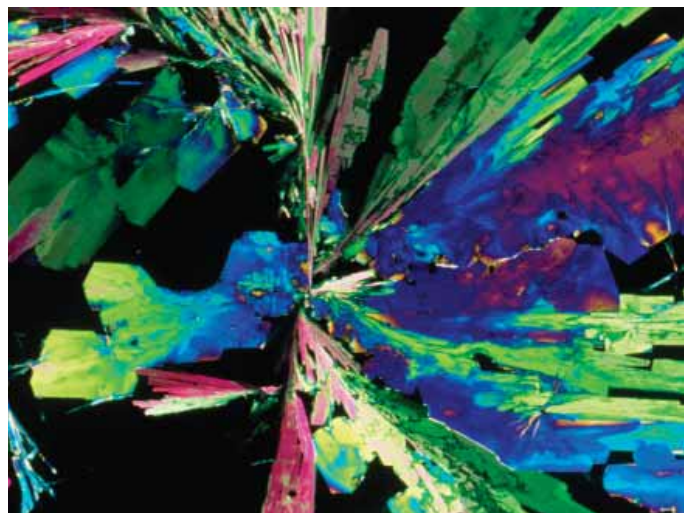


# Hypertension

## — pharmacological management

By Beth Gormer, MPharm, MRPharmS

This article describes the mode of action of drugs used in the treatment of hypertension, their side effects and factors to consider in special patient groups. Recent guidelines from the National Institute for Health and Clinical Excellence are also described



Crystals of the beta-blocker propranolol (polarised light micrograph)

**H**ypertension is a risk factor for many coronary events. However, blood pressure can usually be reduced with appropriate treatment, reducing the risk of stroke, coronary events, heart failure and renal failure.

Many different factors are involved in the pathogenesis of hypertension. These include increased cardiac output, increased peripheral resistance, vasoconstriction and reduced vasodilation. The kidneys also play a role in the regulation of blood pressure by controlling sodium and water excretion, and the secretion of renin, which influences vascular tone and electrolyte imbalance. Neuronal mechanisms such as the sympathetic nervous system and endocrine systems are also involved in blood pressure regulation. These systems are therefore targets for drug therapy to reduce blood pressure.

**Target blood pressures** The optimal systolic blood pressure (SBP) is <140mmHg and the optimal diastolic blood pressure (DPB) is <85mmHg. A target SBP of 130mmHg and DPB of <80mmHg should be considered for patients with established atherosclerotic cardiovascular disease, diabetes or chronic renal failure.<sup>1</sup> Guidance on initiating phar-

macological treatment, as recommended by the British National Formulary, is summarised in Panel 1 (p120).

Regardless of the severity of hypertension, all patients should be offered lifestyle advice to reduce their blood pressure. This includes advice on smoking cessation, weight reduction, exercise, alcohol intake and diet.

**Drug classes** Commonly used classes of antihypertensive drugs are the thiazide diuretics (eg, bendroflumethiazide), beta-blockers (eg, propranolol, atenolol), angiotensin-converting enzyme inhibitors (eg, captopril, enalapril), angiotensin II antagonists (eg, candesartan, losartan), calcium channel blockers (eg, amlodipine, nifedipine) and alpha-blockers (eg, doxazosin).

Less commonly used drugs include vasodilator and centrally acting antihypertensives and, rarely, guanethidine, which is indicated for the treatment of hypertensive crisis.

### Thiazide diuretics

Thiazide diuretics are moderately potent diuretics which lower blood pressure by inhibiting sodium reabsorption at the beginning of the distal convoluted tubule in the kidney, increasing sodium excretion and urine volume. Thiazides also have a direct vasodilatory effect on arterioles, sustaining the antihypertensive effect. They are well

absorbed following oral administration, widely distributed and metabolised in the liver.

The diuretic effect of thiazides occurs within one to two hours of administration and continues for 12–24 hours, allowing once daily administration.

The antihypertensive effect occurs at low thiazide doses and there is no additional benefit to blood pressure from increasing the dose, although additional diuresis can occur at higher doses.

The effects of thiazides on the renal tubule depend on the extent of their excretion, so thiazides may be less effective in patients with renal impairment.

**Side effects** Increased urinary excretion with thiazide diuretics can lead to hypokalaemia, hyponatraemia and hypomagnesaemia. Hypercalcaemia can occur due to reduced excretion of calcium. Interference with the excretion of uric acid can cause hyperuricaemia, so thiazides should be used with caution in patients with gout. Thiazide diuretics can also cause hyperglycaemia due to impaired glucose tolerance (insulin resistance) leading to an increased risk of non-insulin dependent diabetes mellitus.

Other less common side effects include hyperlipidaemia, causing increases in low density lipoprotein and triglycerides and a reduction in high density lipoprotein (HDL). Up to 25 per cent of men treated

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## Panel 1: Target blood pressures for pharmacological treatment<sup>1</sup>

Initial blood pressure	Complications*	Action
Systolic $\geq 220$ mmHg or diastolic $\geq 160$ mmHg	No	Treat immediately
Systolic 180–219mmHg or diastolic 110–119mmHg	No	Confirm over one to two weeks and treat if these readings are sustained
Systolic 160–179mmHg or diastolic 100–109mmHg	Yes	Confirm over three to four weeks and treat if these readings are sustained
Systolic 160–179mmHg or diastolic 100–109mmHg	No	Advise lifestyle changes, initially reassess weekly and treat if these readings are sustained on repeat measurements over four to 12 weeks
Systolic 140–159mmHg or diastolic 90–99mmHg	Yes	Confirm within 12 weeks and treat if these readings are sustained
Systolic 140–159mmHg or diastolic 90–99mmHg	No	Advise lifestyle changes and reassess monthly. Treat persistent mild hypertension if the 10-year cardiovascular disease risk is 20 per cent

\* Cardiovascular complications, target organ damage or diabetes

with thiazide diuretics may experience impotence, which is usually reversible on withdrawal of treatment.

### — Beta-blockers

Beta-blockers block beta-adrenoceptors in the body. These receptors are subclassified as beta-1 receptors or beta-2 receptors. Beta-1 receptors are mainly located in the heart and beta-2 receptors are mostly found in the lung, peripheral blood vessels, and skeletal muscle. However, beta-2 receptors can be found in the heart and beta-1 receptors can also be found in the kidney. Beta-receptors are also found in the brain.

Stimulation of beta-receptors in the brain and periphery promotes the release of neurotransmitters which increase sympathetic nervous system activity. Stimulation of beta-1 receptors in the sino-atrial node and the myocardium increases heart rate and force of contraction. Stimulation of beta-receptors in the kidney promotes renin release, increasing the activity of the renin-angiotensin-aldosterone system. The overall effect of stimulation of these receptors is increased cardiac output, increased peripheral vascular resistance and an increase in aldosterone-mediated sodium and water retention.

Treatment with beta-blockers antagonises all of these effects resulting in a reduction in blood pressure, although the principal anti-

hypertensive mechanism of this group of drugs is unclear.

Selective beta-blockers (commonly called cardioselective beta-blockers), for example bisoprolol, primarily act on beta-1 receptors. However they are not specific for beta-1 receptors so should be used with caution in patients with a history of asthma and bronchospasm. Non-selective beta-blockers (eg, propranolol) block both beta-1 and beta-2 receptors.

Beta-blockers with partial agonist activity (sometimes known as intrinsic sympathomimetic activity), eg acebutolol, act as a beta-stimulant when adrenergic activity is minimal (eg, during sleep) but exert a beta-blocking effect when adrenergic activity is increased (eg, during exercise). This has the benefit of reducing bradycardia during the day. Some beta-blockers, such as labetalol and carvedilol, also block the effects of peripheral alpha-adrenoceptors. Others, such as celiprolol, exert beta-2 agonist or vasodilator activity.

Beta-blockers are excreted hepatically or renally depending on the water or lipid solubility of each drug. Those eliminated by the liver usually require multiple daily dosing while those excreted renally generally have longer half-lives and can be administered once daily. Beta-blockers should never be abruptly stopped but should be withdrawn gradually, especially in patients with angina, or rebound symptoms can occur.

**Side effects** Blockade of beta-2 receptors in the bronchi can precipitate bronchospasm, even when cardioselective beta-blockers are used. Other adverse effects of beta-blockers include bradycardia, impairment of myocardial contractility, and cold extremities caused by vasoconstriction from blockade of beta-2 receptors in the smooth muscle of peripheral blood vessels.

Awareness of hypoglycaemia in some patients with insulin-dependent diabetes mellitus can be reduced. This is because beta-blockers block sympathetic nervous system activity which is responsible for the warning signs of hypoglycaemia. Reduced sympathetic outflow may also account for the feelings of malaise experienced by some patients taking beta-blockers.

Vivid dreams and nightmares can occasionally occur, especially with lipid soluble beta-blockers such as propranolol. Impotence can also occur. The non-selective beta-blockers can cause an increase in serum triglyceride levels and a decrease in HDL.

### — ACE inhibitors

Angiotensin-converting enzyme (ACE) inhibitors competitively inhibit the formation of angiotensin II from its inactive precursor angiotensin I, which is found in the blood, blood vessels, kidney, heart, adrenal gland and brain.

Angiotensin II is a potent vasoconstrictor which also promotes aldosterone release and central and peripheral sympathetic activity. Inhibiting its formation therefore reduces blood pressure. If the renin-angiotensin-aldosterone system is already activated (eg, due to sodium depletion, or diuretic therapy), the antihypertensive effect of ACE inhibitors will be greater.

ACE is also responsible for the breakdown of kinins, including bradykinin, which have a vasodilatory effect. Inhibition of this breakdown effect results in a more pronounced antihypertensive effect.

There are significant pharmacokinetic differences between the ACE inhibitors. Captopril is rapidly absorbed but has a short duration of action, so is useful for initial assessment of how a patient will respond to ACE inhibition. The first dose of an ACE inhibitor should be administered at night because a profound drop in blood pressure may occur; this effect is enhanced in patients with low sodium levels.

### — Angiotensin II antagonists

Angiotensin II receptors are found in blood vessels and other targets. They are subclassified into AT<sub>1</sub> and AT<sub>2</sub> receptors. The AT<sub>1</sub> receptor mediates the pharmacological responses of angiotensin II, such as vasoconstriction and aldosterone release, and is therefore the target for drug treatment. The role of the AT<sub>2</sub> receptor is less well understood.

## Panel 2: New NICE guidelines<sup>2</sup>

The most recent guidance from the National Institute for Health and Clinical Excellence on the treatment of hypertension is as follows:

**Step 1** In hypertensive patients aged 55 years or older or in black patients of any age, first choice therapy should be a calcium channel blocker or thiazide-type diuretic. In patients under 55 years, the first choice for initial therapy should be an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin II receptor antagonist if ACE inhibitors are not tolerated).

**Step 2** If an additional drug is required, adding an ACE inhibitor to a calcium channel blocker or a diuretic (or vice versa) is recommended.

**Step 3** If treatment with three drugs is required then the combination of an ACE inhibitor (or angiotensin II receptor antagonist), calcium channel blocker and thiazide-type diuretic should be used.

**Step 4** If a fourth drug is required then a higher dose of thiazide diuretic should be considered, or an alternative diuretic, beta-blocker or alpha blocker. All drug doses should be up-titrated as per the British National Formulary.

Many tissues contain enzyme pathways which are capable of converting angiotensin I into angiotensin II without using ACE. Therefore there may be advantages in blocking the renin-angiotensin system via the AT<sub>1</sub> receptor antagonist pathway with an angiotensin II receptor antagonist.

Angiotensin II receptor antagonists have many properties similar to those of ACE inhibitors, although they do not inhibit the breakdown of kinins. Because of the renal effects, ACE inhibitors and angiotensin II receptor antagonists are contraindicated in bilateral renal artery stenosis and in severe

stenosis of the artery supplying a single functioning kidney.

### Side effects of ACE inhibitors and angiotensin-II receptor antagonists

Before starting treatment with an ACE inhibitor or angiotensin II receptor antagonist a patient's renal function and electrolyte levels should be checked. This monitoring should continue during treatment because both classes of drug can occasionally impair renal function.

Both ACE inhibitors and angiotensin II receptor antagonists cause hyperkalaemia due to reduced aldosterone production, so potassium supplements and potassium sparing diuretics should be avoided in these patients.

One difference between the two classes is that a dry cough is a common side effect of ACE inhibitors, exhibited in up to 15 per cent of patients. Angiotensin II receptor antagonists are not associated with the cough because they do not interfere with the inhibition of bradykinin breakdown.

### — Calcium channel blockers

Calcium channel blockers (less correctly called calcium channel antagonists) reduce calcium ion influx into myocardial cells, the cells within the specialised conducting

system of the heart, and the cells of vascular smooth muscle. The effect of this is to reduce myocardial contractility, depress the formation and propagation of electrical impulses within the heart and promote vasodilator activity, interfering with the constriction of vascular smooth muscle. All of these are calcium ion-dependent processes.

There are three classes of calcium channel blockers: the dihydropyridines (eg, nifedipine and amlodipine); the phenylalkalamines (verapamil) and the benzothiazepines (diltiazem). The dihydropyridines have distinct peripheral vasodilator properties so are effective antihypertensives while verapamil and diltiazem have cardiac effects and are used to reduce heart rate and prevent angina.

All calcium channel blockers are metabolised by the liver.

**Side effects** Facial flushing, headache and swelling of the ankles are often seen, due to the vasodilatory effect of the dihydropyridine calcium channel blockers. Abdominal pain and nausea may also occur.

The gastrointestinal tract is also affected by the influx of calcium ions so calcium channel blockers often cause gastrointestinal disturbances, which may include constipation.

## Alpha-blockers

Alpha-blockers (alpha-1 adrenoceptor blocking agents) block peripheral alpha-1 adrenoceptors, causing vasodilatory effects due to relaxation of vascular smooth muscle. They are indicated for resistant hypertension.

**Side effects** Alpha-blockers can cause postural hypotension, which is commonly seen after administration of the first dose. Alpha-blockers may be beneficial in older men because they may improve symptoms of prostate enlargement.

## Other groups

Vasodilator antihypertensive drugs (eg, hydralazine, minoxidil) lower blood pressure by relaxation of vascular smooth muscle. Centrally acting antihypertensives (eg, clonidine, methyldopa, moxonidine) act on alpha-2 adrenoceptors or related receptors in the brainstem, reducing sympathetic outflow to the heart, blood vessels and kidneys, leading to a reduction in blood pressure.

**Side effects** Vasodilator antihypertensives can cause fluid retention. Liver function tests should be monitored during treatment with hydralazine because it is hepatically cleared.

Hydralazine has also been associated with systemic lupus erythematosus. Minoxidil has been associated with hypertrichosis (hirsutism) and so may be unsuitable for use in women.

Centrally acting agents are not specific or selective enough to avoid central nervous system side effects such as sedation, dry mouth and drowsiness, which commonly occur. Methyldopa has a similar mechanism of action to clonidine but can cause immunological side effects, including pyrexia, hepatitis and haemolytic anaemia.

## Choice of therapy

An update of the National Institute for Health and Clinical Excellence guideline on hypertension was published last year (see Panel 2, p121),<sup>2</sup> together with the British Hypertension Society, as recently published clinical trials provided further evidence for the treatment of hypertension.<sup>3</sup>

The main changes to the NICE guideline are that beta-blockers are no longer the recommended first line treatment for any patient group. Beta-blockers were found to be less effective at reducing major cardiovascular events, especially stroke, than other types of antihypertensives.<sup>4</sup>

Atenolol was the beta-blocker used in most of the studies. When the trials which used atenolol were excluded from the

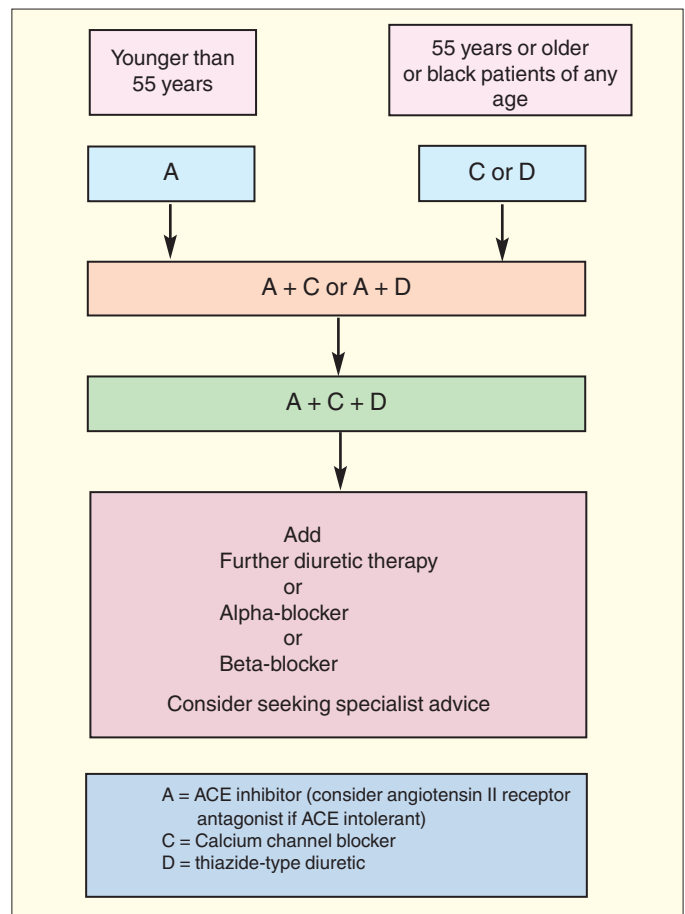


Figure 1: Diagrammatic representation of the National Institute for Health and Clinical Excellence guidelines for the treatment of hypertension (adapted from reference 2).

review, the evidence base for the use of beta-blockers in the treatment of hypertension was much weaker than for the other drug classes. It was concluded that, in the absence of other compelling indications for a beta-blocker (eg, angina), they should not be recommended as an initial treatment for hypertension.

Beta-blockers were also found to be less effective than ACE inhibitors or dihydropyridine calcium channel blockers in reducing the risk of diabetes, especially in patients already taking a thiazide diuretic. If a patient taking beta-blockers requires a second drug, an ACE inhibitor or calcium channel blocker should be added, rather than a thiazide.

## Special considerations

**Pregnancy** Centrally acting agents have a poor CNS profile. However, methyldopa is used in pregnancy, due to its long-term safety data and beta-blockers are used in the third trimester. Intravenous labetalol is reserved for use in pregnancy in a hypertensive crisis. A controlled release formulation of nifedipine has also been used in pregnancy but is unlicensed.

**Ethnic group** Thiazide diuretics and the dihydropyridine calcium channel blockers are more effective than beta-blockers in Afro-Caribbean patients. ACE inhibitors and angiotensin II antagonists have been shown to increase the risk of stroke in this group of patients and are therefore not recommended as first line therapy.<sup>5,6</sup>

**Elderly** The new NICE guidance states that thiazide diuretics or dihydropyridine calcium channel blockers should be the first line therapy in elderly people.<sup>2</sup> However, attention should be paid to renal function during treatment with a thiazide because the elderly are more at risk of renal impairment. Patients over 80 years old should be offered the same treatment as patients aged over 55 years.

**Diabetes** Patients with diabetes may require a combination of antihypertensive drugs to achieve their optimal target blood pressure. ACE inhibitors are the initial treatment of choice because they can delay the progression of microalbuminuria to nephropathy. Patients with diabetic nephropathy should be treated with an ACE inhibitor or an angiotensin II receptor antagonist to minimise the risk of further renal deterioration, even if their blood pressure is normal.

**Renal disease** ACE inhibitors can reduce or abolish glomerular filtration and can cause severe and progressive renal failure. They are therefore contraindicated in patients with bilateral renal artery stenosis. However, ACE inhibitors are unlikely to have an adverse effect on overall renal

function in patients with unilateral renal artery stenosis. A dihydropyridine calcium channel blocker can be added if further blood pressure lowering is required, but thiazide diuretics may be ineffective.

**Systolic hypertension** Isolated systolic hypertension (ISH) is defined as an SBP of greater than 160mmHg with a DBP less than 90mmHg. Patients with ISH should be offered the same treatment as patients with raised SBP and raised DBP, because ISH carries the same risk of complications.<sup>2</sup>

The dihydropyridine calcium channel blockers have been used in the treatment of isolated systolic hypertension in the elderly, especially where a thiazide diuretic is contraindicated.

**Accelerated hypertension** Accelerated or very severe hypertension, defined as a DBP of greater than 140mmHg, requires urgent medical attention. Beta-blockers such as atenolol or labetalol or the dihydropyridine calcium channel blockers are indicated for this condition. DBP should be reduced to 100–110mmHg during the first 24 hours. Blood pressure should be reduced further over the next two to three days using a combination of diuretics, vasodilators and ACE inhibitors, if required.

If intravenous treatment is required then sodium nitroprusside or glyceryl trinitrate is recommended.

## The cardiology pharmacist

As a member of the multidisciplinary team, the pharmacist has an important role to play in the treatment of hypertension.

To aid concordance or ensure compliance with a medication regimen the pharmacist can give information about the benefits and side effects of drugs so that patients can make an informed decision about their treatment. This information should include why the medicine is needed and the risks of not taking it. Practical points, such as ensuring that the medicine is prescribed once daily if possible, may also improve adherence.

Other medicines that a patient is taking should also be reviewed. Concurrent non-steroidal anti-inflammatory drugs, the oral contraceptive pill, glucocorticoids, and sympathomimetics can all increase blood pressure. These medicines, some of which can be bought over the counter, should be avoided in patients with high blood pressure.

It is important to remember that a patient may have additional co-morbidities. The pharmacist can advise and review co-existing disease states to ensure the most appropriate therapy choice is made.

To help reduce costs, pharmacists can also ensure that non-proprietary drugs are prescribed when appropriate.

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## Further reading

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