Changes in Albuminuria Predict Cardiovascular and Renal Outcomes in Type 2 Diabetes − A *Post Hoc* Analysis of the LEADER Trial

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Abstract

OBJECTIVE: A *post hoc* analysis to investigate the association between 1-year changes in albuminuria and subsequent risk of cardiovascular and renal events.

RESEARCH DESIGN AND METHODS: LEADER was a randomized trial of liraglutide up to 1.8 mg/day versus placebo added to standard care for 3.5–5 years, in 9,340 participants with type 2 diabetes and high cardiovascular risk. We calculated change in urinary albumin-to-creatinine ratio (UACR) from baseline to 1 year in participants with >30% reduction (*N*=2,928), 30–0% reduction *N*=1,218) or any increase in UACR (*N*=4,124) irrespective of treatment. Using Cox regression, risks of major adverse cardiovascular events (MACE) were analyzed alongside a composite nephropathy outcome (from 1 year to end of trial in subgroups by baseline UACR [<30 mg/g, 30–300 mg/g or ≥300 mg/g]). The analysis was adjusted for treatment allocation alone as a fixed factor and for baseline variables associated with cardiovascular and renal outcomes.

RESULTS: For MACE, hazard ratios (HRs) for those with >30% and 30%–0% UACR reduction were 0.82 (95% CI 0.71–0.94; *P*=0.006) and 0.99 (0.82–1.19; *P*=0.912), respectively. For the composite nephropathy outcome, respective HRs (95% CI) were 0.67 (0.49–0.93; *P*=0.02) and 0.97 (0.66–1.43; *P*=0.881). Results were independent of baseline UACR and consistent in both treatment groups. After adjustment, HRs were significant and consistent in >30% reduction subgroups with baseline micro- or macroalbuminuria.

CONCLUSIONS: A first-year albuminuria reduction was associated with fewer cardiovascular and renal outcomes, highlighting the importance of measuring albuminuria during treatment to monitor cardiovascular and renal risk.

Evidence from observational studies and clinical trials in diabetes has demonstrated albuminuria to be a strong predictor of cardiovascular (CV) (1; 2) and renal events (3-5). The clinical use of albuminuria groups, i.e. normo-, micro- and macroalbuminuria (based on urinary albumin-to-creatinine ratio [UACR] values of 0−<30 mg/g, 30−300 mg/g and ≥300 mg/g, respectively), and provide useful parameters for treatment decisions. Recent large meta-analyses strengthen an emerging body of evidence for the role of albuminuria as a renal risk factor and its reduction as a target for treatment in kidney disease (6; 7). In the latter meta-analysis, treatment for the most part was based on inhibition of the renin-angiotensin system (RAAS) or other antihypertensive agents.

Recent data from a number of trials indicate that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) lower albuminuria and also provide CV and renal benefits in participants with type 2 diabetes (T2D) (8-12). The GLP-1 RAs liraglutide and semaglutide have shown both CV (9) and renal benefits (10) in participants with T2D and high CV risk in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) and Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN 6) trials (9; 13). In both trials, there was a significant reduction in albuminuria and a prevention of development of macroalbuminuria in the GLP-1 RA-treated groups. In addition, in the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trial, the GLP-1 RA dulaglutide demonstrated a 18% overall reduction in UACR alongside a 15% reduction in the composite renal outcome compared with placebo in a cohort of participants with T2D with and without established CV disease (14).

Using the data from the LEADER trial, we tested the hypothesis that a reduction in UACR is associated with a reduction of CV and renal risks in a cohort treated with a GLP-1 RA or

placebo, on a background of control of established CV risk factors and continuous use of RAAS blockade in the vast majority of participants.

METHODS

The LEADER trial (NCT01179048) design, detailed methods, and primary results have been published previously (9; 15). In brief, 32 countries participated in this randomized, double-blind, placebo-controlled trial, which was designed to assess the CV safety of liraglutide in participants with T2D at high CV risk. A total of 9,340 participants were randomized 1:1 to receive either subcutaneous liraglutide (1.8 mg/day or the maximum tolerated dose of 0.6–1.8 mg/day), or matching placebo, both in addition to standard of care therapy. The treatment period was 3.5–5 years, with a 30-day follow-up period. The vast majority (>80%) of the participants were treated with inhibitors of the RAAS system, more than 40% received insulin, 88% any glucose-lowering agent and 76% lipid-lowering agents.

The primary outcome was the time from randomization to first occurrence of a composite of major adverse CV events (MACE), consisting of CV death, nonfatal myocardial infarction, or nonfatal stroke. Secondary time-to-event outcomes included a four-component nephropathy composite (new onset of persistent macroalbuminuria or a persistent doubling of serum creatinine, i.e. confirmed by a second reading (15) and estimated glomerular filtration rate [eGFR] $\leq$45 ml/min/1.73 m^2, need for continuous renal-replacement therapy [in the absence of an acute reversible cause], and death from renal disease).

In this *post hoc* analysis, we analyzed the risk of MACE and a three-component nephropathy composite (doubling of serum creatinine and eGFR <45 ml/min/1.73m^2, renal replacement therapy, or renal death) in participants with a UACR measurement at baseline and at 1 year after randomization. The component 'new onset of persistent macroalbuminuria' was excluded from the renal composite outcome for this analysis, as one subgroup in the current analysis comprised participants with pre-existing macroalbuminuria. Participants were stratified into three categories according to change in UACR from baseline to 1 year (>30% reduction, 30–0% reduction, and any increase from baseline). These thresholds for changes in albuminuria were chosen based on previous analyses of trials using RAAS inhibition (4; 16; 17). In addition, the analyses were repeated in subgroups with baseline normo-, micro- and macroalbuminuria. For the purposes of comparison, the group with any increase in UACR from baseline served as the reference.

UACR and serum creatinine levels were measured at randomization, after 12 months and annually thereafter, and at trial completion; additionally, serum creatinine level was measured at month 6. All measurements were done centrally (15). UACR or creatinine measurements less than limit of quantification (LLoQ) were imputed using a value of ½ x LLoQ; those measurements greater than the higher limit of quantification (HLoQ) were imputed using the HLoQ value.

CV and renal events included in the composite outcomes were adjudicated by an independent, blinded committee (15). Time to event from 1 year to end of study according to change in UACR from baseline to the 1-year visit, and UACR groups at baseline were analyzed using a Cox proportional-hazards model. The analysis was adjusted for treatment allocation alone (liraglutide versus placebo) as a fixed factor and also for

treatment and covariates (age, gender, systolic and diastolic blood pressure, eGFR, body weight, HbA_{1c}, UACR and smoking status at baseline and changes in systolic and diastolic blood pressure, eGFR, body weight, and HbA_{1c} from baseline to the 1-year visit). All participants who underwent randomization and who had measurements of UACR at baseline and at the 1-year visit were included and, if there was no event, censored from analysis at time of death or the end of follow-up, whichever came first. Events within the first year were excluded from the analysis. Change in UACR at 1 year was analyzed using a mixed-effects model for repeated measures on log-transformed values according to UACR baseline subgroup (normo-, micro- or macroalbuminuria) adjusted for continuous UACR at baseline (log transformed), age, anti-diabetic medication at baseline, gender, and interaction between randomized treatment and UACR subgroup. For each UACR baseline subgroup the change in continuous UACR from baseline was derived as a ratio (summarised in percentages) according to treatment and across treatment.

We assessed the impact of regression to the mean by calculating the 'nonparametric' regression dilution coefficient using the MacMahon-Peto method dividing UACR data into deciles (18) (Supplementary Fig. S1). Additionally, we calculated this coefficient using a linear model with the log-transformed UACR values at 1 year as a dependent variable, and the log transformed UACR values at baseline as a covariate and then used the reciprocal of the regression coefficient to estimate the 'parametric' dilution coefficient. These analyses could be potentially impacted by a survival bias within the first year as patients with a high UACR at baseline risk were at a higher risk for all-cause death, specifically within the first year of follow-up and during the trial.

The trial was approved by ethics committees/institutional review boards, and all patients provided written informed consent. The trial was conducted in accordance with the Declaration of Helsinki.

RESULTS

Of the 9,340 participants randomly assigned in the LEADER trial, 9,113 had UACR measured at baseline (15). The patient disposition is shown in Supplementary Fig. S2. After 1 year, 8,270 patients (89% of the randomized population) had a follow-up albuminuria measurement and were included in this *post hoc* analysis. The demographics of this subgroup population are given in Table 1 and did not differ in any notable way from the full study population.

UACR changes at 1 year

Approximately half of the patients had an increase in albuminuria during the first year of the trial ($n = 4,124$; 47% of the population in this analysis), of which 498 patients (12.1%) experienced CV events and 113 (2.7%) renal events. The remainder of the population had a reduction of up to 30% from baseline ($n = 1,218$; 14%) or >30% reduction ($n = 2,928$; 34%) from baseline UACR during the first year. Overall reduction in UACR was 3.5% (95% CI: 1%−6%); UACR decreased by 15% (95% CI: 13%−18%) in the liraglutide group compared with an estimated increase of 10% (95% CI: 7%−14%) in the placebo group. Compared with any increase in UACR (reference), patients with a decrease of up to 30% had a similar risk of MACE (12.1%) with a hazard ratio (HR) of 0.99 (95% CI 0.82−1.19), P = 0.912. For the composite nephropathy outcome, the HR (95% CI) was 0.97 (0.66−1.43), P = 0.881. For patients with a 1-year reduction in UACR of more than 30% from baseline, the HR (95% CI) for MACE was 0.82 (0.71−0.94), P = 0.006, and 0.67 (0.49−0.93), P =

0.02 for the composite nephropathy outcome. The associations between early change and subsequent MACE and renal outcomes were consistent in the liraglutide and placebo group (*P*-values for interaction were 0.516 and 0.839 for MACE and renal events, respectively). **Subgroups of baseline albuminuria**

In patients with normoalbuminuria at baseline, after 1 year, there was a mean relative reduction in UACR of 14% (95% CI: 9%, 18%). In patients with microalbuminuria, an increase in UACR of 12% (95% CI: 4%, 20%) was estimated, and in those with macroalbuminuria, UACR more than doubled (120% [95% CI: 92%, 153%]). Supplementary Fig. S3A shows the unadjusted HRs for MACE by normo-, micro- and macroalbuminuria subgroups and change in UACR, respectively. An albuminuria reduction of more than 30% from baseline was associated with a reduction in risk of MACE in patients with micro- or macroalbuminuria. The *P*-value for interaction between baseline category and change in UACR adjusted for treatment was 0.26. Fig. 1A shows the adjusted HRs for MACE with a >30% reduction in micro- and macroalbuminuria subgroups significantly associated with lower risk.

Similarly, Supplementary Fig. S3B shows the unadjusted HRs for the composite nephropathy outcome in the same subgroups. Here, a reduction in albuminuria of more than 30% was associated with renal benefit in patients with macroalbuminuria. The *P*-value for interaction between baseline category and change in UACR adjusted for treatment was 0.89. Fig. 1B depicts the same association, but with adjusted HRs and here a >30% reduction was associated with less renal risk in subgroups with baseline micro- or macroalbuminuria. In addition, a minor reduction from baseline albuminuria was associated with less renal risk. The demographics of the subgroups population are given in Supplementary Table S1.

The cumulative distribution of change from baseline to 1-year in UACR (logarithm to the ratio between 1-year measurement and baseline), is shown in Fig. 2. No interactions were seen between UACR change and use of RAAS inhibitors at baseline according to the three UACR groups for the two endpoints (data not shown).

Supplementary analyses

Analyses showed that for each standard deviation (SD) increase in UACR from baseline (log transformed) to 1-year, the HR (95% CI) was 1.19 (1.12−1.27) for MACE, and 1.79 (1.52−2.12) for renal outcome. A 1% decrease in glycated hemoglobin (HbA$_{1c}$) from baseline to 1 year in was associated with change in UACR (β) = 0.14, $P < 0.001$), adjusted for baseline HbA$_{1c}$ and log-transformed UACR.

Additionally, analyses with relative change in UACR between baseline and 1-year were performed. These adjusted analyses showed that for patients with macroalbuminuria, a doubling of UACR increased the risk of first MACE and risk of renal event by 25% (95% CI: 11%−41%) and 44% (95% CI: 27%−65%), respectively. For patients with microalbuminuria and normoalbuminuria, the corresponding numbers were 0−1% and 0−3% for first MACE and first renal event, indicating a very modest risk of UACR increase for these endpoints. We used clinically relevant changes in UACR used in previous studies. (3, 19) **Regression to the mean sensitivity analyses**

Pooled across treatment groups, there was modest evidence of regression to the mean UACR; the nonparametric dilution coefficent (representing regression on the change from baseline) using the MacMahon-Peto method and the parametric dilution coefficient (representing baseline) were 1.24 and 1.22, respectively. Every one SD increase in UACR at baseline was associated with 35% higher risk of first MACE (95% CI 27−43). Applying

the nonparametric dilution coefficient increased this estimate to 43% (95% CI 34−56). Correspondingly, every one SD increase in baseline UACR was associated with a 3.6-fold (95% CI 4.03−5.27) higher risk of a renal event which increased after applying the dilution coefficient to a 5.6-fold (95% CI 5.63−7.85) higher risk.

CONCLUSIONS

The results of this *post hoc* analysis from the LEADER trial indicate that a1-yearreduction in UACR from baseline to 1 year predicts future benefits on CV and renal outcomes. For example, a >30% reduction of UACR from baseline was associated with a reduced risk of the composite nephropathy outcome. These associations were confirmed after adjusting for clinical variables at baseline and changes in covariates up till 1 year. Indeed, approximately a third of the LEADER population experienced a substantial reduction, (i.e. >30%) of UACR which was seen more frequently with liraglutide than with placebo. Nevertheless, no treatment interaction was observed with the association of change in UACR and MACE or renal outcomes, indicating that the renal benefit of UACR reduction was not restricted to liraglutide-treated patients alone.

In subgroups with micro- or macroalbuminuria at baseline, we found that a 1-year reduction in albuminuria >30% was associated with improved CV and renal outcomes. These findings are reassuring, as these subgroups with elevated albuminuria also carry the highest risk of CV and renal events. Any effort to reduce albuminuria should be implemented in routine clinical diabetes care.

These findings from LEADER are of particular interest given that most other evidence of associations of changes in UACR and outcomes have come from trials investigating initiation of RAAS blockade, a well-known mechanism to reduce UACR. In LEADER, the

vast majority of enrolled participants were on standard dose RAAS blockade at randomization and remained on that therapy for the duration of the trial.

Our findings are in line with previous observational and *post hoc* studies (19) and recent meta-analyses (6; 7) performed in cohorts where treatment was mostly based on initiation of RAAS inhibitors or non-GLP-1 RA antihypertensive treatments. .

Of note is the dual benefit associated with a significant reduction of albuminuria for the CV and renal outcomes. We observed a 25% and 58% relative risk reduction of these outcomes, respectively, in the group with baseline microalbuminuria (based on the adjusted analyses); a >30% reduction in albuminuria after 1 year in the group with baseline macroalbuminuria was associated with a 43% lower risk of both CV and renal outcomes. Few other targeted risk factor interventions in T2D are associated with this magnitude of risk reduction.

Previous *post hoc* analyses investigating the benefit of albuminuria reduction are mostly from randomized trials of mono- or dual-RAAS-blocking therapies. In an analysis of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trials, two large CV randomized clinical trials ran in parallel in patients with vascular disease or high risk diabetes, many of whom had albuminuria, Schmieder et al. (20) reported that a two-fold or greater decrease in albuminuria predicted both CV and renal benefit compared to a minor change in albuminuria.

Similarly, in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) it was demonstrated that >30% reduction from baseline albuminuria

was associated with both greater CV and renal protection (4; 21). We chose the same cutoff (>30% reduction) for our analysis, and it is interesting that this is still clinically significant in a modern cohort of patients with T2D, most of whom were on RAAS-blocking treatment. (2).. A large meta-analysis of 41 randomized clinical trials recently demonstrated close associations between albuminuria reduction and lower risk of renal outcome. In the analysis, a 30% decrease in albuminuria was associated with a 27% lower risk for a composite renal endpoint of end-stage renal disease, eGFR <15 ml/min/1.73m^2 or doubling of serum creatinine (6). In addition, in a real-world setting, Italian authors demonstrated that a remission of albuminuria category led to a reduction in renal risk in a cohort gathered from 100 diabetes centers(22).

The novelty of our analysis is that the LEADER trial was not investigating RAAS blocking or antihypertensive treatment, but a diabetes treatment with pleiotropic effects. This supports focus on albuminuria reduction as an overall clinical treatment goal, alongside the reduction in glycemic control, blood pressure, and lipid levels in diabetes treatment guidelines (23). The drawback at present is that we are lacking prospective intervention trials that target higher and lower goals of UACR, and examine renal and CV outcomes, comparable to intensive versus standard goals of blood pressure or glycemic control.

We need a better mechanistic understanding of the potential damage caused by albuminuria in order to develop appropriately targeted therapies. In the meantime, it is comforting that several GLP-1 RAs now have documented albuminuria-lowering effects that may well contribute to their overall renal benefit. Studies have shown reductions in albuminuria of 17−32% with liraglutide (11; 24), 2−39% with lixisenatide (25), and 29% with dulaglutide (26). Dipeptidyl peptidase-4 inhibitors, on the other hand, seem to have less albuminuria-lowering potential, as demonstrated in the placebo-controlled Efficacy,

Safety & Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with LINAgliptin (MARLINA) trial in which linagliptin led to a nonsignificant 6% albuminuria reduction (27). Similar effects sizes were observed in the DELIGHT trial, where saxagliptin was added to dapagliflozin (28). However, the subsequent linagliptin outcome trial Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) (29) showed potential for reduced albuminuria progression, HR 0.86 (0.78–0.95) $P = 0.003$, as did a previous analysis of the Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications (SAVOR-TIMI 53) trial with saxagliptin, which also showed significant reduction of albuminuria in the normoalbuminuric range ($P = 0.021$) (30).

There are limitations to our analysis. Although LEADER was a large trial with a long follow-up, this remains a *post hoc* analysis with all the inherent problems that preclude causal inferences. Firstly, it is not clear whether the reductions in albuminuria are the cause of improved outcomes or merely markers of other factors such as general endothelial integrity. Also, the LEADER trial was conducted in a population with T2D with high CV risk, thus the findings from this analysis may not be generalizable to a broader patient population. UACR measurement was based on a single urine sample, which may lead to higher variability compared to using two or three samples and potential regression to the mean. However, it has been shown that a single sample can be used in a large study population with T2D and macroalbuminuria (31). Morning spot urine samples are well suited for use in clinical trials of albuminuria, and logistically challenging 24-hour urine collections are not needed (32; 33). Futhermore, UACR measurements at an earlier stage of treatment, such as after 3 or 6 months of treatment, would have helped to describe the time course of albuminuria changes. Finally, no control for multiplicity was performed.

In conclusion, the results of the current study in a large, contemporary population of patients with T2D followed for a median of 3.8 years confirm the close association of reductions in UACR with reduced risk for major CV and renal outcomes in patients with T2D at high CV and moderate renal risk. These data strongly support the concept of a randomized controlled trial testing lower and higher target levels of UACR on major CV and renal outcomes.

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Table 1 – Baseline demographics of the LEADER population included in the current *post hoc* analysis according to baseline albuminuria status

	UACR <30 mg/g (*n* = 5,256)	UACR 30–300 mg/g (*n* = 2,180)	UACR ≥300 mg/g (*n* = 834)
Male, *n* (%)	3,277 (62.3)	1,492 (68.4)	569 (68.2)
Age, years	64.0 ± 7.1	64.8 ± 7.1	64.3 ± 7.2
Diabetes duration, years	11.9 ± 7.7	13.5 ± 8.1	15.7 ± 8.0
Geographic region, *n* (%)			
Europe	2,037 (38.8)	739 (33.9)	214 (25.7)
North America	1,479 (28.1)	661 (30.3)	241 (28.9)
Asia	355 (6.8)	212 (9.7)	104 (12.5)
Rest of the world	1,385 (26.4)	568 (26.1)	275 (33.0)
HbA$_{1c}$, %	8.5 ± 1.4	9.0 ± 1.6	9.0 ± 1.7
mmol/mol*	69.2 ± 15.0	74.5 ± 17.7	74.7 ±18.9
BMI, kg/m^2	32.6 ± 6.2	32.3 ± 6.2	32.0 ± 6.4
Body weight, kg	91.8 ± 20.1	91.2 ± 21.4	89.7 ± 21.8
Systolic blood pressure, mmHg	133.5 ± 16.4	138.2 ± 17.7	145.1 ± 20.0
Diastolic blood pressure, mmHg	76.6 ± 9.8	77.7 ± 10.4	79.2 ± 10.6
Heart failure,[†] *n* (%)	759 (14.4)	300 (13.8)	95 (11.4)
Severe or moderate renal disease,[‡] *n* (%)	861 (16.4)	533 (24.5)	426 (51.1)
eGFR, ml/min/1.73m^2	84.3 ± 25.3	79.8 ± 27.5	63.1 ± 28.5

Data are means ± SD or number of patients (% of total liraglutide- or placebo-treated patients).

*Calculated not measured; [†]Chronic heart failure (New York Heart Association class II or III). [‡]Based on MDRD eGFR.
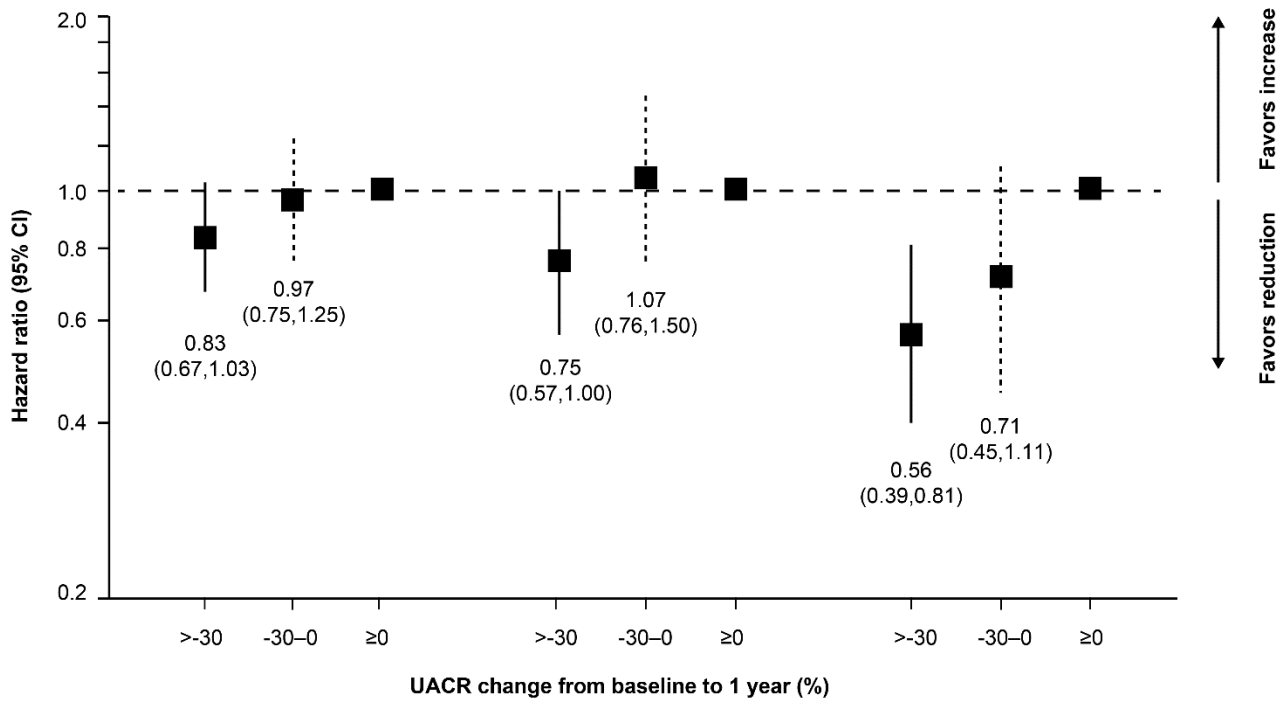BMI, body mass index; MDRD, Modification of Diet in Renal Disease; *n*, number of patients.

Figure legend

Figure 1 – Cardiovascular (A) and renal (B) events by baseline albuminuria and change in albuminuria from 1 year and onwards (adjusted values).
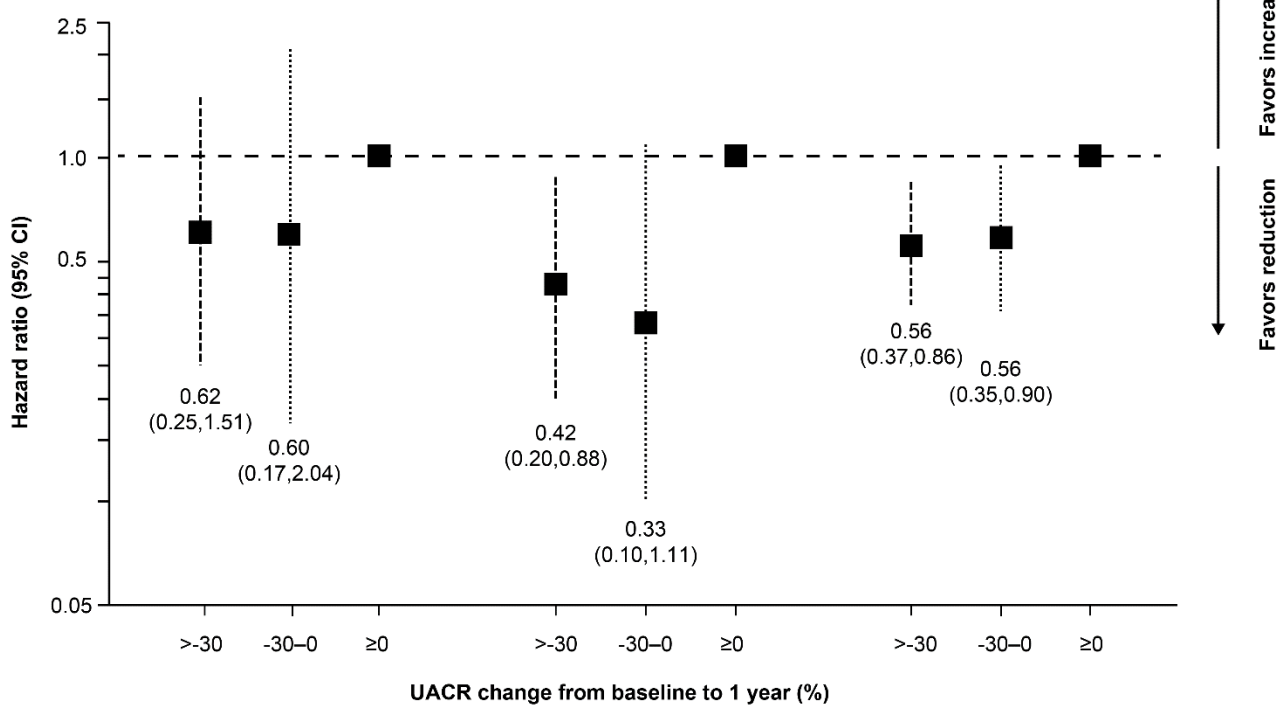
A

	Normoalbuminuria			Microalbuminuria			Macroalbuminuria		
N =	1580	755	2921	978	329	873	371	133	330
N_{events} =	135	74	290	102	47	121	60	26	87
P-value =	0.097	0.796		0.048	0.698		0.002	0.131	

Favors increase

Favors reduction

Hazard ratio (95% CI)

2.0

1.0

0.8

0.6

0.4

0.2

0.83
(0.67,1.03)

0.97
(0.75,1.25)

0.75
(0.57,1.00)

1.07
(0.76,1.50)

0.56
(0.39,0.81)

0.71
(0.45,1.11)

>-30   -30–0   ≥0   >-30   -30–0   ≥0   >-30   -30–0   ≥0

UACR change from baseline to 1 year (%)

B

	Normoalbuminuria			Microalbuminuria			Macroalbuminuria		
N =	1580	755	2921	978	329	873	371	133	330
N_{events} =	8	3	18	14	3	21	40	27	74
P-value =	0.292	0.418		0.021	0.072		0.007	0.018	

Favors increase

Favors reduction

Hazard ratio (95% CI)

2.5

1.0

0.5

0.05

0.62
(0.25,1.51)

0.60
(0.17,2.04)

0.42
(0.20,0.88)

0.33
(0.10,1.11)

0.56
(0.37,0.86)

0.56
(0.35,0.90)

>-30   -30–0   ≥0   >-30   -30–0   ≥0   >-30   -30–0   ≥0

UACR change from baseline to 1 year (%)

Cardiovascular events defined as the time from randomization to first occurrence of a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. Renal events defined as a three-component nephropathy composite (doubling of serum creatinine and eGFR <45 ml/min/1.73m^2, renal replacement therapy.

Figure 2 – Cumulative distribution of UACR from baseline to 1-year

UACR, urinary albumin-to-creatinine ratio.