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Hypertension

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Competing interests: none

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Competing interests: none.

Abstract

Hypertension has high prevalence in the general population, accounts for one in every eight consultations in primary care and is a major risk factor for cardiovascular and renal disease. Despite the wide availability of suitable medicines, only about 25% of all hypertensive patients have their blood pressure controlled adequately. Effective management of patients with hypertension mandates assessment for asymptomatic target organ damage and also for potential secondary causes. Accurate blood pressure measurement is crucial for diagnosis and may require recordings to be made in the clinic and at home, as well as use of ambulatory methods. Treatment is dependent not only on blood pressure level but also on total cardiovascular risk. Evidence-based treatment algorithms exist to simplify the approach to treatment and most patients require at least two medicines to achieve control. Severely elevated blood pressure can lead to acute organ failure that requires emergency treatment but routine management of hypertension relies on the careful combination of different classes of drug and titration of dosage.

Keywords

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

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Introduction

Blood pressure (BP) is continuously related to both cardiovascular (CV) diseases and chronic kidney disease (CKD) (Figure 1). However, to simplify decisions about diagnosis and pharmacotherapy, threshold levels of BP are used in all international guidelines on the management of clinic systolic BP (SBP) >140 mmHg and/or diastolic BP (DBP) >90 mmHg[1,2] (Table 1).

Epidemiology

Hypertension is the largest attributable risk factor for mortality worldwide, and is responsible for more than half of all stroke and coronary heart disease (CHD). The burden of the problem is increasing, with predictions that one-third of adults worldwide will have hypertension by 2025. Despite public health programmes and effective pharmacotherapy for hypertension in developed economies, approximately 25% of adults have hypertension. Hypertension remains untreated in up to 50% of these patients and, disappointingly, BP is controlled to guideline-driven targets in only 50% of those hypertensive patients advised to take treatment.

Hypertension is one of the most common chronic non-communicable diseases and accounts for 12% of all primary care consultations in UK.[1] Blood pressure rises with increasing age and 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, especially the aorta. Increased arterial stiffness causes augmentation of SBP and diminution of DBP and is thus also responsible for the increasing prevalence of isolated systolic hypertension (ISH) in the elderly. Furthermore, hypertension has a higher prevalence in women and ethnic minorities in predominantly Caucasian countries such as the UK and the USA.

Aetiology

Primary hypertension

Hypertension is thought to arise from the interplay of multiple genetic traits that are all individually responsible for only small increases in BP but collectively may be responsible for 30–50% of individual variation, with environmental and lifestyle factors that elevate BP responsible for the rest. Commonly implicated medicines/drugs or foodstuffs that elevate BP include non-steroidal anti-inflammatory drugs (NSAIDs), steroids, calcineurin inhibitors, hormonal oral contraceptives and female hormone replacement, stimulant sympathomimetic medications and illicit drugs, liquorice, salt (sodium chloride) and alcohol. Furthermore, a sedentary lifestyle, and dietary patterns of low fruit and vegetable intake, as well as high saturated fat and carbohydrate-rich diets that lead to obesity, also contribute to raised BP. In such cases where there is no single identifiable cause for hypertension, the term *primary hypertension* is preferred to the historical *essential hypertension.*.

Secondary hypertension

In 5–10% of hypertensive patients, an identifiable, possibly reversible or treatable, cause for hypertension can be elucidated through careful assessment. These are broadly categorized into renal, vascular, endocrine or neural problems (Table 2). In young patients (aged <30 years), patients with sudden-onset, severe hypertension, and patients with *resistant hypertension* (uncontrolled BP despite at least three antihypertensive medicines, including a diuretic), the prevalence of secondary causes increases to between 20% and 60%.[9] The most common secondary causes found in resistant

hypertension are obstructive sleep apnoea (OSA) (through sympathetic overdrive) and hyperaldosteronism (Conn's adenoma or bilateral adrenal hyperplasia causing mineralocorticoid excess).[9]

Diagnosis and evaluation

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

- Is the patient truly hypertensive?
- Is there evidence that hypertension has caused complications (target organ damage (TOD); major CV events)?
- Is a secondary cause identifiable?
- What is the total CV risk of the patient?

BP measurement

Blood pressure is an inherently unstable biological variable, subject to seasonal, circadian, hormonal and immediate external influences. As such, a single point measure of BP is unlikely to represent usual BP. This is particularly important to remember when making a diagnosis or treating a patient for a disease that is largely asymptomatic, the purpose of which is to mitigate future CV and renal risk. It is established practice to take multiple BP readings at one sitting, and to repeat BP measurement over several clinical encounters, to smooth out variation and obtain readings that more closely resemble usual BP.

Clinic BP measurement

Most of our experience in the measurement of BP and the assessment of the beneficial effects of treating hypertension relates to recordings made in front of a health professional (clinic BP). International guidelines require at least two or three sequential recordings obtained in the non-dominant arm (unless BP in the dominant arm is greater than 10 mmHg higher than in the non-dominant) in a seated position after at least 5 minutes rest. Guidelines vary on whether the lowest of these readings or the mean of the second and third reading should be used to indicate the true clinic BP.[1,2] Although traditionally the preferred equipment for BP measurement was the mercury auscultatory sphygmomanometer, the withdrawal of mercuric devices from clinical environments has led increasingly to the use of validated, semi-automatic, oscillometric devices with appropriately sized cuffs, which also allows for the measurement of out-of-office BP (see below). However, these oscillometric monitors are not entirely accurate in patients with irregular arrhythmias, such as atrial fibrillation, in whom manual aneroid auscultation must be used. A number of cuffless BP monitoring devices are on the horizon, and are currently being evaluated in the research setting. Approval of such devices for clinical practice will enable collection of high quality longitudinal BP data, and facilitate remote patient-clinician telemedicine interactions.

Out-of-office BP measurement

Out-of-office BP measurement, such as home BP, is particularly useful for the long-term monitoring of BP control as it allows multiple recordings to be made between clinic visits. The involvement of patients in the management of their disease has benefits for engagement and satisfaction. Furthermore, diagnosis of both white-coat hypertension (WCH: high clinic BP, normal out-of-office BP) and masked hypertension (normal clinic BP, high out-of-office BP) (Table 1) is very important as these conditions can lead to over/under treatment, respectively, and are both associated with increased CV risk compared to having normal clinic and out-of-office BP.[ii] Home BP is usually 5–10 mmHg lower than equivalent clinic recordings, though this is exaggerated/reversed in WCH and masked hypertension, respectively.
As with home BP, ambulatory BP (ABP) monitoring is increasingly used for diagnosis and monitoring.[1,2] Daytime ABP is 5–10 mmHg lower than clinic BP in the same patient but is superior to clinic BP in the determination of CV risk, the ability to rule out WCH in a single event (which may represent 10–30% of all hypertensives),[ii] the provision of multiple readings to provide improved diagnostic accuracy in a single event,[12] and the provision of night-time BP (which may suggest OSA if there is a failure of BP to dip by 10% below day-time readings).[1] Thus, ABP monitoring is mandated by latest UK guidelines when making a diagnosis of hypertension.[2] However for on-going monitoring, clinic BP is considered more appropriate, especially as no major outcome clinical trials have used ABP monitoring to guide pharmacotherapy.[1]

History

Historical questioning should include childhood illnesses, especially recurrent urinary tract infections, and family history, especially of premature vascular disease. In women, evidence of previous pregnancy-related hypertensive disorders should be specifically sought.

Dietary assessment is notoriously imprecise but salt intake can be estimated by asking about consumption of high-salt containing foodstuffs and whether patients add or cook with salt. Alcohol and smoking status should be clarified. Medicines/drugs that interfere with BP (see above) should be asked about specifically as should the use of any over-the-counter medicines, herbal or traditional medicines.

A history of major CV events, such as myocardial infarction, stroke, peripheral arterial disease, heart failure and chronic kidney disease should be obtained. Current and previous medication history (with intolerances or adverse effects and compliance), length of diagnosis and any self-home BP monitoring values should also be collected. Secondary causes may be suggested by abnormal sweating (phaeochromocytoma, OSA, acromegaly); palpitations and anxiety (phaeochromocytoma); postural and post-prandial symptoms (autonomic dysfunction); or witnessed nocturnal apnoeas and daytime somnolence (OSA).

Examination

Examination should focus on looking for evidence of both asymptomatic TOD and secondary causes. TOD can be assessed in three systems: ophthalmic, CV and renal. Direct fundoscopy may reveal different grades of hypertensive retinopathy such as silver wiring (grade 1) and arteriovenous nipping (grade 2) that represent TOD 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 anti-hypertensive therapy. 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 TOD at the bedside.

General appearance may suggest an underlying endocrinopathy (Table 2). Vascular examination in a patient with coarctation may reveal disproportionately cool lower limbs with reduced pulses and either radio-radial or radio-femoral delay, depending on the exact location of the stenosis. A significant coarctation will normally produce a large systolic murmur best heard in the inter-scapular region. Renal bruits may signify either atherosclerotic renal artery stenosis or fibromuscular renal artery dysplasia and both warrant further investigation. Polycystic kidneys should be easily ballotable in the flanks.

Investigation

Investigations should be directed towards exploring underlying asymptomatic TOD and secondary causes, and to provide a full CV risk profile. All hypertensive patients should be offered. [2]

•Serum electrolytes, estimated glomerular filtration rate (eGFR) and protein:creatinine ratio estimation: these will aid detection of asymptomatic chronic kidney disease, and hypokalaemia associated with mineralocorticoid (and glucocorticoid) excess may be picked up.

•Fasting lipids, plasma glucose and glycated haemoglobin: these allow completion of CV-risk estimation equations, such as Q-RISK 2.

•Electrocardiogram (ECG): this will detect electrical left ventricular hypertrophy (LVH), as well as atrial fibrillation, which influences selection of the device that can be used to diagnose and monitor BP accurately.

•Transthoracic echocardiography or cardiac magnetic resonance imaging may be used in specialist settings to give greater sensitivity and specificity for LVH.

Other investigations to look for secondary causes will be patient-specific depending on pre-test probability from the history and examination, and the necessity/utility of making an underlying diagnosis (Table 2). All relatively young patients (aged <40 years) and patients with resistant hypertension should be fully evaluated for secondary causes.[2] A 24-hour urine collection for electrolytes can estimate salt intake. Increasingly, specialists are attempting to determine patient compliance using sophisticated tests such as observed tablet taking and subsequent BP measurements, and analytical drug (or drug metabolite) assays in urine and plasma.[iii] Using urine drug-metabolite assays, it has been estimated non-adherence is as high as 40% and therefore use of these techniques in routine clinical practice may improve identification of true drug-resistant hypertension.

Management

Hypertension is treated to reduce the risk of major CV and renal events. For this reason, treatment of hypertension in isolation from other modifiable CV risk factors (hyperlipidaemia, diabetes, smoking, obesity) is inappropriate. CV-risk equations, such as Q-RISK 2 are useful for integrating different risk factors, to judge when to treat asymptomatic patients and to provide on-going patient education.

Thresholds and targets

BP is a continuous variable. CV risk increases in cohort studies at all levels of clinic BP >115/75 mmHg. However, from intervention trials in uncomplicated hypertension, there is no evidence to support antihypertensive treatment in patients with BP <140/90 mmHg.[1,2] Indeed, in grade 1 hypertension, there is scanty evidence that treatment provides a reduction in CV events,[1,2] in contrast with grade 2 hypertension and above, in which this is well demonstrated. Hence, grade 1 hypertension should be treated only if there is concomitant TOD, total CV risk >20% per year[2] or highly modifiable lifetime risk. In the elderly (aged >80 years), there is even less evidence for treating grade 1 hypertension, and the biggest study (HYVET)[iv] aimed for target BP of 150/90 mmHg with large reductions in CV morbidity. However, when treating patients with diabetes mellitus with or without CKD, or non-diabetic patients with significant proteinuria, one should aim for BP 120–129/<80 mmHg. The most recent American guidelines, based on recent meta-analyses and randomised controlled trials, have redefined stage 1 hypertension as BP 130-139/80-89mmHg, and stage 2 as BP >140/90mmHg; which may pave the way in the future for changes in the threshold for diagnosis in the UK.[4]

Lifestyle interventions

All patients should be counselled and supported to introduce and maintain proven lifestyle interventions to lower BP and CV risk[2] (Table 3):

Pharmacotherapy

Current UK guidelines are predicated on the use of 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 and are less responsive to angiotensin-converting enzyme inhibition or angiotensin II-receptor blockade (Figure 2). Most patients require at least two medicines to control BP[1] and it has been suggested that pharmacotherapy should start with combination therapy (perhaps in a fixed-dose combination single tablet), particularly in those found at the outset to have severe hypertension or those with high total CV risk.[1]

Resistant hypertension is defined as uncontrolled BP despite maximally tolerated doses of three classes of antihypertensive medications including a diuretic (Table 4).[2] At this point, it is recommended that primary care professionals refer the patient for specialist evaluation of secondary causes and treatment. Spironolactone is now the preferred 4th line agent[5].

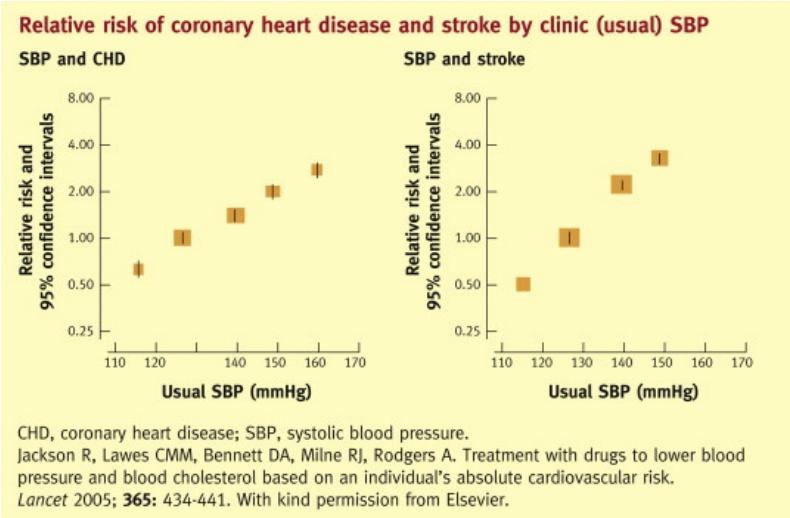
In contrast to other guidelines, UK NICE guidelines have relegated β-adrenoceptor blockers to fifth place,[2] unless there is a pressing indication, because of recent meta-analyses suggesting inferior CV risk reduction despite similar BP-lowering effects. Medicines from different classes are combined 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.

Key Points

- Diagnosis of hypertension now requires ABPM or HBPM, as both have been shown to be superior to clinic BP in the diagnosis and prognosis of hypertension. Although clinic BP is still recommended for monitoring within the clinical setting, engaging patients in HBPM has shown to improve patient education and adherence.

- Most patients require a combination of at least two anti-hypertensive medications to reach target BP, with American and European guidelines changing to suggest initiation of two classes of pharmacotherapy concomitantly at diagnosis

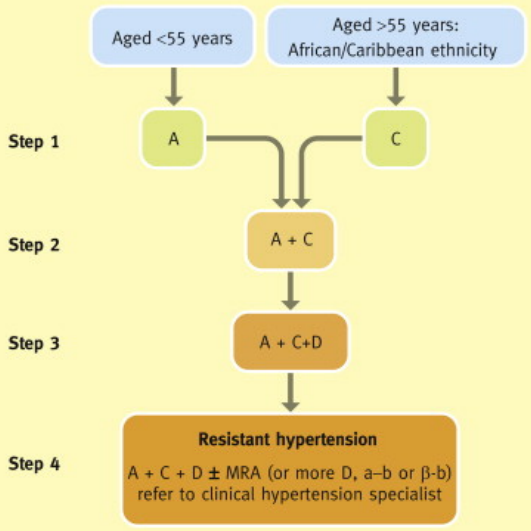
- Patients with uncontrolled hypertension taking step 3 treatment, or young patients with hypertension should be referred for expert evaluation
-
- Spironolactone is now recommended as the preferred fourth line agent



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

Treatment algorithm for hypertension. Adapted from UK NICE guidelines.[3]



A, angiotensin-converting enzyme inhibitor or low-cost angiotensin II-receptor blocker; α-b, α-adrenoceptor blocker; β-b, β-adrenoceptor blocker; C, calcium-channel blocker; D, thiazide-like diuretic; MRA, mineralocorticoid receptor antagonist.

Figure 2

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	<130	<85	n/a	n/a
High-normal BP	130–139	85–89	n/a	n/a
Grade 1 hypertension	140–159	90–99	135–149	85–94
Grade 2 hypertension	160–179	100–109	>150	>95
Grade 3 hypertension	>180	>110	n/a	n/a
Isolated systolic hypertension	>140	<90	>135	<85
White-coat hypertension	>140	>90	<135	<85
Masked hypertension	<140	<90	>135	>85

For diagnosis of different grades of hypertension, the highest categorization of DBP or SBP is used. Diagnosis using ABPM requires only daytime mean (>14 readings to be valid). Data adapted from Mancia et al.[2] and UK NICE guidelines.[1] BP, blood pressure; DBP, diastolic blood pressure; n/a, not applicable; NICE, National Institute for Health and Care Excellence; SBP, systolic blood pressure.

Table 1

Common secondary causes of hypertension and their diagnostic tests	
Secondary causes	**Diagnostic test**
Renal	
Chronic kidney disease (any aetiology)	eGFR, P:CR
Polycystic kidney disease	Renal ultrasound
Reninoma	Plasma renin activity
Page kidney (sub-capsular compression)	Renal ultrasound
Monogenic tubular syndromes (e.g. Liddle's, Gordon's)	Serum electrolytes, plasma aldosterone
Vascular	
Coarctation of aorta	CT/MR aorta
Renovascular diseases	
Atherosclerotic renal stenosis	CT/MR renal angiography
Fibromuscular dysplasia	CT/MR renal angiography
Endocrine	
Hyperaldosteronism	Aldosterone/renin ratio
Hypercortisolaemia	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 steroid synthesis	Measurement of urine steroid precursors
Neural	
Obstructive sleep apnoea	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; MR, magnetic resonance; P:CR, protein:creatinine ratio.

Table 2

Lifestyle interventions	
Intervention	**Approximate SBP reduction**
Regular aerobic exercise (30 minutes/day)	4-9mmHg
Weight reduction (BMI <25 kg/m^2 or waist circumference <102cm men, <88cm women)	5-20mmHg/10kg
DASH eating plan – increased fruits, vegetables, low fat dairy, reduced saturated and total fat intake	8-14mmHg
Dietary salt reduction <6g sodium chloride/day	2-8mmHg
Alcohol (Male < 2units/day, Female <1 unit/day)	2-4mmHg
BMI: Body mass index,	

Table 3

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Antihypertensive medication classes

Class	Example	Mode of action	Duration of action	Adverse effects/monitoring/notes
ACE-i, ARB	Ramipril, Losartan	Reduce Ang II-mediated vasoconstriction	Once or twice daily	Reversible renal decline, cough, angioedema ACE-i contraindicated in bilateral RAS
CCB (DHP)	Amlodipine	Peripheral vasodilator	Once daily	Peripheral oedema, tachycardia, gum hyperplasia
CCB (non-DHP)	Diltiazem	Peripheral vasodilator; negatively chronotropic	Once or twice daily as MR formulation	Peripheral oedema, bradycardia, constipation. Do not co-prescribe with β-blocker
Diuretic (Th-L)	Indapamide	Vasodilator and salt/water excretion	Once daily	Hypokalaemia/hyponatraemia, hyperuricaemia, glucose. Avoid nocturnal dosing
MRA	Spironolactone	Salt/water excretion	Once daily	Hyperkalaemia, painful gynaecomastia Avoid if eGFR <30 mL/min
β-Blocker	Atenolol	Inhibit renin secretion; negatively inotropic/chronotropic	Once daily	Bradycardia, bronchospasm, disturbed sleep, lethargy. Do not co-prescribe with non-DHP CCB
α-Blocker	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. ACE-I, angiotensin-converting enzyme inhibitor; Ang II, angiotensin II; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; M/R, modified-release; MRA, mineralocorticoid receptor antagonist; RAS, renal artery stenosis; Th-L, thiazide-like diuretic.

Table 4

Key References

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A further reading list can be added with a total of 5 entries.

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Self Assessment Questions

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Question 1:

A 64-year-old asymptomatic Caucasian gentleman with a background of well-controlled Type II diabetes mellitus continues to have uncontrolled blood pressure (clinic BP 155/97mmHg, HBPM 148/92mmHg). His current medication includes Ramipril 10mg daily, Amlodipine 10mg daily, Indapamide M/R 1.5mg daily, for which he ensures compliance. His most recent blood tests results are – Na^+142 mmol/L, K^+-3.9 mmol/L, eGFR 72ml/min/1.73m^2.

In addition to emphasizing lifestyle management advice, which of the following management steps is most appropriate?

a. Increase to Ramipril 10mg twice daily

b. Review BP in 6 months

c. Start atenolol 50mg daily

d. Commence spironolactone 25mg daily

e. Refer to cardiologist

Explanation

This gentleman is currently above his BP treatment target; 50% of patients with hypertension are inadequately treated and do not achieve target BP. In addition to lifestyle interventions, a fourth line drug should be added straight away given that delay in treating is associated with increased risk of CV events. Spironolactone has been proven to be superior to non-diuretic add on drugs at lowering blood pressure and is therefore is now the preferred 4th line agent. Monitoring of his renal function will be required.

NICE does recommend referral to a hypertension specialist in if BP uncontrolled on 3 drugs (resistant hypertension) – a list of hypertension specialist referral centres is available on the website of the British & Irish Hypertension Society: https://bihsoc.org/referral-centres/

Question 2:

A 93-year-old asymptomatic lady with a background of osteoarthritis, macular degeneration and irritable bowel syndrome attends clinic with a BP of 148/80mmHg, and domiciliary BP measurements with a validated device are on average less than this. Her current antihypertensive prescription is for ramipril 10mg daily and felodipine 10mg daily and she assures you that she is fully adherent with her medication. Her renal function results are: Na^+139 mmol/L, K^+-4.1 mmol/L, eGFR 50 ml/min/1.73m^2.

In addition to lifestyle recommendations,, which of the following options should be taken in regard with her pharmacotherapy?

a. No changes in medication

b. Initiate indapamide M/R 1.5mg daily

c. Start doxazosin 4mg twice daily

d. Commence spironolactone 25mg daily

e. Refer for ABPM

Explanation

The current evidence base recommends treatment of patients above the age of 80 years to a systolic BP target of < 150mmHg and therefore no further changes in medication are required. Given that she is already on an ACE-I and a CCB, the next drug choice would therefore be indapamide (b), as per the treatment algorithm (figure 2) if the BP control was to deteriorate to levels above target.

Question 3:

A 27-year-old female primary school teacher is referred to the ambulatory clinic with hypertension (182/102mmHg), blurred vision and headaches. She has recently been treated for a urinary tract infection with several courses of antibiotics, and visited the GP in the last 3 months for generalized weakness. She has a family history of hypertension and takes no regular medication. Her renal function results are: Na^+143 mmol/L, K^+-2.9 mmol/L, eGFR 90ml/min/1.73m^2.

What would be the investigation of choice in this patient?

a**. Aldosterone/Renin assay once potassium levels normalised**

b. Low dose dexamethasone suppression test

c. CT angiography of the renal arteries

d. Urine βHCG

e. ABPM

Explanation

Her symptoms, hypokalaemia and positive family history all point to a diagnosis of primary hyperaldosteronism; for which the initial investigation is aldosterone/renin ratio and would demonstrate high aldosterone levels with suppressed plasma renin activity and thus a very high ratio. B is used to diagnose hypercortisolaemia once elevated cortisol excretion is demonstrated. CT angiography is indicated if a diagnosis of renal artery stenosis or fibromuscular dysplasia is suggested in the history/examination or if other secondary causes of hypertension are excluded. A CT scan of the adrenal glands will be necessary following a positive finding of A. Although pregnancy is common in this age group, and should always be tested for in women of childbearing age, her presentation and positive family history make this less likely.