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## RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

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### ABSTRACT

**Background** It is unknown whether either the angiotensin-II-receptor blocker irbesartan or the calcium-channel blocker amlodipine slows the progression of nephropathy in patients with type 2 diabetes independently of its capacity to lower the systemic blood pressure.

**Methods** We randomly assigned 1715 hypertensive patients with nephropathy due to type 2 diabetes to treatment with irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. The target blood pressure was 135/85 mm Hg or less in all groups. We compared the groups with regard to the time to the primary composite end point of a doubling of the base-line serum creatinine concentration, the development of end-stage renal disease, or death from any cause. We also compared them with regard to the time to a secondary, cardiovascular composite end point.

**Results** The mean duration of follow-up was 2.6 years. Treatment with irbesartan was associated with a risk of the primary composite end point that was 20 percent lower than that in the placebo group ( $P=0.02$ ) and 23 percent lower than that in the amlodipine group ( $P=0.006$ ). The risk of a doubling of the serum creatinine concentration was 33 percent lower in the irbesartan group than in the placebo group ( $P=0.003$ ) and 37 percent lower in the irbesartan group than in the amlodipine group ( $P<0.001$ ). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23 percent lower than that in both other groups ( $P=0.07$  for both comparisons). These differences were not explained by differences in the blood pressures that were achieved. The serum creatinine concentration increased 24 percent more slowly in the irbesartan group than in the placebo group ( $P=0.008$ ) and 21 percent more slowly than in the amlodipine group ( $P=0.02$ ). There were no significant differences in the rates of death from any cause or in the cardiovascular composite end point.

**Conclusions** The angiotensin-II-receptor blocker irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes. This protection is independent of the reduction in blood pressure it causes. (N Engl J Med 2001;345:851-60.)

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**D**IABETES mellitus is increasing in prevalence worldwide and is currently estimated to affect more than 6.5 percent of the population of the United States.<sup>1</sup> Diabetes is the most common cause of end-stage renal disease in this country, accounting for 40 percent of cases.<sup>2</sup> Although the inhibition of the effects of angiotensin II has a beneficial effect in patients with nephropathy caused by type 1 diabetes,<sup>3</sup> no published study with definitive renal outcomes has addressed the issue of renoprotection in patients with type 2 diabetes — a population that differs substantially from patients with type 1 diabetes in terms of demographic characteristics, metabolic features, and potential mechanisms of glomerular disease.<sup>4</sup> Several studies have addressed the positive effects of specific antihypertensive agents on cardiovascular morbidity and mortality within this population.<sup>5-8</sup>

We undertook the Irbesartan Diabetic Nephropathy Trial to determine whether the use of an angiotensin-II-receptor blocker or a calcium-channel blocker would provide protection against the progression of nephropathy due to type 2 diabetes beyond that attributable to the lowering of the blood pressure. We also compared the groups assigned to different therapeutic regimens in terms of overall mortality and the rate of cardiovascular events.

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\*The participants in the Collaborative Study Group are listed in the Appendix.

## METHODS

We conducted a prospective, randomized, double-blind clinical trial in 210 clinical centers. The conduct of the study was managed and monitored by the clinical coordinating center and the various committees of the Collaborative Study Group. All decisions regarding the biostatistical protocol, study plans, and analyses, including the data presented to the data safety and monitoring board, were the product of the biostatistical coordinating center of the study group. The biostatistics and data management department of Bristol-Myers Squibb was responsible for data handling, including entry into the master data base, data-base review, and audit. The blinded clinical data base was provided to the biostatistical coordinating center of the Collaborative Study Group for the generation of interim reports and for final statistical analyses for publications. Details of the protocol have been published previously.<sup>9</sup> The institutional review board or ethics committee of each center approved the protocol, and all patients gave written informed consent after reviewing a written summary of the study plan.

### Study Patients

The criteria for eligibility included an age between 30 and 70 years, a documented diagnosis of type 2 diabetes mellitus, hypertension (a systolic blood pressure of more than 135 mm Hg while sitting, a diastolic blood pressure of more than 85 mm Hg while sitting, or documented treatment with antihypertensive agents), and proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. The serum creatinine concentration was required to be between 1.0 and 3.0 mg per deciliter (88 and 265  $\mu\text{mol}$  per liter) in women and 1.2 and 3.0 mg per deciliter (106 and 265  $\mu\text{mol}$  per liter) in men.

### Randomization and Treatment Plan

All angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers, and calcium-channel blockers were discontinued at least 10 days before the screening period, during which time blood pressure was controlled with other agents. Eligible patients were randomly assigned by a central office to one of three treatment regimens: irbesartan (Avapro, Bristol-Myers Squibb, Princeton, N.J.), in a dose titrated from 75 to 300 mg per day; amlodipine (Norvasc, Pfizer, New York), in a dose titrated from 2.5 to 10 mg per day; or placebo. Antihypertensive agents other than ACE inhibitors, angiotensin-receptor blockers, and calcium-channel blockers were used as needed in each group, and the target blood pressure for all patients was the same (a systolic blood pressure of 135 mm Hg or less, or 10 mm Hg lower than the value at screening if that value was more than 145 mm Hg, and a diastolic blood pressure of 85 mm Hg or less). Survival, end-stage renal disease, the cardiovascular end points, the serum creatinine and potassium concentrations, and the 24-hour urinary protein excretion were monitored quarterly. Blood-pressure measurements were reviewed by a clinical management committee that made treatment recommendations. The committee also monitored blood glucose concentrations by measurement of glycosylated hemoglobin. Adherence to the treatment regimen was monitored by means of pill counts. Serum creatinine concentrations were determined by a central laboratory. Serum potassium and urinary protein were measured in four regional laboratories. A protocol was established for the management of hyperkalemia and the detection of early increases in the creatinine concentration that might be caused by renal-artery stenosis.<sup>9</sup> We planned to continue recruitment for three years and to follow all patients for a minimum of two years after the end of recruitment; data were censored on December 31, 2000. The mean arterial blood pressure was calculated as the diastolic blood pressure plus one third of the difference between the systolic blood pressure and the diastolic blood pressure. Values for urinary protein excretion were log-transformed to reduce skewness.

### End Points

The primary end point was the composite of a doubling of the base-line serum creatinine concentration, the onset of end-stage

renal disease (as indicated by the initiation of dialysis, renal transplantation, or a serum creatinine concentration of at least 6.0 mg per deciliter [530  $\mu\text{mol}$  per liter]), or death from any cause. The secondary, cardiovascular end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, heart failure resulting in hospitalization, a permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle. The serum creatinine outcomes were confirmed with the use of centrally determined concentrations of serum creatinine. All outcomes were reviewed and classified by an outcome committee. Adverse events were recorded at quarterly visits.

### Statistical Analysis

Comparisons of base-line values and outcomes that were not time dependent among the three treatment groups were made with the chi-square test (for categorical data) or analysis of variance (for continuous data). The times to the primary end point and its components were compared by means of product-limit survival curves and the log-rank test.<sup>10</sup> All analyses were based on the intention-to-treat principle. Comparisons of the survival curves for the secondary, cardiovascular end point were made by means of the Breslow-Gehan test.<sup>11</sup> Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.<sup>12</sup> Similar proportional-hazards models were used to adjust for time-dependent covariates such as the mean arterial pressure. In calculating the slopes of the rates of change of the serum creatinine concentration and creatinine clearance, a mixed model was used in which the data for patients who reached an end point were censored. Comparisons among subgroups defined according to the frequency of serious adverse events were performed with the use of methods for comparing Poisson counts.<sup>13</sup> All statistical tests were two-sided.

On the basis of the results of our study of type 1 diabetes,<sup>3</sup> in which the three-year rate of a doubling of the base-line serum creatinine concentration, end-stage renal disease, or death was 36 percent, we estimated that we would need 550 patients per treatment group for an analysis of the primary outcome. The sample size was selected to achieve 90 percent power to detect a 26 percent difference in the primary end point between the irbesartan group and the placebo group at a 5 percent alpha level.

An independent data and safety monitoring board monitored the study. The Lan-DeMets alpha spending-function method<sup>13</sup> was used to adjust for interim analyses. Four formal interim analyses were performed. The adjusted level of significance for the final analysis of the primary outcome was  $P=0.04$ .

For all other outcomes, a  $P$  value of 0.05 or less was considered to indicate significance. The protocol defined the comparison of the irbesartan group with the placebo group as the primary comparison and the comparison of the irbesartan group with the amlodipine group as the secondary comparison. Because the protocol identified one primary comparison, the reported  $P$  values were not corrected for multiple comparisons.

## RESULTS

Between March 21, 1996, and February 25, 1999, 1715 patients underwent randomization. The baseline demographic, clinical, and laboratory characteristics of the three groups were similar (Table 1), except that a slightly lower proportion of the patients in the placebo group were female ( $P=0.02$ ). The outcomes for these patients are summarized in Table 2.

### Clinical Management

The blood-pressure measurements for the three groups are shown in Figure 1. In all three groups, the proportion of patients in whom the target blood

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

CHARACTERISTIC	IRBESARTAN GROUP (N=579)	AMLODIPINE GROUP (N=567)	PLACEBO GROUP (N=569)	P VALUE
Age — yr	59.3±7.1	59.1±7.9	58.3±8.2	0.63
Male sex — no. (%)	378 (65)	359 (63)	403 (71)	0.02
Race or ethnic group — no. (%)				0.33
Non-Hispanic white	438 (76)	389 (69)	415 (73)	
Non-Hispanic black	63 (11)	87 (15)	78 (14)	
Hispanic	28 (5)	29 (5)	26 (5)	
Asian or Pacific Islander	24 (4)	34 (6)	27 (5)	
Other	26 (4)	28 (5)	23 (4)	
Body-mass index†	31.0±5.6	30.9±5.9	30.5±5.9	0.34
Blood pressure — mm Hg				
Systolic	160±20	159±19	158±20	0.10
Diastolic	87±11	87±11	87±11	0.97
Insulin use at entry — no. (%)	329 (57)	327 (58)	335 (59)	0.78
History of cardiovascular disease — no. (%)	158 (27)	171 (30)	164 (29)	0.37
Retinopathy — no. (%)	401 (69)	362 (64)	380 (67)	0.19
Serum creatinine — mg/dl‡	1.67±0.53	1.65±0.61	1.69±0.57	0.50
Urinary protein excretion — g/24 hr				
Median	2.9	2.9	2.9	0.40
Interquartile range	1.6–5.4	1.6–5.2	1.8–5.2	
Urinary albumin excretion — g/24 hr				
Median	1.9	1.9	1.9	0.47
Interquartile range	1.0–3.8	1.0–3.5	1.1–3.5	
Glycosylated hemoglobin — %	8.1±1.7	8.2±1.7	8.2±1.7	0.82

\*Plus-minus values are means ±SD.

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

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

pressure was achieved increased and the mean blood pressure decreased over the course of the study; the mean blood pressure at visits after base line was 140/77 mm Hg in the irbesartan group, 141/77 mm Hg in the amlodipine group, and 144/80 mm Hg in the placebo group. The mean arterial pressure was significantly higher (by 3.3 mm Hg) in the placebo group than in the two active-treatment groups ( $P=0.001$  for both comparisons), between which it did not differ significantly. The distribution of classes of nonstudy drugs used to control blood pressure — primarily diuretics, beta-blockers, peripheral alpha-blockers, and central  $\alpha_2$  agonists — was similar in all groups. The patients in the placebo group required an average of 3.3 nonstudy drugs for the control of blood pressure, as compared with an average of 3.0 nonstudy drugs among the patients in the irbesartan and amlodipine groups. The mean glycosylated hemoglobin values did not differ significantly among the treatment groups or vary significantly over time.

#### Primary, Renal Outcome

The proportions of patients in each group who reached the primary end point are shown in Figure 2A. The patients in the irbesartan group had an unadjusted relative risk of reaching the primary end point that was 20 percent lower than that in the pla-

cebo group ( $P=0.02$ ) and 23 percent lower than that in the amlodipine group ( $P=0.006$ ) (Table 3). The relative risk of the primary end point in the placebo and amlodipine groups did not differ significantly. The proportions of patients in each group who reached each of the three components of the primary end point are shown in Figures 2B, 2C, and 2D. Among the patients assigned to irbesartan, the unadjusted relative risk of a doubling of the serum creatinine concentration was 33 percent lower than that among the patients assigned to placebo ( $P=0.003$ ) (Table 3) and 37 percent lower than that among the patients assigned to amlodipine ( $P<0.001$ ). The unadjusted relative risk of end-stage renal disease ( $P=0.07$ ) was 23 percent lower in the irbesartan group than in either the amlodipine group or the placebo group (Table 3). The placebo and amlodipine groups did not differ significantly with respect to the relative risk of a doubling of the serum creatinine concentration or of end-stage renal disease. There was no significant difference among the three groups in the unadjusted risk of death from any cause (Table 3).

#### Secondary, Cardiovascular Outcome

There were no significant differences among the treatment groups in the secondary, cardiovascular outcome (Table 3). The patients assigned to receive ir-

TABLE 2. OUTCOMES ACCORDING TO STUDY GROUP.\*

VARIABLE	IRBESARTAN GROUP (N=579)	AMLODIPINE GROUP (N=567)	PLACEBO GROUP (N=569)	ALL PATIENTS (N=1715)
Primary composite outcome — no. (%)	189 (32.6)	233 (41.1)	222 (39.0)	644 (37.6)
Doubling of serum creatinine concentration	98 (16.9)	144 (25.4)	135 (23.7)	377 (22.0)
End-stage renal disease	82 (14.2)	104 (18.3)	101 (17.8)	287 (16.7)
Death from any cause	87 (15.0)	83 (14.6)	93 (16.3)	263 (15.3)
Secondary composite outcome — no. (%)	138 (23.8)	128 (22.6)	144 (25.3)	410 (23.9)
Never received study medication — no. (%)†	2 (0.3)	8 (1.4)	6 (1.1)	16 (0.9)
Lost to follow-up — no. (%)‡	5 (0.9)	2 (0.4)	4 (0.7)	11 (0.6)
Completed study without primary outcome — no. (%)	385 (66.5)	332 (58.6)	343 (60.3)	1060 (61.8)
Mean duration of follow-up — days§	952	924	921	932

\*The numbers of patients with the composite end points are lower than the sums of those with the various components because some patients reached more than one component.

†Patients who never received study medication were included in all analyses according to the intention-to-treat principle.

‡Data are for patients lost to follow-up before reaching the primary outcome or the last scheduled study visit.

§The duration of follow-up was calculated from the time of randomization to the occurrence of the first primary outcome or the date of the last scheduled visit when data were censored.

besartan had a rate of congestive heart failure necessitating hospitalization that was 23 percent lower than that among the patients assigned to receive placebo. The patients assigned to receive amlodipine had a rate of nonfatal myocardial infarction that was 41 percent lower than that among the patients assigned to receive placebo.

#### Effect of Base-Line Covariates and Achieved Mean Arterial Pressure

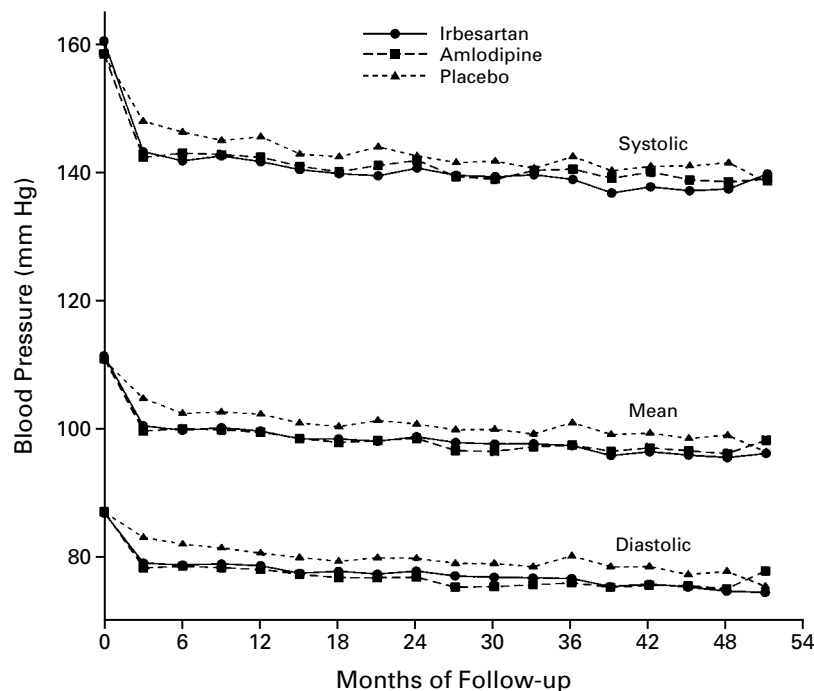
Analyses were performed to ensure that the observed differences in outcomes could not be explained by imbalances in the distribution of the base-line covariates. The inclusion of these base-line covariates in proportional-hazards analyses did not change the conclusions of the primary analyses.

The better renal outcomes in the irbesartan group could not be explained by differences in the mean arterial blood pressure during follow-up. The mean arterial pressure in the irbesartan group was not significantly different from that in the amlodipine group. Furthermore, when we corrected for the mean arterial pressure at each of the quarterly visits in a time-dependent proportional-hazards analysis (Table 3), the results were similar to those of the primary analysis.

#### Changes in Renal Function

The serum creatinine concentration, creatinine clearance, and levels of urinary protein and albumin

excretion were similar in the three groups at base line (Table 1). The serum creatinine concentration increased 24 percent more slowly in the patients in the irbesartan group than in those in the placebo group ( $P=0.008$ ) and 21 percent more slowly than in those in the amlodipine group ( $P=0.02$ ), despite the fact that larger numbers of patients in the placebo and amlodipine groups were excluded from further analyses of the serum creatinine concentration when they reached a renal end point. The serum creatinine slopes in the placebo and amlodipine groups did not differ. The mean ( $\pm$ SE) absolute rates of change in the serum creatinine concentration were  $0.45 \pm 0.04$  mg per deciliter per year in the irbesartan group,  $0.57 \pm 0.04$  mg per deciliter per year in the amlodipine group, and  $0.59 \pm 0.04$  mg per deciliter per year in the placebo group. The mean rate of change in creatinine clearance was  $-5.5 \pm 0.36$  ml per minute per  $1.73 \text{ m}^2$  of body-surface area per year in the irbesartan group,  $-6.8 \pm 0.37$  ml per minute per  $1.73 \text{ m}^2$  per year in the amlodipine group, and  $-6.5 \pm 0.37$  ml per minute per  $1.73 \text{ m}^2$  per year in the placebo group. Proteinuria was reduced on average by 33 percent (mean [ $\pm$ SD] decrease in protein concentration,  $-1.1 \pm 1.7$  g per 24 hours) in the irbesartan group, as compared with 6 percent ( $-0.1 \pm 2.9$  g per 24 hours) in the amlodipine group and 10 percent ( $-0.3 \pm 4.3$  g per 24 hours) in the placebo group. These reductions were maintained throughout the follow-up period.



**Figure 1.** Average Systolic, Mean Arterial, and Diastolic Blood Pressures at Randomization (0 Months) and during Follow-up, According to Treatment Group.

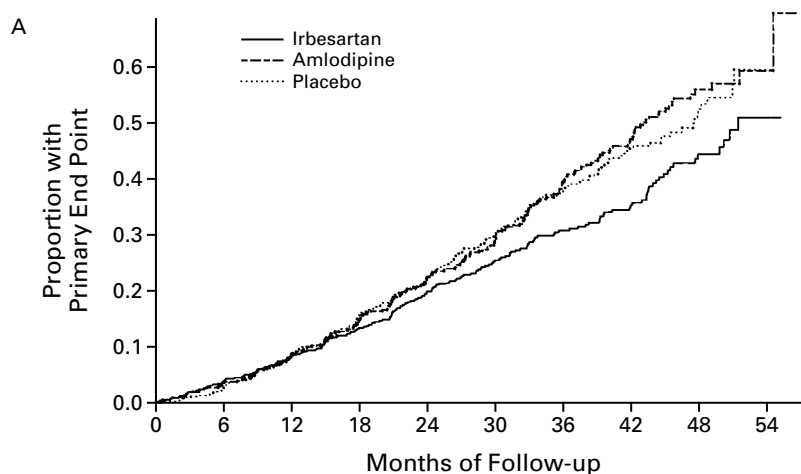
The mean arterial pressure during follow-up was, on average, 3.3 mm Hg lower in the irbesartan and amlodipine groups than in the placebo group.

### Serious Adverse Events

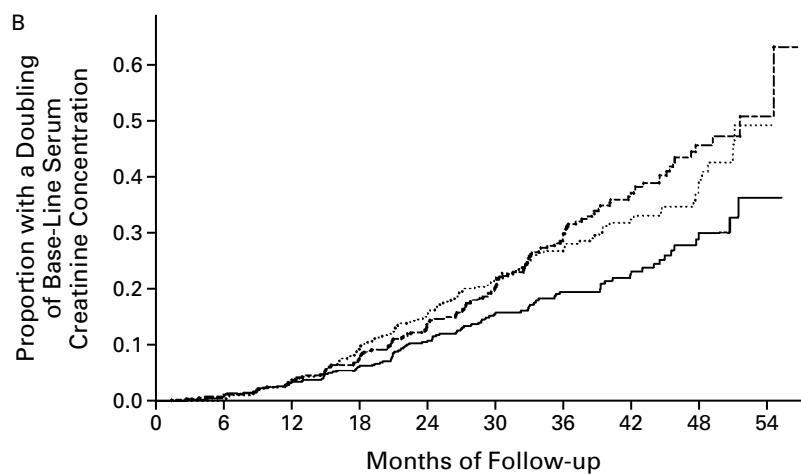
One episode of an early increase in the serum creatinine concentration suggestive of renal-artery stenosis necessitated the stopping of the study medication. Hyperkalemia necessitating a discontinuation of the study medication occurred in 11 of the patients in the irbesartan group (1.9 percent), as compared with 3 of those in the amlodipine group (0.5 percent) and 2 of those in the placebo group (0.4 percent,  $P=0.01$  for both comparisons). Overall, 23.7 percent of the patients stopped receiving the study medication without having reached the primary end point and before their data were censored. The most common reason for the discontinuation of the study medication was the occurrence of a clinical cardiovascular event. These discontinuations were evenly distributed among the treatment groups. The number of patients who had at least one serious adverse event (61 percent of the total cohort) reflected the advanced stage of illness and the numerous risk factors in this population, but the number did not differ significantly among groups. The patients in the irbesartan group had a significantly lower rate of adverse events per 1000 days of treatment than those in the placebo and amlodipine groups ( $P=0.002$ ).

### DISCUSSION

The angiotensin-II-receptor antagonist irbesartan was associated with better renal outcomes than the other agents (amlodipine, placebo, and antihypertensive agents) we used. A slowing of the rate of progression of nephropathy was reflected in a significant increase in the time to a doubling of the serum creatinine concentration, a measure that approximates a halving of the glomerular filtration rate.<sup>3</sup> A diminished rate of progression of disease was not limited to the patients in whom there was a doubling of the serum creatinine concentration during follow-up. The mean increase in the serum creatinine concentration and the mean decrease in creatinine clearance were significantly slower in the entire irbesartan group. The patients in the amlodipine group had worse renal outcomes than those in the irbesartan group, although there was equal control of blood pressure in the amlodipine group. When we adjusted for the disparity in blood-pressure control between the irbesartan and placebo groups, the extent of the estimated renal benefit of irbesartan did not decrease significantly. We interpret these results as demonstrating that irbesartan was renoprotective in these patients with nephropathy due to type 2 diabetes — an effect analogous to



No. AT Risk	
Irbesartan	579 555 528 496 400 304 216 146 65
Amlodipine	565 542 508 474 385 287 187 128 46
Placebo	568 551 512 471 401 280 190 122 53



No. AT Risk	
Irbesartan	579 534 495 457 363 273 191 131 57 5
Amlodipine	567 516 476 439 347 254 166 108 40 5
Placebo	569 527 482 436 360 252 173 107 47 2

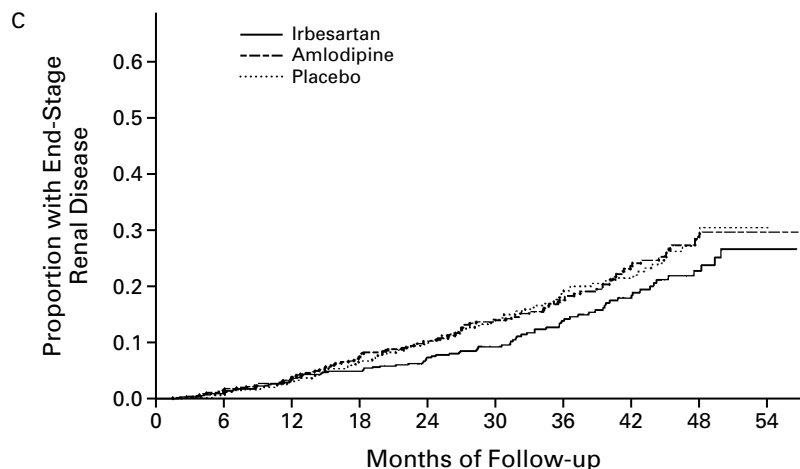
**Figure 2.** Cumulative Proportions of Patients with the Primary Composite End Point (Panel A) and Its Components, a Doubling of the Base-Line Serum Creatinine Concentration (Panel B), End-Stage Renal Disease (Panel C, facing page), and Death from Any Cause (Panel D, facing page).

The date of onset of end-stage renal disease could not be determined for one patient in the placebo group and two patients in the amlodipine group. These three patients were excluded from the analyses shown in Panels A and C.

that of the ACE inhibitor captopril in patients with nephropathy due to type 1 diabetes.<sup>3</sup>

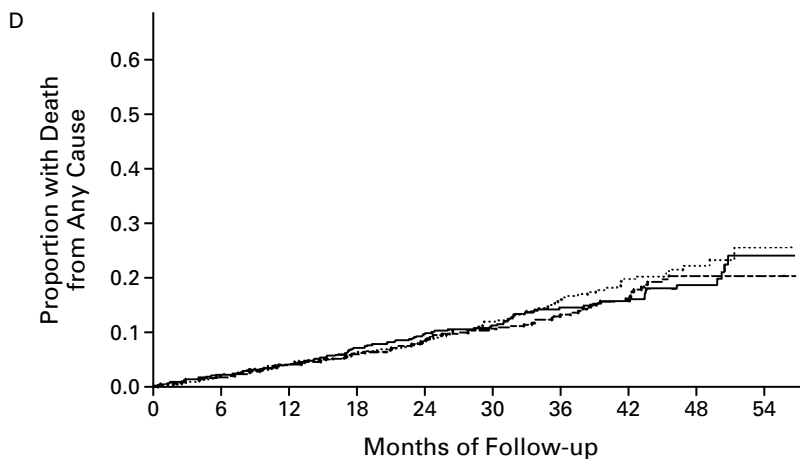
The renoprotection provided by an angiotensin-II-receptor antagonist derives solely from its restriction of angiotensin activity. ACE inhibition may be less specific and less complete. ACE is responsible for the

conversion of angiotensin I to angiotensin II, as well as for the catalytic degradation of bradykinin.<sup>14</sup> The renoprotection associated with ACE inhibition has been shown in rats to be the result of diminished generation of angiotensin and increased bradykinin concentrations.<sup>14</sup> However, studies in humans have sup-



NO. AT RISK

Irbesartan	579	549	523	501	418	327	234	162	78	7
Amlodipine	565	538	510	482	408	310	221	152	58	7
Placebo	568	542	517	487	418	302	205	141	63	2



NO. AT RISK

Irbesartan	579	563	550	530	452	355	264	196	99	10
Amlodipine	567	552	536	524	457	358	266	201	83	9
Placebo	569	553	539	522	465	354	255	185	94	7

ported the notion that ACE inhibitors alter renal hemodynamics primarily by diminishing the action of angiotensin II.<sup>15-17</sup> Thus, in both the renoprotection demonstrated by ACE inhibition in nephropathy due to type 1 diabetes and that of angiotensin-receptor blockers in nephropathy due to type 2 diabetes, the important pharmacologic action appears to be the restriction of intrarenal angiotensin activity. The mechanism of renoprotection by agents that block the action of angiotensin II may be complex, involving hemodynamic factors that lower the intraglomerular pressure,<sup>18</sup> the beneficial effects of diminished pro-

teinuria,<sup>19</sup> and decreased collagen formation<sup>20</sup> that may be related to decreased stimulation of transforming growth factor  $\beta$  by angiotensin II.<sup>21</sup>

We cannot directly address the issue of whether the effects of ACE inhibitors and angiotensin-receptor blockers would be equivalent in the treatment of patients with nephropathy due to type 2 diabetes. It may seem reasonable to assume that agents that primarily reduce the generation or effect of angiotensin II would have similar clinical results. However, it is important to caution that ACE inhibitors and angiotensin-receptor blockers are distinctly different class-

TABLE 3. RELATIVE RISKS OF OUTCOMES.\*

OUTCOME	UNADJUSTED RELATIVE RISK (95% CI)	P VALUE	ADJUSTED RELATIVE RISK (95% CI)†	P VALUE
Primary composite end point				
Irbesartan vs. placebo	0.80 (0.66–0.97)	0.02	0.81 (0.67–0.99)	0.03
Amlodipine vs. placebo	1.04 (0.86–1.25)	0.69	1.07 (0.89–1.29)	0.47
Irbesartan vs. amlodipine	0.77 (0.63–0.93)	0.006	0.76 (0.63–0.92)	0.005
Doubling of serum creatinine concentration				
Irbesartan vs. placebo	0.67 (0.52–0.87)	0.003	0.71 (0.54–0.92)	0.009
Amlodipine vs. placebo	1.06 (0.84–1.35)	0.60	1.15 (0.91–1.46)	0.24
Irbesartan vs. amlodipine	0.63 (0.48–0.81)	<0.001	0.61 (0.48–0.79)	<0.001
End-stage renal disease				
Irbesartan vs. placebo	0.77 (0.57–1.03)	0.07	0.83 (0.62–1.11)	0.19
Amlodipine vs. placebo	1.00 (0.76–1.32)	0.99	1.09 (0.82–1.43)	0.56
Irbesartan vs. amlodipine	0.77 (0.57–1.03)	0.07	0.76 (0.57–1.02)	0.06
Death from any cause				
Irbesartan vs. placebo	0.92 (0.69–1.23)	0.57	0.94 (0.70–1.27)	0.69
Amlodipine vs. placebo	0.88 (0.66–1.19)	0.40	0.90 (0.66–1.21)	0.47
Irbesartan vs. amlodipine	1.04 (0.77–1.40)	0.80	1.05 (0.78–1.42)	0.75
Secondary, cardiovascular composite end point				
Irbesartan vs. placebo	0.91 (0.72–1.14)	0.40	0.91 (0.72–1.14)	0.40
Amlodipine vs. placebo	0.88 (0.69–1.12)	0.29	0.88 (0.69–1.11)	0.27
Irbesartan vs. amlodipine	1.03 (0.81–1.31)	0.79	1.03 (0.81–1.32)	0.78

\*CI denotes confidence interval.

†The relative risks were adjusted for the mean arterial blood pressure during follow-up.

es of drugs and that one cannot assume equivalence between them. The pharmacologic activity of these agents is complex. The effect of ACE inhibition on renal hemodynamics could be limited by the non-ACE-dependent generation of angiotensin II that has been documented in patients in the hyperglycemic state.<sup>17</sup> It is noteworthy that the size-selective dysfunction of glomerular capillary permeability that characterizes diabetic nephropathy is improved by ACE inhibition in patients with type 1 diabetes but not in those with type 2 diabetes.<sup>4</sup> The Ramipril Efficacy in Nephropathy study failed to demonstrate renoprotection in patients with nephropathy due to type 2 diabetes who received ACE inhibitors.<sup>22</sup> Patients who received ramipril lost renal function at a significantly faster rate than those assigned to other antihypertensive agents.<sup>22</sup> A subanalysis of patients in the United Kingdom Prospective Diabetes Study concluded that ACE inhibitors and  $\beta$ -adrenergic-blocking agents were equally effective in preventing renal damage.<sup>8</sup> Since  $\beta$ -adrenergic-blocking agents were commonly used in our placebo group, one must note the contrast between the results of the United Kingdom Prospective Diabetes Study and our results. The population at risk in that study, however, was small, and the comparison between ACE inhibitors and beta-blockers was not part of its primary design. One study of the course of proteinuria in patients with microalbuminuria and type 2 diabetes indicated that ACE in-

hibition slowed the progression of renal disease.<sup>23</sup> In the light of conflicting information from previous reports, we must limit our recommendations to those that can be drawn from the results achieved with the agent and dosage that we used in this study.

It should be noted that, although the differences were not statistically significant, our irbesartan group had lower rates of death from any cause and of the secondary, cardiovascular end point than the placebo group. These differences were slightly smaller than the absolute differences in the risk of death from any cause and the risk of other cardiovascular end points that were reported in the Heart Outcomes Prevention Evaluation Study.<sup>24</sup> However, the statistically robust result reported for that study was the product of its statistical power for the detection of differences in mortality with a total of 9297 patients, 3577 of whom had diabetes. In our study, in which the sample was much smaller, we found no statistically significant differences in the rate of death from any cause or the secondary, cardiovascular end point. Our study was not designed to have adequate statistical power for an analysis of these outcomes.

The amlodipine group had a significantly higher rate of congestive heart failure than the placebo or irbesartan group. This finding is in keeping with the moderately increased risk of congestive heart failure associated with calcium-channel blockers reported in a recent meta-analysis that focused on hypertensive

patients without diabetes.<sup>25</sup> Our report of a lower risk of coronary events associated with calcium-channel-blocker therapy differs from the results of Hansson et al. in a larger trial in elderly hypertensive patients, which found no difference between therapy with a calcium-channel blocker and therapy with an ACE inhibitor with regard to the risk of coronary events.<sup>26</sup> It is possible that calcium-channel blockers are more efficacious in lowering the rate of coronary events in a population with diabetic nephropathy.

Our data reveal that irbesartan is renoprotective in patients with type 2 diabetes and overt nephropathy and that it significantly slows the progression of glomerulopathy. The beneficial effects of irbesartan were accompanied by minimal drug-specific serious adverse effects in our patients.

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## APPENDIX

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