3.3.2 Treatment assignment

Run In: On identification of eligibility, the patient entered a run-in phase. During this time the patient was to receive 2.5mg once daily of active ramipril for 7-10 days followed, after a blood test, by placebo ramipril for 10-14 days. This phase was single blind and was conducted to exclude patients who were unable to tolerate an ACE-I or who were non-compliant.

Randomization: Once identified as eligible, the centre would contact the central randomization service. On confirmation that the patient was eligible they were provided with a 4-digit randomization number (last four digits of the patient ID#). The HOPE study medication kit bearing the randomization number was then given to the patient.

As a result of the two by two factorial design, randomization allocation was done in blocks of 8 and stratified per centre to ensure equal randomization into each of the four cells. For those patients in the SECURE substudy, a three by two factorial design was used. Therefore randomization allocation was done in blocks of 12 and again stratified by centre.

3.3.3 Packaging, labeling, storage and drug destruction

Ramipril: Hoechst Marion Roussel provided the ramipril 2.5mg, 5.0mg and 10.0 mg capsules or tablets and matching placebo. Tablets were used in Europe to comply with approved formulations. Bio-equivalence between the two formulations (capsules and tablets) has been previously demonstrated [18].

Vitamin E: The Natural Source Vitamin E Association provided d-alpha tocopheryl acetate and matching placebo, which was encapsulated by Banner Pharmacaps.

3.3.4 Unblinding

The randomization schedule was stored in the HOPE Project Office in Canada. Central as well as local emergency unblinding was available. Unblinding was only recommended when absolutely necessary in the judgment of the patient's physician. Prior to unblinding, the centre was asked to call the Canadian Project office. Central as well as local (separate sealed envelopes for ramipril and vitamin E arms) unblinding was provided.

3.3.5 Medication compliance

The investigator or delegate at each centre was responsible for ensuring that the patient received a further supply of study medication at each study visit. Centres were encouraged to maintain patients on study medication throughout the study unless the patients clinical condition indicated otherwise. If patients had been withdrawn from treatment for tolerance problems study medication was re-introduced if and when possible.

75% compliance was recorded for each treatment at each visit. This was measured using pre-printed gradations on the side of each medication bottle.

If a lower drug dose of Ramipril was believed to be likely to increase adherence, the dosage could be reduced temporarily. Only in cases of extreme adverse reactions was the study medication withdrawn. If the drug was stopped, every attempt was made to restart it if medically appropriate.

3.3.6 Patient history at study entry

Relevant cardiovascular and medical conditions along with current medications were recorded at entry to the study. Medications were recorded again at the 2-year and penultimate visit.

3.4 Study procedures and schedule

Patients first participated in a run-in phase to determine eligibility. This involved an initial visit and subsequent follow-up blood work. Patients returned approximately 3 weeks later and eligibility for randomization was assessed. If eligible, patients were randomized and follow-up visits occurred at one month and six months and every six months thereafter. Assessments carried out at each of these visits are shown in Figure 1.

3.5 Data collection

3.5.1 Method of data collection

At the outset of the study investigators received appropriate study case report forms all containing a unique barcode for that page and visit. Investigators completed the case report forms and faxed these centrally to the Project Office. The Investigator then kept the original case report form and made any subsequent corrections or additions to this form only, and refaxed the page.

The system used for data collection was the DataFax® software. This software allows for electronic receipt of faxed case report forms. The software then scans the images and uses image character recognition to enter numbers and "checks" directly into the database. The barcode found at the top of each form allows the software to correctly assign the page in the database. An image of this scanned data is then verified against the electronically held faxed form by data entry staff. In addition, text fields are entered at this time. This software also allows for routine monitoring of patient schedules, recruitment rates and medication re-ordering. The DataFax system (a commercially available product) provides substantial gains in accuracy and speed of data collection and is an excellent clinical trial management system for large studies. This software has been used by both academic and industrial clients and has been used for 2 successful NDA applications with the FDA.

All investigators were provided with written guidelines on form completion and use of DataFax. To facilitate form completion and ensure data quality, regional variations (in text only) occurred on some case report forms. It should be noted that the data collected from each region was identical.

3.5.2 Information collected

3.5.2.1 Clinical Data

At each visit a routine clinical examination was carried out, the results of which were recorded on the relevant page of the case report form. A summary of the information collected and frequency with which it was collected is provided below:

Variable	Method Obtained	When Collected
Blood Pressure	2 measurements on each arm: avg of lowest measurement from each arm	Baseline, 2 yrs and end of study
Ankle Blood Pressure	Avg of 2 measurements on one leg	Baseline, 2 yrs and end of study
Heart Rate	Measured for 30 secs in supine	Baseline, 2 yrs and end of study
Waist Measurement	Narrowest part of waist	Baseline
Hip Measurement	Widest part of hips	Baseline
Weight	Measured	Baseline, 2 yrs and end of study
Height	Measured	Baseline, 2 yrs and end of study
Medication Usage	Patient report	Baseline, 2 yrs and end of study
ECG	Measured	Baseline, 2 yrs and end of study (copy sent to the Project Office each time, but not read centrally)

Relevant history and event details were also recorded at each visit and are summarized below:

Variable	Method Obtained	When Collected
Compliance	Patient report and pill review	At every six month visit
Use of open label ACE-I	Patient report	At every six month visit
Use of A2 antagonist	Patient report	At every six month visit from 2 yr visit on
Laser therapy for diabetic retinopathy	Patient report	At every six month visit
Transient Ischemic Attack	Patient report	At every six month visit (note this may also be collected on hospitalization report)
Congestive Heart Failure	Patient report	At every six month visit (note this may also be collected on hospitalization report)
Renal Dialysis	Patient report	At every six month visit (note this may also be collected on hospitalization report

The table below summarizes the schedule by which outcome data were collected:

Variable	When and How Collected
Primary Outcome	
MI*≅	At each six month follow-up visit on specific event reports
Stroke≅	
Cardiovascular Death*≅	
Secondary Outcomes	
Revascularization Procedures≅	At each six month follow-up visit
Hospitalization for Angina≅	
Hospitalization for CHF*≅	
Cancer	
Total Mortality*≅	
Overt Nephropathy *	For diabetic patients: If annual dipstick is positive or if central sample (baseline, 1 yr, end of study) albumin:creatinine ratio is >36 mg/mmol. For non-diabetic patients: If baseline or end of study urine sample albumin:creatinine ration is > 36mg/mmol.
Other Outcomes	
Heart Failure	At each six month follow-up visit by patient report
Cardiac Arrest	At each six month follow-up visit on hospitalization report
Worsening Angina	At each six month follow-up visit by patient report . Worsening of one class according to Canadian Cardiovascular Societies' grading of angina of effort
New diagnosis of diabetes	Annually and at end of study

*specific event forms collected

≅ centrally adjudicated events

3.5.2.2 Laboratory Data

The following laboratory assessments were completed at the times specified:

Assessment	Visits	Patient Group
Local Serum Creatinine	Pre-randomization 1 month Annually	All patients All patients Patients with diabetes
Local Serum Potassium	Pre-randomization 1 month	All patients All patients
Local Glycated Hb	Pre-randomization Annually	Patients with diabetes Patients with diabetes
Local urine dipstick to screen for overt nephropathy	Run-In Annually	All patients Patients with diabetes
Urine sample sent centrally (for assay of albumin and creatinine)	Randomization 1 year End of Study	All patients Patients with diabetes All patients
24 Hour urine sample local	Throughout study when central sample albumin:creatinine ratio > 36 mg/mmol or dipstick was positive	All patients
Blood sample sent centrally **CANADA ONLY**	Randomization	Only in those patients who consented and those centres who were able to comply with requirements for blood collection

3.5.2.3 Safety Data

ACE-I have been used extensively in clinical practice in the last decade. Data from 3 large long-term trials, involving over 9,000 high risk patients treated with enalapril (SOLVD)[3,5] or captopril (SAVE)[6] compared with placebo, over about 3.5 years, indicates substantial safety. In SOLVD, there were only two instances of severe angioneurotic edema among 7,400 patients (both were detected during the run-in phase), and only a few patients with hyperkalemia (4%) elevated creatinine (3%), dizziness (7%) or cough (6%). Most of these effects were mild and did not require stopping the study drug; the excess in the percentage of patients stopping medications for side effects was only 4.8% in SOLVD. Ramipril is an ACE-I with greater tissue specificity than enalapril or captopril and can achieve ACE-inhibition at relatively low doses. Data from controlled trials of Ramipril involving over 4,000 patients indicate that side-effects are few (discontinuations for cough was 1%, for dizziness 0.5% and impotence 0.4%).[19] Ramipril has been registered for use in 24 countries, including Canada and the U.S.

Streamlined adverse event reporting procedures were employed because of the vast amount of safety information already available for ACE-I and in particular ramipril. Information regarding temporary or permanent withdrawal of study medication or dose reduction was collected at each visit. The medical management of adverse reactions was at the discretion of the patient's physician, and depended on the severity of the adverse reaction and the clinical setting in which it occurred. Minor adverse events were not reported to regulatory agencies.

Serious adverse event reporting procedures were also modified. Deaths, primary endpoints and secondary endpoints were all expected in the study. Only those events, which in the view of the investigator were unexpected, serious **and** believed to be associated with the study treatments, were reported. Reporting was done by completion of a Serious Adverse Experience (SAE) Form. Periodic (unblinded) tabulation of adverse events by study group were provided to the independent Data and Safety Monitoring Board and these data would have been shared with the regulatory authorities if necessary. Routinely however, regulatory authorities were kept informed about the progress of the study.

3.6 Withdrawal and replacement procedures

Since this was an intention to treat study there was no withdrawal from follow up. Patients who discontinued study medication continued to be followed up at the intervals specified in the protocol. All patients withdrawn from study medication were included in the analysis. It was not mandatory to withdraw patients from treatment if the code was broken.

3.7 Quality assurance and quality control

Use of the DataFax software permitted immediate identification of data omissions and inconsistencies. Regular summaries (quality control reports) of the outstanding data queries (quality control notes) were compiled and faxed to centres on an ongoing basis throughout the study.

Checks for consistencies within and between forms were run weekly on all data. .

3.7.1 Standardization procedures

Data was collected centrally at the Canadian Cardiovascular Collaboration (CCC) Project Office in Hamilton, Canada. All data checks were applied consistently according to Project Office standard operating procedures and data validation plans.

For logistical reasons there were four laboratories that performed the central urinary albumin and creatinine in the various geographical areas. Reliability studies were undertaken to ensure consistency across labs.

For all local laboratory assessments of creatinine, potassium and glycated Hb the upper limits of normal was collected for each measurement and recorded on the case report form. All of the local laboratories used the local and national guidelines applicable to ensure adequate quality control and standards.

3.7.2 Data quality assurance

Various measures were taken during the study to maintain high quality data. These are summarized below.

3.7.2.1 Training of study personnel

All Project Office staff, monitors and individual centre staff underwent appropriate training sessions prior to study commencement, and on an ongoing basis to ensure uniformity in study procedures and to address any issues. A detailed outline of each step of the protocol was provided to centres. Project Office staff were available to answer questions or to assist with operational issues. Further, a toll-free assistance number was also available to resolve procedural problems. Investigators and study staff were informed of study status and procedural issues at regular intervals. Various methods were used to disseminate this information including study meetings, newsletters and correspondence.

3.7.2.2 Data collection and correction

After forms were completed and faxed, centres would receive feedback within 14 days. Centres were then informed about missing visits, missing variables or inconsistent data via the DataFax quality control (QC) system. This system allowed for easy compilation of all quality control notes (QC notes) that had been placed on records at the time of data validation. The summary of all outstanding QC

notes was sent to the centres via fax as a QC report at regular intervals (usually every two weeks). Procedures for applying and resolving data queries are shown in the data validation plan.

3.7.2.3 Event adjudication procedures

To ensure that a consistent set of definitions for endpoints were applied, a select committee reviewed all primary and secondary endpoints. Definitions for each primary and secondary endpoint can be found as a supplement to this document.

When a patient had either a primary or secondary endpoint occur, the centre first was asked to complete and fax all relevant event reports. Concurrently they were asked to collect supporting documentation for each endpoint (with relevant translations) and send this to the Project Office. Once all relevant information was received, the event was assigned to an adjudicator. If there was disagreement between committee member and investigator the event was then sent to the committee chair for final decision. Only certain committee members were permitted to adjudicate deaths. All outcomes of the adjudication process were entered into the Event Adjudication database.

As a check on the adjudication process, a blinded committee member reviewed 10% of those events confirmed by an adjudicator. The results of this internal quality check indicated there was a high degree of consistency between adjudicators. The results of this quality check were presented to the Steering Committee.

3.7.3 Monitoring and auditing

Monitoring resource varied between countries. Use of the DataFax system and local regional coordinators together with the depth of knowledge of ramipril, permitted an adapted frequency of monitoring. We were able to target monitoring visits to those centres where specific problems were identified. Because of the rapid receipt of data, problems were quickly identified, enabling a response before the problems were perpetuated.

Monitors were not required to do usual case report form checking collection because of the data management system used. Therefore at the monitoring visits they were able to focus on issues such as recruitment, provision of supporting data for endpoints and longstanding or extensive data queries. In addition the following key data points were verified (above and beyond what was requested by protocol) against source data:

Variable	Region	Type of Verification
Informed consent (baseline and extension)	North America	Sent centrally to Project Office
	Europe & Latin America	Verified locally at each centre
Main reason for study entry	All regions	Verified locally at each centre
Verification of primary and secondary endpoints	All regions	Verified centrally
Verification of absence of events – 10% of patients for whom no event reported (to check for underreporting)	All regions	Verified locally

Independent auditing was conducted by HMR clinical quality assurance.

4.0 PRIMARY, SECONDARY AND OTHER OUTCOMES

The primary study outcome was the composite outcome 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 provided as a supplement to this briefing document.

4.1 Important subgroups

The effects of each intervention in the following sub-groups were examined for consistency; patients with coronary disease, with cerebrovascular or peripheral arterial diseases, with diabetes, with hypertension; men or women; and by age group. One further important substudy was MICROHOPE (Microalbuminuria In Cardiac and Renal Outcomes in the HOPE study)[17] which examines the development and progression of microalbuminuria to overt nephropathy in patients with diabetes.

In addition, the effect of treatment among patients with a **documented** ejection fraction of at least 0.40 was collected retrospectively and analyzed (patient was excluded if they had a known ejection fraction of less than 0.40 at baseline).

4.2 Safety variables

The pre-specified outcomes are not included as safety variables. Reasons for the permanent withdrawal of study medication were analyzed. In addition any serious adverse events meeting the protocol criteria will be described in detail.

4.3 Statistical methods

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 time 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.

All primary and secondary outcome analyses include all patients randomized since the original statistical plan called for an intention to treat analysis only.

The Cox model was also be used for treatment effect estimates that were adjusted for baseline-prognostic imbalances. All analyses were carried out using SAS for Unix 6.12.

5.0 DATA AND SAFETY MONITORING BOARD PROCEDURES AND INTERIM ANALYSES

An Independent Data and Safety Monitoring Board (DSMB) monitored the progress of all aspects of the study. Four formal interim analyses were planned originally. Because of the study extension the DSMB met 6 times (1 initial meeting, 4 interim analyses and one final meeting) during the study . The

meeting dates were as follows: 23rd September 1994, 17th October 1995, 27th September 1996, 8th November 1997, 19th November 1998 and 22nd March 1999The statistical monitoring boundary indicating that ramipril had a beneficial effect was a difference in the primary outcome of 4 standard deviations (SD) between groups during the first half of the study and of 3 SD during the second half. The respective boundaries indicating that ramipril may have 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 is April 15 1999.

6.0 RESULTS - STUDY SUBJECTS AND CONDUCT

6.1 Subject accounting

Patients were recruited from December 1993 to August 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. Randomization from each area is summarised in Table 1.

10710 patients were screened for the study of which 134 were not eligible for the run-in period. Reasons for ineligibility for run-in were protein >1+ (96, 0.9%), current use of open label ACE (25, 0.2%) with the inability to discontinue, current use of vitamin E (7 ,0.1%) with the inability to discontinue use and a combination of the above mentioned reasons (6, 0.1%). A total of 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 (also listed in Table 1). A total of 1035 patients were subsequently excluded from randomization. The most common reasons for not continuing in the study were non-compliance and withdrawal of consent. Other reasons included side effects, abnormal serum creatinine or potassium levels, discovery that patients was already receiving ACE inhibitor or vitamin E treatment with the inability to discontinue use (Table 2).

Of the 9541 remaining patients, 4645 were randomly assigned to receive 10 mg of ramipril 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 as shown in the table below.

	Ramipril 10 mg	Ramipril Placebo	Subtotal	Ramipril 2.5 mg	Total
Vitamin E	2326	2311	4637	124	4761
Vitamin E Placebo	2319	2341	4660	120	4780
TOTAL	4645	4652	9297	244	9541

6.2 Protocol deviations and operational issues

The only deviations detected from the protocol were considered of little significance by the Steering Committee, to the outcome of the study. Adherence to the protocol was monitored throughout the study by review of data received and some on site monitoring and any issues arising were resolved as they appeared. Specific points of note are: all patients met the eligibility criteria with the small exception of nine patients who were less than 55 years of age at randomization:

Patient	Age	CALLDATE	DOB
0053571	54	6-May-94	31-Mar-40
5111466	46	20-Sep-94	8-Jan-48
6142593	54	29-Mar-95	2-May-40
6142596	54	29-Mar-95	7-Apr-40
8595113	52	26-Apr-95	17-May-42
8775242	48	24-May-95	10-Aug-46
8775244	46	24-May-95	31-Dec-48
8815305	54	22-Feb-95	7-Jun-40
8815309	54	22-Feb-95	27-Dec-40

Randomization of patients occurred centrally in all regions. In 95 cases the centrally provided randomization number was accidentally not used. 21 of these cases received the correct treatment allocation by chance and did not require re-randomization. In the remaining cases the patient was re-allocated to the correct treatment without the blinding being broken (Table 3A). Although it was unlikely that these errors were caused by local bias, the protocol mandated that randomization could only be performed through a central process. Patients were therefore returned to the centrally allocated treatment with the minimum of delay. Because of the rapid detection and correction in each case there was a minimal time lag until the patients received the correct allocation. Although it is anticipated that this would have had a negligible effect on study outcome, if such an effect did exist it would result in an underestimate in treatment effect

The unblinding envelopes provided for use in emergencies at the site were opened in 16 cases (Table 3B). The most common reason for unblinding was hypotension. In the majority of cases the patient was not given the treatment code and only the investigator was unblinded. Note that all centers were provided with a list of ramipril/placebo treatment allocations on request after the database was closed at the end of the study. Since the vitamin E arm of the study is continuing the unblinding information for this arm of the study has not been provided to centres.

The recruitment strategy for this study was to include patients perceived as high risk and the inclusion criteria were seen as a practical guide to investigators to allow them to accomplish this. In 16 cases investigators included patients they considered to be at 'high risk' despite the fact that they were unable to capture the risk profile on the case report form . The majority of these cases were prior surgery for abdominal aortic aneurysm and were considered high risk by the investigator because of relevant past medical history or existing concomitant conditions or treatment at the time of entry to the study.

6.3 Administration of study medication

Patients were randomized to ramipril (2.5 mg once daily for 1 week then 5 mg once daily for 3 weeks then 10 mg once daily) or placebo and vitamin E 400 IU once daily or placebo utilizing a 2 X 2 "factorial" designThe relevant HOPE Study Medication Kit with the correct randomization number was given to the patient. The option existed for the patient to decrease the dose of ramipril during the study if required. Where patients required open label ACE inhibitor according to the discretion of the treating physician they were encouraged to stop their blinded study medication.

6.3.1 Visit compliance

Patients were encouraged to return to visits whenever possible, but follow-up information could also be obtained by telephone or third party. The number of patients for whom information on vital status was obtained remained high throughout the study, with information on 99.9% of eligible patients being collected at the final visit. For the purposes of the analyses all patients who returned or for whom information was collected by phone were counted as compliant. The number and proportion of patients returning annually is presented in Table 4A. The reasons patients did not return for clinic visits are listed in Table 4B. Since visit compliance was balanced and high for both groups there are no visit compliance issues for this study. Despite intensive efforts there were six patients for whom vital status could not be ascertained at the final visit. A summary of visit compliance for the final study visit can be found in Table 4C.

6.3.2 Medication compliance

A noted difficulty with long-term mortality studies is maintenance of study medication compliance. Measures taken during the study to maintain compliance were clearly effective as can be seen by the high overall medication compliance (Table 5A). The number and percentage of patients still taking each of the blinded study medications at each annual visit is shown in Table 5A. and at the final visit in Table 5B. In addition, those patients who could not tolerate full dose were given the option of taking a lesser dose (2.5 mg, 5.0mg or 7.5 mg and matching placebo). At the one year visit 120 (2.6 percent) of patients in the ramipril group and 58 (1.3 percent) of patients in the placebo group were on a reduced dose of study drug. This had increased slightly by the four year visit with 204 (5.2 percent) of patients in the ramipril group and 107 (2.8 percent) of patients in the placebo group receiving a reduced dose (Table 5A). It was expected that some of the patient population would become more ill as the study progressed and may at sometime require the use of an open label ACE-I, which would dilute the effect of treatment. Table 5C shows the number of patients in each group who received open label ACE-I. Note that the difference between the total number of patients taking ACE-I and the number of patients in the placebo group who received an active ACE-I is known as the "contrast" between the two groups. It is important to maintain high contrast in any study, as this is the only way of testing the true difference between the treatments. The contrast at the end of the study was 66.6%, indicating the results presented below are probably an underestimate of the true effect of ramipril.

Reasons for discontinuation of study medication are discussed in the safety section below.

6.4 Demographics and baseline characteristics

As intended a high risk population was recruited to this study. Tables 6A, 6B and 6C demonstrate the high risk profile of the complete population and the subgroups.

The overall baseline characteristics of the 9297 patients who underwent randomization are shown in Table 6D. The number of patients in each of the important subgroups is shown below. 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. There were no obvious differences in baseline characteristics between the treatment groups and the baseline characteristics in the major subgroups of CAD and patients with diabetes are shown in Tables 6E and 6F to exemplify this.

6.5 Concomitant medication

HOPE study medication was taken in addition to required drug treatment. Table 7 (A, B, C) shows concomitant medication at randomization, 2 years and penultimate study visit. The groups were

balanced at baseline. It is important to note that all of the efficacy data presented in section 7 below shown an effect of ramipril, which is **in addition** to this standard therapy.

6.6 Physical exam and local laboratory determinations

The results of the physical exam and local lab measurements for baseline, 1 month, 2 year and penultimate visits are shown in Tables 8A, B, C and D respectively. Again the groups are evenly matched on all of these variables. From the table it is evident that the patient population had well controlled blood pressure. Some of the derived parameters such as waist to hip ratio and body mass index are slightly higher than normal, which would be expected in this high-risk group.

The results of ECG measurements are shown in Table 9. As expected, approximately 2/3 of the subjects had an abnormal ECG at baseline.

Table 10A shows the number of patients with an abnormal albumin to creatinine ratio (≥ 2.0). There is no difference in the incidence of abnormal ratios between the groups at baseline.

7.0 RESULTS – EFFICACY

Vital status was ascertained for 9535 patients (99.9 percent) at study end. All events occurring up to and including April 15, 1999 are included in these analyses. The results of this study have been published [20] and the NEJM made the unusual step of releasing the paper electronically ahead of its publication date because of the potential therapeutic implications of the results. In addition the results of the study in the diabetic population have also been published separately [21]. As might be expected the collection of outstanding data, resolution of outstanding queries and additional data validation has continued beyond the preparation of the paper and for that reason the numbers presented in this section may differ slightly from those in the publication. In no aspects are any of these differences significant but it was felt appropriate to present the most up to date data known in this report.

7.1 Analyses of primary efficacy variable

There was significant benefit in the ramipril group when the composite primary outcome of myocardial infarction, stroke or cardiovascular death was examined: 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) (Table 11A and Figure 2). As can be seen from the survival curve (Figure 2) the reduction in risk of the composite outcome with ramipril therapy was apparent as early as one year after randomization (169 patients in the ramipril group reached the outcome compared to 198 in the placebo group; relative risk 0.85; 95% confidence interval 0.70 to 1.05). This reduction was significant at two years (326 versus 398 patients, relative risk 0.82; 95 percent confidence interval 0.70 to 0.94). The results are consistent for events as reported by centre (i.e. prior to adjudication) (Table 11B), and with the inclusion of the 244 patients on low dose (2.5mg) in the active ramipril group (Table 11C).

In addition to the effect on the composite primary outcome there were significant reductions in risk when each component of this endpoint was examined separately (Table 11A and Figures 3,4,5): 282 (6.1 percent) patients in the ramipril group died of cardiovascular causes, as compared with 377 (8.1 percent) patients in the placebo group (relative risk, 0.74; 95 percent confidence interval, 0.64 to 0.87; P<0.001); 459 (9.9 percent) patients in the ramipril group had a myocardial infarction, as compared with 570 (12.3 percent) patients in the placebo group (relative risk, 0.80; 95 percent confidence interval, 0.70 to 0.90; P<0.001); and 156 (3.4 percent) patients in the ramipril group had a stroke, as compared with 226 (4.9 percent) 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=0.0053).

As can be seen in Table 12 the event rates for those taking active ramipril together with active vitamin E and for those taking active ramipril but assigned vitamin E placebo were very similar. Treatment with ramipril 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, 0.77; P<0.001; P=0.81 for the test of heterogeneity of two relative risk s).

Although the primary outcome demonstrated considerable benefit, it is important to examine the effect on each of the individual components of the composite to ensure there is consistency. As can be seen in Table 13 there was significant benefit of ramipril on the individual outcome of MI. Event rates categorized by type of MI further support the outcome as relative risk reductions all trend towards a beneficial effect of ramipril. The same supportive trends can be seen with respect to the data on strokes. Again significant benefit of ramipril was seen for the individual outcome of stroke. Table 14A illustrates the benefits seen in each type of stroke. In addition, Table 14B demonstrates the effects by resulting functional disability. Again benefit is seen consistently regardless of whether there are residual functional deficits or if the stroke resulted in fatality. Referring back to Table 11 and Figure 6, there is again a statistically significant effect on the outcome of cardiovascular death. As one would expect, there is no effect on non-cardiovascular death.

Although ejection fractions were not requested at randomization, patients were excluded if they had a known ejection fraction of <0.40 or clinical heart failure. At the end of the study centres were asked to report if the patient has ever had their ejection fraction determined. This retrospective chart review found that 5196 patients had a documented ejection fraction (either before or after randomization). 242 (4.7 %) patients had a low ejection fraction before randomization. As further support to the primary outcome, a separate analysis of the primary outcome was performed for those patients with known preserved ventricular function (either before or after randomization). The treatment was clearly beneficial in this subgroup of 4775 patients with a relative risk, 0.73; 95 percent confidence interval, 0.63 to 0.84; P<0.001 (Table 15).

7.2 Analyses of secondary efficacy variables

The effect of ramipril on the incidence of secondary outcomes is shown in Table 16A. Significantly fewer patients in the ramipril group than in the placebo group underwent revascularization (743 (16.0 percent) vs. 854 (18.4 percent); relative risk, 0.85; P=0.0014), and there was a trend toward fewer hospitalizations for heart failure in the ramipril group (141 (3.2 percent) vs. 161 (3.5 percent); relative risk, 0.87; P=0.22) (Table 16). In addition, significantly fewer patients in the ramipril group than in the placebo group had a cardiac arrest (37 (0.8 percent) vs. 59 (1.3 percent); relative risk, 0.62; P=0.02), worsening angina (1107 (23.8 percent) vs. 1222 (26.3 percent); relative risk, 0.88; P=0.003), heart failure (417 (9.0 percent) vs. 534 (11.5 percent); relative risk, 0.77; P<0.001), a new diagnosis of diabetes (102 (3.6 percent) vs. 155 (5.4 percent)(Figure 6); relative risk, 0.66; P<0.001), or complications related to diabetes (303 (6.5 percent) vs. 356 (7.7 percent); relative risk, 0.85; P=0.038). However, treatment with ramipril had no effect on the likelihood of hospitalization for unstable angina.

Significantly fewer patients in the ramipril treatment group experienced heart failure and this was reflected in the reduced number of patients being withdrawn from study medication to receive open label ACE I treatment in the ramipril group (Table 17A). This effect was consistently seen in patients hospitalized for heart failure, in heart failure death and in cardiovascular death attributed to heart failure (Table 17A).

The percentage of patients who were receiving non-study angiotensin-converting-enzyme inhibitors for heart failure was 240 (5.2 percent) in the ramipril group and 327 (7.0 percent) in the placebo group; 59 (1.3 percent) and 60 (1.3 percent,) respectively, were receiving such drugs because of proteinuria, and 222 (4.8 percent) and 301 (6.5 percent) for control of hypertension (Table 17B). The use of open-label angiotensin II-receptor antagonists in both groups was low (68 (1.6 percent) in the ramipril group and 79 (1.9 percent) in the placebo group (Table 7C), but the reasons for such use were similar to those for angiotensin-converting-enzyme inhibitors.

As noted above significantly fewer patients in the ramipril treatment group underwent revascularization and this effect was consistent for any type of cardiovascular revascularization (Table 18).

The survival curve for the combined endpoint of all relevant outcomes (primary outcome + revascularization + all heart failure) is shown in Figure 7A. 1357 patients in the ramipril group experienced the composite of these endpoints compared to 16 patients in the placebo group (relative risk, 0.81; 95 percent confidence interval 0.75 to 0.87; P<0.001). A similar outcome can be noted for the composite of cardiovascular death and hospitalization for heart failure (Figure 7B).

In addition, treatment with ramipril had a protective effect on the development of overt nephropathy. In the ramipril group 144 (3.1 percent) patients developed overt nephropathy compared to 185(4.0 percent) in the placebo group (relative risk of 0.78; 95 percent confidence interval 0.63 to 0.97; P =0.027) (Table 19, Figure 8). Although not every patient was able to complete a 24-hour urine sample, the majority did and the results in this group are identical to the overall results. The development of new microalbuminuria was also less in the ramipril group (765 (20.7 percent) vs. 847(23.2 percent); relative risk 0.90; P=0.04)(Table 19).

7.3 Subgroup analyses

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 (Figure 9, Table 20). In addition, there was a clear benefit of ramipril among patients with evidence of coronary artery disease at baseline (Table 21) and those with no evidence of it and among those with a history of myocardial infarction and those with no such history.

Patients with Diabetes

As noted above the risk reductions in the ramipril group for both the primary and secondary outcomes were consistent across many sub-groups including the very significant diabetic subgroup randomized to this study. 38% of the patients randomized to the HOPE study had diabetes at baseline and the effects of ramipril on the outcomes in this important group are shown in Table 22 and Figure 10. The effects of ramipril were similar to that seen in the overall group. Specifically the primary outcome, and it's individual components, the need for revascularizations and all reports of heart failure were significantly reduced for those patients with diabetes who were taking ramipril. In addition these effects were seen regardless of whether patients were on insulin or oral hypoglycemics (Figure 11). As shown in Table 23, patients with diabetes who took ramipril also had significantly less overt nephropathy and less progression to microalbuminuria.

Effect on Blood Pressure

The mean blood pressure at entry was 139/79 mmHg in both groups. The mean blood pressure was 133/76 mm Hg in the ramipril group and 137/78 mmHg in the placebo group at one month, 135/76

mmHg and 138/78 mmHg, respectively, at two years, and 136/76 mm Hg and 139/77 mm Hg, respectively, at the end of the study (Table 24). Figures 12 and 13 show the relative risk reductions by baseline systolic and diastolic blood pressure, subdivided by quartiles. Risk reductions are seen in each quartile for both systolic and diastolic blood pressures. As noted above the beneficial effects of ramipril were noted in those with hypertension at base line and those without it. Adjusting the benefit due to ramipril for change in blood pressure during the trial, the relative risk estimate remained the same.

CONCOMITANT MEDICATIONS

Benefits were observed whether or not patients were also taking beta blockers, lipid lowering agents, aspirin, or a combination of the above (Table 25). The tests for heterogeneity are also listed in Table 25.

8.0 RESULTS – SAFETY

Safety data are presented beyond the cut-off date of 15th April, which was used for the efficacy analysis

8.1 Serious adverse

When Serious Adverse Event forms were received at the Project Office, they were reviewed within 24 hours for adherence to the protocol stated definition of a serious adverse event. All serious adverse event were reviewed by the HOPE Clinical Doctor on call at the Project Office. As noted in the methods section pre-specified endpoints of the study were not reported as serious adverse events and only those events that were unexpected, serious and associated were reported as serious adverse events. There was only one serious adverse event that met the criteria for expedited reporting to regulatory authorities. This event was a ruptured esophagus (secondary to excessive coughing) and was in the ramipril group. The patient (6712700) was hospitalized and underwent surgery, symptoms abated 2 days after study medication was stopped. Patient was subsequently discharged without sequelae. The overwhelming majority of reported serious adverse events were incorrectly identified as such by investigators as these were primary or secondary outcomes.

8.2 Adverse events leading to treatment withdrawal

In addition those adverse events resulting in withdrawal of study medication were recorded in the case report form. Brief details of reason for treatment withdrawal where this occurred were given on each follow up visit case report form and are summarized in Table 26. More patients in the ramipril group than in the placebo group stopped treatment because of cough 340 (7.3 percent) vs. 85 (1.8 percent) or hypotension or dizziness 88(1.9 percent) vs. 70 (1.5 percent). By contrast, more patients in the placebo group than in the ramipril group stopped treatment because of uncontrolled hypertension 183 (3.9 percent) vs. 109(2.3 percent) or because of a clinical event – a primary or secondary outcome (8.9 percent vs. 6.6 percent). In the ramipril group, 16(0.3%) patients stopped treatment because of angioedema compared to 6(0.1%) in the placebo group.

Unblinded adverse event data were reviewed by the independent data and safety monitoring board on an ongoing basis. There were no unexpected differences between the groups..

8.3 Laboratory data

RESULTS OF LABORATORY VALUES AT RUN-IN

Serum creatinine and potassium values at 1 month (Table 8B) show that there was no clinically relevant change in levels, confirming tolerability of the drug. Lab values measured during the study

were considered to be part of the efficacy of the study and are therefore discussed in section 6.6 and 7.2.

Exceptionally high potassium or creatinine values occurring at the one month visit were flagged and referred back to investigator for follow-up.

9.0 DISCUSSION AND OVERALL CONCLUSIONS

Our findings show that ramipril, an angiotensin-converting-enzyme inhibitor, is beneficial in a broad range of patients who are at high risk for cardiovascular events including patients with and without diabetes and those without evidence of left ventricular systolic dysfunction or heart failure. 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 the diagnosis 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 complements the results of previous studies of ACE-Inhibitors among patients with low ejection fractions [6] or heart failure and acute myocardial infarction (Table 27 and 28). [16] 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 orrevascularization, unstable angina, or stable angina), a history of cerebrovascular disease or peripheral arterial 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, 1119 of whom had no clinical manifestations of cardiovascular disease, and the event rate in this group for those receiving placebo was about half that in patients with cardiovascular disease who were receiving placebo (9.9 percent vs. 23.9percent). 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, [22]aspirin, [23] and lipid-lowering agents, [24] during four years of treatment. It should be noted that HOPE study medication (ramipril/placebo) was in addition to standard therapy. 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. [25]However, the results of recent studies, such as the Hypertension Optimal Treatment Study, [26]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 [27] 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, [28] the proliferation of vascular smooth-muscle cells, [28] and rupture of plaques [29]; improving vascular endothelial function [28]; reducing left ventricular hypertrophy; and enhancing fibrinolysis. [28]

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 [3] and studies of patients after myocardial infarction, ([28,4,6, 30,31,32]) 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. [32]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, and extensive review of charts identified only 8.2 percent of patients with a low ejection fraction before randomization, and treatment was clearly beneficial in the subgroup of 4775 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, [33] or an effect on abdominal fat. [34] The results are also consistent with the results of the recent Captopril Prevention Project study, [35] 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 II diabetes [36]as well as those without diabetes. [37]

Ramipril was well tolerated and the only adverse event worthy of note is an excess of cough in the ramipril group. More patients in the ramipril group than in the placebo group stopped treatment because of cough (7.3 percent vs. 1.8 percent). There was only one serious adverse event that met the criteria for expedited reporting to regulatory authorities. This event was a ruptured esophagus (secondary to excessive coughing) and was in the ramipril group. The patient was hospitalized and underwent surgery. Symptoms abated and patient was subsequently discharged without sequelae.

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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RESULTS: STUDY SUBJECTS AND CONDUCT

Table 1: Total Patient Recruitment By Centre

Region	Vitamin E		Ramipril 10mg*			
	Active	Placebo	Active	Placebo	Not Randomized	Total
Overall	4761	4780	4645	4652	1035	10576
Canada	2852	2856	2727	2737	702	6410
USA	399	399	399	399	121	919
Europe	984	1002	999	987	152	2138
Latin America	526	523	520	529	60	1109

* Vitamin E/placebo randomization includes the 244 patients in the SECURE substudy on low dose ramipril, who are not included in the analyses of the Ramipril 10mg/placebo data.

Table 2: Reasons for Withdrawal in Run-In

	N	%
No. entering Run-In	10546	100
Randomized	9541	90.2
Not Randomized	1035	9.8
Non compliance (less than 80% of medication taken)	395	3.7
Creatinine >250 mmol/l	13	0.1
Potassium >5.5 meq/L	48	0.5
Cough	39	0.4
Hypotension/dizziness	56	0.5
Angioedema	5	0
Other side effects	182	1.7
Death	11	0.1
Ineligible	215	2.0
Refused	398	3.7
Miscellaneous	4	0

*. Note that 3 reasons for non-randomization could be recorded for each patient

Table 3: Protocol Deviations

3A: RANDOMIZATION IRREGULARITIES BY CENTRE

CANADA

Region	Number of Patients Where Re-Allocation was Required
Canada	48
Europe	33
US	3
Latin America	11

3B: PATIENT UNBLINDING PRIOR TO END OF RAMIPRIL ARM OF STUDY

Pt ID	Date of Unblinding	Date of Notification	Reason for Unblinding	Treatment Arm Unblinded	Who was unblinded?
116431	95/03/11	95/03/11	doc wanted pt on ACE	Ramipril	Investigator and patient
314558	95/02/15	95/02/15	decreased WBC	Ramipril	SS, JB, Dr. Auger, nurse, hematologist
734950	97/08/28	97/12/17	microalbuminuria	Ramipril	Dr. Zinman only
845004	98/02/17	98/02/14	Pt was hypotensive (80/ 50). The GP asked to unblind as the pt had devleped hypotension secondary to extensive progression of cancer (she believes). Pt was also taking metoprolol and she was unsure which medication to stop. She was also concerned about stopping the metoprolol and leaving the patient cardio comprimised.	Ramipril	Only the GP. GP also stated that she would not unblind the pt. Note: GP also started pt on open label vitamin E, but did not unblind.
875102	94/12/21	95/03/14	centre misunderstood QC note	Both	JB, nurse, patient
1082639	96/03/14	96/03/14	pt undergoing surgery - anaesthesiologist wanted to know	ramipril	only anaesthesiologist and JP
1095219	99/04/06	99/04/06	medical examiner request	ramipril	Investigator and study nurse. Documentation put in unblinding file
1182698	95/01/30	95/02/01	Angioedema	ramipril	JP, SR, Dr. E.M. Wagner
1505315	95/09/01	95/09/01	Overdose	ramipril	JB, CCU nurse, attending physician
1526351	99/05/06	99/05/06	Pt is travelling and cannot change medications because of insurance. Pt demanded this information.	ramipril	Dr. Imrie, pt and study nurse Jackie Askew (note this was after study medication had been stopped).
3078193		99/05/31	Husband and wife are both in the study and had switched meds at one visit by accident. Centre called PO to find out what to do. Unsure as to what exactly L. Westfall discussed with centre. AM found letter in centre file during a visit and brought a copy back to the PO. JP confirmed that pts did have same allocation.	Ramipril	To allocation - P Suhan , L. Westfall

3B: PATIENT UNBLINDING PRIOR TO END OF RAMIPRIL ARM OF STUDY

Pt ID	Date of Unblinding	Date of Notification	Reason for Unblinding	Treatment Arm Unblinded	Who was unblinded?
			P Suhan received this info but was not unblinded. Pts are once again taking the correct meds.		
3078199		99/05/31			
6121793	95/04/29	96/10/04	Hypotension	ramipril	Investigator only
6563209	96/11/18	96/12/04	pt had MI	ramipril	Ctr informed that this procedure was incorrect. Investigator, Co-Investigator, study nurse , the intensive care doctor.
7011004	95/12/14	95/12/20	MI, hypotensive	ramipril	Investigator and possibly patient
643 3358	98/12/29	99/04/27	Hospitalization for proteinuria	both	Investigator

Table 4: Visit Compliance

4A: SUMMARY OF OVERALL VISIT COMPLIANCE

	RAMIPRIL ACTIVE			RAMIPRIL PLACEBO		
	ELIGIBLE	N	%	ELIGIBLE	N	%
RANDOMIZED	4645	4645	100.0	4652	4652	100.0
1-YEAR VISIT	4565	4562	99.9	4566	4562	99.9
2-YEAR VISIT	4441	4437	99.9	4451	4451	100.0
3-YEAR VISIT	4343	4336	99.8	4303	4301	100.0
4-YEAR VISIT	4209	3920	93.1	4133	3854	93.2*

Eligible = Alive and having reached each scheduled visit

* Because of study stopping early, not all patients who were eligible for a four year visit had one. Instead they returned for a final visit.

4B: REASONS FOR NOT RETURNING TO CLINIC VISIT

*	RAMIPRIL ACTIVE		RAMIPRIL PLACEBO	
	N	%	N	%
RANDOMIZED	4645	100.0	4652	100.0
HOME VISIT	914	19.7	883	19.0
HOSPITALIZED	26	0.6	33	0.7
ILL	31	0.7	41	0.9
VACATION	23	0.5	14	0.3
REFUSED	482	10.4	417	9.0
TEMPORARILY LOST	114	2.5	114	2.5
OTHER	9	0.2	20	0.4

*not mutually exclusive

4C: FINAL VISIT COMPLIANCE

	RAMIPRIL ACTIVE		RAMIPRIL PLACEBO	
	N	%	N	%
ELIGIBLE FOR VISIT*	4150	100.0	4070	100.0
VITAL STATUS ASCERTAINED	4148	99.9	4068	99.0
EVENT STATUS ASCERTAINED	4126	99.4	4031	99.0
LOST**	4	0.1	2	0.1

*number of patients alive and having reached the scheduled visit

Table 5: Medication Compliance

5A: Summary of Number of patients Taking Study Medication at Indicated Time Point

	Number of patients (%)	
	Ramipril	
	Active	Placebo
Eligible at 1 yr**	4562	4562
On At 1 yr	3904 (85.5)	4072 (89.2)
On full dose study drug at 1 yr	3784 (82.9)	4014 (87.9)
On reduced dose study drug at 1 yr	120 (2.6)	58 (1.3)
Eligible at 2 yrs	4437	4451
On At 2 yrs	3603 (81.1)	3752 (84.3)
On full dose study drug at 2 yrs	3313 (74.6)	3594 (80.7)
On reduced dose study drug at 2 yrs	290 (6.5)	158 (3.5)
Eligible at 3 yrs	4336	4301
On At 3 yrs	3324 (76.6)	3420 (79.5)
On full dose study drug at 3 yrs	3077 (70.9)	3291 (76.5)
On reduced dose study drug at 3 yrs	247 (5.7)	129 (3.0)
Eligible at 4 yrs	3920	3854
On At 4 yrs	2652 (67.6)	2730 (70.8)
On full dose study drug at 4 yrs	2448 (62.4)	2623 (68.0)
On reduced dose study drug at 4 yrs	204 (5.2)	107 (2.8)

**number of patients alive and having completed the visit

5B: SUMMARY OF NUMBER OF PATIENTS TAKING STUDY MEDICATION: FINAL STUDY VISIT

	NUMBER OF PATIENTS (%)	
	RAMIPRIL	
	ACTIVE	PLACEBO
ELIGIBLE FOR FINAL VISIT	4150	4070
ON AT FINAL VISIT	2913 (70.2)	2958 (72.7)
ON FULL DOSE STUDY DRUG AT FINAL VISIT	2700 (65.1)	2854 (70.1)
ON REDUCED DOSE STUDY DRUG AT FINAL VISIT	213 (5.1)	104 (2.6)

5C: COMPLIANCE ADJUSTED FOR OPEN LABEL ACE-I USE
N (% of visit completed)

VISIT	RAMIPRIL ACTIVE						
	ELIGIBLE N	ON STUDY DRUG	ON OPEN LABEL ACE-I	TOTAL ON ANY ACTIVE ACE-I	ELIGIBLE N	RAMIPRIL PLACEBO ON OPEN LABEL ACE-I	CONTRAST %
1 YR	4565	3904 (85.5)	101 (2.2)	3988 (87.4)	4566	153 (3.4)	84.0
2YR	4440	3603 (81.1)	200 (4.5)	3773 (85.0)	4451	265 (6.0)	79.0
3 YR	4339	3324 (76.6)	256 (5.9)	3568 (82.2)	4302	347 (8.1)	74.1
4 YR	3923	2652 (67.6)	307 (7.8)	2946 (75.1)	3855	417 (10.8)	64.3
FINAL VISIT	4150	2913 (70.2)	392 (9.4)	3274 (78.9)	4070	501 (12.3)	66.6

Table 6: Demographics and Baseline Characteristics

6A: Overall Main Reason for Study Entry

	Ramipril Active		Ramipril Placebo	
Reason for Entry	N	%	N	%
CAD	2952	63.6	3087	66.4
PAD	293	6.3	269	5.8
Stroke	128	2.8	112	2.4
Diabetes +1	1272	27.4	1183	25.4
Unknown	0	0	1	0

6B: RISK PROFILE AT RANDOMIZATION

	RAMIPRIL ACTIVE		RAMIPRIL PLACEBO	
REASON FOR ENTRY	N	%	N	%
CAD ALONE	159	3.4	154	3.3
CAD + OTHER RISK FACTOR	3532	76.0	3632	78.1
OTHER RISK FACTOR ALONE	951	20.5	865	18.6

6C: Risk Profile by Baseline Subgroup

Reason for Entry*		N	CAD	PAD	Stroke	Diabetes
CAD	Active	3691	-	611 (16.6)	222 (6.0)	1046 (28.3)
	Placebo	3786	-	666 (17.6)	211(5.6)	1093 (28.9)
PAD	Active	836	611 (73.1)	-	88 (10.5)	311 (37.2)
	Placebo	889	666 (74.9)	-	81 (9.1)	361 (40.6)
Stroke	Active	336	222 (66.1)	88 (26.2)	-	101 (30.1)
	Placebo	337	211 (66.6)	81 (24.0)	-	140 (41.5)
Diabetes	Active	1808	1046 (57.9)	311 (17.2)	101 (5.6)	-
	Placebo	1769	1093 (61.8)	361 (20.4)	140 (7.9)	-

* these categories are not mutually exclusive

6D: OVERALL BASELINE PATIENT CHARACTERISTICS

Characteristic	Ramipril Group (N=4645)*	Placebo Group (N=4652)*
Age – year	66±7	66±7
Blood pressure – mmHg	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 < 1year	452 (9.7)	446 (9.6)
Within > 1year	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 arterial disease + Low AABP– no (%)**	1859 (40.0)	1969 (42.3)
Hypertension – no (%)	2212 (47.6)	2143 (46.1)
Diabetes – no (%)	1808 (38.9)	1769 (38.0)
Documented elevated total cholesterol level or on treatment – 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 anti-platelet 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 (%)	955 (20.6)	1008 (21.7)

*Plus-minus values are means with SD
** Peripheral arterial 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.
The body mass index was calculated as the weight in kilograms divided by the square of the height in metres

6E: BASELINE PATIENT CHARACTERISTICS FOR PATIENTS WITH CAD

Characteristic	Ramipril Group (N=3691)*	Placebo Group (N=3786)*
Age – year	66±7	66±7
Blood pressure – mmHg	137±19/78±10	137±19/78±11
Heart rate – beats/min	67±11	68±11
Body mass index	28±4	28±4
Female sex – no (%)	810 (22.0)	833 (22.0)
Myocardial infarction	2410 (65.3)	2482 (65.6)
Within < 1year	452 (12.3)	446 (11.8)
Within > 1year	1958 (53.1)	2036 (53.8)
Stable angina pectoris	2544 (68.9)	2618 (69.2)
Unstable angina pectoris	1179 (31.9)	1188 (31.4)
CABG	1192 (32.3)	1207 (31.9)
PTCA	853 (23.1)	806 (21.3)
Stroke or transient ischemic attacks - no (%)	357 (9.7)	361 (9.5)
Peripheral arterial disease + Low AABP– no (%)**	1408 (38.2)	1544 (40.8)
Hypertension – no (%)	1662 (45.0)	1670 (44.1)
Diabetes – no (%)	1046 (28.3)	1093 (28.9)
Documented elevated total cholesterol level or on treatment – no (%)	2412 (65.4)	2532 (66.9)
Documented low HDL cholesterol level – no (%)	688 (18.6)	756 (20.0)
Current cigarette smoking – no (%)	425 (11.5)	495 (13.1)
Medications – no (%)		
Beta-blockers	1704 (46.2)	1748 (46.2)
Aspirin or other anti-platelet agents	3185 (86.3)	3282 (86.7)
Lipid Lowering agents	1176 (31.9)	1215 (32.1)
Diuretics	517 (14.0)	546 (14.4)
Calcium channel blockers	1900 (51.5)	1979 (52.3)
Left ventricular hypertrophy on electrocardiography – no (%)	305 (8.3)	330 (8.7)
Microalbuminuria- no (%)	681 (18.5)	742 (19.6)

*Plus-minus values are means with SD
** Peripheral arterial 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.
The body mass index was calculated as the weight in kilograms divided by the square of the height in metres

6F: BASELINE PATIENT CHARACTERISTICS FOR PATIENTS WITH DIABETES

Characteristic	Ramipril Group (N=1808)*	Placebo Group (N=1769)*
Age – year	65±6	66±7
Blood pressure – mmHg	142±20/80±11	142±19/79±11
Heart rate – beats/min	72±11	73±11
Body mass index	29±5	29±5
Female sex – no (%)	696 (38.5)	626 (35.4)
History of coronary artery disease – no (%)	1046 (57.9)	1093 (61.8)
Myocardial infarction	626 (34.6)	663 (37.5)
Within < 1year	109 (6.0)	120 (6.8)
Within > 1year	517 (28.6)	543 (30.7)
Stable angina pectoris	718 (39.7)	769 (43.5)
Unstable angina pectoris	318 (17.6)	336 (19.0)
CABG	321 (17.8)	326 (18.4)
PTCA	205 (11.3)	182 (10.3)
Stroke or transient ischemic attacks - no (%)	153 (8.5)	195 (11.0)
Peripheral arterial disease + Low AABP– no (%)**	753 (41.7)	819 (46.3)
Hypertension – no (%)	1045 (57.8)	951 (53.8)
Documented elevated total cholesterol level or on treatment – no (%)	1174 (64.9)	1161 (65.6)
Documented low HDL cholesterol level – no (%)	370 (20.5)	348 (19.7)
Current cigarette smoking – no (%)	274 (15.2)	270 (15.3)
Medications – no (%)		
Beta-blockers	510 (28.2)	505 (28.6)
Aspirin or other anti-platelet agents	1024 (56.6)	1044 (59.0)
Lipid Lowering agents	409 (22.6)	390 (22.1)
Diuretics	350 (19.4)	350 (19.8)
Calcium channel blockers	776 (42.9)	801 (45.3)
Left ventricular hypertrophy on electrocardiography – no (%)	153 (8.5)	156 (8.8)
Microalbuminuria – no (%)	550 (30.4)	583 (33.0)

*plus-minus values are means with SD
** peripheral arterial 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.
The body mass index was calculated as the weight in kilograms divided by the square of the height in metres

Table 7: Concomitant Medication

7A: RANDOMIZATION

	Ramipril Active		Ramipril Placebo	
	N	%	N	%
Randomized	4645	100.0	4652	100.0
Beta-blockers	1820	39.2	1853	39.8
Aspirin and Other Antiplatelets	3497	75.3	3577	76.9
Aspirin	3368	72.5	3445	74.1
Other Antiplatelet	230	5.0	227	4.9
Non-steroidal Anti-Inflammatory agent	313	6.7	320	6.9
Oral Anticoagulants	185	4.0	172	3.7
Diuretics	713	15.3	706	15.2
Nitrates	1382	29.8	1499	32.2
Any Calcium Channel Blocker	2152	46.3	2228	47.9
Diltiazem/Verapamil	1218	26.2	1299	27.9
Other CCB	962	20.7	958	20.6
Cholesterol Lowering Agent	1318	28.4	1340	28.8
Vitamin C	280	6.0	257	5.5
Beta-carotene	61	1.3	62	1.3
Multivitamins	331	7.1	323	6.9
Estrogen(% of Females only)	115	9.0	151	12.6
Estrogen + Progesterone (Females only)	31	2.4	32	2.7
Insulin (% of Diabetics only)	520	28.8	574	32.4
Oral Hypoglycemic (% of Diabetics only)	1045	57.8	987	55.8

7B: 2 YEARS

	Ramipril Active		Ramipril Placebo	
	N	%	N	%
NO. OF 2 YR VISITS	4437	100.0	4451	100.0
BETA-BLOCKERS	1673	37.7	1802	40.5
ASPIRIN AND OTHER ANTIPLATELETS	3261	73.5	3330	74.8
ASPIRIN	3122	70.4	3192	71.7
OTHER ANTIPLATELET	210	4.7	216	4.9
NON-STEROIDAL ANTI-INFLAMMATORY AGENT	291	6.6	287	6.4
ORAL ANTICOAGULANTS	245	5.5	229	5.1
DIURETICS	738	16.6	854	19.2
NITRATES	1284	28.9	1359	30.5
ANY CALCIUM CHANNEL BLOCKER	1983	44.7	2006	45.1
DILTIAZEM/VERAPAMIL	1026	23.1	1065	23.9
OTHER CCB	926	20.9	965	21.7
CHOLESTEROL LOWERING AGENT	1691	38.1	1711	38.4
VITAMIN C	254	5.7	242	5.4
BETA-CAROTENE	43	1.0	36	0.8
MULTIVITAMINS	302	6.8	281	6.3
ESTROGEN(FEMALES ONLY	130	10.7	155	13.7
ESTROGEN + PROGESTERONE (FEMALES ONLY)	41	3.4	49	4.3
INSULIN (DIABETICS ONLY)	556	12.7	586	13.3
ORAL HYPOGLYCEMIC (DIABETICS ONLY)	963	22.0	977	22.2

7C: PENULTIMATE VISIT

	Ramipril Active		Ramipril Placebo	
	N	%	N	%
NO. OF PENULTIMATE VISITS	4174	100.0	4105	100.0
BETA-BLOCKERS	1565	37.5	1764	43.0
ANY ANTIPLATELET AGENTS	2993	71.7	3055	74.4
ASPIRIN	2807	67.2	2863	69.7
OTHER ANTIPLATELET	256	6.1	277	6.7
A2 ANTAGONISTS	68	1.6	79	1.9
NON-STEROIDAL ANTI-INFLAMMATORY AGENT	253	6.1	237	5.8
ORAL ANTICOAGULANTS	294	7.0	286	7.0
DIURETICS	816	19.5	942	22.9
NITRATES	1100	26.4	1184	28.8
ANY CALCIUM CHANNEL BLOCKER	1670	40.0	1703	41.5
DILTIAZEM/VERAPAMIL	806	20.0	808	20.3
OTHER CCB	894	21.4	928	22.6
CHOLESTEROL LOWERING AGENT	2048	49.1	2022	49.3
VITAMIN C	257	6.2	242	5.9
BETA-CAROTENE	52	1.2	32	0.8
MULTIVITAMINS	406	9.7	367	8.9
ESTROGEN (FEMALE ONLY)	91	8.2	125	12.2
ESTROGEN + PROGESTERONE (FEMALE ONLY)	44	4.0	45	4.4
INSULIN (DIABETICS ONLY)	614	15.3	591	14.9
ORAL HYPOGLYCEMIC (DIABETICS ONLY)	916	22.8	950	23.9

Table 8: Physical Exam and Local Laboratory Determinations

8A: Randomization

Variable	Ramipril Active			Ramipril Placebo		
	N	Mean	SD	N	Mean	SD
Resting Heart Rate beats/min	4644	68.6	11.4	4650	68.8	11.3
Resting Heart Rate - Pt on Anti-anginal	2716	65.3	10.4	2798	66.1	10.7
Resting Heart Rate – Pt Not on Anti-anginal	1928	73.2	11.2	1852	72.9	10.9
arm Systolic Blood Pressure mmHg	4645	138.5	19.7	4649	138.9	19.6
arm Diastolic Blood pressure mmHg	4644	78.9	10.6	4649	78.9	10.5
Ankle Systolic Blood Pressure mmHg	4036	134.2	28.3	4018	133.9	27.7
Ankle:Arm Ratio	4036	0.98	0.19	4017	0.98	0.19
Waist:Hip Ratio	4631	0.93	0.08	4644	0.93	0.08
Female	1277	0.87	0.08	1198	0.87	0.08
Male	3354	0.95	0.07	3446	0.95	0.06
Body Mass Index	4639	27.7	4.4	4646	27.7	4.4
Serum Creatinine (umol/L)	4641	97.0	21.2	4646	96.8	21.9
Potassium (mmol/L)	4642	4.4	0.5	4650	4.4	0.7
Glycated Hb (patients with diabetes only) (% of ULN)	1752	123.1	30.4	1706	124.7	31.7

8B: 1 MONTH

VARIABLE	RAMIPRIL ACTIVE			RAMIPRIL PLACEBO		
	N	MEAN	SD	N	MEAN	SD
ARM SYSTOLIC BLOOD PRESSURE MMHG	4580	133.0	19.2	4589	137.2	19.2
ARM DIASTOLIC BLOOD PRESSURE MMHG	4579	76.2	10.5	4589	78.3	10.7
ANKLE SYSTOLIC BLOOD PRESSURE MMHG	3952	130.4	27.4	3957	133.7	27.8
ANKLE:ARM RATIO	3951	0.99	0.20	3956	0.98	0.19
SERUM CREATININE (UMOL/L)	4538	97.2	22.2	4572	97.1	24.1
POTASSIUM (MMOL/L)	4539	4.4	0.8	4570	4.4	1.8

8C: 2 YEARS

VARIABLE	RAMIPRIL ACTIVE			RAMIPRIL PLACEBO		
	N	MEAN	SD	N	MEAN	SD
ARM SYSTOLIC BLOOD PRESSURE MMHG	4171	135.1	20.0	4204	138.5	19.4
ARM DIASTOLIC BLOOD PRESSURE MMHG	4170	76.1	10.7	4203	77.8	10.4
ANKLE SYSTOLIC BLOOD PRESSURE MMHG	3440	131.7	28.3	3473	133.7	28.4
ANKLE:ARM RATIO	3439	0.99	0.19	3473	0.97	0.20
SERUM CREATININE (UMOL/L)	1615	94.8	26.1	1628	94.0	25.5
GLYCATED HB (PATIENTS WITH DIABETES ONLY)(% OF ULN)	1574	122.5	29.8	1574	125.2	31.2

8D: STUDY END

VARIABLE	RAMIPRIL ACTIVE			RAMIPRIL PLACEBO		
	N	MEAN	SD	N	MEAN	SD
RESTING HEART RATE BEATS/MIN	3672	69.3	11.5	3620	69.0	11.4
RESTING HEART RATE - PT ON ANTI-ANGINAL	2427	67.3	11.4	2521	67.3	11.1
RESTING HEART RATE – PT NOT ON ANTI-ANGINAL	1245	73.2	10.7	1099	73.0	11.1
ARM SYSTOLIC BLOOD PRESSURE MMHG	3683	136.1	19.2	3632	138.7	19.5
ARM DIASTOLIC BLOOD PRESSURE MMHG	3682	75.8	10.5	3632	76.9	10.8
ANKLE SYSTOLIC BLOOD PRESSURE MMHG	2613	132.5	31.6	2595	132.7	30.4
ANKLE:ARM RATIO	2613	0.99	0.24	2593	0.97	0.21
BODY MASS INDEX	3631	27.9	4.5	3586	28.0	4.6
SERUM CREATININE (IN PATIENTS WITH DIABETES ONLY) (UMOL/L)	1145	95.8	27.4	1145	93.7	25.3
GLYCATED HB (IN PATIENTS WITH DIABETES ONLY) (%OF ULN)	1818	124.4	29.5	1819	124.0	29.1

Table 9: ECG Results

9: RANDOMIZATION

	RAMIPRIL ACTIVE		RAMIPRIL PLACEBO	
	N	%	N	%
RANDOMIZED	4645	100.0	4652	100.0
ECG ABNORMAL	2840	61.1	2916	62.7
PATH Q WAVES	1440	31.0	1522	32.7
ST ELEVATION	227	4.9	195	4.2
ST DEPRESSION	439	9.5	475	10.2
T INVERSION	1282	27.6	1288	27.7
LEFT VENTRICULAR HYPERTROPHY	379	8.2	406	8.7
CONDUCTION DEFECT	493	10.6	504	10.8
OTHER	13	0.3	14	0.3

Table 10: Abnormal Albumin to Creatinine Ratios (≥2)

VARIABLE	N	ALL PATIENTS AT BASELINE				N	PATIENTS WITH DIABETES AT BASELINE			
		RAMIPRIL ACTIVE		RAMIPRIL PLACEBO			RAMIPRIL ACTIVE		RAMIPRIL PLACEBO	
		N	%	N	%		N	%		
BASELINE	9043	952	21.1	1004	22.2	3498	550	31.2	583	33.6
1 YEAR	3077	584	36.9	689	43.3	3068	576	37.2	664	43.7
PENULTIMATE VISITS	7222	1172	32.2	1283	35.8	2674	641	46.6	673	51.8

RESULTS: EFFICACY

Table 11: Incidence of the Primary Outcome and of Deaths from Any Cause

11A: ADJUDICATED

OUTCOME	RAMIPRIL GROUP (N=4645) N (%)	PLACEBO GROUP (N=4652) N(%)	RELATIVE RISK (95% CI)*	Z STATISTIC	P VALUE
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 CARDIOIVASCULAR CAUSES$^{\Omega}$	282 (6.1)	377 (8.1)	0.74 (0.64-0.87)	-3.78	<0.001
MYOCARDIAL INFARCTION$^{\Omega}$	459 (9.9)	570(12.3)	0.80(0.70-0.90)	-3.63	<0.001
STROKE$^{\Omega}$	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	0.0053

$^{\Omega}$Not mutually exclusive categories.

11B: AS REPORTED BY CENTRE

OUTCOME	RAMIPRIL GROUP (N=4645) N (%)	PLACEBO GROUP (N=4652) N(%)	RELATIVE RISK (95% CI)*	Z STATISTIC	P VALUE
MYOCARDIAL INFARCTION, STROKE OR DEATH FROM CARDIOVASCULAR CAUSES+	695 (15.0)	850 (18.3)	0.81(0.73-0.89)	-4.22	<0.001
DEATH FROM CARDIOIVASCULAR CAUSES$^{\Omega}$	286 (6.2)	372 (8.0)	0.76(0.66-0.89)	-3.43	<0.001
MYOCARDIAL INFARCTION$^{\Omega}$	462 (10.0)	573(12.3)	0.80(0.71-0.90)	-3.60	<0.001
STROKE$^{\Omega}$	193(4.2)	255(5.5)	0.75(0.62-0.90)	-3.05	0.002
DEATH FROM NONCARDIOVASCULAR CAUSES	196(4.2)	197(4.2)	0.99(0.81-1.20)	0.12	0.91
DEATH FROM ANY CAUSE	482(10.4)	569(12.2)	0.84(0.75-0.95)	-2.79	0.0053

11C: Adjudicated Events With 244 patients randomized to active 2.5 mg (low dose) group

Outcome	Ramipril Group (N=4889) N (%)	Placebo Group (N=4652) N(%)	Relative Risk (95% CI)*	Z Statistic	P Value
Myocardial infarction, Stroke or death from cardiovascular causes*	685 (14.0)	826 (17.8)	0.78 (0.70-0.86)	-4.95	<0.001

Table 12: Outcomes(Event Rates) by Factorial Cells

	Ramipril Active Vitamin E Active N(%)	Ramipril Active Vitamin E Placebo N(%)	Ramipril Placebo Vitamin E Active N(%)	Ramipril Placebo Vitamin E Placebo N(%)
NUMBER RAND	2326	2319	2311	2341
MYOCARDIAL INFARCTION, STROKE OR DEATH FROM CARDIOVASCULAR CAUSES	338 (14.5)	313 (13.5)	421 (18.2)	405 (17.3)
DEATH FROM CARDIOIVASCULAR CAUSES$^{\Omega}$	147 (6.3)	135 (5.8)	192 (8.3)	185 (7.9)
MYOCARDIAL INFARCTION$^{\Omega}$	234 (10.1)	225 (9.7)	290 (12.6)	280 (12.0)
STROKE$^{\Omega}$	80 (3.4)	76 (3.3)	124 (5.4)	102 (4.4)
DEATH FROM ANY CAUSE	248 (10.7)	234 (10.1)	279 (12.1)	290 (12.4)

$^{\Omega}$Not mutually exclusive categories.

Table 13: Detailed Myocardial Infarction Results

Outcome	Event Rates		Relative Risk (95% CI)
	Ramipril N(%)	Placebo N(%)	
Any Myocardial Infarction	459 (9.9)	570 (12.3)	0.80(0.70-0.90)
Fatal Myocardial Infarction	186 (4.0)	219 (4.7)	0.84(0.69-1.03)
Confirmed	47 (1.0)	51 (1.1)	0.92(0.62-1.36)
Unexpected Sudden Death	126 (2.7)	155 (3.3)	0.81(0.64-1.02)
Presumed Myocardial Infarction	13 (0.3)	13 (0.3)	0.99(0.46-2.14)
Non-Fatal Myocardial Infarction	273 (5.9)	351 (7.6)	0.77(0.66-0.90)
Q Wave*	117 (2.5)	140 (3.0)	0.83(0.65-1.06)
Non Q Wave*	216 (4.7)	283 (6.1)	0.76(0.63-0.90)
Other*	16 (0.3)	19 (0.4)	0.84(0.43-1.63)

* not mutually exclusive

Please refer to Event Adjudication Definitions for definitions of above categories.

Table 14: Detailed Stroke Results

14A: Stroke by Type

Outcome	Event Rates		Relative Risk (95% CI)
	Ramipril N(%)	Placebo N(%)	
Overall	156 (3.4)	226 (4.9)	0.68(0.56-0.84)
Ischemic	101 (2.2)	157 (3.4)	0.64(0.50-0.82)
Haemorrhagic	12 (0.26)	16 (0.34)	0.74 (0.35-1.57)
Uncertain	52 (1.1)	65 (1.4)	0.79(0.55-1.14)

14B: Stroke by Severity

Outcome	Event Rates		Relative Risk (95% CI)
	Ramipril N(%)	Placebo N(%)	
Overall	156 (3.4)	226 (4.9)	0.68(0.56-0.84)
Full recovery/non-limiting	49 (1.1)	80 (1.7)	0.61(0.42-0.86)
Some impairment	43 (0.9)	56 (1.2)	0.76(0.51-1.13)
Constant help/incapacitated	50 (1.1)	66 (1.4)	0.75(0.52-1.08)
Fatal	26 (0.4)	40 (1.0)	0.39(0.22-0.67)

Table 15: Patients with Documented Normal Ejection Fraction

N=4775

Outcome	Ramipril Group (N=2381) N (%)	Placebo Group (N=2394) N(%)	Relative Risk (95% CI)
Myocardial infarction, Stroke or death from cardiovascular causes	332(13.9)	451(18.8)	0.73(0.63-0.84)
Death from cardioivascular causes	123(5.2)	181(7.6)	0.68(0.54-0.85)
Myocardial infarction	254(10.7)	337(14.1)	0.75(0.63-0.88)
Stroke	69(2.9)	102(4.3)	0.67(0.50-0.91)
All Heart Failure	206(8.7)	257(10.7)	0.79(0.66-0.95)
Revascularization	475(20.0)	565(23.6)	0.82(0.72-0.92)

Table 16: Incidence of Secondary and Other Outcomes

Outcome	Ramipril Group (N=4645) N (%)	Placebo Group (N=4652) N(%)	Relative Risk (95% CI)	Z Statistic	P Value
Secondary Outcomes					
Revascularization	743(16.0)	854(18.4)	0.85(0.77-0.94)	-3.19	0.0014
Hospitalization for Unstable Angina	554(11.9)	567(12.2)	0.97(0.87-1.09)	-0.47	0.64
Hospitalization for Heart Failure	141(3.2)	161(3.5)	0.87(0.69-1.09)	-1.22	0.22
Other Outcomes					
Complications Related to Diabetes[Ω]	303(6.5)	356(7.7)	0.85(0.73-0.99)	-2.07	0.038
Heart Failure*	417(9.0)	534(11.5)	0.77(0.68-0.87)	-4.06	<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)	1222(26.3)	0.88(0.82-0.96)	-2.96	0.003
New Diagnosis of Diabetes (%of Patients without Diabetes)	102(3.6)	155(5.4)	0.66(0.51-0.85)	-3.31	<0.001

[Ω]Includes diabetic nephropathy, the need for renal dialysis and the need for laser therapy for diabetic retinopathy.

* Includes any report of heart failure (i.e. requiring hospitalisation, required stopping study medication and/or use of an ACE-I, worsening heart failure at any visit, death as a result of heart failure)

**As indicated on follow-up forms

Table 17: Heart Failure

17A: ALL HEART FAILURE

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)	P VALUE
	N (%)	N(%)		
ALL HEART FAILURE*	417(9.0)	534(11.5)	0.77(0.68-0.87)	<0.001
OPEN ACE-I FOR CHF	240(5.2)	327(7.)	0.72(0.61-0.85)	<0.001
HEART FAILURE HOSPITALIZATION	141(3.2)	161(3.5)	0.87(0.69-1.09)	0.22
HEART FAILURE DEATH	24(0.52)	27(0.58)	0.88(0.51-1.53)	0.66
CV DEATH + ALL CHF	624(13.4)	807(17.4)	0.76(0.69-0.84)	<0.001
CV DEATH + CHF HOSPITALIZATION	383(8.3)	491(10.6)	0.77(0.68-0.88)	<0.001

* Includes any report of heart failure (i.e. requiring hospitalisation, required stopping study medication and/or use of an ACE-I, worsening heart failure at any visit, death as a result of heart failure)

17B: REASONS FOR NON-STUDY ACE-I USE

	Ramipril Group (N=4645) N(%)	Placebo Group (N=4652) N(%)
HEART FAILURE	240(5.2)	327(7.0)
PROTEINURIA	59(1.3)	60(1.3)
HYPERTENSION	222(4.8)	301(6.5)
OTHER	294(6.3)	338(7.3)

Table 18: Type of Revascularization

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)	P VALUE
	N (%)	N(%)		
ANY REVASCULARIZATION	743(16.0)	854(18.4)	0.85(0.77-0.94)	0.0014
PTCA/CABG	580(12.5)	688(14.8)	0.83(0.74-0.92)	0.0008
NON CARDIOVASCULAR *	191(4.1)	213(4.6)	0.89(0.73-1.08)	0.24

* Peripheral Angioplasty/Surgery, Limb Amputation, Carotid Endarterectomy, Other

Table 19: Development of Overt Nephropathy

	Ramipril Group (N=4645)	Placebo Group (N=4652)	Relative Risk (95% CI)	P Value
	N(%)	N(%)		
Overt nephropathy	144(3.1)	185(4.0)	0.78(0.63-0.97)	0.027
24 hour test available	116(2.5)	148(3.2)	0.79(0.62-1.01)	0.06
New microalbuminuria (% of non-microalbuminurics at baseline)	765(20.7)	847(23.2)	0.90(0.82-0.99)	0.04

Table 20: Primary Outcome for Important Subgroups

Subgroup	N	Event Rate		Relative Risk (95% CI)	Test for Heterogeneity of Relative Risk Between Groups P-Value
		Ramipril Group %	Placebo Group %		
Cardiovascular Disease	8162	14.9	18.7	0.78(0.70-0.87)	0.88
No Cardiovascular Disease	1135	8.2	10.1	0.81(0.55-1.19)	
Diabetes	3577	15.3	19.8	0.75(0.64-0.88)	0.68
No Diabetes	5720	13.2	16.5	0.79(0.69-0.90)	
Age <65 yr	4169	11.9	14.2	0.83(0.70-0.98)	0.34
Age ≥65 yr	5128	15.7	20.7	0.74(0.65-0.85)	
Male	6817	15.0	18.8	0.78(0.70-0.88)	0.82
Female	2480	11.3	14.8	0.76(0.61-0.95)	
Hypertension	4355	14.7	19.4	0.75(0.65-0.86)	0.48
No Hypertension	4942	13.4	16.3	0.80(0.70-0.93)	
History of CAD	7477	15.0	18.5	0.79(0.71-0.88)	0.50
No History of CAD	1820	10.3	14.2	0.72(0.55-0.93)	
Prior Myocardial Infarction	4892	16.8	20.9	0.78(0.69-0.89)	0.89
No Prior Myocardial Infarction	4405	11.1	14.2	0.77(0.65-0.91)	
Cerebrovascular Disease	1013	19.6	25.9	0.75(0.57-0.97)	0.72
No Cerebrovascular Disease	8284	13.3	16.7	0.78(0.70-0.88)	
Peripheral Arterial Disease	3828	17.1	22.4	0.74(0.64-0.85)	0.25
No Peripheral Arterial Disease	5469	12.0	14.3	0.83(0.72-0.96)	
Microalbuminuria	1963	19.6	26.3	0.71(0.59-0.86)	0.26
No Microalbuminuria	7334	12.6	15.4	0.81(0.72-0.92)	

Table 21: Incidence of Primary and Secondary Outcomes in Patients with Coronary Artery Disease

21A: PRIMARY OUTCOMES

OUTCOME	RAMIPRIL GROUP (N=3691)	PLACEBO GROUP (N=3786)	RELATIVE RISK (95% CI)	P VALUE
	N (%)	N(%)		
MYOCARDIAL INFARCTION, STROKE OR DEATH FROM CARDIOVASCULAR CAUSES	553 (15.0)	703 (18.6)	0.79 (0.71-0.88)	<0.0001
DEATH FROM CARDIOIVASCULAR CAUSES[Ω]	246 (6.7)	336 (8.9)	0.74 (0.63-0.87)	0.0003
MYOCARDIAL INFARCTION[Ω]	401 (10.9)	505 (13.3)	0.8 (0.70-0.91)	0.0009
STROKE[Ω]	121 (3.3)	173 (4.6)	0.71 (0.56-0.89)	0.0032
DEATH FROM ANY CAUSE	392 (10.6)	490 (12.9)	0.81 (0.71-0.92)	0.0018

[Ω]Not mutually exclusive

21B: SECONDARY OUTCOMES

OUTCOME	RAMIPRIL GROUP (N=3691)	PLACEBO GROUP (N=3786)	RELATIVE RISK (95% CI)*	P VALUE
	N (%)	N(%)		
SECONDARY OUTCOMES				
REVASCULARIZATION	658 (17.8)	756 (20.0)	0.87 (0.78-0.97)	0.0088
HOSPITALIZATION FOR UNSTABLE ANGINA	524 (14.2)	546 (14.4)	0.97 (0.86-1.10)	0.66
COMPLICATIONS RELATED TO DIABETES[Ω]	164 (4.4)	213 (5.6)	0.79 (0.64-0.96)	0.021
HOSPITALIZATION FOR HEART FAILURE	119 (3.2)	138 (3.7)	0.87 (0.68-1.11)	0.27
OTHER OUTCOMES				
ALL HEART FAILURE	356 (9.7)	470 (12.4)	0.76 (0.66-0.87)	<0.0001
WORSENING ANGINA	1070 (29.0)	1119 (31.7)	0.89 (0.82-0.96)	0.0037

[Ω]Includes diabetic nephropathy, the need for renal dialysis and the need for laser therapy for diabetic retinopathy.

Table 22: Details on Outcomes in Patients with Diabetes

22A: PRIMARY OUTCOMES

OUTCOME	RAMIPRIL GROUP (N=1808)	PLACEBO GROUP (N=1769)	RELATIVE RISK (95% CI)	P VALUE
	N (%)	N(%)		
MYOCARDIAL INFARCTION, STROKE OR DEATH FROM CARDIOVASCULAR CAUSES	277(15.3)	351(19.8)	0.75(0.64-0.88)	0.0004
DEATH FROM CARDIOVASCULAR CAUSES[Ω]	112(6.2)	172(9.7)	0.63(0.49-0.79)	<0.0001
MYOCARDIAL INFARCTION[Ω]	185(10.2)	229(13.0)	0.78(0.64-0.94)	0.01
STROKE[Ω]	76(4.2)	108(6.1)	0.67(0.50-0.90)	0.0074
DEATH FROM ANY CAUSE	196(10.8)	248(14.0)	0.76(0.63-0.92)	0.004

[Ω]Not mutually exclusive

22B: SECONDARY OUTCOMES

OUTCOME	RAMIPRIL GROUP (N=1808)	PLACEBO GROUP (N=1769)	RELATIVE RISK (95% CI)*	P VALUE
	N (%)	N(%)		
SECONDARY OUTCOMES				
REVASCULARIZATION	255(14.1)	292(16.5)	0.83(0.70-0.98)	0.031
HOSPITALIZATION FOR UNSTABLE ANGINA	213(11.8)	208(11.8)	1.0(0.83-1.21)	0.97
COMPLICATIONS RELATED TO DIABETES[Ω]	278(15.4)	314(17.8)	0.85(0.72-1.00)	0.051
HOSPITALIZATION FOR HEART FAILURE	81(4.5)	79(4.5)	0.99(0.72-1.34)	0.93
OTHER OUTCOMES				
ALL HEART FAILURE	198(11.0)	235(13.3)	0.80(0.66-0.97)	0.022
WORSENING ANGINA	363(20.1)	397(22.4)	0.87(0.76-1.0)	0.057

[Ω]Includes diabetic nephropathy, the need for renal dialysis and the need for laser therapy for diabetic retinopathy.

Table 23: Development of Overt Nephropathy in Patients with Diabetes

	RAMIPRIL GROUP (N=1808)	PLACEBO GROUP (N=1769)	RELATIVE RISK (95% CI)	P VALUE
	N(%)	N(%)		
OVERT NEPHROPATHY	122 (6.8)	151 (8.5)	0.78(0.62-0.99)	0.045
24 HOUR TEST AVAILABLE	101(5.6)	124(7.0)	0.79(0.61-1.03)	0.08
NEW MICROALBUMINURIA (% OF NON-MICROALBUMINURICS AT BASELINE)	431(34.3)	451(38.2)	0.930.81-1.06)	0.28

Table 24: Results by Blood Pressure

24A: BLOOD PRESSURE (MMHG) AS MEASURED AT BASELINE, 1 MONTH, 2 YEARS AND STUDY END

	BASELINE	1 MONTH		2 YEAR		END	
	MEAN(SD)	MEAN (SD)	Δ(SD)	MEAN (SD)	Δ(SD)	MEAN(SD)	Δ(SD)
ARM SYSTOLIC BP							
RAMIPRIL	139(20)	133(19)	-5.5(16.1)	135(20)	-3.3(19.1)	136(19)	-2.2(20.1)
PLACEBO		137(19)	-1.7(15.6)	138(19)	0(19.1)	139(20)	0.4(20.5)
ARM DIASTOLIC BP							
RAMIPRIL	79(11)	76(11)	-2.7(9.6)	76(11)	-2.9(11.0)	76(11)	-3.1(11.4)
PLACEBO		78(11)	-0.6(9.7)	78(10)	-1.0(10.8)	77(11)	-2.1(11.4)

ΔIndicates change from baseline
NOTE: During follow-up periods the numbers of patients having blood pressure measured changes, therefore sum of mean plus delta will not equal baseline value.

Table 25: Event Rates for Outcomes By Key Baseline Treatments

25A: EVENT RATES FOR PRIMARY OUTCOME BY KEY BASELINE TREATMENTS

	N	RAMIPRIL GROUP(N=4645) N(%)	PLACEBO GROUP (N-4652) N(%)	RELATIVE RISK (95% CI)	TEST FOR HETEROGENEITY OF RELATIVE RISK BETWEEN GROUPS P-VALUE
BETA BLOCKER					
+	3673	259(14.2)	338(18.2)	0.77(0.65-0.90)	
-	5624	392(13.9)	487(17.4)	0.78(0.68-0.89)	0.88
LIPID LOWERING AGENT					
+	2658	139(10.6)	187(14.0)	0.75(0.60-0.93)	
-	6639	512(15.4)	638(19.3)	0.78(0.70-0.88)	0.67
ASPIRIN					
+	6813	503(14.9)	594(17.2)	0.86(0.76-0.96)	
-	2484	148(11.6)	231(19.1)	0.59(0.48-0.72)	0.002
ANY BETA BLOCKER/ASPIRIN/LIPID LOWERING AGENT					
+	7730	557(14.5)	685(17.6)	0.81(0.73-0.91)	
-	1567	94(11.7)	140(18.4)	0.61(0.47-0.79)	0.05

25B: EVENT RATES FOR COMPOSITE OUTCOME OF PRIMARY OUTCOME/HOSPITALIZATION FOR HEART FAILURE/ REVASCULARIZATION BY KEY BASELINE TREATMENTS

	N	RAMIPRIL GROUP (N=4645) N(%)	PLACEBO GROUP (N=4652) N(%)	RELATIVE RISK (95% CI)	TEST FOR HETEROGENEITY OF RELATIVE RISK BETWEEN GROUPSP-VALUE
BETA BLOCKER					
+	3673	547(30.1)	663(35.8)	0.82(0.73-0.91)	
-	5624	727(25.7)	866(30.9)	0.80(0.73-0.88)	0.84
LIPID LOWERING AGENT					
+	2658	327(24.8)	405(30.2)	0.79(0.68-0.91)	
-	6639	947(28.5)	1124(33.9)	0.82(0.75-0.89)	0.66
ASPIRIN					
+	6813	982(29.2)	1169(33.9)	0.83(0.76-0.90)	
-	2484	292(22.9)	360(29.8)	0.75(0.64-0.87)	0.24
ANY BETA BLOCKER/ASPIRIN/LIPID LOWERING AGENT					
+	7730	1095(28.5)	1321(34.0)	0.81(0.75-0.88)	
-	1567	179(22.2)	208(27.3)	0.78(0.64-0.96)	0.73

RESULTS: SAFETY

Table 26: Reasons for Discontinuation of Study Treatment

	Ramipril Group (N=4645)	Placebo Group 9N=4652)
Discontinuation at any time	1575(33.9)	1493(32.1)
Permanent discontinuation	1357(29.2)	1284(27.6)
Reasons for Stopping*		
Cough	340(7.3)	85(1.8)
Hypotension/dizziness	88(1.9)	70(1.5)
Angioedema	16(0.3)	6(0.1)
Uncontrolled hypertension	109(2.3)	183(3.9)
Clinical events	306(6.6)	416(8.9)
Nausea	19(0.4)	17(0.4)
Headache	19(0.4)	23(0.5)
Fatigue	34(0.7)	27(0.6)
Refusal	699(15.0)	647(13.9)
Doctor's advice	161(3.5)	156(3.4)

* these categories are not mutually exclusive

DISCUSSION

Table 27: Meta-analysis of Data from Long Term Trials of ACE-I

STUDY	2N PTS	DEATH		MYOCARDIAL INFARCTION		STROKE	
		ACE-I	PLACEBO	ACE-I	PLACEBO	ACE-I	PLACEBO
SOLVD(PREVENTION AND TREATMENT)	6797	22.5	24.8	7.3	9.2	3.5	4.1
POST-MI (SAVE/TRACE/AIRE)	5966	23.4	29.1	10.8	13.2	4.0	3.7
HOPE	9297	10.4	12.2	9.9	12.3	3.4	4.9
TOTAL	22060	17.7	20.7	9.3	11.5	3.6	4.3
OR(95% CI)		0.82 (0.76-0.88)		0.79 (0.73-0.86)		0.83 (0.72-0.95)	
		$P=7x10^{-9}$		$P=1x10^{-7}$		P=0.006	

Table 28: Meta-analysis of Composite Cardiovascular Outcomes from Long Term Trials

STUDY	ACE-I GROUP TOTAL(%)	PLACEBO GROUP TOTAL(%)	OR	95% CI
SOLVD(PREVENTION AND TREATMENT)	3396(27.2)	3401(31.4)	0.87	0.78-0.96
POST-MI (SAVE/TRACE/AIRE)	2995 (31.5)	2971 (37.2)	0.85	0.76-0.94
HOPE	4645(14.0)	4652 (17.8)	0.78	0.70-0.86
TOTAL	11036 (22.9)	11024 (27.2)	0.79	0.74-0.84
	P=0.00000000000003 (P=3 x 10-14)			

FIGURE 1: STUDY ASSESSMENTS

Eligibility & Run-in Visit (-3 weeks)

1. Obtain informed consent.
2. Check urine using dipstick (exclude if proteinuria >1+).
3. Complete one page Run-In form and fax to the CCC Project Office.
4. Start Run-In period with 2.5 mg of ramipril once daily (active for 7-10 days and then placebo for 10-14 days).
5. Obtain creatinine, potassium and glycated Hb(in patients with diabetes only) on last day of active ramipril dose in Run-In.

Randomization Visit (0 weeks)

1. Check compliance and confirm eligibility.
2. Randomize patient by calling project office.
3. Dispense allocated treatment.
4. Complete and fax randomization forms.
5. Make follow-up appointment for one month (+-1 week).

Follow-Up (at 1 month, 6 months then every 6 months)

1. Check for all cardiovascular events and hospitalizations. If these occur, fax relevant event forms and send appropriate supporting documentation centrally.
2. At 1-month visit repeat local creatinine and potassium determination.
3. Dispense medication and encourage compliance.
4. Fax the relevant follow-up forms.

Note because of early closure of the ramipril arm of the study, the penultimate and final study visits were combined for some patients.

FIGURE 2: KAPLAN-MEIER SURVIVAL CURVE: PRIMARY OUTCOME

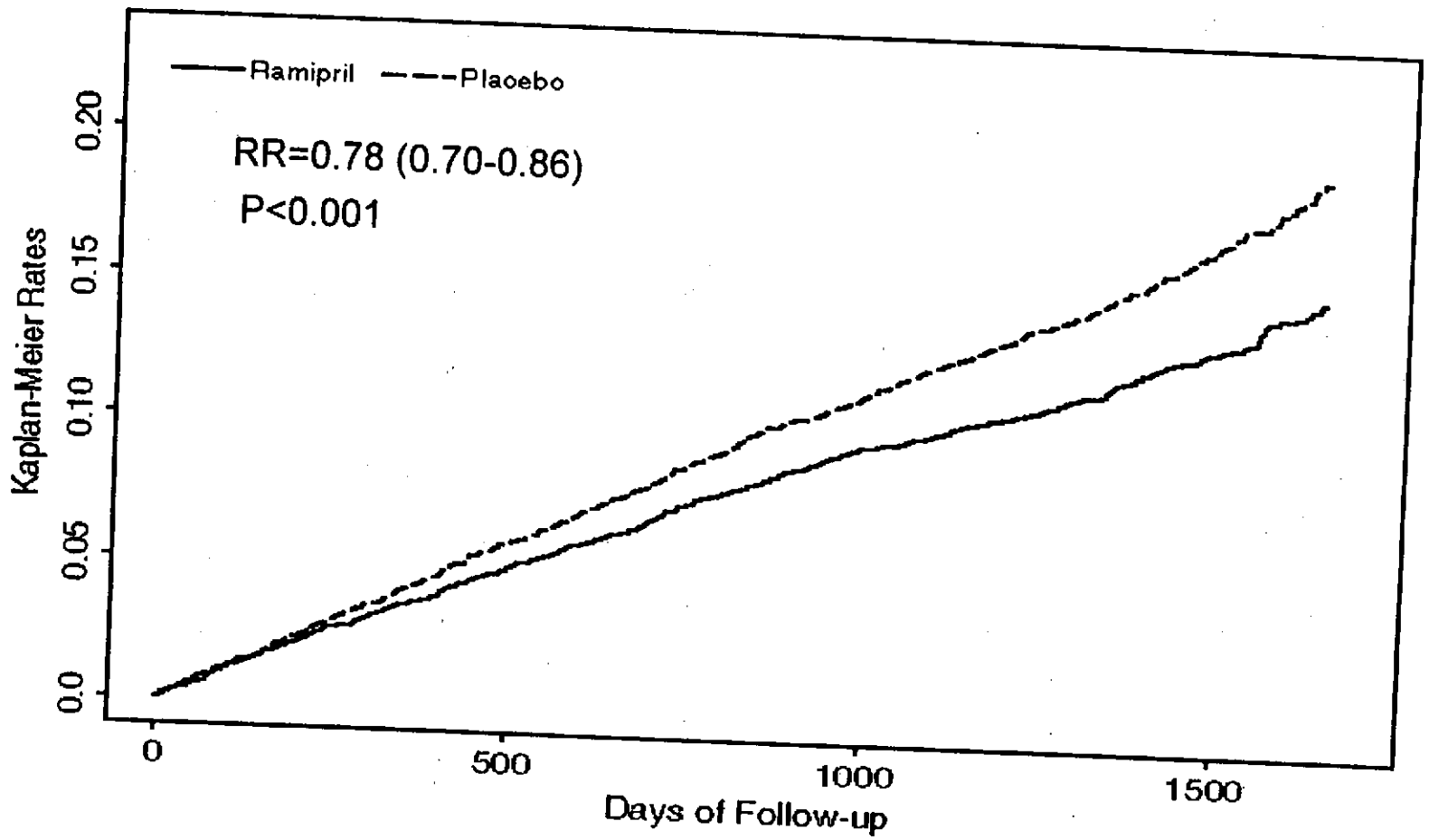


FIGURE 3: KAPLAN-MEIER SURVIVAL CURVE: MYOCARDIAL INFARCTION

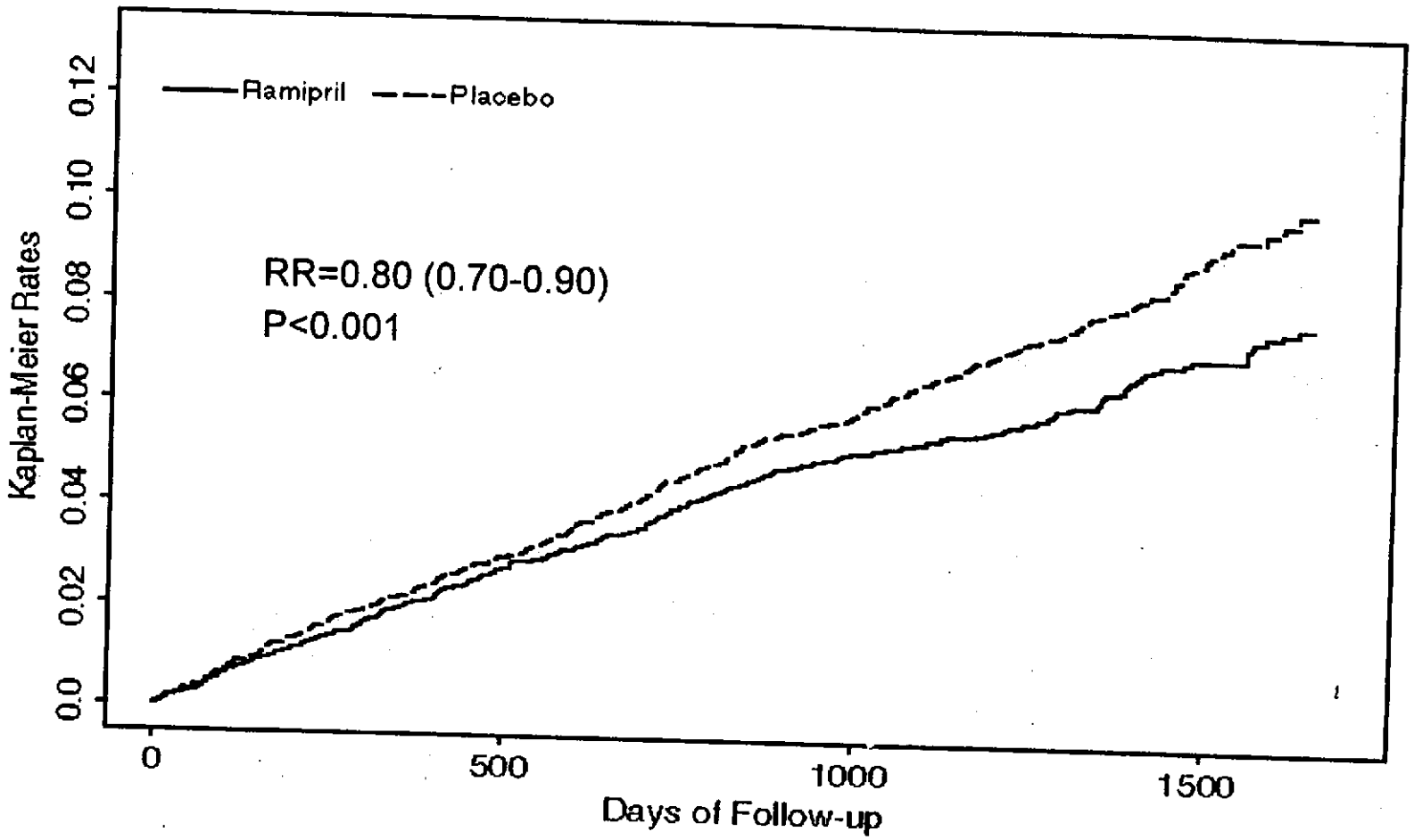


FIGURE 4: KAPLAN-MEIER SURVIVAL CURVE: STROKE

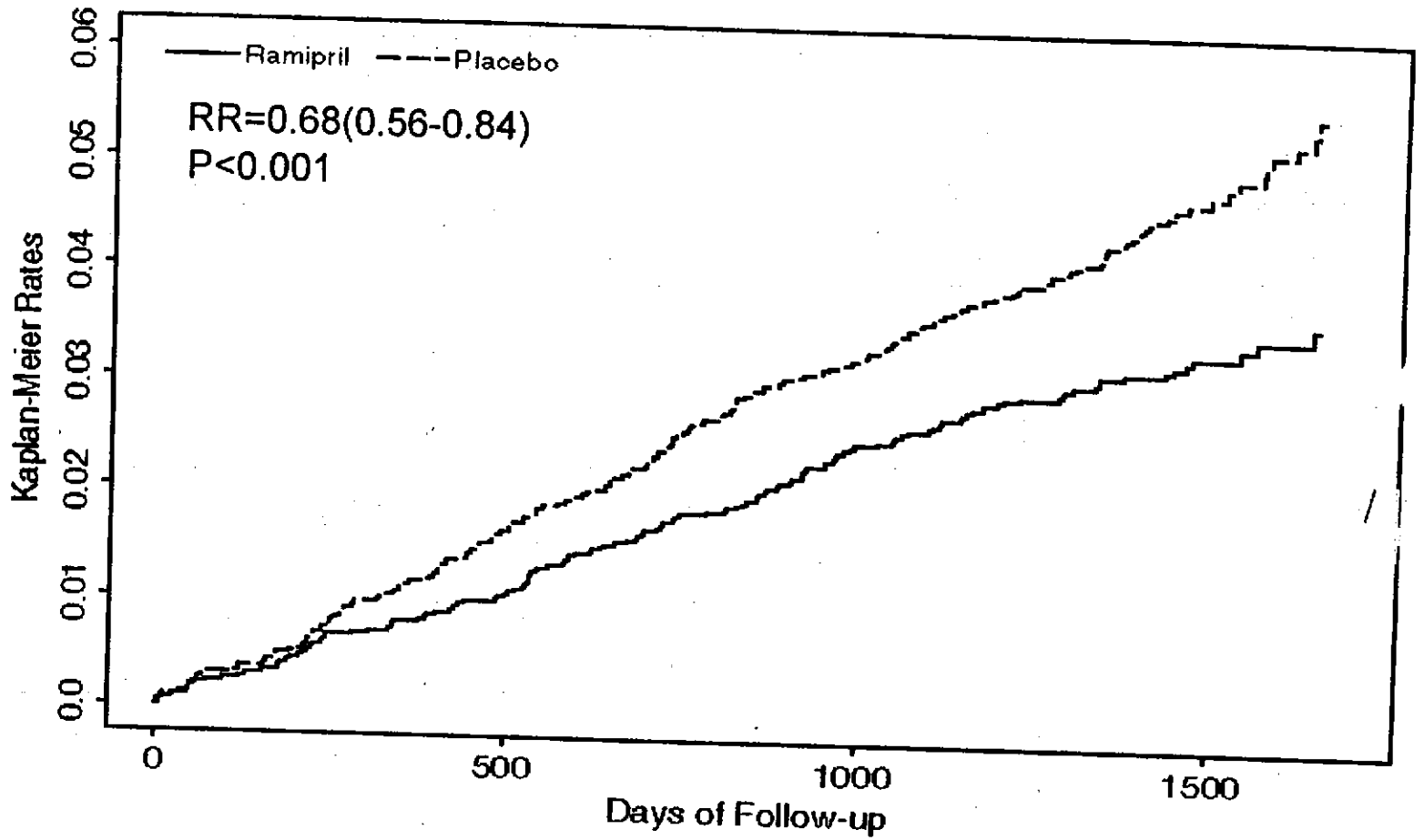


FIGURE 5: KAPLAN-MEIER SURVIVAL CURVE: CARDIOVASCULAR DEATH

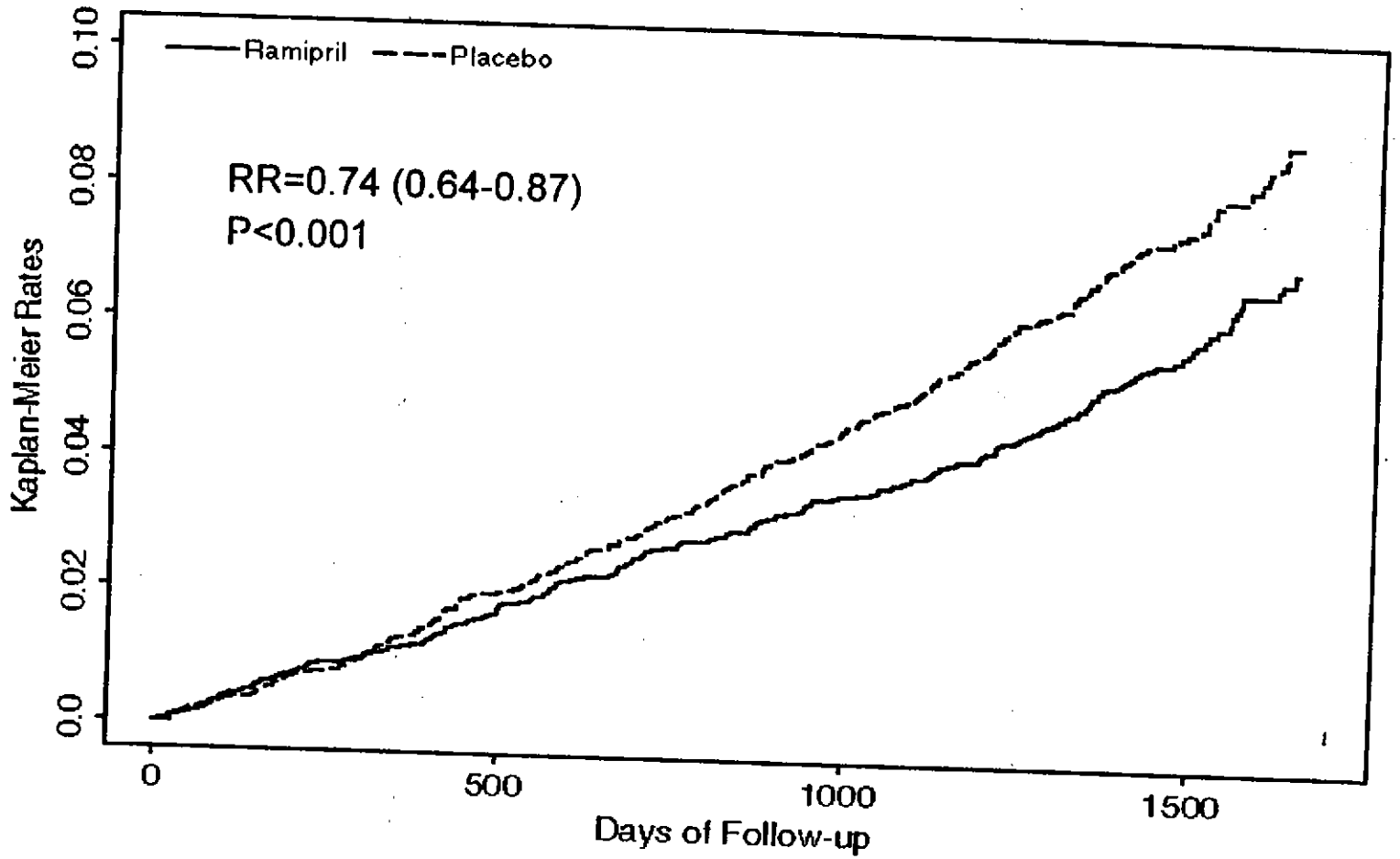
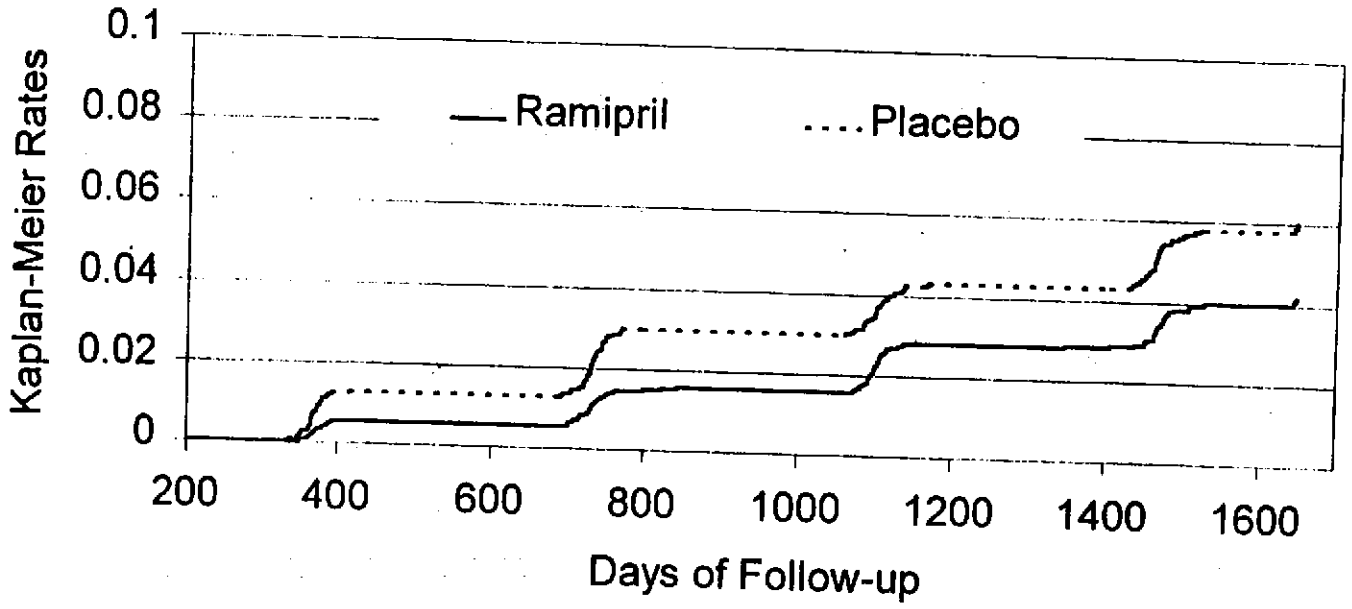


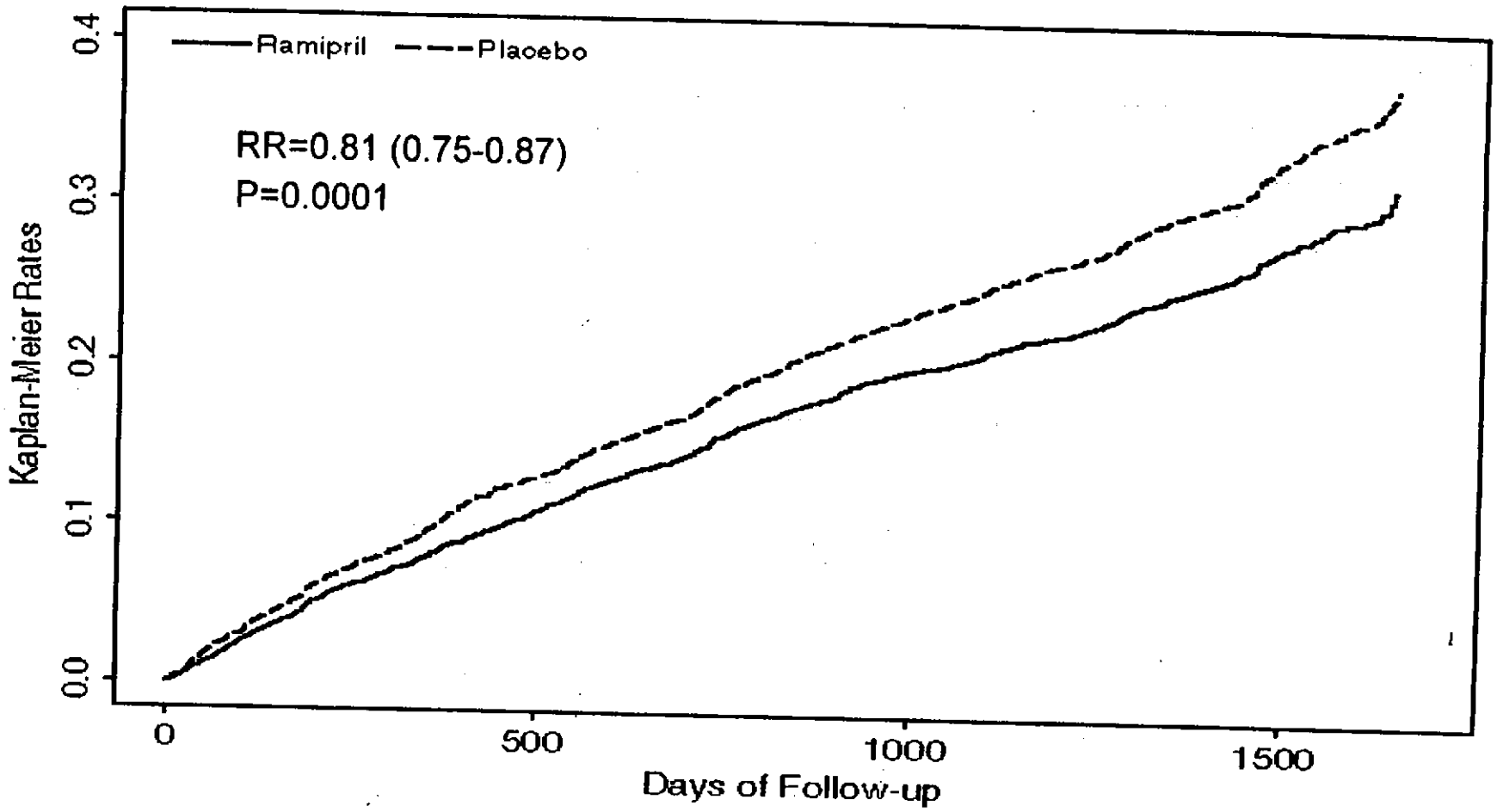
FIGURE 6: KAPLAN-MEIER SURVIVAL CURVE:DEVELOPMENT OF DIABETES



RR =0.66(0.51-0.85) P<0.001

FIGURE 7: KAPLAN-MEIER SURVIVAL CURVE

7A: PRIMARY OUTCOME + REVASCULARIZATION + ALL HEART FAILURE



7B: KAPLAN-MEIER SURVIVAL CURVE: CARDIOVASCULAR DEATH + HOSPITALIZATION FOR HEART FAILURE

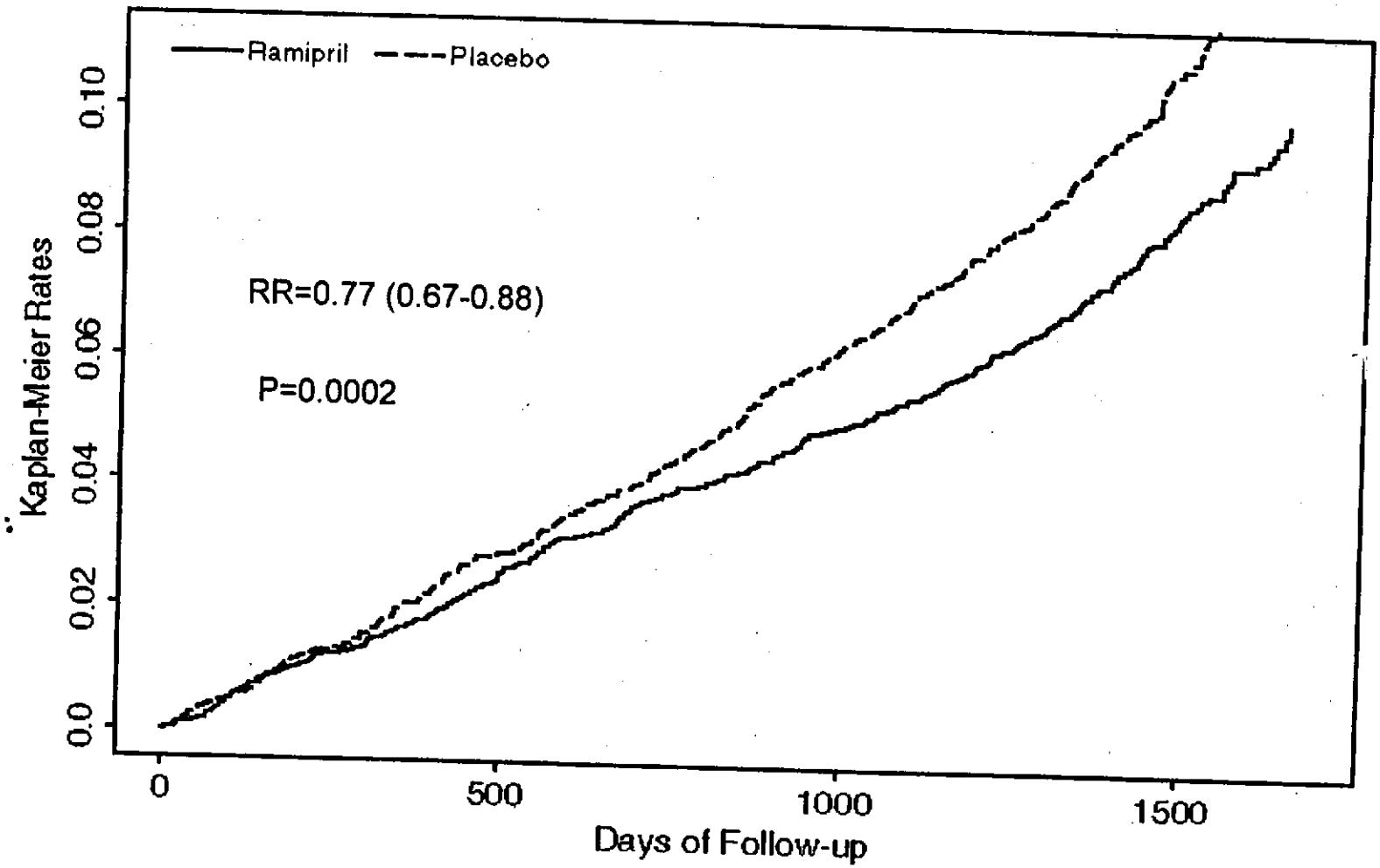


FIGURE 8: RENAL OUTCOMES IN ALL PATIENTS

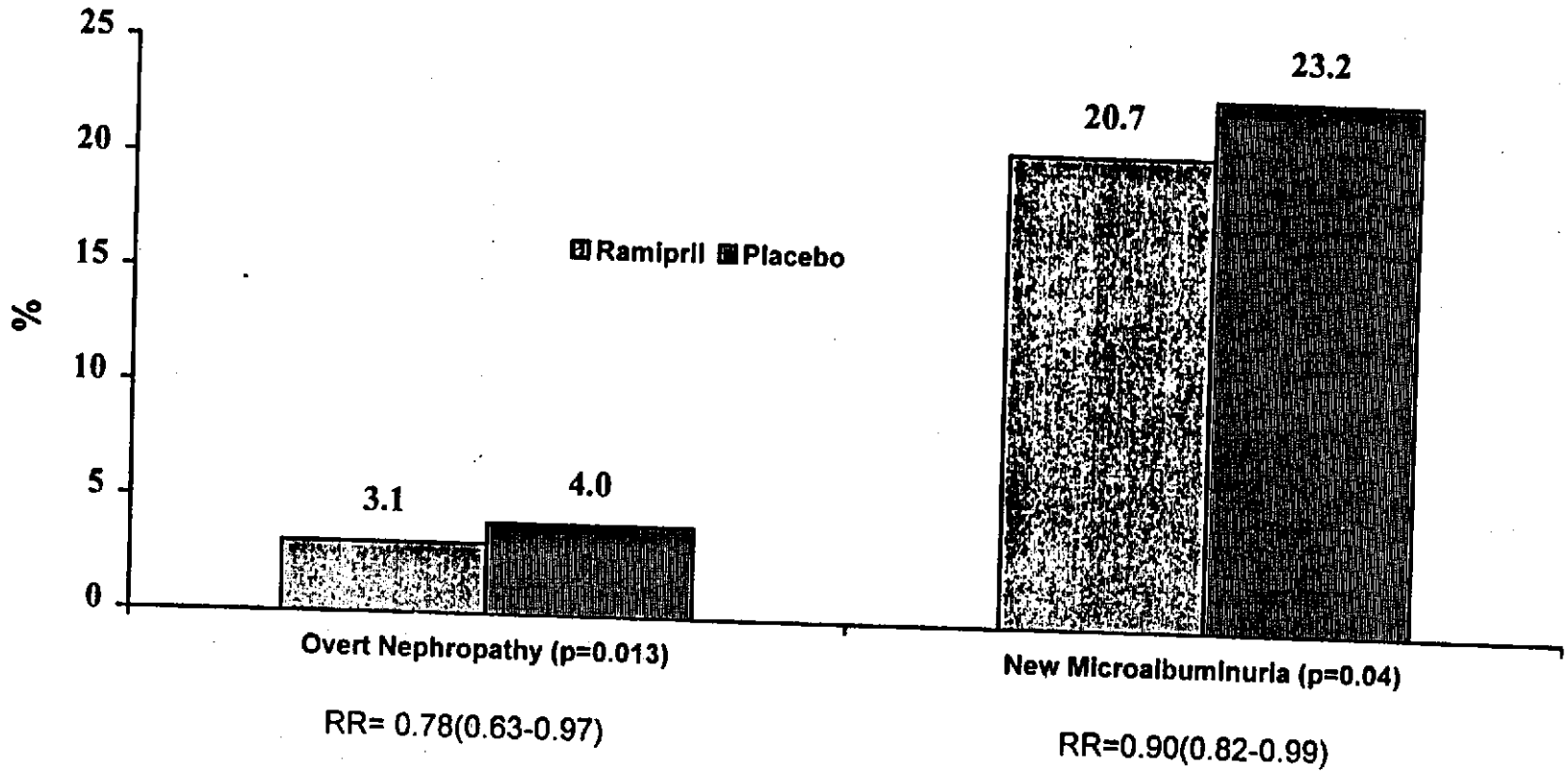


FIGURE 9: THE EFFECT OF RAMIPRIL TREATMENT ON THE COMPOSITE OUTCOME IN PRE-DEFINED SUBGROUPS

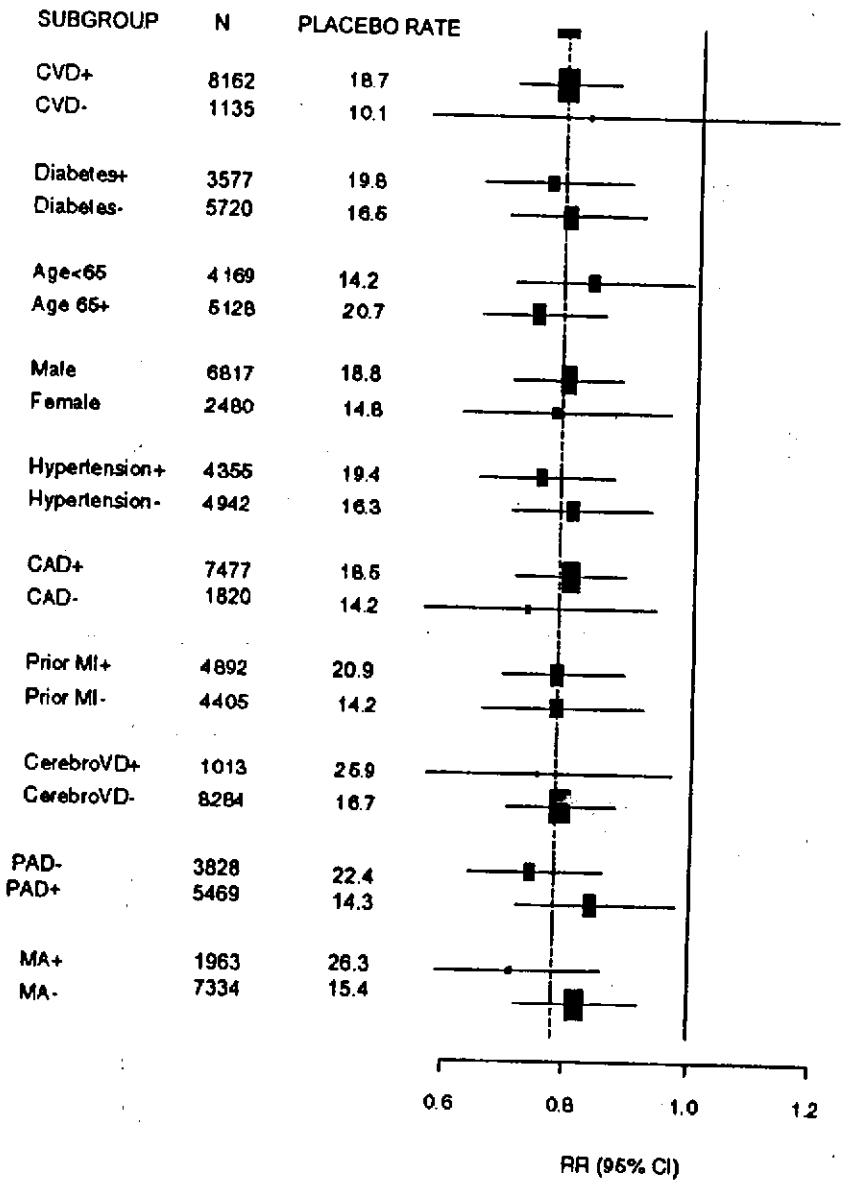
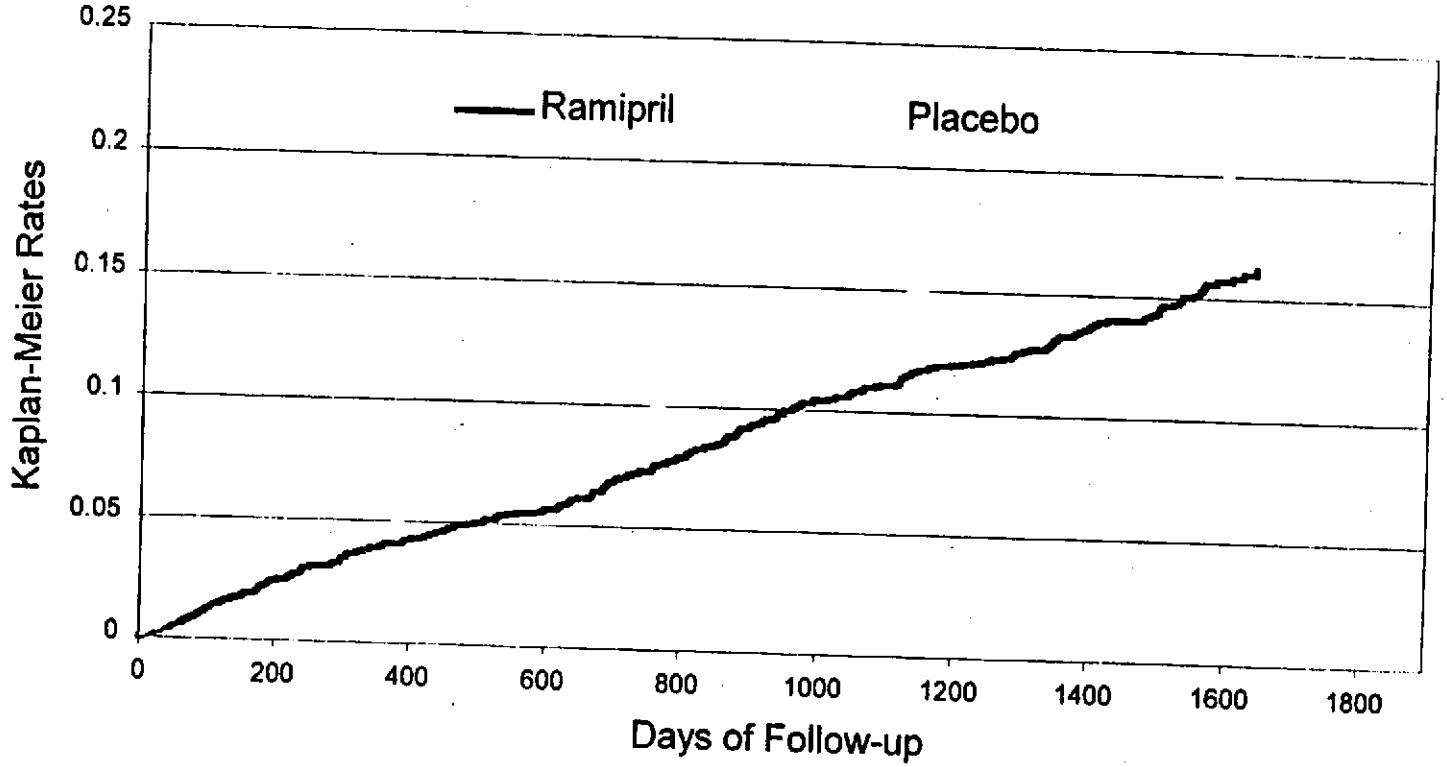


FIGURE 10: KAPLAN-MEIER SURVIVAL CURVE: PRIMARY OUTCOME IN PATIENTS WITH DIABETES ONLY



RR: 0.75(0.64-0.88) P=0.0004

FIGURE 11: PRIMARY OUTCOME IN IMPORTANT DIABETIC SUBGROUPS

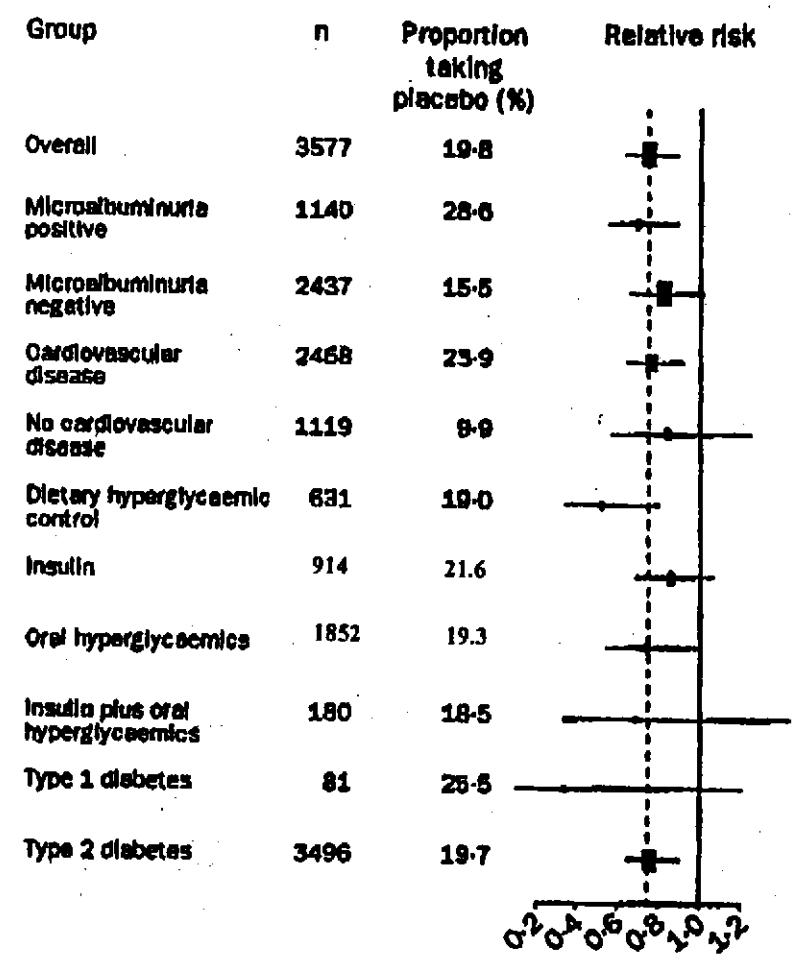


FIGURE 12: RISK OF PRIMARY OUTCOME BY SYSTOLIC BLOOD PRESSURE

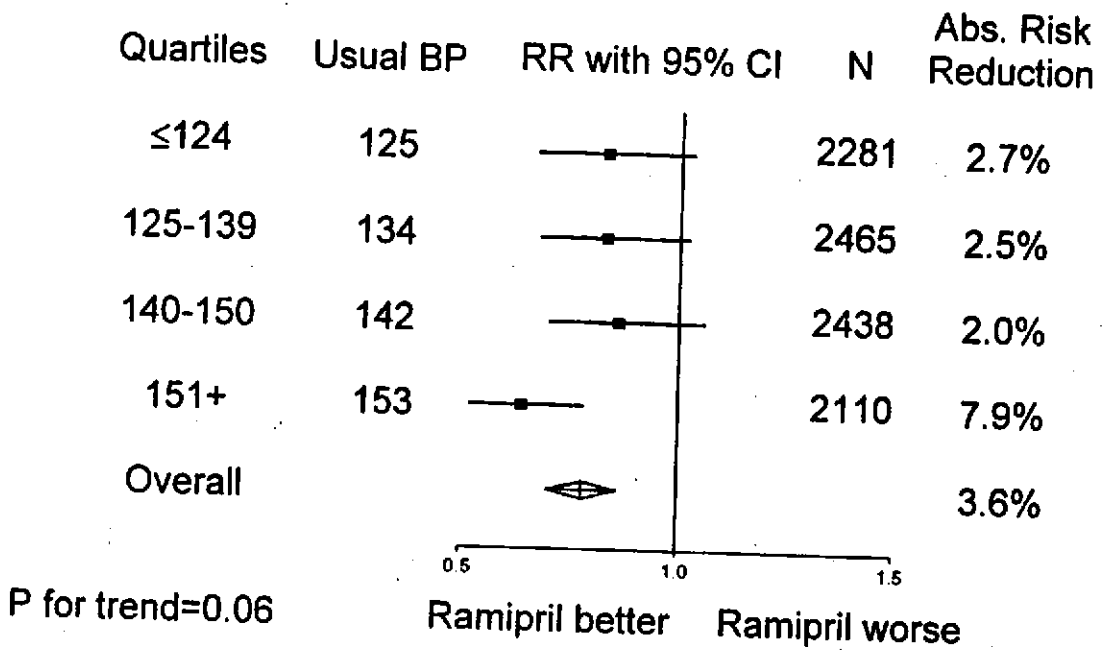
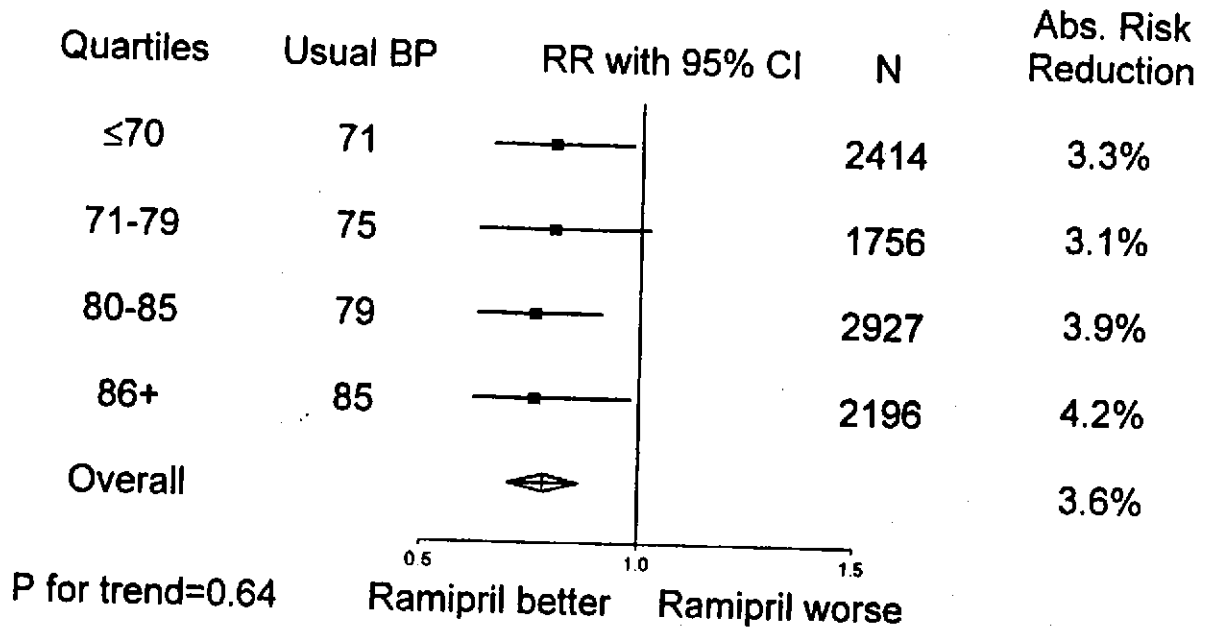


FIGURE 13: RISK OF PRIMARY OUTCOME BY DIASTOLIC BLOOD PRESSURE



ALTACE® Capsules

(ramipril)

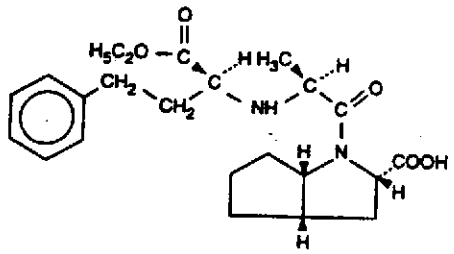
USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE® should be discontinued as soon as possible. **See WARNINGS: Fetal/neonatal morbidity and mortality.**

DESCRIPTION

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. It is a white, crystalline substance soluble in polar organic solvents and buffered aqueous solutions. Ramipril melts between 105° C and 112°C.

The CAS Registry Number is 87333-19-5. Ramipril's chemical name is (2*S*,3a*S*,6a*S*)-1[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl]alanyl]octahydrocyclopenta [*b*]pyrrole-2-carboxylic acid, 1-ethyl ester; its structural formula is:



Its empiric formula is C23H32N2O5, and its molecular weight is 416.5.

Ramiprilat, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group.

ALTACE (ramipril) is supplied as hard shell capsules for oral administration containing 1.25 mg, 2.5 mg, 5 mg, and 10 mg of ramipril. The inactive ingredients present are pregelatinized starch NF, gelatin, and titanium dioxide. The 1.25 mg capsule shell contains yellow iron oxide, the 2.5 mg

blue #1 and FD&C red #40, and the 10 mg capsule shell contains FD&C blue #1.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. In hypertensive patients with normal renal function treated with ALTACE alone for up to 56 weeks, approximately 4% of patients during the trial had an abnormally high serum potassium and an increase from baseline greater than 0.75 mEq/L, and none of the patients had an abnormally low potassium and a decrease from baseline greater than 0.75 mEq/L. In the same study, approximately 2% of patients treated with ALTACE and hydrochlorothiazide for up to 56 weeks had abnormally high potassium values and an increase from baseline of 0.75 mEq/L or greater, and approximately 2% had abnormally low values and decreases from baseline of 0.75 mEq/L or greater. (See **PRECAUTIONS**.) Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity.

The effect of ramipril on hypertension appears to result at least in part from inhibition of both tissue and circulating ACE activity, thereby reducing angiotensin II formation in tissue and plasma. ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of ALTACE remains to be elucidated.

While the mechanism through which ALTACE lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, ALTACE has an antihypertensive effect even in patients with low-renin hypertension. Although ALTACE was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to monotherapy than non-black patients.

Following oral administration of ALTACE, peak plasma concentrations of ramipril are reached within one hour. The extent of absorption is at least 50-60% and is not significantly influenced by the presence of food in the GI tract, although the rate of absorption is reduced.

In a trial in which subjects received ALTACE capsules or the contents of identical capsules dissolved in water, dissolved in apple juice, or suspended in apple sauce, serum ramiprilat levels were essentially unrelated to the use or nonuse of the concomitant liquid or food.

Cleavage of the ester group (primarily in the liver) converts ramipril to its active diacid metabolite, ramiprilat. Peak plasma concentrations of ramiprilat are reached 2-4 hours after drug intake. The serum protein binding of ramipril is about 73% and that of ramiprilat about 56%; *in vitro*, these percentages are independent of concentration over the range of 0.01 to 10µg/ml.

Ramipril is almost completely metabolized to ramiprilat, which has about 6 times the ACE inhibitory activity of ramipril, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat, all of which are inactive. After oral administration of ramipril, about 60% of the parent drug and its metabolites is eliminated in the urine, and about 40% is found in the feces. Drug recovered in the feces may represent both biliary excretion of metabolites and/or unabsorbed drug, however the proportion of a dose eliminated by the bile has not been determined. Less than 2% of the administered dose is recovered in urine as unchanged ramipril.

Blood concentrations of ramipril and ramiprilat increase with increased dose, but are not strictly dose-proportional. The 24-hour AUC for ramiprilat, however, is dose-proportional over the 2.5-20 mg dose range. The absolute bioavailabilities of ramipril and ramiprilat were 28% and 44%, respectively, when 5 mg of oral ramipril was compared with the same dose of ramipril given intravenously.

Plasma concentrations of ramiprilat decline in a triphasic manner (initial rapid decline, apparent elimination phase, terminal elimination phase). The initial rapid decline, which represents distribution of the drug into a large peripheral compartment and subsequent binding to both plasma and tissue ACE, has a half-life of 2-4 hours. Because of its potent binding to ACE and slow dissociation from the enzyme, ramiprilat shows two elimination phases. The apparent elimination phase corresponds to the clearance of free ramiprilat and has a half-life of 9-18 hours. The terminal elimination phase has a prolonged half-life (>50 hours) and probably represents the binding/dissociation

After multiple daily doses of ramipril 5-10 mg, the half-life of ramiprilat concentrations within the therapeutic range was 13-17 hours.

After once-daily dosing, steady-state plasma concentrations of ramiprilat are reached by the fourth dose. Steady-state concentrations of ramiprilat are somewhat higher than those seen after the first dose of ALTACE, especially at low doses (2.5 mg), but the difference is clinically insignificant.

In patients with creatinine clearance less than 40 ml/min/1.73m2, peak levels of ramiprilat are approximately doubled, and trough levels may be as much as quintupled. In multiple-dose regimens, the total exposure to ramiprilat (AUC) in these patients is 3-4 times as large as it is in patients with normal renal function who receive similar doses.

The urinary excretion of ramipril, ramiprilat, and their metabolites is reduced in patients with impaired renal function. Compared to normal subjects, patients with creatinine clearance less than 40 ml/min/1.73m2 had higher peak and trough ramiprilat levels and slightly longer times to peak concentrations. (See **DOSAGE AND ADMINISTRATION.**)

In patients with impaired liver function, the metabolism of ramipril to ramiprilat appears to be slowed, possibly because of diminished activity of hepatic esterases, and plasma ramipril levels in these patients are increased about 3-fold. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function, and the effect of a given dose on plasma ACE activity does not vary with hepatic function.

Pharmacodynamics

Single doses of ramipril of 2.5-20 mg produce approximately 60-80% inhibition of ACE activity 4 hours after dosing with approximately 40-60% inhibition after 24 hours. Multiple oral doses of ramipril of 2.0 mg or more cause plasma ACE activity to fall by more than 90% 4 hours after dosing, with over 80% inhibition of ACE activity remaining 24 hours after dosing. The more prolonged effect of even small multiple doses presumably reflects saturation of ACE binding sites by ramiprilat and relatively slow release from those sites.

Pharmacodynamics and Clinical Effects

Prevention of Myocardial Infarction, Stroke or Death from Cardiovascular Causes

The Heart Outcomes Prevention Evaluation study (HOPE study)[1] was a large, multi-center, random-

ALTACE) who were 55 years or older with 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 HDL levels, cigarette smoking, or documented microalbuminuria). This study was designed to examine the long-term (mean of five years) effects of ALTACE (10 mg orally once a day) on the primary endpoint of myocardial infarction, stroke or death from cardiovascular causes, and the secondary endpoints of death from any cause, the need for coronary artery revascularization, and hospitalization for unstable angina or heart failure.

The HOPE study results showed that ALTACE (10 mg/day) significantly reduced the composite of myocardial infarction, stroke or death from cardiovascular causes (651/4645 *vs.* 826/4652, relative risk 0.78, P<0.001).

Outcome	Altace (N=4645) no. (%)	Placebo (N=4652)	Relative Risk (95% CI)
Combined End-point			
(MI, stroke, or death from CV cause)	651 (14.0%)	826 (17.8%)	0.78 (0.70-0.86), P<0.001
Component End-point			
Death from Cardiovascular Causes	282 (6.1%)	377 (8.1%)	0.74 (0.64-0.87), P<0.001
Myocardial infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70-0.90), P<0.001
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56-0.84), P<0.001
Overall Mortality (Death from any Cause)	482 (10.4%)	569 (12.2%)	0.84 (0.75-0.95), P=0.005

This effect reached significance early in the study and significant differences between active and control continued to be observed throughout the study.

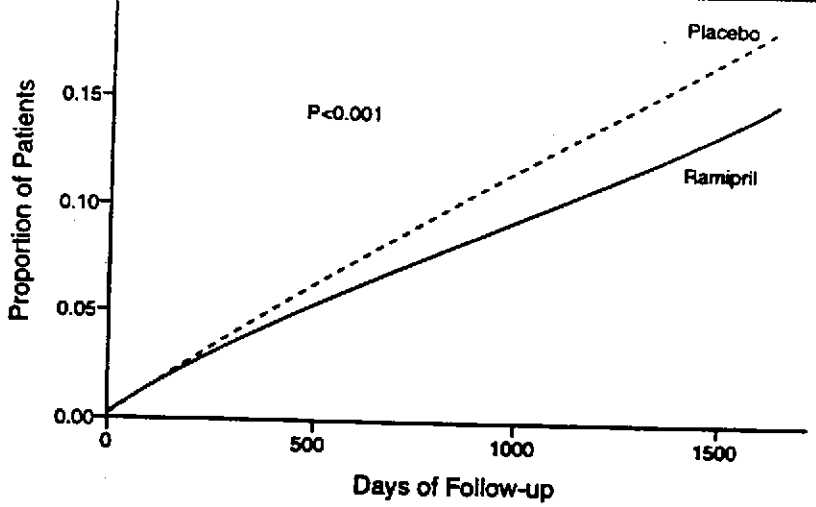
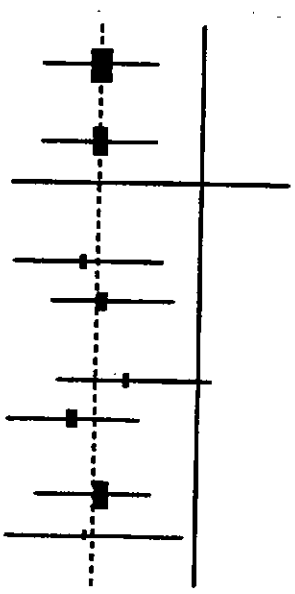


Figure 1: Kaplan-Meier Estimates of the composite outcome of MI, Stroke, or Death from CV causes in the Ramipril Group and the Placebo Group. The relative risk of the composite outcomes in the Ramipril Group as compared with the Placebo Group was 0.78% (95% confidence interval, 0.70–0.86).

The HOPE results were observed in all of the following subgroups:

- Patients with and without hypertension at base line.
- Patients with and without diabetes.
- Men and women;
- Patients with and without evidence of cardiovascular disease.
- Patients who were older or younger than 65 years, and
- Patients with and without microalbuminuria.

	No. of Patients	Incidence of Composite Outcome in Placebo Group
Overall	9297	17.8
Cardiovascular disease	8162	18.7
No cardiovascular disease	1135	10.2
Diabetes	3577	19.8
No diabetes	5720	16.5
Age <65 yr	4169	14.2
Age >65 yr	5128	20.7
Male sex	6817	18.7
Female sex	2480	14.4



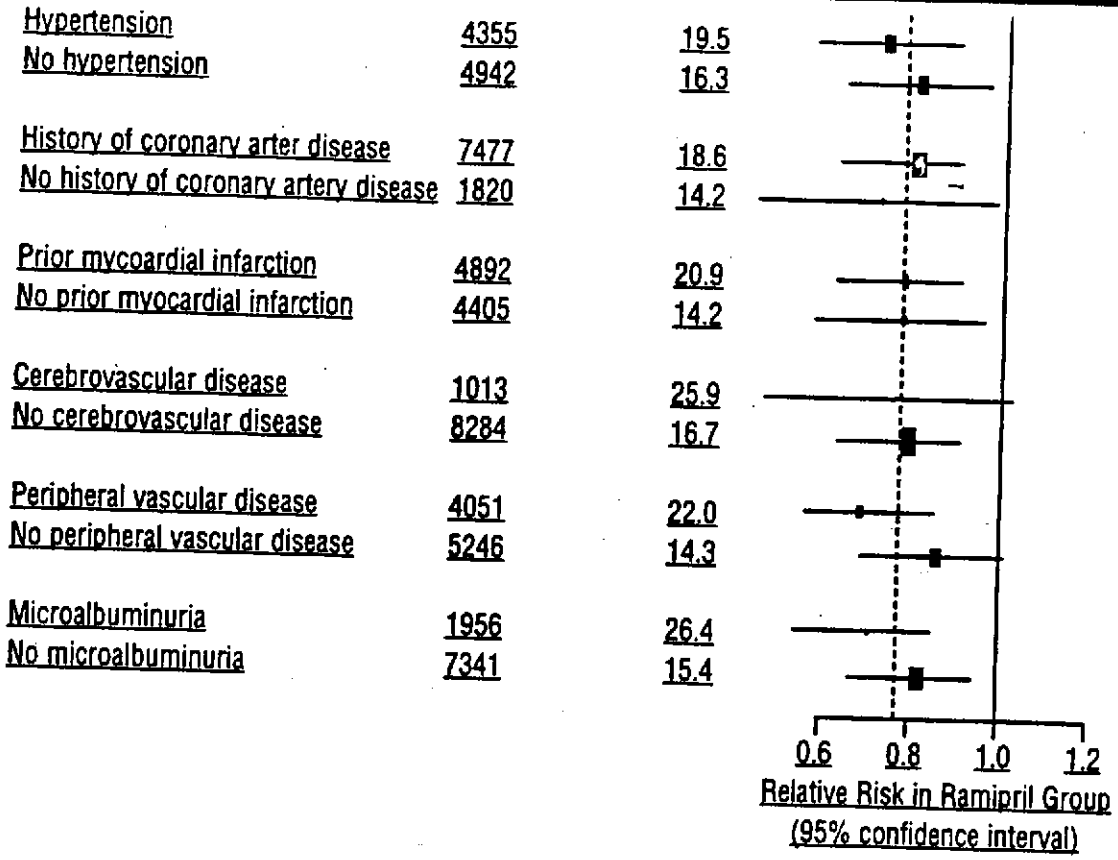


Figure 2. The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes Overall and in Various Predefined Subgroups. Cerebrovascular disease was defined as stroke or transient ischemic attacks. The size of each symbol is proportional to the number of patients in each group. The dashed line indicates overall relative risk.

The significant benefits of ALTACE were observed among patients who were prescribed and taking the treatments already proven to reduce the risk of cardiovascular events [i.e.: aspirin or other anti-platelet agents (75.3%), beta-blockers (39.2%), and lipid-lowering agents (28.4%)] as well as diuretics (15.3%) and calcium channel blockers (46.3%).

It was calculated that the overall incremental reduction in blood pressure attributable to the addition of ALTACE contributed only marginally to the results of the HOPE study since the majority of patients were not hypertensive at baseline and the reduction in blood pressure with ALTACE during the study was extremely small (3/2 mmHg).

Prespecified Secondary Endpoints of Clinical Relevance

The HOPE study also showed that Altace significantly reduced the number of patients who underwent coronary revascularization (742/4645 vs. 852/4652, rr = 0.85, P=0.002), and there was a trend toward fewer hospitalizations for heart failure (141 vs. 160; rr = 0.88; P = 0.25). In addition, Altace

= 0.77; p<0.001), newly diagnosed diabetes (102 vs. 155; rr = 0.66; p<0.001) and complications related to diabetes (299 vs. 354; rr = 0.84; p = 0.03) as shown in the following table.

Outcome	Altace (N=4645) no. (%)	Placebo (N=4652)	Relative Risk (95% CI)
Secondary Outcomes*			
Revascularization	742 (16.0%)	852 (18.3%)	0.85 (0.77-0.94), P=0.002
Complications Related to Diabetes❖◆	299 (6.4%)	354 (7.6%)	0.88 (0.70-0.98), P=0.03
Hospitalization for Heart Failure	141 (3.0%)	160 (3.4%)	0.88 (0.70-1.10), p=0.25
Other Clinical Relevant Outcomes			
Heart Failure◆	417 (9.0%)	535 (11.5%)	0.77 (0.67-0.87), P<0.001
Cardiac Arrest	37 (0.8%)	59 (1.3%)	0.62 (0.41-0.94), p=0.02
New Diagnosis of Diabetes	102 (3.6%)	155 (5.4%)	0.66 (0.51-0.85) P<0.001

* These events were centrally adjudicated

◆ All cases (with or without hospitalization)

❖ Includes diabetic nephropathy (urinary albumin >300mg/day or urine protein of 500 mg/day), need for dialysis, or need for laser therapy of diabetic retinopathy

Clinical Benefits in Diabetics

In the Microalbuminuria, Cardiovascular, and Renal Outcomes substudy (MICRO-HOPE) of HOPE study,[2] the effects of ALTACE (10 mg orally once a day) on the risk of occurrence of myocardial infarction, stroke or death from cardiovascular causes, and development of overt nephropathy (24 hour urine albumin > 300mg/day, 24 hour urine total protein > 500 mg/day, or albumin/creatinine ratio > 36 mg/mmol + clinical evidence of proteinuria) was investigated in 3577 diabetics in a large, multi-center, two by two factorial designed study. Diabetes status was established by history and physical examination at each visit. Participants were judged to have type 2 diabetes if they developed diabetes at age 30 years or older and did not require insulin for control. Glycated hemoglobin (HbA_{1c}) expressed as the percentage higher than the upper limit of normal and serum creatinine were assayed for participants with a history of diabetes. Urinary albumin excretion was measured at baseline, 1 year, and at the end of study (4.5 years) by determination of albumin/creatinine ratio in a first morning urine specimen. Microalbuminuria was defined as a urine albumine/creatinine ratio equal to or greater than 2mg/mmol. Baseline characteristics of the Altace and placebo groups were similar.

	Ramipril (n=1808)	Placebo (n=1769)
Demography		
Mean age (years)	65.3(6-4)	65.6 (6.6)
Female/male	696 (38%)/ 1112 (62%)	626 (35%)/ 1143 (65%)
Clinical characteristics		
Mean (SD) body-mass index (kg/m²)	28.9 (4.8)	28.6 (4.7)
Mean (SD) heart rate (beats/min)	72.3 (11.4)	72.5 (11.0)
Mean (SD) systolic blood pressure (mm Hg)	141.7 (19.6)	142.3 (19.5)
Mean (SD) diastolic blood pressure (mm Hg)	80 (10.6)	79.3 (10.7)
Mean (SD) ankle/arm systolic pressure (mm Hg)	0.97 (0.19)	0.96 (0.18)
Mean (SD) waist/hip ratio	0.93 (0.09)	0.93 (0.08)
Mean (SD) waist circumference (cm)	99.9 (12.7)	99.6 (12.4)
Microalbuminuria	553 (31%)	587 (33%)
Mean (SD) HbA_{1C} (%)*	123 (30)	124 (32)
Mean (SD) serum creatinine (µmol/L)*	93.8 (22.3)	94.0 (27.6)
Mean duration of diabetes (years)	11.1 (10.2)	11.8 (10.7)
Type 2 diabetes	1774 (98%)	1722 (97%)
History of hypertension	1045 (58%)	951 (54%)
Documented cholesterol >5.2 mmol/L	1174 (65%)	1161 (66%)
Current smoker	274 (15%)	270 (15%)
Previous coronary artery disease	1046 (58%)	1093 (62%)
Previous stroke/endarterectomy	124 (7%)	150 (8%)
Previous peripheral vascular disease	311 (17%)	361 (20%)
No previous cardiovascular disease	604 (33%)	515 (29%)
Hyperglycaemic control		
Dietary therapy alone	331 (18%)	300 (17%)
Insulin therapy alone	432 (24%)	482 (27%)
Oral agents alone	957 (53%)	895 (51%)
Insulin plus oral agents	88 (5%)	92 (5%)
Other Drugs		
Acetylsalicylic acid	982 (54%)	998 (56%)
Diurectics	350 (19%)	350 (20%)
B-blockers	510 (28%)	505 (29%)
Calcium-channel blockers	776 (43%)	801 (45%)
Hypolipidaemic drugs	409 (23%)	390 (22%)

*Measured at local laboratories: HbA_{1C} is reported as percentage above upper limit of normal for local laboratory.

Table 1: Baseline characteristics of participants with diabetes

nificantly lower rate of occurence of the combined primary endpoint of mycardial infarction, stroke or death from cardiovascular causes (277/1808 vs 351/1769; relative risk reduction=0.25; P=0.0004), as were the secondary endpoints of death from any cause (196 vs 248; relative risk reduction=0.24; P=0.004), the need for coronary artery revascularization (254 vs 291; relative risk reduction=0.17; P=0.031), and development of overt nephropathy (117 vs 149; relative risk reduction=0.24; p=0.027).

Outcome	Altace (N=1808) no. (%)	Placebo (N=1769)	Relative Risk Reduction (95% CI)
Combined End-point			
(MI, stroke, or death from CV cause)	277 (15.3%)	351 (19.8%)	0.25 (0.12-0.36), P=0.0004
Component End-point			
Death from Cardiovascular Causes	112 (6.2%)	172 (9.7%)	0.37 (0.21-0.51), P=0.0001
Myocardial infarction	185 (10.2%)	229 (12.9%)	0.22 (0.06-0.36), P=0.01
Stroke	76 (4.2%)	108 (6.1%)	0.33 (0.10-0.50), P=0.0074
Secondary Outcomes			
Total Mortality	196 (10.8%)	248 (14.0%)	0.24 (0.08-0.37), P=0.004
Revascularization	254 (14.0%)	291 (16.4%)	0.17 (0.02-0.30), P=0.031
Overt Nephropathy❖	117 (6.5%)	149 (8.4%)	0.24 (0.03-0.40), P=0.027
Other Clinical Relevant Outcomes			
Any Heart Failure	198 (11.0%)	236 (13.3%)	0.20 (0.04-0.34), P=0.019
Transient Ischemic Attacks	80 (4.4%)	104 (5.9%)	0.26 (0.01-0.45), P=0.04
Laser Therapy◆	170(9.4%)	186 (10.5%)	0.22 (-0.09-0.28), P=0.24

❖ Based on positive 24 hour urine collection or albumin/creatinine ration > 36 /mmol, if no 24 hour urine available.

◆ Laser therapy for retinopathy

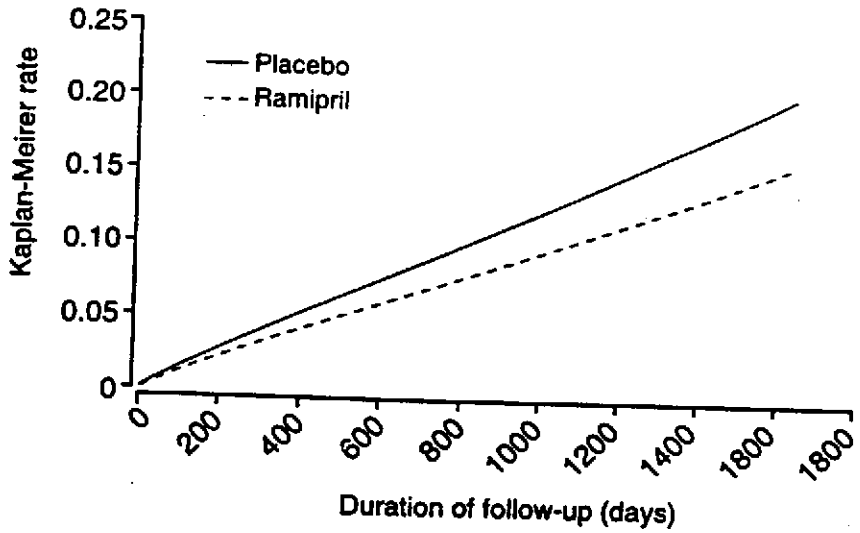


Figure 3: Kaplan-Meier Estimates of the primary outcome of MI, Stroke, or Death from CV causes in the Ramipril Group and the Placebo Group for participants with diabetes. (relative risk reduction 25% [95% CI 12-36], p=0.0004).

During the study, 345 participants developed an albumin/creatinine ratio >36mg/mmol and were asked to provide a urine collection to test for overt nephropathy. Overt nephropathy developed in 117 participants on Altace and 149 on placebo (relative risk redution=0.24, p=0.027). Altace lowered the risk of development of overt nephropathy in both of these groups and in addition led to an albumin/creatinine ratio lower than the placebo group at 1 year and at the end of the study as shown below.

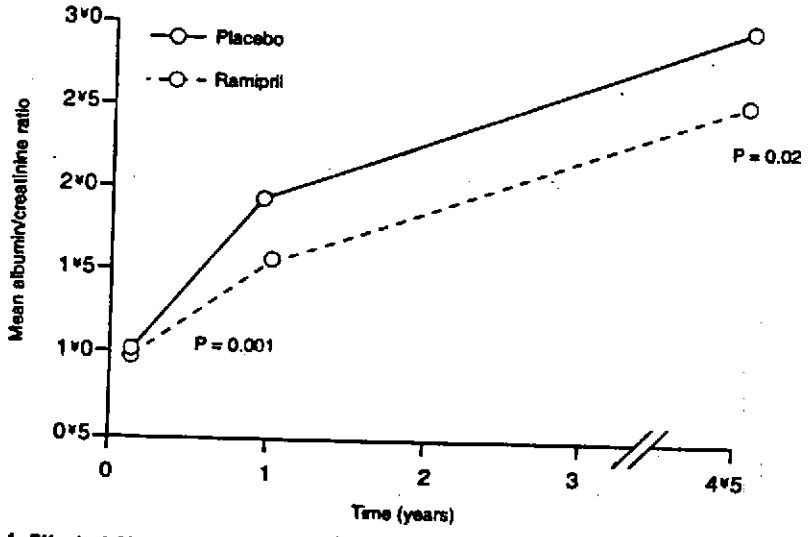


Figure 4: Effect of Altace on degree of albuminuria - Geometric mean albumin/creatinine ratio of all participants with available 24 hr. urine collection, (adjusted for laboratories where assays were performed).

Administration of ALTACE to patients with mild to moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See **WARNINGS.**) Use of ALTACE in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone.

In single-dose studies, doses of 5-20 mg of ALTACE lowered blood pressure within 1-2 hours, with peak reductions achieved 3-6 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In longer term (4-12 weeks) controlled studies, once-daily doses of 2.5-10 mg were similar in their effect, lowering supine or standing systolic and diastolic blood pressures 24 hours after dosing by about 6/4 mm Hg more than placebo. In comparisons of peak vs. trough effect, the trough effect represented about 50-60% of the peak response. In a titration study comparing divided (bid) vs. qd treatment, the divided regimen was superior, indicating that for some patients the antihypertensive effect with once-daily dosing is not adequately maintained. (See **DOSAGE AND ADMINISTRATION.**)

In most trials, the antihypertensive effect of ALTACE increased during the first several weeks of repeated measurements. The antihypertensive effect of ALTACE has been shown to continue during long-term therapy for at least 2 years. Abrupt withdrawal of ALTACE has not resulted in a rapid increase in blood pressure.

ALTACE has been compared with other ACE inhibitors, beta-blockers, and thiazide diuretics. It was approximately as effective as other ACE inhibitors and as atenolol. In both caucasians and blacks, hydrochlorothiazide (25 or 50 mg) was significantly more effective than ramipril.

Except for thiazides, no formal interaction studies of ramipril with other antihypertensive agents have been carried out. Limited experience in controlled and uncontrolled trials combining ramipril with a calcium channel blocker, a loop diuretic, or triple therapy (beta-blocker, vasodilator, and a diuretic) indicate no unusual drug-drug interactions. Other ACE inhibitors have had less than additive effects with beta adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

ALTACE was less effective in blacks than in caucasians. The effectiveness of ALTACE was not influ-

In a baseline controlled study of 10 patients with mild essential hypertension, blood pressure reduction was accompanied by a 15% increase in renal blood flow. In healthy volunteers, glomerular filtration rate was unchanged.

Heart Failure post myocardial infarction

ALTACE was studied in the Acute Infarction Ramipril Efficacy (AIRE) trial. This was a multinational (mainly European) 161-center, 2006-patient, double-blind, randomized, parallel-group study comparing ALTACE to placebo in stable patients, 2-9 days after an acute myocardial infarction (MI), who had shown clinical signs of congestive heart failure (CHF) at any time after the MI. Patients in severe (NYHA class IV) heart failure, patients with unstable angina, patients with heart failure of congenital or valvular etiology, and patients with contraindications to ACE inhibitors were all excluded. The majority of patients had received thrombolytic therapy at the time of the index infarction, and the average time between infarction and initiation of treatment was 5 days.

Patients randomized to ramipril treatment were given an initial dose of 2.5 mg twice daily. If the initial regimen caused undue hypotension, the dose was reduced to 1.25 mg, but in either event doses were titrated upward (as tolerated) to a target regimen (achieved in 77% of patients randomized to ramipril) of 5 mg twice daily. Patients were then followed for an average of 15 months (range 6-46). The use of ALTACE was associated with a 27% reduction ($p=0.002$), in the risk of death from any cause; about 90% of the deaths that occurred were cardiovascular, mainly sudden death. The risks of progression to severe heart failure and of CHF-related hospitalization were also reduced, by 23% ($p=0.017$) and 26% ($p=0.011$), respectively. The benefits of ALTACE therapy were seen in both genders, and they were not affected by the exact timing of the initiation of therapy, but older patients may have had a greater benefit than those under 65. The benefits were seen in patients on, and not on, various concomitant medications; at the time of randomization these included aspirin (about 80% of patients), diuretics (about 60%), organic nitrates (about 55%), beta-blockers (about 20%), calcium channel blockers (about 15%), and digoxin (about 12%).

INDICATIONS AND USAGE

Prevention of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

In patients 55 years or older with a history of coronary artery disease, stroke, peripheral vascular

cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), ALTACE is indicated as an adjunctive therapy to significantly reduce the risk of myocardial infarction, stroke, or death from cardiovascular causes. In addition, ALTACE is indicated to significantly reduce the incidence of these pre-selected clinically relevant secondary end-points: coronary revascularization procedures, complications related to diabetes, and heart failure.

Hypertension

ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See **WARNINGS**.)

In considering use of ALTACE, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients. (See **WARNINGS, Angioedema**.)

Heart Failure post-myocardial infarction

Ramipril is indicated in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of ramipril to such patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risks of failure-related hospitalization and progression to severe/resistant heart failure. (See **CLINICAL PHARMACOLOGY, Heart Failure post-myocardial infarction** for details and limitations of the survival trial.)

CONTRAINDICATIONS

ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ALTACE) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also **CONTRAINDICATIONS.**)

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered. (See ADVERSE REACTIONS.)**

In a large U.S. postmarketing study, angioedema (defined as reports of angio, face, larynx, tongue, or throat edema) was reported in 3/1523 (0.20%) of black patients and in 8/8680 (0.09%) of white patients. These rates were not different statistically.

Anaphylactoid reactions during desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension

ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic

be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Neutropenia/Agranulocytosis

Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/neonatal morbidity and mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or

from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE which crosses the placenta can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

PRECAUTIONS

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone sys-