# Change in Albuminuria Is Predictive of Cardiovascular Outcome in Normotensive Patients With Type 2 Diabetes and Microalbuminuria

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Microalbuminuria is associated with cardiovascular complications and all-cause mortality in patients with diabetes (1–3). Inhibitors of the renin-angiotensin system (RAS) protect renal and cardiac function in these patients, at least partly independent of the associated blood pressure reduction (4–9). Recently, a few studies showed that reduction in albuminuria in hypertensive diabetic patients reduces the risk of subsequent cardiovascular events (10–12). The question remains whether this risk reduction is explained by the reduction of high blood pressure. No data are available for normotensive diabetic patients. Therefore, we investigated whether sustained change in albuminuria independently predicts cardiovascular outcome in patients with type 2 diabetes and microalbuminuria but without hypertension.

## RESEARCH DESIGN AND METHODS

— The present study is a prospective follow-up study of 67 normotensive patients (baseline blood pressure ≤140/90 mmHg without antihypertensive treatment) with type 2 diabetes and microalbuminuria (urinary albumin excretion 20–200 mg/l), who participated in a previously published, larger, randomized, double-blind, placebo-controlled, multicenter trial investigating the short-term effects of the angiotensin-receptor antagonist losartan on microalbuminuria (7). Exclusion criteria included a history of macrovascular complications and a baseline serum creatinine level >150 μmol/l.

After the original 20-week study period, a cohort of 67 patients from that study was prospectively followed during mean ± SEM 4.7 ± 0.1 years. They were recruited on the basis of their address and received standard medical care. Data were collected on current and past health, medication use, blood pressure, renal function, and albuminuria, which was annually assessed in morning spot urines. The end point was a composite of death, cardiovascular disease, cerebrovascular events, and peripheral artery disease.

Paired Student's *t* test was used for comparisons within similar variables. Regarding the rate of change in albuminuria from baseline over each year, three groups were discerned: one with reduction of albuminuria of ≥30%, one with stable albuminuria (change <30%), and one with rapid progression of albuminuria of at least 30%. The correlation between rate of change in albuminuria at 1 year and cumulative event-free survival was analyzed with the Kaplan-Meier method, the log-rank test, and multivariate Cox regression. The 95% CI of the hazard ratio (HR) was calculated as the exponent of the regression coefficient. *P* values <0.05 defined statistical significance. We used SPSS for Windows (version 12.0; SPSS, Chicago, IL) for all analyses.

## RESULTS

— Baseline characteristics of the three groups, including blood pressure and albuminuria, did not differ significantly, with the exception of age, for which we corrected. Albuminuria reduced from 69.1 mg/l at baseline to 39.4 mg/l after 1 year (mean difference −29.7 mg/l [95% CI −39.7 to −19.8], $P < 0.0001$) and returned to 62.0 mg/l at the end of follow-up in the group with albuminuria reduction. In patients with rapid progression of albuminuria, mean levels were 84.3 mg/l at baseline, 223.3 mg/l after 1 year (139.0 mg/l [46.3–209.7], $P < 0.01$), and 354.1 mg/l at the end of follow-up. Albuminuria levels did not change significantly in the group with stable albuminuria. Importantly, the course of blood pressure was similar in the three groups, without significant changes in systolic or diastolic blood pressure (Fig. 1).

During follow-up, 14 patients (21%) reached the composite end point. A significant difference in event-free survival was observed between the three groups ($P = 0.02$). Patients with rapid progression of albuminuria were at highest risk to reach the end point, whereas patients with reduction in albuminuria of ≥30% were at lowest risk. After adjustment for sex, age, systolic blood pressure, total–to–HDL cholesterol ratio, and current smoking in a multivariate Cox regression model, change of albuminuria remained an independent, significant predictor (HR 5.1 [95% CI 1.5–18.1], $P = 0.01$).

Relevant medication during follow-up was used similarly in the three groups. Following the original study protocol, 63 patients (95%) received an RAS inhibitor because of microalbuminuria. At the end of follow-up, 62 patients

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**Abbreviations:** RAS, renin-angiotensin system.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

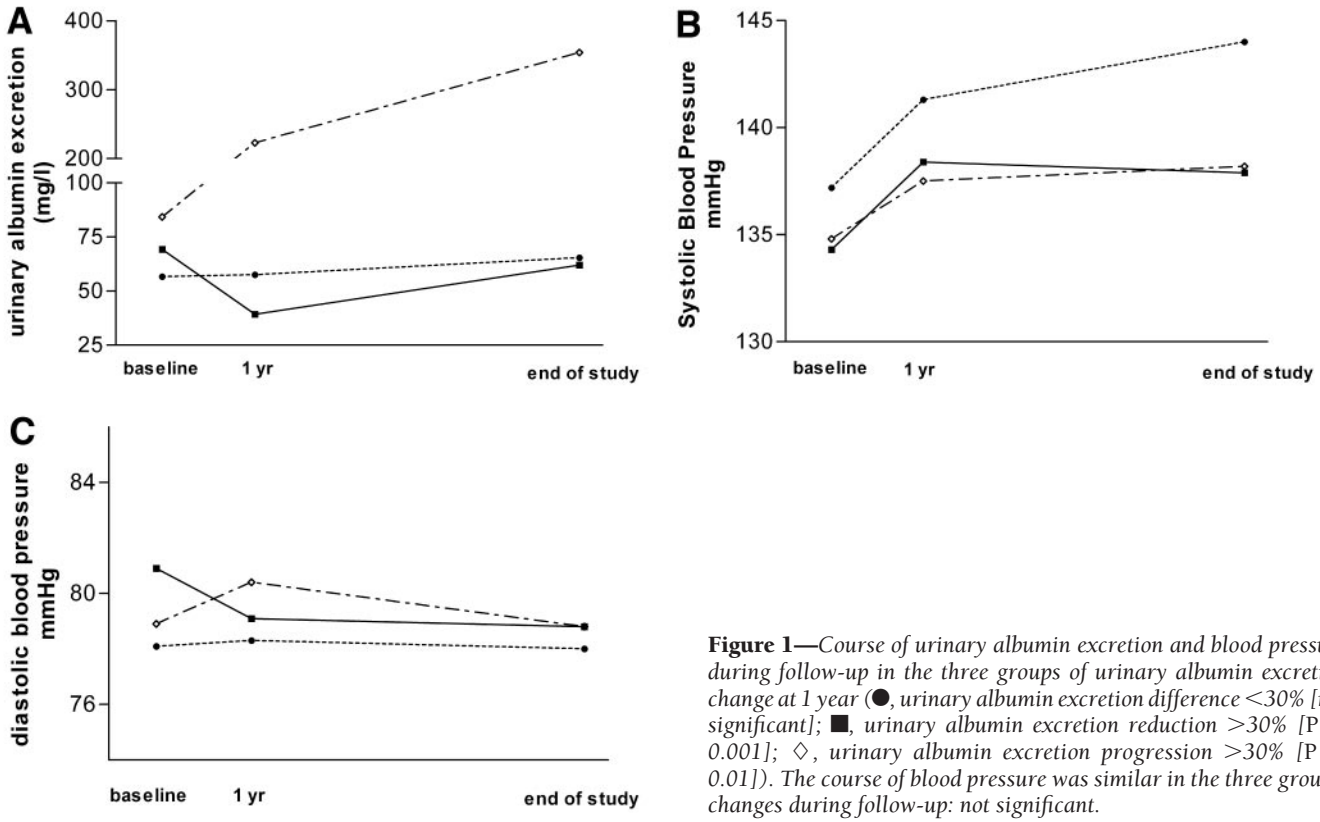


**Figure 1**—*Course of urinary albumin excretion and blood pressure during follow-up in the three groups of urinary albumin excretion change at 1 year (●, urinary albumin excretion difference <30% [not significant]; ■, urinary albumin excretion reduction >30% [P < 0.001]; ◇, urinary albumin excretion progression >30% [P < 0.01]). The course of blood pressure was similar in the three groups; changes during follow-up: not significant.*

(93%) still used RAS inhibition. Moreover, neither statin nor aspirin use differed between groups.

**CONCLUSIONS** — This study demonstrates that normotensive patients with type 2 diabetes and miroalbuminuria run a marked risk for cardiovascular complications. The risk depends on the rate of 1-year change in urinary albumin excretion. Patients with rapid progression of albuminuria were at highest risk, whereas patients with regression of albuminuria had the lowest risk. This association persisted after adjustment for classic cardiovascular risk factors.

Besides reducing blood pressure, RAS inhibitors are effective in preserving renal and cardiac function in diabetic patients (4–9). Moreover, they reduce albuminuria up to 40%, significantly more than other classes of antihypertensive drugs (4). Since albuminuria is strongly associated with cardiovascular outcome, changes in albuminuria during treatment might reflect changes in cardiovascular disease risk (13,14). A few studies recently showed that reduction of albuminuria in hypertensive diabetic patients reduces the risk of subsequent cardiovascular events (10–12,15). However, these studies investigated hypertensive patients, thereby leaving open the possibility that blood pressure lowering explains the cardiovascular risk reduction, with albuminuria change just an innocent bystander. To our knowledge, our study is the first demonstrating that, even with no appreciable changes or even rises in blood pressure, change in albuminuria differentiates the cardiovascular outcome in type 2 diabetic patients without hypertension.

An important limitation of this study is the small sample size. Nonetheless, the association that we observed between changes in albuminuria and cardiovascular outcome was statistically significant in multivariate analysis. The strength of our study lies in the fact that we studied type 2 diabetic patients with microalbuminuria but without hypertension at baseline in a prospective design. Clearly, this study needs further follow-up in larger cohorts.

In summary, sustained reduction in albuminuria reflected cardiovascular risk reduction in type 2 diabetic patients without hypertension. Hence, albuminuria change during treatment seems to reveal therapeutic responsiveness independent of blood pressure changes and is therefore useful as a modifiable treatment goal. These observations advocate a more aggressive approach to treating albuminuria in addition to more aggressive cardioprotective treatment in normotensive diabetic patients with elevated levels of albuminuria.

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