severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE (ramipril). In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See **DRUG INTERACTIONS.**)

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions

With diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently insti-

py with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced. (See DOSAGE AND ADMINISTRATION.)

With potassium supplements and potassium-sparing diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of ALTACE and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate). The co-administration of ALTACE and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, co-administration of ALTACE with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. (For either species, these doses are about 200 times the maximum recommended human dose when compared on the basis of body surface area.) No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy

Fetal/neonatal morbidity and mortality.

Nursing Mothers

Ingestion of single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving ALTACE should not breast feed.

Geriatric Use

Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hypertension

ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were:

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below.

PATIENTS IN US PLACEBO CONTROLLED STUDIES

	ALTACE (n=651)		Placebo (n=286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment.

Heart Failure post-myocardial infarction

Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than one percent of patients with heart failure treated with ALTACE are shown below. The incidences represent the experiences from the AIRE study. The follow-up time was between 6 and 46 months for this study.

Percentage of Patients with Adverse Events Possibly/Probably Related to Study Drug

Placebo-Controlled (AIRE) Mortality Study

Adverse Event	Ramipril (n=1004)	Placebo (n=982)
Hypotension	10.7	4.7
Cough Increased	7.6	3.7
Dizziness	4.1	3.2
Angina Pectoris	2.9	2.0
Nausea	2.2	1.4
Postural Hypotension	2.2	1.4
Syncope	2.1	1.4
Heart Failure	2.0	2.2
Severe/Resistance Heart Failure	2.0	3.0

Vomiting	1.6	0.5
Vertigo	1.5	0.7
Headache	1.2	0.8
Kidney Function	1.2	0.5
Abnormal Chest Pain	1.1	0.9
Diarrhea	1.1	0.4
Asthenia	0.3	0.8

Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Body As a Whole: Anaphylactoid reactions. (See **WARNINGS**.)

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (See **WARNINGS** and **PRECAUTIONS**), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

Hematologic: Pancytopenia, hemolytic anemia and thrombocytopenia.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See **WARNINGS**.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See **WARNINGS**.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See **PRECAUTIONS, Cough** subsection.)

Gastrointestinal: Pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), erythema multiforme, pemphigus, photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia,

disturbances.

Miscellaneous: As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported.

Fetal/neonatal morbidity and mortality. **See WARNINGS: Fetal/neonatal morbidity and mortality.**

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings:

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See **WARNINGS** and **PRECAUTIONS.**) Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See **WARNINGS** and **PRECAUTIONS.**)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnor-

OVERDOSAGE

Single oral doses in rats and mice of 10-11 g/kg resulted in significant lethality. In dogs, oral doses as high as 1 g/kg induced only mild gastrointestinal distress. Limited data on human overdosage are available. The most likely clinical manifestations would be symptoms attributable to hypotension. Laboratory determinations of serum levels of ramipril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of ramipril overdose. No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of ramipril and its metabolites. Similarly, it is not known which, if any, of these substances can be usefully removed from the body by hemodialysis. Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of ramipril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

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

For the prevention of myocardial infarction, stroke, and death from cardiovascular causes, ALTACE® should be given at an initial dose of 2.5 mg. once a day for 1 week, followed by 5 mg. once a day for the next 3 weeks, and then increased to a maintenance dose of 10 mg. once a day.

Hypertension

The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic can be added.

Heart Failure post myocardial infarction

For the treatment of post-infarction patients who have shown signs of congestive failure, the recommended starting dose of ALTACE is 2.5 mg twice daily. A patient who becomes hypotensive at

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ated) toward a target dose of 5 mg twice daily.

After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ALTACE does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The ALTACE Capsule is usually swallowed whole. The ALTACE Capsule can also be opened and the contents sprinkled on a small amount (about 4 oz.) of apple sauce or mixed in 4 oz. (120 ml) of water or apple juice. To be sure that ramipril is not lost when such a mixture is used, the mixture should be consumed in its entirety. The described mixtures can be pre-prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration.

Concomitant administration of ALTACE with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. (See PRECAUTIONS.)

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ALTACE. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with ALTACE. (See WARNINGS.) Then, if blood pressure is not controlled with ALTACE alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used to avoid excess hypotension.

Dosage Adjustment in Renal Impairment

In patients with creatinine clearance <40 ml/min/1.73m^2 (serum creatinine approximately >2.5 mg/dl) doses only 25% of those normally used should be expected to induce full therapeutic levels of ramiprilat. (See CLINICAL PHARMACOLOGY.)

Hypertension: For patients with hypertension and renal impairment, the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg.

recommended initial dose is 1.25 mg ALTACE once daily. The dose may be increased to 1.25 mg b.i.d. and up to a maximum dose of 2.5 mg b.i.d. depending upon clinical response and tolerability.

HOW SUPPLIED

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in hard gelatin capsules, packaged in bottles of 100 capsules. ALTACE is also supplied in blister packages (10 capsules/blister card).

ALTACE 1.25 mg capsules are supplied as yellow, hard gelatin capsules in bottles of 100 (NDC 61570-110-01), and Unit Dose packs of 100 (NDC 61570-110-56).

ALTACE 2.5 mg capsules are supplied as orange, hard gelatin capsules in bottles of 100 (NDC 61570-111-01), and Unit Dose packs of 100 (NDC 61570-111-56).

ALTACE 5 mg capsules are supplied as red, hard gelatin capsules in bottles of 100 (NDC 61570-112-01), and Unit Dose packs of 100 (NDC 61570-112-56).

ALTACE 10 mg capsules are supplied as Process Blue, hard gelatin capsules in bottles of 100 (NDC 61570-120-01).

Dispense in well-closed container with safety closure.

Store at controlled room temperature (59 to 86° F).

Rx only.

REFERENCE

1. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of An Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. N Engl J Med 2000;342;145-153.

2. The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355;253-59.

Prescribing Information as of XXXX

Distributed by: Monarch Pharmaceuticals, Inc., Bristol, TN 37620

Manufactured by: Hoechst Marion Roussel, Inc., Kansas City, MO 64137

########### (Item #)

Monarch Pharmaceuticals®
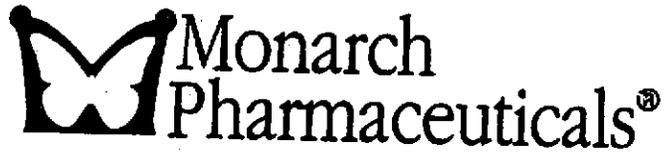
Event Adjudication Definitions

Primary Outcomes

1.0 Cardiovascular Death

1.11 <u>Unexpected Death</u>: Unexpected death presumed to be due to ischemic cardiovascular disease, occurring within 24 hours of the onset of symptoms without confirmation of cardiovascular disease, and without clinical or post mortem evidence of other etiology.

1.12 <u>Fatal myocardial infarction</u> (MI): death within 7 days of the onset of documented MI (see 2.0).

1.13 <u>Congestive heart failure</u> (CHF): death due to clinical, radiological or postmortem evidence of CHF without clinical or postmortem evidence of an acute ischemic event (cardiogenic shock to be included).

1.14 <u>Post cardiovascular invasive interventions</u>: death associated with the intervention: within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

1.15 <u>Documented arrhythmia</u>: death due to bradyarrhythmias or tachyarrhyhthmias not induced by an acute ischemic heart disease (IHD) event

1.16 <u>Death following non-cardiovascular surgery</u>: death due to cardiovascular causes as defined in 1.11-1.15, 1.17-1.18 and within 30 days of surgery.

1.17 <u>Stroke</u>: death due to stroke occurring within 7 days of the signs and symptoms of a stroke (see 3.0).

1.18 <u>Other cardiovascular diseases</u>: death due to other vascular diseases including pulmonary emboli, abdominal aortic aneurysm rupture, ...

1.19 <u>Presumed Cardiovascular Death</u>: Suspicion of cardiovascular death with clinically supporting evidence which may not fulfill criteria otherwise stated. Example: Patient admitted with typical chest pain of 3 hours duration and treated as an MI, but without ECG and enzymatic documentation to meet normal criteria.

NB <u>Accidental Death</u>: Qualifies as a cardiovascular event unless clear evidence of extraneous disease is known.

NB <u>Cardiac transplantation</u> is not a cardiac death.

2.1 <u>Q-Wave MI</u>: in comparison to the last ECG, presence of at least one new significant Q-wave on the standard 12-lead ECG as described in the Minnesota Code 1.1.1. appendix A, and at least one of:

1. Typical symptoms (e.g. typical ischemic chest pain >20 min).
   and/or
2. Significant elevation of serum enzymes - presence of any one of the following criteria:

   a) elevation of CK-MB to twice the upper limit of normal for the laboratory that performed the test.
   b) CK total at least twice the upper limit of normal for the laboratory that performed the test.
   c) SGOT, LDH, or other cardiac enzymes at least twice the upper limit of normal for the laboratory that performed the test with a characteristic pattern.

2.2 <u>Non Q-wave MI</u>: defined as patient with significant elevation of cardiac enzymes (at least twice the upper limit of normal) with or without characteristic pain in absence of new significant Q wave.

2.3 <u>Probable non Q-wave MI</u>: presence of new and persistent ST-T changes (>24 hours in duration) on the ECG with characteristic symptoms of ischemic chest pain without documentation of enzyme elevation.

2.4 <u>Silent MI</u>: development of new significant Q waves (as per the Minnesota Code 1.1.1) in at least 2 adjacent leads in the absence of any other evidence of myocardial infarction (note that the date of event will be assessed as halfway between the date of discovery and last normal ECG).

2.5 <u>Non-fatal MI post cardiovascular invasive interventions</u>: MI (as defined in 2.1, 2.2, 2.3 or 2.4) associated with the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

2.6 <u>Non-fatal MI post non-cardiovascular surgery</u>: MI (as defined in 2.1, 2.2, 2.3 or 2.4) occurring within 30 days of non-cardiovascular surgery.

3.0 Stroke

3.1 <u>Definite ischemic stroke:</u> CT or MRI scan within 14 days of onset of a definite stroke (focal neurological deficit greater than 24 hours) with evidence of infarction, or autopsy confirmation

3.2 <u>Definite hemorrhagic stroke</u> (primary intracerebral, subarachnoid, or secondary to cerebral infarction): confirmation with CT or MRI scan within 14 days of stroke, or at autopsy or by lumbar puncture

3.3 <u>Stroke of unknown etiology</u>: Definite stroke of unknown etiology when CT, MRI or autopsy are not done.

3.4 <u>Non-fatal stroke post cardiovascular invasive interventions</u>: stroke (as defined in 3.1-3.3) associated to the intervention within 30 days of cardiovascular surgery, or within 7 days of cardiac catheterization, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

3.5 <u>Non-fatal stroke post non-cardiovascular surgery</u>: Stroke (as defined in 3.1-3.3) occurring within 30 days of non-cardiovascular surgery.

Secondary Outcomes

4.1 <u>Unstable angina</u>: unstable angina requiring hospitalization because of increased frequency or severity of angina. **Note: If the unstable angina was not the reason for hospitalization then the unstable angina is coded as 411.9.**

4.2 <u>All cardiovascular revascularization procedures</u> to include CABG surgery, coronary interventions, carotid endarterectomy (for stenosis of carotid luminal wall, transient ischemic attacks or stroke), peripheral cardiovascular surgery or angioplasty (for limb ischemia) or limb amputation.

4.21 PTCA

4.22 CABG

4.23 Peripheral Angioplasty

4.24 Peripheral vascular Surgery

4.25 Carotid Endarterectomy

4.26 Limb Amputation: Including partial or digit amputation due to cardiovascular disease.

4.3 <u>Total Mortality</u>. All non-cardiovascular deaths

4.361 Cancer Death: Primary site of cancer is gastrointestinal.

4.362 Cancer Death: Primary site of cancer is lung.

4.363 Cancer Death: Primary site of cancer is breast.

4.364 Cancer Death: Primary site of cancer is prostate.

4.365 Cancer Death: Primary site of cancer is brain.

4.366 Cancer Death: Primary site of cancer is 'other'

4.367 Cancer Death: Primary site of cancer is multi site.

4.368 Cancer Death: Primary site of cancer is genito-urinary.

a) A 24 hour urine protein greater than or equal to 500 mg.

b) A 24 hour urine albumin greater than or equal to 300 mg.

c) A timed albumin excretion rate greater than or equal to 200 microgram/min.

4.5 Hospitalization for congestive heart failure with documented clinical and radiological evidence.Note: If CHF was not the reason for hospitalization then the CHF is coded as 428.

4.6 Cancer or other malignancy by site and morphology.

4.61 Cancer gastrointestinal

4.62 Cancer lung

4.63 Cancer breast

4.64 Cancer prostate

4.65 Cancer brain

4.66 Cancer other site

4.67 Cancer multi site

4.68 Cancer genito-urinary

THE HOPE (Heart Outcomes Prevention Evaluation) Study

A large, simple randomized trial of
ACE-Inhibitors and Vitamin E
in patients at high risk
of cardiovascular
events

Summary: The HOPE (Heart Outcomes Prevention Evaluation) Study

Background: Although it is well established that elevated cholesterol, smoking and hypertension are major risk factors for cardiovascular disease (CVD), these factors do not account fully for the risks of developing CVD in a population. Therefore, identification of other risk factors and modifying them are needed to further reduce death and disability from CVD. Recent epidemiological and experimental 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 inhibitors (ACE-I) which block the activation of the renin-angiotensin system may retard atherosclerosis. Three large clinical trials of ACE-I (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 ($2p < 0.0002$). The reduction in MI in the SOLVD trials was independent of the level of ejection fraction, etiology of low ejection fraction (ischemic or non-ischemic), concomitant use of various cardiac medications, presence or absence of diabetes and blood pressure response, suggesting that ACE-I may have a role in preventing MIs in a much wider range of patients and not just those with low ejection fraction. However, this hypothesis requires direct confirmation by prospective randomized clinical trials.

Atherosclerosis also appears to be increased with oxidation of lipids. Oxidized lipids affect many atherogenic processes and data from epidemiological and laboratory studies suggest that the use of naturally occurring and safe anti-oxidants such as Vitamin E may retard atherosclerosis or its clinical sequelae. However Vitamin E has not been properly evaluated and large-scale randomized clinical trials are needed to establish any efficacy.

We therefore propose to evaluate the effects of an ACE-I, Ramipril and a naturally occurring anti-oxidant, Vitamin E, in a large, simple randomized clinical trial of 8,000 to 9,000 patients in a 2 X 2 factorial design.

Objectives: To evaluate if use of Ramipril and/or Vitamin E, two safe and practicable therapies, reduce myocardial infarction, stroke and cardiovascular death in a broad group of patients at risk for cardiovascular events.

Study design: A randomized, placebo-controlled, double blind clinical trial of 8,000 to 9,000 patients at significant risk of CVD events (including patients with previous MI, *stable and* unstable angina, bypass or angioplasty, previous stroke, peripheral vascular disease and high risk diabetics) utilizing a 2 X 2 factorial design and a simple and focused protocol. Patients will be recruited from approximately 200 centres internationally over a one year time period. After an initial three-week run-in period, patients will be randomized to Ramipril (2.5 mg OD for 1 week then 5.0 mg OD for three weeks then 10 mg OD thereafter) or placebo and Vitamin E (400 IU OD) or placebo. Patients will be followed for an average of 3.5 years at regular six month intervals during which all cardiovascular events and hospitalizations will be monitored.

Importance of the study: If Ramipril and/or Vitamin E is found to be beneficial in this trial, these safe and practicable therapies could be applied world wide and prevent thousands of patients suffering disability or death from CVD.

A LARGE, SIMPLE RANDOMIZED CLINICAL TRIAL OF ACE-INHIBITORS AND VITAMIN E IN PATIENTS AT HIGH RISK FOR CARDIOVASCULAR EVENTS

ELIGIBILITY: MEN OR WOMEN OVER AGE 55 AT HIGH RISK OF CARDIOVASCULAR EVENTS

1. CARDIAC DISEASE: Previous MI, previous stable or unstable angina (with documented multivessel coronary artery disease or a positive stress test), previous multivessel PTCA (more than one month ago), previous multivessel CABG > 4 years ago or with angina, or multivessel coronary disease seen on angiography.

2. OTHER HIGH RISK:

   A. Peripheral vascular disease: Previous limb bypass surgery or angioplasty, previous limb amputation, history of intermittent claudication with leg/arm BP ratio ≤0.80 in at least one side, or significant stenosis by documented angiography or non-invasive testing.

   B. Previous stroke more than one month ago.

   C. Diabetes (type I or II): With one other risk factor: hypertension; (>160 systolic or >90 diastolic or on treatment); total cholesterol > 5.2mmol/L(200 mg/dL); currently smoking; known microalbuminuria; HDL ≤ 0.9 or any evidence of previous vascular disease.

IDENTIFICATION & INVITATION

1. Identify eligible patients from patient lists, procedure logs, coronary care unit logs, referral clinics, etc.
2. Enter brief, key data on patients into H♥PE Screening Log.
3. Invite patient to participate and send Patient Information Pamphlet.

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 (C3PO) at 1-800-268-2376.
4. Start run-in period with 2.5 mg of Ramipril OD (active for 7-10 days and then placebo for 10-14 days).
5. Obtain creatinine, potassium and glycated Hb(the latter in diabetics only), at days 7-10 of Run-In Phase.

RANDOMIZATION VISIT (0 weeks)

1. Check compliance and confirm eligibility.
2. Randomize patient by calling (toll-free) C3PO at 1-800-667-7263 (RAND) between 7:00am and 7:00pm EDT.
3. Dispense allocated medication from H♥PE Medication Kits:
   - Ramipril 2.5 mg OD (increased to 5 mg OD after one week, then increased to 10 mg at one month) or placebo
   - Vitamin E 400 IU OD or placebo
4. Complete and Fax Randomization Forms (including bottom half of Run-In Form) and Fax to 1-800-268-2376.
5. Make follow-up appointment for 1 month (±1 week).

FOLLOW-UP (at 1 month, 6 months, then every 6 months for 3 years)

1. Check for all cardiovascular events and all hospitalizations.
2. At one month visit, repeat local creatinine and potassium determination.
3. Dispense medication and encourage compliance.
4. Fax Follow-Up Form and, as needed, relevant Event Reports to C3PO.

CENTRAL MONITORING FOR SAFETY, EFFICACY & OUTCOMES

1. Fax Hospitalization, Death, MI and Stroke Forms.
2. Send discharge summaries, CT Scans etc., by mail in the HOPE Document Envelope.
3. Send laboratory results when requested to do so.

♥ LOCAL INVESTIGATOR: _____

☎ phone _____ fax _____

C3PO: 237 Barton St. East, Hamilton, Ontario, L8L 2X2. For questions call 1-800-263-9428 (WHA⁻

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The HOPE (Heart Outcomes Prevention Evaluation) Study - A LARGE, SIMPLE RANDOMIZED TRIAL OF ACE-INHIBITORS AND VITAMIN E IN PATIENTS AT HIGH RISK OF CARDIOVASCULAR EVENTS.

BACKGROUND AND RATIONALE

1. REDUCING CARDIOVASCULAR DISABILITY AND UNTIMELY DEATH REQUIRES INTERVENTIONS IN ADDITION TO THE CONTROL OF TRADITIONAL RISK FACTORS.

The sequelae of atherosclerosis, such as coronary artery disease (CAD) or cerebrovascular disease constitute the biggest causes of death, including premature death in Western countries. Approximately 40-50% of all deaths are due to CVD and as the population ages in Western countries, the absolute burden of CVD is certain to rise [1].

Prevention of these cardiovascular diseases (CVD) requires modification of known risk factors for atherosclerosis such as blood pressure, cholesterol and smoking.[2] However, these risk factors only partly account for the risk of premature CVD and it is highly likely that additional factors are of importance.[3] Recent experimental evidence indicates that the formation and progression of atherosclerotic lesions are influenced by a number of additional complex biological processes, such as the post-secretory modifications of low density lipoproteins (LDL). The interaction of oxidized LDL with arterial wall, endothelial cells, macrophages, vascular smooth muscle cells, platelets and circulating coagulation factors promotes atherosclerosis.[4,5] Further, a number of stimuli increase the proliferation of smooth muscle cells in the vascular wall. The role of the above rocesses in increasing the risk of atherosclerosis and its complications is supported by experimental, clinical and epidemiological data. This multi-factorial causation of atherosclerosis suggests that multiple approaches to preventing events in high risk patients are needed.

In this document, we will first summarize several independent but complementary lines of evidence suggesting that angiotensin converting enzyme (ACE) inhibitors (ACE-I) and a naturally occurring anti-oxidant, Vitamin E, may be effective in reducing the risk of clinical sequelae of CVD. Both therapies are simple, safe and are relatively inexpensive, so that they are likely to have substantial public health impact and are potentially applicable worldwide. Second, we will outline a protocol for a large, simple and cost-efficient trial that will definitively and simultaneously test these therapies.

2. USE OF ACE-INHIBITORS (ACE-I) IN PATIENTS WITH LOW EJECTION FRACTION HAS SHOWN A SIGNIFICANT REDUCTION IN MYOCARDIAL INFARCTION.

Three recent large randomized trials in patients with low ejection fractions reported significant reductions in the risk of myocardial infarction (MI) with the use of ACE-I. The results of these studies are summarized in Table 1.

1

Table 1: Reduction in risk of myocardial infarction (MI) in patients with low ejection fractions (EF) in three randomized trials of ACE-inhibitors

Trial/ACE-I used [Ref]	Patient Characteristics	MI/No. Patients		RRR (95% CL)	2P Value
		ACE-I	Placebo		
SOLVD [6,7] Treatment/enalapril	EF<35% *with* CHF	127/1285 (9.9%)	158/1284 (12.3%)	23(2 to 39)	0.02
SOLVD [7,8] Prevention/enalapril	EF<35% *without* CHF	161/2111 (7.6%)	204/2117 (9.1%)	24(6 to 38)	0.01
SAVE/captopril [9]	EF<40% post-MI	133/1115 (11.9%)'	170/1116 (15.2%)	24(5 to 40)	0.02
Total of all three trials		421/4511 (9.3%)	532/4517 (11.8%)	23(12 to 33)	0.0002

In each of the two Studies Of Left Ventricular Dysfunction (SOLVD) trials,[6-8] there was a significant reduction in MI with enalapril versus placebo (for both trials: 23% relative risk reduction or RRR; 95% Confidence Limits = 11% to 34%). Further, there was a highly significant reduction in the risk of unstable angina in each trial (for both trials: 20% RRR; 95% CL = 9% to 29%). In the Survival And Ventricular Enlargement (SAVE) trial,[9] there was a significant reduction in MI (24% RRR; 95% CL = 5% to 40%) and in the need for re-vascularization procedures (23% RRR p <0.001) with use of captopril versus placebo. Reductions in the incidence of myocardial infarction and unstable angina only became apparent in the above three studies after at least 6 months of treatment. Thereafter the difference continued to widen until the end of the study. This delay in the reduction of ischemic events resembles the pattern observed in trials of cholesterol lowering[10] and suggests that the mechanism for this observed anti-ischemic action of ACE-I is not solely related to the beneficial hemodynamic effect of the drug, which is observed early.

Reductions in ischemic events were consistently seen in the SOLVD study among various subgroups defined by differing levels of ejection fraction (EF), etiology (ischemic and non-ischemic) with and without a history of diabetes and against a background of different drugs (beta-blockers, aspirin or calcium blockers).[7] Further, reductions in ischemic events were observed both among patients with congestive heart failure, who might be expected to have high renin profiles and among patients without failure, in whom renin levels were not elevated in the absence of diuretic use.[11] In addition, the effects cannot be explained by the hypotensive actions of ACE-I alone, as the magnitude of risk reduction was substantially more than that expected from short term reductions in blood pressure.[12] Moreover the risk reductions were similar among patients with different degrees of blood pressure reductions.

This evidence suggests that the benefits observed in these trials among patients with low ejection fraction also may occur in a broader group of patients without left ventricular dysfunction and that the mechanisms of benefit are perhaps related to a "cardioprotective" or "cardiovascular-protective" effect. However, since the degree of activation of the renin-angiotensin system, systemically and in localized vascular tissue is not known in patients with preserved ejection fractions (who presumably have no elevation of systemic renin levels), direct proof of the benefits

ACE-I is required in such patients. Moreover, two short-term trials of ACE-I in patients following PTCA did not demonstrate any impact on the degree of re-stenosis.[9a,9d] However, in these trials treatment was for only 6 months and the process of restenosis following PTCA likely differs from native vessel atherosclerosis. Nevertheless, these data emphasize the need for caution in extrapolating the results from the trials in patients with low ejection fraction to other patient groups.

3. LABORATORY AND EXPERIMENTAL EVIDENCE SUGGEST THAT ACE-I MAY REDUCE THE RISK OF CVD EVENTS THROUGH MULTIPLE MECHANISMS.

1. The anti-proliferative action of ACE-I on the myocardium and the vascular wall may be beneficial. The prospective Framingham Heart study has noted that left ventricular mass is an independent predictor of CAD death (1.7 fold risk elevation for men and 2.1 risk elevation for women).[13] ACE-I have been shown to reduce left ventricular mass.[14] Recently, angiotensin II has been found to induce growth and proliferation of vascular smooth muscle cells in culture and in animal models in vivo.[15-19] At the molecular level, angiotensin II increases expression of proto-oncogenes c-myc mRNA and c-fos and of the A-chain of platelet-derived growth factor (PDGF) and these effects are inhibited by the ACE-I saralazin.[20,21] The sequential activation of proto-oncogenes and growth factor genes may represent an important mechanism by which angiotensin II promotes vascular smooth muscle cell growth and proliferation.[21,22] It is possible that the anti-proliferative effects of ACE-I would reduce cardiac hypertrophy and simultaneously have a protective effect on the vascular wall.[23]

Hormonal, vascular and cardio-protective effects may also be involved in the mechanisms of benefit derived from ACE-I. Epidemiological studies have examined the association of renin levels with risk of CAD events. Although two of the early, small retrospective studies reported conflicting results,[24,25] the best epidemiologic evidence is provided by a recent larger prospective cohort study,[26] in which 1717 subjects with hypertension were followed for a mean of 8.3 years. The risk of MI was increased 5.3 fold among subjects with high renin profiles versus those with low renin profiles (95%CL=3.4-8.3), and this effect was independent of other established cardiovascular risk factors such as elevated cholesterol, blood pressure levels and diabetes. Other cardio-protective effects of ACE-I reported include reduction in myocardial oxygen demand through reductions in preload and afterload, prevention of ventricular dilatation[27] and myocardial hypertrophy,[28] blockade of coronary vasoconstrictor and inotropic effects of angiotensin II,[29] decrease in angiotensin II mediated sympathetic activity,[30] increase in cardiac electrical stability demonstrated in animal preparations,[31] improvement in cardiac energetics by inhibition of the renin-angiotensin system,[32] protective effects on endothelial function possibly through bradykinin accumulation[33] and possible antioxidant properties.[34]

3. Evidence for an anti-atherogenic action of ACE-I from animal experiments is substantial. In the normotensive Watanabe heritable hyperlipidemic rabbit, captopril caused a dramatic reduction in atherosclerotic lesions whereas this effect was not seen with beta-blockers or calcium channel blockers in doses producing similar reductions in blood pressure.[35,36] Cellularity and cholesterol content of atherosclerotic plaques were found to be decreased and extracellular matrix was increased by ACE-I, suggesting plaque stabilization. Similar results were obtained in animal studies of ACE-I in monkeys.[37]

.. The antihypertensive action of ACE-I. The link between hypertension and atherosclerosis is well established. Hypertension may contribute to atherogenesis by several mechanisms, including endothelial damage and increased endothelial permeability, facilitating deposition in the arterial

wall of lipoproteins and other circulating substances.[38] Experimental studies suggest that hypertension thickens the arterial intima and media (changes thought to be early atherosclerosis) in the presence of high serum lipids and increases the extent of fatty streaks and atherosclerotic lesions in coronary arteries.[39] Epidemiologic studies demonstrate that blood pressure levels are positively and independently associated with the risk of CAD and stroke, even within the ranges considered to be "normotensive" (eg below 90 mm diastolic). A recent meta-analysis[40] of 9 large prospective observational studies estimated that a prolonged reduction of 5-6 mmHg in diastolic blood pressure is associated with 20-25% reduction in CAD and 35-40% reduction in stroke. An overview of 17 randomized clinical trials[40a] found that a reduction of 5-6 mmHg over 2-3 years (the effective duration of therapy in these trials) resulted in 17% reduction in risk for CAD and a 38% reduction in stroke.

The apparent smaller effect of treatment on CAD observed in these randomized trials (compared to the effect observed in epidemiologic studies), could be related to the relatively short duration of treatment, (possibly insufficient to affect a chronic process such as atherosclerosis), and to the fact that most of these trials used diuretics, whose adverse metabolic effects may partially offset the beneficial effect of blood pressure lowering. ACE-I have no such adverse metabolic effects: they do not raise serum lipids, do not cause hyperglycemia; have no hypokalemic effects and are effective at lowering blood pressure in both hypertensive patients and those with blood pressure in the traditionally normal range.[41] Since most cases of CAD occur among individuals with "normal" BP, and as there is a continuous relationship between BP levels and CAD, lowering BP levels among high risk "normotensive" individuals could be of worthwhile public health benefit.

5. **Genetic studies.** A recent case-control study[42] found that the frequency of an ACE genotype (ACE-DD) was significantly more common in 610 patients with MI than among 733 control subjects (p = 0.007).

In summary, the available data suggest that the benefit derived from ACE-I is not limited to patients with reduced ejection fraction and ACE-I may have a wider role in preventing major CVD events in high risk populations. This effect appears to be attributable to multiple mechanisms including blood pressure reduction, prevention of myocardial hypertrophy, anti-proliferative effects on vascular smooth muscle, and the prevention of atherosclerosis progression. Initial randomized trials in patients with low ejection fraction support the hypotheses. However, direct evidence is necessary before ACE-I can be justified for use in patients with preserved left ventricular function but at high risk of cardiovascular events.

4. ANTIOXIDANTS MAY REDUCE THE PROGRESSION OF ATHEROSCLEROSIS.

1. **Oxidized LDL is atherogenic.** Although there is now strong evidence that LDL is causally related to atherosclerosis, the exact process by which elevated LDL levels cause atherosclerosis is still being unravelled. Laboratory and animal experiments reveal that oxidized LDL is substantially more atherogenic than native LDL and that this occurs through several mechanisms.[4,43,44] Oxidized LDL is chemotactic for monocytes and macrophages, some of which become foam cells (cholesterol-filled cells within arterial walls) that may develop into atherosclerotic plaques. Oxidized LDL is more easily taken up by specific foam cell receptors than non-oxidized LDL. Oxidized LDL is directly cytotoxic to arterial endothelium in vitro studies. Oxidized LDL releases cytokines from macrophages, and inhibits the arterial wall relaxation mediated through endothelial derived relaxation factor. Clinical studies have documented a positive correlation between the extent of atherosclerosis and levels of antioxidant susceptibility[45] as well as with levels of oxidized LDL auto-antibodies.[46]

<u>Vitamin E reduces atherosclerosis in animals</u>. Three of four animal trials reported that Vitamin E-fed animals had between 25% to 50% less atheroma formation than control animals.[47-50] Studies in animals with probucol, an agent with both antioxidant and lipid lowering properties, have also shown slower progression of atherosclerosis.[51] The effect of probucol was independent of any cholesterol-lowering properties of these drugs.[52]

3. <u>Human ecological studies</u>. A cross-sectional survey of 16 different populations suggested that a two-fold difference in serum alpha-tocopherol (Vitamin E) corresponded to an approximately 30% lower rate of CAD deaths,[53] whereas levels of Vitamin A, C and selenium were less consistently associated with CAD. Two other smaller correlation studies did not find an association between Vitamins A, C or E with CAD mortality.[54,55]

4. <u>Retrospective case-control studies</u>. A study of 110 middle aged men with angina and 394 controls found a 2.2 fold elevated risk of angina with the lowest quintile[56] of alpha-tocopherol versus the highest quintile. In a group of patients referred for catheterization, lower levels of serum Vitamin C levels were found in those with angiographically proved CAD compared to those without.[57]

5. <u>Prospective studies</u>. A nested case-control study noted an inverse association between serum beta-carotene levels and risk of MI (RR = 0.42; 95% CL = 0.19-0.89).[58] Two other smaller nested case-control studies on archived blood samples did not find an association with serum Vitamin E or Vitamin C levels and CAD, although prolonged storage is known to reduce alpha-tocopherol.[59,60] One large prospective study of over 87,000 nurses found that those who took vitamin E supplements had a decreased incidence of CAD by 37% (95% CL = 12%-55%) after 8 years of follow up. These results were independent of any effects of supplementation with Beta-carotene or Vitamin C. Another prospective study of over 39,000 male health professionals found Vitamin E supplementation was associated with a 25% lower risk of CAD (95% CL = 7%-34%) after 3.5 years of follow-up, but found only a minimal effect in those taking supplementation for less than two years.[62] Another cohort study among the elderly found an inverse relationship between intake of fruit and vegetables high in beta-carotene and subsequent CAD death (RR = 0.55 95% CL = 0.34-0.87 for highest versus lowest quintile).[63] A cohort of 13,000 U.S. subjects taking Vitamin C supplementation found a standardized mortality ratio of 0.66 (95% CL = 0.53-0.82) for CVD death. A smaller cohort of 1,200 Swedish women found no association of MI or stroke with Vitamin C supplementation.[65]

6. <u>Randomized clinical trials</u>. Given that confounding routinely occurs in ecological and observational studies and may be of the same magnitude as the moderate effects being sought, randomized clinical trials are needed to evaluate definitively the role of antioxidants in the prevention of CVD events. A recent trial of 100 patients assessing the effect of alpha-tocopherol on re-stenosis post-coronary angioplasty, found a re-stenosis rate of 36% in patients receiving 1200 IU of alpha-tocopherol versus a 48% re-stenosis rate in patients receiving placebo (risk reduction = 31%; p = 0.06).[66] A retrospective subgroup analysis of 333 men with pre-existing CAD in the U.S. Physicians' Study[67,68] indicated a significant risk reduction in CVD events with Beta-carotene supplementation. These data-derived subgroup findings, although encouraging, are unreliable. Several other small trials have been conducted[69-71] showing reduction in claudication with Vitamin E supplementation, while another trial showed no effect of Vitamin E on angina pectoris at six months.[72] It appears however that prolonged supplementation or high dietary intake for several years may be required before clinical benefit can be demonstrated from retarding the development or progression of atherosclerosis.[53,61,62]

5. RATIONALE FOR THE CHOICE OF VITAMIN E AS THE SOLE ANTIOXIDANT IN THE TRIAL.

Vitamin E is naturally occurring, very safe and circulates in the blood incorporated into the LDL particle itself.[73] In addition to the anti-atherogenic effects already described, Vitamin E has other potentially beneficial effects, including decreased platelet adhesiveness,[74] deactivation of protein kinase C,[75] protection of prostacyclin PGI2 and stabilization of cardiovascular tone,[76] and infarct size limitation.[77] In several epidemiologic studies,[63,61,62] Vitamin E levels demonstrated a stronger association with CVD than Vitamin C and Beta-carotene.

As dietary intake is complex, and as the intake of various vitamins may be correlated with each other, it is not possible from observational studies of vitamin intake to ascertain definitively which of the naturally occurring antioxidants is most likely to have a benefit on CVD. In addition, there are no substantive human data suggesting that the use of several antioxidants will produce a synergistic response. Furthermore, the primary prevention trial of beta-carotene supplementation in 22,000 male physicians, has now completed at least 11 years of follow-up,[67] and yet has not been terminated. It therefore appears that the benefit from beta-carotene alone cannot be more than modest. For these reasons, we have therefore decided to study the effects of Vitamin E alone (versus a combination of three antioxidant vitamins or an evaluation of Beta-carotene separately in a further 2 X 2 X 2 factorial randomization).

A 400 IU dose of Vitamin E has been found to achieve serum levels of alpha-tocopherol as high as those achieved with higher doses, and achieves serum levels above those of 95% of the US population.[78,79] The doubling of serum alpha tocopherol corresponds to a 30% difference in CAD rates between different populations,[63] thus this dose should be adequate to demonstrate the efficacy of the antioxidant effects of Vitamin E, if they exist.

In summary, an intervention trial of Vitamin E of adequate size can potentially have widespread clinical and public health impact, and if proven effective, would be a low cost and safe means of prevention that could be adopted in most developed and developing countries.

6. RATIONALE FOR INCLUDING A BROAD GROUP OF HIGH RISK INDIVIDUALS.

The various patient populations to be studied in this trial have on average about a 5% risk of a major cardiovascular event per year (Appendix A). Amongst those groups, traditional risk factors increase the risk of CVD regardless of the presence or absence of established cardiovascular disease. Among both diabetic and non diabetic patients elevations of cholesterol, blood pressure, or renin each independently increase the risk of MI. Further data suggest that the rationale for evaluating ACE-I and Vitamin E are applicable across the various groups to be included in this trial. For example, renin levels appear to be a risk factor among both diabetics and non-diabetics, and among those with elevated or normal cholesterol.[26] In diabetic patients, oxidation of lipids appears as important[79] as it does among angina patients.[56] Details of these risk profiles are discussed in Appendix A and Appendix H. The various types of high risk patients that are to be entered into this trial are expected to derive benefits from both interventions.

We propose a large randomized trial, utilizing a 2 X 2 factorial design, that would simultaneously test the efficacy of an ACE-inhibitor, Ramipril, and Vitamin E in reducing cardiovascular events. Key design and organizational aspects of the study include:

1. Inclusion of subjects at high risk of subsequent cardiovascular events independent of the initial mode of presentation.

2. Large size, so that <u>moderate</u>, but <u>important</u> effects on clinically relevant endpoints may be reliably detected or excluded.

3. Clinically important results will be obtained as even <u>modest</u> reductions in risk may be of great public health importance among the millions of people world wide at risk of premature death from CVD.

4. Simplicity in study design in which only key baseline and endpoint measures are recorded in all subjects. This approach increases the feasibility of the study in a wide variety of settings (i.e. University or community hospitals, doctor's offices) and speeds up recruitment.

5. Wide eligibility criteria, so that the results of the trial will be applicable to a hroad, yet high risk, population. Further, the combination of wide entry criteria, simple study design, clinical endpoints and the use of a factorial design considerably lowers the cost of the trial.

o. Factorial design, whereby there is considerable efficiency in simultaneously and independently evaluating two different interventions (Ramipril and Vitamin E).

7. *Inclusion of several studies of mechanism will be achieved by few focused detailed sub-studies on surrogate endpoints (such as carotid atherosclerosis measured by B-mode ultrasound or left ventricular mass) (see Appendix F). Such a tiered approach will further our knowledge of atherosclerosis.*

8. *Publications to be in the names of all wholehearted collaborators.*

Figure 1 (page i) outlines key aspects of the study protocol and design.

STUDY DESIGN: A LARGE, SIMPLE, COST-EFFICIENT TRIAL WITH A MINIMUM OF EFFORT FOR COLLABORATING PHYSICIANS.

1. PRIMARY OBJECTIVES

1. To evaluate if use of an ACE-I (Ramipril) compared with placebo, reduces CVD events in high risk patients.

2. To evaluate if use of Vitamin E compared with placebo, reduces CVD events in high risk patients.

The primary endpoint for this study (CVD events) will be the occurrence of myocardial infarction, stroke or cardiovascular death. Secondary endpoints will add to the primary endpoint,

hospitalization for unstable angina, emergent re-vascularization procedures (CABG or PTCA), carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation. Development of congestive heart failure (for Ramipril) as well as cardiovascular mortality and total mortality will also be secondary endpoints. Among patients with diabetes, a secondary analysis would include nephropathy. The effects of each intervention in different sub-groups (patients with coronary disease, with cerebrovascular or peripheral cardiovascular diseases, with diabetes; men or women; and by age group) will be examined for consistency and coherence. These endpoints have been defined in Appendix E. Endpoints of interest also include cancers (see Appendix B for brief discussion of rationale that Vitamin E may prevent cancers).

2. PARTICIPANT ELIGIBILITY: A WIDE RANGE OF HIGH RISK PATIENTS.

1. _Women and men,aged 55 or above_ at high risk of developing a major cardiovascular event:

    A. Coronary disease: Previous myocardial infarction, _stable or unstable angina with documented multivessel coronary disease* or positive stress (ST depression $\geq$ 2mm or a positive thallium),_ or multivessel PTCA (patients can be entered into Run-in Phase one week after these events but should only be randomized one month after these events), _multivessel CABG(more than 4 years ago or with angina) or multivessel coronary disease* seen on angiography._
    * _multivessel coronary artery disease is defined as > 50% stenosis in at least two major coronary arteries_

    B. Other patients at high risk of developing MI or stroke:

    (i) Peripheral vascular disease: Previous limb bypass surgery or percutaneous trans- luminal 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.

    (ii) Previous stroke (more than one month ago).

    (iii) 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._

2. All patients must provide informed consent (see Appendix C).

3. 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.

    1. 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.

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2. Cardiovascular diseases:

    1. Ejection fraction <40% (only if known).

    2. Hemodynamically significant primary valvular or outflow tract obstruction (eg. mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve).

    3. Constrictive pericarditis.

    4. Complex congenital heart disease.

    5. Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia are not an exclusion criterion).

    6. Planned cardiac surgery or angioplasty within 3 months (patient may be reconsidered for the trial after the procedure).

    7. Uncontrolled hypertension.

    8. Cor pulmonale.

    9. Heart transplant recipient.

3. Other conditions:

    1. Significant renal disease defined as:
      a) renal artery stenosis;
      b) creatine 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.

    2. Any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation.

    3. Patient is simultaneously taking another experimental drug.

    4. Previously randomized to HOPE.

3. SIMPLE SCREENING AND PRE-RANDOMIZATION PHASE.

    1. Overview. The efforts in recruiting each patient are kept to a minimum. Study subjects are to be recruited from among participating hospitals and clinics under the responsibility of a Collaborating Investigator. The enrolment process involves three steps.

    Initial Screening. During the planning phase, investigators will identify the pool of potential study subjects prior to the initiation of the recruitment phase. Each centre will be required to identify at least 30 potentially eligible patients in advance by either reviewing past medical

records and diagnoses, admissions to coronary care units, logs of invasive and non-invasive laboratories and relevant surgical procedures, screening in diabetic clinics, referrals from physicians, or other sources of recruitment. All participants who are found to be eligible, may be entered into the HOPE Screening Log to be provided to each Collaborating Investigator which is sent to the Canadian Cardiovascular Collaboration Project Office (C3PO).

The Log contains basic screening criteria such as diagnosis, key identifiers, contact details, age and sex. If the patient is potentially suitable for the trial, he/she is scheduled for the Eligibility and Run-In Visit. A Patient Information Pamphlet will be provided to aid recruitment.

3. **Eligibility and Run-In Visit: (3 weeks before Randomization)** At this visit the following will be obtained:

   1. Written informed consent, which is then mailed to the C3PO in the HOPE Document Envelope (a copy is kept in the HOPE patient folder).

   2. Assessment if the patient meets inclusion criteria and has no exclusion criteria, including performing a urine dipstick. If it shows ≥ *1+ proteinuria*, the patient is excluded.

   3. Patients who remain eligible for the study will be given a 2.5 mg dose of active Ramipril for 7 to 10 followed by 10 to 14 days of placebo Ramipril. A local determination of serum creatinine and potassium will be made between days 7 and 10 of the Run-In Phase (on active Ramipril). In diabetics, the glycated haemoglobin will also be noted. Following the blood test patients are instructed to use medication from the next row of the calendar pack (i.e. placebo Ramipril, on days 11 to 24 of the Run-In Phase). Patients are instructed to return for the Randomization Visit after an 8 hour (usually overnight) fast for blood collection and with a first morning urine sample. The blood and urine samples, from the Randomization visit will be sent to the HOPE Central Lab.

   4. The first visit also will be an opportunity for ancillary treatments to be optimized in terms of diet, anti-hypertensive therapy, lipid lowering therapy and advice about smoking cessation.

Based on the SOLVD study in 7,400 patients, it is expected that 2% to 3% of patients will report side effects and will not be willing to continue participation in the trial. If a patient fails the first Run-In Phase due to non-compliance, and they are willing to re-enter the study, the Run-In Phase may be repeated once. 3% to 4% of patients will be non-compliant and would therefore not be reliable participants in a long term study.

4. RANDOMIZATION AND TREATMENT REGIME (0 WEEKS).

At this visit any intolerance such as symptomatic hypotension, will be recorded and the results of the local potassium and creatinine tests will be reviewed. Patients who have adhered to the medication regimen (80% or more of Ramipril during the Run-In Phase) are tolerant (no severe adverse effects), show no gross elevations in potassium and creatinine, and didn't show ≥ *1+ proteinuria* at the Run-In Visit may be randomized.

Key details will be provided to the C3PO by a toll-free telephone call between 7:00 AM and 7:00 PM (EDT) 1-800-667-7263 (RAND)). After receipt of complete and appropriate baseline data over

(¸ telephone, the patient is randomized. The Randomization Form is completed and faxed to the .JPO. The original is kept in the HOPE patient folder.

The randomization is to RAMIPRIL (2.5 mg OD for 1 week then 5 mg OD for 3 weeks then 10 mg OD) OR PLACEBO AND VITAMIN E 400 IU OD OR PLACEBO utilizing a 2 X 2 "factorial" design as in Table 2. The HOPE Study Medication Kit bearing the randomization number is assigned to the patient. At 1 month the dose of Ramipril will be increased to 10 mg daily. At the randomization visit, each patient will be given a patient identification card. This card indicates the date of the next visit, provides a brief description of the study, lists a toll free contact number in case of questions or emergency, and provides his or her study physicians' name. The patient is then given a date for a first follow-up visit (1 month ± 1 week). Once randomized, the patient will be followed until the end of the study, and all endpoints will be recorded even if the study medication has been stopped.

Table 2. Factorial Design of Trial of 8,000 Patients		
	Ramipril (4,000) vs placebo (4,000)	
Vitamin E (4,000) vs placebo (4,000)	A. Active Ramipril + Active Vitamin E (2,000)	B. placebo Ramipril + Active Vitamin E (2,000)
	C. Active Ramipril + placebo Vitamin E (2,000)	D. placebo Ramipril + placebo Vitamin E (2,000)

5. FOLLOW-UP AND DATA COLLECTION.

1. **Follow-up schedule: at 1, 6, 12, 18, 24, 30, 36, 42 and 48 months.** The follow-up visits will occur at 1 month (± 1 week), 6 months (± 4 weeks) and every 6 months thereafter until the end of the study. Each visit beyond the first month shall have a designated "window" of plus or minus four weeks. Every attempt should be made to complete the clinic visit during this window period. In unusual circumstances when the participant cannot be seen in the time window, sections of the Follow-Up Form may be completed by phone and medications may be mailed to the patient.

2. **Follow-up procedures.** At each visit, a Follow-Up Form will be completed by the Physician or local study nurse and faxed to the C3PO. These forms will provide data on the occurrence of any major event (which will trigger an event form), on adverse effects and adherence or dosage change of the study medication. Blood pressures and heart rate will be recorded at 1 month and 2 year visits. Adherence to study drugs will be assessed by estimating the remaining pills in the ᵇottle. Reasons for poor adherence will be determined and patients will be appropriately unselled. If a lower drug dose of Ramipril is believed to be likely to increase adherence, the dosage may be reduced temporarily by using the extra 2.5 mg titration capsules provided in the patients medication kit or by calling C3PO to use the Back-up Kit. Only in cases of extreme

adverse reactions will the study medication be withdrawn. If the drug is stopped, every attempt should be made to restart it if medically appropriate. In addition to the above, at first follow-up visit, blood will be drawn locally for creatinine and potassium. Elevations in creatinine or potassium levels could necessitate a reduction in dose or adjustment of concomitant medications (such as diuretics or potassium supplementation). If the patient moves, a Change of Address Report is completed and faxed to C3PO.

3. **Special Event Data.** Event Reports are required for: 1. Every hospitalization, 2. Every myocardial infarction, 3. Every stroke, and 4. Death. One primary diagnosis and several secondary diagnoses for each hospitalization will be recorded. In patients with myocardial infarction, details of the history, cardiac enzymes and ECG changes will be sought. For every stroke, further details (e.g. report of CT or MRI scan) will be collected (see Appendix E). A photocopy of the discharge summary and other documents for each hospitalization is also sent to C3PO in the HOPE Event Document Envelope.

4. **Summary of Forms to be faxed to C3PO.**

a) **Run-In Visit (1 page):** Records patient's principle diagnosis, date of Run-In and ordering of lab tests.

b) **Randomizations Form (5 pages):** Records Randomization Number (after toll free phone call to Randomization operator to obtain Randomization Number) and patient's address, social and medical history, current medications, physical exam and lab test results.

c) **Follow-Up Form (2 to 3 pages at 1 month, 6 months, then every 6 months for up to 4 years):** Records patient compliance with medication, and brief history on endpoints not needing hospitalization.

d) **End of Study Form (2 pages):** Records physical exam, ECG Results and current medication use at the end of the follow-up period.

e) **Hospitalization Report (1 page):** Records all hospitalizations and the primary and secondary reason for them. This is faxed to C3PO. A copy of the discharge summary or other relevant reports is mailed to C3PO in the HOPE Document Envelope within four weeks.

f) **M.I. Report (1 page):** Records all myocardial infarctions. This form is faxed to C3PO. A copy of the hospital discharge summary, diagnostic ECG, autopsy report and other relevant reports are mailed to C3PO in the HOPE Document Envelope within four weeks.

g) **Stroke Report (1 page):** Records all strokes. These forms are faxed to C3PO. A copy of the hospital discharge summary, CT/MRI reports, autopsy reports and other relevant reports are mailed to C3PO in the HOPE Document Envelope within four weeks.

h) **Death Report (1 page):** Records all deaths and their cause. This form is faxed to C3PO. A copy of the death certificate, autopsy report or discharge summary or other relevant reports is mailed to C3PO in the HOPE Document Envelope within four weeks.

i) Change of Address Report (1 page): Faxed to C3PO if patient moves.

(j) Serious Adverse Experience (SAE) Report (1 page): Records all serious adverse experiences *which are unexpected and* attributable to study medications. A copy of the discharge summary or other relevant reports is mailed to C3PO in the HOPE Document Envelope as soon as possible to a maximum of one week.

5. Standardization and Monitoring of Data Quality.
All study staff will undergo a one-day training session prior to study commencement to resolve questions about the study and to ensure uniformity in study procedures. The HOPE Operations Manual will provide a detailed outline of each step of the protocol. The HOPE Coordinator and Regional Coordinators will provide training and information on a regional level and will provide re-training as necessary. Staff from the C3PO will be freely available to answer any questions on the protocol or to help resolve operational problems. Further, a toll-free assistance number will be available to resolve procedural problems.

Data collection will be monitored regularly. For all deaths, a copy of the death certificate, autopsy report (if available) and/or hospital discharge summary will be submitted and for all major cardiovascular events a photocopy of the hospital discharge summary *and other relevant reports* will be mailed. The C3PO will perform the majority of edit checks on the data as they are obtained. Errors, missing items or inconsistent values will be resolved by fax, telephone calls and, if needed, by visits from a member of the C3PO. Regular reports by clinic, and overall, will be generated for the Steering Committee and the independent Data and Safety Monitoring Board (DSMB), outlining recruitment rates, patterns and timeliness of data receipt, consistency of data over forms, adherence rates, losses to follow up, completeness of forms, ascertainment of endpoints, error rates, screening and randomization rates, and participant follow-up. A random sample of forms and key endpoint measures will be compared with hospital records for verification (see Appendix D).

The responsibility of the Collaborating Investigators at each or centre is to ensure that the data from their respective centre are accurate and complete. Prior to the annual meeting, data summaries will be sent to each Investigator so that any difficulties can be discussed in detail at the meeting.

6. Central adjudication of all events.
All suspected cardiovascular deaths or major events for which there is any discrepancy between the Event Reports and hospital discharge summary will be reviewed blind to the study drugs by the Events Adjudication Committee. This will be done for the following events: 1. Deaths classified by cause; 2. Myocardial infarction; 3. Strokes. These events are defined in Appendix E. A study physician at C3PO will compare all discharge summaries with Event Reports for consistency.

7. Central laboratory analysis of biological samples.
At selected centres, patients will have a fasting (8 hour, usually overnight) sample of blood drawn at the Randomization Visit which will be frozen, shipped and stored centrally at the HOPE Central Blood Lab. These blood samples will be analyzed at a future date in nested case-control or correlation studies relating events to factors such as Vitamin E levels, lipids, or other potential risk factors. etc. Two further random samples on 10% of patients will be obtained, one at 6 and another at 18 months. These will be analyzed to measure the size of the regression-dilution bias and the effect on treatments on various biochemical parameters.[811]

(.s well, a first morning urine sample will be collected in all patients at the randomization visit. This will be sent centrally for microalbuminuria testing. Results from this test will be kept centrally.

6. ADVERSE EFFECTS AND MEDICATION SAFETY.

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)[6,8] or captopril (SAVE)[9] 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%).[41,80] Ramipril has been registered for use in 24 countries, including Canada and the U.S. Nonetheless, the study will record details of all adverse events *which result in temporary or permanent withdrawal of study medication or a change in dosage,* and report them periodically to the independent DSMB. The management of adverse reactions will be at the discretion of the patient's physician, and depends on the severity of the adverse reaction and the clinical setting in which it occurs (see Appendix D). All changes in the medication dosage will be recorded with C3PO.

The formulation of Vitamin E will be a d-alpha tocopheryl acetate provided by The Natural Source Vitamin E Association. The bioavailability and pharmacokinetics of this preparation have been well studied[73] (see Appendix B). It is an extremely safe, naturally occurring antioxidant for which no major side-effects have been described.[76]

7. MANAGEMENT OF INTERCURRENT EVENTS.

A number of illnesses and other major events may befall patients during the study. Collaborating Investigators are free to treat each patient according to their best judgment. However, when in doubt they are encouraged to discuss an individual patient's management with the C3PO. It will be recommended that, unless clear contraindications arise, the study drug be continued at the same or lower dose, or only briefly interrupted. Some possible situations are:

1. Congestive heart failure: Congestive heart failure is a clear indication to prescribe diuretics and ACE-I. Therefore, such patients will be given open label ACE-I and discontinue the corresponding Ramipril.

2. Myocardial infarction or unstable angina: The protocol does not require stopping the study drug when a patient develops an acute MI or unstable angina. The continued use of study medications during the event is encouraged. However, the physician may at his/her discretion, stop the Ramipril/placebo during the early phase of convalescence following acute MI. If the study medication has been discontinued, the physician is encouraged to restart within a week of the event.

3. Hospitalization for other medical illnesses or for cardiac or non-cardiac surgery: Although it may be necessary to discontinue the study medication during hospitalization for acute medical illness or for surgical procedure, it should be cautiously re-instituted prior to discharge, increasing the dose to the previous maintenance dose if tolerated. In the event of cardiac transplantation, the trial medications will be stopped permanently.

CABG or PTCA: The study medication could be withheld prior to scheduled surgery or as early as needed for unplanned surgery. Study medication should be re-started as soon as possible.

5. **Azotemia or hyperkalemia:** In patients with azotemia, Ramipril can usually be continued at a lower dose and, if appropriate, by reducing the dosage of concurrent diuretics. Hyperkalemia can be treated by stopping any K^+ supplementation, or K^+ sparing diuretics or by reducing the dose of Ramipril. In patients with $K^+ > 5.5$ MEq/L, the usual medical interventions for hyperkalemia will be followed.

6. **Uncontrolled hypertension:** Physicians will be encouraged initially to employ an antihypertensive drug from a different class, such as diuretics, beta-blockers, calcium blockers, alpha-agonists, etc.

None of these events is an indication to discontinue Vitamin E. All these events will be reported at once to the C3PO. In all cases, including situations when the patient has discontinued study medication or received open-label ACE-I or Vitamin E, the patient will remain in the study and all follow-up visits and events will be reported. Patients will remain in their originally allocated group for analysis.

8. PARTICIPANT SAFETY AND CONFIDENTIALITY.

1. **Overview.** Ensuring the safety of participants and confidentiality of their data are essential. Each collaborating physician will be responsible for the safety of participants under his or her care. The DSMB will have primary responsibility for the monitoring of study data for adverse trends in mortality, morbidity and drug toxicity. All patients with contraindications to Ramipril or Vitamin E will be excluded. Tolerance to Ramipril will be assessed during the Run-In Phase prior to randomization, thereby minimizing the risk for serious early side effects. *Adverse events (both minor - those that result in temporary or permanent withdrawal of study medication or a change in dosage, and serious) will be monitored regularly. Routine 6 monthly reports on adverse events will be generated and shared with the DSMB. These data will be shared in a blinded fashion with regulatory authorities. These reports will not include information about events that constitute the primary outcomes of the trial.*

2. **Emergency Unblinding.** Emergency unblinding will be available locally. Unblinding will only be done when absolutely necessary in the judgment of the patient's physician. Prior to unblinding, a telephone call is made to C3PO. A check list will be completed over the telephone to ensure that unblinding is really necessary and that appropriate steps for patient management are taken. All such patients will continue to be part of the study.

3. **Confidentiality.** The confidentiality of all participants will be protected at both the local centres and at the C3PO. Paper records at clinical centres will receive the same protection as other medical records. Data at the C3PO will be kept secure. No patient identifiers will be presented on any files transmitted to any committee or any clinical centre. *A duplicate copy of the most recent data tapes will be stored securely in a bank vault.*

9. SAMPLE SIZE AND ANALYSES.

Study Power. We are proposing a study of 8,000 to 9,000 subjects recruited in a single year and followed for an additional three years (average follow-up 3.5 years). This total will include about 4,000 to 5,000 cardiac, 1,000 peripheral vascular, and 3,000 to 4,000 high risk diabetics

(including 1,000 to 2,000 with cardiac disease). Based on an extensive review of over 93,000 patients (Appendix A) in the available literature, we anticipate an overall 5% per year event rate for the primary endpoint cluster of MI, stroke, and cardiovascular death. To be prudent, we have also considered the implications of somewhat lower (4% per year) and higher (6% per year) event rates. As the patients included in our trial are older (≥55) than those covered in the extensive review, we anticipate that event rates will be at least 5% and in all likelihood much higher. For example data from ISIS-2 long-term follow-up of post MI patients[15] suggests that death occurred two times more commonly in patients over 55 versus those under 55. A lower age limit of 54 also ensures that many more woman may be randomized into the trial, as most CVD in women occurs after menopause[1].

Based on a total of 8,000 subjects overall and 6,000 patients from North America, we have calculated the estimates of risk reductions (i.e. including non-compliers) which will be detectable with power of 80% and 90% (Table 3). These calculations are based on a constant proportional risk reduction and a Mantel-Haenszel test on an intention-to-treat viewpoint. A 1% per year non-cardiovascular mortality rate has been assumed which reduces time-at-risk for the primary endpoint. *We propose to include an additional 1,000 patients if feasible, to protect against unexpectedly lower event rates, compliance or other reasons that may reduce study power.*

Table 3 Estimates of Detectable Relative Risk Reduction at 80% and 90% Power					
Event Rate Per Year	Power	Number of Patients			
		8,000[1]	6,000[2]	5,000[3]	4,000[4]
4%	80%	17%	19%	20%	22%
	90%	19%	21%	23%	25%
5%	80%	15%	17%	18%	20%
	90%	17%	20%	21%	23%
6%	80%	14%	16%	17%	19%
	90%	16%	18%	19%	21%

[1]Overall sample size. (If possible a further 1,000 patients will be recruited for a total of 9,000 patients).
[2]Overall sample size in Canada and U.S.
[3]Size of subgroup of all patients with previous cardiac disease.
[4]Size of subgroup of diabetic patients.

This trial is not designed primarily for detection of reductions in total CVD mortality. Nonetheless assuming an overall 7.5% CVD death rate in the placebo group, with 8,000 patients there would be 80% power to detect a 24% RRR in mortality and 90% power to detect a 27% RRR.

Risk reductions of 20% to 25% for vascular events are biologically plausible and have been seen with ACE-I in heart failure trials (23% risk reduction). For Vitamin E, epidemiological studies have indicated that prolonged doubling in serum alpha-

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tocopherol levels is associated with a 30% reduction in CAD rates.[53,41,42] Assuming that two-thirds of the reduction observed in epidemiological studies will be apparent over the 3.5 year follow-up period, then a 20% risk reduction could be observed, which should be detected with adequate power by including 8,000 patients (see Appendix B).

From Table 3, it is clear that the study of 6,000 to 8,000 subjects will be able to reliably detect risk reductions in the 15%-20% range associated with either active treatment component. Increasing the study size by a further 1,000 to 1,500 patients protects study power in case of lower event rates than expected. We judge effect sizes in this range to be both clinically important and biologically plausible. A major subanalysis will involve patients with cardiovascular disease (n = 5000) or diabetes (n = 4,000) separately. Analysis of these major subgroups would yield adequate power to detect relative risk reductions (RRR) in the 25-30% range utilizing the primary endpoint and adequate power to detect risk reductions in the 20% to 25% range for the secondary endpoints.

2. Statistical analysis. The primary endpoint is defined as the first occurrence of an event in the cluster of non-fatal MI, non-fatal stroke, or death from a cardiovascular cause. Secondary analyses will broaden the cluster of cardiovascular events to include, in addition, hospitalization for unstable angina, emergency coronary revascularization, carotid endarterectomy, peripheral angioplasty/surgery or limb amputation. Other analyses will also be conducted for cardiovascular mortality and for total mortality and for hospitalization for congestive heart failure (for Ramipril). mong diabetic patients, the incidence of nephropathy will be assessed for each therapy. Data ill be summarized for each treatment group in the form of a survival curve which depicts the proportion of patients remaining event free over time since randomization. Survival curves are estimated using the Kaplan-Meier[93] procedure and compared between treatments using the log-rank test,[94] based on an intention-to-treat approach. The factorial design will require that the comparison of Ramipril will be stratified by Vitamin E (and vice-versa), and clinical centre. We anticipate that the treatment effects of Ramipril and Vitamin E, if present, will act independently and thus that the combined effect of both active agents will be the multiplication of their individual effects on risk reduction. We will, however, investigate the possibility of synergism by formally testing the interaction term in a Cox model[95] allowing for potential non-multiplicative effects. Subgroup analyses (e.g. cardiac patients, diabetics) will be done by retrospective, stratified analysis, including tests of interaction in the Cox model. The Cox model will also be used for treatment effect estimates which are adjusted for baseline-prognostic imbalances. Data derived findings will not have a p value assigned.

3. Interim analysis and data monitoring. The independent DSMB will monitor the progress of all aspects of the study and will ensure that the study meets the highest standards of ethics and patient safety. In particular, data on key study endpoints will be monitored at regular intervals to ensure that the event rates meet protocol projections. If the event rates are lower than expected, the DSMB can recommend an extension in the duration of follow-up to maintain study power. Four formal interim analyses are planned, equally spaced, with respect to accumulating years at risk. Specific statistical guidelines for data monitoring will be discussed and formalized at a later date. *One suggestion for early stopping is that a reduction in events by four standard deviations or a three standard deviation excess in the first half of the trial, or a reduction in events y three standard deviation or a two standard deviation excess in the second half of the trial. This approach has been used in the Digitalis Trial [96], constitutes evidence of benefit and harm, respectively.* The decision to continue or stop the trial would be based on a number of factors in addition to the main results.

4. **Data Verification.** It is expected that the data from HOPE will form the basis of an NDA (New Drug Application). Therefore, the manufacturers of Ramipril, Hoechst and its related companies will arrange for verification of data collected by auditing case-records on a random basis. It is expected that 25% of all patients with a primary event and 5% of those without an event will be audited. However, all centres will be audited at least twice during the study to ensure that they are following the study protocol. These visits will be coordinated by the C3PO and Regional Coordinator.

10. PROPOSED TIMETABLE.

1. Phase I (6 months).

1. Finalizing protocol.
2. Development of forms and pilot centres.
3. Translation of consent form into French and other languages.
4. Identification of centres.
5. Identification by each centre of at least 30 eligible patients for the trial prior to recruitment.
6. Meetings of collaborating investigators for discussion of protocol and training.
7. Establishment of telephone lines.
8. Develop all study aids.
9. Approval of local ethics committees/HPB and FDA forms.
10. Drug packaging and kit preparation and randomization sequence blocks determined and shipping of materials.

2. Phase II (12 months).
Recruitment: 6,000 patients recruited in Canada and the U.S. and 2,000 additional patients from Europe. Careful preparation during Phase I will ensure initiation of recruitment within a 2 month period at all centres and a high rapid rate of recruitment because of previously identified patients. This should minimize the early lag in recruitment seen in several trials. This strategy was successfully used in the SOLVD and DIG trials.

3. Phase III. Follow-Up: The last patient is followed for at least 3 years.

4. Phase IV (12 months): The close out period will be 3 months for scheduling final patient visits, obtaining data, completion of missing data, confirmation and classification of events; data analysis and publication will take an additional 9 months.
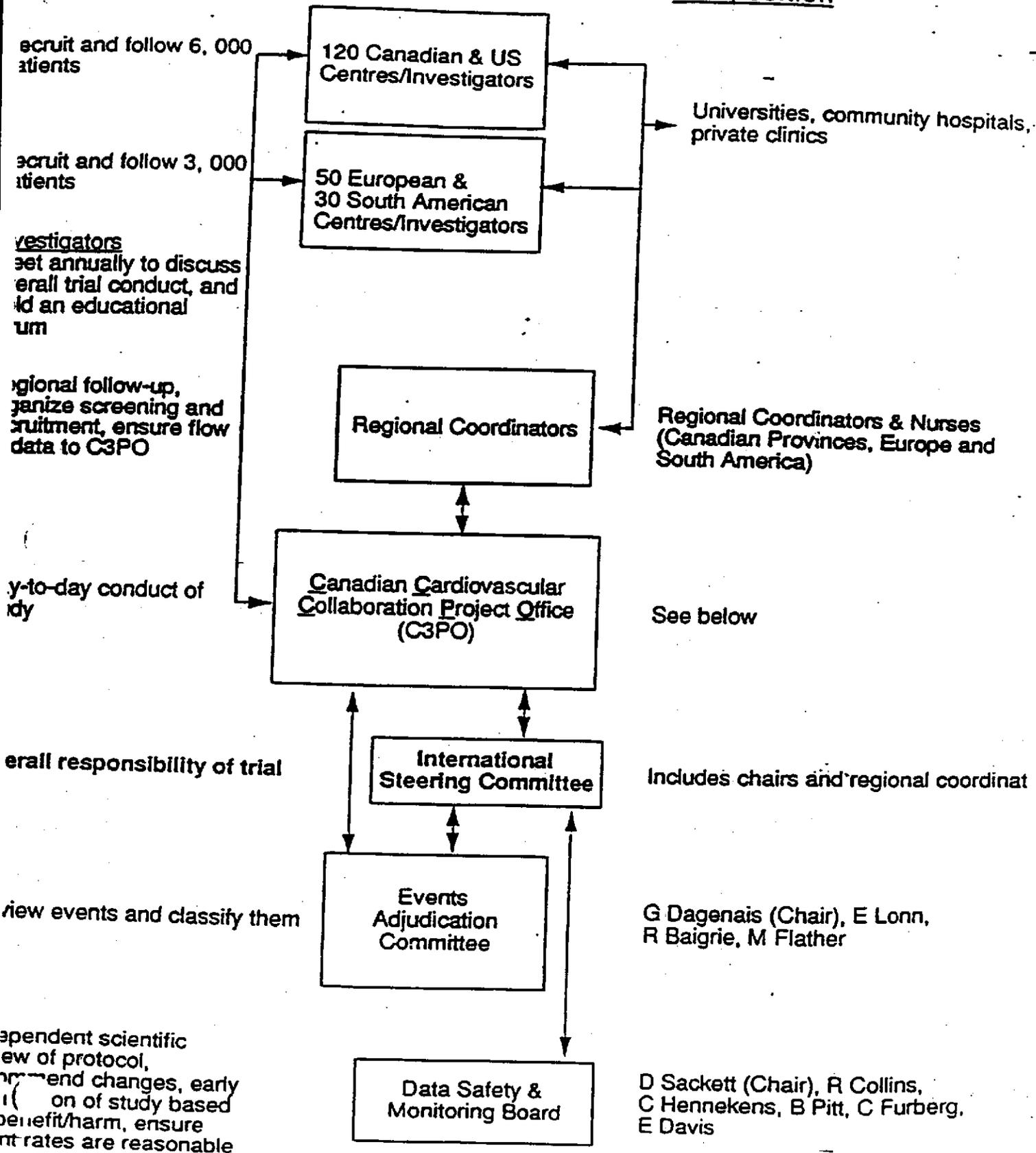
11. FEASIBILITY OF RECRUITMENT.

We propose to include a minimum of 100 to 120 Canadian centres, a minimum of 20-30 U.S. centres, and a maximum of 50 centres in Europe. Each centre would have to agree to recruit at least 50 patients within one year. Although recruitment of 8,000 patients within one year appears to be ambitious, there are several reasons why we are likely to succeed: a) high level of interest in the questions, b) established network of investigators in Canada and in Europe for trials that we have coordinated (DIG, ISIS, CAPRIE, CAMIAT, etc.), c) simplicity in study design, d) wide entry criteria, e) screening from an easily identifiable large prevalent pool of patients and f) provision of recruitment aids to centres and g) initiation of screening prior to the official date of randomization.

An extensive feasibility surveys of 51 hospitals and chart reviews from nearly 1300 patients in thirteen hospitals across Canada indicates that recruitment is highly feasible (Table 4).

12. HOPE STUDY ORGANIZATION. See Figure 2 (next page)

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nal Steering Committee: Co-Chairs: S Yusuf, T Montague, P Sleight; Vice-Chair G Dagenais; Canadian Coordination: M Arnold, R Baigrie. s, R Davies, R Hoeschen, D Johnstone, P Liu, B Mitchell, H Mizgala, A Morris, O Naylor, N Racine, F Sestier, B Sussex, K Teo, P Theroux, CR H Tildesley, R Tsuyuki, G Wiseberg, B Zimman. US Coordination J Probstfield, J Young, European Coordination M Jolly, L Richardson; South

13. THE CANADIAN CARDIOVASCULAR COLLABORATION

The Canadian Cardiovascular Collaboration has been established to successfully conduct trials in cardiovascular disease in Canada, the U.S. and worldwide.

The members of the DSMB are internationally respected for both methodologic contributions and for the conduct of large multi-centre trials. These include Dr. D. Sackett (McMaster), Dr. B. Pitt (U. of Michigan), Dr. C. Hennekens (Harvard), Dr. R. Collins (Oxford University) and Dr. C. Furberg (Bowman Gray Univ.) and Dr. E. Davis (U of N. Carolina).

14. PUBLICATIONS

The main publication(s) from the trial will be in the names of all fully Collaborating Investigators. Subsidiary papers will be authored by study investigators.

IV. POTENTIAL SIGNIFICANCE OF THE STUDY

The scientific questions addressed by the trial are of major public health importance and have the potential of making an impact worldwide. The collaborative structure is broad and will attempt to include every university in Canada and a large number of community based physicians. Furthermore there will be a large number of investigators from the U.S., Europe and S. America. This strategy not only makes the study feasible and efficient, but the results are likely to be readily incorporated into clinical practice.

Number of Eligible Patients

We conducted a survey of the numbers of patients in various categories, other than diabetes, attending 51 Canadian centres. The numbers of potentially eligible patients in the previous year were:

Category:	MI	Unstable Angina	Post-CABG	Post-PTCA	Stroke	PVD
Avg. # per centre	272	282	210	172	116	218

Total number of patients available per centre per year, assuming a 50% overlap of patient categories = 635. Using a prevalent pool of patients (e.g. 3 year review of charts) 1,905 patients should be available.

2. Detailed chart reviews of 1295 patients at 13 Canadian centres.

Centre (Investigator)	Number of Patients Eligible/Reviewed		
	Cardiac	Stroke/PVD	Diabetes*
1. Victoria General, Halifax (D. Johnstone)	37/103	12/32	28/41
2. Sunnybrook, Toronto (R. Baigrie)	25/35	3/30	4/30
3. Royal Victoria, Montreal (N. Racine)	32/35	35/40	-
4. Royal Columbian, Vancouver (R. Tsuyuki)	15/29	12/66	3/6
5. University of Alberta Edmonton (K. Teo)	24/39	17/30	9/39
6. Vancouver General, Vancouver (A. Fung)	12/35	25/34	23/35
7. Queen's, Kingston (A. Abdollah)	24/40	20/30	20/30
8. St. Paul's Hosp. Vancouver (C. Thompson)	30/35	26/30	7/30
9. Hamilton General, Hamilton (E.Lonn)	12/24	18/27	-
10. McMaster University Med. Centre (M. Farkouh)	-	-	16/20
11. Henderson General Hospital, Hamilton (M. Farkouh)	13/21	7/21	7/21
12. Foothills Hospital, Calgary (B. Mitchell)	17/35	13/30	6/30
13. Hopital Notre Dame, Montreal (F. Sestier)	32/65	30/49	30/98
TOTAL NUMBER OF PATIENTS = 1295	273/496 (55%)	218/419 (52%)	153/380 (40%)

*diabetics above age 50

Thus about 1900 patients are available per centre of which about 50% are eligible. Therefore, each centre will have close to 1000 eligible patients, and it should be easily possible to recruit 50 to 100 patients from each centre in one year.

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Appendix A: Rationale for studying a wide range of patients at high risk for cardiovascular events

As atherosclerosis is a complex process which occurs simultaneously in various cardiovascular beds, it may lead to various clinical sequelae.[39] Epidemiological evidence has identified that smoking, hypertension, high serum cholesterol, and diabetes are some of the major determinants of increased risk of developing a clinically-important sequelae of underlying atherosclerosis, such as death, myocardial infarction (MI) or stroke.

"Newer" risk factors which have been identified for atherosclerosis include the activation of the renin-angiotensin system[26] and antioxidants.[4] These risk factors appear to be related to development of both strokes and MI indicating a relationship with cardiovascular disease in general. These risk factors appear to operate independently of the presence or absence not only of each other but also of the presence or absence of established cardiovascular disease. For example, hypercholesterolemia is a risk factor both in post MI patients and those free of any MI,[n,10] smoking is a risk factor among both patients with established stroke or those without stroke.[1] Indeed, patients suffering one sequelae of atherosclerosis such as stroke or peripheral cardiovascular disease have high risk of another cardiovascular endpoint (such as MI) (see Appendix A, Table 1).

This suggests that rather than restricting entry to include only patients post-MI or any other single category, clinical trials should not only target individuals with established diseases of one category, but also individuals at increased risk of clinically important cardiovascular events by virtue of the presence of risk factors or evidence of cardiovascular disease in any territory.

In this context "primary" or "secondary" prevention are imprecise terms and ought to be replaced by risk prevention among patients at increased risk.

Thus the fundamental questions for inclusion of patients from various categories of "disease" are as follows:

1) Do these groups have high rates of clinically important CVD events? (As seen in Table 1, the rates are high, as on average one in 20 individuals from all these groups will have such events every year).
2) Does epidemiological, laboratory or clinical evidence support the idea that the underlying mechanism of atherosclerotic disease in these groups are amenable to intervention with ACE-I and/or Vitamin E?

These are discussed by "disease" category below.

Cardiac Patients:

The rationale for the renin angiotensin system having a role in cardiac patients is extensively discussed in the protocol. Data from the prospective study of 1700 middle-aged men and women by Alderman[26] showed that baseline renin profile was predictive of subsequent risk of MI (relative rate (RR) = 5.3 95% CL = 3.4-8.3). Renin profile was predictive of risk of MI among smokers and non-smokers, those with low or high cholesterol and those with normal/high fasting glucose. The efficacy of ACE-I has been well established in the SOLVD and SAVE trials of patients with ejection fractions below 40%. These showed a reduction in MI (23%, P < 0.0002; Table 1). In the SOLVD trial, treatment effects were similar across a variety of underlying clinical conditions, including ischemic

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(ischemic etiology, presence or absence of diabetes, levels of ejection fraction and concomitant drug use (beta blockers, aspirin etc)[7], suggesting that the reduction in ischemic events may occur across a wider range of patients.

The oxidation of lipids appears to be important in cardiac patients.[43] Low levels of Vitamin E are associated with angina,[56] and atherosclerosis in progression is linked to antibodies against oxidized lipoproteins.[45] A small angiographic trial found a borderline 33% reduction (p = 0.06) in restenosis in angioplasty patients supplemented with Vitamin E.[66]

Stroke/Peripheral Vascular Disease (PVD Patients):

Although the direct role of renin and stroke is not well studied one small retrospective case-control study found elevated renin levels were associated with stroke.[24] The relationship between blood pressure elevation and stroke is well established.[40,40a] In addition, stroke (as well as PVD) patients suffer from relatively high rates of cardiac ischemic events, suggesting that a high proportion of these patients have silent coronary atherosclerosis.

The role of antioxidants in stroke prevention is less well established than that of cardiac ischemia, although free radicals appear to have a role in neurologic ischemia.[87] A recent retrospective study of 80 patients showed that higher levels of antioxidant Vitamin A levels were associated with a better neurologic endpoint.[88] In this study, Vitamin E levels did not show a similar relationship, although the small sample size precludes a definitive null result. However, recent unpublished data .(the prospective Nurses Study indicates an inverse relationship between Vitamin E levels and st .as (personal communication C. Hennekens). The inhibitor effect of Vitamin E on platelet aggregation/platelet adhesion might help retard arterial thrombosis.[74] Several small randomized trials of Vitamin E in a dose of 400-600 mg/day in intermittent claudication suggested improvement in subjective symptoms, distance walked before pain appeared and blood flow in calf muscles.[69-71,99]

Diabetic Patients:

Regardless of the presence or absence of established cardiovascular disease, diabetics have an increased risk of suffering a cardiovascular event. The relative risk for CVD death in the MRFIT cohort study was 2.5 for those with diabetics in comparison to non-diabetics and was independent of other risk factors.[91] In diabetics, a variety of mechanisms may be responsible for accelerated atherosclerosis including vascular injury by sorbitol deposition, altered cardiovascular reactivity, enhanced growth effects of insulin, as well as concomitant dyslipidemias.[100-1] Renin profile is associated with an increased risk of MI in both diabetics and non-diabetics.[26] In addition, it has been found that microalbuminuria (urinary albumin excretion at a rate of 30-300 μg per day) is an independent predictor of CVD.[102] Microalbuminuria, which is found in up to 20% of diabetics, may reflect abnormalities in vascular smooth muscle function.

ACE-I are well tolerated in diabetics with no adverse effects on lipid or sugar profiles. There is evidence that ACE-I reduce microalbuminuria[103] and this beneficial effect on vascular smooth muscle may also reduce left ventricular mass.[104] However, any extrapolation of these results to prevention of CVD events requires large scale clinical trials, of which HOPE is probably the first. In the SOLVD tri' [6-8] beneficial effects of enalapril in reducing ischemic events are seen in both diabetics or non- (ics (unpublished data). Other beneficial effects of ACE-I have been described in diabetics, including improvement of insulin sensitivity and glycemic profile.[102,105]

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Several studies have found that diabetics suffer abnormalities of lipids, which likely predispose to oxidative damage. Diabetics have small dense LDL, low HDL, depletion of ascorbic acid and glycation of LDL, all of which are likely to enhance oxidation.[79,106-7] Therefore, there is a clear rationale for trials of antioxidants in diabetics.

In conclusion, there is sufficient evidence that each of the groups eligible for the HOPE study, regardless of disease category are at high risk and likely to derive benefit from ACE-inhibitors and Vitamin E. Thus the results of the HOPE study will be of great public health importance for a wide variety of individuals at risk of cardiovascular events.

Type of Patient	Source[a,b]	No. CVD events/no. patients	Mean Follow-up (years)	Annualized event rates (%)	Comments
1) Long-term post MI					
Acute and long term post MI	APT Collaboration[162]	1321/9877	2.3	5.8	Event rate in patients on aspirin. Excludes acute MI.
	a) ISIS-1[164]				
	35 days-1 year	625/14822 (deaths)	1.0	4.3*	In ISIS-3, 90% of patients were discharged on aspirin. Data are from a large number of hospitals and therefore are likely to be representative.
	>1 year-2 years	281/10704 (deaths)	1.0	2.6*	
	b) ISIS-2[166]				
	35 days-1 year	817/14535 (deaths)	1.0	5.6*	
	>1 year-2 years	238/9144 (deaths)	1.0	2.6*	
	c) ISIS-3[168]				
	35 days-1 year	1771/37001 (deaths)	1.0	4.8	
	>1 year-2 years	179/7459 (deaths)	1.0	2.5	
2) Unstable angina	APT Collaboration[162]	92/1991	0.9	4.6	Excludes events during first month.
3) Post-CABG	a) CABG Pooling Project[?]	135/1324 (deaths)	5.0	2.0*	Includes peri-operative events. Therefore expect about 4% if patients are entered >1 month post surgery.
	b) VA CABG-antiplatelet trial[?]	382/1113	1.0	10.8	
4) Post-angioplasty	NHLBI Registry[?]	339/1211	4.0	7.0	Includes peri-procedural cardiac events and patients with EF <0.45. However, 50% of patients had only one vessel disease. It is therefore likely that after exclusion of perioperative events and inclusion of strokes in the event rate, and restricting inclusion of patients with at least 2-vessel disease, the event rate would be about 5% per year.

Appendix A, Table 1 (continued). Rates for the combined endpoint of cardiovascular death, myocardial infarction and stroke in various types of patients assuming the use of aspirin in all patients. HOPE assuming the use of aspirin in all patients.
patients that are to be included in

Type of Patient	Source [a]	No. CVD events/no. patients	Mean Follow-up (years)	Annualized event rates (%)	Comments
5) Stable angina (without surgery)	a) APT Collaboration[12]	27/229	3.7	3.2	Excludes patients with more severe angina.
	b) CABG pooling[13] project - medical group	514-1325	10.0	3.2	Excludes patients with severe angina, does not include strokes. 40% of patients underwent CABG surgery by 10 years.
6) Peripheral cardiovascular disease	APT Collaboration[12] a) all patients b) grafting	221/2221 66/771	2.5 1.7	4.1 5.0	
7) Post stroke/TIA	APT Collaboration[12]	1082/5083	2.1	8.9	11% of events MI, 44% strokes and 46% cardiovascular deaths.
8) Diabetes Type II (>50 yrs)	ETDRS[6]	123/507	5.0	4.5	HOPE will include diabetics >55 yrs of age with at least one other risk factor. Therefore, patients meeting the HOPE criteria are likely to have at least a 5% per year event rate. It is estimated that 40%-50% aged diabetics
Men age 50-57	MRFIT[17]	445/2833 (deaths)	12.0	1.5	are smokers, 40% have cholesterol > 6.2 and 47% are hypertensive. Rates for CVD events are likely to be 2
Men and women age 45-84	Finland[18]	18/109 (MI)	5.0	4.0	to 2.5 times death rates.

Total number of patients reviewed: 93,981

• CVD event rates for death, MI and stroke should be 2 to 2.5 times that of death alone.

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Appendix B. Antioxidant Vitamin E

1. Rationale for choice of Natural Source Vitamin E

Vitamin E (d-alpha-tocopheryl acetate) is available either as natural (RRR or d) or fully synthetic (all-racemic or dl).[73] The natural form is one compound, whereas the synthetic form is a mixture of approximately equal amounts of eight closely related compounds (stereoisomers). It is well established that RRR-racemic d-alpha-tocopheryl acetate is more biologically active than all-racemic α-tocopherol. The most extensively used assay has been the rat fetal gestation-resorption assay. In this test RRR-alpha-tocopheryl is about 1.4 times more active than all-racemic-α-tocopherol. A newer deuterium-labelled mass spectrometry assay may be used in humans (G. Burton, work in progress). In this assay, a day or so after swallowing the last dose, the ratio of RRR/all-racemic is 2.0 in plasma and red cells and between 1.3 to 1.7 in other human tissues.

Therefore, we shall use Natural Source Vitamin E in the HOPE trial.

2. Alternatives to the choice of Vitamin E as the sole antioxidant in this trial.

Our rationale for using only Vitamin E as the sole antioxidant has been discussed in the protocol. We did consider the alternatives of a further factorial design in which beta-carotene and/or Vitamin C would also be randomly allocated and therefore evaluated. We felt that this might complicate the trial to the point where patient compliance may be affected. Another option was use a combination of Vitamins within the same intervention-arm versus control. This could produce a bigger treatment effect if these vitamins were additive or synergistic. However, such a design might also adversely affect patient compliance and one would not be able to distinguish which component(s) of the cocktail was responsible for the treatment benefit. Therefore, we have come down on the side of Vitamin E alone to be used in this trial.

3. Plausible risk reduction in endpoints with Vitamin E

The two larger cohort studies of antioxidant Vitamins [61,62] noted a minimal effect of using Vitamin E supplementation for less than two years (RRR 14% in the Nurses study, RRR 5% in the Health Professionals study). It is possible that only half to 2/3 of the 30% RRR seen in epidemiological studies may be detected in the trial with a mean follow up of 3.5 years. With 6,000 to 8,000 patients (and assuming a 5%/yr event rate), risk reductions of 19% and 15% can be detected with 90% power despite the lack of detectable effect in the first two years. However, the DSMB will advise the steering committee if event rates are unexpectedly low and warrant extension of the Vitamin E component for additional time.

4. Rationale for prevention of cancer with Vitamin E

Free radicals may be able to initiate changes in DNA and antioxidants, for example Vitamin E are able to scavenge these free radicals.[107-8] In animal models of chemically induced carcinogenesis, Vitamin E has shown, albeit inconsistently, an ability to reduce the frequency of tumour development.[109-111] Data from epidemiological studies in humans show a variable association of vitamin E intake and cancer. Dietary intake is difficult to assess as up to 16 different isomers of vitamin E with variable bio-activity exist and vitamin levels may be unstable.[73] However, a large case-control study of gastric cancers (1016 cancers and 1159 controls) with a well validated

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dietary questionnaire found that the upper quintile of σ-tocopherol intake was associated with reduced risk of gastric cancer (Odds ratio 0.6 95%CI = 0.4-0.8).[113] Dietary supplementation or serum σ-tocopherol (Vitamin E) levels are somewhat more reliable. A recent large case-control study of oral or pharyngeal cancers (1114 cancers and 1218 controls) found Vitamin E supplementation (> 100 IU OD) significantly protected against cancer (Odds ratio = 0.5, 95% CL = 0.4-0.6).[112]

A total of 10 prospective studies have examined the relation of archived serum tocopherol with subsequent cancer.[114-123] Only two, including the largest[114] of these (766 cancers occurring in 36,365 men and women)[114,123] showed significantly lower levels of σ-tocopherol in all cancer cases versus controls. Another showed a trend towards lower levels.[121] Overall, these studies showed a moderate but significant lower level of σ-tocopherol in cases than controls.[114] The association with specific cancers was variable, with one study showing a five-fold relative risk of breast cancer with low Vitamin E levels[122] whereas others did not find any association of Vitamin E levels with breast cancer.[115,116] Lung cancer was associated with lower Vitamin E levels in two studies.[118,119]

Given that the amount of confounding inherent in these observational studies likely exceed any moderate reduction of cancers by use of Vitamin E in these studies, large scale clinical trials of Vitamin E supplementation are needed to determine any reduction in the risk of cancer. With 8,000 patients, the HOPE trial will be one of the largest trials of Vitamin E supplementation. At 3.5 years of follow-up, approximately 143 cancers in men and 36 cancers in women will be expected to develop. These numbers yield only 65% power to detect a 30% risk reduction (presuming an alpha of 5%). However, with follow-up at 10 years the number of events would be about three times higher and there would be 95% power to detect a 30% risk reduction and 80% power to measure a 25% risk reduction.

We would seek to obtain funding at a later point to follow these individuals, either through annual mail contact or linkage with cancer registries and mortality databases. In addition to examining the effect of Vitamin E supplementation for a few years, the association of baseline Vitamin E levels could be examined in relation to subsequent cancer risk.

Cancers are the second most common cause of death in Canada. Death rates from lung cancer in women are rising. Breast cancer affects one in 11 Canadian women.[124] Therefore, even a small impact of Vitamin E or reducing cancer rates could be of tremendous public health impact.

You have been asked to participate in this trial because you have had some form of heart disease, stroke, blood artery disease or diabetes. These diseases are common and they increase your risk of further complications such as heart attacks or stroke. The Medical Research Council and over 140 Canadian, US and International Hospitals are working to find medications which will reduce the risk of heart attacks and strokes in individuals such as yourself. One promising medication is called Ramipril, which belongs to a class of drugs called ACE-inhibitors and has been shown to be very useful in patients with heart failure. We do not know whether it will be useful in patients like yourself. Another promising, but unproven medication is Vitamin E. We are conducting a study which will be able to tell us with certainty if Ramipril or Vitamin E reduce the risk of heart attacks, stroke and other heart problems.

If you choose to participate in this study, you will have an equal chance of receiving Ramipril or its placebo (an inactive substance) and an equal chance of receiving Vitamin E or placebo. You will take Ramipril (or its placebo) once a day. You will also take one Vitamin E capsule (or its placebo) a day. Ramipril can occasionally cause side effects which are rarely serious but can sometimes be bothersome. The side effects of Ramipril include light headedness, dizziness, cough, nausea or rarely, swelling of the throat. We will carefully observe if those effects occur in you and ensure they are dealt with. Vitamin E is a safe, 100% natural substance and has very few, if any side effects. If side effects occur your doctor may stop or decrease the medication dosage. The treatment may or may not be of personal benefit to you, but the information gathered from the study will be very important in discovering new treatments that could to reduce heart attacks in people like yourselves. You will be one of eight thousand people participating in this trial. Because so many are involved in the trial, we are likely to get a clear answer as to whether Ramipril or Vitamin E work in reducing heart attacks, stroke and other ailments.

After starting the medication, you will be seen at one month and then every six months by a study doctor or nurse. At the visits, information about your medical history will be collected and a brief physical examination will be performed. You will have your blood tested for routine kidney function about three times during the study. Participation in this study will not prolong your usual visits to physician. You will not pay anything for the study drugs, nor for any visits or tests done. Further, you will not be denied any treatment that your doctor believes that you require.

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We will ask for your social insurance number/social security number and your provincial health care number so that the clinic can know if you have needed hospital care. We will also need your pertinent medical information from other hospitals or doctors (such as discharge summaries, CT Scan reports, etc.). This information as well as all other information will be kept strictly confidential and used for medical statistical purposes only. You will never be identified by name in any results.

Your participation in the study is entirely confidential and will not affect any medical care to which you are entitled. An alternative to participating in the study is individualized care by your physician. You are free to refuse to participate or to withdraw from the study at any time without penalty. If you have any questions please contact Dr._____ on telephone number _____. Questions about research related risks can be answered by _____ on telephone number _____.

I agree to participate in the HOPE Study and I have been given a copy of this form.

_____   _____
(Patient signature)   (date)

_____   _____
(Witness signature)   (date)

_____   _____
(Investigator's signature)   (date)

Specific definition of major adverse effects are as follows:

Azotemia: increase in serum creatinine to 200 mEq/L or greater ($\geq$ 2.26 mg/dl).

Hyperkalemia: an increase in serum potassium level greater than 5.5 mEq/L.

Symptomatic hypotension: unexplained syncopal episode or any episode of dizziness or lightheadedness experienced in the upright position, regardless of a blood pressure measurement being taken at the same time.

The recommended management of side effects is as follows:

The side effects listed above and gastrointestinal upset will be dealt with by the individual physician. Other side effects including renal function impairment, angioedema, neutropenia/agranulocytosis and severe neurologic adverse reactions requires reduction in Ramipril, stopping study medication with restarting at a lower dose, or the reduction of other medication such as diuretics or other vasodilators.

SERIOUS ADVERSE EVENTS(SAE)

A   adverse events need not be reported to regulatory agencies. Deaths, primary endpoints and s   idary endpoints are all expected in the study. Only adverse events which in the view of the investigator are unexpected, serious, and believed to be associated with the study treatments will need reporting. Reporting is done by completion of a Serious Adverse Experience (SAE) Form after which details will be obtained by the C3PO. *Based on previous experience, it is expected that less than 1% to 2% of patients will report a SAE during the trial. This corresponds to a total of about 100 such events over 3.5 years or about 30 events per year. Periodic (blinded) tabulation of adverse events by study group will be provided to the independent Data and Safety Monitoring Board. It is expected that this will be provided every 4 months and these "blinded" data will be shared with the regulatory authorities.*

MINOR ADVERSE EVENTS

In addition to serious adverse events as outlined above, information on other events which result in temporary or permanent withdrawal of study medication or a change in dosage will also be recorded at each follow up visit.

MONITORING OF THE STUDY

The study will be monitored to ensure data quality and to facilitate entry of patients into the trial. Monitoring will be done by Hoechst Roussel. All centres will be visited once at the start of the study and once more during the trial. A random 25% of those individuals with a primary endpoint will have chart audits. A random 5% of all individuals not suffering a primary endpoint will have chart audits.

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Appendix E: Draft definition of primary and secondary endpoints.

Primary Endpoints: Cardiovascular Death, Myocardial Infarction and Stroke

Definitions:

1. Cardiovascular Deaths. Any deaths due to myocardial infarction, stroke, pulmonary emboli arrhythmia or other cardiovascular events (i.e. ruptured aorta). This includes sudden deaths without any other documented cause.

2. Myocardial Infarction.

A.   Q-wave MI - presence of one new significant Q-waves ($\geq$ 0.04 seconds duration or 3-4 mm depth and loss in height of ensuing R wave) in at least two leads on the standard 12 lead ECG, and at least one of:

1. Typical symptoms (e.g. chest pain) associated with

and / or

2. Significant elevation of serum enzymes - presence of any one of the following criteria:
a) elevation of CK-MB above the upper limit of normal within 36 hours of onset of acute symptoms of MI.   Total CK at least twice the upper limit of normal for the laboratory that performed the test.
b) SGOT, LDH, or other cardiac enzymes at least twice the upper limit of normal for the laboratory that performed the test with a characteristic pattern.

B. Non Q-wave MI - presence of new and persistent ST changes or T wave changes on the ECG with significant enzyme elevation and/or symptoms of chest pain.

C. Myocardial infarction without ECG changes or minimal ECG changes defined as patient with characteristic symptoms plus significant elevation of cardiac enzymes with characteristic pattern. In such cases the ECG changes may be minimal, transient or non-diagnostic.

D. Silent Q-wave MI - Development of new Q waves in at least 2 adjacent leads.

3. Stroke. Presence of neurological deficits that persist for more than 24 hours. Location and symptoms and severity of stroke will be sought. CT scan or MRI results will also be sought (if done).

On the basics of clinical symptoms, autopsy and/or CT/MRI, strokes are classified as:

A. Definite or probable ischemic stroke (CT, MRI or autopsy exclude haemorrhage).
B. Definite or probable haemorrhagic stroke (CT, MRI or autopsy confirm haemorrhage).
C. Definite stroke, type uncertain (no CT, MRI or autopsy performed).

Secondary Endpoints:

1.   Acute ischemic cardiac syndromes; MI, plus unstable angina, or severe angina requiring emergency CABG or PTCA (i.e. within 7 days of symptom onset).

All cardiovascular revascularization procedures to include CABG surgery, coronary PTCA, carotid endarterectomy (for stenosis of carotid luminal wall, transient ischemic attacks or stroke), peripheral cardiovascular surgery or angioplasty (for limb ischemia), or limb amputation.

3. *Cardiovascular mortality.*

4. *Total Mortality.*

5. *Development of overt nephropathy or dialysis among diabetics.*

6. *Hospitalization for congestive heart failure.*

7. *Cancer by site and morphology.*

Emphasis on data collection will be for the primary endpoints (cardiovascular death, MI and stroke) each of which have a separate detailed form. However, the death certificate and/or discharge summary will be collected on all hospitalizations.

Appendix F: Potential Substudies for HOPE

[NB: it is anticipated that separate funding will be sought for these substudies].

1. Studies of atherosclerosis lesion progression and regression*

    SECURE (Studies to Evaluate Carotid Ultrasound Changes in patients treated with Ramipril and Vitamin E).

2. Assessment of left ventricular mass, function and arrhythmic activity measured by two-dimensional quantitative echocardiography, and Holter monitoring.

3. Assessment of risk factors for atherosclerosis (including conventional risk factors and others, for example antioxidant vitamin levels, insulin levels, Lp(a), fibrinogen and plasminogen activator inhibitor) using a nested case-control study approach*.

4. Assessment of neurohormonal activity (renin angiotensin II, ACE activity) using conventional assay methods.

5. Assessment of Vitamin E levels using deuterium labelled mass spectrometry of samples taken at baseline and during the course of the study.

6. Renal function and microalbuminuria*.

7. Assessment of functional capacity among patients with peripheral cardiovascular disease.

* Separate protocols already developed.

Responsibilities of Investigators at each centre:

Investigators are part of the Canadian (and International) Cardiovascular Collaboration and are responsible for ensuring a successful collaboration. Specific responsibilities include;

1. Familiarization with the protocol.
2. Obtaining local ethical/IRB approval and annual reviewals.
3. Completing forms for regulatory approval
4. Prime responsibilities at each centre for recruitment and follow up of 50 patients.
5. Collection of biological specimens from patients
6. *Maintaining all study records in a safe file and allowing verification by CCC or Hoechst representatives if requested.*
7. Ensuring a suitable replacement for their duties in the event that they leave the centre.
8. Attendance at regional and national meetings of the CCC/Study.

C3PO Responsibilities:

The Canadian Cardiovascular Collaboration Project Office will provide study aids for HOPE, a 24 hour ~emergency line, costs for travel to central and regional meetings (these will include an educational ~ment with educational credits).

Payment Schedule:

To be provided by the HOPE Study:

Randomization of patients	$ 350
Each Follow-Up visit	$ 50
Notification of MI, Stroke, Deaths and Hospitalizations	$ 50

To be provided for by the industry sponsor:

Administrative fee for each monitoring visit	$ 50

Payments will be made on a regular basis after receipt of completed forms (and, where appropriate, supporting documents).

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Appendix H

The H O P E Study Rationale

and Design for Patients with

Diabetes Mellitus

Contents: Page

:cific Objectives Related To Diabetes

n. primary objective of this research is to determine if an ACE-I and/or /Natural Source Vitamin E will protect patients with diabetes from cardiovascular disease.

The specific primary research questions are:
1. In patients with Insulin-Dependent Diabetes Mellitus (IDDM) or Non-Insulin Dependent Diabetes Mellitus (NIDDM) who are ≥ 55 years of age, and who have at least one other cardiac risk factor, does an ACE-I (Ramipril) reduce the occurrence of myocardial infarction, stroke or cardiovascular death?

2. In patients with IDDM or NIDDM who are ≥ 55 years of age, and who have at least one other cardiac risk factor, does Natural Source Vitamin E reduce the occurrence of myocardial infarction, stroke or cardiovascular death?

Secondary questions include:
1. In patients with IDDM or NIDDM who are ≥ 55 years of age, does either an ACE-I or Natural Source Vitamin E decrease the occurrence of other significant cardiovascular events, total cardiovascular mortality or total mortality?

2. In patients with IDDM or NIDDM who are ≥ 55 years of age, does an ACE-I (Ramipril) or Natural Source Vitamin E prevent:
   a) incipient diabetic nephropathy
   b) progression of incipient nephropathy to overt nephropathy needing hospitalization or dialysis deterioration in renal function ..

3. Does an ACE-I or Natural Source Vitamin E:
   a) improve glucose control (HbA1c)
   b) decrease the occurrence of diabetic retinopathy requiring laser therapy, or
   c) decrease the rate of limb amputations and foot infections requiring antibiotics?

4. Analysis of effects amongst all diabetics in the presence or absence of established cardiac disease.

2. Background

1. Annual Cardiovascular Event and Total Mortality Rates In Diabetics

The risk of cardiovascular disease in patients with diabetes mellitus is increased 2-4 fold compared to nondiabetic patients, and is independent of other risk factors including age, smoking, cholesterol elevation, and hypertension; the increased risk is more pronounced in women than in men [101]. The annual rate of cardiovascular disease and mortality in middle-aged diabetic patients has been well-studied. In a cohort study of 5163 diabetic men (age 35-57, follow-up = 12 years) without heart disease, there was a 0.85% annual rate of cardiovascular deaths and 1.6% annual total mortality rate (calculated relative risk = 2.5). In male diabetics with one other risk factor (smoking, hypertension, or elevated cholesterol), the relative risk was 4.8; this excess risk of death increased with the number of risk factors [91]. Another cohort study of NIDDM patients (age > 50, mean follow-up = 5 years) yielded an annualized cardiovascular event rate of 4.5% (3). A third population-based cohort study of 249 patients (median age = 68, mean follow-up = 6.1 years) demonstrated an annualized total mortality rate of 6% and a coronary heart disease mortality rate of 1.8% [90]. Finally, a 5 year study of diabetics aged 45-64 demonstrated an annual mortality rate of 4% [92].

B. Microalbuminuria Increases the Risk of Cardiovascular Disease in Patients with Diabetes

Approximately 15-20% of diabetics [102] have a urinary albumin excretion rate of 30-300 mg/24h or 20-200 micrograms/min (i.e. microalbuminuria or incipient diabetic nephropathy). This abnormality, which may reflect abnormalities in vascular smooth muscle cell function or structure, may be a consequence of one or more of hyperglycemia, protein glycation or genetically acquired abnormalities. It predicts progression to overt nephropathy (urinary albumin excretion rate greater than 300 mg/24h or 200 micrograms/min) in both IDDM and NIDDM; in IDDM, but not necessarily in NIDDM, patients with overt nephropathy will eventually develop end stage renal disease. Microalbuminuria is also associated with a relative risk of cardiovascular mortality of approximately 3 in both IDDM [126] and NIDDM [125,126], compared to normoalbuminuric patients with diabetes, and is an independent predictor of excess mortality in NIDDM [125]. Indeed, in NIDDM, microalbuminuria is more strongly associated with cardiovascular death than with death from end stage renal disease [102]. Moreover, patients with NIDDM who have urinary albumin concentrations of 40-200mg/l have a total and coronary heart disease standardized mortality ratio of 2.4 and 4.1 respectively[125].

C. ACE-I and Cardiovascular Disease in Diabetes

The reasons for suggesting that ACE-I may prevent cardiovascular disease in patients with diabetes are described in detail in the HOPE Study protocol. In addition, ACE-I may decrease insulin resistance and improve glycemic profiles[105,127] and this may decrease atherogenesis and cardiovascular risk. Finally, the well-described salutary effects of ACE-I on incipient and overt diabetic nephropathy (see below) may reflect a reversal of some of the cardiovascular abnormalities in diabetes.

D. Renal Effects of ACE-I in Diabetes

ACE-I reduce the degree of albuminuria in diabetic patients with both overt and incipient nephropathy [103,128,129]. In contrast to most other antihypertensive agents, this reduction is independent of any blood pressure-lowering effect [130] and is observed in normotensive as well as hypertensive patients. Furthermore, in one trial of 409 patients with IDDM and overt nephropathy in whom blood pressure was controlled by other agents, ACE-I decreased the risk of the composite of death, dialysis and renal transplantation[131].

Most of these ACE-I studies have been done in young patients with microalbuminuria; indeed a large number have been restricted to young patients with IDDM, who are at high risk for progression of diabetic nephropathy to end stage renal disease. The clinical impact of ACE inhibition in older diabetic patients with microalbuminuria, who are likely to have other, nondiabetic causes of renal dysfunction and proteinuria, and who have a lower risk of end stage renal disease is therefore unclear. Moreover, as noted above, these older microalbuminuric patients are much more likely to die from cardiovascular disease than significant renal disease.

At present, there is no evidence that reducing microalbuminuria by any therapy, including ACE-I, will decrease the risk of cardiovascular disease[125] in these patients. Moreover, the routine use of ACE-I in normotensive patients with diabetes exposes them to the increased cost and risk of adverse effects associated with these drugs.

E. Renal Effects of Other Antihypertensive Agents in Diabetes

Any antihypertensive agent which reduces the blood pressure of hypertensive diabetic patients will decrease microalbuminuria and the progression of overt nephropathy. Aside from ACE-I, there is evidence that two of the calcium channel blockers (verapamil and diltiazem) may also reduce microalbuminuria independent of blood pressure[128,132].

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.1. potential role for Natural Source Vitamin E in prevention of cardiovascular disease in general is discussed in the HOPE protocol. Diabetics have small, dense LDL, low HDL, depletion of ascorbic acid and glycation of LDL, all of which enhance oxidation[78,106-7]. Thus antioxidants may be of benefit in diabetics at risk of cardiovascular disease.

G. Summary

Patients with diabetes mellitus are at high risk for cardiovascular disease, which can cause significant morbidity and mortality. Although there is reason to believe that this risk may be significantly decreased by both an ACE-I and Natural Source Vitamin E, this is still uncertain. The HOPE study will test this hypothesis and allow a reliable estimate of the size of benefit of these drugs.

Although microalbuminuria (incipient nephropathy) is an important risk factor for cardiovascular disease in diabetes, there is no evidence that reducing it will decrease the cardiovascular risk. There is evidence, however, that ACE-I will decrease mortality and significant morbidity in IDDM patients with overt nephropathy - because of this, both IDDM and NIDDM patients with overt nephropathy (either on the basis of past history or urine dipstick showing ≥ 1 plus proteinuria) will be excluded from the trial.

3. Study Design

A randomized, double blind placebo-controlled factorial design will be used to simultaneously study the effects of an ACE-I and Natural Source Vitamin E. Patients with diabetes who meet the inclusion and exclusion criteria will be randomly allocated to take 2 study medications once daily – Natural e Vitamin E or placebo and Ramipril or placebo. They will be followed every 6 months for up o 5 months and the occurrence of cardiovascular events, deaths or hospitalizations will be recorded.

4. Eligible Diabetic Patients

Patients with both IDDM and NIDDM who are at increased risk for cardiovascular disease will be studied. Two groups of diabetic patients will be included in the HOPE trial - diabetic patients with a history of cardiovascular disease as defined in the HOPE protocol (page 8), and diabetic patients without a history of cardiovascular disease who have at least one other cardiac risk factor.

A. Inclusion Criteria
1. Patients diagnosed with IDDM or NIDDM
2. Age ≥ 55
3. Coronary disease, peripheral vascular or cerebrovascular disease (defined in HOPE protocol) OR at least one of the following:
   a) hypertension (BP > 160 systolic or > 90 diastolic or on treatment)
   b) total cholesterol > 5.2 mmol/l (> 200 mg/dl)
   c) HDL < 0.9 mmol/l (< 35 mg/dl)
   d) currently smoking
   e) known microalbuminuria (urinary albumin excretion 20-200 micrograms/minute)
   f) with any evidence of previous vascular disease
B. All patients must provide written, informed consent.

C. Exclusion Criteria (see protocol)

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.

i. 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.

ii. Cardiovascular diseases:

1. Ejection fraction < 40% (only if known)

2. Hemodynamically significant primary valvular or outflow tract obstruction (eg. mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve).

3. Constrictive pericarditis.

4. Complex congenital heart disease.

5. Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia are not an exclusion criterion).

6. Planned cardiac or other vascular surgery or angioplasty within 3 months (patient may be reconsidered for the trial after the procedure).

7. Uncontrolled hypertension.

8. Cor pulmonale.

9. Heart transplant recipient.

iii. Other conditions:

1. Significant renal disease defined as:
   a) renal artery stenosis
   b) creatine 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

2. Any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation.

3. Patient is simultaneously taking another experimental drug.

5. Additional Data Collection in Diabetics

Patients who meet the eligibility criteria and have no exclusion criteria such as overt nephropathy may be randomized into HOPE. The following additional information will be collected in all diabetics during the Run-In Phase.

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. all diabetic patients an additional urine collection for microalbuminuria will be drawn and sent to a central lab. *At one year central testing will occur, and at years 2, 3 and 4 local testing will occur.* ---

The following additional information on all diabetics will be collected during the Follow-up:
1) Glycated hemoglobin;
2) A history of laser therapy for retinopathy, limb ulcers/infections, amputations, hospitalizations for nephropathy and ketoacidosis.

In diabetic patients from diabetic clinics, urine collection for microalbuminuria will be done at a central lab at baseline, one year and the end of the study. Urine will be tested by dipstick anually and if the results show overt nephropathy or $\geq$ 1+ proteinuria or urinary albumin excretion >200 micrograms/minute, then the collection is repeated locally. If this repeat sample confirms overt nephropathy the patient may be withdrawn from the Ramipril arm of the study, depending on the judgement of the investigator.

6. Co-Intervention

Subjects will be explicitly told that they should not be taking any ACE-I or Vitamin E preparations (other than the study medications). This will be reinforced by physicians at follow-up visits, and will be communicated to family physicians.

Physicians may choose to treat hypertensive patients with diltiazem or verapamil, especially in the presence of microalbuminuria. Second line drugs for hypertension include low dose diuretics or alpha ckers (doxazosin). Patients with microalbuminuria may be put on a low protein diet; extra attention glycemic control may also be appropriate.

7. Endpoints, Sample Size, Analyses and Feasibility

These are described in the HOPE protocol (pages 8, 14-21). Glycated hemoglobin and creatinine will be done locally. Briefly, we expect to enroll between 3,000 and 4,000 patients with diabetes. Assuming an annual event rate of 6% to 7% (i.e. total events of 21% to 24.5%) for 3.5 years, we expect to have 80% power to detect risk reductions of 18% or 19% in the primary endpoint of cardiovascular death, myocardial infarction or stroke.

Journal of Medicine

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

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS*

ABSTRACT

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

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

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

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

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

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

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

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The writing group (Salim Yusuf, D.Phil., Peter Sleight, D.M., Janice Pogue, M.Sc., Jackie Bosch, M.Sc., Richard Davies, Ph.D., and Gilles Dagenais, M.D.) assumes responsibility for the overall content and integrity of the manuscript.

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

METHODS

Study Design

The double-blind, two-by-two factorial, randomized Heart Outcomes Prevention Evaluation study evaluated ramipril and vitamin E in 9541 patients. A substudy compared a low dose of ramipril (2.5 mg per day) with a full dose (10 mg per day) or placebo; there were 244 patients in each group. The results of the placebo-controlled study of full-dose ramipril are given here. The effects of vitamin E are reported in a companion paper.[3] The design of the study has been reported previously[4]; a brief summary follows.

Patients

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

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

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

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

Organization of the Study

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

Outcomes

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

Statistical Analysis

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

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

RESULTS

Characteristics of the Patients

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

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

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

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

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

TABLE 2. REASONS FOR DISCONTINUATION OF TREATMENT.

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

*The categories are not mutually exclusive.

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

Compliance

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

Blood Pressure

The mean blood pressure at entry was 139/79 mm Hg in both groups. The mean blood pressure was 133/76 mm Hg in the ramipril group and 137/78 mm Hg in the placebo group at one month, 135/76 mm Hg and 138/78 mm Hg, respectively, at two years, and 136/76 mm Hg and 139/77 mm Hg, respectively, at the end of the study.
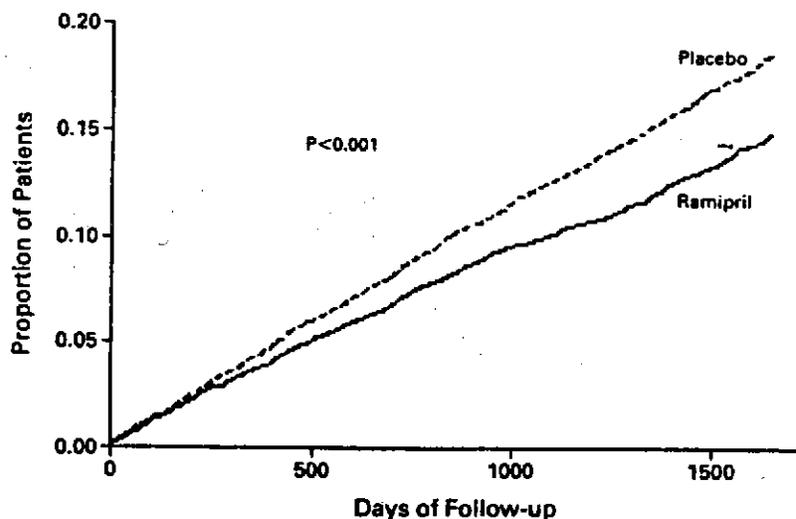
Figure 1. Kaplan–Meier Estimates of the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes in the Ramipril Group and the Placebo Group.

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

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

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

*CI denotes confidence interval.

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

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

§All patients with this outcome are included.

Primary Outcomes and Deaths from Any Cause

A total of 651 patients in the ramipril group (14.0 percent) died of cardiovascular causes or had a myocardial infarction or stroke, as compared with 826 patients in the placebo group (17.8 percent; relative risk, 0.78; 95 percent confidence interval, 0.70 to 0.86; P<0.001) (Fig. 1 and Table 3). Treatment with ramipril also reduced the risk of the primary outcome among patients who were receiving vitamin E (338 patients who received both agents reached the end point, as compared with 421 patients who received only vitamin E; relative risk, 0.79; P=0.001) or its

placebo (313 patients who received ramipril and the vitamin E placebo reached the end point, as compared with 405 patients who received the vitamin E placebo alone; relative risk, 0.76; P<0.001; P=0.79 for the comparison of the two relative risks). In addition, there were significant reductions in risk when each of these end points was analyzed separately: 282 patients in the ramipril group died of cardiovascular causes, as compared with 377 patients in the placebo group (relative risk, 0.74; 95 percent confidence interval, 0.64 to 0.87; P<0.001); 459 patients in the ramipril group had a myocardial infarction, as compared with

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

*CI denotes confidence interval.

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

‡These events were centrally adjudicated.

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

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

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

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

Secondary and Other Outcomes

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

Subgroup Analysis

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

Temporal Trends

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

	No. of Patients	Incidence of Composite Outcome in Placebo Group	
Overall	9297	17.8	
Cardiovascular disease	8162	18.7	
No cardiovascular disease	1135	10.2	
Diabetes	3577	19.8	
No diabetes	5720	16.5	
Age <65 yr	4169	14.2	
Age ≥65 yr	5128	20.7	
Male sex	6817	18.7	
Female sex	2480	14.4	
Hypertension	4355	19.5	
No hypertension	4942	16.3	
History of coronary artery disease	7477	18.6	
No history of coronary artery disease	1820	14.2	
Prior myocardial infarction	4892	20.9	
No prior myocardial infarction	4405	14.2	
Cerebrovascular disease	1013	25.9	
No cerebrovascular disease	8284	16.7	
Peripheral vascular disease	4051	22.0	
No peripheral vascular disease	5246	14.3	
Microalbuminuria	1956	26.4	
No microalbuminuria	7341	15.4	

0.6   0.8   1.0   1.2

Relative Risk in Ramipril Group
(95% confidence interval)

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

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

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

DISCUSSION

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

Our findings indicate that the spectrum of patients who would benefit from treatment with an angio-tensin-converting–enzyme inhibitor is quite broad and complement those of previous studies of patients with low ejection fractions[5] or heart failure and acute myocardial infarction.[7] The underlying rationale for our study was that the inhibition of angiotensin-converting enzyme would prevent events related to ischemia and atherosclerosis, in addition to those related to heart failure and left ventricular dysfunction (although patients with these two conditions were excluded from the study). We therefore included a broad range of patients with any manifestation of coronary artery disease (e.g., a history of myocardial infarction or revascularization, unstable angina, or stable angina), a history of cerebrovascular disease or peripheral vascular disease, or diabetes and one cardiovascular risk factor, and ramipril was beneficial in all these subgroups.

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

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

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

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

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

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

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

APPENDIX

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outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators *

Summary

Background Diabetes mellitus is a strong risk factor for cardiovascular and renal disease. We investigated whether the angiotensin-converting-enzyme (ACE) inhibitor ramipril can lower these risks in patients with diabetes.

Methods 3577 people with diabetes included in the Heart Outcomes Prevention Evaluation study, aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and who were not taking ACE inhibitors, were randomly assigned ramipril (10 mg/day) or placebo, and vitamin E or placebo, according to a two-by-two factorial design. The combined primary outcome was myocardial infarction, stroke, or cardiovascular death. Overt nephropathy was a main outcome in a substudy.

Findings The study was stopped 6 months early (after 4·5 years) by the independent data safety and monitoring board because of a consistent benefit of ramipril compared with placebo. Ramipril lowered the risk of the combined primary outcome by 25% (95% CI 12–36, p=0·0004), myocardial infarction by 22% (6–36), stroke by 33% (10–50), cardiovascular death by 37% (21–51), total mortality by 24% (8–37), revascularisation by 17% (2–30), and overt nephropathy by 24% (3–40, p=0·027). After adjustment for the changes in systolic (2·4 mm Hg) and diastolic (1·0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (12–36, p=0·0004).

Interpretation Ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes. The cardiovascular benefit was greater than that attributable to the decrease in blood pressure. This treatment represents a vasculoprotective and renoprotective effect for people with diabetes.

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Introduction

People with diabetes mellitus are at high risk of cardiovascular disease. Epidemiological studies show that the risk of cardiovascular mortality is two to three times higher in men with diabetes and three to five times higher in women with diabetes than in people without diabetes.[1,2] The age-adjusted prevalence of coronary heart disease in white adults who have diabetes is about 45%, compared with about 25% in individuals without diabetes,[3] and cardiovascular disease accounts for about 70% of all deaths in people with diabetes mellitus.[4]

The presence of other risk factors increases the risk of cardiovascular disease in people with diabetes mellitus. The absolute annual risk of fatal and non-fatal cardiovascular disease in middle-aged and elderly people with type 2 diabetes is 4–5%.[5–13] Despite decreases in the incidence of heart disease in the general population, the decline is much smaller in people with type 2 diabetes, and may even be rising in women with diabetes.[13]

Experimental studies, epidemiological studies, and clinical trials suggest that inhibitors of angiotensin-converting enzyme (ACE) may delay or prevent cardiovascular outcomes. For patients with diabetes, such benefit has been seen after acute myocardial infarction,[14] in the presence of hypertension,[15–19] and in the presence of a low ejection fraction or heart failure.[20] ACE inhibitors may also prevent overt nephropathy and other microvascular outcomes in patients with type 1 or type 2 diabetes.[17,21,22]

Although studies suggest that ACE inhibitors may prevent or delay serious events in some subgroups, their role in a broader group of people with diabetes who are at high risk of cardiovascular events remains unknown. The Heart Outcomes Prevention Evaluation (HOPE) study investigated whether the addition of the ACE inhibitor ramipril to the current medical regimen of high-risk patients with diabetes mellitus can lower the risk of cardiovascular events. In the microalbuminuria, cardiovascular, and renal outcomes (MICRO) HOPE substudy, the effect of this intervention on the risk of overt nephropathy was investigated. We present here the results from these two studies for patients with diabetes mellitus.[22]

Methods

Participants

The HOPE and MICRO-HOPE study protocol has been published.[23,24] Briefly, people with and without diabetes were recruited, who were aged 55 years or older, and who had a history of cardiovascular disease (coronary artery disease, stroke, or peripheral vascular disease) or diabetes plus at least

Clinical characteristics

Mean (SD) body-mass index (kg/m²)	28·9 (4·8)	28·6 (4·7)
Mean (SD) heart rate (beats/min)	72·3 (11·4)	72·5 (11·0)
Mean (SD) systolic blood pressure (mm Hg)	141·7 (19·6)	142·3 (19·5)
Mean (SD) diastolic blood pressure (mm Hg)	80 (10·6)	79·3 (10·7)
Mean (SD) ankle/arm systolic pressure (mm Hg)	0·97 (0·19)	0·96 (0·18)
Mean (SD) waist/hip ratio	0·93 (0·09)	0·93 (0·08)
Mean (SD) waist circumference (cm)	99·9 (12·7)	99·6 (12·4)
Microalbuminuria	553 (31%)	587 (33%)
Mean (SD) HbA₁c (%)*	123 (30)	124 (32)
Mean (SD) serum creatinine (μmol/L)*	93·8 (22·3)	94·0 (27·6)
Mean duration of diabetes (years)	11·1 (10·2)	11·8 (10·7)
Type 2 diabetes	1774 (98%)	1722 (97%)
History of hypertension	1045 (58%)	951 (54%)
Documented cholesterol >5·2 mmol/L	1174 (65%)	1161 (66%)
Current smoker	274 (15%)	270 (15%)
Previous coronary artery disease	1046 (58%)	1093 (62%)
Previous stroke/endarterectomy	124 (7%)	150 (8%)
Previous peripheral vascular disease	311 (17%)	361 (20%)
No previous cardiovascular disease	604 (33%)	515 (29%)
Hyperglycaemic control		
Dietary therapy alone	331 (18%)	300 (17%)
Insulin therapy alone	432 (24%)	482 (27%)
Oral agents alone	957 (53%)	895 (51%)
Insulin plus oral agents	88 (5%)	92 (5%)
Other drugs		
Acetylsalicylic acid	982 (54%)	998 (56%)
Diuretics	350 (19%)	350 (20%)
β-blockers	510 (28%)	505 (29%)
Calcium-channel blockers	776 (43%)	801 (45%)
Hypolipidaemic drugs	409 (23%)	390 (22%)

*Measured at local laboratories; HbA₁c is reported as percentage above upper limit of normal for local laboratory.

Table 1: Baseline characteristics of participants with diabetes

Cough	133 (7%)	37 (2%)
Hypotension/dizziness	30 (2%)	24 (1%)
Angioedema	5 (0·3%)	1 (0·1%)
Hypertension	60 (3%)	100 (6%)
Clinical event	138 (8%)	171 (10%)
Other	511 (28%)	503 (28%)
ACE-inhibitor use		
Non-study use at any time*	366 (20%)	431 (24%)
Reasons for use		
Heart failure	116 (6%)	133 (8%)
Proteinuria	57 (3%)	54 (3%)
Hypertension	123 (7%)	173 (10%)
Other	181 (10%)	191 (11%)

*Categories not mutually exclusive.

Table 2: Reasons for stopping treatment

prevented these outcomes, as well as microalbuminuria or overt nephropathy, in participants with diabetes.[23,24] All primary and secondary outcomes were documented on separate forms and centrally assessed by the event committee (who were unaware of the participants' assigned treatments) according to standard definitions.[13]

Diabetes status and other demographic and clinical variables were established by history and physical examination at each visit. Participants were judged to have type 2 diabetes if they developed diabetes at age 30 years or older or were not taking insulin. We defined a history of hypertension as the taking of drugs to treat hypertension or blood pressure at recruitment higher than 160 mm Hg systolic or 90 mm Hg diastolic. Glycated haemoglobin (HbA₁c) and serum creatinine were assayed for participants with a history of diabetes in each study centre's local laboratory. Results for HbA₁c were expressed as the percentage higher than the upper limit of normal for the assay used. Any admissions for hypoglycaemia were recorded.

As part of the MICRO-HOPE substudy, urinary albumin excretion was measured at baseline, 1 year, and study end (4·5 years) by measuring the albumin/creatinine ratio in a first morning urine sample. Urine was stored at −70°C. The albumin/creatinine ratio was measured in four different laboratories during the study (in Canada, UK, Argentina, and Brazil) by different assay systems.[22] Microalbuminuria was defined in 1993 as a ratio of 2 mg/mmol or higher in men and women.[22]

Participants whose albumin/creatinine ratio was higher than 36 mg/mmol after randomisation were asked to provide a 24 h urine sample that was assayed in their local laboratory for total protein or urinary albumin; assays were chosen according to availability at each clinical site. Overt nephropathy was diagnosed if the 24 h urine albumin was 300 mg or more per day, if the 24 h urine total protein excretion was 500 mg or more per day, or if the measured albumin/creatinine ratio was higher than 36 mg/mmol and no 24 h urine result was available (ie, if there was evidence of clinical proteinuria). The measurements of actual daily excretion of albumin or protein for all 24 h urine collections were sent to the project office and all cases of overt nephropathy were centrally assessed.

Statistical analysis

The HOPE study was designed to recruit up to 4000 participants with diabetes. With the assumption of a constant event rate in participants with diabetes of 5% per year, this sample size would provide 90% power (two-sided $\alpha=0·05$) to detect an 18% relative risk reduction in the rate of myocardial infarction, stroke, or cardiovascular death during the planned mean follow-up period of 5 years. The study was ended 6 months early on the recommendation of the independent data safety and monitoring board. Therefore, we report results for a median follow-up period of 4·5 years.

one other cardiovascular risk factor (total cholesterol >5·2 mmol/L, HDL cholesterol ≤0·9 mmol/L, hypertension, known microalbuminuria, or current smoking). Key exclusion criteria were dipstick-positive proteinuria or established diabetic nephropathy, other severe renal disease, hyperkalaemia, congestive heart failure, low ejection fraction (<0·4), uncontrolled hypertension, recent myocardial infarction or stroke (<4 weeks), and use of or hypersensitivity to vitamin E or ACE inhibitors.[23] The study was done in 19 countries in North and South America and in Europe. The HOPE study protocol was approved by each institution's review board or ethics committee, and all participants provided written, informed consent.

Eligible participants were included who completed a run-in period, during which they received 2·5 mg ramipril daily for 7–10 days, followed by matching placebo for 10–14 days, who were at least 80% compliant, tolerated the drug without side-effects, and maintained a serum creatinine concentration of 200 μmol/L or lower and potassium concentration of 5·5 mmol/L or lower.

Study design

The study had a two-by-two factorial design with randomisation of participants to 10 mg ramipril or placebo taken once daily in the evening and 400 IU vitamin E or placebo daily. Follow-up visits were at 1 month and then every 6 months.

The combined primary endpoint was the development of myocardial infarction, stroke, or cardiovascular death. Secondary endpoints were total mortality, admission to hospital for congestive heart failure or unstable angina, cardiovascular revascularisation, or development of overt nephropathy. Other outcomes were any heart failure, worsening angina, and the development of diabetes in people with no history of the disorder. A preplanned analysis in the HOPE and MICRO-HOPE studies was to find out whether ramipril delayed or

	Ramipril	Placebo	RRR (95% CI)	p value
Cardiovascular death	112 (6·2%)	172 (9·7%)	37% (21 to 51)	0·0001
Secondary outcomes				
Total mortality	196 (10·8%)	248 (14·0%)	24% (8 to 37)	0·004
Unstable angina*	213 (11·8%)	207 (11·7%)	0 (−21 to 17)	0·99
Heart failure*	81 (4·5%)	79 (4·5%)	1% (−34 to 28)	0·93
Revascularisation	254 (14·0%)	291 (16·4%)	17% (2 to 30)	0·031
Overt nephropathy†	117 (6·5%)	149 (8·4%)	24% (3 to 40)	0·027
Other outcomes				
Any heart failure	198 (11·0%)	236 (13·3%)	20% (4 to 34)	0·019
Transient ischaemic attacks	80 (4·4%)	104 (5·9%)	26% (1 to 45)	0·04
Worsening angina	363 (20·1%)	397 (22·4%)	13% (0 to 24)	0·057
Laser therapy‡	170 (9·4%)	186 (10·5%)	22% (−9 to 28)	0·24
Dialysis	10 (0·5%)	8 (0·5%)	−20% (−205 to 53)	0·70
Overt nephropathy,† laser therapy, or dialysis	273 (15·1%)	312 (17·6%)	16% (1 to 29)	0·036

*Requiring admission. †Based on positive 24 h urine collection or albumin/creatinine ratio >36 mg/mmol if no 24 h urine available. ‡Laser therapy for retinopathy.

Table 3: Clinical outcomes for ramipril and placebo groups

We report only analyses done by intention to treat. Analyses were stratified according to randomisation to vitamin E or placebo by Cox's regression, to account for the factorial design. Results are reported as the relative risk reduction (95% CI), defined as 1 minus the relative hazard. Kaplan-Meier curves were used to estimate survival and were compared by log-rank test. Changes in continuous variables (ie, HbA$_{1c}$, albumin/creatinine ratio, blood pressure, serum creatinine) from baseline values, by treatment group, were analysed by ANOVA, adjusted for the baseline value. Albumin/creatinine ratios were transformed to account for non-normality and values were adjusted for the laboratories in which ratios were measured. Statistical tests for interaction were done with Cox's regression to assess the effect on the primary outcome of diabetes type, diabetes treatment, history of previous cardiovascular events, and presence of microalbuminuria or a history of hypertension at randomisation, and a similar approach was used to assess the effect of the presence of baseline microalbuminuria on the

Results

Of all 9541 participants in the HOPE study, 3654 (39·3%) had diabetes at randomisation. 77 people who participated in another substudy in which they received only 2·5 mg ramipril or placebo were excluded from the analysis. Therefore, 3577 people with diabetes were included. The mean age was 65·4 years, 1322 (37%) were women, and 1996 (56%) had a history of hypertension. Baseline characteristics of participants in the ramipril and placebo groups were similar (table 1).

Of surviving participants at 1 year, 1486 (84%) patients in the ramipril group and 1516 (88%) in the placebo group were still taking study drugs, as were 1045 (65%) and 992 (66%), respectively, at the end of the study. At 4 years, 184 (12%) participants initially assigned ramipril and 220 (15%) initially assigned placebo were taking open-label ACE inhibitors. Non-medical reasons for stopping the study drug are shown in table 2. The only notable side-effect that led to excess discontinuation of study drug was cough, which was 5% more frequent among participants taking ramipril than among those taking placebo. The rate of admission to hospital because of hypoglycaemia did not differ between the ramipril and placebo groups (2 vs 2%), nor did the mean change in serum creatinine concentration.

The rate of the combined primary outcome of myocardial infarction, stroke, or cardiovascular death was significantly lower in the ramipril group than in the placebo group (relative risk reduction 25% [95% CI 12–36], p=0·0004). When the outcome components were analysed separately, the rates were also lowered significantly in the ramipril group, as were the secondary
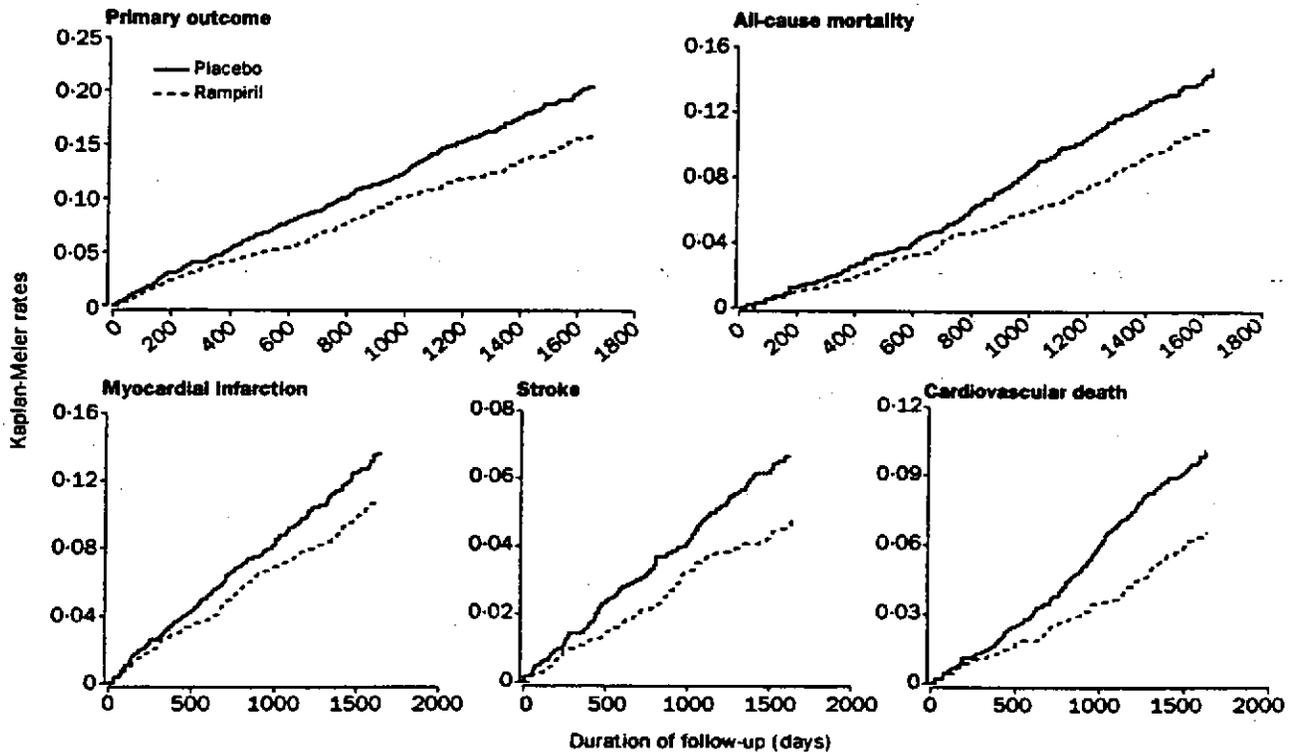
Figure 1: Kaplan-Meier survival curves for participants with diabetes

Subgroup	N	%
Microalbuminuria positive	1140	28.6
Microalbuminuria negative	2437	15.5
Cardiovascular disease	2458	23.9
No cardiovascular disease	1119	9.9
Dietary hyperglycaemic control	631	19.0
Insulin	1852	19.3
Oral hyperglycaemics	914	21.6
Insulin plus oral hyperglycaemics	180	18.5
Type 1 diabetes	81	25.5
Type 2 diabetes	3496	19.7
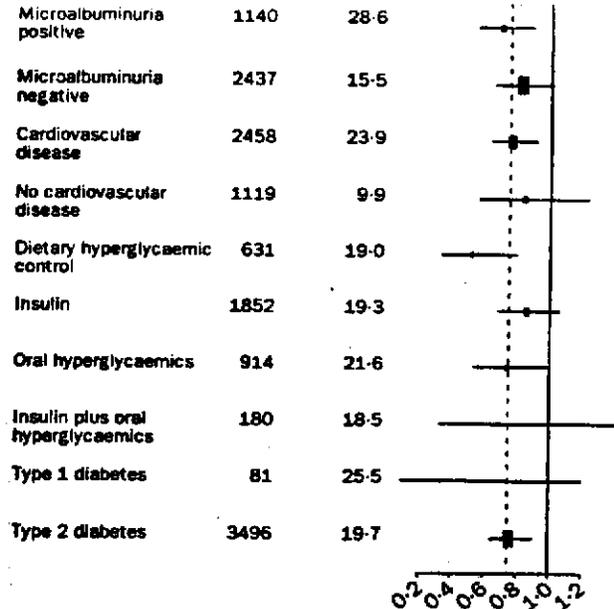
Figure 2: Effect of ramipril on combined primary outcome in subgroups

Size of symbol is proportional to number of participants in subgroup; broken line=overall relative risk.

Figure 3: Effect of ramipril on degree of albuminuria

Geometric mean albumin/creatine ratio of all participants with available 24 h urine collection is shown. Adjusted for laboratory in which assays done.

outcomes (table 3, figure 1). Ramipril lowered the risk of the primary outcome by 16% (−14 to 39, p=0.26) after 1 year, and significantly by 26% (6–41, p=0.011) after 2 years. This effect was maintained at each subsequent year of follow-up.

Ramipril's benefit was noted irrespective of whether participants had a history of cardiovascular events (p for interaction=0.91), hypertension (p for interaction=0.93), or microalbuminuria (p for interaction=0.34), whether or not participants had type 1 or type 2 diabetes (p for interaction=0.32), and irrespective of current treatment for hyperglycaemia (p for interaction=0.51). The effect of ramipril in different diabetes-related subgroups is shown in figure 2.

Compared with baseline, mean absolute HbA_{1c} values increased by absolute amounts of 1.5% higher than the upper limit of normal in the ramipril group and 3.4% in the placebo group at 1 year (p=0.04). They fell by 0.1% among participants taking ramipril and rose by 2.2% among participants taking placebo at 2 years (p=0.016); the change from baseline in HbA_{1c} was the same for both groups at subsequent visits and at the end of the study (2.2% for ramipril and 2.0% for placebo respectively; p=0.8).

Blood pressure (mm Hg)	Baseline	Change at 1 month	Change at 2 years	Change at final visit
Systolic				
Ramipril	141.7	−5.3	−2.7	−1.9
Placebo	142.3	−1.3*	0.6*	0.55†
Diastolic				
Ramipril	80.0	−2.6	−2.6	−3.3
Placebo	79.3	−0.3*	−1.05*	−2.3‡

*p=0.0001. †p=0.0002. ‡p=0.008. p values for difference in change from baseline (ramipril vs placebo).

Table 4: Change in blood pressure with ramipril and placebo

Blood pressure decreased slightly more among participants on ramipril than among those on placebo. By the end of the study, systolic blood pressure had fallen by 1.92 mm Hg and risen by 0.55 mm Hg in participants on ramipril and placebo, respectively (p=0.0002); diastolic blood pressure had fallen by 3.30 mm Hg and 2.30 mm Hg in the ramipril and placebo groups (p=0.008; table 4). After adjustment for changes in blood pressure, ramipril had the same effect on the primary outcome as that before adjustment (relative risk reduction 25% [12–36], p=0.0004).

Albumin/creatinine ratio was measured in 3498 (98%) participants at baseline, 2914 (83%) of 3511 at 1 year, and 2671 (86%) of 3106 at the end of the study. During follow-up, 345 (10%) participants developed an albumin/creatinine ratio of more than 36 mg/mmol and were asked to provide a 24 h urine collection to test for overt nephropathy. Results were available for 295 (85.5%) individuals. 117 (7%) participants on ramipril and 149 (8%) on placebo developed overt nephropathy (24% [3–40], p=0.027). When a more stringent definition of overt nephropathy was used and the analysis was restricted to people in whom 24 h urine results were available, 100 (6%) participants in the ramipril group and 124 (7%) in the placebo group were affected (22% [−2 to 40], p=0.07). Restriction of the definition of overt nephropathy even further to include only people who had a positive 24 h urine collection and who reported a history of laser therapy for retinopathy gave similar results (25% [−39 to 59], p=0.36).

225 (20%) participants with and 41 (2%) without baseline microalbuminuria developed overt nephropathy (relative risk 14.0 [10–19], p<0.0001). Ramipril lowered the risk of overt nephropathy in participants who did and did not have baseline microalbuminuria (p for interaction 0.51). Moreover, ramipril treatment led to a lower albumin/creatinine ratio than placebo at 1 year and at the end of the study end (figure 3). In participants without baseline microalbuminuria, the risk of new microalbuminuria was non-significantly reduced (relative risk reduction 9% [−4 to 20], p=0.17).

The effect of ramipril on a reported history of new laser therapy for diabetic retinopathy, and on a reported history of renal dialysis are shown in table 3. Ramipril reduced the risk of a combined microvascular outcome of overt nephropathy, dialysis, or laser therapy by 16% (1–29, p=0.036).

whether participants had a history of cardiovascular events, hypertension, or microalbuminuria, were taking insulin or oral antihyperglycaemic agents, or had type 1 or type 2 diabetes mellitus. The study had, however, low power to detect different effects in the subgroups. Since adherence to ramipril was 65% at the last visit, our results may underestimate the benefit that would have been seen with higher adherence.

Ramipril also lowered the risk of overt nephropathy, renal failure, or laser therapy. It had no long-term effect on glycaemic control.

When the major cardiovascular and microvascular events are taken into account, 15 high-risk people with diabetes would have to be treated with ramipril for a median of 4·5 years to prevent one individual from having a myocardial infarction, stroke, cardiovascular death, admission to hospital for heart failure, a revascularisation procedure, development of overt nephropathy, laser therapy for retinopathy, or renal dialysis.

We assessed blood pressure by cuff pressures, which is the normal approach in clinical practice and large randomised trials. We did not monitor ambulatory blood pressure and, therefore, excess overnight hypertension in the placebo group cannot be excluded. The risk reduction for cardiovascular events was, however, greater than would be expected from the observed mean difference in blood pressure between groups, which supports the results of the regression model showing that the effect of ramipril was much greater than can be attributed to its effect on blood pressure. For example, in the UK Prospective Diabetes Study (UKPDS),[15] mean differences between groups in systolic and diastolic blood pressures of 10 mm Hg and 5 mm Hg, respectively, lowered the risk of myocardial infarction by 21% and stroke by 44%. Similarly, in participants with diabetes in the Systolic Hypertension in the Elderly (SHEP) study,[26] a decrease in systolic and diastolic pressures of 10 mm Hg and 2 mm Hg, respectively (using a diuretic-based approach), reduced the risk of cardiovascular events by up to 34%. By contrast, in the HOPE study the differences in systolic and diastolic blood pressures were only slight at 2·2 mm Hg and 1·4 mm Hg, yet the decreases in risk of myocardial infarction and stroke were similar to those seen in UKPDS.

These considerations suggest that the observed benefits of ramipril may be due largely to a protective effect of ACE inhibitors on the arterial wall.[27] Angiotensin II is a powerful direct vasoconstrictor, and promotes vascular smooth-muscle growth, possibly by inducing various proto-oncogenes and growth factors. It may also promote plaque rupture, possibly by stimulating release of endothelin, inhibiting fibrinolyis, and promoting thrombosis.[27] Bradykinin is a direct vasodilator and also promotes release of the vasodilating substances nitric oxide and prostacyclin. The effect of ACE inhibitors may, therefore, be mediated by the lowering of angiotensin-II concentrations and the increasing of bradykinin concentrations.

The observed effect of ramipril on cardiovascular outcomes are consistent with the results of other trials of

up those taking captopril had a 14% (95% CI 1–26) lower rate of myocardial infarction, stroke, or cardiovascular death than those taking diuretics and β-blockers.[16] Similarly, the UKPDS study showed that the lowering of blood pressure with captopril or atenolol clearly decreased the risk of cardiovascular and microvascular events, but found no benefit of captopril over atenolol.[17] Because 758 participants were randomly assigned captopril or atenolol and the event rate was 34%, the study had high power (about 80%) to detect large differences (eg, 30% differences in relative risk). However, differences in benefit between two active therapies are likely to be smaller than those between active treatments and placebo, and may typically be about 10%. Such differences could, therefore, have been missed. The results of other trials have supported a beneficial cardiovascular effect of ACE inhibitors over calcium-channel blockers, although this was not the primary aim of these studies.[18,19,28].

For microvascular outcomes, our results are consistent with previous observations in individuals with type 1 and type 2 diabetes that ACE inhibitors lower the risk of diabetic nephropathy[29,30] and renal failure,[31] and are consistent with previous reports suggesting that ACE inhibition with lisinopril reduces the risk of diabetic retinopathy in normotensive people with type 1 diabetes.[21] The findings are limited by the fact that the albumin/creatinine ratio was measured in four different laboratories, and that 24 h urine collections to confirm the presence of overt nephropathy were done in many different laboratories. Nevertheless, we adjusted analysis of the albumin/creatinine ratio for the laboratory in which it was measured and all 24 h urine results were adjudicated centrally. Moreover, a beneficial effect of ramipril was seen despite the increased variability because of the different laboratories, which would lead to an underestimate of the effect of ramipril on overt nephropathy.

The results are also limited by the fact that overt nephropathy was not confirmed by a renal biopsy—a point that may be important because of observations of a high rate of non-diabetic renal disease in people with type 2 diabetes.[32,33] Nevertheless, a report and review of morphological data from several studies suggests that clinical proteinuria is a reliable marker for overt diabetic nephropathy in people with type 2 diabetes.[34] Moreover, our results were unchanged after use of a more stringent definition for diabetic nephropathy (a positive 24 h urine collection plus a history of retinopathy that was treated with laser therapy). In addition, epidemiological studies show a high rate of renal failure in people with type 2 diabetes and overt nephropathy defined on the basis of clinical proteinuria alone.[35] For retinopathy alone, these results are clearly limited by the fact that retinal photographs were not taken. Nevertheless, a history of laser therapy for diabetic retinopathy is likely to be highly specific, but not sensitive, for serious diabetic retinopathy.

Because the HOPE study was not designed to be a trial of the effect of lowering blood pressure, only general comparisons can be made with other studies. In the HOPE study, ramipril was added to participants' current

pressure. Its addition to other proven prevention strategies such as decreasing blood pressure, glycaemic control, lipid lowering, stopping smoking, and aspirin should further lower the risk of cardiovascular and microvascular events in people with diabetes.

VITAMIN E SUPPLEMENTATION AND CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS*

ABSTRACT

Background Observational and experimental studies suggest that the amount of vitamin E ingested in food and in supplements is associated with a lower risk of coronary heart disease and atherosclerosis.

Methods We enrolled a total of 2545 women and 6996 men 55 years of age or older who were at high risk for cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor. These patients were randomly assigned according to a two-by-two factorial design to receive either 400 IU of vitamin E daily from natural sources or matching placebo and either an angiotensin-converting–enzyme inhibitor (ramipril) or matching placebo for a mean of 4.5 years (the results of the comparison of ramipril and placebo are reported in a companion article). The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. The secondary outcomes included unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer.

Results A total of 772 of the 4761 patients assigned to vitamin E (16.2 percent) and 739 of the 4780 assigned to placebo (15.5 percent) had a primary outcome event (relative risk, 1.05; 95 percent confidence interval, 0.95 to 1.16; P=0.33). There were no significant differences in the numbers of deaths from cardiovascular causes (342 of those assigned to vitamin E vs. 328 of those assigned to placebo; relative risk, 1.05; 95 percent confidence interval, 0.90 to 1.22), myocardial infarction (532 vs. 524; relative risk, 1.02; 95 percent confidence interval, 0.90 to 1.15), or stroke (209 vs. 180; relative risk, 1.17; 95 percent confidence interval, 0.95 to 1.42). There were also no significant differences in the incidence of secondary cardiovascular outcomes or in death from any cause. There were no significant adverse effects of vitamin E.

Conclusions In patients at high risk for cardiovascular events, treatment with vitamin E for a mean of 4.5 years has no apparent effect on cardiovascular outcomes. (N Engl J Med 2000;342:154-60.)
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OXIDATIVE modification of low-density lipoprotein is an important step in the development and progression of atherosclerosis in experimental studies,[1,2] and antioxidants such as vitamin E have been shown to slow atherosclerosis.[3-5] An inverse relation has been observed between coronary heart disease and the consumption of fruits, vegetables, and other foods containing vitamins, particularly vitamin E.[6-9] Observational studies have indicated that persons who consume more than 100 IU of vitamin E a day for more than two years have lower rates of coronary events[10,11] and lower rates of progression of coronary artery lesions.[12] However, observational studies cannot distinguish whether the lower risk of coronary heart disease associated with higher levels of vitamin E consumption is due to the vitamin or to other associated lifestyle factors such as increased exercise and other aspects of diet. There have been four randomized, controlled trials of the relation between vitamin E and coronary heart disease,[13-16] but their results are conflicting, perhaps because of the low doses of vitamin E used in some studies,[13,14] the small numbers of events,[15] or the limited duration of treatment.[15,16]

We evaluated a high dose (400 IU per day) of vitamin E from natural sources, which has high bioavailability, in a large, five-year, prospective study of patients at high risk for cardiovascular events. The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. The secondary outcomes included death from any cause, hospitalization for unstable angina or congestive heart failure, revascularization or limb amputation, complications of diabetes, and cancer. The trial was also designed to evaluate the effects of an angiotensin-converting–enzyme inhibitor, ramipril, on the incidence of cardiovascular events. After nearly 4.5 years of follow-up, the collection of data on cardiovascular disease was stopped in April 1999 on the basis of a finding by the independent data and safety monitoring board that the trial had conclusively demonstrated the benefits of ramipril and a lack of effect of vitamin E on cardiovascular events. This report presents our findings relating to the effects of vitamin E on the primary and secondary cardiovascular outcomes. The study has been continued in the majority of centers to evaluate the effects of vitamin E on the incidence of cancer.

METHODS

Study Design

The Heart Outcomes Prevention Evaluation (HOPE) Study is a double-blind, randomized trial with a two-by-two factorial de-

sign, conducted to evaluate the effects of ramipril and vitamin E in 9541 patients at high risk for cardiovascular events. The results of the comparison of ramipril with placebo are reported in a companion article.[17] Details of the methods are given in that article[17] and in a previously published article.[18] Briefly, eligible patients at high risk were randomly assigned to receive either 400 IU of vitamin E from natural sources or an equivalent placebo daily for 4 to 6 years (mean, 4.5) and in addition to receive either 10 mg of ramipril or an equivalent placebo daily. Patients were evaluated every six months for a variety of outcomes.

Outcomes

The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. Deaths classified as due to cardiovascular causes were unexpected deaths presumed to be due to ischemic cardiovascular disease and occurring within 24 hours after the onset of symptoms without clinical or postmortem evidence of another cause; deaths from myocardial infarction or stroke that occurred within seven days after the myocardial infarction or stroke; and deaths from congestive heart failure, dysrhythmia, pulmonary embolism, or ruptured abdominal aortic aneurysm. Deaths for which the cause was uncertain were presumed to be due to cardiovascular disease. Myocardial infarction was diagnosed when two of the following three criteria were met: typical symptoms, increased cardiac enzyme levels (at least twice the upper limit of normal), and diagnostic electrocardiographic changes. Stroke was defined as a neurologic deficit lasting more than 24 hours. A computed tomographic or magnetic resonance imaging examination was recommended to define the type of stroke.

Secondary and other outcomes were death from any cause; unstable angina, defined as worsening angina or angina at rest requiring hospitalization; hospitalization for heart failure with clinical and radiologic signs of congestion; revascularization or limb amputation; the development of overt nephropathy or the need for dialysis or laser therapy among patients with diabetes; and the development of heart failure or new or worsening angina regardless of the need for hospitalization.

RESULTS

Characteristics of the Patients

The characteristics of the 9541 patients are shown in Table 1. The rate of compliance with the assigned regimen was high throughout the study. The percentages of patients who were taking vitamin E in the vitamin E and placebo groups, respectively, were 94.2 percent and 1.0 percent at one year, 93.3 percent and 1.7 percent at two years, 91.3 percent and 2.0 percent at three years, 90.2 percent and 2.7 percent at four years, and 89.2 percent and 3.4 percent at the final visit.

Primary Cardiovascular Outcomes and Deaths from Any Cause

A total of 772 of the 4761 patients who were assigned to receive vitamin E (16.2 percent) and 739 of the 4780 who were assigned to placebo (15.5 percent) had a primary cardiovascular event (relative risk, 1.05; 95 percent confidence interval, 0.95 to 1.16; P=0.33) (Table 2 and Fig. 1). There were no significant differences between the groups in the numbers of deaths from cardiovascular causes (342 in the vitamin E group vs. 328 in the placebo group; relative risk, 1.05), myocardial infarctions (532 vs. 524; relative risk, 1.02), deaths from coronary heart disease

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

CHARACTERISTIC†	VITAMIN E GROUP (N=4761)	PLACEBO GROUP (N=4780)
Age — yr	66±7	66±7
Blood pressure — mm Hg	139±20/79±11	139±20/79±11
Heart rate — beats/min	69±11	69±11
Body-mass index‡	28±4	28±4
Female sex — no. (%)	1263 (26.5)	1282 (26.8)
History of coronary artery disease — no. (%)	3857 (81.0)	3832 (80.2)
Myocardial infarction	2499 (52.5)	2535 (53.0)
Stable angina pectoris	2653 (55.7)	2668 (55.8)
Unstable angina pectoris	1205 (25.3)	1246 (26.1)
CABG	1229 (25.8)	1251 (26.2)
PTCA	851 (17.9)	863 (18.1)
Stroke or transient ischemic attacks — no. (%)	530 (11.1)	500 (10.5)
Peripheral vascular disease — no. (%)§	2109 (44.3)	2037 (42.6)
Hypertension — no. (%)	2219 (46.6)	2222 (46.5)
Diabetes — no. (%)	1838 (38.6)	1816 (38.0)
Known elevated total cholesterol — no. (%)	3109 (65.3)	3171 (66.3)
Known low HDL cholesterol — no. (%)	893 (18.8)	869 (18.2)
Current cigarette smoking — no. (%)	665 (14.0)	679 (14.2)
Medications — no. (%)		
Beta-blockers	1901 (39.9)	1870 (39.1)
Aspirin or other antiplatelet agents	3665 (77.0)	3616 (75.6)
Lipid-lowering agents	1352 (28.4)	1401 (29.3)
Diuretics	728 (15.3)	717 (15.0)
Calcium-channel blockers	2249 (47.2)	2236 (46.8)
Left ventricular hypertrophy on ECG — no. (%)	411 (8.6)	382 (8.0)
Microalbuminuria — no. (%)	1012 (21.3)	976 (20.4)

*Plus–minus values are means ±SD.

†CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, HDL high-density lipoprotein, and ECG electrocardiogram.

‡The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

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

(287 vs. 277; relative risk, 1.06), or strokes (209 vs. 180; relative risk, 1.17) (Fig. 2 and 3). The total numbers of deaths were similar in the two groups (535 vs. 537; relative risk, 1.00). Vitamin E had no significant effect on the primary outcome either among patients who were receiving ramipril (338 events among those who were receiving vitamin E and 313 events among those who were receiving placebo; relative risk, 1.08) or among patients who were not receiving ramipril (421 and 405 events, respectively; relative risk, 1.05).

Secondary Cardiovascular and Combined Outcomes

There were no differences between patients assigned to vitamin E and those assigned to placebo in the number of hospitalizations for unstable angina

TABLE 2. INCIDENCE OF THE PRIMARY OUTCOME AND OF DEATHS FROM ANY CAUSE.

OUTCOME	VITAMIN E GROUP (N=4761)	PLACEBO GROUP (N=4780)	RELATIVE RISK (95% CI)*	P VALUE†
	no. (%)			
Myocardial infarction, stroke, or death from cardiovascular causes‡	772 (16.2)	739 (15.5)	1.05 (0.95–1.16)	0.33
Death from cardiovascular causes§	342 (7.2)	328 (6.9)	1.05 (0.90–1.22)	0.54
Myocardial infarction§	532 (11.2)	524 (11.0)	1.02 (0.90–1.15)	0.74
Stroke§	209 (4.4)	180 (3.8)	1.17 (0.95–1.42)	0.13
Death from any cause	535 (11.2)	537 (11.2)	1.00 (0.89–1.13)	0.99

*CI denotes confidence interval.

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

‡The number of events among those receiving ramipril did not differ significantly between those assigned to receive vitamin E and those assigned to placebo (338 vs. 313). Similar results were observed among those who received matching placebo rather than ramipril (421 vs. 405).

§A patient may have had more than one event.

Primary Outcome
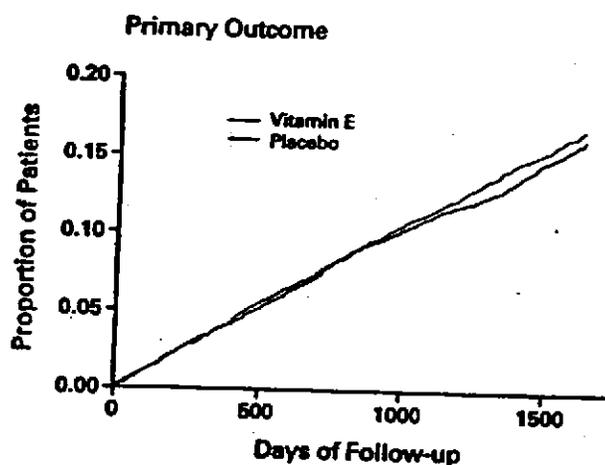
Figure 1. Kaplan–Meier Estimates of the Effect of Vitamin E on the Composite Outcome of Nonfatal Myocardial Infarction, Stroke, or Death from Cardiovascular Causes.

The relative risk of the composite outcome in the vitamin E group as compared with the placebo group was 1.05 (95 percent confidence interval, 0.95 to 1.16; P=0.33).

(586 vs. 569; relative risk, 1.04), hospitalizations for heart failure (160 vs. 144; relative risk, 1.12), or revascularizations or limb amputations (848 vs. 787; relative risk, 1.09) (Table 3). There were no significant differences in the number of patients with angina of new onset (278 vs. 245; relative risk, 1.15) or microvascular complications of diabetes (340 vs. 325; relative risk, 1.06). A combined analysis of the proportion of patients who had any primary or secondary event found a nonsignificantly higher rate among those assigned to vitamin E (1630 vs. 1576; relative risk, 1.05; 95 percent confidence interval, 0.98 to 1.13; P=0.14).

Subgroup Analyses

There was no heterogeneity of results among subgroups defined according to sex, age, previous cardiovascular disease, or use of other drugs with respect to the primary or secondary outcomes (data not shown). Specifically, there was no significant difference in the incidence of the primary outcome among patients with diabetes (325 of those assigned to vitamin E vs. 313 of those assigned to placebo; relative risk, 1.04) or among smokers (135 vs. 139; relative risk, 1.02).

Adverse Effects

There was no significant difference between groups in the incidence of adverse effects or in the number of patients who stopped taking the study medication. There was no increase in hemorrhagic stroke associated with vitamin E use (17 of those assigned to vitamin E had hemorrhagic stroke, as compared with 13 of those assigned to placebo) or among those who were also taking an antiplatelet agent (11 vs. 8).

DISCUSSION

In our study, vitamin E did not reduce the incidence of cardiovascular events, as compared with the incidence among patients assigned to placebo, during a follow-up period of four to six years. Given the large number of events and the consistent lack of difference in all secondary cardiovascular outcomes, it is very unlikely that vitamin E had any clinically worthwhile beneficial effect on cardiovascular disease during four or five years of treatment.

Results have been reported from four randomized trials of the effects of vitamin E on cardiovascular events. In a Chinese study, 29,584 adults from Linxian Province, who did not have cardiovascular disease at entry, were randomly assigned to receive daily vita-
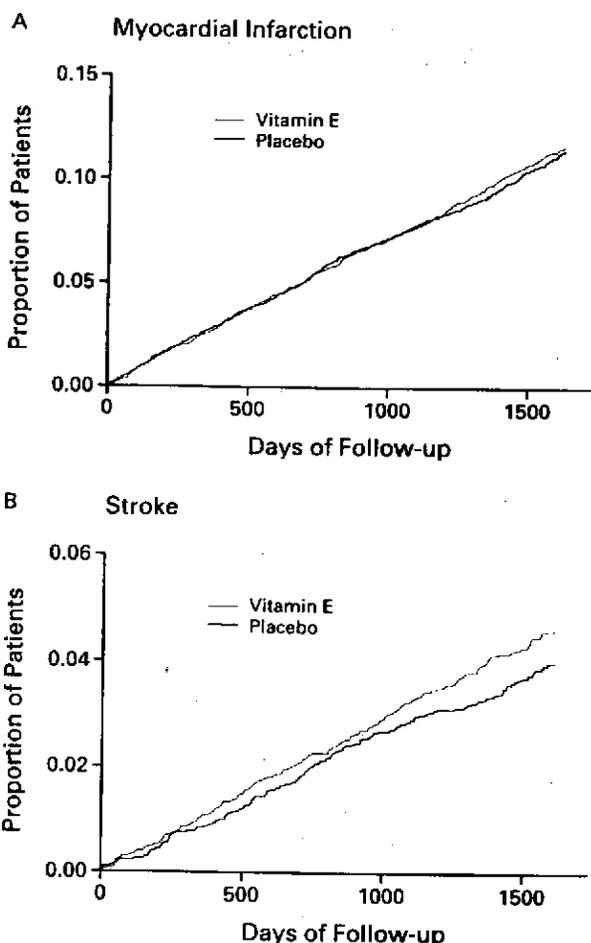
A

Myocardial Infarction

B

Stroke

Figure 2. Kaplan–Meier Estimates of the Effect of Vitamin E on the Incidence of Myocardial Infarction (Panel A) and Stroke (Panel B).

The relative risk of myocardial infarction in the vitamin E group as compared with the placebo group was 1.02 (95 percent confidence interval, 0.90 to 1.15; P=0.74), and the relative risk of stroke was 1.17 (95 percent confidence interval, 0.95 to 1.42; P=0.13).

Death from Any Cause

Figure 3. Kaplan–Meier Estimates of the Effect of Vitamin E on the Incidence of Death from Any Cause.

The relative risk in the vitamin E group as compared with the placebo group was 1.00 (95 percent confidence interval, 0.89 to 1.13; P=0.99).

min E (30 mg), beta carotene, and selenium supplements or to receive placebo.[13] During the 5.2 years of follow-up, there was a 9 percent decrease in deaths from any cause without any significant reduction in cardiovascular events. The dose of vitamin E in this study was small, the nutritional status and cardiovascular risk of this population were very different from those of Western populations, and the beneficial effects on overall mortality cannot be attributed only to vitamin E.

The second trial was the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study, involving 29,133 male smokers who were 50 to 69 years of age.[14] Daily treatment with 50 mg of vitamin E for five to eight years had no effect on the risk of death from coronary heart disease. In a subgroup of 1862 men with a pre-
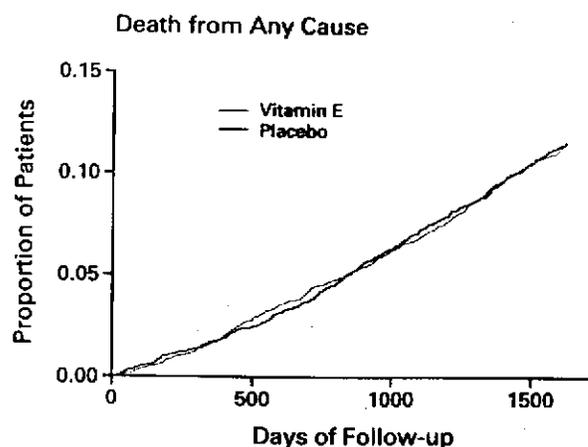
vious myocardial infarction at entry, there was a nonsignificant increase in the risk of death from coronary heart disease (relative risk, 1.33; 95 percent confidence interval, 0.86 to 2.05; P=0.20). However, a reduction in the risk of nonfatal myocardial infarction was documented among men assigned to vitamin E only (40 vs. 55; relative risk, 0.62; 95 percent confidence interval, 0.41 to 0.96), but not among those receiving the combination of vitamin E and beta carotene, in comparison with those receiving placebo only.[19] In this subgroup, the number of events was small. In the remaining patients in this study, there was no significant effect of vitamin E on nonfatal or fatal myocardial infarction, despite large numbers of events (1204 and 907, respectively).[20] Thus, in this well-conducted trial, vitamin E had no effect on coronary heart disease. Although the trial used a low dose of synthetic vitamin E (50 mg per day), the median level of alpha-tocopherol increased significantly, from 28.5 μmol per liter at base line to 42.5 μmol per liter at three months.

The third trial was the Cambridge Heart Antioxidant Study, which randomly assigned 2002 patients with coronary atherosclerosis to receive either vitamin E or placebo.[15] The mean alpha-tocopherol levels increased from 34.2 to 51.1 μmol per liter in patients receiving 400 IU of vitamin E per day and to 64.5 μmol per liter in patients receiving 800 IU per day. The majority of the patients received 400 IU per day. After a median follow-up of 1.4 years, a large reduction in the number of patients with nonfatal myocardial infarction was observed (14 in the vitamin E group vs. 41 in the placebo group; relative risk, 0.53; 95 percent confidence interval, 0.11 to 0.47; P= 0.005), but there was no difference in deaths due to

TABLE 3. INCIDENCE OF SECONDARY AND OTHER OUTCOMES.

Outcome	Vitamin E Group (N=4761)	Placebo Group (N=4780)	Relative Risk (95% CI)*	P Value†
	no. (%)			
Revascularization or limb amputation	848 (17.8)	787 (16.5)	1.09 (0.99–1.20)	0.07
Hospitalization for unstable angina	586 (12.3)	569 (11.9)	1.04 (0.93–1.17)	0.52
New-onset angina	278 (5.8)	245 (5.1)	1.15 (0.97–1.37)	0.11
Worsening angina	1215 (25.5)	1186 (24.8)	1.02 (0.94–1.11)	0.63
Claudication	762 (16.0)	753 (15.8)	1.02 (0.92–1.13)	0.70
Hospitalization for heart failure	160 (3.4)	144 (3.0)	1.12 (0.90–1.41)	0.33
Heart failure	530 (11.0)	457 (9.6)	1.17 (1.03–1.32)	0.02
Complications of diabetes‡	340 (7.1)	325 (6.8)	1.06 (0.91–1.23)	0.47

*CI denotes confidence interval.

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

‡Complications included nephropathy, dialysis, and laser therapy.

TABLE 4. META-ANALYSIS OF THE EFFECTS OF VITAMIN E ON MYOCARDIAL INFARCTION, STROKE, OR DEATH FROM CARDIOVASCULAR CAUSES IN LARGE TRIALS.*

Study	Daily Dose	Duration of Study	Vitamin E	Placebo	Relative Risk (95% CI)
	mg	yr	no. with events/total no. (%)		
ATBC[14]	50	5.0	1889/14,564 (13.0)	1970/14,569 (13.5)	0.96 (0.90–1.03)
CHAOS[11]	>400	1.3	41/1035 (4.0)	64/967 (6.6)	0.60 (0.40–0.89)
GISSI[16]	300	3.5	571/5660 (10.1)	584/5664 (10.3)	0.98 (0.87–1.10)
Current study	400	4.5	772/4761 (16.2)	739/4780 (15.5)	1.05 (0.95–1.16)
Total			3273/26,020 (12.6)	3357/25,980 (12.9)	0.97 (0.92–1.02)†

*CI denotes confidence interval, ATBC Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, CHAOS Cambridge Heart Antioxidant Study, and GISSI Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.

†Relative risks and confidence intervals were derived by the method of Yusuf et al.[31]; P=0.27.

cardiovascular causes (27 vs. 23; relative risk, 1.18; 95 percent confidence interval, 0.62 to 2.27; P=0.61). In this trial, the number of events was small and there were imbalances in several base-line characteristics that call into question whether randomization resulted in truly comparable groups.

Furthermore, the very large reduction in nonfatal myocardial infarction within a relatively short time (median, 1.4 years) is inconsistent with the results of other interventions, such as lipid-lowering agents or antihypertensive medications, that reduce cardiovascular events. It is therefore likely that the results of the Cambridge Heart Antioxidant Study may have been due to chance. This possibility is supported by the results of a recent Italian trial,[16] in which 11,000 patients who had had myocardial infarctions were randomly assigned to receive 300 IU of vitamin E per day or placebo for a median of 3.5 years. The number of patients with nonfatal myocardial infarction was slightly higher in the vitamin E group than the placebo group (295 vs. 284; relative risk, 1.02; 95 percent confidence interval, 0.87 to 1.21), and the number of deaths from coronary heart disease was slightly smaller (227 vs. 249; relative risk, 0.92; 95 percent confidence interval, 0.77 to 1.11). Neither difference was statistically significant.[16]

Our study used a high dose of vitamin E (400 IU per day), had high rates of compliance, and involved high-risk patients. The study had a large number of primary outcomes and therefore had high statistical power (more than 90 percent power to detect a 13 percent relative reduction in the risk of the primary outcome). Furthermore, a large number of secondary outcomes (e.g., revascularization or limb amputation, unstable angina, worsening angina, and heart failure) were examined. Such data are not available from most trials. Combining the data from all trials of vitamin E indicates that such treatment has little effect on the risk of death or cardiovascular events (Table 4), at least over a four-to-six-year period.

Steinberg has hypothesized that unlike agents that lower cholesterol or blood pressure, antioxidants may have to be used for more than five years to have a demonstrable benefit, since the primary mechanism of these agents may be the prevention of new lesions.[22] Therefore, in a population like the one we studied, it may take longer than five years to detect an effect on clinical outcomes. However, the Physicians' Health Study did not find a benefit of beta carotene (another antioxidant with a different action) after 12 years.[23] Similar data are not available for vitamin E, but observational studies that demonstrated a lower rate of coronary heart disease with vitamin E supplementation suggested that a lower risk should be evident after two years.[10,11] In a nested substudy, we are examining whether the thickness of the carotid intima and media (an indication of the risk of early atherosclerosis) can be favorably altered by vitamin E.[24] If so, Steinberg's hypothesis may be worth exploring with more prolonged follow-up or treatment to assess whether such changes in the development of atherosclerosis would translate into a benefit in terms of clinical outcomes.'

Although the moderate duration of vitamin E supplementation (four to six years) and the characteristics of the population may explain our finding of a lack of benefit of vitamin E, another reason may be our use of vitamin E alone, without other antioxidants. In the epidemiologic studies that found an association between higher dietary intake of vitamin E and lower rates of coronary heart disease, higher vitamin E consumption was also associated with higher intake of a number of other antioxidants and micronutrients.[6-9] It is possible that vitamin E supplementation requires these cofactors to have a beneficial effect.[25] Although the existence of interactions between vitamin E and other vitamins,[10] beta carotene,[6,14] or selenium[13] is not supported by the findings of prospective observational studies or randomized trials, this hypothesis can be tested only in trials in which combinations of vitamins are given; some such trials are now in progress.[26-28]

In conclusion, 400 IU of vitamin E administered daily for four to six years had no beneficial effects on cardiovascular outcomes in a high-risk population of patients who were 55 years of age or older. Vitamin E was well tolerated, with no significant adverse events as compared with placebo. This finding provides some reassurance for the conduct of large, longer-term trials to address unanswered questions regarding vitamin E, such as its possible effects in preventing cancer.

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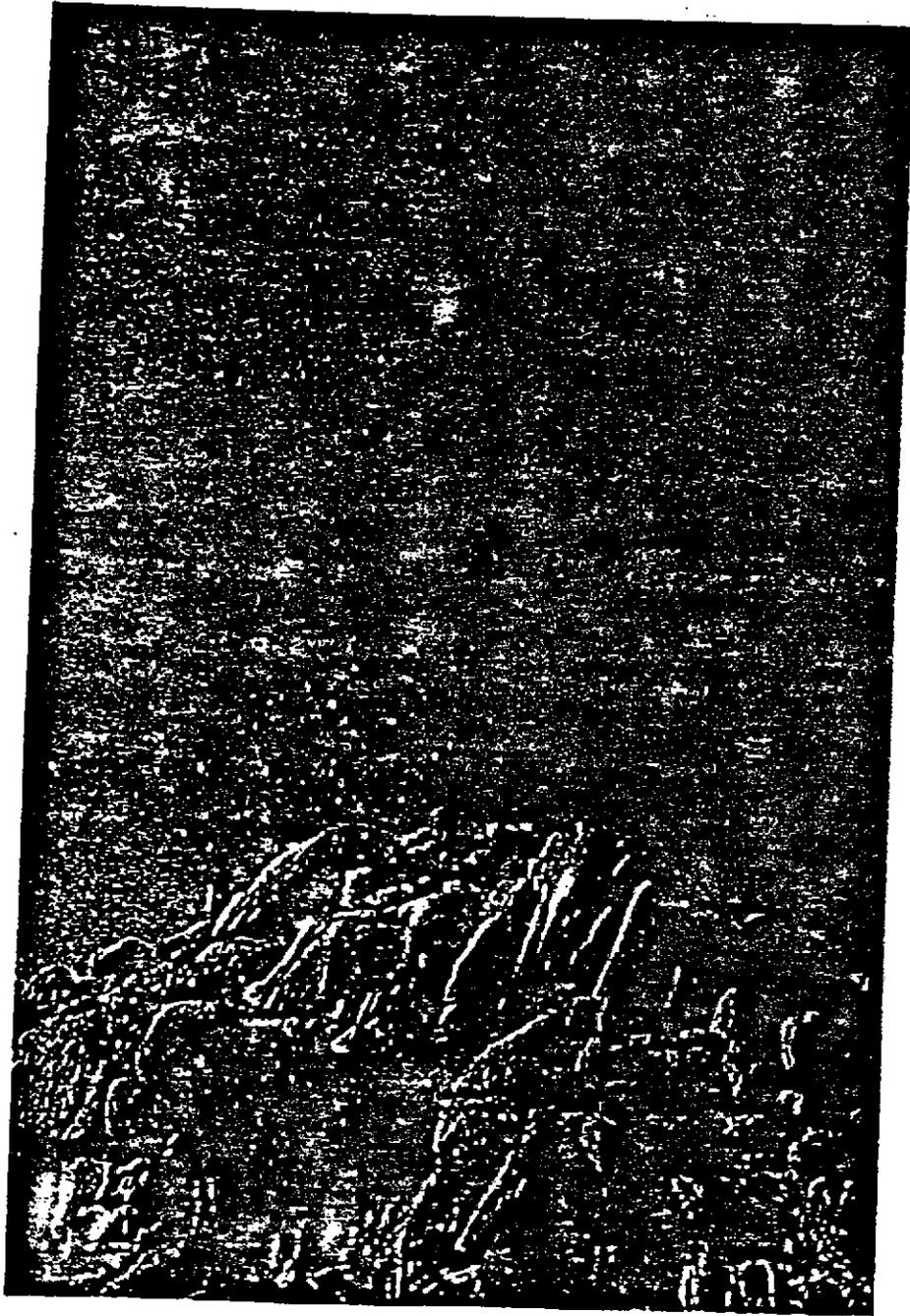
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KEVIN BOBROWSKY, M.D.

The HOPE (Heart Outcomes Prevention Evaluation) Study: The design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events

THE HOPE STUDY INVESTIGATORS

THE HOPE STUDY INVESTIGATORS. The HOPE (Heart Outcomes Prevention Evaluation) Study: The design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events. Can J Cardiol 1996;12(2):127-137.

OBJECTIVE: To describe the design of the HOPE (Heart Outcomes Prevention Evaluation) Study.

DESIGN: Description of the key design features of HOPE, a large, simple randomized trial of two widely applicable treatments – ramipril, an angiotensin-converting enzyme inhibitor; and vitamin E, a naturally occurring antioxidant vitamin – in the prevention of myocardial infarction, stroke or cardiovascular death.

SETTING: Two-hundred and sixty-seven hospitals, physician offices and clinics in Canada, the United States, Mexico, Europe and South America.

PATIENTS: Over 9000 women and men aged 55 years and above at high risk for cardiovascular events such as myocardial infarction and stroke were recruited over 18 months.

INTERVENTIONS: A 2x2 factorial design with ramipril and vitamin E with follow-up for up to four years.

CONCLUSIONS: HOPE will be one of the largest trials of two new interventions to prevent myocardial infarction, stroke or cardiovascular death in high risk patients. The results of HOPE will have direct public health impact and are likely to be readily incorporated into clinical practice. Key design features of HOPE are inclusion of individuals at high risk of cardiovascular disease, inclusion of a substantial proportion of patients with diabetes (36%) and women (27%), and detailed substudies to provide data on mechanisms of benefit.

Key Words: Angiotensin-converting enzyme inhibitors, Cardiovascular prevention, HOPE Study, Randomized trial methodology, Vitamin E antioxidant

L'étude HOPE (Heart Outcome Prevention Evaluation) : modèle d'une grande étude randomisée simple sur un inhibiteur de l'enzyme de conversion de l'angiotensine (ramipril) et la vitamine E chez des patients exposés à un risque cardiovasculaire élevé

OBJECTIF : Décrire le modèle de l'étude HOPE (Heart Outcome Prevention Evaluation).

MODÈLE : Description des caractéristiques clés de l'étude HOPE, un grand essai clinique randomisé simple sur deux thérapeutiques d'application facile, soit le ramipril, inhibiteur de l'enzyme de conversion de l'angiotensine (ECA) et la vitamine E, vitamine antioxydante naturelle, en prévention de l'infarctus du myocarde, de l'ACV ou du décès d'origine cardiovasculaire.

CONTEXTE : Deux cent soixante-sept hôpitaux, cabinets médicaux et cliniques au Canada, aux États-Unis, au Mexique, en Europe et en Amérique du Sud.

PATIENTS : Plus de 9 000 femmes et hommes de 55 ans et plus exposés à un risque cardiovasculaire élevé (d'infarctus du myocarde ou d'ACV, par exemple) ont été recrutés au cours d'une période de 18 mois.

INTERVENTIONS : Modèle factoriel 2 x 2 avec ramipril et vitamine E et suivi échelonné sur un maximum de quatre ans.

CONCLUSIONS : L'essai HOPE sera l'un des plus grands à porter sur deux interventions en prévention de l'infarctus du myocarde, de l'ACV ou de la mort d'origine cardiovasculaire chez des patients à haut risque. Les résultats de l'étude HOPE exerceront un impact direct sur la santé publique et risquent d'être intégrés rapidement à la pratique clinique. Les caractéristiques clés de l'étude HOPE sont l'inclusion de sujets à risque cardiovasculaire élevé, d'une proportion importante de patients diabétiques (36 %) et de femmes (27 %) et la réalisation de sous-études détaillées en vue de produire des données sur les mécanismes des avantages conférés.

health care costs. In Canada, CVD costs total a quarter of all disability pensions and consume about US$12 billion in direct and indirect health care costs every year (1).

Prevention of CVD requires modification of known risk factors such as elevated blood pressure, cholesterol and smoking (2). These risk factors only partly account for the risk of CVD and a number of complex biological processes such as the oxidation of serum lipids (3-4); proliferative, hormonal and vascular stimuli may also have a role in progression of atherosclerosis, the precursor to clinical CVD events (5,6). This multifactorial causation of atherosclerosis suggests that multiple approaches to preventing events are needed in high risk patients.

In this document, we outline the rationale, key methodological and practical steps in the ongoing HOPE (Heart Outcomes Prevention Evaluation) Study. The HOPE Study is a large, randomized clinical trial of the efficacy of an angiotensin-converting enzyme inhibitor (ACE-I), ramipril, and of a naturally occurring antioxidant, vitamin E, in reducing myocardial infarction (MI), stroke or CVD death in over 9000 men and women at high risk of CVD. All design features presented were specified before the trial started. We also briefly present the results for screening, exclusion and distribution of patients across risk groups for the 9541 patients entered.

BRIEF RATIONALE FOR USE OF ACE-I AND VITAMIN E

Data from three large trials in patients with low ejection fraction suggest that ACE-I use leads to about a 23% relative risk reduction (RRR) in MI and other ischemic heart events (7-10). 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 (10). Parallel lines of evidence from observational animal and human studies suggest that ACE-I may provide benefit through several mechanisms, including blood pressure reduction, antiproliferative effects, hormonal/vascular effects and anti-atherogenic effects (5,6,11-15). However, widespread acceptance of ACE-I as a preventive therapy must be preceded by direct proof from randomized trials of benefit in patients with preserved ejection fractions. HOPE is a large randomized controlled trial designed to evaluate whether ACE-I reduces ischemic cardiovascular events.

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 antioxidant (3,4). Several large observational studies have shown that users of vitamin E have a substantially reduced risk of CVD events such as MI and stroke in comparison with nonusers (16-18). However, these observational studies may be subject to considerable bias, such as vitamin E consumers more often adopting other healthy lifestyle changes, eg,

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ELIGIBILITY CRITERIA: Women and men aged 55 years and above at high risk of developing a major cardiovascular event. Any of:

A. Coronary disease:
1. Previous myocardial infarction (>1 month ago)
2. Stable angina or unstable angina (>1 month ago) each with documented multivessel coronary disease*; >50% stenosis in at least two major coronary arteries, or positive stress (ST depression ≥2 mm or a positive thallium)
3. Multivessel PTCA >1 month ago
4. Multivessel CABG >4 years ago or with angina

B. Peripheral vascular disease:
1. Previous limb bypass surgery or percutaneous transluminal angioplasty
2. Previous limb or foot amputation
3. History of intermittent claudication with ankle:arm blood pressure ratio ≤0.80 in at least one side
4. Significant stenosis (>50%) documented by angiography

C. Stroke >1 month ago

D. Diabetes (insulin-dependent or noninsulin-dependent) with one of the following:
1. Hypertension (blood pressure >160 mmHg systolic or >90 mmHg diastolic or on treatment)
2. Total cholesterol >5.2 mmol/L (>200 mg/dL)
3. HDL cholesterol <0.9 mmol/L (<35 mg/dL)
4. Current cigarette smoking
5. Known microalbuminuria
6. Any evidence of previous vascular disease

EXCLUSION CRITERIA: Any of:

A. Drug use:
1. Current use of ACE-I (eg, for congestive heart failure, ejection fraction <40% or severe hypertension) or current use of vitamin E and inability to discontinue these medications
2. Known hypersensitivity to ACE-I or vitamin E

B. Cardiovascular diseases:
1. Ejection fraction known to be <40%
2. Hemodynamically significant primary valvular or outflow tract obstruction (eg, mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve)
3. Constrictive pericarditis
4. Complex congenital heart disease
5. Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia are not an exclusion criterion)
6. Planned cardiac surgery or angioplasty within three months
7. Uncontrolled hypertension
8. Cor pulmonale
9. Heart transplant recipient

C. Other conditions:
1. Significant renal disease defined as: a) renal artery stenosis; b) creatine clearance <0.6 mL/s or serum creatinine ≥200 mEq/L (≥2.26 mg/dL); c) overt nephropathy: ≥1 proteinuria on dipstick or urinary albumin excretion >200 µg/min (>300 mg/24 h); d) hyperkalemia; potassium >5.5 mEq/L
2. Any other major noncardiac illness expected to reduce life expectancy or interfere with study participation
3. Patient is simultaneously taking another experimental drug
4. Previously randomized to HOPE

*Multivessel coronary disease (>50% stenosis in at least two major coronary arteries) seen on angiography. ACE-I Angiotensin-converting enzyme inhibitor; CABG Coronary artery bypass graft; HDL High density lipoprotein; PTCA Percutaneous transluminal coronary angioplasty

Title of substudy	Principal investigator	Objectives	Funding source
1. Study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E	S Yusuf, Eva Lonn, McMaster University; F Hutchinson, V Dzavik, University of Alberta	To test the hypothesis that therapy with ACE-I (ramipril) decreases the rate of progression of atherosclerotic vascular disease in high risk individuals, as assessed by quantitative carotid ultrasound; to test the hypothesis that therapy with vitamin E decreases the rate of progression of atherosclerotic disease in high risk individuals, as assessed by quantitative carotid ultrasound	MRC grant obtained; study ongoing (n=732)
2. Microalbuminuria, Cardiovascular and Renal outcomes (MICROHOPE)	H Gerstein, S Yusuf, DW Taylor, McMaster University; B Zinman, University of Toronto	To determine whether ACE-I prevents overt nephropathy in older patients with diabetes; to determine whether vitamin E prevents overt nephropathy in older patients with diabetes	MRC grant obtained; study ongoing (n=9541)
3. Cataract Risk Reduction by Dietary Supplementation with Mixture of Antioxidants Vitamins C & E and Beta-Carotene	J Trevithick, University of Western Ontario	To investigate the reduction of cataract risk by dietary antioxidants vitamin C, vitamin E and beta-carotene	No extra funding required (n=9230)
4. Cost-effectiveness of ramipril and vitamin E	J Ostergren, Karolinska Institute, Stockholm, Sweden	To assess the costs and effects associated with each treatment and to calculate the incremental cost-effectiveness ratios	Funded by Astra Sweden (n=550)
5. Examining the effect of vitamin E on lipid peroxidation	R Hoeschen, University of Manitoba	To analyze the plasma for total cholesterol, cholesteryl esters, LDL vitamin E content, LDL and LDL cholesterol, resistance of LDL to oxidation by a free radical generating system	Unfunded (n=165)
6. Hostility in Heart Disease	H Arthur, McMaster University	To explore further psychophysiological explanations for the relationship between hostility and CAD	Unfunded (n=375)
7. Assessing Plasma Lipid Levels and Lipoproteins	N Kruseman, Academisch Ziekenhuis, Maastricht, The Netherlands	To elucidate the effects of vitamin E, alone or in combination with ramipril, on the lipid disturbances found in diabetic patients	Unfunded (n=79)
8. Oslo Satellite Study	T Henriksen, University of Oslo	To evaluate the influence of ramipril and/or vitamin E on the plasma levels of factors linked to the development of atherosclerosis	Unfunded (n=56)
9. Study to evaluate impact of long term ACE-I on left ventricular mass and function	E Lonn, S Yusuf, McMaster University	To assess the impact of chronic treatment with ramipril on left ventricular mass in patients without elevated blood pressure or significant left ventricular dysfunction; to assess changes in left ventricular mass and possibly in left ventricular systolic and diastolic function in diabetic patients	Is being done in conjunction with SECURE substudy – no extra funding required; study ongoing (n=375)
10. Evaluation of a 6 min walk test in patients with intermittent claudication participating in the HOPE study	J Ostergren, Karolinska Institute, Stockholm, Sweden	To compare the 6 min walk test with a standardized exercise treadmill test in patients with intermittent claudication and to assess impact of treatment	Unfunded (n=46)
11. Mechanisms Of Reduced End-points in Heart Outcomes Prevention Evaluation (MORE-HOPE)	E Lonn, M McQueen, J Weitz, McMaster University	To determine whether hematological, biochemical and endocrine markers correlate with anatomical extent of atherosclerosis and its progression	MRC/HSFO application to be submitted (n=732)
12. A test of sex differences in the relation between psychological predictors and CAD morbidity and mortality	K Davidson, Dalhousie University; H Arthur, McMaster University	To test the hypothesis that men possess higher levels of certain toxic facets of anger and hostility, and that these facets in turn are independently related to CAD outcomes	Submitted to NHRDP
13. Ambulatory Holter ECG monitoring on diabetic patients in HOPE	R Sarma, Rancho Los Amigos Medical Center, Downey, California	To examine ECG changes in patients with diabetes	Unfunded (n=24)

ACE-I Angiotensin-converting enzyme inhibitor; CAD Coronary artery disease; ECG Electrocardiogram; HSFO Heart and Stroke Foundation of Ontario; LDL Low density lipoprotein; MRC Medical Research Council of Canada; NHRDP National Health Research and Development Program; SECURE Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E

efficient and feasible in a broad group of investigators. Therefore, we have adopted simple entry and follow-up procedures for the main trial and we document only key outcomes. Such an approach has been successfully applied to other large clinical trials in cardiology (26,27).

Substudies to provide information on biological mechanisms and intermediate end-points: Because these substudies are done in parallel with the main study, the link among mechanisms, intermediate end-points and clinical outcomes may be evaluated (Table 4).

Widespread collaboration: The HOPE study involves cardiologists, internists, endocrinologists, family physicians, pharmacists, nurses, statisticians and support staff from over 267 centres in 19 countries.

DESIGN OF THE HOPE STUDY

The study design is summarized in Figure 1.

Objectives: Objectives of the study are to evaluate, first, whether use of an ACE-I (ramipril), compared with placebo, reduces major CVD events in high risk patients; and second, whether use of natural source vitamin E, compared with placebo, reduces major CVD events in high risk patients. The primary end-point for this study (CVD events) will be a combined end-point of the occurrence of MI, stroke or CVD death.

Major secondary end-points will include the following:

- total and CVD mortality;

- development of overt nephropathy or need for dialysis among patients with diabetes;

- hospitalization for congestive heart failure (for ramipril);

- unstable angina requiring hospitalization because of increased frequency of angina;

- all cardiovascular revascularization procedures: coronary artery bypass graft surgery, coronary interventions, carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation;

- cancers (for vitamin E), given the data suggesting that antioxidants may reduce cancer development (28).

Ethics: At the first visit, written informed consent is obtained from each patient. The HOPE protocol has been approved by appropriate regulatory and ethics councils in all participating countries and centres.

Eligibility and exclusion criteria: Eligibility and extension criteria are detailed in Table 1.

Initial screening and prerandomization phase: Eligible patients are drawn from a prevalent pool of patients, namely those with established CVD or diabetes. Potential sources of or referrals from physicians.

About three weeks before randomization, a run-in visit is arranged. At this visit eligible patients provide written informed consent and are given seven to 10 days of 2.5 mg active ramipril followed by 10 to 14 days of placebo ramipril. Serum creatinine and potassium are determined between days 7 and 10 of the run-in phase (on active ramipril) to determine initial safety and tolerance of ACE-I. In total, 10,711 patients attended the eligibility visit. Of these, 135 were found ineligible and 10,576 entered the run-in phase; 1035 patients were withdrawn at the end of the run-in phase and 9541 (90.2%) patients were randomized.

Central telephone randomization: Randomization is done internationally by a telephone call to a central office. After receipt of appropriate baseline data over the telephone, the patient is randomized to ramipril (2.5 mg for one week, then 5 mg every day for three weeks) or matching placebo and vitamin E (400 IU) or matching placebo by a 2x2 factorial design (Table 3). The patient is then given a date for a first follow-up visit (one month plus or minus one week) after which the dose of ramipril is increased to 10 mg daily (vitamin E remains at 400 IU). All randomized patients will be followed until the end of the study, and all end-points will be recorded even if the study medication has been stopped.

Follow-up and data collection: The follow-up visits occur at one month (plus or minus one week), six months (plus or minus four weeks) and every six months thereafter up to the end of the study. The mean duration of follow-up is expected to be approximately four years. At each visit, a follow-up form will be completed by the investigator or study nurse and faxed to the project office. This form records information on the occurrence of any major event or hospitalization and adherence to the medication or dosage change. Special report forms are required for every MI, stroke, death or hospitalization, together with supporting documents.

Standardization and monitoring of data quality: All study staff have undergone a training session to ensure knowledge of key steps in the protocol and to ensure uniformity in study procedures. The HOPE Study Operations Manual provides a detailed outline of each step of the protocol. The HOPE Coordinator and Regional Coordinators provided training and information on a regional level and will provide retraining as necessary. A 24 h toll-free telephone number is available to answer any questions related to the study.

Data management and DataFax use: The system for data collection employed is DataFax (Clinical DataFax Systems Inc) in which standardized forms are read optically. These forms are faxed to the project office on toll-free numbers. Digital reading technology allows most of the information to be read and entered into a computer database directly. The results of the computer-read data are verified against a visual display of the faxed form by project office staff. Any discrepancies are organized into quality control reports and faxed back to the investigator at regular intervals. The system also

addition to the main results. The DSMB chose to use a modified Haybottle-Peto rule to assist in decision regarding early termination. During the first half of the study, a difference of 4 SD in favour of treatment or 3 SD against treatment would trigger discussion regarding early termination. During the second half of the trial, the boundaries of 3 and 2 SD would be used to assess benefit or harm, respectively.

HOPE STUDY ORGANIZATION

HOPE includes 129 Canadian centres, 27 American centres, 76 centres in 14 countries in Europe, 30 centres in two countries in South America and five Mexican centres. (A list of investigators at these centres is given in Appendix B.)

HOPE is being conducted by the Canadian Cardiovascular Collaboration (CCC) in collaboration with other groups. The CCC has been established to conduct trials in CVD in Canada, the United States and worldwide. The key element of the CCC is the wholehearted input and collaboration of physicians, nurses and others at participating centres into the design and conduct of randomized clinical trials. Collaborating investigators have responsibility for recruitment and follow-up of all their patients. They will also attend annual meetings to discuss the study and which provide an educational forum. Day-to-day conduct of the study in North America is done at the project office in Hamilton, Ontario along with 11 regional coordinators. Adjunct project offices in London, England, São Paolo, Brazil and Rosario, Argentina will provide coordination for Europe, Brazil and Argentina, respectively. The overall responsibility for HOPE lies with the Steering Committee (see Appendix B for list of members). The Events Adjudication Committee will review and classify end-points in the trial. The DSMB will have responsibility for independent review of the conduct of the study, protocol changes, recommendations regarding early termination, ensuring overall patient safety and that event rates are adequate.

Drug packaging and distribution for North and South America is being handled by Hoechst-Roussel Canada and by CTS Galen Ltd in London, England for Europe.

PUBLICATIONS

The main publication(s) from the trial will be in the names of all fully collaborating investigators. Subsidiary papers will be written by individual investigators after discussion with the Steering Committee. These papers will include in the authorship the statement "for the HOPE investigators".

PROGRESS UPDATE

As of January 1, 1996 the study has completed randomizing 9541 patients. This includes 2543 women, 7553 patients with previous CVD, 3654 with diabetes and 4406 with hypertension. Approximately half the patients are over 65 years of age.

therapies that may be used by a very wide range of patients. The results of HOPE will have direct public health importance in many different countries to a broad population who are at high risk of cardiovascular events.

APPENDIX A
ORGANIZATIONAL STRUCTURE FOR HOPE

International Steering Committee: Co-Chairs: S Yusuf, T Montague, P Sleight; Vice-Chair: G Dagenais; HOPE Coordinator: J Bosch; Statisticians: J Pogue, W Taylor; Epidemiologist: P Jha; Pacific: R Tsuyuki; Northern Alberta, Saskatchewan, NWT: T Montague, K Teo; Southern Alberta: LB Mitchell; Manitoba: A Morris; Western Ontario: M Arnold; Central Ontario: R Baigrie; Eastern Ontario: R Davies; Southwestern Ontario: E Lonn; Quebec: G Dagenais; Maritimes: D Johnstone; Newfoundland: B Sussex; United States: J Probstfield, J Young; Argentina: R Diaz, E Paolasso; Brazil: A Avezum, L Piegas; Europe: ACN Kruseman, J Östergrens; Mexico: E Meaney. Canadian Regional Coordinators: Pacific: K Stevens; Northern Alberta: L Harris, S Martin; Southern Alberta: B Baptie, J Kellen; Manitoba: D Bedard; Western Ontario: P Squires; Central Ontario: C Liuni; Eastern Ontario: S Hagar; Southwestern Ontario: A Magi; Quebec: D LaForge; Maritimes: S Barnhill; Newfoundland: D Dalton, M Tobin. Canadian Coordination: HOPE Project Office: M Anderson, C Bamsey, J Bosch, L Campbell, A Magi, F Mazur, H McQueen, P Pappin, P Piss, J Pogue, S Reeve, S Scott, W Taylor, J Tucker, L Westfall, S Yusuf. International Coordination: European Coordination: J Clinch, N Raw, L Richardson; European National Coordinators: A Gin, G Heyndrickx, J Kennedy, W Klein, K Kølendorf, B Magnani, J Mann, A Reikvam, G Sanz, O Siitonen, G Spinas; Argentinian Coordination: M Ines Genisans, G Romero; Brazilian Coordination: A Amaki, J Rossi. Diabetic Sub-Committee: Chairs: H Gerstein, B Zinman. Events Adjudication Committee: Chair: G Dagenais; M Arnold, A Avezum, R Baigrie, E Lonn. Events Adjudication Sub-Committee: P Auger, I Bata, V Bernstein, BM Fisher, J Grover, C Gunn, M Gupta, R Hoeschen, S Kouz, E Lonn, J Mann, J Mathew, E Meaney, D Meldrum, J Östergrens, C Pilon, R Ramos, R Roccaforte, R Starra. Substudy Committee: Chair: D Johnstone; R Davies, S Hagar, J Östergrens, J Probstfield. Data Safety and Monitoring Board: Chair: D Sackett (University of Oxford); R Collins (University of Oxford), E Davis (University of North Carolina), C Furberg (Bowman Gray University), C Hennekens (Harvard University), B Pitt (University of Michigan), R Turner (University of Oxford). Writing Committee for this report: P Jha, S Yusuf, T Montague, G Dagenais, J Probstfield, P Sleight, L Richardson, D Johnstone, M Arnold, R Tsuyuki, R Davies, E Lonn, J Bosch.

Uppsala: A Hägg, C Mörlin*, M Pettersson, A Wanders; Växjö: H Björkman*, G Karlsson, H Larsson, Y Lönndahl, P Weber. Switzerland: Lugano: R Corti, P Gerber*, T Moccetti*, E Safwan, F Sessa; Zürich: T Binder, P Boman, W Kiowski, R Lehman, B Lüll, G Spinas*. United Kingdom: Glasgow: A Jamieson, JA Kennedy, C Keason, R Gryczka, P Parker, S Sidiki, M Small, S Struthers; Manchester: JJ Manns, H Smithurst; Paisley: A Begg, BM Fisher; Sheffield: C Bedford, S Heller, S Marlow.

Mexico: Guadalajara: E Cardona Muñoz,* H Hernandez Garcia*, R Olvera Ruiz*; Mexico City: E Meaney*; Monterrey: M Ibarra Flores*. United States: Alabama: Birmingham: E Brown, G Perry*. California: Downey: G Patel, R Sarma*, Y Srlachcic; Los Angeles: J Dorman, B Singh*. Colorado: Denver: G Bailey, L Clegg, L Horwitz*. Connecticut: Derby: J Leahy, A Rashkow*. Florida: Jacksonville: M Hudson, A Miller*; Tampa: J Umberger, R Zoble*. Georgia: Augusta: P Orander, M Sridharan*. Illinois: Chicago: G DeFrancisco, M Davidson*, N Islam, J Mathew*, R Rajanahally. Iowa: Des Moines: D French, W Wickemeyer*. Maryland: Baltimore: M Effron*, M Goldstein, K Utley. Michigan: Minneapolis: G Pierpont*, J Weigenant. Minnesota: Rochester: M Farkouh*, V Kubly. Missouri: St Louis: M Rich*, L Wisneski. New ora, R Kohn*, E Muffoletto; Kingston: D Brink, E Lader*, A Singler; Rochester: P Pande*, J Powers. Ohio: Cleveland: B Hoogwerf*, J Moore, F Yanak; Dayton: S Gupta*, D Williams. Oklahoma: Muskogee: K Danis*, C Kirk, B Wescott. Oregon: Portland: J Grover*, M Mackenzie. Pennsylvania: Pittsburgh: M Amidi*, M Bell. Texas: Houston: J Farmer*, C Kingry, J Young*. Washington: Seattle: V Harms, JW Kennedy*, R Letterer; Wenatchee: C Heller, R Mack, JW Kennedy*.

HOPE Sponsors

Argentina: M Eilez, A Vasquez; Austria: M Gantschacher, W Reinisch; Belgium: D Poelaert, P Spinewine ; Brazil: D Brandao; Canada: Y Berman, B Carter, N Hade, G Heseltine, M Montplaisir, T Pierce, JP St-Pierre; Denmark: P Ronsted, B Wentzer-Petersen; Finland: R Lehtonen; Germany: A Breidstadt, B Rangoonwala, W Schulz, S Stade, W Seix; Italy: P Favini, R La Valle, M Sessa, A Silva, A van Dijk; Mexico: M Bravo, G Cornejo; The Netherlands: AM Engbern, M Mignot; Norway: T Rostad; Spain: J Garcia Barbel, C Pina; Sweden: I Alden, K Fredriksson, C Larsson, A Ljunggren, K Rehn, A Sandberg, G Westergren; Switzerland: W Lilienthal, G Scrub; United Kingdom: J Clinch, P Stonier; United States: P Schorr, H Stanbrook.

* indicates Principal Investigator

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-901/S-028

CORRESPONDENCE

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax: 1-423-989-8055

September 26, 2000

Thomas K. Rogers, III, M.S.
Executive Vice President, Regulatory Affairs

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852-1420

Re: NDA 19-901/S028
Altace® (ramipril) Capsules
User Fee ID #: 3892
Pre-Meeting Information

Dear Dr. Lipicky:

We are most appreciative that upon a very short notice, we have been granted a meeting with FDA to discuss final labeling text relative to our sNDA seeking approval of new indications for Altace Capsules. We look forward to the opportunity for discussion with you, Dr. Temple, and your colleagues on Thursday September 28, 2000 from 10:30 AM to 12:00 PM. Representatives from Wyeth-Ayerst, our co-promotion partner, will accompany us to the meeting. A list of anticipated attendees from King and Wyeth-Ayerst is provided on the following page.

As stated to Ms. Birdsong in our meeting request, we are in essential agreement with the Agency's recommendations; however, there are a few substantive points, as well as several minor points, that we wish to raise for consideration and clarification. From the "marked-up draft labeling" received from FDA via facsimile on September 21, 2000, we prepared revised draft labeling. The draft labeling provided herewith has been revised completely according to the marked-up version received from FDA. All affected areas where we propose further revisions to the text are bolded. Recommended additions are underlined, and recommended deletions have strike-throughs. A brief rationale in support of each of our recommendations is also provided with this package.

Our goal for Thursday's meeting is to reach agreement with FDA on acceptable text for new product labeling so that final draft labeling can be submitted to the Agency the following day in anticipation of a rapid approval. We look forward to receiving your comments on these few remaining issues, and we sincerely appreciate your timely attention to our submission.

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Executive Vice President Regulatory Affairs

Cc: Mr. John M. Gregory
   Mr. Joseph R. Gregory
   Mr. Jefferson J. Gregory

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March 10, 2000

Thomas K. Rogers, III, M.S.
Vice President, Regulatory Affairs

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852-1420

REC'D
MAR 1 3 2000
HFD-110

Re: NDA 19-901/S028
       Altace® (ramipril) Capsules
       User Fee ID# 3892
       General Communication Regarding Advisory Committee Meeting

Dear Dr. Lipicky:

Reference is made to King Pharmaceuticals' January 18, 2000 supplement seeking approval of new indications for the use of Altace. Reference is also made to the teleconference of March 8, 2000 among FDA, Dr. Salim Yusuf and his colleagues, and representatives of the firm.

In the teleconference, there was significant discussion about the clinical relevance of the reduction of proteinuria to the reduction of overt nephropathy and the associated impact of therapeutic doses of ramipril in the prevention of diabetes. Consideration was given to the possibility of including recognized nephrologists and diabetologists as advisors to the Advisory Committee for consideration of this point. The names of several leaders in these fields were mentioned.

As the applicant, we would suggest that it is not appropriate to consider Dr. Edmond Lewis in this role due to a potential conflict of interest on other projects with the firm. As discussed, other nephrologists for consideration may be Dr. George Bakris of the Clinical Research Center in Chicago or Dr. Barry Brenner of the Brigham and Women's Hospital in Boston. We also propose that Dr. William Keane of the University of Minnesota Medical School could be considered as an advisor in this capacity.

Additionally, we suggest that Dr. John Buse of the University of North Carolina Diabetes Care Centre be considered as a recognized diabetologist who could advise the Committee.

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Vice President Regulatory Affairs

Cc: Mr. Jefferson Gregory
    Dr. Henry Richards
    Mr. Ed Reilly
    Dr. Salim Yusuf

King Pharmaceuticals, Inc.
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March 9, 2000

Thomas K. Rogers, III, M.S.
Vice President, Regulatory Affairs

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852-1420

Re: NDA 19-901/S028
Altace® (ramipril) Capsules
User Fee ID #: 3892
Amendment to Supplement

NDA SUPPL AMENDMENT
(BC)
SE1-028

Dear Dr. Lipicky:

Reference is made to King Pharmaceuticals' January 18, 2000 supplement seeking approval of new indications for the use of Altace. Reference is also made to the January 24, 2000 request for information relevant to product patent and exclusivity as affected by the pending Supplement and to the February 10, 2000 request for information pertaining to financial disclosure by clinical investigators. We also refer to subsequent discussions with Ms. Linda Carter, Office of Drug Evaluation I, on February 10 and 24, 2000 concerning specific documentation needed to fulfill the requirements of 21CFR§54.4. Lastly, reference is made to the February 25, 2000 request from Dr. Stuart Zimmerman, Office of New Drug Chemistry, for information on the environmental impact associated with the anticipated increased use of the product.

In response to these requests, we have included within this amendment the following documents:

- Attachment A: Financial Disclosure by Clinical Investigators
    FDA Form 3454
    Complete List of Clinical Investigators

- Attachment B: Environmental Categorical Exclusion Request

- Attachment C: Patent and Exclusivity Information

This amendment is supplied in duplicate as an archival copy (blue binder) and a review copy (red binder). I may be contacted directly at 423-989-8172 if you have further questions on this amendment.

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Vice President Regulatory Affairs

REC'D
MAR 10 2000
HFD-110
CENTER FOR DRUG EVALUATION AND RESEARCH

TKR:upm

March 8, 2000

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852-1420

Re: NDA 19-901/S028
        Altace* (ramipril) Capsules
        User Fee ID #: 3892

Dear Sirs:

Please be advised that King Pharmaceuticals and their predecessor of interest, Hoechst-Marion Roussel, provided substantial support as defined in 21CFR§314.50(j)(4)(iii) for the conduct of the HOPE study.

Yours truly,
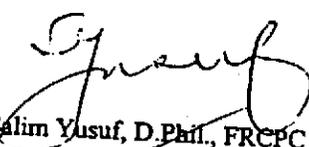
Salim Yusuf, D.Phil., FRCPC

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Study Chairs:
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    Chair:
    Dagenais
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Data Safety &
Monitoring Board
  D. Sackett (Chair)
  R. Collins, C. Furberg,
  C. Hennekens, B. Pitt,
  E. Davis

March 1, 2000

Mr. Thomas Rogers
VP Regulatory Affairs
King Pharmaceuticals, Inc.
501 fifth street
Bristol, Tennessee   37620
USA

Dear Tom,

I am writing to clarify the issue of dispensation of funds to centres in the HOPE Study.

Funding for the HOPE study was derived from the multiple sources that included the Medical Research Council of Canada, Hoechst-Marion Roussel, AstraZeneca, King Pharmaceuticals, Natural Vitamin E Association and Negma, and the Heart and Stroke foundation of Ontario. The collection and dispersment of all funding for the study was directed by the International Steering committee of the HOPE study. Compensation provided to clinical investigators was based solely on patient recruitment and participation in the study. Compensation affected by the outcome of clinical studies was neither offered to nor received by clinical investigators involved with the study.

Please do not hesitate to contact me if you have any questions regarding this issue.

Yours sincerely,

Salim Yusuf, DPhil, FRCPC
HOPE Study Chair
Director, Division of Cardiology
Professor of Medicine
McMaster University

SY/cn

Cc: HOPE FDA Submissions file

King Pharmaceuticals, Inc.
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January 18, 2000

Thomas K. Rogers, III, M.S.
Vice President, Regulatory Affairs

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852-1420

Re: NDA 19-901
        Altace° (ramipril) Capsules
        Prior Approval Supplement – New Labeled Indications
        User Fee ID #: 3892

Dear Dr. Lipicky:

Submission forms for a new Supplemental Application to King Pharmaceuticals' NDA 19-901 for Altace (ramipril) Capsules are enclosed. This supplement seeks approval of new labeled indications for this product as supported by the HOPE study that was conducted by Dr. Salim Yusuf, et al. Results of the HOPE study are reported in the *New England Journal of Medicine* and conclude that "ramipril significantly reduces mortality, myocardial infarction, stroke, revascularization procedures, and heart failure."

Based upon the agreement of our teleconference with you on January 12, 2000, clinical and statistical data to support this supplement are being forwarded to FDA under separate cover directly by Dr. Yusuf. Please contact us if you do not receive these data.

We sincerely appreciate your personal interest in this submission and we look forward to working with the Agency through the review and approval process for this submission.

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Vice President Regulatory Affairs

Cc: Mr. John M. Gregory
      Mr. Jefferson J. Gregory
      Dr. Henry Richards
      Mr. Ed Reilly
      Dr. Salim Yusuf

Shiva Biomedical, LLC

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UAMS MEDICAL CENTER

SUDHIR V. SHAH, M.D.
PROFESSOR AND DIRECTOR

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES
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December 16, 1999

Dr. David Roeder
Division of Cardio-Renal Drug Products
Food and Drug Administration
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Roeder:

I want to thank Dr. Lipicky, you, Sandra Birdsong, and other FDA staff for reviewing the information that I had sent you and making many helpful suggestions. I want to summarize my understanding of the major points that were made at the meeting.

1. Dr. Lipicky recommended that we consider carrying out in vitro studies using human liver slices to identify the metabolites on deferiprone. The rationale for these studies is that we may identify a metabolite that is as effective as the parent compound with less toxicity.

2. Complete a mitogenic screen. You would be sending me details of the nature of the studies that are required for this.

3. Carcinogenic studies following the published guidelines that you would be providing me.

4. To consider the potential toxic effects of the chelated product and to carry out some animal studies to address this issue. As was pointed out in the discussion, this becomes more of an issue if during the course of the human studies we identify that there is in fact accumulation of the chelated product in patients with renal insufficiency.

5. It is my understanding that none of these studies are required to begin the clinical trial the points related which I will outline below, but that the FDA would like to see plans for these studies in the _____ application. FDA recommends that these studies be carried out in parallel with the human studies because they would be required for the NDA approval. If new published data are available that would make carrying out these studies unnecessary, these data should be provided.

The clinical studies in which we presented three protocols, in essence, Dr. Lipicky said to cut to the chase and proceed to study three. The major reason is that proteinuria is a major end-point in Study-1 and that would not satisfy the FDA as a valid end-point in its own right.

In the discussion related to the clinical protocols the following points were made:

1. Must select appropriate definite end-points, which include doubling of the creatinine, death, dialysis. Other end points, of course, could also be included such as proteinuria.

2. There was some concern about maintaining the blind for the patient and for the investigator because deferiprone causes discoloration in a percentage of patients that receive it. Several solutions were discussed, the best of which appears to be to incorporate a substance that would discolor urine in all patients including patients receiving placebo.

3. There was some discussion about the validity of weekly monitoring of white blood count followed by intervals of 3 months. Since the precise mechanism does not appear to be known, Dr. Lipicky suggested that we do the literature search and give some thought to when the white blood count should be monitored, how often, and some rationale for selecting those time points. For example, he said that it may not be necessary after the first month or two to be closely monitoring the white count as opposed to be paying much more attention to the development of infection in the patient which would prompt a visit and measurement of white blood count. In any case, he wanted more details developed on this point.

4. He strongly urged us to reconsider the doses that we were using: 75, 50 and 25 mg/kg/day. He said that, in general, this should be in log order rather than the doses that we selected and although this was our call, he would probably omit the 50-mg. dose.

5. FDA would prefer two separate studies which address the progressive renal failure and some details were discussed related to design which will be incorporated by Dr. Lewis in the protocols that are being developed. Importantly though, at the end of the meeting the transplant patients were brought up and according to the conversation between Dr. Lewis and Dr. Lipicky if we studied transplant patients as a separate protocol and if the rest of the progressive renal failure as another protocol, these two would satisfy the requirement for two separate studies.

6. While the FDA would have no objection to carrying out the study in diabetic patients with microalbuminuria, (or for that matter patients with proteinuria) Dr. Lipicky felt it would be an uphill battle to get NDA approval for this indication. Several strategies related to this were also discussed but it was left to us to decide whether to study these patients and in what manner.

Dr. Roeder, I look forward to your minutes of the meeting as well as the guidelines that we discussed. If there are things in this letter that are not in keeping with our discussions, please do not hesitate to let me know. Thank you, once again.

Yours sincerely,
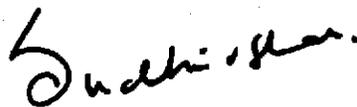
SUDHIR V. SHAH, M.D.
Professor and Director
Division of Nephrology

SVS/jn

1. Based on the collective information available about the toxicity of deferiprone, if you agree that the parameters including monitoring of the white blood cell count and liver function tests, have been appropriately selected.

2. Because there is a fair amount of pharmacological and toxicological information available on deferiprone we do not believe that pharmacokinetic studies are necessary on patients in study protocols 1 and 2 who do not have advanced renal failure. On the other hand, we would like to discuss the extent and nature of pharmacokinetic studies required for study protocol 3 dealing with patient with progressive renal disease.

3. Although not specifically mentioned in protocol 3, we consider the patients with chronic transplant rejection to fall under the category of patients with progressive renal disease. We recognize that additional studies in this particular group of patient will be required including documenting that deferiprone does not interfere with the levels of cyclosporine achieved in renal transplant patients.

We anticipate the following individuals to attend the Pre-IND meeting:

1. Sudhir V. Shah, M.D., Professor of Medicine and Director, Division of Nephrology, University of Arkansas for Medical Sciences, Little Rock, Arkansas.
2. Mahendra Patel, Ph.D., Invamed, Inc., Dayton, New Jersey.
3. Edward Lewis, M.D., Professor of Medicine and Director, Division of Nephrology, University of Chicago, Chicago, Illinois.
4. Julia Breyer-Lewis, M.D., Associate Professor of Medicine, Vanderbilt University Medical Center. Nashville, Tennessee may also attend the meeting.

I am looking forward to visiting with you on December 14, 1999. If you have any questions or need further information, please do not hesitate to contact me.

Sincerely,

Sudhir V. Shah, M.D.

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November 23, 1999

Thomas K. Rogers, III, M.S.
Vice President, Regulatory Affairs

Raymond Lipicky, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

RE: NDA 19-901
Altace® (ramipril) 1.25, 2.5, 5, and 10 mg Capsules
General Correspondence

Dear Dr. Lipicky:

We appreciate the recent opportunity of meeting with Dr. Robert Fenichel and others of your Division on Friday November 19, 1999. The discussion provided valuable guidance for the anticipated submission of important new findings generated from the recently completed HOPE study.

You are aware that Salim Yusuf, D.Phil., FRCPC, FACC, served as the principal investigator for the HOPE study which evaluated the long-term effects of ramipril in preventing cardiovascular death, myocardial infarction, and stroke in 9,297 high risk patients. Ms. Jackie Bosch was the study coordinator for the HOPE study, which was conducted under an investigator IND.

As sponsor of NDA 19-901 for Altace (ramipril) Capsules, King Pharmaceuticals hereby grants complete authority to Dr. Jusuf, Ms. Bosch, and their colleagues at McMaster University, Hamilton, Ontario, Canada, to communicate directly with the Agency on matters associated with a Supplemental Application regarding results of this study.

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Vice President Regulatory Affairs

Cc: Jefferson J. Gregory
John A. A. Bellamy
Ed Reilly
Salim Jusuf
Jackie Bosch