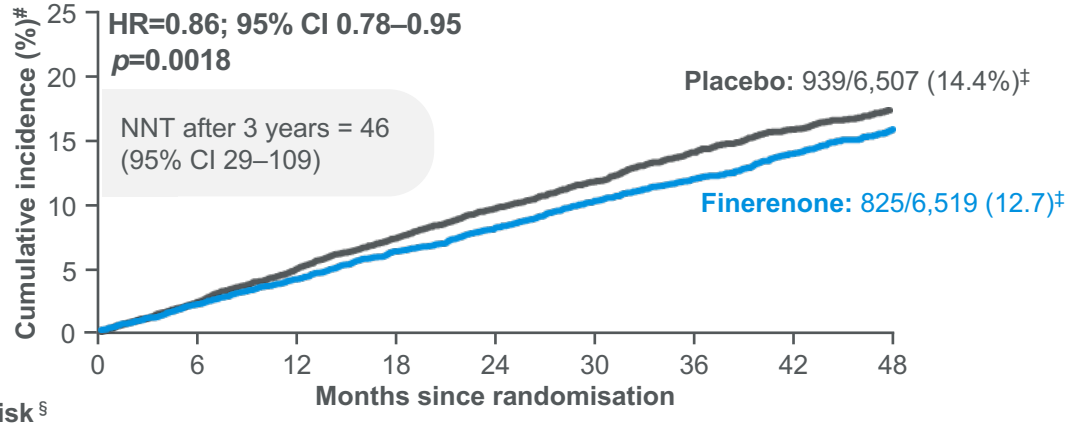
*10 mg if screening eGFR 25–<60 ml/min/1.73 m^2; 20 mg if ≥60 ml/min/1.73 m^2, up-titration encouraged from month 1 if serum [K^+] ≤4.8 mEq/l and eGFR stable
#Kidney failure defined as either ESKD (initiation of chronic dialysis for ≥90 days or kidney transplant) or an eGFR <15 ml/min/1.73 m^2
eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; [K^+], potassium concentration; MI, myocardial infarction; od, once daily; R, randomisation; RASi, renin–angiotensin 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;385:2252−2263; 3. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

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

CV composite

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

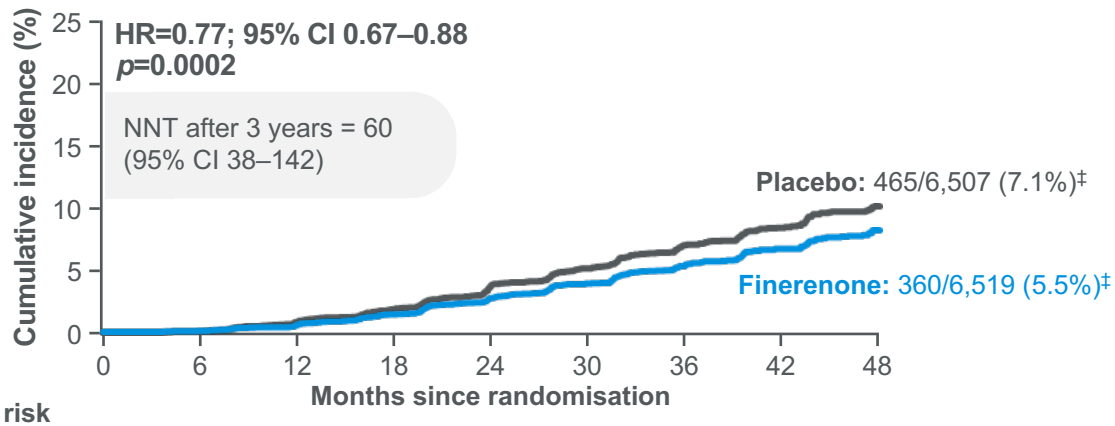


No. at risk §									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

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

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)

*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; HR hazard ratio; KRT, kidney replacement therapy; NNT, number needed to treat

Agarwal R, *et al. Eur Heart J* 2022;43:474–484

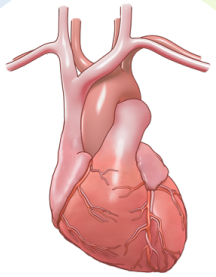
Subgroup analyses of FIDELITY were performed according to the presence of LVH at baseline

FIDELITY
FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis

SUBGROUP ANALYSIS OBJECTIVE:

To evaluate the cardiorenal efficacy and safety of finerenone compared with placebo in patients with CKD associated with T2D, with or without LVH at baseline (included any ECG LVH diagnosis identified from the run-in visit to randomisation)

Diagnosis of LVH was based on ECG findings as per local practice*



9.6% of patients had LVH at baseline (n=1,250/13,026)

9.1% of the finerenone group (n=596/6,519)

10.1% of the placebo group (n=654/6,507)

*No central adjudication of ECGs was performed and no assessment criteria were applied
ECG, electrocardiogram

LVH at baseline was associated with microvascular complications and an increase in HF

Patient characteristics	With LVH (n=1,250)	Without LVH (n=11,776)
Age, years, mean	65	65
Sex, male, %	62	71
SBP/DBP, mmHg, mean	139/78	137/76
BMI, kg/m^2, mean	31	31
Duration of diabetes, years, mean	15	15
HbA1c, %, mean	7.8	7.7
Serum potassium, mmol/l, mean	4.3	4.4
eGFR, ml/min/1.73 m^2, mean	57	58
UACR, mg/g, median	662	502
UACR, mg/g, %		
<30	1	2
30 to <300	27	32
≥300	72	66
hs-CRP, mg/l, mean	5.1	4.7
Serum cholesterol, mg/dl, mean	179	171

Medical history, %	With LVH (n=1,250)	Without LVH (n=11,776)
Diabetic retinopathy	47	37
Diabetic neuropathy	33	26
CAD	36	30
CABG	8	5
PCI	5	5
MI	19	15
Ischaemic stroke	16	12
Atrial fibrillation*	7	9
HF	18	7
Hypertension	97	96
Hyperlipidaemia	34	44

*Includes atrial flutter

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; SBP, systolic blood pressure

Patients with LVH reported higher use of beta blockers and antiplatelet agents at baseline than those without

Medication use at baseline, %	With LVH (n=1,250)	Without LVH (n=11,776)
RASi	99.8	99.8
Alpha blocker	15.8	21.9
Beta blocker	56.6	49.2
Calcium channel blocker	59.4	56.2
Diuretics	49.8	51.7
Statins	71.3	72.2
Potassium supplements	2.0	3.1
Potassium-lowering agents*	1.4	1.4
Oral anticoagulants	6.0	8.0
Platelet aggregation inhibitors#	61.4	55.5
Aspirin	54.6	48.2

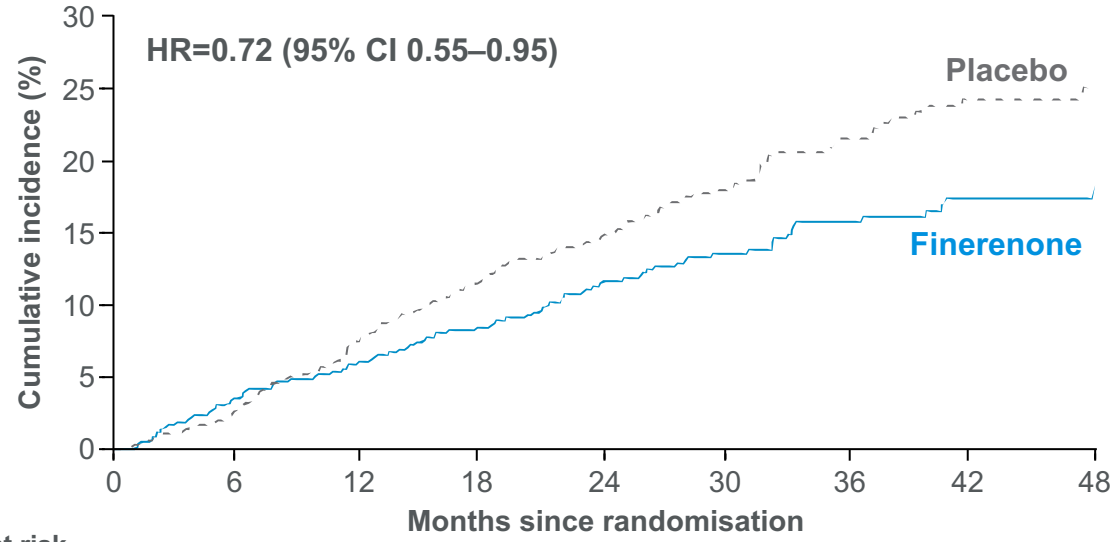
Medication use at baseline, %	With LVH (n=1,250)	Without LVH (n=11,776)
Glucose-lowering therapy	97.5	97.1
Insulin and analogues	57.4	58.7
DPP-4 inhibitors	19.5	25.8
GLP-1RA	3.6	7.6
SGLT-2 inhibitor	3.8	7.0
Biguanides	53.5	58.5
Sulfonylureas	28.8	25.7

*Including binders; #excludes heparin
DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium-glucose co-transporter-2

Finerenone reduced the risk of the CV composite outcome compared with placebo, irrespective of LVH status at baseline

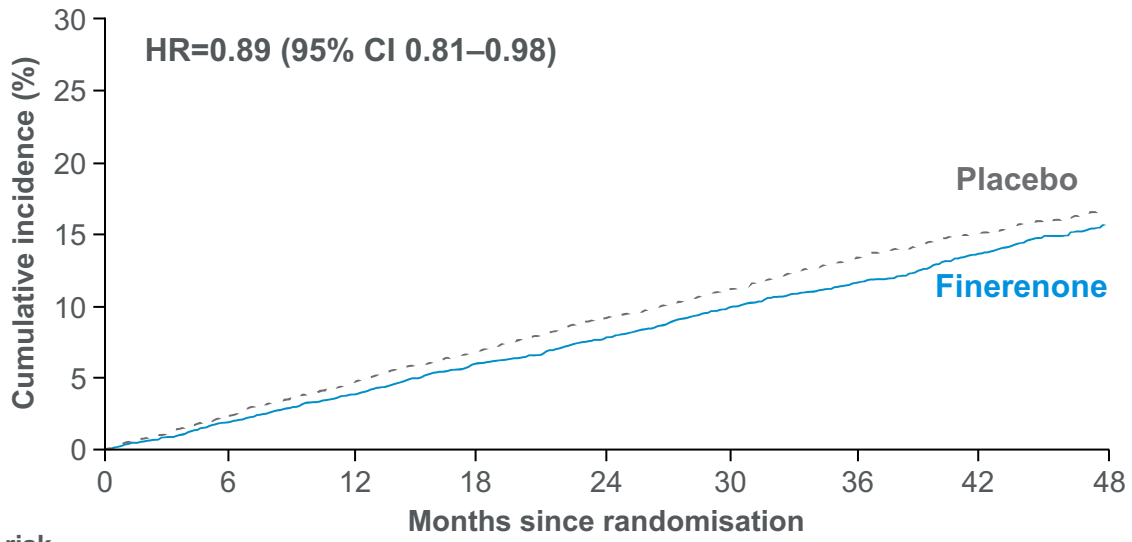
Composite CV outcome (time to CV death, non-fatal MI, non-fatal stroke or HHF) by LVH status at baseline

Patients with LVH at baseline



No. at risk					
Finerenone	596	554	457	247	86
Placebo	654	596	466	227	76

Patients without LVH at baseline



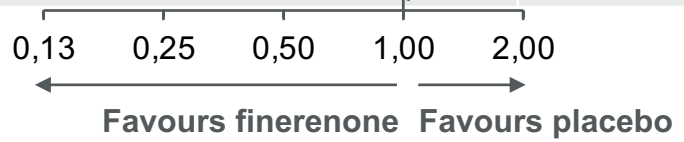
No. at risk					
Finerenone	5,923	5,648	4,816	2,818	1,001
Placebo	5,853	5,529	4,718	2,742	1,006

***p*-value for interaction = 0.108**

LVH at baseline had no impact on the effect of finerenone on CV risk reduction, except for HHF

Components of the CV composite outcome by LVH status at baseline

Endpoint	Population	Finerenone		Placebo		HR (95% CI)	*p*-value for interaction
		n/N (%)	Events per 100 PY	n/N (%)	Events per 100 PY		
HHF	**Overall[1]**	**256/6,519 (3.9)**	**1.31**	**325/6,507 (5.0)**	**1.68**	**0.78 (0.66–0.92)**	
	With LVH	17/596 (2.9)	1.00	52/654 (8.0)	2.94	0.34 (0.19–0.61)	0.002
	Without LVH	239/5,923 (4.0)	1.34	273/5,853 (4.7)	1.55	0.86 (0.72–1.03)	
CV death	**Overall[1]**	**322/6,519 (4.9)**	**1.61**	**364/6,507 (5.6)**	**1.84**	**0.88 (0.76–1.02)**	
	With LVH	49/596 (8.2)	2.84	61/654 (9.3)	3.30	0.96 (0.65–1.42)	0.905
	Without LVH	273/5,923 (4.6)	1.50	303/5,853 (5.2)	1.69	0.89 (0.75–1.04)	
Non-fatal MI	**Overall[1]**	**173/6,519 (2.7)**	**0.88**	**189/6,507 (2.9)**	**0.97**	**0.91 (0.74–1.12)**	
	With LVH	18/596 (3.0)	1.06	27/654 (4.1)	1.50	0.75 (0.41–1.38)	0.498
	Without LVH	155/5,923 (2.6)	0.86	162/5,853 (2.8)	0.92	0.94 (0.75–1.17)	
Non-fatal stroke	**Overall[1]**	**198/6,519 (3.0)**	**1.01**	**198/6,507 (3.0)**	**1.02**	**0.99 (0.82–1.21)**	
	With LVH	19/596 (3.2)	1.12	25/654 (3.8)	1.39	0.75 (0.40–1.40)	0.397
	Without LVH	179/5,923 (3.0)	1.00	173/5,853 (3.0)	0.98	1.03 (0.83–1.26)	



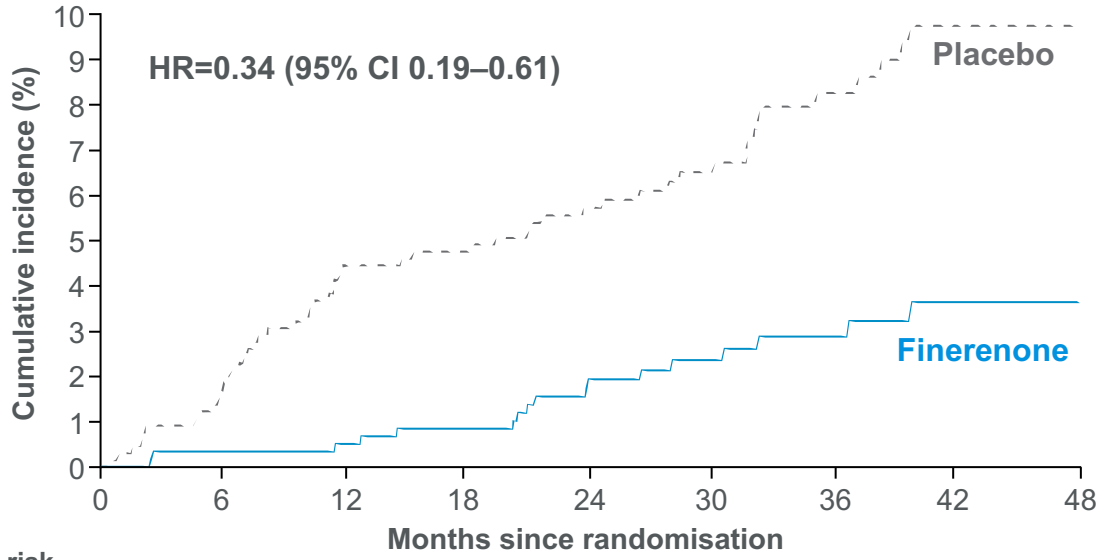
PY, patient-years

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

A lower incidence of HHF was observed early with finerenone compared with placebo in patients with LVH

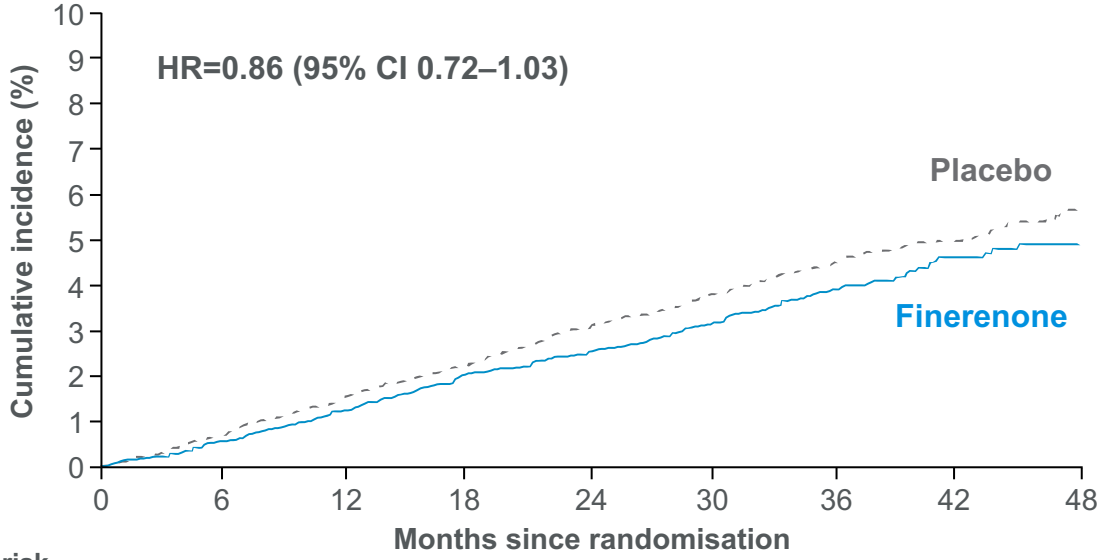
Time to HHF by LVH status at baseline

Patients with LVH at baseline



No. at risk					
Finerenone	596	572	478	256	88
Placebo	654	606	489	245	82

Patients without LVH at baseline



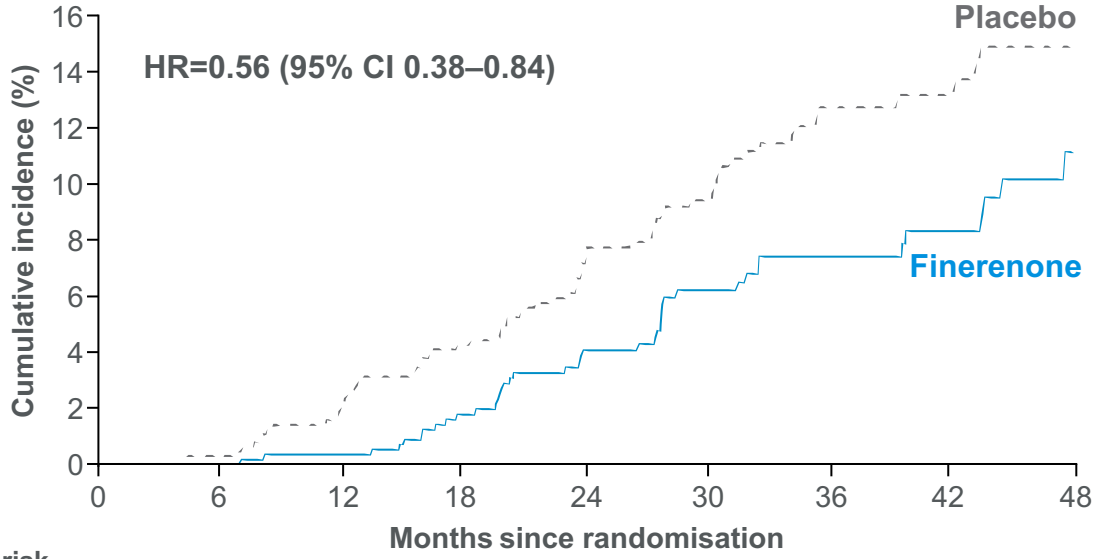
No. at risk					
Finerenone	5,923	5,741	4,972	2,947	1,055
Placebo	5,853	5,640	4,890	2,893	1,062

***p*-value for interaction = 0.002**

Finerenone reduced the risk of the kidney composite outcome compared with placebo, irrespective of LVH status at baseline

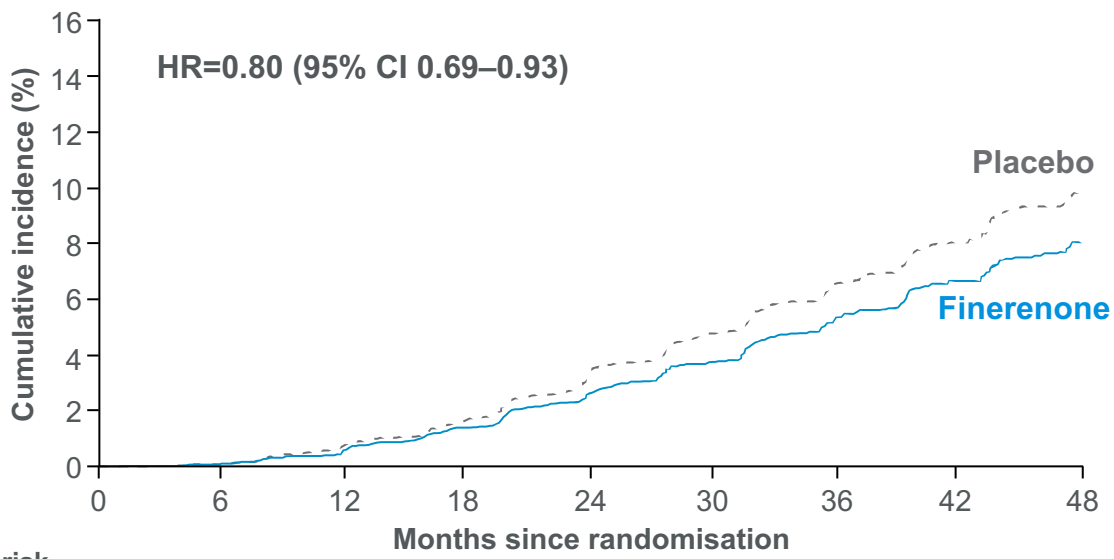
Composite kidney outcome (time to onset of kidney failure, a sustained decrease of eGFR ≥57% from baseline, or renal death) by LVH status at baseline

Patients with LVH at baseline



No. at risk					
Finerenone	596	542	431	213	72
Placebo	654	597	450	205	61

Patients without LVH at baseline



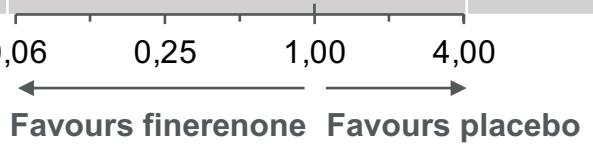
No. at risk					
Finerenone	5,923	5,565	4,596	2,602	887
Placebo	5,853	5,474	4,499	2,593	901

***p*-value for interaction = 0.178**

Finerenone reduced the nonfatal components of the kidney composite outcome compared with placebo, irrespective of LVH status at baseline

Components of the kidney composite outcome by LVH status at baseline

Endpoint	Population	Finerenone		Placebo		Hazard ratio (95% CI)	*p*-value for interaction
		n/N (%)	Events per 100 PY	n/N (%)	Events per 100 PY		
Kidney failure	**Overall[1]**	**254/6,519 (3.9)**	**1.38**	**297/6,507 (4.6)**	**1.62**	**0.84 (0.71–0.99)**	
	With LVH	27/596 (4.5)	1.71	47/654 (7.2)	2.80	0.60 (0.37–0.97)	0.139
	Without LVH	227/5,923 (3.8)	1.35	250/5,853 (4.3)	1.50	0.88 (0.74–1.06)	
≥57% decrease in eGFR from baseline*	**Overall[1]**	**257/6,519 (3.9)**	**1.40**	**361/6,507 (5.5)**	**1.98**	**0.70 (0.60–0.83)**	
	With LVH	27/596 (4.5)	1.72	50/654 (7.6)	3.00	0.51 (0.31–0.84)	0.271
	Without LVH	230/5,923 (3.9)	1.37	311/5,853 (5.3)	1.88	0.73 (0.61–0.87)	
Renal death	**Overall[1]**	**2/6,519 (<0.1)**	**0.01**	**4/6,507 (<0.1)**	**0.02**	**0.53 (0.10–2.91)**	
	With LVH	0/596 (0)	0	0/654 (0)	0	1.00 (1.00–1.00)[#]	0.999
	Without LVH	2/5,923 (<0.1)	0.01	4/5,853 (<0.1)	0.02	0.53 (0.10–2.88)	



*confirmed by two eGFR measurements ≥4 weeks apart; **[#]an unstratified model using Firth's penalised likelihood approach was applied due to zero cell counts and/or convergence issues**

1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

The risk of hyperkalaemia was higher with finerenone irrespective of LVH status, but discontinuation due to hyperkalaemia was low

TEAE, %	With LVH		Without LVH	
	Finerenone (n=595)	Placebo (n=653)	Finerenone (n=5,915)	Placebo (n=5,836)
Any SAE	28	33	32	34
Treatment related	0.7	0.8	1.3	1.0
Leading to treatment discontinuation	1.3	1.7	2.3	2.5
Serious hyperkalaemia	0.1	0	1.1	0.3
Treatment related	0.2	0	0.7	0.1
Leading to hospitalisation	**0.7**	**0**	**1.0**	**0.2**
Leading to treatment discontinuation	**0.2**	**0**	**0.2**	**<0.1**

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

Summary

In a patients 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 RASi:

The CV and kidney benefits of finerenone versus placebo were observed in patients with T2D and CKD irrespective of baseline LVH

A lower incidence of HHF was observed early with finerenone compared with placebo in patients with LVH

Although hyperkalaemia was increased with finerenone for patients in both LVH subgroups, the clinical impact was minimal

Finerenone has shown cardiorenal benefits across the spectrum of patients with CKD and T2D, irrespective of LVH status at baseline

Thank you

48 countries, 33,292 patients enrolled, 13,171 patients randomised

Executive committee
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FIDELITY
FInerenone in chronic kiDney diseasE and type 2 diabetes: Combined FIDELIO-DKD and FIGARO-DKD Trial programme analYsis

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