THE EFFECT OF ANGIOTENSIN-CONVERTING–ENZYME INHIBITION ON DIABETIC NEPHROPATHY

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Abstract *Background.* Renal function declines progressively in patients who have diabetic nephropathy, and the decline may be slowed by antihypertensive drugs. The purpose of this study was to determine whether captopril has kidney-protecting properties independent of its effect on blood pressure in diabetic nephropathy.

Methods. We performed a randomized, controlled trial comparing captopril with placebo in patients with insulin-dependent diabetes mellitus in whom urinary protein excretion was ≥500 mg per day and the serum creatinine concentration was ≤2.5 mg per deciliter (221 μmol per liter). Blood-pressure goals were defined to achieve control during a median follow-up of three years. The primary end point was a doubling of the base-line serum creatinine concentration.

Results. Two hundred seven patients received captopril, and 202 placebo. Serum creatinine concentrations doubled in 25 patients in the captopril group, as compared with 43 patients in the placebo group (P =0.007). The associated reductions in risk of a doubling of the serum creatinine concentration were 48 percent in the captopril group as a whole, 76 percent in the subgroup with a base-line serum creatinine concentration of 2.0 mg per deciliter (177 μmol per liter), 55 percent in the subgroup with a concentration of 1.5 mg per deciliter (133 μmol per liter), and 17 percent in the subgroup with a concentration of 1.0 mg per deciliter (88.4 μmol per liter). The mean (±SD) rate of decline in creatinine clearance was 11±21 percent per year in the captopril group and 17±20 percent per year in the placebo group (P = 0.03). Among the patients whose base-line serum creatinine concentration was ≥1.5 mg per deciliter, creatinine clearance declined at a rate of 23±25 percent per year in the captopril group and at a rate of 37±25 percent per year in the placebo group (P = 0.01). Captopril treatment was associated with a 50 percent reduction in the risk of the combined end points of death, dialysis, and transplantation that was independent of the small disparity in blood pressure between the groups.

Conclusions. Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood-pressure control alone. (N Engl J Med 1993;329: 1456-62.)

PATIENTS with diabetic nephropathy have a progressive decline in glomerular function, and the treatment of hypertension in these patients slows the rate of loss of renal function.[1-5] Angiotensin-converting–enzyme inhibitors have been used in several trials.[6-8] Findings in studies of animals with diabetes mellitus suggested that angiotensin-converting–enzyme inhibitors could reduce glomerular damage by one or more mechanisms independent of their antihypertensive effects.[9-11] We report the results of a trial designed to determine whether the angiotensin-converting–enzyme inhibitor captopril is more effective in slowing the progression of diabetic nephropathy than agents that act primarily by reducing blood pressure.

METHODS

The study was a prospective, double-blind, randomized clinical trial performed in 30 clinical centers. The study protocol was approved by the institutional review board at each center, and all patients gave written informed consent.

Entry and Exclusion Criteria

Patients 18 to 49 years of age were eligible if they had had insulin-dependent diabetes mellitus for at least 7 years, with an onset before the age of 30 years, and had diabetic retinopathy, urinary protein excretion of ≥500 mg per 24 hours, and a serum creatinine concentration of ≤2.5 mg per deciliter (221 μmol per liter). All patients satisfying these criteria during a single examination were eligible for the study, regardless of previous blood-pressure status or a previous need for antihypertensive medication. Patients who were receiving angiotensin-converting–enzyme inhibitors or calcium antagonists were eligible provided their blood pressure could be maintained within the blood-pressure goals required by the trial (see below) without these drugs. Therapy with an angiotensin-converting–enzyme inhibitor, other than the coded medication, and calcium antagonists was not allowed during the trial. Patients were excluded for the following reasons: pregnancy, a dietary evaluation that indicated marked departure from standard dietary recommendations, white-cell count below 2500 per cubic millimeter, congestive heart failure (New York Heart Association class III or worse), and a serum potassium concentration of ≥6 mmol per liter.[12]

Randomization and Treatment Plan

Eligible patients were stratified according to center and randomly assigned to a group according to a standard urn design.[13] Those assigned to the captopril group received a dose of 25 mg three times daily, and those assigned to the control group received identical-appearing placebo tablets three times daily. The specific blood-pressure goals were a diastolic blood pressure below 90 mm Hg and a systolic blood pressure below 140 mm Hg or, if the base-line systolic blood pressure exceeded 150 mm Hg, a subsequent decrease of at least 10 mm Hg and a maximal reading of 160 mm Hg. Blood pressures were measured in seated patients at rest by the nurse coordinator at each center according to a standard technique. The average of two consecutive readings taken 30 seconds apart was recorded as the blood pressure for that visit.

Each patient underwent a dietary evaluation, and recommendations were made according to American Diabetes Association guidelines. The recommended dietary protein intake was 1 g per kilogram of body weight per day. The patient's diabetes was managed in accord with the patient's historical treatment schedule. The extent to which diabetes was controlled was monitored by measurements of glycosylated hemoglobin. After randomization, the patients were seen at two weeks, at one month, and every three months thereafter until they died, required dialysis, or underwent renal transplantation. Compliance in taking the coded medications was determined

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Supported by grants from the Public Health Service (5 R01-DK 39908, 5 R01-DK 39826, MO1-RR00030, MO1-RR00034, MO1-RR00036, MO1-RR00051, MO1-RR00058, MO1-RR00059, and MO1-RR00425) and by the Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, N.J.).

*Members of the Collaborative Study Group are listed in the Appendix.

by the nurse coordinators with the pill-count method. The patients' vital status, need for dialysis, and need for transplantation were monitored until September 30, 1992. Glycosylated hemoglobin, serum creatinine, and 24-hour urinary excretion of creatinine, protein, and urea were measured by the central laboratory at each visit according to standard methods.

End Points

The primary study end point was a doubling of the base-line serum creatinine concentration to at least 2.0 mg per deciliter (177 μmol per liter), confirmed by the central laboratory. Secondary analyses included the length of time to the combined end points of death, dialysis, and transplantation and changes in renal function, assessed in terms of the serum creatinine concentration, 24-hour creatinine clearance, and urinary protein excretion. Other stopping points were defined for patients whose blood pressure could not be maintained within the limits dictated by the study and those with persistent hyperkalemia (potassium level exceeding 6 mmol per liter), adverse drug effects, pregnancy, or intercurrent illness that precluded their continued enrollment in the study.[12]

Statistical Analysis

The results were analyzed with the Statistical Analysis System[14] and StatXact[15] software. Dichotomous and polychotomous base-line characteristics of the groups were compared with Fisher's exact test[16]; continuous base-line characteristics were compared with Wilcoxon rank-sum tests.[17] The mean values of measurements at all follow-up visits were compared with t-tests.[18] For the analysis of the length of time to event end points, product-limit life-table distributions were compared with the log-rank test statistic.[19] Proportional-hazards regression analysis was used to determine interactions between the treatment groups and the base-line and time-dependent covariates, as well as to estimate the percent reduction in the number of events within subgroups and from one subgroup to another.[19,20] Renal-function measurements over time were compared with a two-stage, simple, linear random-effect model,[21] with variables estimated by restricted maximum likelihood and the multivariate Wilcoxon rank-sum test.[22] The analyses included all patients who underwent randomization, with all patients retained in their assigned group regardless of their adherence to the treatment regimen. To protect against increasing the rate of a type I error due to interim analyses, the Lan–DeMets group sequential procedure[23] set the significance level for the primary outcome in the final analysis at 0.044. For other outcomes, a P value of less than 0.05 was considered to indicate statistical significance. All statistical tests were two-sided.

Quality Assurance and Study Monitoring

A clinical review committee, masked to patient assignment, classified all study outcomes. An external advisory board, appointed by the National Institute of Diabetes and Digestive and Kidney Diseases, reviewed all medical, ethical, and statistical considerations.

Results

Four hundred nine patients entered the study at 30 centers between December 1987 and October 1990. Two hundred seven were assigned to the captopril group, and 202 to the placebo group. The demographic, clinical, and laboratory characteristics of the two groups were similar, except that urinary protein excretion was higher in the placebo group than in the captopril group (P = 0.02) (Table 1). A total of 301 patients completed their final scheduled visit (median follow-up, 3 years; range, 1.8 to 4.8). Of the remainder, 50 patients began dialysis, underwent renal transplantation, or died before their final scheduled visit (median follow-up, 1.7 years; maximum, 4.5). The remaining 58 patients (31 in the placebo group and 27 in the captopril group) discontinued their quarterly scheduled visits (median follow-up, 0.7 year; maximum, 3.3), but we were able to determine whether all but 4 of these patients (2 in each group) had died, begun dialysis treatment, or undergone transplantation as of September 30, 1992.

Table 1. Base-Line Characteristics of the Patients with Diabetic Nephropathy in the Captopril and Placebo Groups.*

Characteristic	Captopril (N = 207)	Placebo (N = 202)	P Value†
Age (yr)	35±7	34±8	0.46
Male sex (%)	52	54	0.69
Race (%)			
White	91	87	0.12
Black	5	10	
Duration of diabetes (yr)	22±7	22±7	0.96
Hypertension (%)‡	75	76	0.91
Antihypertensive therapy (%)	60	59	0.84
Systolic blood pressure (mm Hg)§	137±19	140±20	0.21
Diastolic blood pressure (mm Hg)§	85±11	86±12	0.47
Mean arterial pressure (mm Hg)§	102±12	104±13	0.25
Serum creatinine (mg/dl)¶	1.3±0.4	1.3±0.4	0.54
24-Hour urinary protein excretion (mg/day)	2500±2500	3000±2600	0.02
24-Hour urinary urea nitrogen (g/day)‖	11±5	10±5	0.08
24-Hour creatinine clearance (ml/min)	84±46	79±35	0.50
Glycosylated hemoglobin (%)	11.8±2.8	11.6±2.8	0.75

*Plus–minus values are means ±SD.

†For categorical variables the P values were based on Fisher's exact test. The P values for continuous variables were based on the Wilcoxon test.

‡Hypertension was defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg.

§Blood pressure was measured in seated, resting patients during an office visit.

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

‖To convert urinary urea nitrogen values to millimoles per day, multiply by 35.7.

Clinical Management

Only four patients (three in the placebo group and one in the captopril group) were removed from the study because of an inability to meet the predefined blood-pressure goals. The median systolic blood pressure at base line was 135 mm Hg in the captopril group and 138 mm Hg in the placebo group. The median values obtained at quarterly intervals during the study ranged from 128 to 134 mm Hg in the captopril group and from 129 to 136 mm Hg in the placebo group; at most times the difference between groups was no more than 2 mm Hg. The median diastolic blood pressure at base line was 86 mm Hg in both groups. The median diastolic values during the study ranged from 77 to 82 mm Hg in the captopril group and from 80 to 84 mm Hg in the placebo group; the difference between groups was consistently less than 4 mm Hg, with the captopril group having the lower value at most times. The mean (±SD) arterial pressure, averaged over all follow-up visits, was 96±8 mm Hg in the captopril group and 100±8 mm Hg in the placebo group.

The decrease in base-line mean arterial pressure in

the 155 patients in the captopril group who had preexisting hypertension averaged 7±11 mm Hg, and it averaged 5±11 mm Hg in the 153 patients with preexisting hypertension in the placebo group. This difference in blood-pressure control was not significant (P = 0.16). Among patients who were not hypertensive before entry into the trial (52 in the captopril group and 49 in the placebo group), the difference in the control of mean arterial pressure was more pronounced, averaging 5 mm Hg through the follow-up period (P<0.001).

At base line, 59 percent of the patients in the placebo group and 60 percent of those in the captopril group were receiving antihypertensive medication (Table 1). Sixty-four percent of the hypertensive patients in the placebo group were receiving diuretic agents at base line, and this value ranged from 79 to 93 percent during the study. By comparison, 62 percent of the hypertensive patients in the captopril group were receiving diuretic agents at base line, and this value ranged from 74 to 87 percent during the study. At no quarterly interval was the difference between groups statistically significant except at month 24 (P = 0.033). Fifteen percent of the hypertensive patients in the placebo group were receiving β-adrenergic antagonists at base line, and 34 to 46 percent were receiving them during the study, whereas 11 percent of the hypertensive patients in the captopril group were receiving these drugs at base line, and 15 to 53 percent were receiving them during the study. The difference between groups was significant only during the first 12 months of the study. There were no significant differences in the use of other agents, including labetalol, clonidine, methyldopa, prazosin, hydralazine, guanabenz, terazosin, and minoxidil.

The mean changes from base line in the glycosylated hemoglobin concentration (an increase of 0.5 percent) and 24-hour urinary urea nitrogen excretion (a decrease of 0.9 g [32 mmol] per day) were not different between the treatment groups.

Changes in Serum Creatinine Concentrations

Sixty-eight patients had a doubling of serum creatinine concentrations: 25 in the captopril group and 43 in the placebo group (P = 0.007) (Table 2 and Fig. 1A). They included four patients in the captopril group and five patients in the placebo group who had discontinued their visits (and the study drug). The associated reduction in risk in the captopril group was 48 percent (95 percent confidence interval, 16 to 69 percent) (Table 3). The effect of treatment on the primary end point was assessed in subgroups defined by the base-line covariates summarized in Table 1. The beneficial effect of captopril was not altered by any of these covariates except for the base-line creatinine concentration. A higher base-line serum creatinine value was significantly associated (P = 0.02) with a decreased risk of a twofold increase in serum creatinine in the captopril group (Table 3).

Table 2. Outcome Events in Patients with Diabetic Nephropathy in the Captopril and Placebo Groups.

Event	Captopril (N = 207)	Placebo (N = 202)
	number of patients	
Death*	8	14
Dialysis or transplantation	20	31
Death, dialysis, or transplantation	23	42
Stopping points†		
Doubling of serum creatinine‡	25	43
Neutropenia	1	1
Captopril-specific side effect	2	1
Nonspecific side effect	3	3
Hyperkalemia	3	0
Failed blood-pressure control	1	3
Intercurrent illness or condition	11	7
Pregnancy	1	1
Study medication discontinued for other reasons	19	11
Scheduled follow-up visits discontinued*	27	31

*Includes patients who had previously reached other stopping points.

†Includes patients reaching stopping points who stopped taking their coded medication but continued their scheduled visits.

‡The primary end point was a doubling of the base-line serum creatinine concentration to at least 2.0 mg per deciliter.

Figure 2A shows the cumulative incidence curves for the primary end point in the subgroup of 102 patients with a base-line serum creatinine concentration of ≥1.5 mg per deciliter (133 μmol per liter) (P<0.001; risk reduction, 68 percent; 95 percent confidence interval, 39 to 83 percent) and in the subgroup of 307 patients with a base-line serum creatinine concentration below 1.5 mg per deciliter (P = 0.31; risk reduction, 33 percent; 95 percent confidence interval, −44 to 69 percent). The difference in the risk of a doubling of the serum creatinine concentration remained after adjustments for differences in mean arterial pressure[20] (Table 3).

Death, Dialysis, and Transplantation

As of September 30, 1992, 65 patients had died or required dialysis or renal transplantation: 23 in the captopril group and 42 in the placebo group (P = 0.006) (Table 2 and Fig. 1B). Of these 65 patients, 7 in the captopril group and 8 in the placebo group reached one or more of these three end points after they discontinued their scheduled visits. Treatment with captopril was associated with a 50 percent reduction in the risk of the combined end points of death, dialysis, and transplantation (95 percent confidence interval, 18 to 70 percent) (Table 3). The beneficial effect of captopril on the three end points was consistent over the range of measurements of each covariate (Table 1) except the base-line serum creatinine concentration (P = 0.02). The reduction in the combined risk increased as the base-line serum creatinine concentration increased (Table 3). Figure 2B shows the cumulative incidence curves for the combined end points in the subgroup of 102 patients with a base-line serum creatinine concentration of ≥1.5 mg per deciliter (P = 0.002; risk reduction, 61 percent; 95 percent confidence inter-

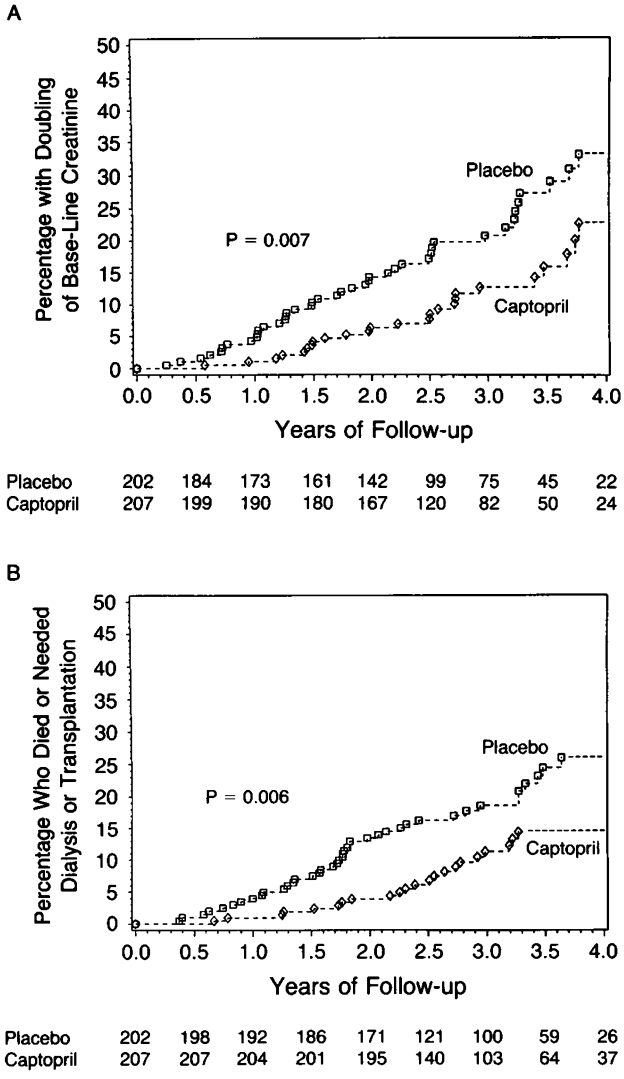

Figure 1. Cumulative Incidence of Events in Patients with Diabetic Nephropathy in the Captopril and Placebo Groups.

Panel A shows the cumulative percentage of patients with the primary end point: a doubling of the base-line serum creatinine concentration to at least 2.0 mg per deciliter. Panel B shows the cumulative percentage of patients who died or required dialysis or renal transplantation. The numbers at the bottom of each panel are the numbers of patients in each group at risk for the event at base line and after each six-month period.

val, 26 to 80 percent) and in the subgroup of 307 patients with a base-line serum creatinine concentration below 1.5 mg per deciliter (P = 0.14; risk reduction, 46 percent; 95 percent confidence interval, 22 to 76 percent).

Sequential Measurements of Renal Function

Among the 405 patients who had 2 or more determinations of serum creatinine (median, 13 determinations; maximum, 27) during an average follow-up of 2.7 years per patient (maximum, 4.8), the mean rate of increase in serum creatinine in the patients in the captopril group was 0.2±0.8 mg per deciliter per year (22±67 μmol per liter per year), which was significantly lower (P = 0.004) than that in the patients in the placebo group, in whom the values increased at a rate of 0.5±0.8 mg per deciliter per year (42±67 μmol per liter per year). Among the patients with base-line serum creatinine concentrations of less than 1.5 mg per deciliter, the increase was 0.1±0.4 mg per deciliter per year (11±37 μmol per liter per year) in the captopril group and 0.2±0.4 mg per deciliter per year (17±37 μmol per liter per year) in the placebo group (P = 0.15). Among the patients with base-line serum creatinine concentrations of ≥1.5 mg per deciliter, the increase in serum creatinine in the captopril group was 0.6±1.2 mg per deciliter per year (72±102 μmol per liter per year), as compared with 1.4±1.2 mg per deciliter per year (122±102 μmol per liter per year) in the placebo group (P = 0.002). For the sequential measurements of creatinine clearance, a logarithmic transformation was used to improve the distributional assumptions of the simple, linear random-effects model. The rate of decline in 24-hour creatinine clearance in the 402 patients with 2 or more determinations (maximum, 21) was 11±21 percent per year in the captopril group and 17±20 percent per year in the placebo group (P = 0.03). The rate of decline was more pronounced among patients who had a base-line serum creatinine concentration of ≥1.5 mg per deciliter: 23±25 percent per year in the captopril group and 37±25 percent per year in the placebo group (P = 0.01).

The median urinary protein excretion of the patients in the captopril group had decreased 0.3 g per day by the first quarterly visit, and it remained lower

Table 3. Percent Reduction in the Overall Risk of Progression of Diabetic Nephropathy with Captopril Treatment and According to the Base-Line Serum Creatinine Concentration.*

Event	Percent Reduction in Risk (95 Percent Confidence Interval)	
	Unadjusted for Mean Arterial Pressure	Adjusted for Mean Arterial Pressure
Doubling of base-line serum creatinine		
All patients	48 (16 to 69)	43 (6 to 65)
Base-line serum creatinine†		
1.0 mg/dl	17 (−97 to 65)	4 (−121 to 58)
1.5 mg/dl	55 (25 to 73)	50 (16 to 70)
2.0 mg/dl	76 (55 to 87)	74 (52 to 86)
Death, dialysis, or transplantation		
All patients	50 (18 to 70)	46 (10 to 68)
Base-line serum creatinine†		
1.0 mg/dl	7 (−127 to 62)	4 (−129 to 16)
1.5 mg/dl	54 (22 to 73)	51 (16 to 71)
2.0 mg/dl	78 (57 to 89)	75 (51 to 87)

*Proportional-hazards regression analysis was used to estimate the 95 percent confidence interval of the percent reduction in risk with mean arterial pressure as a time-dependent covariate and without it; a negative number indicates an increase in risk. The chi-square statistic for the interaction of the base-line serum creatinine concentration with the effect of captopril on the risk of doubling the concentration was 5.09 (P = 0.02) without adjustment for mean arterial pressure and 6.10 (P = 0.014) after adjustment for mean arterial pressure; that for the interaction with the effect of captopril on the combined end points of death, dialysis, and renal transplantation was 5.97 (P = 0.02) without adjustment for mean arterial pressure and 5.34 (P = 0.021) after adjustment for mean arterial pressure.

†The results given are for patients with the exact serum creatinine concentrations shown, as representative of the continuum of base-line serum creatinine concentrations.

in this group than in the placebo group throughout most of the remainder of the trial. An aggregate analysis over the four years of the study revealed significantly less proteinuria in the captopril group (P = 0.001).

Compliance with Treatment and Adverse Events

The number of patients taking their study drug at the one-year visit was similar in the captopril (170 of 185 patients, 92 percent) and placebo (160 of 169 patients, 95 percent) groups. At the last scheduled visit, 128 of the 153 patients remaining in the captopril group (84 percent) who had not reached the primary end point were still taking the study drug, as compared with 110 of the 121 patients remaining in the placebo group (91 percent) (P = 0.10).

Captopril or placebo was discontinued before the serum creatinine concentration doubled or death occurred in 68 patients for reasons summarized in Table 2. The most frequent intercurrent illnesses or conditions that prompted discontinuation of treatment were myocardial infarction (seven patients), congestive heart failure (three patients), and stroke (three patients). Eleven other patients were thought by their physicians to require therapy with an angiotensin-converting–enzyme inhibitor or a calcium antagonist. A physician discontinued the study medication for other reasons in 7 patients, and 12 patients stopped taking the study medication on their own initiative.

Discussion

We found that captopril significantly retarded the rate of loss of renal function in this group of patients with diabetic nephropathy. In the captopril group, the risk of a doubling of the serum creatinine concentration was reduced by almost one half, as was the combined risk of death, dialysis, or transplantation. The study was designed to determine whether captopril was associated with an effect that was independent of its role as an antihypertensive agent. The magnitude of the blood-pressure reduction in the two groups was comparable, the median systolic blood pressure being very similar in the groups and the disparity between

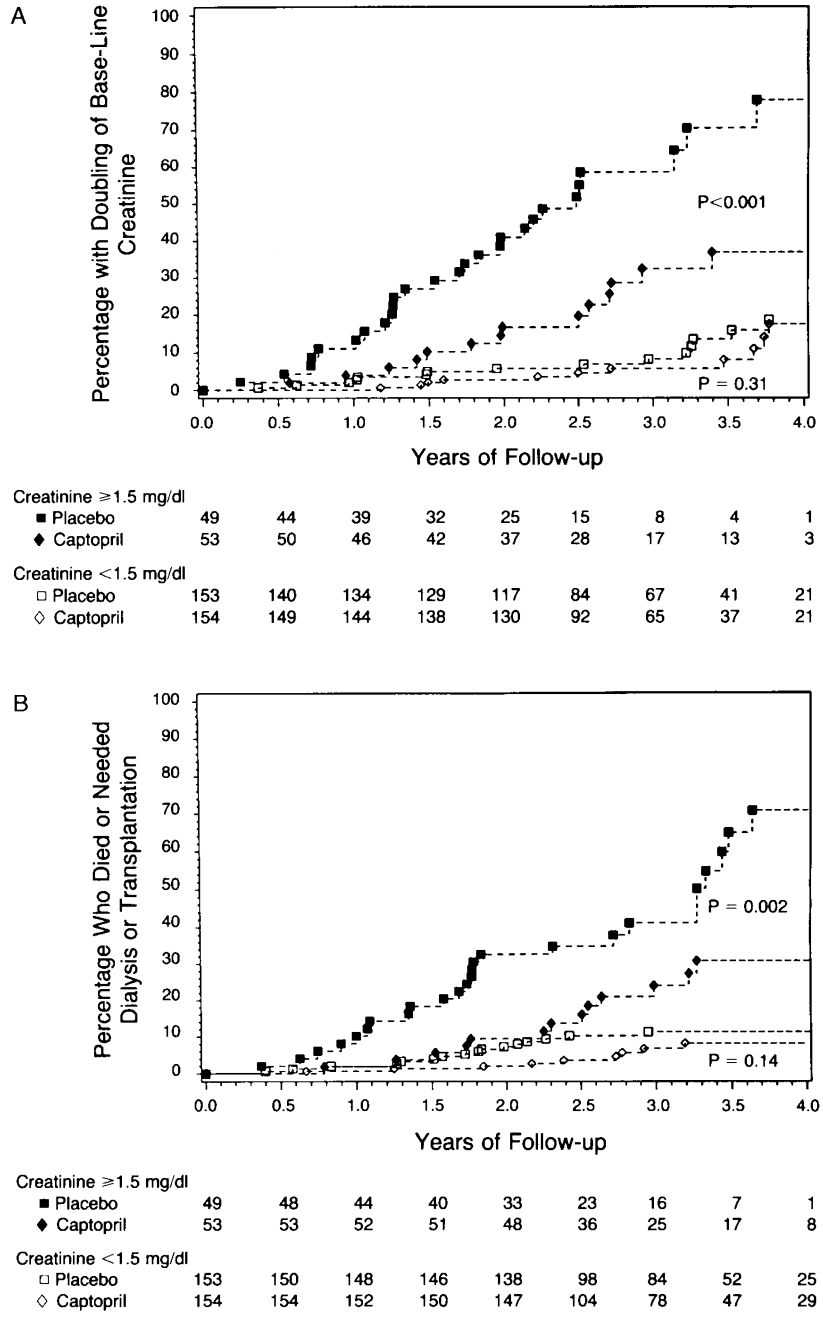

Figure 2. Cumulative Incidence of Events in Patients with Diabetic Nephropathy in the Captopril and Placebo Groups, According to the Base-Line Serum Creatinine Concentration.

A total of 102 patients had a base-line serum creatinine concentration of ≥1.5 mg per deciliter, and 307 had a base-line serum creatinine concentration below 1.5 mg per deciliter. Panel A shows the cumulative percentage of patients in each subgroup who had a doubling of the serum creatinine concentration to at least 2.0 mg per deciliter. Panel B shows the cumulative percentage of patients in each subgroup who died or required dialysis or renal transplantation. The numbers at the bottom of the figure are the numbers of patients in each subgroup at risk for the event at base line and after each six-month period.

groups in median diastolic blood pressure tending to be no more than 2 to 3 mm Hg throughout the study, although the patients treated with captopril did have a marginally lower average mean arterial pressure. This difference was not significant among the patients with preexisting hypertension, and 85 percent of the patients who had a twofold increase in serum creatinine were in this subgroup. The inclusion of mean arterial pressure during the study as a time-dependent covariate did not alter the estimated reduction in the risk of a doubling of the serum creatinine concentration in the captopril group, nor did it affect the decreased combined risk of death, dialysis, or transplantation in the captopril group. The beneficial effect of captopril was therefore not explained by the small differences in the level of blood-pressure control between the two groups.

Our results support the proposal that captopril slows the progression of diabetic nephropathy by a mechanism that is independent of its antihypertensive properties. It has been proposed that angiotensin-converting–enzyme inhibition can beneficially influence the altered glomerular hemodynamics in patients with diabetes. Glomerular efferent arteriolar tone is increased in diabetic animals, and as a result there is an increase in transcapillary hydraulic pressure.[9,10] These alterations may decrease the functional integrity of the glomerular capillary wall. Removal of the tonic constrictor effect of angiotensin II on efferent arterioles would be expected to lower glomerular intracapillary pressure while preserving renal plasma flow. In rats with diabetes, the long-term administration of an angiotensin-converting–enzyme inhibitor diminishes the functional and morphologic evidence of glomerular injury and decreases glomerular transcapillary pressure[11]; other antihypertensive agents do not have these effects.[11] There are other possible explanations for the beneficial intrarenal actions of angiotensin-converting–enzyme inhibitors. They may interfere with trophic properties of angiotensin II to promote cellular and glomerular hypertrophy[24-26] or diminish the accumulation of mesangial matrix.[27] Either of these processes could be an important initial step leading to glomerular scarring.

The results achieved in the placebo group in this study serve as a measure of the expected clinical course of patients with diabetic nephropathy who have their blood pressure maintained at normal levels. We were unable to confirm previous reports suggesting that the progressive loss of renal function could be markedly diminished by blood-pressure control with agents other than angiotensin-converting–enzyme inhibitors.[1,3,4,6,8] The patients who received only antihypertensive treatment lost renal function at a rate substantially higher than would be predicted from the existing literature.

Other studies have supported the notion that therapy with an angiotensin-converting–enzyme inhibitor preserves renal function. Björck et al. reported a reduction in the pretreatment rate of decline of renal function with the use of captopril.[7] In small, short-term studies, patients with diabetic nephropathy, both those with hypertension[8] and those without hypertension,[28] had a slower rate of decline of renal function when treated with captopril than untreated patients. Others have focused attention on the short-term antiproteinuric effect of angiotensin-converting–enzyme inhibitors at various stages of diabetes.[29,30] Whether a specific kidney-protecting effect was operative in these trials is difficult to judge, since the mean arterial pressure in the untreated patients was higher than in the captopril-treated patients.[8,28]

Angiotensin-converting–enzyme inhibitors are known to decrease urinary protein excretion in patients with diabetes and other glomerulopathies.[31-33] In our study, the administration of captopril led to decreased proteinuria. This decrease could be explained by a beneficial effect of the drug on glomerular hemodynamics and glomerular pathology. It has been suggested that the magnitude of proteinuria itself may be associated with the rate of progression of kidney damage.[34] We cannot rule out the possibility that the amelioration of the proteinuria may have been pathogenetically relevant in the captopril-treated patients in this study.[34]

Our results indicate that captopril therapy is kidney-protecting in patients with insulin-dependent diabetes who have established nephropathy. The beneficial effects of this therapy were accompanied by relatively few serious side effects specifically attributable to the drug. We propose that this therapy be used in normotensive and hypertensive patients with diabetes and clinically evident nephropathy.

Appendix

The following institutions and persons participated in the Collaborative Study Group trial: *Clinical Coordinating Center,* Rush–Presbyterian–St. Luke's Medical Center, Chicago — E.J. Lewis, R. Rohde, and M. Nemcek; University of Iowa, Iowa City — L.G. Hunsicker; *Biostatistical Coordinating Center,* George Washington University, Washington, D.C. — R.P. Bain, J. Lachin, S.W. Greenhouse, D.A. Verme, T.R. Turlington, and P.K. Burrows; *Collaborating Clinics and Investigators:* Case Western Reserve University, Cleveland — J. Wish and J. Sheehan; Cleveland Clinic, Cleveland — M. Pohl; University of Colorado, Denver — T. Berl; Henry Ford Hospital, Detroit — G. Santiago; Medical College of Wisconsin, Milwaukee — J. Lemann, Jr., S. Blumenthal, and B.A. Bresnahan; Ohio State University, Columbus — L. Hebert and N.S. Nahman, Jr.; University of Pennsylvania, Philadelphia — S. Goldfarb and S. Kobrin; Rush–Presbyterian–St. Luke's Medical Center, Chicago — R. Rodby; University of Illinois, Chicago — S. Lietz and D. Valaitis; New England Medical Center, Boston — A. Levey and M. McLaughlin; Joslin Diabetes Center, Boston — M. Williams; Washington University, St. Louis — J. McGill; Affiliated Hospitals of Canton, Canton, Ohio — F. Whittier; University of Toronto, Toronto — D. Cattran; Loyola Medical Center, Maywood, Ill. — J. Hano; Indiana University, Indianapolis — D. Maxwell; Brookdale Hospital Medical Center, Brooklyn, N.Y. — J. Porush and S. Spitalewitz; Nyack Hospital, Nyack, N.Y. — K. Shapiro; Harbor–UCLA Medical Center, Torrance, Calif. — S. Adler; Syracuse, N.Y. — N. Tolchin; Lovelace Institutes, Albuquerque, N.M. — W. Hoy and R. Bernstein; Duke University, Durham, N.C. — L. Svetkey; Atlanta Nephrology Referral Center, Decatur,

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