Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study)

The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators

Summary

Background Treatment with angiotensin-converting-enzyme (ACE) inhibitors reduces the rate of cardiovascular events among patients with left-ventricular dysfunction and those at high risk of such events. We assessed whether the ACE inhibitor perindopril reduced cardiovascular risk in a low-risk population with stable coronary heart disease and no apparent heart failure.

Methods We recruited patients from October, 1997, to June, 2000. 13 655 patients were registered with previous myocardial infarction (64%), angiographic evidence of coronary artery disease (61%), coronary revascularisation (55%), or a positive stress test only (5%). After a run-in period of 4 weeks, in which all patients received perindopril, 12 218 patients were randomly assigned perindopril 8 mg once daily (n=6110), or matching placebo (n=6108). The mean follow-up was 4·2 years, and the primary endpoint was cardiovascular death, myocardial infarction, or cardiac arrest. Analysis was by intention to treat.

Findings Mean age of patients was 60 years (SD 9), 85% were male, 92% were taking platelet inhibitors, 62% β blockers, and 58% lipid-lowering therapy. 603 (10%) placebo and 488 (8%) perindopril patients experienced the primary endpoint, which yields a 20% relative risk reduction (95% CI 9–29, p=0·0003) with perindopril. These benefits were consistent in all predefined subgroups and secondary endpoints. Perindopril was well tolerated.

Interpretation Among patients with stable coronary heart disease without apparent heart failure, perindopril can significantly improve outcome. About 50 patients need to be treated for a period of 4 years to prevent one major cardiovascular event. Treatment with perindopril, on top of other preventive medications, should be considered in all patients with coronary heart disease.

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Introduction

Cardiovascular disease remains the leading cause of death in most regions of the world, mostly in the form of coronary heart disease.[1] Over the past few decades, preventive and therapeutic measures have substantially improved the prognosis of these patients.[2,3] Nevertheless, the risk of cardiovascular complications remains high and progression can be halted only in a few patients, despite treatment with aspirin, statins, and β blockers.[4] More effective secondary preventive strategies are needed, and angiotensin-converting-enzyme (ACE) inhibitors could fill an important gap. ACE inhibitors effectively reduce mortality and morbidity among patients with heart failure, left-ventricular dysfunction, after myocardial infarction, with hypertension, and among other high-risk patients.[5–11] In particular, previous ACE-inhibitor studies have suggested a reduction in the rate of myocardial infarction and the need for revascularisation in patients with heart failure and left-ventricular dysfunction.[12,13] The Heart Outcomes Prevention Evaluation (HOPE) study[11] confirmed the benefits of ACE inhibition in patients aged 55 years or older at high risk of cardiovascular complications, characterised by a high prevalence of diabetes, hypertension, stroke, and obstructive peripheral vascular disease. In addition to lowering blood pressure, ACE inhibitors possess direct cardiovascular protective effects through angiotensin II reduction and increased bradykinin availability.[14] Consequently, ACE inhibition may result in antiatherosclerotic effects, reduced neointimal formation, and improved endothelial function, plaque stabilisation, and fibrinolysis.[15–17] In animal models, ACE inhibitors reverse atherosclerosis.[18] This multifactorial antiatherosclerotic profile of ACE inhibition suggests that its application might be extended to all patients with established coronary heart disease and should not be restricted to patients with impaired left-ventricular function, heart failure, or a high risk of atherosclerotic events.[11–13]

Therefore, in the EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) study, we aimed to assess the ability of the ACE inhibitor perindopril to reduce cardiovascular death, myocardial infarction, and cardiac arrest in a broad population of patients with stable coronary heart disease and without heart failure or substantial hypertension. We used perindopril, a long-acting ACE inhibitor, because, in addition to its blood-pressure-lowering properties, it has documented anti-ischaemic and antiatherogenic effects, as well as an effect on cardiovascular remodelling.[19–23]

Patients and methods

We did a randomised, double-blind, placebo-controlled, multicentre study. The design of the trial has been described previously.[24]

Patients

Between October, 1997, and June, 2000, we recruited men and women aged at least 18 years without clinical evidence of heart failure and with evidence of coronary heart disease, documented by previous myocardial infarction (>3 months before screening), percutaneous or surgical coronary revascularisation (>6 months before screening), or angiographic evidence of at least 70% narrowing of one or more major coronary arteries. Men could also be recruited if they had a history of chest pain and a positive electrocardiogram, echo, or nuclear stress test. Exclusion criteria included: clinical evidence of heart failure, planned revascularisation, hypotension (sitting systolic blood pressure <110 mm Hg), uncontrolled hypertension (systolic blood pressure >180 mm Hg, diastolic blood pressure >100 mm Hg, or both), recent (<1 month) use of ACE inhibitors or angiotensin-receptor blockers, renal insufficiency (creatinine >150 μmol/L), and serum potassium higher than 5·5 mmol/L. Informed consent was obtained from all patients.

Methods

In a run-in period, enrolled patients received 4 mg oral perindopril once daily, in the morning, for 2 weeks in addition to their normal medication, followed by 8 mg oral perindopril once daily, in the morning, for 2 weeks if the lower dose was well tolerated. Patients aged 70 years or older were given 2 mg perindopril in the first week of screening, followed by 4 mg daily in the second week, and 8 mg daily in the last 2 weeks. At the end of the run-in period, patients were randomly assigned perindopril 8 mg (two tablets) or placebo once daily for at least 3 years. If this dose was not tolerated, it could be reduced to 4 mg once daily or matching placebo (figure 1).

We saw patients at 3, 6, and 12 months, and every 6 months thereafter. Blood pressure, recorded twice with a standard sphygmomanometer after at least 5 min of rest, and heart rate were measured at each visit in a sitting position. We measured sodium, potassium, and creatinine concentrations in serum during the run-in period and at randomisation, and once-yearly thereafter.

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and cardiac arrest with successful resuscitation. Secondary endpoints were: the composite of total mortality, non-fatal myocardial infarction, hospital admission for unstable angina, and cardiac arrest with successful resuscitation; cardiovascular mortality and non-fatal myocardial infarction, as well as the individual components of these secondary outcomes and revascularisation (coronary artery bypass graft or percutaneous coronary intervention), stroke, and admission for heart failure. A diagnosis of myocardial infarction was based on the recommendations of the European Society of Cardiology and the American College of Cardiology.[25]

Towards the end of the initial proposed follow-up period, we changed the definition of the primary endpoint to the above. The primary endpoint was initially defined as the composite of total mortality, non-fatal myocardial infarction, unstable angina, and cardiac arrest with successful resuscitation. The following reasons prompted this modification to the protocol. First, new methods were introduced in clinical practice, which allowed more sensitive and accurate detection of myocardial infarction among patients with acute coronary syndromes. According to the recommendations of the European Society of Cardiology and the American College of Cardiology, all patients with raised markers of myocardial necrosis (creatine kinase-MB mass, cardiac troponin T, or cardiac troponin I) should be labelled as myocardial infarction and distinguished from unstable angina without myocardial necrosis.[25] Unstable angina without myocardial necrosis was no longer judged an appropriate endpoint given its subjective diagnosis and favourable prognosis; accordingly, we removed it from the primary endpoint. Second, the contribution of cardiovascular mortality to the overall mortality in our population proved to be lower, around 60%, than expected. Since ACE inhibition would probably not affect non-cardiovascular mortality, we included cardiovascular mortality in the primary endpoint instead of overall mortality. The original study endpoint was maintained as the first secondary endpoint. These modifications were agreed by the EUROPA trial steering committee in January, 2002, more than 1 year before the trial was completed, with no knowledge of the trial outcome findings at that time. For the new primary endpoint, 775 events would be needed to provide at least 90% power in order to detect a 21% relative reduction in the primary

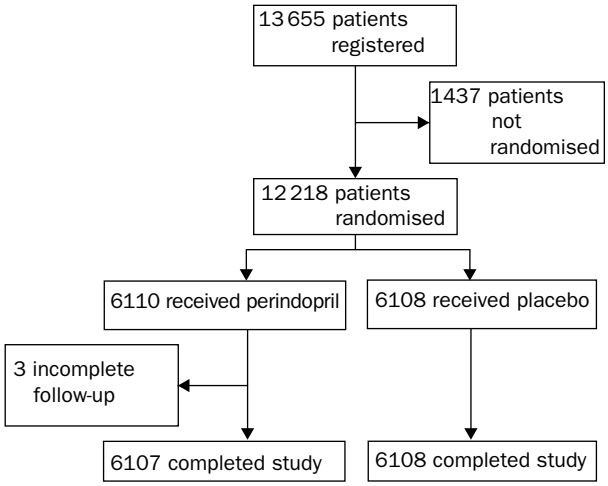


Figure 1: **Trial profile**

	Perindopril (n=6110)	Placebo (n=6108)
Characteristics		
Mean (SD) age (years)	60 (9)	60 (9)
Female sex	884 (14·5%)	895 (14·7%)
History of coronary artery disease		
MI	3962 (64·9%)	3948 (64·7%)
PCI	1773 (29·0%)	1800 (29·5%)
CABG	1790 (29·3%)	1797 (29·4%)
Documented coronary artery disease based on		
Angiographic evidence (stenosis >70%)	3693 (60·4%)	3696 (60·5%)
Positive stress test (in men)	1380 (22·6%)	1422 (23·3%)
Previous stroke or TIA	210 (3·4%)	199 (3·3%)
Peripheral vascular disease	432 (7·1%)	451 (7·4%)
Hypertension*	1650 (27·0%)	1662 (27·2%)
Diabetes mellitus	721 (11·8%)	781 (12·8%)
Hypercholesterolaemia†	3869 (63·3%)	3868 (63·3%)
Medication		
Platelet inhibitors	5613 (91·9%)	5662 (92·7%)
Lipid-lowering therapy	3534 (57·8%)	3499 (57·3%)
β blockers	3790 (62·0%)	3745 (61·3%)
Calcium-channel blockers	1935 (31·7%)	1891 (31·0%)
Nitrates	2613 (42·8%)	2629 (43·0%)
Diuretics	555 (9·1%)	573 (9·4%)
Mean (SD) heart rate (beats/min)	68 (10)	68 (10)
Mean (SD) systolic blood pressure (mm Hg)	137 (16)	137 (15)
Mean (SD) diastolic blood pressure (mm Hg)	82 (8)	82 (8)

Values are n (%) unless marked otherwise. MI=myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary bypass surgery. TIA=transient ischaemic attack. *Blood pressure >160/95 mm Hg or receiving antihypertensive treatment. †Cholesterol >6·5 mmol/L or receiving lipid-lowering treatment.

Table 1: **Baseline characteristics**

	Perindopril (n=6110)	Placebo (n=6108)
Withdrawal from treatment		
Total	1391 (22·8%)	1266 (20·7%)
Cough	162 (2·7%)	32 (0·5%)
Hypotension	60 (1·0%)	17 (0·3%)
Kidney failure	20 (0·3%)	16 (0·3%)
Intolerance	144 (2·4%)	80 (1·3%)
Study endpoint	376 (6·2%)	460 (7·5%)
Hypertension	22 (0·4%)	46 (0·8%)
Refusal to continue	261 (4·3%)	257 (4·2%)
Other reason	347 (5·7%)	359 (5·9%)

Table 2: **Reasons for permanent treatment withdrawal**

endpoint. To accrue the required number of events, the anticipated duration of the trial was extended by 1 year. Patients were scheduled to have their last study visit or contact between Oct 1, 2002, and April 30, 2003.

An independent critical event committee adjudicated all suspected events with source documentation, and an independent data safety monitoring board reviewed outcome data on four occasions during the trial.

Statistical analysis

We used the logrank test in an intention-to-treat analysis for the time to first occurrence of a primary endpoint. The cumulative distribution of events over time was examined with the Kaplan-Meier method. Cox's proportional-hazards model was used to assess risk reduction for the primary and secondary clinical endpoints. We compared event rates between treatment groups with 95% CI.

A descriptive analysis of the primary endpoint was also done in clinically defined subgroups of patients. All analyses were based on intention to treat. For the primary endpoint, the significance level was adjusted to 0·041 to account for four interim analyses.[26] For other endpoints, $p<0·05$ was deemed significant.

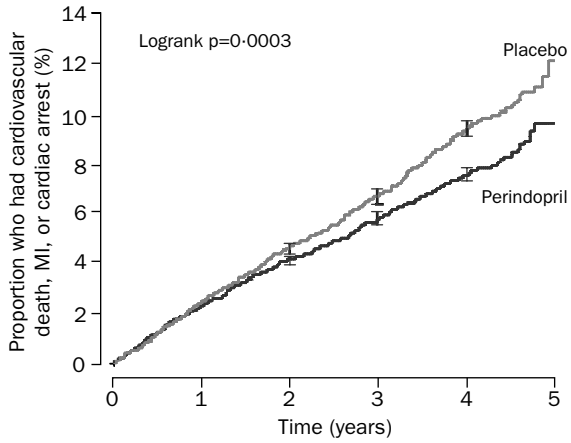
Role of the funding source

Representatives of the sponsor were non-voting members of the study executive committee and were involved with the executive committee in the study design, interpretation of the data, the writing of the report and the decision to submit the paper for publication. However, the sponsor was not involved in the data collection and data analysis.

Results

13 655 patients were registered; 8775 (64%) had a history of myocardial infarction, 8302 (61%) of angiography with substantial stenoses, 7550 (55%) of previous revascularisation, and 1670 (12%) of diabetes mellitus. 603 (5%) men were registered with only an abnormal stress test. After the run-in period, 12 218 patients were randomised: 10 439 (85%) men and 1779 (15%) women (figure 1). Reasons for registered patients not proceeding to randomisation were: hypotension (290), raised potassium or creatinine concentrations (149), other intolerance (332), major clinical events (75), poor adherence to treatment (80), exclusion or non-inclusion criteria (44), withdrawn consent (nine), unspecified stop reason (446), and patients never randomised (12). Mean follow-up was 4·2 years and study endpoints were ascertained for all but three patients during the predefined time period. 1588 (13%) of the patients did not take part in the extension of the trial made necessary by the redefined primary endpoint (unable, or refused to restart or continue study medication).

The mean age was 60 years (SD 9), 7910 (65%) had had a previous myocardial infarction, 5709 (55%; some patients underwent both procedures) had previously undergone revascularisation, 1670 (12%) had diabetes



Patients at risk

Placebo	6108	5943	5781	5598	4450	71
Perindopril	6110	5957	5812	5653	4515	64

Figure 2: **Time to first occurrence of primary endpoint**
SE are indicated.

mellitus (known history of diabetes or were taking antidiabetic agents), 3312 (27%) hypertension (blood pressure >160/95 mm Hg or receiving antihypertensive treatment), and 7737 (63%) had hypercholesterolaemia (cholesterol >6·5 mmol/L or on lipid-lowering therapy, table 1). At randomisation, 81% of patients had no angina, 17% had mild angina (Canadian Cardiovascular Society class II), and 2% had moderate or severe angina (Canadian Cardiovascular Society class III–IV). Past history of congestive heart failure was recorded in 1·3% of the population, but no patient had clinical signs of heart failure, with 10% in New York Heart Association class I and none in class II or higher. At randomisation, 92% of the patients were taking platelet inhibitors, 62% β blockers, and 58% lipid-lowering therapy. At 3 years of follow-up, concomitant medication was recorded in 11 547 (95%) patients: 91% were taking platelet inhibitors, 63% β blockers, and 69% lipid-lowering agents.

During the run-in period, during which all patients received perindopril, blood pressure was reduced from 137/82 to 128/78 mm Hg. After randomisation, systolic and diastolic blood pressures among patients treated with perindopril were maintained and the average blood pressure during double-blind treatment was 5/2 mm Hg (SD 15/9) higher in the placebo group. After randomisation, study medication was well tolerated (table 2). At 3 years, 81% of patients assigned perindopril and 84% of placebo patients were taking study medication. Most patients assigned perindopril continued on 8 mg—eg, only 7% had dropped to 4 mg at 3 years. The average use of study medication was 3·7 years of 4·2 years follow-up.

	Perindopril (n=6110)	Placebo (n=6108)	Relative risk reduction (95% CI)	p
Cardiovascular mortality, MI, or cardiac arrest	488 (8·0%)	603 (9·9%)	20% (9 to 29)	0·0003
Cardiovascular mortality	215 (3·5%)	249 (4·1%)	14% (–3 to 28)	0·107
Non-fatal MI	295 (4·8%)	378 (6·2%)	22% (10 to 33)	0·001
Cardiac arrest	6 (0·1%)	11 (0·2%)	46% (–47 to 80)	0·22
Total mortality, non-fatal MI, unstable angina, cardiac arrest	904 (14·8%)	1043 (17·1%)	14% (6 to 21)	0·0009
Total mortality	375 (6·1%)	420 (6·9%)	11% (–2 to 23)	0·1

Table 3: **Frequency of primary and selected secondary outcomes**

	Number of patients	Primary events (%) Perindopril	Placebo
Male	10 439	8·2	10·1
Female	1779	6·9	8·8
Age (years)			
⩽55	3948	6·5	8·9
56–65	4439	6·9	8·1
>65	3831	10·7	12·9
Previous MI	7910	8·9	11·3
No previous MI	4299	6·4	7·3
Previous revascularisation	6709	6·6	8·0
No previous revascularisation	5509	9·6	12·2
Hypertension	3312	9·8	12·0
No hypertension	8906	7·3	9·1
Diabetes mellitus	1502	12·6	15·5
No diabetes mellitus	10 716	7·4	9·0
Lipid-lowering drug	6831	7·0	8·3
No lipid-lowering drug	5387	9·3	11·9
β blockers	7650	7·6	10·2
No β blockers	4568	8·7	9·4
Calcium-channel blockers	3955	9·9	11·7
No calcium-channel blockers	8263	7·1	9·0

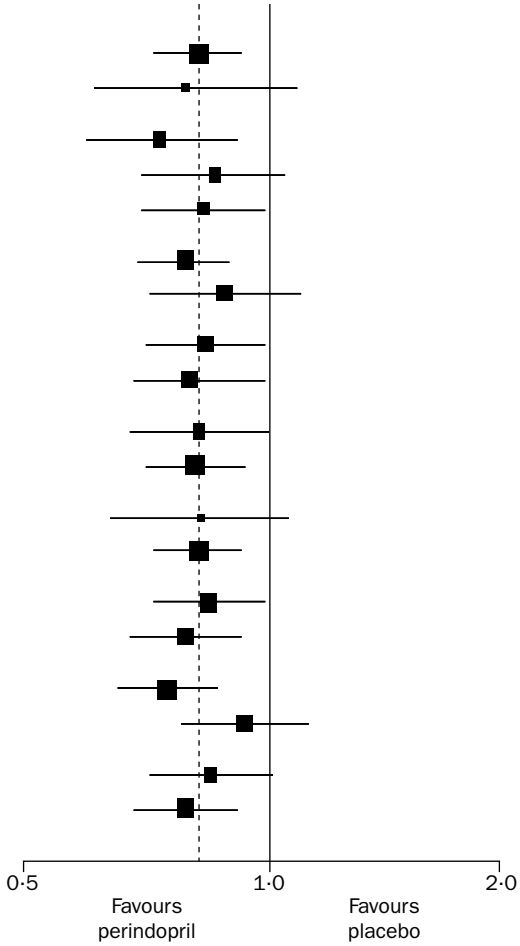


Figure 3: **Beneficial effect of treatment with perindopril on primary endpoint in predefined subgroups**
MI=myocardial infarction. Size of squares proportional to number of patients in that group. Dashed line indicates overall relative risk.

Perindopril treatment was associated with a significant reduction in the primary endpoint (cardiovascular mortality, non-fatal myocardial infarction, and resuscitated cardiac arrest, p=0·0003; figure 2). Among patients in this group, 488 (8%) reached the primary endpoint compared with 603 (10%) in the placebo group. This finding yields a 20% relative risk reduction (95% CI 9–29, table 3), and a 1·9% absolute risk reduction. The benefit began to appear at 1 year (relative risk reduction 10%, p=0·35) and gradually increased throughout the trial.

The beneficial effect of perindopril on the primary endpoint was consistent across all predefined subgroups, although it was not significant for some subgroups (figure 3). Outcome was improved in all age-groups among patients with and without hypertension, diabetes mellitus, or previous myocardial infarction. Importantly, we noted treatment benefit in patients taking lipid-lowering therapy and β blockers. Most of the patients (>90%) used platelet inhibitors (mainly aspirin).

Compared with placebo treatment with perindopril was associated with reductions in all secondary endpoints, although not significantly for some endpoints (figure 4). In particular, there was a 14% reduction in total mortality, non-fatal myocardial infarction, unstable angina, and cardiac arrest (95% CI 6–21, p=0·0009), which was the initial primary endpoint. Total mortality was 11% lower with perindopril but this finding was not significant. Revascularisation, stroke, and heart failure were infrequent, 9·6%, 1·6%, and 1·4% respectively. Hospital admission for heart failure was significantly reduced with perindopril, by 39% (17–56, p=0·002).

Discussion

We show a substantial benefit with perindopril in a broad population of patients with stable coronary artery disease and no evidence of heart failure or notable hypertension. Cardiovascular death, myocardial infarction, cardiac arrest, acute coronary syndromes, and development of heart failure were all reduced. Our findings confirm the reduction in myocardial infarction with ACE inhibitors originally noted in earlier studies of patients with heart failure or left-ventricular dysfunction.[12,13] Furthermore, the study extends the observations of the HOPE study,[11] in which cardiovascular events were reduced with ACE inhibition in high-risk patients with coronary heart disease. By contrast with previous studies, we did not note a significant reduction in revascularisation, which might be explained by the low rate of percutaneous coronary intervention or coronary artery bypass grafting, as is expected in a low-risk asymptomatic population.

The risk level in our patients was lower than that in HOPE, which selected patients aged 55 years or older who had cardiovascular disease or diabetes plus at least one additional cardiovascular risk factor. In our study, almost a third were younger than 55 years, fewer had diabetes and hypertension, and more used aspirin, β blockers,

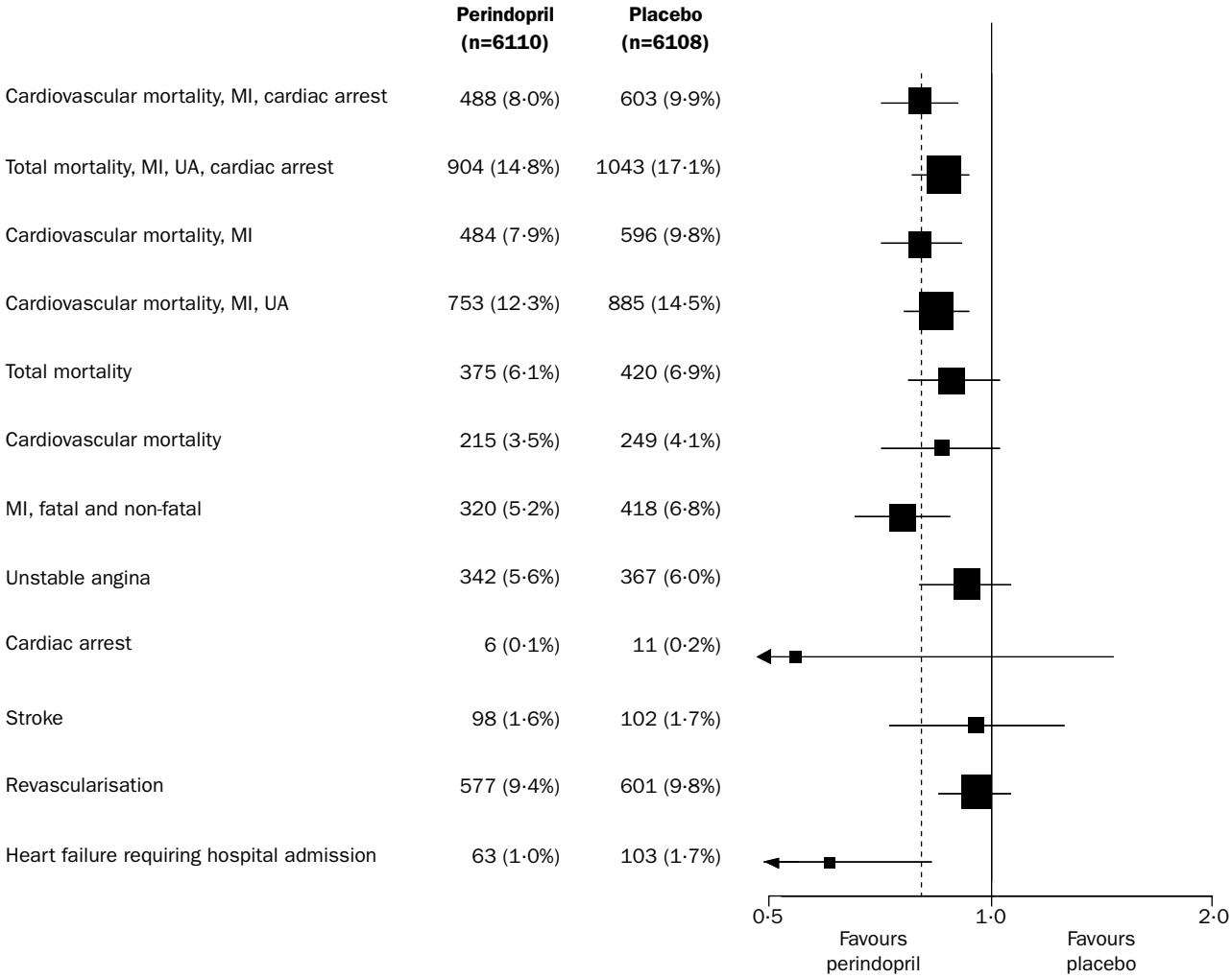


Figure 4: **Beneficial effect of treatment with perindopril on primary endpoint and selected secondary endpoints**
MI=myocardial infarction. UA=unstable angina. Size of squares proportional to number of patients in that group. Dashed line indicates overall relative risk.

and lipid-lowering drugs. At a mean follow-up of 4·5 years, HOPE reported a placebo mortality of 12%, cardiovascular mortality of 8%, and Q-wave myocardial infarction of 3%, compared with 7%, 4%, and 2%, respectively, in our study at 4·2 years of follow-up. Thus, the major annual event rates in HOPE were 40% to 80% higher than those in EUROPA. The frequency of clinical myocardial infarction and cardiovascular death was reduced by 21% with ACE inhibition in HOPE. We saw a similar 20% reduction, from 10% to 8% at 4·2 years. At 3 years of follow-up, concomitant medication was recorded in 11 547 (95%) patients—platelet inhibitors (91%), lipid-lowering agents (69%), and β blockers (63%). Thus, the benefits of ACE inhibition were still evident on top of current recommended secondary preventive measures.

The 8 mg dose of perindopril, once daily, used in our study was well tolerated. Around 10% of patients did not continue after the open-label dose-titration phase for various reasons. Specific adverse effects, such as cough, hypotension, or abnormal creatinine rise were infrequent. After randomisation, withdrawals from treatment were similar to those for placebo; cough was a reason for withdrawals in 2·7% of perindopril treated patients compared with 0·5% on placebo.

We recruited patients without heart failure. Although 65% of patients had had previous myocardial infarction, only 1·4% developed heart failure during the study period. This proportion contrasts with about 25% of new-onset heart failure among patients who have pre-existing left-ventricular dysfunction in the Studies of Left Ventricular Dysfunction prevention study,[7] and provides some support that our patients did not have left-ventricular dysfunction.

The effects of perindopril on the primary outcome seem to begin after 1 year of treatment, after which the event curves continued to separate throughout the remaining study period. Differences between the event curves were significant at 3 years of follow-up and beyond. The gradual onset of effect and progressive benefit over time is consistent with the antiatherosclerotic and antihypertensive properties of ACE inhibition.

In several studies ACE inhibitors have modulated various components of the atherosclerotic process by inhibiting angiotensin II formation and by reducing bradykinin breakdown.[14–18,27–29] Angiotensin II increases lipid peroxidation and oxyradical formation, and stimulates the expression of proinflammatory genes, such as chemoattractant protein and leucocyte adhesion molecules, resulting in endothelial dysfunction. In addition, angiotensin II improves vascular smooth-muscle proliferation and stimulates the production of PAI-I. Conversely, bradykinin counteracts the negative action of angiotensin II and improves endothelial function by increasing expression and activity of the constitutive nitric-oxide synthase, the enzyme that produces nitric oxide. Bradykinin also inhibits the expression of monocytes and adhesion molecules, has an antiproliferative effect,

and stimulates the synthesis of tissue plasminogen activator. By favouring the balance between angiotensin II and bradykinin, ACE inhibitors are likely to maintain endothelial function and counteract initiation and progression of atherosclerosis. However, quantitative differences do exist among ACE inhibitors, and tissue ACE inhibitors (such as ramipril, perindopril) are highly lipophilic and have strong enzyme-binding capabilities; such ACE inhibitors probably provide greater penetration into the atherosclerotic plaque.

In hypertensive patients, long-term blood-pressure reduction with different antihypertensive drugs, can reduce subsequent cardiovascular events.[30] However, among patients with a normal blood pressure, the effect of blood-pressure lowering on improving cardiovascular outcome is unclear. We noted a similar treatment effect among patients with treated hypertension and those without hypertension. Furthermore, the reduction in cardiovascular events was greater than may be expected for the observed reduction in blood pressure (mean 5/2 mm Hg) achieved with perindopril. This finding implies that the specific antiatherosclerotic effects of ACE inhibition should not be neglected. This effect will probably be elucidated by EUROPA substudies that will focus on the development of atherosclerosis and endothelial function.[24]

Unusually, the EUROPA steering committee felt obliged to change the primary endpoint towards the end of the initial proposed follow-up period, because of evolving concepts in the recognition and the understanding of acute coronary syndromes, as well as appreciation of the continuing reduction in cardiovascular mortality among our patients. Nevertheless, the results are similar for the redefined and original primary endpoints. As a consequence of this decision, the anticipated follow-up needed to be prolonged. Unfortunately, 13% of the patients did not take part in the extension of the trial. The average use of study medication was 3·7 years during 4·2 years of follow-up. Thus the reported improved outcome is a conservative estimate of the benefit of perindopril.

The benefits we report for perindopril were in addition to other preventive measures, including aspirin, β blockers, and lipid-lowering drugs, and were consistent for all patients. We estimate that 50 patients need to be treated with perindopril for a period of 4 years, to prevent one major cardiovascular event. These results provide strong support for considering this ACE inhibitor perindopril, in addition to other preventive treatments, irrespective of cardiac function or risk factors for all patients with coronary heart disease.

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