The role of angiotensin-converting enzyme inhibitors in coronary artery disease

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Perindopril has recently been granted a licence extension for the treatment of stable coronary artery disease, to reduce the risk of cardiac events in patients with a history of myocardial infarction (MI) and/or revascularisation. Dr Kristian Bailey and Professor Alistair Hall review the evidence behind this extended role for angiotensin-converting enzyme (ACE) inhibitors and discuss whether this role applies across the whole class.

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Introduction

Cardiovascular disease remains the leading cause of death in the UK, with coronary artery disease (CAD) being the single largest contributory factor. Despite a steady reduction in mortality from acute MI over the past 20 years, the mortality and morbidity of CAD continue to increase, partially as a result of the improvements made in care in the acute setting. Between 1994 and 2003 the overall prevalence of CAD in men in the UK rose from 6.0% to 7.4%, while in women a smaller increase was seen, from 4.1% to 4.5%. Among older age groups, CAD is far more prevalent: 26.4% of men and 18.4% of women over the age of 75 live with CAD.[1]

In 2003, the estimated cost of CAD to the National Health Service (NHS) in the UK was £3,527 million per annum, of which inpatient care and ongoing medication accounted for 95% of the total costs. When effects of CAD mortality and morbidity are taken into account, the estimated cost to the UK economy is £7,910 million per annum.[2] Improvements in care that reduce morbidity and hospitalisation will be beneficial not only to patients themselves, but will also reduce the burden on the NHS and greater economy.

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Guidelines on use of ACE inhibitors

Hypertension

ACE inhibitors are currently recommended as either first- or second-line therapy for the treatment of hypertension in adults. The British Hypertension Society guidelines published in 2004 (BHS IV) recommend the use of blockers of the renin-angiotensin system (ACE inhibitors or angiotensin-II receptor blockers [ARBs]) or beta blockers as first-line treatment for hypertension in younger patients (under 55 years) and non-black patients, and as second-line agents in black patients and those over 55 years, should adequate blood pressure control not be achieved with thiazide diuretics or calcium channel antagonists.[3] This difference in approach is based on the physiological principle that the renin-angiotensin system is more active in younger and non-black patients and therefore greater reductions in blood pressure are likely to result from use of ACE inhibitors/ARBs in this population.

The National Institute for Clinical Excellence (NICE) published guidelines for the treatment of hypertension in 2004, and these differed from the BHS guidelines in recommending initial therapy with thiazide-type diuretics for all patients.[4] NICE recommends use of ACE inhibitors as second-line therapy for patients with uncontrolled hypertension who are at high risk of developing new-onset diabetes. The NICE guidelines take into account the cost of generic thiazide diuretics, and beta blockers such as atenolol, in assessing the overall cost-effectiveness of blood pressure control.

At the time of writing, the NICE and BHS guidelines are under review following the recent publication of the findings from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which looked at treatment of hypertension in patients with no history of coronary heart disease but with at least three other cardiac risk factors.[5] A total of 19,257 patients with untreated or suboptimally treated hypertension were randomised to one of two antihypertensive treatment regimes, either amlodipine ± perindopril or atenolol ± bendroflumethiazide. Patients with a known diagnosis of CHD were excluded to allow open-label treatment with ACE inhibitors. The primary end point was non-fatal myocardial infarction and fatal CAD.

The study was stopped prematurely after a median of 5.5 years' follow-up: at this point fewer patients in the amlodipine ± perindopril group had suffered a primary end point, although this was not statistically significant (429 *vs.* 474; unadjusted HR 0·90, 95% CI 0·79-1·02; p=0·1052). Patients in the amlodipine ± perindopril group did, however, show a statistically significant

Table 1. Comparison of current heart failure guidelines in relation to use of ACE inhibitors

Updated	NICE[6] 2003	ESC[7] 2005	ACC/AHA[8] 2005
Which patients should be considered for ACE inhibitors?	All patients with heart failure due to LV dysfunction	All patients with evidence of LV dysfunction	All patients with heart failure due to LV dysfunction
When should ACE inhibitors be initiated?	Prior to treatment with beta blockers	First-line therapy	First-line therapy
Do patients need to be symptomatic?	Not specifically mentioned	No	No
What dose of ACE inhibitor?	Maximum tolerated. Up-titrated to target dose used in clinical trials	Maximum tolerated. Up-titrated to target dose used in clinical trials	Maximum tolerated. Up-titrated to target dose used in clinical trials
Use for transient heart failure following acute MI	Not specifically mentioned	Yes	Not specifically mentioned
Renal impairment	Mild increases in creatinine from baseline acceptable	Moderate renal impairment not a contraindication (creatinine < 250 µmol/L)	Use with caution if creatinine > 3 mg/dL (265 µmol/L)
Hypotension	Asymptomatic hypotension not a contraindication	Moderate hypotension not a contraindication (≈ 90 mmHg systolic) in patient is asymptomatic	Discontinue therapy if patient becomes severely hypotensive and symptomatic

Key: LV = left ventricular; ACE = angiotensin-converting enzyme; MI = myocardial infarction; NICE = National Institute for Clinical Excellence; ESC = European Society of Cardiology; ACC/AHA = American College of Cardiology/American Heart Association

reduction in most of the secondary end points, including the risk of fatal and non-fatal stroke (327 *vs.* 422; 0·77, 0·66–0·89; p=0·0003), total cardiovascular events and procedures (1,362 *vs.* 1,602; 0·84, 0·78–0·90; p<0·0001), and all-cause mortality (738 *vs.* 820; 0·89, 0·81–0·99; p=0·025). The incidence of new-onset diabetes, a tertiary end point, was also less on the amlodipine ± perindopril regimen (567 *vs.* 799; 0·70, 0·63-0·78; p<0·0001).

Heart failure

Trials have consistently shown a benefit from ACE inhibitors in patients with heart failure, reducing both morbidity and mortality. For this reason all guidelines for the management of heart failure recommend the routine use of ACE inhibitors in patients with left ventricular dysfunction. Table 1 summarises the main guidelines.[6-8]

ACE inhibitors in CAD – the evidence so far

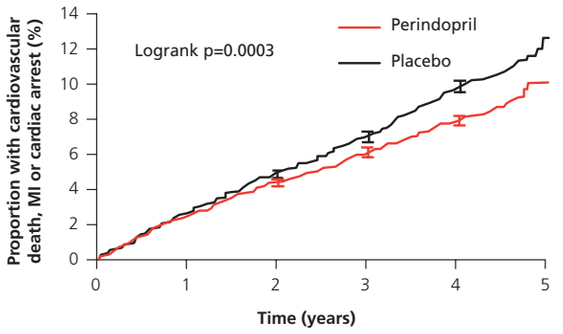
A number of trials have demonstrated the beneficial effects of ACE inhibitors in patients with CAD. These trials have involved patients with acute MI, stable coronary disease, impaired left ventricular function and some with normal left ventricular ejection fractions.

The Survival And Ventricular Enlargement (SAVE) study randomised 2,231 patients with acute MI and ejection fraction < 40%, but without overt symptoms of heart failure, to either captopril or placebo.[9] Patients were followed up for a mean of 42 months. All-cause mortality was reduced in the captopril group compared to placebo (228 *vs.* 275 deaths; relative risk reduction 19%; p=0.019). In addition, there was a 20–25% reduction in the incidence of each of the following end points: death from cardiovascular causes, development of severe heart failure, congestive heart failure requiring hospitalisation and recurrent MI. Each of these reductions reached statistical significance. These benefits were seen irrespective of therapy with thrombolytics, aspirin or beta blockers, suggesting an independent benefit from treatment with captopril.

A similar benefit was demonstrated in patients treated with ramipril in the Acute Infarction Ramipril Efficacy (AIRE) trial.[10] AIRE randomised 2,006 patients with clinical evidence of heart failure following acute MI to receive either ramipril or placebo. Patients with severe heart failure in whom the use of ACE inhibitors was deemed mandatory were excluded. Follow-up was for a minimum of six months and a mean of 15 months. All-cause mortality was significantly lower in those patients treated with ramipril as compared to placebo (170 *vs.* 222 deaths; relative risk reduction 27%; p=0.002). There was a 19% relative reduction in the combined end points of death, severe/resistant heart failure, MI or stroke (p=0.008). This benefit from ramipril was seen as early as 30 days following initiation of treatment and it persisted throughout follow-up.

The Studies Of Left Ventricular Dysfunction (SOLVD) trials enrolled 6,797 patients with left ventricular ejection fraction < 35% and randomised them to treatment with either enalapril or placebo. The patients were assigned to a treatment trial if they displayed clinical features of heart failure (n=2,569) or to a prevention trial if they had no clinical features of heart failure (n=4,228). In both trials, treatment with enalapril significantly reduced the risk of MI (treatment trial: 158 placebo *vs.* 127 enalapril, p<0.02; prevention trial: 204 placebo *vs.* 161 enalapril, p<0.01) and the development of unstable angina (treatment trial: 240 placebo *vs.* 187 enalapril, p<0.001; prevention trial: 355 placebo *vs.* 312 enalapril, p<0.05).[11] Although this was a

Figure 1. Time to first occurrence of primary end point in the EUROPA trial



Patients at risk						
Placebo	6,108	5,943	5,781	5,598	4,450	71
Perindopril	6,110	5,957	5,812	5,653	4,515	64

Figure adapted from *Lancet* 2003;**362**:782-8

Table 2. Frequency of primary and selected secondary outcomes in the EUROPA trial

	Perindopril (n=6,110)	Placebo (n=6,108)	Relative risk reduction (95% CI)	p value
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%)	1,043 (17·1%)	14% (6 to 21)	0·0009
Total mortality	375 (6·1%)	420 (6·9%)	11% (-2 to 23)	0·1

Data taken from *Lancet* 2003;**362**:782-8

trial of ACE inhibitor use in heart failure, it provided further evidence of the beneficial effects of ACE inhibitors in coronary disease.

In the Heart Outcomes Protection Evaluation (HOPE) study, a total of 9,297 high-risk patients aged ≥ 55 years (80% of whom had known coronary disease) but without evidence of left ventricular dysfunction were randomised to treatment with either ramipril or placebo.[12] Follow-up was for a mean of five years and the primary outcome was a composite of myocardial infarction, stroke or death from cardiovascular causes. There was a reduction in the primary outcome in the active treatment group compared to placebo (651 *vs.* 826; relative risk 0.78; p<0.001), with significant reductions in the individual end points of death from cardiovascular causes, myocardial infarction, stroke, death from any cause, revascularisation procedures, cardiac arrest, heart failure and complications from diabetes.

In the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), some 13,665 patients with stable coronary disease and without known left ventricular dysfunction were randomised to either perindopril 8 mg or placebo.[13] There was a 20% relative reduction (488 *vs.* 603; p=0.0003) in the primary end point of cardiovascular death, myocardial infarction or cardiac arrest in those patients who received perindopril (figure 1, table 2). Thus, the HOPE and EUROPA trials seem to confirm the benefits of ACE inhibitors in patients with CAD but without LV dysfunction.

Does blood pressure reduction alone explain the results?

In EUROPA 27% percent of patients were hypertensive on entry into the trial. Mean systolic blood pressure at baseline was 137 mmHg in both the perindopril and the placebo group. During the course of the trial the mean blood pressure in those patients on perindopril was 5/2 mmHg lower than those on placebo. Is it possible that the reduction in cardiovascular events resulted purely from overall improvement in blood pressure control?

A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION trial) explored the effects of nifedipine in stable coronary disease. ACTION randomised 3,825 patients with stable symptomatic coronary disease to long-acting nifedipine (60 mg daily) or placebo.[14] Follow-up was for a mean of 4.9 years and the primary end point was a composite of death, acute myocardial infarction, refractory angina, new overt heart failure, debilitating stroke and peripheral revascularisation. A greater proportion of patients in ACTION (52%) were known to be hypertensive than in EUROPA but mean baseline systolic blood pressure was similar (137 mmHg). The difference in blood pressure between the two groups observed throughout the trial (6/3 mmHg) was similar to that in EUROPA (5/2 mmHg).

There was no reduction seen in the primary end point with nifedipine treatment. Rates for the individual end points of cardiovascular mortality, myocardial infarction, refractory angina and coronary revascularisation were similar between the two groups. There was a reduction in the total number of cardiovascular procedures, due to a significant decrease in the number of patients requiring coronary angiography and interventions in the nifedipine group. This reduction is probably the result of better angina symptom control with nifedipine treatment.

The results of EUROPA would appear to suggest that the benefits observed with ACE inhibitors are attributable to mechanisms of action other than blood pressure reduction. In order to explore the mechanisms by which ACE inhibitors reduce cardiovascular events, a substudy of EUROPA measured the effects of perindopril on various markers of inflammation and endothelial dysfunction. The PERindopril Thrombosis InflammatioN

Endothelial dysfunction and Neurohormonal activation Trial (PERTINENT) measured the effects of perindopril *vs.* placebo on levels of fibrinogen, D-dimer, C-reactive protein, von Willebrand factor, tumour necrosis factor (TNF) α and chromogranin-A in 300 EUROPA participants.[15] The predictive role of C-reactive protein and von Willebrand factor as markers of future cardiovascular events was studied in 1,200 subjects.

Treatment with perindopril for one year resulted in improvements in endothelial nitric oxide synthase (NOS) activity, reduction of TNFα, and reduction in endothelial apoptosis. This combination of effects seen with perindopril treatment would be expected to attenuate the atherosclerotic process and offers a possible explanation for the beneficial cardiovascular effects seen with ACE inhibitors.

In ASCOT there was a slightly greater reduction in blood pressure in the amlodipine $\pm$ perindopril group than in the atenolol $\pm$ thiazide group, which was statistically significant (p=0.001). The maximal difference was 5.9/2.4 mmHg seen at three months; by the end of the trial the difference was 1.6/1.8 mmHg. The mean difference in blood pressure throughout the course of the trial was 2.7/1.9 mmHg in favour of the amlodipine $\pm$ perindopril group. The authors calculated that such differences in blood pressure would result in a maximal reduction of 8% for coronary events and 14% for stroke, which was far less than the reductions seen within the amlodipine $\pm$ perindopril group.[5]

Are the effects the same for all ACE inhibitors?

The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial studied the effects of trandolapril in patients who had stable coronary disease without evidence of left ventricular dysfunction.[16] In PEACE 8,290 patients were randomised to receive either trandolapril 4 mg or placebo. Follow-up was for a mean of 4.8 years. The mean age was 64$\pm$8 years, mean blood pressure on enrolment was 133$\pm$17/78$\pm$10 mmHg, and mean left ventricular ejection fraction was 58$\pm$9%. There was no difference in the primary end point of death from cardiovascular causes, myocardial infarction or coronary revascularisation between the two groups (hazard ratio for the trandolapril group 0.96; 95% CI 0.88-1.06; p=0.43).

Although the authors of PEACE attribute the lack of clinical benefit to an event rate that was 'lower than the event rates in the placebo groups in two previous trials' (HOPE and EUROPA), the annualised all-cause mortality was similar between all three trials (PEACE 1.6% per annum, EUROPA 1.5% per annum and HOPE 2.3% per annum). These similarities were present despite higher proportions of lipid-lowering therapy use and revascularisation in PEACE (70% and 72%, respectively) compared to EUROPA (57% and 55%, respectively) and HOPE (29% and 44%, respectively).

Why should some ACE inhibitors have different effects?

ACE is present in both a plasma form and a tissue form. Different ACE inhibitors have varying affinities for plasma and tissue ACE. It is postulated that the short-term effects of ACE inhibitors, i.e. blood pressure lowering, are achieved by inhibition of plasma ACE, whereas the long-term cardiovascular benefits arise from inhibition of tissue ACE. The degree of affinity for tissue ACE is dependent upon the lipophilicity of the individual drug. Both ramipril and perindopril are highly lipophilic and therefore have a greater affinity for tissue ACE than less lipophilic ACE inhibitors.[17,18] This lipophilicity offers a possible explanation for the greater cardioprotective effects observed in HOPE and EUROPA.

High tissue affinity may not be the only factor affecting the benefit afforded by ACE inhibitors. The QUinapril Ischaemic Event Trial (QUIET) failed to show an overall reduction in cardiovascular events in patients with CAD but without left ventricular dysfunction, even though quinapril has a high affinity for tissue ACE.[19] This result is likely to have been influenced by the small study size.

Duration of action is another factor thought to influence the effects of individual ACE inhibitors. Although all ACE inhibitors have a plasma half-life of only a few hours, ramipril, perindopril, quinapril and trandolapril have metabolites with a greater degree of ACE inhibition than the parent compounds. These active metabolites have varying plasma elimination half-lives: quinaprilat two hours, trandolaprilat 10 hours, perindoprilat 10 hours and ramiprilat 9–18 hours. The active metabolites display a two-phase elimination, with a prolonged late phase reflecting slow dissociation from tissue ACE. The elimination half-life for the slow phase of ramiprilat is > 50 hours and for perindoprilat 30–120 hours.[20] Both ramipril and perindopril therefore have much longer durations of action than other ACE inhibitors, resulting in a more sustained inhibition of ACE. These differences in pharmacokinetics, together with the frequency of administration, also appear to influence the effects of different ACE inhibitors.[21]

Conclusions

ACE inhibitors have consistently been proven to be beneficial in patients with CAD and left ventricular dysfunction, following an acute event or in stable disease. Mortality and cardiovascular morbidity are significantly reduced in these patients when ACE inhibitors are used. All patients with evidence of left ventricular dysfunction should be prescribed ACE inhibitors, if these agents are tolerated.

In patients with coronary disease but without left ventricular dysfunction the evidence to support the use of ACE inhibitors is less clear. HOPE and EUROPA showed a benefit whereas PEACE and QUIET did not. It is possible that different ACE inhibitors have individual properties that confer different levels of benefit. The similar outcomes in HOPE and EUROPA may lead us to suppose that treatment using ACE inhibitors with high tissue affinity and prolonged duration of action is beneficial in stable patients with coronary disease, even in the absence of left ventricular dysfunction. This benefit may result from mechanisms other than blood pressure reduction alone.

Conflicts of interest

KMB has received honoraria from AstraZeneca for speaking at

educational meetings and has received support for attending conferences from AstraZeneca, Pfizer and Servier.

ASH has received research grants and also speaker fees from pharmaceutical companies including Pfizer, AstraZeneca, Servier and Sanofi-Aventis.

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Prescribing Information.
Refer to Summary of Product Characteristics (SPC) before prescribing.

Presentation: 2 mg, 4 mg and 8 mg tablets. Indications: Hypertension. Symptomatic Heart Failure. Stable Coronary Artery Disease: reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation. Dosage and Administration: Coversyl® should be taken in the morning before food. Hypertension: 4 mg once a day is the recommended starting dose. Titrate dose to gain optimum blood pressure control. Maximum daily dose is 8 mg once daily. Patients with a strongly activated renin-angiotensin-aldosterone system should be initiated on 2 mg under close medical supervision (see SPC). Diuretic-treated Patients: stop the diuretic 2-3 days before starting Coversyl® at 2mg. Diuretics can be re-started later if required, preferably at the lowest dose. Elderly: Start treatment at 2mg daily. Symptomatic Heart Failure: Coversyl®, generally associated with a non-potassium sparing diuretic and/or digoxin and/or a beta-blocker, should be initiated under close supervision (particularly in higher risk patients) at a starting dose of 2 mg, which may be increased to 4 mg if tolerated (see SPC). As with other ACE inhibitors, blood pressure, renal function and serum potassium should be monitored. Stable coronary artery disease: Start at 4 mg once daily for two weeks, then increase to 8 mg once daily, depending on renal function and provided that 4 mg is well tolerated. Elderly: Start at 2 mg once daily for one week, then if well tolerated titrate to 4 mg once daily the next week, then to 8 mg once daily depending on renal function (see SPC). Impaired Renal Function: The dosage should be based on the creatinine clearance (see SPC). Children: Not recommended. Contraindications: Patients with a history of hypersensitivity to Coversyl®, any of the excipients or any other ACE inhibitor; angioneurotic oedema associated with previous ACE inhibitor therapy; hereditary or idiopathic angioedema. Pregnancy and lactation: do not use. Precautions: Stable coronary artery disease: If unstable angina pectoris occurs during the first month of treatment, perform a careful appraisal of the benefit/risk before treatment continuation. Hypotension: Symptomatic hypotension may occur, particularly in patients who are volume depleted, receiving diuretics or suffering from severe heart failure. Aortic and mitral valve stenosis/hypertrophic cardiomyopathy: use with caution. Renal Impairment/Renovascular Hypertension: renal function should be closely monitored. Haemodialysis patients or patients receiving LDL apheresis or desensitisation treatment: anaphylactoid reactions have been reported. Hypersensitivity/Angioedema: discontinue Coversyl® promptly (see SPC). Development of hepatic failure: discontinue the ACE inhibitor. Patients with compromised immune system: use with extreme care (see SPC). Surgery/Anaesthesia: hypotension may occur. Other: Hyperkalaemia has been observed in some patients treated with ACE inhibitors (see SPC). Coversyl, like other ACE inhibitors, may be less effective in black patients. Interactions: Potassium supplements, potassium sparing diuretics, potassium-containing salt substitutes and lithium are not recommended. For other interactions, see SPC. Side Effects: Common: cough, dyspnoea, hypotension, headache, dizziness, vertigo, asthenia, paraesthesia, muscle cramps, vision disturbance, tinnitus, nausea, vomiting, abdominal pain, dysgeusia, dyspepsia, diarrhoea, constipation, rash, pruritus. Uncommon: mood or sleep disturbances, bronchospasm, dry mouth, renal insufficiency, impotence, sweating, angioedema, urticaria. For very rare events: see SPC. Laboratory parameters: Increases in blood urea and plasma creatinine, hyperkalaemia reversible on discontinuation may occur. Rarely, elevation of liver enzymes and serum bilirubin. Consult SPC for full list of side effects. NHS Price: 2mg tablets: £10.95 per pack of 30. 4mg tablets: £10.95 per pack of 30. 8mg tablets: £10.95 per pack of 30. Legal Category: POM. Product Licence Numbers: 2mg tablets: 5815/0001. 4mg tablets: 5815/0002. 8mg tablets: 5815/0023. Further Information: Servier Laboratories Ltd Gallions, Wexham Springs, Slough SL3 6RJ Tel (01753) 662744. Date of Revision: December 2005.

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Adverse events should also be reported to Servier Laboratories Ltd.
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