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EFFECTS OF AN ANGIOTENSIN-CONVERTING–ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS*

ABSTRACT

Background Angiotensin-converting–enzyme inhibitors improve the outcome among patients with left ventricular dysfunction, whether or not they have heart failure. We assessed the role of an angiotensin-converting–enzyme inhibitor, ramipril, in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure.

Methods A total of 9297 high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg once per day orally) or matching placebo for a mean of five years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

The trial was a two-by-two factorial study evaluating both ramipril and vitamin E. The effects of vitamin E are reported in a companion paper.

Results A total of 651 patients who were assigned to receive ramipril (14.0 percent) reached the primary end point, as compared with 826 patients who were assigned to receive placebo (17.8 percent) (relative risk, 0.78; 95 percent confidence interval, 0.70 to 0.86; $P<0.001$). Treatment with ramipril reduced the rates of death from cardiovascular causes (6.1 percent, as compared with 8.1 percent in the placebo group; relative risk, 0.74; $P<0.001$), myocardial infarction (9.9 percent vs. 12.3 percent; relative risk, 0.80; $P<0.001$), stroke (3.4 percent vs. 4.9 percent; relative risk, 0.68; $P<0.001$), death from any cause (10.4 percent vs. 12.2 percent; relative risk, 0.84; $P=0.005$), revascularization procedures (16.0 percent vs. 18.3 percent; relative risk, 0.85; $P=0.002$), cardiac arrest (0.8 percent vs. 1.3 percent; relative risk, 0.63; $P=0.03$), heart failure (9.0 percent vs. 11.5 percent; relative risk, 0.77; $P<0.001$), and complications related to diabetes (6.4 percent vs. 7.6 percent; relative risk, 0.84; $P=0.03$).

Conclusions Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure. (N Engl J Med 2000;342:145-53.)

ALTHOUGH dyslipidemia, diabetes, smoking, and hypertension are major risk factors for cardiovascular disease, they do not fully account for the risk. Therefore, other risk factors must be identified in order to reduce mortality and morbidity even further. Epidemiologic and experimental data suggest that activation of the renin–angiotensin–aldosterone system has an important role in increasing the risk of cardiovascular events.[1] Angiotensin-converting–enzyme inhibitors block the activation of the renin–angiotensin system and could retard the progression of both heart failure and atherosclerosis. In a meta-analysis of three studies[1-3] that included more than 9000 patients with low ejection fractions, treatment with angiotensin-converting–enzyme inhibitors reduced the risk of myocardial infarction by 23 percent. This finding, which has not been widely accepted, was independent of the ejection fraction, the cause of heart disease, concomitant use of medications, diabetes status, and blood pressure, suggesting that angiotensin-converting–enzyme inhibitors may have a role in preventing myocardial infarction in a broad range of patients, not just those with low ejection fractions. Angiotensin-converting–enzyme inhibitors may also reduce the risk of stroke, by lowering blood pressure, and may prevent complications related to diabetes.[4] These hypotheses require direct confirmation in prospective, randomized clinical trials.

Therefore, in a high-risk population, we evaluated the effects of an angiotensin-converting–enzyme inhibitor, ramipril, in preventing the primary out-

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come, which was a composite of death from cardiovascular causes, myocardial infarction, or stroke, as well as each outcome separately. Secondary outcomes included death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes. Other outcomes included worsening angina, heart failure, and the development of diabetes.

METHODS

Study Design

The double-blind, two-by-two factorial, randomized Heart Outcomes Prevention Evaluation study evaluated ramipril and vitamin E in 9541 patients. A substudy compared a low dose of ramipril (2.5 mg per day) with a full dose (10 mg per day) or placebo; there were 244 patients in each group. The results of the placebo-controlled study of full-dose ramipril are given here. The effects of vitamin E are reported in a companion paper.[5] The design of the study has been reported previously[6]; a brief summary follows.

Patients

Men and women who were at least 55 years old were eligible for the study if they had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria).[6] Patients were excluded if they had heart failure, were known to have a low ejection fraction (<0.40), were taking an angiotensin-converting–enzyme inhibitor or vitamin E, had uncontrolled hypertension or overt nephropathy, or had had a myocardial infarction or stroke within four weeks before the study began. All patients provided written informed consent.

In this large study it was impractical to measure left ventricular function in all patients. Instead, echocardiograms were obtained at three centers in 496 patients who were enrolled in a substudy. Of these patients, 2.6 percent had an ejection fraction of less than 0.40. A subsequent review of the charts of randomized patients showed that ventricular function had been evaluated before randomization in 5193. Only 421 of these patients (8.1 percent) had a low ejection fraction, and none had heart failure before randomization. We performed a separate analysis of the 4772 patients who were documented to have a normal ejection fraction.

All 10,576 eligible patients participated in a run-in phase in which they received 2.5 mg of ramipril orally once daily for 7 to 10 days followed by matching placebo for 10 to 14 days. A total of 1035 patients were subsequently excluded from randomization because of noncompliance (<80 percent of pills taken), side effects, abnormal serum creatinine or potassium levels, or withdrawal of consent. Of the 9541 remaining patients, 4645 were randomly assigned to receive 10 mg of ramipril once per day, 4652 were randomly assigned to receive matching placebo, and 244 were randomly assigned to receive a low dose (2.5 mg per day) of ramipril. Treatment was scheduled to last five years.

At randomization, patients were assigned to receive ramipril (or matching placebo) at a dose of 2.5 mg once a day for one week, 5 mg for the next three weeks, and then 10 mg. In addition, all patients were randomly assigned to receive 400 IU of vitamin E per day or matching placebo. Follow-up visits occurred at one month and six months and every six months thereafter. At each visit, data were collected on the outcome events, compliance, and side effects leading to a discontinuation of study medications. All primary and secondary events were documented and were centrally adjudicated with the use of standardized definitions.[5]

Organization of the Study

Patients were recruited from December 1993 to June 1995 at 129 centers in Canada, 27 centers in the United States, 76 centers in 14 western European countries, 30 centers in Argentina and Brazil, and 5 centers in Mexico. The review board at each institution approved the protocol. The study was organized and coordinated by the Canadian Cardiovascular Collaboration Project Office at McMaster University in Hamilton, Ontario. Adjunct offices were located in London, United Kingdom; São Paulo, Brazil; and Rosario, Argentina. An independent steering committee oversaw the study.

Outcomes

The primary study outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Each of these outcomes was also analyzed separately. Secondary outcomes were death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes (whether or not hospitalization was required). Other outcomes were worsening angina, cardiac arrest, heart failure (whether or not hospitalization was required), unstable angina with electrocardiographic changes, and the development of diabetes. These outcomes are defined in a companion paper.[5]

Statistical Analysis

The study was originally designed to follow participants for a mean of 3.5 years. However, before the end of this period, the steering committee (whose members were unaware of any of the results) recommended increasing the duration of follow-up to five years to account for the impact of a possible lag before treatment had its full effect. Assuming an event rate of 4 percent per year for five years, we calculated that 9000 patients would be required for the study to have 90 percent power to detect a 13.5 percent reduction in the relative risk with a two-sided alpha level of 0.05 and with data analyzed on an intention-to-treat basis. Survival curves were estimated according to the Kaplan–Meier procedure, and treatments were compared with use of the log-rank test. Because of the factorial design, all analyses were stratified for the randomization to vitamin E or placebo. Subgroup analyses were conducted with the use of tests for interactions in the Cox regression model. This model was used to estimate the effects of treatment after stratification for randomization to vitamin E or its placebo.

An independent data and safety monitoring board monitored the progress of all aspects of the study. Four formal interim analyses were planned. The statistical monitoring boundary indicating that ramipril had a beneficial effect was a difference in the primary outcome of 4 SD between groups during the first half of the study and of 3 SD during the second half. The respective boundaries indicating that ramipril had a harmful effect were 3 SD and 2 SD. On March 22, 1999, the monitoring board recommended termination of the study because of the clear evidence of a beneficial effect of ramipril (consistent crossing of the monitoring boundaries in two consecutive reviews). At that time, the data showed a 20 percent reduction in the relative risk of the primary outcome (95 percent confidence interval, 12 percent to 28 percent; z statistic, −4.5; $P<0.001$). The results of the study were disclosed to the investigators at two meetings held on April 17 and April 24, 1999. The cutoff date for all events included in the main analysis was set for April 15, 1999, and final visits were scheduled to be completed by June 30, 1999. Vital status was ascertained for 9535 of the 9541 randomized patients (99.9 percent) at the end of the study.

RESULTS

Characteristics of the Patients

The base-line characteristics of the 9297 patients who underwent randomization are shown in Table 1. There were 2480 women, 5128 patients who were at least 65 years old, 8162 who had cardiovascular disease, 4355 who had hypertension, and 3577 who had diabetes.

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

CHARACTERISTIC	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)
Age — yr	66±7	66±7
Blood pressure — mm Hg	139±20/79±11	139±20/79±11
Heart rate — beats/min	69±11	69±11
Body-mass index	28±4	28±4
Female sex — no. (%)	1279 (27.5)	1201 (25.8)
History of coronary artery disease — no. (%)	3691 (79.5)	3786 (81.4)
Myocardial infarction	2410 (51.9)	2482 (53.4)
Within ≤1 year	452 (9.7)	446 (9.6)
Within >1 year	1958 (42.2)	2036 (43.8)
Stable angina pectoris	2544 (54.8)	2618 (56.3)
Unstable angina pectoris	1179 (25.4)	1188 (25.5)
CABG	1192 (25.7)	1207 (25.9)
PTCA	853 (18.4)	806 (17.3)
Stroke or transient ischemic attacks — no. (%)	500 (10.8)	513 (11.0)
Peripheral vascular disease — no. (%)†	1966 (42.3)	2085 (44.8)
Hypertension — no. (%)	2212 (47.6)	2143 (46.1)
Diabetes — no. (%)	1808 (38.9)	1769 (38.0)
Documented elevated total cholesterol level — no. (%)	3036 (65.4)	3089 (66.4)
Documented low HDL cholesterol level — no. (%)	842 (18.1)	881 (18.9)
Current cigarette smoking — no. (%)	645 (13.9)	674 (14.5)
Medications — no. (%)		
Beta-blockers	1820 (39.2)	1853 (39.8)
Aspirin or other antiplatelet agents	3497 (75.3)	3577 (76.9)
Lipid-lowering agents	1318 (28.4)	1340 (28.8)
Diuretics	713 (15.3)	706 (15.2)
Calcium-channel blockers	2152 (46.3)	2228 (47.9)
Left ventricular hypertrophy on electrocardiography — no. (%)	379 (8.2)	406 (8.7)
Microalbuminuria — no. (%)	952 (20.5)	1004 (21.6)

*Plus–minus values are means ±SD. The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, and HDL high-density lipoprotein.

†Peripheral vascular disease included claudication, a history of peripheral arterial disease, or a ratio of blood pressure in the ankle to blood pressure in the arm of less than 0.90.

TABLE 2. REASONS FOR DISCONTINUATION OF TREATMENT.

VARIABLE	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)
	no. of patients (%)	
Discontinuation at any time	1511 (32.5)	1430 (30.7)
Permanent discontinuation	1343 (28.9)	1268 (27.3)
Reasons for stopping*		
Cough	340 (7.3)	85 (1.8)
Hypotension or dizziness	88 (1.9)	70 (1.5)
Angioedema	17 (0.4)	7 (0.2)
Uncontrolled hypertension	109 (2.3)	183 (3.9)
Clinical events	309 (6.7)	418 (9.0)
Other	1101 (23.7)	1074 (23.1)
Use of nonstudy angiotensin-converting–enzyme inhibitor at any time*†	648 (14.0)	839 (18.0)
Reasons for use		
Heart failure	249 (5.4)	335 (7.2)
Proteinuria	59 (1.3)	60 (1.3)
Hypertension	222 (4.8)	300 (6.4)
Other	294 (6.3)	335 (7.2)

*The categories are not mutually exclusive.

†Clinical progression of disease may have resulted in the need for open-label angiotensin-converting–enzyme inhibitors.

Compliance

Among the patients who were randomly assigned to the ramipril group, 87.4 percent were taking ramipril or an open-label angiotensin-converting–enzyme inhibitor at one year, 85.0 percent were doing so at two years, 82.2 percent were doing so at three years, 75.1 percent were doing so at four years, and 78.8 percent were doing so at the final follow-up visit. The percentage of patients who were receiving 10 mg of ramipril per day was 82.9 percent at one year, 74.6 percent at two years, 70.9 percent at three years, 62.4 percent at four years, and 65.0 percent at the last visit. Among the patients who were randomly assigned to receive placebo, 3.4 percent were receiving an angiotensin-converting–enzyme inhibitor at one year, 6.0 percent were doing so at two years, 8.1 percent were doing so at three years, 10.8 percent were doing so at four years, and 12.3 percent were doing so at five years. The most common reasons for discontinuing treatment are outlined in Table 2. More patients in the ramipril group than in the placebo group stopped treatment because of cough (7.3 percent vs. 1.8 percent) or hypotension or dizziness (1.9 percent vs. 1.5 percent). By contrast, more patients in the placebo group than in the ramipril group stopped treatment because of uncontrolled hypertension (3.9 percent vs. 2.3 percent) or because of a clinical event — a primary or secondary outcome (8.9 percent vs. 6.6 percent). The percentage of patients who were receiving nonstudy angiotensin-converting–enzyme inhibitors for heart failure was 5.4 percent in the ramipril group and 7.2 percent in the placebo group; 1.3 percent and 1.3 percent, respectively, were receiving such drugs because of proteinuria, and 4.8 percent and 6.4 percent for control of hypertension. The use of open-label angiotensin II–receptor antagonists in both groups was low (1.6 percent in the ramipril group and 1.8 percent in the placebo group), but the reasons for such use were similar to those for angiotensin-converting–enzyme inhibitors.

Blood Pressure

The mean blood pressure at entry was 139/79 mm Hg in both groups. The mean blood pressure was 133/76 mm Hg in the ramipril group and 137/78 mm Hg in the placebo group at one month, 135/76 mm Hg and 138/78 mm Hg, respectively, at two years, and 136/76 mm Hg and 139/77 mm Hg, respectively, at the end of the study.

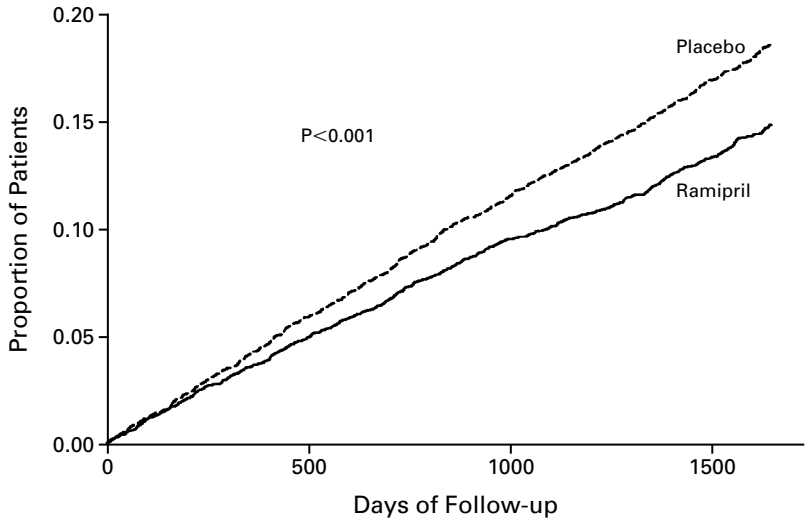

Figure 1. Kaplan–Meier Estimates of the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes in the Ramipril Group and the Placebo Group.

The relative risk of the composite outcome in the ramipril group as compared with the placebo group was 0.78 (95 percent confidence interval, 0.70 to 0.86).

TABLE 3. INCIDENCE OF THE PRIMARY OUTCOME AND OF DEATHS FROM ANY CAUSE.

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	z STATISTIC	P VALUE†
	no. (%)				
Myocardial infarction, stroke, or death from cardiovascular causes‡	651 (14.0)	826 (17.8)	0.78 (0.70–0.86)	−4.87	<0.001
Death from cardiovascular causes§	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	−3.78	<0.001
Myocardial infarction§	459 (9.9)	570 (12.3)	0.80 (0.70–0.90)	−3.63	<0.001
Stroke§	156 (3.4)	226 (4.9)	0.68 (0.56–0.84)	−3.69	<0.001
Death from noncardiovascular causes	200 (4.3)	192 (4.1)	1.03 (0.85–1.26)	0.33	0.74
Death from any cause	482 (10.4)	569 (12.2)	0.84 (0.75–0.95)	−2.79	0.005

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡In the substudy, 34 of 244 patients (13.9 percent) assigned to take a low dose of ramipril (2.5 mg per day) reached the composite end point, as compared with 31 of 244 assigned to take 10 mg of ramipril per day (12.7 percent) and 41 of 244 assigned to placebo (16.8 percent). The inclusion of the data from the low-dose group did not change the overall results (relative risk of the primary outcome, 0.78; 95 percent confidence interval, 0.70 to 0.86).

§All patients with this outcome are included.

Primary Outcomes and Deaths from Any Cause

A total of 651 patients in the ramipril group (14.0 percent) died of cardiovascular causes or had a myocardial infarction or stroke, as compared with 826 patients in the placebo group (17.8 percent; relative risk, 0.78; 95 percent confidence interval, 0.70 to 0.86; P<0.001) (Fig. 1 and Table 3). Treatment with ramipril also reduced the risk of the primary outcome among patients who were receiving vitamin E (338 patients who received both agents reached the end point, as compared with 421 patients who received only vitamin E; relative risk, 0.79; P=0.001) or its placebo (313 patients who received ramipril and the vitamin E placebo reached the end point, as compared with 405 patients who received the vitamin E placebo alone; relative risk, 0.76; P<0.001; P=0.79 for the comparison of the two relative risks). In addition, there were significant reductions in risk when each of these end points was analyzed separately: 282 patients in the ramipril group died of cardiovascular causes, as compared with 377 patients in the placebo group (relative risk, 0.74; 95 percent confidence interval, 0.64 to 0.87; P<0.001); 459 patients in the ramipril group had a myocardial infarction, as compared with

TABLE 4. INCIDENCE OF SECONDARY AND OTHER OUTCOMES.

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	z STATISTIC	P VALUE†
	no. (%)				
Secondary outcomes‡					
Revascularization	742 (16.0)	852 (18.3)	0.85 (0.77–0.94)	−3.17	0.002
Hospitalization for unstable angina	554 (11.9)	565 (12.1)	0.98 (0.87–1.10)	−0.41	0.68
Complications related to diabetes§¶	299 (6.4)	354 (7.6)	0.84 (0.72–0.98)	−2.16	0.03
Hospitalization for heart failure	141 (3.0)	160 (3.4)	0.88 (0.70–1.10)	−1.16	0.25
Other outcomes					
Heart failure§	417 (9.0)	535 (11.5)	0.77 (0.67–0.87)	−4.09	<0.001
Cardiac arrest	37 (0.8)	59 (1.3)	0.62 (0.41–0.94)	−2.28	0.02
Worsening angina§	1107 (23.8)	1220 (26.2)	0.89 (0.82–0.96)	−2.91	0.004
New diagnosis of diabetes‖	102 (3.6)	155 (5.4)	0.66 (0.51–0.85)	−3.31	<0.001
Unstable angina with electrocardiographic changes‡	175 (3.8)	180 (3.9)	0.97 (0.79–1.19)	−0.30	0.76

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡These events were centrally adjudicated.

§All cases are included, whether or not hospitalization was required.

¶Complications related to diabetes include diabetic nephropathy (defined as urinary albumin excretion of at least 300 mg per day or urinary protein excretion of 500 mg per day), the need for renal dialysis, and the need for laser therapy for diabetic retinopathy.

‖The denominator in the ramipril group is the 2837 patients who did not have diabetes at base line. The denominator in the placebo group is the 2883 patients who did not have diabetes at base line.

570 patients in the placebo group (relative risk, 0.80; 95 percent confidence interval, 0.70 to 0.90; P< 0.001); and 156 patients in the ramipril group had a stroke, as compared with 226 patients in the placebo group (relative risk, 0.68; 95 percent confidence interval, 0.56 to 0.84; P<0.001). The risk of death from any cause was also significantly reduced by treatment with ramipril (relative risk, 0.84; 95 percent confidence interval, 0.75 to 0.95; P=0.005).

Secondary and Other Outcomes

Significantly fewer patients in the ramipril group than in the placebo group underwent revascularization (742 vs. 852; relative risk, 0.85; P=0.002), and there was a trend toward fewer hospitalizations for heart failure in the ramipril group (141 vs. 160; relative risk, 0.88; P=0.25) (Table 4). However, treatment with ramipril had no effect on the likelihood of hospitalization for unstable angina. In addition, significantly fewer patients in the ramipril group than in the placebo group had a cardiac arrest (37 vs. 59; relative risk, 0.62; P=0.02), worsening angina (1107 vs. 1220; relative risk, 0.89; P=0.004), heart failure (417 vs. 535; relative risk, 0.77; P<0.001), a new diagnosis of diabetes (102 vs. 155; relative risk, 0.66; P<0.001), or complications related to diabetes (299 vs. 354; relative risk, 0.84; P=0.03).

Subgroup Analysis

The beneficial effect of treatment with ramipril on the composite outcome was consistently observed among the following predefined subgroups: patients with diabetes and those without diabetes, women and men, those with evidence of cardiovascular disease and those without such evidence, those younger than 65 years of age and those 65 years of age or older, those with hypertension at base line and those without it, and those with microalbuminuria and those without it (Fig. 2). In addition, there was a clear benefit of ramipril among patients with evidence of coronary artery disease at base line and those with no evidence of it, among those with a history of myocardial infarction and those with no such history, and among those with a documented ejection fraction of 0.40 or greater (332 of 2379 patients reached the end point in the ramipril group vs. 451 of 2393 patients in the placebo group; relative risk, 0.73; 95 percent confidence interval, 0.63 to 0.84; P<0.001). Benefits were also observed whether or not patients were also taking aspirin or other antiplatelet agents, beta-blockers, lipid-lowering agents, or antihypertensive drugs at randomization.

Temporal Trends

The reduction in the risk of the composite outcome with ramipril therapy was evident within one year after randomization (169 patients reached the end point in the ramipril group, as compared with 198 in the placebo group; relative risk, 0.85; 95 percent confidence interval, 0.70 to 1.05) and was significant at two years (326 vs. 398 patients; relative risk, 0.82; 95 percent confidence interval, 0.70 to 0.94).

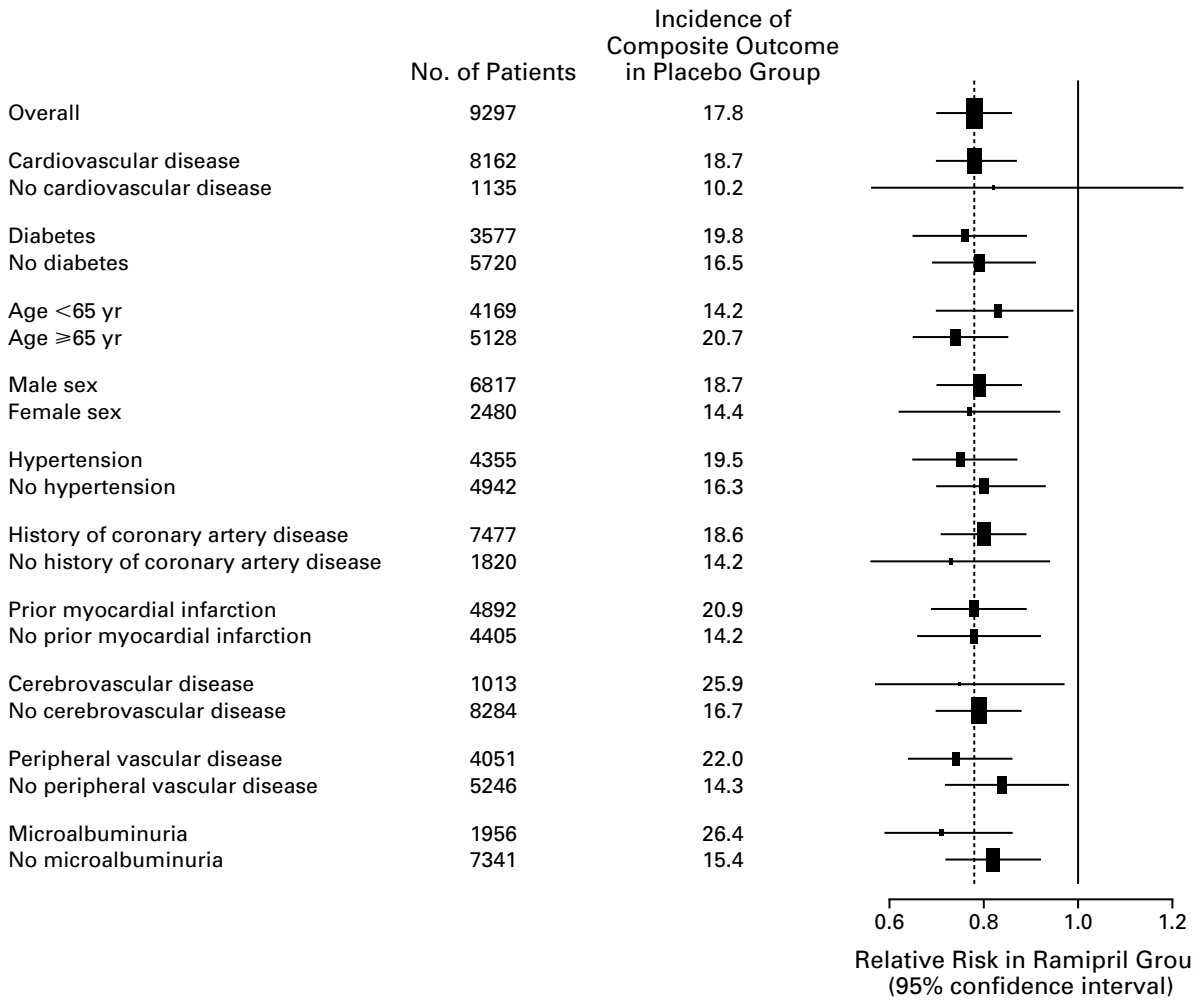

Figure 2. The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes Overall and in Various Predefined Subgroups.

Cerebrovascular disease was defined as stroke or transient ischemic attacks. The size of each symbol is proportional to the number of patients in each group. The dashed line indicates overall relative risk.

The relative risk was 0.78 in the second year, 0.73 in the third year, and 0.74 in the fourth year, when the data on patients who were still alive at the end of the preceding year were analyzed.

DISCUSSION

Our findings show that ramipril, an angiotensin-converting–enzyme inhibitor, is beneficial in a broad range of patients without evidence of left ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events. Treatment with ramipril reduced the rates of death, myocardial infarction, stroke, coronary revascularization, cardiac arrest, and heart failure as well as the risk of complications related to diabetes and of diabetes itself.

Our findings indicate that the spectrum of patients who would benefit from treatment with an angiotensin-converting–enzyme inhibitor is quite broad and complement those of previous studies of patients with low ejection fractions[3] or heart failure and acute myocardial infarction.[7] The underlying rationale for our study was that the inhibition of angiotensin-converting enzyme would prevent events related to ischemia and atherosclerosis, in addition to those related to heart failure and left ventricular dysfunction (although patients with these two conditions were excluded from the study). We therefore included a broad range of patients with any manifestation of coronary artery disease (e.g., a history of myocardial infarction or revascularization, unstable angina, or stable angina), a history of cerebrovascular disease or peripheral vascular disease, or diabetes and one cardiovascular risk factor, and ramipril was beneficial in all these subgroups.

A total of 3577 patients in our study had diabetes, 1135 of whom had no clinical manifestations of cardiovascular disease, and the event rate in this group was about half that in the other patients (10.2 percent vs. 18.7 percent). Nonetheless, overall, treatment with ramipril was beneficial in patients with diabetes.

The magnitude of the benefit of treatment with ramipril with respect to the primary outcome was at least as large as that observed with other proven secondary prevention measures, such as treatment with beta-blockers,[8] aspirin,[9] and lipid-lowering agents,[10] during four years of treatment. In addition, there were reductions in the rates of revascularization, heart failure, complications related to diabetes, and new cases of diabetes. The rapid and sustained response to ramipril and the continuing divergence in results between the ramipril group and the placebo group indicate that longer-term treatment may yield even better results. Ramipril was also well tolerated.

The benefits of ramipril were observed among patients who were already taking a number of effective treatments, such as aspirin, beta-blockers, and lipid-lowering agents, indicating that the inhibition of angiotensin-converting enzyme offers an additional approach to the prevention of atherothrombotic complications. Only a small part of the benefit could be attributed to a reduction in blood pressure, since the majority of patients did not have hypertension at base line (according to conventional definitions) and the mean reduction in blood pressure with treatment was extremely small (3/2 mm Hg). A reduction of 2 mm Hg in diastolic blood pressure might at best account for about 40 percent of the reduction in the rate of stroke and about one quarter of the reduction in the rate of myocardial infarction.[11] However, the results of recent studies, such as the Hypertension Optimal Treatment study,[12] suggest that for high-risk patients (e.g., those with diabetes), it may be beneficial to lower blood pressure even if it is already within the "normal" range. Moreover, a recent reanalysis of 20 years of blood-pressure data from the Framingham Heart Study[13] suggests that the degree of benefit expected from a decrease in blood pressure may have been underestimated. Despite these considerations, it is likely that angiotensin-converting–enzyme inhibitors exert additional direct mechanisms on the heart or the vasculature that are important. These may include antagonizing the direct effects of angiotensin II on vasoconstriction,[1] the proliferation of vascular smooth-muscle cells,[1] and rupture of plaques[14]; improving vascular endothelial function[1]; reducing left ventricular hypertrophy; and enhancing fibrinolysis.[1]

We also observed a reduction in the incidence of heart failure in patients with no evidence of impairment of left ventricular systolic dysfunction. These data complement those of a study of patients with a low ejection fraction[15] and studies of patients after myocardial infarction,[1-3,7,16,17] which demonstrated that treatment with angiotensin-converting–enzyme inhibitors prevents heart failure, and the studies of patients with documented low ejection fractions and heart failure, which indicated that angiotensin-converting–enzyme inhibitors reduced the rate of hospitalization for heart failure.[17] Both these results and our findings suggest that angiotensin-converting–enzyme inhibitors will be beneficial for patients who are at high risk for heart failure, irrespective of the degree of left ventricular systolic dysfunction.

We believe that the extent to which our results may have been affected by the inclusion of patients with undiagnosed low ejection fractions is very small, because a large substudy of 496 consecutive patients at three centers indicated that only 2.6 percent had an ejection fraction of less than 0.40, an extensive review of charts identified only 8.1 percent of patients with a low ejection fraction before randomization, and treatment was clearly beneficial in the subgroup of 4772 patients who were documented to have preserved ventricular function (relative risk, 0.73; 95 percent confidence interval, 0.63 to 0.84; $P<0.001$) and in those with no history of myocardial infarction (relative risk, 0.77; 95 percent confidence interval, 0.65 to 0.91; $P=0.002$).

We observed a marked reduction in the incidence of complications related to diabetes and new cases of diabetes. These effects may be mediated by improved insulin sensitivity, a decrease in hepatic clearance of insulin, an antiinflammatory effect, improved blood flow to the pancreas,[18] or an effect on abdominal fat.[19] The results are also consistent with the results of the recent Captopril Prevention Project study,[20] which indicated a lower rate of newly diagnosed diabetes in patients who were randomly assigned to receive captopril than in those who were assigned to receive a diuretic or beta-blocker, and with the results of other trials, which reported that treatment with an angiotensin-converting–enzyme inhibitor slowed the progression of nephropathy among patients with type 2 diabetes[21] as well as those without diabetes.[22]

Our findings clearly demonstrate that ramipril, a long-acting angiotensin-converting–enzyme inhibitor, reduces the rates of death, myocardial infarction, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes, and new cases of diabetes in a broad spectrum of high-risk patients. Treating 1000 patients with ramipril for four years prevents about 150 events in approximately 70 patients.

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