

DRUG CLASSES

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

Drugs from this class have an increasing role in cardiovascular risk management including hypertension.

Examples

- Captopril
- Enalapril
- Fosinopril
- Lisinopril
- Perindopril
- Quinapril
- Ramipril
- Trandolapril

Mechanism of action

These drugs inhibit competitively the activity of ACE (also termed kininase II) to prevent formation of the active octapeptide, angiotensin II, from the inactive decapeptide, angiotensin I. This occurs in blood and tissues including kidney, heart, blood vessels, adrenal gland and brain. Angiotensin II is a potent vasoconstrictor, promotes aldosterone release, facilitates sympathetic activity and has other potentially harmful effects on the cardiovascular system. Reduction in blood pressure secondary to vasodilatation following ACE inhibition is greatest when the renin-angiotensin system is stimulated (e.g. following salt restriction, diuretic therapy or in renal artery stenosis) but ACE inhibitors also lower blood pressure when there is normal or low activity of the renin-angiotensin system. Nevertheless, Afro-Caribbeans and elderly individuals, who tend to have low renin hypertension, respond less well to ACE inhibitors. Inhibition of ACE (kininase II) also leads to accumulation of kinins including bradykinin which promotes vasodilator activity and may contribute to the overall effectiveness of ACE inhibitors.

Pharmacokinetics

All ACE inhibitors bind to tissue and plasma protein. Whereas free drug is eliminated relatively rapidly by the kidney predominantly by glomerular filtration, binding to tissue sites means that the plasma concentration-time profile shows a long lasting terminal elimination phase. The prototype ACE inhibitor, captopril, is absorbed and eliminated rapidly. Enalapril, like most of the later ACE inhibitors, is an inactive pro-drug that requires hydrolysis during or active absorption to general the active acid form, enalaprilat. Lisinopril is an analogue of enalapril and is itself active.

Adverse effects

ACE inhibitors are generally well tolerated but some adverse effects can be observed.

- Dry, irritant cough in about 15% (10% men and 20% women) attributable to accumulation of bradykinin. **Not uncommon and should trigger switching to an angiotensin receptor blocker.**
- Angioedema also attributable to kinin potentiation. **Rare but potentially fatal.**
- Hyperkalaemia due to potassium retention mediated by reduction of aldosterone. **Rare except in renal impairment.**
- First dose hypotension of renin-angiotensin system activated. **Rare in essential hypertension.**
- Impairment of renal function. **Caution if bilateral renal artery stenosis suspected.**
- Taste disturbance. **Very rare**
- Skin rashes. **Very rare**
- Urticaria. **Very rare.**

Practical issues

The ACE inhibitor dose-blood pressure response relationship is linear at low doses, but a “plateau” is reached quickly within the therapeutic range. Further increases in dosage does not increase the peak blood pressure reduction but prolong the duration of action. The fall in blood pressure following ACE inhibition is not associated with changes in heart rate; in particular, there is no reflex tachycardia.

ACE inhibitors vary in efficacy and duration of action with some but not others being suitable for once-daily dosing. Captopril has the shortest duration of action and has to be administered twice or thrice daily to provide blood pressure lowering over 24 hours. Although many ACE inhibitors are recommended for once daily dosing, for some, such as enalapril, a more consistent response is achieved by twice daily administration. Since duration of blood pressure reduction is dose-dependent, with most ACE inhibitors, smooth blood pressure lowering over 24 hours is only achieved at the maximum recommended dose. To avoid precipitous initial fall in blood pressure or decline in renal

function, it is generally advised to start therapy with low dosages in the elderly, and in patients with compromised renal function or heart failure.

In general ACE inhibitors are well tolerated. Other than cough and other non-specific upper respiratory symptoms, side effects are rare. Cough is not dose-dependent and is a class effect. Altering dose or ACE inhibitor is not helpful. Concern about first dose hypotension arose from experience in patients with heart failure, accelerated hypertension or essential hypertension treated with excessive doses of diuretics and consequent sodium/volume depletion with activation of the renin-angiotensin system. This is uncommon with current low dose diuretic regimens. Impairment of renal function may arise in patients with bilateral renal artery stenosis which should be suspected if there is evidence of peripheral vascular disease. Renal failure, reversible on discontinuation of ACE inhibitor, may be precipitated. However, ACE inhibitors can protect renal function in patients with chronic renal failure and hypertension. To avoid the risks of abrupt reduction in renal function and hyperkalaemia, serum creatinine and potassium should be measured before and soon after starting an ACE inhibitor. Only if serum potassium rises above the reference range or serum creatinine rises by more than 20% (and is above the reference range), need the ACE inhibitor be discontinued and further investigations of renal structure and function should be considered. In addition, patients should be advised to temporarily suspend the use of ACE inhibitors during dehydrating illnesses such as diarrhoea and vomiting to avoid postural hypotension and acute kidney injury. ACE inhibitors should be avoided in women of child bearing potential because of the danger of foetal maldevelopment. The risk of new onset diabetes appears to be less with ACE inhibitors than with many other classes of antihypertensive drugs.

ACE inhibitors combine well with thiazide and thiazide-like diuretics and with calcium channel blockers to produce overall antihypertensive effects which are at least additive. However, care should be taken when these drugs are co-administered with potassium salts and potassium sparing diuretics because of the risk of hyperkalaemia, especially if there is pre-existing renal impairment. Similar caution is advised if non steroidal anti-inflammatory drugs are prescribed with ACE inhibitors.

ACE inhibitors are available in fixed-dose combinations with a thiazide or thiazides-like diuretic or a calcium channel blocker. These preparations may improve compliance and should be considered, provided there is no cost disadvantage.

Large-scale prospective outcome trials have demonstrated benefits in cardiovascular protection with ACE inhibitors equivalent to those with other antihypertensive drugs. Furthermore, cardiovascular and renal protective effects beyond that to be expected

from blood pressure reduction have been reported in various groups of patients at high risk.

Compelling indications include heart failure, left ventricular dysfunction, post myocardial infarction or established coronary heart disease, type 1 diabetic nephropathy and secondary stroke prevention in combination with a thiazide or thiazide-like diuretic.

Possible indications include chronic renal disease (with caution, close supervision and specialist advice when there is established and significant renal impairment), type 2 diabetic nephropathy and proteinuric renal disease. ACE inhibitors can be useful in subjects who have headaches or migraine.

Caution is advised if there is renal impairment or peripheral vascular disease because of the association with renovascular disease.

Compelling contraindications are pregnancy and renovascular disease, although ACE inhibitors are sometimes used in renovascular disease under specialist supervision. ACE inhibitors should not be combined with direct renin inhibitors and not with angiotensin receptor blockers. They are also contra-indicated with sacubitril/valsartan.

In the absence of a compelling indication for another drug or contraindication to an ACE inhibitor, these drugs should be used as recommended in the NICE/BHS algorithm.

- **step 1** in Caucasian people aged less than 55 years
- **step 2** with a calcium channel blocker or thiazide-like diuretic
- **step 3** with a calcium channel blocker plus a thiazide-like diuretic

BIHS