Effect of Losartan on Microalbuminuria in Normotensive Patients with Type 2 Diabetes Mellitus

A Randomized Clinical Trial

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Background: **Angiotensin-converting enzyme inhibitors have shown antiproteinuric effects in normotensive and hypertensive diabetic patients. Angiotensin-receptor antagonists reduce urinary albumin excretion and the risk for renal and cardiovascular complications in hypertensive patients with type 2 diabetes mellitus. The effect of angiotensin-receptor antagonists in normotensive diabetic patients with microalbuminuria has not yet been reported.**

Objective: **To assess the antiproteinuric effects of losartan in normotensive patients with type 2 diabetes and microalbuminuria.**

Design: **Multicenter randomized, double-blind, placebo-controlled clinical trial.**

Setting: **19 outpatient clinics in the Netherlands.**

Patients: **147 normotensive patients with type 2 diabetes mellitus and microalbuminuria.**

Intervention: **74 patients were randomly assigned to receive losartan and 73 patients were assigned to receive placebo for 10 weeks; 71 patients in each group completed the study. The losartan dose was 50 mg during the first 5 weeks and 100 mg during the subsequent 5 weeks.**

Measurements: **Change in urinary albumin excretion rate after 5 and 10 weeks, change in creatinine clearance and blood pressure, and safety and tolerability of losartan.**

Results: **A significant 25% relative reduction in the albumin excretion rate occurred after 5 weeks of the 50-mg losartan dose, with further improvement over the subsequent 5 weeks with the 100-mg dose (relative reduction, 34%). In the losartan group, creatinine clearance did not improve and blood pressure decreased slightly. Side effects did not differ between treatment groups.**

Conclusions: **The angiotensin-receptor antagonist losartan reduces urinary albumin excretion in normotensive patients with type 2 diabetes and microalbuminuria. In multivariate analysis, the antiproteinuric effect of losartan was independent of the associated reduction in blood pressure. Losartan was safe and well tolerated in these normotensive patients.**

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Diabetes mellitus is an important cause of nephropathy, end-stage renal disease, and cardiovascular events. Nephropathy occurs in about 40% of patients with type 2 diabetes, and 25% to 40% of diabetic patients in Europe and the United States develop end-stage renal disease. Increased urinary albumin excretion, the first marker of kidney damage, carries an increased risk for renal as well as cardiovascular disease (1–5). Because reduction in microalbuminuria is associated with marked renal protection, the delay or retardation of the disease process is important in the management of diabetes mellitus (1).

Angiotensin-converting enzyme (ACE) inhibitors reduce albumin excretion in both normotensive and hypertensive patients with type 1 or type 2 diabetes. The antiproteinuric effects appear to be at least partly independent of the reduction in blood pressure caused by these agents (6–11), although some studies have not confirmed this finding (12). Angiotensin II is thought to play a prominent role in the pathogenesis of diabetic nephropathy. Therefore, both preventing the formation of angiotensin II by ACE inhibition and blockade of the angiotensin receptor might be renoprotective.

The trials of angiotensin-receptor antagonists in hypertensive patients with type 1 or 2 diabetes mellitus and microalbuminuria showed a reduction in albumin excretion, regardless of pretreatment levels (13–20). Recently, the angiotensin-receptor antagonist irbesartan retarded progression from microalbuminuria to overt proteinuria in hypertensive patients with type 2 diabetes (21). In RENAAL (The Reduction of Endpoints in NIDDM [non–insulin-dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan study) and IDNT (Irbesartan Diabetic Nephropathy Trial), losartan and irbesartan, respectively, reduced proteinuria and slowed the progression of diabetic nephropathy in hypertensive patients with type 2 diabetes (22–24).

Therefore, therapy that interferes with the renin–angiotensin–aldosterone system should probably be initiated when microalbuminuria develops in order to reduce albumin excretion and the associated risk for overt nephropathy. All previous studies on this subject investigated hypertensive patients. Therefore, we conducted a multicenter randomized, double-blind, placebo-controlled, clinical trial with forced dose titration to investigate the effects of losartan on urinary albumin excretion rate in normotensive patients with type 2 diabetes and microalbuminuria. Secondary objectives were to determine the time course of the antiproteinuric effect, the optimal dose of losartan, effects on creatinine clearance and blood pressure, and the safety and tolerability of losartan in normotensive patients.

METHODS

Study Design

In 19 outpatient clinics in the Netherlands, we conducted a 20-week randomized, placebo-controlled trial. The trial consisted of a 5-week screening and washout period, a 10-week double-blind treatment period, and a 5-week placebo washout period. The study was performed according to the guidelines of good clinical practice and was approved by the institutional review board at each center. All patients gave written informed consent.

Patients

From March 1999 through August 2001, all outpatients with type 2 diabetes mellitus, microalbuminuria, and a sitting blood pressure of 150/90 mm Hg or less were invited to participate. Type 2 diabetes mellitus was defined as diabetes diagnosed at age older than 30 years or controlled by diet or blood glucose–lowering agents for at least 6 months. Microalbuminuria was defined as a urinary albumin excretion rate of 20 to 200 μg/min.

The current definition of normotension is a blood pressure less than 140/90 mm Hg, with a blood pressure–lowering target of less than 130/80 mm Hg in hypertensive adults with diabetes mellitus (25, 26); however, we developed the protocol for this study in 1998, when normotension was defined as a sitting blood pressure of 160/90 mm Hg or less. Because of this and the fact that the mean baseline blood pressures appeared to be 135.9/78.8 mm Hg for the losartan group and 138.3/80.3 mm Hg for the placebo group, our study sample can be considered normotensive.

We excluded patients with a myocardial infarction in the preceding 6 months, cerebrovascular events within the past year, unstable angina pectoris, or symptomatic heart failure; patients with electrocardiographic abnormalities (atrioventricular conduction disturbances, sick sinus syndrome, atrial fibrillation, or other clinically significant rhythm disturbances), acute renal failure, chronic glomerulonephritis, polycystic kidney disease, or a serum creatinine level greater than 150 μmol/L (1.7 mg/dL); and patients with a glycosylated hemoglobin level greater than 10% or other relevant laboratory abnormalities. Concomitant use of antihypertensive agents, ophthalmic preparations containing β-blocking agents, steroids, or lithium was not allowed.

Eligible patients were included in the screening and washout period (weeks −5 to 0). In patients not taking blood pressure–lowering or renoprotective medication, microalbuminuria was assessed by two sequential 24-hour urine collections before the randomization visit (week 0). Patients could be randomly assigned if the average of these two measurements confirmed microalbuminuria as defined above. Eligible patients who were receiving ACE inhibitors, angiotensin-receptor antagonists, or other antihypertensive agents first entered a 5-week washout period. In these patients, microalbuminuria was assessed after this period. If therapy with such medication had been initiated to normalize known hypertension, the patient was excluded.

Context

Angiotensin-receptor antagonists reduce renal and cardiovascular complications in patients with type 2 diabetes and hypertension. The effect of these drugs on normotensive patients with type 2 diabetes is not known.

Contribution

This 10-week randomized, placebo-controlled trial showed that in normotensive diabetic patients receiving losartan, albumin excretion rate was significantly reduced and blood pressure slightly decreased.

Cautions

The study included patients with systolic blood pressure up to 150 mm Hg and was too brief to evaluate progression of clinical renal disease. Angiotensin-receptor antagonists hold promise in preserving renal function in patients with type 2 diabetes without marked hypertension, but they warrant further study.

–The Editors

Interventions

Patients who met all study criteria were randomly assigned in a double-blind fashion to receive losartan, 50 mg once daily, or matching placebo (week 0). After 5 weeks of treatment, patients initially assigned to receive 50 mg of losartan had fixed-dose titration to 100 mg of losartan; patients initially assigned to receive placebo continued to receive placebo. Treatment was continued at this dose for another 5 weeks, after which all patients were switched to single-blind placebo for the last 5 weeks. At the end of this washout period, patients returned for their final visit (week 15).

The study sponsor, Merck, Sharpe & Dohme, provided each center with the study medication and randomly assigned the patients in blocks of four. The investigators dispensed the study medication and provided the patient with the first available allocation number. In each center, the allocation numbers were assigned in consecutive order. The patients had an equal probability of assignment to either group. The randomization list was inaccessible to all investigators. No randomization code was broken, so all investigators and participants remained blinded to treatment assignment during the entire study.

Throughout the study, patients received the standard of care for diabetes. They were instructed not to change their physical exercise patterns significantly because doing so may influence proteinuria.

Outcomes

The primary end point was the change in urinary albumin excretion rate from baseline to week 10. Secondary end points were change in albumin excretion rate at week 5, change in creatinine clearance from baseline to week 10,

Table 1. **Baseline Characteristics of the Full-Analysis Study Sample***

Characteristic	Losartan Group ($n = 74$)	Placebo Group ($n = 73$)
Age, *y*	56.9 ± 11.0	58.5 ± 12.3
Men, *n (%)*	50 (68)	51 (70)
Race or ethnicity, *n (%)*		
White	59 (80)	63 (86)
Black	5 (7)	3 (4)
Asian	2 (3)	0 (0)
Other	8 (11)	7 (10)
Body mass index, *kg/m²*	32.0 ± 16.2	28.7 ± 4.5
Blood pressure, *mm Hg*		
Systolic	135.9 ± 10.4	138.3 ± 9.7
Diastolic	78.8 ± 9.4	80.3 ± 7.5
Pulse, *beats/min*	79.2 ± 11.5	76.4 ± 11.3
Biochemistry		
Serum creatinine level, *μmol/L (mg/dL)*	87.6 ± 20.8 (1.0 ± 0.2)	87.7 ± 17.5 (1.0 ± 0.2)
Total cholesterol level, *mmol/L (mg/dL)*	5.3 ± 1.0 (204.6 ± 38.6)	5.4 ± 0.9 (208.4 ± 34.7)
HDL cholesterol level, *mmol/L (mg/dL)*	1.2 ± 0.3 (46.3 ± 11.6)	1.2 ± 0.5 (46.3 ± 19.3)
LDL cholesterol level, *mmol/L (mg/dL)*	3.1 ± 0.9 (119.7 ± 34.7)	3.2 ± 0.8 (123.5 ± 30.9)
Triglyceride level, *mmol/L (mg/dL)*	22.4 ± 1.7 (212.6 ± 150.6)	2.3 ± 2.0 (203.7 ± 177.1)
Glycosylated hemoglobin value, *%*	8.0 ± 1.2	7.5 ± 1.1
Urinalysis		
Creatinine level, *mmol/L (mg/dL)*	7.4 ± 2.7 (0.08 ± 0.03)	7.5 ± 2.9 (0.08 ± 0.03)
Albumin excretion rate, *μg/min*	78.6 ± 51.3	89.4 ± 57.0
Creatinine clearance, *mL/s*		
As measured	1.77 ± 0.49	1.68 ± 0.58
Calculated with Cockcroft–Gault formula	1.71 ± 0.60	1.64 ± 0.57

* Values given with a plus/minus sign are the mean ± SD. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

and change in systolic and diastolic blood pressures at weeks 5 and 10. Tertiary end points were safety and tolerability of losartan.

Measurements

At each visit, the same investigator measured blood pressure and pulse. Blood pressure was measured by a sphygmomanometer, with the patient seated for 5 minutes before the first measurement. Three replicate measurements, obtained 1 minute apart, were averaged.

In each center, microalbuminuria was measured just before every visit in two sequential 24-hour urine collections by using an immunonephelometric assay on an automated analyzer (Beckman Coulter, Brea, California). The measurements of the two samples were averaged. Complete laboratory evaluations (biochemistry, hematology) were conducted at weeks 0 and 10; at weeks 5 and 15, only renal function and electrolytes were checked. A virtual central laboratory recalculated all laboratory results, including microalbuminuria, and corrected them for possible bias.

At weeks 0, 5, 10, and 15, adverse events were recorded, and medication use and adherence were checked by counting pills. Patients were considered adherent if at least 75% of the study drug had been taken.

Statistical Analysis

Primary and secondary end points were analyzed in the full-analysis study sample, which consisted of all patients randomly assigned (intention-to-treat analysis). The statistical method used was the generalized linear mixed model for longitudinal data, which compares the differences in trends over time between both treatment groups (27). Baseline values were used as covariates in this model, and outcomes were adjusted by using treatment, visit, center, and the corresponding interaction terms as fixed effects.

A generalized linear mixed model was also applied to evaluate whether the observed changes in albumin excretion rate were consistent across different baseline blood pressures. Furthermore, an additional analysis using analysis of variance was performed to evaluate whether changes in blood pressure affected the observed changes in albumin excretion rate.

Safety data were analyzed for all patients who took at least one dose of study medication and for whom at least one safety assessment was available. Statistical analysis of these data was not done.

The study had 92% power with an α level of 0.05 to detect a 30% difference in the change in albumin excretion rate between the treatment groups. We used SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina), for all statistical analyses.

Role of the Funding Source

The funding source had no role in the collection, analysis, or interpretation of the data or the decision to submit the manuscript for publication.

RESULTS

Patients

Of the 236 patients enrolled in the screening period, 49 used an ACE inhibitor or angiotensin-receptor antagonist before enrollment and underwent initial washout. Of

the 236 patients, 147 were randomly assigned. The main reason for exclusion before randomization was a screening-phase albumin excretion rate less than 20 μg/min, despite levels between 20 and 200 μg/min before enrollment. Of the 147 patients (full-analysis study sample), 74 were allocated to losartan and 73 were allocated to placebo.

In the losartan group, 3 patients discontinued treatment before the end of the study: 1 just after week 0 because the baseline urinary albumin excretion rate was retrospectively discovered to be greater than 200 μg/min, 1 after week 5 because of a cerebrovascular event within the preceding year, and 1 just after week 5 because of dizziness and headache after ingestion of 100 mg of losartan. In the placebo group, 2 patients discontinued treatment: 1 patient at week 5 because of a protocol violation (medication of wrong allocation number was given) and 1 at week 10 because the baseline urinary albumin excretion rate was retrospectively discovered to exceed 200 μg/min.

The remaining 142 patients (71 in each group) completed the entire study. Baseline characteristics did not significantly differ between groups (**Table 1**).

Albumin Excretion Rate

After 5 weeks of treatment with losartan, 50 mg, the mean albumin excretion rate was reduced from 78.6 μg/min at baseline to 59.3 μg/min (relative reduction, 24.6%) (**Table 2**). In the placebo group, the albumin excretion rate decreased from 89.4 μg/min to 83.3 μg/min (relative reduction, 6.8%). The adjusted mean difference in albumin excretion rate between the losartan and placebo groups was −16.9 μg/min (95% CI, −26.7 to −7.0 μg/min; $P < 0.001$).

At week 5, patients in the losartan group had a fixed-dose titration to 100 mg of losartan, and patients in the placebo group continued to receive placebo. After 5 weeks of treatment with this dose, the mean albumin excretion rate in the losartan group decreased further, from 78.6 μg/min at baseline to 51.9 μg/min at week 10 (relative reduction, 34%). In the placebo group, the mean albumin excretion rate at week 10 was 97.3 μg/min (increase, 10.3%). The difference in the adjusted mean albumin excretion rate between the losartan and placebo groups (−39.1 μg/min [CI, −48.9 to −29.2 μg/min]) was statistically significant ($P < 0.001$). After 10 weeks of treatment with losartan, 8 patients returned to normoalbuminuria (albumin excretion rate < 20 μg/min). In the placebo group, the minimum urinary albumin excretion rate after 10 weeks was 21 μg/min.

The adjusted mean albumin excretion rate decreased by 8.3 μg/min (CI, 0.04 to 16.5 μg/min; $P = 0.049$) when the losartan dose was increased from 50 mg to 100 mg. The antiproteinuric effect of losartan was reversible after discontinuation of treatment (**Table 2**, **Figure**).

Secondary End Points

Losartan was associated with a 9.7% relative reduction in measured creatinine clearance after 10 weeks of treatment, whereas this measure remained unchanged in the placebo group (adjusted difference between losartan and placebo groups, −0.16 mL/s [CI, −0.29 to −0.03 mL/s]; $P = 0.014$). When calculated with the Cockcroft–Gault formula, creatinine clearance decreased 3.3% in the losartan group and increased 2.7% in the placebo group; this difference was not statistically significant.

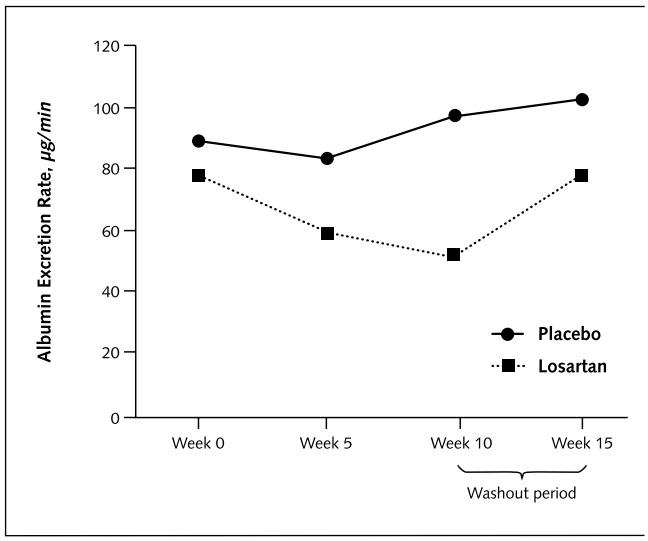
Blood pressure at baseline did not significantly differ between the losartan and placebo groups. After 5 weeks of treatment with losartan, 50 mg, mean blood pressure was reduced from 135.9/78.8 mm Hg to 132.4/76.8 mm Hg; in the placebo group, blood pressure decreased from 138.3/80.3 mm Hg to 136.1/79.7 mm Hg. The difference in mean blood pressure reduction between the losartan and placebo groups was not statistically significant. After 5 weeks of losartan, 100 mg, mean blood pressure decreased to 131.3/75.8 mm Hg. After 10 weeks of placebo use, mean blood pressure was 138.4/79.8 mm Hg (adjusted difference in mean systolic blood pressure between the lo-

Table 2. **Effects of Losartan and Placebo on Urinary Albumin Excretion Rate, Creatinine Clearance, and Blood Pressure***

End Point	Week 0 (Baseline)	Week 5 (50 mg of Losartan or Placebo)	Week 10 (100 mg of Losartan or Placebo)	Week 15 (Washout Period)
Albumin excretion rate, *μg/min*				
Losartan	78.6 ± 51.3	59.3 ± 37.0	51.9 ± 36.8	78.6 ± 64.8
Placebo	89.4 ± 57.0	83.3 ± 57.0	97.3 ± 66.4	102.5 ± 72.8
Creatinine clearance (as measured), *mL/s*				
Losartan	1.77 ± 0.49	1.70 ± 0.64	1.60 ± 0.49	1.72 ± 0.85
Placebo	1.68 ± 0.58	1.67 ± 0.64	1.67 ± 0.60	1.64 ± 0.64
Creatinine clearance (calculated with Cockcroft–Gault formula), *mL/s*				
Losartan	1.71 ± 0.56		1.65 ± 0.59	
Placebo	1.64 ± 0.57		1.69 ± 0.63	
Systolic blood pressure, *mm Hg*				
Losartan	135.9 ± 10.4	132.4 ± 13.5	131.3 ± 15.6	137.6 ± 10.4
Placebo	138.3 ± 9.7	136.1 ± 12.7	138.4 ± 12.9	141.2 ± 11.3
Diastolic blood pressure, *mm Hg*				
Losartan	78.8 ± 9.4	76.8 ± 9.4	75.8 ± 8.6	78.0 ± 9.1
Placebo	80.3 ± 7.5	79.7 ± 7.9	79.8 ± 7.0	80.7 ± 7.8

* Data are given as the mean ± SD.

Figure. **Time course of the effect of losartan and placebo on mean urinary albumin excretion rate.**



sartan and placebo groups, −3.8 mm Hg [CI, −6.5 to −1.1 mm Hg; $P = 0.006$]; difference in diastolic blood pressure, −2.7 mm Hg [CI, −4.5 to −0.8 mm Hg; $P = 0.005$]) (**Table 2**). Blood pressure returned to pretreatment levels after the 5-week placebo washout period.

Influence of Blood Pressure on Albumin Excretion Rate

At baseline, 62 patients had a blood pressure greater than 140/90 mm Hg to 150/90 mm Hg, 53 had a pressure greater than 130/80 to 140/90 mm Hg, and 32 had a pressure of 130/80 mm Hg or less. The change in mean albumin excretion rate from baseline to week 10 was independent of blood pressure at baseline in both the losartan and placebo groups ($P > 0.2$ for the interaction between baseline blood pressure and effect of treatment on albumin excretion rate in the losartan group and for the interaction in the placebo group).

Furthermore, in multivariate analysis, the reduction in albumin excretion rate was independent of the reduction in blood pressure associated with losartan ($P > 0.2$ for the interaction between changes in blood pressure and changes in albumin excretion rate and $P < 0.001$ for the interaction between treatment group and changes in albumin excretion rate).

Adherence, Tolerability, and Safety

Adherence was high in both treatment groups and at both doses, ranging from 94.4% in the placebo group to 100% in the 50-mg losartan group.

During the first 5 weeks of treatment, 10 and 12 adverse events, possibly related to the study drug, occurred in the placebo group and losartan group, respectively. During the subsequent 5 weeks, the corresponding figures were 3 and 2. All adverse events were mildly or moderately severe. No patients died.

Laboratory evaluations showed no significant changes in either treatment group. Neither losartan nor placebo affected serum potassium, sodium, uric acid, or glycosylated hemoglobin A levels.

DISCUSSION

To our knowledge, this study is the first randomized, placebo-controlled trial showing that the angiotensin-receptor antagonist losartan reduces urinary albumin excretion in normotensive patients with type 2 diabetes mellitus and microalbuminuria. Because 100 mg of losartan reduced the albumin excretion rate significantly more than did the 50-mg dose, our data also show the incremental benefit of a higher dose. The antiproteinuric effect was reversible upon discontinuation of losartan therapy. Losartan was well tolerated at both doses.

Treatment with losartan, 50 mg, reduced blood pressure slightly, but the effect was not significantly different from that in the placebo group. Losartan, 100 mg, resulted in a somewhat higher but still modest blood pressure reduction. However, the reduction in albumin excretion rate was independent of the decrease in blood pressure associated with losartan. These findings confirm an independent renoprotective effect, as postulated in previous studies (6–8, 21–23). Furthermore, the antiproteinuric effect of losartan was consistent across different baseline blood pressures, including patients who are normotensive according to the current definition.

The IRMA (Irbesartan Type II Diabetes with Microalbuminuria) trial studied the effect of the angiotensin-receptor antagonist irbesartan on the progression of microalbuminuria to overt proteinuria in hypertensive patients with type 2 diabetes (21). In that study, 150 and 300 mg of irbesartan were compared with placebo for the time to onset of overt nephropathy, changes in albuminuria, and creatinine clearance. The albumin excretion rate decreased by 24% with 150 mg of irbesartan and by 38% with 300 mg. The steepest decrease in albumin excretion rate occurred within the first 3 months of treatment. In our study, 50 mg of losartan resulted in a 25% relative reduction in the albumin excretion rate, compared with a 34% reduction with 100 mg. Thus, the antiproteinuric effects of losartan in our study appear to be qualitatively and quantitatively comparable to those of losartan and irbesartan in previous studies in hypertensive patients with diabetes mellitus (14, 16, 18, 19).

As stated, the IRMA trial showed a significant additional 14–percentage point reduction in microalbuminuria with a double dose of irbesartan (21), a finding similar to ours. As shown in previous studies that investigated the time course of the antiproteinuric response of angiotensin-receptor antagonists and ACE inhibitors (28–30), the incremental reduction in albumin excretion with losartan, 100 mg, appears attributable to a dose response rather than a time response. In patients with type 1 diabetes and microalbuminuria, the antiproteinuric response to losartan

was maximal within 1 week of treatment, and these changes paralleled those in blood pressure and renal hemodynamics (28). In nondiabetic patients with proteinuria and patients with type 1 diabetes mellitus and macroproteinuria, the antiproteinuric effects of losartan and enalapril were maximal within 4 weeks of treatment. Increasing the dose further reduced albuminuria; maximal effect was seen within 4 weeks (29, 30).

In the losartan-treated patients, the measured creatinine clearance decreased compared with baseline levels and compared with the placebo recipients. The difference between the measured and calculated clearance can be explained by inaccuracy of urine collection; the Cockcroft–Gault formula corrects this discrepancy. As known from other studies of ACE inhibitors and losartan in patients with early diabetic nephropathy, creatinine clearance stabilizes after prolonged treatment (6, 10, 11, 14, 17, 21–23, 31). The initial decrease is thought to result from renal hemodynamic factors and is reversible after withdrawal of medication (10, 17). The extent of the reduction in creatinine clearance in our study is similar to that seen in other studies.

Losartan at both doses was well tolerated, with a safety profile similar to that of placebo. These findings parallel observations made by others studying the nephroprotective effect of losartan in hypertensive diabetic patients (13, 14, 23). Of note, our study shows that normotensive patients can be treated safely with the antihypertensive drug losartan.

A possible site of action of angiotensin-receptor antagonists in normotensive diabetic patients is the vascular endothelium. Endothelial dysfunction has been associated with increased urinary albumin excretion, as well as with an increased risk for cardiovascular events in type 2 diabetes (32, 33). Inhibition of urinary albumin excretion may reflect recovery of endothelial function and may predict a reduction in the risk for complications.

One of the main limitations of our study is the brief follow-up period. However, the study was established to investigate whether losartan reduced microalbuminuria in normotensive patients with type 2 diabetes, since to our knowledge it is the first trial reported in this patient population. Furthermore, our study evaluated the effect of losartan on surrogate outcomes (albumin excretion rate), and therefore our findings cannot be extrapolated to hard clinical end points; however, microalbuminuria is considered to be predictive of renal and cardiovascular morbidity (2–5, 32).

A comparison with an ACE inhibitor or other antihypertensive drug would be of interest. However, when we developed the protocol, antihypertensive treatment of patients with type 2 diabetes mellitus and a blood pressure of 150/90 mm Hg or less was not the standard of care, nor was ACE inhibitor treatment of normotensive patients with type 2 diabetes and microalbuminuria. Accordingly, we had no reason to include a comparison group beyond placebo. Furthermore, investigating whether angiotensin-receptor antagonists have an advanced antiproteinuric effect over ACE inhibitors in this population would require an extremely large study because of the expected similar effects of both agents.

In conclusion, our data show that the angiotensin-receptor antagonist losartan reduces urinary albumin excretion in normotensive patients with type 2 diabetes mellitus and microalbuminuria. The antiproteinuric effects of ACE inhibitors and angiotensin antagonists in hypertensive diabetic patients decrease the risk for overt nephropathy, end-stage renal disease, and cardiovascular events (9, 11, 14, 21–24). Therefore, a long-term, large-scale clinical trial, preferably comparing losartan with an ACE inhibitor and other antihypertensive agents, is required to investigate the effects of losartan on hard clinical end points in normotensive patients with type 2 diabetes, with treatment started at a stage as early as microalbuminuria.

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Appendix

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