

The clinical application of ACE inhibitors in coronary artery disease

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Abstract

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the pathogenesis of cardiovascular disease. Blockade of this system results in a number of biologically important beneficial effects, including inhibition of the breakdown of bradykinin, reduction in blood pressure and inhibition of neuroendocrine activity, as well as reversal of endothelial dysfunction. Angiotensin-converting enzyme (ACE) inhibitors have an established role in the management of hypertension and heart failure. More recently, for instance in the HOPE trial, they have been investigated in patients with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor, but with preserved left ventricular function. Treatment with ramipril was shown to reduce cardiovascular events significantly, especially in patients who had diabetes. Two further ongoing trials – EUROPA (with perindopril) and PEACE (with trandolapril) – are described, which have important differences in trial design and which will further assess the protective effects of ACE inhibition in patients with stable coronary artery disease.

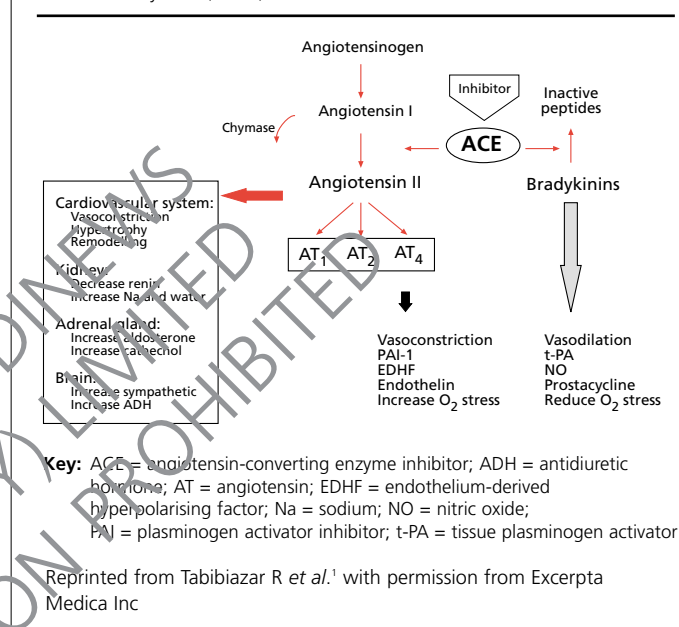
Key words: ACE inhibitors, coronary artery disease, HOPE, EUROPA, PEACE.

Introduction

Atherosclerosis appears to be clearly associated with abnormalities of the renin-angiotensin-aldosterone system (RAAS). There are likely to be several other causes of atherosclerosis, but study of the RAAS has produced a great deal of direct and circumstantial evidence, and this is primarily the subject of this review. Abnormality of the RAAS usually involves the over-production of angiotensin II, the upregulation of its receptors, the under-production of the potent vasodilator, bradykinin, or some per-

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Figure 1. Biological properties of the renin-angiotensin-aldosterone system (RAAS)



mutation of all of these. The RAAS can be conveniently interrupted by angiotensin-converting enzyme (ACE) inhibitors: most investigations, whether animal studies or clinical trials, show that these drugs do indeed inhibit certain stages of atherosclerosis, including coronary atherosclerosis.

Endothelial dysfunction underlies many stages in the progression of the disease, and under normal circumstances angiotensin II (whose effects in excess are harmful) is kept in check by the activities of vasodilator agents (primarily nitric oxide [NO]) and prostaglandins produced by the endothelium. Figure 1 summarises the 'harmful' and 'good' sides of the balance: normally, bradykinin stimulates the release of NO from the endothelium, which not only dilates the vessel but also prevents platelet aggregation, the activity of white cells (monocytes, especially) and smooth muscle hypertrophy, all of which result from the activities of angiotensin II.

Damage to the endothelium through smoking, hypercholesterolaemia, diabetes, hypertension or superoxides inhibits NO release, allowing angiotensin II to exert its harmful effects (see the left side of figure 1). It seems likely that endothelial damage acts primarily on nitric oxide synthase, the enzyme in the endothelium responsible for synthesising NO.

Once the endothelium is damaged, NO loses its restraining influence and white cell activity, platelet aggregation and smooth muscle hypertrophy begin the serious structural damage of atherosclerosis. Angiotensin II, some of which is produced locally by tissue angiotensin converting enzyme (ACE), stimulates the conversion of monocytes to lipid-laden macrophages. As might be expected, long-term treatment with ACE inhibitors decreases the ratio of angiotensin II to angiotensin I and also increases the plasma level of bradykinin. Earlier animal studies suggest that the increased availability of NO associated with ACE inhibitor use is mediated via endothelial bradykinin receptors.

A large number of clinical trials, some of them reviewed below, suggest that these putative mechanisms of action translate into clinical benefits.

ACE inhibitors in coronary angioplasty

In the TREND study,² 105 patients were randomised to quinapril (40 mg/day) or placebo for six months. The patients all had documented coronary artery disease (CAD) and no heart failure. Target segments of coronary artery were examined using quantitative coronary angiography (QCA) at baseline and at six months. At baseline, the quinapril and placebo groups had graded doses of acetylcholine infused into these target segments: the groups showed comparable vasoconstrictor responses, implying inadequate endothelial production of NO. Patients who showed no constrictor activity at baseline were excluded.

After six months, repeat acetylcholine infusions showed the quinapril group to have reversed their vasoconstrictor response: for acetylcholine concentrations of 10^{-6} mol/L the flow was increased by 4.5% and of 10^{-4} mol/L, by 12.1%. No vasodilator change was seen in the placebo group ($p=0.002$). The findings offer great encouragement to any long-term study of ACE inhibition on coronary artery disease, for an early stage of atherosclerosis is shown to be reversible. In further clinical studies, however, ACE inhibitors have failed to prevent hyperplasia (restenosis) following coronary angioplasty.

The MERCATOR study (1992)³ involved 595 patients taking cilazapril (5 mg/twice a day) or placebo treatment beginning on the same day as their angioplasty. Treatment lasted for six months and, at the end of this time, there was no difference in the restenosis rates. The 'big brother' of MERCATOR was MARCATOR.⁴ This studied 1,436 post-angioplasty subjects, who received 2, 10 or 20 mg/day cilazapril or placebo for six months, beginning at angioplasty. These larger doses are 2–4 times the maximum recommended dose of cilazapril (5 mg/day), which was an attempt to make the situation analogous to that seen in earlier successful animal experiments. None of the three groups of patients showed clinical or angiographic features different from the placebo group.

A third study, QUIET,⁵ involved 453 post-angioplasty patients taking quinapril 20 mg/day, or placebo, for three years. The drug treatment began on day 1; once again, there was no difference in the restenosis rate between quinapril and placebo-treated patients.

Was this lack of efficacy a problem of timing rather than one

of dosing, and should the ACE inhibitor have been given before angioplasty in an attempt to raise local NO levels and prevent angiotensin II from triggering muscle hyperplasia? A small study from Japan tried to address this.⁶ Some 167 patients were randomised to either cilazapril or placebo, starting seven days before angioplasty. Unfortunately, only 128 patients finished the study, but the restenosis rates were 29% in the cilazapril group and 50% in the placebo group ($p < 0.02$) at six months. Since this study (which was performed in 1995) was apparently the first successful prevention of restenosis using ACE inhibitors, it seems surprising that it has not been repeated.

ACE inhibitors in ischaemic heart failure

ACE inhibitors are much used in ischaemic heart failure, and the larger trials showed a significant reduction in the risk of myocardial infarction. Clearly, an anti-atherosclerotic effect could contribute to such findings. Thus the SOLVD⁷ study in heart failure patients showed a risk reduction of 23% in myocardial infarction and 20% in unstable angina. In the SAVE⁸ study there was also a 25% reduction in recurrent myocardial infarction and a significant reduction in the revascularisation rate in patients receiving captopril. The difference between drug and placebo lines in the Kaplan-Meier plots becomes evident within a few months of treatment, and becomes progressively greater with time.

The falls in blood pressure seen in the active groups of these studies were not considered large enough to explain the infarction differences between the two groups: in SOLVD, for example, there was a fall of 4 mmHg in the diastolic pressure of the treatment arm. This was associated with a 23% reduction in fatal or non-fatal myocardial infarction (see discussion of the HOPE trial below). Such evidence adds further support to the idea that ACE inhibitors produce structural, rather than haemodynamic, effects on the circulation. These heart failure trials were a great stimulus to setting up the atherosclerosis studies that we shall describe here.

ACE inhibitors in atherosclerosis

At the time of writing, three multicentre, randomised, double-blind, placebo-controlled trials exist. Each study is 3–5 years long. One (HOPE) is finished; the two incomplete trials (EUROPA and PEACE) will be described first.

EUROPA

The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA)⁹ involves 12,236 randomised patients from 24 European countries. The patients are randomised to 8 mg/day perindopril or placebo; they all have proven coronary artery disease but do not have heart failure or ventricular dysfunction. The primary outcome of EUROPA is to determine whether the addition of the ACE inhibitor perindopril to standard therapy decreases the incidence of cardiovascular death, myocardial infarction and resuscitated cardiac arrest in patients with stable coronary artery disease but without evidence of heart failure. In this population, 15% of the patients are diabetic (which makes an interesting contrast to the HOPE trial,

where 39% are diabetic). Recruitment began in November 1997 and ended in March 1999. All patients will be followed-up until January–April 2003.

A number of substudies have been undertaken in order to develop a better understanding of the mechanisms of perindopril in coronary artery disease. These substudies 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 (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 (eNOS) for endothelial function. This substudy has two parts: part A includes 345 patients and looks at the concentration of the above factors at baseline and at one year whereas, part B, which includes 1,282 patients, only examines C-reactive protein and von Willebrand factor, measured at baseline and at one year.

PERFECT (PERindopril Function of the Endothelium in Coronary artery disease Trial). 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 substudy, blood flow in the brachial artery is measured using an echo duplex scanner at rest and after four minutes of ischaemia during the run-in period, at the time of randomisation and at six, 12, 24 and 36 months thereafter. The primary end point is the percentage change in the flow-mediated vasodilatation of the brachial artery between baseline and 36 months and 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) aims to investigate the effects of perindopril administration on the progression and regression of coronary atherosclerosis using quantitative 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 the main parameters measured by IVUS are plaque volume, plaque area and lumen area. Some 319 patients have been recruited from those within the main study needing angiography. The primary objective of this substudy 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 36 months of 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), a further substudy, examines diabetic patients in EUROPA (who made up 15% of the study population). The main efficacy variable is to determine the effects of perindopril in the diabetic population in terms of the primary and secondary end points. The primary end points are those of the EUROPA study. It will also detect the progression of diabetic nephropathy as assessed by albumin:creatinine ratio.

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

PEACE

The design of the (predominantly American) Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE)¹⁰ study is very similar to that of EUROPA. In PEACE, 8,100 patients with CAD and an ejection fraction greater than 40% have been randomised to trandolapril (4 mg/day) or placebo for five years. The primary end point is cardiovascular mortality, non-fatal myocardial infarction or revascularisation. Recruitment was planned to end when 8,100 patients were randomised or when the end of 1999 was reached. Follow-up will end in the year 2003, when the median follow-up time is projected to be 4.5 years.

HOPE

The (predominantly Canadian) Heart Outcomes Prevention Evaluation study (HOPE),¹¹ which reported in 2000, involved a comparison of ramipril (10 mg/day) and placebo in patients with cardiovascular disease. The study involved a total of 9,297 patients, with 39% of them diabetic. Patients were over 55 years old and had no heart failure or ventricular dysfunction. The range of cardiovascular conditions in the study was very wide: patients could have a history of proven CAD or stroke, peripheral vascular disease or diabetes and one other additional risk factor such as hypertension or dyslipidaemia. Some 80% of them had CAD. Diabetic patients were encouraged to enter the study, provided that they had one coronary risk factor as well as diabetes. Thus, a diabetic who smoked was eligible, even though he might have no evidence of vascular disease.

The study was a 2x2 factorial design, with patients randomly assigned to ramipril (10 mg/day) or placebo, and to vitamin E or placebo. Patients took these drugs for a mean of 4.5 years. The primary end point was composite: myocardial infarction, stroke or death from cardiovascular causes. Secondary end points are also included in table 1.

Table 1. Principal findings from the HOPE study

	Ramipril	Placebo	Relative risk	p value
Patients reaching primary end point				
● Combined	14.0%	17.8%	0.78	<0.001
● Cardiovascular death	6.1%	8.1%	0.74	<0.001
● Myocardial infarction	9.9%	12.3%	0.80	<0.001
● Stroke	3.4%	4.9%	0.68	<0.001
Patients reaching secondary end point				
● Death (any cause)	10.4%	12.2%	0.84	0.005
● Revascularisation	16.0%	18.3%	0.85	0.03
● Cardiac arrest	0.8%	1.3%	0.63	0.03
● Heart failure	9.0%	11.5%	0.77	<0.001
● New diagnosis of diabetes	3.6%	5.4%	0.66	<0.001

Table 2. Principal findings from MICRO-HOPE

	Ramipril	Placebo	p value
Patients reaching primary end point			
● Combined	15.3%	19.8%	0.004
● Myocardial infarction	10.2%	12.9%	0.01
● Stroke	4.2%	6.1%	0.0074
● CV death	6.2%	9.7%	0.0001
Patients reaching secondary end point			
● Total mortality	10.8%	14.0%	0.004
● Revascularisation	14.0%	16.4%	0.031
● Overt nephropathy	6.5%	8.4%	0.027
● All heart failure	11.0%	13.2%	0.019
● All worsening diabetic outcomes	15.1%	17.6%	0.036

Blood pressure was 139/79 mmHg in both groups at entry. By the end of the study, the blood pressure of the ramipril patients was 136/76 mmHg and of the placebo patients was 139/77 mmHg. The authors concluded that the significantly better event rate seen in patients taking ramipril was apparently not the result of this very small fall in blood pressure. No significant findings emerged for patients taking vitamin E.

The diabetic patients (of whom 97% had type II disease) were analysed separately in a substudy, MICRO-HOPE,¹² which was published simultaneously with HOPE. These 3,577 patients had no clinical proteinuria, but were admitted if their diabetes was accompanied by one or more risk factors - total cholesterol > 5.2 mmol/L, HDL-cholesterol < 0.9 mmol/L, hypertension, known microalbuminuria or current smoking.

The baseline characteristics of patients taking ramipril (n=1,808) were virtually identical with those taking placebo (n=1,769). Both HOPE and MICRO-HOPE were stopped six



Key messages

- The renin-angiotensin-aldosterone system (RAAS) is critically involved in the pathogenesis of cardiovascular disease
- Blockade of this system is clinically beneficial
- ACE inhibitors have an established role in hypertension and heart failure
- ACE inhibitors also prevent cardiovascular events in patients with established coronary artery disease and preserved left ventricular function

months early (at 4.5 years) for the same reason: a consistent benefit of ramipril over placebo. The end point findings in MICRO-HOPE are shown in table 2.

Glycated haemoglobin did not change for the two groups at the end of the study. This would suggest that ramipril had no influence on the disease process itself, even though it significantly improved vascular status and nephropathy. The fall in blood pressure in ramipril patients was -1.9/-3.3 mmHg and in placebo patients 0.55/-2.3 mmHg over the study: both systolic and diastolic changes were significant (p=0.0002 and p=0.008, respectively). Adjustment for changes in blood pressure on the primary end point did not change the relative risk reduction of 25%. As in HOPE, the beneficial effect of ramipril was not primarily due to lowering of blood pressure.

A remarkable feature of MICRO-HOPE is that the outcome for diabetic patients taking ramipril was better than that for non-diabetics taking placebo. This confirms that the drug markedly reduces the effect of diabetes. It has previously been shown that hyperinsulinism sensitises the cardiovascular system to the trophic effects of angiotensin II and aldosterone.^{13,14} Such a mechanism would provide a basis for part of the protective effects of ACE inhibitors on the arterial disease of diabetics. It can be argued that all diabetic patients, irrespective of any evidence of arterial disease, should be given an ACE inhibitor for primary prevention, especially since these are drugs with few side effects.

Conclusion

Provided that EUROPA and PEACE show findings that are similar to HOPE, it is clear that ACE inhibitors have a very significant role to play in coronary artery disease. Indeed, in the future it may be an achievement to find a cardiovascular patient (diabetic or otherwise) who would not benefit from an ACE inhibitor.

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