Effect of finerenone on cardiovascular outcomes in patients with chronic kidney disease and type 2 diabetes: results of the FIGARO-DKD trial

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

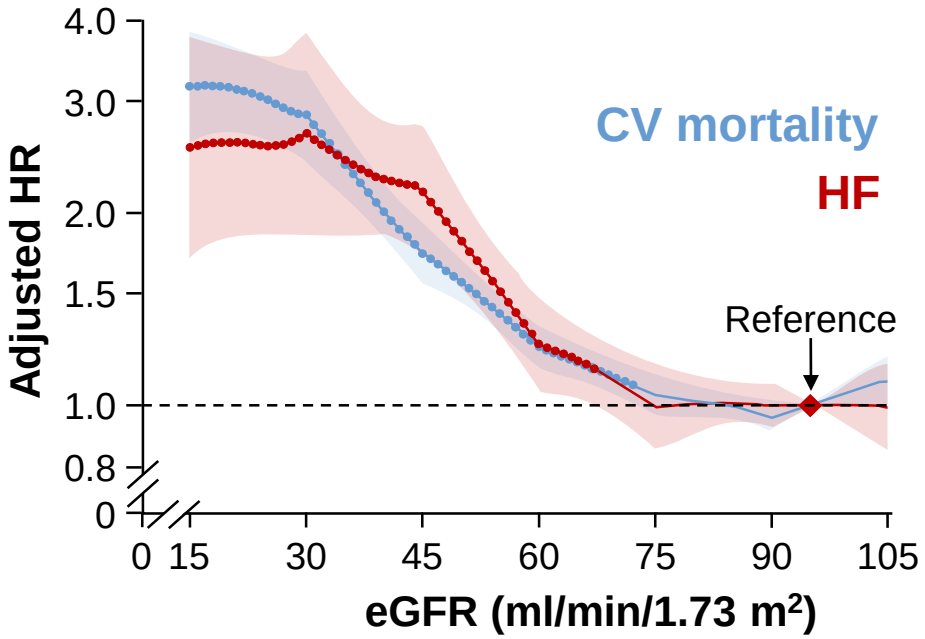
28 August 2021

FIGARO-DKD
FInerenone in reducinG cArdiovascular moRtality and mOrbidity in DKD

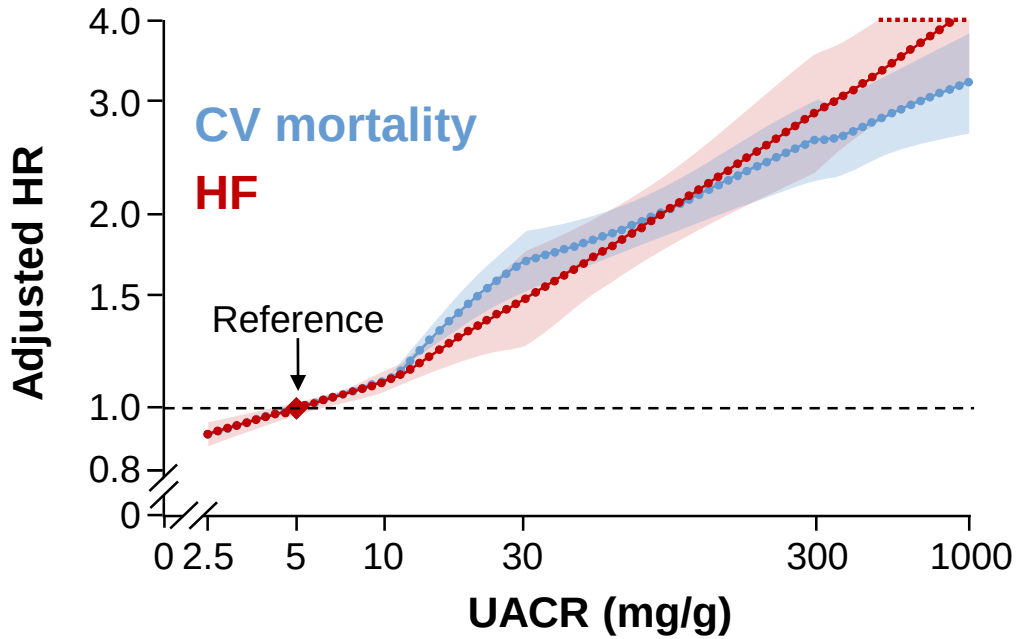
Patients with CKD and T2D have a high risk of hospitalisation for HF and CV death

- CV risk increases as eGFR falls below ~75 ml/min/1.73 m^2

eGFR (ml/min/1.73 m^2)*#,2



UACR (mg/g)*,2



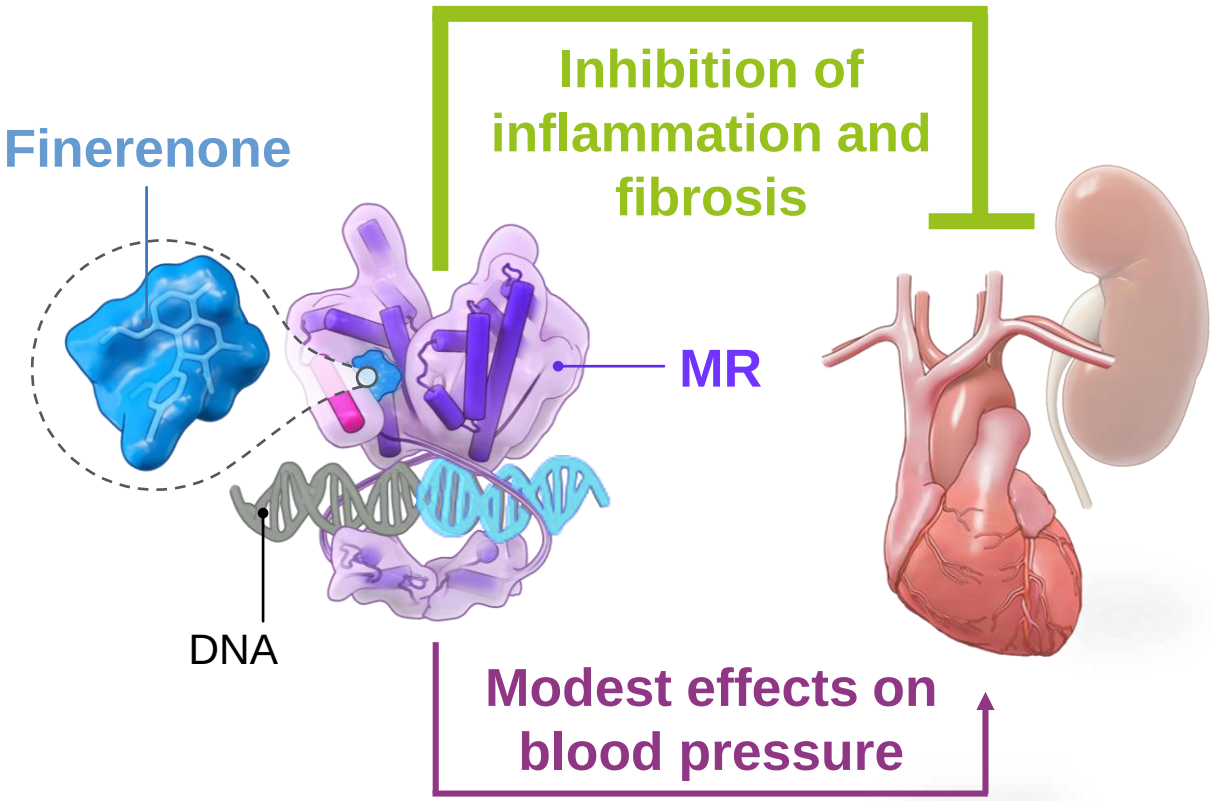
*Adjusted for age, sex, race or ethnic origin, smoking, SBP, antihypertensive drugs, diabetes, total and high-density lipoprotein cholesterol concentrations, and albuminuria (UACR or dipstick) or eGFR, as appropriate; #Figure adapted from Matsushita K, *et al.* 2015

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; SBP, systolic blood pressure; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Matsushita K, *et al. Lancet Diabetes Endocrinol* 2015;3:514–525; 2. Fox CS, *et al. Lancet* 2012;380:1662–1673

Finerenone is a selective nonsteroidal MRA that interacts with the MR in a different way to steroidal MRAs

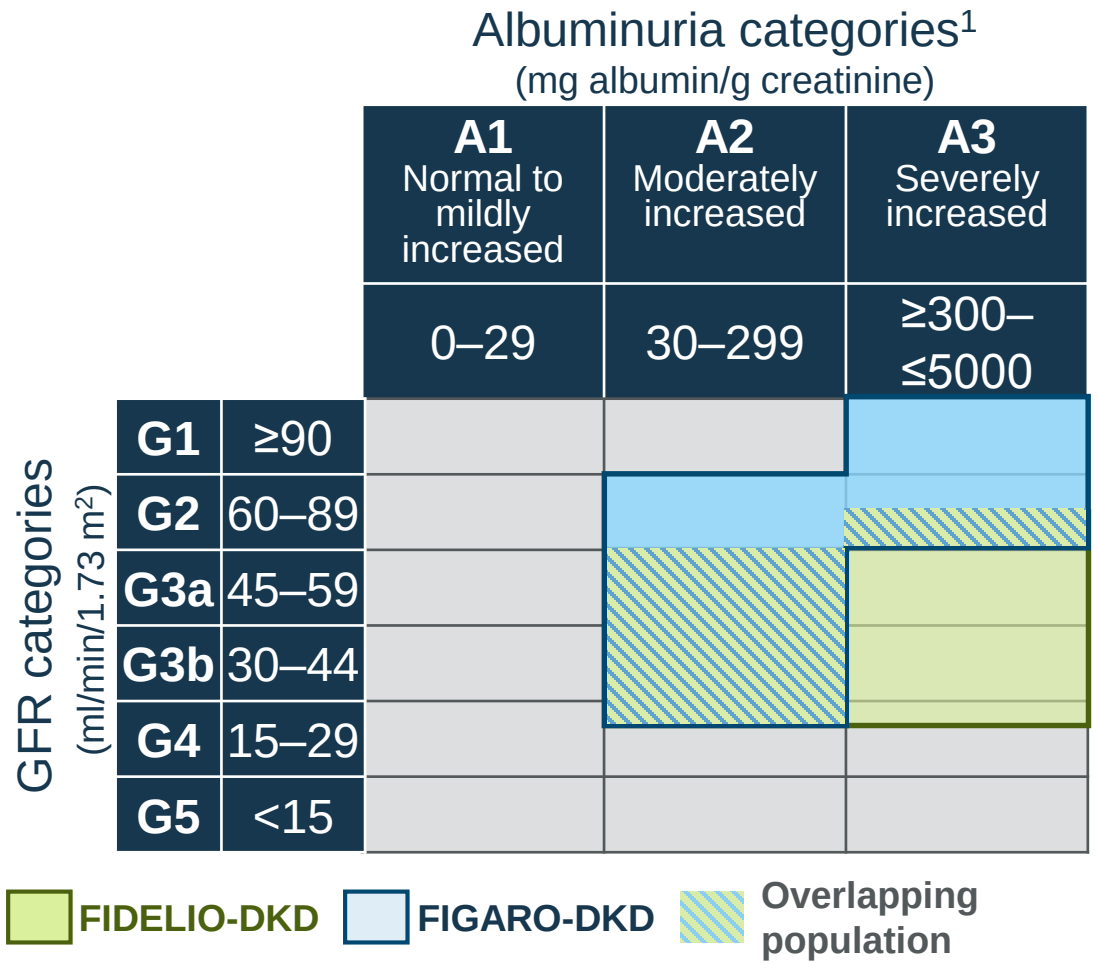
- Finerenone blocks MR overactivation, which contributes to inflammation and fibrosis, leading to kidney and CV damage[1,2]
- Finerenone has a unique binding mechanism and distribution vs steroidal MRAs, which results in high potency, selectivity and a differential effect on MR cofactor binding[1,2]
- In FIDELIO-DKD, finerenone slowed CKD progression and improved CV outcomes in patients with CKD and T2D[3]
  - The incidence of hyperkalaemia leading to permanent discontinuation was low



DNA, deoxyribonucleic acid; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist

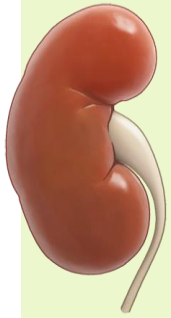
1. Agarwal R, *et al. Eur Heart J* 2021;42:152–161; 2. Agarwal R, *et al. Nephrol Dial Transplant* 2020; doi: 10.1093/ndt/gfaa294; 3. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229

FIGARO-DKD is the second phase III trial in the finerenone clinical programme



FIDELIO-DKD[2]

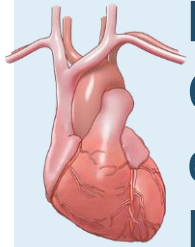
Primary outcome: Kidney composite



Finerenone significantly **slowed CKD progression** by **18%** vs placebo in patients with **advanced CKD in T2D, irrespective** of **baseline use of SGLT-2is and GLP-1RAs**

FIGARO-DKD[3]

Primary outcome: CV composite



Hypothesis: Finerenone reduces CV morbidity and mortality, and expands the evidence base to cover a broader CKD in T2D population

GLP-1RA, glucagon-like peptide-1 receptor agonist; GFR, glomerular filtration rate; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

1. Kidney Disease Improving Global Outcomes. *Kidney Int* 2013;3:1–150; 2. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229; 3. Ruilope L, *et al. Am J Nephrol* 2019;50:345–356

FIGARO-DKD study design

19,381 patients enrolled

Run-in (4–16 weeks) → Screening → **R**

7437 patients randomised

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

3.4 years' median follow-up

Key inclusion criteria

- Aged ≥18 years with T2D
- eGFR ≥25[#] ml/min/1.73 m^2
- UACR ≥30–≤5000 mg/g
- On maximum tolerated dose of RAS inhibitor for ≥4 weeks
- Serum [K$^+$] ≤4.8 mmol/l

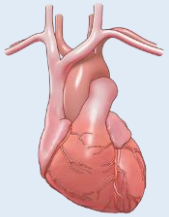
Key exclu criter

- **HFrEF with NYH Class II–I**
- Uncontroll arterial hypertens

Key 'time-to-event' outcomes

Primary CV composite

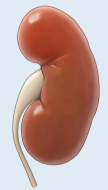
CV death, non-fatal MI, non-fatal stroke, or HHF



≥40% eGFR kidney composite

≥57% eGFR kidney composite

Kidney failure,[§] sustained **≥40% or ≥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 potassium ≤4.8 mmol/land eGFR stable; [#]either eGFR ≥25–≤90 ml/min/1.73 m^2 in patients with a UACR ≥30–<300 mg/g and eGFR ≥60 ml/min/1.73 m^2 in patients with a UACR ≥300–≤5000 mg/g; [‡]mean sitting SBP ≥170 mmHg or mean sitting DBP ≥110 mmHg at the run-in visit or mean sitting SBP ≥160 mmHg or mean sitting DBP ≥100 mmHg at the screening visit [§]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
DBP, diastolic blood pressure; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; od, once daily; R, randomisation; RAS, renin–angiotensin system

Patients had well-controlled blood pressure and HbA1c at baseline and were on optimised CV medications

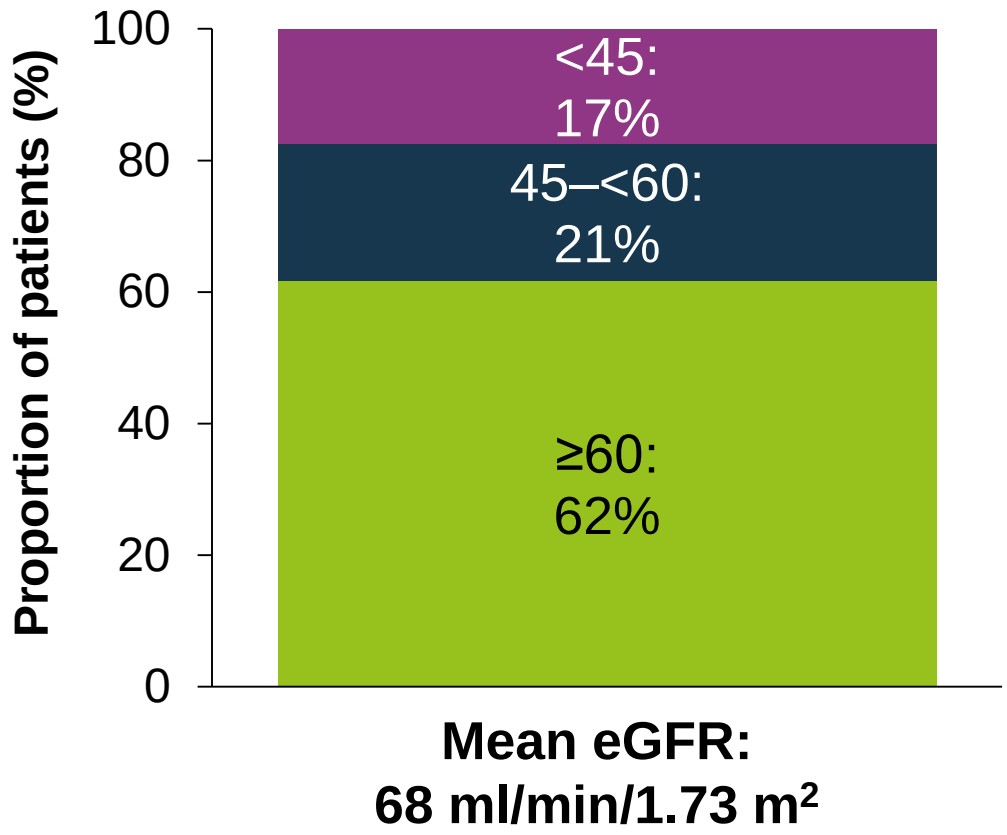
Characteristic*	Total (n=7352)
Age, years	64
Male, %	69
Duration of T2D, years	14.5
HbA1c, %	7.7
SBP/DBP, mmHg	**136/77**
History of CV disease, %	**45**
History of HF, %	**7.8**

Medications, %	Total (n=7352)
CV medications	
RASi	**7343 (100)**
Statins	**5184 (71)**
Beta-blockers	3536 (48)
Calcium antagonists	3773 (51)
Diuretics	3496 (48)
Glucose-lowering therapies	7196 (98)
Metformin	5067 (69)
Insulin	3993 (54)
GLP-1RAs	**550 (7.5)**
SGLT-2i	**618 (8.4)**

*Data expressed as means unless otherwise stated

62% of patients had albuminuric CKD with preserved kidney function (eGFR ≥60 ml/min/1.73 m²)

eGFR at baseline (ml/min/1.73 m²)*



UACR is an important indicator for kidney damage[1]

Median UACR = 308 mg/g

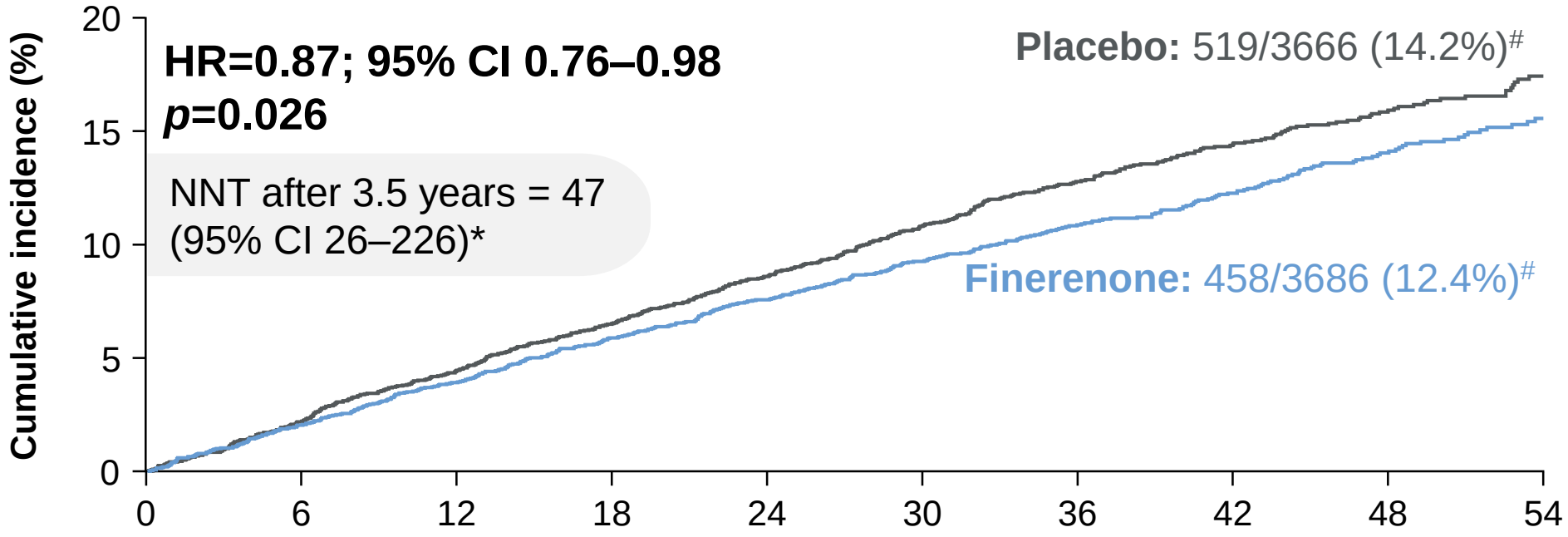
Patients with **eGFR ≥60 ml/min/1.73 m²** had **albuminuric CKD** with a **UACR ≥30 mg/g**

*Data were missing for 0.04% of patients

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

On top of optimised RAS blockade, finerenone significantly reduced the risk of the primary CV outcome by 13% vs placebo

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



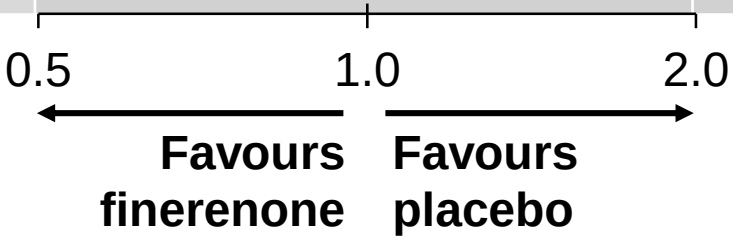
No. at risk

Finerenone	3686	3600	3517	3427	3320	2781	2184	1712	1093	598
Placebo	3666	3577	3479	3389	3267	2730	2125	1657	1076	585

*NNT calculations based on an absolute risk reduction after 3.5 years of 2.1% (95% CI 0.4–3.8); #number of patients with an event over a median of 3.4 years of follow-up
CI, confidence interval; HR, hazard ratio; NNT, number needed to treat

The CV benefit of finerenone was primarily driven by a reduction in HHF, despite exclusion of patients with symptomatic HFrEF

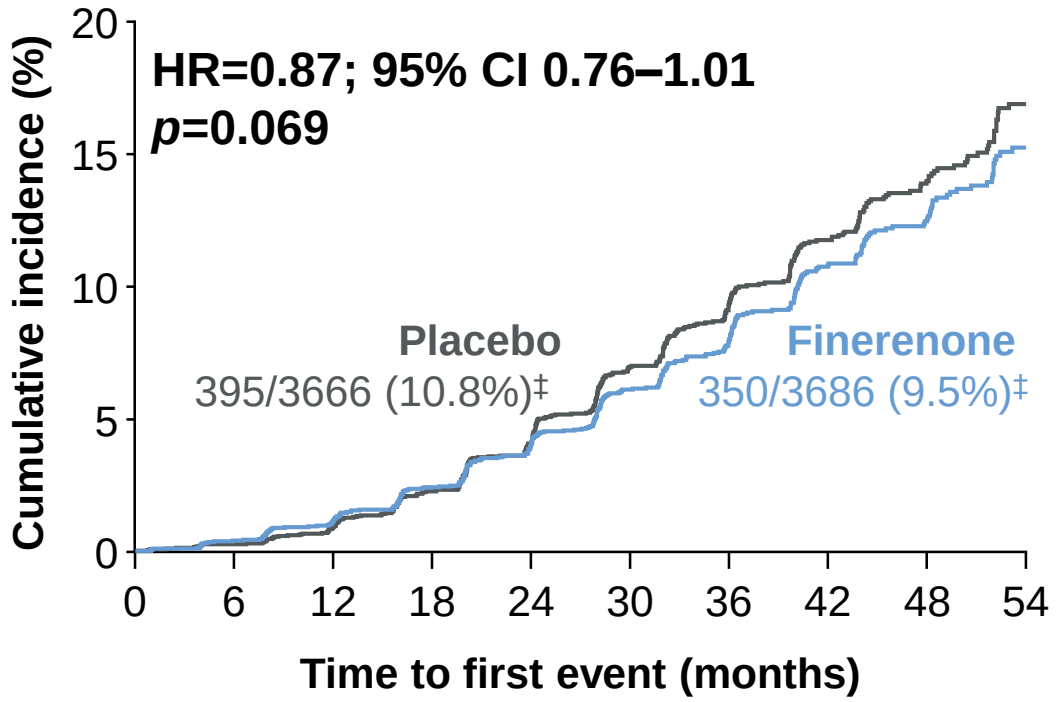
Outcome	Finerenone (n=3686) n (%)	Placebo (n=3666) n (%)	Hazard ratio (95% CI)	*p*-value*
Primary outcome#	458 (12.4)	519 (14.2)	0.87 (0.76–0.98)	**0.026**
HHF	**117 (3.2)**	**163 (4.4)**	0.71 (0.56–0.90)	**0.004**
CV death	194 (5.3)	214 (5.8)	0.90 (0.74–1.09)	0.274
Non-fatal MI	103 (2.8)	102 (2.8)	0.99 (0.76–1.31)	0.963
Non-fatal stroke	108 (2.9)	111 (3.0)	0.97 (0.74–1.26)	0.793



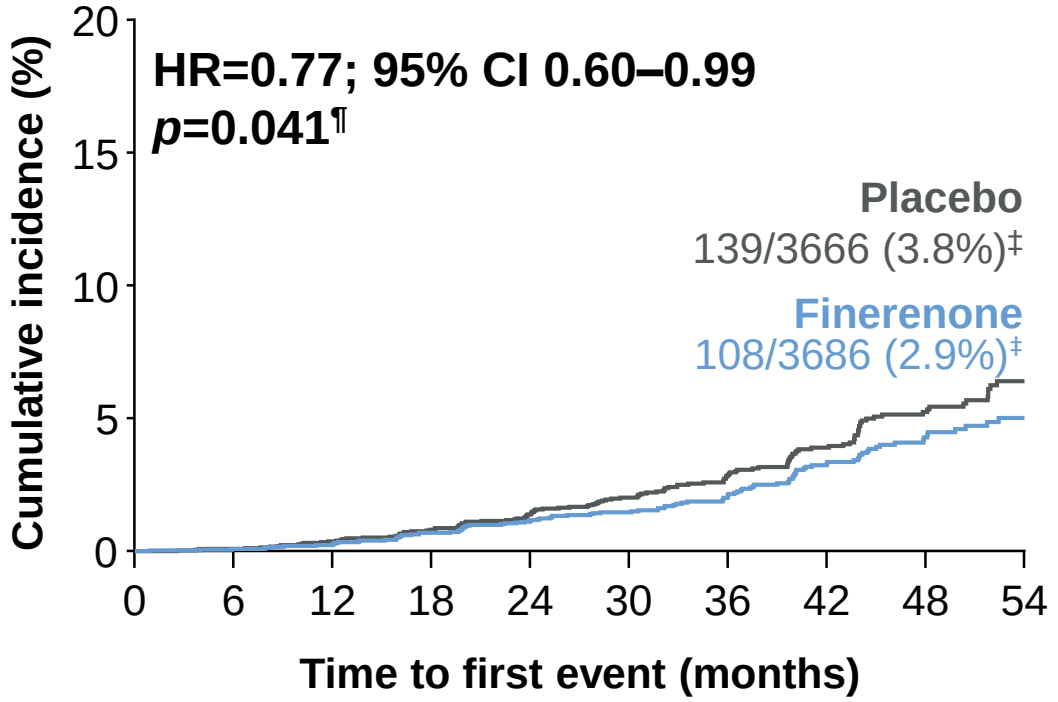
**p*-values for components are exploratory; #composite of CV death, non-fatal MI, non-fatal stroke, or HHF

Finerenone did not significantly reduce the ≥40% eGFR kidney outcome

Kidney failure,* sustained ≥40% decrease in eGFR from baseline, or renal death#



Kidney failure, sustained ≥57% decrease in eGFR from baseline,§ or renal death#



ESKD occurred in 0.9% vs 1.3% of finerenone vs placebo recipients (HR=0.64; 95% CI 0.41–0.995; *p*=0.046¶)

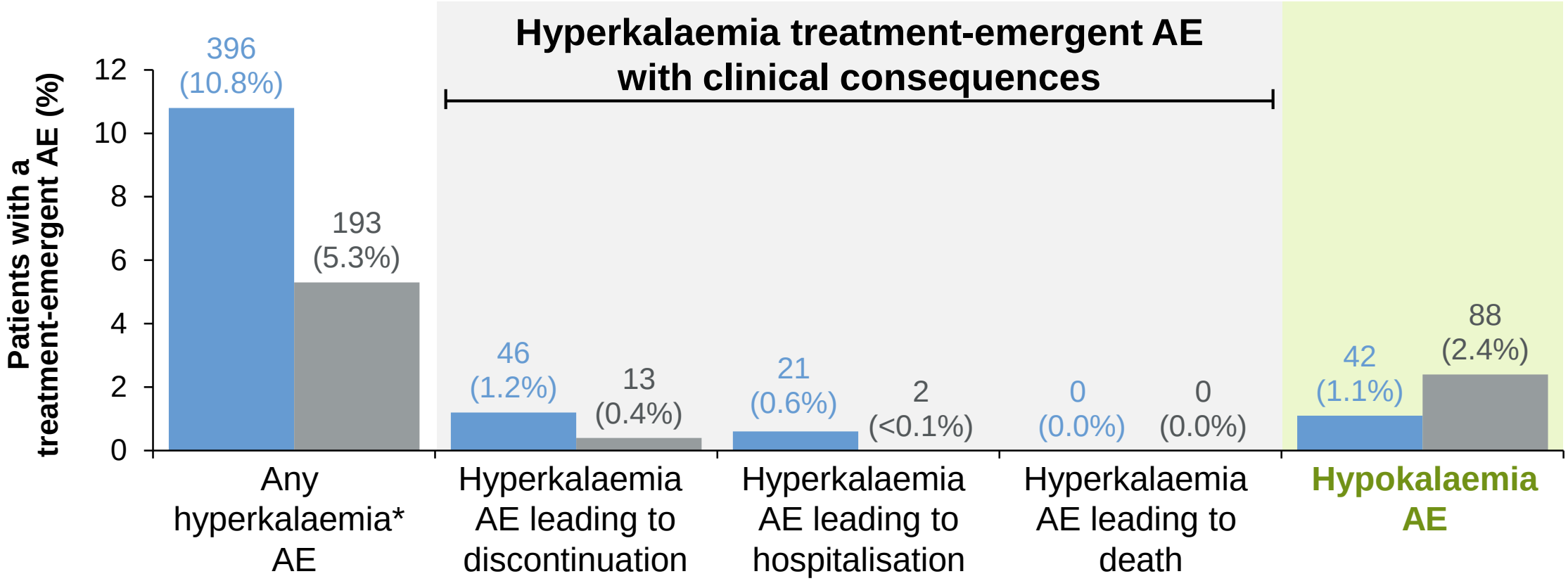
*ESKD or an eGFR <15 ml/min/1.73 m^2; #events were classified as renal death if: (1) the patient died; (2) kidney replacement therapy had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; ‡ number of patients with an event over a median of 3.4 years of follow-up

The overall incidence of treatment-emergent adverse events was similar between the finerenone and placebo groups

Treatment-emergent AE, n (%)	Finerenone (n=3683)	Placebo (n=3658)
Any AE	3134 (85.1)	3129 (85.5)
AE related to study drug	560 (15.2)	413 (11.3)
AE leading to treatment discontinuation	207 (5.6)	183 (5.0)
Any serious AE	1158 (31.4)	1215 (33.2)
Serious AE related to study drug	35 (1.0)	27 (0.7)
Serious AE leading to treatment discontinuation	70 (1.9)	76 (2.1)
AE with outcome death	79 (2.1)	100 (2.7)

AE, adverse event

Effect of finerenone on hyperkalaemia and hypokalaemia versus placebo



*Investigator-reported AEs using the MedDRA preferred terms 'hyperkalemia' and 'blood potassium increased'
MedDRA, Medical Dictionary for Regulatory Activities

Other effects of finerenone were consistent with its mechanism of action

Finerenone **is highly selective for the MR**:
there were **no** '*off-target*' **sexual side effects** associated with finerenone treatment

Hypertension occurred in **fewer patients on finerenone than placebo** (5.6% vs 8.4%)
Hypotension occurred in more patients on finerenone than **placebo** (4.2% vs 2.5%),
but **discontinuation due to hypotension was uncommon** (<0.1% vs 0.0%)

Finerenone had a modest effect on SBP

Overall LS mean difference (finerenone vs placebo):
–2.71 mmHg

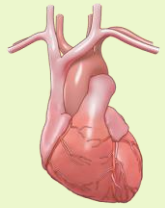
Finerenone had no effect on HbA1c

Overall LS mean difference (finerenone vs placebo):
0.03%

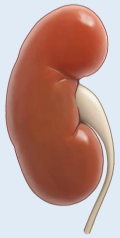
FIGARO-DKD summary

In patients with CKD stage 1–4 with moderate-to-severely elevated albuminuria (UACR ≥30 mg/g), well-controlled SBP and HbA1c, treated with optimised RAS blockade, finerenone:

- **Significantly reduced the risk of CV morbidity and mortality by 13%**
  The benefit of finerenone was driven by a reduction in HHF despite the exclusion of patients with HFrEF



- **Had a favourable trend on kidney outcomes**
  Although finerenone had a non-significant effect on the ≥40% eGFR composite outcome, exploratory findings show that finerenone significantly reduced the incidence of ESKD and the ≥57% eGFR composite outcome



- **Was associated with a similar incidence of AEs to placebo**
  Low incidence permanent discontinuation due to hyperkalaemia (1.2% vs 0.4%)

Conclusion

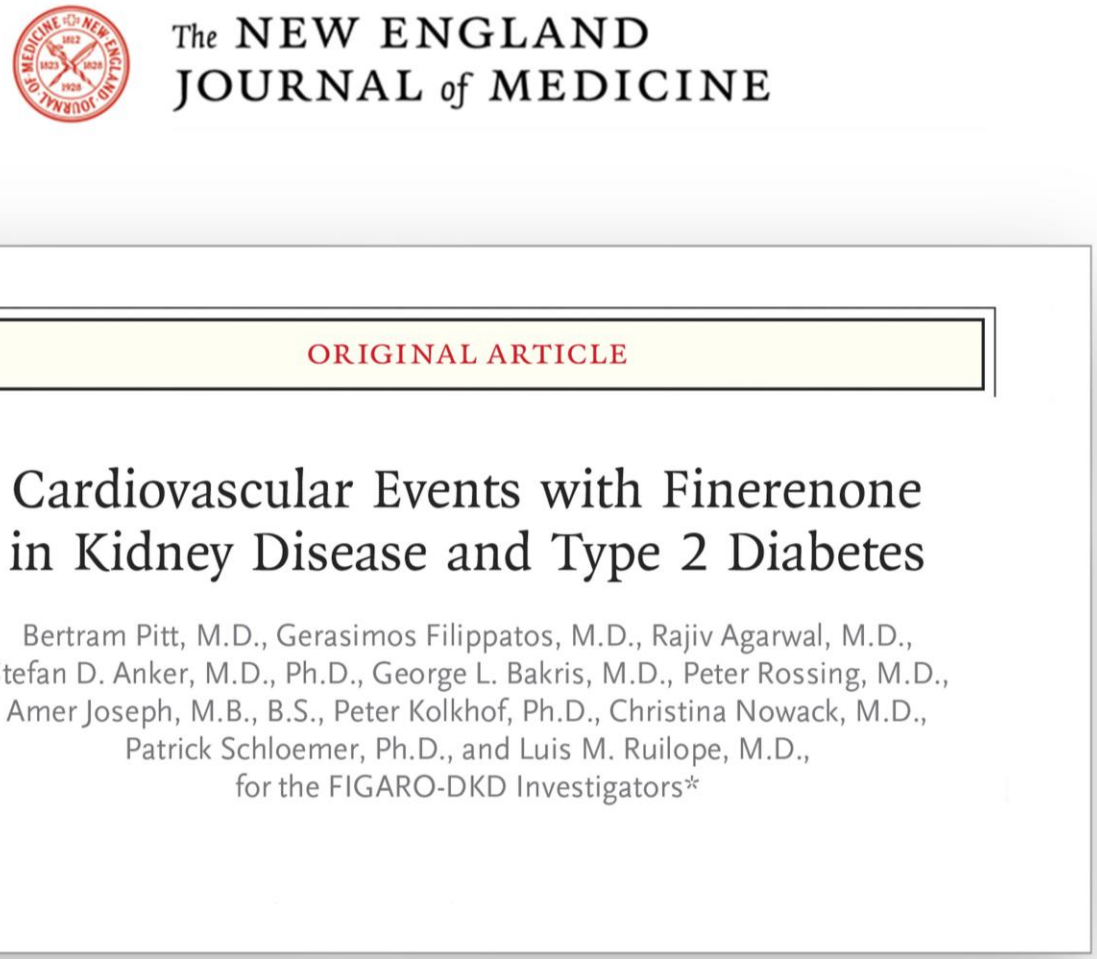
The results of FIGARO-DKD highlight:

- The need for **early CKD treatment** to **reduce the CV and HF burden** in this patient population
- The importance of **UACR monitoring** in **patients with T2D and an eGFR ≥60 ml/min/1.73 m²**

Together, the results of **FIGARO-DKD and FIDELIO-DKD[1]** suggest **finerenone provides kidney and CV benefits across the spectrum of patients with CKD and T2D**

1. Bakris GB, *et al. N Engl J Med* 2020;383:2219–2229

Results from the FIGARO-DKD trial are now available in:



Thank you

48 countries, 19,381 patients enrolled, 7437 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

FIGARO-DKD

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