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Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL

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Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL.

Background. Proteinuria or albuminuria is an established risk marker for progressive renal function loss. Albuminuria can be effectively lowered with antihypertensive drugs that interrupt the renin-angiotensin system (RAS). We investigated whether albuminuria could not only serve as a marker of renal disease, but also function as a monitor of the renoprotective efficacy of RAS intervention by the angiotensin II (Ang II) antagonist, losartan, in patients with diabetic nephropathy.

Methods. The data from the RENAAL (Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) study, a double-blind, randomized trial, were used to examine the effects of losartan on the renal outcome [i.e., the primary composite end point of doubling of serum creatinine, end-stage renal disease (ESRD) or death] in 1513 type 2 diabetic patients with nephropathy. We examined the effect of the degree of albuminuria at baseline, initial antiproteinuric response to therapy, and the degree of remaining (residual) albuminuria on renal outcome (either the primary composite end point of RENAAL or ESRD). We also evaluated the contribution to renal protection of the antiproteinuric effect of losartan independently of changes in blood pressure.

Results. Baseline albuminuria is almost linearly related to renal outcome, and is the strongest predictor among all measured well-known baseline risk parameters. After adjusting for baseline risk markers of age, gender, race, weight, smoking, sitting diastolic blood pressure, sitting systolic blood pressure, total cholesterol, serum creatinine, albuminuria, hemoglobin, and hemoglobin A_{1c} (HbA_{1c}) patients with high baseline albuminuria (≥3.0 g/g creatinine) showed a 5.2-fold (95% CI 4.3–6.3) increased risk for reaching a renal end point, and a 8.1-fold (95% CI 6.1–10.8) increased risk for progressing to ESRD, compared to the low albuminuria group (<1.5 g/g). The changes in albuminuria in the first 6 months of therapy are roughly linearly related to the degree of long-term renal protection: every 50% reduction in albuminuria in the first 6 months was associated with a reduction in risk of 36% for renal end point and 45% for ESRD during later follow-up. Albuminuria at month 6, designated residual albuminuria, showed a linear relationship with renal outcome, almost identical to the relationship between baseline albuminuria and renal risk. Losartan reduced albuminuria by 28% (95% CI −25% to −36%), while placebo increased albuminuria by 4% (95% CI +8% to −1%) in the first 6 months of therapy. The specific (beyond blood pressure lowering) renoprotective effect of the Ang II antagonist, losartan, in this study is for the major part explained by its antialbuminuric effect (approximately 100% for the renal end point, and 50% for ESRD end point).

Conclusion. Albuminuria is the predominant renal risk marker in patients with type 2 diabetic nephropathy on conventional treatment; the higher the albuminuria, the greater the renal risk. Reduction in albuminuria is associated with a proportional effect on renal protection, the greater the reduction the greater the renal protection. The residual albuminuria on therapy (month 6) is as strong a marker of renal outcome as is baseline albuminuria. The antiproteinuric effect of losartan explains a major component of its specific renoprotective effect. In conclusion, albuminuria should be considered a risk marker for progressive loss of renal function in type 2 diabetes with nephropathy, as well as a target for therapy. Reduction of residual albuminuria to the lowest achievable level should be viewed as a goal for future renoprotective treatments.

Key words: proteinuria, albuminuria progressive renal function loss, angiotensin II antagonism, type 2 diabetes.

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It is estimated that type 2 diabetes affects more than 150 million people worldwide and its prevalence is projected to double in the next 25 years [1, 2]. Diabetic nephropathy is characterized by hypertension, macroalbuminuria (proteinuria), progressive loss of renal function, plus a high incidence of cardiovascular morbidity and mortality. The four most important risk factors and/or markers for these outcomes are hyperglycemia, hypertension,

hyperlipidemia, and proteinuria or albuminuria. Treatment of type 2 diabetes has focused on attenuating hyperglycemia, hypertension, and dyslipidemia [3–5].

The predictive power of proteinuria (>500 mg/day) or albuminuria for progressive renal insufficiency has been previously demonstrated in patients with diabetic or nondiabetic renal disease [3, 6, 7]. This risk appears to be independent of other established risk markers such as hyperglycemia and hypertension. Several therapeutic options are available to reduce proteinuria. Interruption of the renin-angiotensin system (RAS) with either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II (Ang II) antagonists is frequently used. These drugs also lower blood pressure, which has made it difficult to separate antihypertensive from antiproteinuric effects as the mediator of renoprotection. To date, no clinical trial has been performed with the primary objective of studying the effect of suppressing albuminuria without reducing blood pressure on outcomes of renal function. Data from several clinical trials and a meta-analysis indicate that blocking the RAS with ACE inhibitors is more renoprotective than other blood pressure–lowering strategies; the benefit coincided with a reduction in albuminuria in both nondiabetic and type 1 diabetic subjects [6, 8, 9]. Results from two large clinical trials using Ang II antagonists to treat type 2 diabetic patients with albuminuria, the IDNT Trial [10] and the RENAAL Study [11], reveal the striking benefits of blocking the RAS on preserving renal function. We decided to examine if the renoprotective property of RAS intervention could be attributed to a reduction in albuminuria, which could be separated from blood pressure reduction.

Specifically, we examined whether albuminuria is an independent renal risk marker in type 2 diabetes with kidney disease. Second, we examined whether the degree of initial reduction in albuminuria would be an indicator of long-term renal protection. Finally, we examined whether the degree of albuminuria found during continued therapy (residual albuminuria) was as important risk factor for kidney damage as was the degree of albuminuria at baseline. If these questions are answered positively, it would suggest that albuminuria is a specific therapeutic target for treating patients with kidney disease in addition to blood pressure reduction [12].

METHODS

Patients and study design

Results from RENAAL, a multinational, double-blind, randomized trial comparing losartan versus placebo, each in addition to conventional antihypertensive therapy, excluding ACE inhibitors and other Ang II antagonists, were examined. RENAAL was performed in 28 countries and in 250 centers and involved 1513 patients. The study design, inclusion/exclusion criteria, and the treatment protocols have been reported previously [11, 13]. Participants were considered to have type 2 diabetes if they were older than 30 years at time of diagnosis of diabetes, had no history of diabetic ketoacidosis, and did not require insulin within 6 months of diagnosis. As an index of nephropathy, urinary albumin:creatinine ratio >300 mg/g in a first morning void or a 24-hour urine protein >500 mg was defined as an entry criterion. At the time of randomization, patients were stratified according to degree of albuminuria (<2000 mg/g or ≥2000 mg/g). A serum creatinine >1.5 mg/dL in males (>1.3 mg/dL in females or males <60 kg) to 3.0 mg/dL, a glycosylated hemoglobin A_{1c} (HbA_{1c}) <12%, and an age of 31 to 70 years were also part of the inclusion criteria. Patients with type 1 diabetes or a history of nondiabetic kidney disease were excluded. Non-ACE inhibitors or Ang II antagonist antihypertensive therapy (including diuretics, beta blockers, calcium channel blockers, alpha blockers, or centrally acting agents) was maintained during the baseline phase. After the 6-week baseline period, patients were randomized to treatment with either losartan or placebo, and were followed for a mean of 3.4 years. All patients signed informed consent prior to enrollment, and the study was approved by the local Institutional Review Board of each participating center.

Prior to randomization and every 3 months post-randomization, blood samples were obtained to measure chemistry and hematologic parameters, and a first-morning urine sample was obtained to measure the albumin:creatinine ratio (g/g). In a subset of patients 24-hour urine samples also were collected in order to measure total protein. All blood and urine tests were performed in a central laboratory. Seated trough blood pressure was measured three times in a sitting position after a resting period of at least 5 minutes, and prior to ingestion of daily antihypertensive medications. The average of these measurements was recorded. Glomerular filtration rates (GFR) were not measured in the study, but estimated for each patient using the modified Modification of Diet in Renal Disease (MDRD) Study formula and expressed per 1.73 m^2 of body surface area (BSA) [abstract; Levey AS, et al, *J Am Soc Nephrol* 11:155A, 2000). The target blood pressure was diastolic <90 mm Hg and systolic <140 mm Hg.

The primary efficacy parameter was a composite end point of time to the first event of doubling of serum creatinine, end-stage renal disease (ESRD), or death. Doubling of serum creatinine was defined as the first serum creatinine value that was twice the baseline value, confirmed with a second serum creatinine value obtained at least 4 weeks after the initial doubling. ESRD was defined as the need for chronic dialysis or renal transplantation. Analyses of the components of the primary composite end points also were prespecified. Albuminuria

(proteinuria) reduction over time between two treatment groups was one of the secondary end points.

Data analysis

The target of the current analysis focuses on the secondary end point of albuminuria. Albuminuria was assessed using the ratio of albumin (g/L) to creatinine (g/L) concentrations from a first-morning urine sample, and designated "albuminuria" throughout the **Results** section. In a subset of patients actual 24-hour urine was collected and total protein was measured. For comparison, baseline 24-hour proteinuria data from this subset are presented as part of the demographic tables. According to the study protocol, albuminuria should have been collected during the baseline period, and every 3 months postrandomization for the duration of the study. Baseline albuminuria was determined by the average of the last two measurements prior to randomization. Postrandomization albuminuria at each visit was determined by a prespecified time window around each scheduled visit.

To analyze therapy-induced changes in albuminuria, baseline albuminuria was compared with the albuminuria at month 6 or the last postrandomization value prior to the renal event if the event of interest occurred before month 6. If no postrandomization value was observed an imputed albuminuria value was used (see **Statistical Analysis** section). The 6-month time point for therapy-induced changes of specified variables was chosen because this was the earliest time point that most variables of interest are available, the therapy effect was considered fully present, and few renal events occurred before month 6. The albuminuria reduction at month 6 was calculated as 100% $\times$ (1 ratio of albuminuria at month 6 over baseline).

In the current analysis, the renal end points are defined as follows: (*1*) the primary combined end point of doubling of serum creatinine, ESRD, or death, designated renal end point; and (*2*) individual component of ESRD.

For patients who had multiple end points of different types, only the first occurrence of a renal event was considered for the renal end point. There were no lost to follow-up patients; therefore, ESRD or death outcomes were collected for all randomized patients; collection of the doubling of serum creatinine component of the renal end point was considered to be incomplete, due to patient discontinuation prior to reaching doubling of serum creatinine. Patients who did not have an end point of interest during the study were considered censored at the study cutoff date.

Statistical analysis

All 1513 randomized participants in RENAAL were included in the analysis from randomization through the study termination date. Patient characteristics, blood pressure, and laboratory parameters at baseline were summarized either by treatment group or baseline albuminuria categories. Prognostic factors over the study follow-up were summarized by treatment group. Patients with a missing value for a given variable at a given time-point were not included in this summary. Month 6 changes from baseline in prognostic factors were assessed by month 6 albuminuria categories. For this summary, missing values for a given variable were imputed (see below). Mean and standard deviation were provided for continuous variables, and statistical significance for the between group comparison was determined based on a two-sample *t* test. Number of patients was provided for categorical variables. Since albuminuria shows a skewed distribution in this study, averages were expressed as geometric mean at baseline. Month 6 change from baseline was expressed as geometric mean ratio (post versus baseline) by using the natural log (albuminuria) in calculation.

In order to identify risk factors at baseline and therapy-induced changes in risk factors at month 6 that were independent predictors of the renal end points, baseline and baseline and change at month 6 multivariate Cox models were performed. Baseline risk factors were selected among the following covariates: age, gender, race, weight, smoking, sitting diastolic blood pressure, sitting systolic blood pressure, total cholesterol, serum creatinine, hemoglobin, HbA_{1c}, and albuminuria. Risk factors for the therapy induced change analysis were selected among month 6 changes for weight, sitting diastolic blood pressure, sitting systolic blood pressure, serum creatinine, and $HbA_{1c,}$ and albuminuria on the natural log scale. The change was defined by the difference between month 6 and baseline. The month 6 data were selected in the day range of 138 to 228 and prior to an end point of interest. Few patients had events prior to month 6, and the most recent postrandomization value prior to month 6 was used. For all multivariate analyses, including those described in the following paragraphs, a backward selection method was used with the significance level <0.01 for removing a covariate from the model. The strength of a risk factor as an independent predictor included in the final analysis for each endpoint was determined by its magnitude of significance using chi-squared statistics.

The association between albuminuria and the renal and ESRD end points were estimated using the Kaplan-Meier procedure, with baseline albuminuria stratified into three, post hoc subgroups: <1.5 g/g, $\geq 1.5 < 3.0$ g/g, and ≥ 3.0 g/g. To estimate a risk increase over the subgroup <1.5 g/g, a multivariate Cox regression model was performed with indicators of baseline albuminuria subgroups as a factor. A similar analysis also was done when adjusting for other baseline covariates described above (with the exception of albuminuria). To further explore the hazard risk profile (when adjusting for other baseline covariates), finer categories (<0.5, $\geq 0.5 < 1.5$, $\geq 1.5 < 3.5$, and ≥ 3.5 g/g) in both

baseline albuminuria and month 6 residual albuminuria were used in a similar Cox model with the lowest category as a common reference to compute the hazard ratio and 95% CI for the remainder of the categories. For comparison in risk profile (adjusted for other baseline covariates) between two treatment groups, the same categories (<0.5, $\geq 0.5<1.5$, $\geq 1.5<3.5$, and ≥ 3.5 g/g) in baseline and month 6 residual albuminuria were used in the analysis. The lowest category was used as a common reference for the placebo treatment group. For the losartan treatment group, the hazard ratio with 95% CI was referenced by the corresponding placebo category. Again, the finer categories were chosen post hoc, with the aim of providing a smooth risk profile, when adjusting for other baseline risk factors.

To estimate the effect of albuminuria change on renal and ESRD end points, analyses similar to baseline albuminuria were performed including the Kaplan-Meier estimates and multivariate Cox regression models when patients were stratified by three response groups in albuminuria reduction at month 6: $<0\%$, $\geq 0<30\%$, and $\geq 30\%$. In additional to baseline covariates, the previously described month 6 change variables (with the exception of log albuminuria) were also included in the adjusted multivariate analyses. To further explore the hazard risk profile, finer categories in albuminuria reduction (<-40, $\geq -40<-10$, $\geq -10<10$, $\geq 10<40$, $\geq 40<60$, and $\geq 60\%$) were used in a similar Cox model with the lowest category as a common reference to compute the hazard ratio and 95% CI for the remainder of the categories. Again, these categories were chosen post hoc, with the aim of providing a smooth risk profile, when adjusting for other baseline risk factors.

Some patients had missing values for relevant baseline and month 6 parameters. The number (%) of patients with missing baseline values are as follows: hemoglobin, 45 (3.0%); HbA_{1c}, 17 (1.1%); total cholesterol, 15 (1.0%); smoking, 4 (0.3%). It is important to note that no patients had missing baseline albuminuria or serum creatinine values. The number (%) of patients with missing month 6 values (prior to the renal end point) are as follows: HbA_{1c}, 197 (13.0%); albuminuria, 43 (2.8%); serum creatinine, 9 (0.6%); weight, 8 (0.5%); and sitting diastolic blood pressure or sitting systolic blood pressure, 6 (0.4%). In order to include all randomized patients into the multivariate Cox models (especially to compare the losartan with placebo groups), missing values either at baseline or month 6 were populated initially by imputation using linear regression models. Each dependent variable at baseline (or month 6) was run in the model with a set of baseline variables with complete baseline measurements (independent variables), including age, gender, race, region, blood pressure, weight, prior therapies, and lab parameters (i.e., serum creatinine, estimated GFR, albuminuria, blood urea nitrogen (BUN), glucose, serum potassium, sodium, chloride, and uric acid). A backward selection method was performed to identify covariates with a significance level of alpha $= 0.05$. The independent variables in the final model served as the predictors for patients who had either missing baseline or month 6 values.

The statistical package SAS version 8 was used for this analysis.

RESULTS

Baseline albuminuria as predictor of renal outcome

Table 1 show the baseline data and risk markers of the placebo and losartan subgroups, as well as the entire group of patients. Albuminuria was 1.8 g/g creatinine, which is equivalent to a proteinuria of 3 g/day with a range from 0.1 to 15.1 g/day. The degree of proteinuria was comparable with that measured in the subset of patients in whom 24-hour urine was collected (3.4 g/day). Of all the baseline risk markers (age, gender, smoking, ethnicity, weight, blood pressure, cholesterol, serum creatinine, albuminuria, hemoglobin, and HbA_{1c}) albuminuria was by far the strongest predictor of both the renal end point and ESRD (Table 2). Figure 1 shows the Kaplan-Meier curves for renal end points for three different baseline albuminuria subgroups. Clearly, the high (≥ 3.0 g/g) as well as the intermediate ($\geq 1.5<3.0$ g/g) albuminuria group show significantly more renal events (unadjusted hazard ratios listed in the figure). Table 3 shows the concurrent baseline values of the other risk parameters in the three albuminuria groups. Although the baseline values in the three albuminuria groups were numerically comparable, there were many small statistically significant differences observed between the three groups. However, the effect of these differences on the hazard ratio for albuminuria was limited. Adjusted hazard ratios were very similar for both renal end point and ESRD (Fig. 1). Comparing the outcomes of patients in the three groups, and when adjusting for baseline risk markers, we found that the renal endpoint was 5.2-fold higher (95% CI 4.3–6.3) in the high versus the low (<1.5 g/g) albuminuria group. The high albuminuria group had an 8.1-fold (95% CI 6.1–10.8) increased risk of progressing to ESRD compared to the low albuminuria group. To better discern the adjusted risk associated with different levels of albuminuria, we analyzed finer categories of albuminuria against the renal end points. Controlling for other (baseline) risk markers, we found an almost linear positive relationship between the degree of baseline albuminuria and the risk for having a renal endpoint or for progressing to ESRD (Fig. 2, left panels).

Reduction in albuminuria as a predictor of renal outcome

Table 4 shows the results of changes in albuminuria, blood pressure, and other variables from baseline values

Table 1. Patient demographic and other baseline characteristics in all patients, and stratified for the protocol treatment

Variables	Losartan ($N = 751$)			Placebo ($N = 762$)			Total ($N = 1513$)		
	Number	Mean	SD	Number	Mean	SD	Number	Mean	SD
Gender *female/male*	289/462			268/494			557/956		
Race									
Asian	117			135			252		
African American	125			105			230		
Hispanic	140			137			277		
Other	11			8			19		
White	358			377			735		
Smoking *yes/no*	145/604			128/632			273/1236		
Age *years*	751	60.0	7.4	762	60.3	7.5	1513	60.2	7.4
Weight *kg*	751	82.6	20.6	762	81.7	20.9	1513	82.2	20.7
Sitting systolic blood pressure *mm Hg*	751	151.8	18.7	762	153.2	19.9	1513	152.5	19.3
Sitting diastolic blood pressure *mm Hg*	751	82.4	10.3	762	82.4	10.6	1513	82.4	10.4
Cholesterol *mg/dL*	743	227.4	55.6	755	228.7	55.4	1498	228.1	55.5
GFR *mL/min/1.73 m*^{2}	751	39.7	12.0	762	40.0	12.7	1513	39.8	12.3
Hemoglobin A_{1c}%	742	8.5	1.7	754	8.4	1.6	1496	8.5	1.6
Hemoglobin *g/dL*	732	12.5	1.8	736	12.5	1.8	1468	12.5	1.8
Serum creatinine *mg/dL*	751	1.9	0.5	762	1.9	0.5	1513	1.9	0.5
Albuminuria *mg/g*	751	1873	1831	762	1743	1543	1513	1808	1693
(Geometric mean)		(1172)	.		(1148)	.		(1160)	.
Proteinuria *mg/day*[a]	350	3478	3487	360	3494	3587	710	3486	3536
(Geometric mean)		(2232)	.		(2216)	.		(2224)	.

GFR is estimated glomerular filtration rate.
Data are given a mean (SD) for continuous variables, and counts for class variables. Smoking status is defined by one year window prior to randomization.
[a]Subgroup of patients in whom 24-hour urine was collected (see **Methods** section).

Table 2. Multivariate analysis for the effect of baseline risk markers as well as for the therapy induced change in these risk markers on renal end point (ordered by statistical significance)

End point	Multivariate risk markers	Hazard ratio	95% CI Low	95% CI Up	Chi-square	*P* value
	At baseline					
Renal	Albuminuria *g/g*	1.41	1.36	1.47		<0.0001
	Serum creatinine *mg/dL*	1.91	1.64	2.23	66.9	<0.0001
	Hemoglobin *g/dL*	0.89	0.85	0.93	24.5	<0.0001
	Hemoglobin A_{1c}%	1.07	1.02	1.12	8.9	.0028
ESRD	Albuminuria *g/g*	1.45	1.39	1.52	288.7	<.0001
	Serum creatinine *mg/dL*	3.51	2.83	4.36	130.9	<.0001
	Hemoglobin *g/dL*	0.86	0.81	0.92	20.0	<.0001
	Age *10 years*	0.81	0.70	0.93	9.0	0.0026
	At baseline and change at month 6					
Renal	Serum creatinine change at month 6 *mg/dL*	4.51	3.84	5.30	332.8	<0.0001
	Albuminuria *g/g*	1.36	1.31	1.42	249.2	<0.0001
	Albumin change at month 6 natural *log*	1.91	1.69	2.16	109.0	<0.0001
	Serum creatinine *mg/dL*	1.45	1.23	1.70	20.0	<0.0001
	Hemoglobin *g/dL*	0.94	0.90	0.98	7.5	0.006
ESRD	Serum creatinine change at month 6 *mg/dL*	3.76	3.13	4.51	201.3	<0.0001
	Albuminuria *g/g*	1.43	1.36	1.51	185.1	<0.0001
	Serum creatinine *mg/dL*	3.43	2.74	4.29	115.2	<0.0001
	Albumin change at month 6 *on log*	2.38	1.99	2.84	91.3	<0.0001
	Hemoglobin A_{1c} change at month 6 %	0.86	0.80	0.92	19.0	<0.0001

ESRD is end-stage renal disease.
Top: Baseline risk factors included in the multivariate model are summarized in the **Statistical analysis** section.
Bottom: Risk factors at baseline and month 6 changes included in the multivariate model are summarized in the **Statistical analysis** section.
Risk factors are ordered by magnitude of significance as indicated by chi-square statistics.

to those found at 6 months, 1, 2, and 3 years. Results are available for the total study group as well as for the subgroups randomized to losartan and placebo treatment groups. Albuminuria was changed by −14% (95% CI −11% to −17%) in the first 6 months in the total study group, by +4% (95% CI +8 to −1%) in the placebo group, and by −28% (95% CI −25% to −36%) in the losartan group. The level of albuminuria remained relatively stable during follow-up in the placebo group. The apparent "fall" observed at 24 and 36 months is likely linked to "drop out" of patients with high albuminuria in the placebo group. In the losartan group a slight further decrease occurred also possibly due to drop out of high albuminuria subjects. Additionally, the losartan treatment

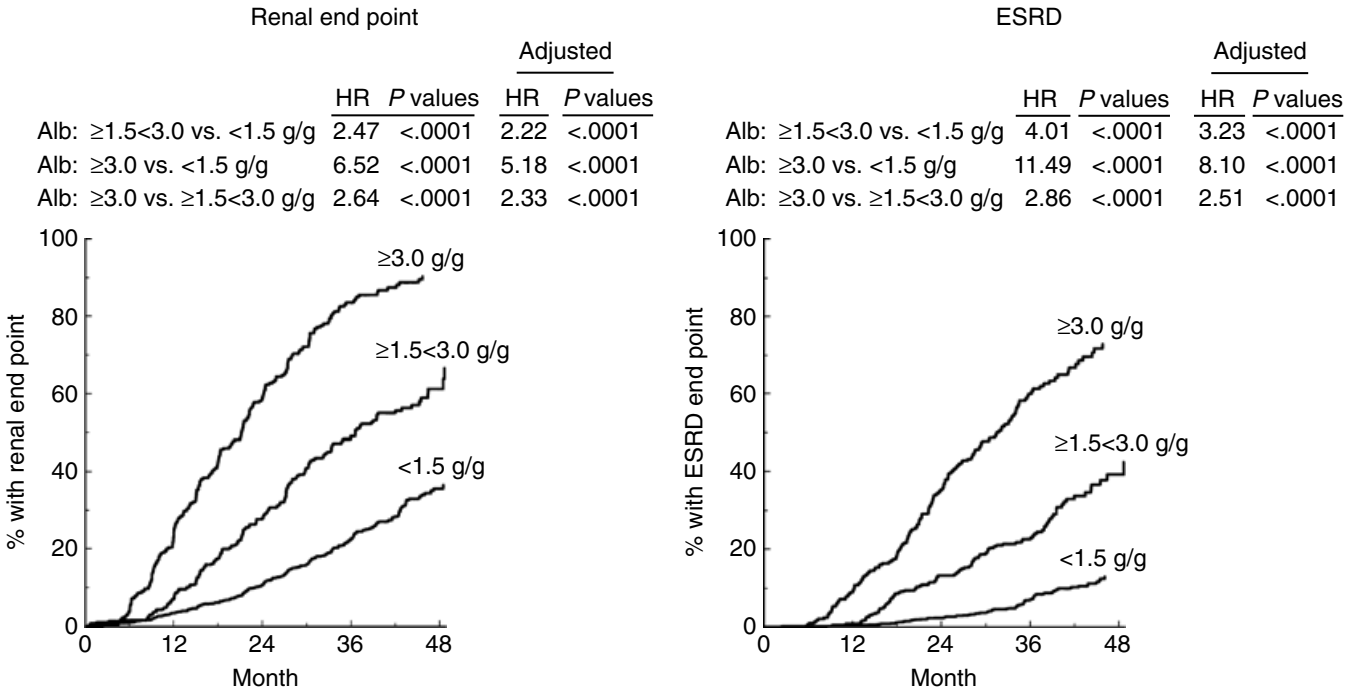

Fig. 1. Event rate of renal end points stratified by baseline albuminuria. The hazard ratio (HR) is shown at the top of each figure. The adjusted HR is corrected for all measured baseline risk markers summarized in the **Statistical analysis** section.

Table 3. Patient demographic and other baseline characteristics stratified by baseline albuminuria

	Baseline albuminuria								
	<1.5 ($N = 859$)			≥1.5<3.0 ($N = 365$)			≥3.0 ($N = 289$)		
	Number	Mean	SD	Number	Mean	SD	Number	Mean	SD
Gender *female/male*	270/589			134/231			153/136		
Race									
Asian	123			73			56		
African American	163			45			22		
Hispanic	127			70			80		
Other	10			2			7		
White	436			175			124		
Smoking *yes/no*	150/706			67/297			56/233		
Age *years*	859	61.0	7.2	365	59.7[a]	7.5	289	58.1[a]	7.8
Weight *kg*	859	83.7	19.8	365	81.3	21.1	289	78.5[a]	22.4
Sitting systolic blood pressure *mm Hg*	859	149.4	18.6	365	154.5[a]	19.1	289	159.5[a]	19.5
Sitting diastolic blood pressure *mm Hg*	859	82.1	10.7	365	82.2	10.2	289	83.8[a]	10.0
Cholesterol *mg/dL*	848	213.2	46.3	364	233.5[a]	52.3	286	265.3[a]	64.9
GFR *mL/min/1.73 m²*	859	42.6	12.2	365	38.0[a]	11.7	289	33.8[a]	11.0
Hemoglobin A_{1c}%	849	8.5	1.6	363	8.4	1.5	284	8.6	1.7
Hemoglobin *g/dL*	832	12.8	1.8	353	12.3[a]	1.8	283	11.8[a]	1.7
Serum creatinine *mg/dL*	859	1.8	0.4	365	1.9[a]	0.5	289	2.1[a]	0.5
Albuminuria *mg/g*	859	695	380	365	2173[a]	448	289	4652[a]	1543
(Geometric mean)		(571)			(2121)[a]			(4449)[a]	
Proteinuria *mg/day*[b]	442	1617	1110	142	4476[a]	1995	126	8926[a]	4333
(Geometric mean)		(1294)			(3865)[a]			(7966)[a]	.

GFR is estimated glomerular filtration rate.
Analysis based on observed data without imputing missing values.
Data are given a mean (SD) for continuous variables, and counts for class variables. Smoking is indicated as the status 1 year prior to randomization.
[a]The ≥1.5<3.0 g/g or ≥3.0 g/g groups were compared to the <1.5% g/g group. Statistical significance for these comparisons was based on a two-sample *t* test, $P < 0.05$; [b]Subgroup of patients in whom 24-hour urine was collected (see **Methods** section).

effect on reduction of albuminuria may have contributed to the late decline in albuminuria. Systolic blood pressure changed by −3% (95% CI −4% to −2%), +1% (95% CI −1% to 2%), and −1% (95% CI −2% to 0%) in the losartan, placebo, and total groups, respectively. Diastolic blood pressure changed by −3% (95% CI −4% to −2%), 0% (95% CI −1% to +1%), and −1% (95% CI −2% to −1%) in the losartan, placebo, and total groups,

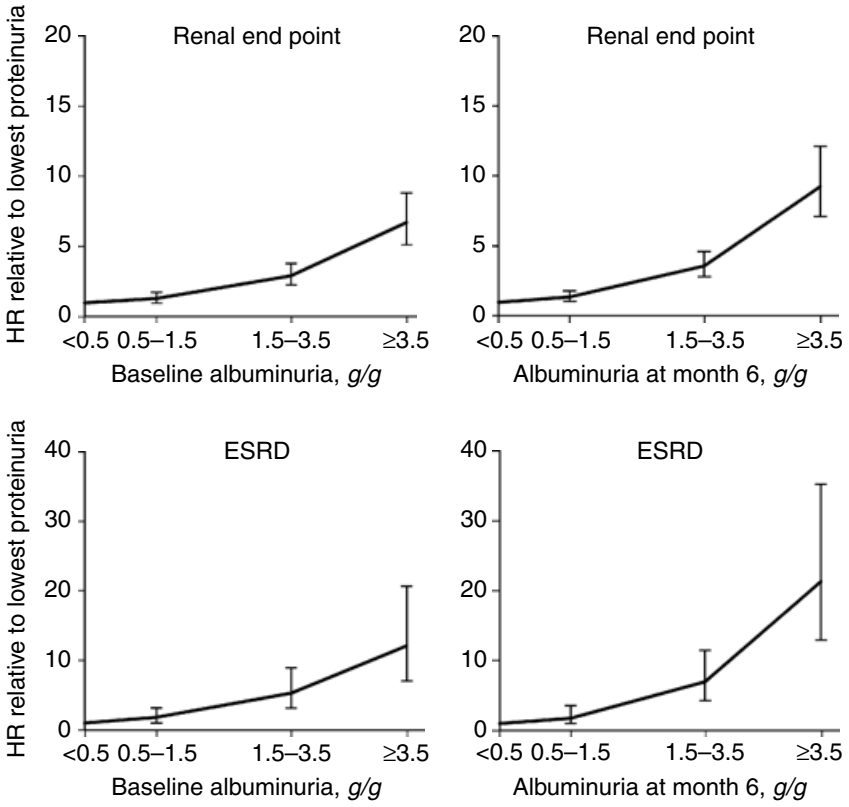

Fig. 2. Hazard ratio for renal events versus baseline albuminuria (left panels) and versus albuminuria at month 6 after treatment start (right panels). The hazard ratio (HR) with 95% CI is referenced at albuminuria <0.5 g/g. Relation is corrected for all baseline risk markers summarized in the **Statistical analysis** section.

respectively. Cholesterol and hemoglobin parameters were not collected at month 6. GFR fell slightly more in the losartan (10%) group versus placebo (8%, $P < 0.09$, NS). Modeling of the initial 6 months change in these different risk parameters for predicting the long-term renal and cardiovascular risk showed that initial albuminuria reduction is one of the strongest independent predictors of both renal outcomes (Table 2).

The change in albuminuria from baseline to 6 months was highly variable in the total study cohort, and in both the losartan and placebo-treated groups. When we subdivided the total population into three subgroups according to their initial (6 months) antialbuminuric response (<0%, ≥0<30%, and ≥30% response), renal events occurred more frequently in the groups that had little to no suppression of albuminuria. In contrast, the groups that had significant reduction in albuminuria showed fewer renal events during follow-up (Fig. 3). The changes in many parameters were significantly greater in the high (≥30%) albuminuria response group compared to the low-response (<0%) group (Table 5). However, even after correcting for these changes in other parameters plus baseline risk factors, the relative importance of suppressing albuminuria remained strong, since there was little change in the hazard ratios adjusted for these changes (see the unadjusted and adjusted hazard Rratios in Fig. 3). To better discern the adjusted risk associated with different response levels, we analyzed finer categories of antialbuminuric response versus the risk for renal outcome. As shown in Figure 4, for each increase in antialbuminuric response, there is a decrease in the frequency of renal events even after correcting for the differences in other risk factors and baseline risk factors. An increase in albuminuria in the first 6 months resulted in an increased renal risk.

Contribution of the antialbuminuric effect to the renoprotection induced by losartan

Losartan affords renoprotection beyond its blood pressure–lowering effects [11]. To examine if this additional renoprotection can be attributed to its antialbuminuric effect, we followed two strategies. First, we analyzed the hazard risk for renal events over albuminuria at both baseline and after at least up to 6 months of treatment. In patients starting with the same baseline albuminuria subsequently randomized to losartan or placebo, those receiving losartan had a lower risk for a renal event compared to those treated with placebo, particularly in those with the high baseline albuminuria ranges (Fig. 5, left panels, all corrected for other baseline risk markers). Second, an impact of reduction in albuminuria over time on the losartan treatment effect was investigated. When we adjusted for residual albuminuria (on the natural logarithm scale), prior to the renal end point, the treatment effect of losartan on the renal end

Table 4. Time course of risk markers in all patient and stratified by treatment group

Variable	Time Month	Losartan		Placebo		Total	
		Number	Mean	Number	Mean	Number	Mean
Albuminuria *mg/g*	Baseline	751	1172	762	1148	1513	1160
	6	679	817	672	1185	1351	983
	12	636	714	598	1087	1234	875
	24	517	567	500	854	1017	693
	36	306	451	269	702	575	555
Sitting systolic blood pressure *mm Hg*	Baseline	751	151.8	762	153.2	1513	152.5
	6	714	146.7	706	152.3	1420	149.5
	12	674	146.1	657	149.7	1331	147.9
	24	562	143.3	534	144.6	1096	143.9
	36	334	139.8	288	144.0	622	141.8
Sitting diastolic blood pressure *mm Hg*	Baseline	751	82.4	762	82.4	1513	82.4
	6	714	79.7	706	81.6	1420	80.7
	12	674	78.3	657	79.9	1331	79.1
	24	562	77.0	534	77.4	1096	77.2
	36	334	74.7	288	76.2	622	75.4
Cholesterol *mg/dL*	Baseline	743	227.4	755	228.7	1498	228.1
	6	35	217.1	41	213.3	76	215.1
	12	631	214.3	613	226.4	1244	220.3
	24	524	206.9	506	209.9	1030	208.4
	36	302	198.1	266	206.4	568	202.0
Serum creatinine *mg/dL*	Baseline	751	1.9	762	1.9	1513	1.9
	6	701	2.1	691	2.1	1392	2.1
	12	647	2.3	632	2.3	1279	2.3
	24	543	2.5	530	2.6	1073	2.5
	36	327	2.8	287	2.7	614	2.7
Hemoglobin A_{1c}%	Baseline	742	8.53	754	8.43	1496	8.48
	6	619	8.59	626	8.56	1245	8.58
	12	633	8.55	604	8.51	1237	8.53
	24	513	8.58	490	8.51	1003	8.54
	36	298	8.38	257	8.41	555	8.39
Hemoglobin *mg/dL*	Baseline	732	12.5	736	12.5	1468	12.5
	6	37	11.7	45	12.0	82	11.9
	12	625	11.9	598	12.4	1223	12.1
	24	516	11.9	489	12.3	1005	12.1
	36	298	11.9	258	12.3	556	12.1

Analysis based on observed data without imputing missing values. All laboratory measures occurred prior to end-stage renal disease (ESRD).
Albuminuria is presented as geometric mean.
At each post-randomization time point, a day range was prespecified (for example, days 138 to 228 for month 6 and days 321 to 410 for month 12). If a patient had more than one measurement in a day range, the measurement in the range which is closest to the center day (day 365 for month 12) was used in the analysis.

point was eliminated: 16.1% (95% CI 2.5% to 27.8%) to 1.7% (95% CI −14.5% to 15.5%). This suggests that the albuminuria effect is a strong predictor for the renal protection in this study. A similar analysis was performed for ESRD alone, demonstrating that when albuminuria was adjusted over the entire study prior to ESRD, the risk reduction for ESRD was reduced from 28.6% (95% CI 11.5% to 42.4%) to 14.1% (95% CI −6.6% to 30.8%).

Residual albuminuria

Albuminuria at 6 months is designated as residual albuminuria, reflecting the albuminuria that remains despite "maximal" treatment per protocol. Interestingly, the residual albuminuria also demonstrated a relationship with long-term renal outcome. Specifically, the more albumin that is excreted in the urine, the more risk for a subsequent renal event (Fig. 2, right panels). In fact, when comparing the relationship between baseline albuminuria and renal risk with the 6 months residual albuminuria and renal risk, these curves show complete overlap. The importance of residual albuminuria even during therapy is further shown by the finding that the residual albuminuria level after reduction with losartan confers the same renal risk as such a (unchanged) albuminuria level in a placebo patient (Fig. 5, right panels).

DISCUSSION

Results from the current study show that albuminuria is the most powerful marker for subsequent renal events in type 2 diabetic subjects with nephropathy. Reduction of albuminuria during the first 6 months of treatment was clearly evident in patients treated with the Ang II antagonist, losartan. The antiproteinuric effect of losartan appears to explain most of the renoprotection conferred by this agent, and is beyond that which could be attributed to the effect of this agent on blood pressure. Suppression of albuminuria was an independent predictor of long-term protection from renal events. Interestingly, the degree of

Renal end point	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.88	0.1570	0.76	0.0028
Δ Alb: ≥30 vs. <0%	0.60	<.0001	0.46	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.68	0.0003	0.61	<.0001

ESRD	Unadjusted		Adjusted	
	HR	*P* values	HR	*P* values
Δ Alb: ≥0<30 vs. <0%	0.82	0.1242	0.62	<.0003
Δ Alb: ≥30 vs. <0%	0.51	<.0001	0.37	<.0001
Δ Alb: ≥30 vs. ≥0<30%	0.62	0.0019	0.60	0.0010

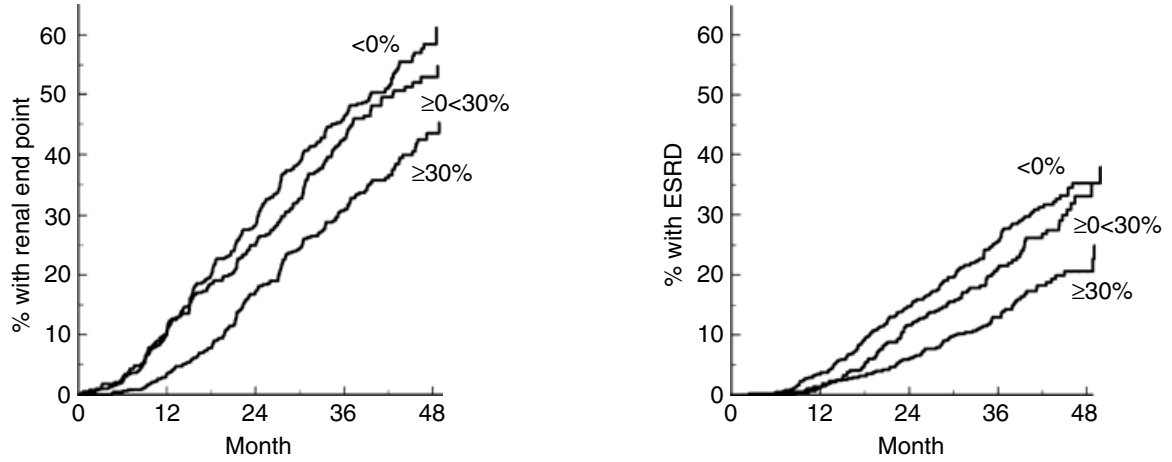

Fig. 3. Event rate of renal end points stratified by albuminuria change from baseline to 6 months. The hazard ratio (HR) is shown at the top of each figure. The adjusted HR is corrected for all measured baseline risk markers, and month-6 changes summarized in the **Statistical analysis** section.

Table 5. Response of different risk markers to antihypertensive treatment in the first 6 months stratified according to albuminuria reduction at month 6

Variable for change from baseline at month 6	Albuminuria reduction at month 6					
	<0% ($N = 631$)		≥0<30% ($N = 393$)		≥30% ($N = 489$)	
	Mean change	SD	Mean change	SD	Mean change	SD
Weight *kg*	0.7	2.8	0.3[a]	2.9	0.4	3.3
Sitting systolic blood pressure *mm Hg*	1.0	16.7	−3.9[a]	16.2	−6.6[a]	16.5
Sitting diastolic blood pressure *mm Hg*	−0.0	8.9	−2.2[a]	8.0	−3.8[a]	7.9
Hemoglobin A_{1c} %	0.1	1.4	0.1	1.4	0.1	1.5
GFR *mL/min*	−2.6	6.4	−3.6[a]	5.7	−3.8[a]	5.8
Serum creatinine *mg/dL*	0.3	0.5	0.3	0.5	0.3	0.4
Albuminuria mg/g	634	775	−339[a]	399	−884[a]	905
Albuminuria reduction %	+50		−20[a]		−60[a]	

GFR is estimated glomeruclar filtration rate. The analysis was based on all randomized patients whose missing data at baseline and month 6 were imputed, see details in **Statistical analysis** section. Only the observed data prior to end-stage renal disease (ESRD) was included in the analysis.

Albuminuria reduction was geometric mean ratio at month 6 over baseline, expressed as % change from baseline.

[a]The ≥0<30% or ≥30 % reduction groups were compared to the <0% group. Statistical significance for these comparisons was based on a two-sample *t* test, $P < 0.05$.

residual albuminuria remains proportionally associated with renal risk, and its relationship is similar as that observed with albuminuria before start of treatment. Thus, suppressing albuminuria is associated with a reduction in risk and it is predicted that additional suppression of albuminuria would be associated with additional end-organ protection. Specifically, we demonstrated that the greater the reduction in albuminuria over the initial 6 months, and the lower the albuminuria after 6 months of treatment, the less likely the patient would experience a renal outcome. Therefore, albuminuria should be further explored as a prime target in type 2 diabetic patients with nephropathy, potentially, and should be a key consideration in determining drug choice as well as the drug dose, irrespective of the blood pressure.

Albuminuria has long been known to be a marker of the severity of kidney disease [14]. The prevailing opinion was that albuminuria was primarily a marker of renal injury and that the more the kidney was damaged, the more it would leak plasma proteins. Remuzzi and Bertani [15] challenged this idea and hypothesized that albuminuria itself could damage the kidney cell. Although a cause-effect relationship for albuminuria and progressive kidney damage is hard to identify clinically, albuminuria is a strong risk marker in diabetes [16–18] as well as in non-diabetic renal disease [19]. The results from the present

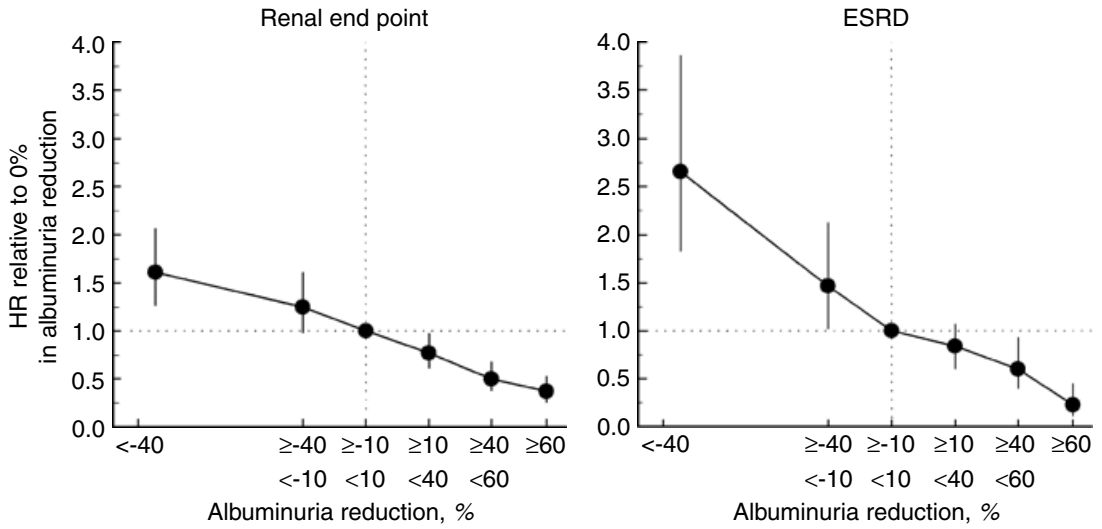

Fig. 4. Change in albuminuria (baseline compared to month 6) versus the hazard ratio of renal end point. The hazard ratio (HR) is adjusted for all baseline risk markers as well as the initial 6-month changes summarized in the **Statistical analysis** section. The HR with 95% CI is calculated relative to 0% change in albuminuria.

study obtained in this large, prospective clinical trial show that this phenomenon also applies to the clinical context of the patient with type 2 diabetes.

Since the discovery that blood pressure and cholesterol are independent risk markers for renal events, therapeutic strategies have been designed and tested to lower the blood pressure and serum cholesterol. These studies determined that lowering blood pressure and/or serum cholesterol appeared to be associated with reduced kidney risks [20, 21]. There are therapeutic strategies that can reduce the degree of albuminuria, including low protein diet [22], indomethacin [23], the antihypertensive agents such as ACE inhibitors [24, 25], or Ang II antagonists [26, 27]. In particular, the latter two drug classes are well known for their antiproteinuric effect in a variety of renal diseases. Large clinical trials such as the collaborative trial [9] in type 1 diabetes, and the AIPRI study [28] in nondiabetic renal disease have shown that the renal protection of RAS intervention is associated with a lower level of albuminuria. Unfortunately in those studies, the RAS intervention led to lower blood pressure levels than observed with the control therapies. Thus, it remained speculative whether the changes in albuminuria per se affected the renal endpoints independently of blood pressure. However, the REIN study in nondiabetic renal disease clearly showed that lowering of albuminuria in the ACE inhibitor arm is associated with renal protection beyond blood pressure effects [29].

The current study has clearly demonstrated that albuminuria reduction in type 2 diabetic nephropathy is associated with renal protection. One of the arguments in favor of albuminuria itself being detrimental to the kidney has been the fact that the degree of reduction of albuminuria predicts the renal outcome. This has been demonstrated in relatively small studies in type 1 diabetes [30] and in nondiabetic renal disease [31]. Confirmed by retrospective analysis in large trials in type 1 diabetes [17], and in nondiabetic patients in the MDRD [19], these results positioned albuminuria next to high blood pressure as a potential independent target for therapy. The current study for the first time shows on a large scale, in a prospective manner that the degree of albuminuria reduction is related in a linearly manner to the subsequent renal protection in type 2 diabetes. A particularly important finding of the present study was the fact that the relationship between albuminuria and renal risk remains present both before and after albuminuria lowering therapy. For example, 2 g albuminuria in a patient not taking losartan carries the same risk as 2 g albuminuria in a patient receiving losartan. This would imply that albuminuria is a damaging marker irrespective of the absence or presence of Ang II inhibition/antagonism. This would suggest that further lowering of the residual albuminuria by additional approaches should still be considered.

Blood pressure control was an important part of the treatment of all patients participating in this trial. The use of other antihypertensive drugs was well balanced between the different albuminuria subgroups and the albuminuria response groups, even though patients were not randomized into albuminuria subgroups. These groups did have small differences in responses of other risk markers such as blood pressure and cholesterol but the impact of these changes did not explain the observed "antialbuminuric effect." Regardless, we recognize there could have been other characteristics coinciding with the presence or the change in albuminuria that we did not

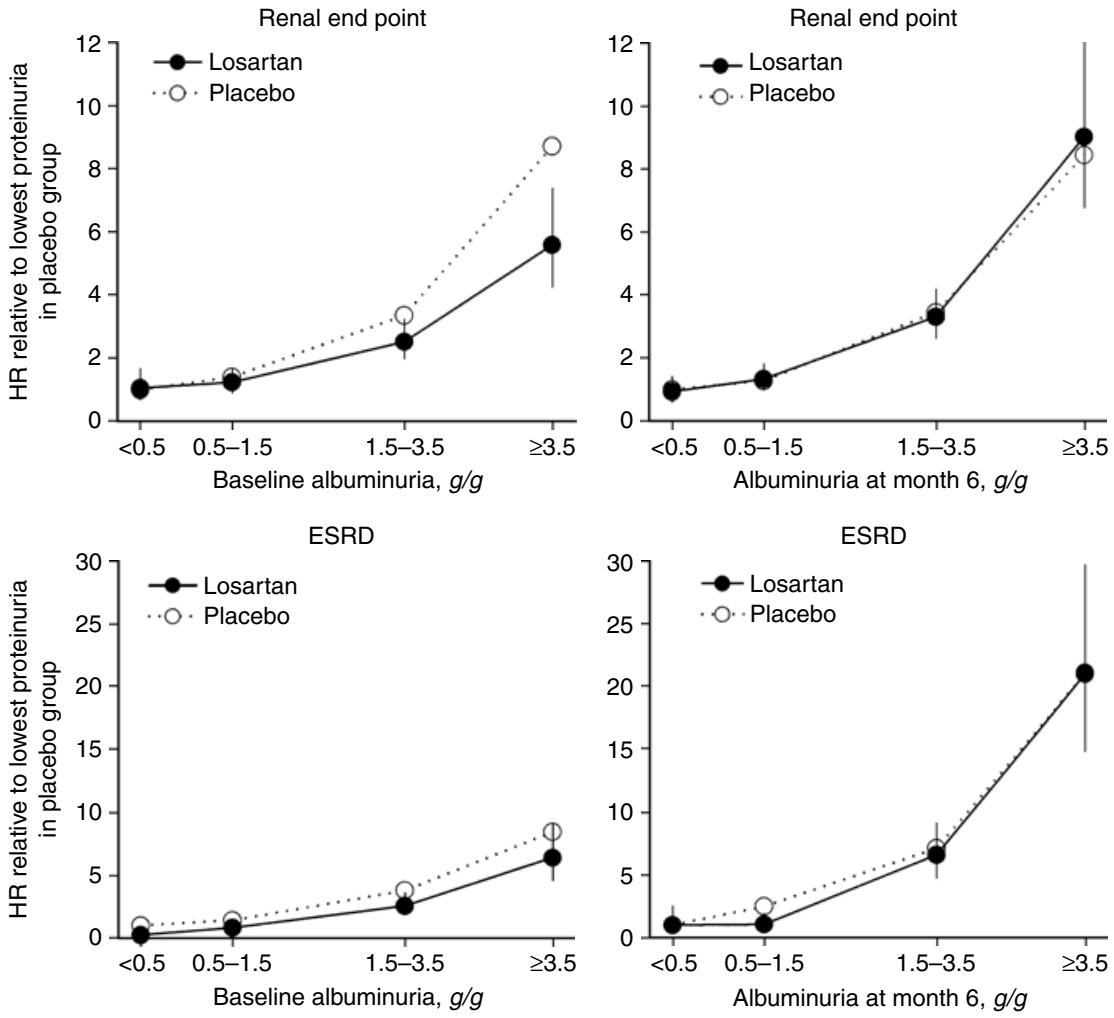

Fig. 5. Hazard ratio for renal events versus albuminuria stratified for study drug. The left panel is the relation of the renal end point and end-stage renal disease (ESRD) against baseline albuminuria, The right panel is the relation between the renal end point and ESRD against month 6 albuminuria. Relation is corrected for baseline risk markers, as summarized in the **Statistical analysis** section. The <0.5 g/g category in the placebo group was used as a common reference for the losartan and placebo groups.

measure, and that such changes may have influenced the outcome. However, the current results indicate the need to design future studies by assigning special attention to changes in albuminuria as an index of the risk of renal outcomes, especially when other clinical outcome studies confirm the finding from the RENAAL Study.

The findings of the RENAAL Study extend the concept that suppressing albuminuria should be further explored as a goal of therapy to achieve optimal renal protection in the individual patient with type 2 diabetes. The drug of choice would very likely be an ACE inhibitor or an Ang II antagonist. One could argue that titration of drug dosage based on changes in blood pressure would be sufficient to ensure an optimal antiproteinuric effect, but from other studies in type 1 diabetes and nondiabetic renal disease, the dose-response curve for blood pressure and albuminuria appear to be different [32–34]. These data emphasize the need for new studies where the primary target is reduction of albuminuria. It is our advice that guidelines on individual therapies in type 2 diabetes should not only mention albuminuria as an important risk factor/marker, but should also define albuminuria as a target for therapy choice as well as dose of treatment, independent of blood pressure. As with blood pressure, therapy strategies should be guided with the sole aim to reduce albuminuria to the lowest achievable level.

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