dures, p.1181), use of abciximab as an adjunct to heparin and aspirin improves short-term[1-3] and long-term[4,5] outcomes in various groups of patients, including those receiving coronary stents.[6-8] Most benefit has been seen in patients given abciximab as a bolus injection immediately before intervention followed by intravenous infusion for 12 hours,[1,2] and in a study[9] in which abciximab was given for 18 to 24 hours before angioplasty and for 1 hour after, the initial benefit was not maintained at 6 months.

For patients undergoing PCI who are pretreated with both aspirin and clopidogrel, the role of abciximab is less clear. In stable patients undergoing elective PCI, no benefit was found at 30 days,[10] or at 1 year.[11] A study[12] in diabetic patients also found no effect on mortality or risk of myocardial infarction at 1 year, despite their higher risk, although restenosis was reduced. However, in patients undergoing PCI for non-ST elevation acute coronary syndromes, use of abciximab in addition to aspirin and clopidogrel pretreatment improved clinical outcomes at 30 days, although this effect was restricted to patients with raised troponins.[13] Positive results have also been reported[14,15] with abciximab given as a single bolus injection without subsequent infusion in patients undergoing coronary stenting.

In *acute ST-elevation myocardial infarction* (p.1175), abciximab has been used as an adjunct to primary PCI, including coronary stenting, and has been shown to reduce reinfarction rates and mortality,[16] with benefit persisting long-term.[17] There is some evidence that starting treatment as soon as possible rather than immediately before the procedure may provide additional benefit.[18,19] Abciximab has also been used as an adjunct to thrombolysis and some benefit has been shown,[20] but this appears to be offset by an increased bleeding rate, even when reduced doses of thrombolytics are used.[21,22] In patients with *unstable angina* (p.1157) receiving noninterventional treatment, a large study[23] with abciximab failed to show any benefit over placebo, although other glycoprotein IIb/IIIa inhibitors have a role in such patients.

Some promising results have been reported with intracoronary abciximab in patients with acute coronary syndromes,[24] and with abciximab-coated stents in patients with acute myocardial infarction.[25]

1. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994; **330:** 956–61.
2. Topol EJ, *et al.* Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994; **343:** 881–6.
3. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997; **336:** 1689–96.
4. Topol EJ, *et al.* Long-term protection from myocardial ischemic events in a randomized trial of brief integrin β blockade with percutaneous coronary intervention. *JAMA* 1997; **278:** 479–84.
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9. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997; **349:** 1429–35. Correction. *ibid.*; **350:** 744.
10. Kastrati A, *et al.* The Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) Study Investigators. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004; **350:** 232–8.
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13. Kastrati A, *et al.* Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial. *JAMA* 2006; **295:** 1531–8.
14. Bertrand OF, *et al.* The Early Discharge After Transradial Stenting of Coronary Arteries (EASY) Study Investigators. A randomized study comparing same-day home discharge and abciximab bolus only to overnight hospitalization and abciximab bolus and infusion after transradial coronary stent implantation. *Circulation* 2006; **114:** 2636–43.
15. Marmur JD, *et al.* Bolus-only platelet glycoprotein IIb/IIIa inhibition during percutaneous coronary intervention. *J Invasive Cardiol* 2006; **18:** 521–6.
16. De Luca G, *et al.* Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA* 2005; **293:** 1759–65.
17. The ADMIRAL Investigators. Three-year duration of benefit from abciximab in patients receiving stents for acute myocardial infarction in the randomized double-blind ADMIRAL study. *Eur Heart J* 2005; **26:** 2520–3.
18. Gödicke J, *et al.* Early versus periprocedural administration of abciximab for primary angioplasty: a pooled analysis of 6 studies. Abstract: *Am Heart J* 2005; **150:** 1015. Full version: http://download.journals.elsevierhealth.com/pdfs/journals/0002-8703/PIIS0002870305007544.pdf (accessed 24/10/07)
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22. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; **358:** 605–13.
23. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet* 2001; **357:** 1915–24.
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25. Kim W, *et al.* The clinical results of a platelet glycoprotein IIb/IIIa receptor blocker (abciximab: ReoPro)-coated stent in acute myocardial infarction. *J Am Coll Cardiol* 2006; **47:** 933–8.

Preparations

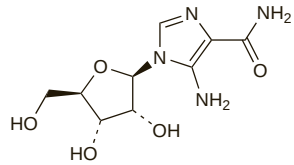
Proprietary Preparations (details are given in Part 3)
Arg.: ReoPro†; ***Austral.:*** ReoPro; ***Austria:*** ReoPro; ***Belg.:*** ReoPro; ***Braz.:*** ReoPro; ***Canad.:*** ReoPro; ***Chile:*** ReoPro; ***Cz.:*** ReoPro; ***Denm.:*** ReoPro; ***Fin.:*** ReoPro; ***Fr.:*** ReoPro; ***Ger.:*** ReoPro; ***Gr.:*** ReoPro; ***Hong Kong:*** ReoPro; ***India:*** ReoPro; ***Irl.:*** ReoPro; ***Israel:*** ReoPro; ***Ital.:*** ReoPro; ***Malaysia:*** ReoPro; ***Mex.:*** ReoPro; ***Neth.:*** ReoPro; ***Norw.:*** ReoPro; ***NZ:*** ReoPro; ***Pol.:*** ReoPro; ***Port.:*** ReoPro; ***Rus.:*** ReoPro (Реопро); ***S.Afr.:*** ReoPro; ***Singapore:*** ReoPro; ***Spain:*** ReoPro; ***Swed.:*** ReoPro; ***Switz.:*** ReoPro; ***Thai.:*** ReoPro; ***UK:*** ReoPro; ***USA:*** ReoPro.

Acadesine *(BAN, USAN, rINN)*

Acadesina; Acadésine; Acadesinum; AICA Riboside; GP-1-110; GP-1-110-0. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide.

Акадезин

$C_9H_{14}N_4O_5$ = 258.2.
CAS — 2627-69-2.
ATC — C01EB13.
ATC Vet — QC01EB13.



Profile

Acadesine is a purine nucleoside analogue reported to have cardioprotective effects. It is being investigated in the management of myocardial ischaemia, particularly in patients undergoing coronary artery bypass graft surgery. Acadesine may protect against further ischaemia by influencing metabolism in ischaemic cells, enhancing the release of adenosine in preference to inosine after the breakdown of adenosine monophosphate.

Acadesine is also under investigation for chronic lymphocytic leukaemia.

◊ References.

1. Leung JM, *et al.* An initial multicenter, randomized controlled trial on the safety and efficacy of acadesine in patients undergoing coronary artery bypass graft surgery. *Anesth Analg* 1994; **78:** 420–34.
2. Alkhulaifi AM, Pugsley WB. Role of acadesine in clinical myocardial protection. *Br Heart J* 1995; **73:** 304–5.
3. Mangano DT. Effects of acadesine on myocardial infarction, stroke, and death following surgery: a meta-analysis of the 5 international randomized trials. *JAMA* 1997; **277:** 325–32.
4. Mangano DT, *et al.* Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Post-reperfusion myocardial infarction: long-term survival improvement using adenosine regulation with acadesine. *J Am Coll Cardiol* 2006; **48:** 206–14.

ACE Inhibitors

Angiotensin-converting Enzyme Inhibitors; Inhibidores de la ECA.

There appear to be few significant differences between ACE inhibitors. They may be distinguished from each other by the presence or absence of a sulfhydryl group, whether they are prodrugs or not, their route of elimination, and their affinity for angiotensin-converting enzyme in vascular and other tissue, although whether these characteristics modify pharmacodynamics and therefore clinical efficacy is uncertain. Differences in these characteristics do however influence onset and duration of action of ACE inhibitors.

Adverse Effects and Treatment

Many of the adverse effects of ACE inhibitors relate to their pharmacological action and all therefore have a similar spectrum of adverse effects. Some effects, such as taste disturbances and skin reactions, were at one time attributed to the presence of a sulfhydryl group (as in captopril) but have now also been reported with other ACE inhibitors; however, they may be more common with captopril.

The most common adverse effects are due to the vascular effects of ACE inhibitors and include hypotension, dizziness, fatigue, headache, and nausea and other gastrointestinal disturbances.

Pronounced hypotension may occur at the start of therapy with ACE inhibitors, particularly in patients with heart failure and in sodium- or volume-depleted patients (for example, those given previous diuretic therapy). Myocardial infarction and stroke have been reported and may relate to severe falls in blood pressure in patients with ischaemic heart disease or cerebrovascular disease. Other cardiovascular effects that have occurred include tachycardia, palpitations, and chest pain.

Deterioration in renal function, including increasing blood concentrations of urea and creatinine, may occur, and reversible acute renal failure has been reported. Renal effects are most common in patients with existing renal or renovascular dysfunction or heart failure, in whom vasodilatation reduces renal perfusion pressure; it may be aggravated by hypovolaemia. Proteinuria has also occurred and in some patients has progressed to nephrotic syndrome. Hyperkalaemia and hyponatraemia may develop due to decreased aldosterone secretion.

Other adverse effects include persistent dry cough and other upper respiratory tract symptoms, and angioedema; these may be related to effects on bradykinin or prostaglandin metabolism. Skin rashes (including erythema multiforme and toxic epidermal necrolysis) may occur; photosensitivity, alopecia, and other hypersensitivity reactions have also been reported.

Blood disorders have been reported with ACE inhibitors and include neutropenia and agranulocytosis (especially in patients with renal failure and in those with collagen vascular disorders such as systemic lupus erythematosus and scleroderma), thrombocytopenia, and anaemias.

Other less common adverse effects reported with ACE inhibitors include stomatitis, abdominal pain, pancreatitis, hepatocellular injury or cholestatic jaundice, muscle cramps, paraesthesias, mood and sleep disturbances, and impotence.

ACE inhibitors have been associated with fetal toxicity (see Pregnancy under Precautions, below).

Most of the adverse effects of ACE inhibitors are reversible on withdrawing therapy. Symptomatic hypotension, including that after overdosage, generally responds to volume expansion with an intravenous infusion of sodium chloride 0.9%.

◊ General reviews.

1. Parish RC, Miller LJ. Adverse effects of angiotensin converting enzyme (ACE) inhibitors: an update. *Drug Safety* 1992; **7:** 14–31.
2. Alderman CP. Adverse effects of the angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1996; **30:** 55–61.
3. Agusti A, *et al.* Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction : meta-analysis of randomised clinical trials. *Drug Safety* 2003; **26:** 895–908.
4. Adam A, *et al.* Physiopathologie des effets secondaires aigus des inhibiteurs de l'enzyme de conversion de l'angiotensine. *Bull Acad Natl Med* 2007; **191:** 1433–43.

Angioedema. See under Hypersensitivity, below.

Cough. Treatment with ACE inhibitors has been associated with the development of cough in up to 20% of hypertensive patients; cough may be less troublesome in those with heart failure,[1] although the incidence may be higher.[2] The cough is reported to be persistent, paroxysmal, and non-productive; it causes irritation of the throat, may be accompanied by voice changes (hoarseness or huskiness), and is often worse when lying down.[1,3,4] It is more common in women and non-smokers, and may be delayed in onset by weeks or even months.

The majority of reports of this adverse effect concern captopril and enalapril,[3,4] but it has also occurred in patients receiving many of the other ACE inhibitors,[5] suggesting that the effect is common to all drugs of this class.

The mechanism that produces the reaction is uncertain but appears to be related to the non-specific blockade of ACE since angiotensin II receptor antagonists are associated with a much lower incidence of cough.[6] The sensitivity of the cough reflex is increased.[7] Prostaglandins released in the respiratory tract have been proposed as mediators,[3] but other mediators such as bradykinin[8] or substance P,[9] both of which are substrates for ACE, have been suggested. However, attempts to show a link between the effects of ACE inhibitors on cough, and bronchial hyperreactivity of the type found in obstructive airways disease and asthma have produced conflicting evidence, with bronchial hyperreactivity being shown in some studies[10] but not in others.[11]

Where the patient can tolerate the cough, it may be reasonable to continue treatment; in some cases reducing the dose may help. Spontaneous recovery or improvement in the cough has been reported.[12] Changing to an alternative ACE inhibitor is not advised since it is rarely effective.[7] Drugs that inhibit prostaglandin synthesis, including the NSAIDs sulindac[13] and indometacin,[14] have been reported to suppress the cough, but NSAIDs and ACE inhibitors may interact adversely (see under Interactions, below). The calcium-channel blocker nifedipine also reduced cough, although to a lesser extent than indometacin, possibly by a similar mechanism.[14] Inhaled bupivacaine,[15] inhaled sodium cromoglicate,[16,17] oral baclofen,[18] oral picotamide,[19] and oral ferrous sulfate,[20] have also been reported to be of help. However, in many patients there will be no alternative but to withdraw the ACE inhibitor, and this is recommended by some in all patients presenting with ACE-inhibitor induced cough.[21] Angiotensin II receptor antagonists may be a suitable alternative in patients with hypertension.[21]

1. Anonymous. Cough caused by ACE inhibitors. *Drug Ther Bull*. 1994; **32:** 28 and 55–6.
2. Ravid D, *et al.* Angiotensin-converting enzyme inhibitors and cough: a prospective evaluation in hypertension and congestive heart failure. *J Clin Pharmacol* 1994; **34:** 1116–20.
3. Coulter DM, Edwards IR. Cough associated with captopril and enalapril. *BMJ* 1987; **294:** 1521–3.
4. Berkin KE, Ball SG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; **296:** 1279–80.
5. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. *Ann Intern Med* 1992; **117:** 234–42.
6. Pylypchuk GB. ACE inhibitor- versus angiotensin II blocker-induced cough and angioedema. *Ann Pharmacother* 1998; **32:** 1060–6.
7. Overlack A. ACE inhibitor-induced cough and bronchospasm. *Drug Safety* 1996; **15:** 72–8.
8. Ferner RE, *et al.* Effects of intradermal bradykinin after inhibition of angiotensin converting enzyme. *BMJ* 1987; **294:** 1119–20.
9. Morice AH, *et al.* Angiotensin-converting enzyme and the cough reflex. *Lancet* 1987; **ii:** 1116–18.
10. Bucknall CE, *et al.* Bronchial hyperreactivity in patients who cough after receiving angiotensin converting enzyme inhibitors. *BMJ* 1988; **296:** 86–8.
11. Boulet L-P, *et al.* Pulmonary function and airway responsiveness during long-term therapy with captopril. *JAMA* 1989; **261:** 413–16.
12. Reisin L, Schneeweiss A. Spontaneous disappearance of cough induced by angiotensin-converting enzyme inhibitors (captopril or enalapril). *Am J Cardiol* 1992; **70:** 398–9.
13. Nicholls MG, Gilchrist NL. Sulindac and cough induced by converting enzyme inhibitors. *Lancet* 1987; **i:** 872.
14. Fogari R, *et al.* Effects of nifedipine and indomethacin on cough induced by angiotensin-converting enzyme inhibitors: a double-blind, randomized, cross-over study. *J Cardiovasc Pharmacol* 1992; **19:** 670–3.
15. Brown RC, Turton CWG. Cough and angiotensin converting enzyme inhibition. *BMJ* 1988; **296:** 1741.
16. Keogh A. Sodium cromoglycate prophylaxis for angiotensin-converting enzyme inhibitor cough. *Lancet* 1993; **341:** 560.
17. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin-converting enzyme inhibitor cough. *Lancet* 1995; **345:** 13–16.
18. Dicpinigaitis PV. Use of baclofen to suppress cough induced by angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1996; **30:** 1242–5.
19. Malini PL, *et al.* Thromboxane antagonism and cough induced by angiotensin-converting-enzyme inhibitor. *Lancet* 1997; **350:** 15–18.
20. Lee S-C, *et al.* Iron supplementation inhibits cough associated with ACE inhibitors. *Hypertension* 2001; **38:** 166–70.
21. Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129** (suppl): 169S–173S.

Effects on the blood. Blood disorders have occurred in patients receiving ACE inhibitors, although there have been few reports in the literature. A reduction in haemoglobin concentration and haematocrit may occur but is not usually clinically significant, although an unfavourable effect on recovery from anaemia has been reported;[1] ACE inhibitors have also been used therapeutically to reduce the haematocrit (see Erythrocytosis under Uses, below). Cases of neutropenia and agranulocytosis (particularly in patients with renal or collagen vascular disorders), and thrombocytopenia have been noted. Aplastic anaemia has also occurred[2,3] and may be fatal.[3]

1. Ripamonti V, *et al.* Angiotensin-converting enzyme inhibitors slow recovery from anemia following cardiac surgery. *Chest* 2006; **130:** 79–84.
2. Kim CR, *et al.* Captopril and aplastic anemia. *Ann Intern Med* 1989; **111:** 187–8.
3. Harrison BD, *et al.* Fatal aplastic anaemia associated with lisinopril. *Lancet* 1995; **346:** 247–8.

Effects on the kidneys. ACE inhibitors have complex effects on the kidney;[1,2] they have established renoprotective effects but also cause acute deterioration in renal function in some patients. These apparently contradictory effects are related to the action of ACE inhibitors on the renin-angiotensin-aldosterone system.

The renin-angiotensin-aldosterone system has an important role in maintaining normal renal blood flow and renal function. A reduction in renal perfusion, for example due to hypovolaemia, heart failure, or renal artery stenosis, leads to activation of this system and an increase in angiotensin II release. This results mainly in post-glomerular renal vasoconstriction, which maintains renal glomerular pressure and thus glomerular filtration, despite the fall in renal blood flow.

In normal individuals with unrestricted sodium intake, the renin-angiotensin-aldosterone system is suppressed and ACE inhibitors have little effect on renal function. In patients with essential hypertension ACE inhibitors generally increase renal blood flow despite the reduction in arterial blood pressure, since this is exceeded by the effects of renal vasodilatation. However, filtration fraction falls since the pressure within the glomerulus is reduced, and there are only minor changes in glomerular filtration rate. The increase in renal blood flow is more pronounced during sodium restriction and in younger patients.

These effects are generally beneficial. However, in patients with reduced renal perfusion, glomerular filtration rate may be critically dependent on the renin-angiotensin-aldosterone system and the use of ACE inhibitors may provoke problems. Severe renal function loss or even anuria have been reported in patients with a single transplanted kidney with renal artery stenosis, or patients with bilateral renal artery disease. The stenotic kidney maintains its filtering capacity by preferential vasoconstriction of the efferent arterioles, a mechanism mainly mediated by the renin-angiotensin system; under ACE inhibition, vasodilatation of the efferent arterioles combined with the drop in arterial pressure can result in a critical decrease in filtration pressure. Hypovolaemia or sodium depletion, for example due to diuretics, also leads to activation of the renin-angiotensin-aldosterone system and predisposes patients to renal impairment. Most patients developing renal insufficiency have been using diuretics and sodium repletion can restore renal function despite continuing ACE inhibition.

Patients with heart failure may also be at risk of a decline in renal function on long-term ACE inhibitor therapy. This is because in chronic heart failure, angiotensin-II mediated systemic and renal vasoconstriction is again important in the maintenance of renal perfusion pressure. The decline may be alleviated by reduction of the dosage of diuretics or liberalisation of dietary salt intake, despite continuing the ACE inhibitor. An additional risk factor in elderly patients with heart failure is the high incidence of occult renovascular disease in these patients.[3]

Moderate impairment of renal function either before or during use of ACE inhibitors is not necessarily an indication to stop therapy. The effects of ACE inhibitors on renal function are generally reversible, and the reduction in filtration pressure may result in renoprotection. A review[4] of studies of the use of ACE inhibitors in patients with renal impairment found that those who initially lost renal function had the greatest long-term benefit.

In addition to pathophysiological effects ACE inhibitors may induce membranous glomerulopathy or interstitial nephritis. The former has been associated with captopril use, particularly at high doses, but is rare, and seems less likely to occur at the lower doses favoured today. The proteinuria usually clears without appreciable renal function loss irrespective of whether or not the drug is continued, although persistent proteinuria and renal function loss have been described. Proven interstitial nephritis has also been reported rarely, and may possibly be due to an allergic mechanism.

1. Navis G, *et al.* ACE inhibitors and the kidney: a risk-benefit assessment. *Drug Safety* 1996; **15:** 200–11.
2. Schoolwerth AC, *et al.* Renal considerations in angiotensin converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 2001; **104:** 1985–91.
3. MacDowall P, *et al.* Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998; **352:** 13–16.
4. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000; **160:** 685–93.

Effects on the liver. Hepatotoxicity has been reported with ACE inhibitors, including captopril,[1,2] enalapril,[2] lisinopril,[2] and ramipril.[3] Most reports have been associated with captopril. In a report[1] of 3 cases of liver disease apparently caused or aggravated by captopril, it was noted that jaundice due to captopril is usually mainly cholestatic in nature but acute hepatocellular injury has also been seen. Of 29 cases of liver dysfunction due to captopril and reported to the UK CSM, 9 had hepatocellular jaundice, with 2 deaths; 8 were cholestatic jaundice, with 1 fatality; and 3 patients had hepatorenal syndrome, all of whom died. Worldwide, excluding the UK, 164 cases of hepatic adverse reactions had been notified to the WHO by January 1989. The incidence of such reactions is estimated at 0.09 per 1000 patients but this is likely to be an underestimate. Resolution may take a long time and captopril should be withdrawn immediately at the earliest hint of liver sensitivity.

1. Bellary SV, *et al.* Captopril and the liver. *Lancet* 1989; **ii:** 514.
2. Hagley MT, *et al.* Hepatotoxicity associated with angiotensin-converting enzyme inhibitors. *Ann Pharmacother* 1993; **27:** 228–31.
3. Yeung E, *et al.* Ramipril-associated hepatotoxicity. *Arch Pathol Lab Med* 2003; **127:** 1493–7.

Effects on the mouth. Aphthous and tongue ulcers may occur during treatment with ACE inhibitors. There have been a few reports of a 'scalded mouth syndrome', described as similar to being scalded by hot liquids, associated with captopril,[1] enalapril,[1] and lisinopril[2] therapy.

1. Vlasses PH, *et al.* "Scalded mouth" caused by angiotensin-converting enzyme inhibitors. *BMJ* 1982; **284:** 1672–3.
2. Savino LB, Haushalter NM. Lisinopril-induced "scalded mouth syndrome." *Ann Pharmacother* 1992; **26:** 1381–2.

Effects on the nervous system. Encephalopathy and focal neurological signs,[1] and peripheral neuropathy,[2,3] including Guillain-Barré neuropathy,[3] have been reported in patients receiving captopril. Some CNS effects of captopril may be attributable to alterations in cerebral blood flow. In a study in patients with severe heart failure, cerebral blood flow in patients aged under 65 was improved by a single dose of captopril 12.5 mg, but in patients aged over 70 there was a 13% reduction.[4] Two patients in whom captopril 6.25 mg produced impaired consciousness and paraesthesias, and dizziness, blurred vision, and aphasia, were found to have stenosis of the carotid arteries.[5] Agitation, panic, extreme depression, and insomnia was reported in a patient 4 weeks after starting treatment with enalapril; depressive episodes recurred on rechallenge.[6] There have been reports of mania possibly precipitated by captopril,[7] and visual hallucinations have been reported in association with captopril and enalapril therapy.[8]

1. Rapoport S, Zyman P. Captopril and central nervous system effects. *Ann Intern Med* 1983; **98:** 1023.
2. Samanta A, Burden AC. Peripheral neuropathy due to captopril. *BMJ* 1985; **291:** 1172.
3. Chakraborty TK, Ruddell WSJ. Guillain-Barré neuropathy during treatment with captopril. *Postgrad Med J* 1987; **63:** 221–2.
4. Britton KE, *et al.* Angiotensin-converting-enzyme inhibitors and treatment of heart failure. *Lancet* 1985; **ii:** 1236.
5. Jensen H, *et al.* Carotid artery stenosis exposed by an adverse effect of captopril. *BMJ* 1986; **293:** 1073–4.
6. Ahmad S. Enalapril-induced acute psychosis. *DICP Ann Pharmacother* 1991; **25:** 558–9.
7. Peet M, Peters S. Drug-induced mania. *Drug Safety* 1995; **12:** 146–53.
8. Haffner CA, *et al.* Hallucinations as an adverse effect of angiotensin converting enzyme inhibition. *Postgrad Med J* 1993; **69:** 240.

Effects on the pancreas. The manufacturers of captopril, enalapril, and lisinopril have all been reported[1] to have data on file on drug-associated pancreatitis. In 1994 the UK CSM[2] noted that there had been 23 reports of pancreatitis associated with ACE inhibitors (captopril 11, enalapril 10, fosinopril 1, and quinapril 1) although whether or not this was causal was not certain.

1. Dabaghi S. ACE inhibitors and pancreatitis. *Ann Intern Med* 1991; **115:** 330–1.
2. Committee on Safety of Medicines/Medicines Control Agency. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)

Effects on the respiratory system. Cough is a recognised adverse effect of ACE inhibitors but evidence for a link with bronchial hyperreactivity or airways obstruction is controversial (see Cough, above). In reports of adverse respiratory reactions to ACE inhibitors submitted to the Swedish Adverse Drug Reactions Advisory Committee and to WHO, symptoms of airway obstruction such as dyspnoea, asthma, and bronchospasm occurred rarely, usually within the first few weeks of treatment.[1] However, the evidence for a causal link between ACE inhibitors and these symptoms was questioned.[2]

Severe nasal obstruction was associated with enalapril treatment in a 45-year-old woman with a history of mild rhinorrhoea and sneezing. Symptoms cleared within 2 days of stopping enalapril and recurred on rechallenge.[3] Another woman taking enalapril developed obstructive sleep apnoea,[4] which improved when the enalapril was stopped.

There have been case reports of pneumonitis associated with treatment with captopril[5] and perindopril.[6]

1. Lunde H, *et al.* Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1994; **308:** 18–21.
2. Inman WHW, *et al.* Angiotensin converting enzyme inhibitors and asthma. *BMJ* 1994; **308:** 593–4.
3. Fennerty A, *et al.* Enalapril-induced nasal blockage. *Lancet* 1986; **ii:** 1395–6.

4. Cicolin A, *et al.* Angiotensin-converting enzyme inhibitors and obstructive sleep apnea. *Mayo Clin Proc* 2006; **81:** 53–5.
5. Kidney JC, *et al.* Captopril and lymphocytic alveolitis. *BMJ* 1989; **299:** 981.
6. Benard A, *et al.* Perindopril-associated pneumonitis. *Eur Respir J* 1996; **9:** 1314–16.

Effects on skeletal muscle. Severe muscle pain and weakness, accompanied by morning stiffness, was reported[1] in a patient taking enalapril. Symptoms resolved within a few days of stopping the drug.

1. Leloët X, *et al.* Pseudopolymyalgia rheumatica during treatment with enalapril. *BMJ* 1989; **298:** 325.

Effects on the skin. Skin rashes may occur during treatment with ACE inhibitors; they have been reported in 1 to 6% of patients receiving captopril. Angioedema is also an adverse effect of ACE inhibitors (see Hypersensitivity, below). There have been reports of bullous pemphigoid,[1] hyperhidrosis,[2] Kaposi's sarcoma,[3] lichen planus,[4] onycholysis,[5,6] pemphigus,[7,8] and cutaneous hypersensitivity vasculitis[9] associated with use of captopril. Kaposi's sarcoma has also been reported[10] with lisinopril. Onycholysis has also occurred with enalapril,[11] pemphigus with enalapril[12,13] and ramipril,[14] and bullous pemphigoid with lisinopril.[15] Lichen planus pemphigoides has been reported with ramipril.[16] A severe cutaneous reaction, resembling early mycosis fungoides, and possibly allergic in nature, has been reported after use of captopril or enalapril.[17] Captopril has also been reported to exacerbate psoriasis.[18] Vulvovaginal pruritus with dysuria[19] has been noted in a patient receiving enalapril.

1. Mallet L, *et al.* Bullous pemphigoid associated with captopril. *DICP Ann Pharmacother* 1989; **23:** 63.
2. Morse MH. Hyperhidrosis: a possible side effect of captopril treatment. *BMJ* 1984; **289:** 1272.
3. Puppin D, *et al.* Kaposi's sarcoma associated with captopril. *Lancet* 1990; **336:** 1251–2.
4. Cox NH, *et al.* Lichen planus associated with captopril: a further disorder demonstrating the 'tin-tack' sign. *Br J Dermatol* 1989; **120:** 319–21.
5. Brueggemeyer CD, Ramirez G. Onycholysis associated with captopril. *Lancet* 1984; **i:** 1352–3.
6. Borders JV. Captopril and onycholysis. *Ann Intern Med* 1986; **105:** 305–6.
7. Parfrey PS, *et al.* Captopril-induced pemphigus. *BMJ* 1980; **281:** 194.
8. Butt A, Burge SM. Pemphigus vulgaris induced by captopril. *Br J Dermatol* 1995; **132:** 315–16.
9. Miralles R, *et al.* Captopril and vasculitis. *Ann Intern Med* 1988; **109:** 514.
10. Bilen N, *et al.* Possible causal role of lisinopril in a case of Kaposi's sarcoma. *Br J Dermatol* 2002; **147:** 1042–4.
11. Gupta S, *et al.* Nail changes with enalapril. *BMJ* 1986; **293:** 140.
12. Kuechle MK, *et al.* Angiotensin-converting enzyme inhibitor-induced pemphigus: three case reports and literature review. *Mayo Clin Proc* 1994; **69:** 1166–71.
13. Frangogiannis NG, *et al.* Pemphigus of the larynx and esophagus. *Ann Intern Med* 1995; **122:** 803–4.
14. Vignes S, *et al.* Ramipril-induced superficial pemphigus. *Br J Dermatol* 1996; **135:** 657–8.
15. Kalińska-Bienias A, *et al.* Can pemphigoid be provoked by lisinopril? *Br J Dermatol* 2006; **155:** 854–5.
16. Ogg GS, *et al.* Ramipril-associated lichen planus pemphigoides. *Br J Dermatol* 1997; **136:** 412–14.
17. Furness PN, *et al.* Severe cutaneous reactions to captopril and enalapril; histological study and comparison with early mycosis fungoides. *J Clin Pathol* 1986; **39:** 902–7.
18. Hamlet NW, *et al.* Does captopril exacerbate psoriasis? *BMJ* 1987; **295:** 1352.
19. Heckerling PS. Enalapril and vulvovaginal pruritus. *Ann Intern Med* 1990; **112:** 879–80.

Gynaecomastia. Painful unilateral gynaecomastia was reported in a patient with systemic lupus erythematosus and renal impairment who was given captopril for hypertension.[1] In view of reports of breast enlargement in women given penicillamine it was suggested that the sulfhydryl structure might be responsible; however, gynaecomastia has also been reported in 2 patients receiving enalapril,[2,3] which does not contain the sulfhydryl grouping.

1. Markusse HM, Meyboom RHB. Gynaecomastia associated with captopril. *BMJ* 1988; **296:** 1262–3.
2. Nakamura Y, *et al.* Gynaecomastia induced by angiotensin converting enzyme inhibitor. *BMJ* 1990; **300:** 541.
3. Llop R, *et al.* Gynecomastia associated with enalapril and diazepam. *Ann Pharmacother* 1994; **28:** 671–2.

Hypersensitivity. Some of the adverse effects of ACE inhibitors might be mediated by the immune system, but evidence of specific **hypersensitivity reactions** seems to be limited. The presence of an IgG antibody to captopril was demonstrated in the serum of 2 of 45 patients taking the drug but the clinical significance was unclear.[1] A reaction resembling serum sickness was reported in a patient given captopril, with deposition of immune complexes in the glomerular basement membrane, and symptoms of rash, arthralgia, epidermolysis, fever, and lymphadenopathy.[2] Eosinophilia has also been reported in a number of patients.[3] The formation of antinuclear antibodies and lupus-like reactions have been described.[4,5]

Treatment with ACE inhibitors (enalapril, captopril, or lisinopril) has been associated with the development of **anaphylactoid reactions** in patients undergoing high-flux haemodialysis using polyacrylonitrile membrane (AN69).[6,7] The UK CSM has advised that the combined use of ACE inhibitors and such membranes should be avoided.[8] Similar anaphylactoid reactions have occurred in patients taking ACE inhibitors while being treated for severe hypercholesterolaemia by extracorporeal removal of low-density lipoproteins (LDL-apheresis) with dextran sulfate columns.[9] These reactions are thought to be bradykinin-mediated. Prolonging the interval between the last dose of ACE inhibitor and dextran sulfate apheresis has averted the reaction;[10] successful prevention has also been reported with the bradykinin receptor antagonist icatibant acetate (p.2324).[11] Hypotensive reactions associated with blood transfusion through bedside leucoreduction filters in patients taking ACE inhibitors have also been attributed to bradykinin.[12] There have also been rare reports of severe allergic reactions, including anaphylaxis, occurring in patients taking ACE inhibitors who were stung by insects or during desensitisation with Hymenoptera venom (e.g. bee or wasp venom).[13]

Angioedema, a known adverse effect of ACE inhibitors,[14-17] is reported to occur in 0.1 to 0.2% of patients.[16,17] The incidence may be higher in black American[18] or Afro-Caribbean[19] patients. There is no evidence that it results from an immunological mechanism in these patients and it has been suggested that the effect is due to impaired kinin degradation. However, angioedema has been reported with lisinopril in a patient who had previously tolerated captopril.[20] The onset of angioedema has usually been within hours or at most a week of starting treatment with the ACE inhibitor,[16] but can occur after prolonged therapy for several months or years.[21-24] It may also occur episodically with long symptom-free intervals.[24] Visceral angioedema presenting as abdominal pain with diarrhoea, nausea, and vomiting, has also been reported.[25,26] If angioedema occurs the ACE inhibitor should be withdrawn and if there is swelling affecting the tongue, glottis, or larynx likely to cause airway obstruction, adrenaline should be given (see p.1204). Fatalities have occurred.[27] Angiotensin II receptor antagonists have been suggested as an alternative in patients unable to tolerate ACE inhibitors, but there have also been reports of angioedema associated with their use (see under Losartan Potassium, p.1326). For a report of angioedema occurring after use of alteplase for stroke in patients taking ACE inhibitors, see under Interactions of Alteplase, p.1207.

1. Coleman JW, *et al.* Drug-specific antibodies in patients receiving captopril. *Br J Clin Pharmacol* 1986; **22:** 161–5.
2. Hoorntje SJ, *et al.* Serum-sickness-like syndrome with membranous glomerulopathy in patient on captopril. *Lancet* 1979; **ii:** 1297.
3. Kayanakis JG, *et al.* Eosinophilia during captopril treatment. *Lancet* 1980; **ii:** 923.
4. Schwartz D, *et al.* Enalapril-induced antinuclear antibodies. *Lancet* 1990; **336:** 187.
5. Pelayo M, *et al.* Drug-induced lupus-like reaction and captopril. *Ann Pharmacother* 1993; **27:** 1541–2.
6. Verresen L, *et al.* Angiotensin-converting-enzyme inhibitors and anaphylactoid reactions to high-flux membrane dialysis. *Lancet* 1990; **336:** 1360–2.
7. Tielmans C, *et al.* ACE inhibitors and anaphylactoid reactions to high-flux membrane dialysis. *Lancet* 1991; **337:** 370–1.
8. Committee on Safety of Medicines. Anaphylactoid reactions to high-flux polyacrylonitrile membranes in combination with ACE inhibitors. *Current Problems 33* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 04/04/08)
9. Olbricht CJ, *et al.* Anaphylactoid reactions, LDL apheresis with dextran sulphate, and ACE inhibitors. *Lancet* 1992; **340:** 908–9.
10. Keller C, *et al.* LDL-apheresis with dextran sulphate and anaphylactoid reactions to ACE inhibitors. *Lancet* 1993; **341:** 60–1.
11. Davidson DC, *et al.* Prevention with icatibant of anaphylactoid reactions to ACE inhibitor during LDL apheresis. *Lancet* 1994; **343:** 1575.
12. Quillen K. Hypotensive transfusion reactions in patients taking angiotensin-converting-enzyme inhibitors. *N Engl J Med* 2000; **343:** 1422–3.
13. Stumpf JL, *et al.* Safety of angiotensin-converting enzyme inhibitors in patients with insect venom allergies. *Ann Pharmacother* 2006; **40:** 699–703.
14. Wood SM, *et al.* Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. *BMJ* 1987; **294:** 91–2.
15. Hedner T, *et al.* Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1992; **304:** 941–6.
16. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. *Ann Intern Med* 1992; **117:** 234–42.
17. Vleeming W, *et al.* ACE inhibitor-induced angioedema. *Drug Safety* 1998; **18:** 171–88.
18. Brown NJ, *et al.* Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther* 1996; **60:** 8–13.
19. Gibbs CR, *et al.* Angioedema due to ACE inhibitors: increased risk in patients of African origin. *Br J Clin Pharmacol* 1999; **48:** 861–5.
20. McElligott S, *et al.* Angioedema after substituting lisinopril for captopril. *Ann Intern Med* 1992; **116:** 426–7.
21. Chin HL, Buchan DA. Severe angioedema after long-term use of an angiotensin-converting enzyme inhibitor. *Ann Intern Med* 1990; **112:** 312–13.
22. Edwards TB. Adverse effects of ACE inhibitors. *Ann Intern Med* 1993; **118:** 314.
23. Chu TJ, Chow N. Adverse effects of ACE inhibitors. *Ann Intern Med* 1993; **118:** 314.
24. Adverse Drug Reactions Advisory Committee (ADRAC). Angioedema – still a problem with ACE inhibitors. *Aust Adverse Drug React Bull* 2005; **24:** 7. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.htm (accessed 06/11/06)
25. Mullins RJ, *et al.* Visceral angioedema related to treatment with an ACE inhibitor. *Med J Aust* 1996; **165:** 319–21.
26. Byrne TJ, *et al.* Isolated visceral angioedema: an underdiagnosed complication of ACE inhibitors? *Mayo Clin Proc* 2000; **75:** 1201–4.
27. Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. *S Afr Med J* 2007; **97:** 244–5.

Overdosage. There have been reports of overdosage with captopril,[1,2] enalapril,[3-6] and lisinopril.[7,8] The main adverse effect is hypotension which usually responds to supportive treatment and volume expansion. Activated charcoal may be given in severe overdosage if the patient presents within 1 hour of ingestion. If hypotension persists, sympathomimetics may be given, although they are not usually required. Specific therapy with angiotensinamide (p.1216) may be considered if conventional therapy is ineffective,[5,6,8] but it is not widely available. There has also been a report[9] of the successful use of naloxone after captopril overdosage.

1. Augenstein WL, *et al.* Captopril overdose resulting in hypotension. *JAMA* 1988; **259:** 3302–5.
2. Graham SR, *et al.* Captopril overdose. *Med J Aust* 1989; **151:** 111.
3. Waeber B, *et al.* Self poisoning with enalapril. *BMJ* 1984; **288:** 287–8.
4. Lau CP. Attempted suicide with enalapril. *N Engl J Med* 1986; **315:** 197.
5. Jackson T, *et al.* Enalapril overdose treated with angiotensin infusion. *Lancet* 1993; **341:** 703.
6. Newby DE, *et al.* Enalapril overdose and the corrective effect of intravenous angiotensin II. *Br J Clin Pharmacol* 1995; **40:** 103–4.
7. Dawson AH, *et al.* Lisinopril overdose. *Lancet* 1990; **335:** 487–8.
8. Trilli LE, Johnson KA. Lisinopril overdose and management with intravenous angiotensin II. *Ann Pharmacother* 1994; **28:** 1165–8.
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 1991; **20:** 1125–7.

Precautions

ACE inhibitors are usually contra-indicated in patients with aortic stenosis or outflow tract obstruction (but see below). They should not generally be used in patients with renovascular disease or suspected renovascular disease, but are occasionally necessary for severe resistant hypertension in such patients, when they should only be given with great caution and under close specialist supervision. The elderly, or patients with peripheral vascular diseases or generalised atherosclerosis, may be at high risk because they may have clinically silent renovascular disease. Renal function should be assessed in all patients before use of ACE inhibitors and should be monitored during therapy. Patients with existing renal disease or taking high doses should be monitored regularly for proteinuria. Regular white blood cell counts may be necessary in patients with collagen vascular disorders, such as systemic lupus erythematosus and scleroderma, or in patients receiving immunosuppressive therapy, especially when they also have impaired renal function. ACE inhibitors should be used with caution in patients with a history of idiopathic or hereditary angioedema.

Patients with heart failure and patients who are likely to be sodium or water depleted (for example, those receiving treatment with diuretics or dialysis) may experience symptomatic hypotension during the initial stages of ACE inhibitor therapy. Treatment should therefore be started under close medical supervision, using a low dose and with the patient in a recumbent position to minimise this effect.

Anaphylactoid reactions have occurred in patients taking ACE inhibitors during haemodialysis using high-flux polyacrylonitrile membranes, during LDL-apheresis with dextran sulfate columns, and during desensitisation with wasp or bee venom (see Hypersensitivity under Adverse Effects, above).

ACE inhibitors have been associated with fetal toxicity and should not be used during pregnancy (see below).

Aortic stenosis. Vasodilators, including ACE inhibitors, are usually contra-indicated in obstructive cardiac disorders such as aortic stenosis since cardiac output cannot increase to compensate for systemic vasodilatation and there is a risk of severe hypotension. However, a study[1] in patients with symptomatic aortic stenosis found that enalapril was well-tolerated and improved symptoms, and a drug withdrawal study[2] in hypertensive patients with asymptomatic aortic stenosis suggested that ACE inhibitors had beneficial haemodynamic effects. Another study[3] in patients with heart failure and perceived contra-indications to ACE inhibitors (including 17.3% with aortic stenosis) found that survival was improved in those given ACE inhibitors. There is also some evidence that ACE inhibitors may slow the progression of calcific aortic stenosis, but this remains to be confirmed.[4]

1. Chockalingam A, *et al.* Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: Symptomatic Cardiac Obstruction-Pilot study of Enalapril in Aortic Stenosis (SCOPE-AS). *Am Heart J* 2004; **147:** E19.

2. Jiménez-Candil J, *et al.* Effects of angiotensin converting enzyme inhibitors in hypertensive patients with aortic valve stenosis: a drug withdrawal study. *Heart* 2005; **91:** 1311–18.
3. Ahmed A, *et al.* A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. *Am Heart J* 2005; **149:** 737–43.
4. Newby DE, *et al.* Emerging medical treatments for aortic stenosis: statins, angiotensin converting enzyme inhibitors, or both? *Heart* 2006; **92:** 729–34.

Diarrhoea. Several reports have indicated that life-threatening hypotension and signs of renal failure may develop in patients receiving captopril[1-3] or enalapril[3] after volume depletion due to diarrhoea.

1. McMurray J, Matthews DM. Effect of diarrhoea on a patient taking captopril. *Lancet* 1985; **i:** 581.
2. Benett PR, Cairns SA. Captopril, diarrhoea, and hypotension. *Lancet* 1985; **i:** 1105.
3. McMurray J, Matthews DM. Consequences of fluid loss in patients treated with ACE inhibitors. *Postgrad Med J* 1987; **63:** 385–7.

Ethnicity. ACE inhibitors are less effective as antihypertensives in Afro-Caribbean black patients than in white patients. A similar difference has been reported in heart failure; in a pooled analysis[1] of the Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials, treatment with enalapril significantly reduced the risk of hospitalisation for heart failure in white patients with left ventricular dysfunction, but not in similar black patients. However, analysis[2] of the prevention arm alone showed that enalapril reduced the relative risk of disease progression to a similar extent in black and white patients.

1. Exner DV, *et al.* Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *N Engl J Med* 2001; **344:** 1351–7.
2. Dries DL, *et al.* Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. *J Am Coll Cardiol* 2002; **40:** 311–17. Correction. *ibid.*; 1019.

Hepatic cirrhosis. It has been suggested that in patients with cirrhosis, captopril could cause a marked reduction in arterial pressure and severely compromise renal function, since maintenance of glomerular filtration rate might be mediated by angiotensin II in these patients.[1] This theory was supported by a report of a reduction in glomerular filtration rate in response to a fall in mean arterial pressure in 4 patients with resistant ascites secondary to hepatic cirrhosis.[2] The fall in mean arterial pressure was associated with orthostatic hypotension and increasing encephalopathy. Severe confusion has also been reported in 2 patients with cirrhosis during treatment with captopril 6.25 to 12.5 mg three times daily.[3]

1. Ring T. Captopril and resistant ascites: a word of caution. *Lancet* 1983; **ii:** 165.
2. Wood LJ, *et al.* Adverse effects of captopril in treatment of resistant ascites, a state of functional bilateral renal artery stenosis. *Lancet* 1985; **ii:** 1008–9.
3. Jørgensen F, *et al.* Captopril and resistant ascites. *Lancet* 1983; **ii:** 405.

Huntington's disease. The condition of a woman with Huntington's disease deteriorated dramatically during treatment with captopril and improved on withdrawal of the drug.[1]

1. Goldblatt J, Bryer A. Huntington's disease: deterioration in clinical state during treatment with angiotensin converting enzyme inhibitor. *BMJ* 1987; **294:** 1659–60.

Peripheral vascular disease. Patients with peripheral vascular disease may have a high incidence of renal artery stenosis and are therefore at high risk of renal failure with ACE inhibitor therapy (see Effects on the Kidneys, above). Mild renal artery stenosis was found in 64 of 374 patients (17%) with peripheral vascular disease, and severe renal artery stenosis in 52 (14%); the stenosis was bilateral in 43 (12%).[1] Renal function should be carefully monitored in any patient with peripheral vascular disease who receives ACE inhibitors.

1. Salmon P, Brown MA. Renal artery stenosis and peripheral vascular disease: implications for ACE inhibitor therapy. *Lancet* 1990; **336:** 321.

Pregnancy. There is evidence from *animal* studies that use of ACE inhibitors during pregnancy is associated with fetal toxicity and an increase in still-births.[1] In humans, the main effect of ACE inhibitors is on the kidneys. Several case reports have described the development of fetal renal failure, with oligohydramnios or neonatal anuria, in the offspring of mothers receiving captopril[2-4] or enalapril;[5] there have been fetal[4] and neonatal[3] deaths. A literature search up to the end of 1989 indicated that the use of ACE inhibitors during pregnancy can cause severe disturbances of fetal and neonatal renal function, long-lasting neonatal anuria, and pulmonary hypoplasia.[6] There are also 2 case reports in which maternal captopril[7] or enalapril[8] therapy, in association with other drugs, was associated with birth defects including defective ossification of the skull. A registry study[9] found that 2 of 19 infants exposed to ACE inhibitors during pregnancy had serious life-threatening conditions: one had prolonged anuria requiring dialysis; the other had microcephaly and a large occipital encephalocele.

The FDA has re-emphasised that ACE inhibitors can cause injury and even death to the developing fetus in the second and third trimester.[10] Although use of ACE inhibitors in the first trimester had been thought to carry a lesser risk,[11-13] a review of the available experimental and clinical data concluded that the use of ACE inhibitors should be avoided throughout pregnancy.[14] Also, a later cohort study[15] of 29 507 infants found a significantly increased risk of major congenital malformations in 209 who had been exposed to ACE inhibitors alone in the first trimester and concluded that such use should be avoided.

1. Broughton Pipkin F, *et al.* Possible risk with captopril in pregnancy: some animal data. *Lancet* 1980; **i:** 1256.
2. Boutroy M-J, *et al.* Captopril administration in pregnancy impairs fetal angiotensin converting enzyme activity and neonatal adaptation. *Lancet* 1984; **ii:** 935–6.
3. Guignard JP, *et al.* Persistent anuria in a neonate: a side effect of captopril? *Int J Pediatr Nephrol* 1981; **2:** 133.
4. Knott PD, *et al.* Congenital renal dysgenesis possibly due to captopril. *Lancet* 1989; **i:** 451.
5. Schubiger G, *et al.* Enalapril for pregnancy-induced hypertension: acute renal failure in a neonate. *Ann Intern Med* 1988; **108:** 215–16. Correction. *ibid.*: 777.
6. Hanssens M, *et al.* Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. *Obstet Gynecol* 1991; **78:** 128–35.
7. Duminy PC, Burger P du T. Fetal abnormality associated with use of captopril during pregnancy. *S Afr Med J* 1981; **60:** 805.
8. Mehta N, Modi N. ACE inhibitors in pregnancy. *Lancet* 1989; **ii:** 96.
9. Piper JM, *et al.* Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors. *Obstet Gynecol* 1992; **80:** 429–32.
10. Nightingale SL. Warnings on use of ACE inhibitors in second and third trimester of pregnancy. *JAMA* 1992; **267:** 2445.
11. CDC. Postmarketing surveillance for angiotensin-converting enzyme inhibitor use during the first trimester of pregnancy—United States, Canada, and Israel, 1987-1995. *JAMA* 1997; **277:** 1193–4.
12. Lip GYH, *et al.* Angiotensin-converting-enzyme inhibitors in early pregnancy. *Lancet* 1997; **350:** 1446–7.
13. Steffensen FH, *et al.* Pregnancy outcome with ACE-inhibitor use in early pregnancy. *Lancet* 1998; **351:** 596.
14. Shotan A, *et al.* Risk of angiotensin-converting enzyme inhibition during pregnancy: experimental and clinical evidence, potential mechanisms, and recommendations for use. *Am J Med* 1994; **96:** 451–6.
15. Cooper WO, *et al.* Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; **354:** 2443–51.

Interactions

Excessive hypotension may occur when ACE inhibitors are used with diuretics, other antihypertensives, or other agents, including alcohol, that lower blood pressure. An additive hyperkalaemic effect is possible in patients receiving ACE inhibitors with potassium-sparing diuretics, potassium supplements (including potassium-containing salt substitutes), or other drugs that can cause hyperkalaemia (such as ciclosporin or indometacin), and serum-potassium concentrations should be monitored. Potassium-sparing diuretics and potassium supplements should generally be stopped before starting ACE inhibitors in patients with heart failure. However, ACE inhibitor therapy does not obviate the possible need for potassium supplementation in patients given potassium-wasting diuretics and potassium concentrations should also be monitored in these patients. The adverse effects of ACE inhibitors on the kidneys may be potentiated by other drugs, such as NSAIDs, that can affect renal function.

◊ General references.

1. Shionoiri H. Pharmacokinetic drug interactions with ACE inhibitors. *Clin Pharmacokinet* 1993; **25:** 20–58.
2. Mignat C, Unger T. ACE inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–7.

Allopurinol. For reports of reactions in patients taking captopril and allopurinol, see p.553.

Antacids. Use of captopril with antacids reduced the bioavailability of captopril although this did not significantly alter the effects on blood pressure and heart rate.[1] The bioavailability of fosinopril, and possibly other ACE inhibitors, may also be reduced by use with antacids.

1. Mäntylä R, *et al.* Impairment of captopril bioavailability by concomitant food and antacid intake. *Int J Clin Pharmacol Ther Toxicol* 1984; **22:** 626–9.

Antidiabetics. Hypoglycaemia was noted in 3 type 1 diabetics when captopril was added to their therapeutic regimen; it was also seen in a type 2 diabetic, in whom withdrawal of hypoglycaemic drugs became necessary.[1] Subsequent study suggested that the effect was due to enhanced insulin sensitivity.[1] Similar instances of a reduction in blood sugar in both non-diabetic[2] and diabetic[3] patients given enalapril have occurred. Two case-control studies in diabetic patients receiving insulin or oral hypoglycaemics suggested that patients treated with ACE inhibitors were at increased risk of developing severe hypoglycaemia.[4,5] However, other studies in diabetic patients given captopril or enalapril have failed to find any significant alterations in blood-glucose control,[6,7] and ACE inhibitors are widely used in the treatment of hypertension in diabetic patients (see p.1171) and also have a role in the management of diabetic complications such as nephropathy (see Kidney Disorders under Uses, below).

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
2. Helgeland A, *et al.* Enalapril, atenolol, and hydrochlorothiazide in mild to moderate hypertension: a comparative multicentre study in general practice in Norway. *Lancet* 1986; **i:** 872–5.
3. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
4. Herings RMC, *et al.* Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345:** 1195–8.
5. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
6. Passa P, *et al.* Enalapril, captopril, and blood glucose. *Lancet* 1986; **i:** 1447.
7. Winocour P, *et al.* Captopril and blood glucose. *Lancet* 1986; **ii:** 461.

Azathioprine. Leucopenia has been reported in a patient given captopril with azathioprine; the effect did not occur when either drug was given alone.[1] In a similar report, neutropenia in a patient taking a regimen including azathioprine and captopril did not recur when captopril was reintroduced after stopping azathioprine.[2]

1. Kirchertz EJ, *et al.* Successful low dose captopril rechallenge following drug-induced leucopenia. *Lancet* 1981; **i:** 1363.
2. Edwards CRW, *et al.* Successful reintroduction of captopril following neutropenia. *Lancet* 1981; **i:** 723.

Ciclosporin. An additive hyperkalaemic effect with ACE inhibitors and ciclosporin is possible. Also, acute renal failure has been reported in 2 patients on ciclosporin after renal transplantation who were given enalapril.[1] Renal function recovered when the ACE inhibitor was withdrawn.

1. Murray BM, *et al.* Enalapril-associated acute renal failure in renal transplants: possible role of cyclosporine. *Am J Kidney Dis* 1990; **16:** 66–9.

Digoxin. For reports of an increase in serum-digoxin concentrations during therapy with ACE inhibitors, see p.1261.

Diuretics. Excessive hypotension may occur when ACE inhibitors are used with diuretics. Deterioration in renal function has also been reported with *metolazone* (see p.1337). Severe hyperkalaemia may occur if ACE inhibitors are used with *spironolactone* (see p.1401).

Epoetins. An additive hyperkalaemic effect may occur when ACE inhibitors are given with epoetins. ACE inhibitors have also been reported to antagonise the haematopoietic effects of epoetins.

General anaesthetics. Marked hypotension may occur during general anaesthesia in patients taking ACE inhibitors. In addition corrected cerebral blood flow was significantly lower in 11 patients who took captopril before general anaesthesia induced with thiopental and maintained with nitrous oxide and enflurane, than in 9 patients pretreated with metoprolol and 9 untreated controls.[1] Although there were no complications of anaesthesia associated with captopril pretreatment, stopping ACE inhibitor therapy before anaesthesia should be considered. However, others have suggested[2] that since there is no clear evidence for stopping them, ACE inhibitors may be continued with care.

1. Jensen K, *et al.* Cerebral blood flow during anaesthesia: influence of pretreatment with metoprolol or captopril. *Br J Anaesth* 1989; **62:** 321–3.
2. Anonymous. Drugs in the peri-operative period: 4 – cardiovascular drugs. *Drug Ther Bull* 1999; **37:** 89–92.

Gold salts. The nitritoid reaction (flushing, nausea, dizziness, and hypotension associated with the first weeks of gold treatment) occurred soon after commencing treatment with an ACE inhibitor (captopril, lisinopril, or enalapril) in 4 patients who had been receiving sodium aurothiomalate for at least 2 years.[1]

1. Healey LA, Backes MB. Nitritoid reactions and angiotensin-converting-enzyme inhibitors. *N Engl J Med* 1989; **321:** 763.

Interferons. Severe granulocytopenia has been reported[1] in 3 patients with mixed cryoglobulinaemia treated with interferon alfa-2a who also received ACE inhibitors. The effect was considered to be due to synergistic haematological toxicity. However, in a further report,[2] 2 patients developed only mild granulocytopenia that was reversible despite continued therapy, while a third patient retained a normal granulocyte count.

1. Casato M, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1995; **99:** 386–91.
2. Jacquot C, *et al.* Granulocytopenia after combined therapy with interferon and angiotensin-converting enzyme inhibitors: evidence for a synergistic hematologic toxicity. *Am J Med* 1996; **101:** 235–6.

Interleukin-3. Marked hypotension occurred in 3 patients[1] receiving ACE inhibitors who were given interleukin-3 following chemotherapy; blood pressure returned to normal when the ACE inhibitors were stopped.

1. Dercksen MW, *et al.* Hypotension induced by interleukin-3 in patients on angiotensin-converting enzyme inhibitors. *Lancet* 1995; **345:** 448.

Lithium. For reports of lithium toxicity in patients taking ACE inhibitors, see p.404.

Muscle relaxants. For a report of severe hypotension in a patient taking lisinopril and tizanidine, see p.1898.

NSAIDs. *Indometacin* and possibly other NSAIDs, including aspirin, have been reported to reduce or abolish the hypotensive action of ACE inhibitors. A similar effect has been reported[1] with *rofecoxib*. NSAIDs cause sodium and water retention and thus may attenuate the effects of various antihypertensives. It has also been suggested that part of the hypotensive effect of ACE inhibitors is prostaglandin-dependent, which might explain this interaction with drugs such as NSAIDs that block prostaglandin synthesis. However, in a double-blind study designed to assess the role of prostaglandins,[2] indometacin did not influence the hypotensive effect of captopril or enalapril, suggesting that the effects on prostaglandins are not significant.

The possibility of an interaction between low-dose *aspirin* and ACE inhibitors has caused concern.[3-5] Retrospective analysis of some studies of ACE inhibitors in patients with heart failure after myocardial infarction suggested that outcome was poorer in those who were also receiving aspirin. A number of small studies have investigated the effects of aspirin plus ACE inhibitors on haemodynamic parameters, but results have been conflicting and the clinical relevance of these findings is not clear. Given the well-established benefits of both ACE inhibitors and aspirin in patients with heart failure associated with ischaemic heart disease, it is generally recommended that patients should continue to receive treatment with both.[4,5] A systematic review[6] of long-term studies using ACE inhibitors came to a similar conclusion, and an observational study[7] in patients with both ischaemic and non-ischaemic heart failure found that ACE inhibitors improved outcomes, irrespective of whether or not patients were taking aspirin.

The combination of NSAIDs and ACE inhibitors may also have variable effects on renal function since they act at different parts of the glomerulus.[8] When given to patients whose kidneys are underperfused, for example because of heart failure, liver cirrhosis, or haemorrhage, renal function may deteriorate. Use of NSAIDs in patients taking ACE inhibitors with diuretics may be particularly hazardous.[9] However, specific patient groups without reduced renal perfusion may benefit from combining an NSAID with an ACE inhibitor.

Indometacin, and possibly other NSAIDs, may have an additive hyperkalaemic effect.

1. Brown CH. Effect of rofecoxib on the antihypertensive activity of lisinopril. *Ann Pharmacother* 2000; **34:** 1486.
2. Gerber JG, *et al*. The hypotensive action of captopril and enalapril is not prostacyclin dependent. *Clin Pharmacol Ther* 1993; **54:** 523–32.
3. Stys T, *et al*. Does aspirin attenuate the beneficial effects of angiotensin-converting enzyme inhibition in heart failure? *Arch Intern Med* 2000; **160:** 1409–13.
4. Mahé I, *et al.* Interaction between aspirin and ACE inhibitors in patients with heart failure. *Drug Safety* 2001; **24:** 167–82.
5. Olson KL. Combined aspirin/ACE inhibitor treatment for CHF. *Ann Pharmacother* 2001; **35:** 1653–8.
6. Teo KK, *et al*. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin: a systematic review. *Lancet* 2002; **360:** 1037–43. Correction. *ibid.* 2003; **361:** 90.
7. McAlister FA, *et al*. Aspirin use and outcomes in a community-based cohort of 7352 patients discharged after first hospitalization for heart failure. *Circulation* 2006; **113:** 2572–8.
8. Sturrock NDC, Struthers AD. Non-steroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors: a commonly prescribed combination with variable effects on renal function. *Br J Clin Pharmacol* 1993; **35:** 343–8.
9. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Beware the triple whammy! *Aust Adverse Drug React Bull* 2006; **25:** 18. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0610.pdf (accessed 04/04/08)

Probenecid. Giving probenecid to 4 healthy subjects during intravenous infusion of captopril caused increases in the steady-state plasma-captopril concentration. The interaction was considered to be due to a reduction of tubular secretion of captopril by probenecid.[1]

1. Singhvi SM, *et al*. Renal handling of captopril: effect of probenecid. *Clin Pharmacol Ther* 1982; **32:** 182–9.

Pharmacokinetics

Most ACE inhibitors are given orally. Apart from captopril and lisinopril, they are generally prodrugs and after absorption undergo rapid metabolism by ester hydrolysis to the active diacid form; for example, enalapril is converted to enalaprilat. Metabolism occurs mainly in the liver. Excretion as active drug or active metabolite is principally in the urine; some, such as benazeprilat and fosinoprilat, are also excreted via the biliary tract. Elimination of the diacid is polyphasic and there is a prolonged terminal elimination phase, which is considered to represent binding to the angiotensin-converting enzyme at a saturable binding site. This bound fraction does not contribute to accumulation of drug following multiple doses. The terminal elimination half-life does not therefore predict the kinetics observed with multiple dosing and the effective half-life for accumulation is the value usually quoted.

◊ Reviews.

1. Burnier M, Biollaz J. Pharmacokinetic optimisation of angiotensin converting enzyme (ACE) inhibitor therapy. *Clin Pharmacokinet* 1992; **22:** 375–84.
2. Hoyer J, *et al*. Clinical pharmacokinetics of angiotensin converting enzyme (ACE) inhibitors in renal failure. *Clin Pharmacokinet* 1993; **24:** 230–54.
3. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; **41:** 207–24.

Uses and Administration

ACE inhibitors are antihypertensive drugs that act as vasodilators and reduce peripheral resistance. They inhibit angiotensin-converting enzyme (ACE), which is involved in the conversion of angiotensin I to angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent direct vasoconstrictor effect. ACE is identical to bradykininase (kininase II) and ACE inhibitors also reduce the degradation of bradykinin, which is a direct vasodilator and is also involved in the generation of prostaglandins. The pharmacological actions of ACE inhibitors are thought to be primarily due to the inhibition of the renin-angiotensin-aldosterone system, but since they also effectively reduce blood pressure in patients with low renin concentrations other mechanisms are probably also involved. ACE inhibitors produce a reduction in both preload and afterload in patients with heart failure. They also reduce left ventricular remodelling, a process that sometimes follows myocardial infarction. Normally, renal blood flow is increased without a change in glomerular filtration rate. ACE inhibitors also reduce proteinuria associated with glomerular kidney disease.

ACE inhibitors are used in the treatment of hypertension and heart failure and are given to improve survival after myocardial infarction and for the prophylaxis of cardiovascular events in patients with certain risk factors. They are also used in the treatment of diabetic nephropathy. They are generally given orally.

In some hypertensive patients there may be a precipitous fall in blood pressure when starting therapy with an ACE inhibitor and the first dose should preferably be given at bedtime; if possible, any diuretic therapy should be stopped a few days beforehand and resumed later if necessary.

In patients with heart failure taking loop diuretics, severe first-dose hypotension is common on introduction of an ACE inhibitor, but temporary withdrawal of the diuretic may cause rebound pulmonary oedema. Thus treatment should start with a low dose under close medical supervision.

◊ Reviews.

1. Lopéz-Sendón J, *et al*. The Task Force on ACE-inhibitors of the European Society of Cardiology. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. *Eur Heart J* 2004; **25:** 1454–70. Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-ACEI-FT.pdf (accessed 25/07/08)

Action. The renin-angiotensin system plays a major role in regulation of cardiovascular and renal function and blockade of this system has complex physiological effects.[1] Although the main target for ACE inhibitors was initially thought to be the endocrine renin-angiotensin system in the circulation this mechanism alone cannot readily explain all the actions of ACE inhibitors.[2] Endogenous renin-angiotensin systems exist in many tissues and ACE inhibitors also have localised effects.[3] This may underlie some of the long-term effects of ACE inhibition, including improved endothelial function, increased arterial wall compliance, improved left ventricular function in heart failure, regression of vascular and left ventricular hypertrophy, and delayed progression of diabetic nephropathy. ACE inhibitors differ in their degree of binding to tissue ACE and in their tissue distribution, but the clinical significance of this is not clear. In one study[4] endothelial function improved with quinapril, which has high tissue specificity, but a similar effect was not seen with the less-specific enalapril, despite an earlier study[5] showing it to be effective.

ACE inhibitors also have effects on the kinin system and there is some evidence that the cardiovascular actions of ACE inhibitors also involve localised accumulation of kinins.[6-8] It has been suggested[9] that the free radical scavenging property of captopril may contribute to some of its actions, although not all studies have confirmed this effect.[10]

1. Schmieder RE, *et al.* Renin-angiotensin system and cardiovascular risk. *Lancet* 2007; **369:** 1208–19.
2. Tabibiazar R, *et al.* Formulating clinical strategies for angiotensin antagonism: a review of preclinical and clinical studies. *Am J Med* 2001; **110:** 471–80.
3. Zarnke KB, Feldman RD. Direct angiotensin converting enzyme inhibitor-mediated venodilation. *Clin Pharmacol Ther* 1996; **59:** 559–68.
4. Anderson TJ, *et al.* Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study). *J Am Coll Cardiol* 2000; **35:** 60–6.
5. O'Driscoll G, *et al.* Improvement in endothelial function by angiotensin converting enzyme inhibition in insulin-dependent diabetes mellitus. *J Clin Invest* 1997; **100:** 678–84.
6. Linz W, *et al.* Contribution of kinins to the cardiovascular actions of angiotensin-converting enzyme inhibitors. *Pharmacol Rev* 1995; **47:** 25–49.
7. Bönner G. The role of kinins in the antihypertensive and cardioprotective effects of ACE inhibitors. *Drugs* 1997; **54** (suppl 5): 23–30.
8. Gainer JV, *et al.* Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. *N Engl J Med* 1998; **339:** 1285–92.
9. Chopra M, *et al.* Captopril: a free radical scavenger. *Br J Clin Pharmacol* 1989; **27:** 396–9.
10. Lapenna D, *et al.* Captopril has no significant scavenging antioxidant activity in human plasma in vitro or in vivo. *Br J Clin Pharmacol* 1996; **42:** 451–6.

Bartter's syndrome. Captopril has been reported to produce beneficial responses in patients with Bartter's syndrome[1-5] (p.1670), which is characterised by hyperaldosteronism, hypokalaemia, and hyperreninaemia, but with normal or reduced blood pressure. Captopril may also be used diagnostically with scintigraphy.[6]

1. Aurell M, Rudin A. Effects of captopril in Bartter's syndrome. *N Engl J Med* 1981; **304:** 1609.
2. Hené RJ, *et al.* Long-term treatment of Bartter's syndrome with captopril. *BMJ* 1982; **285:** 695.
3. James JM, Davies D. The use of captopril in Bartter's syndrome. *BMJ* 1984; **289:** 162.
4. Savastano A, *et al*. Treatment of Bartter's disease with captopril: a case report. *Curr Ther Res* 1986; **39:** 408–13.
5. Jest P, *et al.* Angiotensin-converting enzyme inhibition as a therapeutic principle in Bartter's syndrome. *Eur J Clin Pharmacol* 1991; **41:** 303–5.
6. Dondi M, *et al.* Bartter's syndrome: renal scintigraphic appearance after captopril administration. *J Nucl Med* 1996; **37:** 1688–90.

Diabetic complications. Control of blood pressure plays a major role in the prevention of the sequelae of diabetes mellitus (p.433). ACE inhibitors have been reported[1] to reduce the risk of major cardiovascular events in patients, including a broad range of diabetics, with either a history of cardiovascular disease or at least one additional cardiovascular risk factor. A study[2] of diabetics with no cardiovascular disease (but unknown risk factors) also found a reduction in mortality with use of ACE inhibitors. Some of the studies of ACE inhibitors for cardiovascular risk reduction have also suggested that ACE inhibitors may prevent the development of diabetes in non-diabetic patients,[3-7] but a randomised study[8] in subjects with moderately impaired glucose metabolism but low cardiovascular risk was unable to confirm this effect.

ACE inhibitors may also have benefits in other diabetic complications. They have an established role in the management of nephropathy in patients with type 1 and type 2 diabetes (see Kidney Disorders, below).

It has been reported[9] that ACE inhibitors may reduce the progression of retinopathy in normotensive patients with type 1 diabetes mellitus. However, progression of retinopathy was a secondary end-point of the study and it was suggested that further studies were needed to confirm the beneficial results.

A preliminary report[10] has suggested that ACE inhibitors may improve peripheral neuropathy in diabetic patients, but again further studies are needed.

1. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355:** 253–9. Correction. *ibid.*; **356:** 860.
2. Eurich DT, *et al.* Reduced mortality associated with the use of ACE inhibitors in patients with type 2 diabetes. *Diabetes Care* 2004; **27:** 1330–4.
3. Yusuf S, *et al.* Ramipril and the development of diabetes. *JAMA* 2001; **286:** 1882–5.
4. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; **27:** 247–55.
5. Gillespie EL, *et al.* The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28:** 2261–6.
6. Abuissa H, *et al.* Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46:** 821–6.
7. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; **66:** 1169–77.
8. Bosch J, *et al.* DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006; **355:** 1551–62.

9. Chaturvedi N, *et al.* Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. *Lancet* 1998; **351:** 28–31.
10. Malik RA, *et al.* Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double-blind controlled trial. *Lancet* 1998; **352:** 1978–81.

Erythrocytosis. Secondary erythrocytosis (secondary polycythaemia) is an absolute increase in red cell mass that may occur as a result of tissue hypoxia (as in chronic obstructive airways disease), or excessive erythropoietin production (as in some renal tumours or after renal transplantation). Treatment may be necessary for hyperviscosity symptoms and to reduce the risk of thromboembolic complications, and mainly involves removal of red blood cells by venesection and the use of drugs such as ACE inhibitors that inhibit erythropoiesis.

Post-transplantation erythrocytosis may resolve spontaneously in some patients but for the remainder the aim of therapy is to minimise the risk of thromboembolic and other complications by reducing the haematocrit to less than 45%. Originally treatment was by venesection but this led to severe iron deficiency. There is now evidence of beneficial effects using ACE inhibitors[1-4] or angiotensin II receptor antagonists such as losartan[5-9] and current guidelines recommend these drugs for first-line therapy.[10,11] Theophylline may also be used but appears to be less effective than ACE inhibitors[1] and is usually reserved for patients who do not respond to first-line therapy; it may also be used with an ACE inhibitor but venesection may need to be used until the haematocrit falls to 45%.

Guidelines[11] recommend that patients who develop **erythrocytosis secondary to hypoxic pulmonary disease** should first be considered for methods to improve oxygenation, including long-term oxygen therapy. Those who have hyperviscosity or a haematocrit greater than 56% should undergo venesection. ACE inhibitors or angiotensin II receptor antagonists might be of use for patients who do not tolerate venesection;[11] beneficial responses have been reported with enalapril in altitude polycythaemia,[12] and with losartan in erythrocytosis secondary to chronic obstructive pulmonary disease.[13] Theophylline has also been reported to be of benefit.

1. Ok E, *et al.* Comparison of the effects of enalapril and theophylline on polycythemia after renal transplantation. *Transplantation* 1995; **59:** 1623–45.
2. Beckingham IJ, *et al.* A randomized placebo-controlled study of enalapril in the treatment of erythrocytosis after renal transplantation. *Nephrol Dial Transplant* 1995; **10:** 2316–20.
3. Hernández E, *et al.* Usefulness and safety of treatment with captopril in posttransplant erythrocytosis. *Transplant Proc* 1995; **27:** 2239–41.
4. MacGregor MS, *et al.* Treatment of postrenal transplant erythrocytosis. *Nephron* 1996; **74:** 517–21.
5. Klaassen RJL, *et al.* Losartan, an angiotensin-II receptor antagonist, reduces hematocrits in kidney transplant recipients with posttransplant erythrocytosis. *Transplantation* 1997; **64:** 780–2.
6. Navarro JF, *et al.* Effects of losartan on the treatment of post-transplant erythrocytosis. *Clin Nephrol* 1998; **49:** 370–2.
7. Julian BA, *et al.* Losartan, an angiotensin II type 1 receptor antagonist, lowers hematocrit in posttransplant erythrocytosis. *J Am Soc Nephrol* 1998; **9:** 1104–8.
8. Iñigo P, *et al.* Treatment with losartan in kidney transplant recipients with posttransplant erythrocytosis. *Transplant Proc* 1999; **31:** 2321.
9. Yildiz A, *et al.* Comparison of the effects of enalapril and losartan on posttransplantation erythrocytosis in renal transplant recipients: prospective randomized study. *Transplantation* 2001; **72:** 542–5.
10. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.9.3. Haematological complications: erythrocytosis. *Nephrol Dial Transplant* 2002; **17** (suppl 4): 49–50. Also available at: http://ndt.oxfordjournals.org/cgi/reprint/17/suppl_4/49-a.pdf (accessed 20/11/06)
11. McMullin MF, *et al.* British Committee for Standards in Haematology. Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130:** 174–95. Also available at: http://www.bcshguidelines.com/pdf/polycythaemia_05.pdf (accessed 20/11/06)
12. Plata R, *et al.* Angiotensin-converting-enzyme inhibition therapy in altitude polycythaemia: a prospective randomised trial. *Lancet* 2002; **359:** 663–6.
13. Vlahakos DV, *et al.* Losartan reduces hematocrit in patients with chronic obstructive pulmonary disease and secondary erythrocytosis. *Ann Intern Med* 2001; **134:** 426–7.

Genetic disorders. Small studies have suggested that ACE inhibitors may be of benefit in patients with cardiac disorders associated with Marfan syndrome,[1,2] as well as in Duchenne muscular dystrophy.[3,4]

1. Yetman AT, *et al.* Usefulness of enalapril versus propranolol or atenolol for prevention of aortic dilation in patients with the Marfan syndrome. *Am J Cardiol* 2005; **95:** 1125–7.
2. Ahimastos AA, *et al.* Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: a randomized controlled trial. *JAMA* 2007; **298:** 1539–47.
3. Duboc D, *et al.* Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005; **45:** 855–7.
4. Duboc D, *et al.* Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. *Am Heart J* 2007; **154:** 596–602.

Heart failure. ACE inhibitors given orally produce clinical benefit in all stages of chronic heart failure (p.1165) additional to that seen with diuretics. They relieve symptoms and improve survival and reduce the progression of mild or moderate heart failure to more severe stages. Thus, it is now recommended that all patients with heart failure due to left ventricular systolic dysfunction should receive ACE inhibitors, even if they are asymptomatic with diuretics alone. The studies that have shown a benefit with ACE inhibitors have tended to use higher doses than those used in practice. A study[1] with lisinopril found that higher doses reduced the combined end-point of death or hospitalisation more than low doses and were equally well tolerated, suggesting that higher doses should be used. Studies with enalapril have failed to show a benefit of standard doses over lower doses,[2] or high doses over standard doses.[3] It is now recommended[4,5] that doses should be titrated to those found to be effective in randomised trials, rather than according to symptomatic response, although lower doses may still be of benefit if higher doses are not tolerated.[4] Combination of ACE inhibitors with angiotensin II receptor antagonists to produce a more complete blockade of the renin-angiotensin system may also be of benefit,[6-8] and may therefore be considered[4,5] in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers. ACE inhibitors may also have a role in patients with asymptomatic left ventricular dysfunction, although this is less well established; no effect on short-term mortality was found in asymptomatic patients in the SOLVD trial, but a significant survival benefit was found on long-term follow-up.[9] In patients with heart failure and preserved left ventricular function (diastolic dysfunction) the role of ACE inhibitors is unclear, although they may provide symptomatic benefit.[10] ACE inhibitors may be beneficial in patients with heart failure associated with valve disorders (but see under Precautions, above for discussion of their use in aortic stenosis). There is also some evidence that ACE inhibitors may prevent the development of antineoplastic-induced cardiotoxicity,[11] although this remains to be confirmed.

The mechanism of action in heart failure is not established. ACE inhibitors have beneficial haemodynamic effects; they produce arterial and venous dilatation,[12] reducing both preload and afterload and thus improving cardiac output without increasing heart rate. Their neurohormonal effects also play a part,[13] as do their effects on cytokines. Further actions that may contribute include reduction of left ventricular hypertrophy, and an indirect action to prevent cardiac arrhythmias.[14-16]

Captopril and enalapril have both been used in infants with severe heart failure (see Administration in Children, p.1240, and p.1277, respectively).

1. Packer M, *et al.* Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; **100:** 2312–18.
2. The NETWORK investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J* 1998; **19:** 481–9.
3. Nanas JN, *et al.* Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: a multicenter study. *J Am Coll Cardiol* 2000; **36:** 2090–5.
4. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Full version: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 25/07/08)
5. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). Executive summary: *Eur Heart J* 2005; **26:** 1115–40. Full text: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-CHF-FT.pdf (accessed 25/07/08)
6. Struckman DR, Rivey MP. Combined therapy with an angiotensin II receptor blocker and an angiotensin-converting enzyme inhibitor in heart failure. *Ann Pharmacother* 2001; **35:** 242–8.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667–75.
8. McMurray JJV, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.
9. Jong P, *et al.* Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 2003; **361:** 1843–8.
10. Cleland JGF, *et al.* PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27:** 2338–45.
11. Cardinale D, *et al.* Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006; **114:** 2474–81.
12. Capewell S, *et al.* Acute and chronic arterial and venous effects of captopril in congestive cardiac failure. *BMJ* 1989; **299:** 942–5.
13. Deedwania PC. Angiotensin-converting enzyme inhibitors in congestive heart failure. *Arch Intern Med* 1990; **150:** 1798–1805.
14. Wesseling H, *et al.* Cardiac arrhythmias—a new indication for angiotensin-converting enzyme inhibitors? *J Hum Hypertens* 1989; **3** (suppl 1): 89–95.
15. Campbell RWF. ACE inhibitors and arrhythmias. *Heart* 1996; **76** (suppl 3): 79–82.
16. Healey JS, *et al.* Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; **45:** 1832–9.

Hypertension. ACE inhibitors have an established role in the management of hypertension (p.1171) and appear to have comparable effects to the other main groups of antihypertensives.[1] The Captopril Prevention Project (CAPPP) trial,[2] which compared captopril-based therapy with beta blocker- or diuretic-based therapy, suggested that cardiovascular mortality was lower with captopril, although the risk of stroke was increased in those receiving captopril and overall mortality did not differ between the groups. In the large ALLHAT study,[3] which compared an ACE inhibitor with a calcium-channel blocker or a diuretic, overall mortality did not differ significantly between any of the groups, although there were slightly higher rates of stroke and heart failure in those given the ACE inhibitor compared with the diuretic group. ACE inhibitors are particularly recommended in diabetic patients with nephropathy as they may have beneficial effects on the kidney, and also in patients with heart failure. Other advantages that have been suggested include their lack of adverse effects on serum lipids, a reduction in left ventricular hypertrophy,[4] and a reduction in plasma fibrinogen levels,[5] but the clinical significance of these effects is not established.

The antihypertensive actions of ACE inhibitors may be potentiated by drugs that activate the renin-angiotensin system. Hence, combination therapy with diuretics or with calcium-channel blockers may be particularly useful.

1. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362:** 1527–35.
2. Hansson L, *et al.* Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; **353:** 611–16.
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.* 2003; **289:** 178.
4. Schmieder RE, *et al.* Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. *JAMA* 1996; **275:** 1507–13.
5. Fogari R, *et al.* Effects of different antihypertensive drugs on plasma fibrinogen in hypertensive patients. *Br J Clin Pharmacol* 1995; **39:** 471–6.

DIAGNOSIS OF RENOVASCULAR HYPERTENSION. Captopril has been used to diagnose renovascular hypertension, since the increase in plasma renin activity after blockade of the conversion of angiotensin I to angiotensin II is greater in renovascular hypertension than in primary hypertension.[1] However, a meta-analysis[2] of various tests used for the diagnosis of renovascular hypertension found that the accuracy of the captopril test is low when compared with imaging methods such as computed tomography or magnetic resonance angiography. Captopril is also used to enhance the sensitivity and specificity of renal scintigraphy.[3] For reference to the use of captopril scintigraphy to diagnose Bartter's syndrome see above.

1. Muller FB, *et al.* The captopril test for identifying renovascular disease in hypertensive patients. *Am J Med* 1986; **80:** 633–44.
2. Vasbinder GBC, *et al.* Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. *Ann Intern Med* 2001; **135:** 401–411.
3. Dowling RJ, *et al.* Imaging and stenting for renal artery stenosis. *Hosp Med* 1999; **60:** 329–34.

Ischaemic heart disease. ACE inhibitors have clinical benefits in patients with ischaemic heart disease and other atherosclerotic conditions. They have an established role in the treatment of patients after acute myocardial infarction (see below) and may also have a preventative effect; in the SAVE[1] and SOLVD[2] studies, use of ACE inhibitors in patients with heart failure was noted to lead to a reduction in the incidence of myocardial infarction. In the HOPE study,[3] treatment with ramipril significantly reduced the rate of death, myocardial infarction, and stroke in patients at high risk for cardiovascular disease, while in the EUROPA study[4] perindopril was found to reduce cardiovascular events in patients with stable ischaemic heart disease. In the QUO VADIS study,[5] giving quinapril for 1 year after coronary artery bypass grafting reduced the incidence of clinical ischaemic events although there was no effect on ischaemia during exercise testing or Holter monitoring.

The mechanisms by which ACE inhibitors produce benefit in these patients is less clear. Although a direct action to reduce atherosclerosis (p.1159) has been suggested, studies have failed to confirm this effect. In the TREND study,[6] giving quinapril for 6 months was reported to improve endothelial dysfunction in patients with ischaemic heart disease, but apparently no effects on the progression of atherosclerosis or the incidence of cardiac events were found in the QUIET study[7] which used a lower dose of quinapril given for 3 years. In the PART-2 study,[8] ramipril had no effect on the progression of carotid atherosclerosis, while the PARIS study[9] found an increase in angiographic restenosis after use of quinapril.

A lack of acute anti-ischaemic effect has been found with short-term use of captopril and enalapril in patients with stable angina,[10] and with enalapril in Prinzmetal's angina;[11] however, a further study[12] in patients with stable angina reported an improvement in the results of maximal exercise testing after sublingual captopril dosage. Symptomatic benefit has also been reported[13] in patients with atherosclerotic peripheral arterial disease, and a case-control study[14] has suggested that patients with

aortic disease may have a lower risk of ruptured aortic aneurysm if they are taking ACE inhibitors.

1. Pfeffer MA, *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.
2. Yusuf S, *et al.* Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992; **340:** 1173–8.
3. The Heart Outcomes Prevention Evaluation 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.
4. 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.
5. Oosterga M, *et al.* Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study): QUinapril on Vascular Ace and Determinants of Ischemia. *Am J Cardiol* 2001; **87:** 542–6.
6. Mancini GBJ, *et al.* Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND (Trial on Reversing Endothelial Dysfunction) study. *Circulation* 1996; **94:** 258–65.
7. Cashin-Hemphill L, *et al.* Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet. *Am J Cardiol* 1999; **83:** 43–7.
8. MacMahon S, *et al.* Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. *J Am Coll Cardiol* 2000; **36:** 438–43.
9. Meurice T, *et al.* Effect of ACE inhibitors on angiographic restenosis after coronary stenting (PARIS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2001; **357:** 1321–4.
10. Longobardi G, *et al.* Failure of protective effect of captopril and enalapril on exercise and dipyridamole-induced myocardial ischemia. *Am J Cardiol* 1995; **76:** 255–8.
11. Guazzi M, *et al.* Ineffectiveness of angiotensin converting enzyme inhibition (enalapril) on overt and silent myocardial ischemia in vasospastic angina and comparison with verapamil. *Clin Pharmacol Ther* 1996; **59:** 476–81.
12. Gemici K, *et al.* The effects of sublingual administration of captopril on parameters of exercise test and neurohormonal activation in patients with stable angina pectoris. *Int J Angiol* 1998; **7:** 238–43.
13. Ahimastos AA, *et al.* Ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial. *Ann Intern Med* 2006; **144:** 660–4.
14. Hackam DG, *et al.* Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. *Lancet* 2006; **368:** 659–65.

Kidney disorders. The effects of ACE inhibitors on the kidney are complex. Although they may reduce renal function and should be used with caution in patients with renal impairment (see Adverse Effects and Treatment, above), ACE inhibitors may also have beneficial effects in diabetic and nondiabetic renal disease. Reducing blood pressure protects renal function regardless of the class of antihypertensive used,[1] since hypertension and the resultant proteinuria both cause kidney damage. A number of studies have shown that ACE inhibitors and other drugs that block the renin-angiotensin-aldosterone system (RAS), such as angiotensin II receptor antagonists, are particularly effective[1] and they may therefore be preferred for blood pressure control in kidney disorders. However, whether they have a specific renoprotective effect beyond their antihypertensive effect is unclear.[2]

Most experience has been gained in patients with diabetic nephropathy (see Diabetic Complications, p.433), which is often associated with hypertension and may progress from microalbuminuria to the nephrotic syndrome and end-stage renal failure. In patients with proteinuria, the use of ACE inhibitors now appears to be of established benefit, whether they are hypertensive or normotensive or whether they have type 1 or type 2 diabetes mellitus. Angiotensin II receptor antagonists are also effective[3,4] and may be used as an alternative, although only ACE inhibitors have been shown to have a mortality benefit;[5] dual therapy with an ACE inhibitor and an angiotensin II receptor antagonist has also been tried and may be more effective than either alone.[6,7] In patients with early diabetic nephropathy, ACE inhibitors also slow progression of microalbuminuria,[4,8] and they have been recommended, in conjunction with tight glycaemic control, in all diabetic patients with microalbuminuria.[9] They may also have benefits in patients with normal renal albumin excretion and have been reported to reduce the incidence of microalbuminuria in both hypertensive and normotensive type 2 diabetics,[10] although the clinical significance remains to be established.

ACE inhibitors may also be of benefit in renal disease unrelated to diabetes, although their role is less established. Proteinuria is an important indicator of glomerular kidney disease (p.1504) of various causes and may range from asymptomatic to severe. A number of studies[11-18] have reported that ACE inhibitors reduce both proteinuria and the rate of decline of renal function in patients with various non-diabetic renal disorders. Meta-analyses[19,20] have concluded that ACE inhibitors are more effective than other antihypertensives, although others suggest this is uncertain.[2] As in diabetic nephropathy, dual therapy with an ACE inhibitor and an angiotensin II receptor antagonist may provide additional benefit,[6] although there is less evidence for angiotensin II receptor antagonists alone in non-diabetic renal disease.[3]

Patients with systemic sclerosis (see Scleroderma, p.1817) are considered to be at high risk of adverse effects from ACE inhibitors; however there is evidence that these drugs are of benefit in the management of scleroderma-associated hypertension and renal crisis.[21]

1. Ravera M, *et al.* Importance of blood pressure control in chronic kidney disease. *J Am Soc Nephrol* 2006; **17** (4 suppl 2): S98–S103.
2. Casas JP, *et al.* Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; **366:** 2026–33.
3. Thurman JM, Schrier RW. Comparative effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on blood pressure and the kidney. *Am J Med* 2003; **114:** 588–98.
4. Thomas MC, Atkins RC. Blood pressure lowering for the prevention and treatment of diabetic kidney disease. *Drugs* 2006; **66:** 2213–34.
5. Strippoli GFM, *et al.* Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 25/04/08).
6. MacKinnon M, *et al.* Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. *Am J Kidney Dis* 2006; **48:** 8–20.
7. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148:** 30–48.
8. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001; **134:** 370–9.
9. Mogensen CE, *et al.* Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; **346:** 1080–4.
10. Strippoli GFM, *et al.* Antihypertensive agents for preventing diabetic kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 04/04/08).
11. Gansevoort RT, *et al.* Long-term benefits of the antiproteinuric effect of angiotensin-converting enzyme inhibition in nondiabetic renal disease. *Am J Kidney Dis* 1993; **22:** 202–6.
12. Hannedouche T, *et al.* Randomised controlled trial of enalapril and β blockers in non-diabetic chronic renal failure. *BMJ* 1994; **309:** 833–7.
13. Maschio G, *et al.* Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996; **334:** 939–45.
14. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; **349:** 1857–63.
15. Ruggenenti P, *et al.* Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 1998; **352:** 1252–6.
16. Ruggenenti P, *et al.* Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; **354:** 359–64.
17. Agodoa LY, *et al.* Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001; **285:** 2719–28.
18. Hou FF, *et al.* Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006; **354:** 131–40.
19. Giatras I, *et al.* Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. *Ann Intern Med* 1997; **127:** 337–45.
20. Jafar TH, *et al.* Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: a meta-analysis of patient-level data. *Ann Intern Med* 2001; **135:** 73–87.
21. Steen VD, *et al.* Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990; **113:** 352–7.

Malignant neoplasms. *Animal* and *in vitro* studies have suggested that ACE inhibitors may protect against the development of cancer, and there has been a case report[1] of regression of Kaposi's sarcoma in a patient treated with captopril (but see Effects on the Skin, above). A retrospective cohort study[2] suggested that the incidence of cancer in hypertensive patients receiving ACE inhibitors was lower than expected. However, a subsequent case control study[3] in postmenopausal women found no evidence of a reduced risk of breast cancer associated with ACE inhibitor therapy.

See under Heart Failure, above for a suggestion that ACE inhibitors may protect against antineoplastic-induced cardiotoxicity.

1. Vogt B, Frey FJ. Inhibition of angiogenesis in Kaposi's sarcoma by captopril. *Lancet* 1997; **349:** 1148.
2. Lever AF, *et al.* Do inhibitors of angiotensin-I-converting enzyme protect against risk of cancer? *Lancet* 1998; **352:** 179–84.
3. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; **160:** 349–53.

Marfan syndrome. For mention of the use of ACE inhibitors in patients with Marfan syndrome see Genetic Disorders, above.

Migraine. Observations that attacks of migraine occurred less frequently in hypertensive patients treated with lisinopril, were confirmed by a small placebo-controlled study[1] in 47 non-hypertensive patients with migraine (p.616).

1. Schrader H, *et al.* Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. *BMJ* 2001; **322:** 19–22.

Muscular dystrophy. For reference to the use of ACE inhibitors in patients with Duchenne muscular dystrophy see Genetic Disorders, above.

Myocardial infarction. ACE inhibitors may be of benefit in both the prevention and treatment of myocardial infarction (p.1175). They reduce left ventricular remodelling, a process which sometimes follows myocardial infarction and is a recognised precursor of symptomatic heart failure. Studies in patients with evidence of left ventricular dysfunction have shown benefit from long-term oral use of ACE inhibitors such as captopril (the SAVE study),[1] ramipril (the AIRE and AIRE extension (AIREX) studies),[2-4] or trandolapril (the TRACE study)[5,6] started about 3 days, or more, after infarction, and long-term ACE inhibitors are now established therapy in such patients.[7,8]

Early treatment with ACE inhibitors as an adjunct to standard thrombolytic therapy is less well established. Favourable results have been reported in the GISSI-3[9] and the ISIS-4[10] studies where lisinopril and captopril, respectively, were given orally starting within 24 hours of the onset of chest pain and in the Chinese Cardiac Study[11] (CCS-1) where captopril was given orally within 36 hours of the onset of symptoms. In the GISSI-3 study the beneficial effects were maintained at 6 months.[12] However, the CONSENSUS II study was stopped early when it was found that enalapril, given intravenously as enalaprilat and begun within 24 hours of the onset of chest pain, did not improve survival during the 180 days after infarction.[13] A substudy on some of the patients did however suggest that they may have benefited from early treatment since left ventricular dilatation was attenuated.[14] An interaction between aspirin and enalapril was postulated as one of the reasons for the overall lack of benefit seen, and further analysis of the CONSENSUS II results found that the beneficial effect of enalapril was reduced in those patients already taking aspirin,[15] although a systematic overview[16] failed to support this finding. A systematic review of the CONSENSUS II, GISSI-3, ISIS-4, and CCS-1 studies found lower 30-day cumulative mortality and incidence of non-fatal heart failure among ACE inhibitor recipients.[17] However, the size of benefit in these studies of largely unselected patients is much smaller than in the studies of patients with left ventricular dysfunction, and there remains no clear consensus as to whether all patients should be given ACE inhibitors or only those who develop evidence of left ventricular dysfunction.

1. Pfeffer MA, *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.
2. The Acute Infarction Ramipril Efficacy (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.
3. Hall AS, *et al.* Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE extension (AIREX) study. *Lancet* 1997; **349:** 1493–7.
4. Cleland JGF, *et al.* Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure: a report from the AIRE study investigators. *Eur Heart J* 1997; **18:** 41–51.
5. Køber L, *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.
6. Torp-Pedersen C, Køber L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. *Lancet* 1999; **354:** 9–12.
7. Borghi C, Ambrosioni E. A risk-benefit assessment of ACE inhibitor therapy post-myocardial infarction. *Drug Safety* 1996; **14:** 277–87.
8. Murdoch DR, McMurray JJV. ACE inhibitors in acute myocardial infarction. *Hosp Med* 1998; **59:** 111–15.
9. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994; **343:** 1115–22.
10. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; **345:** 669–85.
11. Chinese Cardiac Study collaborative group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995; **345:** 686–7.
12. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Six-month effects of early treatment with lisinopril and transdermal glyceryl trinitrate singly and together withdrawn six weeks after acute myocardial infarction: the GISSI-3 trial. *J Am Coll Cardiol* 1996; **27:** 337–44.
13. Swedberg K, *et al.* Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992; **327:** 678–84.
14. Bonarjee VVS, *et al.* Attenuation of left ventricular dilatation after acute myocardial infarction by early initiation of enalapril therapy. *Am J Cardiol* 1993; **72:** 1004–9.
15. Nguyen KN, *et al.* Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol* 1997; **79:** 115–19.
16. Latini R, *et al.* Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96,712 randomized patients. *J Am Coll Cardiol* 2000; **35:** 1801–7.
17. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. *Circulation* 1998; **97:** 2202–12.

Raynaud's syndrome. ACE inhibitors are among many drugs that have been tried in Raynaud's syndrome, a vasospastic peripheral vascular disease (p.1178). Variable effects have been reported. In a patient with Raynaud's syndrome captopril improved blood circulation in the fingers both acutely and during long-term therapy with a dose of 37.5 mg daily; the effect was apparently related to its effects on kinins rather than inhibition of angiotensin II formation.[1] However, a double-blind crossover study in 15 patients with Raynaud's phenomenon given captopril 25 mg or placebo three times daily for 6 weeks found that the drug improved blood flow but not the frequency or severity of attacks,[2] and a similar study in patients given enalapril failed to find any subjective or objective benefits.[3]

There has also been a report[4] of a patient in whom peripheral ischaemia induced by ergotamine was rapidly reversed by captopril.

1. Miyazaki S, *et al.* Relief from digital vasospasm by treatment with captopril and its complete inhibition by serine proteinase inhibitors in Raynaud's phenomenon. *BMJ* 1982; **284:** 310–11.
2. Rustin MHA, *et al.* The effect of captopril on cutaneous blood flow in patients with primary Raynaud's phenomenon. *Br J Dermatol* 1987; **117:** 751–8.
3. Challenor VF, *et al.* Subjective and objective assessment of enalapril in primary Raynaud's phenomenon. *Br J Clin Pharmacol* 1991; **31:** 477–80.
4. Zimran A, *et al.* Treatment with captopril for peripheral ischaemia induced by ergotamine. *BMJ* 1984; **288:** 364.

Stroke. Antihypertensive therapy reduces the risk of stroke (p.1185) in patients with hypertension. However, in patients who have had a stroke, antihypertensive therapy has often been avoided due to the perceived risk of reducing cerebral perfusion. A study[1] of blood-pressure lowering with the ACE inhibitor perindopril, alone or with a diuretic, found that the risk of recurrent stroke was reduced in patients with a history of stroke or transient ischaemic attack, irrespective of whether they had a normal or raised blood pressure at study entry. Retrospective studies[2,3] have also suggested that stroke severity may be reduced in patients who are already taking ACE inhibitors. The beneficial effects of ACE inhibitors in stroke may not be entirely due to their antihypertensive effects; in the HOPE study,[4] ramipril reduced the incidence of stroke in patients with high cardiovascular risk despite only a small reduction in blood pressure.

There have also been reports[5,6] that ACE inhibitors may reduce the risk of pneumonia in patients with a history of stroke, possibly by an effect on symptomless dysphagia.[7]

1. 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. Corrections. *ibid.*; 1556 and 2002; **359:** 2120.
2. Kumar S, *et al.* Antiplatelets, ACE inhibitors, and statins combination reduces stroke severity and tissue at risk. *Neurology* 2006; **66:** 1153–8.
3. Chitravas N, *et al.* Is prestroke use of angiotensin-converting enzyme inhibitors associated with better outcome? *Neurology* 2007; **68:** 1687–93.
4. Bosch J, *et al.* Use of ramipril in preventing stroke: double blind randomised trial. *BMJ* 2002; **324:** 699–702.
5. Sekizawa K, *et al.* ACE inhibitors and pneumonia. *Lancet* 1998; **352:** 1069.
6. Arai T, *et al.* ACE inhibitors and pneumonia in elderly people. *Lancet* 1998; **352:** 1937–8.
7. Arai T, *et al.* ACE inhibitors and symptomless dysphagia. *Lancet* 1998; **352:** 115–6.

Acebutolol *(BAN, USAN, rINN)* ⊗

Acébutolol; Acebutololum; Asebutolol; Asebutololi. (±)-3′-Acetyl-4′-(2-hydroxy-3-isopropylaminopropoxy)butyranilide.

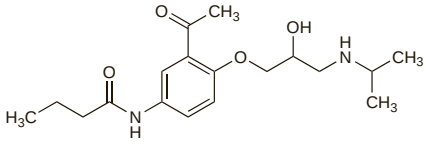
Ацебутолол

$C_{18}H_{28}N_2O_4$ = 336.4.

CAS — 37517-30-9.

ATC — C07AB04.

ATC Vet — QC07AB04.



Acebutolol Hydrochloride *(BANM, rINNM)* ⊗

Acébutolol, chlorhydrate d'; Acebutolol-hidroklorid; Acebutolol-hydrochlorid; Acebutololhydroklorid; Acebutololi hydrochloridum; Acebutololio hidrochloridas; Acebutololu chlorowodorek; Asebutololihydrokloridi; Hidrocloruro de acebutolol; IL-17803A; M&B-17803A.

Ацебутолола Гидрохлорид

$C_{18}H_{28}N_2O_4$,HCl = 372.9.

CAS — 34381-68-5.

ATC — C07AB04.

ATC Vet — QC07AB04.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Acebutolol Hydrochloride). A white or almost white crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

USP 31 (Acebutolol Hydrochloride). A white or almost white crystalline powder. Soluble in water and in alcohol; very slightly soluble in acetone and in dichloromethane; practically insoluble in ether. pH of a 1% solution in water is between 4.5 and 7.0. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Concentrations of acebutolol and its active metabolite diacetolol in breast milk are higher than those in maternal plasma.[1] Pharmacological effects in the neonate, including hypotension, bradycardia, and tachypnoea, have been reported,[1] and the American Academy of Pediatrics therefore considers[2] that acebutolol should be given with caution to breast-feeding mothers.

1. Boutroy MJ, *et al.* To nurse when receiving acebutolol: is it dangerous for the neonate? *Eur J Clin Pharmacol* 1986; **30:** 737–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on the liver. Six cases of hepatotoxicity associated with acebutolol were reported[1] in the USA to the FDA between 1985 and 1989. The syndrome consisted of markedly elevated transaminase concentrations, moderately elevated alkaline phosphatase concentrations, and other constitutional symptoms such as fever, nausea, abdominal pain, and headache. The duration of therapy before onset of symptoms ranged from 10 to 31 days; 5 patients received a daily dose of 400 mg; the dose was unspecified in the sixth patient. The syndrome resolved when acebutolol was stopped but reappeared in 2 patients who were rechallenged.

1. Tanner LA, *et al.* Hepatic toxicity after acebutolol therapy. *Ann Intern Med* 1989; **111:** 533–4.

Effects on respiratory function. Bronchospasm is a recognised adverse effect of beta blockers, but other respiratory disorders have also been reported. Pleurisy and pulmonary granulomas developed in a patient given acebutolol and a diuretic; acebutolol was considered to be responsible.[1] Hypersensitivity pneumonitis has also been reported in a patient taking acebutolol.[2]

1. Wood GM, *et al.* Pleurisy and pulmonary granulomas after treatment with acebutolol. *BMJ* 1982; **285:** 936.
2. Akoun GM, *et al.* Acebutolol-induced hypersensitivity pneumonitis. *BMJ* 1983; **286:** 266–7.

Hypersensitivity. See Effects on Respiratory Function, above and Lupus, below.

Lupus. An increase in antinuclear antibodies has been seen with acebutolol.[1] A report of a lupus syndrome in an elderly patient given acebutolol and clonidine described remission of symptoms when acebutolol was withdrawn, but the high antinuclear antibody titre persisted for more than 9 months.[2] Acebutolol was also reported to have caused subacute cutaneous lupus erythematosus in a 57-year-old woman. The condition had resolved completely 4 months after acebutolol was stopped.[3] The authors noted that there had been 9 previous reports of lupus in patients taking acebutolol, but only one had skin manifestations.

1. Wilson JD. Antinuclear antibodies and cardiovascular drugs. *Drugs* 1980; **19:** 292–305.
2. Hourdebaigt-Larrusse P, *et al.* Une nouvelle observation de lupus induit par acébutolol. *Ann Cardiol Angeiol (Paris)* 1985; **34:** 421–3.
3. Fenniche S,*et al.* Acebutolol-induced subacute cutaneous lupus erythematosus. *Skin Pharmacol Physiol* 2005; **18:** 230–3.

Pregnancy. Both acebutolol and its active metabolite diacetolol cross the placenta. In a study[1] in 29 pregnant women who had received acebutolol for at least one month before delivery, there was evidence of bradycardia in 12 of the 31 offspring and tachypnoea in 6.

1. Boutroy MJ, *et al.* Infants born to hypertensive mothers treated by acebutolol. *Dev Pharmacol Ther* 1982; **4** (suppl 1): 109–15.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Pharmacokinetics

Acebutolol is well absorbed from the gastrointestinal tract, but undergoes extensive first-pass metabolism in the liver. Although the bioavailability of acebutolol is reported to be only about 40%, the major metabolite diacetolol is active. After oral doses, peak plasma concentrations of acebutolol and diacetolol are reached in about 2 and 4 hours, respectively.

Acebutolol and diacetolol are widely distributed in the body, but they have low to moderate lipid solubility and penetration into the CSF is poor. They cross the placenta and higher concentrations are achieved in breast milk than in maternal plasma. Acebutolol is only about 26% bound to plasma proteins, but is about 50% bound to erythrocytes. The plasma elimination half-lives for acebutolol and diacetolol are 3 to 4 hours and 8 to 13 hours respectively. Half-life values for acebutolol and diacetolol may be increased in the elderly and the half-life for diacetolol may be prolonged up to 32 hours in patients with severe renal impairment. Acebutolol and diacetolol are excreted in the urine and in the bile and may undergo enterohepatic recycling; acebutolol is also reported to be excreted directly from the intestinal wall, and more than 50% of an oral dose can be recovered from the faeces. Acebutolol and diacetolol are removed by dialysis.

Uses and Administration

Acebutolol is a cardioselective beta blocker (p.1225). It is reported to have some intrinsic sympathomimetic activity and membrane stabilising properties.

Acebutolol is used in the management of hypertension (p.1171), angina pectoris (p.1157), and cardiac arrhythmias (p.1160).

Acebutolol is used as the hydrochloride, but doses are usually expressed in terms of the base; 110.8 mg of acebutolol hydrochloride is equivalent to 100 mg of base. It is generally given orally although slow intravenous injection has been used for the emergency treatment of arrhythmias.

In **hypertension** the usual initial oral dose is 400 mg once daily or 200 mg twice daily, increased if necessary after 2 weeks to 400 mg twice daily. Doses up to 1.2 g daily in divided doses may be given.

The usual oral dose for **angina pectoris** is 400 mg once daily or 200 mg twice daily, but up to 300 mg three times daily may be required for severe cases and total daily doses of 1.2 g have been given.

The usual initial oral dose for **cardiac arrhythmias** is 200 mg twice daily, increased according to response; up to 1.2 g daily in divided doses has been required.

Reduced doses may be required in patients with impaired renal function (see below). Elderly patients may also require lower maintenance doses; doses greater than 800 mg daily should be avoided.

Action. Acebutolol is generally considered to be a cardioselective beta blocker but there has been considerable controversy as to the degree of its selectivity and the selectivity of its primary metabolite, diacetolol.[1-3] In a review of beta blockers,[4] acebutolol was stated to be less cardioselective than other drugs such as atenolol or metoprolol. It was proposed[5] that this may be because the metabolite accumulates during chronic dosage to reach concentrations that affect both $beta_1$ and $beta_2$ receptors since cardioselectivity is only a relative and dose-related phenomenon. This remains uncertain and there is some evidence[6] that at least after single doses, diacetolol is actually more cardioselective than acebutolol itself.

1. Whitsett TL, *et al.* Comparison of the beta and beta adrenoceptor blocking properties of acebutolol and propranolol. *Chest* 1982; **82:** 668–73.
2. Nair S, *et al.* The effect of acebutolol, a beta adrenergic blocking agent, and placebo on pulmonary functions in asthmatics. *Int J Clin Pharmacol Ther Toxicol* 1981; **19:** 519–26.
3. Leary WP, *et al.* Respiratory effects of acebutolol hydrochloride: a new selective beta-adrenergic blocking agent. *S Afr Med J* 1973; **47:** 1245–8.
4. Feely J, *et al.* Beta-blockers and sympathomimetics. *BMJ* 1983; **286:** 1043–7.
5. Feely J, Maclean D. New drugs: beta blockers and sympathomimetics. *BMJ* 1983; **286:** 1972.
6. Thomas MS, Tattersfield AE. Comparison of beta-adrenoceptor selectivity of acebutolol and its metabolite diacetolol with metoprolol and propranolol in normal man. *Eur J Clin Pharmacol* 1986; **29:** 679–83.

Administration in renal impairment. The dose of acebutolol should be reduced in patients with renal impairment. It is recommended that the dose should be reduced by 50% in patients with a creatinine clearance between 25 and 50 mL/minute and by 75% in those with a creatinine clearance of less than 25 mL/minute. The dose frequency should not exceed once daily.