Randomized, Placebo-Controlled Trial of the Angiotensin-Converting Enzyme Inhibitor, Ramipril, in Patients With Coronary or Other Occlusive Arterial Disease

Stephen MacMahon, PhD, MPH, FACC,* Norman Sharpe, MD, FRACP, FACC,† Greg Gamble, MSc,† Alison Clague, RN,‡ Cliona Ni Mhurchu, PhD,‡ Taane Clark, MSc,‡ Hamish Hart, MB, ChB, FRACP,§ John Scott, MD, FRACP,‡ Harvey White, DSc, FRACP, FACC,‡ for the PART-2 Collaborative Research Group

Sydney, Australia and Auckland, New Zealand

OBJECTIVES The primary objective of this study was to investigate the effects of the angiotensin-converting enzyme (ACE) inhibitor, ramipril, on carotid atherosclerosis in patients with coronary, cerebrovascular or peripheral vascular disease.

BACKGROUND Angiotensin-converting enzyme inhibitors have been shown to reduce the risk of coronary events in various patient groups and to prevent the development of atherosclerosis in animal models. It has been hypothesized that the clinical benefits of ACE inhibitors may, therefore, be mediated by effects on atherosclerosis.

METHODS Six hundred seventeen patients were randomized in equal proportions to ramipril (5–10 mg daily) or placebo. At baseline, two years and four years, carotid atherosclerosis was assessed by B-mode ultrasound, and left ventricular mass was assessed by M-mode echocardiography.

RESULTS Blood pressure (BP) was reduced by a mean of 6 mm Hg systolic and 4 mm Hg diastolic in the ramipril group compared with the placebo group (p < 0.001). There was no difference between groups in the changes in common carotid artery wall thickness (p = 0.58) or in carotid plaque (p = 0.93). Left ventricular mass index decreased by 3.8 g/m² (4%) in the ramipril group compared with the placebo group (2p = 0.04).

CONCLUSIONS The results provide no support for the hypothesis that reduced atherosclerosis is responsible for the beneficial effects of ACE inhibitors on major coronary events. It is more likely that the benefits are due to lower BP, reduced left ventricular mass or other factors such as reversal of endothelial dysfunction. (J Am Coll Cardiol 2000;36:438–43) © 2000 by the American College of Cardiology

Among patients with heart failure or left ventricular dysfunction, long-term treatment with angiotensin-converting enzyme (ACE) inhibitors has been shown to reduce the risk of major coronary events (1) as well as the risks of cardiovascular death and heart failure–related morbidity (2). A recent report from the Heart Outcomes Prevention Evaluation (HOPE) Study (3) indicates that these benefits extend to a variety of other patient groups without impaired left ventricular (LV) function but at high risk for coronary events. It has been suggested that the effects of ACE inhibitors on coronary events may be mediated by unique vascular protective effects that involve the regression or prevention of atherosclerosis (4). This hypothesis was based primarily on the evidence of anti–atherosclerotic and anti-proliferative effects of ACE inhibitors in animal models (5–8). However, there is little direct evidence about the effects of ACE inhibitors on atherosclerosis in man. This study was conducted to determine the effects of the ACE inhibitor, ramipril, on carotid atherosclerosis and other outcomes, including LV hypertrophy, in patients with a history of coronary or other occlusive arterial disease.

METHODS

Patients. The study participants were recruited from four collaborating centers in metropolitan Auckland: the Auckland, Green Lane, Middlemore and North Shore Hospitals. Approval for the conduct of the study in each of these institutions was provided by the Auckland Regional Ethics Committee. Patients aged 75 years or younger who provided written informed consent to participate were eligible for inclusion if they had a hospital diagnosis (within five years of enrollment) of any of the following: acute myocardial infarction (MI), angina with coronary disease confirmed by angiography or exercise electrocardiogram, transient ischemic attack (TIA) or intermittent claudication. Individuals were not eligible if they had congestive heart failure (CHF) or any other definite indication for treatment with an ACE inhibitor, a contraindication to treatment with an ACE inhibitor, serious nonvascular disease, a diastolic blood pressure (BP) >100 mm Hg, a systolic BP >160 mm Hg or <100 mm Hg during the...
prerandomization run-in period, or were of childbearing potential without adequate contraception.

**Design and study treatment.** Prior to randomization, potentially eligible patients entered a two-week tolerability phase during which they received ramipril 5 mg daily for the first week and ramipril 10 mg daily for the second week. The purpose of this open-treatment phase was to identify patients who could not tolerate even a short course of treatment with ramipril or who were unlikely to comply with treatment or follow-up procedures. Those compliant patients who tolerated at least 5 mg ramipril daily were then randomized to continue active treatment or to receive placebo in a double-blind, parallel-group design. Depending on the outcome in the tolerability phase, patients received either 5 mg or 10 mg ramipril once daily or matching placebo. Treatment assignment was obtained by telephone call to the Clinical Trials Research Unit randomization service in Auckland. Randomization was performed by computer using a minimization algorithm that balanced treatment assignment by center, disease inclusion criteria and current use of a beta-adrenergic blocking agent. The double-blind treatment and follow-up phase was scheduled to continue for a minimum of four years, during which patients were seen at three monthly clinic visits throughout.

**Study outcomes.** At baseline, two years and four years, B-mode ultrasound recordings of the carotid arteries and M-mode echocardiograms were performed in the Cardiovascular Research Laboratory of the University of Auckland Department of Medicine. Ultrasound images of common and internal carotid arteries were captured with an Acuson 128 ultrasound machine and 10-MHz linear transducer (Mountainview, California). Images were digitized and stored for off-line analysis. For each patient, three views of the right and left common carotid arteries were collected, maximizing the lumen diameter to ensure that the plane of interrogation was orthogonal to the artery wall. All discrete plaques (>1.2 mm in height) in the internal, external and common carotid arteries and bulb were also recorded. Three ultrasonographers, blind to study treatment allocation, performed all examinations using a standardized protocol.

The images collected at baseline, two and four years were measured at the end of the study by an ultrasonographer and a radiologist blind to study treatment allocation but not to the order of scans. Throughout the measurement period, checks were conducted to assess the reliability of the measurements obtained. Measurements of carotid artery far wall thickness and lumen diameter were made on a 1 cm length of the right and left common carotid artery immediately proximal to the bulb, using methods described previously (9). This method of estimating carotid far wall thickness is reproducible (limits of agreement = 8%) and has previously been shown to closely resemble total carotid wall thickness measured histologically (10). Mean carotid artery far wall thickness was prespecified as the primary study outcome. Discrete plaques (as defined above) in the internal, external and common carotid arteries and bulb were identified, and the sum of the heights of all such plaques in the entire carotid tree on both the left and right sides was calculated for each patient (carotid plaque score).

Left ventricular dimensions were measured using two-dimensionally guided M-mode echocardiography. An M-mode view of the LV from the parasternal long axis with the M-mode cursor perpendicular to both the LV septum and posterior wall at the level of the mitral valve chordae was recorded, and LV mass was determined using the American Society of Echocardiography modified Penn convention. The LV mass index was calculated as LV mass (g) divided by body surface area (m²).

Throughout follow-up, systolic and diastolic BPs were measured in duplicate at every clinic visit using a standard mercury sphygmomanometer, following a standardized protocol. Details of all clinical events resulting in death, hospitalization or withdrawal from study treatment were also recorded throughout follow-up.

**Statistical methods.** The study sample size was calculated to provide 80% power (with \( p = 0.05 \)) to detect a 0.05 mm difference between groups in the primary study outcome, mean carotid artery far wall thickness. All outcome analyses were conducted according to the intention-to-treat principle. The effect of treatment on all continuous outcome variables was tested using analysis of variance to estimate main and interaction effects for repeated observations over time. A maximum likelihood approach was used to impute missing at-random data within this model. The variables used in the minimization algorithm to balance the groups at randomization were included as terms in the model. Post hoc tests of significant main and interaction effects were performed using the methods of Tukey. The same methods were used to test differences between randomized groups in the change in other carotid artery measurements, LV mass and BP levels during follow-up. All \( p \) values were calculated from two-tailed tests of statistical significance. A 5% significance level was maintained throughout these analyses. Relative risk of major nonfatal and fatal events was estimated using Cox proportional hazards models adjusted for the variables used in the minimization algorithm. The frequency of hospital admissions was analyzed using chi-square tests. The study was not designed to determine the effects of treatment on mortality or morbidity, but analyses were prespecified for the following clinical outcomes: total cardiovascular events (death from cardiovascular disease or hospitalization for MI, unstable angina, stroke or CHF),
RESULTS

A total of 617 patients were randomized in this study. Characteristics of the participants at entry to the study are given in Table 1. The mean age of participants was 61 years, 82% were men, and 16% were current smokers. The average BP at entry was 133/79 mm Hg, and the average total cholesterol concentration was 6.1 mmol/l. Sixty-eight percent of patients had a history of coronary heart disease, 20% had a history of peripheral vascular disease, and 10% had a history of ischemic stroke or TIA. Forty-three percent of patients were receiving a beta-blocker, 25% a calcium antagonist, 29% a cholesterol lowering drug and 81% an antiplatelet agent.

A total of 744 potentially eligible patients entered the prerandomization run-in period, of which 617 patients (83%) were randomized. Of the 17% who withdrew before randomization, the reasons for withdrawal were ineligibility in 7%, suspected adverse reaction in 7% and patient preference in 3%. Three hundred eight patients were assigned treatment with ramipril, and 309 were assigned placebo. Of those randomized to ramipril, 83% received 10 mg daily and 17% received 5 mg daily. At the year 4 examination, 72% of patients who had been assigned ramipril and 75% of patients who had been assigned placebo were still taking study treatment. By the same time, 3% of patients who had been assigned ramipril and 7% of patients who had been assigned placebo had begun nonstudy treatment with an ACE inhibitor. The main reasons for stopping randomized treatment were suspected adverse drug reactions (10% in the ramipril group, 1% in the placebo group) and patient preference (7% in both groups). Data from carotid B-mode ultrasound examinations were available from all randomized patients at baseline and between 88% and 95% of patients during follow-up. Data from M-mode echocardiography examinations were available from 94% of patients at baseline and between 77% and 81% of patients during follow-up. Data on vital status at the end of follow-up were available for all but one patient (assigned placebo). The average duration of total follow-up was 4.7 years.

On average overall follow-up, there was a 6 mm Hg reduction in systolic BP and a 4 mm Hg reduction in diastolic BP in the ramipril group compared with the placebo group (both p < 0.0001) (Table 2). The sizes of the reductions in BP at year 2 and year 4 were similar. There was no significant difference in the change in common carotid far wall thickness from baseline to follow-up between ramipril and placebo groups (0.01 mm, p = 0.58) nor was there any difference between groups in the change in carotid plaque score (p = 0.93) (Table 3 and Fig. 1). There was a small increase in the common carotid artery lumen diameter in the placebo group compared with the ramipril group during follow-up (0.06 mm, p = 0.02). After adjustment for the expected effects of these differences in lumen diameter on carotid artery wall thickness (assuming conservation of wall mass and an inverse relationship between change in radius and change in wall thickness), there was still no evidence of any effect of study treatment on far wall thickness (p = 0.98). By year 4, there was a 3.8 g/m² reduction in LV mass index in the ramipril group compared with the placebo group (p = 0.04). This change was associated with a small increase in LV end diastolic dimension in the placebo group compared with the ramipril group (p = 0.004). The differences between groups in LV mass index and end diastolic dimension were similar at years 2 and 4.

During follow-up, 41 patients died (16 in the ramipril group and 25 in the placebo group, p = 0.17), and 279 people in the ramipril group and 289 in the placebo group were admitted to the hospital at least once (p = 0.18) (Table 4). For the combined end point of death from cardiovascular disease or hospital admission for MI, unstable angina, CHF
or stroke, there was no evidence of a difference in the frequency of this outcome in the ramipril and placebo groups (relative risk 0.95), but the confidence interval was wide (0.69–1.31). There were nonsignificant trends toward fewer deaths from cardiovascular disease in the ramipril group (relative risk 0.43, 95% confidence interval 0.19–1.03) and fewer major coronary events (death from coronary disease or nonfatal MI) in the ramipril group (relative risk 0.66, 95% confidence interval 0.39–1.14).

**DISCUSSION**

This randomized trial is the largest completed study of the effects of any ACE inhibitor on atherosclerosis in any patient population. Its results provide no evidence of an effect of long-term treatment with ramipril on carotid atherosclerosis among patients with coronary or other occlusive vascular disease. There was more than 80% power to detect a difference of 0.05 mm in carotid wall thickness between patients assigned ramipril or placebo, so it is unlikely that any real effect of treatment greater than about 5% would have gone undetected. However, the study would not have been able to reliably detect smaller effects of treatment on carotid atherosclerosis. With regard to the sensitivity of the study to detect plausible treatment effects, it is noteworthy that in a trial of similar size and duration using the same ultrasound methods, cholesterol lowering with an 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor was shown to produce a clear reduction in the progression of carotid atherosclerosis among patients with coronary heart disease (9). This study recorded too few major cardiovascular events to provide reliable evidence about moderate effects of treatment on such outcomes; however, the 95% confidence intervals for the estimates of treatment effect were consistent with those effects observed in the HOPE study (3) and others (1,2).

The absence of any demonstrable effect of ramipril on carotid atherosclerosis in this study is consistent with the findings of the only other major randomized controlled trial that has reported effects of an ACE inhibitor on atherosclerosis. In the atherosclerosis substudy of the QUIET (Quinapril Ischemic Events Trial) trial, 453 patients with coronary heart disease were randomized to receive quinapril or placebo, and after three years there was no evidence of any effect of study treatment on coronary atherosclerosis assessed by angiography (11). The only other moderate-to-large-scale studies to have investigated the effects of these agents on the coronary arteries are those trials of ACE inhibitors in patients undergoing coronary angioplasty, which showed no effect of treatment on the rate of restenosis (12–14). These negative trial results in humans contrast with the evidence of marked anti-atherosclerotic and anti-proliferative effects of very high-dose ACE inhibition in studies of diet- or endothelial injury–induced atherosclerosis in animals (5–8). These observations raise doubts about the value of some animal models of atherosclerosis for the

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**Table 3.** Common Carotid Artery and Left Ventricular Measurements in Randomized Groups at Baseline and Follow-up

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Year 2</th>
<th>Year 4</th>
<th>p Value*</th>
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*Two-sided p value for interaction between treatment group and time of measurement.

**Figure 1.** Common carotid artery wall thickness (A) and carotid plaque score (B) in placebo and ramipril groups at baseline and at follow-up.
investigation of drug effects and of the use of drug doses in experimental studies so far outside the range of that typically used in humans.

The results of this trial suggest that mechanisms other than reduced progression of atherosclerosis are likely to mediate the main effects of ACE inhibitors on the risk of coronary events and other serious cardiovascular outcomes. The results of this study suggest that reduced BP and LV mass among patients treated with an ACE inhibitor may be more relevant. Both these outcomes have been shown to predict coronary disease and other cardiovascular events in various populations (15–18). Similar effects of ACE inhibitors have previously been observed in trials in hypertensive patients with LV hypertrophy (19,20). Whether such effects on BP and LV mass account for all of the reduction in coronary events observed in trials of ACE inhibitors is uncertain. From epidemiological data (15) it can be estimated that the reduction in BP observed in this study could account for as much as a 15% reduction in coronary events (i.e., about three-quarters of the reduction in coronary events observed in the previous trials of ACE inhibitors [1–3]). However, it is also possible that there are other mechanisms by which ACE inhibitors might alter coronary risk, including reversal of endothelial dysfunction (21), leading, perhaps, to increased plaque stability and reduced risk of plaque rupture. Further research on the mechanisms of benefit from ACE inhibition is required.

In summary, the results of this trial provide no evidence of any substantial effect of ACE inhibitors on carotid atherosclerosis. However, the results extend to nonhypertensive patients the evidence that treatment with these agents not only reduces BP but also reduces LV mass. Changes in these or other mechanisms, rather than changes in atherosclerosis, appear more likely to mediate the beneficial effects of ACE inhibitors on coronary events and other serious cardiovascular outcomes observed in randomized controlled trials. Whether other BP-lowering drugs have effects on atherosclerotic progression is still somewhat uncertain. Two large studies comparing the effects of calcium antagonist- and diuretic-based therapy in hypertensive patients have provided weak evidence of reduced atherosclerotic progression among patients assigned the calcium antagonist (22,23). The clinical consequences of any such differences between the effects of BP-lowering drugs are uncertain, but these should be determined by the ongoing large-scale trials comparing the effects of various agents on cardiovascular disease mortality and morbidity (24).

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Reprint requests and correspondence: Dr. Stephen MacMahon, Institute for International Health, The University of Sydney, PO Box 1225, Crows Nest, Sydney NSW 1585, Australia.
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