1422-059

Effect of baseline lipid levels or statin use on finerenone treatment outcomes in patients with chronic kidney disease and type 2 diabetes: A FIDELITY post hoc analysis

Ashish Verma,[1,2] Rajiv Agarwal,[3] Stefan D. Anker,[4] Sophie E. Claudel,[1,2] Bertram Pitt,[5] Peter Rossing,[6,7] Luis M. Ruilope,[8,9] Melinda Solomon,[10] Anand Vaidya,[11] Sushrut Waikar,[2] Rania Dayoub,[12,13] Sonia Gomez,[14] Zihe Zheng,[15] Gerasimos Filippatos,[16] for the FIDELIO-DKD and FIGARO-DKD Investigators

[1]Department of Medicine, Boston Medical Center, Boston, MA, USA; [2]Department of Medicine, Section of Nephrology, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA; [3]Indiana University School of Medicine and Richard L. Roudebush VA Medical Center, Indianapolis, IN, USA; [4]Department of Cardiology (CVK) of German Heart Center Charité; German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany; [5]Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI, USA; [6]Steno Diabetes Center Copenhagen, Copenhagen, Denmark; [7]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [8]Cardiorenal Translational Laboratory and Hypertension Unit, Institute of Research imas12, Madrid, Spain; [9]CIBER-CV, Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Department of Medicine, Newton-Wellesley Hospital, Newton, MA, USA; [11]Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [12]Global Medical & Evidence CV and Heme, Bayer AG, Berlin, Germany; [13]Children's University Hospital (KUNO), University Hospital Regensburg, Regensburg, Germany; [14]Syneos Health LLC (providing service to Bayer), Morrisville, NC, USA; [15]Medical Affairs Cardio-Renal Division, Bayer U.S. LLC, Whippany, NJ, USA; [16]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece

Presenting author: Zihe Zheng; Medical Affairs Cardio-Renal Division, Bayer U.S. LLC. Whippany, NJ, USA; emma.zheng@bayer.com

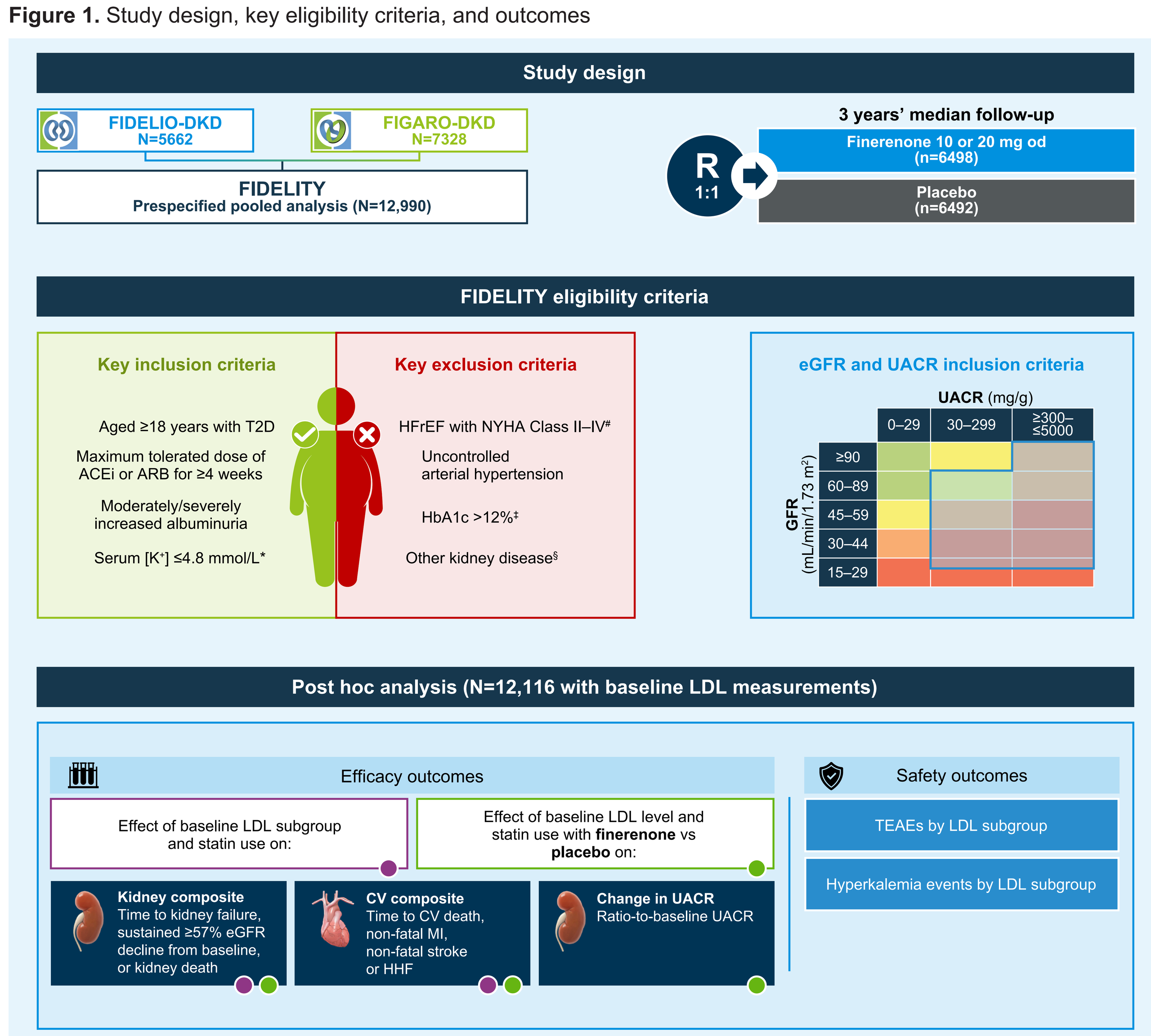
Background

- Altered lipid metabolism is associated with increased risk of cardiovascular (CV) events and chronic kidney disease (CKD) progression in patients with CKD and type 2 diabetes (T2D)[1–4]
  - Lowering low-density lipoprotein (LDL) levels with statins reduces risk of CV disease[5]
  - Statin use is recommended in patients with CKD over 50 years of age and in younger patients with risk factors for CV disease[5]
- Serum lipid concentrations are related to aldosterone concentration,[6] and aberrant activation of the associated mineralocorticoid receptor has been linked to lipid metabolic disorders[7]
- Finerenone, a nonsteroidal mineralocorticoid receptor antagonist, improved CV and kidney outcomes versus placebo in participants with CKD and T2D in FIDELITY, a prespecified pooled analysis of the phase III FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) trials[8]
- Here, we examine whether baseline LDL levels and statin use modified finerenone treatment effects in the FIDELITY dataset

Methods

- Key elements of the study design and eligibility criteria for the studies comprising the FIDELITY dataset are shown in **Figure 1**
  - Participants were adults with CKD and T2D on optimal renin–angiotensin system inhibition
    - CKD requirements: Urine albumin-to-creatinine ratio (UACR) 30–299 mg/g and estimated glomerular filtration rate (eGFR) 25–≤90 mL/min/1.73 m² or UACR 300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m²
  - Eligible participants were randomized 1:1 to receive once-daily treatment with finerenone or placebo

Figure 1. Study design, key eligibility criteria, and outcomes



*At run-in or screening visit; #run-in only; ‡at the run-in or screening visit; §known significant non-diabetic kidney disease, including clinically relevant renal artery stenosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; [K+], potassium concentration; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association od, once daily; R, randomization; T2D, type 2 diabetes; TEAE, treatment-emergent adverse event; UACR, urine albumin-to-creatinine ratio

Outcomes

- The outcomes assessed in this post hoc analysis are described in **Figure 1**
- The effects of baseline LDL levels and statin use on the occurrence of the composite CV and kidney outcomes were assessed
- The main outcome assessed the effect of baseline LDL levels and statin use on the efficacy and safety of finerenone versus placebo
  - Efficacy outcomes assessed included:
    - Composite CV outcome: time to CV death, non-fatal stroke, non-fatal myocardial infarction, or hospitalization for heart failure
    - Composite kidney outcome: time to kidney failure, sustained decrease in eGFR ≥57% from baseline over at least 4 weeks, or kidney-related death
    - Ratio to baseline of UACR
- Treatment-emergent adverse event (TEAE) incidence by LDL subgroup was determined

Statistical analysis

- Baseline characteristics and efficacy analyses were performed using the full analysis set, which included all randomized participants except those with critical Good Clinical Practice violations
- Safety assessments were performed using the safety analysis set (all randomized participants without critical Good Clinical Practice violations who took ≥1 dose of study drug)
- Participants were split into subgroups based on baseline LDL levels (<70 mg/dL, 70–100 mg/dL, >100 mg/dL) and baseline statin use (yes/no)
- The effect of baseline LDL and statin use on efficacy outcomes was assessed using stratified Cox proportional hazards models, using the stratification factors geographical region, eGFR and albuminuria category at screening, history of CV disease and study and adjusted for treatment
- A stratified Cox proportional hazards model including treatment was calculated by subgroup, with treatment outcomes expressed as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs)
- Treatment effect on UACR was analyzed for each subgroup using a mixed model with factors treatment group, region, eGFR category at screening, type of albuminuria at screening, CVD 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 covariates
- All analyses were performed using SAS software version 9.4 (SAS Institute)

Results

Baseline characteristics

- Among 12,116 participants with baseline LDL measurements, 7421 (61.2%) had LDL ≥70 mg/dL (**Table 1**)

Table 1. Baseline demographics and clinical characteristics by LDL subgroup (full analysis set*)

Characteristic	Baseline LDL <70 mg/dL (n=4695)	Baseline LDL 70–100 mg/dL (n=3905)	Baseline LDL >100 mg/dL (n=3516)
Age, years, mean (SD)	66.2 (9.0)	65.3 (9.4)	63.1 (9.7)
Sex, male, n (%)	3610 (76.9)	2719 (69.6)	2126 (60.5)
Race, n (%)			
White	3228 (68.8)	2605 (66.7)	2344 (66.1)
Black/African American	179 (3.8)	173 (4.4)	152 (4.3)
Asian	1050 (22.4)	920 (23.6)	757 (21.5)
Others#	238 (5.1)	207 (5.3)	263 (7.5)
eGFR, mL/min/1.73 m², mean (SD)	56.0 (20.5)	56.7 (21.7)	60.5 (22.4)
UACR, mg/g, median (Q1–Q3)	430.7 (151.7–967.2)	500.4 (192.1–1090.6)	628.6 (273.8–1385.1)
Statin use, n (%)	4171 (88.8)	2873 (73.6)	1755 (49.9)
CV disease in medical history, n (%)	2487 (53.0)	1697 (43.5)	1393 (39.6)
Systolic blood pressure, mmHg, mean (SD)	135.6 (14.6)	137.3 (14.0)	137.1 (13.8)
Diastolic blood pressure, mmHg, mean (SD)	74.7 (9.8)	76.3 (9.6)	78.2 (9.0)
Hs-CRP, mg/dL, mean (SD)	4.3 (10.1)	4.7 (10.4)	5.3 (9.4)
HbA1c, mean (SD)	7.6 (1.3)	7.6 (1.3)	7.8 (1.4)
BMI, kg/m², mean (SD)	31.4 (6.1)	31.1 (6.0)	31.0 (5.9)
HDL ≥40/50 mg/dL for men/women, n (%)	2232 (47.5)	2306 (59.1)	2054 (58.4)
Triglycerides <150 mg/dL, n (%)	1955 (41.6)	1631 (41.8)	1223 (34.8)
SGLT-2i use, n (%)	398 (8.5)	215 (5.5)	161 (4.6)
GLP-1RA use, n (%)	451 (9.6)	259 (6.6)	145 (4.1)

*Data not shown for 329 participants in the finerenone arm and 333 participants in the placebo arm with missing LDL data at baseline; #includes American Indian, Alaska native, native Hawaiian, Pacific Islander, participants who reported that they belong to more than one race, and participants whose race was not reported

BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Q, quartile; SGLT-2is, sodium-glucose co-transporter-2 inhibitors; SD, standard deviation; UACR, urine albumin-to-creatinine ratio

- Overall, baseline statin use was high (9241/12,778; 72.3%)
- Baseline characteristics were generally balanced between the LDL subgroups, with some notable differences
  - Compared with participants in the lowest LDL category (<70 mg/dL), those in the highest LDL category (>100 mg/dL) had:
    - Lower statin use
    - Higher eGFR and UACR
    - Less history of CV disease
    - Higher mean systolic and diastolic blood pressure
    - Higher glycated hemoglobin levels
    - Higher levels of high-sensitivity C-reactive protein
    - Lower use of sodium-glucose co-transporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Association of composite CV and kidney outcomes with baseline lipid levels and statin use

- Baseline LDL <70 mg/dL, compared with LDL ≥70 mg/dL, was significantly associated with reduced risks of composite CV outcomes (HR=0.86; 95% CI 0.79–0.93; p=0.0003; **Figure 2A**). It was not significantly associated with kidney outcomes (HR=0.94; 95% CI 0.83–1.05; p=0.2725)
- Baseline statin use was similarly associated with reduced CV risk (HR=0.81; 95% CI 0.72–0.90; p=0.0001; **Figure 2B**)
  - Statin use was also associated with reduced risk of composite kidney outcomes (HR=0.76; 95% CI 0.65–0.89; p=0.0006)

Figure 2. Risk of composite CV and kidney outcomes by baseline LDL level and statin use in FIDELITY (full analysis set*)

A. Baseline LDL subgroup

	LDL <70 mg/dL		LDL ≥70 mg/dL			
	n/N	n/100 PY	n/N	n/100 PY	Hazard ratio (95% CI)	p-interaction
Composite CV outcome#	591/4695	4.28	1050/7421	4.93	0.86 (0.79–0.93)	0.0003
Composite kidney outcome‡	244/4695	1.83	507/7421	2.46	0.94 (0.83–1.05)	0.2725

Axis: 0.5, 1, 2; ← Decreased risk with LDL <70 mg/dL; Increased risk with LDL <70 mg/dL →

B. Baseline statin use

	Statins used		Statins not used			
	n/N	n/100 PY	n/N	n/100 PY	Hazard ratio (95% CI)	p-interaction
Composite CV outcome#	1255/9241	4.69	478/3537	4.67	0.81 (0.72–0.90)	0.0001
Composite kidney outcome‡	564/9241	2.17	247/3537	2.52	0.76 (0.65–0.89)	0.0006

Axis: 0.5, 1, 2; ← Decreased risk with statin use; Increased risk with statin use →

*A total of 329 participants in the finerenone arm and 333 participants in the placebo arm with missing LDL data at baseline were excluded from this analysis; #time to CV death, non-fatal stroke, non-fatal myocardial infarction, or hospitalization for heart failure; ‡time to kidney failure, sustained decrease in eGFR ≥57% from baseline over at least 4 weeks, or kidney-related death. Stratified Cox proportional hazards model with geographical region, eGFR and albuminuria category at screening, history of CV disease and study as stratification factors. The statistical significance of statin use and baseline LDL was assessed by the type III p-value of the main effect.

CI, confidence interval; CV, cardiovascular; LDL, low-density lipoprotein; PY, patient-years

Effect of finerenone versus placebo on composite CV and kidney outcomes by baseline lipid levels and statin use

- Finerenone reduced risks of composite CV (**Figure 3A**) and kidney (**Figure 3B**) outcomes versus placebo (HR=0.86; 95% CI 0.79–0.95 and HR=0.77; 95% CI 0.67–0.88, respectively) with no heterogeneity between lipid and statin use subgroups ($p_{interactions}$≥0.10)
  - The effect of finerenone on risk of CV (**Figure 4A**) and kidney (**Figure 4B**) composite outcomes remained consistent relative to placebo across the spectrum of baseline LDL levels
- At month 4, there was a significant reduction in UACR with finerenone versus placebo across all baseline LDL subgroups that was sustained through 48 months (p<0.05 at all visits; **Figure 5A**). Similarly, finerenone significantly improved ratio to baseline UACR versus placebo regardless of baseline statin use, starting at month 4 and maintained for 48 months (p<0.002 at all visits; **Figure 5B**)

Figure 3. The effect of finerenone versus placebo on composite CV and kidney outcomes by baseline LDL level and statin use in FIDELITY (full analysis set)

A. Composite CV outcome*

	Finerenone		Placebo			
	n/N	n/100 PY	n/N	n/100 PY	Hazard ratio (95% CI)	p-interaction
Overall	811/6383	4.35	922/6385	5.02	0.86 (0.79–0.95)	
LDL at baseline						
Missing LDL	38/329	3.94	54/333	5.79	0.73 (0.47–1.13)	0.5401
<70 mg/dL	274/2346	3.94	317/2349	4.62	0.83 (0.70–0.97)	
70–100 mg/dL	243/1952	4.20	284/1953	5.00	0.86 (0.72–1.02)	
>100 mg/dL	256/1766	5.21	267/1750	5.44	0.94 (0.79–1.12)	
Statin use at baseline						
Statins used	569/4581	4.27	686/4660	5.11	0.83 (0.74–0.93)	0.3046
Statins not used	242/1812	4.57	236/1725	4.78	0.92 (0.77–1.11)	

Axis: 0.25, 0.5, 1, 2, 4; ← Favors finerenone; Favors placebo →

B. Composite kidney outcome#

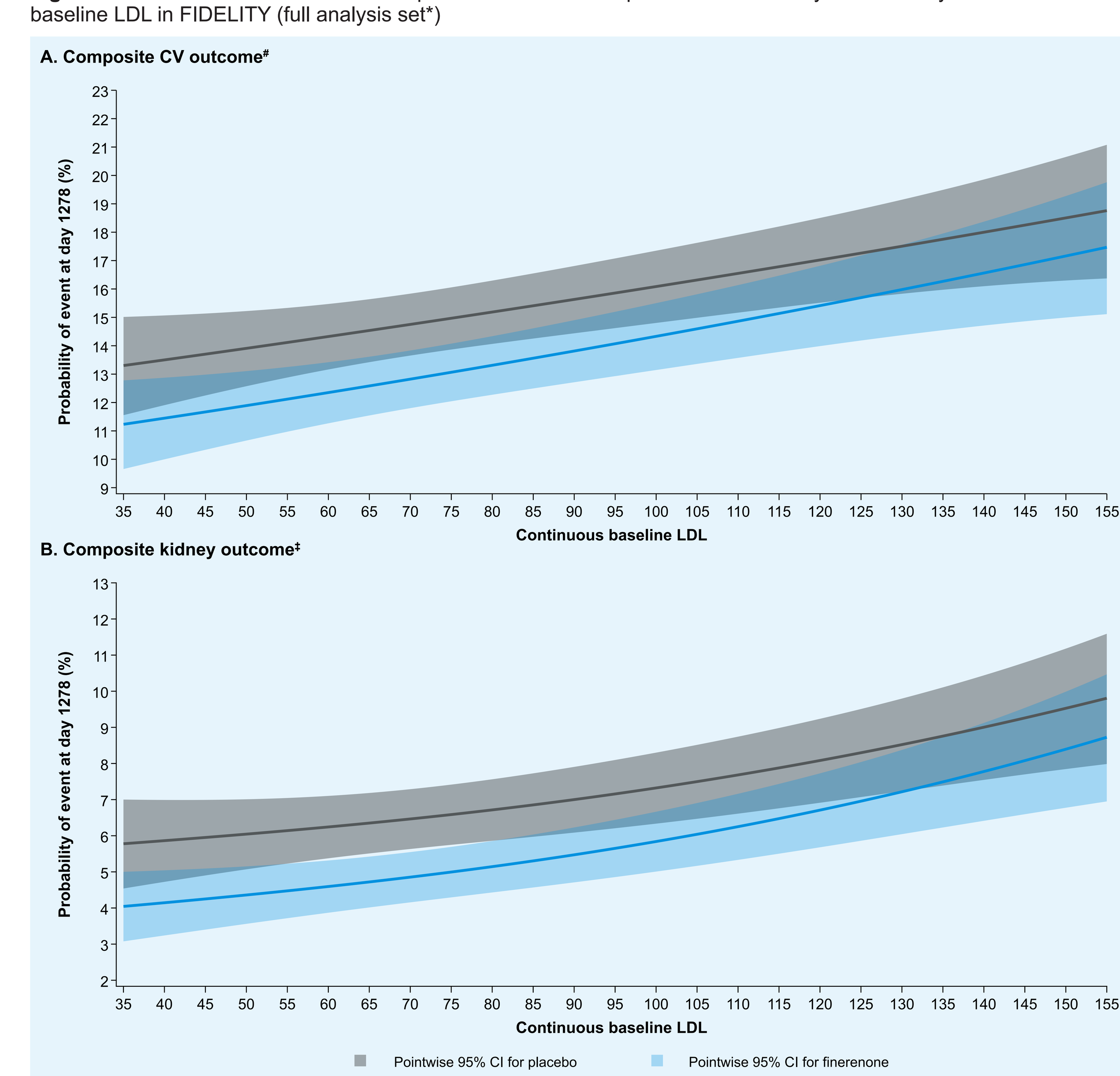
	Finerenone		Placebo			
	n/N	n/100 PY	n/N	n/100 PY	Hazard ratio (95% CI)	p-interaction
Overall	353/6393	1.97	458/6385	2.56	0.77 (0.67–0.88)	
LDL at baseline						
Missing LDL	25/329	2.74	35/333	3.76	0.63 (0.36–1.08)	0.7348
<70 mg/dL	100/2346	1.5	144/2349	2.16	0.72 (0.55–0.93)	
70–100 mg/dL	107/1952	1.9	124/1953	2.25	0.81 (0.62–1.06)	
>100 mg/dL	121/1766	2.54	155/1750	3.27	0.81 (0.64–1.04)	
Statin use at baseline						
Statins used	241/4581	1.87	323/4660	2.46	0.75 (0.64–0.89)	0.5255
Statins not used	112/1812	2.21	135/1725	2.84	0.81 (0.62–1.04)	

Axis: 0.25, 0.5, 1, 2, 4; ← Favors finerenone; Favors placebo →

*Time to CV death, non-fatal stroke, non-fatal myocardial infarction, or hospitalization for heart failure; #time to kidney failure, sustained decrease in eGFR ≥57% from baseline over at least 4 weeks, or kidney-related death. Stratified Cox proportional hazards model including treatment calculated by subgroup. Interaction p-values were calculated based on a stratified Cox proportional hazards model including treatment, subgroup, and treatment by subgroup interaction. The statistical significance of statin use and baseline LDL by treatment group was assessed by the type III p-value of the interaction effect.

CI, confidence interval; CV, cardiovascular; LDL, low-density lipoprotein; PY, patient-years

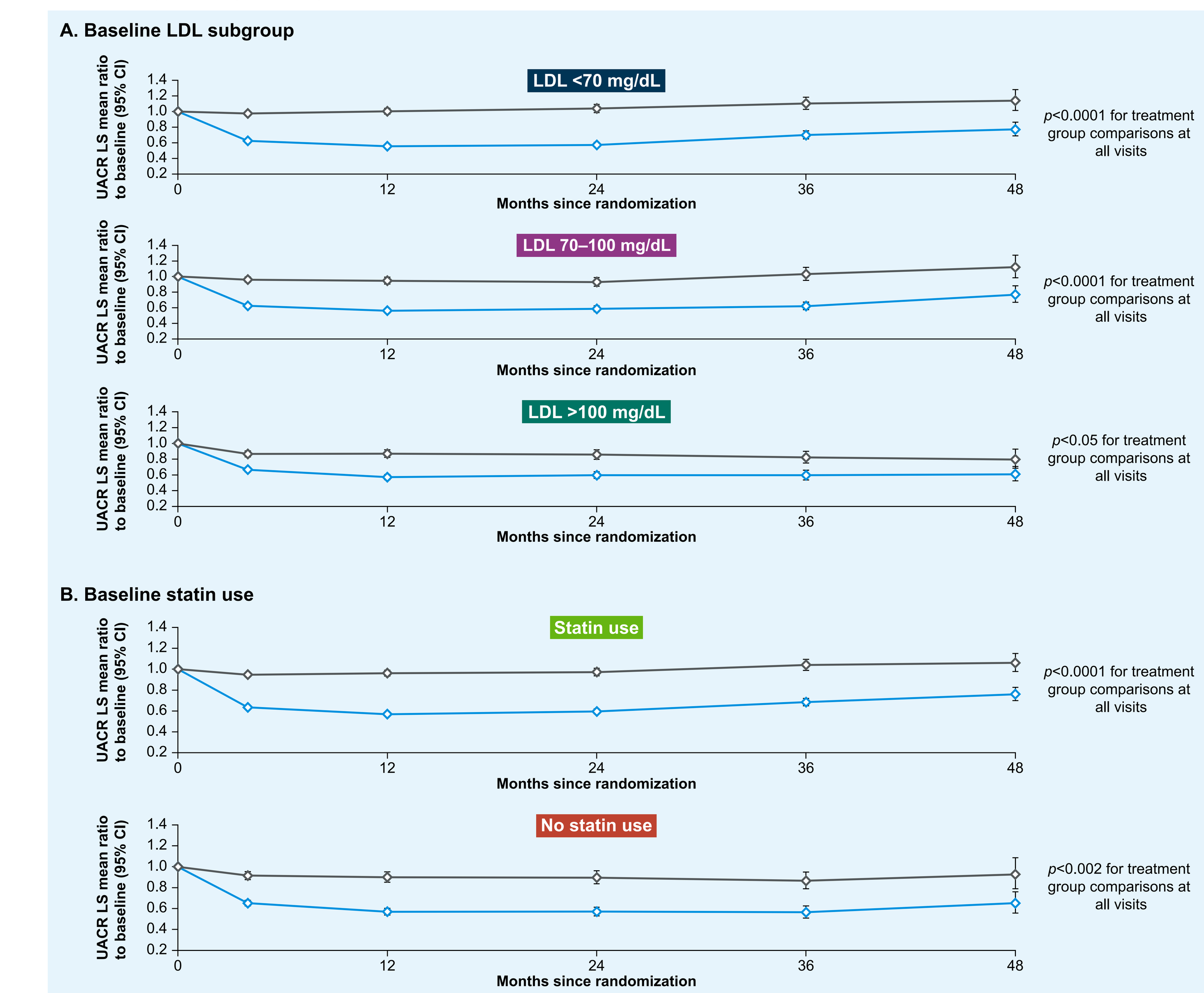
Figure 4. The effect of finerenone versus placebo on risk of composite CV and kidney outcomes by continuous baseline LDL in FIDELITY (full analysis set*)



*A total of 329 participants in the finerenone arm and 333 participants in the placebo arm with missing LDL data at baseline were excluded from this analysis; #time to CV death, non-fatal stroke, non-fatal myocardial infarction, or hospitalization for heart failure; ‡time to kidney failure, sustained decrease in eGFR ≥57% from baseline over at least 4 weeks, or kidney-related death. The overlapping confidence intervals indicated by the shaded areas represent non-statistically significant difference between treatment effects at that LDL value.

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein

Figure 5. The effect of finerenone versus placebo on changes in UACR by baseline LDL level and statin use in FIDELITY (full analysis set*)



*Data not shown for 329 participants in the finerenone arm and 333 participants in the placebo arm with missing LDL data at baseline. Models were run separately for each subgroup. LS mean and 95% CI from mixed model with factors of treatment group, region, eGFR category at screening, type of albuminuria at screening, history of CV disease, study, time, treatment by time, baseline value nested within eGFR category at screening, and baseline value by time as covariates. Type III p-values of the interaction effect were used to assess the significance of the treatment effect over time.

CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; LS, least squares; UACR, urine albumin-to-creatinine ratio

Safety outcomes

- The proportion of participants experiencing any TEAE and any serious TEAE was similar between LDL subgroups and treatment arms (**Table 2**)
- Rates of hyperkalemia were higher with finerenone than with placebo across all baseline LDL subgroups. Rates of hyperkalemia and serious hyperkalemia were similar between LDL subgroups within treatment arms
  - Discontinuation and hospitalization due to hyperkalemia were low in both treatment arms

Table 2. TEAEs by LDL subgroup (safety analysis set*)

	Baseline LDL <70 mg/dL		Baseline LDL 70–100 mg/dL		Baseline LDL >100 mg/dL	
TEAE, n (%)	Finerenone (n=2343)	Placebo (n=2339)	Finerenone (n=1951)	Placebo (n=1951)	Finerenone (n=1764)	Placebo (n=1747)
Any TEAE	2086 (89.0)	2075 (88.7)	1688 (86.5)	1680 (86.1)	1441 (81.7)	1464 (83.8)
Leading to discontinuation	160 (6.8)	145 (6.2)	123 (6.3)	102 (5.2)	96 (5.4)	80 (4.6)
Leading to death	37 (1.6)	61 (2.6)	30 (1.5)	33 (1.7)	37 (2.1)	49 (2.8)
SAEs	808 (34.5)	855 (36.6)	620 (31.8)	643 (33.0)	504 (28.6)	551 (31.5)
Leading to discontinuation	51 (2.2)	67 (2.9)	50 (2.6)	40 (2.1)	33 (1.9)	40 (2.3)
TEAEs of Hyperkalemia						
Any	380 (16.2)	166 (7.1)	256 (13.1)	134 (6.9)	213 (12.1)	117 (6.7)
Leading to permanent discontinuation	52 (2.2)	17 (0.7)	24 (1.2)	11 (0.6)	25 (1.4)	8 (0.5)
SAEs	28 (1.2)	4 (0.2)	18 (0.9)	10 (0.5)	18 (1.0)	2 (0.1)
Leading to permanent discontinuation	4 (0.2)	1 (<0.1)	3 (0.2)	0	2 (0.1)	1 (<0.1)
Leading to hospitalization	25 (1.1)	2 (<0.1)	15 (0.8)	7 (0.4)	17 (1.0)	1 (<0.1)
Leading to death	0	0	0	0	0	0

*Data not shown for 329 participants in the finerenone arm and 333 participants in the placebo arm with missing LDL data at baseline
LDL, low-density lipoprotein; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Conclusions

- Higher LDL at baseline was associated with risk factors for CV disease and CKD progression
  - A large proportion of participants with high baseline LDL were not receiving statin therapy as recommended, though the generalizability of this finding in trial participants to the overall patient population is unknown
- Lower LDL and use of statins at baseline were associated with reduced risk of CV outcomes in the FIDELITY dataset of participants with CKD and T2D
  - Statin use was also associated with reduced risk of kidney outcomes
- Finerenone reduced the risk of CV and kidney outcomes regardless of baseline LDL level and statin use status. Adverse events were generally consistent between LDL subgroups within treatment arms and hyperkalemia events were manageable

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References

Disclosures

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