Management of coronary artery disease: implications of the EUROPA trial

KIM M FOX

Abstract

The recent EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) examined the effect of treatment with the angiotensin-converting enzyme (ACE) inhibitor perindopril in 12,218 patients with stable coronary artery disease (CAD). After 4.2 years, treatment with perindopril 8 mg once daily resulted in a 20% relative risk reduction in the primary end point, a composite of cardiovascular death, non-fatal myocardial infarction, and cardiac arrest (p=0.0003). Risk reductions were also observed for secondary end points, including fatal and non-fatal myocardial infarction (24% reduction, p<0.001) and hospitalisation for heart failure (39% reduction, p=0.002). These benefits were observed on top of standard recommended preventive therapies such as antiplatelet agents, beta blockers and lipid-lowering drugs. Benefits were consistent for all patients with CAD, irrespective of the presence or absence of risk factors such as age, diabetes, hypertension, previous myocardial infarction, or previous revascularisation. Perindopril, a lipophilic tissue ACE inhibitor which binds strongly to ACE, has several anti-atherogenic actions and vascular properties which may contribute to its protective effect. EUROPA is the first trial to show the benefit of ACE inhibition in a broad population often seen in daily clinical practice. The results suggest that perindopril should be added to other recommended preventive treatments in all patients with CAD.

Key words: EUROPA, coronary artery disease, perindopril, ACE inhibition.

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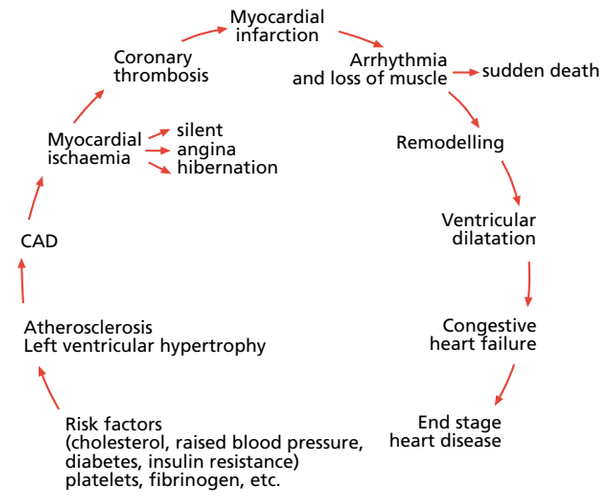
Kim M Fox

Introduction

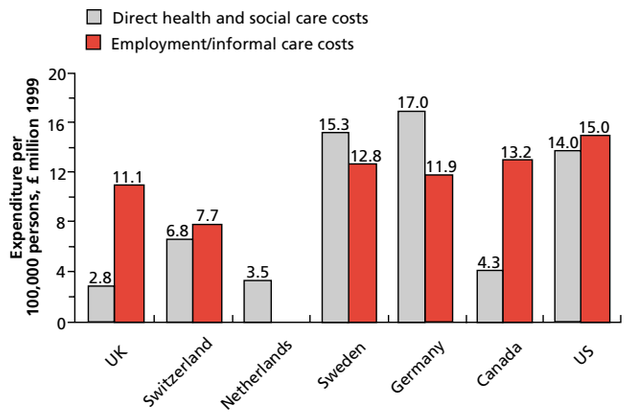
Cardiovascular disease is currently responsible for approximately 16 million deaths yearly, which represents one-third of global deaths,[1] a burden predicted to significantly rise to 37% by 2020. Coronary artery disease (CAD) underlies many of the cardiac manifestations of cardiovascular disease (figure 1).[2] It is the major

Figure 1. The chain of cardiovascular events that can arise from underlying coronary artery disease (CAD)[2]



Cardiology Department, Royal Brompton Hospital, Sydney Street, London, SW3 6NP.
Kim M Fox, Professor of Clinical Cardiology
Correspondence to: Professor KM Fox
(email: k.fox@rbh.nthames.nhs.uk)

Figure 2. Expenditure on coronary artery disease per 100,000 persons in selected countries[8]



cause of premature death and disability in the Western world and most European countries.[3,4] In Europe, CAD alone (i.e. excluding other forms of cardiovascular disease) accounts for approximately two million deaths each year, which represents about half of all deaths from cardiovascular disease. In the UK, CAD is the most common cause of death, accounting for more than 120,000 deaths in 2001.[5] Moreover, CAD not only represents a healthcare burden in its own right (when it is defined as angina or myocardial infarction [MI]) but also contributes to the mortality and morbidity associated with other forms of cardiovascular disease. A study in the UK, for example, concluded that CAD is the single most important aetiology in incident cases of heart failure, accounting for 52% of cases in patients aged < 75 years.[6] In the USA it was estimated that 60% of heart failure cases in the general population might be attributable to CAD.[7]

The costs of CAD in the UK in 1999 were estimated as £1.73 billion: £2.42 billion in informal care, and £2.91 billion in lost productivity (figure 2).[8] Direct and indirect costs of CAD in the USA were estimated as US $129.9 billion in 2003.[9] Unlike diseases which affect predominantly elderly patients, CAD is a prominent cause of death or disability in adults at the peak of their productive lives, when their earning capacity is high;[9] this accounts in part for the heavy economic burden imposed by CAD.

Background

In recent decades, the use of aspirin, beta blockers and statins in patients who have already experienced a cardiovascular event, and of statins in patients with elevated cholesterol levels, has improved the prognosis of patients with CAD. However, these patients are still at an increased risk of developing the manifestations of cardiovascular disease shown in figure 1. In light of the above mentioned costs (medical, social, and economic), it is clear that more effective secondary prevention strategies are needed.

The recent EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) has provided definitive evidence that long-term treatment with the angiotensin-converting enzyme (ACE) inhibitor perindopril reduces the risk of cardiovascular end points in all CAD patients, regardless of their level of risk.[10] This article reviews the rationale for and results of EUROPA, and considers the implications of this trial for the management of patients with CAD.

Table 1. Trials showing the benefit of ACE inhibitors in patients at risk of developing cardiovascular end points

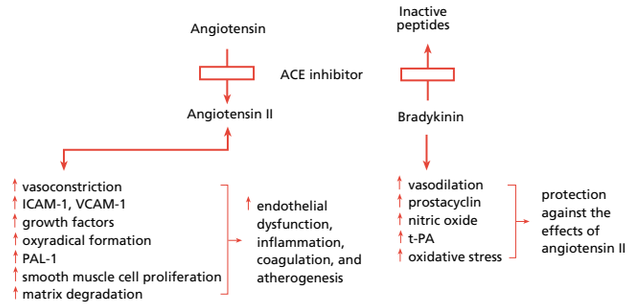
Date (ref)	Trial	n	ACE inhibitor	Patients in whom benefit was shown
1987[12]	CONSENSUS	253	Enalapril	CAD and heart failure
1991[13]	SOLVD	2,569	Enalapril	CAD and heart failure
1992[14]	SOLVD-prevention	4,228	Enalapril	CAD and left ventricular dysfunction
1992[15]	SAVE	2,231	Captopril	Post-MI with left ventricular dysfunction
1993[16]	AIRE	2,006	Ramipril	Post-MI with heart failure
1995[17]	TRACE	1,749	Trandolapril	Post-MI with left ventricular dysfunction
2000[18]	HOPE	9,297	Ramipril	High cardiovascular risk: aged ≥ 55 years and with cardiovascular disease or diabetes and at least one additional risk factor (including patients without CAD)
2003[10]	EUROPA	12,218	Perindopril	All patients with CAD, regardless of their level of cardiovascular risk and in addition to other recommended preventive treatments

Key: n = number of patients; ACE = angiotensin-converting enzyme; CAD = coronary artery disease; MI = myocardial infarction; AIRE = Acute Infarction Ramipril Efficacy study; CONSENSUS = Cooperative New Scandinavian Enalapril Survival Study; EUROPA = EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; HOPE = Heart Outcomes Prevention Evaluation study; SAVE = Survival And Ventricular Enlargement study; SOLVD = Studies Of Left Ventricular Dysfunction; TRACE = TRAndolapril Cardiac Evaluation

Rationale of ACE inhibition in the treatment of CAD

In addition to their established efficacy in lowering blood pressure, ACE inhibitors have been shown to have the broadest impact of any drug in cardiovascular medicine, reducing the risk of death, MI, stroke, diabetes mellitus and renal impairment.[11] Also, previous trials had already shown that ACE inhibitors reduce morbidity and mortality in high-risk CAD patients, such as those with heart failure or left ventricular systolic dysfunction, and in post-MI patients (table 1).[10,12-18] The Heart Outcomes Prevention Evaluation (HOPE) trial extended these findings to patients at high risk for developing cardiovascular events, including those who were at least 55 years old and with a history of CAD, stroke, peripheral vascular disease, or diabetes mellitus plus

Figure 3. Atherosclerosis-promoting actions of angiotensin II and protective effects of bradykinin. ACE inhibition blocks the production of angiotensin II and the breakdown of bradykinin



Key: ACE = angiotensin-converting enzyme; ICAM-1 = intracellular adhesion molecule 1; PAI-1 = plasminogen activator inhibitor 1; t-PA = tissue plasminogen activator; VCAM-1 = vascular cell adhesion molecule 1

at least one other cardiovascular risk factor, such as hypertension, hypercholesterolaemia, reduced high-density lipoprotein, microalbuminuria, or smoking.[18] The EUROPA trial was designed to assess whether the protective effects of ACE inhibition, using perindopril, would extend even further, to a younger and broader population of CAD patients, regardless of their level of risk and in addition to currently recommended treatments.

In addition to evidence from the trials above, a possible protective effect of ACE inhibition in CAD also has a sound theoretical basis, considering the role of angiotensin II and bradykinin in atherogenesis. Concentrations of ACE are elevated in CAD and other cardiovascular disease states. As a result, there is an increase in angiotensin II levels. This has generally harmful, vasoconstrictive effects that increase oxidative stress, promote inflammation and thrombosis, damage the endothelium, and lead to the development of atherosclerosis. ACE also breaks down bradykinin, which has vasodilatory and protective effects that counteract the negative effects of angiotensin II[19] (figure 3).

The use of an ACE inhibitor can help to restore the balance between angiotensin II and bradykinin. While blockade of angiotensin II receptors with an angiotensin II receptor blocker will also reduce the harmful effects of angiotensin II, it will not restore levels of bradykinin. Indeed, it has been shown that the beneficial effects of bradykinin are augmented in the presence of ACE inhibition.[20]

The effectiveness of an ACE inhibitor in counteracting the atherosclerotic process depends, to some extent, on how strongly it binds to ACE and how well it can penetrate into atherosclerotic plaques. More than 90% of ACE is present in tissue, rather than as a circulating enzyme in the plasma,[21] and ACE inhibitors differ in their affinity for tissue ACE. Lipophilic tissue ACE inhibitors are likely to penetrate into atherosclerotic plaques more successfully than ACE inhibitors which do not share these properties.

Table 2. Properties of perindopril that may play a role in preventing cardiovascular end points in coronary artery disease (CAD)

- Once-daily dosing and long-acting 24-hour blood pressure control[22]
- High affinity for tissue ACE[23,24]
- Anti-ischaemic effects in CAD[25]
- Reduces serum ACE and increases plasma bradykinin concentrations[25]
- Reduces neointimal proliferation in coronary arteries[26]
- Prevents the progression of atherosclerosis[27,28]
- Enhances the expression of nitric oxide synthase in coronary arteries[24]
- Improves endothelial function[29]
- Improves the fibrinolytic balance[30,31]

Key: CAD = coronary artery disease; ACE = angiotensin-converting enzyme

Choice of perindopril for EUROPA

The combination of several essential criteria resulted in the selection of perindopril as the ACE inhibitor for the EUROPA trial (table 2).[22-31] In addition to being a highly lipophilic tissue ACE inhibitor which binds strongly to ACE,[21] perindopril has several properties, observed in human and animal studies, which suggest that it could be useful in preventing the progression of CAD and reducing cardiovascular remodelling. For example, perindopril reduced the progression of atherosclerosis in an experimental model, whereas the angiotensin II receptor blocker losartan did not.[27] In addition, in a study in apolipoprotein E-deficient mice, perindopril prevented the accelerated development of atherosclerotic lesions that is seen in diabetes.[28] In patients with CAD, perindopril reduced both plasma and vascular levels of ACE, and increased levels of endothelial nitric oxide synthase, providing evidence of the ability to restore endothelial dysfunction in patients with hypertensive and cardiovascular disorders.[24] In addition, in two further studies, perindopril improved flow-mediated dilatation in hypertensive patients,[29] and reduced plasma levels of plasminogen activator inhibitor-1 in hypertensive type 2 diabetic patients.[30] In the latter two studies, the same effect was not observed with a comparator angiotensin II receptor blocker (telmisartan and losartan, respectively).

In addition to these anti-atherogenic and anti-ischaemic effects, and reducing remodelling, perindopril has been documented to provide long-acting 24-hour blood pressure control (terminal half-life of 25–30 h) with once-daily dosing.[22] The importance of once-daily dosing in terms of increasing patient compliance, as well as reducing target organ damage, has recently been underlined once again.[32] Perindopril was already known to have a good efficacy and tolerability profile in hypertension, heart failure, and even after stroke.[33-37]

Design and results of the EUROPA study

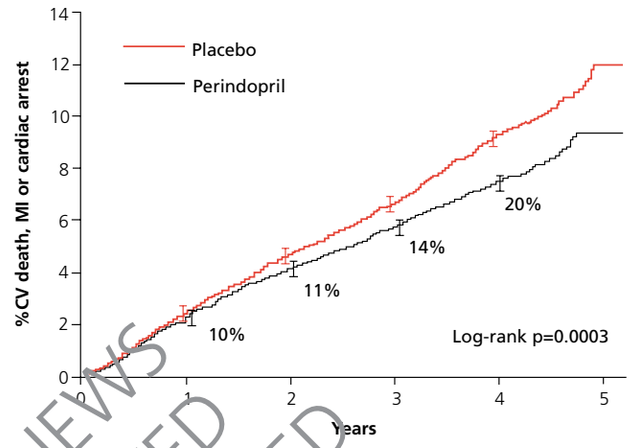
EUROPA was a randomised, double-blind, placebo-controlled study that involved 424 centres in 24 European countries.[10] Male and female patients aged ≥ 18 years were recruited to the study if they had evidence of stable CAD, with no clinical evidence of

Table 3. Baseline characteristics of the patients in the EUROPA study. Values are given as mean ± standard deviation or as percentages

	Perindopril n=6,110	Placebo n=6,108
Age (years)	60 ± 9	60 ± 9
Female (%)	14.5	14.7
Weight (kg)	81 ± 12	80 ± 12
Heart rate (bpm)	68 ± 10	68 ± 10
SBP (mmHg)	137 ± 16	137 ± 15
DBP (mmHg)	82 ± 8	82 ± 8
Current smoker (%)	15.4	15.1
Medical history (%)		
- prior MI	64.9	64.7
- prior revascularisation	54.7	55.2
- hypertension	27.0	27.2
- diabetes mellitus	11.8	12.8
- hypercholesterolaemia	63.3	63.3
Baseline medication (%)		
- platelet inhibitors	91.9	92.7
- beta blockers	62.0	61.3
- lipid-lowering drugs	57.8	57.3

Key: DBP = diastolic blood pressure; SBP = systolic blood pressure; MI = myocardial infarction

Figure 4. Over a mean follow-up period of 4.2 years, patients who received perindopril 8 mg once daily experienced a 20% reduction in the risk of cardiovascular death, myocardial infarction (MI), and cardiac arrest, relative to placebo[10]



Adapted from *Lancet*[10] with permission
Key: CV = cardiovascular; MI = myocardial infarction

heart failure or left ventricular systolic dysfunction. CAD had to be documented by one of the following parameters:

- an MI more than three months before the study
- percutaneous or surgical coronary revascularisation more than six months before the study
- angiographic evidence of ≥ 70% narrowing of a major coronary artery
- in men, a history of chest pain and a positive electrocardiogram, echocardiogram, or nuclear stress test.

The main exclusion criteria were clinical evidence of heart failure, planned revascularisation, hypotension, uncontrolled hypertension (systolic blood pressure [SBP] > 180 mmHg, diastolic blood pressure [DBP] > 110 mm Hg, or both), recent use of ACE inhibitors or angiotensin II receptor blockers, and renal insufficiency.

During an initial run-in period, patients received perindopril 4 mg once daily for two weeks, then perindopril 8 mg once daily for a further two weeks. Patients (n=12,218) were then randomised to perindopril 8 mg once daily or placebo for at least three years. The patients' baseline characteristics are shown in table 3. Perindopril or placebo were administered in addition to recommended modern standards of secondary prevention for CAD. This can be confirmed by comparison of the baseline characteristics of the EUROPA patients with those of 3,379 hospitalised patients with CAD studied in the EUROASPIRE II survey, conducted in nine European countries between 1999 and 2000.[38,39] Notably, 92% of the EUROPA patients were receiving a platelet inhibitor (mainly aspirin), 62% a beta blocker, and 58% a lipid-lowering drug. In EUROASPIRE II, 84% of patients were receiving a platelet inhibitor, 66% a beta blocker, and 63% a lipid-lowering drug. The added risk due to the presence of treated diabetes was possibly even under-reflected in the EUROPA population, since diabetes was present in only 12% of patients, versus 22% in EUROASPIRE.

After a mean follow-up period of 4.2 years, treatment with perindopril resulted in a 20% relative risk reduction in the primary end point, which was a composite of cardiovascular death, non-fatal MI, and cardiac arrest with successful resuscitation (p=0.0003) (figure 4). Importantly, as for the primary end point, treatment with perindopril was also associated with notable reductions in all secondary end points, such as a 14% reduction in the combined end point of MI, total mortality, unstable angina, and cardiac arrest (p=0.0009), a 24% reduction in fatal and non-fatal MI (p<0.001), and a 39% reduction in hospital admission for heart failure (p=0.002) (table 4). These results were evident on top of recommended preventive therapies and were consistent for all patients with CAD, irrespective of their age and whether they were diabetic, hypertensive, or had had a previous MI.

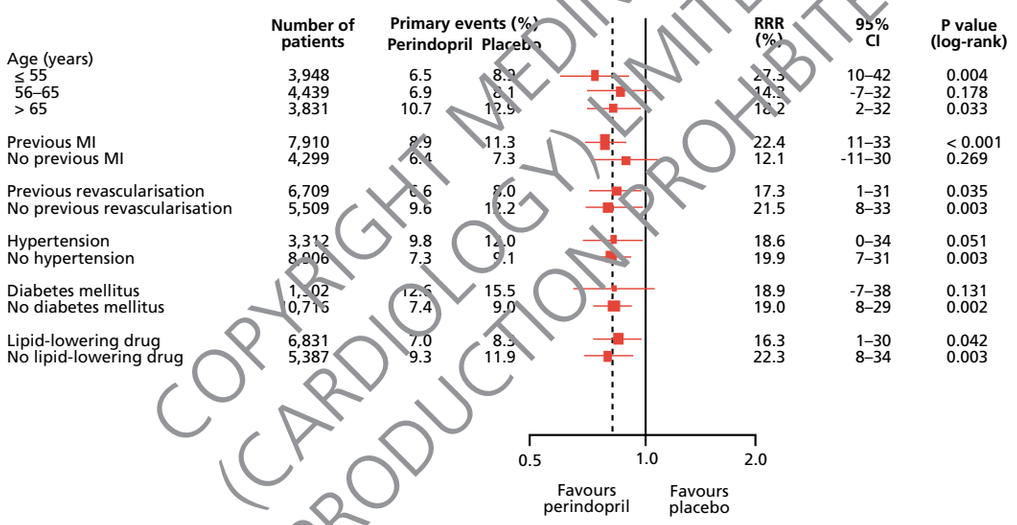
The onset of the benefits of perindopril became evident from one year of treatment (RRR 10%, p=0.35) achieving statistical significance after three years of follow-up and beyond (RRR 14%; 95% CI 0.5–25.2%). The beneficial effect of perindopril might be due to the blood pressure reduction (5/2 mmHg on average), although the gradual onset of effect and progressive benefits observed over time are most probably also related to the anti-atherosclerotic properties of ACE inhibition with perindopril. Moreover, throughout the study period, perindopril was well tolerated, since adherence to treatment was identical to the placebo group. Among the perindopril-treated patients, 1% withdrew

Table 4. Beneficial effect of treatment with perindopril on the primary end point and selected secondary end points in EUROPA[10]

Outcomes	Number of events		Relative risk reduction	95% confidence interval	p value Log-rank
	Perindopril n=6,110	Placebo n=6,108			
Primary end point					
CV mortality, MI, cardiac arrest	488	603	20%	9 to 29%	0.0003
Secondary end points					
Total mortality, non-fatal MI, unstable angina, cardiac arrest	904	1,043	14%	6 to 21%	0.0009
Fatal and non-fatal MI	320	418	24%	12 to 34%	< 0.001
Hospitalisation for heart failure	63	103	39%	17 to 56%	0.002

Key: CV = cardiovascular; MI = myocardial infarction

Figure 5. In EUROPA, treatment with perindopril was associated with a reduction in the relative risk of cardiovascular death, myocardial infarction, and cardiac arrest in predefined subgroups[10]



Adapted from *Lancet*[10] with permission

Key: RRR = relative risk reduction; CI = confidence interval; MI = myocardial infarction

due to hypotension, compared with 0.3% in the placebo group, and 2.7% due to cough, compared with 0.5% in the placebo group.

Implications of the EUROPA study

Unlike previous trials with ACE inhibitors showing that this class of drugs provides benefits in high-risk CAD patients, EUROPA is the first trial demonstrating that a thoroughly representative population with CAD, regardless of their level of risk and already receiving recommended preventive therapy, can benefit from treatment with perindopril 8 mg once daily, not only in terms of reduced risk of a first event, but also the risk of subsequent events. Since the beneficial effects of perindopril on the cardiovascular events were consistent across all predefined subgroups (although, due to lack of statistical power, not significant for some subgroups), the implications of the EUROPA study for daily clinical practice might be far-reaching. A selection of frequently encountered patients with stable CAD in whom treatment with perindopril 8 mg once daily should be considered is detailed below.

Implications for CAD patients with or without a history of MI or revascularisation

The beneficial effects of perindopril treatment on the primary end point were consistent for all patients, including those with or without a history of MI or revascularisation. Even though 65% of

the patients had a history of MI (> 3 months before screening), the EUROPA trial cannot be defined as a post-MI trial, since the MI had occurred more than one year previously in 80%, and more than five years previously in 33%. In the overall population (i.e. irrespective of a history of MI), fatal or non-fatal MI was reduced by 24% (95% CI 12–34%, p<0.001) among patients receiving perindopril, and non-fatal MI by 22% (95% CI 10–33%, p=0.001). Among patients with a history of MI, 704 (8.9%) reached the primary end point with perindopril compared with 894 patients (11.3%) in the placebo group, indicating a relative risk reduction of 22% (p<0.001). Among patients without a history of MI, the cardiovascular outcome was improved by 12% (figure 5).

Regarding revascularisation procedures, 55% of the EUROPA population had a history at randomisation of either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG), or both (> 6 months before screening). Although the result did not reach significance due to the limited number of patients requiring this type of procedure, treatment with perindopril reduced the risk of revascularisation by 4.2% in the overall population. A subgroup analysis of patients with and without a history of revascularisation showed that addition of perindopril to standard therapies significantly reduced development of cardiovascular events by 17% in those with a history of revascularisation (p=0.035) and by 22% in those without a history (p=0.003) (figure 5). Thus, addition of perindopril 8 mg once daily to the existing treatment regimens may provide substantial benefits for stable CAD patients with or without a history of MI or of revascularisation (by PTCA or CABG).

Implications for CAD patients with or without major cardiovascular risk factors

The prognosis and impact of treatment of stable CAD depend largely on cardiovascular risk factors, as well as demographic factors and co-morbidities. The beneficial effects of treatment with perindopril on major risk factors such as hypertension and heart failure have been reported elsewhere and are therefore not discussed in this paper. The results of EUROPA have shown that treatment with perindopril in addition to standard treatment reduced cardiovascular events independently of some of the major risk factors, such as age, hypertension, diabetes mellitus, or hypercholesterolaemia.

1. Age

By lowering the minimum age of recruitment to 18 years, the EUROPA study involved relatively young patients with stable CAD as well as older patients. Therefore, unlike previous trials conducted in this field, EUROPA is the first trial including a thoroughly representative population. The mean age ranged from 26 to 89 years (mean 60 years, SD 9) with almost one third of patients being younger than 55 years. Although beneficial effects on cardiovascular events were consistent across all age strata, the observed 27% risk reduction in the group younger than 55 years is of particular interest (p=0.004) (figure 5).

2. Hypertension, diabetes mellitus and hypercholesterolaemia

Since the aim of the EUROPA study was to include a clinically representative population with stable CAD, only 27% of patients had hypertension (blood pressure > 160/95 mmHg or receiving antihypertensive treatment), 12% had diabetes mellitus (known history of diabetes or taking antidiabetic drugs), and 67% had hypercholesterolaemia (cholesterol > 6.5 mmol/L or receiving lipid-lowering therapy). Similar treatment effects were observed in patients with hypertension and those without hypertension: the primary end point was significantly improved by 19.9% in patients without hypertension as compared with the placebo group (p=0.003) (figure 5). Hypertensive patients also benefited from an 18.6% risk reduction. Perindopril similarly reduced the primary end point in both the diabetic population (by 18.9%, p=0.131) and the non-diabetic population (by 19.0%, p=0.002). In patients with and without lipid-lowering drug treatment, cardiovascular outcome was significantly improved by 16.3% (p=0.042) and 22.3% (p=0.003), respectively.

The data from EUROPA provide strong evidence that the recommended medications and lifestyle changes for stable CAD should be extended to include perindopril 8 mg once daily for all patients with one or more cardiovascular risk factors, such as hypertension, diabetes mellitus, or hypercholesterolaemia.

Independent treatment benefits

Importantly, treatment benefits were noted in patients receiving lipid-lowering drugs, beta blockers and calcium antagonists. A formal interaction analysis was performed to detect whether the effect of perindopril on the outcome was related to the other treatment regimen. The analysis showed no significant interaction effect in any of the three analyses and thus confirmed that the effect of perindopril was independent of the other drugs. Thus, the prognosis of all CAD patients can potentially be improved by treatment with perindopril independently of current recommended preventive therapy.

Implications for other patients at high risk of cardiovascular events

Hypertension and diabetes are risk factors for developing cardiovascular disease, and some patients with these conditions already have CAD.[40] An elevated blood pressure and associated conditions such as endothelial dysfunction, cardiovascular remodelling, atherosclerotic balance, and perturbation of fibrinolytic balance, are commonly shared in both conditions, and heart failure is an important outcome that will markedly worsen the prognosis. Perindopril has been demonstrated to act on all these associated conditions. As shown in the EUROPA study, it not only lowered blood pressure effectively in the short and long term, but also had a favourable tolerability profile and significantly reduced cardiovascular morbidity and mortality. As such, perindopril fulfils the criteria for effective preventive therapy as defined in the recent European guidelines on the prevention of cardiovascular disease.[4] Therefore, perindopril can be beneficial in other patients who need effective cardiovascular protection with 24-hour efficacy

and benefits beyond blood pressure control, such as patients with hypertension, diabetes, or heart failure.

Implications for guidelines

The British guidelines on the treatment of CAD currently recommend an ACE inhibitor for patients with heart failure or left ventricular systolic dysfunction,[41] and the European guidelines suggest that ACE inhibitors should be considered in patients with symptoms or signs of left ventricular systolic dysfunction due to CAD and/or arterial hypertension.[4] These and other guidelines will need updating in light of the results of the EUROPA trial. The current edition of the American guidelines for the management of chronic stable angina, published while EUROPA was still in progress, recognised that the results of EUROPA were expected to show whether the protective effect of ACE inhibition in CAD patients could extend to patients not just at high risk.[42] Currently, these guidelines suggest that ACE inhibitors should be used as routine secondary prevention for patients with known CAD, particularly in diabetic patients without severe renal disease.

Furthermore, the recently issued European guidelines on hypertension list heart failure and left ventricular dysfunction as 'compelling indications' for ACE inhibitors;[43] in the light of EUROPA, there is a strong case for adding CAD to this list. The recently published complete version of the Seventh American Joint National Committee hypertension guidelines (JNC 7), recommends that hypertensive patients with a compelling cardiovascular risk factor, such as a high risk for coronary disease, should start initial therapy with an antihypertensive drug that has been proven to effectively reduce this cardiovascular risk factor.[40]

Cost implications

Fifty patients with CAD need to be treated with perindopril 8 mg once daily for four years in order to prevent one cardiovascular death, non-fatal MI, and cardiac arrest. In a country of 60 million inhabitants, this means that perindopril over a four-year period could prevent 50,000 heart attacks or cardiovascular deaths. For Europe as a whole, treatment of CAD patients with perindopril could prevent about 330,000 deaths or MIs every four years.

In the UK, the total amount spent on the prevention and detection of CAD, and on the treatment and rehabilitation of patients with this condition, is currently much lower than the lost productivity it generates.[8] It is expected, therefore, that the use of perindopril in secondary prevention is likely to be cost-effective. Pharmacoeconomic analyses are currently ongoing to confirm whether this is the case.

Drug-specific or class effect?

The question of whether the results seen in EUROPA are specific to perindopril or are a 'class effect' of ACE inhibitors is an important one, but difficult to answer. As mentioned earlier, the lipophilic tissue ACE inhibitors, such as perindopril, probably penetrate more successfully into atherosclerotic plaques. They could therefore be expected to inhibit the onset and progression of the atherosclerotic process, and plaque rupture, more effectively than the less lipophilic 'plasma' ACE inhibitors. In this age of evidence-based medicine, it cannot be assumed that the effects of one drug will be reproduced by others in its class: small differences in chemical structure may sometimes produce profound pharmacological differences. Thus, the EUROPA findings may not be applicable across the wide range of available ACE inhibitors with varying properties and administration schedules.[11] Substudies of EUROPA are currently attempting to elucidate the effects of perindopril on the development of atherosclerosis and endothelial function, in order to clarify more fully how it exerts its beneficial effect.

The issue of dosing is also important. Equipotency in one measure (such as blood-pressure lowering) may not equate to an equally beneficial effect on another outcome (such as atherogenesis), and the optimal dosage for a particular therapeutic benefit needs to be established. For example, with ACE inhibitors, the importance of providing an adequate dose in order to achieve a satisfactory response in heart failure has been emphasised.[44] EUROPA has provided the evidence that perindopril at the highest recommended dose for the treatment of hypertension, 8 mg once daily, is effective and extremely well tolerated for the treatment of CAD.

In summary, it is possible that other tissue ACE inhibitors may share some of the protective effects of perindopril, but the evidence for this has to be provided by other trials.

Key messages

- In EUROPA, patients who received perindopril 8 mg once daily benefited from a 20% reduction in risk of the primary composite end point of cardiovascular death, myocardial infarction, and cardiac arrest. Secondary end points, such as hospitalisation for heart failure and fatal and non-fatal myocardial infarction, were reduced by 39% and 24%, respectively
- EUROPA has shown that long-term treatment with perindopril reduces the risk of cardiovascular end points in a broad population of CAD patients, regardless of their level of risk
- The protective effect of perindopril was apparent on top of standard recommended preventive therapies such as antiplatelet agents, beta blockers and lipid-lowering drugs
- Perindopril has a number of anti-atherogenic actions which probably contribute to this protective effect
- It cannot be assumed that other ACE inhibitors will necessarily have a similar protective effect
- The results of EUROPA suggest that perindopril should be added to other recommended preventive treatments in all patients with CAD, such as those with stable angina, a history of myocardial infarction or revascularisation

Conclusion

Clinical trials have consistently shown that ACE inhibitors provide the broadest impact of any drug in cardiovascular medicine. They benefit both hypertensive and normotensive patients in reducing the risk of morbidity and mortality from heart failure, MI, stroke, diabetes, and renal impairment. In spite of the abundant evidence of benefit and the existence of guidelines, implementation in clinical practice often remains inadequate.[39] Many patients do not yet receive adequate lifestyle and therapeutic interventions to reduce high blood pressure and cardiovascular disease.

In the light of the anticipated increase in the number of patients with CAD, the new evidence obtained with EUROPA might have far-reaching clinical consequences for the management of patients with stable CAD. The study results are clear-cut and were obtained on a thoroughly representative population: EUROPA is the first trial extending the life-saving effects of an ACE inhibitor, perindopril, to a broad population often seen in daily clinical practice. If statins can be considered as being one of the biggest drug advances of the past decade in the management of cardiovascular disease, then perindopril is probably the next major advance likely to change clinical practice. Therefore, treatment with perindopril 8 mg once daily should be considered for all patients with stable CAD, irrespective of their cardiovascular risk profile and additional treatment.

Conflict of interest

KMF has received honoraria and research grants from the study sponsor, Servier.

References

1. WHO report. Risks to health 2002. Geneva, Switzerland: WHO, 2002.
2. Dzau VJ. Resolved and unresolved issues in the prevention and treatment of coronary artery disease. *Am Heart J* 1991;**121**:1244-53.
3. Petersen S, Rayner M. *Coronary heart disease statistics: 2002 edition*. London: British Heart Foundation Statistics Database, 2002:1-164.
4. De Backer G, Ambrosioni E, Borch-Johnsen K *et al*. European guidelines on cardiovascular disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil* 2003;**10**(suppl 1):S1-S78.24:1601-10.
5. British Heart Foundation Statistics Database 2003. *Coronary heart disease statistics*. http://www.bhf.org.uk/professionals/uploaded/bhf%20heartstats%202003%20-%204-page.pdf
6. Fox KF, Cowie MR, Wood DA *et al.* Coronary artery disease as the cause of incident heart failure in the population. *Eur Heart J* 2001;**22**:228-36.
7. He J, Ogden L, Bazzano L *et al*. Risk factors for congestive heart failure in US men and women. *Arch Intern Med* 2001;**161**:996-1002.
8. Liu JL, Maniadakis N, Gray A, Rayner M. The economic burden of coronary heart disease in the UK. *Heart* 2002;**88**:597-603.
9. American Stroke Association/American Heart Association. Heart disease and stroke statistics – 2003 update. http://www.americanheart.org/presenter.jhtml?identifier=3000090
10. EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease investigators. 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). *Lancet* 2003;**362**:782-8.
11. White HD. Should all patients with coronary disease receive angiotensin-converting-enzyme inhibitors? *Lancet* 2003;**362**:755-6.
12. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;**316**:1429-35.
13. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293-302.
14. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;**327**:685-91.
15. Pfeffer MA, Braunwald E, Moye LA *et al*. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. *N Engl J Med* 1992;**327**:669-77.
16. AIRE Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821-8.
17. Kober L, Torp-Pedersen C, Carlsen JE *et al*. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;**333**:1670-6.
18. HOPE study investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 2000;**342**:145-53.
19. Dzau VJ, Bernstein K, Celermajer D *et al*. The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. *Am J Cardiol* 2001;**88**(suppl):1L-20L.
20. Minai K, Matsumoto T, Horie H *et al*. Bradykinin stimulates the release of tissue plasminogen activator in human coronary circulation: effects of angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2001;**37**:1565-70.
21. Dell'Italia LJ, Kicic P, Luchesi PA. Use of tissue angiotensin-converting enzyme inhibitors in patients with diabetes and coronary artery disease. *Curr Probl Cardiol* 2002;**27**:4-36.
22. Myers MG. A dose-response study of perindopril in hypertension: effects on blood pressure 6 and 24 h after dosing. Perindopril Multicenter Dose-Response study Group. *Can J Cardiol* 1996;**12**:1191-6.
23. Zhuo J, Broomes P, Casley D *et al*. Perindopril chronically inhibits angiotensin-converting enzyme in both the endothelium and adventitia of the internal mammary artery in patients with ischemic heart disease. *Circulation* 1997;**96**:174-82.
24. Zhuo J, Mendelsohn F, Ohishi M. Perindopril alters vascular angiotensin-converting enzyme, AT1 receptor, and nitric oxide synthase expression in patients with coronary heart disease. *Hypertension* 2002;**39**(part 2):634-8.
25. Morishita T, Tsutsui M, Shimokawa H *et al*. Long-term treatment with perindopril ameliorates dobutamine-induced myocardial ischemia in patients with coronary artery disease. *Jpn J Pharmacol* 2002;**88**:100-07.
26. Schwarzkopff B, Brehm M, Mundhenke M, Strauer BE. Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. *Hypertension* 2000;**36**:220-5.
27. Fennessy P, Campbell J, Mendelsohn F *et al*. Angiotensin-converting enzyme inhibitors and atherosclerosis: relevance of animal models to human disease. *Clin Exp Pharmacol Physiol* 1996;**23**(suppl 1):S30-S32.
28. Candido R, Jandeleit-Dahm A, Cao Z *et al*. Prevention of accelerated atherosclerosis by angiotensin-converting enzyme inhibition in diabetic apolipoprotein E-deficient mice. *Circulation* 2002;**106**:246-53.
29. Ghiadoni L, Magagna A, Versari D *et al*. Different effect of antihypertensive drugs on conduit artery endothelial function. *Hypertension* 2003;**41**:1281-6.
30. Fogari R, Mugellini A, Zoppi A *et al*. Losartan and perindopril effects on plasma plasminogen activator inhibitor-1 and fibrinogen in hypertensive type 2 diabetic patients. *Am J Hypertens* 2002;**15**:316-20.
31. Matsumoto T, Minai K, Horie H *et al*. Angiotensin-converting enzyme inhibition but not angiotensin II type 1 receptor antagonism augments coronary release of tissue plasminogen activator in hypertensive patients. *J Am Coll Cardiol* 2003;**41**:1373-9.
32. Mead M. The need for 24-hour blood pressure control. *Br J Cardiol* 2003;**10**:310-14.
33. Hurst M, Jarvis B. Perindopril. An updated review of its use in hypertension. *Drugs* 2001;**61**:867-96.
34. Simpson D, Noble S, Goa K. Perindopril in congestive heart failure. *Drugs* 2002;**62**:1367-77.
35. Hutcheon SD, Gillespie ND, Crombie IK, Struthers AD, McMurdo MET. Perindopril improves six minute walking distance in older patients with left ventricular systolic dysfunction: a randomised double blind placebo

controlled trial. *Heart* 2002;**88**:373-7.
36. MacFadyen RJ, Lees KR, Reid JL. Differences in first dose response to angiotensin converting enzyme inhibition in congestive heart failure: a placebo controlled study. *Br Heart J* 1991;**66**:206-11.
37. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;**358**:1033-41.
38. EUROASPIRE I and II Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. *Lancet* 2001;**357**:995-1001.
39. EUROSPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: principal results from EUROSPIRE II Euro Heart Survey programme. *Eur Heart J* 2001; **22**:554-72.
40. Chobanian AV *et al*. JNC 7 – complete version. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;**42**:1206-52.
41. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, British Diabetic Association. Joint British recommendations on prevention of coronary heart disease in clinical practice: summary. *BMJ* 2000;**320**:705-08.
42. Gibbons RJ, Abrams J, Chatterjee K *et al.* ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. http://www.acc.org/clinical/guidelines/stable/stable_clean.pdf
43. Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;**21**:1011-53.
44. Task Force for the Diagnosis and Treatment of Chronic Heart Failure, ESC. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;**22**:1527-60.