Association of urine albumin-to-creatinine ratio and its early change with cardiorenal outcomes in FIDELIO-DKD: A mediation analysis

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RATIONALE AND OBJECTIVE

- In the phase III FIDELIO-DKD trial, finerenone showed kidney and CV benefits in patients with CKD and T2D[1]
- This analysis investigates the association of UACR and its early change with the magnitude of cardiorenal protection with finerenone in patients with CKD in T2D

KEY FINDINGS

- Changes in baseline albuminuria are associated with the risk of clinically relevant cardiorenal events
- The effect of finerenone on cardiorenal risk versus placebo is observed irrespective of change in UACR from baseline to month 4

FIDELIO-DKD
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

CKD, chronic kidney disease; CV, cardiovascular; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

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

DISCLOSURES
Dr Agarwal has received the following:

Personal fees and/or non-financial support from:
Bayer Healthcare Pharmaceuticals Inc., Akebia Therapeutics, Janssen, Relypsa, Vifor Pharma, Boehringer Ingelheim, Sanofi, Eli Lilly, AstraZeneca, Fresenius, Ironwood Pharmaceuticals, Merck & Co., Lexicon, Reata, Otsuka America, Pharmaceuticals, Opko Pharmaceuticals, E. R. Squibb & Sons

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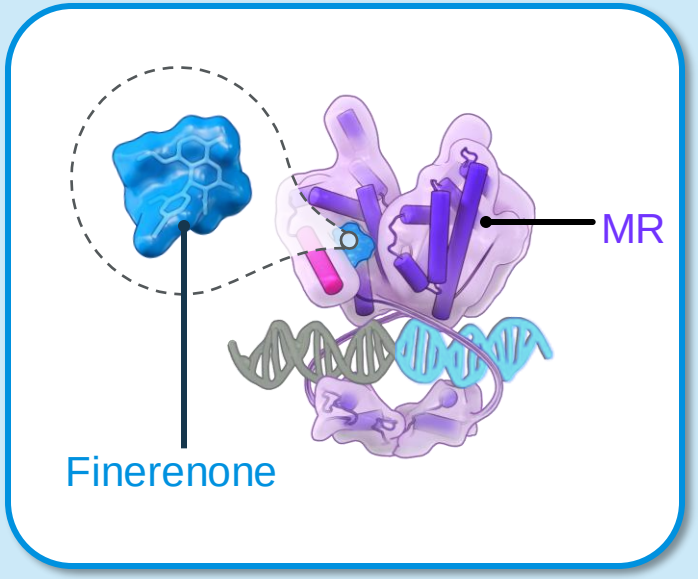
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

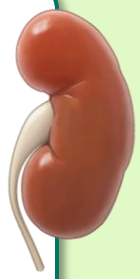
Finerenone showed cardiorenal benefits in patients with CKD and T2D in the phase III FIDELIO-DKD trial[1]

Finerenone is a **new, selective, nonsteroidal MRA** that **inhibits inflammation and fibrosis**[2]

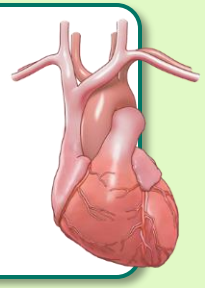


In **FIDELIO-DKD**, finerenone[1]

- **Significantly reduced** the risk of the **primary endpoint*** by **18% (NNT=29#)**
- Led to a **31% reduction in UACR** at month 4 versus placebo



- **Significantly reduced** the risk of the **CV composite endpoint‡** by **14% (NNT=42#)**



*Kidney failure (ESKD or an eGFR <15 mL/min/1.73 m^2), sustained ≥40% decrease in eGFR from baseline, or renal death; #NNT to prevent one event based on absolute risk reductions at 3 years; ‡time to cardiovascular death, nonfatal MI, nonfatal stroke, or HHF

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; MI, myocardial infarction; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat

1. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 2. Agarwal R, *et al. Eur Heart J* 2021;42:152–161

FIDELIO-DKD
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This analysis evaluated the association between UACR change and cardiorenal protection in the FIDELIO-DKD trial population

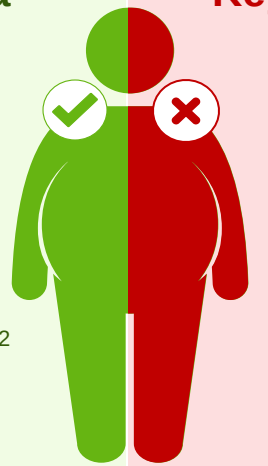
5674 patients randomized

R 1:1

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

Key inclusion criteria

- Aged ≥18 years with T2D
- On maximum tolerated dose of ACEi or ARB for ≥4 weeks
- **UACR ≥30–≤5000** mg/g and eGFR 25–75 mL/min/1.73 m^2
- Serum [K^+] ≤4.8 mmol/L at screening



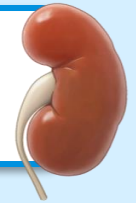
Key exclusion criteria

- HFrEF with NYHA Class II–IV
- Uncontrolled arterial hypertension#
- HbA1c >12%
- Other kidney disease‡

Key endpoints

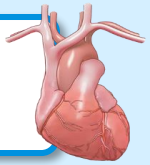
Kidney composite

Time to kidney failure, sustained ≥40% decrease in eGFR ≥4 weeks from baseline, or renal death



CV composite

Time to CV death, nonfatal MI, nonfatal stroke, or HHF



Objective: To investigate the association of UACR and its early change with the magnitude of cardiorenal protection in patients with CKD in T2D

*10 mg if screening eGFR <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/L and eGFR stable; a decrease in the dose from 20 to 10 mg od was allowed anytime after the initiation of finerenone or placebo; #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; ‡known significant nondiabetic kidney disease, including clinically relevant renal artery stenosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; [K^+], potassium concentration; NYHA, New York Heart Association; od, once daily; R, randomization; SBP, systolic blood pressure

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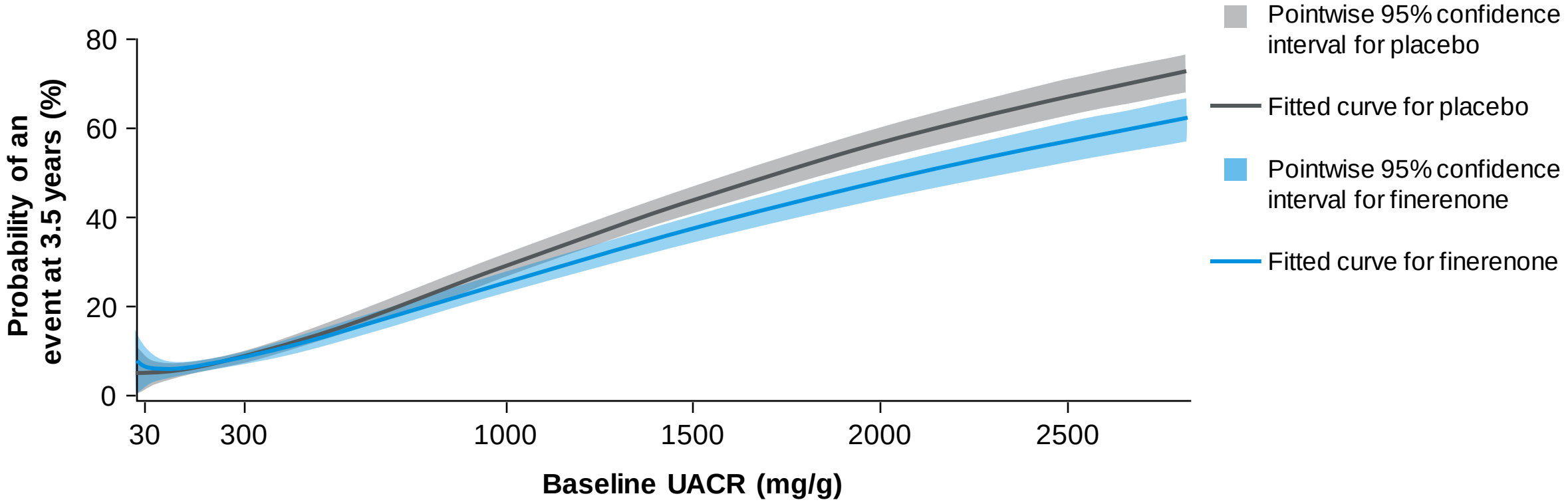
Increasing baseline albuminuria was associated with an increasing risk of the kidney composite outcome

Event probability at 3.5 years for time to onset of the kidney composite outcome* by continuous variable UACR



Greater benefit was observed with finerenone in patients with higher UACR at baseline

Full analysis set. Cox proportional hazards model is fitted with covariates treatment, baseline UACR (log-transformed), region, sex, and continuous covariates age. Splines used with knots at UACR=30, 300, 1000. AIC: 16717.7

*Time to kidney failure, sustained ≥40% decrease in eGFR ≥4 weeks from baseline, or renal death

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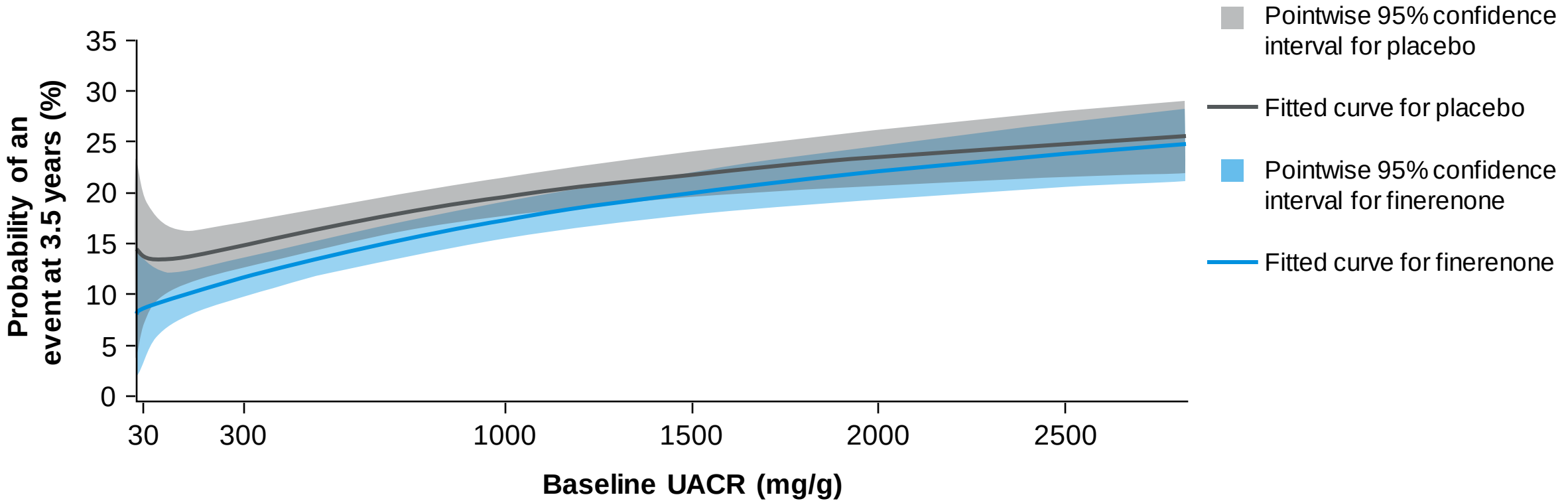
Increasing baseline albuminuria was associated with an increasing risk of the CV composite outcome

Event probability at 3.5 years for time to the CV composite outcome* by continuous variable baseline UACR



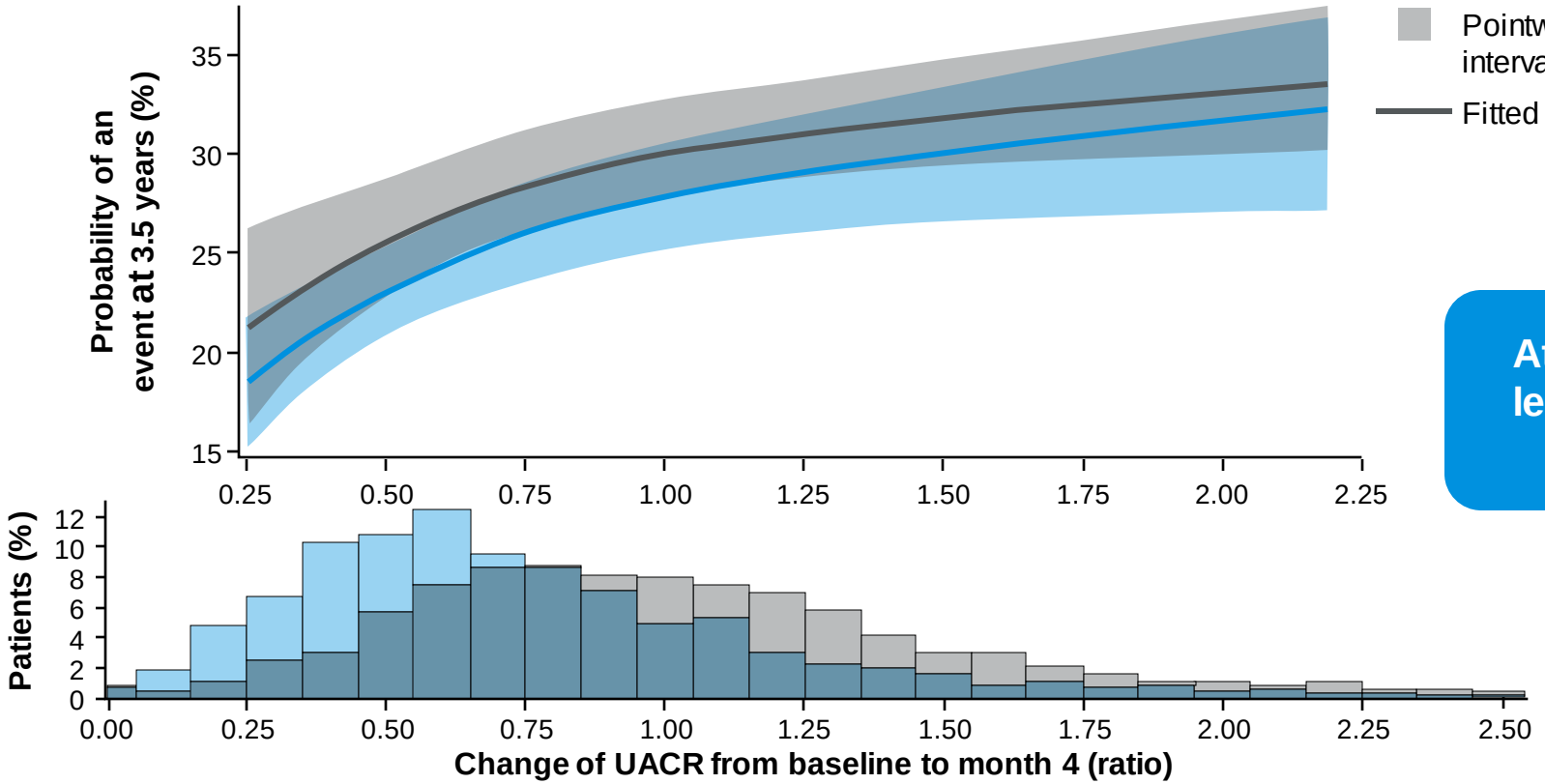
Full analysis set. Cox proportional hazards model is fitted with covariates treatment, baseline UACR (log-transformed), region, sex, and continuous covariates age. Splines used with knots at UACR=30, 300, 1000. AIC: 12937.8

*Time to CV death, nonfatal MI, nonfatal stroke, or HHF

FIDELIO-DKD
FInerenone in reducing kiDnEy faiLure and dIsease prOgression in DKD

The risk of the kidney composite outcome was reduced with finerenone versus placebo, irrespective of change in albuminuria from baseline to month 4

Event probability at 3.5 years for time to the kidney composite outcome* by continuous variable change of UACR from baseline to month 4



At 4 months, treatment with finerenone led to a 31% greater reduction in UACR than placebo[1]

Full analysis set. Cox proportional hazards model is fitted with covariates treatment, change of UACR from baseline to Month 4 (mg/g) (log-transformed), region, sex, and continuous covariates age. Splines used with knots at 33rd, 66th and 99th percentile of ratio of change of UACR. AIC: 17069.8

*Time to kidney failure, sustained ≥40% decrease in eGFR ≥4 weeks from baseline, or renal death

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

FIDELIO-DKD
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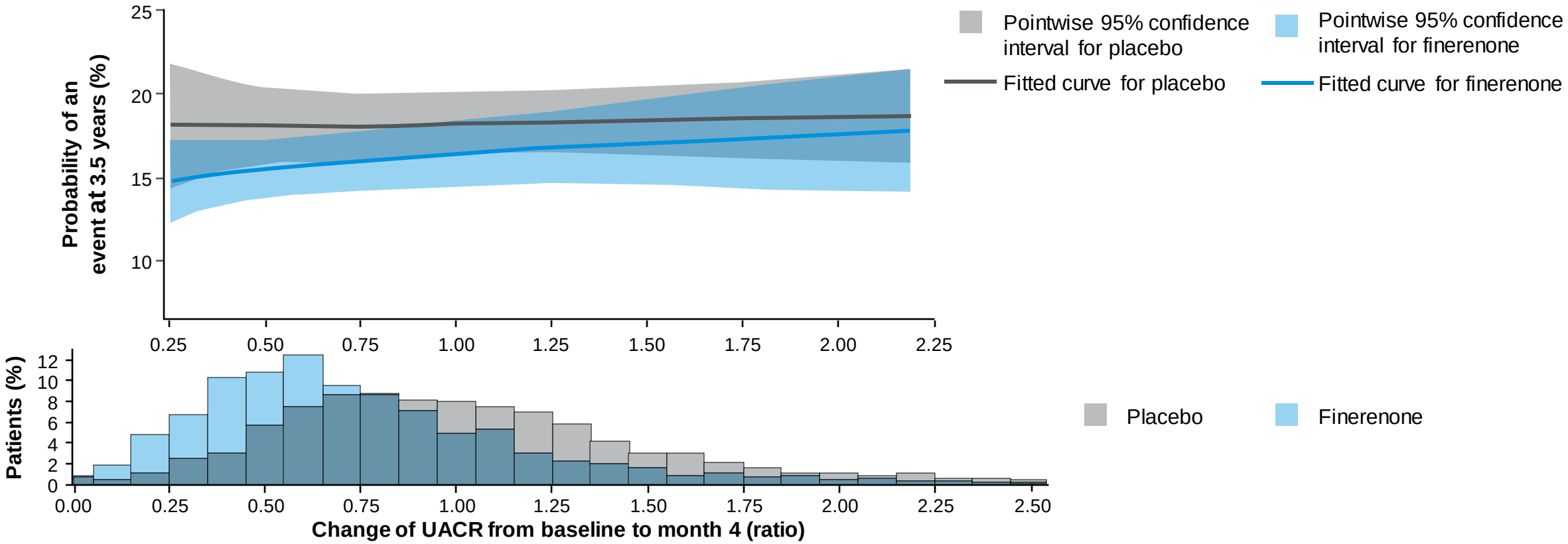
The risk of the CV composite outcome was reduced with finerenone versus placebo irrespective of change in albuminuria from baseline to month 4

Event probability at 3.5 years for time to the CV composite outcome* by continuous variable change of UACR from baseline to month 4



Full analysis set. Cox proportional hazards model is fitted with covariates treatment, change of UACR from baseline to Month 4 (mg/g) (log-transformed), region, sex, and continuous covariates age. Splines used with knots at 33rd, 66th and 99th percentile of ratio of change of UACR. AIC: 11916.6

*Time to CV death, nonfatal MI, nonfatal stroke, or HHF

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Summary and conclusions

In patients with CKD and T2D, treated with optimized RAS blockade:

- **There is a linear relationship between baseline UACR and risk of clinically important kidney and CV outcomes**
  - Finerenone's benefit on the kidney composite outcome appears to be most important in patients with severely increased albuminuria (UACR ≥300 mg/g) at baseline
  - In the case of the CV composite outcome, finerenone benefit observed across baseline albuminuria

Albuminuria at baseline is predictive of CV and kidney outcomes

- **An early reduction in UACR is associated with protection against risk of kidney events**
  - At 4 months, treatment with finerenone led to a 31% greater reduction in UACR than placebo[1]
- **In addition, finerenone reduces kidney and CV risk versus placebo irrespective of change in UACR from baseline to month 4**

Kidney and CV risk is lower when patients receive finerenone, even if UACR is increased or unchanged

RAS, renin–angiotensin system

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