ORIGINAL ARTICLE

Angiotensin-Receptor Blockade versus Converting–Enzyme Inhibition in Type 2 Diabetes and Nephropathy

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ABSTRACT

BACKGROUND

Few studies have directly compared the renoprotective effects of angiotensin II–receptor blockers and angiotensin-converting–enzyme (ACE) inhibitors in persons with type 2 diabetes.

METHODS

In this prospective, multicenter, double-blind, five-year study, we randomly assigned 250 subjects with type 2 diabetes and early nephropathy to receive either the angiotensin II–receptor blocker telmisartan (80 mg daily, in 120 subjects) or the ACE inhibitor enalapril (20 mg daily, in 130 subjects). The primary end point was the change in the glomerular filtration rate (determined by measuring the plasma clearance of iohexol) between the baseline value and the last available value during the five-year treatment period. Secondary end points included the annual changes in the glomerular filtration rate, serum creatinine level, urinary albumin excretion, and blood pressure; the rates of end-stage renal disease and cardiovascular events; and the rate of death from all causes.

RESULTS

After five years, the change in the glomerular filtration rate was −17.9 ml per minute per 1.73 m² of body-surface area, where the minus sign denotes a decrement, with telmisartan (in 103 subjects), as compared with −14.9 ml per minute per 1.73 m² with enalapril (in 113 subjects), for a treatment difference of −3.0 ml per minute per 1.73 m² (95 percent confidence interval, −7.6 to 1.6 ml per minute per 1.73 m²). The lower boundary of the confidence interval, in favor of enalapril, was greater than the predefined margin of −10.0 ml per minute per 1.73 m², indicating that telmisartan was not inferior to enalapril. The effects of the two agents on the secondary end points were not significantly different after five years.

CONCLUSIONS

Telmisartan is not inferior to enalapril in providing long-term renoprotection in persons with type 2 diabetes. These findings do not necessarily apply to persons with more advanced nephropathy, but they support the clinical equivalence of angiotensin II–receptor blockers and ACE inhibitors in persons with conditions that place them at high risk for cardiovascular events.

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In persons with type 2 diabetes mellitus, hypertension and increased urinary albumin excretion are features of diabetic nephropathy. Diabetic persons with this complication are at increased risk for cardiovascular events and, if untreated, have a relentless decline in renal function.[1] Although death from cardiovascular causes commonly occurs before end-stage renal failure, diabetic nephropathy is now the most common reason for renal-replacement therapy, accounting for about half the new cases in the United States.[2]

Angiotensin-converting–enzyme (ACE) inhibitors, which competitively block the renin–angiotensin system, decrease glomerular capillary pressure and prevent the progression of microalbuminuria to overt proteinuria.[3] The results of clinical trials suggest that ACE inhibitors reduce loss of kidney function in persons with diabetic nephropathy, above and beyond any such effect attributable to a reduction in blood pressure.[4,5] At the time the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study was designed (1996), ACE inhibition was first-line treatment for nephropathy in persons with type 1 and type 2 diabetes. The DETAIL study was designed to demonstrate that the renoprotective effect of telmisartan (Micardis, Boehringer Ingelheim), an angiotensin II–receptor blocker, was similar (i.e., not inferior) to that of once-daily enalapril (Innovace, Merck Sharp & Dohme), the most commonly used ACE inhibitor.

Subsequently, three studies examined the use of angiotensin II–receptor blockers in subjects with type 2 diabetes and nephropathy. Two studies evaluated cohorts with overt albuminuria and found that angiotensin II–receptor blockers reduced the number of patients who had progression to end-stage renal failure or a doubling of the serum creatinine level, independently of a reduction in blood pressure.[6,7] The third study, assessing progression from microalbuminuria to albuminuria, reported a beneficial effect associated with angiotensin II–receptor blockade, again independently of a reduction in blood pressure.[8] One study included a comparison with a calcium-channel blocker,[7] but none allowed the use of ACE inhibitors in either the treatment group or control group. Since these data were reported, the Food and Drug Administration has named renal disease in type 2 diabetes an indication for the use of losartan and for the use of irbesartan, and many guidelines recommend use of an angiotensin II–receptor blocker as first-line therapy for diabetic nephropathy.[9]

There is a need for head-to-head comparison of ACE inhibition and angiotensin II–receptor blockade in diabetic nephropathy. The aim of the DETAIL study was thus to compare the effect of telmisartan and enalapril on the change in the glomerular filtration rate (assessed by measuring the plasma clearance of iohexol) over a five-year period.[10]

METHODS

STUDY DESIGN

This prospective, randomized, double-blind, double-dummy, parallel-group study was conducted at 39 centers in northern Europe. It was led by academic investigators and managed and coordinated by an independent scientific steering committee. The protocol was approved by the institutional review board at each center.[11] All the subjects provided written informed consent. Data handling and trial management were supported by Boehringer Ingelheim. The main database was held by the principal investigator (Dr. Barnett), and the statistical analyses, predetermined by the scientific steering committee, were performed by an independent statistical consultant in collaboration with Drs. Barnett and Bain. Drs. Barnett and Bain prepared the manuscript.

SUBJECTS

The subjects could be male or female, white or Asian (as determined by the local investigator), and 35 to 80 years of age. All had to have type 2 diabetes that had been treated by diet, diet plus oral hypoglycemic drugs (for at least one year), or insulin preceded by treatment with oral agents (also for at least one year). Among those whose diabetes was treated with insulin, the onset of diabetes had to have occurred after the age of 40 years and the body-mass index (the weight in kilograms divided by the square of the height in meters) had to be more than 25 at the time of diagnosis. All the subjects had to have mild-to-moderate hypertension, with a resting blood pressure of less than 180/95 mm Hg after at least three months of ACE-inhibitor therapy before entry into the study. Other inclusion criteria included normal renal morphology; a urinary albumin excretion rate (mean of three consecutive overnight values) between 11 and 999 μg per minute, with two values greater than 10 μg per minute; a glycosylated hemoglobin value below 12 percent; a serum creatinine level below 1.6 mg per deciliter (141 μmol per liter); and a glomerular filtration rate

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Table 1. Baseline Characteristics of the Subjects.*

Variable	Telmisartan Group (N=120)	Enalapril Group (N=130)
Age — yr	61.2±8.5	60.0±9.1
Male sex — no. of subjects (%)	87 (72.5)	95 (73.1)
White race — no. of subjects (%)†	118 (98.3)	128 (98.5)
Body-mass index‡	30.8±4.4	30.6±5.1
Blood pressure — mm Hg		
Systolic	152.6±16.6	151.6±15.8
Diastolic	85.4±8.8	85.9±7.8
Heart rate — beats/min	73.6±10.2	75.7±10.0
Duration of hypertension — yr		
Median	8.0	5.5
Range	0–34	0–49
Duration of diabetes — yr		
Median	8.0	8.0
Range	0–25	0–37
History of cardiovascular disease — no. of subjects (%)	59 (49.2)	63 (48.5)
Glomerular filtration rate — ml/min/1.73 m²	91.4±21.5	94.3±22.1
Serum creatinine — mg/dl	1.02±0.21	0.99±0.20
Urinary albumin excretion rate — μg/min		
Median	46.2	60.0
Range	4–1011	9–969
Microalbuminuria — no. of subjects (%)§	98 (81.7)	106 (81.5)
Macroalbuminuria — no. of subjects (%)§	22 (18.3)	23 (17.7)
Cholesterol — mg/dl¶		
Total		
Mean	224±41	222±40
Range	152–344	142–353
High-density lipoprotein		
Mean	48±13	48±12
Range	29–115	17–108
Low-density lipoprotein		
Mean	136±35	137±33
Range	48–249	62–232

above 70 ml per minute per 1.73 m² of body-surface area. Exclusion criteria included any condition (other than cardiovascular disease) that could restrict long-term survival and known allergy to study drugs or iohexol.

RANDOMIZATION AND TREATMENT PLAN

During the one-month screening period, the subjects continued to receive antihypertensive medication, which was required to include an ACE inhibitor. Thereafter, this medication was stopped, and the subjects were randomly assigned at a central location to receive 40 mg of telmisartan once daily or 10 mg of enalapril once daily, with mandatory forced titration after four weeks to 80 mg once daily and 20 mg once daily, respectively. Randomization was based on permuted blocks, with a block size of four. At the discretion of the local investigator, the dose of study drug could be reduced after two months of treatment; a subsequent increase was not permitted.

Additional antihypertensive medication (not an

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Table 1. (Continued.)

Variable	Telmisartan Group (N=120)	Enalapril Group (N=130)
Triglycerides — mg/dl¶		
Mean	202±134	210±136
Range	66–675	50–742
Uric acid — mg/dl¶		
Mean	5.2±1.4	5.2±1.4
Range	2.1–8.4	1.8–8.8
Glycosylated hemoglobin — (%)¶		
Mean	8.4±1.4	8.3±1.5
Range	5.5–11.9	5.5–12.4
Smoking history — no. of subjects (%)		
Never smoked	41 (34.2)	47 (36.2)
Previously smoked	54 (45.0)	55 (42.3)
Currently smokes	25 (20.8)	28 (21.5)
Alcohol use — no. of subjects (%)		
None	29 (24.2)	35 (26.9)
Average	90 (75.0)	94 (72.3)
Excessive	1 (0.8)	1 (0.8)

* Plus–minus values are means ±SD. Differences between the treatment groups were not statistically significant. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for total, high-density lipoprotein, and low-density lipoprotein cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for uric acid to millimoles per liter, multiply by 0.0595.
† Racial group was assigned by the local investigator.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Microalbuminuria is defined as a urinary albumin excretion rate of 200 μg per minute or less and macroalbuminuria as a urinary albumin excretion rate of more than 200 μg per minute.
¶ This variable was not evaluated in all the subjects at baseline.

ACE inhibitor or angiotensin II–receptor blocker) was allowed after two months, if the resting systolic blood pressure exceeded 160 mm Hg or the resting diastolic blood pressure exceeded 100 mm Hg. The target blood pressure was initially less than 160/90 mm Hg, but lower targets were subsequently allowed as local or national guidelines changed during the study. Blood pressure was evaluated after 2 weeks, after 1, 2, 3, 6, 9, and 12 months, and then every 6 months over a 5-year period or until treatment was discontinued. On clinic-visit days, the subjects took their study medication after examination (23 to 26 hours after the previous drug administration) to ensure that blood pressure was measured when antihypertensive drugs were at trough levels. Throughout the study, the treatment of diabetes was at the local investigator's discretion. At each visit, the use of concomitant medication was recorded, and compliance with study treatment was checked by pill count.

END POINTS

All analyses were performed centrally. The primary end point was the change in the glomerular filtration rate (determined by measurement of the plasma clearance of iohexol) after five years.[10] Secondary end points were the annual changes in the glomerular filtration rate, urinary albumin excretion (determined by rate nephelometry, with the use of timed overnight samples obtained on three consecutive nights), the serum creatinine level, and blood pressure; the rates of clinical events (end-stage renal disease, myocardial infarction, stroke, and congestive heart failure); the rate of death from all causes; the rate of adverse events; and laboratory abnormalities.

STATISTICAL ANALYSIS

An analysis-of-covariance model was used to evaluate differences according to treatment with respect to the change in the glomerular filtration rate, with the country and the baseline rate fitted as co-

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variates. The treatment-by-country interaction was also examined. Changes from baseline in the serum creatinine level and log changes in the urinary albumin excretion rate were also compared with the use of analysis of covariance. Analyses included all the randomized subjects. The change in the glomerular filtration rate after five years was based on year 5 values for subjects who completed the study but on the last available values for subjects who dropped out before year 5, with no adjustment in standard errors for this imputation.

A clinically significant difference between the groups in the change in the glomerular filtration rate was predefined as a difference of −10.0 ml per minute per 1.73 m² or more. The standard deviation of the change in the glomerular filtration rate was estimated to be 12.0 ml per minute per 1.73 m², based on the data available in the literature.[5,12,13] It was also noted that the daily change in the glomerular filtration rate can vary by 5 to 10 percent and that the stage of disease at the time of entry into the study would have an effect on this variable. If the lower boundary of the 95 percent confidence interval of the difference between the telmisartan and enalapril groups was greater than −10.0 ml per minute per 1.73 m², in favor of enalapril, then telmisartan was to be judged to be noninferior to the ACE inhibitor. All reported P values were two-sided, and no interim analyses were conducted.

It was determined that 64 evaluable subjects in each treatment group would be required to achieve a power of 95 percent at a one-sided alpha level of 5 percent. Assuming a 25 percent dropout rate per year, a recruitment target of 272 subjects (136 in each treatment group) was set. The alpha level was subsequently changed to 2.5 percent to meet regulatory guidelines,[14] increasing the necessary number of subjects who could be evaluated to 78. However, because the actual dropout rate was lower than the expected annual 25 percent, the recruitment targets were not changed.

RESULTS

The baseline characteristics of the 250 subjects who underwent randomization were similar in the two treatment groups (Table 1). The study was completed by 82 of the 120 subjects in the telmisartan group (68 percent) and 86 of the 130 subjects in the enalapril group (66 percent). In both groups, the most common reason for dropping out was an adverse event. Twenty subjects in the telmisartan group and 30 in the enalapril group had adverse events necessitating discontinuation, despite the fact that all had received ACE-inhibitor therapy for at least three months before the study. An additional 32 subjects (18 in the telmisartan group and 14 in the enalapril group) withdrew for reasons other than adverse events: withdrawal of consent (12 subjects), noncompliance with the protocol (9), lack of efficacy as

Table 2. Concomitant Cardiovascular Medications Used for a Minimum of Six Consecutive Months before and during the Study.*

Medication	Telmisartan Group (N=120)		Enalapril Group (N=130)	
	Before Study	During Study	Before Study	During Study
	number of subjects (percent)			
Any	104 (86.7)	102 (85.0)	122 (93.8)	106 (81.5)
Angiotensin-converting–enzyme inhibitors†	92 (76.7)	NA	110 (84.6)	NA
Diuretics	26 (21.7)	63 (52.5)	29 (22.3)	67 (51.5)
Beta-blockers	23 (19.2)	47 (39.2)	23 (17.7)	51 (39.2)
Calcium-channel blockers	32 (26.7)	55 (45.8)	33 (25.4)	60 (46.1)
Other antihypertensive agents	14 (11.7)	42 (35.0)	18 (13.8)	46 (35.4)
Aspirin	21 (17.5)	44 (36.7)	26 (20.0)	54 (41.5)
Statins	14 (11.7)	51 (42.5)	22 (16.9)	54 (41.5)

* Medications listed as having been taken during the study are in addition to the randomly assigned trial medication. NA denotes not applicable.
† Subjects had to have received an angiotensin-converting–enzyme inhibitor for a minimum of three months before the study.

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judged by the local investigator (3), loss to follow-up (2), and other reasons (6). Subjects who withdrew were followed for an additional 28 days for the assessment of safety. The use of concomitant cardiovascular medications (antihypertensive agents, aspirin, and statins) increased during the study, in keeping with changes in clinical guidelines (Table 2).

PRIMARY END POINT

The glomerular filtration rate was measured at baseline and then yearly for five years or until dropout (whichever occurred first). After baseline, glomerular filtration rates were determined in 216 subjects (103 in the telmisartan group and 113 in the enalapril group). Actual five-year values were available for 62 subjects in the telmisartan group and 74 in the enalapril group, and analyses of values based on the last observation carried forward were performed for all 103 and 113 subjects, respectively, in whom the glomerular filtration rates were determined. Subjects who dropped out before the year 1 visit (10 in the telmisartan group and 15 in the enalapril group) were excluded from the analysis of this end point. Dropout rates were higher in those with macroalbuminuria at baseline than in those with microalbuminuria at baseline (44 percent vs. 29 percent, $P=0.04$). After five years, the mean change in the glomerular filtration rate was −17.9 ml per minute per 1.73 m² (where the minus sign denotes a decrement) in the telmisartan-treated subjects, as compared with −14.9 ml per minute per 1.73 m² in the enalapril-treated subjects; the treatment difference was thus −3.0 ml per minute per 1.73 m² (95 percent confidence interval, −7.6 to 1.6 ml per minute per 1.73 m²). The lower boundary of −7.6, in favor of enalapril, was greater than the predefined value of −10.0, indicating that telmisartan was not inferior to enalapril.

Of the 168 subjects who completed the five-year follow-up, 32 did not have valid year 5 data for the glomerular filtration rate, mainly because the assay was performed after discontinuation of the study medication. Analysis of the change in the glomerular filtration rate in the subgroup of 136 subjects who completed the study showed a mean change of −18.7 ml per minute per 1.73 m² in telmisartan-treated subjects, as compared with −15.8 ml per minute per 1.73 m² in enalapril-treated subjects (95 percent confidence interval for the difference, −9.2 to 3.4 ml per minute per 1.73 m²), a finding consistent with the noninferiority of telmisartan relative to enalapril.

SECONDARY END POINTS

Renal Variables

Annual changes from baseline in the glomerular filtration rate for the analysis of the last observation carried forward and for actual five-year values are shown in Figure 1. The rates of decrease in the glomerular filtration rate — 7.6, 5.6, and 3.6 ml per minute per 1.73 m² in years 1, 2, and 3, respectively, and negligible in years 4 and 5 — were similar in the two groups. The changes in secondary renal end points after five years are summarized in Table 3. The annual changes in the urinary albumin

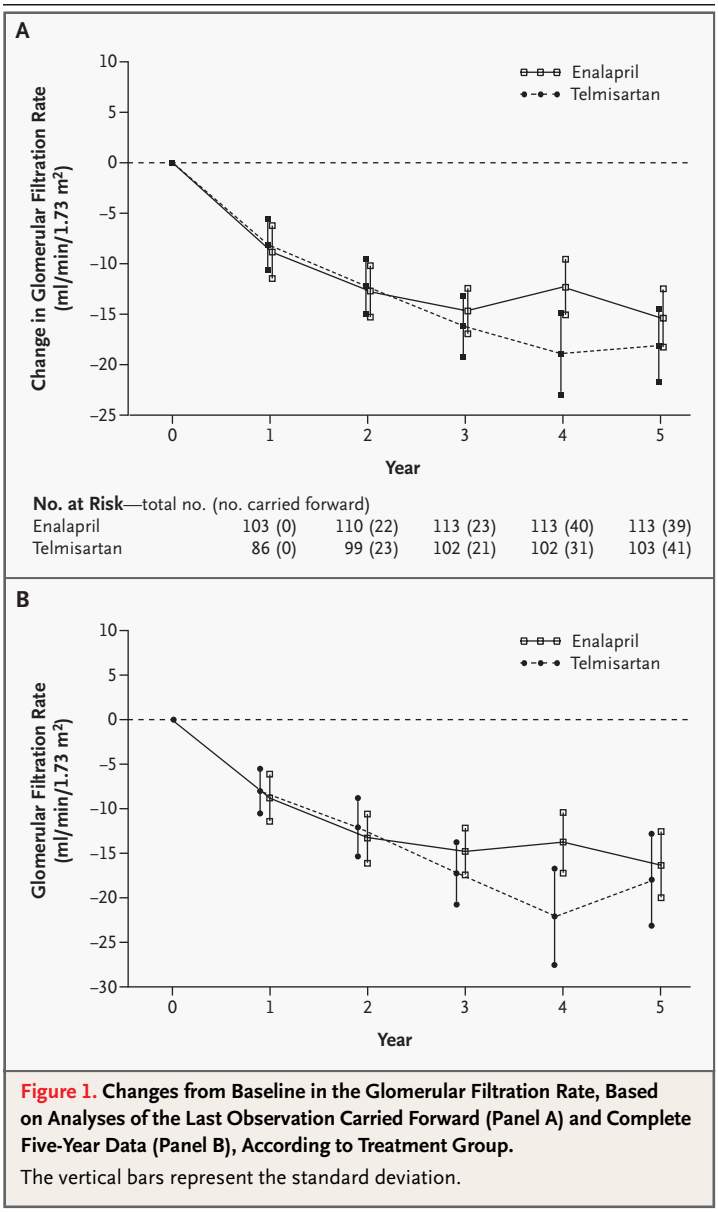

Figure 1. Changes from Baseline in the Glomerular Filtration Rate, Based on Analyses of the Last Observation Carried Forward (Panel A) and Complete Five-Year Data (Panel B), According to Treatment Group.

The vertical bars represent the standard deviation.

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Table 3. Secondary Renal End Points after Five Years of Treatment, According to Analysis of the Last Observation Carried Forward.*

End Point	Change from Baseline		Difference between Groups (95% CI)
	Telmisartan Group	Enalapril Group	
Serum creatinine (mg/dl)	0.10	0.10	0 (–0.66 to 0.65)
Urinary albumin excretion (ratio)†	1.03	0.99	1.04 (0.71 to 1.51)‡

* One hundred sixteen subjects (35 with the last observation carried forward) in the telmisartan group and 128 (44 with the last observation carried forward) in the enalapril group were included in the analysis of serum creatinine, and 115 (35 with the last observation carried forward) and 125 (42 with the last observation carried forward), respectively, were included in the analysis of urinary albumin excretion.

† Urinary albumin excretion rates were determined as the ratio of the final value to the baseline value.

‡ The ratio of the difference between treatment groups is shown. Because of the skewed distribution of the albumin excretion rate, the log analysis (when log values are converted back to nonlog values, or "anti-logged") yields treatment ratios, both for treatment means (ratio of year 5 value to baseline value) and treatment differences (ratio of telmisartan to enalapril).

excretion rate were highly variable, with large 95 percent confidence intervals; the overall change in both groups was small. The effects of telmisartan on the change in the serum creatinine level from baseline and the percentage change in urinary albumin excretion were not significantly different from the effects of enalapril on those variables.

Blood-Pressure Changes

Forced titration of the study drugs meant that 93 percent of subjects assigned to telmisartan received a dose of 80 mg daily and 93 percent of the subjects assigned to enalapril received a dose of 20 mg daily. Reductions from baseline in systolic and diastolic blood pressure were observed over five years (Fig. 2). The adjusted mean reduction in systolic blood pressure with telmisartan was 6.9 mm Hg, as compared with 2.9 mm Hg with enalapril (95 percent confidence interval, –8.5 to 0.5 mm Hg). At the end of the study, 75 percent of the subjects had a systolic pressure of less than 160 mm Hg and 42 percent had a systolic pressure of less than 140 mm Hg; there was no significant difference between groups in this respect.

SAFETY

Adverse events occurred in 115 subjects in the telmisartan group and in all 130 subjects in the enalapril group, leading to study discontinuation in 20 subjects (17 percent) and 30 subjects (23 percent), respectively. In each group, there were six strokes and two cases of a raised serum creatinine level (in both, to less than 2.3 mg per deciliter [200 μmol per liter]). In the telmisartan group, nine cases of congestive heart failure and nine nonfatal myocardial infarctions occurred. In the enalapril group, seven subjects had congestive heart failure, and six had a nonfatal myocardial infarction. During the study, six deaths occurred in each treatment group. In the telmisartan group, cardiovascular events (stroke, myocardial infarction, or cardiac insufficiency) accounted for three of the deaths; in the enalapril group, myocardial infarction accounted for two. There were no changes in routine hematologic or blood chemical values in either group.

DISCUSSION

In this long-term, head-to-head comparison of renal outcomes with the use of an angiotensin II–receptor blocker and an ACE inhibitor in subjects with type 2 diabetes and early nephropathy, we determined that telmisartan was not inferior to enalapril in preventing the progression of renal dysfunction, measured as the decline in the glomerular filtration rate. A decline in the glomerular filtration rate is a key determinant of end-stage renal disease, and measurement in terms of iohexol clearance is regarded as highly accurate.

In the design of the DETAIL study, a high dropout rate was anticipated. It was predicted to be 25 percent per year on the basis of reports of high rates of cardiovascular events in subjects with type 2 diabetes and increased urinary albumin excretion.[15-18] In the current study, almost 50 percent of the subjects had a baseline history of cardiovascular disease, but there were few cardiovascular events in either treatment group and 12 deaths among subjects taking study medication. Nevertheless, there was a high dropout rate (approximately one third), mainly because of adverse events; half of these subjects left the study within the first two years. Subjects who left the study were followed for an additional 28 days, but data were not collected thereafter. Since the number of dropouts and reasons for withdrawal were similar in the two treatment groups, we believe our estimates of the change in the glomerular filtration rate at year 5 are similar to those based on data from the subjects who completed the study. However, we acknowledge that imputing data may narrow the confidence intervals and hence bias the

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result toward noninferiority. For this reason, we have performed additional analyses — for example, by estimating missing data that include the anticipated decline in the glomerular filtration rate over the study period or by using off-medication glomerular filtration rates. All of these analyses, including the analysis of subjects who completed the study, support the noninferiority outcome.

The high dropout rate, however, may have influenced some study outcomes. For example, the decrease in the glomerular filtration rate was greatest during the initial year of the study. Although this effect is commonly seen when patients first begin taking ACE inhibitors, all the subjects had received an ACE inhibitor before randomization. This initial decrease may have been a true effect; however, another explanation is that subjects with the largest decreases in the glomerular filtration rate were more likely to withdraw from the study, leading to a more gradual change in the slope of the decline.

This contention is supported by the observation that dropouts were overrepresented in the subgroup with the highest albumin excretion rate at baseline. Unfortunately, in most of the subjects who dropped out, the glomerular filtration rate was measured only once, at year 1, rendering it impossible to assess their subsequent rates of decline. Another confounder is an effect of the analysis based on the last observation carried forward. Because of the typical decline in the glomerular filtration rate over time, carrying forward data points tends to raise the level of the glomerular-filtration-rate plot. Finally, an effect of concomitant cardiovascular therapies cannot be ruled out.

In comparison with recent long-term outcome studies of diabetic nephropathy, the cohort in the DETAIL study is most like that of the study by Parving et al.,[8] in which the subjects had a similar age, duration of diabetes, blood pressure, and urinary albumin excretion. In that large cohort of subjects with microalbuminuria, irbesartan (300 mg once daily) exerted a renoprotective effect that was independent of a reduction in blood pressure; over a two-year period, diabetic nephropathy (defined as an albumin excretion rate above 200 μg per minute and at least 30 percent higher than the baseline value) developed in 5.2 percent of the treated subjects. Applying the same end point to our own, longer-term study, microalbuminuria progressed in 17 percent of our subjects over the five-year study period, although this result must be interpreted with caution given the absence of follow-up data for subjects who dropped out. The results with respect to renoprotection in the current study are consistent with those reported by Parving and colleagues, who described a rapid early decline in creatinine clearance and a low rate of death from cardiovascular causes.[8]

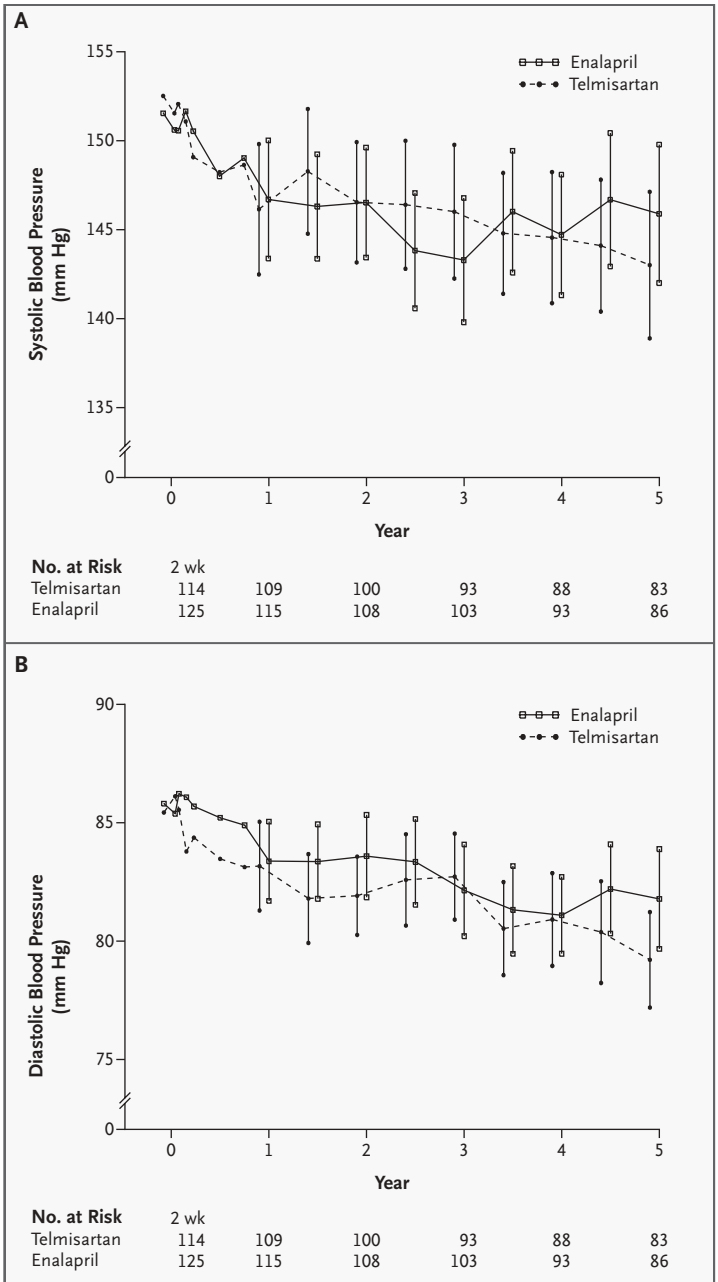

Figure 2. Changes from Baseline in Systolic Blood Pressure (Panel A) and Diastolic Blood Pressure (Panel B), According to Treatment Group.

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To our knowledge, there has been one clinical study that has directly compared the effect of an angiotensin II–receptor blocker (losartan) with that of an ACE inhibitor (enalapril) in subjects with type 2 diabetes and early nephropathy.[19] That short-term study indicated that both drugs reduced urinary albumin excretion; differences between the treatments were not significant. Three other studies have compared treatment with an angiotensin II–receptor blocker and an ACE inhibitor, two in patients who had had a myocardial infarction and one in patients who had heart failure.[20-22] In these studies, the ACE inhibitor captopril, administered three times daily (titrated to a dose of 50 mg three times daily), was compared with once-daily losartan (50 mg) or twice-daily valsartan (160 mg). In all three trials, the two drug classes had an equivalent effect on the primary end point: the rate of death from all causes. The nonsuperiority of losartan was attributed to the low dose used,[20,21] although this reason could not be cited in the study involving valsartan.[22] Likewise, in the DETAIL study, the forced-titration regimen led to use of the maximal recommended telmisartan dose in more than 90 percent of the subjects.

Taken together, our data indicate that telmisartan is not inferior to enalapril in providing renoprotection in subjects with type 2 diabetes and early nephropathy. This result is consistent with emerging data that support the clinical equivalence of angiotensin II–receptor blockers and ACE inhibitors in various conditions associated with high cardiovascular risk.

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APPENDIX

The following persons participated in the DETAIL study: Scientific Steering Committee: A.H. Barnett (chair), S.C. Bain, P. Bouter, B. Karlberg, S. Madsbad, J. Jervell, and J. Mustonen. Investigators: *Denmark* — O. Ortved Andersen, J. Faber, K. Kolendorf, T. Krarup, S. Madsbad, A. Prange Hansen, and O. Snorgaard; *Finland* — H. Jarvinen, L. Juurinen, J. Mustonen, L Niskanen, and J. Saltevo; *the Netherlands* — K.P. Bouter and H. de Valk; *Norway* — A. Fehn, K. Furuseth, G. Mouland, P. Olsen, and S. Skeie; *Sweden* — P. Andersson, A. Hanni, U. Hollertz, P. Katzman, A. Sjostrand, P. Sjostrom, C. Voss, A. Tisell, and S. Wide; *United Kingdom* — S.C. Bain, A.H. Barnett, D. Cavan, C. Fox, J. Gill, G. Gooding, S. Marshall, S. Matthews, C. Morgan, P. O'Hare, and R. Ryder.

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