

Hypertension

Disease characteristics

The cause of essential hypertension is not known but may be multifactorial. Indeed, rather than a disease in its own right, we may view hypertension as blood pressure (BP) that is associated with significant cardiovascular risk. The cut-off point between normal BP and hypertension is arbitrary, and is now generally regarded as a sustained diastolic BP >90 mmHg or systolic BP >140 mmHg.

Over the years alterations in many cardiovascular control mechanisms (nitric oxide, endothelins, renin–angiotensin system and sympathetic nervous system) have been proposed as causing essential hypertension but there is no convincing evidence to support a ‘universal cause’. Far less commonly, however, hypertension (<10%) may be secondary to another condition: renal disease, renovascular disease, Conn’s syndrome (primary hyperaldosteronism), polycythaemia, Cushing’s syndrome, hyperthyroidism, pheochromocytoma and pregnancy, and these should be excluded. Drugs that may cause hypertension include:

- oral contraceptives
- sympathomimetics
- corticosteroids
- non-steroidal anti-inflammatory drugs (NSAIDs)
- ketoconazole
- moclobemide
- erythropoietin
- ciclosporin
- venlafaxine
- sibutramine.

Clinical features

Hypertension is almost always asymptomatic and often detected by routine measurement. The main complications are due to end-organ damage, principally left ventricular hypertrophy, ischaemic heart disease, renal failure, retinopathy and peripheral vascular disease. Ultimately, hypertension is a major risk factor for stroke (especially), myocardial infarction and the development of chronic heart failure, hence the need to treat this condition effectively.

Goals of treatment

The clear goal is a reduction in BP and, when this involves drug treatment, this should be with as few side-effects as possible. The joint guidelines of the National Institute for Health and Clinical Excellence (NICE) and British Hypertension Society (BHS) specify a target systolic BP of <140 mmHg and a target diastolic BP of <90 mmHg (80 mmHg in people with diabetes), whereas the Hypertension Optimal Treatment (HOT) trial (HOT Study Group 1998) indicated that there is little benefit from lowering BP further.

As a consequence of treatment the following are ideal goals:

- reduction in cardiovascular damage
- preservation of renal function
- limitation or reversal of left ventricular hypertrophy
- prevention of coronary artery disease and chronic heart failure
- reduction in mortality due to stroke and myocardial infarctions.

Pharmacological basis of management

Diuretics: thiazides and related agents, e.g. bendroflumethiazide, indapamide, metolazone

Diuretics are first-line drugs in the management of hypertension and cause a reduction in circulating volume, thus reducing preload and afterload, and hence cardiac work. In addition, they may have direct vascular effects leading to vasodilatation, which further reduces preload and/or afterload.

Thiazides act in the distal convoluted tubule to inhibit Na^+/Cl^- reabsorption, leading to diuresis. Loop diuretics, which are occasionally used when thiazides (except metolazone) are likely to be ineffective in renal impairment, act via inhibition of the $\text{Na}^+/\text{K}^+/\text{Cl}^-$ transporter in the thick ascending limb of the loop of Henle.

It should be noted that, with bendroflumethiazide, the most widely used agent, there is no benefit from increasing the dose above the optimum of 2.5 mg, because there is little additional antihypertensive effect and side effects are substantially increased.

The effectiveness of thiazide diuretics has been established over many years and was confirmed by the ALLHAT trial (2002), which demonstrated that they were effective at preventing cardiovascular disease and supported their use as first-line antihypertensives.

ACE inhibitors, e.g. captopril, enalapril, lisinopril, perindopril, ramipril

Angiotensin-converting enzyme (ACE) inhibitors are now recognized as having an important role in hypertension but are no more effective than other agents (CAPP Study Group 1999). By inhibiting ACE, they lead to reductions in angiotensin II, which in turn leads to:

- reductions in arterial and venous vasoconstriction (reduced total peripheral resistance)
- reduced aldosterone production, which leads to reductions in salt and water retention, hence reduced circulating volume (reduced cardiac output).

Clinical use

ACE inhibitors may cause pronounced first-dose hypotension and are best given initially on retiring at night. A low starting dose should be used and titrated up to the maximum effective and tolerated dose.

The renin–angiotensin system is activated in renovascular disease (atheroma of the renal artery) in order to maintain renal perfusion and filtration. Hence, ACE inhibitors may cause deterioration of renal function in pre-existing renal disease and these patients should be identified by measuring plasma creatinine and should not receive an ACE inhibitor.

A build-up of bradykinin, usually broken down by ACE, may produce a troublesome dry cough in some patients (10%) treated with ACE inhibitors.

Angiotensin II receptor antagonists, e.g. candesartan, irbesartan, losartan, valsartan

This new class of drugs blocks the action of angiotensin II at the angiotensin (AT_1) receptor. Hence these agents have similar consequences to ACE inhibitors but do not give rise to a cough. The Lifestyle Intervention for Endpoint Reduction in Hypertension (LIFE) trial (2002) reported that losartan was more effective than atenolol at reducing mortality in hypertensive patients, largely through a reduction in the incidence of stroke. In patients with diabetes with hypertension, the effects of losartan were even more impressive at reducing overall mortality, cardiovascular mortality and the development of heart failure. In both classes of hypertensive patients, losartan was also more effective than atenolol at reversing left ventricular hypertrophy. Current guidelines recommend that AT_1 -receptor antagonists be used when ACE inhibitors are indicated but not tolerated, e.g. due to a cough.

Calcium channel blockers, e.g. diltiazem, felodipine, nifedipine, verapamil

There are three main classes of calcium channel blockers: (1) verapamil; (2) dihydropyridines –

nifedipine, nicardipine, amlodipine, lacidipine, nisoldipine; and (3) diltiazem. Verapamil exerts most of its effects on the heart compared with dihydropyridine effects, which target arteriolar smooth muscle. The activity of diltiazem is between class 1 and 2. Worldwide, calcium channel blockers are currently the most widely used antihypertensives and they act principally to inhibit voltage-operated calcium channels on vascular smooth muscle, leading to vasodilatation and a reduction in BP.

β Blockers: acebutolol, atenolol, bisoprolol, metoprolol, nadolol, pindolol, propranolol

β Blockers were once viewed as first-line drugs and have been widely used over many years. Their precise antihypertensive effect is unclear but it is thought to involve a reduction in sympathetic drive to the heart, reducing cardiac output, and a reduction in sympathetically evoked renin release from the kidneys. However, in 2006 joint guidance from NICE and the BHS recommended that they should no longer be used as first-line antihypertensives, based on their reduced effectiveness at reducing cardiovascular outcomes compared with other antihypertensives, as established by the ASCOT trial (2005).

α Blockers, e.g. doxazosin, prazosin

These should generally be regarded as agents of last choice, being added to therapy that has not achieved target BP. They are competitive receptor antagonists, inhibiting sympathetic activation of α_1 -adrenoceptors on vascular smooth muscle, leading to vasodilatation and a drop in BP. As a result of this non-selective action, they lead to widespread side effects, making them poorly tolerated. They may, however, be useful for patients with diabetes or a lipid disorder (when diuretics or β blockers are sometimes avoided) or in older men with prostatic symptoms.

Centrally acting agents, e.g. clonidine, α -methyldopa, moxonidine

These agents are occasionally used, e.g. α -methyldopa in pregnancy or when other treatments have failed. Their action is on central vasomotor centres and they lead to a decrease in sympathetic output, causing a fall in BP. The interference with the sympathetic nervous system leads to widespread side effects. In the case of clonidine and moxonidine (an imidazoline receptor agonist), they should not be withdrawn suddenly, because there is a risk of a hypertensive crisis. For withdrawal, if moxonidine is used together with a β blocker, then the β blocker should be withdrawn slowly, several days before the centrally acting agent.

The beneficial pharmacological targets of cardiovascular drugs are listed in Table 11.1. Consideration of the distribution in the body of the sites of action for these drugs also explains some of the unwanted but predictable type A adverse drug reactions (Table 11.1).

Management of hypertension

Lifestyle measures play an important role both before and alongside drug therapy. Lifestyle modifications may involve weight reduction, reducing fat and salt intake, increasing fruit and oily fish in the diet, increasing exercise and stopping smoking. It has been reported that a sustained weight loss of 4.5 kg was associated with an 8–9 mmHg drop in diastolic and systolic BP (Stevens et al 2001) and made a significant contribution to blood pressure reduction. Particular attention should be paid to alcohol consumption, because excessive alcohol intake is closely associated with hypertension. In many patients the initial treatment will involve lifestyle changes to see whether these bring about a reduction in BP. During this process the patient's BP should be measured on several occasions to determine whether hypertension is established and to exclude 'white-coat' hypertension.

Table 11.1 Examples of principal type A adverse reactions of drugs used in hypertension

Drug	Pharmacological activity	Unwanted clinical effects
Thiazides	Act on the Na ⁺ /Cl ⁻ transporter of the renal distal convoluted tubule to cause diuresis and reduce circulating volume. May also have vasodilator actions	<ul style="list-style-type: none"> • Postural hypotension • Adversely alter lipid profile • May induce diabetes
Calcium channel blockers	Vascular smooth muscle: arteriolar relaxation (mainly dihydropyridines)	Headache, facial flushing, peripheral oedema (ankles), postural hypotension, gum hyperplasia
(1) Verapamil	CNS Smooth muscle: GI tract Sinus or AV nodes: negative inotrope Myocardium	Depression, extrapyramidal symptoms Constipation Bradycardia or heart block Reduced cardiac output
(2) Dihydropyridines	Reflex sympathomimetic stimulation	Tachycardia or palpitations
(3) Diltiazem	Sinus or AV nodes: negative inotrope Smooth muscle: GI tract	Bradycardia or heart block Constipation
β Blockers	Myocardium: sympathetic drive mediated by β ₁ -adrenoceptors	Bradycardia, cardiac failure, conduction disorders
Hydrophilic (atenolol, acebutolol)	Smooth muscle: bronchoconstriction Reduce lacrimation Peripheral vascular smooth muscle: constriction Lipids Liver and pancreas	Bronchoconstriction Dry eyes Raynaud's phenomenon, impotence Adversely affect lipid profile: increase LDL and decrease HDL Decrease glycogenolysis, and decrease secretion of insulin
Sotalol (hydrophilic)	As above + prolongation of Q-T interval	No longer licensed for hypertension
Lipophilic (propranolol, timolol, metoprolol, labetalol)	As above + CNS effects	Lethargy, depression, nightmares

AV, atrioventricular; CNS, central nervous system; GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Choice of drugs

If lifestyle measures do not bring about a satisfactory reduction in BP, the joint NICE and BHS guidelines (2006a, 2006b) suggest that drug treatment should be initiated in patients with BP that is consistently >160/100 mmHg or when the BP is 140/90 mmHg and cardiovascular disease is present, in patients with elevated cardiovascular risk (>20% over 10 years) or end-organ damage (such as left ventricular hypertrophy or renal damage).

The management of hypertension has been the subject of controversy with clinical trials

giving different results regarding drug choice and the existence of conflicting guidelines. In 2006 the NICE and the BHS produced consensus guidelines that attempted to resolve these issues. The so-called Cambridge AB/CD rules were modified and adopted as 'A/CD' guidelines. These guidelines divide patients into groups under and over 55 years of age, with black patients of any age being treated as the latter group. The rationale for this is that younger patients are deemed to have high renin hypertension and respond best to ACE inhibitors (A) whereas older patients or black patients are initially treated with calcium channel blocker (C) or diuretic (D).

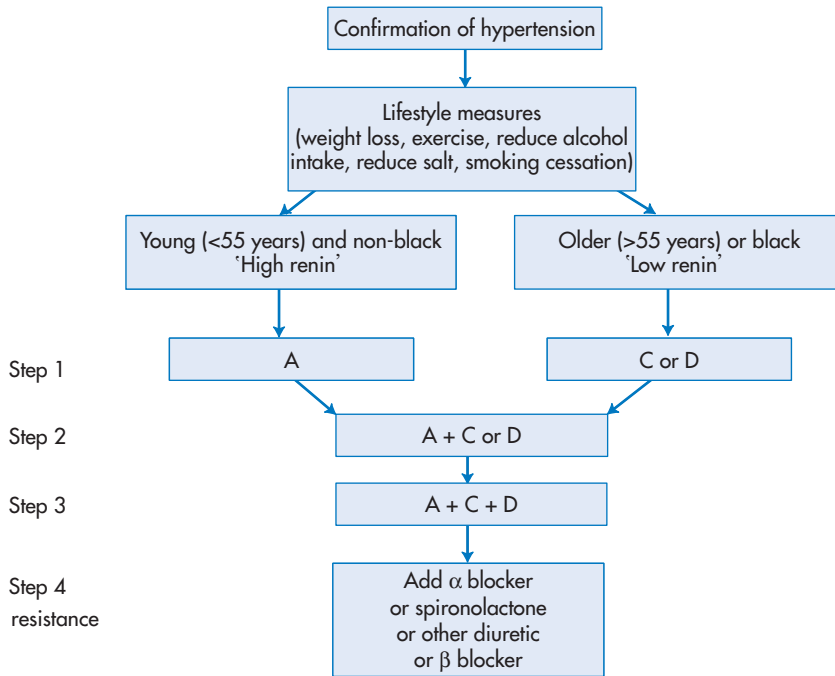


Figure 11.1 This is a summary of guidance from the National Institute for Health and Clinical Excellence (NICE 2006b) on the management of hypertension using the A/CD rules where A = ACE (angiotensin-converting enzyme) inhibitor, C = calcium channel blocker and D = diuretic. The stepwise care is shown and, once lifestyle measures have failed to control confirmed hypertension, patients are treated on the basis of age and ethnicity.

It is then acknowledged that most patients require more than one drug, so drug treatment is stepped up using an agent from the other group, e.g. patients who are younger than 55 years would normally be initiated on a ACE inhibitor and, if this failed to control their BP, they would then be additionally prescribed either a calcium channel blocker (C) or a diuretic (D) (step 2). After this the third step would involve adding the remaining class of drug. In cases of resistance (step 4), an additional diuretic, β blocker or α blocker should be added to therapy. In some cases, the aldosterone antagonist spironolactone is effective because the patient may have undiagnosed Conn's syndrome with high aldosterone. β Blockers are also reserved for patients who are intolerant to ACE inhibitors and used in pregnancy.

Concurrent illnesses

In addition to the A/CD rules, concurrent illnesses also influence drug choice, for example asthma is a reason to avoid β blockers. Some reasons to favour or avoid certain antihypertensives are summarized in Table 11.2.

Hypertension is a major risk factor for cardiovascular disease, so the patient may have other related conditions. Hyperlipidaemia is common in the population at risk of hypertension and should be managed, usually with a statin (see Chapter 12). The NICE guidelines point to using a statin in patients with a 20% or greater 10-year risk of coronary artery disease. In addition, evidence from small-scale studies has also suggested that statins may themselves cause modest reductions in BP and, when used in combination with antihypertensives, may augment the regression of left ventricular hypertrophy, an effect

Table 11.2 Compelling indications and contraindications for antihypertensives

Condition	Drug indicated	Drugs contraindicated or used with caution
Ischaemic heart disease	β Blockers; diltiazem verapamil, long-acting dihydropyridines	Short-acting dihydropyridines – associated with increased mortality
Heart failure	ACE inhibitors and AT ₁ -receptor antagonists; diuretics; β blockers with caution (see Chapter 15)	Diltiazem and verapamil – due to negative inotropic effects
Left ventricular hypertrophy (LVH)	The AT ₁ -receptor antagonist, losartan, has been shown to be particularly effective at reversing LVH (LIFE trial)	
Diabetes mellitus	ACE inhibitors – they are renally and vasoprotective in diabetes (HOPE trial). The AT ₁ -receptor antagonist, losartan, reduces mortality more than atenolol in diabetic patients with hypertension (LIFE trial). Centrally acting agents and calcium channel blockers are also suitable	Thiazides and β blockers may cause hyperglycaemia. Thiazides may adversely affect the lipid profile. β Blockers may also mask signs of hypoglycaemia (e.g. tachycardia; see Chapter 35)
Elderly people	Thiazides	
Chronic obstructive pulmonary disease (COPD) and asthma	Centrally acting agents are safe	β Blockers are contraindicated in asthma, although in the absence of an alternative, β_1 -receptor antagonists may be used with extreme caution. In COPD, cardioselective agents are used with caution
History of stroke	Perindopril and indapamide reduce the risk of stroke in both hypertensive and normotensive patients (PROGRESS trial); this may apply to any ACE inhibitor plus a thiazide	
Renal impairment		Thiazides less effective. Dose reduction of hydrophilic β blockers (atenolol, celiprolol, nadolol) may be necessary. Caution with ACE inhibitors. ACE inhibitors and AT ₁ -receptor antagonists should not be used in renovascular disease
Prostatic hypertrophy	β Blocker	Diuretics
Pregnancy	Methyldopa; β blockers (third trimester)	Consider all other agents
Gout	Centrally acting agents safe	Thiazides
Migraine	β Blocker; clonidine	
Resistant hypertension	α Blocker; minoxidil, hydralazine, sodium nitroprusside	
Depression		Side effect of β blockers, calcium channel blockers, clonidine and methyldopa
Parkinsonism		Indoramin has extrapyramidal side effects

ACE, angiotensin-converting enzyme; AT₁, angiotensin; HOPE, Heart Outcomes Prevention Evaluation; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; PROGRESS, Perindopril Protection Against Recurrent Stroke Study.

that is independent of lipid lowering (Glorioso *et al* 1999; Borghi *et al* 2000; Su *et al* 2000). The concurrent use of a statin would have no bearing on the choice of antihypertensive regimen.

Diabetes mellitus often coexists with hypertension and, as indicated above, may be a compelling reason to use an ACE inhibitor. Clinical trials certainly suggest that ACE inhibitors are less likely to cause diabetes and many clinicians favour them in patients with diabetes to reduce the chances of renal nephropathy. Both thiazides and β blockers may worsen glucose tolerance, so their use in combination is often avoided in diabetes and patients at risk of developing diabetes.

Heart failure is often a consequence of untreated hypertension and, as reviewed in Chapter 15, may well be treated with an ACE inhibitor, diuretic, β blocker or spironolactone, all of which

are also indicated for hypertension. In the case of a β blocker, a very low dose would be introduced in heart failure, initially under the supervision of an appropriately experienced clinician.

Drug interactions

Given the diversity of drugs used in the treatment of hypertension there is a range of drug interactions. Some important interactions of antihypertensive drugs are summarized in Table 11.3.

General counselling

As outlined earlier, lifestyle changes (including weight reduction, increased exercise, smoking

Table 11.3 Summary of important interactions within drugs used in hypertension

Interacting drugs	Consequences	Comments
β Blockers with β agonists	Pharmacological antagonism	Bronchoconstriction may occur due to inhibition of bronchial β_2 -adrenoceptors
α Antagonists with calcium channel blockers or β blockers	Hypotension	Additive effects require close monitoring and counselling
Calcium channel blockers with β blockers	Some combinations are safe (e.g. felodipine and β blockers). Bradycardia and heart block with verapamil or diltiazem and β blockers (avoid combination or monitor closely); dihydropyridines with β blockers are usually safe but should be monitored	Additive negative inotropic effects. Increased plasma levels of β blockers metabolized by the liver
ACE inhibitors with NSAIDs	Risk of renal impairment	Both associated with renal toxicity
Grapefruit juice with nifedipine (and possibly nicardipine, amlodipine)	Increased effects of calcium channel blockers	Inhibition of cytochrome P450, therefore reduced metabolism
Alcohol with antihypertensives	<ul style="list-style-type: none"> • Chronic: increase in blood pressure • Acute: postural hypotension and dizziness 	<ul style="list-style-type: none"> • Evidence of reduced blood pressure when moderate-heavy drinkers taking antihypertensives; reduce alcohol intake • Acutely, alcohol causes vasodilatation

ACE, angiotensin-converting enzyme; NSAIDs, non-steroidal anti-inflammatory drugs.

cessation, a low salt diet and reduction in alcohol consumption) should be advocated. Failure of lifestyle changes alone would then indicate drug treatment. In talking to patients about drug treatment it should be stressed that the purpose is to lower their BP and this should reduce their risk of having a heart attack, stroke or kidney problems. Although hypertension has no symptoms and the drugs may have side effects, it is important to take the drugs; however, if they find the side effects intolerable, they may find that changing their drug is beneficial.

Diuretics

- Diuretics (or 'water tablets') will cause an increase in urine flow, which may subside after a couple of weeks.
- It is best to take the diuretic in the morning to limit sleep disturbance. A dose may be taken later in the day to avoid the need for urination interfering with social engagements during the day.
- Diuretic use in elderly people is associated with increased incidence of falls.
- Diuretics may cause impotence and this should be discussed with the patient.

ACE inhibitors

- Patients may experience pronounced first-dose hypotension that may be worse if the patient is also taking diuretics; it is best to take the ACE inhibitor on retiring to bed at night. Discuss any cough with their GP. Patients should be encouraged to persist with the ACE inhibitor, because this is an effective treatment.
- Consult a pharmacist before purchasing other medicines or supplements, e.g. avoid the use of potassium salts (salt substitute, effervescent preparations, cystitis treatments) and use NSAIDs with caution.
- If patients experience any lip, facial or tongue swelling (angio-oedema), they should stop taking the ACE inhibitor and seek immediate medical advice.

Calcium channel blockers

- Calcium channel blockers may cause flushing, constipation and ankle swelling. Gentle exercise or elevation of the foot may reduce ankle swelling. These side effects should improve after a few weeks. If the side effects become troublesome, patients should discuss this with their general practitioner.
- Avoid grapefruit juice if taking a dihydropyridine.

β Blockers

- Male patients may experience impotence.
- Report any additional breathlessness (due to worsening of symptoms or blockade of bronchial β_2 -adrenoceptors); cold extremities or peripheral weakness may reflect blockade of vasodilator β_2 -adrenoceptors.
- Do not stop taking the tablets suddenly (because this may increase the risk of myocardial infarction). β Blockers should be withdrawn gradually over at least a week.

α Blockers

- Patients should be alert to first-dose hypotension.
- Patients may also experience urinary incontinence.
- Take care when driving, because of possible drowsiness.

Centrally acting drugs

- Take care when driving, because of possible drowsiness.
- Do not stop taking the tablets suddenly (particularly clonidine).

Monitoring

Home and pharmacy blood pressure measurements

Automated devices are available for home monitoring by the patient. These devices measure BP on different principles from auscultation with a sphygmomanometer. Indeed, some devices

measure at the wrist rather than the brachial artery and very few of these are accurate. Hence, they may give differing absolute values and only a few of the devices have been validated: further details may be obtained from the BHS. The machine should be calibrated annually. Other sources of inaccuracy in home measuring may be poor technique such as cuff placing and inadequate resting before measurement.

'White-coat' hypertension is a well-recognized clinical phenomenon whereby the patient's BP is significantly higher when recorded by a doctor, and is thought to be induced by anxiety. In a proportion of cases, 'white-coat' hypertension is so pronounced that patients who are normotensive under normal conditions may be classed and treated as hypertensive on the basis of measurements made by a doctor. However, 'white-coat' hypertension may be eliminated by nurses or patients themselves measuring BP. Similarly, the BHS (O'Brien *et al* 2000) has produced guidelines regarding the use of ambulatory BP monitoring, which also overcomes the problems of 'white-coat' hypertension.

Prior to treatment

The following may be assessed:

- An electrocardiogram (ECG) to test for left ventricular hypertrophy, because up to a third of people with hypertension have left ventricular hypertrophy. There may also be the need for an echocardiogram.
- Electrolytes, especially potassium, because a reduced level may reflect hyperaldosteronism. This is particularly important when initiating diuretics and ACE inhibitors.
- Plasma lipids and glucose: these may be adversely affected by β blockers and diuretics.
- Renal function; plasma creatinine: this will influence drug choice because thiazides, except metolazone, are ineffective in moderate renal failure and ACE inhibitors may make renal impairment worse. Dose reduction with close monitoring is required if glomerular filtration rate (GFR) is <50 mL/min.
- Urinalysis, because protein and/or blood might indicate renal damage.
- Full blood count.

- Liver function test, with mean corpuscular volume to assess for excess alcohol consumption.
- Thyroid function test.

During treatment

- Measurement of BP.
- Monitor renal function and proteinuria (annually).
- Monitor electrolytes, especially potassium, with diuretics and ACE inhibitors.

Over-the-counter considerations

Most patients should be considered for low-dose aspirin therapy because this has been shown to reduce the incidence of myocardial infarction in hypertensive patients. Although NSAIDs should not generally be used with ACE inhibitors or thiazides, low-dose aspirin (75 mg) appears to be safe. Indeed, the HOT trial indicated that low-dose aspirin reduced cardiovascular events but not stroke. The BHS recommends that low-dose aspirin be used in primary prevention in people with hypertension who are aged over 50 years and have controlled BP ($<150/90$ mmHg), and those with end-organ damage, diabetes or a 15% or greater risk of coronary artery disease over 10 years. Even low-dose aspirin is associated with gastric damage and bleeding, to which the patient should be alerted. Ibuprofen may oppose the beneficial effects of aspirin (see Chapter 14).

There is some evidence that fish oil supplementation may cause a modest reduction in BP, although this has not been universally reported. None the less, fish oil supplementation appears a sensible approach to reducing overall cardiovascular risk and is advocated by the American Heart Association (Kris-Etherton *et al* 2002).

Some considerations of over-the-counter (OTC) medicines and their use in hypertension are detailed in Table 11.4.

Alternative remedies

Consideration should be given to herbal preparations and supplements with sympathomimetic

Table 11.4 Summary of the use of over-the-counter (OTC) medicines in hypertension

OTC medicine	Effects	Comments
Low-dose aspirin	Reduces risk of myocardial infarction and stroke	Need to select high-risk patients due to the risk of gastric damage associated with even low doses. Proton pump inhibitor may be used for prophylaxis
Aspirin or ibuprofen	May reduce effects of captopril	Caution: blood pressure should be monitored
Antacids	Aspirin (300 mg) may reduce the effects of enalapril Interaction with ACE inhibitors to reduce their absorption	Paracetamol is a safe alternative analgesic Separate doses
Cimetidine	May increase plasma concentrations of diltiazem and nifedipine	Ranitidine may be used as an alternative
Systemic sympathomimetic decongestants	Weak pressor effects	Use topical agents (if not swallowed), steam or saline drops

ACE, angiotensin-converting enzyme.

activity (see Chapter 4). Diuretic effects of herbal preparations may also increase side effects in combination with antihypertensives.

There has been recent interest in non-pharmacological treatment using devices that aim to lower BP by guiding patients to control their breathing to a rate of 10 breaths/min for a short period each day. However, the effectiveness of these devices requires confirmation in large trials, although small studies have reported modest BP responses. There is also evidence for a lack of efficacy in patients with diabetes and hypertension (Logtenberg *et al* 2007). It could be that these devices may be of benefit in cases of selected patients with mild hypertension or as an adjunct to drug treatment.

Future developments

The currently available drug treatments for hypertension are extensive and, in the absence of a single identifiable cause, future directions are limited. Having said that, renin inhibitors are under investigation as possible novel antihypertensives.

Practice points

- The BHS and NICE have produced joint guidelines. The guidelines recommend the A/CD algorithm. β Blockers are no longer recommended as first-line antihypertensives.
- Most patients do not have their BP adequately controlled by the first drug used.
- Patients should be warned about first-dose hypotension with ACE inhibitors and α blockers (extra caution in combination with diuretics) due to the risk of falls.
- Monitor patients for hypertension secondary to drug treatment, e.g. NSAIDs, oral contraceptives, sympathomimetics, corticosteroids, ketoconazole, moclobemide, venlafaxine and ciclosporin.
- In treatment failure consider OTC drugs, alcohol consumption and compliance.
- The aim of antihypertensive treatment is to reduce cardiovascular risk, reduce/limit end-organ damage, especially kidneys, left ventricular hypertrophy, and reduce the risk of heart failure.
- Aim for BP control without unacceptable side effects, because hypertension is generally asymptomatic.
- Always enquire about side effects, particularly impotence.

Self-assessment

Consider whether the following statements are true or false. In the management of hypertension:

1. ACE inhibitors are associated with causing first dose hypotension.
2. Thiazide diuretics are most effective at lowering blood pressure in patients with moderate-to-severe renal impairment.
3. β Blockers should be avoided in concurrent ischaemic heart disease.
4. Most patients require more than one drug to control their BP to target levels.
5. AT₁-receptor antagonists are usually used in combination with ACE inhibitors.



CASE STUDY

Mr AH was found by his GP during a routine check-up to have a BP of 180/100 mmHg. Mr AH is 58 years old, smokes 20 cigarettes a day, drinks 'several pints each night', has a body mass index (BMI) of 28, but is otherwise healthy. His father died of 'heart trouble' in his 50s.

1. What would be the first steps in the management of Mr AH?
 - 180/100 mmHg is moderate hypertension; there is a need to confirm that this is sustained on several occasions (typically, three readings over 2 months). There is also a need to exclude 'white-coat' hypertension. In the meantime this is not a medical emergency. It is important to encourage the patient to 'own' the problem and to change his risks, rather than simply leave it as a problem to be solved with tablets. He should be advised to reduce alcohol intake (a risk factor for essential hypertension), reduce his BMI to <25 (risk factor), cease smoking (although not a risk factor for hypertension, smoking greatly enhances the cardiovascular risk from hypertension; smoking is a major risk factor for ischaemic heart disease) and increase exercise.
- Two months later Mr AH's BP was 170/98 mmHg.
2. Suggest clinical tests that might be carried out:
 - if not carried out at the initial appointment, physical examination: retina for vascular damage, auscultation of heart (and kidneys for renal bruits?)
 - ECG to test for left ventricular hypertrophy (up to a third of people with hypertension have left ventricular hypertrophy)
 - echocardiogram to determine his ejection fraction
 - electrolytes – especially potassium (a reduced level may reflect hyperaldosteronism; Conn's syndrome)
 - plasma lipids, cholesterol, glucose
 - renal function: plasma creatinine (this may influence drug choice; thiazides, except metolazone, are ineffective in moderate renal failure)
 - urine: protein/blood may indicate renal damage
 - the above would be the ideal, but monitoring may be poor in the community, which may lead to increased hospitalization, e.g. hypokalaemia.

continued


CASE STUDY (continued)

3. What active treatment is he likely to receive?
 - According to the A/CD rules he should be prescribed a thiazide or calcium channel blocker as a first pharmacological step.

Following 2 months of treatment with 2.5 mg bendroflumethiazide tablets every morning his BP is now 166/96 mmHg.
4. Why was the bendroflumethiazide every morning?
 - The diuresis would interfere with sleep if taken at night.
5. Given the poor response to bendroflumethiazide, should the dose be increased to 5 mg?
 - With thiazides, increasing the dose has no additional benefit and increases the side effects. Also, thiazides become ineffective in moderate renal failure – this could of course be the explanation for the failure of the thiazide, and so it may be worth measuring creatinine levels.
6. Draw up a plan with the various steps to continue the patient's management:
 - step 1: thiazides as a first pharmacological step. Cheap and effective. Potassium supplements are not normally needed but plasma potassium should be checked after 3–4 weeks
 - step 2: add an ACE inhibitor as step 2 of the A/CD rules
 - step 3: add a long-acting calcium channel blocker
 - step 4: consider an α blocker, a β blocker or additional diuretic.
7. What counselling is appropriate for Mr AH if he subsequently receives lisinopril (2.5 mg/day) in addition to bendroflumethiazide?
 - He may experience a dry cough, which he should report to his GP. He should take the first dose of lisinopril at night and the diuretic in the morning due to the risk of first-dose hypotension.
9. What are the goals of treatment for Mr AH?
 - target BP of systolic <140 mmHg and diastolic <90 mmHg; lowering diastolic BP by 5 mmHg reduces the risk of ischaemic heart disease by 21%
 - reduce cardiovascular risk (both stroke and myocardial infarction)
 - reduce/limit end-organ damage, especially the kidneys
 - reduce the risk of heart failure
 - BP control without unacceptable side effects, because hypertension is generally asymptomatic.

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Online resources

www.bhf.org.uk

The website of the British Heart Foundation, providing patient information (accessed April 2008).

www.bpassoc.org.uk

The website of the Blood Pressure Association, providing patient information (accessed April 2008).

www.bhsoc.org

The website of the British Hypertension Society, providing professional guidance, including the validation of BP-measuring devices (accessed April 2008).

