In patients with type 2 diabetes, chronic kidney disease is a modifiable cardiovascular risk factor

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Background

- In patients with type 2 diabetes (T2D), chronic kidney disease (CKD) is associated with an increased risk of cardiovascular (CV) events[1]
- Albuminuria and lower levels of estimated glomerular filtration rate (eGFR) are associated with a higher risk of mortality, CV events and hospitalisation[1,2]
- The modifiability of CKD-associated CV risk in patients with T2D across a spectrum of CKD stages remains unknown

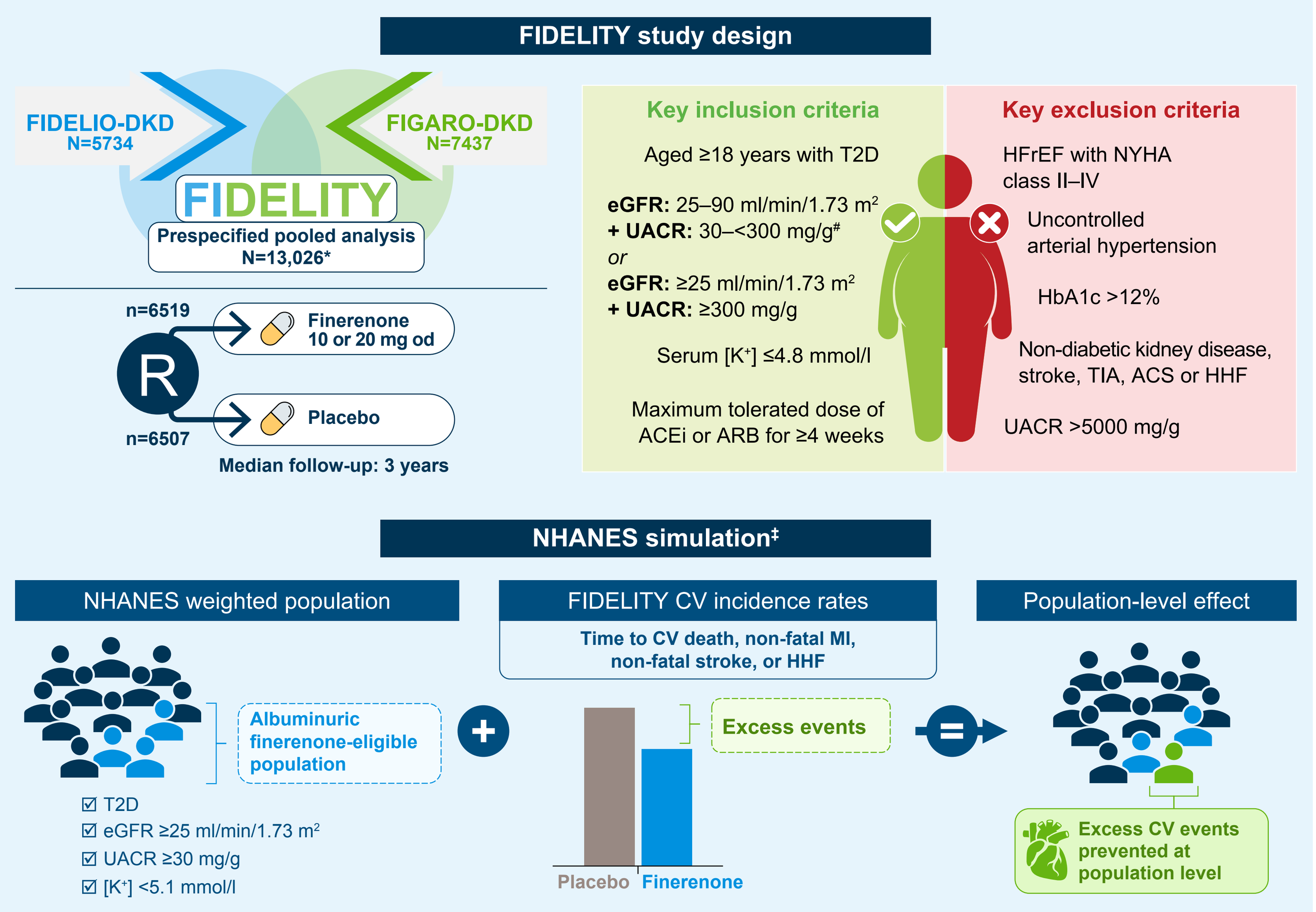
Purpose

- To evaluate whether CKD, as defined jointly by eGFR and albuminuria (urine albumin-to-creatinine ratio [UACR]), is a modifiable CV risk factor in patients with T2D
- Furthermore, to estimate the population-wide reduction in first CV events in the United States (US) if all eligible patients were treated with finerenone

Methods

- FIDELITY, a prespecified pooled analysis of two phase III trials (FIGARO-DKD and FIDELIO-DKD), included 13,026 patients with T2D and a wide spectrum of CKD, forming the largest dedicated CKD in T2D programme to date, as previously published[3] (**Figure 1**)
- In this subanalysis, incidence rates of CV events (composite of CV death, non-fatal stroke, non-fatal myocardial infarction, or hospitalisation for heart failure; primary and secondary endpoints of FIGARO-DKD and FIDELIO-DKD, respectively) were estimated by eGFR and albuminuria categories for the finerenone and placebo groups
- The National Health and Nutrition Examination Survey (NHANES) was used to estimate the number of albuminuric finerenone-eligible individuals in the US population (as per the US label),[4] which was then combined with the FIDELITY incidence rates to simulate the potential number of first CV events prevented per year with finerenone at a population level (**Figure 1**)
- The excess number of events was calculated based on a two-step Monte Carlo simulation with 10,000 iterations. This utilised a normal distribution based on NHANES data per Kidney Disease: Improving Global Outcomes (KDIGO) category for simulating population counts and the Poisson distribution with FIDELITY incidence rates (in each arm) per KDIGO category for simulating events

Figure 1. Study design[3]



FIDELITY study design
FIDELIO-DKD N=5734
FIGARO-DKD N=7437
FIDELITY
Prespecified pooled analysis N=13,026*
Key inclusion criteria
Aged ≥18 years with T2D
eGFR: 25–90 ml/min/1.73 m² + UACR: 30–<300 mg/g#
or
eGFR: ≥25 ml/min/1.73 m² + UACR: ≥300 mg/g
Serum [K+] ≤4.8 mmol/l
Maximum tolerated dose of ACEi or ARB for ≥4 weeks
Key exclusion criteria
HFrEF with NYHA class II–IV
Uncontrolled arterial hypertension
HbA1c >12%
Non-diabetic kidney disease, stroke, TIA, ACS or HHF
UACR >5000 mg/g
n=6519
Finerenone 10 or 20 mg od
R
n=6507
Placebo
Median follow-up: 3 years
NHANES simulation‡
NHANES weighted population
Albuminuric finerenone-eligible population
☑ T2D
☑ eGFR ≥25 ml/min/1.73 m²
☑ UACR ≥30 mg/g
☑ [K+] <5.1 mmol/l
FIDELITY CV incidence rates
Time to CV death, non-fatal MI, non-fatal stroke, or HHF
Excess events
Placebo
Finerenone
Population-level effect
Excess CV events prevented at population level

*Prospective exclusion of 145 patients; #in FIDELIO-DKD, patients with moderately elevated albuminuria were required to also have diabetic retinopathy, ‡Figures are illustrative only

ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; [K+], potassium concentration; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; NYHA, New York Heart Association; od, once daily; R, randomisation; T2D, type 2 diabetes; TIA, transient ischaemic attack; UACR, urine albumin-to-creatinine ratio

Results

Baseline characteristics

- Mean eGFR was 57.6 ml/min/1.73 m² and median UACR was 515 mg/g
- Overall, 10.2%, 41.0% and 48.3% of patients had moderate, high and very high KDIGO risk scores, respectively
- Baseline characteristics were largely balanced between eGFR and UACR categories (**Table 1**)

Table 1. Baseline characteristics of the FIDELITY study sample

Characteristic*	eGFR, ml/min/1.73 m²					UACR, mg/g	
	<30 (n=890)	30–<45 (n=3504)	45–<60 (n=3434)	60–<90 (n=3876)	≥90 (n=1319)	<300 (n=4329)	≥300 (n=8692)
Age, years	66.9 ± 8.6	67.3 ± 9.0	66.5 ± 8.8	63.4 ± 9.1	56.0 ± 8.8	67.6 ± 8.6	63.3 ± 9.7
Male sex, n (%)	570 (64.0)	2399 (68.5)	2468 (71.9)	2768 (71.4)	883 (66.9)	3018 (69.7)	6068 (69.8)
HbA1c, %	7.6 ± 1.3	7.6 ± 1.3	7.6 ± 1.3	7.7 ± 1.4	8.1 ± 1.5	7.6 ± 1.3	7.8 ± 1.4
Systolic blood pressure, mmHg	136.0 ± 16.2	136.9 ± 14.7	136.6 ± 14.0	137.1 ± 13.9	136.1 ± 12.8	134.2 ± 14.4	138.0 ± 13.9
History of CV disease, n (%)	448 (50.3)	1856 (53.0)	1746 (50.8)	1505 (38.8)	378 (28.7)	2279 (52.6)	3655 (42.1)
Baseline medications, n (%)							
RAS inhibitors	888 (99.8)	3501 (>99.9)	3424 (99.7)	3868 (99.8)	1319 (100)	4321 (99.8)	8677 (99.8)
Statins	685 (77.0)	2665 (76.1)	2580 (75.1)	2671 (68.9)	796 (60.3)	3237 (74.8)	6159 (70.9)
Insulin	614 (69.0)	2185 (62.4)	1963 (57.2)	2131 (55.0)	735 (55.7)	2361 (54.5)	5266 (60.6)
GLP-1RAs	57 (6.4)	245 (7.0)	250 (7.3)	290 (7.5)	102 (7.7)	330 (7.6)	614 (7.1)
SGLT-2is	13 (1.5)	129 (3.7)	241 (7.0)	344 (8.9)	150 (11.4)	299 (6.9)	578 (6.6)
eGFR, ml/min/1.73 m²	26.9 ± 2.3	37.7 ± 4.3	52.0 ± 4.3	73.2 ± 8.6	99.7 ± 7.6	53.8 ± 18.3	59.5 ± 22.9
eGFR, ml/min/1.73 m², n (%)							
<30	–	–	–	–	–	255 (5.9)	635 (7.3)
30–<45	–	–	–	–	–	1298 (30.0)	2206 (25.4)
45–<60	–	–	–	–	–	1471 (34.0)	1962 (22.6)
60–<90	–	–	–	–	–	1094 (25.3)	2780 (32.0)
≥90	–	–	–	–	–	211 (4.9)	1108 (12.7)
UACR, mg/g, median (IQR)	720 (242–1642)	516 (163–1250)	389 (127–1009)	546 (262–1100)	604 (376–1103)	114 (61–196)	871 (513–1564)
UACR, mg/g, n (%)							
<30	16 (1.8)	68 (1.9)	82 (2.4)	51 (1.3)	13 (1.0)	230 (5.3)	0
30–<300	239 (26.9)	1230 (35.1)	1389 (40.4)	1043 (26.9)	198 (15.0)	4099 (94.7)	0
≥300	635 (71.3)	2206 (63.0)	1962 (57.1)	2780 (71.7)	1108 (84.0)	0	8692 (100)

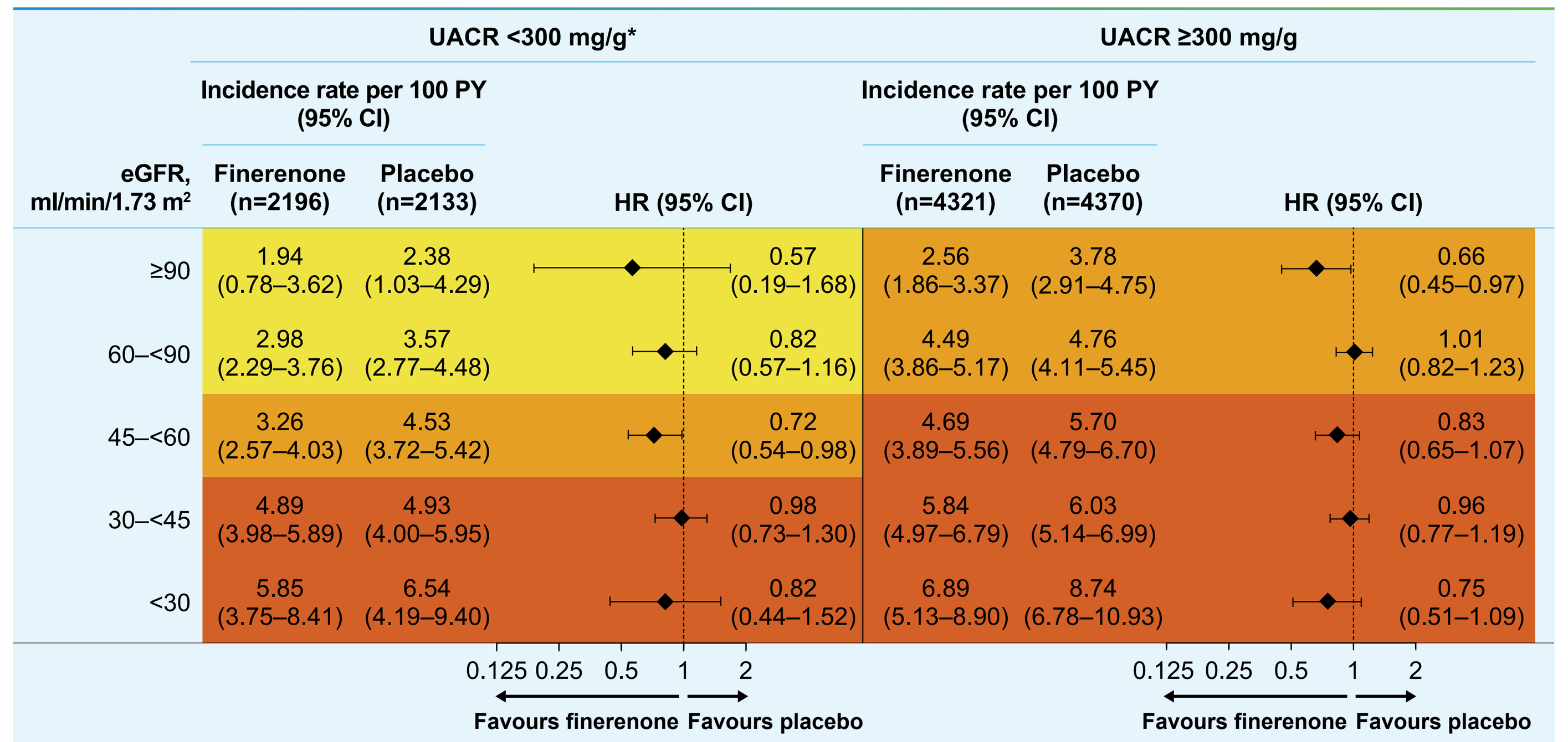
*Plus–minus values indicate mean ± SD

eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; IQR, interquartile range; RAS, renin–angiotensin system; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

CV event incidence rates in FIDELITY

- Lower eGFR and higher albuminuria were associated with higher incidences of CV events (**Figure 2**)
  - In placebo recipients with eGFR ≥90 ml/min/1.73 m², incidence rates per 100 patient-years were 2.38 and 3.78 in those with UACR <300 and ≥300 mg/g, respectively
  - In patients with eGFR <30 ml/min/1.73 m², incidence rates were 6.54 and 8.74, respectively
- Lower levels of eGFR were associated with a higher risk of a CV event at 4 years in both patients with UACR <300 and ≥300 mg/g (**Figure 3A, B**)
  - Similarly, higher levels of albuminuria were associated with a higher risk of CV events in both those with eGFR <60 and ≥60 ml/min/1.73 m² (**Figure 3C, D**)
- CV risk was reduced with finerenone (hazard ratio: 0.86; 95% confidence interval [CI] 0.78–0.95; *p*=0.0018) across all ranges of UACR and eGFR, with no significant interaction (*p*-interaction=0.66)

Figure 2. Incidence rates of CV events in FIDELITY



UACR <300 mg/g*
UACR ≥300 mg/g
Incidence rate per 100 PY (95% CI)
eGFR, ml/min/1.73 m²
Finerenone (n=2196)
Placebo (n=2133)
HR (95% CI)
Finerenone (n=4321)
Placebo (n=4370)
HR (95% CI)
≥90 | 1.94 (0.78–3.62) | 2.38 (1.03–4.29) | 0.57 (0.19–1.68) | 2.56 (1.86–3.37) | 3.78 (2.91–4.75) | 0.66 (0.45–0.97)
60–<90 | 2.98 (2.29–3.76) | 3.57 (2.77–4.48) | 0.82 (0.57–1.16) | 4.49 (3.86–5.17) | 4.76 (4.11–5.45) | 1.01 (0.82–1.23)
45–<60 | 3.26 (2.57–4.03) | 4.53 (3.72–5.42) | 0.72 (0.54–0.98) | 4.69 (3.89–5.56) | 5.70 (4.79–6.70) | 0.83 (0.65–1.07)
30–<45 | 4.89 (3.98–5.89) | 4.93 (4.00–5.95) | 0.98 (0.73–1.30) | 5.84 (4.97–6.79) | 6.03 (5.14–6.99) | 0.96 (0.77–1.19)
<30 | 5.85 (3.75–8.41) | 6.54 (4.19–9.40) | 0.82 (0.44–1.52) | 6.89 (5.13–8.90) | 8.74 (6.78–10.93) | 0.75 (0.51–1.09)
0.125 0.25 0.5 1 2
Favours finerenone
Favours placebo

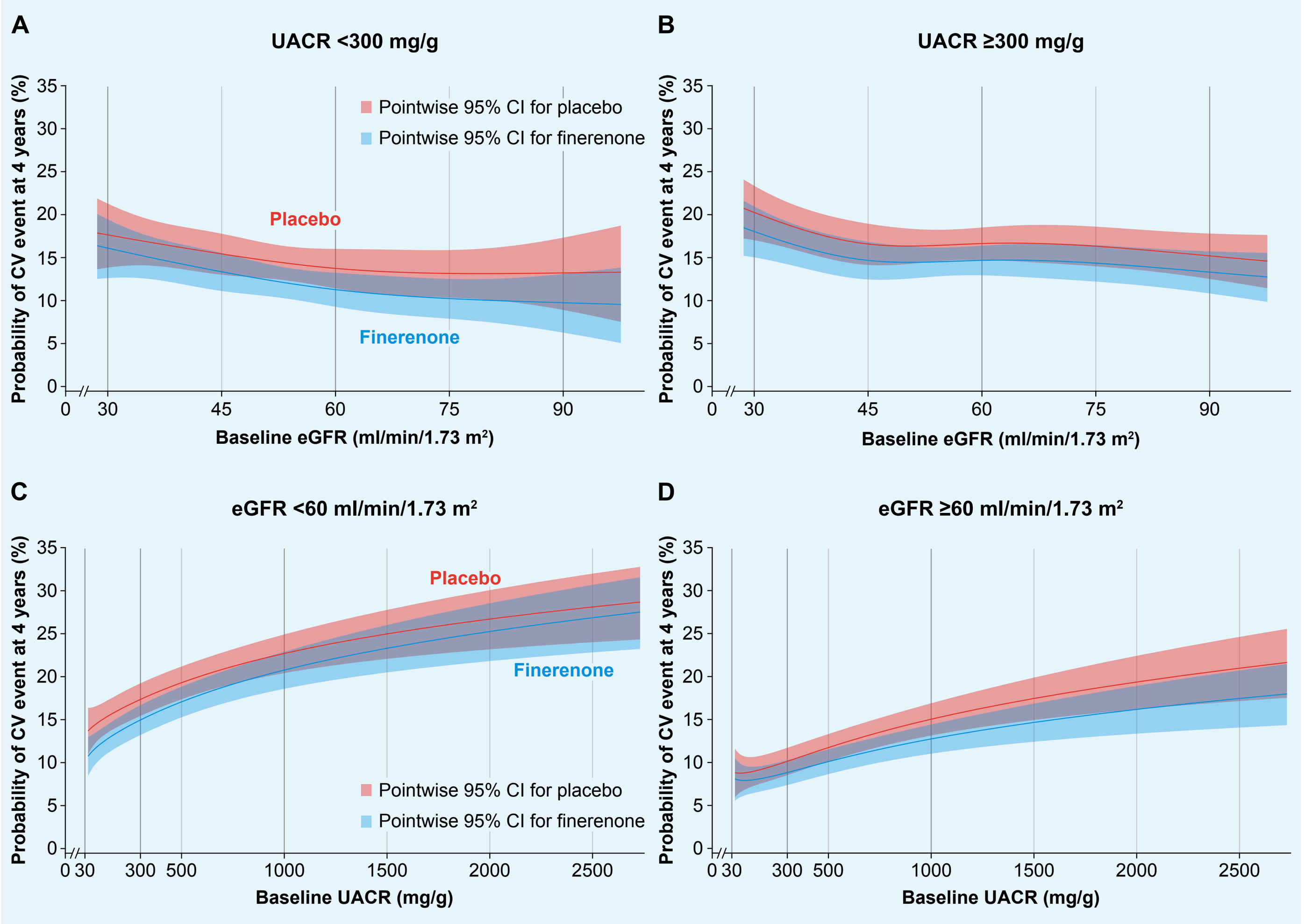
p-interaction=0.6629

Colours represent KDIGO risk categories

*230 patients with UACR <30 mg/g were included in FIDELITY because of variability between screening and baseline UACR values

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDIGO, Kidney Disease: Improving Global Outcomes; PY, patient-years; UACR, urine albumin-to-creatinine ratio

Figure 3. Predicted probability of a CV event at 4 years by eGFR in patients with UACR <300 mg/g (**A**) or ≥300 mg/g (**B**); and by UACR in patients with eGFR <60 ml/min/1.73 m² (**C**) or ≥60 ml/min/1.73 m² (**D**)



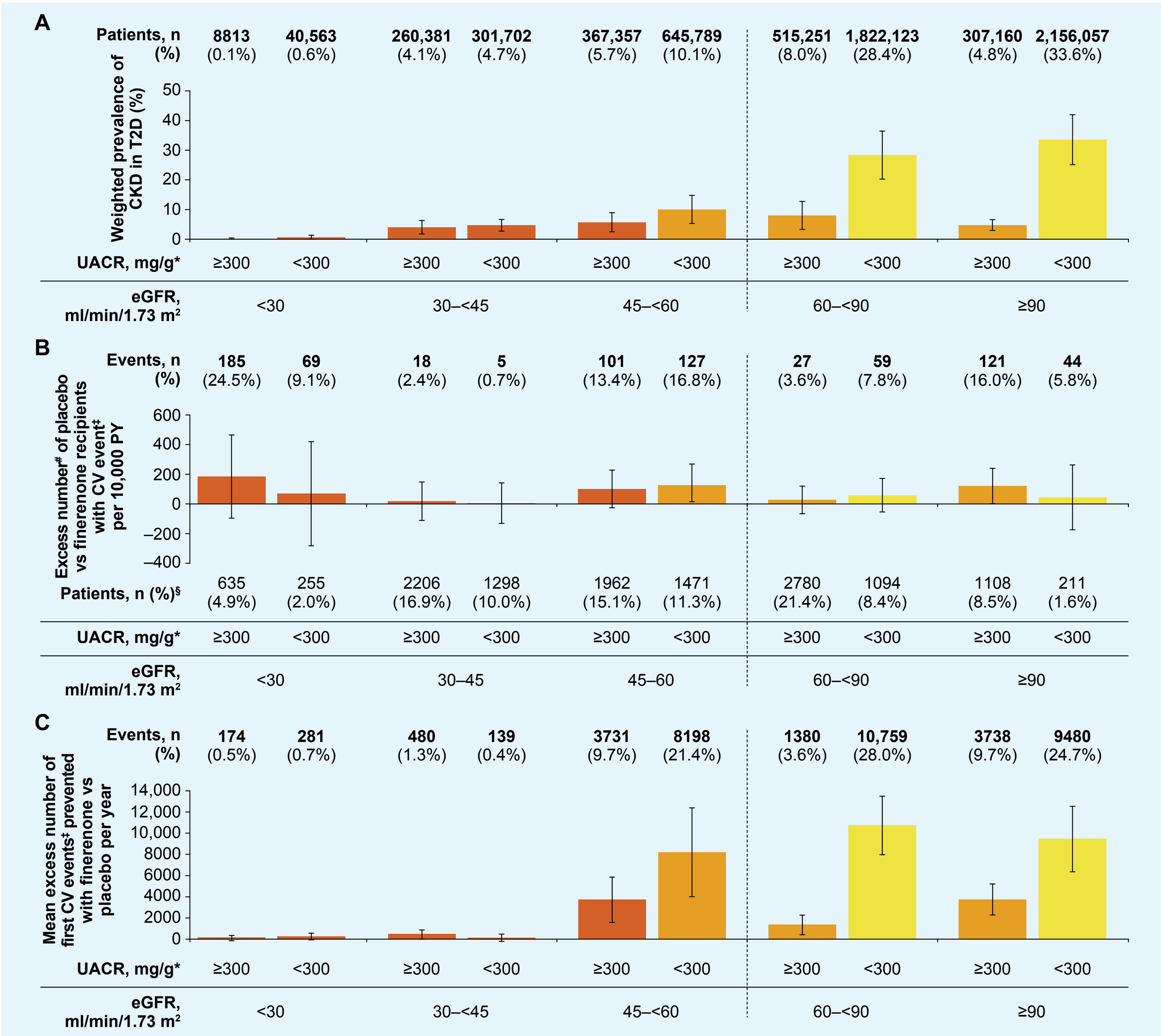
The Cox proportional hazards model was fitted with the covariates treatment, study, CV disease history, region, sex, and race, and the continuous covariates age, HbA1c, systolic blood pressure, and baseline log-transformed UACR and eGFR. Cubic B-splines were used for baseline eGFR (**A, B**) and log-transformed UACR (**C, D**)

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; UACR, urine albumin-to-creatinine ratio

Simulation of population-level first CV event prevention

- Out of the NHANES-estimated 318.7 million non-institutionalised population in the US, 6.4 million (2.6%) finerenone-eligible individuals with T2D and albuminuric CKD were identified
  - The majority had higher eGFR (≥60 ml/min/1.73 m²) and lower UACR (<300 mg/g) levels (**Figure 4A**)
- In FIDELITY, finerenone prevented excess first CV events across eGFR and UACR categories, with a total excess number of prevented events of 67 per 10,000 patient-years (95% CI 24–111) (**Figure 4B**)
  - Based on the finerenone-eligible NHANES population, a simulated 38,359 CV events could be prevented per year with finerenone treatment
  - Of these, 25,357 (66.1%) CV events could be prevented in patients that would be diagnosed with CKD based on albuminuria alone (UACR ≥30 mg/g and eGFR ≥60 ml/min/1.73 m²) (**Figure 4C**)

Figure 4. CV risk reduction by finerenone across eGFR and albuminuria categories in FIDELITY and at a population level



A
Patients, n (%)
8813 (0.1%) | 40,563 (0.6%) | 260,381 (4.1%) | 301,702 (4.7%) | 367,357 (5.7%) | 645,789 (10.1%) | 515,251 (8.0%) | 1,822,123 (28.4%) | 307,160 (4.8%) | 2,156,057 (33.6%)
Weighted prevalence of CKD in T2D (%)
UACR, mg/g*
≥300 <300 ≥300 <300 ≥300 <300 ≥300 <300 ≥300 <300
eGFR, ml/min/1.73 m²
<30 30–<45 45–<60 60–<90 ≥90
B
Events, n (%)
185 (24.5%) | 69 (9.1%) | 18 (2.4%) | 5 (0.7%) | 101 (13.4%) | 127 (16.8%) | 27 (3.6%) | 59 (7.8%) | 121 (16.0%) | 44 (5.8%)
Excess number# of placebo vs finerenone recipients with CV event‡ per 10,000 PY
Patients, n (%)§
635 (4.9%) | 255 (2.0%) | 2206 (16.9%) | 1298 (10.0%) | 1962 (15.1%) | 1471 (11.3%) | 2780 (21.4%) | 1094 (8.4%) | 1108 (8.5%) | 211 (1.6%)
UACR, mg/g*
eGFR, ml/min/1.73 m²
<30 30–45 45–60 60–<90 ≥90
C
Events, n (%)
174 (0.5%) | 281 (0.7%) | 480 (1.3%) | 139 (0.4%) | 3731 (9.7%) | 8198 (21.4%) | 1380 (3.6%) | 10,759 (28.0%) | 3738 (9.7%) | 9480 (24.7%)
Mean excess number of first CV events‡ prevented with finerenone vs placebo per year
UACR, mg/g*
eGFR, ml/min/1.73 m²
<30 30–<45 45–<60 60–<90 ≥90

Error bars represent 95% confidence intervals

Colours represent KDIGO risk categories

NHANES-estimated prevalence of finerenone-eligible individuals with CKD and T2D in the United States by KDIGO, eGFR and albuminuria categories (**A**); excess number# of patients with first CV event‡ per 10,000 PY in FIDELITY with finerenone versus placebo across KDIGO, eGFR and albuminuria categories (**B**); simulated number of excess first CV events‡ prevented with finerenone versus placebo per year in finerenone-eligible US individuals with CKD and T2D by KDIGO, eGFR and albuminuria categories (**C**)

*Individuals with UACR 30–<300 mg/g were included in NHANES, although 230 patients with UACR <30 mg/g were included in FIDELITY because of variability between screening and baseline results; #based on differences of FIDELITY incidence rates between the finerenone and placebo groups; ‡composite of time to CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for heart failure; §data on baseline eGFR and UACR categories were missing for 6 patients in FIDELITY

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NHANES, National Health and Nutrition Examination Survey; PY, patient-years; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

Conclusions

- In patients with T2D, CKD is a modifiable CV risk factor in part mediated by mineralocorticoid receptor overactivation
- Population-level benefits of finerenone are expected in patients with UACR ≥30 mg/g and eGFR ≥60 ml/min/1.73 m², highlighting the need to screen for UACR in addition to eGFR to identify albuminuric patients with stage 1–2 CKD who could derive benefit from treatment

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References

1. Go AS, *et al*. *N Engl J Med* 2004;351:1296–1305.
2. Matsushita K, *et al*. *Lancet Diabetes Endocrinol* 2015;3:514–525.
3. Agarwal R, *et al*. *Eur Heart J* 2022;43:474–484.
4. Bayer Healthcare Pharmaceuticals Inc. KERENDIA (finerenone) Prescribing Information. 2021. https://labeling.bayerhealthcare.com/html/products/pi/Kerendia_PI.pdf [accessed 28 Apr 2022].

Disclosures

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