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## Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events

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### ABSTRACT

#### BACKGROUND

In patients who have vascular disease or high-risk diabetes without heart failure, angiotensin-converting-enzyme (ACE) inhibitors reduce mortality and morbidity from cardiovascular causes, but the role of angiotensin-receptor blockers (ARBs) in such patients is unknown. We compared the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes.

#### METHODS

After a 3-week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

#### RESULTS

Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mm Hg greater reduction) and the combination-therapy group (a 2.4/1.4 mm Hg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94 to 1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%,  $P<0.001$ ) and angioedema (0.1% vs. 0.3%,  $P=0.01$ ) and a higher rate of hypotensive symptoms (2.6% vs. 1.7%,  $P<0.001$ ); the rate of syncope was the same in the two groups (0.2%). In the combination-therapy group, the primary outcome occurred in 1386 patients (16.3%; relative risk, 0.99; 95% CI, 0.92 to 1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%,  $P<0.001$ ), syncope (0.3% vs. 0.2%,  $P=0.03$ ), and renal dysfunction (13.5% vs. 10.2%,  $P<0.001$ ).

#### CONCLUSIONS

Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit. (ClinicalTrials.gov number, NCT00153101.)

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\*The Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial (ONTARGET) investigators are listed in the Appendix.

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**R**ANDOMIZED, CONTROLLED TRIALS INVOLVING about 150,000 patients have convincingly demonstrated that angiotensin-converting–enzyme (ACE) inhibitors reduce rates of death, myocardial infarction, stroke, and heart failure among patients with heart failure,<sup>1</sup> left ventricular dysfunction,<sup>2-4</sup> previous vascular disease alone,<sup>5-7</sup> or high-risk diabetes.<sup>8</sup> ACE inhibitors do not block the production of all angiotensin II, so direct receptor blockade might be more effective. ACE inhibitors reduce bradykinin degradation, which enhances vasodilatation, but increase the rates of angioedema and cough. In patients with heart failure, angiotensin II levels may increase and symptoms worsen, despite the use of ACE inhibitors.<sup>9</sup> The use of an angiotensin-receptor blocker (ARB), as compared with placebo, reduced the rate of death or hospitalization for heart failure in patients with a low ejection fraction and heart failure who either could not tolerate an ACE inhibitor<sup>10</sup> or were already receiving one.<sup>11,12</sup> As compared with beta-blockers, ARBs also reduced vascular events in high-risk patients with hypertension and left ventricular hypertrophy.<sup>13</sup> Nevertheless, in other high-risk populations, the role of ARBs as an alternative or in addition to ACE inhibitors to prevent cardiovascular outcomes is not known.

We evaluated whether the ARB telmisartan was not inferior to the ACE inhibitor ramipril and whether a combination of the two drugs was superior to ramipril alone as a treatment to prevent vascular events in high-risk patients who had cardiovascular disease or diabetes mellitus but did not have heart failure. We used a dose of ramipril that had previously been shown to be effective for this outcome.

## METHODS

### STUDY DESIGN

The design of the study has been described previously.<sup>14</sup> We enrolled patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage. Patients who could not tolerate ACE inhibitors were randomly assigned to receive either telmisartan or placebo in a parallel trial.<sup>14</sup> Detailed eligibility criteria have also been described previously<sup>14</sup> (for details, see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). The primary objectives of our study were to determine the effectiveness of 80 mg of telmisartan daily, as com-

pared with 10 mg of ramipril daily. If the noninferiority of telmisartan was demonstrated, we would test the superiority of telmisartan over ramipril. We would also determine whether the combination of the two drugs was more effective than ramipril alone in reducing the composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.

The main secondary outcome was a composite of death from cardiovascular causes, myocardial infarction, or stroke, which was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.<sup>5</sup> Other secondary outcomes were new heart failure, diabetes mellitus, atrial fibrillation, dementia or cognitive decline, nephropathy, and revascularization procedures. Other outcomes were death from any cause or from noncardiovascular causes, angina, transient ischemic attack, development of left ventricular hypertrophy, microvascular complications of diabetes, changes in blood pressure or in the ankle-to-arm ratio of blood pressure, and new cancers.

National coordinators and clinical monitors supervised the recruitment of patients at 733 centers in 40 countries. The trial was coordinated and data were gathered and analyzed by the Population Health Research Institute at McMaster University and Hamilton Health Sciences, with coordinating suboffices at Oxford University and the University of Auckland. The steering committee designed and oversaw the trial. An operations committee, with representatives from the three coordinating centers and the sponsor (Boehringer Ingelheim), met regularly to evaluate progress.

All main study outcomes (death according to any cause, myocardial infarction, stroke, and hospitalization for heart failure) were adjudicated by a central committee whose members were unaware of study-group assignments, with the use of standard criteria.<sup>14</sup> All serious adverse events were reviewed by an independent data and safety monitoring board.

The initial draft of the manuscript was written by Dr. Yusuf and the writing committee, who vouch for the data, with input from the steering committee. The protocol was approved by regulatory authorities and the ethics review committee at each participating institution.

### RUN-IN PERIOD AND RANDOMIZATION

After written informed consent was obtained, patients entered a single-blind run-in period in which

they received 2.5 mg of ramipril once daily for 3 days, followed by 40 mg of telmisartan and 2.5 mg of ramipril once daily for 7 days and then 5 mg of ramipril plus 40 mg of telmisartan for 11 to 18 days. Of the 29,019 patients who entered the run-in period, 3399 (11.7%) were excluded from the study: 1123 (3.9%) had poor compliance, 597 (2.1%) withdrew from the study, 492 (1.7%) had symptomatic hypotension, 223 (0.8%) had an elevated potassium level, 64 (0.2%) had an elevated creatinine level, 872 (3.0%) had other reasons for exclusion, and 27 (0.1%) died.

A total of 25,620 patients underwent randomization and were stratified according to site with the use of permuted blocks through a central automated telephone service. For the first 2 weeks after randomization, 8542 patients were assigned to receive 80 mg of telmisartan once daily, 8576 were assigned to receive 5 mg of ramipril once daily, and 8502 were assigned to receive a combination of the two drugs (combination therapy). After 2 weeks, the dose of ramipril was increased to 10 mg per day. Follow-up visits occurred at 6 weeks, at 6 months, and then every 6 months until the last scheduled visit.

#### INTERIM ANALYSIS AND DATA MONITORING

An independent data and safety monitoring board of cardiologists, statisticians, and clinical-trial experts met twice yearly; three formal interim analyses were conducted when 25%, 50%, and 75% of the events accrued. A modified Haybittle–Peto approach<sup>15</sup> guided decisions (i.e., a boundary of 4 SD in the first half of the trial and 3 SD in the second half for efficacy; for safety, if boundaries of 3 SD and 2 SD, respectively, were crossed in a second analysis 4 to 6 months later, it would trigger consideration of stopping).

#### STATISTICAL ANALYSIS

The number of patients was based on the rate of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure associated with ramipril in the HOPE trial, in which the Kaplan–Meier estimate for the primary outcome was 0.0397 per year. A determination of noninferiority required a hazard ratio for telmisartan as compared with ramipril that was below a predefined margin, with most of ramipril's effect, as compared with placebo, retained by telmisartan.

The margin was determined by the results of the HOPE trial, in which the hazard ratio with

10 mg of ramipril, as compared with placebo, was 0.775 for a composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure; this was similar to the hazard ratios in other studies comparing ACE inhibitors with placebo.<sup>6,7</sup> We chose the 40th percentile (0.794) as a more robust reference to describe the effect of ramipril. The relative risk was translated into an excess risk for placebo as compared with ramipril of 1.26. Thus, a margin of 1.13 ensured that telmisartan retained at least half the effect of ramipril, if the upper limit of the one-sided 97.5% confidence interval for the hazard ratio was less than this value. We also evaluated whether the combination of telmisartan plus ramipril was superior to ramipril alone.

We tested both hypotheses using group sequential tests with a one-sided type I error of 0.025, with three planned interim analyses. If one of the two comparisons did not reject the null hypothesis, the other comparison needed an alpha of 0.0125. The original planned sample size of 7800 patients who were followed for a mean of 4.5 years provided a power of 93% for the superiority hypothesis, if the hazard ratio was 0.87. For noninferiority, the expected power was 89%, for a hazard ratio of 1.00.

The primary analysis used a time-to-event approach, counting the first occurrence of any component of the composite outcome, and included all randomized patients. All reported P values (other than for noninferiority) are two-sided. Consistency of treatment effects in prespecified subgroups was explored by the Cox regression model, with tests for interaction.<sup>16,17</sup> We performed a sensitivity analysis according to the protocol by censoring data from patients who took the study drugs for less than 50% of the study period.

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## RESULTS

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#### CHARACTERISTICS OF THE PATIENTS

Characteristics of the 25,620 patients who underwent randomization were similar in the three study groups (Table 1); 27% were women, 85% had cardiovascular disease, 69% had hypertension, and 38% had diabetes. A high proportion of patients had previously received proven therapies: statins (61.6% at baseline, increasing to 70.6% by the end of the study), antiplatelet therapy (80.9% and 77.5%, respectively), beta-blockers (56.9% and 56.9%), and diuretics (28.0% and 32.5%).

<b>Table 1. Baseline Characteristics of the Patients.*</b>			
<b>Characteristic</b>	<b>Ramipril (N=8576)</b>	<b>Telmisartan (N=8542)</b>	<b>Combination Therapy (N=8502)</b>
Age — yr	66.4±7.2	66.4±7.1	66.5±7.3
Blood pressure — mm Hg†	141.8±17.4/82.1±10.4	141.7±17.2/82.1±10.4	141.9±17.6/82.1±10.4
Heart rate — beats/min	67.9±12.2	68.0±12.3	67.7±12.2
Body-mass index‡	28.1±4.5	28.1±4.6	28.0±4.5
Cholesterol — mmol/liter			
Total	4.9±1.1	4.9±1.1	5.0±1.2
LDL	2.9±1.0	2.9±1.0	2.9±1.0
HDL	1.3±0.4	1.3±0.4	1.3±0.4
Triglycerides — mmol/liter	1.7±1.1	1.7±1.1	1.7±1.1
Glucose — mmol/liter	6.7±2.6	6.7±2.5	6.7±2.6
Creatinine — μmol/liter	93.5±22.8	93.8±22.8	93.8±22.8
Potassium — mmol/liter	4.4±0.4	4.4±0.4	4.4±0.5
Female sex — no. (%)	2331 (27.2)	2250 (26.3)	2250 (26.5)
Ethnic group — no. (%)§			
Asian	1182 (13.8)	1172 (13.7)	1167 (13.7)
Arab	102 (1.2)	106 (1.2)	106 (1.2)
African	206 (2.4)	215 (2.5)	208 (2.4)
European	6273 (73.1)	6213 (72.7)	6222 (73.2)
Native or aboriginal	747 (8.7)	756 (8.9)	728 (8.6)
Other ethnic group	64 (0.7)	77 (0.9)	69 (0.8)
Missing data	2 (<0.1)	3 (<0.1)	2 (<0.1)
Clinical history — no. (%)			
Coronary artery disease	6382 (74.4)	6367 (74.5)	6353 (74.7)
Myocardial infarction	4146 (48.3)	4214 (49.3)	4189 (49.3)
Angina pectoris			
Stable	3039 (35.4)	2958 (34.6)	2960 (34.8)
Unstable	1257 (14.7)	1296 (15.2)	1264 (14.9)
Stroke or transient ischemic attacks	1805 (21.0)	1758 (20.6)	1779 (20.9)
Peripheral artery disease	1136 (13.2)	1161 (13.6)	1171 (13.8)
Hypertension	5918 (69.0)	5862 (68.6)	5827 (68.5)
Diabetes	3146 (36.7)	3246 (38.0)	3220 (37.9)
Left ventricular hypertrophy	1085 (12.7)	1120 (13.1)	1082 (12.7)
Microalbuminuria¶	929 (13.1)	923 (13.2)	929 (13.3)
Previous procedures — no. (%)			
Coronary-artery bypass grafting	1862 (21.7)	1920 (22.5)	1893 (22.3)
Percutaneous transluminal coronary angioplasty	2527 (29.5)	2476 (29.0)	2434 (28.6)
Smoking status — no. (%)			
Current smoker	1062 (12.4)	1062 (12.4)	1101 (12.9)
Past smoker	4463 (52.0)	4468 (52.3)	4345 (51.1)

**Table 1. (Continued.)**

Characteristic	Ramipril (N = 8576)	Telmisartan (N = 8542)	Combination Therapy (N = 8502)
Medication — no. (%)			
Statin	5234 (61.0)	5294 (62.0)	5255 (61.8)
Beta-blocker	4847 (56.5)	4860 (56.9)	4876 (57.4)
Aspirin	6473 (75.5)	6469 (75.7)	6461 (76.0)
Clopidogrel or ticlopidine	927 (10.8)	966 (11.3)	931 (11.0)
Antiplatelet agent	6903 (80.5)	6926 (81.1)	6898 (81.1)
Diuretic	2454 (28.6)	2359 (27.6)	2351 (27.7)
Calcium-channel blocker	2821 (32.9)	2787 (32.6)	2864 (33.7)

\* Plus-minus values are means ±SD. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein.

† A total of 13,386 patients had a systolic blood pressure of more than 140 mm Hg.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Ethnic group was self-reported.

¶ The percentage is based on 21,074 patients who underwent baseline urinary analysis: 7073 patients in the ramipril group, 7013 patients in the telmisartan group, and 6988 patients in the combination-therapy group.

**FOLLOW-UP AND ADHERENCE**

A total of 25,577 patients (99.8%) were followed until a primary event occurred or until the end of the study (median, 56 months). Among patients in the ramipril group, 92.2% were taking an ACE inhibitor and 1.0% were taking an ARB at 1 year, with respective proportions of 89.4% and 1.8% at 2 years, 87.5% and 2.0% at 3 years, 86.6% and 2.4% at 4 years, and 84.7% and 3.3% at the end of the study. Among patients in the telmisartan group, 93.9% were taking an ARB and 2.6% were taking an ACE inhibitor at 1 year, with respective proportions of 91.2% and 4.2% at 2 years, 89.3% and 4.6% at 3 years, 87.7% and 5.0% at 4 years, and 85.6% and 6.4% at the end of the study. Among patients in the combination-therapy group, 85.5% received both drugs, 2.8% received an ACE inhibitor only, and 3.5% received an ARB only at 1 year; the respective proportions were 81.5%, 4.2%, and 4.8% at 2 years; 78.7%, 4.5%, and 5.4% at 3 years; 76.8%, 4.7%, and 5.7% at 4 years; and 73.6%, 6.0%, and 6.4% at the end of the study.

The proportion of patients receiving the full dose of ramipril at 2 years was 81.7% in the ramipril group and 75.3% in the combination-therapy group. The proportion of patients receiving the full dose of telmisartan at 2 years was 88.6% in the telmisartan group and 84.3% in the combination-therapy group. The study drug was discontinued by 2029 patients (23.7%) in the ramipril group and 1796 (21.0%) in the telmisartan group. In the combination-therapy group, 1929

patients (22.7%) discontinued both drugs, and an additional 566 (6.7%) stopped taking one drug.

The most important reasons for permanent discontinuation of a study drug are summarized in Table 2. More patients discontinued ramipril (either as monotherapy or with telmisartan) because of cough or angioedema than discontinued telmisartan alone. In the combination-therapy group, an increased number of patients stopped taking a study drug because of hypotensive symptoms, syncope, diarrhea, or renal impairment, as compared with the ramipril groups.

**BLOOD PRESSURE, POTASSIUM, AND CREATININE**

Before the run-in period, the mean blood pressure was 141.8/82.1 mm Hg. At 6 weeks, the mean blood pressure was reduced by 6.4/4.3 mm Hg in the ramipril group, by 7.4/5.0 mm Hg in the telmisartan group, and by 9.8/6.3 mm Hg in the combination-therapy group. Patients in the telmisartan group and the combination-therapy group continued to have slightly lower blood-pressure levels throughout the study period (average reductions, 0.9/0.6 mm Hg and 2.4/1.4 mm Hg, respectively) than did patients in the ramipril group. The numbers of patients who had a doubling of the creatinine level were similar in the three groups (159 in the ramipril group, 170 in the telmisartan group, and 180 in the combination-therapy group). The numbers of patients who had an increase in the potassium level of more than 5.5 mmol per liter were similar in the ramipril group (283 pa-

**Table 2. Discontinuation of Study Medications and Selected Reasons for Permanent Discontinuation.\***

Variable	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril		Combination Therapy vs. Ramipril	
				Relative Risk	P Value	Relative Risk	P Value
	<i>number (percent)</i>						
Total no. of discontinuations†	2099 (24.5)	1962 (23.0)	2495 (29.3)	0.94	0.02	1.20	<0.001
Reason for permanent discontinuation							
Hypotensive symptoms	149 (1.7)	229 (2.7)	406 (4.8)	1.54	<0.001	2.75	<0.001
Syncope	15 (0.2)	19 (0.2)	29 (0.3)	1.27	0.49	1.95	0.03
Cough	360 (4.2)	93 (1.1)	392 (4.6)	0.26	<0.001	1.10	0.19
Diarrhea	12 (0.1)	19 (0.2)	39 (0.5)	1.59	0.20	3.28	<0.001
Angioedema	25 (0.3)	10 (0.1)	18 (0.2)	0.4	0.01	0.73	0.30
Renal impairment	60 (0.7)	68 (0.8)	94 (1.1)	1.14	0.46	1.58	<0.001

\* There were no predefined criteria for each of the adverse events listed. Reasons listed are those provided by the investigator for the discontinuation of study drug.

† A patient could have multiple discontinuations, since patients were encouraged to restart study medications whenever possible after discontinuation.

tients) and the telmisartan group (287 patients), but the number was significantly higher in the combination-therapy group (480 patients,  $P<0.001$  for the comparison between the combination-therapy group and the ramipril group).

#### PRIMARY OUTCOMES AND DEATH

The primary outcome occurred in 1412 patients (16.5%) in the ramipril group, in 1423 patients (16.7%) in the telmisartan group, and in 1386 patients (16.3%) in the combination-therapy group (Fig. 1 and 2 and Table 3). The upper boundary of the confidence interval (1.09) for the relative risk of the primary outcome in the telmisartan group as compared with the ramipril group was significantly lower than the predefined noninferiority boundary of 1.13 ( $P=0.004$ ). However, the lower boundary of the confidence interval (0.94) indicates that telmisartan was not superior to ramipril. The secondary outcome — death from cardiovascular causes, myocardial infarction, or stroke — occurred in 1210 patients (14.1%) in the ramipril group and in 1190 patients (13.9%) in the telmisartan group (relative risk, 0.99; 95% confidence interval [CI], 0.91 to 1.07;  $P=0.001$  for noninferiority). The results were consistent for all components of the primary outcome. Combination therapy was not significantly better than ramipril alone (relative risk, 0.99; 95% CI, 0.92 to 1.07). Adjustments for the small differences in

blood pressure did not materially alter the results for the primary outcome (relative risk for telmisartan vs. ramipril, 1.02; 95% CI, 0.95 to 1.10; relative risk for combination therapy vs. ramipril, 1.00; 95% CI, 0.93 to 1.07).

There was no significant difference in the total number of deaths between the ramipril group and the telmisartan group (1014 deaths and 989 deaths, respectively; relative risk in the telmisartan group, 0.98; 95% CI, 0.90 to 1.07); the number of deaths was higher in the combination-therapy group than in the ramipril group (1065 deaths vs. 1014 deaths; relative risk in the combination-therapy group, 1.07; 95% CI, 0.98 to 1.16), but the difference was not significant. Analyses of the cause of death did not indicate significant differences with respect to any particular cause (data not shown).

#### SECONDARY AND OTHER OUTCOMES

There were no significant differences in the rates of secondary outcomes (Table 4), except for renal dysfunction, which occurred in 871 patients (10.2%) in the ramipril group, 906 patients (10.6%) in the telmisartan group, and 1148 patients (13.5%) in the combination-therapy group. As compared with the ramipril group, the telmisartan group had a similar relative risk of renal impairment (1.04), whereas the combination-therapy group had a significant increase in the relative risk (1.33,

P<0.001). The rate of renal dialysis was the same in the ramipril group and the telmisartan group, with 48 patients (0.6%) and 52 patients (0.6%), respectively, undergoing dialysis, whereas the rate was increased in the combination-therapy group, with 65 patients (0.8%) undergoing dialysis (P=0.10 for the comparison with the ramipril group).

**SUBGROUP ANALYSES**

Comparisons of key subgroups showed similar results between the ramipril group and the telmisartan group (Fig. 3A) and between the ramipril group and the combination-therapy group (Fig. 3B). The results for both comparisons were also consistent in analyses that were adjusted for the patients' use of various concomitant drugs (e.g., statins, antiplatelet agents, beta-blockers, diuretics, and calcium-channel blockers) (data not shown).

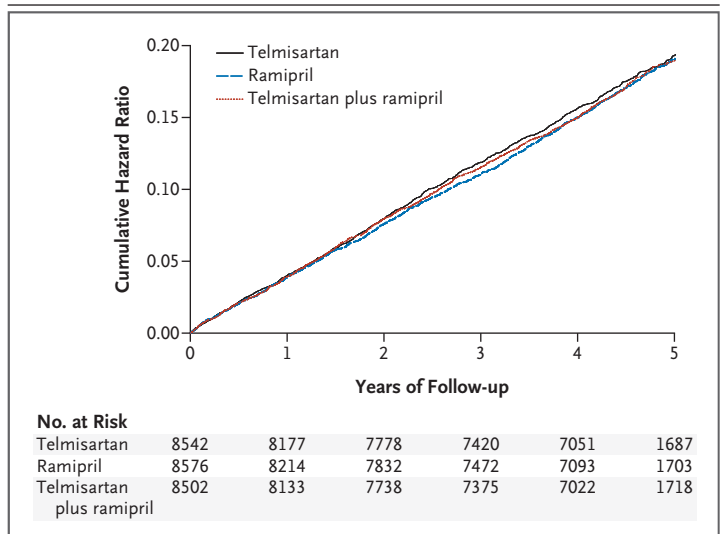
**PER-PROTOCOL ANALYSIS**

For the primary outcome with telmisartan as compared with ramipril, the per-protocol analysis showed a relative risk of 1.00 (95% CI, 0.92 to 1.09; P=0.006 for noninferiority). Analyses comparing combination therapy with ramipril showed results similar to those of the intention-to-treat analysis (relative risk, 0.98; 95% CI, 0.90 to 1.07).

**DISCUSSION**

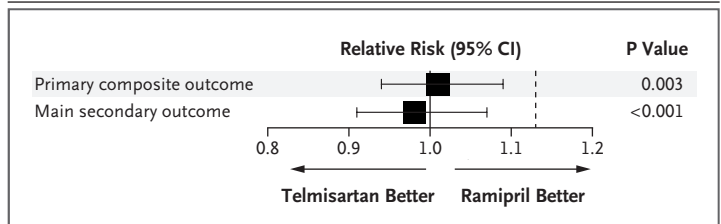
ACE inhibitors have been convincingly shown to reduce rates of death, myocardial infarction, stroke, heart failure, and revascularization among patients with previous cardiovascular disease and high-risk diabetes. Therefore, to provide clinically relevant information, trials evaluating ARBs in these patients must include proven doses of an ACE inhibitor, either as background therapy or as a comparator.

In our study, we evaluated both approaches in a population similar to the one studied in the HOPE trial. Telmisartan was clearly not inferior to ramipril for both the prespecified primary outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure and for the primary outcome in the HOPE trial (death from cardiovascular causes, myocardial infarction, or stroke). Similarities in the telmisartan group and the ramipril group in the proportions of patients who had heart failure, underwent revascularization, or had renal dysfunction (outcomes that were reduced by



**Figure 1. Kaplan–Meier Curves for the Primary Outcome in the Three Study Groups.**

The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure.



**Figure 2. Relative Risk of the Primary Outcome and of the Main Secondary Outcome.**

The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. The main secondary outcome was death from cardiovascular causes, myocardial infarction, or stroke, which was used as the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.<sup>5</sup> The P value is for the comparison with the noninferiority margins.

ramipril in the HOPE trial) and the high rates of adherence to both drug regimens provided additional confidence in establishing the noninferiority of telmisartan. As compared with the ramipril group, the telmisartan group had significantly fewer episodes of cough or angioedema, but this benefit was partially offset by higher rates of hypotensive symptoms (but not syncope). Higher rates of hypotension-related symptoms are consistent with the slightly lower blood-pressure levels associated with telmisartan, although the lower levels did not lead to further benefit. The

**Table 3. Incidence of the Primary Outcome, Its Components, and Death from Any Cause.**

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	
				number (percent)	risk ratio (95% CI)
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94–1.09)	0.99 (0.92–1.07)
Death from cardiovascular causes, myocardial infarction, or stroke†	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91–1.07)	1.00 (0.93–1.09)
Myocardial infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79–1.05)	0.93 (0.81–1.07)
Hospitalization for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97–1.29)	0.95 (0.82–1.10)
Death from cardiovascular causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Death from noncardiovascular causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83–1.10)	1.10 (0.96–1.26)
Death from any cause	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90–1.07)	1.07 (0.98–1.16)

\* Patients could have multiple events in this category. The numbers of events were 2058 (24.0%) in the ramipril group, 2042 (23.9%) in the telmisartan group, and 2000 (23.5%) in the combination-therapy group. The differences were not significant ( $P=0.83$  for telmisartan vs. ramipril, and  $P=0.38$  for combination therapy vs. ramipril).

† This composite was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.<sup>5</sup>

‡ Patients could have multiple events in this category. The category includes both fatal and nonfatal events.

**Table 4. Secondary and Other Outcomes.**

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	
				number (percent)	relative risk (95% CI)
Revascularization	1269 (14.8)	1290 (15.1)	1303 (15.3)	1.03 (0.95–1.11)	1.04 (0.97–1.13)
Hospitalization for angina	925 (10.8)	954 (11.2)	952 (11.2)	1.04 (0.95–1.14)	1.04 (0.95–1.14)
Worsening or new angina	567 (6.6)	536 (6.3)	538 (6.3)	0.95 (0.84–1.07)	0.96 (0.85–1.08)
New diagnosis of diabetes*	366 (6.7)	399 (7.5)	323 (6.1)	1.12 (0.97–1.29)	0.91 (0.78–1.06)
Any heart failure	514 (6.0)	537 (6.3)	478 (5.6)	1.05 (0.93–1.19)	0.94 (0.83–1.07)
New atrial fibrillation†	570 (6.9)	550 (6.7)	537 (6.5)	0.97 (0.86–1.09)	0.96 (0.85–1.07)
Renal impairment‡	871 (10.2)	906 (10.6)	1148 (13.5)	1.04 (0.96–1.14)	1.33 (1.22–1.44)§
Renal failure requiring dialysis	48 (0.6)	52 (0.6)	65 (0.8)	1.09 (0.74–1.61)	1.37 (0.94–1.98)

\* The numbers of patients included in this analysis were 5427 in the ramipril group, 5294 in the telmisartan group, and 5280 in the combination-therapy group.

† This category includes only patients who did not have atrial fibrillation at baseline: 8296 in the ramipril group, 8259 in the telmisartan group, and 8218 in the combination-therapy group.

‡ No specific definitions were used. A determination of renal impairment was based on the clinical investigator's report of an event that led to the discontinuation of a study drug.

§  $P<0.001$ .

benefits of ARBs are being evaluated in three other placebo-controlled trials that are expected to be completed in 2008.<sup>14,18,19</sup>

Our results parallel the findings of the Valsartan in Acute Myocardial Infarction Trial (VALIANT),<sup>20</sup> which established the noninferiority of valsartan, as compared with captopril, in

patients with left ventricular dysfunction or heart failure after myocardial infarction. The upper boundaries of the confidence intervals and the noninferiority margins were almost identical in the two studies, even though they enrolled different patient populations. The side effects in our study were similar to those in the VALIANT study,

which showed lower rates of cough and angioedema in the valsartan group than in the captopril group but higher rates of hypotension-related symptoms. There were more dose reductions (but not discontinuations) because of renal complications in the valsartan group than in the captopril group, an association that was not observed in our study.

In order to establish noninferiority, a rigorous trial design is required that includes a patient population similar to that in the reference trial, a similar drug regimen, high adherence rates, outcomes that the comparator is known to affect, and high statistical power to exclude clinically important differences. All these criteria were satisfied in our study. The entry criteria for our study and the event rates in the ramipril group were similar to those in the HOPE trial, with high follow-up rates in both trials. Moreover, the adherence rate was higher in the ramipril group (89.4% at 2 years and 84.7% at the end of the study among patients receiving either ramipril or an open-label ACE inhibitor) than that in the HOPE trial (85.0% and 78.8%, respectively). A sensitivity analysis that was restricted to patients who adhered to their allocated drug regimen for more than 50% of the study period showed the consistency of our results and confirmed the robustness of noninferiority.

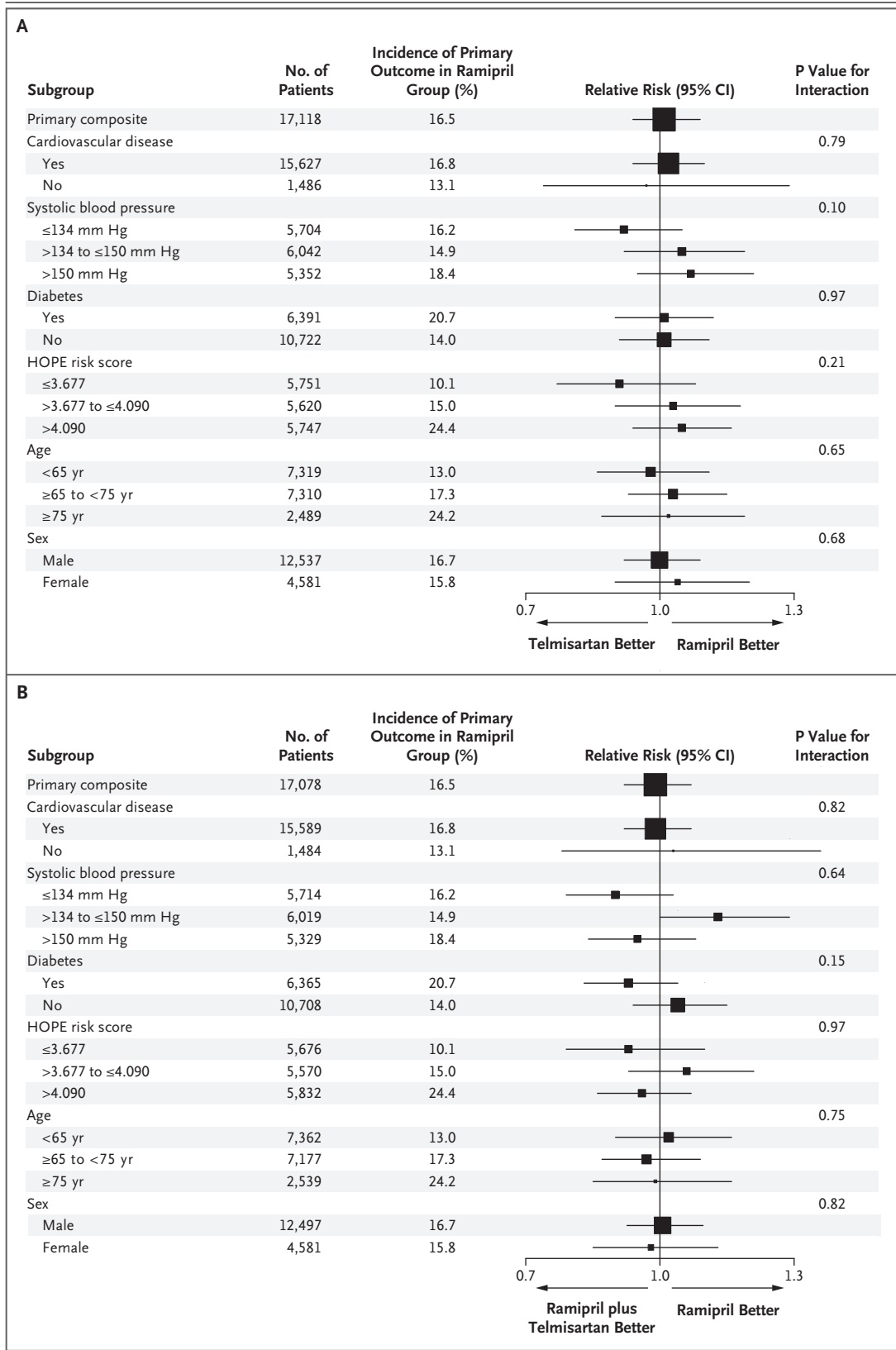
In our study, we confirmed the statistical noninferiority of telmisartan, as compared with ramipril, since the upper boundary of the 97.5% confidence interval (1.09) was lower than the predefined margin of 1.13 for both the primary outcome ( $P=0.004$ ) and the primary outcome used in the HOPE trial ( $P=0.001$ ). Telmisartan preserved about 95% (95% CI, 83.2 to 106.3) of the benefits of ramipril over placebo with respect to the primary outcome and preserved 105% (95% CI, 91.6 to 119.0) of the benefits with respect to the outcome of death from cardiovascular causes, myocardial infarction, or stroke that were observed in the HOPE trial. Use of the method of Hasselblad and Kong<sup>21</sup> to impute effects of telmisartan versus placebo (based on the benefits of ramipril over placebo in the HOPE trial) indicates a relative risk of 0.79 (95% CI, 0.70 to 0.89) for the primary outcome. The number of patients who discontinued therapy was significantly smaller in the telmisartan group than in the ramipril group, although the absolute difference in the discontinuation rate was modest, be-

cause we used an active run-in phase that selected patients for randomization only if they tolerated both medications. After randomization, we vigorously reinforced adherence and encouraged patients who stopped medications to restart them. In clinical practice, the rates of discontinuation might be higher.

We also evaluated whether the combination of telmisartan and ramipril (with both drugs targeted to the full dose) would be superior to ramipril alone. Surprisingly, despite a reduction in systolic blood pressure of 2 to 3 mm Hg in the combination-therapy group, as compared with the ramipril group — a decrease that should have translated into a risk reduction of 4 to 5% — no significant benefit was seen in the primary outcome among patients receiving the two-drug therapy. However, combination therapy significantly increased the risk of hypotension, syncope, renal dysfunction, and hyperkalemia, with a trend toward an increased risk of renal dysfunction requiring dialysis. These results are similar to the analysis of the combined effects of an ARB and an ACE inhibitor, as compared with an ACE inhibitor alone, in four previous trials.<sup>22</sup> Therefore, even though combination therapy had a larger biologic effect (as suggested by greater blood-pressure lowering and changes in potassium), dual blockade did not produce any additional clinical benefit in this population.

In this regard, our results are also similar to those of the VALIANT study, in which the combination of a full dose of captopril plus valsartan (the latter at a dose of 80 mg per day, which was lower than the 160 mg per day used in the valsartan-only group) did not significantly reduce the occurrence of the primary outcome but did increase hypotension.<sup>20</sup> Taken together, these two studies showed no additive effect for an ARB in conjunction with a full dose of a proven ACE inhibitor.

However, our findings contrast with those of two other studies. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study,<sup>12</sup> which involved patients who had symptomatic heart failure and had been hospitalized in the previous 6 months, candesartan, when added to existing therapy with any ACE inhibitor used at variable doses (with less than half the patients receiving full doses), was superior to placebo in reducing death or hospitalization for heart failure. Similarly, a reduction



**Figure 3 (facing page). Relative Risks in Prespecified Subgroups.**

Shown are the comparisons between the telmisartan group and the ramipril group (Panel A) and between the combination-therapy (telmisartan plus ramipril) group and the ramipril group (Panel B). The risk score from the Heart Outcomes Prevention Evaluation (HOPE) trial<sup>5</sup> ranges from 2.350 to 5.928, with higher scores indicating higher risk. The sizes of the squares are proportioned to the numbers of events.

in hospitalization for heart failure was observed in the Valsartan Heart Failure Trial,<sup>11</sup> which compared valsartan with placebo in patients with heart failure, with about 90% of patients receiving background therapy with ACE inhibitors at variable doses. Both trials differed from both our study and the VALIANT study in that decisions regarding the dose and choice of an ACE inhibitor were left to individual physicians, and there was no attempt to titrate the ACE inhibitor to the maximum dose. Furthermore, patients had symptomatic heart failure despite receiving an ACE inhibitor.

The lack of an additional benefit of a substantial lowering of blood pressure is puzzling, both in our study and in the VALIANT study. These results may have been due to previous successful treatment of patients with other drugs so that little further clinical benefit was possible with the addition of full doses of multiple drugs that block the renin-angiotensin system. Alternatively, some harm from combined therapy with ACE inhibitors and ARBs used at full doses may offset

any potential gains. Further information is expected regarding the role of ARBs as compared with placebo in patients after stroke,<sup>18</sup> in high-risk patients with vascular disease who are unable to tolerate an ACE inhibitor,<sup>14</sup> and in patients with atrial fibrillation.<sup>19</sup>

In conclusion, our data show that in patients who have vascular disease or high-risk diabetes but do not have heart failure, telmisartan is an equally effective alternative to ramipril and is less likely to cause angioedema. The choice between the two agents will depend on the preferences of patients and physicians and the individual patient's susceptibility to specific adverse events. There is no additional advantage (and there is some harm) from the combination of telmisartan and ramipril used in full doses in this population, as compared with ramipril alone.

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