

## *The EUROPA Trial: Design, Baseline Demography and Status of the Substudies*

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**Summary. Background:** Angiotensin-converting enzyme inhibitors do reduce both mortality and morbidity in patients with left ventricular dysfunction, recent myocardial infarction and hypertension. However, the long-term effects in patients with coronary artery disease have not been established. The EUROPA study is designed to assess the long-term (3–4 years) effects of perindopril on the reduction of cardiac events in patients with proven stable coronary artery disease but with no evidence of heart failure.

**Study Design and Methods:** EUROPA is a 12236 patient, randomised, double-blind, placebo-controlled and multicentre trial. EUROPA had an initial run-in period of 4 weeks during which patients received 4 and then 8 mg of perindopril daily to assess tolerance to maximum dose. This was followed by a double-blind randomisation to either perindopril or placebo. Patients were followed-up at 3 and 6 months and then 6 monthly until the last patient included in the main study completes the 3-year follow-up. EUROPA includes five sub-studies. Each of these sub-studies investigates the effects of perindopril on a different aspect of coronary artery disease: endothelial dysfunction, atherosclerosis progression or regression, diabetes mellitus, inflammation, thrombosis, neurohormonal activation. Patients are characterised genetically to assess characteristics associated with improved or unfavourable outcome. The final results of EUROPA will be available in 2002.

**Key Words.** coronary artery disease, diabetes, EUROPA, angiotensin-converting enzyme inhibitors, perindopril

### *Introduction*

Coronary artery disease is the most important cause of death in the western world. Although there has been considerable success in relieving the symptoms of angina only statins and aspirin have been shown to improve mortality.

Angiotensin-converting enzyme (ACE) inhibitors have well-established roles in the reduction of mortality and morbidity in patients with heart failure, recent myocardial infarction (MI) and hypertension. In recent years, it has been suggested to extend these indications to coronary artery disease, because the drugs have been shown to be effective in reversing atherosclerosis in animal models [1–3] and because in earlier heart failure studies ACE inhibitors significantly lowered

the incidence of myocardial infarction [4–6]. The current generation of large ACE inhibitor/atherosclerosis studies (HOPE [7], EUROPA [8] and PEACE [9]) include 4–5 years follow up. HOPE results have already been published and showed a favourable effect of ACE inhibition. This trial studied high-risk patients of vascular disease who did not necessarily suffer from coronary artery disease. In contrast, EUROPA and PEACE will demonstrate the long-term effects of ACE inhibition in patients with proven coronary artery disease, not particularly at high-risk. This paper examines the preliminary baseline and demographic findings of EUROPA and also details on its sub-studies. Recruitment was completed in February 1999 and in June 1999 for the patients entering the substudies. 12236 patients have been randomised and the results are expected to be reported in 2002.

### *Methodology*

#### *The study organization*

EUROPA is a multicentre European trial, involving 424 centres in 24 countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Spain, Slovakia, Sweden, Switzerland, Turkey and the United Kingdom; See Appendix).

#### *The study population*

The study recruited men and women aged  $\geq 18$  years without clinical evidence of heart failure and with evidence of coronary artery disease documented by either previous MI for at least 3 months prior to the selection visit, percutaneous or surgical coronary revascularisation for at least 6 months before the selection visit or angiographic evidence of  $\geq 70\%$  narrowing

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of  $\geq 1$  major coronary artery. Men were also recruited if they had history of chest pain and a positive exercise test or regional wall motion abnormalities during stress echocardiography or nuclear scintigraphy or with transient perfusion defects during scintigraphy perfusion imaging. Patients were not scheduled for coronary revascularisation procedures at the time of selection visit and informed consents were obtained from all patients. Exclusion criteria are reported in Table 1.

**The study design**

EUROPA is a large simple study (Fig. 1). The study comprises of a first run-in period of two weeks during which patients received perindopril 4 mg/day in addition to their usual medication, a second run-in period of two weeks during which patients received perindopril 8 mg/day in addition to their usual medication provided that the 4 mg/day of perindopril was well tolerated in the first run-in period. Patients 70 years or older started with 2 mg/day the first week, 4 mg/day the second, and 8 mg/day the last 2 weeks of the run-in period, if well tolerated. At the end of the run-in period, a double-blind treatment period of at least 36 months started during which patients receive either perindopril 8 mg/day or placebo. Patients will continue in the study until the last patient included completes the 3-year follow-up period.

**Follow-up assessment**

Patients were seen at 2 and 4 weeks during the run-in period. Following randomisation patients are seen at

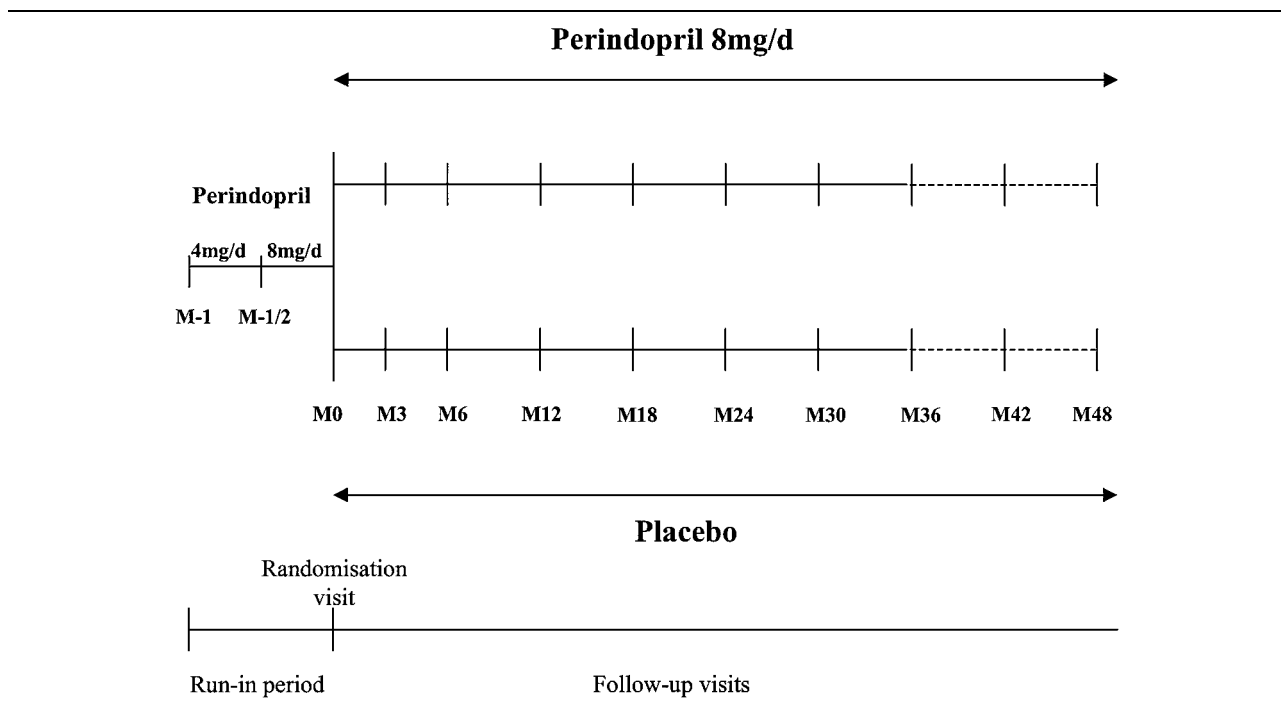
**Table 1. Exclusion criteria**

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- Women of child-bearing potential without contraception;
- Participation in a drug or device trial within the previous 30 days;
- Compliance with the treatment or the visits likely to be inadequate;
- Patients who previously did not tolerate ACE inhibitors because of side effects;
- A history of alcohol or drug abuse;
- Clinical signs of heart failure requiring treatment;
- Supine hypotension with a systolic blood pressure <110 mm Hg;
- Uncontrolled treated hypertension, as defined by a systolic blood pressure >180 mm Hg and/or a diastolic blood pressure >100 mm Hg;
- Clinically significant obstructive valvular disease;
- Hypertrophic cardiomyopathy;
- Use of ACE inhibitors within one month before the first selection visit;
- Use of angiotensin II receptor inhibitors within one month prior to the first selection visit;
- Renal failure with serum creatinine >150  $\mu\text{mol/l}$ ;
- Bilateral renal artery stenosis;
- Serum potassium >5.0 mmol/l;
- Liver disease: ASAT or ALAT >3 times the upper normal values;
- A history of stroke or cerebral transient ischemic attacks within the preceding 3 months;
- Any other serious disease likely to interfere with the conduct of the study;

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3, 6 and 12 months and thereafter at 6 monthly interval. Follow-up is scheduled to end in March 2002 at which time average duration of follow-up will be 3.5 years.



**Fig. 1. EUROPA study Design.**

### The study end-points

The *primary* objective of EUROPA is to assess the effect of perindopril on the combined end-point of total mortality, non-fatal acute myocardial infarction, hospital admission for unstable angina pectoris and cardiac arrest with successful resuscitation and alive after 28 days thereafter.

The *secondary* objectives are to assess the effect of perindopril in reducing the rate of the following events: total mortality, cardiac mortality, cardiac mortality and non fatal acute MI, cardiac mortality, non fatal MI and unstable angina pectoris (UA), fatal and non fatal MI and UA, non fatal MI, UA, cardiac arrest with successful resuscitation and alive 28 days thereafter, revascularisation (CABG or PTCA), heart failure and stroke.

### The study power and sample size determination

In calculating the sample size for EUROPA, the following assumptions were made: with a primary event rate of 4% per year, in order to detect a relative reduction of 16% with a power of greater than 90% and a two-sided type I error rate of 0.05, 750 events are required in the control group. Assuming an average follow-up of 3 years and 9 months, a total of 10500 patients are required.

## Results

### Recruitment

At the end of the recruitment period, which was June 1999, 12236 patients had been randomised. Their average age was 61 years (range 24–90); 83% were male. Their histories showed that 62% had suffered a previous myocardial infarction, 60% documented >70% coronary stenosis, 54% previous revascularisation, 15% had a history of diabetes mellitus or impaired glucose tolerance, 26% hypertension and 63% hypercholesterolaemia as shown in Table 2.

The majority, 76%, had no evidence of angina and only 4.4% of the patients were enrolled with coronary artery disease documented solely by a history of chest pain or abnormal stress test. At entry, 91.9% of the randomised patients were on platelet inhibitors, 62.6% on beta blockers and 47.5% on statins as shown in Table 3.

**Table 2.** EUROPA study baseline characteristics

Mean age (range) (years)	61 (24–90)
Males (%)	83
Documented coronary artery disease: $\geq$ 70% stenosis (%)	60
Previous myocardial infarction (%)	62
Previous revascularisation (%)	54
Diabetes mellitus or impaired glucose tolerance (%)	15
Hypertension (%)	26
Hypercholesterolaemia (%)	63

**Table 3.** Concomitant medications of the randomised patients

No drug treatment	0.3%
Platelets inhibitors	91.9%
Oral anticoagulants	4.5%
Nitrates	44.2%
Beta blockers	62.6%
Calcium blockers	32.3%
Digitalis	1.6%
ACE inhibitors	0.0%
ATII blockers	0.0%
Other vasodilators	4.0%
Potassium sparing diuretics	2.1%
Other diuretics	7.6%
Anti-arrhythmics	2.3%
Lipid lowering agents	55.8%
Statins	47.5%
Other drug treatment	32.2%

**Table 4.** Reasons for drop-outs during the screening period

Intolerance (including cough)	2.4%
Hypotension	1.9%
Creatinine/potassium rise	0.9%
Poor compliance	0.8%
Study event (including angina without hospitalisation)	0.5%
'Other' or 'unknown'	4.4%

Between screening and randomisation, 10.9% of patients were excluded from the trial. The reasons provided for drop-outs are shown in Table 4.

The number of patients in whom the study drug has been withdrawn after randomisation is low indicating good tolerance to perindopril. Mostly are for reaching a study end-point but a very small number (2.4%) are for intolerance including cough.

### EUROPA sub-studies

A number of sub-studies have been undertaken. The purpose of these sub-studies is to develop a better understanding of the actions of perindopril in coronary artery disease. These sub-studies investigate the effects of the drug on neurohormonal activation, thrombosis, endothelium, inflammation and coronary anatomy. In view of the known effects of ACE inhibitors in diabetes, this population has been specifically investigated. Finally, the genetic characterisation of the study population will be studied.

PERTINENT [10] (PERindopril-Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial) evaluates the predictive value of several plasma and serum markers associated with atherosclerosis and the effects of perindopril on their levels. These markers are fibrinogen as a marker for coagulation, C-reactive protein (CRP) as a marker for inflammation, D-dimer for thrombogenesis, von Willebrand factor (vWf) for endothelial activation/coagulation, Cromogranin A (CgA) for neurohormonal

activation and Nitric Oxide synthase (ecNOS) for endothelial function. In addition, angiotensin converting enzyme activity is measured.

This substudy has two parts: Part A includes 345 patients and compares the effect of perindopril and placebo on these plasma markers at baseline and after one year of treatment.

Part B which includes 1282 patients, evaluates whether the effect of perindopril on CRP and vWf is related to its effect on cardiovascular endpoints, both primary and secondary.

PERFECT (PERindopril Function of the Endothelium in Coronary artery disease Trial) [10]: Forearm circulation and flow-mediated vasodilatation of the brachial artery reflect endothelial functional changes similar to those in the coronary arteries of patients with coronary artery disease. In this sub-study, blood flow in the brachial artery will be measured using B-mode imaging with Duplex scanning with a 7–10 MHz linear array transducer. Scanning is performed at rest, during and for 5 minutes after four minutes of ischaemia and during and for 10 minutes after cold pressure testing. Consecutive studies are carried out during the run-in period, at the time of randomisation and at 6, 12, 24, and 36 months thereafter. At baseline and at the end of the study nitroglycerin is administered sublingually to study non-endothelial dependent vasodilation. Plasma levels of von Willebrand factor are assessed during each study.

The primary end-point is the percentage change in the flow-mediated vasodilation of the brachial artery between baseline and 36 months and also the percentage change in neurohormonal-mediated vasoconstriction of the brachial artery.

A total of 345 patients have been enrolled in this substudy.

PERSPECTIVE (PERindopril'S Prospective Effect on Coronary aTherosclerosis by angiographical and IntraVascular ultrasound Evaluation) [10] aims to investigate the effects of perindopril administration on the progression and regression of coronary atherosclerosis using qualitative coronary angiography (QCA) and intravascular ultrasound (IVUS). QCA provides reproducible assessment of the coronary arterial dimensions with main outcome parameters of mean lumen diameter and minimal lumen diameter whereas IVUS main parameters are plaque volume, plaque area and lumen area. 319 patients have been recruited from those within the main study needing angiography. The primary objective of this sub-study is to compare the effects of perindopril and placebo on the progression and regression of coronary atherosclerosis after 36 months of treatment as measured by QCA. The secondary objective is to compare the effects of perindopril and placebo on the progression and regression of plaque and lumen changes following a 36-month treatment as measured by IVUS and the development of new lesions as detected by using QCA and IVUS.

PERSUADE (PERindopril SUBstudy in Coronary Artery Disease and diabEtes) [10] is a substudy that examines diabetic patients in EUROPA (15% of the study population).

The main efficacy variable in this substudy is to determine the effects of perindopril in diabetic population in terms of the primary and secondary end-points. The primary end-points are those of the EUROPA study. We will also detect the progression of diabetic nephropathy as assessed by albumin:creatinine ratio.

PERGENE is a sub-study that will look at the genetic characterisation of all patients in the EUROPA population. A sample of blood is taken from every EUROPA patient which is stored to the end of the study, when the most up-to-date gene polymorphism will be explored.

## Discussion

ACE inhibitors confer unequivocal beneficial effects in treating patients with all degrees of ischaemic heart failure (as demonstrated in CONSENSUS-1, VHeFT-I, VHeFT-II and SOLVD), asymptomatic left ventricular dysfunction (SOLVD) and after acute myocardial infarction (ISIS-4, SAVE, GISSI-3, AIRE, SMILE, TRACE) [11]. SOLVD [12] and SAVE [13] trials demonstrated that patients receiving ACE inhibitors have less myocardial ischaemic events on long-term therapy. This delay in the reduction of ischaemic events suggests that ACE inhibitors may have structural effects, affecting the underlying pathophysiology for coronary atherosclerosis, rather than the acute haemodynamic effects. The possible mechanisms for this observed anti-ischaemic effects of ACE inhibition are discussed below.

### Structural cardiac and vascular effects

ACE inhibitors may reduce myocardial ischaemia through several different mechanisms [14,15]. Firstly, ACE inhibitors induce cardioprotective effects, which are related to a reduction in inappropriate cardiac hypertrophy and a decrease in cardiac enlargement. Under conditions of volume or pressure overload or following myocardial infarction, cardiac ACE expression increases and enhances local tissue angiotensin II formation. Angiotensin II has growth promoting effects and may stimulate cardiac fibrosis, either directly or through activation of aldosterone [16]. Reduction of cardiac tissue angiotensin II by ACE inhibition may counteract cardiac remodelling following long-term overloading of the heart or following an infarct [17,18]. This effect is direct and does not result from blood pressure reduction or other indirect effects of the ACE inhibition [19]. In addition, ACE inhibition leads to increased bradykinin production. Bradykinin induces nitric oxide production and increases prostaglandin formation which may be involved in bradykinin's anti-proliferative effects. Whereas the anti-remodelling effect of the ACE inhibitor results in an improvement

of cardiac function and hemodynamics, the extra spin off, in particular the volume effect, relates to a decrease in myocardial oxygen demand, less ischaemia and an improvement of myocardial energetics. Secondly, long-term administration of ACE inhibitors may result in vasculoprotective effects. Of these, an improvement or even normalisation of endothelial dysfunction is probably the most important. *In vitro* studies indicate that ACE inhibition improves endothelial nitric oxide production, which appears related to its effect on bradykinin formation. In animal models, in which endothelial dysfunction is induced, ACE inhibition improves endothelial function, an effect which is counteracted by bradykinin antagonists. In humans with hypertension or heart failure and endothelial dysfunction, the latter improves following ACE inhibitor therapy [20]. In particular, the TREND [21] study indicated that 6-month treatment with the ACE inhibitor, quinapril, significantly improved coronary endothelial function in normotensive patients with moderate coronary artery disease and without heart failure. Besides their effect on endothelial function, ACE inhibitors have anti-proliferative and, possibly, anti-atherogenic properties [22,23]. The expression of ACE and angiotensinogen increases following angioplasty in small animal models [24] and precedes neointima proliferation. ACE inhibition diminishes intimal hyperplasia in these models, again linked to its effect on bradykinin degradation [25]. Yet, in human coronary angioplasty trials, 6-month ACE inhibition failed to prevent subsequent restenosis [26], which may be related to timing of onset of treatment or to the fact that the main mechanism of restenosis after balloon angioplasty is vascular remodelling and the drug was mainly directed to prevent neo-intimal hyperplasia or due to the fact that the vascular lesion which results from balloon procedures is so significant that neither repair nor prevention of stenosis recurrence is to be expected from any pharmacological intervention. The latter may also be the reason for lack of clinical improvement observed in the QUIET trial, in which patients were treated with quinapril or placebo for a period of 3 years after coronary angioplasty [27]. Although there was a trend towards reduction of events, the combined primary endpoint of cardiovascular death, non-fatal MI, revascularisation procedures and hospitalisation for unstable angina was not significantly reduced ( $p=0.6$ ). Indeed, animal studies suggest that the ACE inhibitor dosage needed to produce anti-proliferative effect exceeds that causing changes in blood pressure [28].

#### **Anti-thrombotic effects**

ACE inhibitors may induce antiplatelet effects through bradykinin. Moreover, they may improve the balance between plasminogen activator inhibitor-1 (PAI-1) and tissue type plasminogen activator (t-PA), also favouring anti-thrombotic effects [29]. ACE inhibitors

therefore may improve endogenous fibrinolytic function in man, although this needs further confirmation.

#### **Neurohormonal effects of ACE inhibition which may add to their anti-ischaemic profile**

In addition to the structural effects on the vasculature described above, ACE inhibitors may exert functional effects which are more direct, but are likely to become more prominent with time when endothelial function recovers.

Episodes of stress-induced myocardial ischaemia result in activation of the sympathetic system with an increase in circulating levels of norepinephrine and epinephrine, unrelated to the presence or absence of angina [30,31]. More severe ischaemia stimulates the circulating renin-angiotensin system [31]. The increase in these circulating vasoconstricting neurohormones results in systemic vasoconstriction, particularly in the absence of normal endothelium. Thus, a vicious circle ensues whereby ischaemia-induced neurohormonal activation leads to systemic vasoconstriction, an increase in after-load and in myocardial oxygen demand, and to coronary vasoconstriction, at least in the coronary lesion area, further jeopardising coronary flow. ACE inhibition limits this neurohormonal activation and vasoconstriction during ischaemia [15].

As angiotensin II is a potent direct systemic and coronary vasoconstrictor, we may expect a direct effect through a reduction in circulating angiotensin II following ACE inhibition. Moreover, bradykinin has a direct vasodilator effect and suppresses platelet adhesion and aggregation (via the release of nitric oxide and prostacyclin).

ACE inhibition with enalaprilat has been shown to ameliorate pacing-induced angina [15], while perindoprilat lessens angina and post-anginal left ventricular filling pressure. Perindoprilat also reverses the increase in arterial norepinephrine levels during ischaemia and significantly diminishes net cardiac norepinephrine release, compared with placebo [32]. As a result of this, systemic vasoconstriction is reduced and myocardial ischaemia diminishes. It is likely that this acute effect of the ACE inhibitor may become more pronounced and more efficient with ongoing treatment when endothelial function improves. This may explain why the reduction in ischaemic events such as observed in large clinical trials takes a relatively long time to become discernible.

*In summary*, ACE inhibitors may reduce myocardial ischaemia through various mechanisms which induce inhibition of angiotensin II production, anti-adrenergic properties and bradykinin formation. As a consequence, ACE inhibitors improve endothelial function over time. In addition, ACE inhibitors avoid cardiac remodelling with a reduction in ventricular volume, mass and wall stress, together leading to a reduction in myocardial oxygen demand and, possibly, an improvement in subendocardial flow. Animal experiments clearly indicate anti-proliferative

and anti-atherogenic properties. In addition, ACE inhibitors may have antiplatelet effects (bradykinin) and improve the balance between plasminogen activator inhibitor-1 and tissue type plasminogen activator. These properties could lead to plaque stabilisation and prevent plaque rupture. Finally, ACE inhibitors modulate ischaemia-induced neurohormonal activation, coronary and systemic vasoconstriction. As such they could override coronary vasoconstriction in the lesion area, particularly in unstable angina. These findings and observations gave a stimulus for large controlled trials which examine the long-term effects of ACE inhibitors in patients with stable coronary artery disease as studied in EUROPA or in patients at high risk of cardiovascular events as studied in HOPE.

In the *EUROPA trial*, perindopril has been used which is a long-acting ACE inhibitor first synthesised [33] in the early 1980s and now registered in over 100 countries worldwide with the hypertension and heart failure indications. It is well tolerated even in at risk patients such as the elderly [34] or patients with recent ischaemic stroke, in whom it causes no change in cerebral circulation [35]. Perindopril at the initiating dose of 2 mg in heart failure has been demonstrated in several controlled studies to minimise the risk of first dose hypotension [36,37]. The effects of perindopril on cardiovascular remodelling are well documented: perindopril improves arterial compliance in large arteries and restores the structure of small resistance arteries [38]. In addition, perindopril restores flow-mediated coronary vasodilation in hypertensive patients [39] and reverses the endothelial dysfunction observed in patients with heart failure [40]. These effects are produced via potentiation of the bradykinin-mediated release, not only of nitric oxide but also endothelium-derived hyperpolarisation factor [41]. Perindopril has been shown to reduce myocardial ischaemia relative to placebo treatment in pacing induced angina, furthermore the increase in arterial norepinephrine levels is reversed and the net cardiac norepinephrine release is significantly diminished [32]. In an experimental model of atherosclerosis, perindopril significantly modified the atherosclerotic process [23]: a reduction in the atherosclerotic lesion size, a decrease in lipid-laden macrophages and less fragmentation of arterial elastic tissue were seen. Furthermore, perindopril not only reduced the size of the lesions but made them more stable and less likely to rupture.

Therefore, we have an extensive body of evidence from both animal and human research that support the hypothesis for the EUROPA trial that perindopril will improve the clinical outcome in patients with stable coronary artery disease. The mechanisms discussed above are verified in the different EUROPA substudies.

In the *HOPE trial*, a total of 9297 high-risk patients who had evidence of vascular disease or diabetes

**Table 5.** *EUROPA v HOPE (Demography)*

	EUROPA	HOPE
Total patients randomised	12236	9297
Mean age (range)	61 (24-90)	66 (>55)
Females (%)	17	27
Evidence of coronary artery disease (%)	100	81
Previous myocardial infarction (%)	62	53
Previous revascularization (%)	54	44
Peripheral vascular disease	7	43
Stroke or transient ischemic attack	3	10.8
Hypertension (%)	26	47
Peripheral vascular disease (%)	7	43
Stroke (%)	3	11
Diabetes mellitus (%)	15	38

plus one other cardiovascular risk factor without evidence of heart failure were randomly assigned to receive ramipril (10 mg once daily orally) or matching placebo. The trial was a two-by-two factorial study evaluating both ramipril and vitamin E. Ramipril significantly reduces the rate of deaths, MI, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure [7].

Comparison of the demographics of HOPE with those of EUROPA illustrates the rather different patient populations of the two studies. HOPE patients were not required to have coronary artery disease; it was enough for them to have diabetes and one clinical risk factor (smoking, for example). Consequently, the proportion of diabetic patients was strikingly higher than in EUROPA. Also, there were more patients with hypertension, peripheral vascular disease and stroke in HOPE.

In contrast, documentation of coronary artery disease is essential for EUROPA and the ratio of diabetic patients in EUROPA represents the true incidence of diabetes in coronary artery disease population. Table 5 shows the demography of the two studies. Two of the important questions which were raised as a result of the HOPE trial are: what will be the effect of ACE inhibition in patients who are not at high risk? and the second question is: can the beneficial effects of ramipril shown in HOPE be reproduced by other ACE inhibitors? These questions and many others will be answered when EUROPA results are available.

## Appendix

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