Cardiovascular Outcomes in the Irbesartan Diabetic Nephropathy Trial of Patients with Type 2 Diabetes and Overt Nephropathy

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Background: **Patients with diabetes have increased risk for adverse cardiovascular events. Angiotensin-converting enzyme inhibitors are protective in type 1 diabetes. However, no definitive studies have examined the use of angiotensin-receptor blockers in patients with type 2 diabetes and overt nephropathy. The primary outcomes of the Irbesartan Diabetic Nephropathy Trial were doubling of serum creatinine levels, end-stage renal disease, and death from any cause.**

Objective: **To compare rates of cardiovascular events among patients with type 2 diabetic nephropathy who received conventional antihypertensive therapy with an angiotensin-receptor blocker (irbesartan) or a calcium-channel blocker (amlodipine), or placebo.**

Design: **Randomized double-blind, placebo-controlled trial with a median follow-up of 2.6 years. A time event analysis was used.**

Setting: **209 centers in the Americas, Europe, Israel, and Australasia.**

Participants: **1715 adults with type 2 diabetic nephropathy and hypertension; serum creatinine levels of 89 μmol/L (1.0 mg/dL) to 266 μmol/L (3.0 mg/dL) in women and 106 μmol/L (1.2 mg/dL) to 266 μmol/L (3.0 mg/dL) in men; and urinary protein excretion rates of at least 900 mg/d.**

Intervention: **Treatment with irbesartan, amlodipine, or placebo.**

Measurements: **Time to cardiovascular death, myocardial infarction, congestive heart failure, strokes, and coronary revascularization.**

Results: **The three groups were not statistically different in the composite of cardiovascular events. Among the components of the composite, there was a trend toward a decrease in strokes in patients receiving amlodipine versus those receiving placebo (hazard ratio, 0.65 [95% CI, 0.35 to 1.22]; $P = 0.18$). Likewise, patients receiving amlodipine had a significantly lower rate of myocardial infarction when compared with placebo recipients (hazard ratio, 0.58 [CI, 0.37 to 0.92]; $P = 0.02$). In contrast, patients receiving irbesartan had a significantly lower incidence of congestive heart failure when compared with placebo recipients (hazard ratio, 0.72 [CI, 0.52 to 1.00]; $P = 0.048$) or amlodipine recipients (hazard ratio, 0.65 [CI, 0.48 to 0.87]; $P = 0.004$).**

Conclusion: **The composite cardiovascular event rate did not differ in patients with type 2 diabetes and overt nephropathy treated with irbesartan, amlodipine, or placebo in addition to conventional antihypertensive therapy.**

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Patients with diabetes have an increased risk for cardiovascular complications and death (1). Studies that analyzed the effects of inhibition of the renin–angiotensin system on the risk for cardiovascular complications included a substantial number of patients with diabetes (2–5) or were done exclusively in patients with diabetes (6–8). The meta-analysis of these studies (9), the analysis of the diabetic cohorts in the Heart Outcomes Prevention Evaluation (HOPE) study (2), and the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial (5) demonstrated that angiotensin-converting enzyme (ACE) inhibitors (2, 9) and angiotensin-receptor blockers (5) had a statistically significant advantage over placebo or alternative agents in decreasing the risk for several cardiovascular events. These studies randomly assigned few patients with renal involvement and overt proteinuria. Overt proteinuria occurred in fewer than 20% of the 470 patients in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial (6), and only 11% of the 1195 patients in the LIFE trial (5). The Captopril Prevention Project (CAPP) (3) and the Swedish Trial in Old Patients with Hypertension-2 (STOP Hypertension-2) (4) did not state the number of patients with diabetes and overt proteinuria. There were no such patients in the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) (7), and patients with dipstick-positive albuminuria were excluded from the HOPE trial (2). Since proteinuria is an independent risk factor for cardiovascular disease (10, 11), the data obtained in the aforementioned trials cannot be extrapolated to patients with type 2 diabetes and overt nephropathy. Trials performed in such patients have reported a blood pressure–independent effect of two different angiotensin-receptor blocker agents to protect against nephropathy (12, 13) without a change in all-cause mortality. Apart from studies in heart failure, few cardiovascular data exist for receptor blockers compared with either placebo or calcium-channel blockers. We report on the analysis of the cardiovascular end points that were monitored as secondary end points in the Irbesartan Diabetic Nephropathy Trial (IDNT) (12) and assess whether an angiotensin II receptor blocker or a calcium-channel blocker alters the risk for cardiovascular events beyond those observed by blood pressure reduction alone without such agents.

METHODS

Patients

The IDNT was a randomized, double-blind study on the effect of treatment with irbesartan or amlodipine com-

pared with placebo in patients with type 2 diabetic nephropathy. The protocol of this study has been published (12, 14). Entry criteria required that patients be between 30 and 70 years of age and have type 2 diabetes mellitus and overt nephropathy, as evidenced by current treatment for hypertension or by a protein excretion rate of 900 mg/d or greater, serum creatinine level of 89 μmol/L (1.0 mg/dL) to 266 μmol/L (3.0 mg/dL) in women or of 106 μmol/L (1.2 mg/dL) to 266 μmol/L (3.0 mg/dL) in men, and baseline seated blood pressure greater than 135/85 mm Hg. The institutional review boards of each center approved the protocol. All patients gave written informed consent.

Treatment and Randomization

Patients were randomly assigned centrally by computer to receive treatment with irbesartan, 300 mg/d (Avapro, Bristol-Myers Squibb, Princeton, New Jersey); amlodipine, 10 mg/d (Norvasc, Pfizer, New York); or matched placebo. To minimize any center effect, randomization was blocked by center. All patients had blood pressure controlled to the same blood pressure goal of less than 135/85 mm Hg by using antihypertensive agents other than ACE inhibitors, angiotensin II receptor blocking agents, or calcium-channel blockers. For the analysis of cardiovascular end points, patients were followed to initiation of treatment for end-stage renal failure (dialysis or renal transplantation), reaching a serum creatinine level of 530.4 μmol/L (6.0 mg/dL) or higher, death, or administrative censoring in December 2000.

Context

Previously published results of this randomized, double-blind trial showed that high-risk patients with type 2 diabetic nephropathy had better renal protection if they were treated with irbesartan rather than amlodipine in addition to conventional antihypertensive therapy.

Contribution

These detailed analyses showed no differences in overall cardiovascular outcomes between patients given irbesartan or amlodipine. Fewer patients given irbesartan had heart failure and fewer patients given amlodipine had heart attacks.

Cautions

The trial had limited power to detect important differences between groups in mortality or strokes, and most patients received several antihypertensive agents.

–The Editors

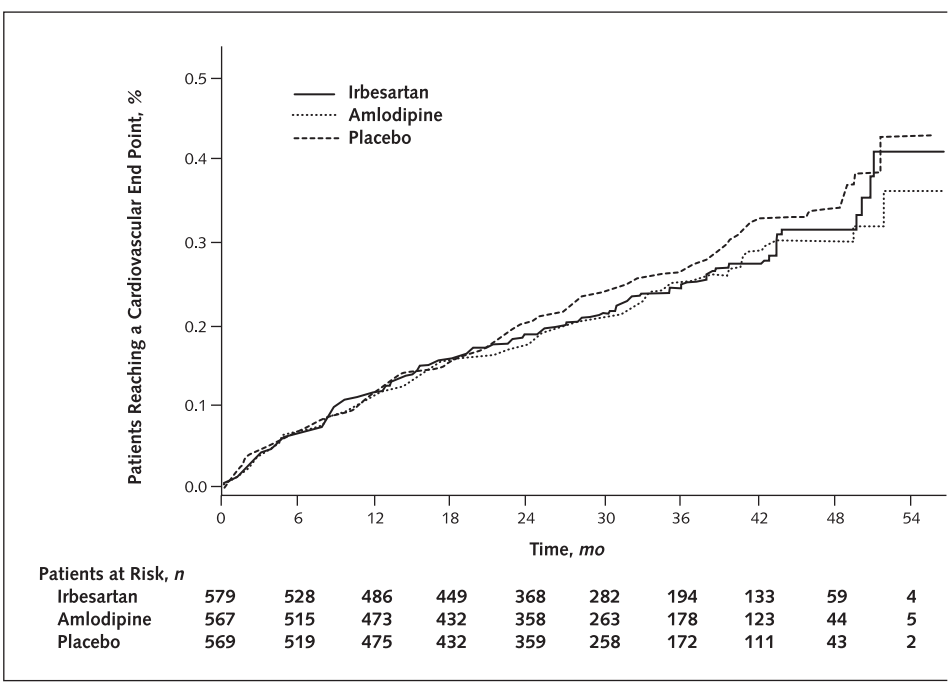
Outcomes

We prospectively established cardiovascular outcomes, defined in the **Appendix Table** (available at www.annals.org).

Ascertainment of Cardiovascular Events

Information about hospitalizations and adverse events were screened at Bristol-Myers Squibb, Princeton, New

Figure. **Time to first cardiovascular composite event as a function of treatment assignment.**



The numbers of patients at risk in each treatment group at 6-month intervals are shown on the x-axis. There was no statistically significant overall difference among treatment groups ($P > 0.05$) or for any specific pairwise comparison.

Table 1. **Baseline Characteristics***

Characteristic	Irbesartan Group (*n* = 579)	Amlodipine Group (*n* = 567)	Placebo Group (*n* = 569)
Age, *y*	59.3 ± 7.1	59.1 ± 7.9	58.3 ± 8.2
Men, *n (%)*	378 (65)	359 (63)	403 (71)
Race/ethnicity, *n (%)*			
White	438 (76)	389 (69)	415 (73)
African American	63 (11)	87 (15)	78 (14)
Hispanic	28 (5)	29 (5)	26 (5)
Asian/Pacific Islander	24 (4)	34 (6)	27 (5)
Other	26 (4)	28 (5)	23 (4)
Body mass index, kg/m^2	31.0 ± 5.6	30.9 ± 5.9	30.5 ± 5.9
Systolic blood pressure, *mm Hg*	160 ± 20	159 ± 19	158 ± 20
Diastolic blood pressure, *mm Hg*	87 ± 11	87 ± 11	87 ± 11
Patients receiving insulin at entry, *n (%)*	329 (57)	327 (58)	335 (59)
Previous cardiovascular disease, *n (%)*	158 (27)	171 (30)	164 (29)
Retinopathy, *n (%)*	401 (69)	362 (64)	380 (67)
Serum creatinine level, *μmol/L (mg/dL)*	148 ± 47 (1.67 ± 0.53)	146 ± 54 (1.65 ± 0.61)	150 ± 50 (1.7 ± 0.57)
Urinary protein excretion rate, *g/d*	2.9 (1.6–5.4)	2.9 (1.6–5.2)	2.9 (1.8–5.2)
Urinary albumin excretion rate, *g/d*	1.9 (1.0–3.8)	1.9 (1.0–3.5)	1.9 (1.1–3.5)
Hemoglobin A_{1c} level, %	8.1 ± 1.7	8.2 ± 1.7	8.2 ± 1.7

* Values expressed with a plus/minus sign are means ± SD.

Jersey, by trained, blinded clinical research associates to identify potential cardiovascular events. Investigators used study forms to report and characterize all cardiovascular outcomes. For all potential events, records, including laboratory values, electrocardiograms, and radiographic reports were obtained for clarification. Since myocardial infarctions may go unrecognized, a central electrocardiogram reading center was established at Brigham and Women's Hospital, Boston, Massachusetts, where two cardiologists reviewed every electrocardiogram. Electrocardiography was performed at baseline, 6 months, 12 months, and annually thereafter. A total of 5698 electrocardiograms were reviewed at the center. When a new Q-wave infarction was found, the cardiologists asked whether a clinical myocardial infarction was reported. Even when myocardial infarctions were not clinically reported, these Q-wave infarctions were adjudicated as myocardial infarctions.

Adjudication of Cardiovascular Events

Investigators at each center reported cardiovascular events, defined in the **Appendix Table**. The information on all potential events was referred to one member of the Outcomes Confirmation and Classification Committee (Appendix, available at www.annals.org). If the committee member agreed with the judgment of the center investigator, their combined judgment was accepted. If the center investigator and the committee member differed, the case material was reviewed by the membership of the committee, whose decision was accepted. Deaths were adjudicated by a Mortality Committee (Appendix). Each death was reviewed by two members of the committee and presented to the membership, whose decision was accepted as final.

Statistical Analysis

For graphical presentation (**Figure**) and overall testing for statistically significant differences among the three treatment groups, time to the first occurrence of either a specific cardiovascular outcome or one of the composite outcomes was analyzed by product-limit survival curves and the log-rank test (15). We used proportional hazards modeling to determine hazard ratios. For the cardiovascular death outcome, which could occur only once, we used the standard proportional hazards model (16), with treatment assignment as the only independent covariate. For other cardiovascular outcomes, which could occur more than once, we used the Anderson–Gill formulation of the proportional hazards model (17), in which patients are considered at risk for the first event from randomization to the first event, at risk for the second event from the day following the first event to the second event, and so forth, permitting use of all the data. In accordance with the method of Lee and colleagues (18), we used a robust variance estimate that accounts for the possibility of correlation of risk for several events within a patient. We believed that occurrence of a first event of a given type increases the likelihood of a subsequent similar event. Therefore, both treatment assignment and a time-dependent covariate indicating whether the event was the first of its type or a subsequent event were included in these analyses. The time-dependent covariate was statistically significant in each case, confirming the above assumption. There was no statistically significant interaction between treatment and the time-dependent covariate—the effects of treatment assignment were similar for first and subsequent events—and inclusion of the time-dependent covariate did not change either the estimates of the treatment effect or their statistical significances.

Data management and computations were done by using SAS software for Windows, version 8 (SAS Institute, Inc., Cary, North Carolina), or S-Plus for Windows, version 6.0 (Insightful Corp., Seattle, Washington). Statistical tests were two sided. A *P* value of 0.05 or less, unadjusted

for the multiple comparisons, was considered statistically significant.

Role of the Funding Sources

The funding sources were involved in the data collection but not in the analysis or interpretation or the decision to submit the manuscript for publication.

RESULTS

The baseline characteristics of the three groups are shown in **Table 1**. A flow diagram of the study is shown in the **Appendix Figure** (available at www.annals.org).

Clinical Management

During the study, the blood pressure decreased from the baseline values to 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. Blood pressure in the two active treatment groups did not differ; values in both groups were statistically significantly lower than in the placebo group ($P = 0.001$). The distribution of nonstudy drugs used to achieve the target blood pressure was similar in the three groups (**Table 2**). The placebo group received an average of 3.3 nonstudy drugs, and the other two groups received an average of 3.0 drugs. Fewer patients assigned to irbesartan received diuretics than patients assigned to amlodipine or placebo. Patients assigned to amlodipine received potassium-sparing and combination diuretics more frequently than patients assigned to irbesartan or placebo. More patients assigned to placebo received each of the other classes of ancillary antihypertensive agents than patients assigned to either of the active treatments.

Composite Cardiovascular Outcomes

Of the 1715 randomly assigned patients, 518 patients sustained 821 cardiovascular events (**Table 3**). The time to the first cardiovascular composite events (**Figure**) did not significantly differ among the three groups; paired comparisons between any two groups were also not significantly different. A total of 172 of 579 (29.7%) patients receiving irbesartan, 161 of 567 (28.3%) patients receiving amlodipine, and 185 of 569 (32.5%) patients receiving placebo had a cardiovascular event before renal failure, death, or censorship.

Components of the Composite Cardiovascular Outcome

Differences between treatment groups emerged in the analysis of the components of the composite. In 225 patients, 336 episodes of heart failure occurred; 320 episodes necessitated hospitalization. Only 60 patients whose initial therapy was irbesartan had congestive heart failure (10.4%), as compared with 93 patients whose initial therapy was amlodipine (16.4%) and 72 patients who initially received placebo (12.7%). Time to the first episode significantly differed among the three treatment groups ($P = 0.007$). Assignment to initial treatment with irbesartan was associated with a statistically significantly longer time ($P = 0.002$) to the first congestive heart failure episode compared with amlodipine. The analysis of time to the first congestive heart failure event showed no statistical difference between amlodipine and placebo and between irbesartan and placebo. However, when the relative hazard ratio for all congestive heart failure events was analyzed, there was a statistically significant difference in the irbesartan–placebo comparison (hazard ratio, 0.72 [CI, 0.52 to 1.00]; $P = 0.048$) (**Table 3**).

The three groups also differed in the time to the first myocardial infarction. Among 117 patients sustaining a total of 128 myocardial infarctions, all but 13 infarctions were confirmed by elevated enzyme levels or electrocardiogram changes. Of patients with infarctions, 44 patients were in the group initially assigned to irbesartan (7.6%), 46 patients were in the placebo group (8.1%), and 27 patients were in the amlodipine group (4.7%). Amlodipine was associated with a statistically significantly longer time

Table 2. **Use of Antihypertensive Agents during Follow-up***

Agent	Irbesartan Group ($n = 579$)	Amlodipine Group ($n = 567$)	Placebo Group ($n = 569$)	*P* Value†
	← *n (%)* →			
Diuretics				
Thiazides	181 (31.3)	192 (33.9)	198 (34.8)	>0.2
Loop agents	388 (67.1)	411 (72.5)	405 (71.2)	0.11
Potassium-sparing	26 (4.5)	44 (7.8)	25 (4.4)	0.018
Combination	24 (4.2)	46 (8.1)	33 (5.8)	0.018
ACE inhibitors‡	36 (6.2)	48 (8.5)	38 (6.7)	>0.2
Angiotensin-receptor blockers‡	13 (2.3)	14 (2.5)	9 (1.6)	>0.2
Calcium-channel blockers‡	41 (7.1)	48 (8.5)	47 (8.1)	>0.2
β-Blockers	251 (43.4)	227 (40.0)	293 (51.5)	0.001
α- or β-Antagonists	249 (43.0)	232 (40.9)	271 (47.6)	0.066
Central adrenergic agonists	205 (35.4)	167 (29.5)	225 (39.5)	0.002
Peripheral adrenergic blockers	154 (26.6)	129 (22.8)	176 (30.9)	0.008
Vasodilators	113 (19.5)	107 (18.9)	132 (23.2)	0.15

* ACE = angiotensin-converting enzyme.
† Exact permutation probability was obtained by using StatXact (Cytel Software Corp., Cambridge, Massachusetts).
‡ Prescribed principally during periods in which treatment was stopped temporarily because of intercurrent illness thought by the attending physician to require treatment with known ACE inhibitor, angiotensin-receptor blocker, or calcium-channel blocker.

($P = 0.02$) to first infarction compared with placebo and a marginally statistically significantly longer time ($P = 0.06$) when compared with irbesartan. A statistically significant reduction in relative hazard ratio with amlodipine when compared with placebo is evident when all myocardial infarctions are considered (hazard ratio, 0.58 [CI, 0.37 to 0.92]; $P = 0.021$) (**Table 3**). The comparison of irbesartan with amlodipine did not reach statistical significance (hazard ratio, 1.54 [CI, 0.97 to 2.45]; $P = 0.068$).

Several tracked cardiovascular events did not differ between groups (**Table 3**). The percentage of patients with cardiovascular deaths and coronary revascularization was similar among the three groups. In 69 patients sustaining 76 strokes, all but 19 strokes were confirmed by radiographic imaging. Time to first stroke did not differ statistically significantly among the three groups. However, although 28 patients initially given irbesartan (4.8%) and 26 patients in the placebo group (4.6%) had strokes, only 15 patients in the amlodipine group (2.6%) had such an event. Considering all strokes, the hazard ratio was 0.65 (CI, 0.35 to 1.22) in the amlodipine–placebo comparison and 1.55 (CI, 0.84 to 2.87) in the irbesartan–amlodipine comparison, but these hazard ratios did not differ significantly.

DISCUSSION

The IDNT was designed to compare the effect of therapy with the angiotensin-1 antagonist irbesartan, the calcium-channel blocker amlodipine, or placebo for similar decrement in blood pressure on the occurrence of various cardiovascular events. Neither drug nor placebo was superior in the time to the composite cardiovascular end points (**Figure**) (CI, 0.74 to 1.10 in the irbesartan–placebo comparison, 0.83 to 1.21 in the amlodipine–placebo comparison, and 0.74 to 1.10 in the irbesartan–amlodipine comparison). The effect of this original assignment could be modified by differences in ancillary therapy during the follow-up period, resulting from initial randomization. The effect of baseline covariates will be analyzed. The placebo group had more men; however, adjustment for sex differences did not significantly affect the analysis. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, which studied a similar group of patients, also showed no difference in composite cardiovascular outcomes between the group receiving the angiotensin-receptor blocker losartan and the placebo group (13).

Reviews (19) and meta-analyses (19, 20) on the effects

Table 3. **Risk for Cardiovascular Outcomes by Treatment Group***

Cardiovascular Event	Events/Patients			Hazard Ratio (95% CI)†	*P* Value
	Irbesartan Group ($n = 579$)	Amlodipine Group ($n = 567$)	Placebo Group ($n = 569$)		
	← *n/n* →				
Cardiovascular composite	259/172	278/161	284/185		
Irbesartan vs. placebo				0.90 (0.74–1.10)	>0.2
Amlodipine vs. placebo				1.00 (0.83–1.21)	>0.2
Irbesartan vs. amlodipine				0.90 (0.74–1.10)	>0.2
Cardiovascular death	52/52	37/37	46/46		
Irbesartan vs. placebo				1.08 (0.72–1.60)	>0.2
Amlodipine vs. placebo				0.79 (0.51–1.22)	>0.2
Irbesartan vs. amlodipine				1.36 (0.89–2.07)	0.155
Congestive heart failure	80/60	143/93	113/72		
Irbesartan vs. placebo				0.72 (0.52–1.00)	0.048
Amlodipine vs. placebo				1.11 (0.83–1.50)	>0.2
Irbesartan vs. amlodipine				0.65 (0.48–0.87)	0.004
Myocardial infarction	48/44	29/27	51/46		
Irbesartan vs. placebo				0.90 (0.60–1.33)	>0.2
Amlodipine vs. placebo				0.58 (0.37–0.92)	0.021
Irbesartan vs. amlodipine				1.54 (0.97–2.45)	0.068
Cerebrovascular accident	30/28	18/15	28/26		
Irbesartan vs. placebo				1.01 (0.61–1.67)	>0.2
Amlodipine vs. placebo				0.65 (0.35–1.22)	0.18
Irbesartan vs. amlodipine				1.55 (0.84–2.87)	0.165
Cardiac revascularization	31/27	32/28	39/36		
Irbesartan vs. placebo				0.80 (0.49–1.30)	>0.2
Amlodipine vs. placebo				0.86 (0.54–1.38)	>0.2
Irbesartan vs. amlodipine				0.93 (0.55–1.55)	>0.2

* All patients received conventional antihypertensive therapy that was initiated with irbesartan, amlodipine, or placebo.
† Hazard ratio for cardiovascular death (single end point) was estimated by using proportional hazards (Cox) regression modeling. Risk for subsequent events was estimated by using the counting process method of Anderson and Gill as modified by Lee et al. (18) to account for possible correlation of risk for events within patients.

of antihypertensive agents on the overall risk for cardiovascular events in various populations of hypertensive patients have yielded conflicting results. One study found a significantly higher risk for cardiovascular events in patients given a calcium-channel blocker (relative risk, 1.10 [CI, 1.02 to 1.18]; $P = 0.018$) (19), while another study found that calcium-channel blockers were similar to diuretics and β-blockers (relative risk, 1.02 [CI, 0.95 to 1.10]; $P > 0.05$), superior to placebo (relative risk, 0.72 [CI, 0.59 to 0.87]), and only marginally inferior to ACE inhibitors (20). The shortcomings of meta-analyses have been the subject of substantial criticism (21, 22). The largest study comparing conventional antihypertensive agents with ACE inhibitors and calcium-channel blockers (23) showed no difference between these agents in overall cardiovascular events. A comparison between an angiotensin-receptor blocker and a β-blocker in patients with hypertension and left ventricular hypertrophy showed a 13% risk reduction ($P = 0.021$) in favor of the former (24). In an analysis of the subgroup of patients with diabetes in our study that compared patients receiving one of the three regimens, no superiority emerges (25). It must be noted, however, that the subgroup of patients with diabetes in the LIFE trial, few of whom had overt nephropathy, also showed a significant risk reduction in the primary composite end point favoring the angiotensin-receptor blocker (5).

It is difficult to attribute effects of single agents when patients are receiving multiple therapies. Nonetheless, our analysis of treatment assignments on components of the composite cardiovascular events revealed differences. Our results demonstrate a protective effect of an angiotensin-receptor blocker on the development of congestive heart failure (**Table 3**). Initial irbesartan treatment was associated with a statistically significant reduction in hazard ratio compared with patients who initially received placebo or amlodipine. This agrees with results of trials using ACE inhibitors (25); the RENAAL trial, which used another angiotensin-receptor blocker (13); the analysis of the subgroup of patients with diabetes in the LIFE trial (5); and a study of another angiotensin-receptor blocker in a cohort of patients with heart failure (26). Trials directly comparing calcium-channel blockers with ACE inhibitors have also reported a decrease in congestive heart failure with the latter (23), but this benefit was not observed in the subgroup of patients with diabetes (4). In our trial, amlodipine was not significantly different from placebo with respect to congestive heart failure; this finding is in line with the above-mentioned meta-analysis (20). The criteria for adjudication of heart failure were strict and frequently led to hospitalization. This avoided classifying patients who develop peripheral edema in a study using a calcium-channel blocker.

We found a statistically significant difference among agents in the risk for myocardial infarction. While the placebo and irbesartan groups did not differ, amlodipine reduced the hazard ratio of a myocardial infarction compared with placebo ($P = 0.02$) and tended to do so in the comparison with irbesartan. The results of previous studies comparing calcium-channel blockers with other agents on the rate of myocardial infarctions have had varying results. In a large sample of elderly patients with hypertension, diltiazem was as effective as a β-blocker or diuretic in preventing myocardial infarction (27). A similar conclusion was reached in a meta-analysis of studies that used both dihydropyridine and a nondihydropyridine calcium-channel blocker (20). In contrast, the hypertensive arm of the ABCD trial was prematurely terminated because the incidence of nonfatal myocardial infarctions was greater in the patients given the calcium-channel blocker than in those given an ACE inhibitor (6). Likewise, the analysis of diabetic patients in the STOP Hypertension-2 group also revealed a significant decrease in myocardial infarctions in patients receiving ACE inhibitors compared with those receiving calcium-channel blockers (4). Our trial thus suggests that angiotensin-receptor blockers and ACE inhibitors may have differential effects in these patients. A prospective trial of the coronary effects of ACE inhibitors versus angiotensin-receptor blockers versus calcium-channel blockers in patients with type 2 diabetes and overt nephropathy may be warranted.

Several components of the composite cardiovascular outcome did not differ in the three groups (**Table 3**). Amlodipine tended to have a somewhat decreased hazard ratio for strokes in the amlodipine–placebo and irbesartan–amlodipine comparisons. These hazard ratios are similar to those seen with myocardial infarctions. The hazard ratio of these two comparisons (approximately 1.5, with an upper-bound CI as high as 2.45 and 2.87) does not allow the exclusion for potential harm for one drug over the other. A similar trend favoring calcium-channel blockers was noted in the Nordic Diltiazem (NORDIL) study (27) and in the previously mentioned meta-analyses (20). It must be recognized that the cardiovascular events in our study were secondary outcomes of a trial primarily designed and powered to study renal outcomes. It is possible that with many cardiovascular events, differences not seen here would have emerged.

In summary, there is a consensus that reducing blood pressure provides both renal (28) and cardiovascular (29, 30) protection in patients with diabetes. Overwhelming evidence suggests that agents that inhibit the renin–angiotensin system have renoprotective effects, both in type 1 diabetes (ACE inhibitors [31, 32]) and in type 2 diabetes (angiotensin-receptor blockers [12, 13]). The beneficial effect of one class of agents over another is substantially less compelling when cardiovascular protection is analyzed. Thus, although most drugs are superior to placebo comparators, when compared to each other the cumulative available data provide no clear and consistent pattern of superiority (25). This neutral effect may be a consequence of the fact that composite cardiovascular events frequently involve several components whose pathophysiology is not

uniform. The mechanisms that underlie progressive heart failure and occlusive coronary and cerebrovascular events may well be different.

The preponderance of studies with ACE inhibitors, as well as our present study with angiotensin-receptor blockers, reveals a decrement in hospitalizations due to heart failure. However, when analyzed together with other outcomes, the overall composite loses statistical significance. This is even more the case when two agents have an opposing effect on two outcomes, as in our study. Furthermore, in some settings a component of the cardiovascular outcomes is significant when analyzed in an overall sample, but not in the subgroup of patients with diabetes, as with heart failure in the STOP Hypertension-2 study (4, 23) or strokes in the LIFE study (5, 24); this further emphasizes the need to clearly define the patients being studied. Therefore, it cannot be assumed a priori, for example, that cardiovascular protection observed in patients with diabetes given an ACE inhibitor in the HOPE trial (2) (which excluded patients with overt nephropathy) or those given an angiotensin-receptor blocker in the LIFE trial (in which a minority of patients had overt albuminuria) can be extrapolated to patients with renal insufficiency and overt nephropathy, such as those described in our study. Since such patients almost always require several agents to attain adequate blood pressure control, combined use of these agents should be encouraged to reach the desired blood pressure target (125/75 mm Hg) (28). To this end, an inhibitor of the renin–angiotensin system should be the primary agent. However, the use of a calcium-channel blocker as tertiary therapy (after addition of a diuretic), if needed to achieve the above blood pressure target, is appropriate.

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APPENDIX

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Appendix Table. **Classification for Fatal and Nonfatal Cardiovascular Events***

1. Cardiovascular deaths
2. Myocardial infarction defined as:
   - A. Clinical report of a myocardial infarction from the investigator and the presence of one of the following:
     Creatine kinase level increased ≥2 times the upper limit of normal for the given hospital without other explanation supported by an elevation of a cardiac enzyme level above the normal range (for example, creatine kinase–MB, cardiac troponin T, or cardiac troponin I); or
     Without cardiac-specific enzyme determination, a typical evolutionary pattern defined as creatine kinase level increased 2 times the upper limit of normal for the given hospital followed by a decrease of at least 50%.
   - B. Appearance of new pathologic (>30 msec) Q waves in ≥2 contiguous leads or the appearance of an R wave (>30 msec) with R–S ratio in lead V1 > 1.0 (without other causes, such as right ventricular hypertrophy or right bundle-branch block) in patients with or without a clinical report of myocardial infarction from the center and without one of the following conditions on their baseline electrocardiogram: pathologic WQ waves, Wolff–Parkinson–White syndrome, intraventricular conduction defects, or left ventricular hypertrophy.
   - C. Myocardial infarction requiring hospitalization and documented by a clinical report from the investigator but lacking confirmation of elevated cardiac enzyme levels.
3. Heart failure
   - A. Requiring hospitalization. Hospital records were reviewed for supporting documentation, which indicates that the patient was admitted for dyspnea or other symptoms of heart failure and required therapy with either an inotropic agent, vasodilator, or ACE inhibitor; an increase in the dose of diuretic; or ultrafiltration or dialysis.
   - B. Not requiring hospitalization. Heart failure requiring therapy with an ACE inhibitor or angiotensin II receptor antagonist.
4. Permanent neurologic deficit of at least 24-hour duration attributed to stroke, requiring hospitalization, and either confirmed or not confirmed by radiographic imaging (CT, MRI, etc.)
5. Unplanned (at the time of randomization) coronary artery revascularization procedure (coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, which includes laser therapy, atherectomy, standard balloon dilatation, or stent placement)

* ACE = angiotensin-converting enzyme; CT = computed tomography; MRI = magnetic resonance imaging.

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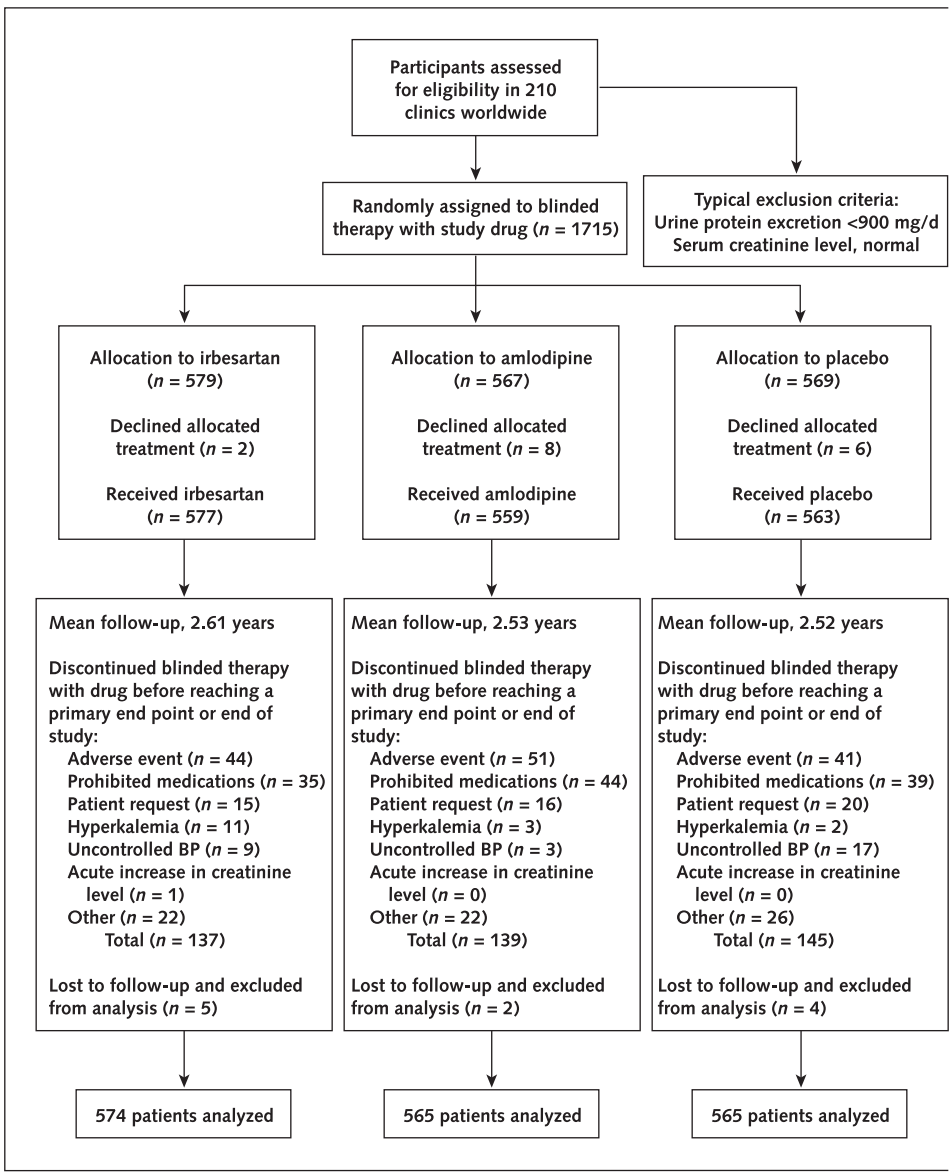
Appendix Figure. **Flow diagram for the Irbesartan Diabetic Nephropathy Trial.**



Administrative censoring took place on 21 December 2000. Final analysis was by intention to treat. Enrollment period was 1 March 1996 to 25 February 1999. BP = blood pressure.

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