Does Albuminuria Predict Cardiovascular Outcomes on Treatment With Losartan Versus Atenolol in Patients With Diabetes, Hypertension, and Left Ventricular Hypertrophy?

The LIFE study

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OBJECTIVE — Our current aims were to investigate whether *1*) baseline urinary albumin-to-creatinine ratio (UACR) predicted cardiovascular outcomes, *2*) changes in UACR differed between treatments, *3*) benefits of losartan were related to its influence on UACR, and *4*) reduction in albuminuria reduced cardiovascular events.

RESEARCH DESIGN AND METHODS — In 1,063 patients with diabetes, hypertension, and left ventricular hypertrophy, UACR was measured for a mean of 4.7 years. The primary composite end point included cardiovascular death, myocardial infarction, and stroke. Cox models were run including and excluding baseline and time-varying UACR.

RESULTS — Increasing baseline albuminuria related to increased risk for cardiovascular events. Reductions in UACR at years 1 and 2 were ~33% for losartan vs. 15% for atenolol ($P < 0.001$). Benefits of losartan seem to be most prominent in patients with the highest level of baseline UACR, although treatment by albuminuria interaction was only significant for total mortality. Approximately one-fifth of the superiority of losartan was explained by the greater reduction of albuminuria. Risk of the primary end point was related to the in-treatment UACR.

CONCLUSIONS — Lowering of albuminuria in patients with hypertension and diabetes appears to be beneficial and should be the subject of additional study in future clinical trials.

Diabetes Care 29:595–600, 2006

Assessment of urinary albumin excretion has become an important independent marker of cardiovascular and/or total mortality in diabetic and nondiabetic hypertensive patients and in the general population (1–4). We have previously shown that even a low level of albuminuria was a powerful predictor of risk for cardiovascular events in patients with hypertension and electrocardiogram (ECG)-documented left ventricular hypertrophy in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study (3,5,6). Treatment with losartan in the LIFE study resulted in a greater reduction in albuminuria compared with atenolol for the same reduction in blood pressure (6). Approximately one-fifth of the superiority of losartan versus atenolol on the primary composite end point in the LIFE study was due to its effect on albuminuria (6). The decrease in albuminuria during treatment was accompanied by a decrease in cardiovascular events (6,7).

The present report describes patients in the LIFE study with diabetes at baseline. The aims were to investigate whether *1*) baseline urinary albumin-to-creatinine ratio (UACR) predicted cardiovascular outcomes on losartan versus atenolol, *2*) changes in UACR across the study differed on losartan versus atenolol, *3*) benefits of losartan related to its influence on UACR, and *4*) reduction in albuminuria translated to reduction in cardiovascular events during treatment.

RESEARCH DESIGN AND METHODS

— As previously described, the LIFE study compared the effects of losartan- versus atenolol-based antihypertensive treatment on a primary composite end point (consisting of cardiovascular mortality plus nonfatal myocardial infarction and nonfatal stroke) in patients aged 55–80 years with hypertension and ECG-verified left ventricular hypertrophy. The study design and patient characteristics for the total population (8) and for the patients with diabetes (9) have been reported. An inclusion criterion was through sitting systolic blood pressure of 160–200 mmHg and/or sitting diastolic blood pressure of 95–115 mmHg after 1–2 weeks of single-blind placebo treatment. The diagnosis of diabetes was investigator reported and based on 1985 World Health Organiza-

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Received for publication 14 September 2005 and accepted in revised form 14 December 2005.

Abbreviations: ECG, electrocardiogram; LIFE, Losartan Intervention For Endpoint reduction in hypertension; UACR, urinary albumin-to-creatinine ratio.

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

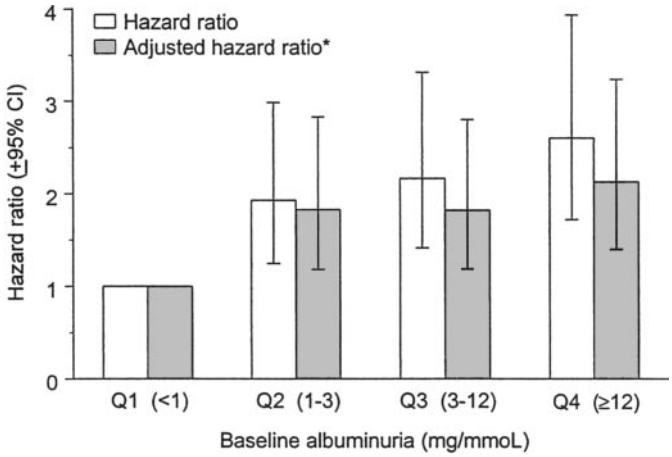

Figure 1—*Adjusted and unadjusted risks for primary composite end point. *Adjusted for ECG left ventricular hypertrophy, Framingham risk score, and treatment.*

tion criteria (10). Patients gave informed consent, and the study was approved by all relevant ethics committees.

A morning spot-urine sample was collected at baseline and annually. Urine albumin concentration was determined by a standard turbidometric method on a single urine specimen. Serum and urine creatinine concentrations were analyzed using the Jaffé reaction without deproteinizing and quantified by a photometric method using the same analyzer. Urine albumin concentration (mg/l) was expressed as a ratio to urinary creatinine concentration (mmol/l) (i.e., UACR, mg/mmol). Cross-laboratory validation studies were performed between the two central laboratories, which did not reveal any differences (6).

An independent committee adjudicated all end points. This report on 1,063 patients with diabetes and available UACR data are based on 260 primary composite end points and the following secondary end points: 91 cardiovascular deaths, 73 fatal and nonfatal myocardial infarctions, 100 fatal and nonfatal strokes, and 149 cases of total mortality.

Statistical methods

SPSS Version 10.1 (SPSS, Chicago, IL) and SAS Version 8.2 (SAS Institute, Cary, NC) statistical software were used. Clinical events were analyzed using Cox proportional hazards models, and reported *P* values and estimates of hazard ratios (HRs) are based on these models.

To examine whether the benefit effect of losartan versus atenolol on events differed across the different levels of baseline UACR, patients were stratified into the following quartiles according to baseline UACR: ≤1, 1–3, 3–12, and ≥12 mg/mmol. Tests for the effects of losartan were based on a Cox proportional hazards model with baseline left ventricular hypertrophy, baseline Framingham risk score, and treatment as covariates. The *P* values and estimates of HR of experiencing an end point on losartan compared with atenolol were reported for each subgroup. Median changes in albuminuria over time were calculated within each treatment group, and the effects of losartan compared with atenolol were tested using the nonparametric Wilcoxon's rank-sum test. To determine the proportion of the treatment effect explained by in-treatment UACR, a covariate for treatment was added to a Cox regression model that included baseline UACR and in-treatment UACR (after log transformation) as a time-varying covariate. The coefficient for the treatment effect from this model was compared with that in a simple model including only treatment. The proportion of the treatment explained by UACR was calculated by comparing the unadjusted HR for treatment with the HR adjusted for in-treatment UACR (11). In-treatment values of UACR were classified into four strata (according to baseline quartiles of UACR), and cardiovascular events were displayed using modified Kaplan-Meier curves; the modification is that the risk sets for each UACR category change over time, and patients can shift among the different cohorts as their UACR level changes over the study process.

Table 1—*Baseline characteristics*

	Losartan	Atenolol
n	524	539
Age (years)	67.3 (54.1–80.5)	67.3 (53.3–81.3)
Female (%)*	51.7 (47.3–56.1)	53.4 (49.1–57.7)
BMI (kg/m^2)	29.9 (19.6–40.2)	30.1 (19.3–40.9)
Blood pressure (mmHg)	176.2 (148.6–203.9)/96.6 (78.7–114.5)	176.9 (149.3–204.4)/95.8 (75.8–115.8)
Heart rate (bpm)	75.6 (52.5–98.8)	76.0 (53.8–98.2)
Cornell product (mV × ms)	2,895 (1,043–4,747)	2,913 (1,040–4,786)
Sokolow-Lyon (mV)	28.7 (8.8–48.6)	28.5 (8.4–48.7)
Framingham risk score	30.3 (13.9–46.8)	31.1 (14.3–47.8)
Smokers (%)*	12.0 (9.4–15.1)	15.1 (12.5–18.7)
Medical history (%)*		
Isolated systolic hypertension (>160/<90 mmHg)	17.8 (14.6–21.3)	22.5 (19.0–26.2)
Angina pectoris	15.3 (12.3–18.6)	13.9 (11.1–17.1)
Ischemic heart disease	7.6 (5.5–10.2)	10.4 (7.9–13.3)
Myocardial infarction	7.8 (5.7–10.5)	7.8 (5.7–10.4)
Heart failure	3.4 (2.0–5.4)	4.5 (2.9–6.6)

Data are means (95% CI). *95% CI by Exact method.

Table 2—*Adjusted event rates for end points according to baseline urinary albumin-to-creatinine quartile value*

End point	Losartan	Atenolol	HR (95% CI)	*P*
n	524	539		
Composite				
Baseline albuminuria quartile				
1	16/140 (11.4)	16/126 (12.7)	0.859 (0.428–1.720)	0.667
2	28/137 (20.4)	25/128 (19.5)	1.076 (0.623–1.857)	0.794
3	23/113 (20.4)	38/153 (24.8)	0.847 (0.504–1.425)	0.533
4	28/134 (20.9)	42/132 (31.8)	0.590 (0.365–0.954)	0.031*
Cardiovascular death				
Baseline albuminuria quartile				
1	6/140 (4.3)	6/126 (4.8)	0.865 (0.276–2.710)	0.804
2	13/137 (9.5)	10/128 (7.8)	1.355 (0.581–3.158)	0.482
3	8/113 (7.1)	16/153 (10.5)	0.708 (0.302–1.657)	0.426
4	10/134 (7.5)	22/132 (16.7)	0.392 (0.185–0.831)	0.015*
Myocardial infarction†				
Baseline albuminuria quartile				
1	7/140 (5.0)	11/126 (8.7)	0.534 (0.206–1.383)	0.196
2	9/137 (6.6)	8/128 (6.3)	0.969 (0.371–2.529)	0.949
3	11/113 (9.7)	13/153 (8.5)	1.179 (0.526–2.642)	0.690
4	11/134 (8.2)	13/132 (9.8)	0.789 (0.353–1.767)	0.565
Stroke†				
Baseline albuminuria quartile				
1	6/140 (4.3)	3/126 (2.4)	1.751 (0.437–7.013)	0.429
2	17/137 (12.4)	14/128 (10.9)	1.151 (0.561–2.360)	0.701
3	9/113 (8.0)	21/153 (13.7)	0.609 (0.278–1.333)	0.215
4	12/134 (9.0)	18/132 (13.6)	0.600 (0.228–1.248)	0.172
Total mortality				
Baseline albuminuria quartile				
1	11/140 (7.9)	11/126 (8.7)	0.899 (0.389–2.079)	0.803
2	20./137 (14.6)	24/128 (18.8)	0.780 (0.427–1.423)	0.418
3	14/113 (12.4)	21/153 (13.7)	0.939 (0.477–1.850)	0.856
4	12/134 (9.0)	36/132 (27.3)	0.292 (0.151–0.563)	<0.001‡

Data are *n* events/*n* patients in each quartile (event rate %), unless otherwise indicated. Adjusted for ECG left ventricular hypertrophy, Framingham risk score, and treatment. Quartile 1: ≤1, quartile 2: 1–3, quartile 3: 3–12, quartile 4: ≥12 mg/mmol. *$P < 0.05$; †Fatal plus nonfatal; ‡$P < 0.01$. No significant treatment by albuminuria interaction except for total mortality. $P = 0.04$.

RESULTS — Patient characteristics, treatment, and results for the LIFE study population with diabetes at baseline have been reported (9). Of 1,195 patients with diabetes at baseline, 1,063 had the baseline UACR measurements necessary for inclusion in these analyses (Table 1).

Albuminuria and cardiovascular morbidity and mortality

The risk of the primary composite end point increased significantly across quartiles of baseline UACR with or without adjustment for baseline ECG left ventricular hypertrophy, Framingham risk score, and treatment (Fig. 1). There was a 2.6-fold increase in the unadjusted and 2.1-fold increase in the adjusted HRs for the primary composite end points from the lowest (UACR ≤1 mg/mmol) to the highest (UACR ≥12 mg/mmol) quartile.

Baseline albuminuria and outcomes on losartan versus atenolol treatment

The crude event rates by treatment for the primary composite end point, cardiovascular mortality, and total mortality by quartile of baseline UACR were lower in the losartan than in the atenolol group (Table 2). The outcomes for the upper quartiles are consistent, especially with regard to cardiovascular mortality and total mortality. The test for treatment-albuminuria interaction was significant for total mortality only ($P = 0.04$).

Changes in albuminuria during treatment

The decrease in UACR across the mean 4.7 years of follow-up was more pronounced on losartan- versus atenolol-based treatment (Fig. 2). From baseline to year 1 or 2, the reduction on losartan was ~33% compared with ~15% on atenolol. The risk reduction for the composite end point with losartan with treatment and albuminuria in the model was 21.7%, and with treatment only in the model it was 26.8%. This implies that 5.1 of 26.8% (i.e., 19% [95% CI 9–61]) of the benefit of the superiority of losartan over atenolol was explained by its influence on UACR.

Changes in albuminuria and outcome

The primary composite end point rate was displayed according to time-varying UACR during >5 years of follow-up (Fig. 3). It is clearly shown that the risk of the primary end point was closely related to the in-treatment levels of UACR. The end point rate increased twofold from the lowest to the highest strata when exam-

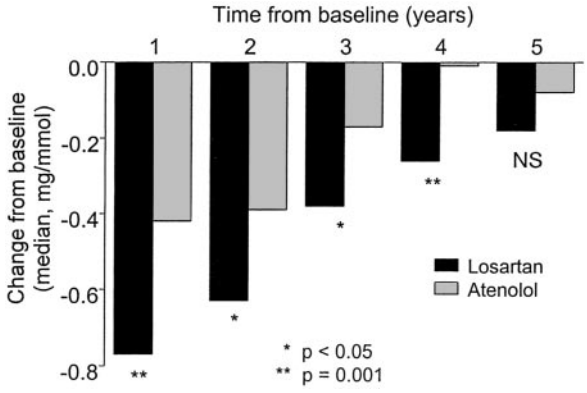

Figure 2—*Changes in median UACR (mg/mmol).*

ined by time-varying UACR. The number of at-risk patients in the strata indicates that patients tended to shift from a higher level of UACR at baseline to a lower level at years 2 and 4. This implies that when UACR is reduced by one strata or more, the cardiovascular event rate is reduced accordingly. When baseline and in-treatment levels of systolic blood pressure were introduced into the Cox proportional hazards model, the HR for in-treatment UACR was only slightly modified; for example, the HR for the composite end point changed from 1.113 to 1.111. In time-varying covariate analysis, a twofold increase in the in-treatment UACR level corresponded to an increase in the risk for the composite end point of 11% (HR 1.111, $P < 0.001$). For cardiovascular mortality and stroke, a higher UACR level corresponded to higher risk as well (results not shown).

CONCLUSIONS — In concordance with earlier LIFE study publications, our data showed that the risk for cardiovascular end points increased in a stepwise fashion with higher values for UACR in the patients with diabetes, a population for which the median baseline value of UACR was 3.05 mg/mmol (versus 1.28 mg/mmol in the overall population [3]). The risk for the composite end point in patients with diabetes was increased by UACR ≥1.94 mg/mmol (3). Our data indicate that albuminuria at a lower level than what is usually utilized as a cut point in patients with diabetes defines patients at increased risk of cardiovascular morbidity and mortality. UACR did not predict risk of myocardial infarction. The reason might be that diabetes in itself is a strong predictor for cardiovascular morbidity and mortality, partly overriding the influence of albuminuria as a risk factor in the present population with rather low levels of albuminuria. Defined by classical criteria, 34% had microalbuminuria (3.5–35.0 mg/mmol) and 13% had macroalbuminuria (>35 mg/mmol). The benefit for losartan compared with atenolol was twice as high in the diabetic population compared with the total LIFE study population: the relative risk reduction for the primary composite end point was ~25% (9).

We aimed to elucidate whether the beneficial outcome on losartan was especially confined to the subset of diabetic patients with a high baseline level of albuminuria. When divided into quartiles of baseline UACR, the outcome in favor of losartan was especially pronounced in the upper quartile. The risk reduction for total mortality was ~60% with significant treatment-albuminuria interaction. Tests for interaction were insignificant for other end points. Lack of statistical power might have jeopardized our possibility to definitively prove whether the outcome on losartan versus atenolol was related to baseline level of UACR.

The reduction in the degree of albuminuria over the 4.7 years of follow-up in the diabetic population of the LIFE study was more pronounced for losartan- versus atenolol-based treatment. Time-varying covariate analyses indicated that about one-fifth (19%, with a wide 95% CI of 9–61) of the superiority of losartan over atenolol was explained by an influence on albuminuria. Whether this is a cause-and-effect relationship or an indirect reflection of other pathophysiological variables remains unclear. Because the blood pressure–lowering effects were comparable in the two treatment arms, it is not likely that the results were a consequence of blood pressure reduction.

There are few studies to clarify whether different antihypertensive regiments confer differences in the level/reduction of albuminuria during treatment in diabetic patients. In a short-term study, the angiotensin II receptor antagonist valsartan caused a greater reduction in albuminuria compared with the calcium channel antagonist amlodipine for the same blood pressure reduction (12). This is in agreement with other stud-

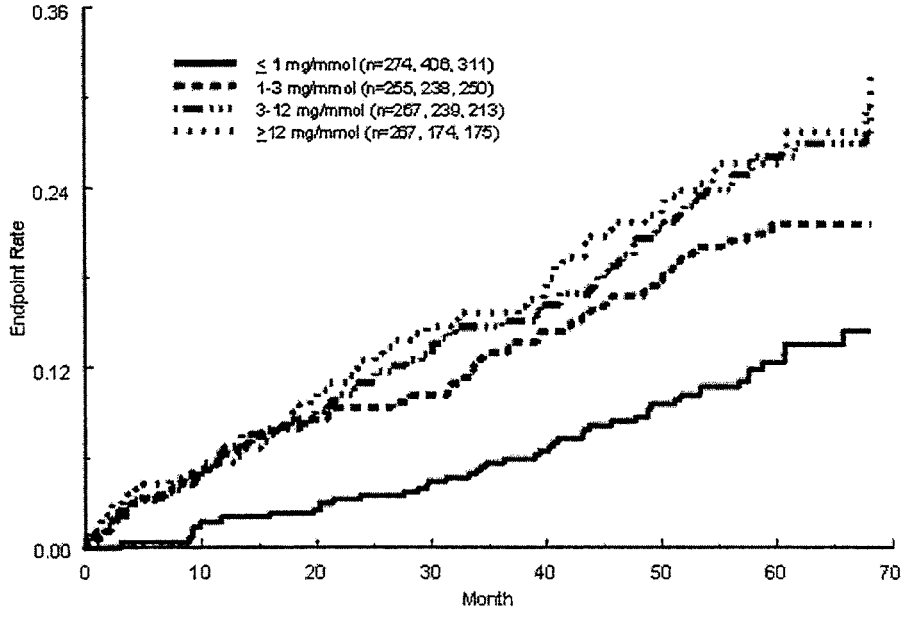

Figure 3—*Composite end point stratified by time-varying albumin-to-creatinine ratio. The numbers in parentheses refer to the numbers of at-risk patients in each range at baseline and at years 2 and 4.*

ies comparing irbesartan with amlodipine (13) and trandolapril with verapamil (14). In the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) Study (15), treatment with telmisartan compared with enalapril influenced albuminuria comparably, although the overall change in both groups was small and highly variable. The issue of whether further benefits are obtained by dual blockade (combination of an angiotensin II receptor antagonist plus an ACE inhibitor) is not settled (16,17).

The effect of lowering UACR was further analyzed by the time-varying albuminuria model. This model assumes that an individual can change stratum of albuminuria by increasing or decreasing UACR within the four strata specified in the analysis. The clinical interpretation is that an individual with high UACR at baseline whose UACR decreases during antihypertensive treatment will accordingly have a decrease in cardiovascular risk. When baseline and in-treatment values of systolic blood pressure were introduced in a Cox proportional hazards model for time-varying UACR, the risk assessment expressed by UACR was only modified to a minor degree. This indicates that a major part of the risk predicted by values of albuminuria during treatment was not explained by the level of systolic blood pressure. The data presented correlated to our data from the total LIFE study population (7,8). Other studies (18,19) in patients with diabetes and established microalbuminuria or proteinuria suggest that the rate of change in albuminuria independently predicts total mortality and cardiovascular events. There are some limitations to these analyses. Albuminuria was characterized by determination of UACR from single spot-urine collection at baseline and annually. Our findings are limited to a sample size of 1,063 patients and 260 primary end points.

In summary, in patients with hypertension, diabetes, and ECG-documented left ventricular hypertrophy, increasing levels of baseline albuminuria were related to increased risk for cardiovascular morbidity and mortality. Approximately one-fifth of the superiority of losartan versus atenolol was explained by the greater reduction of albuminuria associated with treatment with losartan. The risk for cardiovascular events was closely related to the in-treatment level of UACR, i.e., a reduction in albuminuria translated to a reduction in cardiovascular events. Our findings support the concept of monitoring of albuminuria in patients with hypertension and diabetes as part of proper disease management.

Acknowledgments— This work was supported in part by a grant from Merck.

We thank Anne-Grethe Thorn for secretarial services.

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