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### ACE inhibitors

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Also known as angiotensin converting enzyme inhibitors.

#### Captopril

#### Enalapril

#### Fosinopril

#### Lisinopril

#### Perindopril

#### Quinapril

#### Ramipril

#### Trandolapril

### Mode of action

ACE inhibitors block conversion of angiotensin I to angiotensin II and also inhibit the breakdown of bradykinin. They reduce the effects of angiotensin II-induced vasoconstriction, sodium retention and aldosterone release. They also reduce the effect of angiotensin II on sympathetic nervous activity and growth factors.

### Indications

Hypertension

Chronic systolic heart failure as part of standard treatment (eg with beta-blocker, diuretics)

Diabetic nephropathy

Prevention of progressive renal failure in patients with persistent proteinuria (>1 g daily)

Post MI

### Precautions

*Volume or sodium depletion*—may activate the renin-angiotensin system; this may result in excessive hypotension when an angiotensin-blocking drug is started; correct (eg by reducing diuretic dosage) before treatment and/or monitor carefully.

*Primary hyperaldosteronism*—an ACE inhibitor may be ineffective; seek specialist advice.

*Black African or Caribbean descent*—antihypertensive effect of ACE inhibitor monotherapy may be reduced (generally a calcium channel blocker or thiazide diuretic is more effective).

*Treatment with drugs that can increase potassium concentration, eg trimethoprim, ciclosporin*—increases risk of hyperkalaemia; avoid combination or monitor potassium concentration.

### Cardiovascular

Limited data suggest that ACE inhibitors are beneficial in selected patients with aortic stenosis (theoretically they may cause coronary hypoperfusion, systemic hypotension and reduced renal function); caution is needed to avoid hypotension.

Patients with peripheral vascular disease or atherosclerosis may be more likely to have renal artery stenosis, increasing the risk of renal failure.

### Angioedema

Treatment with sacubitril with valsartan is contraindicated with an ACE inhibitor due to the increased risk of angioedema (allow 36 hours between stopping an ACE inhibitor and starting sacubitril with valsartan).

ACE inhibitors increase the risk of further episodes of angioedema in people with hereditary, idiopathic or ACE inhibitor-induced angioedema; use alternative class or seek specialist advice.

Treatment with an mTOR inhibitor (eg everolimus), a dipeptidyl peptidase-4 inhibitor (eg sitagliptin), or alteplase may also increase the risk of angioedema.

## Renal

Renal impairment increases risk of hyperkalaemia and may affect the excretion of some ACE inhibitors; use lower initial doses and monitor potassium concentration.

Renal impairment may worsen, especially in people with hypovolaemia, or if used with NSAIDs (including selective COX-2 inhibitors).

Serum creatinine may increase after starting treatment or increasing the dose (usually stabilises within the first 2 months):

- if increase is <30% or glomerular filtration rate (GFR) reduction is <25%, there is no need to adjust dose
- if increase is >30% (or GFR reduction is >25%), investigate other causes and if necessary, reduce dose or stop ACE inhibitor and consider specialist referral.

ACE inhibitors increase risk of renal failure in bilateral renal artery stenosis.

Haemodialysis with high flux polyacrylonitrile membranes (AN 69) may result in anaphylactoid reactions; similar reactions may occur in patients on low density lipoprotein apheresis with dextran sulfate.

## Surgery

Excessive hypotension may occur during anaesthesia and after surgery.

## Elderly

May be more predisposed to first-dose hypotension, hyperkalaemia and renovascular disease than younger patients. Start treatment with lower doses; monitor renal function closely.

## Women

Avoid in women planning to conceive or who are using inadequate contraception.

## Pregnancy

Avoid use; change women to an alternative antihypertensive as soon as possible during the first trimester. Use in the second and third trimesters may cause fetal renal dysfunction and oligohydramnios, and subsequently fetal death. Contraindicated by manufacturers.

## Breastfeeding

No adverse effects in infants reported with captopril or enalapril; insufficient information to confirm safety of other ACE inhibitors.

## Adverse effects

### Common (>1%)

hypotension, headache, dizziness, cough (below), hyperkalaemia, fatigue, nausea, renal impairment

### Infrequent (0.1–1%)

angioedema (below), rash (especially captopril), diarrhoea, elevated hepatic aminotransferases and bilirubin

### Rare (<0.1%)

hepatitis (cholestatic or hepatocellular), pancreatitis, hyponatraemia, photosensitivity, psoriasis

## Cough

A persistent, nonproductive cough is common; it is not dose-dependent and is unlikely to respond to treatment. It can occur within days to months of starting treatment. The cough may be mild and tolerable, however, some patients need to stop treatment (usually improves within 1–4 weeks of stopping).

## Angioedema

May affect the face, lips, tongue, upper airway, and less often, the GI tract (causing abdominal pain, vomiting and diarrhoea). It can occur within the first week of treatment, but is possible months or years later.

## Comparative information

Advantages for specific ACE inhibitors are claimed based on pharmacokinetic, metabolic or tissue ACE-binding characteristics, however, these do not translate into significant clinical differences.

Most (except captopril) maintain an antihypertensive effect for up to 24 hours and can be given once daily. Most are available as [fixed-dose combinations](#) with a diuretic (hydrochlorothiazide or indapamide) or a calcium channel blocker.

## Dosage in heart failure

Begin with a low dose (risk of hypotension, particularly if the patient is elderly or taking a diuretic), then gradually titrate upwards at short intervals (eg every 2–4 weeks) to the highest tolerable maintenance dose. A more rapid dose escalation may be possible in closely monitored situations.

### Counselling

You may feel dizzy when you start taking this medicine. Get up gradually from sitting or lying to minimise this effect; sit or lie down if you become dizzy or light-headed.

Do not take potassium supplements while you are taking this medicine unless your doctor tells you to.

### Practice points

- when starting an ACE inhibitor:
  - stop potassium supplements and potassium-sparing diuretics
  - in heart failure, consider reducing dose or withholding other diuretics for 24 hours before starting an ACE inhibitor
  - review use of NSAIDs (including selective COX-2 inhibitors)
  - start with a low dose
- check renal function and electrolytes before starting an ACE inhibitor and review after 1-2 weeks

### Treatment with an ACE inhibitor and a sartan

See also [Table – Management of systolic heart failure](#)

- in trials the combination worsened renal function and increased the risk of symptomatic hypotension and hyperkalaemia
- the combination did not provide additional benefit in patients at high risk of vascular disease nor improve survival in patients with left ventricular failure/dysfunction after MI
- despite conflicting trial results, it may be an option, eg for selected patients with chronic heart failure or non-responsive BP, seek specialist advice

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