Reduction in Albuminuria Translates to Reduction in Cardiovascular Events in Hypertensive Patients

Losartan Intervention for Endpoint Reduction in Hypertension Study

Hans Ibsen, Michael H. Olsen, Kristian Wachtell, Knut Borch-Johnsen, Lars H. Lindholm, Carl Erik Mogensen, Björn Dahlöf, Richard B. Devereux, Ulf de Faire, Frej Fyhrquist, Stevo Julius, Sverre E. Kjeldsen, Ole Lederballe-Pedersen, Markku S. Nieminen, Per Omvik, Suzanne Oparil, Ying Wan

Abstract—Few data are available to clarify whether changes in albuminuria over time translate to changes in cardiovascular risk. The aim of the present study was to examine whether changes in albuminuria during 4.8 years of antihypertensive treatment were related to changes in risk in 8206 patients with hypertension and left ventricular hypertrophy in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. Urinary albumin/creatinine ratio (UACR) was measured at baseline and annually. Time-varying albuminuria was closely related to risk for the primary composite end point (ie, when UACR decreased during treatment, risk was reduced accordingly). When the population was divided according to median baseline value (1.21 mg/mmol) and median year 1 UACR (0.67 mg/mmol), risk increased stepwise and significantly for the primary composite end point from those with low baseline/low year 1 (5.5%), to low baseline/high year 1 (8.6%), to high baseline/low year 1 (9.4%), and to high baseline/high year 1 (13.5%) values. Similar significant, stepwise increases in risk were seen for the components of the primary composite end point (cardiovascular mortality, stroke, and myocardial infarction). The observation that changes in UACR during antihypertensive treatment over time translated to changes in risk for cardiovascular morbidity and mortality was not explained by in-treatment level of blood pressure. We propose that monitoring of albuminuria should be an integrated part of the management of hypertension. If albuminuria is not decreased by the patient’s current antihypertensive and other treatment, further intervention directed toward blood pressure control and other modifiable risks should be considered. (Hypertension. 2005;45:198-202.)

Key Words: albuminuria ■ angiotensin antagonist ■ blood pressure ■ cardiovascular diseases

Assessment of small amounts of urinary albumin excretion, so-called microalbuminuria, has become an integrated marker of cardiovascular risk in diabetic as well as nondiabetic populations.1-4 We published data recently from a large group of patients with essential hypertension and ECG-verified left ventricular hypertrophy (LVH) from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study showing a 4- to 5-fold increase in risk for cardiovascular events from the lowest to the highest decile of baseline urinary albumin excretion rate.3 In another publication from the same hypertensive population, we showed that high urinary albumin excretion rate was related to LVH and was independent of age, blood pressure, diabetes, race, serum creatinine, or smoking.5 This suggested cardiac organ damage was paralleling increased renal albumin excretion rate, which itself was most likely a marker of generalized hypertension-related damage to the peripheral vasculature.6,7

Although baseline level of urinary albumin excretion is a powerful risk predictor, there are no data from a comprehensive study population to clarify whether a reduction in albuminuria during antihypertensive treatment relates to a reduction in cardiovascular risk. The aim of the present study was to examine whether changes in albuminuria during antihypertensive treatment in the LIFE study predicted changes in cardiovascular risk.

Methods

Patient Population
Details on the LIFE study design, inclusion/exclusion criteria, patient characteristics, and results have been reported previously.8

Received September 8, 2004; first decision September 28, 2004; revision accepted December 13, 2004.

From the Glostrup University Hospital (H.I., M.H.O., K.W.), Denmark; Steno Diabetes Centre (K.B.-J.), Gentofte, Denmark; Umeå University Hospital (L.H.L.), Sweden; Århus University Hospital (C.E.M.), Denmark; Sahlgrenska University Hospital/Ostra (B.D.), Göteborg, Sweden; Weill Medical College of Cornell University Hospital (R.B.D.), New York, NY; Karolinska University Hospital (U.de F.), Stockholm, Sweden; Helsinki University Hospital (F.F., M.S.N.), Finland; University of Michigan (S.J.), Ann Arbor; Ullevaal University Hospital (S.E.K.), Oslo, Norway; Viborg Hospital (O.L.-F.), Denmark; Haukeland University Hospital (P.O.), Bergen, Norway; University of Alabama (S.O.), Birmingham; and Merck Research Laboratories (Y.W.), West Point, PA.

Correspondence to Hans Ibsen, Chief Physician, Medical Department M, Glostrup Hospital, DK-2600 Glostrup, Denmark. E-mail haih@glostruphosp.kbhamt.dk

Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000154082.72286.2a
The present population included 8206 men and women, 55 to 80 years old, with ECG-verified LVH and mean trough sitting systolic blood pressure between 160 and 200 mm Hg or mean sitting diastolic blood pressure between 95 and 115 mm Hg after 1 to 2 weeks of single-blind placebo treatment, who had a valid prerandomization measurement of urinary albumin/creatinine ratio (UACR).1,2 Important exclusion criteria were myocardial infarction or stroke within 6 months; heart failure or known left ventricular ejection fraction <40%, or renal insufficiency (serum creatinine >160 mmol/L or 1.8 mg/dL). After 2 weeks of placebo treatment, patients were randomized to losartan- or atenolol-based antihypertensive treatment and followed for a mean of 4.8 years. Patients gave informed consent, and ethics committees approved the protocols. The present analyses were prespecified as part of the LIFE albuminuria substudy protocol.

**Urine Albumin Measurement**

A morning spot-urine sample was collected in 90% of the overall LIFE study population at baseline and repeated each year of follow-up. Urine albumin concentration was determined by a standard turbidometric method on a single urine specimen. Serum and urine creatinine concentrations were analyzed using the Jaffe 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) to provide a composite measure of renal glomerular capillary permeability adjusting for urine dilution (that is, UACR, mg/mmol). To derive US measures of UACR in mg/g, UACR in mg/mmol is multiplied by 8.84, indicating that the “traditional” limits for microalbuminuria, UACR 30 to 300 mg/g, is very close to UACR 0.5 mg/mmol, 0.5 to 1 mg/mmol, 1 to 3 mg/mmol, divided into 4 groups, according to the median value of UACR at baseline. The present analyses were prespecified in the LIFE albuminuria substudy protocol.

**End Points**

This report is based on analyses of 971 primary composite end points, which were defined as the first occurrence of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction. Further analyses were conducted on the individual components of the primary end point: cardiovascular death (without regard to any previous nonfatal end points; n = 383), fatal and nonfatal myocardial infarction (without regard to any previous stroke; n = 344), and fatal and nonfatal stroke (without regard to any previous myocardial infarction; n = 479). An independent committee adjudicated all end points based on definitions provided in an end point classification manual.

**Statistics**

The present analyses were prespecified as part of the LIFE albuminuria protocol. SPSS version 10.1 statistical software (SPSS) and SAS 8.2 (SAS Institute) were used. Clinical events were analyzed using Cox proportional hazard models, and reported hazard ratios are based on these models. Baseline and in-treatment values of UACR were classified into 4 categories (≤0.5 mg/mmol, 0.5 to 1 mg/mmol, 1 to 3 mg/mmol, and >3 mg/mmol) and were included as time-varying covariates in Cox regression models. To determine whether in-treatment UACR was predictive of cardiovascular outcomes, hazard ratios for in-treatment UACR were calculated. The results of this analysis are 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 because their UACR level changes over the study process. Note that in-treatment values of UACR were used in these analyses rather than changes from baseline because changes are highly correlated with baseline values. For example, decreases tend to occur in patients with the highest baseline values (ie, those at highest cardiovascular risk), which would bias an analysis of changes. In another attempt to circumvent the problem that those with high baseline values and high risk have the greatest reduction in UACR, the patient population was divided into 4 groups, according to the median value of UACR at baseline (1.21 mg/mmol) and the median value at year 1 of treatment (0.67 mg/mmol). We display the result by calculating crude event rates within the 4 subgroups. In this part of the analysis, patients with a cardiovascular end point within the first year of treatment were disregarded because of a possible influence of an end point on the level of UACR at year 1.

**Results**

Baseline characteristics for the total LIFE study population and relations of albuminuria to cardiovascular risk factors have been reported previously.3,9 Of the 9193 patients participating in the LIFE study, 8206 had baseline measurements necessary for inclusion in this analysis (Table 1). Compared with the patients who did not deliver a urine sample, there were no differences in age, gender, race, body mass index, blood pressure, ECG-LVH, Framingham risk score, or in the prevalence of known diabetes, coronary or peripheral vascular disease, and smoking habits (data not shown).3,5 The number of patients with UACR values available during treatment varies for each year.

Figure 1 shows the rate of primary composite end point according to 4 levels of baseline and in-treatment value of UACR (≤0.5 mg/mmol, 0.5 to 1 mg/mmol, 1 to 3 mg/mmol, >3 mg/mmol). Cut points were chosen to create reasonably large sample sizes in each of the strata. Figure 1 shows that the risk for a subsequent cardiovascular end point increases 3- to 4-fold from the lowest (≤0.5 mg/mmol) to the highest (>3 mg/mmol) strata. 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 from the >3 mg/mmol level to the ≤0.5 mg/mmol level the risk is reduced accordingly. When baseline and in-treatment levels of systolic blood pressure are introduced into the Cox proportional hazard model, the hazard ratio for in-treatment UACR is only slightly modified; for example, the hazard ratio for the

**TABLE 1. Baseline Clinical Characteristics**

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Losartan n = 4126</th>
<th>Atenolol n = 4080</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66.9</td>
<td>66.9</td>
</tr>
<tr>
<td>Female, %</td>
<td>53.9</td>
<td>54.7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>174.2/97.8</td>
<td>174.4/97.7</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73.7</td>
<td>73.7</td>
</tr>
<tr>
<td>Cornell product, mV · ms</td>
<td>2836</td>
<td>2822</td>
</tr>
<tr>
<td>Sokolow–Lyon, mV</td>
<td>30.0</td>
<td>30.2</td>
</tr>
<tr>
<td>Framingham risk score, %</td>
<td>22.3</td>
<td>22.5</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>15.8</td>
<td>16.7</td>
</tr>
<tr>
<td>Previously untreated, %</td>
<td>24.8</td>
<td>25.8</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Isolated systolic hypert.</td>
<td>14.7</td>
<td>14.8</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>14.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Cerebrovascular disease, including transient ischemic attack</td>
<td>7.9</td>
<td>7.5</td>
</tr>
</tbody>
</table>
This implies that only a small fraction of the risk expressed by time-varying UACR is explained by relation to in-treatment systolic blood pressure. If antihypertensive treatment (losartan versus atenolol) is introduced into the model as a covariate, the pattern of the curves is only slightly modified, in accordance with the findings that the superior effect of losartan on reduction in albuminuria compared with atenolol only explained a minor part of the benefit in favor of losartan observed in the LIFE study.

Table 2 and Figure 2 display the end point rates for the 4 groups of patients, subdivided according to above or below the median value of UACR at baseline (1.21 mg/mmol) and above or below median value at year 1 (0.67 mg/mmol). Data show that risk increases stepwise in each group from the group with low baseline/low year 1 level to the group with high baseline/high year 1 level; for example, the primary composite end point rate increases from 5.5% to 8.6% to 9.4% to 13.5%. Note that the rates for those with values below the median at baseline and above the median at year 1 were similar to the rates for those with values above the median at baseline and below the median at year 1. The rates for the individual end points follow the same pattern of stepwise increases in risk.

Data for the composite end point are displayed as a Kaplan–Meier curve in Figure 2, which shows the likelihood of the primary composite end point during 60 months of treatment. Comparing the group with low baseline/low year 1 value to the group with high baseline/high year 1 value, the probability of the event increases from ≈5% to 14%. When this analysis is adjusted for baseline and year 1 systolic blood pressure in a Cox proportional hazard model, the risk estimate is not significantly modified (data not shown). Again, this indicates that the level of systolic blood pressure during treatment does not influence the risk conferred by UACR to any important degree during treatment.

**Discussion**

We and others have shown that baseline level of albuminuria is a powerful predictor for subsequent risk for cardiovascular complications in patients with essential hypertension. Table 2 presents the end point rates subdivided according to UACR above or below the median value at baseline and at year 1. The present study shows that the level of albuminuria during antihypertensive treatment with either losartan- or atenolol-based therapy is closely related to the risk during treatment, implying that changes in albuminuria translate to changes in risk.

**TABLE 2. End Point Rates Subdivided According to UACR Above or Below the Median Value at Baseline and at Year 1**

<table>
<thead>
<tr>
<th>Median UACR, mg/mmol</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Composite n/N (%)</th>
<th>Cardiovascular Mortality n/N (%)</th>
<th>Stroke n/N (%)</th>
<th>Myocardial Infarction n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.21 &lt; 1.21</td>
<td>&lt;0.67</td>
<td>144/2622 (5.5)</td>
<td>47/2638 (1.8)</td>
<td>67/2632 (2.5)</td>
<td>55/2628 (2.1)</td>
<td></td>
</tr>
<tr>
<td>1.21 &gt; 0.67</td>
<td>85/984 (8.6)</td>
<td>27/994 (2.7)</td>
<td>42/988 (4.3)</td>
<td>33/990 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.21 ≥ 0.67</td>
<td>92/978 (9.4)</td>
<td>34/996 (3.4)</td>
<td>44/984 (4.5)</td>
<td>37/990 (3.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>351/2601 (13.5)</td>
<td>161/2643 (6.1)</td>
<td>169/2616 (6.5)</td>
<td>123/2628 (4.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

χ² = 99, χ² = 73, χ² = 47, χ² = 27

P < 0.001, P < 0.001, P < 0.001, P < 0.001

*n indicates No. of patients with the end point; N, sample size for end point.
Sample sizes differ for each end point because patients with an end point before year 1 were excluded, and that No. differs for each end point. χ² indicates Pearson χ² test.
Our analyses were confined to in-treatment levels of albuminuria instead of the magnitude of changes from baseline during treatment. This approach was used to circumvent the problem that patients with the highest baseline value, and the highest cardiovascular risk, most likely also would have the greatest changes in albuminuria. In fact, of the 3606 patients with UACR below the baseline median value, only 801 (22%) had a decrease greater than the median year 1 change, whereas 2784 of 3574 (78%) patients with UACR above the median baseline value had a decrease above the median year 1 change, which was as expected because of blood pressure lowering and a regression-toward-the-mean phenomenon. Therefore, an analysis focusing on changes would bias the results. Thus, we analyzed the data based on dichotomization according to the median values of UACR at baseline and year 1. With this analysis, we found a stepwise decrease in event rate, indicating that lowering of UACR would also lead to a lowering of risk in those with high, as well as low, UACR at baseline.

The effects of lowering UACR were 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 4 strata specified in the analysis. The clinical interpretation is that an individual with high UACR at baseline whose UACR decreased (by ≥1 strata) during antihypertensive treatment will accordingly have a decreased cardiovascular risk.

One of the important correlates for baseline and in-treatment level of albuminuria is the level of blood pressure.5 However, when baseline and in-treatment values of systolic blood pressure were introduced in a Cox proportional hazard model for time-varying UACR, the risk assessment expressed by UACR was only modified to a minor degree. Accordingly, when our analysis on the groups divided according to median baseline in year 1 level of UACR were adjusted for baseline and in-treatment level of systolic blood pressure, the hazard ratios were not influenced to any significant 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.

Why is the level of albuminuria a risk predictor independent of other established risk factors? We and others have proposed that albuminuria is an integrated marker of structural and functional abnormalities in hypertension, such as hypertensive vascular abnormalities, endothelial dysfunction, hypertensive cardiac abnormalities, and impairment of renal function.4,7,10–13 Consequently, reductions in levels of albuminuria during treatment translate to regression of a number of vascular abnormalities in hypertension, and thereby a decrease in risk in general. Albuminuria is believed to be a measure of generalized vascular leakiness for albumin.8 This proposition is strengthened by our finding of parallel relationship between albuminuria and degree of LVH.5,8

We have shown previously that treatment with losartan confers a greater reduction in albuminuria during the study period compared with atenolol.10 We also showed that only part of the benefit of losartan relative to atenolol (≈17% with very wide 95% confidence limits between 9% to 66%) was explained by its superior influence on albuminuria.10 In concordance, the outcome of the time-varying albuminuria model does not change substantially when treatment (losartan versus atenolol) is introduced as a covariate in the model.

We are not aware of any other data from a large group of hypertensive patients elucidating the influence of antihypertensive treatment on change in albuminuria and its relationship to risk. In type 2 diabetes with diabetic nephropathy,14–16 but also in nondiabetic renal disease,17 there are data that indicate that the magnitude of decreases in albuminuria during renin-angiotensin-aldosterone system intervention relates to the degree of renal protection but also to the degree of reduction in cardiovascular risk.16

We believe that our data show the importance of monitoring of albuminuria in hypertensive individuals before, as well as during, treatment, a concept strongly argued for by de Zeeuw et al in patients with type 2 diabetes.14,18 Based on the present results and our previously published data,1 the risk for serious cardiovascular events already increases significantly at a level of UACR of ≥1.2 mg/mmol in a hypertensive population with LVH. This is a level that is much lower than the classical definition of microalbuminuria defined from diabetic population (ie, ≥3.5 mg/mmol), a level at which the risk in the present LIFE population already is increased ≈2- to 3-fold compared with the level ≤0.5 mg/mmol. We propose that measurement of albuminuria should be an integrated part of the management of arterial hypertension. It should be assessed before treatment and measured at yearly intervals. If the level remains high (ie, >1.0 mg/mmol) or not influenced by antihypertensive treatment, the clinician should carefully consider whether blood pressure is adequately controlled or whether other modifiable risk factors, such as smoking, lipid abnormalities, and glucose metabolism, need further intervention to decrease patient risk.

There are some limitations to this analysis. In the present study, albuminuria was characterized by determination of UACR in a single spot-urine collection at baseline and each year of follow-up; however, previous studies have documented a close correlation between spot-urine UACR and measures of albuminuria from overnight or 24-hour urine collection.19 Considering the variability in determination of UACR, only 1 measurement at each time point will weaken the relationship between UACR and outcome measures. On the other hand, this will be balanced to a major extent by the large sample size in this analysis. Patients qualified for enrollment into the study by specified ECG-LVH criteria, and hence, these results might not strictly apply to patients without ECG-LVH.

Conclusion
In hypertensive individuals, baseline and in-treatment levels of albuminuria are powerful predictors for subsequent cardiovascular morbidity and mortality. Reduction in albuminuria during treatment translates to reduction in cardiovascular events.

Perspectives
Our results indicate that measurement of albuminuria should be an integrated part of management of patients with hypertension. Reduction in albuminuria might be a therapeutic goal.
We thank Paulette A. Lyle for assistance with preparation of this manuscript and Anne-Grethe Thorn for secretarial services.

Acknowledgments
This work was supported in part by a grant from Merck & Co., Inc.

References
Reduction in Albuminuria Translates to Reduction in Cardiovascular Events in Hypertensive Patients: Losartan Intervention for Endpoint Reduction in Hypertension Study
Hans Ibsen, Michael H. Olsen, Kristian Wachtell, Knut Borch-Johnsen, Lars H. Lindholm, Carl Erik Mogensen, Björn Dahlöf, Richard B. Devereux, Ulf de Faire, Frej Fyhrquist, Stevo Julius, Sverre E. Kjeldsen, Ole Lederballe-Pedersen, Markku S. Nieminen, Per Ömvik, Suzanne Oparil and Ying Wan

*Hypertension.* 2005;45:198-202; originally published online January 17, 2005; doi: 10.1161/01.HYP.0000154082.72286.2a

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/45/2/198

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org//subscriptions/