

EFFECTS OF LOSARTAN ON RENAL AND CARDIOVASCULAR OUTCOMES  
IN PATIENTS WITH TYPE 2 DIABETES AND NEPHROPATHY

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**ABSTRACT**

**Background** Diabetic nephropathy is the leading cause of end-stage renal disease. Interruption of the renin-angiotensin system slows the progression of renal disease in patients with type 1 diabetes, but similar data are not available for patients with type 2, the most common form of diabetes. We assessed the role of the angiotensin-II-receptor antagonist losartan in patients with type 2 diabetes and nephropathy.

**Methods** A total of 1513 patients were enrolled in this randomized, double-blind study comparing losartan (50 to 100 mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment (calcium-channel antagonists, diuretics, alpha-blockers, beta-blockers, and centrally acting agents), for a mean of 3.4 years. The primary outcome was the composite of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death. Secondary end points included a composite of morbidity and mortality from cardiovascular causes, proteinuria, and the rate of progression of renal disease.

**Results** A total of 327 patients in the losartan group reached the primary end point, as compared with 359 in the placebo group (risk reduction, 16 percent;  $P=0.02$ ). Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25 percent;  $P=0.006$ ) and end-stage renal disease (risk reduction, 28 percent;  $P=0.002$ ) but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction, 32 percent;  $P=0.005$ ). The level of proteinuria declined by 35 percent with losartan ( $P<0.001$  for the comparison with placebo).

**Conclusions** Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated. (N Engl J Med 2001;345:861-9.)

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**I**NTERRUPTION of the renin-angiotensin system with angiotensin-I-converting enzyme inhibitors slows the progression of renal disease both in patients with type 1 diabetes and in non-diabetic patients who have overt nephropathy.<sup>1-3</sup> However, postponing end-stage renal disease in patients with type 2 diabetes, the leading cause of chronic renal failure in many countries, remains an elusive goal. We

undertook a study in patients with type 2 diabetes and nephropathy in order to determine whether the angiotensin-II-receptor antagonist losartan, alone or in combination with conventional antihypertensive therapy, would increase the time to a doubling of the serum creatinine concentration, the onset of end-stage renal disease, or death. In addition, we assessed the effects of losartan and placebo on the following secondary end points: a composite of morbidity and mortality from cardiovascular causes, proteinuria, and the rate of progression of renal disease.

**METHODS****Study Design**

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study was an investigator-initiated, multinational, double-blind, randomized, placebo-controlled study designed to evaluate the renoprotective effects of losartan in 1513 patients with type 2 diabetes and nephropathy. The study design has been described previously.<sup>4</sup> In brief, 250 centers in 28 countries in Asia, Europe, Central America, South America, and North America participated. The study protocol was approved by the institutional review board of each center, and all patients gave written informed consent. The study was overseen by steering and safety committees, each of which contained one nonvoting member who was an employee of the sponsoring pharmaceutical company. The steering committee oversaw the study design, the conduct of the trial, and the management and analysis of the data. A writing subcommittee of the steering committee prepared this report. An independent end-points committee whose members were unaware of the patients' treatment assignments reviewed the data to determine which patients had reached the end points.

We planned to complete the study 3.5 years after the last patient underwent randomization, which would have resulted in a mean follow-up time of 4.5 years. However, the study was discontinued early (February 10, 2001) by a unanimous vote of the steering committee, whose members were unaware of the treatment assignments. Their decision was based on new evidence suggesting that angiotensin-I-converting enzyme inhibitors, which were excluded by design from the study, may be effective in reducing the incidence of cardiovascular events in patients with renal impairment, includ-

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\*The investigators who participated in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study are listed in the Appendix.

ing those with diabetes.<sup>5</sup> Therefore, the results reported here represent a mean follow-up time of 3.4 years (range, 2.3 to 4.6).

### Patients

The study involved male and female patients, ranging in age from 31 to 70 years, who had received diagnoses of type 2 diabetes and nephropathy. Nephropathy was defined by the presence on two occasions of a ratio of urinary albumin (measured in milligrams per liter) to urinary creatinine (measured in grams per liter) from a first morning specimen of at least 300 (or a rate of urinary protein excretion of at least 0.5 g per day) and serum creatinine values between 1.3 and 3.0 mg per deciliter (115 and 265  $\mu$ mol per liter), with a lower limit of 1.5 mg per deciliter (133  $\mu$ mol per liter) for male patients weighing more than 60 kg. Patients were excluded if they had received a diagnosis of type 1 diabetes or nondiabetic renal disease, including renal-artery stenosis. We also excluded patients who had had a myocardial infarction or had undergone coronary-artery bypass grafting within the previous month, who had had a cerebrovascular accident or had undergone percutaneous transluminal coronary angioplasty within the previous six months, who had had a transient ischemic attack within the previous year, or who had any history of heart failure before enrollment.<sup>4</sup>

### Treatment

During the six-week screening phase, patients with hypertension continued to receive their standard antihypertensive therapy. If they had been taking angiotensin-I-converting enzyme inhibitors or angiotensin-II-receptor antagonists, however, these medications were discontinued and replaced by alternative open-label medications (diuretics, calcium-channel antagonists, alpha- or beta-blockers, centrally acting agents, or some combination of these types of medication). Patients were stratified according to their base-line level of proteinuria (a urinary albumin-to-creatinine ratio <2000 or  $\geq$ 2000) and randomly assigned to receive either losartan (50 mg) or placebo once daily, along with conventional antihypertensive therapy. After four weeks, the dose of losartan or placebo was increased to 100 mg or the placebo equivalent once daily if the trough blood pressure with the patient sitting was above the target level of a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg. After an additional eight weeks, antihypertensive agents of the types described above (but not angiotensin-I-converting enzyme inhibitors or angiotensin-II-receptor antagonists) were added or their doses increased to achieve the target blood pressure.

Throughout the study, patients received the standard of care for the treatment of diabetes, including measurements of glycosylated hemoglobin and fasting serum glucose concentrations. Visits were scheduled every three months, or more often if necessary, to monitor the blood pressure and laboratory measurements and to assess whether adverse events had occurred or end points had been reached. Patients who discontinued the study drugs early had follow-up visits every three months until the end of the study; at these visits, the primary and secondary end points reached were recorded, the blood pressure was measured, and laboratory measurements were performed. Those who could not return for clinic visits or a family member was contacted by telephone to determine whether they had reached the end points of the initiation of dialysis, renal transplantation, or death.

### Outcome Measures

The primary efficacy measure was the time to the first event of the composite end point of a doubling of the serum creatinine concentration, end-stage renal disease, or death. The doubling of the serum creatinine concentration was defined as the first serum creatinine value that was twice the base-line value, as confirmed by a second serum creatinine value obtained at least four weeks after the initial doubling. End-stage renal disease was defined by the need for long-term dialysis or renal transplantation. The prespecified secondary end point, morbidity and mortality from cardiovascular

causes, was a composite of myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or death from cardiovascular causes. Analyses of the components of both the primary and secondary composite end points were also prespecified. Other secondary end points included the progression of renal disease<sup>6</sup> and changes in the level of proteinuria.

### Statistical Analysis

Analyses of the primary and secondary end points were performed according to the intention-to-treat principle; we included data from all randomized patients (with the exception of three patients who were lost to follow-up), from the time of randomization through the date of study termination. In a second, per-protocol analysis, we excluded patients who violated the criteria for inclusion and exclusion and censored patients' data 14 days after they permanently discontinued the study medication. A Cox regression model<sup>7</sup> that included the base-line level of proteinuria as a stratification factor and the geographic region as a covariate was used to determine the hazard ratio for the primary end point and its 95 percent confidence interval. The risk reduction was calculated as 100 percent  $\times$  (1 - hazard ratio). In analyses of nonfatal end points, data for the patients who had died were considered to have been censored. Event curves are based on Kaplan-Meier analysis.<sup>8</sup> We examined the effect of differences between the groups in the control of blood pressure by adding the mean arterial pressure during treatment as a time-dependent covariate in the Cox model and comparing the effect of losartan estimated by this model with that estimated by the primary analysis.

The analyses of the progression of renal disease and changes in the level of proteinuria were based on an on-treatment approach. For the analysis of the progression of renal disease, we compared the slopes of the reciprocal of the serum creatinine concentration<sup>6</sup> of the two treatment groups using a linear random-effects model. Changes in the level of proteinuria in the two groups were compared by means of a mixed-effects model<sup>9</sup> whose terms included the treatment at each point and the base-line level of proteinuria.

Because one interim analysis used a stopping boundary that was based on an alpha spending function of the O'Brien-Fleming type,<sup>10</sup> a critical P value of 0.048 was required for the primary hypothesis. For other outcomes, a P value of less than 0.05 was considered to indicate statistical significance. All statistical tests were two-sided.

## RESULTS

A total of 1513 patients were randomly assigned to receive losartan or placebo once daily, along with conventional antihypertensive therapy as needed but excluding angiotensin-I-converting enzyme inhibitors and angiotensin-II-receptor antagonists. The daily dose of losartan ranged from 50 to 100 mg, with 71 percent of the patients receiving 100 mg. The base-line characteristics were similar in the two groups (Table 1). More patients discontinued the study treatment in the placebo group (53.5 percent) than in the losartan group (46.5 percent). Adverse clinical events resulted in discontinuation in 17.2 percent of the patients in the losartan group, as compared with 21.7 percent of those in the placebo group. Increased serum concentrations of creatinine or potassium led to the discontinuation of the study medication in 1.5 percent and 1.1 percent, respectively, of the patients in the losartan group, as compared with 1.2 percent and 0.5 percent of the patients in the placebo group. A total of 7.5 percent of the patients in the losartan

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	LOSARTAN GROUP (N=751)	PLACEBO GROUP (N=762)
Age — yr	60±7	60±7
Sex — no. (%)		
Male	462 (61.5)	494 (64.8)
Female	289 (38.5)	268 (35.2)
Race or ethnic group — no. (%)		
Asian	117 (15.6)	135 (17.7)
Black	125 (16.6)	105 (13.8)
White	358 (47.7)	378 (49.6)
Hispanic	140 (18.6)	136 (17.8)
Other	11 (1.5)	8 (1.0)
Body-mass index†	30±6	29±6
Blood pressure — mm Hg		
Systolic	152±19	153±20
Diastolic	82±10	82±11
Mean arterial‡	105.5±10.9	106.0±11.6
Pulse§	69.4±17.4	70.8±18.1
Medical history — no. (%)		
Use of antihypertensive drugs	693 (92.3)	721 (94.6)
Angina pectoris	65 (8.7)	75 (9.8)
Myocardial infarction	75 (10.0)	94 (12.3)
Coronary revascularization procedure	1 (0.1)	1 (0.1)
Stroke	0	1 (0.1)
Lipid disorder	234 (31.2)	271 (35.6)
Amputation	65 (8.7)	69 (9.1)
Neuropathy	375 (49.9)	379 (49.7)
Retinopathy	494 (65.8)	470 (61.7)
Current smoking	147 (19.6)	130 (17.1)
Laboratory variables		
Median urinary albumin:creatinine ratio	1237	1261
Serum creatinine — mg/dl¶	1.9±0.5	1.9±0.5
Serum cholesterol — mg/dl		
Total	227±56	229±55
Low-density lipoprotein	142±47	142±45
High-density lipoprotein	45±16	45±15
Serum triglycerides — mg/dl**	213±180	225±200
Hemoglobin — g/dl††	12.5±1.9	12.5±1.8
Glycosylated hemoglobin — %	8.5±1.7	8.4±1.6

\*Plus-minus values are means ±SD. The differences between the treatment groups were not statistically significant.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡The mean arterial pressure was calculated as diastolic arterial pressure + (systolic arterial pressure – diastolic arterial pressure) ÷ 3.

§The pulse pressure was calculated as systolic arterial pressure – diastolic arterial pressure.<sup>11</sup>

¶To convert values to micromoles per liter, multiply by 88.4.

||To convert values to millimoles per liter, multiply by 0.02586.

\*\*To convert values to millimoles per liter, multiply by 0.01129.

††To convert values to millimoles per liter, multiply by 0.6206.

group and 7.8 percent of those in the placebo group withdrew their consent. We were able to determine the status of all patients (except for three patients in the losartan group who could not be contacted) with respect to dialysis, transplantation, and death.

### Blood Pressure

At base line, 93.5 percent of the patients (92.3 percent in the losartan group and 94.6 percent in the

placebo group) were receiving antihypertensive therapy. An additional 3 percent of the patients had hypertension but were not receiving antihypertensive therapy. The trough blood pressure declined progressively during the course of the study. The trough blood pressure at base line averaged 152/82 mm Hg in the losartan group and 153/82 mm Hg in the placebo group; the mean arterial pressure was 105.5 mm Hg in the losartan group and 106.0 mm Hg in the placebo group ( $P=0.38$ ); and the pulse pressure was 69.4 mm Hg in the losartan group and 70.8 mm Hg in the placebo group ( $P=0.13$ ). At one year, the values averaged 146/78 mm Hg in the losartan group and 150/80 mm Hg in the placebo group (mean arterial pressure, 100.9 mm Hg and 103.1 mm Hg, respectively [ $P<0.001$ ]; pulse pressure, 67.8 mm Hg and 69.8 mm Hg, respectively [ $P=0.05$ ]); at two years, the values were 143/77 mm Hg and 144/77 mm Hg, respectively (mean arterial pressure, 99.1 mm Hg and 99.7 mm Hg, respectively [ $P=0.38$ ]; pulse pressure, 66.2 mm Hg and 67.1 mm Hg, respectively [ $P=0.37$ ]); and at the end of the study they were 140/74 mm Hg and 142/74 mm Hg, respectively (mean arterial pressure, 95.9 mm Hg and 96.8 mm Hg, respectively [ $P=0.59$ ]; pulse pressure, 66.7 mm Hg and 67.4 mm Hg, respectively [ $P=0.77$ ]). The various classes of conventional antihypertensive drugs that were used before and during the study are listed in Table 2.

### Primary Outcomes

According to the intention-to-treat analysis, the primary composite end point of a doubling of the serum creatinine concentration, end-stage renal disease, or death was reached in 327 patients in the losartan group (43.5 percent), as compared with 359 in the placebo group (47.1 percent) (Fig. 1A). Treatment with losartan resulted in a 16 percent reduction in the risk of the primary composite end point ( $P=0.02$ ) (Table 3). The decrease in risk remained essentially unchanged (15 percent) after adjustment for blood pressure ( $P=0.03$ ). Furthermore, according to the per-protocol analysis, among the patients who continued to receive their assigned study treatment, losartan conferred a 22 percent reduction in the risk of the primary composite end point ( $P=0.008$ ).

The intention-to-treat analyses of the individual components of the primary composite end point are also shown in Table 3. The risk of a doubling of the serum creatinine concentration was 25 percent lower in the losartan group than in the placebo group ( $P=0.006$ ) (Fig. 1B). Losartan also reduced the risk of end-stage renal disease by 28 percent ( $P=0.002$ ) (Fig. 1C). Approximately 20 percent of the patients died, but there was no significant difference in mortality between the two groups ( $P=0.88$ ). The risk of the combined end point of end-stage renal disease or death was 20 percent lower in the losartan group

**TABLE 2.** USE OF CONVENTIONAL ANTIHYPERTENSIVE MEDICATIONS AT BASE LINE AND DURING STUDY TREATMENT.

CLASS OF MEDICATION	AT BASE LINE		DURING STUDY TREATMENT	
	LOSARTAN GROUP (N=751)	PLACEBO GROUP (N=762)	LOSARTAN GROUP (N=751)	PLACEBO GROUP (N=762)
	number (percent)			
Calcium-channel antagonist	532 (70.8)	546 (71.6)	585 (77.9)	618 (81.1)
Dihydropyridine	406 (54.1)	411 (53.9)	456 (60.7)	487 (63.9)
Diuretic	442 (58.9)	436 (57.2)	629 (83.8)	640 (84.0)
Alpha-blocker	180 (24.0)	184 (24.1)	302 (40.2)	348 (45.7)
Beta-blocker	137 (18.2)	140 (18.4)	256 (34.1)	280 (36.7)
Centrally acting agent	80 (10.7)	84 (11.0)	135 (18.0)	165 (21.7)
Angiotensin-I-converting enzyme inhibitor or angiotensin II antagonist	400 (53.3)	376 (49.3)	Excluded, per protocol	

than in the placebo group ( $P=0.01$ ) (Fig. 1D and Table 3). The reductions in the risk of end-stage renal disease and of end-stage renal disease or death changed little after correction for blood pressure (26 percent,  $P=0.007$ , and 19 percent,  $P=0.02$ , respectively).

#### Secondary Outcomes

There was no significant difference between the losartan group and the placebo group in the composite end point of morbidity and mortality from cardiovascular causes. Approximately one third of the patients had a fatal or nonfatal cardiovascular event (247 in the losartan group [32.9 percent] and 268 in the placebo group [35.2 percent]; risk reduction, 10 percent;  $P=0.26$ ). There were no significant differences in the rates of most of the cardiovascular end points; the exception was the first hospitalization with heart failure (89 patients in the losartan group [11.9 percent], as compared with 127 in the placebo group [16.7 percent]), for which the risk was reduced by 32 percent ( $P=0.005$ ) (Fig. 2). There was a difference between the number of myocardial infarctions in the losartan group (50 patients [6.7 percent]) and the number in the placebo group (68 patients [8.9 percent]; risk reduction, 28 percent), but this difference was not statistically significant ( $P=0.08$ ).

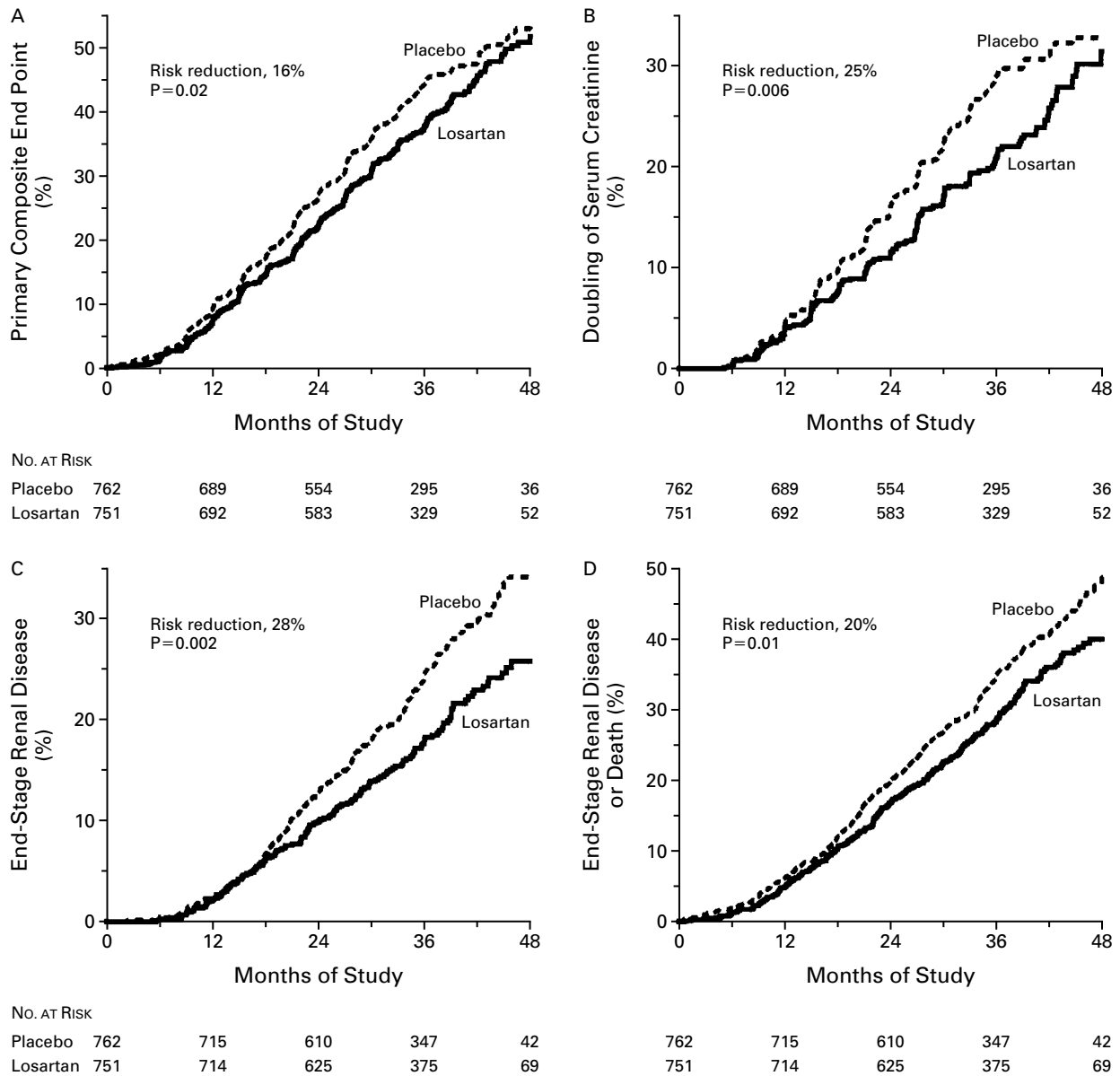
Losartan also led to an average reduction in the level of proteinuria (the urinary albumin-to-creatinine ratio) of 35 percent, whereas in the patients in the placebo group, the urinary albumin-to-creatinine ratio tended to increase ( $P<0.001$  for the overall treatment effect) (Fig. 3). Losartan reduced the rate of decline in renal function, as assessed by the reciprocal of the serum creatinine concentration, by 18 percent (median slope,  $-0.056$  dl per milligram per year in the losartan group, as compared with  $-0.069$  dl per

milligram per year in the placebo group;  $P=0.01$ ). Likewise, losartan was associated with a 15.2 percent reduction in the estimated decline in the glomerular filtration rate (median rate of decline, 4.4 ml per minute per 1.73 m<sup>2</sup> of body-surface area per year in the losartan group, as compared with 5.2 ml per minute per 1.73 m<sup>2</sup> per year in the placebo group;  $P=0.01$ ).<sup>12,13</sup> These reductions in the rate of decline are far smaller than those reported for captopril as compared with placebo in patients with type 1 diabetes nearly a decade ago.<sup>1</sup>

#### DISCUSSION

Our study establishes that losartan, along with conventional antihypertensive treatment as needed, confers strong renal protection in patients with type 2 diabetes and nephropathy. The risk of the primary end point, a composite of a doubling of the serum creatinine concentration, end-stage renal disease, or death from any cause, was reduced by 16 percent with losartan. The primary benefit appeared to be the effect on the renal components of this composite end point. In particular, the risk of end-stage renal disease was reduced by 28 percent with losartan during an average follow-up of 3.4 years. Extrapolating from the observed data, we estimate that this reduction corresponds to an average delay of two years in the need for dialysis or transplantation. The risk of a doubling of the serum creatinine concentration was also reduced by 25 percent with losartan. The difference between the slopes of the reciprocals of the serum creatinine values and the lower level of proteinuria provide further evidence of global renal protection with losartan.

There was a small, time-averaged difference in the trough blood pressure between the losartan group



**Figure 1.** Kaplan–Meier Curves of the Percentage of Patients with the Primary Composite End Point (Panel A) and Its Individual Components, a Doubling of the Serum Creatinine Concentration (Panel B), End-Stage Renal Disease (Panel C), and the Combined End Point of End-Stage Renal Disease or Death (Panel D).

The mean follow-up time was 3.4 years (42 months).

and the placebo group. We cannot exclude the possibility that this small difference had a beneficial effect on the renal outcomes. However, statistical analysis that corrected for these small differences confirmed that the renal protection conferred by losartan exceeded that attributable to any small differences in blood pressure. This study extends our knowledge of the efficacy of antihypertensive therapy in patients

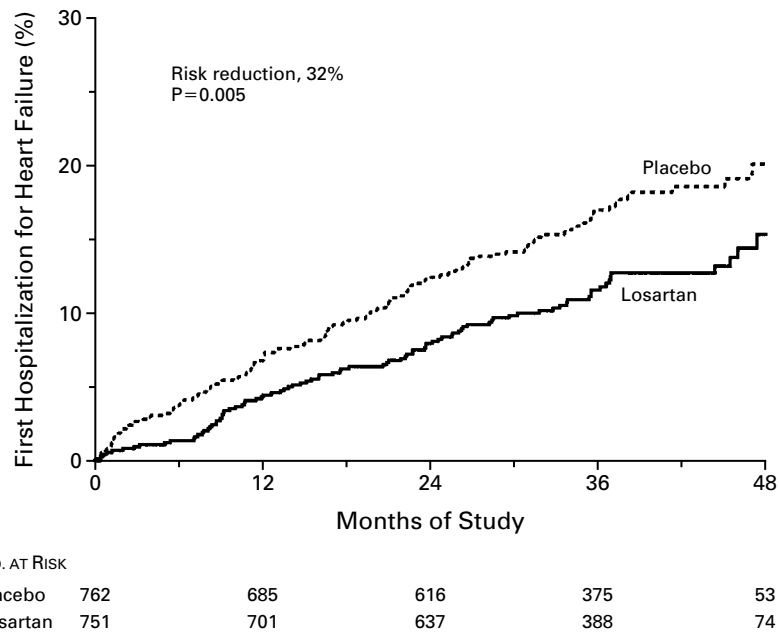
with type 2 diabetes and nephropathy. Previous studies involving angiotensin-I–converting enzyme inhibitors have demonstrated beneficial effects on proteinuria but have not demonstrated the superiority of blockade of the renin–angiotensin system in slowing the progression to end-stage renal disease over non-blockade forms of therapy.<sup>14–20</sup> Indeed, studies of the effects of angiotensin-I–converting enzyme inhibitors

**TABLE 3.** INCIDENCE OF THE PRIMARY COMPOSITE END POINT AND ITS COMPONENTS.\*

END POINT	LOSARTAN GROUP (N=751)		PLACEBO GROUP (N=762)		P VALUE	RISK REDUCTION % (95% CI)
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		
Primary composite end point†	327 (43.5)	15.9	359 (47.1)	18.1	0.02	16 (2 to 28)
Doubling of serum creatinine concentration	162 (21.6)	7.9	198 (26.0)	10.0	0.006	25 (8 to 39)
End-stage renal disease	147 (19.6)	6.8	194 (25.5)	9.1	0.002	28 (11 to 42)
Death	158 (21.0)	6.8	155 (20.3)	6.6	0.88	-2 (-27 to 19)
End-stage renal disease or death	255 (34.0)	11.7	300 (39.4)	14.1	0.01	20 (5 to 32)
Doubling of serum creatinine concentration and end-stage renal disease	226 (30.1)	11.0	263 (34.5)	13.2	0.01	21 (5 to 34)

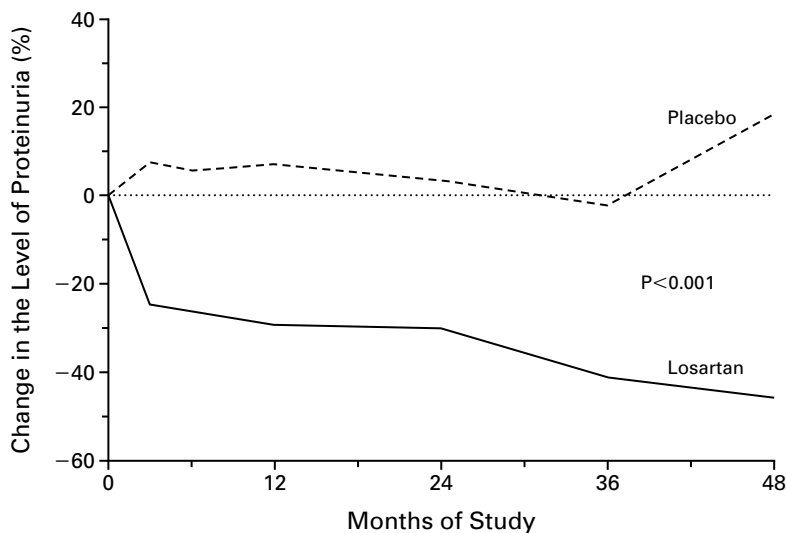
\*In end-point trials, there is often a difference between the risk reduction as determined on the basis of the Cox regression model and the risk reduction as determined on the basis of the crude rates of events. The difference results in part from the fact that the Cox regression model accounts for the time at risk — i.e., the longer average follow-up in the losartan group than in the placebo group. To address this aspect of the difference, we present the numbers of events per 100 patient-years of follow-up. In addition, the Cox model accounts for the base-line level of proteinuria (which was a stratification factor) and the geographic region, as prespecified in the data analysis plan. CI denotes confidence interval.

†The primary end point was a composite of a doubling of the serum creatinine concentration, end-stage renal disease, or death.



**Figure 2.** Kaplan–Meier Curves of the Percentage of Patients with a First Hospitalization for Heart Failure in the Losartan and Placebo Groups.

Subsequent hospitalizations for heart failure were not assessed. There were 88 patients (44 in each group) who had preexisting heart failure at the time of randomization. When these patients were excluded from the analysis of this component, there remained a significant difference in the rate of first hospitalization for heart failure between the two treatment groups. The mean follow-up time was 3.4 years (42 months).



NO. AT RISK					
Placebo	762	632	529	390	130
Losartan	751	661	558	438	167

**Figure 3.** Median Changes from Base Line in the Level of Proteinuria.

Proteinuria was measured as the urinary albumin-to-creatinine ratio in a first morning specimen. The mean follow-up time was 3.4 years.

on the progression of renal disease and end-stage renal failure have yielded conflicting results.<sup>14,15,20-24</sup> Therefore, in the absence of a direct comparison between angiotensin-I–converting enzyme inhibitors and angiotensin II antagonists, any extrapolation from the results obtained with different classes of drugs is speculative at best.

The benefits of losartan were observed among our patients, many of whom were already receiving other therapies, such as aspirin, beta-blockers, and lipid-lowering agents, as part of sound medical practice. Similarly, simultaneous therapy with calcium-channel antagonists did not detract from the beneficial effects of losartan, despite the recent controversy regarding the role of calcium-channel antagonists in the protection of the kidneys and the heart.<sup>25-27</sup> In this regard, it should be noted that in related studies in patients with type 1 and type 2 diabetes,<sup>1,28,29</sup> the benefits of captopril or irbesartan were not tested in the presence of concurrent calcium-channel-antagonist therapy. Furthermore, calcium-channel antagonists have been shown to augment the production of angiotensin II,<sup>30</sup> a response that may be counteracted by concomitant angiotensin-II–receptor blockade.

There was no significant difference between the losartan group and the placebo group in the composite secondary end point of morbidity and mortality from cardiovascular causes. This similarity of in-

cidence may have resulted in part from the relatively small sample and the strict criteria for enrollment that excluded patients at high risk for cardiovascular events including heart failure. We did find a significant difference in favor of losartan with regard to the rate of a first hospitalization for heart failure, a component of this secondary composite end point. This finding in patients without clinical heart failure at base line accords well with findings from the Studies of Left Ventricular Dysfunction Prevention study.<sup>31</sup> That study, however, did not include patients with impaired renal function. The Heart Outcomes Prevention Evaluation (HOPE) Study<sup>32</sup> and its substudy of patients with diabetes, MICRO-HOPE,<sup>20</sup> showed benefits of angiotensin-I–converting enzyme inhibition in terms of the signs and symptoms of heart failure but failed to show significant differences in hospitalizations for heart failure. Furthermore, the evaluation of a subgroup of the HOPE population with renal insufficiency<sup>5</sup> did not show a significant effect on this outcome. Our findings suggest that angiotensin II blockade in patients with renal disease decreases the risk of overt heart failure resulting in hospitalization.

In this population, losartan (plus conventional antihypertensive therapy) demonstrated excellent tolerability, similar to that of placebo (plus conventional antihypertensive therapy), as evidenced by the similar numbers of patients in the two groups in whom

the study treatment was discontinued because of adverse events. The addition of losartan to a conventional antihypertensive treatment regimen did not increase the incidence of adverse events.

End-stage renal disease continues to be a worldwide public health concern. Recent estimates by the National Institutes of Health indicate that diabetes represents the single largest cause of end-stage renal disease, accounting for approximately 40 percent of all cases in the United States between 1994 and 1998.<sup>33</sup> Furthermore, the incidence of end-stage renal disease in patients with type 2 diabetes is rising sharply in many regions of the world and is expected to double by 2010. The annual costs associated with end-stage renal disease in the United States reached \$12 billion in 1998 and are expected to surpass \$28 billion by 2010.<sup>34</sup> Preventing or delaying the progression of diabetic nephropathy is therefore an essential management goal. We believe our findings go a long way toward achieving this goal and may also have an important economic effect.

In summary, losartan led to significant improvement in renal outcomes that was beyond that attributable to blood-pressure control in patients with type 2 diabetes and nephropathy.

Supported by Merck and Company.

Dr. Brenner has served as a consultant to Merck, Bayer, Bristol-Myers Squibb, Aventis, AstraZeneca, Glaxo, and King. He has received research grants from Merck, Bayer, Bristol-Myers Squibb, and Novartis. He has been a member of speakers' bureaus sponsored by Merck, AstraZeneca, Bristol-Myers Squibb, and Novartis.

Dr. Cooper has served as a consultant to Pfizer, Sanofi, and Alteon. He has received research grants from AstraZeneca, Bristol-Myers Squibb, Merck, and Servier. He has been a member of speakers' bureaus sponsored by AstraZeneca and Solvay.

Dr. de Zeeuw has served as a consultant to Boehringer Ingelheim, Dade Behring, Merck Sharp & Dohme, Pfizer, Takeda, and Yamanouchi. He has received research grants from Bristol-Myers Squibb, Boehringer Ingelheim, Dade Behring, Merck Sharp & Dohme, Sanofi, and Yamanouchi. He has been a member of speakers' bureaus sponsored by Bristol-Myers Squibb, Dade Behring, and Merck Sharp & Dohme.

Dr. Keane has served as a consultant to Bayer, Merck, AstraZeneca, and Monarch. He has received research grants from Bayer and Merck. He has been a member of speakers' bureaus sponsored by Bayer, Merck, AstraZeneca, and Monarch.

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Dr. Parving has served as a consultant to Merck, Bristol-Myers Squibb, Sanofi, Pfizer, and BioStratum. He has received research grants from Merck, Bristol-Myers Squibb, Sanofi, and AstraZeneca. He has been a member of speakers' bureaus sponsored by Merck, Bristol-Myers Squibb, Sanofi, Pfizer, and AstraZeneca.

Dr. Remuzzi has received research grants from Aventis Pharma.

Drs. Snapinn, Zhang, and Shahinfar are employees of Merck and may own stock or hold stock options in Merck.

We are indebted to Roger L. Simpson, Denise R. Ramjit, Dr. Raymond P. Bain, and Dr. David J. van Dijk for their substantial contributions.

## APPENDIX

The following persons participated in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study: Independent Steering Committee: B.M. Brenner, M.E. Cooper, D. de Zeeuw, J.P. Grunfeld, W.F. Keane, K. Kurokawa, J. McGill, W.E. Mitch, H.-H. Parving, G. Remuzzi, A.B. Ribeiro, M. Schluchter; Independent Data Safety Monitoring Committee: C.E. Mogensen, M. Fifer, L. Fisher, P. Kowey, D. Schlon-

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