
**International Task Force for Prevention
Of Coronary Heart Disease**



*Clinical management of risk factors
of coronary heart disease and stroke*

Major recent drug trials

**The Heart Outcomes
Prevention Evaluation Study**

TABLE OF CONTENT

Slide 1: Objective and design	3
Slide 2: Eligibility	4
Slide 3: Baseline characteristics of patients	5
Slide 4: Compliance with study medications	6
Slide 5: Blood pressure	7
Slide 6: Ramipril: Incidence of the primary outcome and of deaths from any cause	8
Slide 7: Incidence of secondary and other outcomes	9
Slide 8: Incidence of coronary events and revascularisation	10
Slide 9: Clinical outcomes in patients with diabetes: Results of the MICRO-HOPE substudy	11
Slide 10: Incidence of primary and other outcomes in women and men	12
Slide 11: Vitamin E: Incidence of the primary outcome and of deaths from any cause	13
Slide 12: Conclusions	14

Slide 1:

Objective and design



The Heart Outcomes Prevention Evaluation (HOPE) Study



Objective

- **Assessment of the effects of an angiotensin-converting-enzyme inhibitor, ramipril, and of the antioxidant vitamin E in patients at high risk for cardiovascular events but without left ventricular dysfunction or heart failure**

Primary Outcome

- **Myocardial infarction, stroke or death from cardiovascular causes**

Design

- **Two-by-two factorial, placebo-controlled, double-blind, randomised study for a mean duration of five years**

Source: The Heart Outcomes Prevention Evaluation Study Investigators, *N Engl J Med* 2000;342:145-153

Objective and design

This slide shows the objective and design of the Heart Outcomes Prevention Evaluation (HOPE) study. Epidemiological and experimental data suggest that blocking the activation of the renin-angiotensin-aldosterone system by an angiotensin-converting-enzyme inhibitor may have an important role in reducing the risk of cardiovascular events. Observational studies have indicated that a high intake of vitamin E may result in lower rates of coronary events and lower rates of progression of coronary artery lesions. This study is designed to evaluate the effects of both medications independently on cardiovascular and other outcomes. Patients were randomly assigned to receive ramipril (up to 10 mg/day), vitamin E (400 IU/d), their combination, or matching placebos.

Slide 2:

Eligibility



ELIGIBILITY



- **Men and women**
- **Age \geq 55 years**
- **History of coronary artery disease, stroke, peripheral vascular disease or diabetes plus at least one other cardiovascular risk factor**



Source: The Heart Outcomes Prevention Evaluation Study Investigators, N Engl J Med 2000;342:145-153

Eligibility

This slide shows the eligibility criteria for the participants of the HOPE study. Other cardiovascular risk factors included hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria.

Slide 3:

Baseline characteristics of patients

 Baseline Characteristics of Patients 			
Characteristic	Ramipril (n=4645)	Placebo (n=4652)	
Age (y)	66	66	
Blood pressure (mm Hg)	139/79	139/79	
Heart rate (beats/min)	69	69	
BMI (kg/m²)	28	28	
Female sex (%)	27.5	25.8	
History of coronary artery disease (%)	79.5	81.4	
Stroke or transient ischemic attacks (%)	10.8	11.0	
Peripheral vascular disease (%)	42.3	44.8	
Hypertension (%)	47.6	46.1	
Diabetes (%)	38.9	38.0	
Documented elevated total cholesterol level (%)	65.4	66.4	
Documented low HDL-cholesterol level (%)	18.1	18.9	
Current cigarette smoking (%)	13.9	14.5	
Microalbuminuria (%)	20.5	21.6	

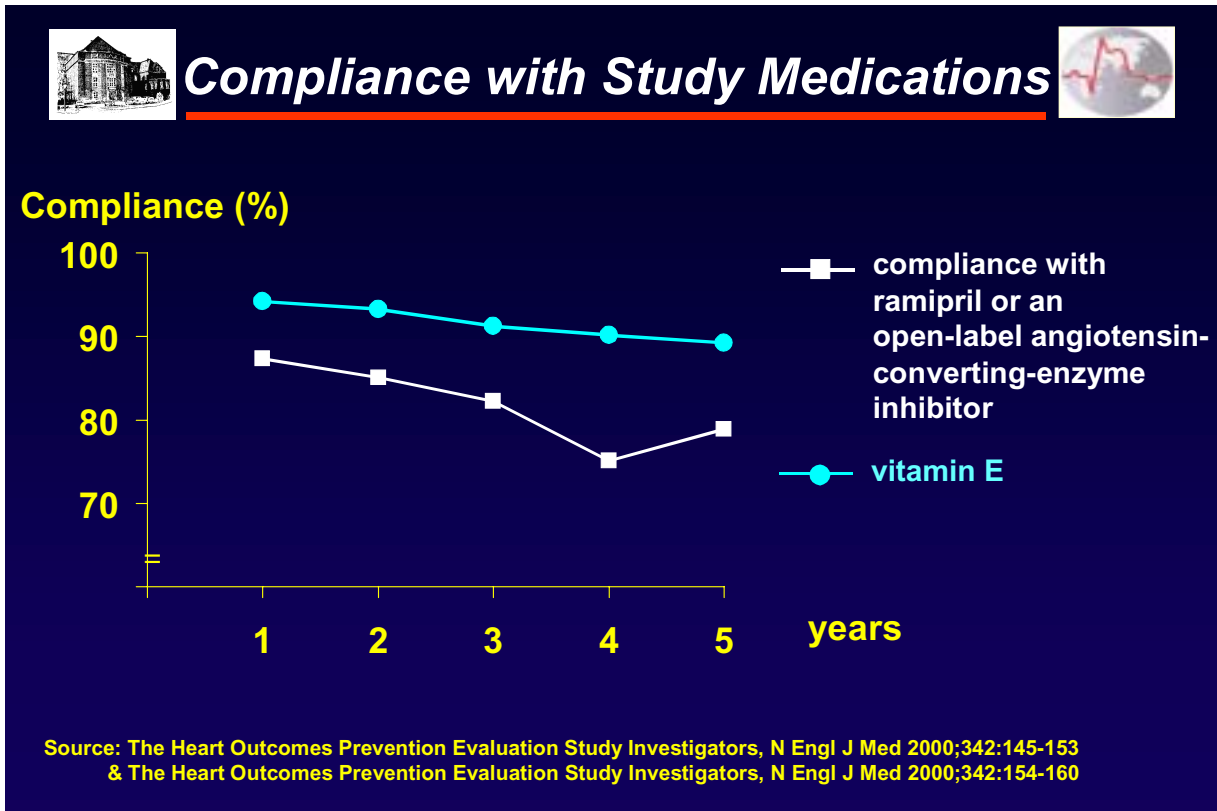
Source: The Heart Outcomes Prevention Evaluation Study Investigators, N Engl J Med 2000;342:145-153

Baseline characteristics of patients

This slide shows baseline characteristics of the HOPE-participants. Patients were recruited from December 1993 to June 1995 at 129 centres in Canada, 27 centres in the United States, 76 centres in 14 western European countries, 30 centres in Argentina and Brazil, and 5 centres in Mexico. Of the total of 9541 patients, 4645 were randomly assigned to ramipril (10mg/d), 4652 to placebo and 244 to a low dose of ramipril (2.5 mg/d). In addition, all patients were randomly assigned to receive 400 IU of vitamin E per day or matching placebo.

Slide 4:



Compliance with study medications



Compliance with study medications

This slide shows the compliance with the study medications vitamin E and the combined compliance of ramipril or an open-label angiotensin-converting-enzyme inhibitor.

Slide 5:
Blood pressure



Blood Pressure

	Ramipril	Placebo
Baseline mean blood pressure	139/79	139/79
at one month	133/76	137/78
at two month	135/76	138/78
at end of study	136/76	139/77

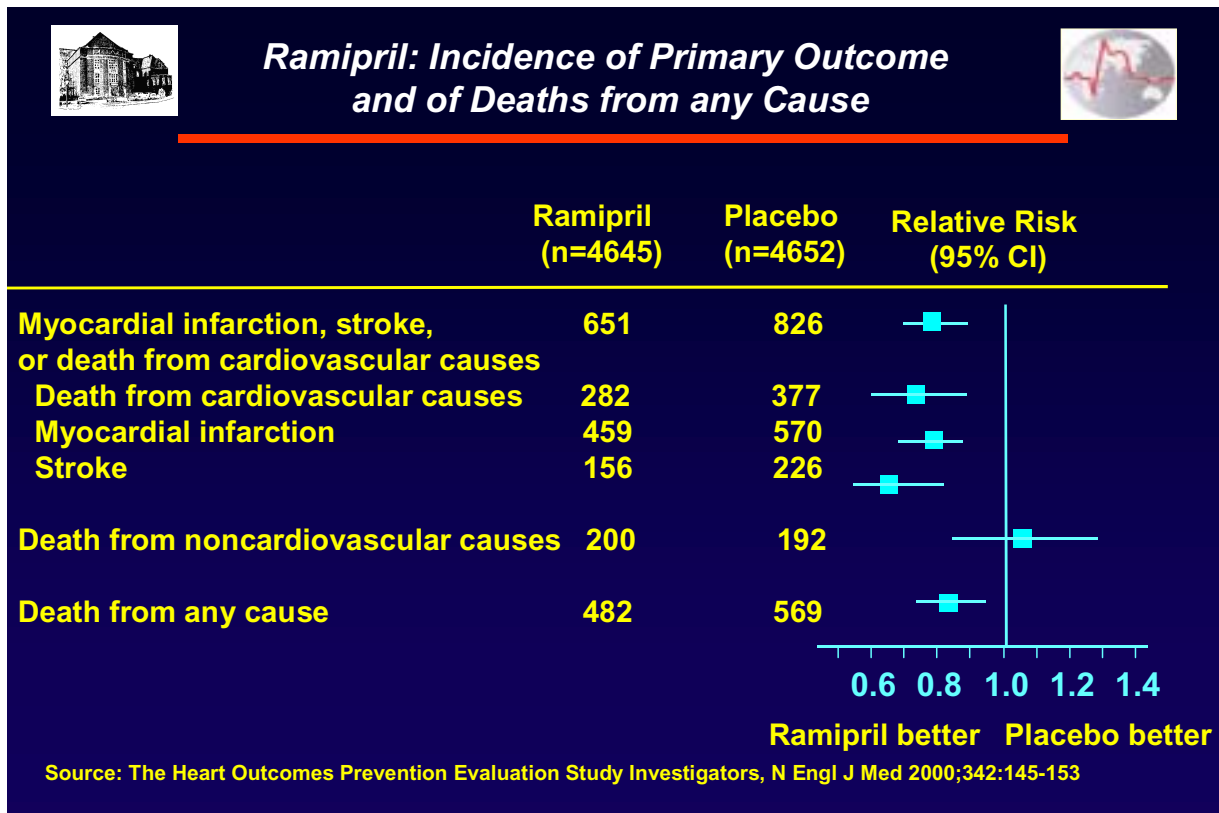
Source: The Heart Outcomes Prevention Evaluation Study Investigators, N Engl J Med 2000;342:145-153

Blood pressure

This slide shows mean blood pressure values at different points during study follow-up.

Slide 6:

Ramipril: Incidence of the primary outcome and of deaths from any cause



Ramipril: Incidence of the primary outcome and of deaths from any cause

Treatment with ramipril significantly reduced the risk of the primary outcome, the risk of each component of the primary outcome (myocardial infarction, stroke or death from cardiovascular cause) and the risk of death from any cause as compared with placebo.

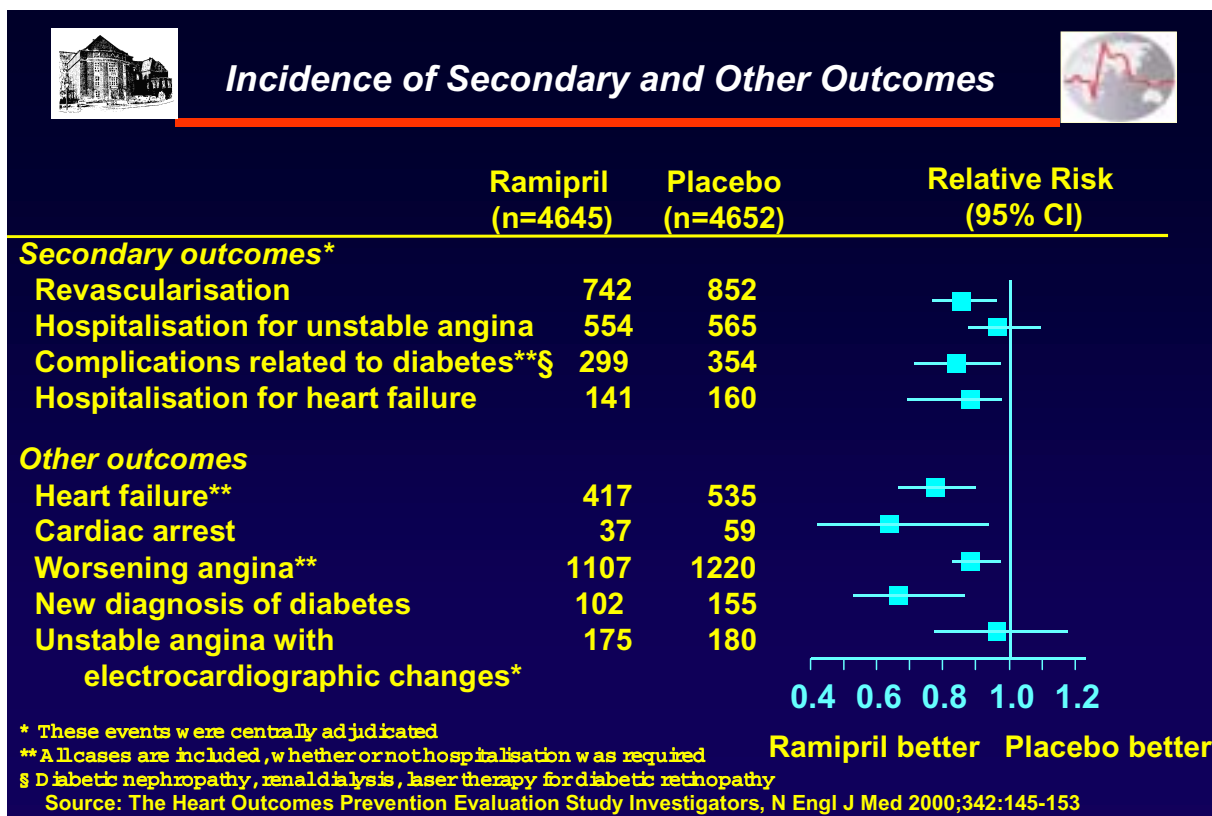
In a substudy with a low dose of ramipril (2.5 mg/day), 34 of 244 patients (13,9%) reached the composite end point, as compared with 31 of 244 assigned to take 10 mg of ramipril per day (12,7%) and 41 of 244 assigned to placebo (16,8%). The inclusion of the data from the low-dose group did not change the overall results (relative risk of the primary outcome, 0.78 [95 % CI, 0.70-0.86]).

Only a small part of the benefit of treatment with ramipril is related to a reduction in blood pressure. It is likely that angiotensin-converting-enzyme inhibitors exert additional direct mechanisms on the heart or the vasculature. These may include antagonizing the direct effects of angiotensin II on vasoconstriction, the proliferation of vascular smooth-muscle cells, and rupture of plaques, improving vascular endothelial function, reducing left ventricular hypertrophy and enhancing fibrinolysis.

The benefits of treatment with ramipril were additive to other cardioprotective medications such as beta-blockers, aspirin or other antiplatelet agents, lipid-lowering agents, diuretics and calcium-channel blockers.

Slide 7:

Incidence of secondary and other outcomes

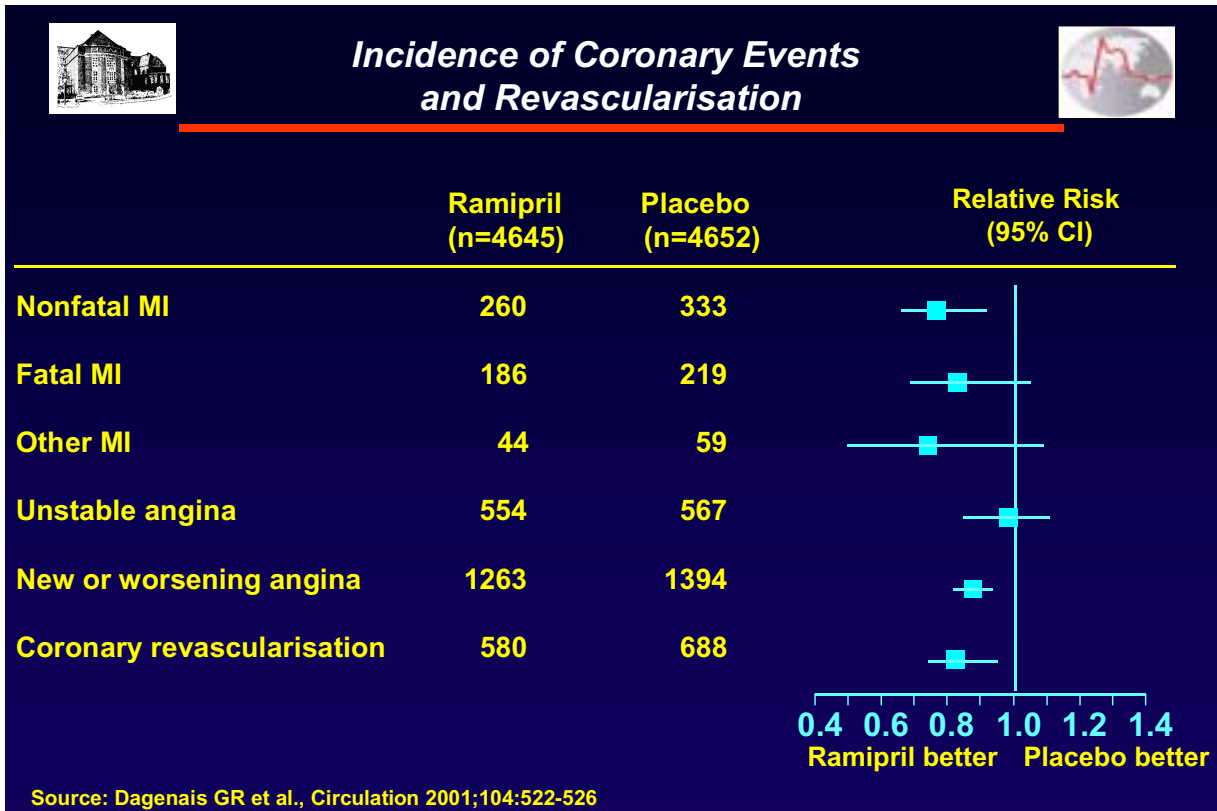


Incidence of secondary and other outcomes

Significantly fewer patients in the ramipril group than in the placebo group underwent revascularisation. There was a trend toward fewer hospitalisations for heart failure in the ramipril group, but no effect on the likelihood of hospitalisation for unstable angina. Significantly fewer patients in the ramipril group than in the placebo group had a cardiac arrest, worsening angina, heart failure, a new diagnosis of diabetes or complications related to diabetes such as diabetic nephropathy, need for renal dialysis or need for laser therapy for diabetic nephropathy.

Slide 8:

Incidence of coronary events and revascularisation



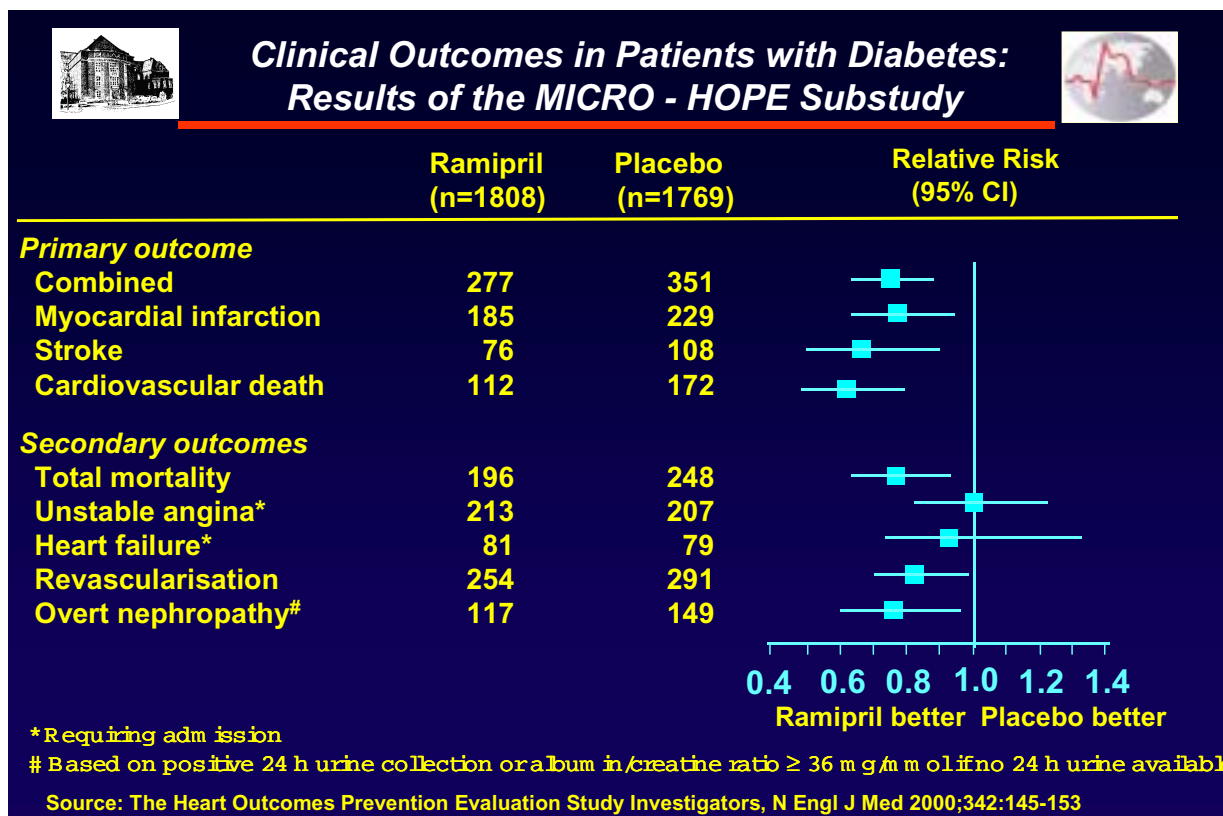
Incidence of coronary events and revascularisation

This slide shows greater details on a range of coronary events and coronary revascularisation. Patients in the ramipril group had reduced relative risk of nonfatal myocardial infarction. There was a trend toward fewer fatal and other myocardial infarction in the ramipril group. Ramipril significantly lowered the rates of new and worsening angina, but not of unstable angina. This apparently inconsistent finding may be due to subjective and variable definitions of this event, the practice patterns in different regions, and the play of chance. Ramipril was associated with a significant lower rate of coronary revascularisation procedures in comparison to placebo.

The beneficial impact of ramipril on the occurrence of myocardial infarction was observed in those taking or not taking antiplatelet agents, lipid-lowering agents, and/or β -blockers, indicating that the effects are independent and additive to those agents.

Slide 9:

Clinical outcomes in patients with diabetes: Results of the MICRO-HOPE substudy



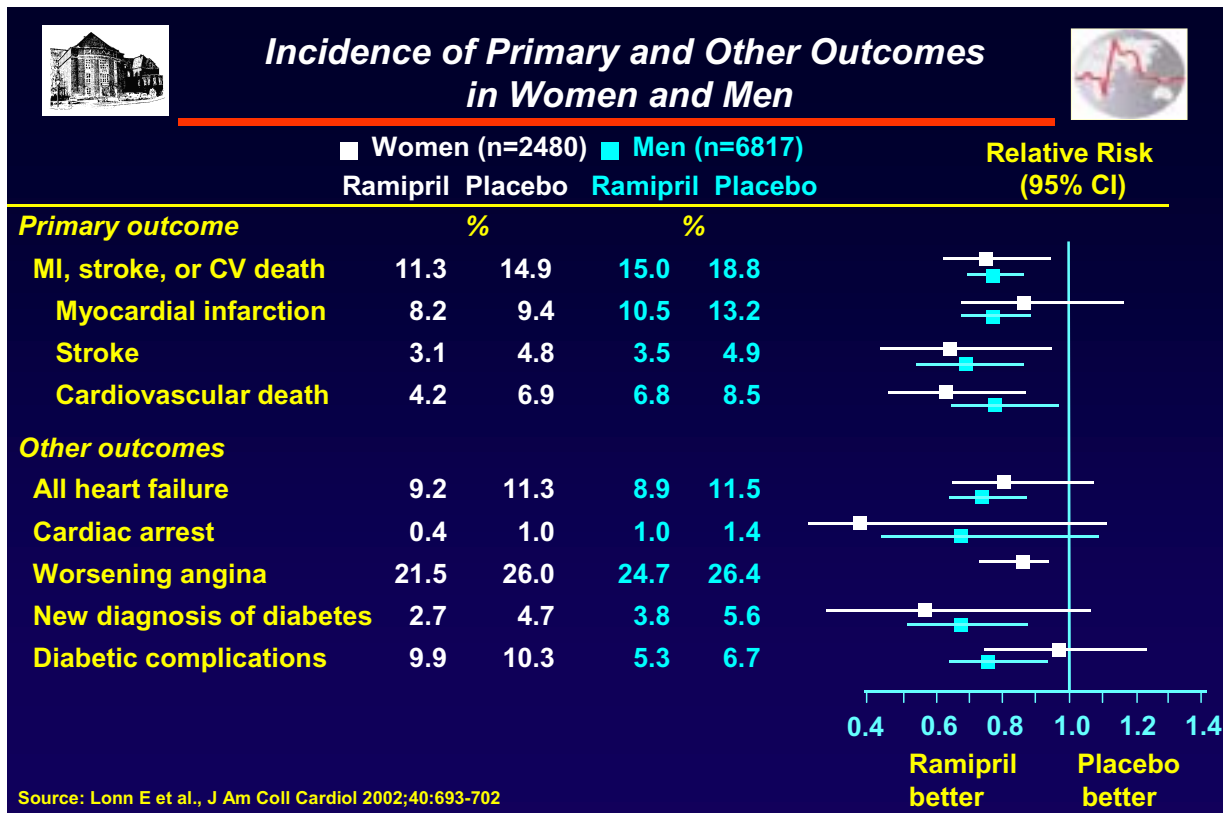
Clinical outcomes in patients with diabetes: Results of the MICRO-HOPE substudy

Of all 9541 participants in the HOPE study 3654 (39.3 %) had diabetes without clinical proteinuria at randomisation. Ramipril significantly lowered the rates of the combined primary outcome of myocardial infarction, stroke, or cardiovascular death and of the single components of the combined outcome compared with placebo. There was a significant treatment effect of ramipril on secondary outcomes such as total mortality, revascularisation and overt nephropathy, but no effect on unstable angina and heart failure compared with placebo.

The cardiovascular benefit was greater than that attributable to the decrease in blood pressure (systolic Bp (2.4 mmHg); diastolic Bp (1.0 mmHg)). Treatment with ramipril represents a vasculoprotective and renoprotective effect for persons with diabetes.

Slide 10:

Incidence of primary and other outcomes in women and men



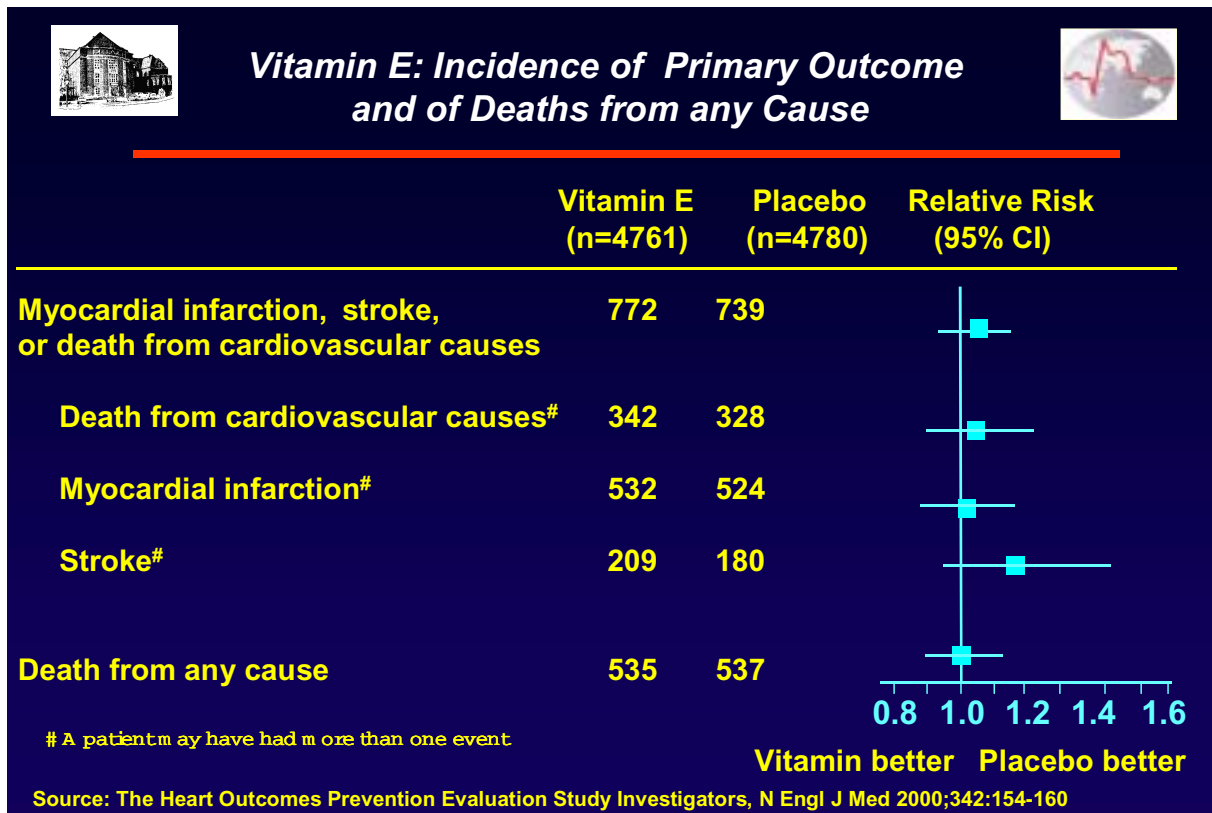
Incidence of primary and other outcomes in women and men

This slide presents the results of the preplanned analysis of the effects of ramipril in women in the HOPE study. The study included 2,480 women aged 55 years with vascular disease or diabetes and at least one additional cardiovascular risk factor and without heart failure or a known low LV ejection fraction.

Treatment with ramipril significantly reduced the risk of major vascular events in women. Women in the ramipril arm of the study had significantly fewer major vascular events, deaths from cardiovascular causes, strokes and episodes of worsening angina. The effects of ramipril appeared to be similar in women and in men; this lack of gender-based difference was noted after controlling for baseline differences and other predictors of risk between women and men. Similar to the overall HOPE study results (see slide 5-8), the magnitude of the benefit on major clinical outcomes in women appeared to exceed the small reduction in blood pressure attained (3mm Hg systolic/1.5 mm Hg diastolic) and is likely to be related to a wide range of cardiac and vascular protective actions of long-term ACE inhibitor therapy, in addition to blood pressure lowering. The benefits of treatment with ramipril were additive to other cardioprotective medications.

Slide 11:

Vitamin E: Incidence of the primary outcome and of deaths from any cause



Vitamin E: Incidence of the primary outcome and of deaths from any cause

This slide shows the results of the vitamin arm of the HOPE study. Treatment with vitamin E (400 IU) for a mean of 4.5 years had no apparent effect on cardiovascular outcomes in patients at high risk for cardiovascular events. The number of events among those receiving ramipril did not differ significantly between those assigned to receive vitamin E and those assigned to placebo (338 vs 313). Similar results were observed among those who received matching placebo rather than ramipril (421 vs. 405).

Slide 12:

Conclusions



Conclusions



In patients at high risk for cardiovascular events, but without a low ejection fraction or heart failure,

- **treatment with vitamin E for a mean of 4.5 years has no apparent effect on cardiovascular outcomes**
- **treatment with ramipril**
 - ◆ **significantly reduces the rates of death, myocardial infarction, stroke, and revascularisations. This effect appears to be similar in women and men.**
 - ◆ **significantly reduces complications related to diabetes and new diagnosis of diabetes**
 - ◆ **has a vasculoprotective and venoprotective effect for patients with diabetes**

Source: The Heart Outcomes Prevention Evaluation Study Investigators, N Engl J Med 2000;342:145-153 and N Engl J Med 2000;342:154-160 and Lancet 2000;355:253-59 and Lonn E et al. JACC 2002;40:693-702

Conclusions

This slide presents the conclusions of the HOPE study and its substudies.