Role of ACE inhibitors in hypertension complicated by vascular disease

Gordon T McInnes

Hypertension is an important risk factor for vascular disease. Therefore, it is not surprising that many patients with hypertension have widespread atherosclerotic disease. Treatment with conventional antihypertensive drugs can be problematic in such patients. In this article I consider the use of angiotensin converting enzyme (ACE) inhibitors in managing hypertension complicated by vascular disease, paying particular attention to cerebrovascular disease and peripheral vascular disease affecting the legs. Coronary artery disease and atherosclerotic renovascular disease are considered only briefly.

ACE inhibitors reduce blood pressure in hypertensive patients by decreasing peripheral resistance with little effect on cardiac output or heart rate. The lack of reflex tachycardia is likely to be due to downward resetting of baroreceptor reflexes, though ACE inhibitor induced venodilatation or modification of parasympathetic activity may contribute. The increase in arterial compliance due to ACE inhibition can influence regional haemodynamics, with redistribution of blood flow in favour of vital organs. ACE inhibitors increase blood flow and decrease vascular resistance in the regions supplied by the renal, carotid, and brachial arteries both in healthy subjects and in patients with hypertension. Unlike some other antihypertensive agents, such as β blockers, ACE inhibitors do not interfere with the normal haemodynamic responses to stress or exercise while blood pressure reduction is maintained. As a consequence of these haemodynamic properties, ACE inhibitors might be particularly suitable for the treatment of hypertension complicated by atherosclerosis.

The beneficial haemodynamic effects of ACE inhibitors in hypertension are mediated primarily by inhibition of ACE and the consequent withdrawal of the vasoconstricting action of endogenous angiotensin II. Since ACE can also affect bradykinin degradation, some of the vascular actions of some ACE inhibitors might be mediated by changes in concentrations of vasoactive kinins and prostanooids. Although the effects of captopril may depend partly on such mechanisms, studies with other ACE inhibitors have failed to show changes in prostaglandin metabolism.

Animal studies suggest that tissue ACE and angiotensin II (particularly in the vasculature) may be more important than plasma concentrations in determining the haemodynamic effects of ACE inhibitors. It is unclear whether the local effects of ACE inhibitors are entirely due to inhibition of local angiotensin II or interference with other peptide systems.

Locally produced angiotensin II may exert a significant effect on vascular tone directly by contracting smooth muscle and indirectly by releasing catecholamines from surrounding nerve endings. Direct clinical evidence suggests that tissue actions may influence regional blood flow. Thus, enalapril, at a dose which did not induce significant humoral or systemic haemodynamic effects, reduced left ventricular inotropic state and increased coronary blood flow when infused into the coronary bed and increased forearm blood flow when infused into the forearm.1

Vascular angiotensin II may be a major pathological factor in the development of atherosclerosis (figure), mediating the proliferation of arterial smooth muscle cells by many mechanisms, including a direct effect on growth factor production and reciprocal suppression of arterial bradykinin concentrations.

The effects of ACE inhibition on progression of atherosclerosis has been reviewed recently by Sharpe.2 Early studies showed no beneficial effect on aortic atherosclerosis in rabbits fed cholesterol, but in more recent work captopril was effective in Watenabe rabbits, which have an inherited tendency to secondary hyperlipidaemia, without affecting serum cholesterol concentration; total aortic surface involvement and the cellularity of atherosclerotic lesions were reduced. In cynomolgus monkeys fed cholesterol, low and high doses of captopril reduced atherosclerotic lesions in carotid arteries by 80% and 95% respectively; coronary arteries were almost free of atherosclerosis after ACE inhibition. Continuous treatment with cilazapril or captopril prevented neointimal proliferation after carotid endotheial denudation injury by balloon catheterisation; this was not primarily due to blood pressure reduction as verapamil was ineffective. Similar findings have been reported with lisinopril and perindopril in various animal models of atherosclerosis. These actions are likely to be due to blockade of angiotensin II since the same effect has been seen with an AT1 receptor antagonist.3 Preservation of

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1. Vascular angiotensin II as a pathological factor in the development of atherosclerosis.
endothelial function with ACE inhibitors has been shown in the aortic segments of rabbits on a long term atherogenic diet, possibly through accumulation of bradykinin, which enhances release of endothelial derived relaxing factor and production of cyclic AMP (cAMP). Thus ACE inhibitors may prevent or retard the development of atherosclerosis. Table 1 lists potential mechanisms.

**Peripheral vascular disease**

Intermittent claudication is the primary symptom of chronic occlusive peripheral vascular disease of the legs. Like hypertension, its prevalence increases with age. Its pattern is similar to that of angina but it occurs 10 years later; 3–20% of subjects over 65 years are affected. Atheroma is a generalised disease, and intermittent claudication might be expected to coexist with coronary artery disease and cerebrovascular disease. About 50% of sufferers have evidence of myocardial ischaemia; a smaller proportion have cerebrovascular disease. About 15% have myocardial infarction and 5% a stroke within five years.

Only two approaches have been shown to be of benefit in improving symptoms: stopping smoking and regular exercise. Angioplasty or reconstructive surgery offers good relief of symptoms if there is continuous serious handicap for at least one year despite conservative measures; pain at rest; or gangrene. Medical treatment of coexistent hypertension, hyperlipidaemia, and diabetes mellitus may be required, but there is no evidence that this leads to symptomatic improvement.

The optimal choice of treatment for hypertension complicated by peripheral vascular disease is limited by the unwanted effects on peripheral vascular resistance and regional haemodynamics of many of the most effective drugs currently available. Antihypertensive drugs should not lower blood flow to the legs as symptoms of peripheral vascular disease may be exaggerated. In peripheral vascular disease arterioles in the leg may already be dilated maximally because of local production of muscle metabolites. Atheromatous blood vessels may also be so sclerotic that they are unable to dilate further, and use of a vasodilator may divert or “steal” blood flow away from the worst affected areas. Thus generalised vasodilatation does not improve intermittent claudication and may even make it worse. By contrast, β blockers reduce blood flow during exercise perhaps because of diminished blood pressure, reduced cardiac output, or blockade of β2 receptors in the vessels supplying working muscles. No change in claudication was seen with atenolol, which does not antagonise β2 receptors, but patients could not walk as far when the cardioselective β blocker was combined with nifedipine. This tends to support the notion that drugs with vasodilating properties may direct blood flow to unaffected vascular beds.

Patients with hypertension and peripheral vascular disease might be expected to respond well to ACE inhibitors, which are associated with decreased sympathetic drive and increased compliance of large vessels. The vasodilating action of ACE inhibitors on peripheral vessels might lead to improved blood flow to the limbs. Ancillary actions such as inhibition of platelet aggregation and thromboxane A2 release after captopril may be particularly advantageous since hyperaggregability of platelets may contribute to the atherogenic process and to formation of mural thrombi and platelet emboli.

In healthy subjects ACE inhibitors have been reported to increase blood flow to the arms and legs. Blood flow to skeletal muscle and skin is augmented because of an action on large arteries and arterioles and because of improved compliance. By contrast, other studies have indicated no change in limb blood flow with captopril in hypertensive subjects. Peripheral vasodilatation is offset by lowered perfusion pressure and flow is unaltered; the normal response to exercise is maintained. These effects may not be accompanied by clear clinical advantages. Herrick et al found no difference between enalapril and atenolol in exercise duration, subjective dyspnoea, or tiredness in hypertensive patients.

Anecdotal reports suggest that the symptoms of peripheral vascular disease seen with β blockers may improve dramatically by switching to treatment with an ACE inhibitor. Properly conducted studies of ACE inhibitors in hypertensive patients with peripheral vascular disease are difficult to find. Uncontrolled observations in 20 patients treated with captopril 50 mg daily for eight weeks indicated improvement in ankle/arm pressure index at rest and after exercise, in absolute pain free interval, and in reduction in blood pressure.

Libretti and Catalano also compared captopril at the same dose with chlorothalidone 25 mg daily in hypertensive patients with Fontaine stage IIIa and IIb peripheral vascular disease. Only captopril reduced blood pressure significantly, increased ankle/arm arterial pressure index at rest and on exercise, and increased relative and absolute pain free intervals on exercise. This study had several shortcomings: only subjects previously shown to be “responders” to captopril were included; the treatments do not seem to have been allocated at random and were open labelled; the groups were not well matched at outset; and the drugs were not compared directly. Inspection of the data suggests no significant differences between captopril and chlorothalidone for any of the variables.

Roberts et al conducted one of the few adequate studies on this subject. In a randomised, placebo controlled, crossover trial they compared captopril 25 mg twice daily, atenolol 100 mg once daily, labetalol 200 mg twice daily, and pindolol 10 mg twice daily for one month in 23 patients with mild to moderate hypertension and chronic stable intermittent claudication. Peripheral arterial disease was confirmed by clinical observation (including pedalbrachial systolic pressure ratio <0.9) and aortofemoral angiography.
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patients were withdrawn from the study because of other cardiovascular events (two with non-fatal myocardial infarctions and one with transient ischaemic attacks), reflecting the high morbidity of this condition. All treatments were equally effective in reducing blood pressure, and there were no differences between treatments in resting blood flow measured by occlusion plethysmography. Postexercise calf blood flow was reduced by labetalol and pindolol, and all β blockers improved the recovery in calf blood flow after exercise, which was reduced by captopril. Labetalol and pindolol reduced pain free walking distance; atenolol reduced total walking distance. Captopril did not alter either walking distance. Increases in the frequency and severity of symptoms of intermittent claudication were seen only with labetalol and pindolol. There were no correlations between calf blood flow indices and walking distances. This study indicates that captopril has advantages over β blockers, regardless of their ancillary properties. The lack of effect on resting calf blood flow suggests little (or no) direct or compensatory action on vessels distal to the arterial obstruction, probably because of medial atrophy in the arterial wall. The preservation of limb flow with captopril strongly supports an action of this drug in maintaining the collateral circulation.

ACE inhibitors may be appropriate antihypertensive agents in peripheral vascular disease, particularly if this is associated with good collateral flow. The incidence of coexisting renal artery stenosis in such patients is, however, high, with consequent risk of acute renal failure induced by ACE inhibition (see later). A prospective study of renal arteriography in 100 patients referred for investigation of peripheral vascular disease found that many patients had bilateral renal artery stenosis; seven had a single functioning kidney. Peripheral vascular disease is the best clinical marker of anatomical renal artery stenosis. Normal renal function has been assumed to preclude renal artery stenosis, but as most patients in this study had normal serum creatinine concentrations this is clearly not the case. In patients with peripheral vascular disease ACE inhibitors should be used with caution. Consideration should be given to coexistent renal artery stenosis.

Cerebrovascular disease

Hypertension and other risk factors for atheroma such as smoking, diabetes, and hyperlipidaemia predispose to cerebrovascular disease. If hypertension is long standing, the risk of development of stenosis in extracranial and intracranial segments of major arteries supplying the brain is increased. As a result, cerebral blood flow is reduced; the decline is particularly well documented in elderly people. Cerebral blood flow is usually autoregulated. It is kept constant during wide changes in perfusion pressure by an intrinsic mechanism mediated by variations in the calibre of cerebral arteries and small arteries, which respond to increases in perfusion pressure by constriction and to decreases in perfusion pressure by dilatation. Below a certain perfusion pressure, autoregulatory vasodilatation is inadequate; flow decreases with the risk of ischaemia. With acute increases in blood pressure beyond a certain level, autoregulatory vasoconstriction is overridden, with consequent increase in cerebral blood flow. Thus, there is an upper and lower limit of autoregulation. Atheromatous narrowing of intracranial arteries, either within or outside the cranium, may limit autoregulation in response to a fall in perfusion pressure, and, at regional level, fixed obstruction (due to vascular disease) in the larger intracranial vessels may lead to local ischaemia when blood pressure fails.

In chronic hypertension the absolute value of cerebral blood flow is the same as that in normal subjects, but autoregulation of cerebral blood flow is adapted to higher pressure. The lower limit of autoregulation is shifted to the right on the blood pressure axis in proportion to the severity of hypertension. This increases the risk of ischaemic effects as blood pressure falls. The shift is probably due to structural changes in hypertensive resistance vessels, which are narrowed and have thickened walls and thus have a restricted capacity for vasodilatation. A shift in the upper limit probably explains tolerance to very high blood pressures, which would precipitate hypertensive crises in normal subjects. However, the shift towards higher pressure of the upper limit of autoregulation may be less obvious than the shift in the lower limit, such that the autoregulatory plateau may be shorter in some patients with hypertension than in normal subjects. Resting cerebral blood flow is nearer the threshold for cerebral ischaemia, particularly in elderly patients.

Antihypertensive treatment protects against cerebrovascular events. In most cases the benefit is much greater than the risk of ischaemia from lowering blood pressure. Although the autoregulatory curve is shifted upwards, there is still a considerable reserve between resting pressure and the lower limit of autoregulation and between resting pressure and the even lower pressure at which clinical symptoms of brain hypoperfusion are seen. The cerebral circulation might also readapt during long term treatment, with consequent shift of the lower end of the cerebral blood flow autoregulation curve towards normal. In animals the shift in the lower limit is completely reversed by antihypertensive treatment. This finding may be relevant in treating young or middle aged patients who have had hypertension for a short time. Whether more longstanding hypertensive adaptation of cerebral circulation with degenerative changes in cerebral vessels could be reversed by antihypertensive treatment is unknown, although at least partial reversal would be expected. Reversal of the shift in the upper limit of autoregulation has not been shown.
Evidence in humans is sparse. Observations during long term treatment of patients with hypertension suggests similar changes in autoregulation, at least in some. Groups at particular risk of cerebral ischaemia include those with malignant hypertension during the early phase of treatment, those with acute stroke with high blood pressure, and elderly people with hypertension. Although elderly people are at particular risk of stroke, they often complain of increased dizziness after treatment, and occasional strokes follow overzealous treatment. Elderly people cannot be expected to show noticeable readaptation of hypertensive vascular changes, and treatment should probably be conservative.

Numerous studies in experimental models of hypertension have shown that treatment with ACE inhibitors normalises blood pressure and restores autoregulation of cerebral blood flow. Thus cerebral blood flow is maintained at normal levels despite a measurable decrease in perfusion pressure, although there remains doubt about distribution of blood flow within different brain areas. ACE inhibitors seem to influence cerebral blood flow uniquely since both lower and upper limits are shifted to lower pressure. These changes improve tolerance to acute hypotension and, if confirmed in humans, might explain why ACE inhibitors are seldom associated with orthostatic hypotension. As yet, studies of long term treatment are awaited.

After ACE inhibition in healthy human volunteers the diameter of and flow in carotid arteries increase in a dose-dependent manner. Despite reduction in blood pressure, ACE inhibitors do not significantly affect cerebral blood flow. The mechanism of action of ACE inhibitors on cerebral blood flow may include inhibition of local angiotensin II at the luminal membrane of cerebral arteries, which leads to dilatation of the arteries and large cerebral resistance vessels, with compensatory constriction of smaller cerebral arteries; this explains a shift mainly of the lower limit of autoregulation of cerebral blood flow towards lower blood pressures.

Changes in carotid artery haemodynamics after ACE inhibition in hypertensive patients are similar to those seen in normal subjects. Clinical studies of short and long term ACE inhibition show total and regional cerebral blood flow is unchanged even though blood pressure is reduced. Therefore autoregulation seems to be intact, but no consistent effect on the lower limit of autoregulation has been shown.

Patients presenting with acute stroke are particularly prone to develop further ischaemia during acute antihypertensive treatment since autoregulatory capacity is lost in the partially ischaemic areas of brain surrounding the infarcted area. ACE inhibitors do not change ischaemic regional cerebral blood flow in acute stroke.

Elderly patients and those with severe atheroma have rigid vessels, which make them particularly sensitive to hypotension. The development of stroke after reduction in blood pressure with ACE inhibitors is well recognised in these circumstances. Symptomatic hypotension is no more common in elderly subjects than in the overall population treated with ACE inhibitors. The cautious use of most antihypertensive agents in elderly people, however, does not compromise cerebral blood flow.

In addition to the above properties, ACE inhibitors may have an advantage in inhibiting thrombosis and the atherosclerotic process in patients with cerebral atherosclerotic disease. Platelet angiotensin concentration is increased after cerebral infarction, and at least some ACE inhibitors reduce platelet angiotensin II in this context. Recent animal studies support a possible beneficial effect of ACE inhibitors on the cerebral vasculature in hypertensive patients. ACE inhibitors may protect cerebral vessels by a number of mechanisms (table 2).

### Coronary artery disease

Coronary artery disease is the most common vascular complication of mild to moderate hypertension. Plaques in coronary vessels are particularly likely to be symptomatic since the myocardium in hypertension has an increased oxygen demand because of hypertrophy and increased afterload. Some antihypertensive drugs such as β blockers and calcium antagonists have well recognised antianginal properties, but the reflex tachycardia and non-specific coronary vasodilatation caused by arterial vasodilators such as hydralazine may precipitate or worsen angina.

A series of controlled studies has failed to show a difference between ACE inhibitors and placebo. More recently, a comparison of placebo and captopril in patients with heart failure and angina suggested that the ACE inhibitor may exacerbate the symptoms of angina and increase nitrate consumption; exercise performance was reduced and thus increased mobility could not account for the deterioration in symptoms. This topic is explored further in this supplement by Davies.

Beneficial effects on coronary events have also been shown in studies of long term outcome in patients with heart failure, suggesting that ACE inhibitors may have secondary protective effects in human coronary artery disease. A series of large outcome trials are currently under way to test this hypothesis, the most important of which is the quinapril ischaemic event trial (QUIET). The QUIET study has several substudies, which will investigate various aspects of coronary vessel structure and function, as well as produce cost-benefit analyses.

In conclusion, ACE inhibitors may be useful in the treatment of hypertensive patients with coronary artery disease. It is premature to consider these drugs as an alternative treatment for coronary heart disease. Published work is heavily weighted by poor quality studies. Properly conducted, randomised, double blind clinical trials are required to settle the issue.

### Table 2 Possible mechanisms of protective effect of ACE inhibitors on cerebral vessels in hypertension

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<th>Mechanism</th>
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<tr>
<td>Normalisation of cerebral vascular reserve</td>
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<tr>
<td>Decrease in vascular hypertrophy</td>
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<tr>
<td>Increase in external diameter</td>
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<tr>
<td>Normalisation of endothelial function</td>
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<td>Vascular mechanisms</td>
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<tr>
<td>Antithrombotic effect:</td>
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<tr>
<td>Decrease in proliferation of smooth muscle cells*</td>
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<td>Prevention of endothelial infiltration of macrophages*</td>
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*Characteristic steps of early phase of atherosclerosis.
†Later form “foam cells,” in which cholesterol accumulates.
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Renovascular disease
Renovascular hypertension probably occurs in no more than 2–5% of hypertensive patients but is a frequent cause of drug-resistant hypertension. Such patients often have widespread vascular disease, of which renal vascular atheroma is only one component. Further consideration is given to this topic in this supplement by Fluck and Raine.²

Conclusions

Theoretical considerations support a role for ACE inhibitors in hypertension complicated by vascular disease, particularly in the management of cerebrovascular disease, where ACE inhibitors seem capable of preserving autoregulation of flow. Few patients, however, are at risk of cerebral underperfusion, and most antihypertensive drugs are well tolerated if used sensibly. ACE inhibitors do not seem to worsen symptoms in most hypertensive patients with angina, but their antianginal effect is modest at best. β Blockers or calcium antagonists are more effective options in patients with symptoms. Although ACE inhibitors are widely advocated as anti-hypertensive agents in patients with peripheral vascular disease, there is a high risk of unsuspected renal artery disease in such patients and renal function, as for patients with known renal artery stenosis, must be monitored carefully.

ACE inhibitors have the potential to cause regression of atherosclerosis or even prevent it. If preliminary findings in animals are confirmed in humans the application of ACE inhibitors in hypertensive patients with vascular disease will be greatly widened. Such patients are at great risk of vascular events, and even a modest benefit would have an enormous clinical impact. Clinical confirmation, or otherwise, awaits the outcome of long-term trials. In the meantime, there is a dearth of good quality evidence to guide clinical decisions. Well controlled clinical trials of ACE inhibitors in hypertensive patients with all forms of vascular disease are needed.

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