The importance of screening for albuminuria to prevent CV disease in patients with CKD and T2D: The FIDELITY analysis

Rajiv Agarwal and Gerasimos Filippatos
Bertram Pitt, Stefan D. Anker, Peter Rossing,
Amer Joseph, Peter Kolkhof, Christina Nowack,
Martin Gebel, Luis M. Ruilope, George L. Bakris,
on behalf of the FIDELIO-DKD and
FIGARO-DKD Investigators

28 August 2021

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

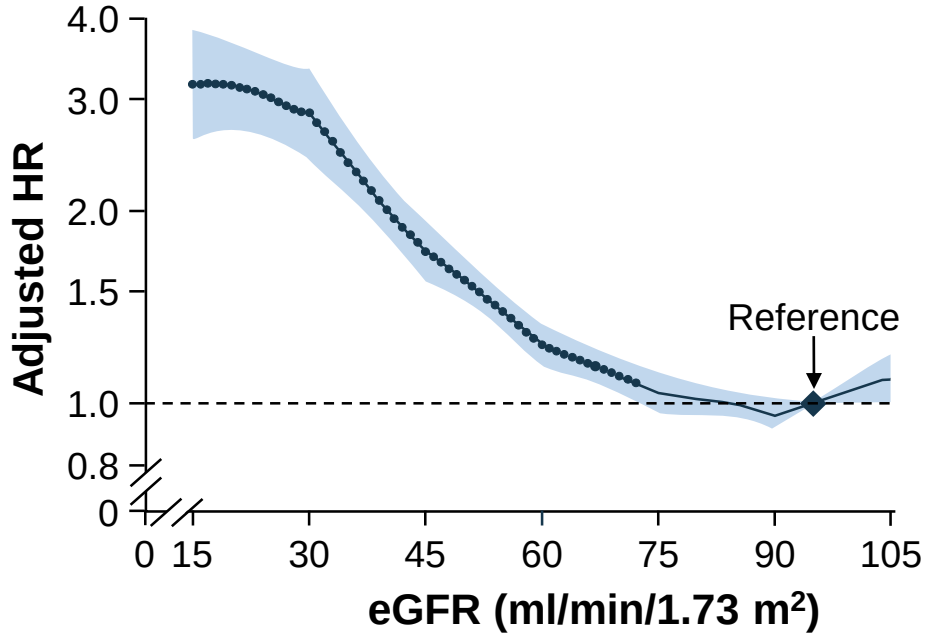
CV risk in patients with CKD and T2D increases as eGFR falls and as UACR rises

CKD = eGFR <60 ml/min/1.73 m² for >3 months[1]

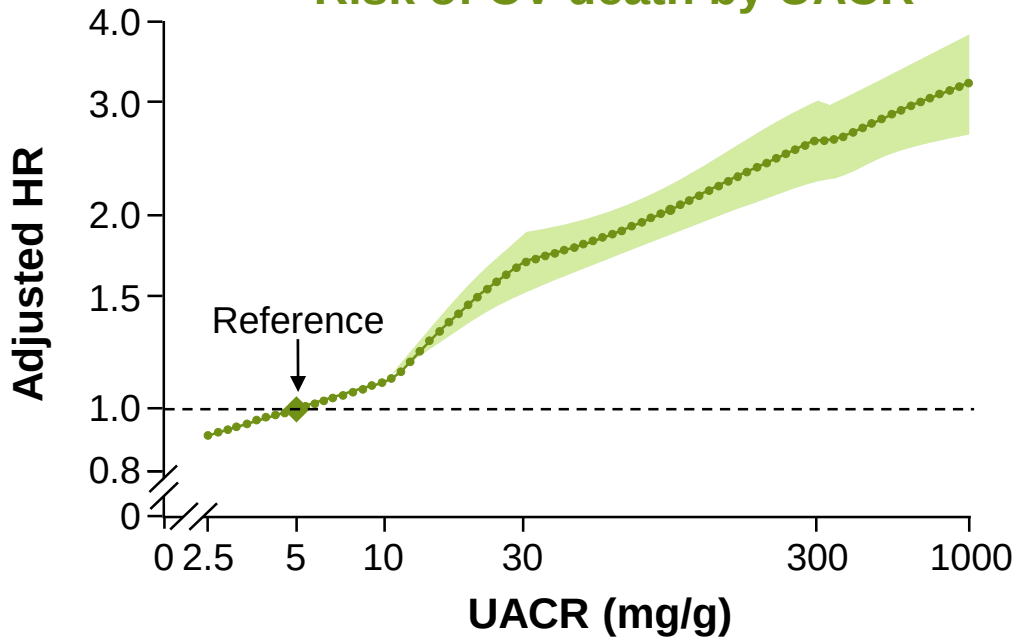
and
OR

CKD = albuminuria
UACR >30 mg/g for >3 months[1]

Risk of CV death by eGFR*#,2



Risk of CV death by UACR*2



*Adjusted for age, sex, race or ethnic origin, smoking, SBP, antihypertensive drugs, diabetes, total and HDL cholesterol concentrations, and albuminuria (UACR or dipstick) or eGFR, as appropriate;
#Figure adapted from Matsushita K, *et al.* 2015
CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Kidney Disease Improving Global Outcomes. *Kidney Int* 2013;3:1–150; 2. Matsushita K, *et al. Lancet Diabetes Endocrinol* 2015;3:514–525

Risk of adverse outcomes in patients with CKD and T2D increases as eGFR falls and as UACR rises

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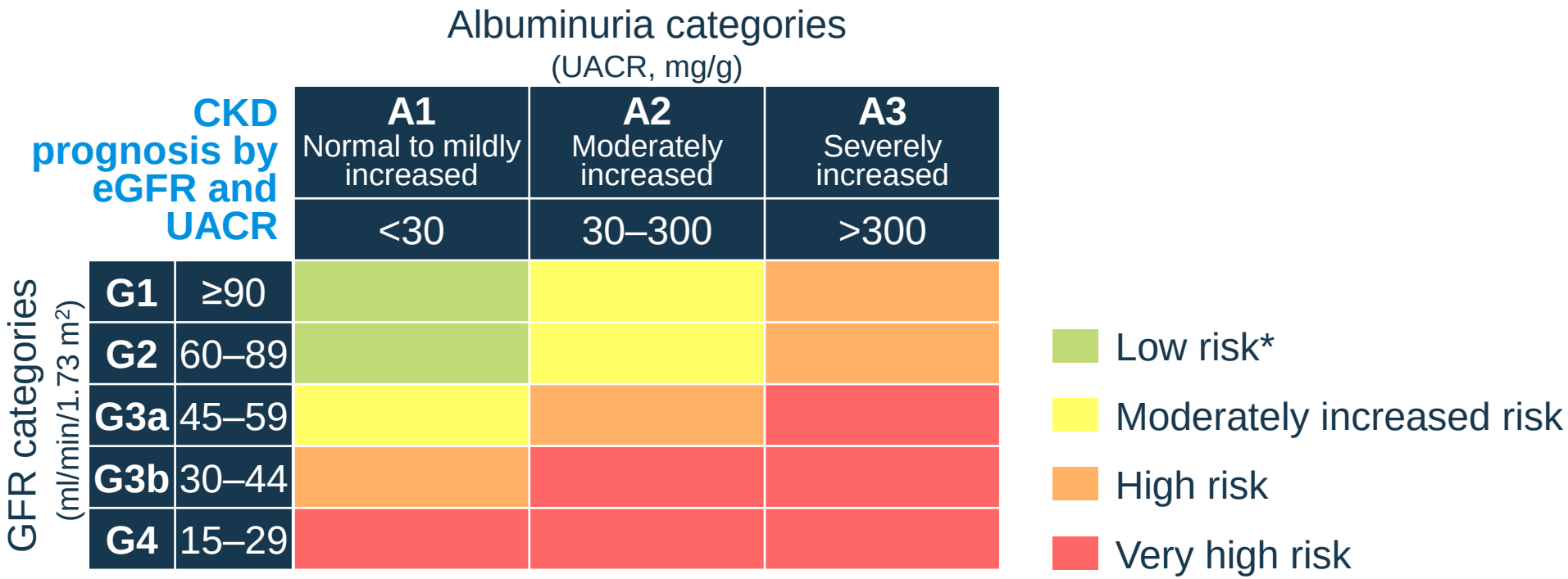


*If no other markers of kidney disease, no CKD

1. Kidney Disease Improving Global Outcomes. *Kidney Int* 2013;3:1–150

FIDELITY is a large individual patient data pooled analysis of FIDELIO-DKD[1] and FIGARO-DKD[2]

48 countries

13,171 patients randomised

3 years' median follow-up

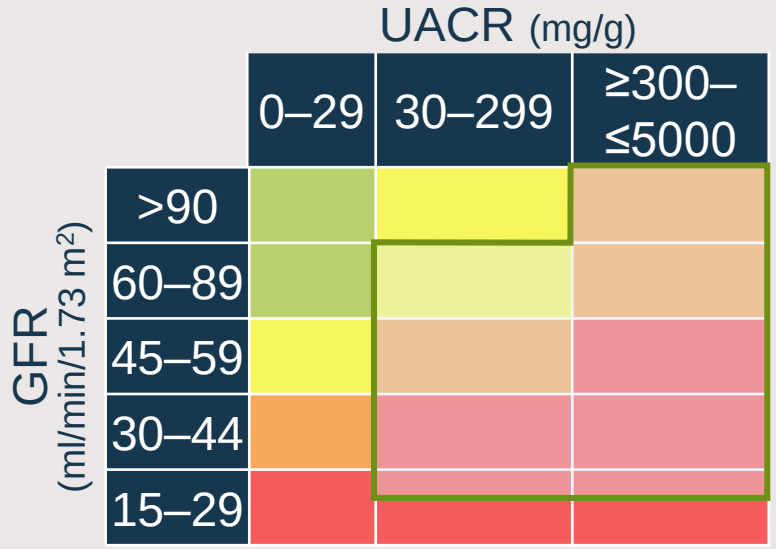
R

Finerenone 10 or 20 mg od*

Placebo

Key eligibility criteria

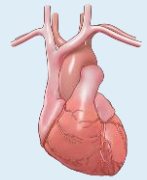
- ✓ T2D
- ✓ CKD
- ✓ On single RASi
- ✓ Serum [K^+] ≤4.8 mmol
- ✗ Symptomatic HFrEF



Key outcomes

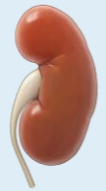
CV composite

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 renal 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 sustained decrease in eGFR <15 ml/min/1.73 m^2; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HHF, hospitalisation for heart failure; HFrEF, heart failure with reduced ejection fraction; [K^+], potassium concentration; MI myocardial infarction; RASi, renin–angiotensin system inhibitor; od, once daily

1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, presented at ESC congress 2021

At baseline, patients had well-controlled blood pressure and HbA1c, and CV medications were used by most patients

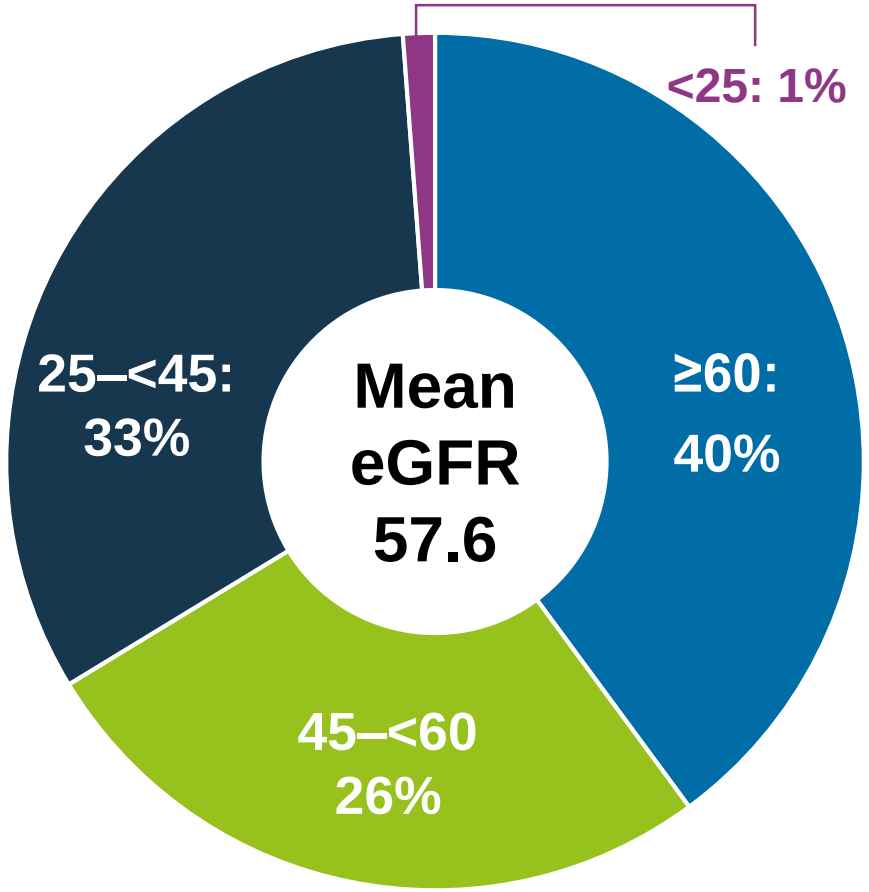
Characteristic	Total (n=13,026)
Age, years	65
Male, %	70
Duration of T2D, years	15.4
HbA1c, %	7.7
SBP/DBP, mmHg	**137/76**
History of CV disease, n (%)	**5935 (46)**
History of HF, %	**1007 (7.7)**
Serum [K^+], mmol/l	4.4

Medications, n (%)	Total (n=13,026)
CV medications	
RASi	**13,003 (100)**
Statins	**9399 (72)**
Beta-blockers	6504 (50)
Calcium antagonists	7358 (57)
Diuretics	6710 (52)
Glucose-lowering therapies	12,720 (98)
Metformin	7557 (58)
Insulin	7630 (59)
GLP-1RAs	944 (7.2)
SGLT-2is	877 (6.7)

GLP-1RA, glucagon-like peptide-1 receptor antagonist; HbA1c, glycated haemoglobin; HF, heart failure; SBP, systolic blood pressure; SGLT-2, sodium-glucose co-transporter-2 inhibitors

40% of patients had albuminuric CKD with preserved kidney function (eGFR ≥60 ml/min/1.73 m²)

Baseline eGFR (ml/min/1.73 m²)



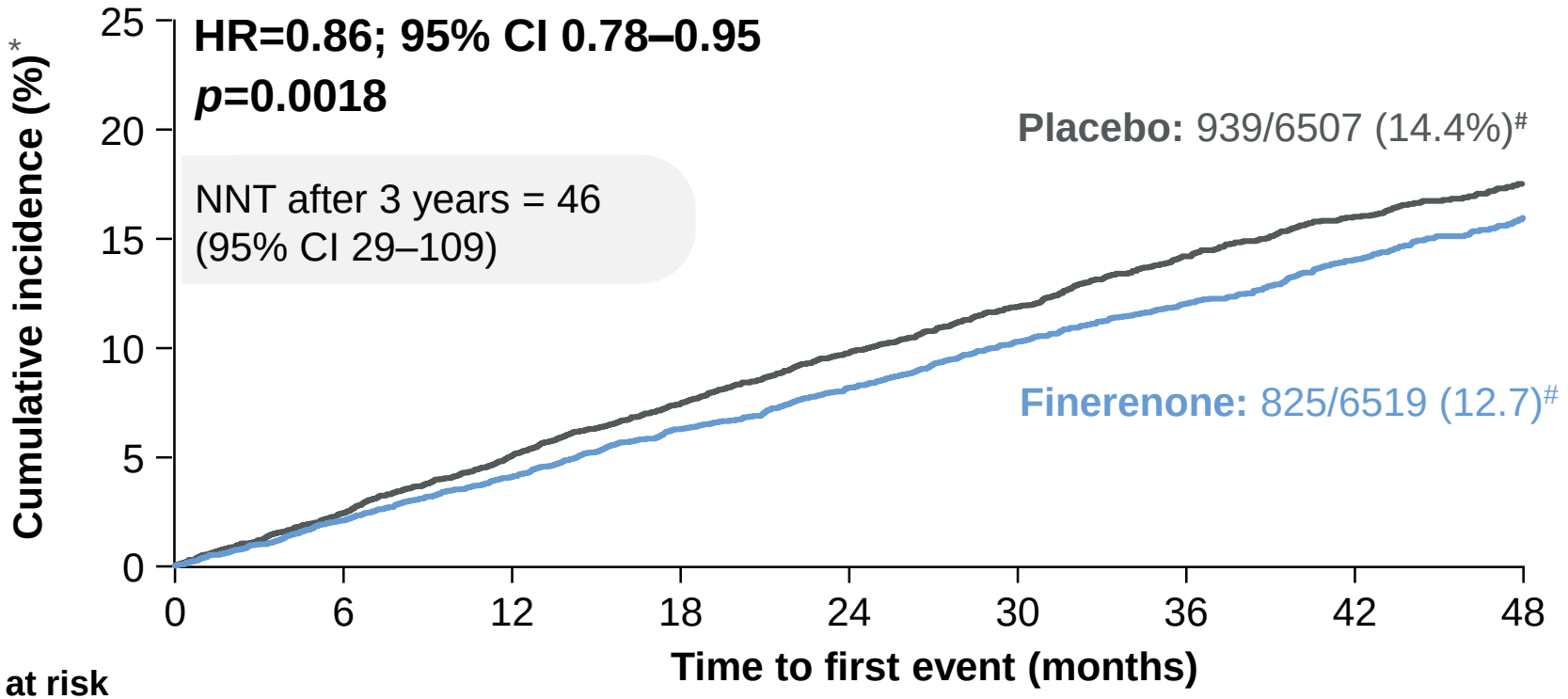
Baseline eGFR and UACR (KDIGO categories)*

GFR categories (ml/min/1.73 m²)	Data presented as n (%)	A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
		Albuminuria categories (mg albumin/g creatinine)		
		0–<30	30–<300	≥300–≤5000
G1	≥90	**13 (<0.1)**	**198 (1.5)**	**1108 (8.5)**
G2	60–89	**51 (0.4)**	**1043 (8.0)**	**2780 (21)**
G3a	45–59	82 (0.6)	1389 (11)	1962 (15)
G3b	30–44	68 (0.5)	1230 (9.4)	2206 (17)
G4	15–29	16 (0.1)	239 (1.8)	635 (4.9)

*Data were missing for 3 patients
KDIGO, Kidney Disease Improving Global Outcomes

On top of optimised RAS blockade, finerenone significantly reduced the risk of the composite CV outcome by 14%

Time to CV death, non-fatal MI, non-fatal stroke, or hospitalisation for HF

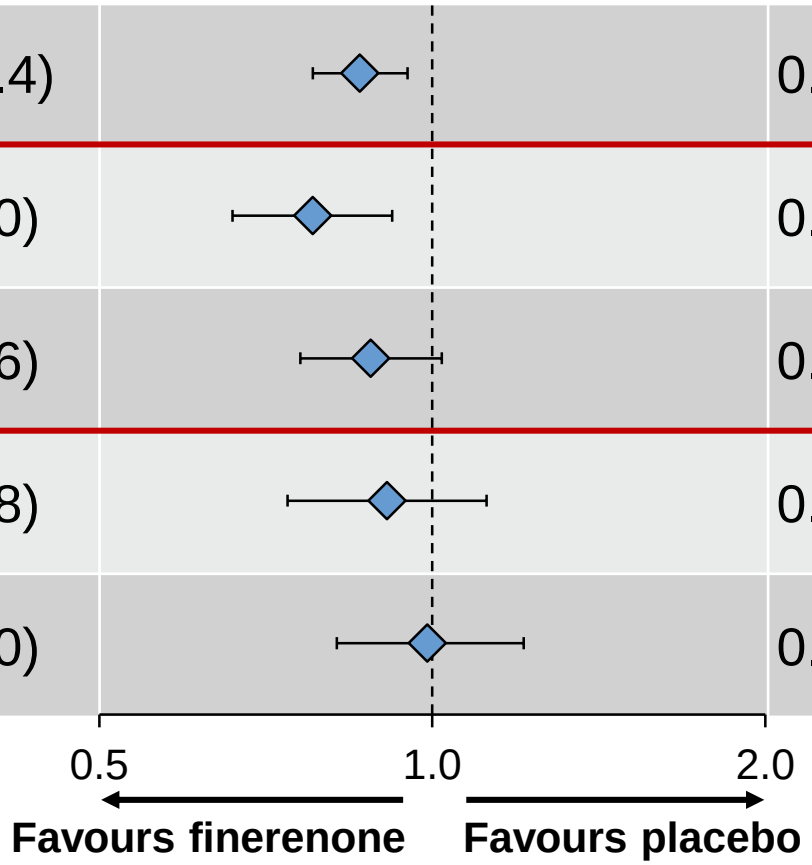


No. at risk									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

*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
CI, confidence interval; HR, hazard ratio; NNT, number needed to treat

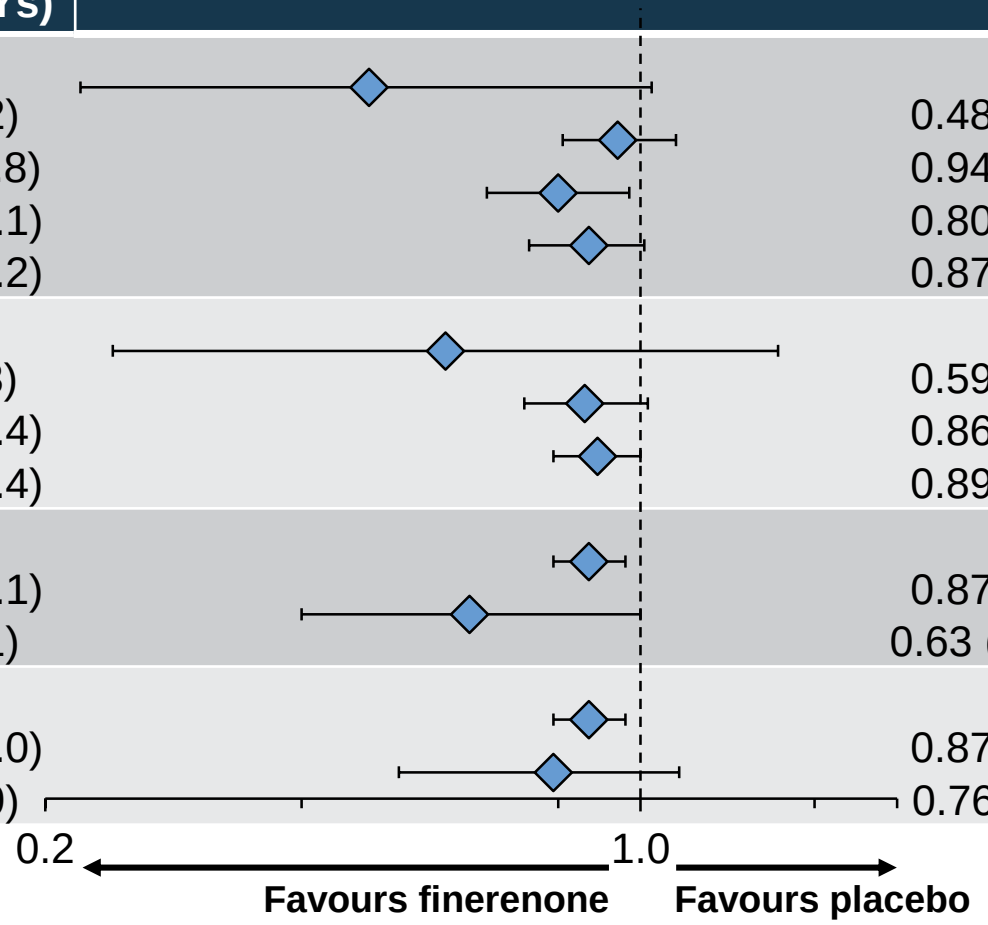
The CV benefits of finerenone were primarily driven by reduction in HHF, and also CV death

Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	*p*-value
Composite CV outcome	825 (12.7)	939 (14.4)	0.86 (0.76–0.95)	0.0018
HHF	256 (3.9)	325 (5.0)	0.78 (0.66–0.92)	0.0030
CV death	322 (4.9)	364 (5.6)	0.88 (0.76–1.02)	0.092
Non-fatal MI	173 (2.7)	189 (2.8)	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	198 (3.0)	0.99 (0.82–1.21)	0.95



The CV benefits of finerenone were consistent regardless of baseline eGFR or UACR, and use of SGLT-2is or GLP-1RAs

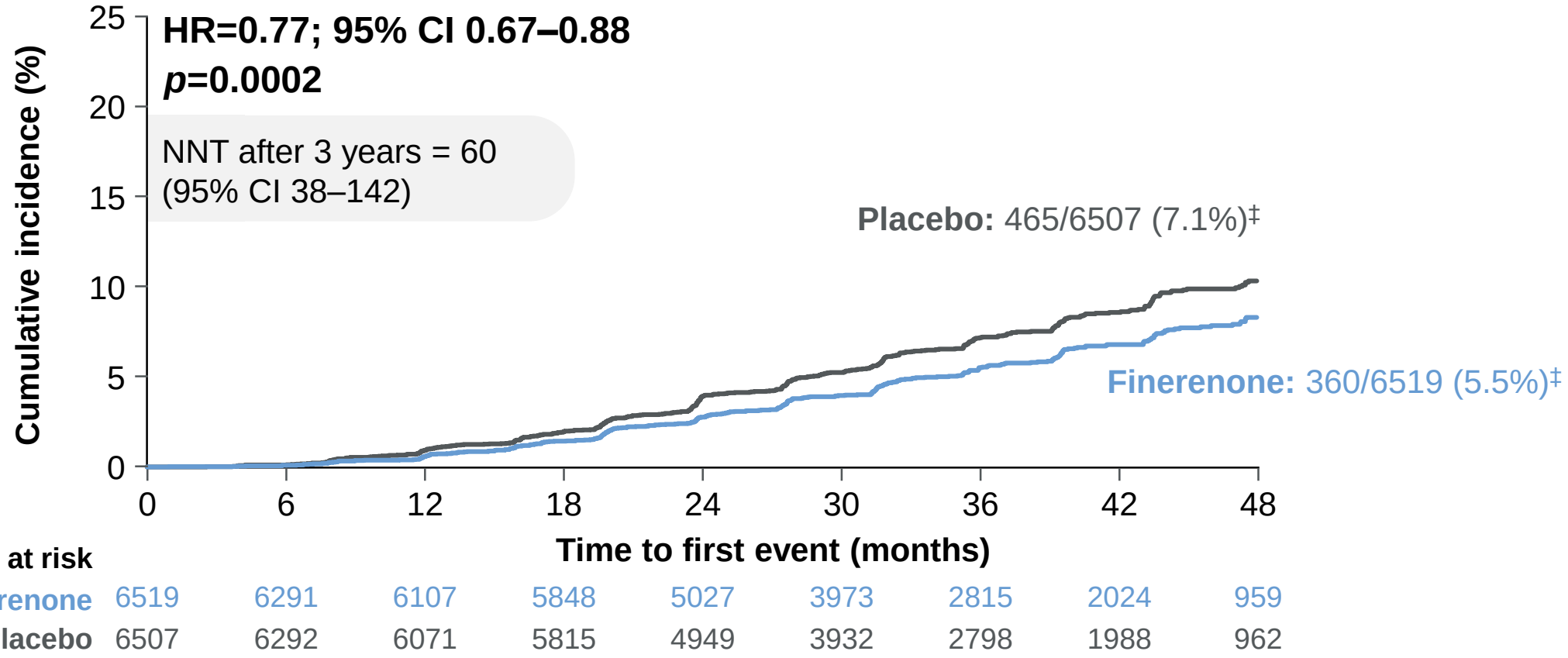
Category	Finerenone (n=6519)	Placebo (n=6507)	HR (95% CI)	$p_{interaction}$
	n/N (n/100PYs)	n/N (n/100PYs)		
Baseline eGFR, ml/min/1.73 m²				0.14
<25	11/81 (5.2)	23/81 (12.2)	0.48 (0.22–1.03)	
25–<45	321/2117 (5.7)	331/2115 (5.8)	0.94 (0.81–1.10)	
45–<60	197/1717 (4.0)	247/1717 (5.1)	0.80 (0.66–0.97)	
≥60	295/2603 (3.6)	337/2592 (4.2)	0.87 (0.74–1.01)	
Baseline UACR, mg/g				0.41
<30	10/120 (2.4)	15/110 (4.3)	0.59 (0.24–1.45)	
30–<300	260/1076 (3.8)	292/2023 (4.4)	0.86 (0.73–1.02)	
≥300	554/4321 (4.7)	631/4371 (5.4)	0.89 (0.79–1.00)	
Baseline SGLT-2i				0.41
No	786/6081 (4.4)	887/6068 (5.1)	0.87 (0.79–0.96)	
Yes	39/438 (3.0)	52/439 (4.1)	0.63 (0.40–<1.00*)	
Baseline GLP-1RA				0.63
No	767/6022 (4.4)	875/6060 (5.0)	0.87 (0.79–0.96)	
Yes	58/497 (3.8)	64/447 (4.9)	0.76 (0.52–1.11)	



*Upper CI=0.996
PY, patient-year; SGLT-2i

Finerenone significantly reduced the risk of the ≥57% eGFR kidney composite outcome by 23%

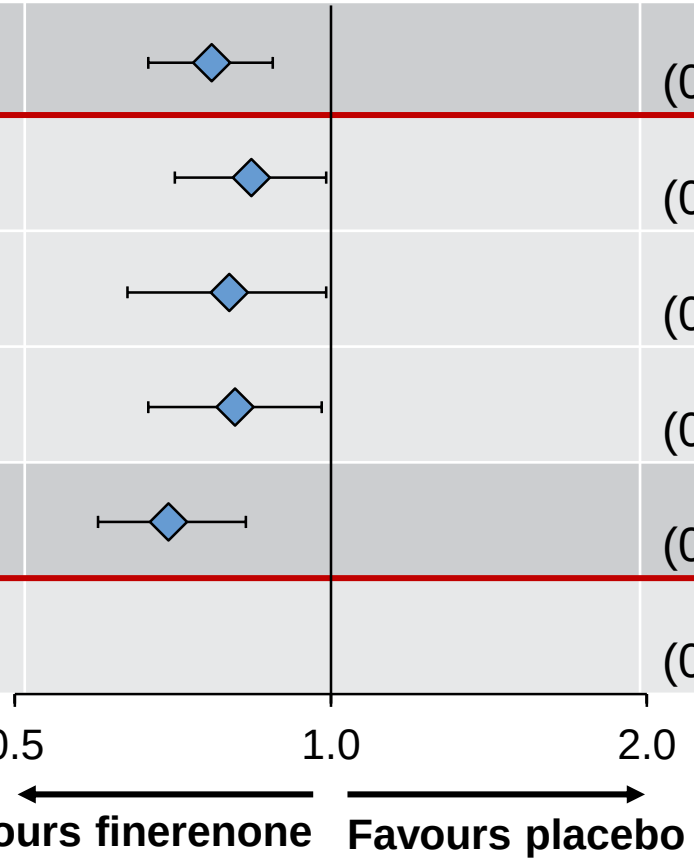
Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or renal death#



*ESKD or an eGFR <15 ml/min/1.73 m^2; #events were classified as renal death if: (1) the patient died; (2) kidney replacement therapy 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

Finerenone significantly reduced the incidences of all components of the kidney composite outcome (except renal death*)

Outcome	Finerenone (n=6519)	Placebo (n=6507)	HR (95% CI)	*p*-value
	n (%)	n (%)		
eGFR 57% composite kidney outcome	360 (5.5)	465 (7.1)	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESKD[#]	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040‡
eGFR <15 ml/min/1.73 m^2¶	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026‡
≥57% decrease in eGFR from baseline¶	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	–



≥57% decrease in eGFR is equivalent to doubling of serum creatinine

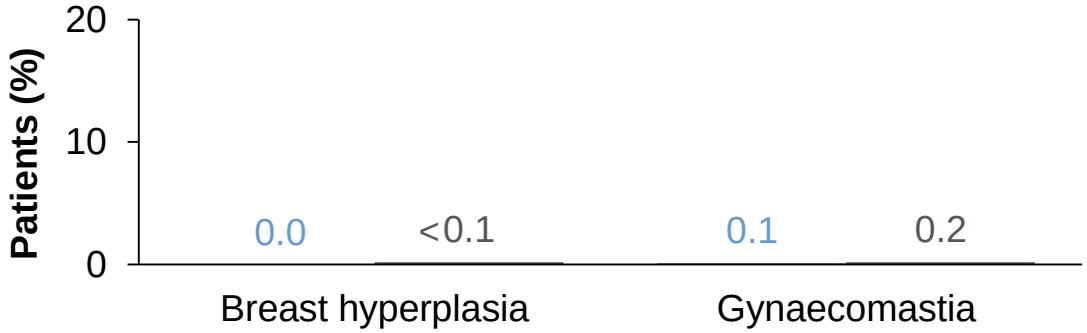
*Only 6 patients experienced renal death; [#]initiation of chronic dialysis for ≥90 days or kidney transplant; ‡analysis for *p*-values not prespecified; ¶confirmed by two eGFR measurements ≥4 weeks apart

Finerenone showed modest effects on SBP and no sexual side effects. Hyperkalemia was increased but clinical impact was low

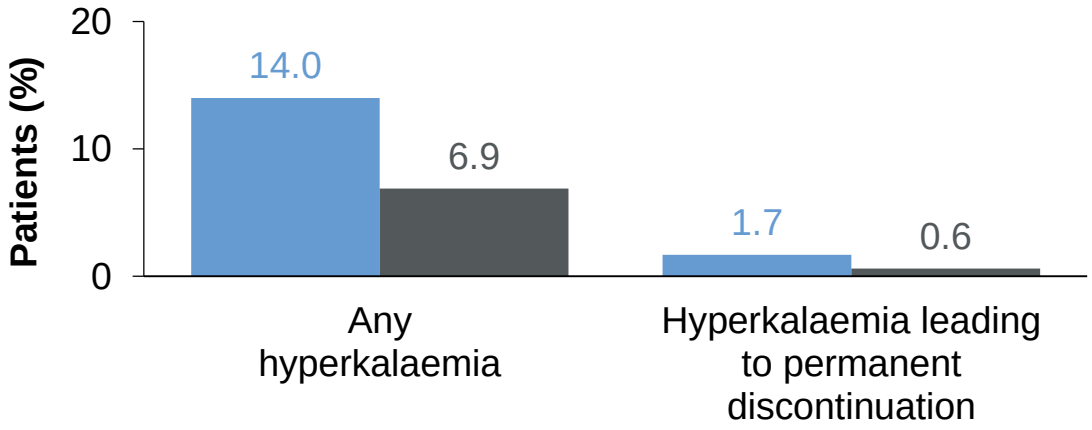
Modest effect on systolic blood pressure

Placebo-corrected change in mean SBP of **-3.7 mmHg** at 4 months

No sexual side-effects



Increased hyperkalaemia with minimal impact



Finerenone (n=6510)
Placebo (n=6489)

FIDELITY summary and conclusions

Finerenone is an effective treatment option for CV and kidney protection in patients with mild-to-severe CKD and T2D

UACR monitoring in patients with T2D is important for the identification of patients who can benefit from treatment with finerenone, independent of eGFR

FIDELIO-DKD[1] and FIGARO-DKD[2]

The increase in hyperkalaemia with finerenone was manageable, and routine potassium monitoring minimised its clinical impact

1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, presented at ESC congress 2021

Thank you

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

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

Independent data monitoring committee
Murray Epstein; Aldo Maggioni; Glenn Chertow; Gerald DiBona; Tim Friede; Jose Lopez-Sendon; Jean Rouleau

Clinical event committee
Rajiv Agarwal; Stefan Anker; Phyllis August; Andrew Coats; Hans Diener; Wolfram Döhner; Barry Greenberg; Stephan von Haehling; James Januzzi; Alan Jardine; Carlos Kase; Sankar Navaneethan; Lauren Phillips; Piotr Ponikowski; Pantelis Sarafidis; Titte Srinivas; Turgut Tatlisumak; John Teerlink.

National lead investigators
Augusto Vallejos; Richard MacIsaac; Guntram Schernthaner; Pieter Gillard; Maria Eugenia F. Canziani; Theodora Temelkova-Kurktschiev; Ellen Burgess and Sheldon Tobe; Fernando González; Zhi-Hong Liu; Andrés Ángelo Cadena Bonfanti and Carlos Francisco Jaramillo; Martin Prazny; Peter Rossing; Jorma Strand; Michel Marre; Roland Schmieder and Christoph Wanner; Pantelis A. Sarafidis; Juliana Chan; László Rosivall; Joseph Eustace; Ehud Grossman and Yoram Yagil; Giuseppe Remuzzi; Daisuke Koya and Takashi Wada; Luis Alejandro Nevarez Ruiz; Ron Gansevoort and Adriaan Kooy; Trine Finnes; Froilan De Leon; Janusz Gumprecht; Fernando Teixeira e Costa; Alexander Dreval; Anantharaman Vathsala; Aslam Amod; Sin Gon Kim and Byung Wan Lee; Julio Pascual Santos; Bengt-Olov Tengmark; Michel Burnier; Chien-Te Lee; Sukit Yamwong; Ramazan Sari; Kieran McCafferty; Borys Mankovsky; Sharon Adler, Linda Fried, Robert Toto, and Mark Williams; Tran Quang Khanh

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