Myocardial ischaemia: new evidence for angiotensin-converting enzyme inhibition

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Angiotensin-converting enzyme (ACE) inhibitors undoubtedly represent a milestone in cardiovascular therapy. They are known to halt the progression of coronary artery disease by interrupting the series of events that lead to end-stage ischaemic heart disease. Moreover, in patients with severe heart failure, ACE inhibitors, quite surprisingly, reduce the recurrence of angina pectoris and myocardial infarction, hospitalization for ischaemic heart disease, and the rate of coronary artery bypass surgery or angioplasty. More recently ACE inhibitors have been postulated to reduce vascular hypertrophy, attenuate atherosclerosis and influence mortality and hospitalization when used in patients with left ventricular dysfunction without overt heart failure. The results of the Heart Outcomes Prevention Evaluation (HOPE) study confirm that this is the case, and that these agents can reduce the incidence of coronary events. Two other major trials, on the same subject but substantially different from HOPE, namely the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) and the Prevention of Events with ACE inhibitors (PEACE) study, are underway. The clinical hypothesis to be tested is that prolonged ACE inhibition reduces the progression of coronary atherosclerosis; the biological hypothesis is that prolonged ACE inhibition reduces or even reverses endothelial dysfunction to normal—a mechanism in which bradykinin might be significantly involved. This is the main topic of the present article.

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Introduction

During ischaemia, both the circulating renin-angiotensin system and local angiotensin-converting enzyme (ACE) are activated. The circulating renin-angiotensin system has a short-term role in the regulation of the cardiovascular system. Its aim is to restore blood pressure and cardiac homeostasis. Activation of the local system causes long-term regulation of cardiovascular homeostasis via sustained activation of local angiotensin and degradation of bradykinin. This results in the secondary permanent structural changes that underlie many aspects of coronary artery disease (CAD). It was recently shown that ACE inhibition is useful in the early and late phases of myocardial infarction. ACE inhibitors have also been shown to reduce in-vitro vascular hypertrophy and attenuate atherosclerosis, and to maintain endothelial function. Interestingly, unexpected data from trials in heart failure have shown that patients receiving ACE inhibitors have a reduced incidence of infarction, hospitalization...
for cardiovascular disease, and need for coronary artery bypass grafting (CABG) or angioplasty, suggesting that this class of drug could also prevent the occurrence of cardiovascular disease and acute coronary syndromes. These beneficial effects of ACE inhibitors can be classified as cardioprotective and ‘vasculo’-protective, and appropriate clinical trials are underway to test the hypothesis that prolonged ACE inhibition can reduce the incidence of ischaemic heart disease.

The present review addresses the evidence for and the possible mechanisms of a protective effect of ACE inhibitor in myocardial ischaemia.

**Pharmacological effects of angiotensin-converting enzyme inhibitors**

ACE inhibitors differ with respect to chemical structure, potency, bioavailability, plasma half-life, distribution, elimination and, more importantly, in their affinity for tissue-bound ACE. They can be classified into three groups according to the chemical structure of their active moiety. Some contain a sulphydryl group, and captopril is the prototype of this type. In-vitro data suggest that the presence of the sulphydryl group may confer properties other than ACE inhibition, such as free radical scavenging and effects on prostaglandins. The clinical relevance of these actions, however, has never been demonstrated. Fosinopril is the prototype of ACE inhibitors that contain a phosphinyl group as its reactive moiety. The others contain a carboxyl moiety.

The majority of ACE inhibitors are administered as prodrugs, and these prodrugs have enhanced oral bioavailability as compared with the active drugs. There are differences in the relative tissue affinity of ACE inhibitors, with perindoprilat, quinaprilat and benazepril having the highest affinity for heart homogenates. This may be important because several investigators have shown that the effects of ACE inhibitors on blood pressure correlate better with tissue ACE levels than with circulating ACE levels.

Equally, their relative potency in enhancing bradykinin levels versus reducing angiotensin II may be important. Little is known about this. Campbell et al. showed that perindopril increases bradykinin levels at doses much lower than those required to reduce angiotensin II levels. Furthermore, perindoprilat is more powerful in increasing bradykinin levels than is enaprilat when tested in dogs with pacing-induced congestive heart failure (CHF).

Pharmacologically, ACE inhibitors block the pressure response to intravenous angiotensin I but not that to angiotensin II. When given as short-term treatment, endogenous levels of angiotensin II and aldosterone decrease, whereas renin activity and angiotensin I increase. The resulting increase in angiotensin I levels may result in degradation of angiotensin I to angiotensin 1-7, a vasodilator, or in the formation of angiotensin II via non-ACE-mediated pathways.

Whereas the reduction in angiotensin II levels is pivotal in blood pressure regulation by ACE inhibitors, the contribution of bradykinin to the haemodynamic effects of ACE inhibitors is uncertain. Bradykinin has a short half-life and is difficult to measure. It has been reported to be either increased or unchanged in patients treated with ACE inhibitors. With the recent availability of specific bradykinin (B2) receptor antagonists, however, it has been shown in animal models that coadministration of ACE inhibitors with bradykinin antagonists attenuates the antihypertensive effect of the ACE inhibitors.

The main pharmacological effect of ACE inhibitors is a reduction in systemic vascular resistance with or without minor changes in heart rate. In normotensive and hypertensive individuals with normal left ventricular function, ACE inhibitors have little effect on cardiac output or pulmonary capillary wedge pressure. In the kidneys, ACE inhibitors cause increased renal plasma flow and promote salt secretion. In patients with CAD, with or without CHF, ACE inhibitors improve haemodynamics and energy supply to the myocardium by causing coronary and peripheral dilatation. Despite this positive haemodynamic action, the effects of ACE inhibitors on angina pectoris are not clear. A number of small-scale clinical trials on the severity of angina pectoris and/or myocardial ischaemia have reported conflicting results, with benefits in some patients, no benefit or even exacerbation of angina, and no effect on exercise-induced ischaemia in others.

This indicates that, although they restore the balance between oxygen supply and demand, ACE inhibitors fail to exert consistent antianginal effects. This contrasts with the beneficial results obtained in long-term studies in post-acute myocardial infarction (post-AMI) patients and implies that ACE inhibitors possess other, more structural effects that underlie their anti-ischaemic action. These effects probably rely on the so-called ‘biological effects’ of ACE inhibitors, which are at the basis of the antiatherosclerotic and antiremodelling actions of these drugs.
What evidence is there that angiotensin-converting enzyme inhibitors have anti-ischaemic properties?

Several small trials, generally of short duration, have assessed the potential anti-ischaemic effects of ACE inhibition on severity of angina pectoris and/or on objective measures of myocardial ischaemia based on the assumption that, being vasodilators, these agents may diminish myocardial energy and oxygen consumption. Although those studies reported conflicting results, the overall conclusion is that ACE inhibitors do not have consistent short-term antianginal effects. Apart from the ancillary reasons for this statement, the short duration of the studies precludes conclusions regarding long-term benefits of ACE inhibitors.

Recently, however, Bartels et al. investigated the effect of perindopril on pacing-induced ischaemia in a double-blind trial conducted in CAD patients with exertional angina with or without left ventricular dysfunction. After perindopril administration, the pacing-induced increase in systemic vascular resistance and left ventricular end-diastolic pressure were significantly reduced. Lactate release was also reduced. These findings, suggesting an acute anti-ischaemic effect of perindopril, were concomitant with a reduction in pacing-induced release of atrial natriuretic peptide and cardiac uptake of noradrenaline (norepinephrine). It follows that the anti-ischaemic effect of perindopril may be the consequence of either a reduction in myocardial oxygen demand or of reduced neurohormonal activation, with particular reference to the sympathetic nervous system. As a consequence of this sympatholytic activity, perindopril causes coronary vasodilatation and may reduce ischaemic damage.

The potential of ACE inhibitors to reduce short-term stress-induced myocardial ischaemia as a result of their neurohormonal modulating and subsequently vasodilating effects was further supported by data reported by Morishita et al. Those investigators investigated whether 1 month of treatment with perindopril ameliorates dobutamine-induced myocardial ischaemia in CAD patients. Treatment significantly improved the time to onset of symptoms while reducing the magnitude of ECG ST-segment changes and left ventricular wall motion score. Interestingly, the extent of reduction in left ventricular wall motion score by perindopril closely correlated with that of inhibition of serum ACE activity and with that of increase in plasma bradykinin concentrations. Once again, this suggests that the biological effects of ACE inhibition, in addition to the haemodynamic effects, may be central to the anti-ischaemic action of ACE inhibitors.

More recently, attention has focused on the potential long-term benefits of ACE inhibitors in preventing ischaemic events in patients with stable CAD. This hypothesis was generated by unexpected data from large clinical trials conducted in patients with severe, moderate and mild heart failure. For example, the combined arms of the Studies Of Left Ventricular Dysfunction (SOLVD) demonstrated a reduction in risk for myocardial infarction (either first or recurrent) of 23% and in risk for unstable angina of 20% in the enalapril group. In the Survival And Ventricular Enlargement (SAVE) study there was also a 25% reduction in recurrent myocardial infarction as well as a significant reduction in the rate of revascularization (including percutaneous transluminal coronary angioplasty and CABG) in the captopril group (Fig. 1). It is unlikely that the observed reduction in ischaemic events can be accounted for by the blood pressure-lowering action of ACE inhibitors alone, because the magnitude of risk reduction was substantially larger than that expected from short-term, modest reductions in blood pressure. In a recent meta-analysis of 14 randomized clinical trials of antihypertensive therapy, diastolic blood pressure reductions of 5—6 mmHg for about 4—5 years were associated with a 14% reduction in fatal and non-fatal coronary heart disease events. In the combined SOLVD trials, diastolic blood pressure was reduced by an average of 4 mmHg; this was associated with a 23% reduction in fatal or non-fatal myocardial infarction, and a 21% reduction in cardiac deaths. Moreover, the risk reductions in ischaemic events were similar in patients with different levels of systolic and diastolic blood pressure at baseline and, although there was a trend toward larger reductions in the risk for myocardial infarction and unstable angina among those with a greater reduction in blood pressure, this did not reach statistical significance.

These considerations suggest that the reduction in major ischaemic events observed with ACE inhibitor therapy is at least partly due to mechanisms that are unrelated to the hypotensive effects of these drugs and, again, the possible ‘biological’ effects of these drugs resulting in vascular and cardiac protection may be important.
Angiotensin-converting enzyme inhibitors in ischaemic patients with congestive heart failure

ACE inhibitors favourably alter the haemodynamics of patients with CHF. They reduce afterload, preload and systolic wall stress such that cardiac output increases without an increase in heart rate. For this reason, enalapril was utilized in the COoperative North Scandinavian ENalapril SUrvival Study (CONSENSUS) I.\(^{11}\) The clear data obtained had a major impact not only on the management of CHF but also on our pathophysiological understanding of the CHF syndrome. It immediately became evident that the positive effects of enalapril were due both to its pharmacological action and to biological improvement, resulting in a reduction in the deleterious effects of the neuroendocrine response.

Accordingly, it is now believed that most of the beneficial actions of ACE inhibitors in CHF are due to their antineuroendocrine effect, which ultimately results in the following: promotion of salt excretion by augmenting renal blood flow as a result of a reduction in the production of aldosterone and antidiuretic hormone; promotion of coronary, renal and peripheral dilatation by counteracting the vasoconstrictor effect of angiotensin II and of the sympathetic system; and an antiremodelling effect by contrasting the proproliferative and proapoptotic effects of angiotensin II. The CONSENSUS I study was also a milestone in the design of subsequent trials in CHF patients, and since 1987 several large, prospective, randomized placebo-controlled trials have demonstrated that treatment with ACE inhibitors results in a reduction in overall mortality in patients with CHF due to systolic dysfunction.\(^{12,13}\) The available meta-analysis of these trials shows that the reduction in mortality is present even in asymptomatic patients, although to a lesser extent. The prognostic improvement is the consequence of a reduction in the progression of CHF (mainly an antiremodelling effect), although the incidence of sudden death and AMI may also decrease.\(^{12,13}\)

It is not clear to what extent bradykinin contributes to these positive effects. The studies with specific angiotensin II receptor blockers, such as Evaluation of Losartan In The Elderly (ELITE) II, Optimal Trial in Myocardial infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) and the Valsartan Heart Failure Trial (Val-HeFT), failed to show superiority over ACE inhibitors despite a more profound and complete effect on angiotensin II. This unexpected finding may indirectly suggest that bradykinin has a pathophysiological role.

Fig. 1  (a) Reduction in the incidences of acute myocardial infarction in the Studies Of Left Ventricular Dysfunction (SOLVD) combined trial (left panel) and Survival And Ventricular Enlargement (SAVE) study (right panel). (b) Reduction in the need for revascularization in the SAVE study with coronary artery bypass grafting (left panel) and percutaneous transluminal coronary angioplasty (right panel) treatment.
Little is known regarding the effect of ACE inhibitors in elderly patients with CHF or in patients with CHF due to diastolic dysfunction. A meta-analysis of the effects of several anti-hypertensive agents suggested that ACE inhibitors are the most effective agents in reducing left ventricular hypertrophy, which is one of the causes of diastolic dysfunction, thus providing some hope even in this indication.\textsuperscript{14} The Perindopril and Remodelling in Elderly with Acute Myocardial Infarction (PREAMI) study, investigating the effects of perindopril in elderly patients with moderate left ventricular dysfunction, is in progress.\textsuperscript{14}

Angiotensin-converting enzyme inhibitors in patients after myocardial infarction

During the past decade, following the striking beneficial results of prolonged ACE inhibition in patients with left ventricular dysfunction due to ischaemic heart disease, a series of very large trials addressed the role of ACE inhibition in unselected patients.\textsuperscript{12,13} In those trials, ACE inhibitors were implemented early during the first days or even hours after AMI (Fig. 2). Overall, these trials indicated a small but definite benefit of around five lives saved for every 1000 patients treated. Therefore, there is a clear decrease in the relative size of the beneficial effect associated with a broadening of the population treated. Despite this, there is no doubt that ACE inhibitors should be used early after AMI in all patients and particularly in those at high risk. The major questions were for how long and what should be the criteria for withdrawal or continuation. Actually, this is no longer a debatable question because the results of the Heart Outcomes Prevention Evaluation (HOPE) study\textsuperscript{15} in high-risk patients have shown that ACE inhibition is indicated for secondary prevention of CAD.

From the pathophysiological point of view, the results appear to fit with the remodelling hypothesis based on experimental studies. The data from the echocardiographic subgroup of Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI) 3 confirm this in a large, unselected population treated very early after AMI.\textsuperscript{16} Although the changes observed in left ventricular volumes were small, they were clinically and statistically relevant.

In addition, activation of the renin-angiotensin system during the first few days after AMI is known to increase heart rate and systemic vascular resistance and decrease coronary perfusion, which leads to infarct expansion. When taken together, all of these data suggest an anti-ischaemic effect of ACE inhibitors.

\textbf{Fig. 2} The plot represents the efficacy of the different clinical trials of angiotensin-converting enzyme (ACE) inhibition, given as therapeutic or preventive treatment.
Anti-ischaemic effect of angiotensin-converting enzyme inhibitors

Interestingly and unexpectedly, several trials in CHF showed that ACE inhibition also reduces ischaemic events such as recurrence of angina pectoris and AMI, hospitalization for ischaemic heart disease, and the rates of CABG or of angioplasty.17 The recently published Perindopril PROtection Against REcurrent Stroke Study (PROGRESS) showed a 38% reduction in the occurrence of non-fatal AMI.18 In the Treatment to Prevent Heart Attack (ALLHAT) trial, and Enalapril Coronary Atherosclerosis Trial (PEACE), the Simvastatin and Angiotensin Converting Enzyme Inhibitors study (EUROPA), Prevention of Events With ACE inhibition (PROGRESS) and the Heart Outcomes Prevention Evaluation (HOPE) trial showed that ACE inhibitors have achieved widespread use in the treatment of cardiovascular and renal diseases. They were developed as therapeutic agents targeted for the treatment of hypertension. Since the initial application of these agents, several additional clinical indications have been identified, and these drugs have been approved for the treatment of CHF and AMI. More recently, ACE inhibitors have been proven able not only to treat but also to prevent ischaemic heart disease. The intimate molecular mechanism of this effect is not known at the present time. It is likely that these drugs exert a favourable ‘biological’ action on the endothelium and vessel wall, thus delaying or preventing the progression of the atherosclerotic process.

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References


