Finerenone and effects on mortality in chronic kidney disease and type 2 diabetes: A FIDELITY analysis

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On behalf of Stefan D. Anker, Phyllis August, Andrew Coats, James L. Januzzi, Boris Mankovsky, Peter Rossing, Luis M. Ruilope, Bertram Pitt, Pantelis Sarafidis, John R. Teerlink, Martin Gebel, Meike Brinker, Amer Joseph, Andrea Lage, George L. Bakris, Rajiv Agarwal and the FIDELIO-DKD and FIGARO-DKD investigators

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FIDELITY

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

Disclosures

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- Senior Consulting Editor: *JACC – Heart Failure*
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An excess risk of mortality is associated with CKD and T2D[1]

- **T2D and early CKD may reduce life expectancy by up to 16 years[1]**
  - CV-related mortality is the main cause of death in patients with CKD and T2D, where a 6-fold increased risk was observed compared with the general population[2–4]

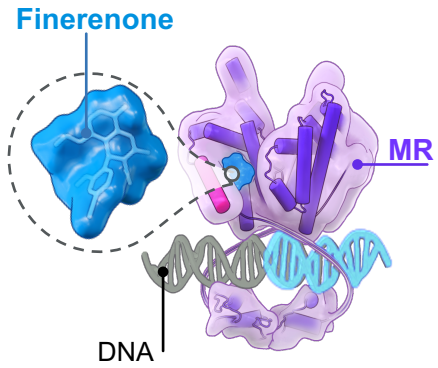
- **ACEis and ARBs reduce the risk of CKD progression in patients with CKD and T2D,[5] but an effect on all-cause mortality has not been reported[6]**

- **While the effect of steroidal MRAs on mortality in patients with CKD and T2D has not been evaluated, reduced CV mortality was reported in patients with HF[7,8]**
  - However, the use of steroidal MRAs is limited by off-target side effects[9]

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; T2D, type 2 diabetes

1. Wen CP, *et al. Kidney Int* 2017;92:388–396; 2. Afkarian M, *et al. J Am Soc Nephrol* 2013;24:302–308; 3. Ang YG, *et al. J Clin Transl Endocrinol* 2016;4:1–6; 4. Charytan DM, *et al. Am J Kidney Dis* 2015;66:196–205; 5. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2020;98:S1–S115; 6. Sarafidis PA, *et al. Am J Hypertens* 2008;21:922–992; 7. Pitt B, *et al. N Engl J Med* 1999;341:709–717; 8. Pitt B, *et al. J Am Col Cardiol* 2005;46:425–431; 9. Agarwal R, *et al. Eur Heart J* 2021;42:152–161

Finerenone is a selective, non-steroidal MRA that has demonstrated CV and kidney benefits in patients with CKD and T2D



FIDELIO-DKD[3]
N=5674*

+

FIGARO-DKD[4]
N=7352*

FIDELITY

Prespecified individual patient-data pooled analysis of FIDELIO-DKD and FIGARO-DKD[6]

Total N=13,026*

Finerenone is a **distinct, nonsteroidal MRA that selectively blocks MR overactivation.**
MR overactivation is thought to contribute to kidney and CV damage[1,2]

In FIDELIO-DKD and FIGARO-DKD, **finerenone significantly improved CV outcomes and slowed CKD progression** in patients with CKD and T2D[3–5]

FIDELITY includes a **broad spectrum of patients** with CKD and T2D[6]

*Patients analysed
DNA, deoxyribonucleic acid

1. Agarwal R, *et al. Eur Heart J* 2021;42:152–161; 2. Agarwal R, *et al. Nephrol Dial Transplant* 2020;gfaa294; 3. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 4. Filippatos G, *et al. Circulation* 2021;143:540–552; 5. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263; 6. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

FIDELITY

FIDELITY is a large, prespecified analysis of individual patient data from FIDELIO-DKD and FIGARO-DKD trials[1–3]

Patients from 48 countries participated
(September 2015 to October 2018)

13,026 patients analysed

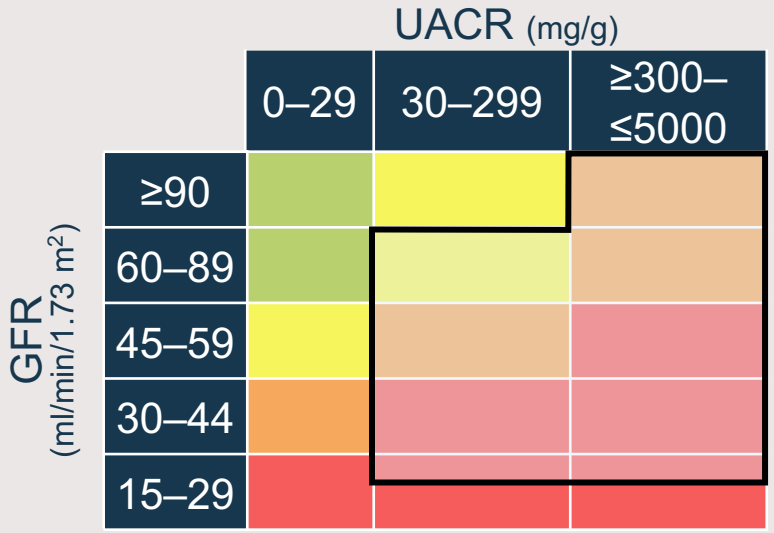
3 years' median follow-up

R

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

Key eligibility criteria

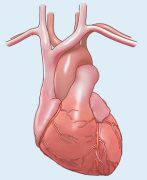
- ✓ **T2D**
- ✓ **CKD**
- ✓ On maximum tolerated dose of a single RASi
- ✓ Serum [K^+] ≤4.8 mmol/l
- ✗ Symptomatic HFrEF



Key outcomes

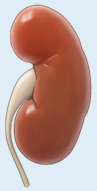
CV composite

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 renal 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 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* 2022;43:474–484

FIDELITY

FIDELITY included patients with CKD and T2D, with a mean age of 65 years, well-controlled HbA1c and BP, and 46% had a history of CV disease

Patient characteristics	Patients (N=13,026)*
Age, years, mean	65
Sex, male, %	70
Race, %	
White	68
Black/African American	4
Asian	22
SBP/DBP*, mmHg, mean	137/76
Duration of diabetes, years, mean	15
HbA1c, %, mean	7.7
Laboratory parameters at baseline	
Serum potassium, mmol/l, mean	4.4
hs-CRP*, mg/l, mean	4.7
eGFR, ml/min/1.73 m^2, mean	58
UACR, mg/g, median	515

Medical history, %	Patients (N=13,026)*
CV disease	46
Ischaemic stroke	12
Atrial fibrillation or flutter	8
Heart failure#	8
Diabetic retinopathy	38
Diabetic neuropathy	27
Hypertension	96
Hyperlipidaemia	43

*Full analysis set; #patients with symptomatic HFrEF were excluded from the study
BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure

FIDELITY

In FIDELITY, all patients were optimised on RASi therapy and most were on CV medications and glucose-lowering therapies

Medication use at baseline, %	Patients (N=13,026)*
RASis	>99
ACEis	39
ARBs	61
Alpha blockers	21
Beta blockers	50
Calcium channel blockers	57
Diuretics	52
Statins	72
Potassium supplements	3
Potassium-lowering agents#	1
Oral anticoagulants	8
Aspirin	49

Medication use at baseline, %	Patients (N=13,026)*
Insulin and analogues	59
DPP-4 inhibitors	25
GLP-1RAs	7
SGLT-2 inhibitors	7
Biguanides	58
Sulfonylureas	26

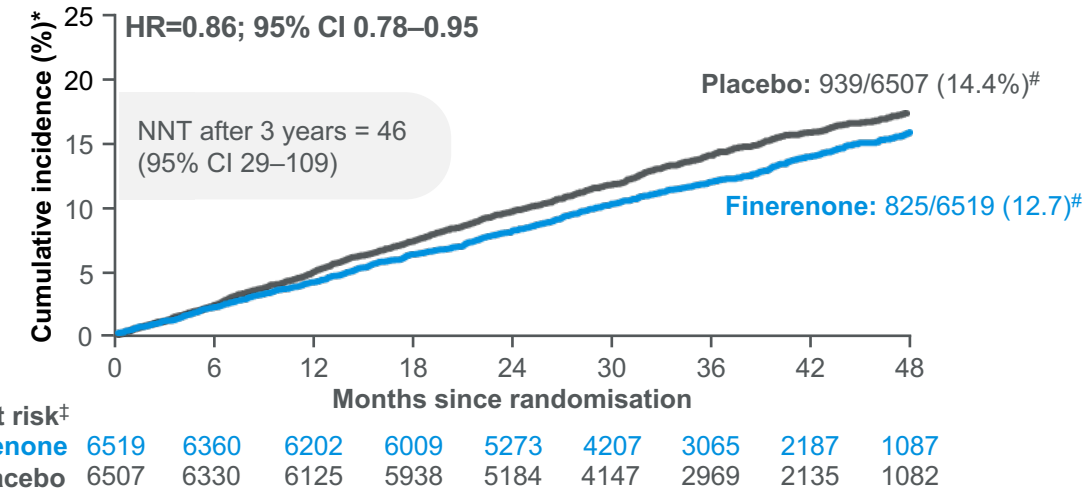
*Full analysis set; #including binders
DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium-glucose co-transporter-2

FIDELITY

In FIDELITY, on top of optimised RASi, finerenone significantly reduced the risk of the composite CV and kidney outcomes

CV composite

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

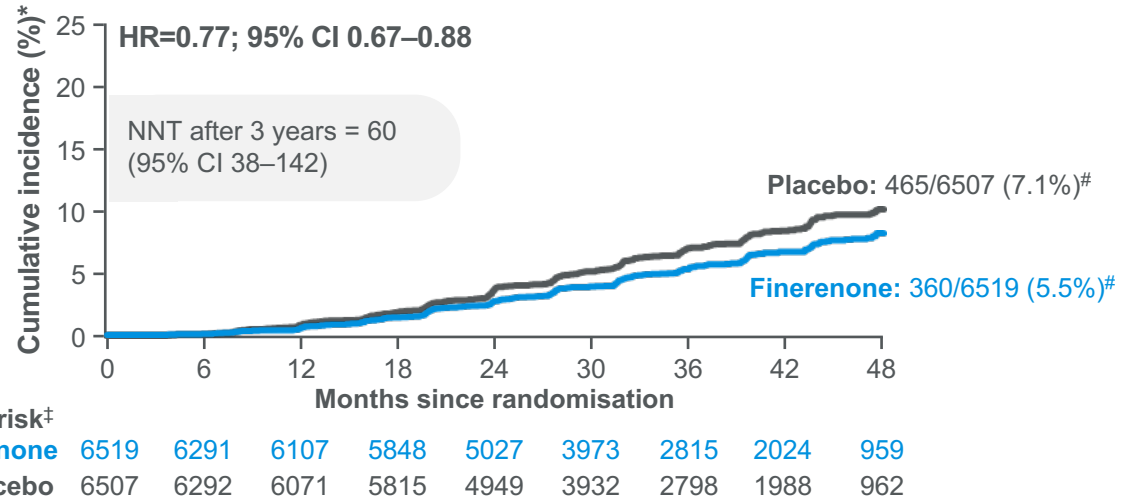


No. at risk‡									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

14% reduced **risk of CV morbidity and mortality** versus placebo (HR=0.86; 95% CI 0.78–0.95); *p*=0.0018

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*** versus placebo (HR=0.77; 95% CI 0.67–0.88); *p*=0.0002

*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; § ESKD or an eGFR <15 ml/min/1.73 m^2;
CI, confidence interval; HR hazard ratio; NNT, number needed to treat

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

FIDELITY

This FIDELITY sub-analysis explored the causes of mortality in patients with T2D and CKD treated with finerenone versus placebo

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

Objective:

To present a **comprehensive analysis on the causes of mortality** in patients with T2D across the spectrum of CKD severity treated with finerenone or placebo

Key outcomes:

- **All-cause mortality**
- **CV mortality** defined as sudden cardiac death,* undetermined mortality,# mortality due to acute MI, HF, stroke or CV procedures, or mortality due to other CV causes‡

All events were **adjudicated prospectively** by an **independent clinical event committee** blinded to treatment allocation

*Defined as any mortality that occurred unexpectedly and was not within 30 days of an acute MI; #defined as any mortality occurring in a patient who was not observed alive within 24 hours and without any other likely cause of mortality. All patients who died from undetermined causes were considered as CV mortality due to the patient population and competing causes of mortality within that population; ‡included CV haemorrhage (such as non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture [e.g. aortic rupture] or haemorrhage causing cardiac tamponade), PE or PAD
PAD, peripheral artery disease; PE, pulmonary embolism

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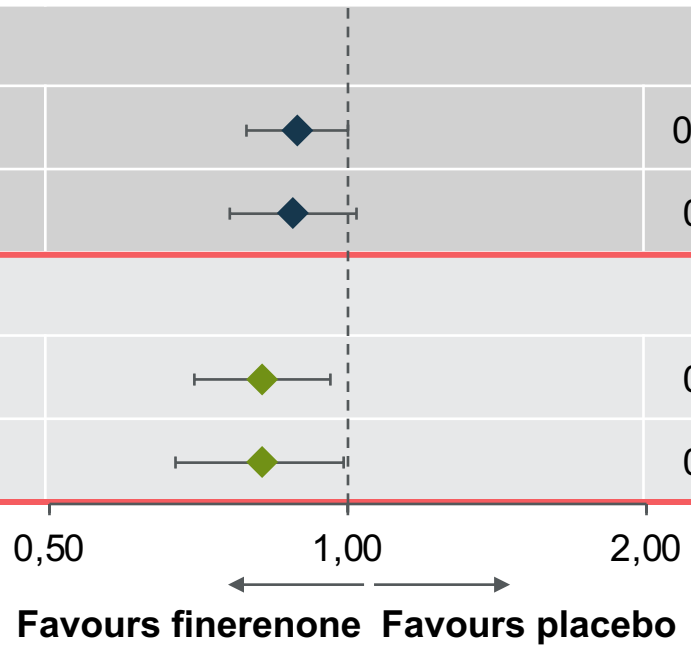
Prespecified on-treatment analysis* showed that all-cause mortality and CV mortality were reduced with finerenone versus placebo

Risk of all-cause mortality and CV mortality

Endpoint	Finerenone (n=6519)		Placebo (n=6507)		HR (95% CI)	*p*-value
	n (%)	Events per 100 PY	n (%)	Events per 100 PY		
Intention to treat (primary) analysis[1]						
All-cause mortality	552 (8.5)	2.76	614 (9.4)	3.10	0.89 (0.79–>1.00)	0.051
CV mortality	322 (4.9)	1.61	364 (5.6)	1.84	0.88 (0.76–1.02)	0.092
On-treatment analysis*						
All-cause mortality	280 (4.3)	1.62	344 (5.3)	1.98	0.82 (0.70–0.96)	0.014
CV mortality	189 (2.9)	1.09	233 (3.6)	1.34	0.82 (0.67–0.99)	0.040



*Time frame of the primary analysis was restricted up to 30 days after last study drug intake
PY, patient-years
1. Agarwal R, *et al. Eur Heart J* 2022;43:474–484

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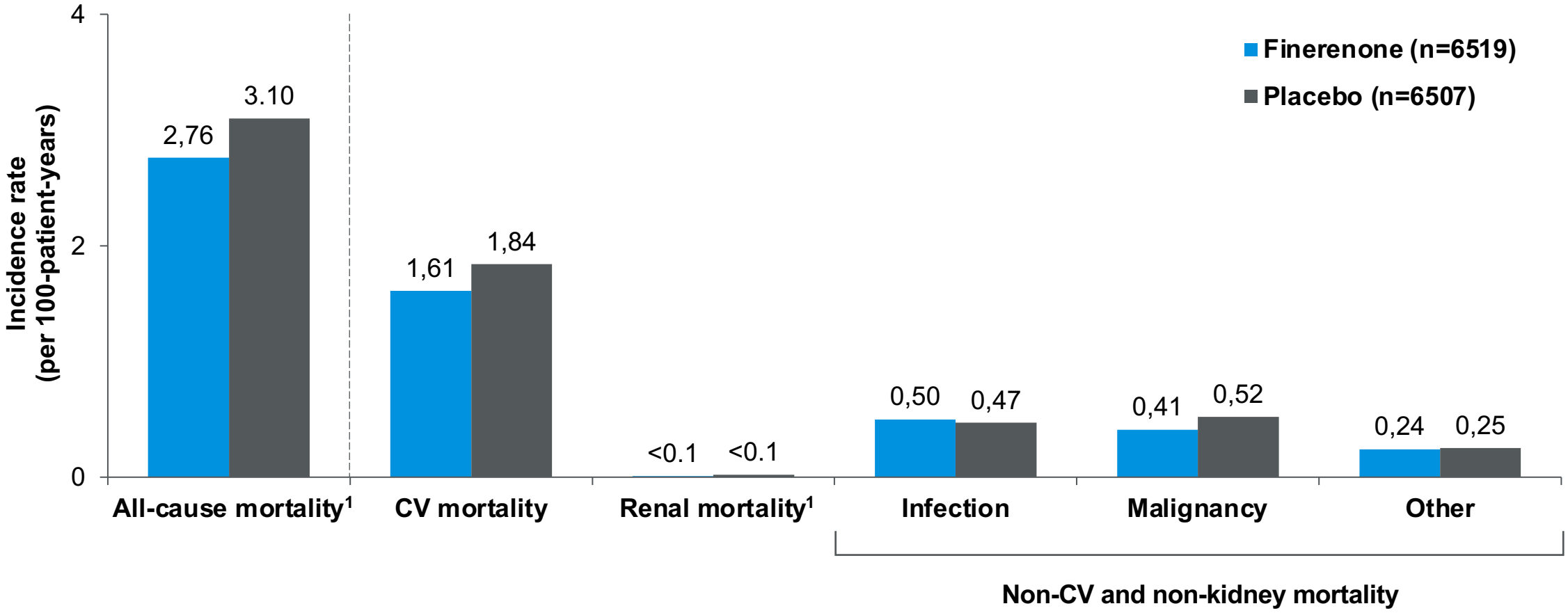
The most common cause of mortality in the overall FIDELITY population was related to CV events

Causes of mortality following treatment with finerenone versus placebo



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

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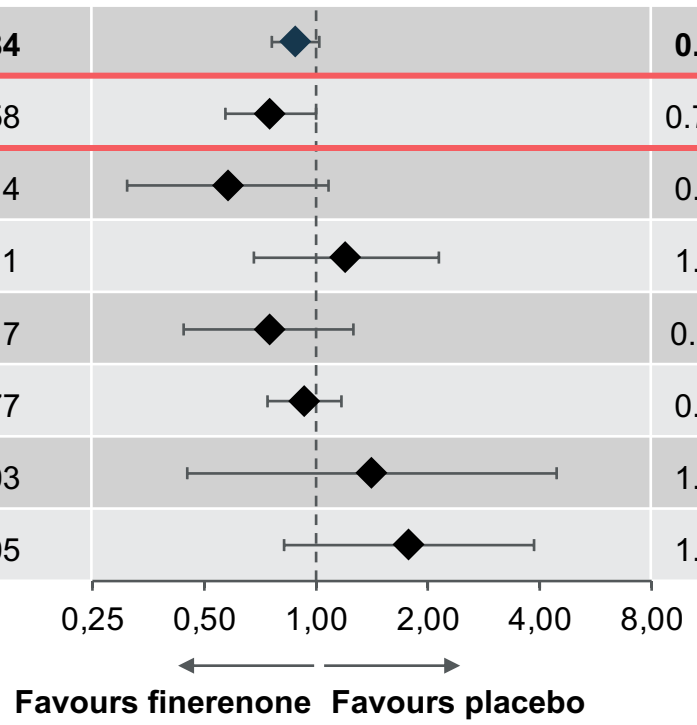
Finerenone reduced the risk of sudden cardiac death versus placebo

Risk of CV mortality and its components

Endpoint	Finerenone (n=6519)		Placebo (n=6507)		HR (95% CI)	*p*-value
	n (%)	Events per 100 PY	n (%)	Events per 100 PY		
CV mortality	**322 (4.9)**	**1.61**	**364 (5.6)**	**1.84**	**0.88 (0.76–1.02)**	**0.092**
Sudden cardiac death	88 (1.3)	0.44	115 (1.8)	0.58	0.75 (0.57–<1.00)	0.046#
Fatal HF	15 (0.2)	0.08	27 (0.4)	0.14	0.58 (0.31–1.08)	0.083#
Death due to acute MI	26 (0.4)	0.13	21 (0.3)	0.11	1.20 (0.68–2.14)	0.531#
Fatal stroke	25 (0.4)	0.13	33 (0.5)	0.17	0.75 (0.44–1.26)	0.268#
Undetermined death	143 (2.2)	0.72	153 (2.4)	0.77	0.93 (0.74–1.17)	0.552#
Death due to CV procedures	7 (0.1)	0.04	5 (<0.1)	0.03	1.41 (0.45–4.44)	0.557#
Death due to other CV causes	18 (0.3)	0.09	10 (0.2)	0.05	1.78 (0.82–3.86)	0.139#

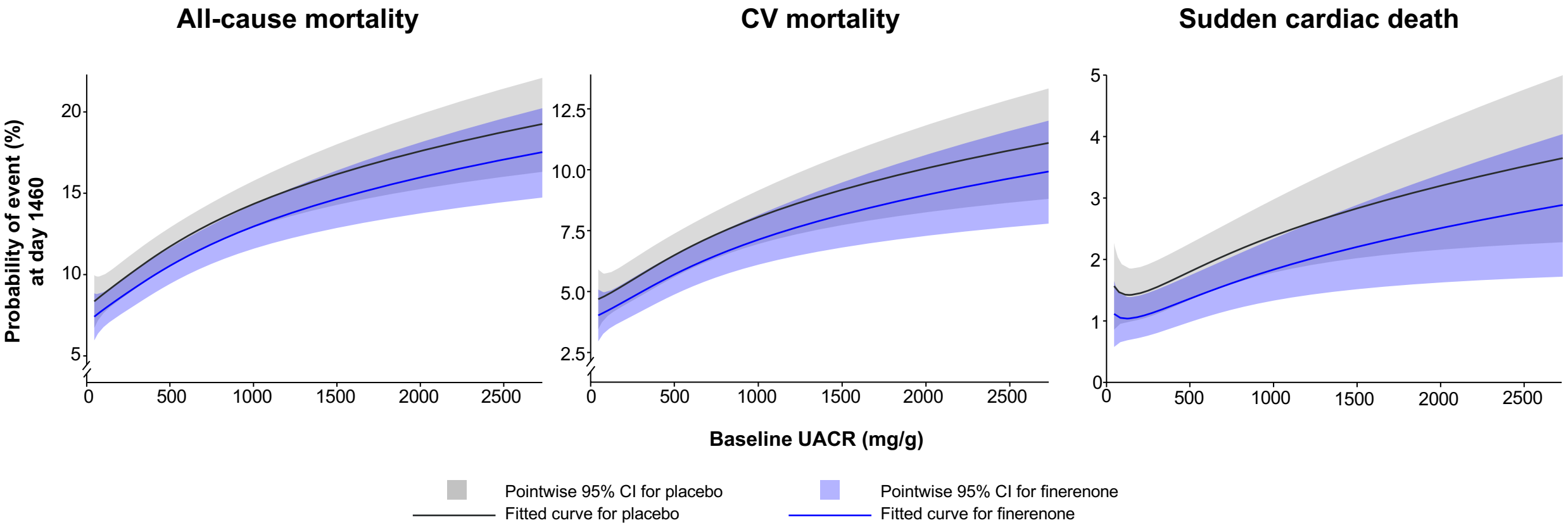


#*p*-value was calculated in a post hoc analysis

FIDELITY

The effect of finerenone on mortality outcomes was consistent versus placebo irrespective of baseline UACR

Event probability analysis of time to mortality outcome at 4 years



Cox proportional hazards model was fitted with covariates baseline eGFR (for continuous variable baseline eGFR) or baseline UACR (log-transformed; for continuous variable baseline UACR), treatment, study, CVD history, region, sex, race and continuous covariates age, HbA1c, SBP, baseline UACR (log-transformed; for continuous variable baseline eGFR) or baseline eGFR (for continuous variable baseline UACR). Splines were used with knots at UACR 30, 300 and 1000 mg/g

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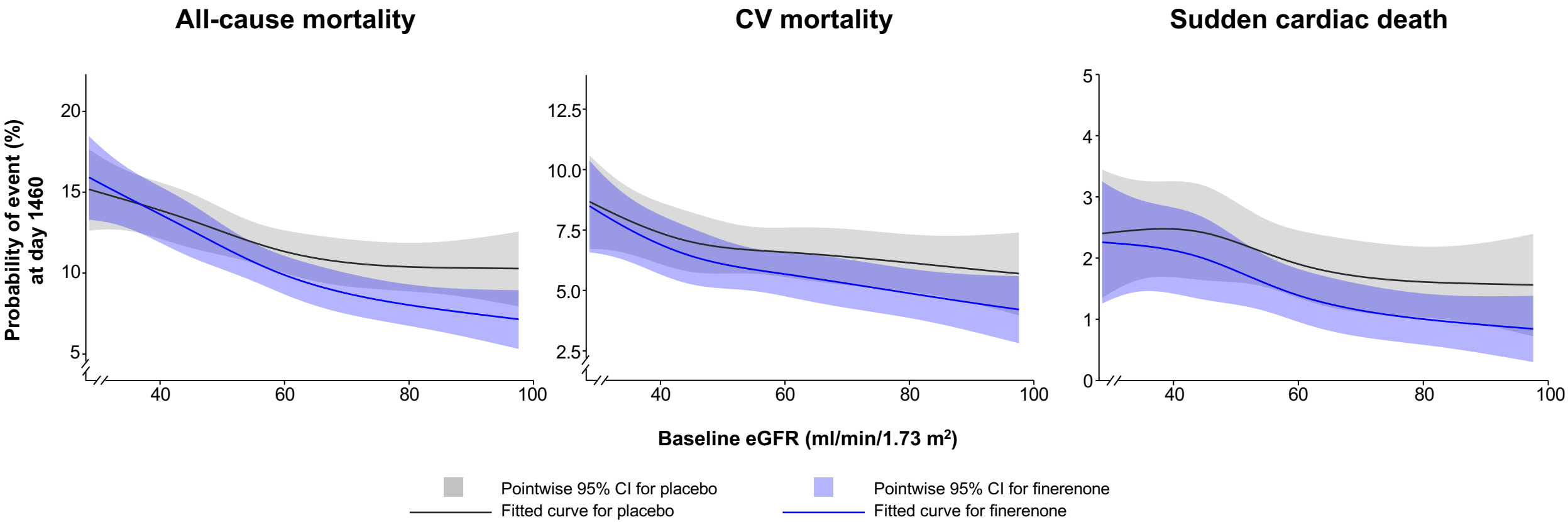
The effect of finerenone on mortality outcomes was seemingly more pronounced in patients with higher baseline eGFR

Event probability analysis of time to mortality outcome at 4 years



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Summary

In patients with T2D across a broad spectrum of CKD stages and severity, with well-controlled blood pressure and HbA1c, and treated with a RASi at the maximum tolerated dose:

The most common cause of mortality was related to CV events

Finerenone reduced the risk of all-cause and CV mortality versus placebo, and lowered the risk of sudden cardiac death

The effect on all three mortality outcomes with finerenone
was consistent irrespective of baseline UACR
but appeared to be more pronounced in patients with a higher baseline eGFR

FIDELITY

Thank you

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

Executive committee
Rajiv Agarwal; Stefan D. Anker; George L. Bakris; Gerasimos Filippatos; Bertram Pitt; Luis M. Ruilope

Independent data monitoring committee
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The FIDELIO-DKD and FIGARO-DKD teams would also like to thank all participating investigators, the centres, and the patients and their families