

## EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY

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**Abstract Background.** Drugs that inhibit angiotensin-converting enzyme slow the progression of renal insufficiency in patients with diabetic nephropathy. Whether these drugs have a similar action in patients with other renal diseases is not known. We conducted a study to determine the effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases.

**Methods.** In a three-year trial involving 583 patients with renal insufficiency caused by various disorders, 300 patients received benazepril and 283 received placebo. The underlying diseases included glomerulopathies (in 192 patients), interstitial nephritis (in 105), nephrosclerosis (in 97), polycystic kidney disease (in 64), diabetic nephropathy (in 21), and miscellaneous or unknown disorders (in 104). The severity of renal insufficiency was classified according to the base-line creatinine clearance: 227 patients had mild insufficiency (creatinine clearance, 46 to 60 ml per minute), and 356 had moderate insufficiency (creatinine clearance, 30 to 45 ml per minute). The primary end point was a doubling of the base-line serum creatinine concentration or the need for dialysis.

**Results.** At three years, 31 patients in the benazepril group and 57 in the placebo group had reached the primary end point ( $P < 0.001$ ). In the benazepril group, the reduction in the risk of reaching the end point was 53 percent overall (95 percent confidence interval, 27 to 70 percent), 71 percent (95 percent confidence interval, 21 to 90 percent) among the patients with mild renal insufficiency, and 46 percent (95 percent confidence interval, 12 to 67 percent) among those with moderate renal insufficiency. The reduction in risk was greatest among the male patients; those with glomerular diseases, diabetic nephropathy, or miscellaneous or unknown causes of renal disease; and those with base-line urinary protein excretion above 1 g per 24 hours. Benazepril was not effective in patients with polycystic disease. Diastolic pressure decreased by 3.5 to 5.0 mm Hg in the benazepril group and increased by 0.2 to 1.5 mm Hg in the placebo group.

**Conclusions.** Benazepril provides protection against the progression of renal insufficiency in patients with various renal diseases. (N Engl J Med 1996;334:939-45.)

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**I**N animals with experimentally induced renal disease, drugs that inhibit angiotensin-converting enzyme reduce glomerular-capillary pressure, inhibit renal cellular growth, and reduce glomerular-capillary permeability to protein, thus reducing proteinuria and preventing the development of glomerulosclerosis.<sup>1-4</sup> Whether this protective effect also occurs in humans is less clear. In patients with diabetes and incipient nephropathy, angiotensin-converting-enzyme inhibitors prevent the progression from microalbuminuria to proteinuria,<sup>5,6</sup> whereas in patients with overt nephropathy, these drugs provide protection against a deterioration in renal function, an effect that is independent of their antihypertensive properties.<sup>7</sup> Small studies suggest that the drugs may have a similar kidney-protecting effect in patients with other renal diseases.<sup>8-11</sup> The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study was designed to determine whether benazepril, a nonsulfhydryl angiotensin-con-

verting-enzyme inhibitor, is safe and effective in slowing the progression of renal dysfunction in patients with mild-to-moderate renal insufficiency.

### METHODS

We conducted a prospective, double-blind, randomized study involving 49 European hospitals. The protocol was approved by the institutional review board of each hospital, and all the patients gave written informed consent.

### Patients

Men and women between the ages of 18 and 70 years who had chronic renal insufficiency caused by various diseases were eligible for the study if they met the following criteria: a serum creatinine concentration of 1.5 to 4.0 mg per deciliter (133 to 354  $\mu\text{mol}$  per liter) and a 24-hour estimated creatinine clearance<sup>12</sup> of 30 to 60 ml per minute, with variations of less than 30 percent in at least three measurements of creatinine clearance during a three-month screening period and less than 15 percent during a subsequent two-week, single-blind placebo period. Patients with hypertension were treated with a stepwise approach involving the use of various antihypertensive drugs during the screening period to maintain the diastolic pressure while supine at or below 90 mm Hg. Patients already receiving an angiotensin-converting-enzyme inhibitor were switched to alternative medications.

The exclusion criteria were therapy-resistant edema; treatment with corticosteroids, nonsteroidal antiinflammatory drugs, or immunosuppressive drugs; a value for urinary protein excretion over 10 g per 24 hours and a value for serum albumin under 25 g per liter (each measured at least three times, and twice during the screening period); renovascular hypertension; malignant hypertension or a myocardial infarction or cerebrovascular accident in the six months preceding the study; congestive heart failure (New York Heart Association class III or IV); insulin-dependent diabetes mellitus; elevated serum aminotransferase concentrations; collagen disease; obstructive uropathy; cancer; chronic cough; a history of allergy to an angiotensin-converting-enzyme inhibitor; drug or alcohol abuse; and pregnancy. The

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\*The members of the study group are listed in the Appendix.

cause of renal disease in each patient was determined on the basis of the history, physical examination, urinalysis, biochemical tests, and radiologic or ultrasonographic studies, as well as renal biopsies in most of the patients with proteinuria. All diagnoses were confirmed by a quality-control and end-point-evaluation committee.

### Study Design

All eligible patients were screened for three months (to determine whether their renal function was stable and to control blood pressure) and then received one placebo tablet once daily for two weeks. They were subsequently stratified into two groups: those with mild renal insufficiency (creatinine clearance, 46 to 60 ml per minute) and those with moderate insufficiency (creatinine clearance, 30 to 45 ml per minute). The patients in each group were then randomly assigned to receive 10 mg of benazepril or placebo once daily. Randomization was balanced for disease severity at each center.

Each patient was examined by a physician, who was unaware of the group assignment, every two weeks during the first month of treatment, monthly for two months, and then every three months. The study period was three years. At each examination, blood pressure was measured in supine patients 3 to 4 hours after ingestion of the drug, and serum creatinine and electrolyte concentrations, other serum biochemical values (uric acid, glucose, cholesterol, triglycerides, liver enzymes, and bilirubin), and a complete blood count were determined, as well as 24-hour urinary protein excretion. Antihypertensive therapy was adjusted as necessary to maintain the target value for diastolic pressure.

All the patients were advised to reduce their salt intake to approximately 3 g per day and to eat 0.8 g of protein per kilogram of ideal body weight per day. Dietary compliance during the study, assessed by evaluating 24-hour urinary urea excretion, was similar in the two groups, although protein intake was higher than suggested (0.9 g per kilogram per day).

### Outcome Measures

The primary outcome measure (end point) was the time from the initiation of benazepril therapy or placebo to a doubling of the serum creatinine concentration, confirmed one month later, or the need for dialysis. The secondary outcome measures were changes over time in the values for serum creatinine, urinary protein excretion, and diastolic pressure and adjustments in antihypertensive therapy.

Serum and urinary creatinine concentrations were measured with an AutoAnalyzer, and urinary protein excretion was determined by a standard method at each center. Benazepril (like other angiotensin-converting-enzyme inhibitors) does not alter creatinine metabolism in vivo or affect the concentration in vitro.

A policy committee, whose members were not otherwise involved in the study, reviewed all medical, ethical, and statistical issues. A quality-control and end-point-evaluation committee confirmed all the diagnoses and all the instances in which end points were reached.

### Statistical Analysis

The primary outcome measure was analyzed with the log-rank test, with the status of renal survival determined as of the last day of the third year of treatment. For all patients who did not complete the three-year study, including those who died, data were censored after the last visit. To protect against a type I error due to the one planned interim analysis, the significance level for the primary outcome measure in the final analysis was set at 0.031 (on the basis of a two-tailed test). Proportional-hazards regression was used to determine possible interactions between the treatment groups and the following covariates: disease severity (mild or moderate), sex, base-line 24-hour urinary protein excretion ( $\leq 1$  g,  $>1$  g to  $<3$  g,  $\geq 3$  g), and base-line normotension or hypertension (including supine diastolic pressure  $\leq 90$  mm Hg or  $>90$  mm Hg in the hypertensive patients), as well as supine diastolic pressure and 24-hour urinary protein excretion over time. The relative benefit of the treatment was evaluated by calculating the number of patients who needed to be treated for three years to prevent the occurrence of one end point.<sup>13</sup>

The secondary outcomes were analyzed descriptively in four cohorts of patients: those still participating in the study at 6 months and at 12, 24, and 36 months. This approach had the advantage of elimi-

Table 1. Characteristics of the Patients in the Benazepril and Placebo Groups at Base Line.\*

CHARACTERISTIC	BENAZEPRIL (N = 300)	PLACEBO (N = 283)
Age (yr)	51 ± 13	51 ± 12
Male sex — no. of patients (%)	220 (73)	201 (71)
Creatinine clearance — ml/min	42.9 ± 11.6	42.3 ± 10.6
Severity of renal insufficiency — no. of patients (%)†		
Mild	120 (40)	107 (38)
Moderate	180 (60)	176 (62)
Serum creatinine — mg/dl	2.1 ± 0.6	2.1 ± 0.6
Urinary protein excretion — g/day	1.8 ± 2.6	1.8 ± 2.2
Urinary urea nitrogen excretion — g/day	15.3 ± 7.8	15.1 ± 7.5
Serum potassium — mmol/liter	4.5 ± 0.5	4.4 ± 0.5
Hemoglobin — g/dl	13.7 ± 1.5	13.7 ± 1.6
Blood pressure — mm Hg		
Systolic	142 ± 17	144 ± 17
Diastolic	87 ± 9	88 ± 9
Hypertension — no. of patients (%)‡	244 (81)	234 (83)
Antihypertensive therapy — no. of patients (%)	234 (78)	222 (78)
Antihypertensive agent — no. of patients (%)		
Calcium antagonist	141 (47)	140 (49)
β-Adrenergic antagonist	113 (38)	107 (38)
Diuretic	60 (20)	72 (25)
Centrally acting drug	33 (11)	38 (13)
Vasodilator	15 (5)	25 (9)
α-Adrenergic antagonist	15 (5)	19 (7)
Other	10 (3)	9 (3)

\*Plus-minus values are means ± SD. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. To convert values for urinary urea nitrogen to millimoles per day, multiply by 35.7.

†Mild insufficiency was defined as a creatinine clearance of 46 to 60 ml per minute, and moderate insufficiency as a creatinine clearance of 30 to 45 ml per minute.

‡Patients who had a supine diastolic pressure over 90 mm Hg or were receiving antihypertensive therapy were considered to have hypertension.

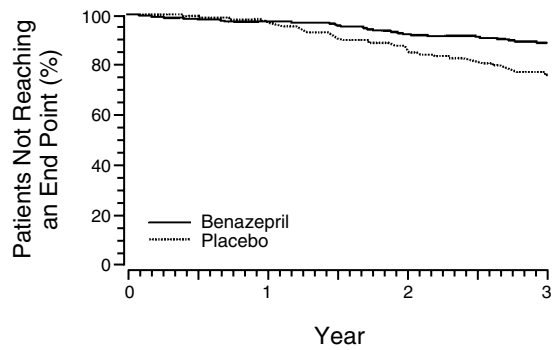
nating the potentially misleading contribution of data from the patients who withdrew from the study early, because the reasons the patients reached the end points were not independent of the evaluated variables.

Fisher's exact test was used to analyze nonparametric safety variables. The analyses were performed with Statistical Analysis System software.

## RESULTS

Between January 1989 and December 1990, 668 patients were screened for the study, and 583 were randomly assigned to receive benazepril or placebo (398 in Italy, 119 in Germany, and 66 in France). Eighty-five patients were screened but not randomized: 3 patients died (1 died suddenly of a cardiac cause, and 1 each died of stroke and myocardial infarction), 8 had concomitant diseases (2 had bladder cancer, 2 had strokes, and 1 each had acute pyelonephritis, worsening mitral insufficiency, nephrotic syndrome, and a possible cervical tumor), 38 had serum creatinine concentrations outside the allowed range or progressive renal insufficiency, and 36 did not participate for administrative reasons.

The characteristics of the two randomized groups were similar (Table 1). The underlying renal diseases included glomerular disease (in 192 patients), interstitial nephritis (in 105), nephrosclerosis (in 97), polycystic kidney disease (in 64), diabetic nephropathy (in 21), and chronic renal insufficiency of miscellaneous or unknown



NO. OF PATIENTS	300	275	259	252	230	219	82
Benazepril	300	275	259	252	230	219	82
Placebo	283	252	236	217	198	179	53

Figure 1. Kaplan-Meier Estimates of Renal Survival among Patients with Chronic Renal Insufficiency Who Were Receiving Benazepril or Placebo.

cause (in 104). Renal insufficiency was mild in 227 patients (39 percent) and moderate in 356 (61 percent).

The overall median duration of treatment was 3.0 years for the benazepril group and 2.9 years for the placebo group.

**Renal Survival**

Eighty-eight patients (31 in the benazepril group and 57 in the placebo group) reached the primary end point within three years: 86 patients had a doubling of the base-line serum creatinine concentration, and 2 required dialysis. Renal survival was significantly better in the benazepril group (P<0.001) (Fig. 1). Among the patients with mild renal insufficiency, 5 of 120 in the benazepril group reached the primary end point, as compared with 15 of 107 in the placebo group (P=0.01). Among the patients with moderate renal insufficiency, 26 of 180 in the benazepril group reached the primary end point, as compared with 42 of 176 in the placebo group (P=0.01). The differences were similar in all three countries.

The overall unadjusted reduction in the risk of progressive renal insufficiency was 53 percent in the benazepril group (71 percent among the patients with mild insufficiency and 46 percent in those with moderate insufficiency) (Table 2). After an adjustment for differences in supine diastolic pressure and urinary protein excretion over time, the overall risk reduction in the benazepril group was still significant (38 and 39 percent, respectively). To prevent one occurrence of an end point, 11 patients would have to receive benazepril for three years (or 11 patients with base-line 24-hour urinary protein excretion >1 g and 5 with urinary protein excretion ≥3 g).

The proportion of patients reaching the primary end point was lower in the benazepril group than in the placebo group among the patients with glomerular disease (11 of 94 patients in the benazepril group vs. 27 of 98 in the placebo group), diabetic nephropathy (1 of 6 vs. 7 of 15), or miscellaneous or unknown renal disorders (6 of 61 vs. 9 of 43), but not among those with polycys-

tic kidney disease (8 of 30 vs. 9 of 34). The proportion of patients reaching the end point was low among the patients with nephrosclerosis (2 of 52 patients in the benazepril group and 1 of 45 in the placebo group) and those with interstitial nephritis (3 of 57 and 4 of 48, respectively).

**Serum Creatinine and Urinary Protein Excretion**

During the first 2 months of treatment, the serum creatinine concentration increased to a greater extent in the benazepril group than in the placebo group; thereafter, it was lower in the benazepril group than the placebo group in the 12-, 24-, and 36-month cohorts (Fig. 2). Urinary protein excretion decreased after only two months of treatment in the benazepril group, whereas it increased slightly in the placebo group (Fig. 3). The final changes from base line in the 6-, 12-, 24-, and 36-month cohorts were -31, -40, -30, and -29 percent, respectively, among the patients receiving benazepril and +15, +14, +14, and +9 percent, respectively, among those receiving placebo.

**Blood Pressure and Antihypertensive Therapy**

In comparison with the base-line values, the mean diastolic pressure in the supine position during the study decreased by 3.5 to 5.0 mm Hg in the benazepril group and increased by 0.2 to 1.5 mm Hg in the placebo group; in both groups the pressure remained below 90 mm Hg (Fig. 3). The mean systolic pressure in the supine position decreased by 4.5 to 8.0 mm Hg in the benazepril group and increased by 1.0 to 3.7 mm Hg in the placebo group.

During the study, the percentage of patients with uncontrolled hypertension decreased from 28 to 18 percent in the benazepril group but increased from 27 to

Table 2. Reduction in the Overall Risk of Progressive Renal Insufficiency in the Benazepril Group at Three Years, According to Base-Line Prognostic Factors and Adjusted for Changes in Diastolic Pressure in the Supine Position and Urinary Protein Excretion.

BASE-LINE FACTOR	REDUCTION IN RISK		
	UNADJUSTED	ADJUSTED FOR DIASTOLIC PRESSURE	ADJUSTED FOR CHANGES IN URINARY PROTEIN EXCRETION
	% (95% confidence interval)		
Creatinine clearance	53 (27 to 70)	38 (3 to 61)	39 (5 to 61)
>45 ml/min	71 (21 to 90)	66 (6 to 88)	65 (4 to 87)
≤45 ml/min	46 (12 to 67)	26 (-23 to 55)	27 (-21 to 56)
Sex			
Male	56 (28 to 73)	42 (4 to 65)	40 (2 to 64)
Female	40 (-59 to 77)	22 (-107 to 71)	35 (-69 to 75)
Normal blood pressure	58 (-72 to 89)	37 (-153 to 84)	30 (-187 to 83)
Treated hypertension			
Diastolic pressure ≤90 mm Hg	51 (13 to 73)	42 (-4 to 68)	37 (-13 to 65)
Diastolic pressure >90 mm Hg	50 (-8 to 76)	32 (-47 to 68)	42 (-24 to 73)
24-Hr urinary protein excretion			
≤1 g	31 (-67 to 71)	3 (-137 to 60)	26 (-79 to 69)
>1 to <3 g	53 (-14 to 81)	45 (-35 to 77)	44 (-36 to 77)
≥3 g	66 (34 to 82)	56 (15 to 78)	52 (5 to 76)

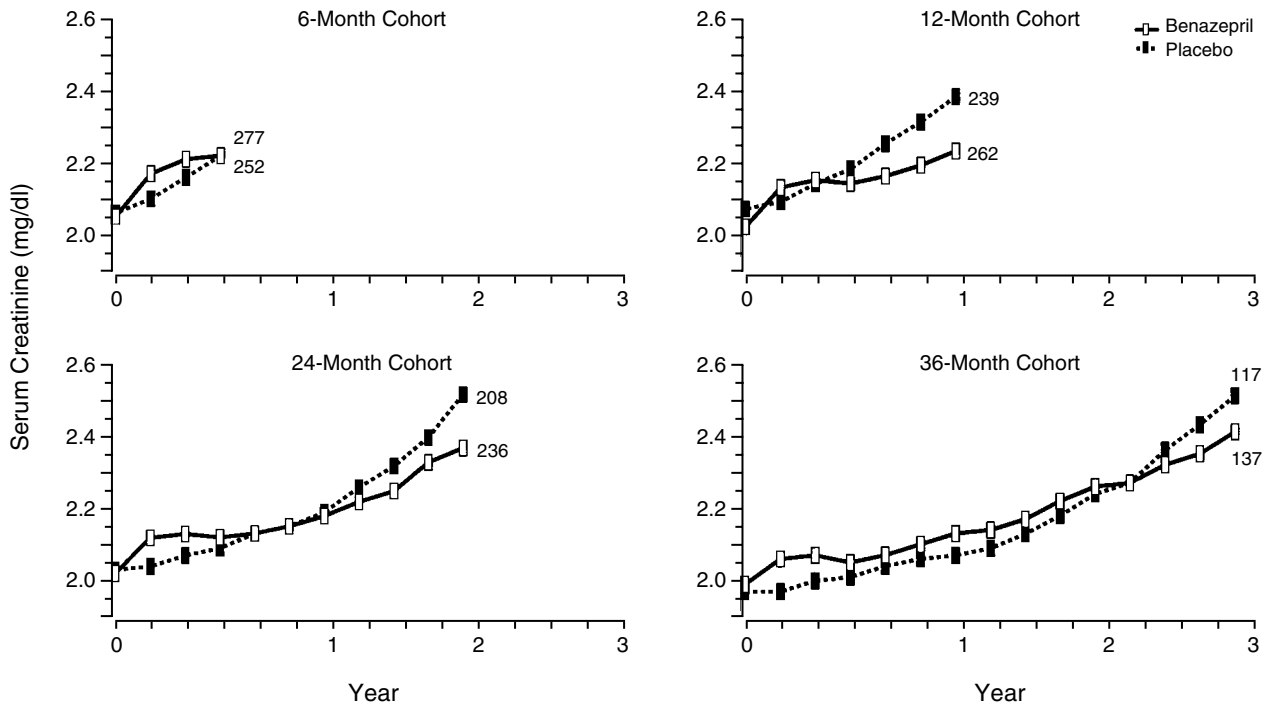


Figure 2. Mean Serum Creatinine Concentrations in the 6-, 12-, 24-, and 36-Month Cohorts, According to Treatment Group. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. The numbers next to the curves denote the numbers of patients remaining in the trial.

32 percent in the placebo group. The average number of antihypertensive drugs required to control blood pressure was smaller in the benazepril group (1.7 drugs per patient at base line and at three years) than in the placebo group (1.9 and 2.1 drugs per patient, respectively).

#### Deaths and Withdrawal from the Study

Sixty-eight patients in the benazepril group and 61 in the placebo group did not complete the study because of death, other adverse events, lack of cooperation, or protocol violations (Table 3).

Eight patients in the benazepril group and one in the placebo group died (four had mild renal insufficiency, and five had moderate insufficiency) (Table 3). Three patients in the benazepril group died suddenly from cardiac causes, three had a fatal myocardial infarction, and two died from other causes. Seven of these eight patients had controlled hypertension, three had had a previous myocardial infarction, two had diabetes mellitus, one had a mitral-valve prosthesis, and one had a history of alcohol abuse. The patient in the placebo group, a diabetic with controlled hypertension, died suddenly. Four of these deaths occurred at one center. None of the patients had high serum potassium concentrations at the time of the last measurement. The death rates in the benazepril group and placebo groups were 1 death per 93 patient-years and 1 per 656 patient-years, respectively ( $P=0.04$ ). (The death rate during the screening period was 1 death per 59 patient-years.)

The numbers of patients with nonfatal cardiovascular events requiring withdrawal from the study were

similar in the two groups, except that four patients in the placebo group had a hypertensive crisis. Six patients in the placebo group, as compared with three in the benazepril group, had worsening renal insufficiency judged as life-threatening by the investigators (without reaching the end point).

Serum potassium concentrations did not change over time in the placebo group but increased in the benazepril group; the average increase was 0.5 mmol per liter or less. Five patients in the benazepril group and three in the placebo group withdrew from the study because of severe hyperkalemia.

In each treatment group, three patients withdrew from the study because of local or systemic allergic reactions. Twenty-five patients in the benazepril group and 10 in the placebo group reported a cough, which caused 1 patient in the benazepril group and 2 in the placebo group to discontinue treatment.

A total of 23 patients in the benazepril group and 12 in the placebo group discontinued treatment for other reasons (Table 3). Thirteen patients (eight in the benazepril group and five in the placebo group) had cancer ( $P$  not significant).

#### DISCUSSION

We found that benazepril provides protection against progressive deterioration of renal function in patients with various renal diseases. Patients with glomerular diseases and diabetes benefited the most from treatment with benazepril, and those with polycystic disease benefited the least. The results in the patients with polycystic disease are not unexpected, since the course

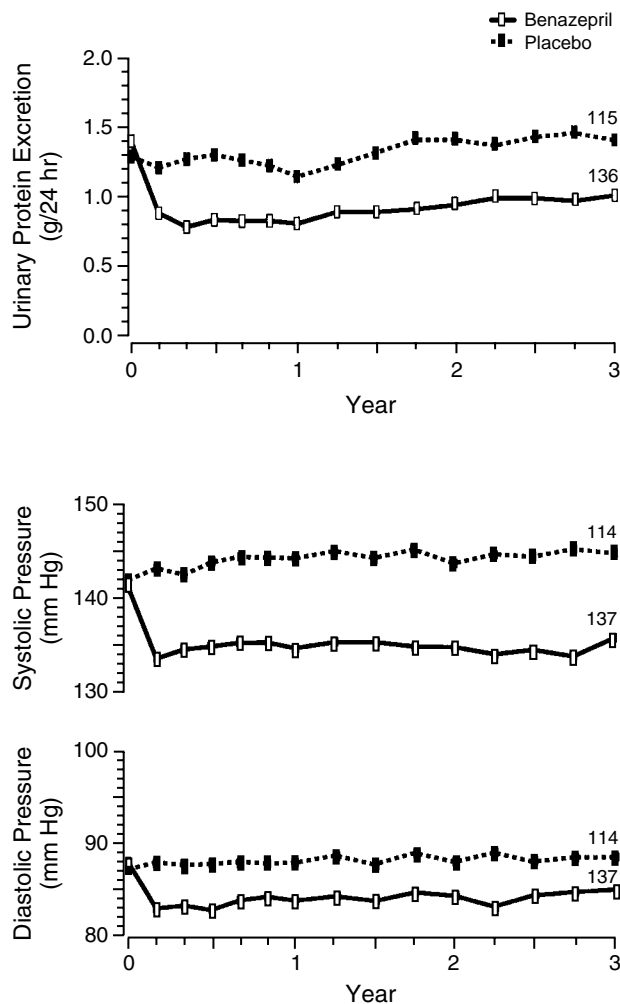


Figure 3. Mean 24-Hour Urinary Protein Excretion and Blood Pressure in the 36-Month Cohort, According to Treatment Group. The numbers next to the curves denote the numbers of patients who remained in the trial at 36 months. Some patients did not undergo the full set of measurements. Blood pressure was measured with the patients supine.

of disease is only minimally affected by the restriction of dietary protein<sup>14-16</sup> or the control of blood pressure.<sup>11,15</sup> Few of the patients with nephrosclerosis, interstitial nephritis, or miscellaneous other nephropathies reached any of the end points, suggesting that the study period may have been too short to identify treatment-related differences among the patients with these slowly progressive diseases. The increase in serum creatinine values during the first two months of treatment with benazepril is reminiscent of the effect of dietary protein restriction on the glomerular filtration rate, as reported in the Modification of Diet in Renal Disease Study<sup>15</sup>; blockade of the renin-angiotensin system and decreased blood pressure may have caused a transient, hemodynamically mediated reduction in glomerular filtration.

Our study was also designed to determine whether the protective effect of benazepril on renal function is independent of antihypertensive action. Blood pressure

was satisfactorily controlled at base line in most of the patients, but the addition of benazepril led to a further reduction in pressure in the hypertensive patients and also to a fall in pressure in the normotensive patients, perhaps in part because blood pressure was measured at about the time of the drug's peak effect.<sup>17</sup> Blood pressure increased slightly in the patients in the placebo group. This difference raises the question of how much the protective effect of benazepril on renal function may be related to changes in systemic and renal hemodynamics rather than to a blockade of the renin-angiotensin system within the kidney. When adjustments were made for changes in diastolic pressure, only part of the reduction in the risk of reaching a primary end point among the patients receiving benazepril was found to be due to the drug's antihypertensive action.

The beneficial effects of angiotensin-converting-enzyme inhibitors may be attributable to mechanisms other than a reduction in blood pressure.<sup>7-11</sup> The protective effect of benazepril on renal function was greatest in the patients with substantial proteinuria, even after adjustments were made for diastolic pressure or changes in urinary protein excretion over time. Benazepril greatly reduced urinary protein excretion, as do other angiotensin-converting-enzyme inhibitors.<sup>18-20</sup> This reduction may be mediated by hemodynamic changes or by a direct effect of the drug on the glomerular basement membrane.<sup>21,22</sup> In either case, reduced urinary protein excretion may provide protection against the progression of disease, the postulated mechanisms be-

Table 3. Reasons for Withdrawal from the Trial.

REASON	no. of patients	
	BENAZEPRIL	PLACEBO
Adverse event		
Death		
Sudden	3	1
From myocardial infarction	3	0
From pulmonary embolism	1	0
From rupture of esophageal varices	1	0
Nonfatal cardiovascular event		
Myocardial infarction	2	2
Stroke	2	3
Transient ischemic attack	1	1
Angina	1	1
Hypertensive crisis	0	4
Hypotension or dizziness	3	3
Other nonfatal event		
Worsening renal insufficiency (end point not reached)	3	6
Hyperkalemia	5	3*
Local or systemic allergic reaction	3	3
Cough	1	2
Other†	23‡	12*
Total adverse events	52‡	41‡
Lack of cooperation	13	15
Protocol violations	5	7
Reached end point	31	57

\*Includes one patient who reached an end point.

†Thirteen patients had cancer: eight in the benazepril group (two with bladder cancer, two with pancreatic cancer, and one each with skin cancer, gastric cancer, non-Hodgkin's lymphoma, and lung cancer) and five in the placebo group (one each with plasmacytoma, gastric cancer, breast cancer, anal cancer, and malignant lymphoma). The incidence of cancer did not differ significantly between the two groups.

‡Includes two patients who reached an end point.

ing a reduction in mesangial-cell protein traffic and decreases in serum lipid concentrations and platelet hyperaggregability.<sup>23</sup>

The overall mortality rate in the benazepril group was 1 death per 93 patient-years, which was higher than the rate in the placebo group (1 per 656 patient-years). The overall number of deaths from cardiac causes was low in comparison with the relatively high prevalence of mortality from cardiovascular disease reported in studies involving similar patients in Europe<sup>24</sup> and the United States.<sup>15</sup> This difference may be due to the large geographic variation in the reported incidence of cardiovascular disease: our study included many patients from Italy and France, where the rate of mortality from cardiovascular disease is low.<sup>25</sup> It is not clear why there were more deaths in the benazepril group than in the placebo group.

It is unlikely that angiotensin-converting-enzyme inhibitors, which reduce mortality from cardiovascular causes,<sup>26</sup> are responsible for deaths from coronary heart disease; it also seems unlikely that hyperkalemia could have caused sudden death, since the four patients who died suddenly had normal serum potassium concentrations at the time of the last measurement.

In conclusion, benazepril provides protection against the loss of renal function in patients with chronic renal insufficiency caused by various disorders. This protective effect is associated with a substantial decrease in blood pressure and urinary protein excretion.

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#### APPENDIX

The following investigators participated in the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study: Lecco, Italy — F. Locatelli, P. Marai, D. Marcelli, and F. Tentori; Dolo, Italy — M. Andriani, G. Drago, and G. Meneghel; Verona, Italy — G. Maschio, L. Oldrizzi, and C. Rugiu; Pavia, Italy — A. Salvadeo, G. Villa, and L. Picardi; Treviglio, Italy — M. Borghi, M. Moriggi, and G. Vendramin; Ravenna, Italy — M. Fusaroli, E. Degli Esposti, and A. Fabbri; Hannover, Germany — K.M. Koch, U. Frey, and J. Schaeffer; Heidelberg, Germany — E. Ritz, J. Mann, and C. Schweitzer; Bologna, Italy — A. Zuccalà and R. Gaggi; Frankfurt, Germany — R. Stohla and C. Blaser; Milan, Italy — C. Ponticelli, E. Rivolta, and G. Buccianti; Varese, Italy — L. Gastaldi and M. Baratelli; Annecy, France — F. Ducret and P. Pointet; Nuernberg, Germany — J.F.E. Mann, R. Sterzel, and E. Oberdorf; Trescore Balneario, Italy — L. Pedrini and P. Faranna; Desio, Italy — G. Cairo and L. Ferrari; Chieti, Italy — A. Albertazzi and P. Cappelli; Gallarate, Italy — P. Cantù and A. Limido; Magdeburg, Germany — L. Lachhein and H.-P. Bosselmann; Udine, Italy — G. Mioni and D. Montanaro; Arezzo, Italy — M. Sasdelli and P. Imperiali; Rostock, Germany — R. Schmidt and I. Handschuck; Jena-Lobeda, Germany — G. Stein; Rimini, Italy — L. Cagnoli and A. Rigotti; Melegnano, Italy — C. Grassi and E. Orazi; Reggio Emilia, Italy — P.P. Borgatti and A. Stefani; Mâcon, France — G. Janin and H. Nefti; Monza, Italy — B. Redaelli and M.R. Viganò; Busto Arsizio, Italy — A. Giangrande; Chambéry, France — J. Maret; Berlin, Germany — R. Natusch and H.R. Laske; Pinerolo, Italy — A. Ramello; Brest, France — J. Clodes; Grenoble, France — D. Cordonnier and K. Sirajedine; Sondrio, Italy — E. Imbasciati; Pisa, Italy — R. Palla; Vimercate, Italy — A. Sessa; Cagliari, Italy — P. Altieri; Bordeaux, France — M. Aparicio; Novara, Italy — G. Verzetti; Mantova, Italy — C. Baroni; Modica, Italy — R. Costanzo; Paris — J.P. Mery, J.M. Idatte, and

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