THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Background Microalbuminuria and hypertension are risk factors for diabetic nephropathy. Blockade of the renin–angiotensin system slows the progression to diabetic nephropathy in patients with type 1 diabetes, but similar data are lacking for hypertensive patients with type 2 diabetes. We evaluated the renoprotective effect of the angiotensin-II–receptor antagonist irbesartan in hypertensive patients with type 2 diabetes and microalbuminuria.

Methods A total of 590 hypertensive patients with type 2 diabetes and microalbuminuria were enrolled in this multinational, randomized, double-blind, placebo-controlled study of irbesartan, at a dose of either 150 mg daily or 300 mg daily, and were followed for two years. The primary outcome was the time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a urinary albumin excretion rate that was greater than 200 μg per minute and at least 30 percent higher than the base-line level.

Results The base-line characteristics in the three groups were similar. Ten of the 194 patients in the 300-mg group (5.2 percent) and 19 of the 195 patients in the 150-mg group (9.7 percent) reached the primary end point, as compared with 30 of the 201 patients in the placebo group (14.9 percent) (hazard ratios, 0.30 [95 percent confidence interval, 0.14 to 0.61; $P<0.001$] and 0.61 [95 percent confidence interval, 0.34 to 1.08; $P=0.08$] for the two irbesartan groups, respectively). The average blood pressure during the course of the study was 144/83 mm Hg in the placebo group, 143/83 mm Hg in the 150-mg group, and 141/83 mm Hg in the 300-mg group ($P=0.004$ for the comparison of systolic blood pressure between the placebo group and the combined irbesartan groups). Serious adverse events were less frequent among the patients treated with irbesartan ($P=0.02$).

Conclusions Irbesartan is renoprotective independently of its blood-pressure–lowering effect in patients with type 2 diabetes and microalbuminuria. (N Engl J Med 2001;345:870-8.)

DIABETIC nephropathy develops in approximately 40 percent of all patients with type 2 diabetes and has become the leading cause of end-stage renal disease in Europe, Japan, and the United States, accounting for 25 to 42 percent of cases. Therefore, the early identification and subsequent renoprotective treatment of all patients at risk are of utmost importance. The screening of urine for albumin has revealed that patients with type 2 diabetes and so-called microalbuminuria — i.e., a urinary albumin excretion rate of 20 to 200 μg per minute — have a risk of diabetic nephropathy that is 10 to 20 times that of patients with normoalbuminuria.[1-6] Diabetic nephropathy develops in 5 to 10 percent of patients with type 2 diabetes and microalbuminuria each year.[1-5] Blockade of the renin–angiotensin system slows the progression to diabetic nephropathy in patients with type 1 diabetes and microalbuminuria,[7] but similar data are not available for hypertensive patients with type 2 diabetes.

We therefore undertook a multinational, double-blind, randomized study to evaluate the effectiveness of the angiotensin-II–receptor antagonist irbesartan in delaying or preventing the development of diabetic nephropathy in hypertensive patients with type 2 diabetes and persistent microalbuminuria. The optimal renoprotective dose of irbesartan was also evaluated.

METHODS

Study Design

In a randomized, double-blind, placebo-controlled study conducted in 96 centers worldwide, we evaluated the renoprotective effect of irbesartan in 590 hypertensive patients with type 2 diabetes and persistent microalbuminuria. At the enrollment visit, 1469 patients were eligible. This visit was followed by a single-blind, three-week run-in screening period during which all antihypertensive treatment was discontinued and replaced by placebo. Blood pressure was measured every week, and overnight urine specimens were obtained for the measurement of albumin concentrations on three consecutive days at the end of the run-in period. A total of 858 patients were excluded during the run-in period, and 611 patients underwent randomization, of whom 18 had no measurement of albuminuria and 3 received no drug treatment. Therefore, a total of 590 randomized patients were followed for a median of two years. The patients were randomly assigned to receive irbesartan in a dose of 150 mg once daily, irbesartan in a dose of 300 mg once daily, or matching placebo once daily. The dose of medication was increased to the target level in two stages lasting two weeks each.

The study protocol was in accordance with the Declaration of Helsinki and was approved by the institutional review board at each center; all patients gave written informed consent. The study

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was overseen by steering and safety committees; the steering committee included two nonvoting members from the sponsoring company, Sanofi–Synthelabo. The steering committee oversaw the study design, the conduct of the trial, and the management and analysis of the data. An independent, blinded end-point committee adjudicated all major cardiovascular events.

Patients

The trial involved hypertensive patients, ranging in age from 30 to 70 years, with type 2 diabetes, persistent microalbuminuria (defined as an albumin excretion rate of 20 to 200 μg per minute in two of three consecutive, sterile, overnight urine samples) and a serum creatinine concentration of no more than 1.5 mg per deciliter (133 μmol per liter) for men and no more than 1.1 mg per deciliter (97 μmol per liter) for women. Hypertension was defined by the finding on at least two of three consecutive measurements obtained one week apart during the run-in period of a mean systolic blood pressure of more than 135 mm Hg or a mean diastolic blood pressure of more than 85 mm Hg, or both. Type 2 diabetes was diagnosed according to the criteria of the World Health Organization. The criteria for exclusion included nondiabetic kidney disease, cancer, life-threatening disease with death expected to occur within two years, and an indication for angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-II–receptor antagonists.

Procedures, Measurements, and Outcome

The procedures and measurements were specified in a manual of operations. The patients were examined at the time of randomization, 2 and 4 weeks after randomization, and at 3, 6, 12, 18, and 22 to 24 months. A clinical examination, measurements of the blood pressure, the urinary albumin excretion, the serum creatinine concentration, and the glycosylated hemoglobin concentration and other laboratory evaluations were performed at each visit. All assessments of urine and blood were performed at a central laboratory. The urinary albumin concentration was determined by nephelometry[8] and the serum creatinine concentration by Jaffe reaction with the use of a Hoffmann–LaRoche kit.[9] Creatinine clearance was estimated on the basis of the Cockroft–Gault formula as validated previously in diabetic nephropathy.[10] Glycosylated hemoglobin (normal range, 2.7 to 5.8 percent) was measured by ion-exchange high-performance liquid chromatography.[11] The lowest arterial blood pressure during a 24-hour period (Korotkoff phase I/V) was measured with the use of an appropriate cuff with a sphygmomanometer with the patient in the sitting position after at least 10 minutes of rest. Two measurements to the nearest 2 mm Hg were obtained, two minutes apart at each time point, and the average of the two was used for the calculation of the 24-hour trough level. The mean arterial blood pressure was calculated as the diastolic pressure plus one third of the pulse pressure. The target blood pressure three months after randomization was less than 135/85 mm Hg for all three groups. Additional antihypertensive drugs used by patients included diuretics, beta-blockers, calcium-channel blockers (except dihydropyridines), and alpha-blockers; ACE inhibitors were not allowed. Patients continued to receive their usual care for diabetes. No restriction on dietary salt or protein was implemented.

The primary efficacy measure was the time from the base-line visit to the first detection of overt nephropathy, defined by a urinary albumin excretion rate in an overnight specimen that was greater than 200 μg per minute and at least 30 percent higher than the base-line rate on at least two consecutive visits.[12] The secondary end points were changes in the level of albuminuria, changes in creatinine clearance, and the restoration of normoalbuminuria (a urinary albumin excretion rate of less than 20 μg per minute) by the time of the last visit.

Statistical Analysis

Analyses of the primary and secondary efficacy end points were based on the intention-to-treat principle; data from the date of randomization through the date of study termination for all 590 patients who underwent randomization were included in the analyses. The event curves for the incidence of diabetic nephropathy were based on the Kaplan–Meier method[13] and the Mantel–Haenszel test.[14] A Cox proportional-hazards regression model[15] was used to estimate the hazard ratios and 95 percent confidence intervals for each dose of irbesartan as compared with placebo. In a secondary analysis, the estimates of the effect of the treatment regimens on the time to the onset of diabetic nephropathy (hazard ratios) were adjusted for the base-line level of albuminuria and the time-dependent mean arterial blood pressure during treatment, which were used as covariates in the Cox model. Dichotomous variables were compared with use of the chi-square test. For continuous variables, the results are reported as means ±SD or ±SE. The level of albuminuria and the creatinine clearance were log-transformed before analysis. All pairwise comparisons between treatment groups at any time point were performed with use of the t-test. In the analysis of the differences among treatment groups in the overall changes in the level of albuminuria and the creatinine clearance, we used adjusted means derived from an analysis-of-variance model with terms for the treatment group and time (month).

The significance level for the primary end point was set at 0.025 with the use of Bonferroni's correction. For other outcomes, a P value of less than 0.05 was considered to indicate statistical significance. All statistical tests were two-sided.

The calculation of sample size for this trial was based on the assumption that the two-year incidence of diabetic nephropathy would be 21 percent in the placebo group and 7 percent in one of the irbesartan groups, with an overall dropout rate of 20 percent.[12] In order to have 90 percent power to detect differences at a 2.5 percent level of significance (in a two-tailed test adjusted for analyses of both doses), the trial required the enrollment of at least 522 patients.

RESULTS

A total of 30 patients in the placebo group, 27 in the group assigned to receive 150 mg of irbesartan per day, and 20 in the group assigned to receive 300 mg of irbesartan per day withdrew from the study for various reasons (Fig. 1). These patients were included in the intention-to-treat analyses. Base-line demographic, clinical, and biochemical characteristics were balanced among the three groups (Table 1). The types of medications taken by the participants are shown in Table 2. Fifty-six percent of the patients in the placebo group were receiving blood-pressure–lowering therapy at the end of the two years of follow-up. Adherence to the study medication was satisfactory, with an average of 81 percent of the irbesartan being taken at the end of the study in the 150-mg group and 89 percent being taken in the 300-mg group.

Primary Outcome

During the 24-month study, nephropathy developed in 30 patients in the placebo group, as compared with 19 patients in the 150-mg group ($P=0.08$) and 10 patients in the 300-mg group ($P<0.001$) (Fig. 2). The Kaplan–Meier curves for the placebo group and the 300-mg group separated at the three-month visit and continued to diverge. The unadjusted hazard ratio for diabetic nephropathy was 0.61 (95 percent confidence interval, 0.34 to 1.08; $P=0.08$) in the 150-mg group and 0.30 (95 percent confidence interval, 0.14 to 0.61; $P<0.001$) in the 300-mg group. After adjustment for the base-line level of microalbuminuria and the blood pressure achieved dur-

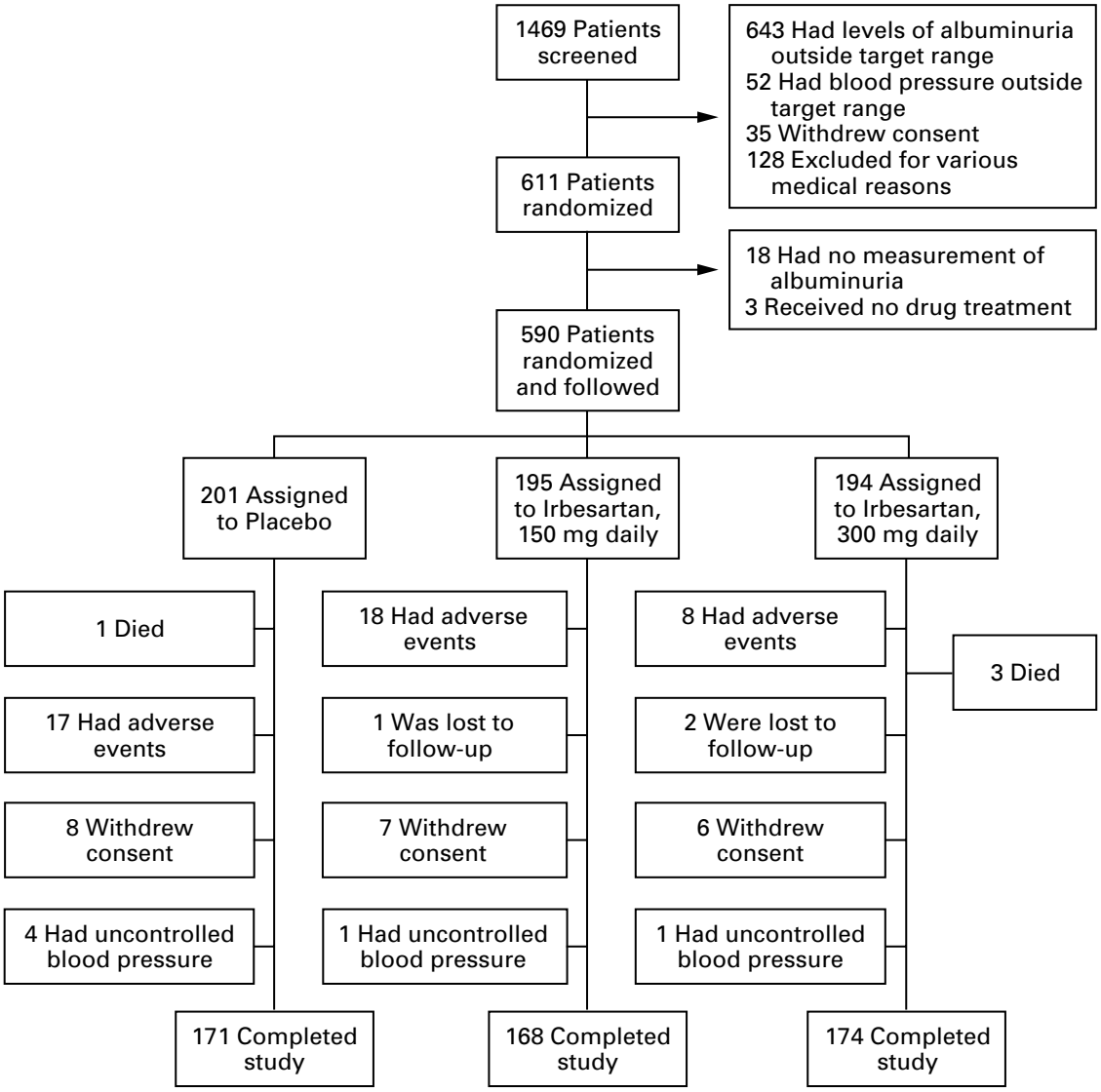


Figure 1. Profile of the Trial.
All 590 patients who underwent randomization and follow-up were included in the intention-to-treat analyses.

ing the study, the hazard ratio for diabetic nephropathy was 0.56 in the 150-mg group (95 percent confidence interval, 0.31 to 0.99; $P=0.05$) and 0.32 in the 300-mg group (95 percent confidence interval, 0.15 to 0.65; $P<0.001$).

Secondary Outcomes

The percent changes from each time point to the next in the level of urinary albumin excretion during the two-year study period are shown in Figure 3. The curves for placebo and the 300-mg dose of irbesartan separated at the three-month visit and continued to diverge.

The decline in creatinine clearance (measured in milliliters per minute per 1.73 m^2 of body-surface area per month) during the initial 3-month period was greater than the sustained decline from 3 months to 24 months; the initial declines were 0.9, 1.0, and 1.9 in the placebo, 150-mg, and 300-mg groups, respectively, as compared with declines between months 3 and 24 of 0.1, 0.2, and 0.2 (Fig. 3). Neither the initial decline nor the sustained decline differed significantly among the three groups.

The trough blood pressure (the blood pressure measured immediately before the administration of medication or placebo) at base line was nearly identi-

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

CHARACTERISTIC	PLACEBO GROUP (N=201)	150-mg IRBESARTAN GROUP (N=195)	300-mg IRBESARTAN GROUP (N=194)
Demographic characteristics			
Age — yr	58.3±8.7	58.4±8	57.3±7.9
Male sex — no. (%)	138 (68.7)	129 (66.2)	137 (70.6)
Race — no. (%)			
White	197 (98.0)	190 (97.4)	187 (96.4)
Nonwhite	4 (2.0)	5 (2.6)	7 (3.6)
Clinical characteristics			
Body-mass index†	30.3±4.4	29.9±3.8	30.0±4.3
Known duration of diabetes — yr	10.4±8.6	9.5±6.9	9.2±6.9
Retinopathy — no. (%)‡			
None	110 (55.3)	105 (55.0)	122 (64.2)
Simplex	50 (25.1)	59 (30.9)	37 (19.5)
Maculopathy	4 (2.0)	8 (4.2)	5 (2.6)
Proliferative	7 (3.5)	7 (3.7)	9 (4.7)
Laser treatment	28 (14.1)	12 (6.3)	17 (8.9)
Smoking — no. (%)			
Never	96 (47.8)	81 (41.5)	80 (41.2)
Formerly	69 (34.3)	72 (36.9)	82 (42.3)
Currently	36 (17.9)	42 (21.5)	32 (16.5)
Medical history			
Known cardiovascular disorders — no. (%)§	47 (23.4)	59 (30.3)	51 (26.3)
Myocardial infarction — no. (%)	3 (1.5)	9 (4.6)	6 (3.1)
Coronary artery disease — no. (%)¶	6 (3.0)	10 (5.1)	11 (5.7)
Peripheral arterial disease — no. (%)	8 (4.0)	13 (6.7)	10 (5.2)
Venous insufficiencies — no. (%)	5 (2.5)	6 (3.1)	4 (2.1)
Stroke or transient ischemic attack — no. (%)	7 (3.5)	6 (3.1)	5 (2.6)
Laboratory variables			
Glycosylated hemoglobin — %	7.1±1.6	7.3±1.7	7.1±1.7
Blood pressure — mm Hg			
Systolic	153±15	153±14	153±14
Diastolic	90±9	90±9	91±10
Urinary albumin excretion — μg/min‖	54.8±2.5	58.3±2.7	53.4±2.2
Serum creatinine — mg/dl**			
Male patients	1.1±0.1	1.1±0.2	1.1±0.2
Female patients	0.9±0.1	0.9±0.1	1.0±0.2
Creatinine clearance — ml/min/1.73 m^2 of body-surface area‖	109±2	110±2	108±2
Triglycerides — mg/dl††	168.5±105.6	184.1±110.2	187.3±117.7
Cholesterol — mg/dl‡‡			
Total	223.2±42.1	227.4±54.2	222.2±46.9
Low-density lipoprotein	143.0±36.9	142.4±46.4	134.6±36.6
High-density lipoprotein	44.9±11.9	43.0±10.6	42.8±12.1

*Differences between groups were not statistically significant. Plus–minus values are means ±SD, unless otherwise indicated.

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

‡Data were missing for two patients in the placebo group, four in the 150-mg group, and four in the 300-mg group.

§Data include patients with arrhythmia, pericarditis, valvular disease, and previous heart failure, in addition to the disorders listed.

¶Data are for patients with angina but no myocardial infarction.

‖Values are geometric means ±SE.

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

††To convert values to millimoles per liter, multiply by 0.113.

‡‡To convert values to millimoles per liter, multiply by 0.259.

TABLE 2. SIMULTANEOUS TREATMENTS IN PATIENTS WITH TYPE 2 DIABETES AND MICROALBUMINURIA AT THE BEGINNING AND THE END OF THE STUDY.*

TREATMENT	BEGINNING OF STUDY			END OF STUDY		
	PLACEBO GROUP (N=201)	150-mg IRBESARTAN GROUP (N=195)	300-mg IRBESARTAN GROUP (N=194)	PLACEBO GROUP (N=201)	150-mg IRBESARTAN GROUP (N=195)	300-mg IRBESARTAN GROUP (N=194)
	number (percent)					
Glucose lowering						
Diet alone	27 (13.4)	32 (16.4)	22 (11.3)	21 (10.4)	21 (10.8)	24 (12.4)
Oral hypoglycemic agent	100 (49.8)	104 (53.3)	115 (59.3)	92 (45.8)	101 (51.8)	106 (54.6)
Insulin and oral hypoglycemic agent	28 (13.9)	27 (13.8)	24 (12.4)	35 (17.4)	37 (19.0)	32 (16.5)
Insulin alone	46 (22.9)	32 (16.4)	33 (17.0)	53 (26.4)	36 (18.5)	32 (16.5)
Antihypertensive agents†						
Any	—	—	—	113 (56.2)	88 (45.1)	84 (43.3)
Diuretics	—	—	—	51 (25.4)	42 (21.5)	37 (19.1)
Beta-blockers	—	—	—	38 (18.9)	27 (13.8)	26 (13.4)
Calcium-channel blockers (nondihydropyridine)	—	—	—	55 (27.4)	35 (17.9)	45 (23.2)
Others	—	—	—	30 (14.9)	22 (11.3)	34 (17.5)
Lipid-lowering agents						
Any	36 (17.9)	37 (19.0)	31 (16.0)	52 (25.9)	52 (26.7)	47 (24.2)
Statin alone	21 (10.4)	23 (11.8)	16 (8.2)	38 (18.9)	37 (19.0)	29 (14.9)
Fibrate alone	14 (7.0)	12 (6.2)	13 (6.7)	12 (6.0)	11 (5.6)	14 (7.2)
Statin and fibrate	1 (0.5)	2 (1.0)	2 (1.0)	2 (1.0)	4 (2.1)	4 (2.1)
Aspirin (≤325 mg daily)	19 (9.5)	31 (15.9)	26 (13.4)	29 (14.4)	42 (21.5)	32 (16.5)

*Differences between groups were not statistically significant, except in the use of antihypertensive agents, for which P=0.03 for the comparison between the placebo group and the 150-mg group and P=0.01 for the comparison between the placebo group and the 300-mg group.

†All antihypertensive agents were discontinued during the three-week run-in screening period.

cal in the three groups (Table 1). The average trough blood pressure throughout the study was 144/83 mm Hg in the placebo group, 143/83 mm Hg in the 150-mg group, and 141/83 mm Hg in the 300-mg group (P=0.004 for the comparison of systolic blood pressure between the combined irbesartan groups and the placebo group). The average trough mean arterial blood pressure during the study was 103 mm Hg in the placebo group, 103 mm Hg in the 150-mg group, and 102 mm Hg in the 300-mg group (P=0.005 for the comparison between the 300-mg group and the placebo group) (Fig. 3).

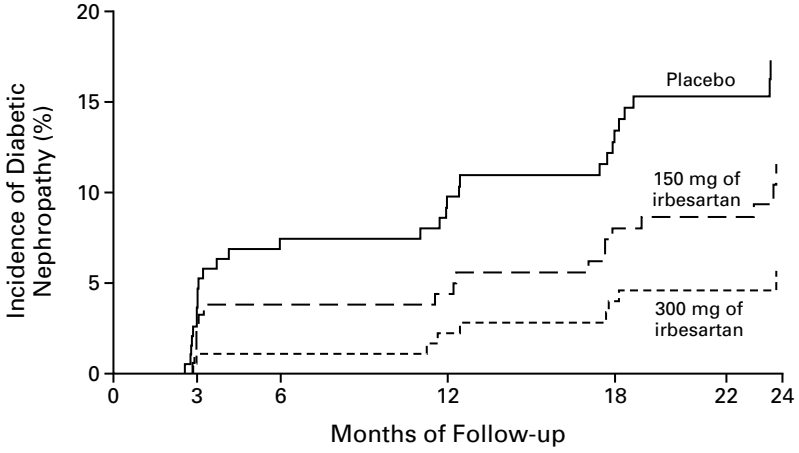
Irbesartan reduced the level of urinary albumin excretion throughout the study; in the 150-mg group, it decreased by 24 percent (95 percent confidence interval, 19 to 29 percent), and in the 300-mg group, it decreased by 38 percent (95 percent confidence interval, 32 to 40 percent), whereas there was a decrease of 2 percent in the placebo group (95 percent confidence interval, −7 to 5 percent; P<0.001 for the comparison between placebo and the combined irbesartan groups). There was a significantly smaller reduction in the level of albuminuria in the 150-mg group than in the 300-mg group (P<0.001).

The restoration of normoalbuminuria (urinary albumin excretion of less than 20 μg per minute) by the last visit was more frequent in the patients treated with the higher dose of irbesartan — 34 percent in the 300-mg group (95 percent confidence interval, 26 to 40 percent), 24 percent in the 150-mg group (95 percent confidence interval, 18 to 30 percent), and 21 percent in the placebo group (95 percent confidence interval, 15 to 26 percent; P=0.006 for the comparison between the placebo group and the 300-mg group). The glycosylated hemoglobin values increased to the same extent in the placebo group and the combined irbesartan groups (0.3 percent and 0.4 percent, respectively).

Serious adverse events during treatment and up to two weeks after treatment were recorded in 22.8 percent of the patients in the placebo group and 15.4 percent of those in the combined irbesartan groups (P=0.02). Nonfatal cardiovascular events were slightly more frequent in the placebo group (8.7 percent, vs. 4.5 percent in the 300-mg group; P=0.11). The study medication was permanently discontinued in 18.9 percent of the patients in the placebo group, as compared with 14.9 percent of those in the combined irbesartan groups (P=0.21).

Subgroup Analysis

The beneficial effect of a daily dose of 300 mg of irbesartan on the primary end point, progression to nephropathy, was examined in many predefined sub-



No. at Risk							
Placebo	201	201	164	154	139	129	36
150 mg of irbesartan	195	195	167	161	148	142	45
300 mg of irbesartan	194	194	180	172	159	150	49

Figure 2. Incidence of Progression to Diabetic Nephropathy during Treatment with 150 mg of Irbesartan Daily, 300 mg of Irbesartan Daily, or Placebo in Hypertensive Patients with Type 2 Diabetes and Persistent Microalbuminuria.

The difference between the placebo group and the 150-mg group was not significant ($P=0.08$ by the log-rank test), but the difference between the placebo group and the 300-mg group was significant ($P<0.001$ by the log-rank test).

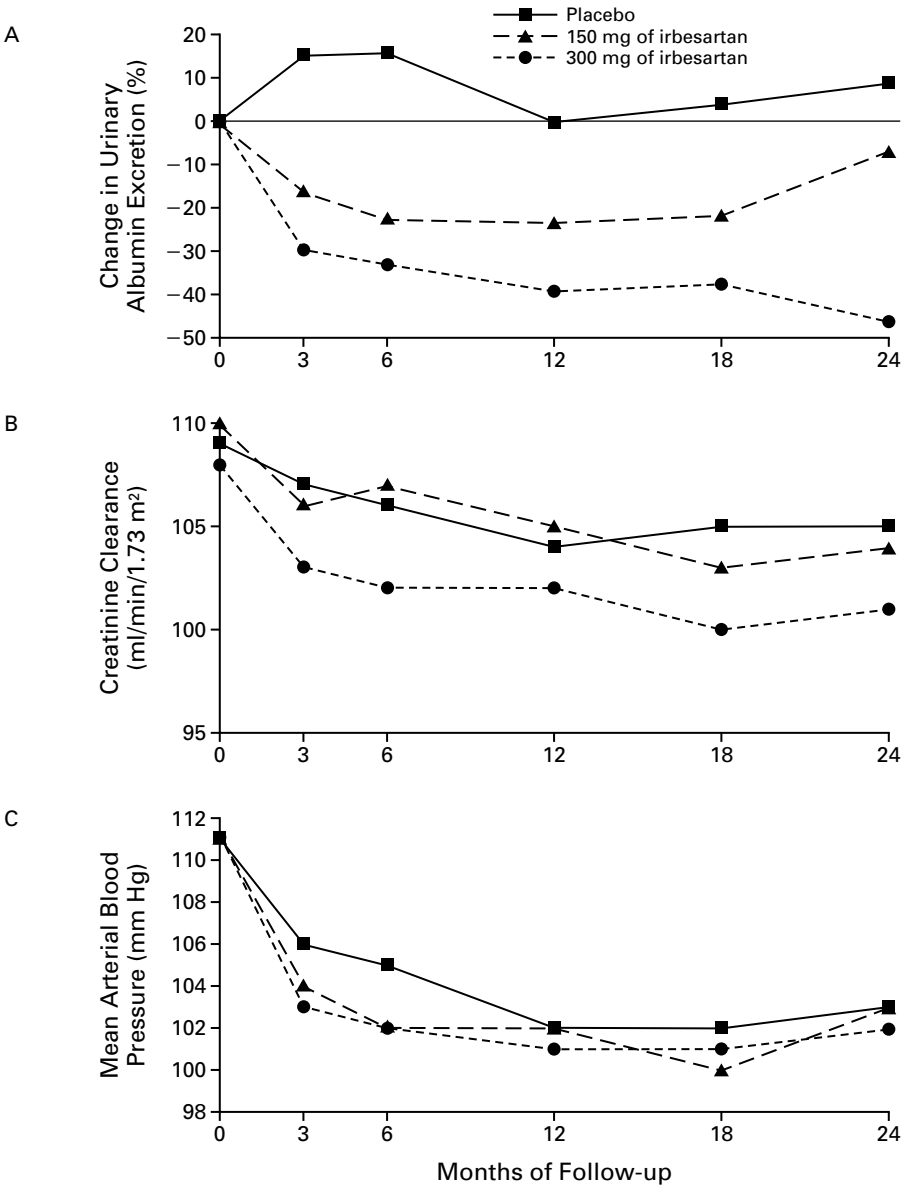
groups. There were no significant differences in the response to irbesartan treatment among the subgroups (data not shown).

DISCUSSION

Our study demonstrates that treatment with irbesartan significantly reduces the rate of progression to clinical albuminuria, the hallmark of overt diabetic nephropathy in patients with type 2 diabetes. Furthermore, the restoration of normoalbuminuria was significantly more common in the group receiving irbesartan at a dose of 300 mg daily. These benefits appear to be independent of the systemic blood pressure, since the average trough blood pressure during the study was only minimally lower in the irbesartan groups than in the placebo group, with no difference in diastolic blood pressure and a difference of 1 to 3 mm Hg in systolic blood pressure. Furthermore, a statistical analysis that adjusted for these small differences confirmed the renoprotective effect of irbesartan. Finally, kidney function remained well preserved in all groups.

Our study confirms and extends the finding that antihypertensive treatment has a renoprotective effect in hypertensive patients with type 2 diabetes and microalbuminuria.[4,5,16-23] There has been conflicting evidence regarding the existence of a specific renoprotective effect — that is, a beneficial effect on kidney function beyond the hypotensive effect — of agents, such as angiotensin-I–converting enzyme inhibitors, that block the renin–angiotensin system in patients with type 2 diabetes and microalbuminuria.[4,5,16-23] The inconclusive nature of the previous evidence may have been due in part to the small size of the study groups and the short duration of antihypertensive treatment in most previous trials; an exception is the long-lasting United Kingdom Prospective Diabetes Study, which suggested the equivalence of a beta-blocker and an angiotensin-I–converting enzyme inhibitor.[21] The rapid and sustained response to irbesartan and the continuing divergence in renal outcomes between the 300-mg group and the placebo group in our study suggest that longer-term therapy may result in an even better prognosis. The rate of progression to diabetic nephropathy in the placebo group in our study is similar to those found in other studies conducted in similar populations.[1-5]

Interruption of the renin–angiotensin system with an angiotensin-I–converting enzyme inhibitor probably induces the same degree of renoprotection as the use of an angiotensin-II–receptor antagonist. However, this possibility needs to be evaluated in a head-to-head comparison of the type performed in patients with heart failure.[24] Angiotensin-I–converting enzyme inhibition is indicated in the 20 to 30 percent of our patients with cardiovascular disease, as documented in the Heart Outcomes Prevention Evaluation Study.[5] Unfortunately, our findings do not enable us to eval-



No. at Risk

Placebo	201	192	179	158	146	140
150 mg of irbesartan	195	185	170	166	156	151
300 mg of irbesartan	194	187	183	170	162	157

Figure 3. Geometric Mean Rate of Urinary Albumin Excretion (Panel A), Estimated Mean Creatinine Clearance (Panel B), and Trough Mean Arterial Blood Pressure (Panel C) in Hypertensive Patients with Type 2 Diabetes and Persistent Microalbuminuria, According to Treatment Group.

The average urinary albumin excretion rate (geometric mean) was significantly reduced in both irbesartan groups ($P<0.001$). There were no significant differences among the three groups in the initial or the sustained (3-to-24-month) rate of decline in creatinine clearance. The average trough mean arterial blood pressure during the study was 103 mm Hg in the placebo group, 103 mm Hg in the 150-mg group, and 102 mm Hg in the 300-mg group ($P=0.005$ for the comparison between the 300-mg group and the placebo group).

uate whether there are differences in the renoprotective capacity of irbesartan according to the race of the patient. Patients in our study were allowed to use only nondihydropyridine calcium-channel antagonists, since verapamil and diltiazem have been reported to have the same antiproteinuric effect as angiotensin-I–converting enzyme inhibitors in patients with type 2 diabetes.[25]

Measurement of urinary albumin excretion is used to determine both the diagnosis of diabetic nephropathy and its progression in patients with type 2 diabetes. Persistent albuminuria heralds progressive kidney disease characterized by a relentless decline in kidney function, ultimately leading to end-stage renal disease. Conversely, an initial and sustained reduction in albuminuria during antihypertensive treatment is associated with a diminished rate of decline in the glomerular filtration rate and consequently with an improved prognosis.[26,27] Increased urinary albumin excretion may contribute to the pathogenesis of glomerular lesions,[28] and persistent clinical albuminuria is now considered the most important surrogate end point in clinical trials aimed at the prevention of diabetic nephropathy.[1,4,5,16,23]

The initial drop in the glomerular filtration rate during the first three months of our study was steeper than the sustained decline during the remainder of the two-year study period. There were no significant differences in the sustained decline in creatinine clearance among the three groups. Previous studies suggest that the faster initial decline in the glomerular filtration rate is due to a functional (hemodynamic) effect of antihypertensive treatment and that it is reversible when treatment is discontinued. By contrast, the sustained but slower decline in the glomerular filtration rate reflects the beneficial effect of treatment on the progression of diabetic nephropathy.[29] The sustained rate of decline in kidney function found in our study was slightly higher than the rate of decline in the glomerular filtration rate of 1 ml per minute per year that has been attributed to aging in subjects without kidney disease.[30]

Preventing or delaying the development of diabetic nephropathy is a major goal of treatment. Our findings indicate that this goal can be achieved if high-risk patients are identified early in the course of disease and are then given appropriate renoprotective therapy with irbesartan. According to published guidelines for the treatment of diabetic kidney disease, routine screening of urine for microalbuminuria should be performed in all patients with diabetes,[31] just as these patients are routinely screened for diabetic retinopathy. Unfortunately, patients at high risk for diabetic nephropathy are rarely identified early, which may help explain why diabetes represents the single most important cause of end-stage renal disease in Europe, Japan, and the United States.[1] We have previously demonstrated that in patients with type 2 diabetes, proteinuria, and retinopathy, diabetic glomerulosclerosis is the cause of albuminuria, whereas in approximately 30 percent of patients with type 2 diabetes and proteinuria but no retinopathy, the glomerular structure is normal or nondiabetic kidney diseases are present.[32] In the present study, there was no difference in glycemic control among the three treatment groups; therefore, metabolic factors cannot be considered to have played a part in conferring renoprotection. Nevertheless, it must be emphasized that improvement in glycemic control slows the increase in the level of albuminuria and postpones the occurrence of overt diabetic nephropathy in patients with type 2 diabetes.[33]

In conclusion, irbesartan is renoprotective independently of its blood-pressure–lowering effect in hypertensive patients with type 2 diabetes and microalbuminuria.

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APPENDIX

The following persons participated in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study: Scientific Committee — P. Arner, H.-H. Parving, J. Bröchner-Mortensen, R. Gomis, H. Lehnert, G. Frangin, M. Grégoire; Data and Safety Monitoring Committee — J.-P. Boissel, W. Kiowski, L. Monnier; Investigators: *Argentina* — L.I. Juncos, C. Ferrer, J.N. Waitman, C. Larrusse, J.A. Vallejos, M. del Carmen Bangher, J. Herrera, M.E. Martin; *Australia* — P. Phillips, D.K. Yue, M. Hooper, D. Wilson, G. Jerums, M. Kotowicz, P. Howe; *Austria* — G. Schernthaner; *Belgium* — A. Scheen, I. Dumont, J.C. Daubresse, L. Van Gaal; *Canada* — J.D. Spence, K. Dawson, A. Belanger, V. Woo, R. Aronson, B. St. Pierre; *Croatia* — V. Profozic, I. Nazar; *Czech Republic* — A. Starek, H. Rosolova, J. Charvat; *Denmark* — H.-H. Parving, S. Andersen, P. Hovind, H.P. Hansen, P.K. Christensen, K. Kolendorf; *Estonia* — T. Podar, V. Ilmoja; *Finland* — K. Harno, K. Harno; *France* — H. Affres, G. Charpentier, C. Petit, M. Rieu, B. Charbonnel, B. Anton, C. Le Devehat, J.J. Altman, N. Elian, E. Verlet, D. Bensoussan; *Germany* — H. Lehnert, J. Adler, J. Hensen, R. Landgraf, K. Mann, G. Woywod, H.U. Häring, G. Klausmann, P. Schwandt, P. Weisweiler, W. Stürmer, D. Krakow, R. Ziegler; *Greece* — N. Karatzas, T. Mountokalakis, A. Achimastos, M. Papavassiliou, M. Kakou, E. Diamantopoulos, E. Andreadis, D. Papadogianis, I. Avramopoulos, K. Siamopoulos, J. Theodorou; *Hungary* — A. Gyimesi, M. Dudás, J. Fövényi, E. Thaisz, Z. Kerényi, P. Stella, G. Tamás, Á. Gy Tabák; *Italy* — F. Quarello, E.D. Esposti, P. Bajardi, M. Sasdelli; *the Netherlands* — C.A.J.M. Gaillard, O. de Vries, P.F.M.J. Spooren; *Norway* — P. Mathisen, K. Birkeland, O.G. Nilsen; *Poland* — B. Krupa-Wojciechowska; *Portugal* — A. Almeida Dias, S. Fortunato, M. Pimenta; *South Africa* — R. Moore, Y.K. Seedat, G. Ellis; *Spain* — R. Garcia-Robles, F. Fernandez Vega, A. Roca-Cusachs, T. Benet, R. Gomis, M.J. Coves, C. Calvo, J. Garcia Puig, E. Montanya, F. de Alvaro, J.L. de Miguel; *Sweden* — P. Arner, J. Bolinder, H. Arnqvist; *Switzerland* — P. Gerber; *United Kingdom* — P. Rylance, J. Vora, H. Llewelyn, M. Sampson, R.L. Kennedy.

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