# THE HOPE (HEART OUTCOMES PREVENTION EVALUATION) STUDY

## A large, randomized trial of the ACE inhibitor, ramipril, and Vitamin E

## in patients at high risk of cardiovascular events

| | |
|---|---|
| Investigators: | Multinational study |
| | Principal Investigator:<br>Prof S Yusuf, McMaster University, Hamilton, CA |
| | Co-Principal Investigators: |
| | Prof P Sleight, Oxford University, Oxford, UK<br>Dr. G. Dagenais, University of Laval, Quebec City, CA |
| Date first subject was enrolled: | 23rd December 1993 |
| Date last subject completed the study: | July 1999 |
| Study manager: | J Bosch Canadian Project Office, Hamilton General Hospital, Ontario, Canada |
| | L Richardson European Project Office<br>Bucks, England |
| Biostatistician: | J Pogue Canadian Project Office, Hamilton General Hospital, Ontario, Canada |
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## STUDY SYNOPSIS

### Title

THE HOPE (HEART OUTCOMES PREVENTION EVALUATION) STUDY: A large, randomized trial of the ACE inhibitor, ramipril, and Vitamin E in patients at high risk of cardiovascular events

### Investigator(s), study site(s)

This was a multicentre study conducted in 267 centres in 19 countries as follows: 129 in Canada, 76 in Europe, 27 in the USA, 30 in South America and 5 in Mexico.

### Objectives

- to compare the effects of treatment with ramipril or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high risk patients

- to compare the effects of treatment with Vitamin E or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high risk patients

Secondary objectives included the investigation of treatment differences incidence of hospitalizations for unstable angina or revascularization procedures (CABG or PTCA), carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation, development of congestive heart failure (for ramipril), cardiovascular mortality and total mortality.

A prospective secondary analysis of incidence of nephropathy was included for diabetic patients. Consistency of results were investigated by examining the effects of treatment across various sub-groups i.e. patients with coronary disease, with cerebrovascular or peripheral cardiovascular diseases, with diabetes, male and female and by age.

### Design

The study was a randomized placebo-controlled, double blind clinical trial designed to recruit at least 9000 patients who were at significant risk of CVD events (including patients with previous MI, previous angina, previous multivessel CABG or multivessel PTCA, multivessel coronary disease seen on angiography, previous stroke, peripheral arterial disease, diabetics with at least one other risk factor) using a 2 x 2 factorial design and a simple and focused protocol.

### Methods

9541 patients were entered into the programme. 244 of these patients were entered into the low dows (2.5 mg per day) arm of the SECURE substudy. 9297 patients were included in the main study. These were high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure. They were randomly assigned to receive ramipril (10 mg per day orally) or matching placebo or vitamin E (400 IU per day orally) or matching placebo for a mean of five years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

Following a screening and run-in phase eligible patients were randomized. Follow-up visits occurred at one month, six months and then every six months thereafter. At each visit a routine clinical examination was carried out, the results of which were recorded on the relevant page of the case report forms. Relevant history and event details were also recorded. In addition, at baseline, 2 years and end of study, centres were asked to collect an electrocardiogram (ECG) on each patient.

For each primary outcome, centres were asked to complete a seperate event form (i.e. MI, stroke or death). In addition secondary outcome data were collected on hospitalization forms. Specific forms recorded hospitalizations as a result of unstable angina or congestive heart failure. Assessments of local serum creatinine, local serum potassium, local glycated Hb, local urine dipstick, local 24-hour urine collections and central assay or urinary albumin and creatinine were carried out at various intervals during the study.

**Study duration and dates**

Patients were recruited from December 1993 to August 1995 and were all followed until the study was terminated in April 1999 because of clear benefit from ramipril. Final Visits took place between May and August 1999. The majority of patients are currently continuing in the vitamin E extension of the study.

**Statistical Procedures**

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 unblinded 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, 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. This model was used to estimate the effects of treatment after stratification for randomization to vitamin E or its placebo. Subgroup analyses were conducted with the use of tests for interactions in the Cox regression model.

**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 4 times during the study (plus one additional confirmation meeting). On March 22, 1999, the monitoring board recommended termination of the ramipril arm of the study because of the clear evidence of a beneficial effect of ramipril .

**Results**

Note that since the vitamin E arm of the study is continuing only limited data on the vitamin E arm of the study are presented in this report.

**Results – Study Subjects and Conduct**

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.

Of the 9541 randomized patients, 4645 were assigned to receive 10 mg of ramipril per day, 4652 were randomly assigned to receive matching placebo, and 244 were assigned to receive a low dose (2.5 mg per day) of ramipril. Only the primary he results from the 244 patients who received a 2.5mg dose are included in this report.

As intended a high risk population was recruited to this study. The number of patients in each of the important subgroups was as follows: 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 significant differences in baseline characteristics between the treatment groups.

The number of patients for whom information on status was obtained remained high throughout the study with information on 99.9% (9,537 of 9,541) of eligible patients being collected at the final visit. Since visit compliance was balanced and comprehensive for both groups there are no visit compliance issues for this study.

**Results - Efficacy**

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).

In addition there were significant benefits in the ramipril group across most of the secondary outcomes. 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 towards 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). 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) ; 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.

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.

**Results - Safety**

Ramipril was well tolerated and the only adverse event worthy of note is an increase in the number of patients experiencing 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 the patient was subsequently discharged without sequelae.

**Conclusions**

Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure. This effect is consistent across many important subgroups including those with and without cardiovascular disease, those with and without hypertension, those with and without diabetes and in both older and younger patients.

The magnitude of the benefit of treatment with ramipril with respect to the primary outcome is at least as large as that observed with other proven secondary prevention measures, such as treatment with beta-blockers, aspirin, and lipid-lowering agents, over four years. In addition, there were reductions in the rates of revascularization, heart failure, complications related to diabetes, and new diagnoses 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.

It should be noted that HOPE study medication (ramipril/placebo) was in addition to standard therapy. 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.

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Please note: Ramipril Active/Placebo in Table Headings always refers to the 10 mg group unless otherwise specified

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## ABBREVIATIONS AND DEFINITIONS

| Abbreviation | Definition |
|---|---|
| AABP | Ankle Arm Blood Pressure Ratio |
| ACE | Angiotensin converting enzyme |
| AE | Adverse event |
| BP | Blood pressure |
| CABG | Coronary artery bypass graft |
| CAD | Coronary artery disease |
| CCC | Canadian Cardiovascular Collaboration |
| CCU | Coronary care unit |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| CRF | Case report form |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DM | Diabetes Mellitus |
| DSMB | Data and Safety Monitoring Board |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| GCP | Good clinical practice |
| Hb | Hemoglobin |
| HMR | Hoechst Marion Roussel |
| HOPE | Heart Outcomes Prevention Evaluation |
| IRB | Institutional review board |
| MI | Myocardial infarction |
| PAD | Peripheral arterial disease |
| PTCA | Percutaneous transluminal angioplasty |
| QC | Quality Control |
| SD | Standard deviation |
| UA | Unstable angina |
| UK | United Kingdom |
| ULN | Upper Limit of Normal |

## 1.0 INTRODUCTION AND STUDY RATIONALE

Cardiovascular disease remains the primary cause of death in the western world despite advances in medical care. Although it is well established that elevated cholesterol, smoking and hypertension are major risk factors for cardiovascular disease[1] (CVD), these factors do not fully account for the risks of developing CVD in a population[2]. Therefore, identification and modification of other risk factors is needed to further reduce death and disability from CVD.

Epidemiological and molecular data suggest that activation of the renin-angiotensin system has a strong role in increasing the risk of CVD events, such as myocardial infarction (MI). Additionally, studies in animals suggest that angiotensin converting enzyme (ACE)-inhibitors which block the activation of the renin-angiotensin system may retard atherosclerosis. Three large clinical trials of ACE inhibitors (SOLVD trials and the SAVE trial) which randomized more than 9000 patients with low ejection fractions found a significant 23% reduction in risk of MI ($2p<0.0002$)[3,4,5,6]. This benefit was seen in a wide range of patients in these trials and raises the possibility that reductions in ischemic heart events may be applicable to a wider range of patients, including those with preserved ejection fractions. Parallel lines of evidence from observational animal and human studies suggest that ACE

inhibitors may provide benefit through several mechanisms, including blood pressure reduction, antiproliferative effects, hormonal/vascular effects and anti-atherogenic effects[7,8,9,10]. However, widespread acceptance of ACE-Inhibitors as preventive therapy must be preceded by direct proof of benefit from randomized trials in patients with preserved ejection fractions. The Heart Outcomes Prevention Evaluation (HOPE) study is a large randomized controlled trial designed to evaluate whether ACE inhibition reduces ischemic cardiovascular events in this group.

Evidence from experimental studies suggests that oxidation of lipids may be important in the formation and progression of atherosclerosis and that vitamin E is an effective anti-oxidant[11,12]. Several large observational studies of vitamin E have shown that users of vitamin E have a substantially reduced risk of events such as MI and stroke in comparison with non-users[13,14,15]. However these observational studies may be subject to considerable bias, such as vitamin E consumers more often adopting other healthy lifestyle changes e.g. exercise, less smoking etc. It is therefore possible that the degree of benefit apparent from antioxidant use may be overestimated by the non randomized studies. The efficacy of vitamin E should be established by large randomized clinical trials before its use becomes widespread.

The study was organized and coordinated by the Canadian Cardiovascular Collaboration Project Office at McMaster University in Hamilton, Ontario. Adjunct offices were located in London, United Kingdom; Sao Paulo, Brazil; and Rosario, Argentina. The overall responsibility for HOPE rested with the independent steering committee. Two important sub-committees of the steering committee were the Events Adjudication committee and the sub-study/publication policy committee. An independent Data and Safety Monitoring Board monitored the progress of all aspects of the study and carried out the appropriate unblinded interim analyses.

On March 22, 1999 the independent Data and Safety Monitoring board recommended early termination of the ramipril arm of the study due to clear benefit. Subsequently on April 17$^{th}$ the Steering Committee accepted this recommendation and the relevant study close-out procedures were implemented. The vitamin E arm of the study is continuing and therefore only minimal data regarding that arm of the study is included in this report.

## 2.0 STUDY OBJECTIVES

### 2.1 Primary objective

The objective of the study was to compare the effects of treatment with ramipril (10mg/day) or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high-risk patients, and/or to compare the effects of treatment with Vitamin E (400IU/day) or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high risk-patients.

### 2.2 Secondary objectives

Secondary objectives were to investigate treatment effects on the incidence of hospitalizations for unstable angina, the need for revascularization procedures (including coronary artery bypass graft (CABG), percutaneous transluminal angioplasty (PTCA), carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation), hospitalization for congestive heart failure, overt nephropathy and total mortality.

Additionally the effect of treatment on important subgroups (women, older patients (>65 years), patients with hypertension, patients with coronary disease, patients with cerebrovascular disease, patients with peripheral arterial disease and patients with diabetes) were to be examined. Diabetic patients were seen to be a particularly important group because of their known high risk of cardiovascular disease.

## 3.0 INVESTIGATIONAL PLAN

### 3.1 Study design

The HOPE study was a randomized placebo-controlled, double blind clinical trial, the design of which has been previously published[16]. The original design included 9000 high-risk patients, however to ensure high statistical power in all important subgroups the sample size was increased to 9,500 prior to the start of the study. The study used a 2 x 2 factorial design to examine the effects of ramipril (10mg/day) versus placebo and/or vitamin E versus placebo on cardiovascular outcomes. The study starting recruiting patients in December 1993 and randomizing patients in January 1994. Randomization was complete in August 1995. Initially follow up was scheduled for an average of 3.5 years however as a result of emerging information indicating a possible time-lag in full treatment effect, while still blinded, the steering committee agreed to extend the study to an average of 4.5 years of follow-up. One of the main strengths of the study was its simple and focused protocol.

#### 3.1.1 Logistics

The study was carried out in the following regions; Canada, Europe (Austria, Belgium, Denmark, Finland, France, Germany, Holland, Italy, Ireland, Norway, Spain, Sweden, Switzerland and the United Kingdom), Latin America (Argentina, Brazil and Mexico) and the United States of America.

Protocol: The development and design of the HOPE study took place over many months between early 1992 and late 1993 and various draft versions of the protocol were developed. Patient enrollment was completed on version 13 of the protocol. There was one protocol amendment that allowed for an extension of the follow up period. A summary of the protocol versions is shown below.

| | Version | Dates |
|---|---|---|
| North American Protocol (English)<br>* Also used in Argentina and Mexico | V11 | August 1993 (used in early IRB submissions in North America) |
| | V12 | December 1993 (incorporated corrections to version 11) |
| | V13 | March 1994<br>* Differences between V13 and previous versions are noted in italics in protocol |
| European Protocol (English)<br>* European Investigators also used North American protocol | | February 1994 (based on V12) |
| Brazilian Protocol (Portuguese) | | March 1994 (based on V13) |

Minor variations in the content of each protocol have arisen due to errors in transcription etc. but since all centres also received the North American protocol and other instructions on study conduct, these differences are not considered significant and are not discussed in detail. Essentially all centres met the standards of version 13 of the protocol and the same data were collected in all areas.

Regulatory and Ethics Submissions: Regional/national submissions were made to regulatory authorities as/if required. In addition, each centre submitted the protocol to appropriate local ethics committees. The approvals for each centre are available at the Canadian Project Office. Ethics approval (both original and extension if required) is available for all 267 centres.

Informed Consent: Written informed consent was obtained prior to the conduct of any study-related procedures. Site-specific versions are archived at the Canadian Project Office. Note that in some countries/centres a new consent form for the extension study was not required.

Investigators: Since the patient population recruited spanned a wide area of medical care, participating investigators could be from a variety disciplines (i.e. cardiology, neurology, surgeons, diabetologists, primary care). One physician at each centre took overall responsibility for the study.

Signed agreement letters, curricula vitae and regulatory forms (where applicable) are available at the Project Office for these individuals. In some countries investigators were asked to sign a contractual agreement while in others, agreement to participate in the study was confirmed by signature on a protocol signature page. The principle investigator at each site was responsible for signing these agreements. Centres 120 and 123 amalgamated during the study as did centres 11 and 146 as a result of physician re-location. Two new sites were established in the UK during the study to follow two patients that moved from Canada to the UK.

### 3.2 Selection of Subjects

The wide inclusion criteria allowed us to capture a truly high-risk population. There were several groups within this population that were of particular interest and recruitment efforts were targeted at these groups. They included:

- Women: Every effort was made to recruit as many female patients as possible (as historically this is an underrepresented group in cardiovascular clinical trials).
- Patients with diabetes and high risk of cardiovascular disease: This group was of specific interest because of the known high rate of cardiovascular morbidity and mortality. In addition, MICROHOPE [17]study examined the progression of microalbuminuria in-patients with diabetes.

#### 3.2.1 Inclusion Criteria

Patients were included in the study if they were 55 years of age or older and at high risk of developing cardiovascular disease. This included patients with:

- coronary disease (previous myocardial infarction, stable or unstable angina with documented multivessel coronary disease (>50% stenosis in at least two major coronary arteries) or positive stress testing (ST depression ≥ 2mm or a positive thallium), or multivessel PTCA (patients could be entered into Run-in Phase one week after these events but could only be randomized one month after these events), multivessel CABG (more than 4 years prior to randomization or with angina) or multivessel coronary disease seen on angiography)

- cerebrovascular disease (previous stroke more than one month ago)

- peripheral arterial disease (previous limb bypass surgery or percutaneous transluminal angioplasty, previous limb or foot amputation, history of intermittent claudication with ankle/arm blood pressure ratio of 0.80 or lower in at least one side, significant stenosis *(>50%)* documented by angiography),

- Diabetes (insulin-dependent or non-insulin dependent) with one of the following cardiovascular risk factors: hypertension, (B.P. >160 mmHg systolic or >90 mmHg diastolic or on treatment); total cholesterol>5.2 mmol/L (>200 mg/dl); HDL cholesterol < 0.9 mmol/l(3.5 mg/dl); current cigarette smoking; known microalbuminuria or any evidence of previous vascular disease.

#### 3.2.2 Exclusion Criteria

Exclusion criteria relate primarily to absolute indications or contra-indications for the use of ACE-I or Vitamin E, and to the presence of other medical problems that would either interfere with participation in the trial or lead to the inability to complete the trial. These include:

- Drug use: Current use of ACE-I (eg, for congestive heart failure, EF<40% or severe hypertension) or current use of Vitamin E and inability to discontinue these medications; or known hypersensitivity to ACE-I or Vitamin E.

- Cardiovascular diseases:

- Ejection fraction <40% (only if known).
- Hemodynamically significant primary valvular or outflow tract obstruction (eg. mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve).
- Constrictive pericarditis.
- Complex congenital heart disease.
- Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia were not an exclusion criterion).
- Planned cardiac surgery or angioplasty within 3 months (patient could be reconsidered for the trial after the procedure).
- Uncontrolled hypertension.
- Cor pulmonale.
- Heart transplant recipient.

- Other conditions:
  - Significant renal disease defined as: a) renal artery stenosis; b) creatinine clearance <0.6 ml/second or serum creatinine ≥ 200 mEq/L (≥2.26 mg/dl); c) overt nephropathy: ≥1 plus proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hrs); d) hyperkalemia; K>5.5 mEq/L.
  - Any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation.
  - Patient is simultaneously taking another experimental drug.
  - Previously randomized to HOPE.

### 3.3 Study treatments

After an initial single blind run-in period, during which patients received 2.5mg once daily of active ramipril for 7-10 days followed by placebo ramipril for 10-14 days, patients were randomized (in a double blind fashion) to ramipril (2.5mg once daily for 7 days followed by 5.0mg once daily for 21-31 days, then 10mg once daily for the remainder of the study) or placebo and Vitamin E (400 IU once daily) or placebo, using a factorial 2 x 2 design. Patients were followed on a regular basis at six month intervals during which all cardiovascular events and hospitalizations were monitored.

#### 3.3.1 Details of study treatments

Patients were to be randomized to ramipril (10mg/day) or placebo and/or Vitamin E (400 IU/day) or placebo using a 2x2 factorial design as shown below:

| | Ramipril Active | Ramipril Placebo |
|---|---|---|
| Vitamin E Active | Vitamin E Active + Ramipril Active | Vitamin E Active + Ramipril Placebo |
| Vitamin E Placebo | Vitamin E Placebo + Ramipril Active | Vitamin E Placebo + Ramipril Placebo |

The dose of ramipril was 2.5mg once daily for 7 days followed by 5.0mg once daily for 21-31 days, then 10mg once daily for the remainder of the study. The dose of Vitamin E was 400 IU once daily throughout. Details of dose adjustments are shown below (see 3.3.5).

### 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.<br>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<br>1 month<br>Annually | All patients<br>All patients<br>Patients with diabetes |
| Local Serum Potassium | Pre-randomization<br>1 month | All patients<br>All patients |
| Local Glycated Hb | Pre-randomization<br>Annually | Patients with diabetes<br>Patients with diabetes |
| Local urine dipstick to screen for overt nephropathy | Run-In<br>Annually | All patients<br>Patients with diabetes |
| Urine sample sent centrally (for assay of albumin and creatinine) | Randomization<br>1 year<br>End of Study | All patients<br>Patients with diabetes<br>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) | PLACEBO GROUP (N=4652) | RELATIVE RISK (95% CI)* | Z STATISTIC | P VALUE |
|---|---|---|---|---|---|
| | N (%) | N(%) | | | |
| 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) | Placebo Group (N=4652) | Relative Risk (95% CI) | Z Statistic | P Value |
|---|---|---|---|---|---|
| | n (%) | N(%) | | | |
| 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) N (%) | PLACEBO GROUP (N=4652) N(%) | RELATIVE RISK (95% CI) | P VALUE |
|---|---|---|---|---|
| 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 CARDIOIVASCULAR CAUSES$^{\Omega}$ | 112(6.2) | 172(9.7) | 0.63(0.49-0.79) | <0.0001 |
| MYOCARDIAL INFARCTION$^{\Omega}$ | 185(10.2) | 229(13.0) | 0.78(0.64-0.94) | 0.01 |
| STROKE$^{\Omega}$ | 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 |

$^{\Omega}$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$^{\Omega}$ | 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 |

$^{\Omega}$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) | 0.88 |
| - | 5624 | 392(13.9) | 487(17.4) | 0.78(0.68-0.89) | |
| LIPID LOWERING AGENT | | | | | |
| + | 2658 | 139(10.6) | 187(14.0) | 0.75(0.60-0.93) | 0.67 |
| - | 6639 | 512(15.4) | 638(19.3) | 0.78(0.70-0.88) | |
| ASPIRIN | | | | | |
| + | 6813 | 503(14.9) | 594(17.2) | 0.86(0.76-0.96) | 0.002 |
| - | 2484 | 148(11.6) | 231(19.1) | 0.59(0.48-0.72) | |
| ANY BETA BLOCKER/ASPIRIN/LIPID LOWERING AGENT | | | | | |
| + | 7730 | 557(14.5) | 685(17.6) | 0.81(0.73-0.91) | 0.05 |
| - | 1567 | 94(11.7) | 140(18.4) | 0.61(0.47-0.79) | |

**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) | 0.84 |
| - | 5624 | 727(25.7) | 866(30.9) | 0.80(0.73-0.88) | |
| LIPID LOWERING AGENT | | | | | |
| + | 2658 | 327(24.8) | 405(30.2) | 0.79(0.68-0.91) | 0.66 |
| - | 6639 | 947(28.5) | 1124(33.9) | 0.82(0.75-0.89) | |
| ASPIRIN | | | | | |
| + | 6813 | 982(29.2) | 1169(33.9) | 0.83(0.76-0.90) | 0.24 |
| - | 2484 | 292(22.9) | 360(29.8) | 0.75(0.64-0.87) | |
| ANY BETA BLOCKER/ASPIRIN/LIPID LOWERING AGENT | | | | | |
| + | 7730 | 1095(28.5) | 1321(34.0) | 0.81(0.75-0.88) | 0.73 |
| - | 1567 | 179(22.2) | 208(27.3) | 0.78(0.64-0.96) | |

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**

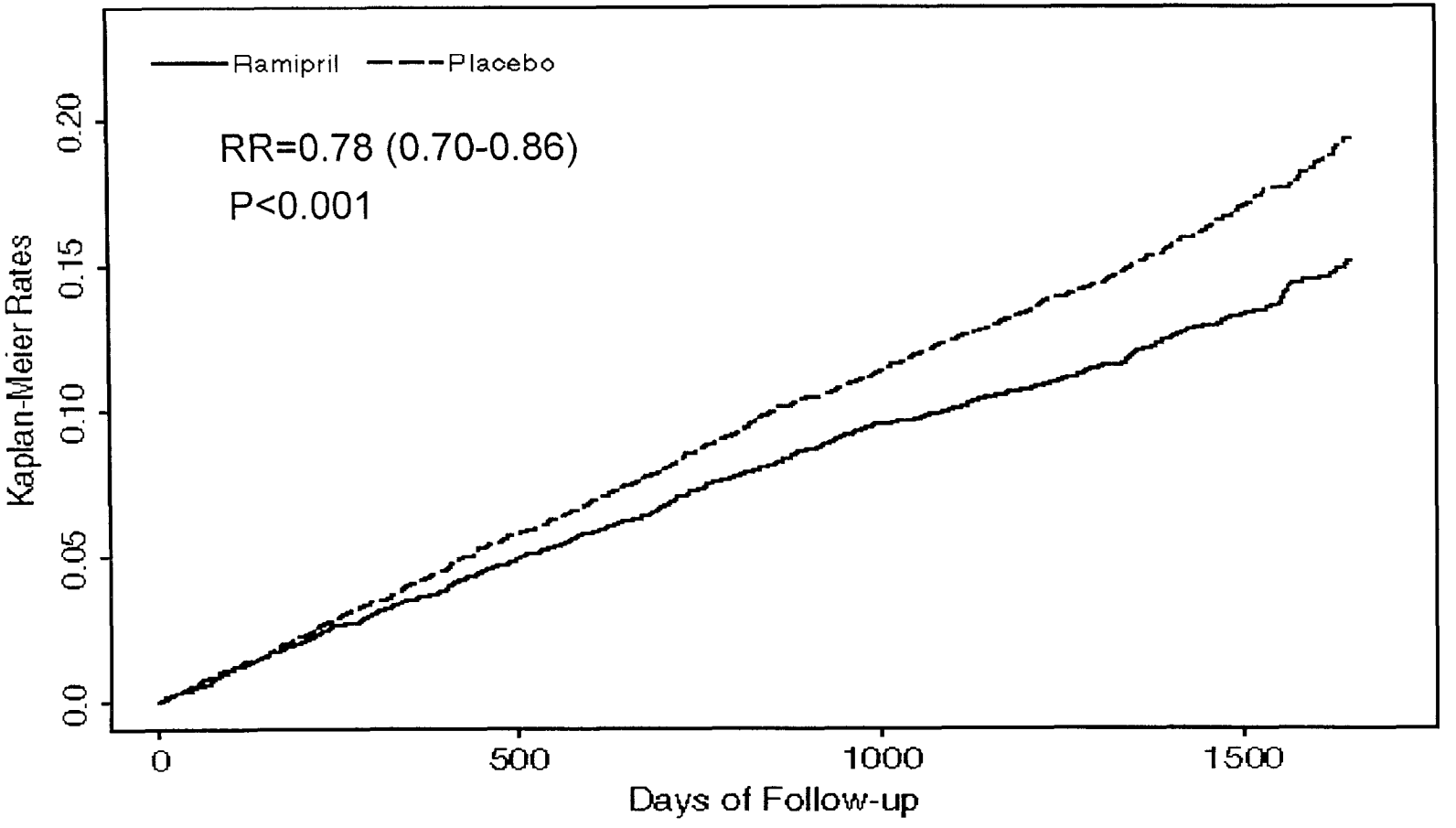


**FIGURE 3: KAPLAN-MEIER SURVIVAL CURVE: MYOCARDIAL INFARCTION**

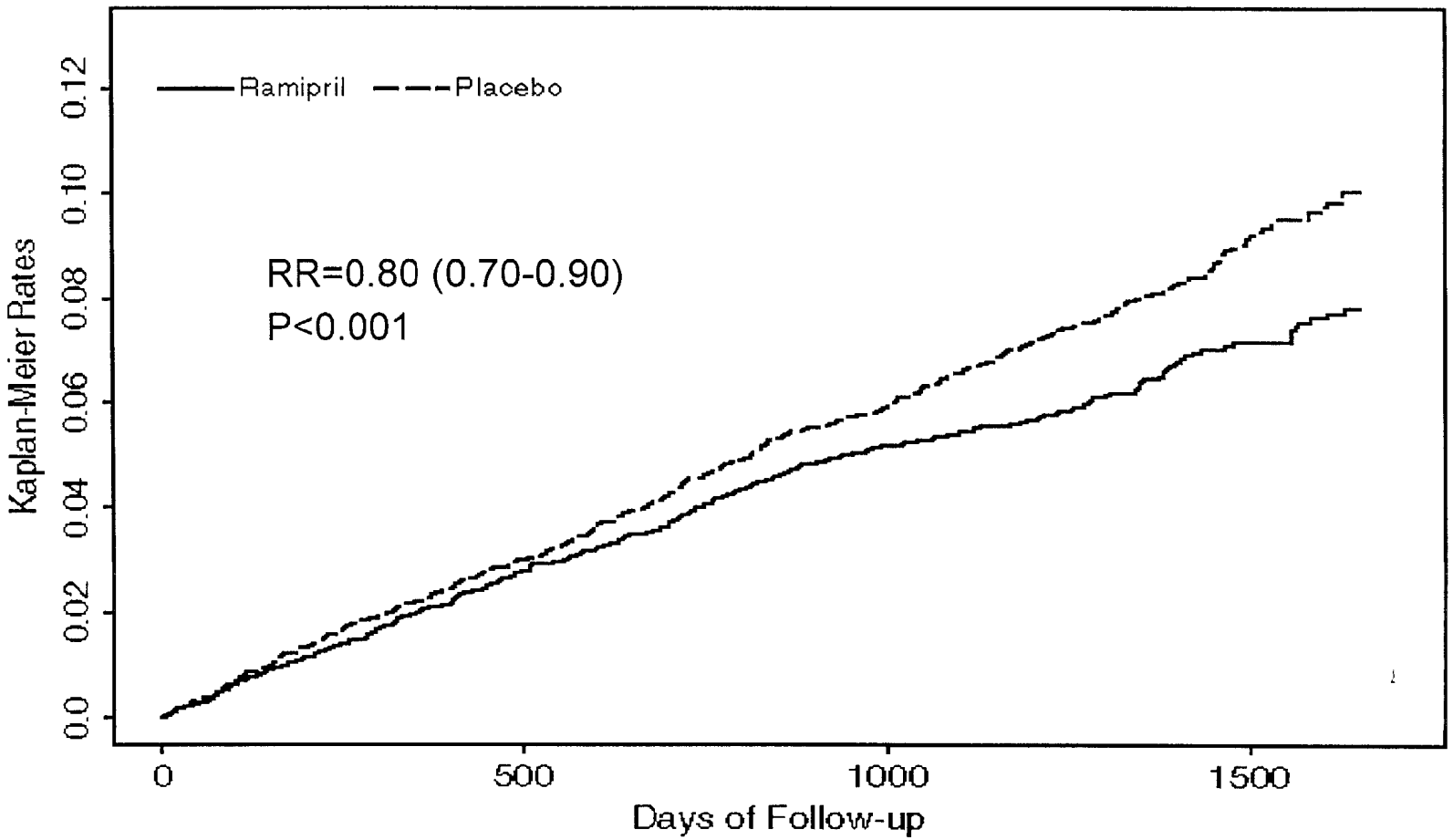


**FIGURE 4: KAPLAN-MEIER SURVIVAL CURVE: STROKE**

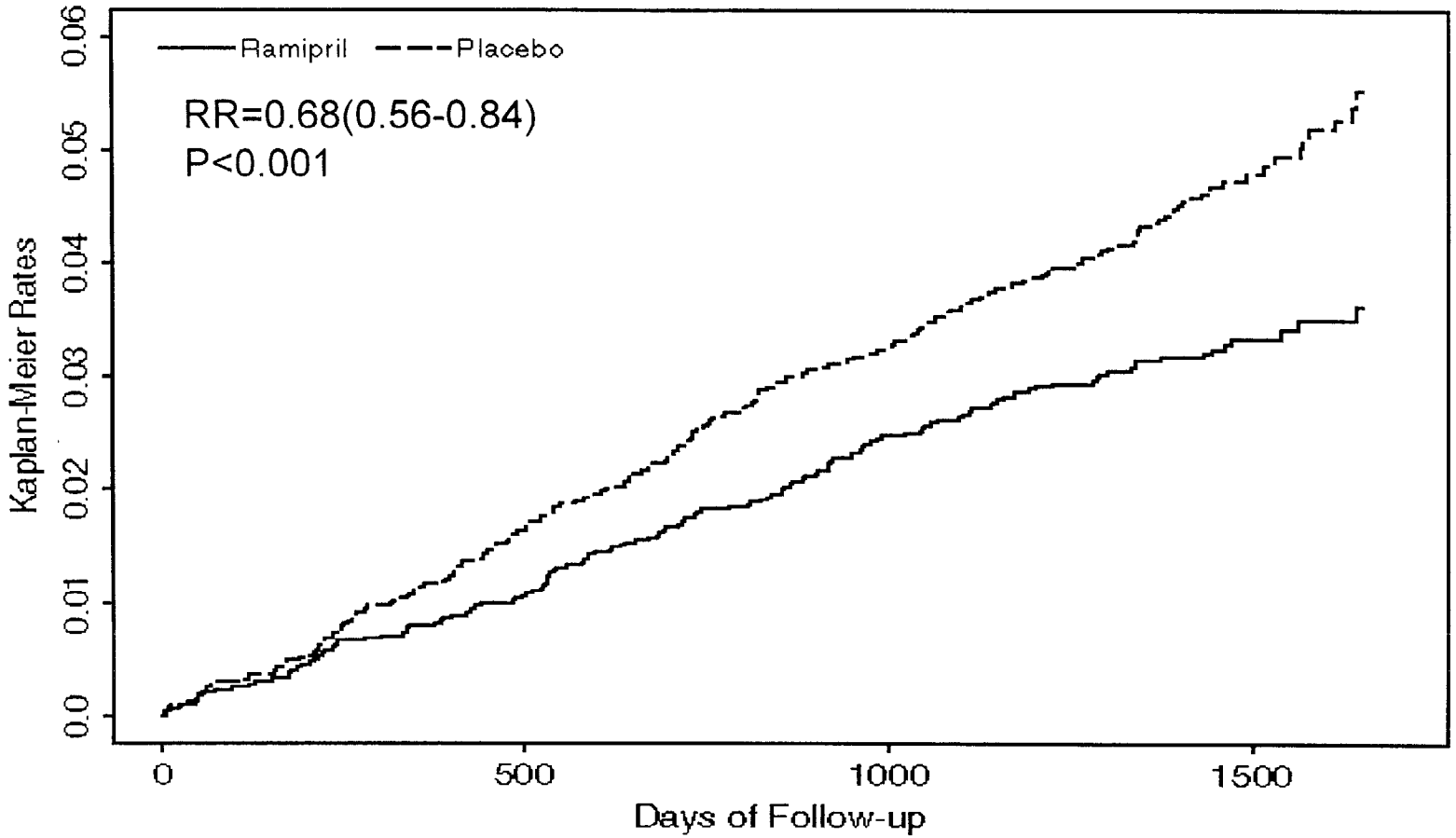


**FIGURE 5: KAPLAN-MEIER SURVIVAL CURVE: CARDIOVASCULAR DEATH**

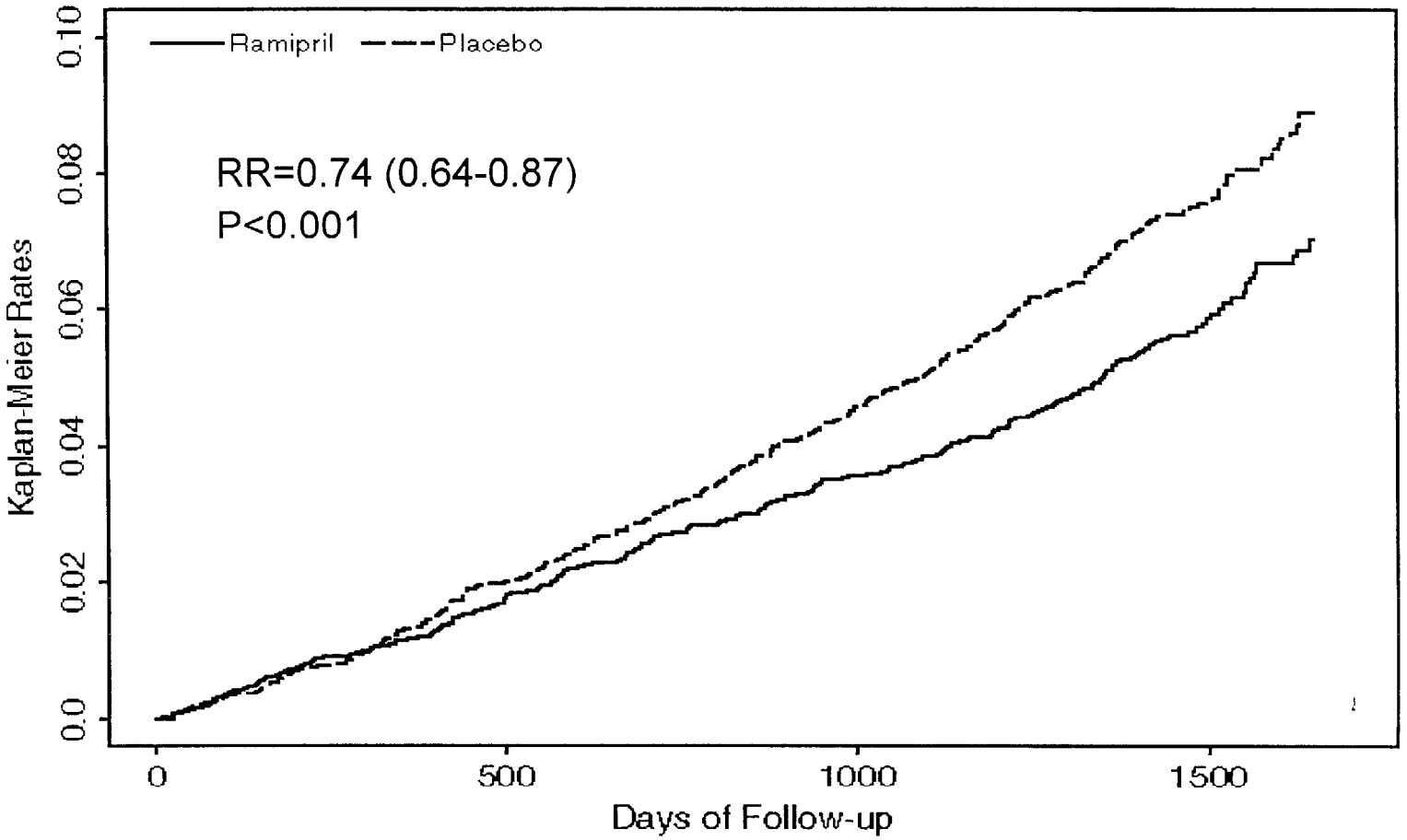
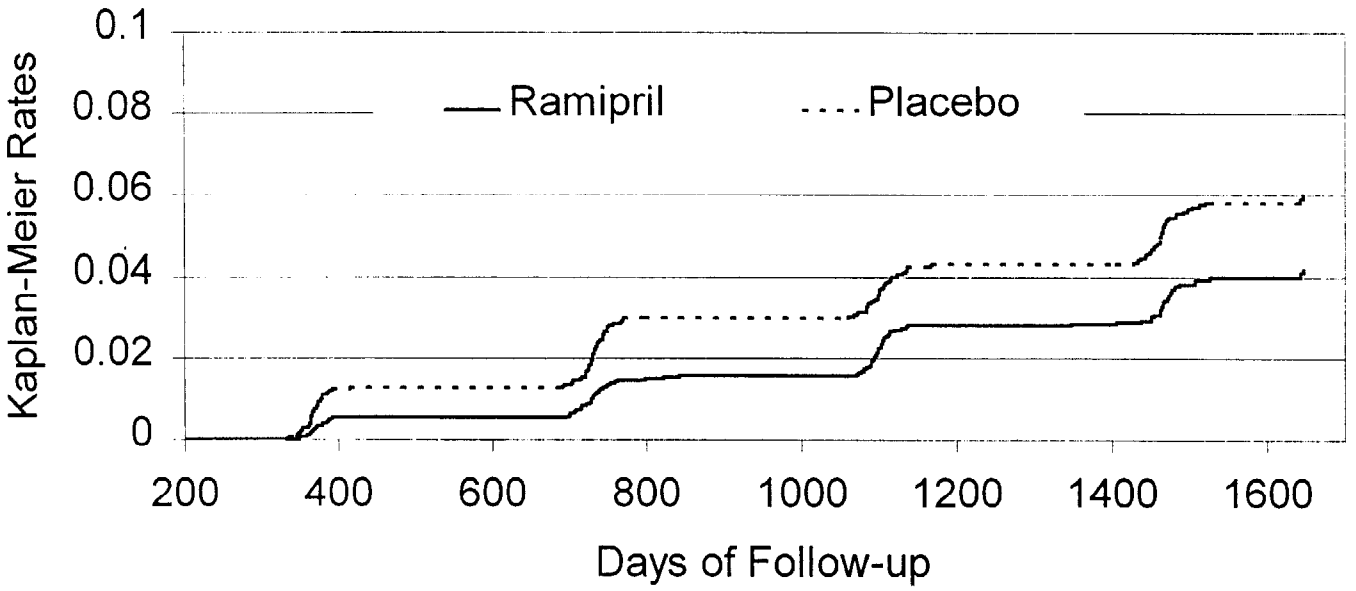


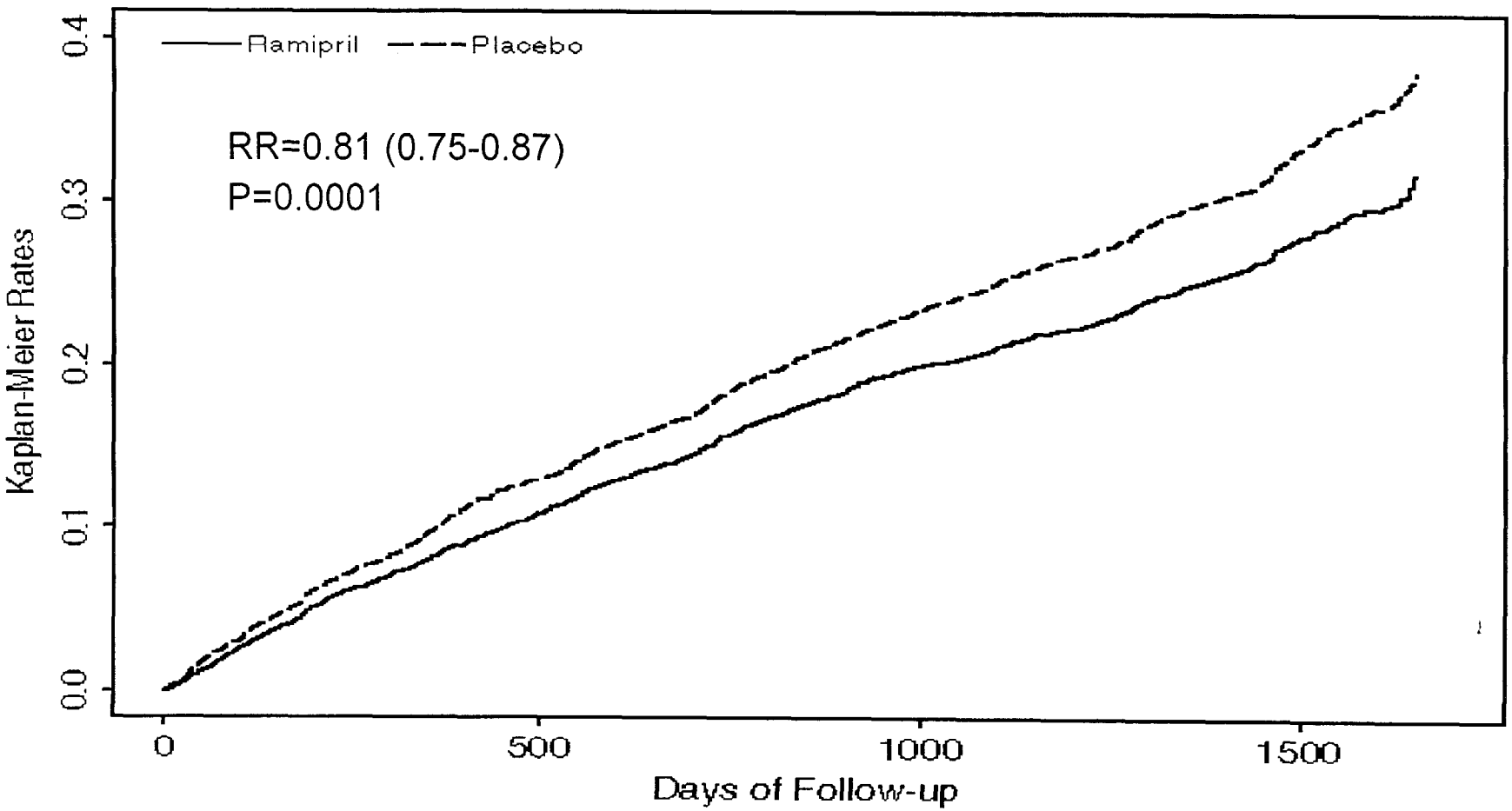
**FIGURE 6: KAPLAN-MEIER SURVIVAL CURVE:DEVELOPMENT OF DIABETES**




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

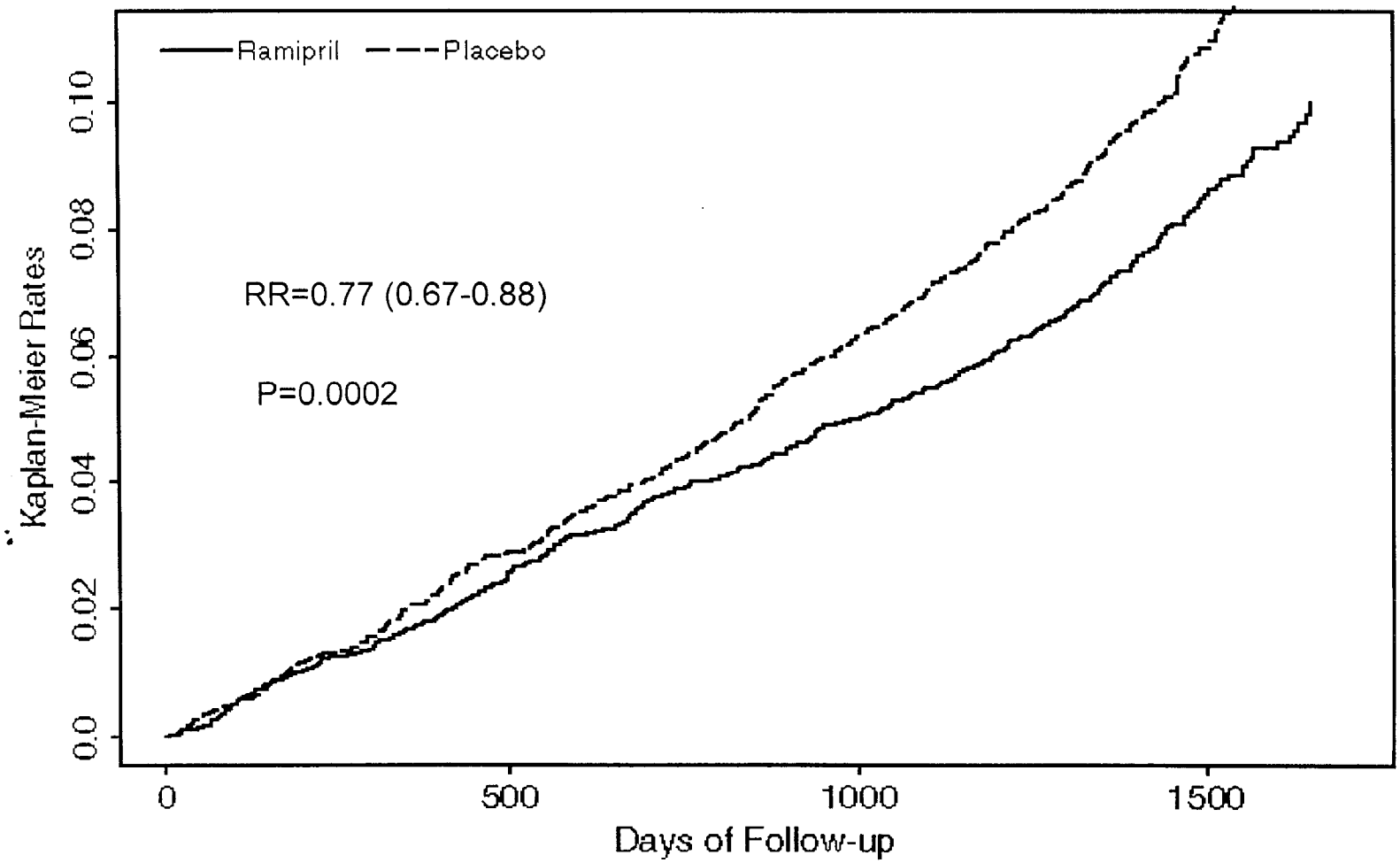


**FIGURE 8: RENAL OUTCOMES IN ALL PATIENTS**

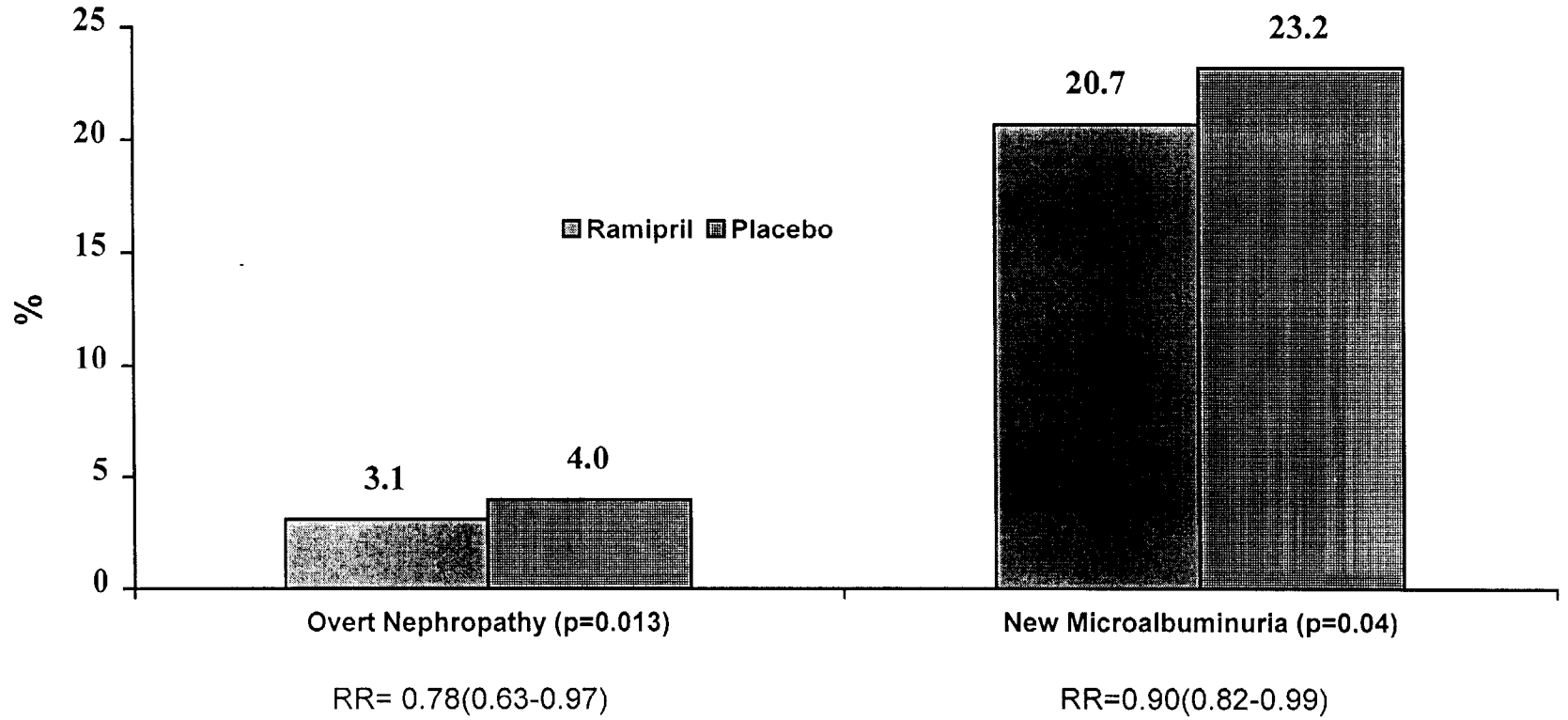


**FIGURE 9: THE EFFECT OF RAMIPRIL TREATMENT ON THE COMPOSITE OUTCOME IN PRE-DEFINED SUBGROUPS**

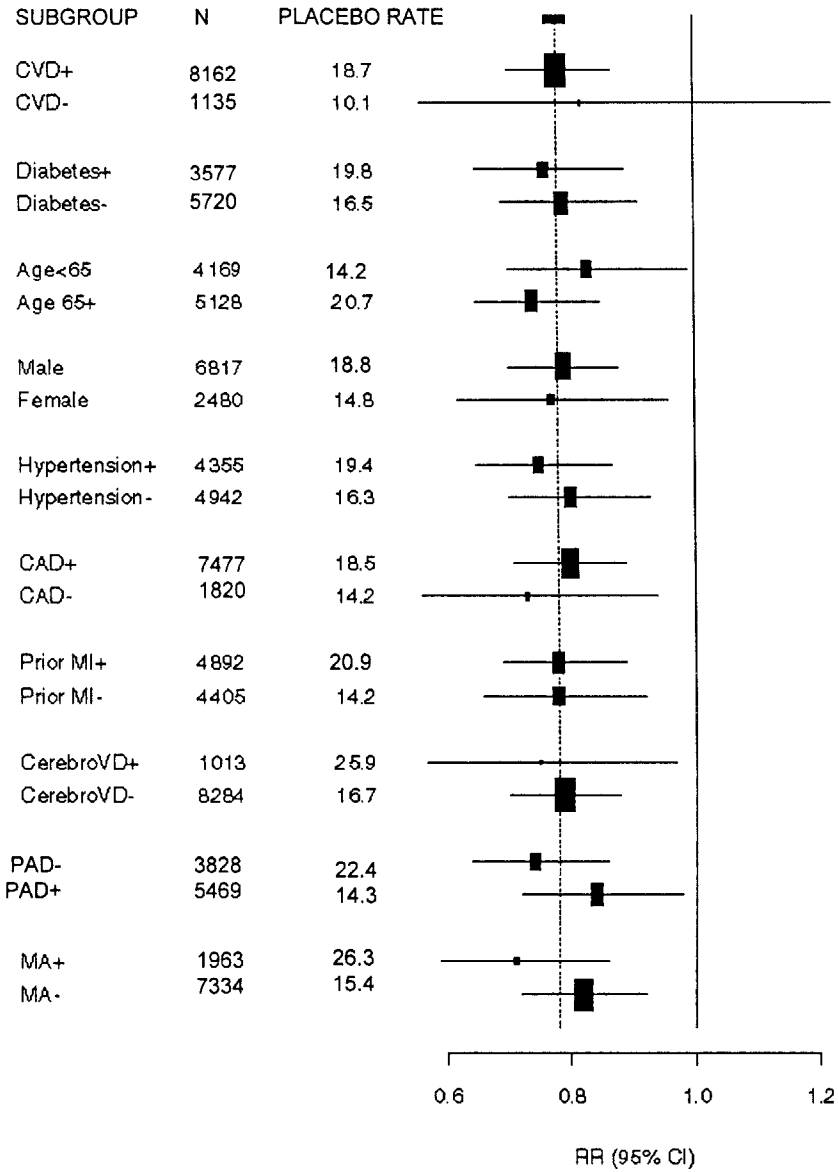
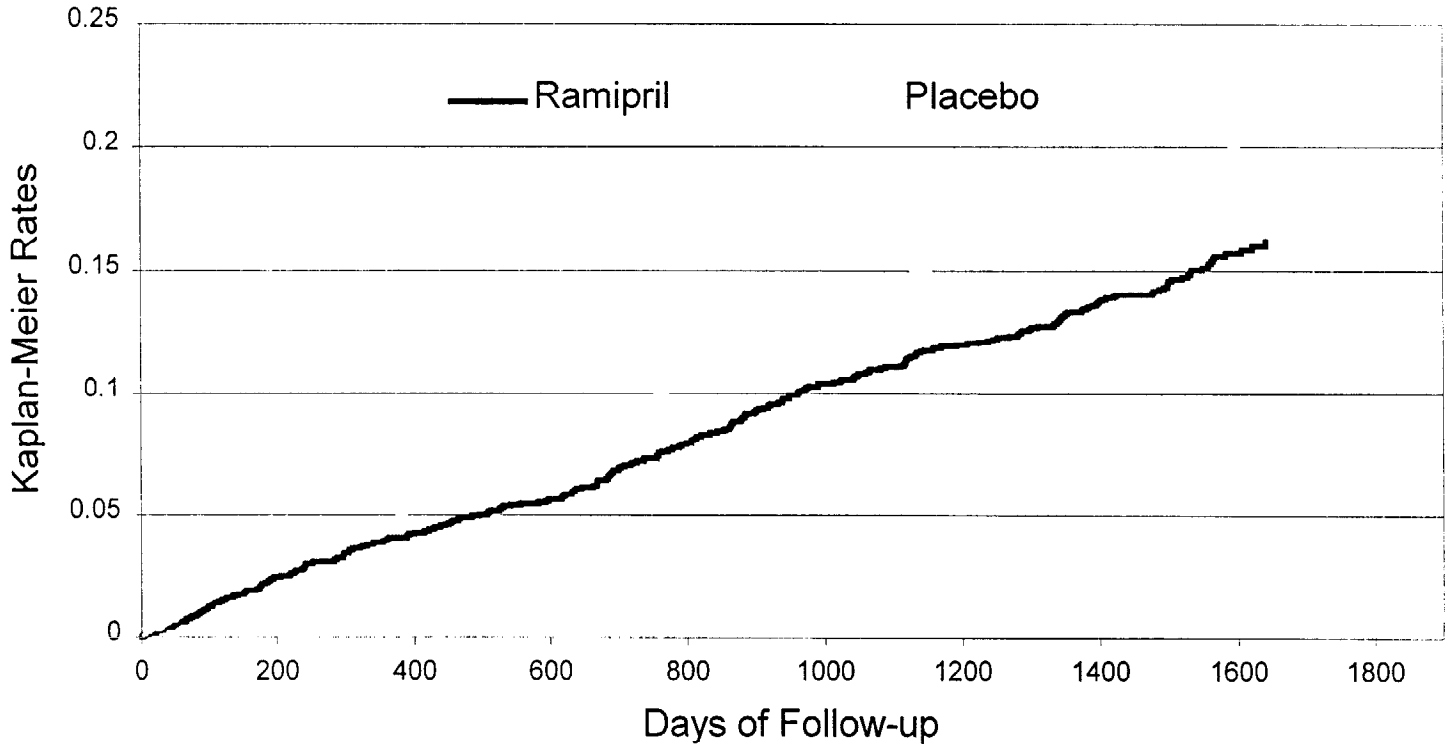


FIGURE 10: KAPLAN-MEIER SURVIVAL CURVE: PRIMARY OUTCOME IN PATIENTS WITH DIABETES ONLY




RR: 0.75(0.64-0.88) P=0.0004

FIGURE 11: PRIMARY OUTCOME IN IMPORTANT DIABETIC SUBGROUPS

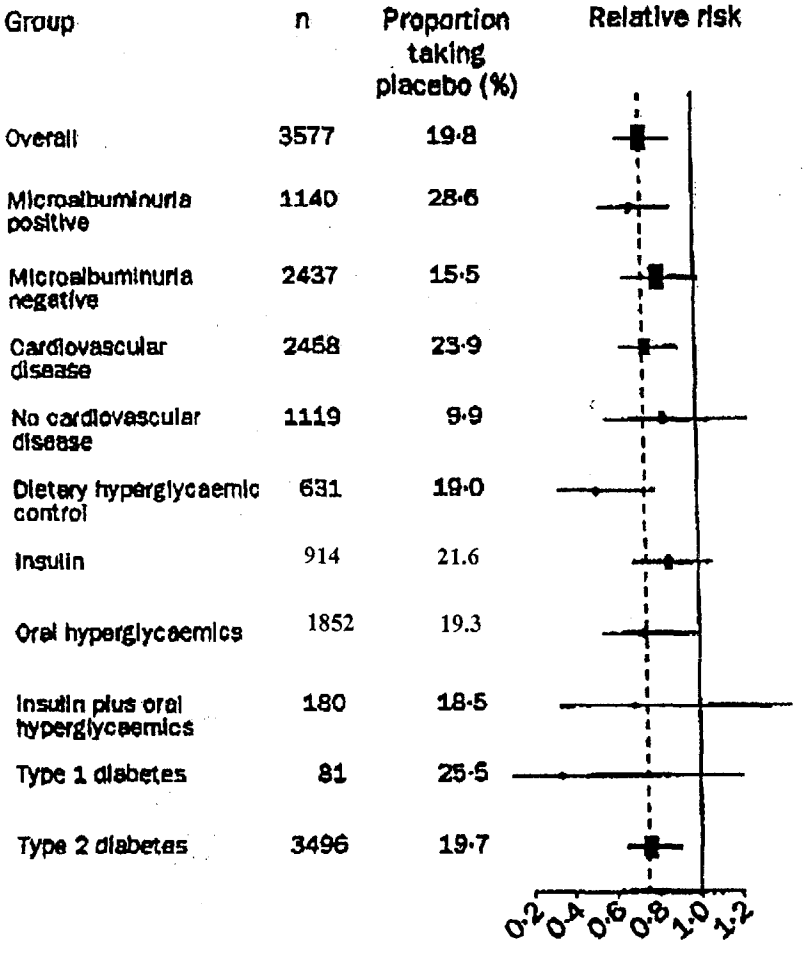


**FIGURE 12: RISK OF PRIMARY OUTCOME BY SYSTOLIC BLOOD PRESSURE**

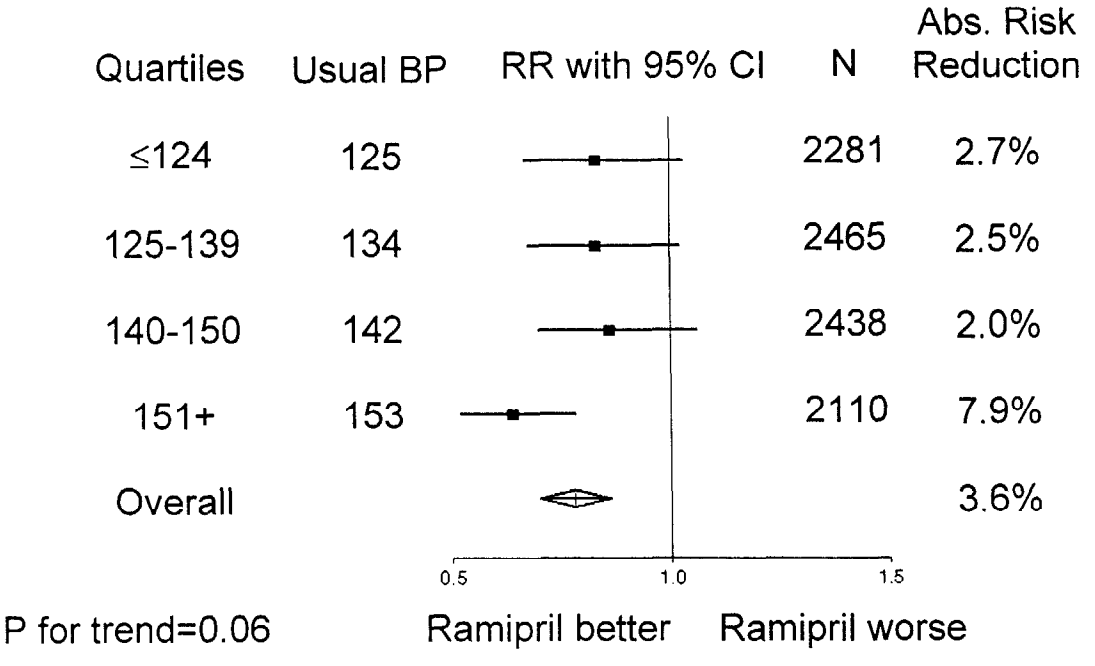


**FIGURE 13: RISK OF PRIMARY OUTCOME BY DIASTOLIC BLOOD PRESSURE**