Hypertension

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Abstract

Hypertension is one of the most prevalent modifiable conditions contributing to global morbidity and mortality. It is a risk factor for cardiovascular and renal disease as well as cognitive decline and premature death. In the UK, hypertension affects around a quarter of adults and accounts for 1 in 8 consultations in primary care. Despite the wide availability of suitable medicines, only approximately 21% of hypertensive patients have their blood pressure adequately controlled. Effective management of hypertension mandates assessment for target organ damage and potential secondary causes. Accurate blood pressure measurement is crucial for diagnosis and can require recordings to be made in the clinic and at home, as well as using ambulatory methods. Treatment depends on both blood pressure level and total cardiovascular risk. Evidence-based treatment algorithms exist to simplify the approach to treatment, and most patients require at least two medications to achieve adequate control. Severely elevated blood pressure can lead to acute organ failure that requires emergency treatment. Routine management of hypertension relies on careful combinations of different classes of drugs and titration of dosage, as well as patient education, lifestyle modifications and adherence to therapy.

Keywords Ambulatory blood pressure monitoring; antihypertensive medications; blood pressure; cardiovascular risk; hypertension; resistant hypertension; secondary hypertension

Key points

- Diagnosis of hypertension requires ambulatory or home blood pressure (BP) monitoring; both have been shown to be superior to clinic BP measurements in the diagnosis and prognosis of hypertension. Although clinic BP is still recommended for monitoring within the clinical setting, home BP monitoring has been shown to improve patient engagement and adherence
- Most patients require a combination of at least two antihypertensive medications to reach their target BP. American and European guidelines advise the initiation of two classes of pharmacotherapy concomitantly at diagnosis, whereas UK guidance recommends starting with monotherapy
- Patients with resistant hypertension and young patients with hypertension should be referred for expert evaluation

Introduction

Hypertension is the largest attributable risk factor for mortality worldwide, and is responsible for more than half of all instances of stroke and coronary heart disease (CHD). Blood pressure (BP) is continuously related to both cardiovascular disease (Figure 1) and chronic kidney disease. However, to simplify decisions on diagnosis and pharmacotherapy, threshold levels of BP are used. This article gives an overview of the important features of hypertension, relating to causes, diagnosis, evaluation and management.

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Epidemiology

The prevalence of hypertension is rising. The World Health Organization estimates that 1.28 billion adults worldwide currently have hypertension, a number that has doubled since 1990. This increase is largely attributed to population growth and ageing.[1] Hypertension remains untreated in 42% of these individuals. Disappointingly, BP is controlled to guideline-driven targets in only 50% of hypertensive patients advised to take treatment.[2] In the UK, a quarter of adults have hypertension. It accounts for 12% of all primary care consultations and £2.1 billion of the NHS health expenditure.[3]

BP rises with increasing age, and with it the prevalence of hypertension. This is thought to reflect environmental and lifestyle factors, as well as changes in haemodynamics caused by arterial stiffness in the major elastic arterial vasculature, notably the aorta. Increased arterial stiffness causes augmentation of systolic BP (SBP) and diminution of diastolic BP (DBP), which is also responsible for the increasing prevalence of isolated systolic hypertension in elderly individuals.

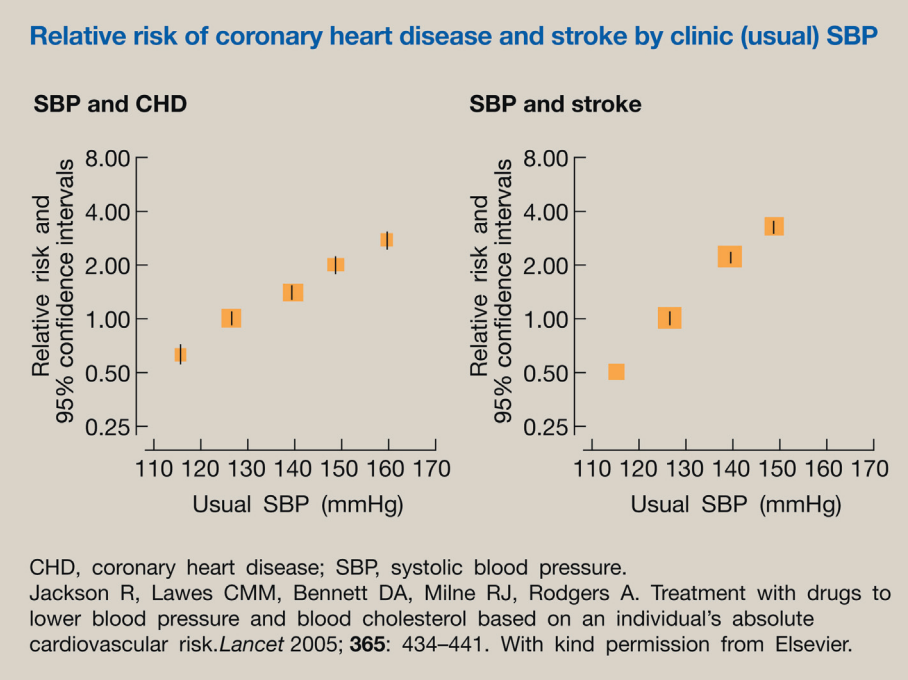
Men tend to have higher BP levels than women up to the age of 65 years, but after this the relationship is reversed. People from certain ethnic groups are disproportionately affected by hypertension. The highest prevalence is among black African Caribbean men and women.

Aetiology

Primary hypertension

Hypertension is thought to arise from the interplay of multiple genetic traits that individually are responsible for only small increases in BP, but collectively could be responsible for 30–50% of individual variation; environmental and lifestyle factors elevating BP are responsible for the rest.

Commonly implicated medicines/drugs or foodstuffs that increase BP include non-steroidal anti-inflammatory drugs,



CHD, coronary heart disease; SBP, systolic blood pressure.
Jackson R, Lawes CMM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk.*Lancet* 2005; **365**: 434–441. With kind permission from Elsevier.

Figure 1

corticosteroids, calcineurin inhibitors, hormonal oral contraceptives and female hormone replacements, stimulant sympathomimetic medications and illicit drugs, liquorice, salt (sodium chloride) and alcohol. Furthermore, a sedentary lifestyle and poor dietary fruit and vegetable intake, as well as high saturated fat and carbohydrate-rich diets that lead to obesity, also contribute. In addition, psychosocial stress is being increasingly recognized as a driver for elevated BP. In cases with no single identifiable cause for hypertension, the term *primary hypertension* is preferred to the historical term *essential hypertension*.

Secondary hypertension

In 5–15% of hypertensive patients, an identifiable and possibly reversible or treatable cause for hypertension can be found through careful assessment. These aetiologies are broadly categorized into renal, vascular, endocrine and neural (see below). In young patients (aged <40 years), individuals with a sudden onset of severe hypertension, and those with *resistant hypertension* (uncontrolled BP despite taking at least three antihypertensive medicines, including a diuretic), the prevalence of secondary causes increases to 20–60%.The most common secondary causes in resistant hypertension are obstructive sleep apnoea (OSA; through sympathetic overdrive) and primary hyperaldosteronism (Conn adenoma or bilateral adrenal hyperplasia, causing mineralocorticoid excess).

Hypertensive emergencies

Hypertensive emergencies are defined as presentations with severe hypertension (usually SBP ≥180 mmHg and/or DBP ≥110mmHg) and evidence of acute, evolving hypertension-mediated organ damage (HMOD) necessitating urgent and careful BP reduction to prevent further deterioration and fatality. HMOD is also referred to as target organ damage.

These emergencies can present in a number of ways depending on the underlying cause and organs affected. Cardiovascular hypertensive emergencies include acute aortic dissection, myocardial ischaemia or heart failure. Neurological presentations of hypertensive emergencies include acute stroke or encephalopathy. Malignant hypertension, a somewhat outdated term, is another emergency presentation; it refers to elevated BP associated with advanced hypertensive retinopathy, often accompanied by acute kidney injury and neurological signs. Hypertensive emergencies can occur in pregnancy, leading to conditions such as pre-eclamptic toxaemia. Other important causes include phaeochromocytoma and the ingestion of sympathomimetic drugs such as cocaine, although most commonly it results from worsening primary hypertension.

Management depends on the exact presentation, but the general approach is to promptly reduce BP or mean arterial pressure to prevent or reverse target organ damage, but in a controlled manner to avoid ischaemia resulting from tissue hypoperfusion. Most presentations require immediate BP reduction to specific targets; for example, in acute aortic dissection, guidance advises immediate SBP reduction to <120 mmHg.[4] These conditions are often managed in a high-dependency environment because of clinical acuity and the need for invasive BP monitoring and intravenous drug therapy.

If there is no evidence of acute target organ damage, severe hypertension (archaically referred to as a hypertensive urgency) can be treated with routine oral antihypertensive pharmacotherapy as well as assessment for and management of the drivers of an acute elevation of BP such as pain or stress. Patients presenting with severe hypertension do not usually require admission for this and can be discharged after a brief period of observation, with uptitration of oral medications.

Diagnosis and evaluation

Hypertension is normally asymptomatic, although many patients ascribe symptoms such as epistaxis, headaches, lethargy and dizziness to their raised BP. Hence, clinical assessment should be tailored to four key questions:

1. Is the patient truly hypertensive?
2. Is there evidence that hypertension has caused complications such as HMOD or major cardiovascular events?
3. Is a secondary cause identifiable?
4. What is the individual's total cardiovascular risk?

BP thresholds for diagnosis

This article mostly refers to three of the main hypertension guidance documents: the UK guidance provided by the National Institute for Health and Care Excellence (NICE)[3]; European guidance from the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)[4]; and American guidance from the joint American College of Cardiology (ACC) and American Heart Association (AHA) task force.[5]

Although BP is a continuous physiological parameter, thresholds for diagnosis are required to guide management. For the most part, hypertension is diagnosed in patients who have a clinic SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg, or daytime ambulatory or home monitoring averages of SBP $\geq$135 mmHg and/or DBP $\geq$85 mmHg.[3,4]

The terms 'grades' and 'stages' are both used to classify degrees of hypertension. NICE guidance refers to the categories as stages.[3] The ESC/ESH guidance refers to them as grades.[4] Table 1 outlines a summary of these thresholds from the NICE and ESC/ESH guidance. ACC/AHA guidance refers to 2 hypertension stages: stage 1 is diagnosed when SBP is 130–139 mmHg or DBP is 80–69 mmHg, and stage 2 refers to BPs above this.[5] For simplicity, the ESC/ESH guidance grade system will be used in this article.

BP measurement

BP is an inherently unstable biological variable, subject to seasonal, circadian, hormonal and immediate external influences. As such, a single point measure is unlikely to represent the individual's usual BP. It is particularly important to remember this when making a diagnosis or treating a patient for a disease that is largely asymptomatic, with the purpose of mitigating future cardiovascular and renal risk. It is established practice to take multiple BP readings at one sitting, and to repeat BP measurements over several clinical encounters, to account for regression to the mean and obtain readings that more closely resemble the usual BP.

Currently, the most commonly used method of measuring BP in clinical practice involves validated, semi-automatic, oscillometric devices with appropriately sized cuffs. This also allows for out-of-office BP measurements (see below). There are now a wide range of validated devices with cuffs for both upper arm and wrist. However, these oscillometric monitors are not entirely accurate in individuals with irregular arrhythmias, such as atrial fibrillation, in whom manual aneroid auscultation should be used instead.

There is growing interest in cuffless BP monitoring devices although none have yet been approved for clinical use. New validation protocols need to be agreed ahead of independent validation studies of such devices before they can be recommended for personal or clinical use.

Clinic (office) BP measurement: most experience of measuring BP and assessing the beneficial effects of treating hypertension relates to recordings made in the presence of a health professional (clinic or office BP). International guidelines require at least two or three sequential recordings obtained from the non-dominant arm (unless BP in the dominant arm is >10 mmHg higher than in the non-dominant arm, in which case the arm with higher BP levels is used), in a seated position after at least 5 minutes' rest. Guidelines vary on whether the lowest of these readings or the mean of the lowest two readings should be used to indicate the true clinic BP.[3–5]

Out-of-office BP measurements: out-of-office BP measurements refer to either ambulatory or home BP measurements. These are more predictive of hypertension-related outcomes than clinic BP and are particularly useful for long-term monitoring of BP control as they allow multiple recordings to be made between clinic visits. Involving patients in the management of their condition also improves engagement and satisfaction.

Furthermore, this approach can detect both white-coat hypertension (high clinic BP but normal out-of-office BP) and masked hypertension (normal clinic BP, high out-of-office BP) (Table 1). White-coat hypertension is estimated to account for 30–40% of patients with an elevated clinic BP. Masked hypertension can be identified in around 15% of patients with a normal clinic BP. This is very important as these conditions can lead to over- and undertreatment, respectively. They are also both associated with increased cardiovascular risk compared with patients with normal clinic and out-of-office BPs. Home BP is usually 5–10 mmHg lower than equivalent clinic recordings, although this is exaggerated and reversed in white-coat hypertension and masked hypertension, respectively.

Ambulatory BP monitoring is increasingly used for diagnosis and monitoring. Ambulatory monitoring can also rule out white-coat hypertension in a single event, provide multiple readings to allow improved diagnostic accuracy, and provide a night-time BP profile. For example, a failure of nocturnal dipping by <10% compared with daytime readings could indicate underlying OSA. Furthermore, nocturnal BP is an even stronger predictor of cardiovascular outcomes than daytime BP. Thus, ambulatory BP monitoring is mandated by the latest NICE guidelines when making a diagnosis of hypertension, unless this is unsuitable or the patient cannot tolerate it, and then home BP monitoring is advised.[3]

For continued monitoring after diagnosis, however, clinic BP is considered more appropriate, especially as no major outcome clinical trials have used ambulatory or home monitoring to guide pharmacotherapy.[4]

Postural BP measurement: NICE guidance recommends measuring standing and seated BP in hypertensive patients who are aged 80 years or more, or have type 2 diabetes or known postural hypertension. In individuals with a significant BP postural drop or symptoms suggestive of orthostatic hypotension, the advice is to use the standing BP to guide management.[3]

Definitions and classification of BP levels/patterns by different methods of measurement

Category	Clinic BP (mmHg)		Ambulatory BP (mmHg)	
	SBP	DBP	SBP	DBP
Optimal BP	<120	<80	n/a	n/a
Normal BP	120–129	85–84	n/a	n/a
High-normal BP	130–139	85–89	n/a	n/a
Grade/stage 1 hypertension	140–159	90–99	135–149	85–94
Grade/stage 2 hypertension	160–179	100–109 (ESC/ESH) or 100–119 (NICE)[a]	>150	>95
Grade/stage 3 hypertension	≥180	≥110 (ESC/ESH) or ≥120 (NICE)[a]	n/a	n/a
Isolated systolic hypertension	≥140	<90	≥135	<85
White-coat hypertension	≥140	≥90	<135	<85
Masked hypertension	<140	<90	≥135	≥85

The highest categorization of DBP and/or SBP is used for the diagnosis of different grades of hypertension. Diagnosis using ambulatory BP monitoring requires only daytime mean (>14 readings to be valid).[3]
n/a, not applicable.
Data adapted from the ESC/ESH (Williams et al. 2018)[4] and NICE (2019)[3] guidelines.
[a] This indicates where NICE and ESC/ESH guidance BP thresholds differ.

Table 1

History

A comprehensive medical history should be obtained including:

- evaluation of previous major cardiovascular events, such as myocardial infarction, stroke, peripheral arterial disease, heart failure and chronic kidney disease
- current and previous BP measurements, in particular home BP measurements
- current and previous medication history (with intolerances or adverse effects and compliance); medicines and drugs that interfere with BP should be specifically asked about (see above), as should the use of over-the-counter, herbal or traditional medicines
- family history, especially of premature vascular disease
- in women, specifically seeking evidence of previous pregnancy-related hypertensive disorders as well as the timing of the onset of the menopause where applicable
- lifestyle evaluation: dietary assessment is notoriously imprecise, but salt intake can be estimated by asking about the consumption of high-salt containing foodstuffs and whether individuals add or cook with salt; alcohol and smoking status should be clarified
- secondary causes, which can be suggested by accompanying symptoms such as abnormal sweating (phaeochromocytoma, OSA, acromegaly), palpitations and anxiety (phaeochromocytoma), postural and postprandial symptoms (autonomic dysfunction) and witnessed nocturnal apnoeas or daytime somnolence (OSA).

Examination

Examination should focus on assessing for evidence of both HMOD and secondary causes. HMOD can be assessed in three systems: ophthalmic, cardiovascular and renal.

Direct fundoscopy can reveal different grades of hypertensive retinopathy such as silver wiring (grade 1) and arteriovenous nipping (grade 2), which represent HMOD that is commonly seen in long-standing, poorly controlled hypertension. Flame haemorrhages (grade 3) or papilloedema (grade 4) and severe hypertension indicate a diagnosis of *malignant hypertension*, mandating immediate antihypertensive therapy (see above). Cardiovascular examination should include looking for asymptomatic, atherosclerotic arterial disease, such as carotid and femoral bruits and abdominal aortic aneurysms. Use of microalbuminuria and proteinuria urine-testing strips can quickly assess renal HMOD at the bedside.

The individual's general appearance can suggest an underlying endocrinopathy (see Table 2 for a list). Vascular examination in patients with coarctation can reveal disproportionately cool lower limbs with reduced pulses and either radio-radial or radio-femoral delay, depending on the location of the stenosis. A significant coarctation normally produces a large systolic murmur best heard in the interscapular region. Renal bruits can signify either atherosclerotic renal artery stenosis or fibromuscular renal artery dysplasia; both warrant further investigation. Polycystic kidneys should be easily ballotable in the flanks.

Investigation

Investigations should be directed towards exploring underlying asymptomatic HMOD and secondary causes and providing a full cardiovascular risk profile. All hypertensive patients should be offered the following:[4]

- Serum electrolytes, estimated glomerular filtration rate and albumin:creatinine ratio estimation aid the detection of asymptomatic chronic kidney disease. In addition, hypokalaemia associated with mineralocorticoid (and glucocorticoid) excess may be identified.
- Lipid profile, fasting plasma glucose and glycated haemoglobin allow cardiovascular risk estimation equations, such as QRISK3, to be completed.
- An electrocardiogram can detect electrical left ventricular hypertrophy as well as atrial fibrillation, which influences the selection of the device used to diagnose and monitor BP accurately (transthoracic echocardiography or cardiac

magnetic resonance imaging can be used in specialist settings to give greater sensitivity and specificity for left ventricular hypertrophy).
- Renal imaging, such as renal ultrasonography, can assess renal parenchyma.

Other investigations to look for secondary causes are patient-specific, depending on the pre-test probability from the history and examination, and the usefulness of making an underlying diagnosis (Table 2). All relatively young patients (aged <40 years) and those with resistant hypertension should be fully evaluated for secondary causes.[3,4] A 24-hour urine collection for electrolytes can estimate salt intake.

Common secondary causes of hypertension and their diagnostic tests

Secondary causes	Diagnostic test
Renal	
Chronic kidney disease (any aetiology)	Plasma creatinine and electrolytes, eGFR, protein:creatinine or albumin:creatinine ratio Renal ultrasound
Polycystic kidney disease	Renal ultrasound
Reninoma	Plasma renin activity
Page kidney (subcapsular compression)	Renal ultrasound
Monogenic tubular syndromes (e.g. Liddle, Gordon)	Plasma electrolytes, plasma aldosterone
Vascular	
Coarctation of aorta	Echocardiogram CT/MR of the aorta
Renovascular diseases	Doppler ultrasonography of the renal arteries CT/MR renal angiography
Atherosclerotic renal stenosis	CT/MR renal angiography
Fibromuscular dysplasia	CT/MR renal angiography
Endocrine	
Hyperaldosteronism	Aldosterone:renin ratio
Hypercortisolaemia	24-hour urinary free cortisol Low-dose dexamethasone suppression
Phaeochromocytoma	Plasma or 24-hour urine metanephrines
Acromegaly	Serum IGF-1, glucose tolerance test
Hyperthyroidism/hypothyroidism	Thyroid function tests
Disorders of corticosteroid synthesis	Measurement of urine corticosteroid precursors
Hyperparathyroidism	Parathyroid hormone, Ca^{2+}
Neural	
OSA	Full polysomnography
Autonomic failure	Autonomic function testing
Other	
Pregnancy	Urine or serum β-hCG

CT, computed tomography; eGFR, estimated glomerular filtration rate; hCG, human chorionic gonadotropin; IGF-1, insulin-like growth factor-1; MR, magnetic resonance.

Table 2

Management

Hypertension is treated to reduce the risk of major cardiovascular and renal events. Therefore, treatment in isolation from other modifiable cardiovascular risk factors (hyperlipidaemia, diabetes mellitus, smoking, obesity) is inappropriate. Cardiovascular risk equations such as QRISK3 are useful for integrating different risk factors, to judge when to treat asymptomatic patients and to provide continuing patient education.

Threshold for treatment and targets

BP is a continuous variable. Cardiovascular risk increases in cohort studies at all levels of clinic BP >115/75 mmHg. However, from intervention trials in uncomplicated hypertension, there is limited evidence to support antihypertensive treatment in patients with a clinic BP <140/90 mmHg.[4] In individuals with high-normal BP and low-moderate cardiovascular risk, lifestyle interventions are advised in the first instance.

For patients with grade 2 and 3 hypertension, or grade 1 hypertension with high cardiovascular risk or HMOD, the recommendation across the international guidelines is management with drug therapy.[3–5] In patients with grade 1 hypertension and low cardiovascular risk, guidance varies because of the lack of robust evidence in this group. The ESC/ESH advise lifestyle interventions in the first instance.[4] NICE guidance advises considering drug treatment in this group alongside lifestyle changes.[3] ACC/AHA guidance recommends commencing pharmacotherapy in these patients.[5]

In elderly individuals (>80 years), there is less evidence for treating grade 1 hypertension, and the management of hypertension is complicated by augmented postural BP variations and associated morbidity. Trials have evaluated target BPs in which the cardiovascular risk reduction outweighs the risk of treatment-related complications.[4] The Hypertension in the Very Elderly Trial (HYVET), the largest BP study aimed at the older population, demonstrated that a target BP of 150/80 mmHg was associated with large reductions in cardiovascular morbidity. The guidelines differ slightly in values for initiating drug therapy in the elderly (see Further reading). ESC/ESC guidance suggests starting drug therapy when clinic BP is ≥160/90 mmHg, whereas NICE guidelines recommend using a threshold of ≥145/90 mmHg.[3,4]

Lifestyle interventions

All patients should be counselled and supported to introduce and maintain proven lifestyle interventions to lower BP and cardiovascular risk (Table 3).

Pharmacotherapy

Most patients require at least two medications to control BP. Medications from different classes are combined in order to target multiple pathophysiological processes (Table 4). A combination of different classes is significantly more effective than increasing the dose of a single agent, which increases the risk of adverse effects (see Further reading).

Lifestyle interventions

Intervention	Approximate SBP reduction
Regular aerobic exercise (30 minutes/day)	5–8 mmHg
Weight reduction (body mass index <25 kg/m^2 or waist circumference <102 cm in men, <88 cm in women)	1 mmHg per 1 kg weight loss
DASH eating plan – increased fruit and vegetables, low-fat dairy products, reduced saturated and total fat intake	11 mmHg
Dietary salt reduction <6 g sodium chloride per day	5–6 mmHg
Enhanced dietary potassium 3500–5000 mg per day	4–5 mmHg
Alcohol (men <2 units/day, women <1 unit/day)	4 mmHg

DASH, Dietary Approach to Stop Hypertension.
Source: ACC/AHA guidelines. Whelton et al. 2017.[5]

Table 3

Guidelines differ regarding starting with monotherapy or combination therapy (perhaps in a fixed-dose combination single tablet), particularly in individuals found at the outset to have severe hypertension and those with high total cardiovascular risk. In the UK, monotherapy is advised (Figure 2) whereas European (Figure 3) and American guidance advocates a combination approach.[4,5]

The updated 2019 NICE guidance places emphasis on the presence of type 2 diabetes in deciding drug class, advising angiotensin-converting enzyme inhibition or angiotensin II receptor blockade as the first step in these patients. For individuals without type 2 diabetes, management is directed using age and ethnicity as a surrogate for plasma renin status: older age (aged >55 years) and African/Caribbean ethnicity are associated with low plasma renin activity; these patients are less responsive to therapies targeted at the renin–angiotensin–aldosterone system (RAAS) so should be offered a calcium channel blocker instead.

Timing of pharmacotherapy: studies evaluating circadian patterns of BP variability and health outcomes indicate that the sleeping or night-time mean is a better predictor of cardiovascular morbidity than the awake or total 24-hour mean. Most

Main classes of antihypertensive medication

Class	Example	Mode of action	Frequency of administration	Adverse effects/monitoring/notes
ACEi, ARB	Ramipril, losartan	Reduce angiotensin II-mediated vasoconstriction	Once or twice daily	Reversible renal decline, cough, angioedema ACEi contraindicated in bilateral renal artery stenosis
CCB (dihydropyridine)	Amlodipine	Peripheral vasodilator	Once daily	Peripheral oedema, tachycardia, gum hyperplasia
CCB (non-dihydropyridine)	Diltiazem	Peripheral vasodilator; negatively chronotropic	Once or twice daily as a modified-release formulation	Peripheral oedema, bradycardia, constipation. Do not co-prescribe with β-adrenoceptor blockers
Diuretic (thiazide-like)	Indapamide	Vasodilator and salt/water excretion	Once daily	Hypokalaemia/hyponatraemia, hyperuricaemia, Hyperglycaemia. Avoid nocturnal dosing
Mineralocorticoid receptor antagonist	Spironolactone	Salt/water excretion	Once daily	Hyperkalaemia, painful gynaecomastia Avoid if eGFR <30 ml/minute/1.73 m^2
β-Adrenoceptor blockers	Atenolol	Inhibit renin secretion; negatively inotropic/chronotropic	Once daily	Bradycardia, bronchospasm, disturbed sleep, lethargy. Do not co-prescribe with non-dihydropyridine CCB
α-Adrenoceptor blockers	Doxazosin	Peripheral vasodilator	Twice daily	Postural hypotension, urge incontinence, peripheral oedema
Central agent	Clonidine	Reduce central sympathetic outflow	Three times daily	Dry mouth, disturbed sleep, sedation Be wary of rebound hypertension at end of use

Different classes of medicines used for hypertension and their mode of action, important and common adverse effects, monitoring requirements. For a comprehensive list of significant medicine–medicine interactions, please consult the *British National Formulary*.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate.

Table 4

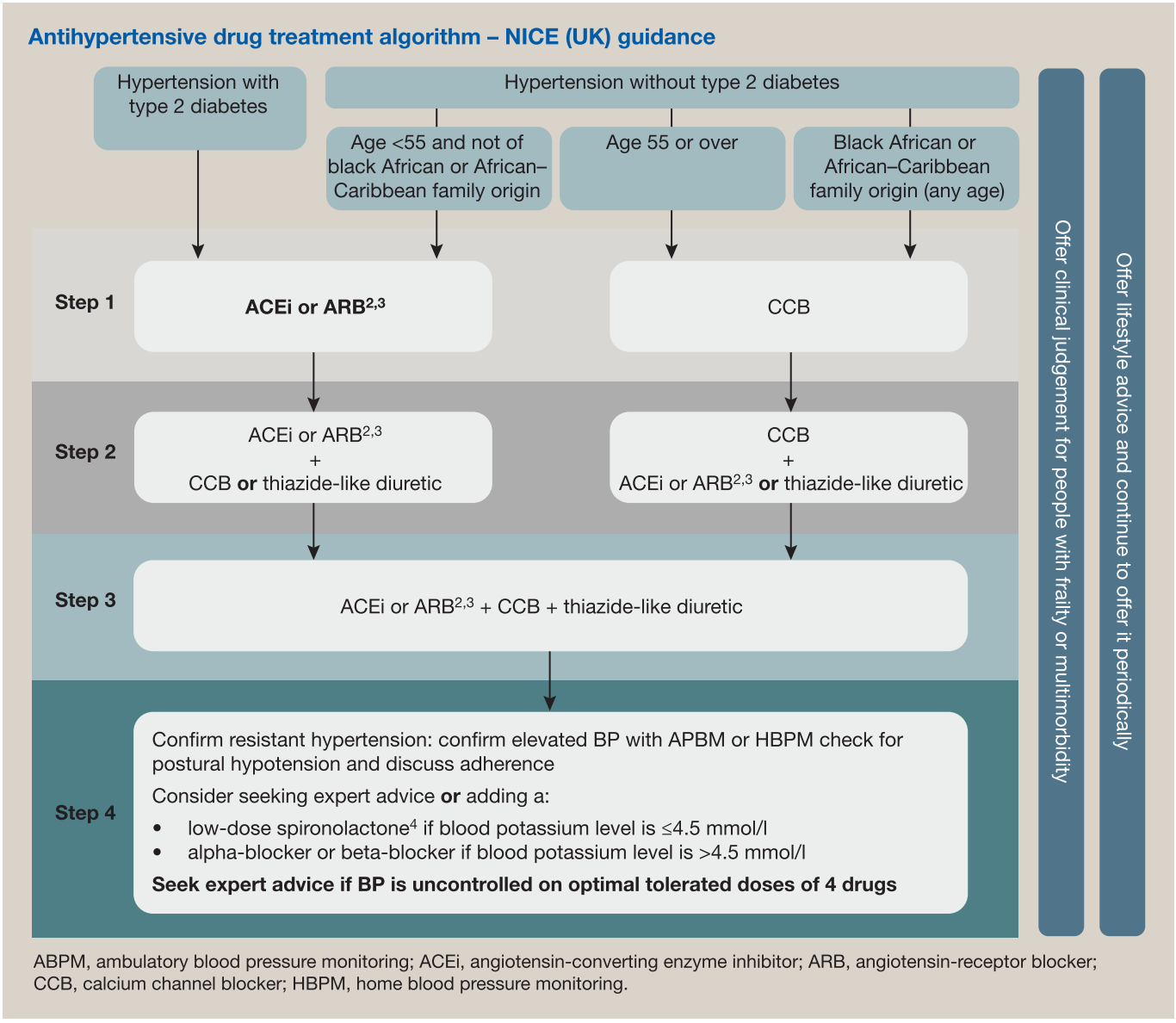


Figure 2 Source: NICE guideline (2019).[3]

cardiovascular medications, including antihypertensive agents, are administered in the morning. Large outcomes studies investigating routine morning or bedtime dosing of antihypertensive medication are in progress. Current available guidance does not feature chronotherapeutic antihypertensive strategies.

Special pharmacotherapeutic considerations

Resistant hypertension: resistant hypertension is defined as uncontrolled BP despite maximally tolerated doses of three classes of antihypertensive medication, including a diuretic.[4] It affects 10–15% of all treated hypertensive patients.[4] It is recommended that primary care professionals refer patients with resistant hypertension for specialist evaluation to assess for secondary causes and optimize treatment.[3]

Non-adherence: for patients in whom the current treatment fails to adequately control BP, particularly those diagnosed with resistant hypertension, non-adherence to prescribed medications could be a contributing factor and should be explored. Non-adherence to medications presents a major clinical challenge, particularly in hypertension, where treatment for a largely asymptomatic condition can result in adverse effects. Improving adherence requires an individualized approach that aims to identify barriers and work collaboratively with patients to overcome them.

Specialists are increasingly attempting to determine patient compliance using tests such as observed tablet-taking with subsequent BP measurements, and analytical drug (or drug metabolite) assays in urine and plasma. Using urine drug metabolite assays, it has been estimated that non-adherence is as high as 40%[4]; therefore the use of these techniques in routine clinical practice might improve the identification of poorly controlled BP caused by non-adherence versus true drug-resistant hypertension.

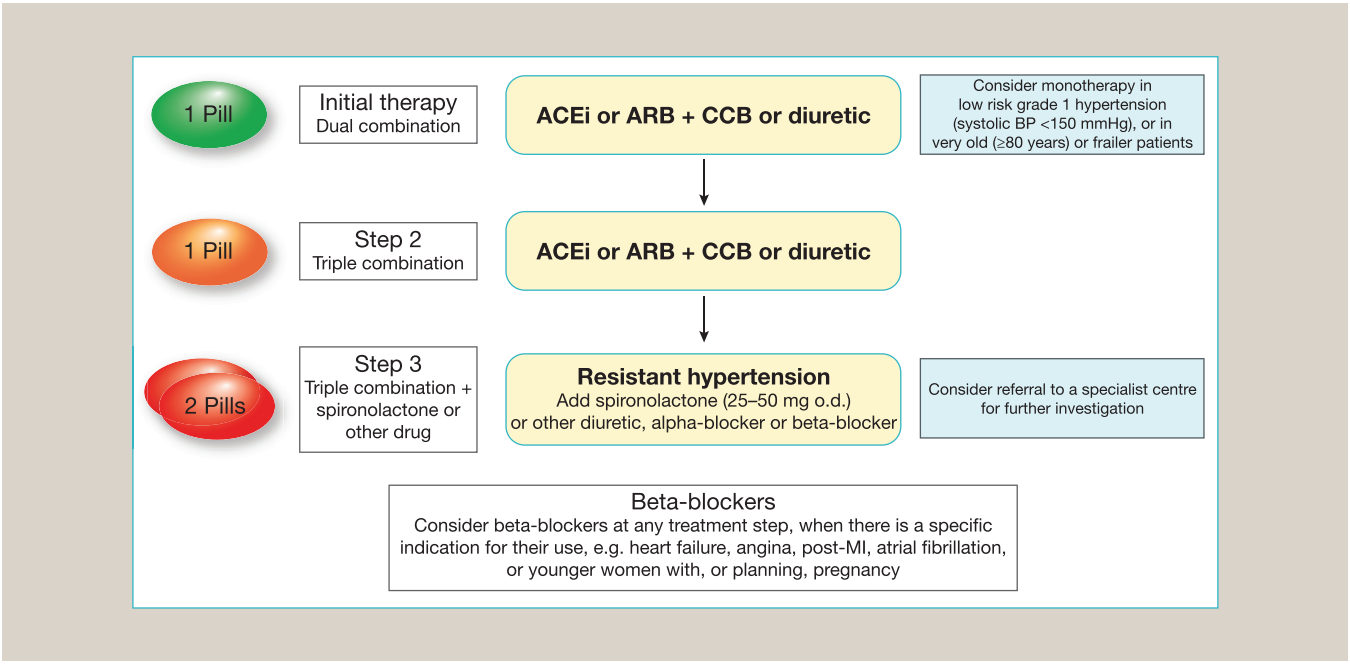


Figure 3 Antihypertensive drug treatment algorithm – ESC/ESH guidance. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium channel blocker; MI, myocardial infarction; o.d., omni die (every day). Reproduced with permission from Williams et al. (2018).[4]

Multiple drug intolerance (MDI): there can be challenges in achieving adequate BP control in individuals who have had several adverse drug reactions. MDI syndrome is diagnosed in those who have had non-immunological reactions to three or more classes of medications. This has a prevalence of 2–5% in the general population, but in a single-centre study of hypertensive patients referred to a tertiary BP centre, MDI was identified in >10% (see Further reading). This study used a stratified approach to manage drug treatment in these hypertensive patients and demonstrated improved BP control through the use of novel antihypertensive strategies such as fractional dosing of solid forms of medications, liquid formulations and transdermal preparations.

Device-based therapies

Interventional technologies are an emerging therapeutic area for the treatment of resistant hypertension. Currently, these are predominantly used in research settings, and further robust evidence is required to assess long-term efficacy and safety before they are recommended for use in standard clinical care.

Carotid baroreceptor stimulation or baroreflex amplification therapy: carotid baroreceptors play an important role in the adrenergic control of BP. Stimulation of these receptors reduces sympathetic outflow and decreases BP. This can be achieved either externally, using an implantable pulse generator, or internally, with an implantable device that distends the carotid bulb. Randomized controlled trials with sham-operations have shown a sustained reduction in BP using these devices but more research is still required with a view to gaining insight into the longer term safety and efficacy.[4]

Renal denervation: the renal vasculature and RAAS are influenced by sympathetic control. Renal denervation involves using methods such as radiofrequency or ultrasound energy to interrupt the sympathetic neural drive to the kidneys. Modest BP-lowering effects have been shown in studies such as the RADIANCE SOLO and SPYRAL trials and no safety signal has emerged in the medium term (3–5 years) (see Further reading). ◆

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