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

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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.

Figure 1:

H♥PE (Heart Outcomes Prevention Evaluation) Study Summary

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 processes 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.

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.[9b,9c] 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]

Vitamin E reduces atherosclerosis in animals. 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. Human ecological studies. 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. Retrospective case-control studies. 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. Prospective studies. 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. Randomized clinical trials. 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,[53,61,62] 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.[78,99] The doubling of serum alpha tocopherol corresponds to a 30% difference in CAD rates between different populations,[53] 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.

VIEW OF PROPOSED TRIAL.

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 moderate, but important effects on clinically relevant endpoints may be reliably detected or excluded.

3. Clinically important results will be obtained as even modest 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 broad, 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.

6. 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 ≥ 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 transluminal angioplasty, previous limb or foot amputation, history of intermittent claudication with ankle/arm blood pressure ratio of 0.80 or lower *in at least one side*, significant stenosis *(>50%)* documented by angiography.

   (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.

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 $\geq 1+$ *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 $\geq 1+$ *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

e telephone, the patient is randomized. The Randomization Form is completed and faxed to the C3PO. 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 counselled. 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.[81]

As 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-

tocopherol levels is associated with a 30% reduction in CAD rates.[53, 61, 62] 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). Among diabetic patients, the incidence of nephropathy will be assessed for each therapy. Data will 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 by 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.

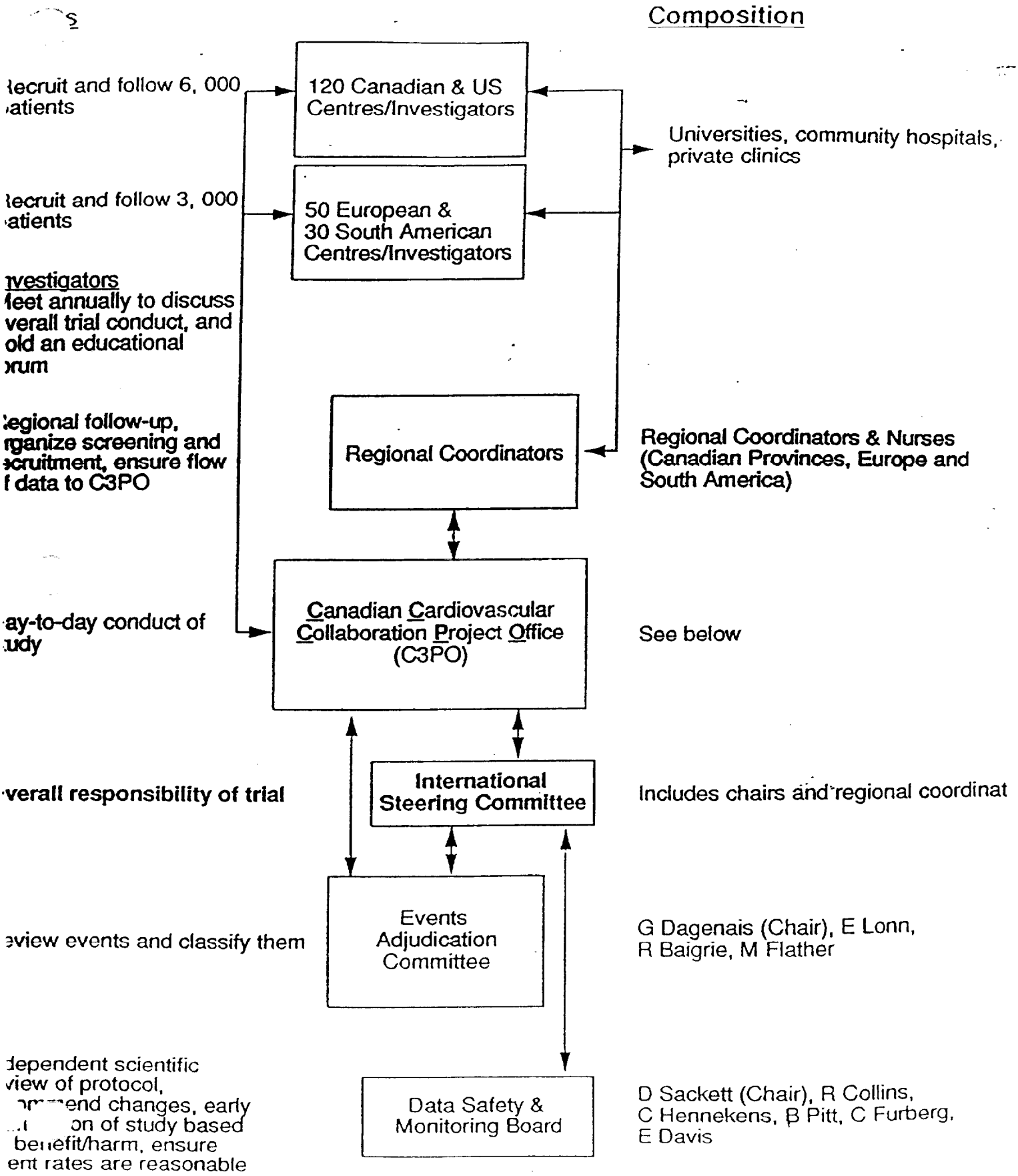
11. FEASIBILITY OF RECRUITMENT.

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)

Figure 2: HOPE Study Organization



tional Steering Committee: *Co-Chairs:* S Yusuf, T Montague, P Sleight; *Vice-Chair* G Dagenais; *Canadian Coordination:* M Arnold, R Baigrie, ars, R Davies, R Hoeschen, D Johnstone, P Liu, B Mitchell, H Mizgala, A Morris, D Naylor, N Racine, F Sestier, B Sussex, K Teo, P Theroux, CR on, H Tildesley, R Tsuyuki, G Wisenberg, B Zinman; *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.

Table 4: Feasibility of Recruitment of 8,000 patients in one year

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,[1, 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

of non-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.[97] A recent retrospective study of 80 patients showed that higher levels of antioxidant Vitamin A levels were associated with a better neurologic endpoint.[98] 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 from the prospective Nurses Study indicates an inverse relationship between Vitamin E levels and stroke (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 trial[6-8] beneficial effects of enalapril in reducing ischemic events are seen in both diabetics or non-diabetics (unpublished data). Other beneficial effects of ACE-I have been described in diabetics, including improvement of insulin sensitivity and glycemic profile.[102,105]

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.[79,106-71] 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.

Appendix A, Tab[illegible]. Rates for the combined endpoint of cardiovascular death, myocardial inf[illegible] and strokes in various types of patients that are to be included in HOPE assuming the [illegible]of aspirin in all patients.

Type of Patient	Source [ref]	No. CVD events/no. patients	Mean Follow-up (years)	Annualized event rates (%)	Comments
1) Long-term post MI	APT Collaboration[82]	1321/9877	2.3	5.8	Event rate in patients on aspirin. Excludes acute MI.
Acute and long term post MI	a) ISIS-1[84]				
	35 days-1 year	625/14622 (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	2.8*	
	b) ISIS-2[85]				
	35 days-1 year	817/14535 (deaths)	1.0	5.6*	
	>1 year-2 years	238/9144 (deaths)	1.0	2.8*	
	c) ISIS-3[80]				
	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[83]	92/1991	0.9	4.6	Excludes events during first month.
3) Post-CABG	a) CABG Pooling Project[87]	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[88]	382/1113	1.0	10.8	
4) Post-angioplasty	NHLBI Registry[89]	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 rates, 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 strokes in various types of patients that are to be included in HOPE assuming the use of aspirin in all patients.**

Type of Patient	Source [*,**]	No. CVD events/no. patients	Mean Follow-up (years)	Annualized event rates (%)	Comments
5) Stable angina (without surgery)	a) APT Collaboration[83]	27/229	3.7	3.2	Excludes patients with more severe angina.
	b) CABG pooling[87] 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[83]				
	a) all patients	221/2221	2.6	4.1	
	b) grafting	65/771	1.7	5.0	
7) Post stroke/TIA	APT Collaboration[83]	1082/5083	2.1	8.9	11% of events MI, 44% strokes and 46% cardiovascular deaths.
8) Diabetes Type II (>50 yrs)	ETDRS[90]	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 are smokers, 40% have cholesterol >6.2 and 47% are hypertensive. Rates for CVD events are likely to be 2 to 2.5 times death rates.
Men age 50-57	MRFIT[91]	445/2833 (deaths)	12.0	1.5	
Men and women age 45-64	Finland[92]	18/109 (MI)	5.0	4.0	
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.

Appendix B. Antioxidant Vitamin E

1. Rationale for choice of Natural Source Vitamin E

Vitamin E (d-alpha-tocepheryl 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 to 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 amin 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

dietary questionnaire found that the upper quintile of α-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 α-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 α-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 α-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.[115,118] 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.

ndix C: Outline of Consent Form for HOPE Study

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.

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)

ndix D: Adverse Reactions of Ramipril and Monitoring

Specific definition of major adverse effects are as follows:

Azotemia: increase in serum creatinine to 200 mEq/L or greater (≥ 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[illegible] adverse events need not be reported to regulatory agencies. Deaths, primary endpoints and s[illegible]dary 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.

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 (≥ 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.

...dix G: Responsibilities of Investigators and Payment Schedule

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 ...rgency 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).

Appendix H

The H O P E Study Rationale and Design for Patients with Diabetes Mellitus

Contents:

ecific Objectives Related To Diabetes

The 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

A. 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].

amin E and Cardiovascular Risk in Diabetes

A 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[79,106-7]. 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 Source Vitamin E or placebo and Ramipril or placebo. They will be followed every 6 months for up to 5 years 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.

1) Glycated hemoglobin (or value within the last four weeks)

, 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.