Beyond CKD progression: Cardiorenal protection across the spectrum of CKD in patients with T2D

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Animated slide

4 months after initiating treatment with finerenone, Julia's UACR has reduced by 31%

Julia*

- 67-year-old female
- T2D and CKD

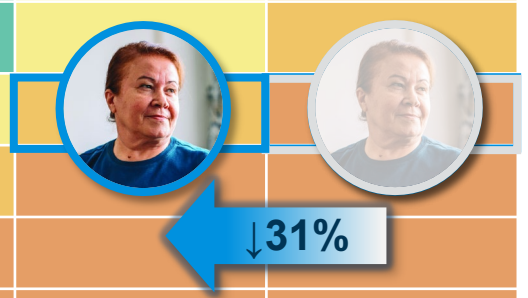
- RASi
- Finerenone#
- SGLT-2i#

- HbA1c 7.8%
- Blood pressure 135/83 mmHg

- eGFR 53 ml/min/1.73 m^2
- **UACR 262 mg/g**
  - Reduced from 380 mg/g at the start of treatment

Albuminuria categories (mg albumin/g creatinine)[1]

GFR categories (ml/min/1.73 m^2)		A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–300 mg/g (3–30 mg/mmol)	A3 Severely increased >300 mg/g (>30 mg/mmol)
G1	≥90			
G2	60–89			
G3a	45–59			
G3b	30–44			
G4	15–29			
G5	<15			



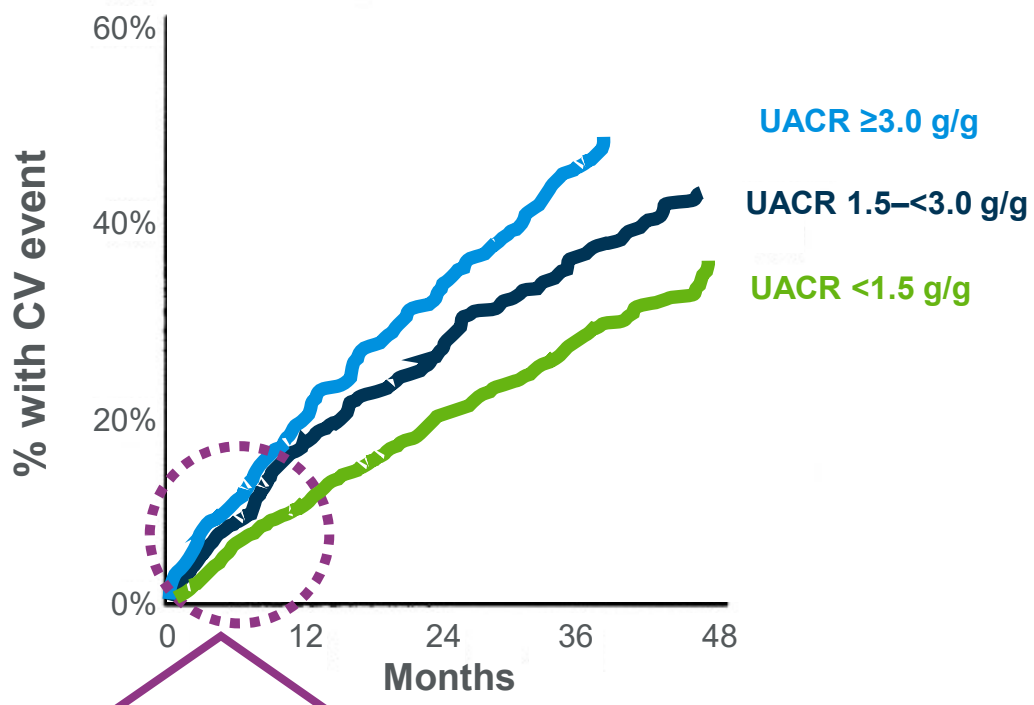
What does this mean for Julia's prognosis?

*Fictitious patient case; #on top of a maximum tolerated dose of RASi

Albuminuria is predictive of CV and kidney events

CV composite outcome

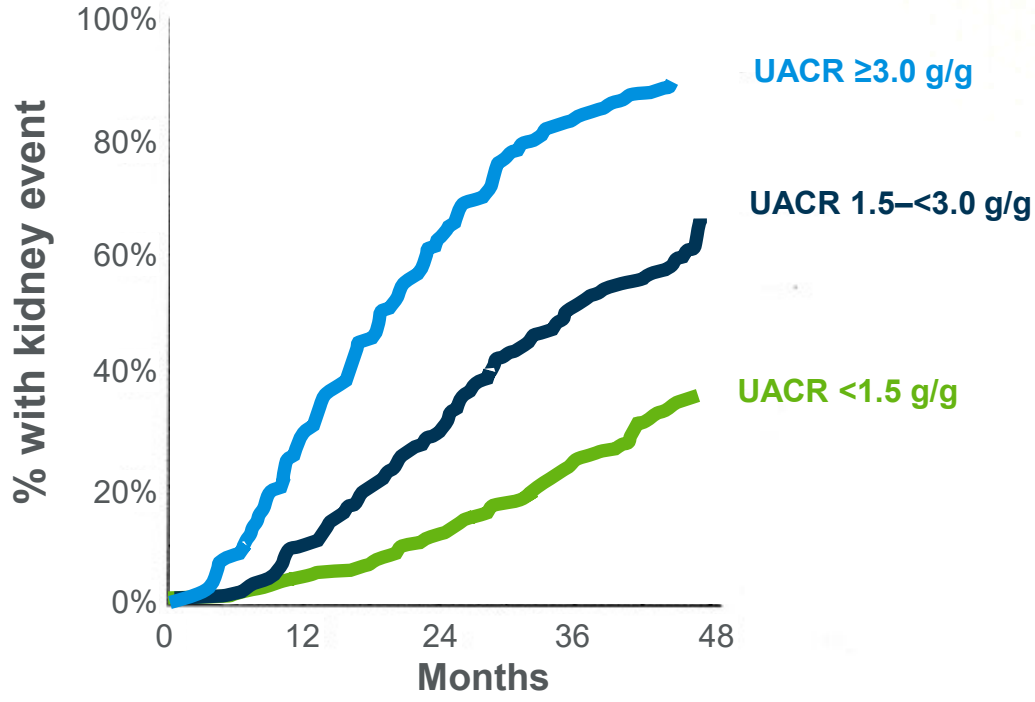
Composite of MI, stroke, first HHF or unstable angina, coronary ıth



CV events are common within 6–12 months

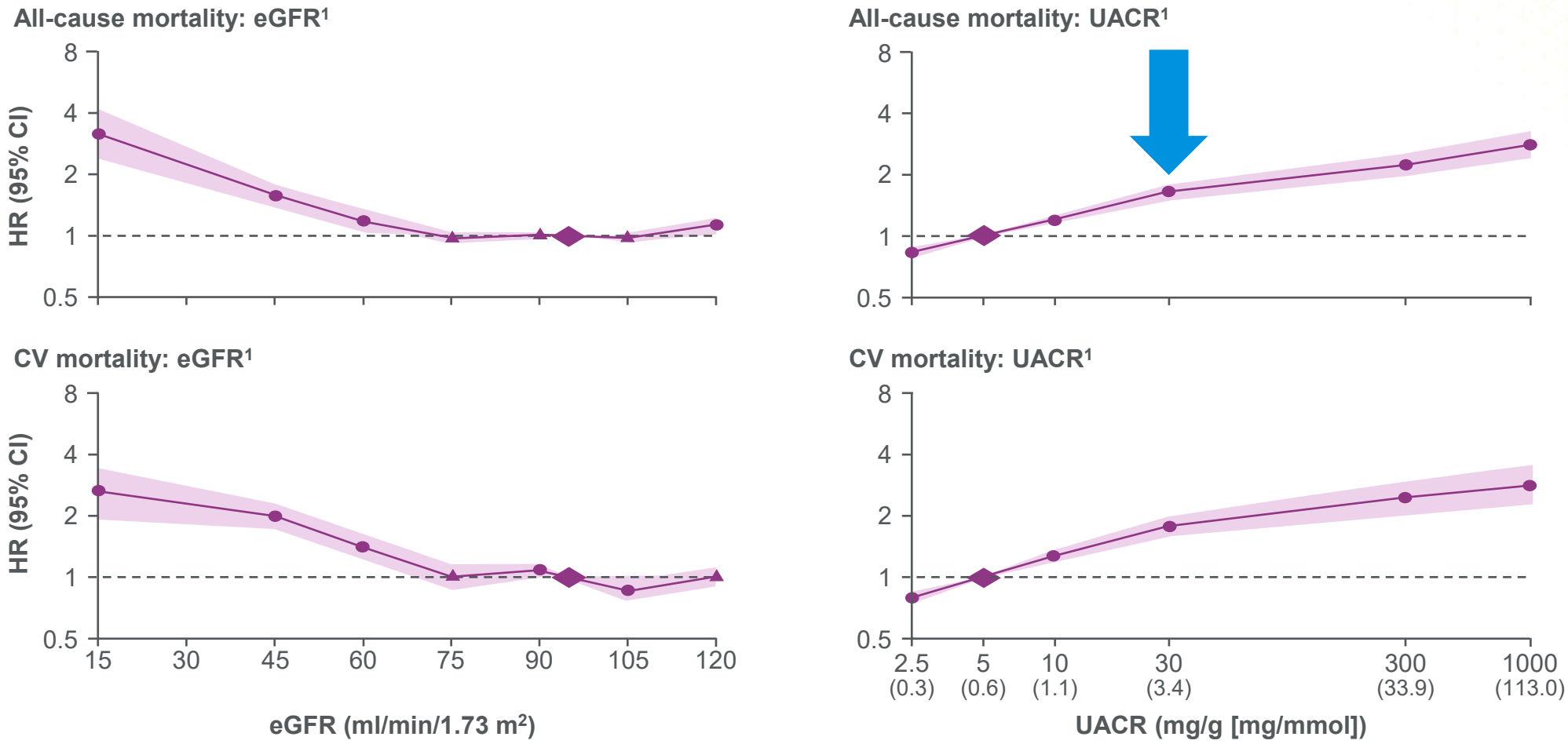
Kidney composite outcome

Composite of the time to first doubling of serum creatir



de Jong PE. *J Nephrol* 2007;20:375–380

UACR as low as ≥30 mg/g is associated with an increased risk of all-cause and CV mortality in CKD[1,2]



Blue arrow indicates UACR 30 mg/g. Diamonds represent reference points (eGFR 95 ml/min/1.73m^2 and UACR 5 mg/g)
Dots are statistically significant; triangles are not statistically significant

1. Matsushita K, *et al. Lancet* 2010;375:2073–2081; 2. Scirica BM, *et al. JAMA Cardiol* 2018;3:155–163

In addition to its importance for CKD diagnosis, UACR is now recognised by major guidelines as a treatment target to reduce the risk of CKD progression

The ADA and FDA have recommended a ≥30% reduction in UACR to slow CKD progression in people with UACR ≥300 mg/g

ADA recommendation 11.6:

'In people with CKD who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow CKD progression'[1]

B

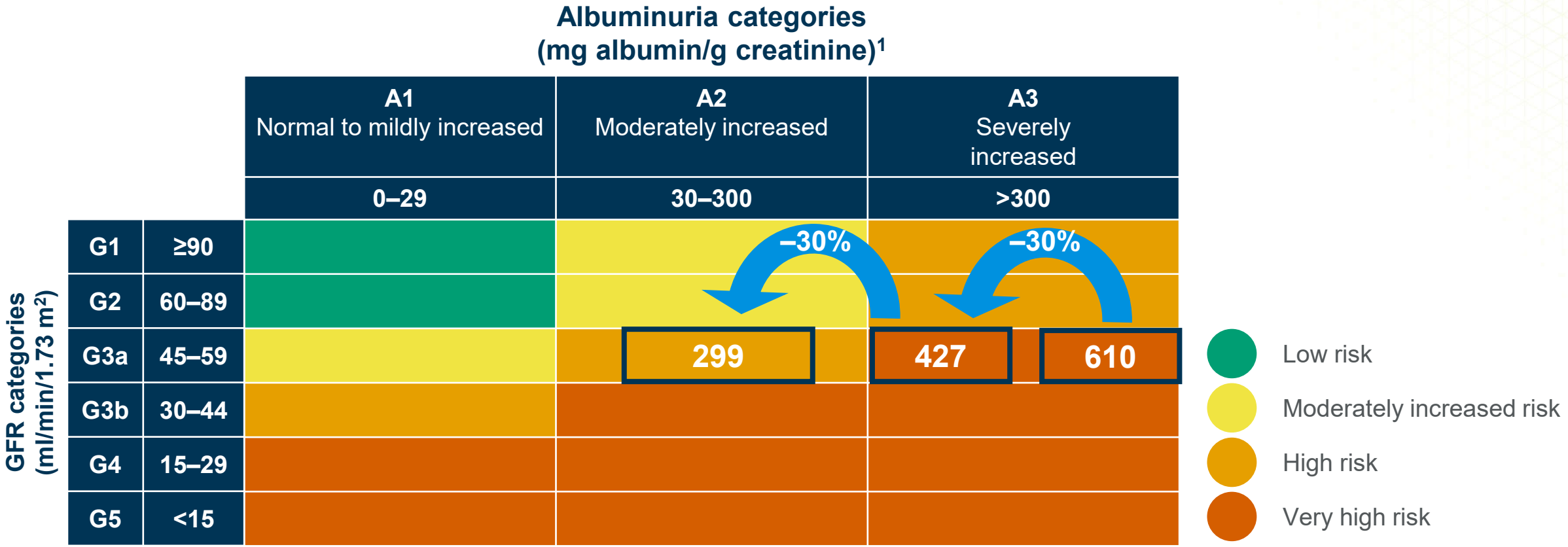
> **"An initial reduction of >30% below where it was initially measured, subsequently maintained over at least 2 years, is considered a valid surrogate for renal benefit by the Division of Cardiology and Nephrology of the FDA*,[2]"**

*This conclusion is based on the outcomes of a workshop sponsored by the National Kidney Federation, FDA and EMA, which evaluated changes in UACR and GFR as surrogate endpoints for CKD progression[2]

FDA, US Food and Drug Administration

1. American Diabetes Association. *Diabetes Care* 2023;46(Suppl 1):S191–S202; 2. Levey AS, *et al. Am J Kidney Dis* 2020;75:84–104

Each 30% reduction in UACR leads to kidney benefit, with the potential to reduce the risk of CKD progression from severe to moderate



Kidney Disease: Improving Global Outcomes. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2022;102:S1–S127

Benefits of UACR screening and early detection include reductions in CV death, dialysis and healthcare costs

Regular **UACR testing** is associated with **increased costs**

This is **offset by**:

Lower rates of **CV death**

Lower rates of **dialysis**

Additional life years gained **in total and before ESKD**

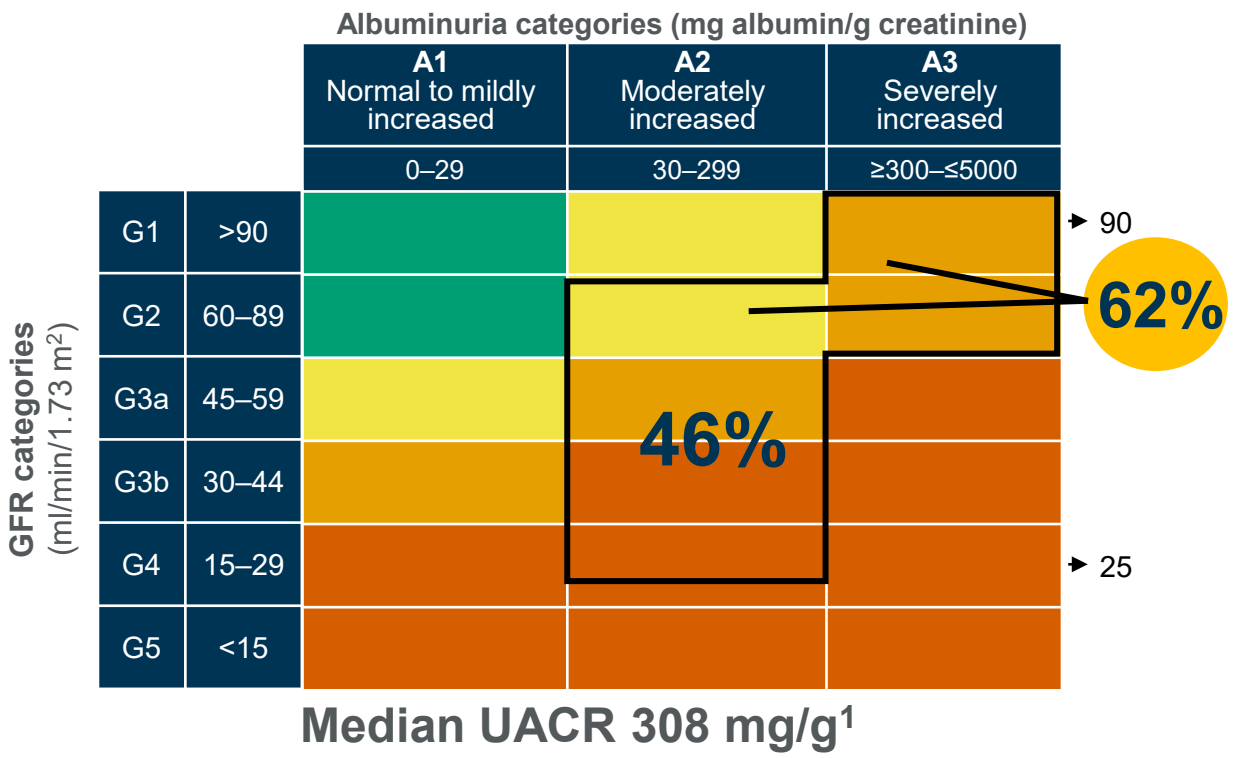
<£5750 per QALY*

Regular UACR testing in early stages of CKD is predicted to be **cost-effective**

*Based on the United Kingdom's willingness to pay threshold of £20,000 per QALY
QALY, quality-adjusted life year
Mernagh P, *et al*. *ERA* 2022; abstract MO375

In FIGARO-DKD, 46% of patients had moderately increased albuminuria and 62% had albuminuric CKD with preserved kidney function (eGFR ≥60 ml/min/1.73 m²) at baseline*,[1]

eGFR and UACR categories[2]



Outcomes

32% reduction in UACR
at month 4 vs placebo[3]

Reduced risk with finerenone# vs placebo[1] for:

- **≥40% eGFR kidney composite outcomes‡** (HR=0.87; 95% CI 0.76–1.01)
- **≥57% eGFR kidney composite outcomes‡** (HR=0.77; 95% CI 0.60–0.99)
- **ESKD** (HR=0.64; 95% CI 0.41–0.995)

Finerenone# significantly reduced the primary CV outcome§ by 13%
(HR=0.87; 95% CI 0.76–0.98; *p*=0.03)[1]

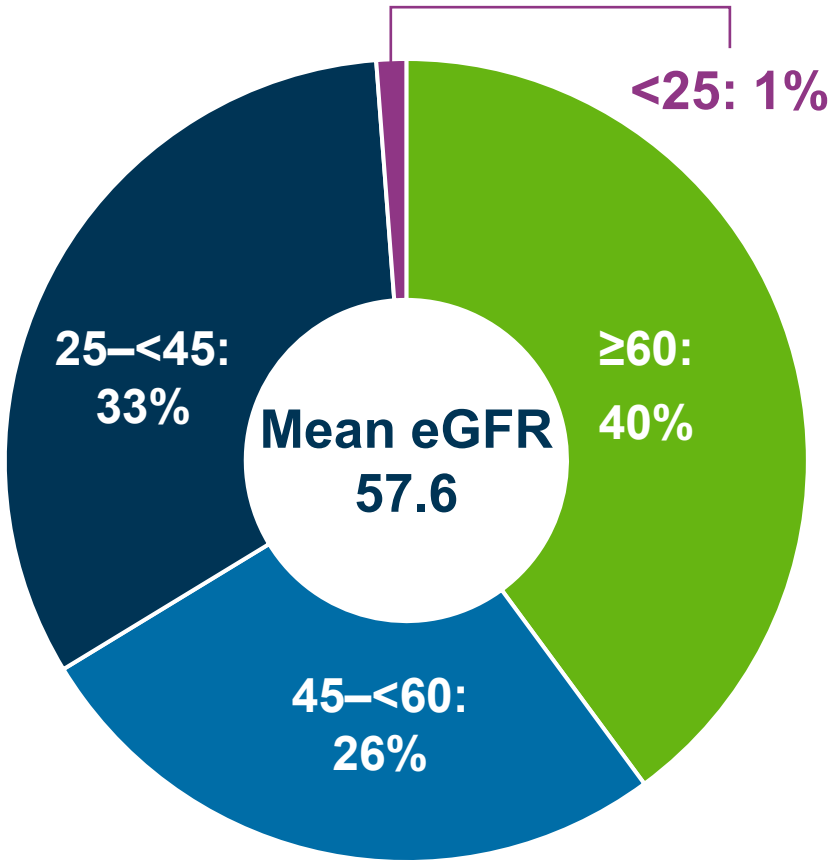
G1: high and optimal; G2: mild; G3a: mild to moderate; G3b: moderate to severe; G4: severe; G5: kidney failure
*eGFR and UACR data missing for 1 and 2 patients, respectively, at baseline; #on top of maximum tolerated RAS therapy; ‡ kidney failure (ESKD or an eGFR <15 ml/min/1.73 m²), sustained decrease in eGFR from baseline or kidney-related death. Events were classified as kidney-related 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; § time to CV death, non-fatal MI, non-fatal stroke or HHF

1.Pitt B, *et al. N Engl J Med* 2021;385:2252–2263; 2. Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int Suppl* 2013;3:1–150;
3. Ruilope LM, *et al. Nephrol Dial Transplant* 2023;38:372–383

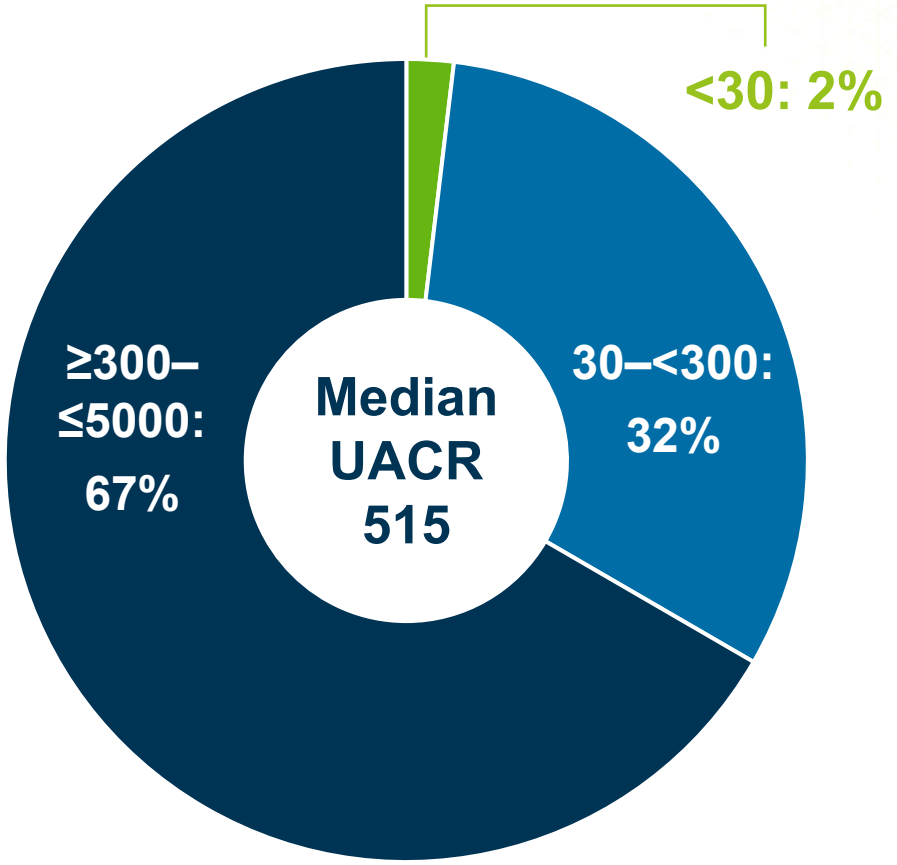
FIGARO-DKD

In FIDELITY, 40% of patients had albuminuric CKD with preserved kidney function (eGFR ≥60 ml/min/1.73 m^2)

Baseline eGFR (ml/min/1.73 m^2)*



Baseline UACR (mg/g)#



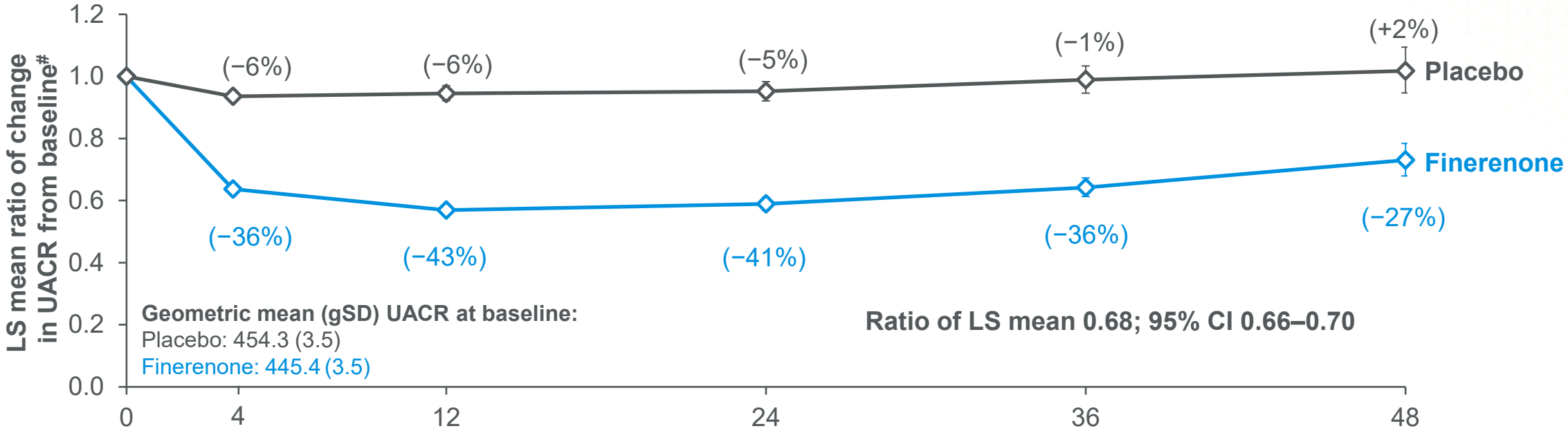
*Data were missing for 3 patients; #data were missing for 5 patients

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

FIDELITY

In FIDELITY, finerenone reduced UACR by 32% between baseline and month 4 versus placebo*

A lower mean UACR with finerenone versus placebo was maintained throughout the study



No. at risk						
Finerenone	6517	6273	5988	4867	2745	899
Placebo	6504	6239	5973	4829	2706	872

Data in parentheses are mean changes from baseline. *Full analysis set. Mixed model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CV disease history, time, treatment*time, study, study*treatment, log-transformed baseline value nested within type of albuminuria at screening and log-transformed baseline value*time as covariate. Separate unstructured covariance patterns are estimated for each treatment group; #data are LS mean ± SD

gSD, geometric standard deviation

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

FIDELITY

A meta-analysis of clinical trials suggests a 30% reduction in UACR reduces the risk of CKD progression

Association between treatment effects on change in UACR and treatment effects on composite kidney outcome* in patients with baseline UACR ≥30 mg/g (N=22,544)

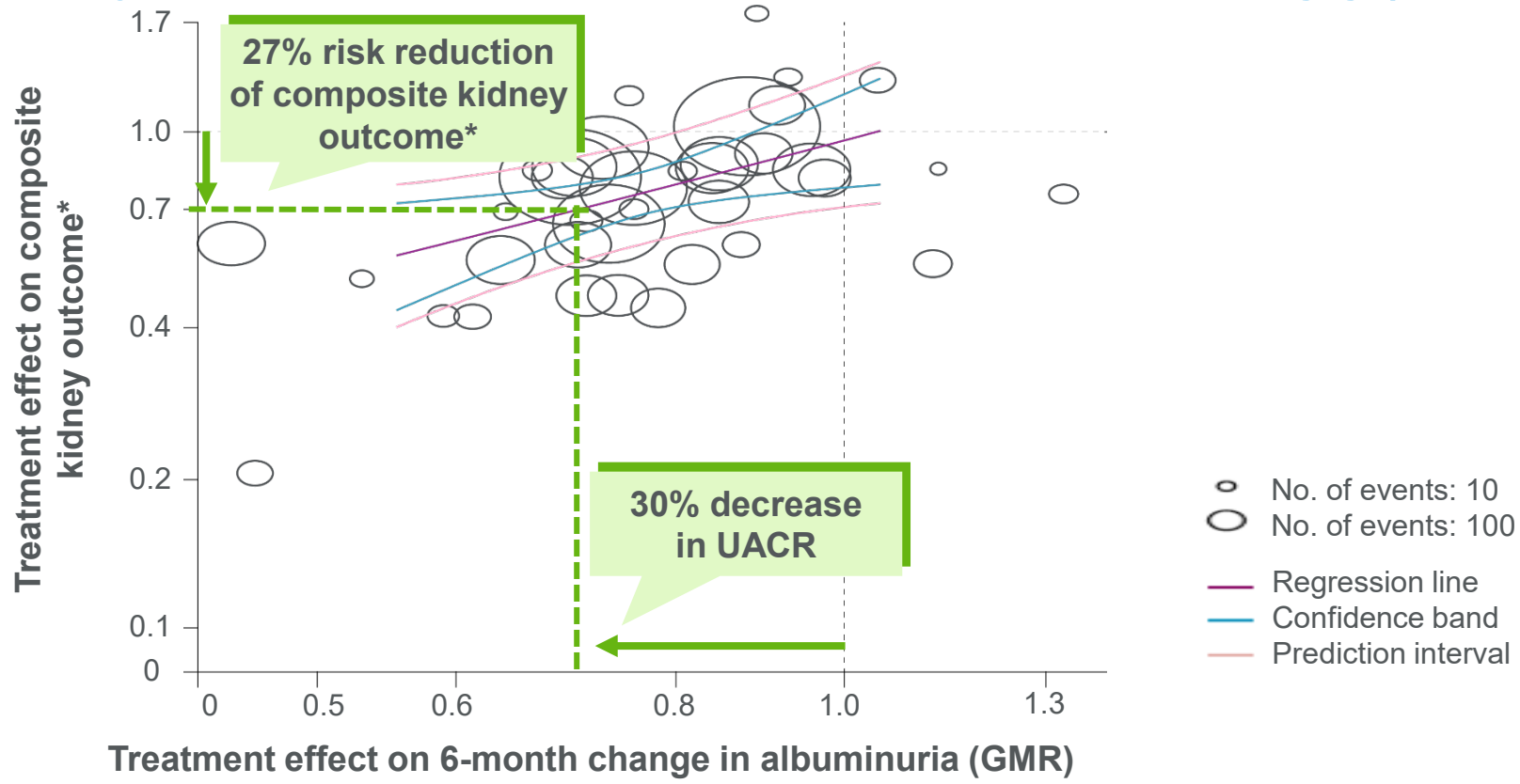


Figure adapted from: Heerspink HJL, *et al. Lancet Diabetes Endocrinol* 2019;7:128–139

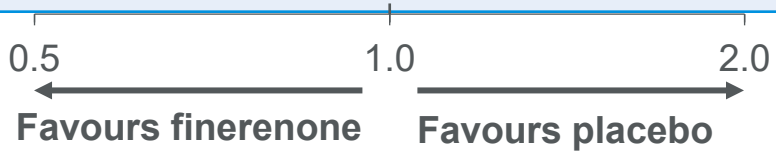
*Time to treatment of ESKD (initiation of chronic treatment with dialysis or kidney transplantation), eGFR <15 ml/min/1.73 m^2 or doubling of SCr sustained at the next visit

GMR, geometric mean ratio

Heerspink HJL, *et al. Lancet Diabetes Endocrinol* 2019;7:128–139

In a FIDELITY subanalysis, finerenone was found to reduce the risk of the ≥57% eGFR kidney composite outcome, irrespective of baseline eGFR or UACR

	Finerenone	Placebo	HR (95% CI)	$p_{interaction}$
	n/N (n per 100 PY)			
Overall	**360/6519 (1.96)**	**465/6507 (2.55)**	**0.77 (0.67–0.88)**	
Baseline eGFR (ml/min/1.73 m²)*				
25–<45	188/2117 (3.42)	225/2115 (4.14)	0.83 (0.68–1.01)	0.6244
45–<60	62/1717 (1.31)	87/1717 (1.83)	0.72 (0.52–1.00)	
≥60	90/2603 (1.14)	130/2592 (1.66)	0.70 (0.53–0.92)	
Baseline UACR (mg/g)#				
30–<300	38/2076 (0.57)	40/2023 (0.62)	0.94 (0.60–1.47)	0.6673
≥300	321/4321 (2.85)	424/4371 (3.71)	0.75 (0.65–0.87)	



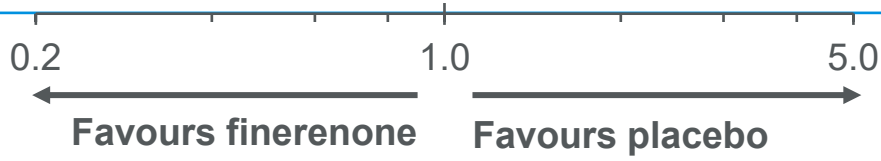
*p-value for interaction also includes data from eGFR <25 ml/min/1.73 m² categories (HR=0.83; 95% CI 0.42–1.61)
#p-value for interaction also includes data from UACR <30 mg/g categories (HR=0.78; 95% CI 0.05–12.5)

Bakris G, *et al. Kidney Int* 2023;103:196–206

FIDELITY

Similarly, the effects of finerenone on the composite CV outcome were consistent regardless of baseline eGFR or UACR

	Finerenone (n=6519)	Placebo (n=6507)	HR (95% CI)	$p_{interaction}$
	n/N (n/100 PY)			
Baseline eGFR (ml/min/1.73 m²)*				
25–<45	321/2117 (5.7)	331/2115 (5.8)	0.94 (0.81–1.10)	0.14
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				
30–<300	260/2076 (3.8)	292/2023 (4.4)	0.86 (0.73–1.02)	0.41
≥300	554/4321 (4.7)	631/4371 (5.4)	0.89 (0.79–<1.00)	



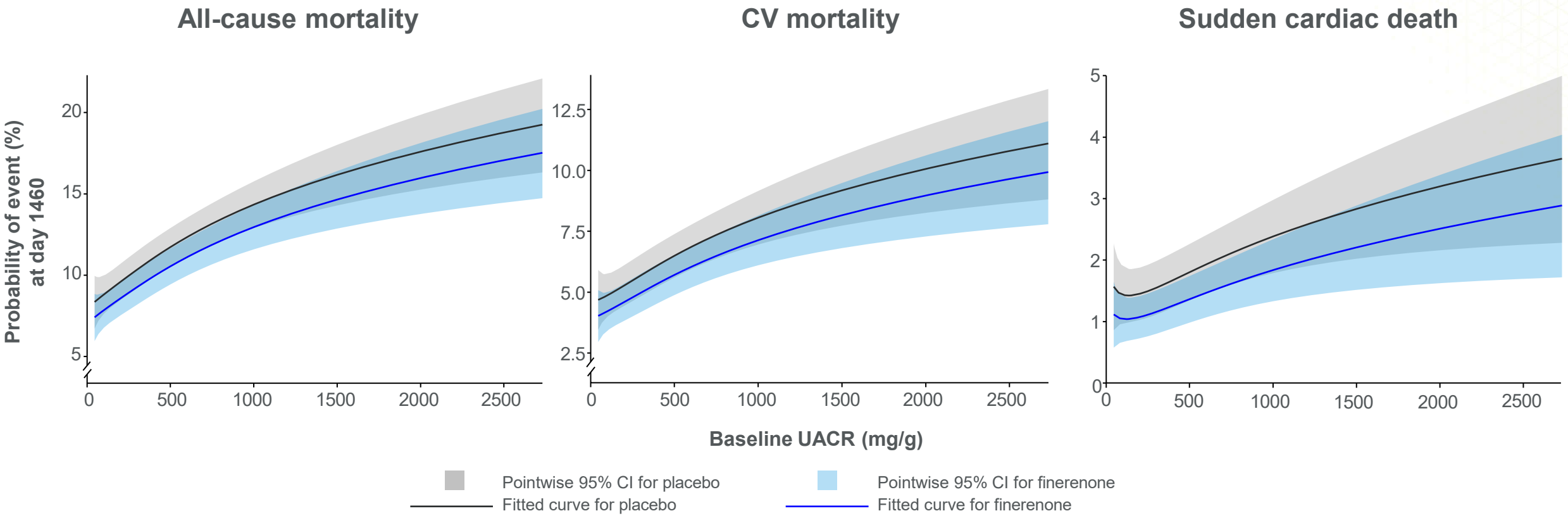
*p-value for interaction also includes data from eGFR <25 ml/min/1.73 m² categories (HR=0.48; 95% CI 0.22–1.03)
#p-value for interaction also includes data from UACR <30 mg/g categories (HR=0.59; 95% CI 0.24–1.45)

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

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

Filippatos G, *et al. Eur Heart J Cardiovasc Pharmacother*. 2023;9:183–191

FIDELITY

Summary

UACR is an important **marker of kidney damage**; in patients with CKD, **increasing UACR** is **associated with** an **increased risk** of CV and kidney outcomes[1,2]

Early detection and treatment of CKD **improve outcomes** for patients and **reduce healthcare costs**[3]

Nephrologists play a key role in advocating for **early UACR screening**!

Finerenone reduces UACR by >30% and has cardiorenal benefits in patients across the spectrum of CKD severity[4–6]

1. Fox CS, *et al. Lancet* 2013;381:532–533; 2. Matsushita K, *et al. Lancet* 2013;375:2073–2081; 3. Mernagh P, *et al. ERA* 2022; abstract MO375;
4. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 5. Ruilope LM, *et al. Nephrol Dial Transplant* 2023;38:372–383; 6. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263