16.17.2 Essential hypertension Diagnosis, assessme

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16.17.2 Essential hypertension: Diagnosis, assessment, and treatment 3753 Devereux RB, et al. (2004). Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA, 292, 2386–8. Drukteinis J, et al. (2007). Cardiac and systemic hemodynamic characteristics of hypertension and prehypertension in ado- lescents and young adults: the Strong Heart Study. Circulation, 115, 221–7. Elliott WJ, Meyer PM (2007). Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet, 369, 201–7. Jin H, Huang Y, Yang G (2019). Association between α-adducin rs4961 polymorphism and hypertension: a meta-analysis based on 40432 subjects. J Cell Biochem, 120, 4613–19. Lip GYH, Blann AD (2000). Does hypertension confer a prothrombotic state? Virchow's triad revisited. Circulation, 101, 218–20. Mancia G, et al. (2007). The sympathetic nervous system and the metabolic syndrome. J Hypertens, 25, 909–20. Mancini JGB, et al. (2004). Surrogate markers for cardiovascular dis- ease. Circulation, 109 Suppl, IV 22–30. Mason JM, et al. (2005). The diabetogenic potential of thiazide-type diuretic and beta-blocker combinations in patients with hyperten- sion. J Hypertens, 23, 1777–81. Okin PM, et al. (2004). Electrocardiographic strain pattern and prediction

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vascular pathology and provides important prognostic information. Three grades are recognized: (1) mild—generalized and focal arteriolar narrowing, arteriolar wall opacification, and arteriovenous nipping; (2) moderate—as (1) plus flame-shaped blot haemorrhages and/or cotton wool spots and/or hard exudates and/or microaneurysms; and (3) severe—as (2) plus swelling of the optic disc. Aside from measurement of blood pressure and fundal examin- ation as just detailed, particular features to look for on examination

section 16 Cardiovascular disorders 3754 are evidence of secondary effects of sustained hypertension on the heart, and features that might suggest the presence of a secondary cause of hypertension (coarctation—absent/delayed femoral pulses, cardiac murmur; and renovascular disease—renal bruit). Patients with essential hypertension need only a limited number of routine investigations, namely (1) urine strip test for blood and urinary albumin:creatinine ratio (ACR) for proteinuria; (2) serum creatinine and electrolytes; (3) blood glucose—ideally fasted; (4) cholesterol and HDL-cholesterol—ideally fasted; and (5) 12-lead electrocardiogram (ECG).
Management The treatment of hypertension is directed towards reducing risk rather than treating symptoms, and best advice and treatment is informed by formal estimation of a patient's overall cardiovascular risk. Most international guidelines recommend that, for office blood pressure, an optimal treatment target should be less than 140/90 mm Hg in patients under the age of 60 years. The 2018 European guide- lines differ, stating that—provided treatment is well tolerated—treated BP should be targeted to less than 130/80 mm Hg in most patients. Recommendations differ for older patients: current American guide- lines suggest treating to a goal of less than 150/90 mm Hg for patients aged over 60 years; the British Hypertension Society/NICE guideline recommends the same higher target for those over 80 years; and the 2018 European guideline recommends a target of SBP 130–139 mm Hg
'if tolerated'. Most international guidelines no longer recommend lower blood pressure targets for populations at higher cardiovascular risk. Although early studies focused primarily on DBP as the treatment target, SBP is the more important prognostic factor, is invariably more difficult to control, and should be the main focus of treatment. The most effective lifestyle interventions for reducing blood pressure are (1) modifications to diet to induce weight loss, (2) regular aerobic ex- ercise, and (3) reduction of excessive alcohol and/or sodium intake; all smokers should be offered advice and help to quit to reduce cardiovas- cular (and other) risks. Many patients will require more than one drug to control blood pressure: monotherapy is rarely sufficient. The blood pressure response to an individual class of blood pressure lowering medication is heterogeneous, hence there is no 'perfect drug' for every patient, but some trials have indicated that certain comorbidities or target organ damage provide compelling indications for inclusion of specific classes of drug therapy in the treatment regimen. There is wide variation in the international guidelines with re- gard to the preferred initial therapy for essential hypertension: (1) the (American) Joint National Committee (JNC) 8 guideline recom- mends initial drug treatment with an angiotensin converting enzyme inhibitor (ACE inhibitor), angiotensin receptor blocker (ARB), calcium channel blocker (CCB), or thiazide-type diuretic (TTD) in nonblack hypertensive patients, with a CCB or TTD preferred in black patients; (2) the 2018 European guideline suggests that initial therapy should be with two drugs—an ACEi or ARB combined with a CCB or TTD in a single pill combination; (3) the British Hypertension Society/NICE guideline suggests that the most appropriate initial blood pressure lowering agent for (a) people aged 55 years or over (without type 2 diabetes), and for black people of African or Caribbean family origin of any age (without type 2 diabetes), is a CCB, with a TTD preferred if a CCB is not suitable, and (b) for people under 55 years of age, or any patient with type

2 diabetes, an ACE inhibitor or a low-cost ARB is preferred initial therapy. All guidelines recognize that combinations of blood pressure lowering drugs are often required to achieve recommended blood pressure goals. The British guideline provides explicit guidance on preferred combinations of treatment if one agent fails to achieve ad- equate control: step 2—a CCB combined with either an ACE inhibitor or ARB; step 3—add a TTD; step 4—add higher-dose TTD, spironolac- tone, an α-blocker or a β-blocker. European and American recom- mendations are similar. Patients with hypertension and deemed to be at high cardiovas- cular risk (>10% over 10 years) should receive advice to adjust their lifestyles and be considered for treatment with statin therapy and low-dose aspirin to optimize their risk reduction. Indications for specialist referral include uncertainty about the decision to treat, investigations to exclude secondary hypertension, severe and complicated hypertension, and resistant hypertension. Introduction There are several important issues that must be considered in the as- sessment of people presenting with an elevated blood pressure: • Does the patient have hypertension (i.e. is the blood pressure per- sistently elevated?) • Are there any associated clinical features that might warrant fur- ther evaluation to exclude secondary causes of hypertension? (see next and Chapter 16.17.3) • Are there factors that might be contributing to an elevated blood pressure, including lifestyle or dietary factors, or concomitant medication? • Is there any associated target organ damage or comorbidity that influences the overall cardiovascular disease risk and subsequent treatment of the patient? These factors, along with the age and ethnicity of the patient, will inform the decision to treat, the urgency of the need to treat, the need for further investigation, and the choice of treatment. Symptoms Essential hypertension is invariably symptomless and usually de- tected by routine screening or opportunistic measurement of blood pressure. However, once a patient has been labelled as ‘hypertensive’ it is not uncommon for them to associate preceding symptoms with their elevated blood pressure. Some patients will claim that they can recognize when their blood pressure is elevated, usually on the basis of symptoms such as plethoric features, palpitations, dizziness, or a feeling of tension. Screening surveys have demonstrated that these symptoms occur no more commonly in untreated hypertensive pa- tients than they do in the normotensive population. However, there are two important caveats to the symptomless nature of essential hypertension: (1) symptoms may develop as a consequence of target organ damage, (2) headache may be a feature of severe hypertension. Headache Most headaches in hypertensive patients are tension headaches, not related to blood pressure at all, although they become more common

 when patients become aware of the diagnosis. The classic hyperten- sive headache is present on waking in the morning, situated in the occipital region, radiating to the frontal area, throbbing in quality, and wears off during the course of the day. It is generally associated with more severe hypertension. Effective treatment of hypertension reduces the incidence of such headaches. Morning headaches in obese hypertensive patients may be related to sleep apnoea. Epistaxis Epistaxis is not associated with mild hypertension but is more common in moderate to severe hypertension. However, the associ- ated anxiety can elevate blood pressure when patients present with bleeding, hence it is particularly important that patients are not automatically labelled as hypertensive, with care taken to dissociate hypertension as a cause of epistaxis from a pressor response to the epistaxis itself. Male impotence Patients rarely volunteer information about impotence, but there is an increased prevalence of erectile dysfunction in untreated hyper- tensive men. This is related to two factors: remodelling of small ar- teries and increased risk of atheroma, both of which vascular changes can reduce penile blood flow despite the elevation in blood pressure. Furthermore, erectile

dysfunction can develop or worsen as a con- sequence of treatment, for the most part related to the reduction in blood pressure before any concomitant change in vascular structure. Nocturia This is common in people with untreated hypertension as a conse- quence of a reduction in urine-concentrating capacity. The symp- toms usually improve with treatment. Symptoms associated with target organ damage If patients develop cardiac, vascular, cerebrovascular, and/or renal complications as a consequence of long-standing untreated or poorly treated hypertension, then symptoms related to these complications may be present. Target organ damage and associated symptoms are discussed in Chapter 16.17.1. Physical examination Blood pressure measurement Large variations in blood pressure measured in a single individual are normal, hence it should be measured as accurately as possible using the British Hypertension Society (BHS) protocol (Box 16.17.2.1). Blood pressure should initially be measured in both arms because there can be large interarm difference in blood pressure. The finding of a difference of greater than 20 mm Hg may indicate the presence of underlying vascular disease, especially subclavian stenosis. When there is a significant interarm difference in blood pressure reading, the arm with the higher pressure should be used for all subsequent measurements. All adults should have their blood pressure measured routinely at least every 5 years. Those with high-normal blood pressure (sys- tolic blood pressure (SBP) 130–139 mm Hg or diastolic blood pres- sure (DBP) 85–89 mm Hg) and those who have had high blood pressure readings at any time previously should have their blood pressure remeasured annually. These measurements can be made in the clinic, in the home setting, or using ambulatory blood pressure monitoring (ABPM), as described later in the chapter. Seated blood pressure recordings have been the standard method for diagnosing hypertension for more than 100 years, are the method used most often in epidemiological studies and clinical out- come trials, and are unequivocally linked to clinical outcomes and mortality in a graded way. However, recordings are often performed badly and can underestimate or overestimate BP in comparison with ABPM, even when performed well. The patient should be seated and rested for a few minutes beforehand. At least two measurements should be taken, and if the first measurement is more than 10 mm Hg higher than the subsequent one, then it should be discarded and a further reading taken. Standing blood pressure (after at least 2 min standing) should be measured in elderly or diabetic patients to ex- clude significant orthostatic hypotension. The timing of blood pressure measurement should take account of the timing of medication. Treatment decisions should not be based on single blood pressure readings: the average of two read- ings at each of at least three visits (depending on severity) should be used to guide the decision to treat. The time between visits will vary according to the severity of the hypertension, ranging from days or weeks to months. In patients with severe hypertension, especially when there is unequivocal evidence of target organ damage, the de- cision to treat may be made at the time of first presentation. When measuring blood pressure, the upper arm should be sup- ported at heart level during recordings, and it is important that an appropriate cuff size is used, with the bladder encircling at least 80% of the upper arm. Using too large a cuff results in an underestimation of blood pressure and too small a cuff will lead to overestimation. If the auscultatory method is used to measure blood pressure, then Korotkoff phase I (first appearance of sound) and phase V sounds (disappearance of sound) should be taken for SBP and DBP, respect- ively. If phase V goes to zero, then phase IV (muffling of sound) should be recorded. The beat-to-beat variability associated with atrial fibrillation can make blood pressure measurement difficult and semiautomatic or Box 16.17.2.1 British Hypertension Society protocol for blood pressure measurement • Use a properly maintained, calibrated, and validated device • Measure sitting blood pressure routinely: standing blood pressure should be recorded at the initial estimation in elderly and diabetic patients • Remove light clothing, support arm at heart level,

ensure hand is re- laxed, and avoid talking during the measurement procedure • Use cuff of appropriate size, and rapidly inflate the cuff to 20 mm Hg above the point where the brachial pulse disappears • Lower cuff pressure slowly (2 mm/s) • Read blood pressure to the nearest 2 mm Hg • Measure diastolic as disappearance of sounds (phase V) • Take the mean of at least two readings: more recordings are needed if marked differences between initial measurements are found • Do not treat on the basis of an isolated reading Reprinted by permission from Williams B, et al. (2004). Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV. Journal of Human Hypertension, 18, 139–85.

section 16 Cardiovascular disorders 3756 automated devices can be very inaccurate in such circumstances, in which case multiple readings of auscultatory measurements are recommended. Blood pressure monitors The sphygmomanometer has been the mainstay of blood pressure measurement for over 100 years, but its use is likely to decline as a consequence of the decommissioning of mercury-based devices and the emergence of automated and semiautomated devices for routine blood pressure measurement in the office and home and for ABPM. It is important to note that there are different diagnostic thresh- olds for the diagnosis of hypertension dependent on the method of measurement; that is, when using multiple home or ambula- tory blood pressure values to measure an average blood pressure, then the average value used to define hypertension is lower than the equivalent office blood pressure threshold of 140/90 mm Hg (Table 16.17.2.1) and it should be noted—as stated earlier—that automated devices are inaccurate in patients with atrial fibrillation, in whom blood pressure should be measured manually. Detailed guidance on blood pressure measurement and a wide range of val- idated monitors is available from http://www.bhsoc.org. Ambulatory blood pressure measurements (ABPM) ABPM recordings improve the sensitivity and specificity of the diag- nosis of hypertension compared to clinic and home blood pressure monitoring, although they cannot be used for people with signifi- cant pulse irregularity (e.g. atrial fibrillation), who require manual auscultation. They also provide much more information regarding the efficacy of treatment of hypertension. When compared to office blood pressure, there is a much steeper relationship between ABPM averages and target organ damage indices and cardiovascular events, no doubt reflecting that fact that more measurements are obtained and the ‘white coat’ or ‘office’ effect (see ‘White coat’ or isolated of- fice hypertension) is eliminated. Generally, ABPM devices are pro- grammed to record blood pressure at 20 min intervals during the day and 30 min intervals at night. A diary is provided to record activity and sleep patterns. In addition to the 24 h blood pressure average, ABPM also provides information on blood pressure profiles (e.g. daytime and night-time averages), the ‘dipper status’ (i.e. the re- lationship between night-time and daytime blood pressure averages, blood pressure variability throughout the day, the morning surge in blood pressure, and—more recently—indices of aortic function via the ambulatory stiffness index). Each of these parameters adds value over and above the assessment of office blood pressure, hence such techniques are increasingly used for the assessment of people with hypertension. Clinical indications for the use of ABPM are shown in Box 16.17.2.2. Home blood pressure measurements (HBPM) It is increasingly common for patients to measure their own blood pressure at home using monitors that measure blood pressure on the upper arm, wrist, or finger. The average of frequent measurements may be more reproducible and reliable than clinic measures, and HBPM has been shown to be a better predictor of clinical outcomes. Validated devices should be used, with an average of duplicate morning and evening HBPM recorded daily for at least 4 days and ideally for 7 days. The measurements should be recorded seated after 5 min rest, with those taken on the first day discarded. Advocates of HBPM

argue that it may reduce unnecessary treatment (by revealing the diagnosis of ‘white coat’ hypertension) and increase treatment compliance, against which must be balanced the fact that in some patients it can lead to inappropriate concern and anxiety. Other features Fundal examination Fundoscopy is the most convenient method of directly visualizing vascular pathology and provides important prognostic informa- tion. Signs of hypertensive retinopathy are frequently seen in adults 40 years and older, and are predictive of incident stroke, congestive heart failure, and cardiovascular mortality—independently of trad- itional risk factors. The Keith Wagener classification of fundal appearances has been used for many years, but has serious shortcomings. This classifica- tion identified four grades of hypertensive retinopathy. Grade I and II changes, which result from arteriolar thickening, are often diffi- cult to differentiate from each other, and the prognostic significance of the grade I and II subclassification is unclear. A more practical three-grade classification (i.e. mild, moderate, and severe) has been proposed (Table 16.17.2.2). The mild changes of generalized retinal– arteriolar narrowing and arteriovenous nipping are related to both the blood pressure at diagnosis and chronic exposure to an elevated blood pressure, hence they appear to be an index of the chronicity of blood pressure elevation (Fig. 16.17.2.1a). The changes of mod- erate hypertensive retinopathy are the changes of mild retinopathy plus flame-shaped or blot-shaped haemorrhages, cotton wool spots, hard exudates, microaneurysms, or a combination of all of these fac- tors. Severe retinopathy (malignant or accelerated hypertension) is characterized by all of the aforementioned changes plus swelling of the optic disc (Fig. 16.17.2.1b). These moderate and severe fundal changes are more closely related to more recent elevation of blood Table 16.17.2.1 Diagnostic thresholds for hypertension according to different methods of measurement SBP (mm Hg) DBP (mm Hg) Office or clinic 140 90 24 hour 125 80 Day 135 85 Night 120 70 Home 135 85 DBP, diastolic blood pressure; SBP, systolic blood pressure. Box 16.17.2.2 Possible indications for ambulatory blood pressure monitoring • Unusual blood pressure variability • Possible ‘white coat’ hypertension • Informing equivocal treatment decisions • Evaluation of nocturnal hypertension • Evaluation of drug-resistant hypertension • Determining the efficacy of drug treatment over 24 h • Diagnosis and treatment of hypertension in pregnancy • Evaluation of symptomatic hypotension

 pressure, suggesting they are the consequence of more transient and severe blood pressure elevation. The flame-shaped haemorrhages are superficial and shaped due to constraints imposed by nerve fibres. Dot and blot haemorrhages are deeper than the nerve fibres and thus are not so constrained. Haemorrhages usually disappear after a few weeks of effective blood pressure control. There are two types of exudates: hard or waxy exudates represent the end result of fluid leakage into the fibre layers of the retina from damaged vessels, with fluid re- absorption leaving a protein–lipid residue that is slowly removed by macrophages; soft exudates or cotton wool patches are usu- ally larger than hard exudates and have a woolly, ill-defined edge, but they are not true exudates, rather nerve fibre infarcts caused by hypertensive vascular occlusion. Unlike hard exudates, these lesions disappear within a few weeks of establishing adequate antihypertensive therapy. Severe fundal changes are characterized by disc swelling (i.e. papilloedema) resulting from raised pressure in the disc head sec- ondary to severe vascular damage and increased permeability. Venous distension is followed by increased vascularity of the optic disc, which has a pink appearance with blurring of the disc mar- gins and loss of the optic cup. Raising of the optic disc with anterior displacement of the vessels occurs later. The surrounding retina often shows oedema, small radial haemorrhages, and cotton wool exudates. Moderate or severe fundal changes represent malignant

or accelerated hypertension and carry the same adverse prognosis and should be treated as a medical urgency (see Chapter 16.17.5). Other fundal changes associated with hypertension Hypertension also predisposes to the development of several sight- threatening complications that can be detected by fundoscopy. Retinal vein occlusion This is characterized by dilated and tor- tuous retinal veins and the presence of retinal haemorrhages, cotton wool spots, and oedema of the macula and optic disc. In the case of central retinal vein occlusion, all four fundal quadrants are involved (Fig. 16.17.2.2a); only one fundal quadrant is involved if there is a branch vein occlusion (Fig. 16.17.2.2b). Central retinal vein occlusion can either be ischaemic or nonischaemic, patients with an ischaemic central retinal vein occlusion typically having poor visual acuity and a relative afferent pupillary defect. Ophthalmic follow-up is needed to diagnose and prevent the two main com- plications of retinal vein occlusion, namely neovascularization and macular oedema. Retinal arteriolar embolization Due to cholesterol crystals, platelet/fibrin clot, or calcium, this is twice as common in people with hypertension compared to those who are normotensive, with the risk further accentuated in cigarette smokers and those with diabetes. Retinal artery occlusion Also more common in people with hypertension, central retinal artery occlusion typically presents with a sudden, painless, unilateral loss of vision, associated with a cherry red spot (Fig. 16.17.2.3a). Branch retinal artery occlusion (Fig. 16.17.2.3b) will present with a sudden, painless, visual field defect: there may be only minimal impairment of central vision. Retinal arterial macroaneurysms These can be either fusiform or saccular. They are uncommon, but are rarely seen in patients without hypertension. When they occur, about 20% are bilateral and 10% are multiple. They are usually discovered by routine fundoscopy in Table 16.17.2.2 Modern classification of hypertensive retinopathy Mild hypertensive retinopathy Retinal arteriolar signs, such as generalized and focal arteriolar narrowing, arteriolar wall opacification, and arteriovenous nipping Moderate hypertensive retinopathy The signs above plus flame-shaped or blot- shaped haemorrhages, cotton wool spots, hard exudates, microaneurysms, or a combination of all of these factors Severe hypertensive retinopathy The signs above plus swelling of the optic disc) b ( )a (AVN AVN CWS FH DS
Fig. 16.17.2.1 (a) Signs of mild hypertensive retinopathy. (b) Signs of severe hypertensive retinopathy. AVN, arteriovenous nipping; CWS, cotton wool spots; DS, swelling of the optic disc; FH, flame-shaped retinal haemorrhage. Reprinted from The Lancet, Vol. 369, Wong T, Mitchell P, The eye in hypertension, pp. 425–35. Copyright (2007), with permission from Elsevier.

section 16 Cardiovascular disorders 3758 asymptomatic hypertensive patients, but can present acutely, with visual loss secondary to haemorrhage or exudation. Nonarteritic ischaemic optic neuropathy This is also more common in people with hypertension, occurring (in one series) with a yearly incidence of 1 in 10 000. It presents with sudden unilateral visual loss and optic disc oedema. There is no effective treatment and prospects for visual recovery are poor. General physical examination All patients with hypertension should have a thorough phys- ical examination. Aside from measurement of blood pressure and fundal examination as just detailed, particular features to look for are evidence of secondary effects of sustained hypertension on the heart, features that might suggest the presence of a secondary cause of hypertension, and evidence of other vascular pathology (absent pulses, arterial bruits) (Box 16.17.2.3). Cardiac examination may reveal a sustained apex beat, or fea- tures of cardiac failure that might be secondary to hypertension. It is sometimes said that the second component of the aortic sound is loud in moderate or severe hypertension, but this is not a reliable finding. In coarctation of the aorta the femoral pulses will be absent or di- minished and delayed, and there may be various murmurs (usually a systolic murmur at the sternal border and a continuous murmur at the back of the

chest), also visible or palpable collateral arteries on the back of the chest or in the axillae. Blood pressure measured in the legs will be lower than that in the arms. An abdominal bruit is reported in 4–20% of normal people, most commonly in those aged over 40 years, when it is typic- ally systolic and audible only between the xiphisternum and the umbilicus. In patients with severe hypertension that is difficult to control, the finding of an abdominal bruit in both systole and AVN BRVO (a) (b) Fig. 16.17.2.2 (a) Central retinal vein occlusion involving all four fundal quadrants. (b) Branch retinal vein occlusion (BRVO) involving a single fundal quadrant, also showing a good example of arteriovenous nipping (AVN). Reprinted from The Lancet, Vol. 369, Wong T, Mitchell P, The eye in hypertension, pp. 425–35. Copyright (2007), with permission from Elsevier.) b BRAO RE ( )a (Fig. 16.17.2.3 (a) Central retinal artery occlusion with a characteristic cherry red spot. (b) Retinal–arteriolar emboli (RE) and retina branch artery occlusion (BRAO). Reprinted from The Lancet, Vol. 369, Wong T, Mitchell P, The eye in hypertension, pp. 425–35. Copyright (2007), with permission from Elsevier.

16.17.2 Essential hypertension: Diagnosis, assessment, and treatment 3759 diastole strongly supports the diagnosis of renovascular hyper- tension, but a bruit confined to systole is much less likely to be of significance. Diagnosis and categories of hypertension Different categories of hypertension can be recognized on the basis of the results of clinic and ambulatory blood pressure meas- urements (Fig. 16.17.2.4). ‘White coat’ or isolated office hypertension In some patients office blood pressure is persistently elevated al- though their 24 h blood pressure or home blood pressure aver- ages are within the normal range. This has been termed white coat hypertension or isolated office hypertension, and is diagnosed when clinic BP is more than 140/90 mm Hg on at least three oc- casions and more than 20/10 mm Hg more than ABPM or home average readings. It is important to note that blood pressure will generally fall with repeated readings in all patients, hence it is the chronicity of the office blood pressure elevation that is important to establish the diagnosis. Surveys suggest that white coat or isolated office hypertension may be present in as many as 15% of the general population and about 25% of all hypertensives (usually grade 1). There is consid- erable debate about its prognostic significance: some studies report association with evidence of hypertensive target organ damage, but others do not. However, overall it appears that white coat hyper- tension is not benign, with the associated risk probably sitting be- tween those with hypertension confirmed by office readings and ABPM, and those with definitively normal pressures by all methods of measurement. When white coat hypertension is diagnosed, the best advice is to monitor blood pressure and target organ damage via ABPM or home blood pressure averages and not treat unless these pressures are persistently elevated. Masked hypertension Less attention has been paid to masked hypertension (i.e. patients with a normal office blood pressure but elevated ABPM or home blood pressure averages) than to those with white coat hyperten- sion. Estimates of prevalence range from 10% to 30% of the popula- tion, and as HBPM becomes more popular the detection of masked hypertension will increase. Most of these will be prehypertensive, with clinic BP 130–139/85–89 mm Hg, but these patients are likely to have target organ damage and are at increased cardiovascular risk, probably more so than those with white coat hypertension (Fig. 16.17.2.5). Masked uncontrolled hypertension is common in people with treated hypertension and should be considered particularly in pa- tients who have clinical evidence of hypertensive target organ damage, but in whom office blood pressure appears normal. ABPM should be used to confirm BP control (including nocturnal read- ings), particularly in higher-risk groups and/or those with border- line control of clinic BP, and treatment should be offered to control ABPM average. Cost-effectiveness of different methods of

diagnosing hypertension A more expensive method of confirming a diagnosis of hyperten- sion may be more cost-effective if, by increasing the accuracy of diagnosis, it avoids treatment costs in some patients. There are no Box 16.17.2.3 Initial assessment of the patient with hypertension • Identifiable causes of hypertension: − Drugs (NSAIDs, oral contraceptive, steroids, liquorice, sympatho- mimetics, i.e. some cold cures) − Renal disease (present, past or family history, proteinuria and/or haematuria: palpable kidney(s)—polycystic) − Renovascular disease (abdominal or loin bruit) − Obstructive sleep apnoea (snoring, daytime somnolence) − Coarctation (radiofemoral delay or weak femoral pulses) − Phaeochromocytoma (paroxysmal symptoms) − Conn's syndrome (tetany, muscle weakness, polyuria, hypokalaemia) − Cushing's (classical clinical characteristics) − Hypothyroidism or hyperthyroidism (classical clinical characteristics) − Acromegaly (classical clinical characteristics) • Contributory factors − Overweight − Excess alcohol (>3 units/day) − Excess salt intake − Lack of exercise − Environmental stress • Complications of hypertension/target organ damage − Stroke, TIA, dementia, carotid bruits − LVH and/or LV strain on ECG, heart failure − Myocardial infarction, angina, CABG, or angioplasty − Peripheral vascular disease − Fundal haemorrhages or exudates, papilloedema − Proteinuria − Renal impairment (raised serum creatinine) • Cardiovascular disease risk factors − Smoking − Diabetes − Total cholesterol:high-density lipoprotein-cholesterol ratio − Family history − Age − Sex • Drug contraindications CABG, coronary artery bypass graft; LVH, left ventricular hypertrophy; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischaemic attack. White coat hypertension Elevated Elevated Normal Normal Ambulatory blood pressure Clinic blood pressure Sustained normotension Sustained hypertension Masked hypertension Fig. 16.17.2.4 Categories of hypertension dependent on clinic and ambulatory blood pressure measurements.

section 16 Cardiovascular disorders 3760 studies that have compared clinic blood pressure monitoring with both ABPM and HBPM from a cost-effectiveness perspective, but the NICE analysis of 2011 concluded that ABPM was the most cost- effective option. It is appropriate to note, however, that arguments about cost-effectiveness depend on a wide range of assumptions, including the costs of ABPM and HBPM, the frequency and cost of subsequent measurements of blood pressure in those deemed not to be hypertensive, and the costs of treatment of those declared to have hypertension. Establishing the diagnosis of hypertension In most healthcare systems hypertension will and should continue to be diagnosed on the basis of office blood pressure measurements. Within the United Kingdom, the NICE recommendations are that, unless severe hypertension (>180/110 mm Hg) is found, a clinic measurement above 140/90 mm Hg should be followed by ABPM, with at least two measurements taken per hour during the person's normal waking hours and an average value of at least 14 readings used to confirm the diagnosis (>135/85 mm Hg). HBPM can be used if the patient cannot tolerate ABPM. The most recent American guidelines (JNC8) do not make new comment on diagnosis of hypertension, although the US Preventive Services Task Force (2015) recommends ABPM. European guide- lines (2018) use conventional office blood pressure measurements or ABPM/HBPM as an alternative strategy. Routine investigation Patients with essential hypertension need only a limited number of routine investigations, which must include: • urine strip test for haematuria • urinary albumin:creatinine ratio (ACR) for proteinuria • serum creatinine (estimated GFR) and electrolytes • glycated haemoglobin (HbA1c) • cholesterol and HDL-cholesterol—ideally fasted • ECG These routine investigations help inform the assessment of target organ damage and cardiovascular disease risk. With regard to renal function, it is now almost universal laboratory practice to report an 'estimated' GFR (eGFR) calculated using an algorithm based on the serum creatinine measurement and the

patient’s age. Testing for proteinuria should be by quantification on a spot urine sample of the urinary albumin/creatinine ratio (ACR). More sophisticated assessment tools are available, but the aforementioned list is suffi- cient for routine clinical practice. Note that only two of these rou- tine investigations contribute to the detection of underlying causes of hypertension, namely urinalysis (renal causes) and serum cre- atinine and electrolytes (renal causes and mineralocorticoid ex- cess), although the ECG may very rarely show U waves as a clue to one of the hypokalaemic syndromes. Indications for further investigation for causes of secondary hypertension are given in Chapter 16.17.3. A chest radiograph and urine microscopy are not routinely re- quired. Echocardiography is more sensitive at detecting left ven- tricular hypertrophy than an ECG, but is not required routinely, although it is valuable to confirm or refute the presence of left ven- tricular hypertrophy when the ECG shows voltage criteria sug- gestive of this. Assessment of cardiovascular disease risk The cardiovascular risk associated with hypertension is not elim- inated by the treatment of blood pressure alone. This is because many patients have established cardiovascular damage which may not necessarily reverse with treatment of blood pressure, also life- style habits such as smoking and dietary factors that may not have changed since therapy was initiated. Other factors are also im- portant: patients with high blood pressure often have associated disturbances in their metabolic profile (especially lipids and glucose 40 Cardiovascular events, untreated Total mortality, untreated P<0.0001 P<0.0001 35 30 25 Event (%) 20 15 10 5 0 40 35 30 25 20 15 10 5 0 0 3 6 9 12 0 3 6 9 12 Sustained hypertensives Masked hypertensives White-coat hypertensives Normotensives Fig. 16.17.2.5 Prognosis of white coat and masked hypertension. Data includes 6458 participants with 714 events. Adapted from Stergiou GS, et al. (2014). Prognosis of white-coat and masked hypertension: International database of home blood pressure in relation to cardiovascular outcome. Hypertension, 63, 675–82.

 tolerance) that contribute to their risk, which has led many inter- national guidelines to recommend that cardiovascular risk should be formally assessed in all patients with hypertension to determine whether they are at low, medium, or high risk. Risk calculations based on the Framingham cohort have been used in the United States of America and the United Kingdom, and European guidelines have used a risk score based on mortality data from European countries. Pragmatism in risk assessment is im- portant, with the risk factors cited in the guidelines being conventional markers that can easily be documented in a basic clinical setting (i.e. SBP, age, gender, low-density lipoprotein (LDL) cholesterol, presence of diabetes, smoking history, and the presence or absence of structural damage, e.g. ECG evidence of left ventricular hypertrophy). Recent surveys suggest that more than 90% of population-attributable risk for cardiovascular disease can be explained by these risk factors. The use of more sophisticated risk assessment by adding any of the recently advocated biomarkers, such as C-reactive protein, adds little to the conventional methods of cardiovascular risk estimation. Cardiovascular disease risk thresholds for intervention currently define ‘high-risk’ patients as having a 10-year Framingham-derived cardiovascular disease risk of 10% or more, and such patients should be offered antihypertensive drug treatment if their blood pressure is elevated. The typical hypertensive male aged 55 years or more has this level of cardiovascular disease risk. Formal cardiovascular dis- ease risk estimation is not necessary for patients with hypertension and established cardiovascular disease, diabetes, or overt end organ damage: they are already at sufficient cardiovascular disease risk to benefit from multifactorial risk factor intervention. Patients with hypertension and deemed to be at high risk should receive strong advice to adjust their lifestyles and be considered for treatment with statin therapy and low-dose

aspirin to optimize their risk reduction (see next section). Clinical management Initial considerations Blood pressure is elevated sporadically in everybody. Key objectives in the assessment of essential hypertension are to establish whether blood pressure is persistently elevated; the level to which blood pres- sure is elevated (i.e. the severity of hypertension); and the presence or absence of hypertension-mediated target organ damage. The initial assessment is usually followed by a period of observation, the dur- ation of which will be dependent on the severity of the hypertension and the associated cardiovascular disease risk and damage. Lifestyle advice should be provided during this observation period, with drug therapy initiated depending on the level of blood pressure and overall cardiovascular disease risk at the end of the observation period. Establishing the diagnosis Patients with essential hypertension usually present in one of three ways: • as an asymptomatic individual whose blood pressure has been meas- ured at routine examination for employment, insurance, or as a re- sult of screening or preoperatively—the most common presentation; • as a patient whose blood pressure has been measured opportunis- tically when presenting with an unrelated disorder; or • as a result of symptoms produced by hypertension, or by the acute or chronic complications of hypertension—the least common presentation. Repeated blood pressure measurements over a period of obser- vation are usually necessary to establish the diagnosis. Exceptions to this are patients presenting with severe hypertension in whom fundal examination or other assessment of target organ damage (e.g. left ventricular hypertrophy or renal impairment) clearly reveals the presence of hypertension-mediated damage, indicative of the fact that the blood pressure needs treatment. The period of observation required before initiating drug therapy is dependent on the severity of the hypertension and the presence or absence of cardiovascular disease, diabetes, and/or target organ damage. Those with more severe hypertension and disease require emergency or urgent intervention with drug therapy to lower their blood pressure, whereas those with less severe hypertension and/ or the absence of damage or disease can be monitored over a longer period—up to many months—before initiating drug therapy. This period of observation is important because it is used to repeat blood pressure measurements, confirm the presence of sustained hyperten- sion, and get a more accurate appreciation of the associated risk, also to implement lifestyle interventions that may reduce blood pressure. Diagnostic thresholds for therapeutic intervention, the observation period, and treatment targets The diagnostic thresholds and appropriate interventions for the levels of hypertension severity are shown in Fig. 16.17.2.6, and the recommended period of observation for different grades of hyper- tension are shown in Table 16.17.2.3. Although there is general consensus about the management of grade II (i.e. ≥160/100 mm Hg) or more severe hypertension, the British guidelines have trad- itionally been more cautious than other guidelines with regard to drug therapy for uncomplicated grade I hypertension (140–159/ 90–99 mm Hg; see Fig. 16.17.2.6 and Table 16.17.2.3). Most other guidelines recommend treating all patients under the age of 60 years with a blood pressure sustained above 140/90 mm Hg, and the 2018 European guidelines state that treatment can be considered for pa- tients with high normal BP (130–139/85–89 mm Hg) when cardio- vascular risk is very high due to established cardiovascular disease, whereas the 2019 British (NICE) guidelines have recommended drug therapy for those with grade I hypertension only when there is associated cardiovascular disease or target organ damage, or a calculated risk of cardiovascular disease at least 10% over 10 years. There is genuine uncertainty about the cost-effectiveness of treating otherwise low-risk people with grade I hypertension, but this must be balanced by recognition that the greatest burden of blood pressure-attributable disease in populations is in those with grade I hypertension because it is so common. Moreover, blood pressure will invariably continue to rise in

patients with grade I hyperten- sion, and there is concern that the subtle vascular damage that is occurring while these patients remain untreated may not be revers- ible when treatment is eventually initiated at higher levels of pres- sure. Thus, while a prolonged period of observation and lifestyle intervention for uncomplicated, low-risk, grade I hypertension is considered acceptable, it is inevitable that most of these patients will eventually (if not immediately) require drug treatment. Further differences between guidelines relate to older patients: current

section 16 Cardiovascular disorders 3762 American guidelines suggest treating to a goal of less than 150/ 90 mm Hg for patients over 60 years of age; the British guideline recommends the same higher target for those over 80 years of age; and the 2018 European guideline suggests a systolic target of 130–139 mm Hg in patients over 80 years of age ‘if tolerated’. The reason that the 2018 European guidelines recommend a lower treatment threshold than most other guidelines is worthy of some comment. The SPRINT trial, published in 2015, found that patients at high risk of cardiovascular events but without diabetes (excluded because of the findings of the ACCORD trial) had lower rates of fatal Clinic blood pressure < 140/90 mm Hg Normotensive Clinic blood pressure ≥ 140/90 mm Hg Clinic blood pressure ≥ 180/110 mm Hg Refer same day for specialist care Consider starting antihypertensive drug treatment immediately Offer ABPM3 (or HBPM4 if ABPM is declined or not tolerated) Offer to assess cardiovascular risk and target organ damage ABPM/HBPM < 135/85 mm Hg Normotensive ABPM/HBPM ≥ 135/85 mm Hg Stage 1 hypertension ABPM/HBPM ≥ 150/95 mm Hg Stage 2 hypertension Offer antihypertensive drug treatment Consider specialist referral Offer lifestyle interventions Offer patient education and interventions to support adherence to treatment Offer to check blood pressure at least every 5 years, more often if blood pressure is close to 140/90 mm Hg 1 Signs of papilloedema or retinal haemorrhage 2 Labile or postural hypotension, headache, palpitations, pallor and diaphoresis 3 Ambulatory blood pressure monitoring 4 Home blood pressure monitoring Offer annual review of care to monitor blood pressure, provide support and discuss lifestyle, symptoms and medication Consider alternative causes for target organ damage If evidence of target organ damage If target organ damage present, established cardiovascular disease, renal disease, diabetes or 10-year cardiovascular risk > 10% If younger than 40 years If accelerated hypertension1 or suspected phaeochromocytoma2 Fig. 16.17.2.6 Thresholds and appropriate inventions depending on blood pressure. Note: if ABPM or HBPM are not available, then proceed as advised in Table 16.17.2.3. From National Clinical Guideline Centre (2011). Hypertension—the clinical management of primary hypertension in adults. Clinical Guideline 127, with modification from National Clinical Guideline Centre (2019) Hypertension in adults: diagnosis and management. Clinical Guideline 136.

16.17.2 Essential hypertension: Diagnosis, assessment, and treatment 3763 and nonfatal major cardiovascular events and deaths from any cause (composite main end-point 1.65%/year versus 2.19%/year) if treated to a target of systolic BP less than 120 mm Hg (121.4 mm Hg achieved) compared to less than 140 mm Hg (136.2 mm Hg achieved), albeit at the expense of a higher burden of some adverse events. Some com- mentators argue that these findings are not representative for trials with baseline normotension and low levels of previous cardiovas- cular disease, in which antihypertensive treatment does not protect against death or major cardiovascular events, and they also note that the way in which blood pressure was measured gives lower readings than those obtained in other clinical trials and in routine clinical practice. However, the SPRINT findings—along with some recent meta-analyses—led the 2018 European guideline authors to state that, provided treatment is well tolerated, treated BP should be targeted

to less than 130/80 mm Hg in most patients, whilst noting that in some groups of patients the evidence for this is ‘less compelling’. Explanation to the patient The treatment of hypertension is directed towards reducing risk rather than treating symptoms. It is imperative, therefore, to explain the significance of high blood pressure at the earliest op- portunity. Many patients find difficulty in grasping the concept of blood pressure variability and are often alarmed by the inevitable occasional high reading. Discussion of the rationale for evalu- ation and treatment, together with an explanation of the nature of high blood pressure and its very high prevalence, reassures patients and may improve adherence to treatment. Further com- prehensive advice for patients may be obtained from http://www. bpassoc.org.uk. Lifestyle advice Blood pressure is strongly influenced by lifestyle factors such as diet and exercise and their consequences such as on body weight. Effective lifestyle modification for patients with grade I hyperten- sion may lower blood pressure as much as a single blood pressure lowering drug, and combinations of two or more lifestyle modifi- cations may be even more effective. Lifestyle interventions may re- duce the need for drug therapy for people with mild hypertension, can enhance the antihypertensive effects of blood pressure lowering medication, and can favourably influence overall cardiovascular disease risk. The most effective lifestyle interventions for reducing blood pres- sure in clinical trials are modifications to diet to induce weight loss, regular aerobic exercise, and restrictions in alcohol and sodium intake. The expected reductions in blood pressure with these life- style manoeuvres are shown in Table 16.17.2.4, and recommended Table 16.17.2.3 Typical observation periods for different grades of hypertension and associated cardiovascular disease, diabetes, and/or target organ damage Grade of hypertension Typical observation period Accelerated (malignant) hypertension (papilloedema and/or fundal haemorrhages and exudates, or with acute cardiovascular complications e.g. aortic dissection) Immediate treatment—usually requiring acute hospital admission (see Chapter 16.17.5) BP ≥220/120 mm Hg Treat immediately—hospital admission not usually required Grade III hypertension BP >180–219/110–119 mm Hg Confirm by repeated measurements over 1–2 weeks, then treat Grade II hypertension BP 160–179/100–109 mm Hg In the presence of cardiovascular disease, diabetes, or target organ damage: confirm over 3–4 weeks, then treat No cardiovascular disease, diabetes, or target organ damage: lifestyle measures, re-measure weekly initially, and treat if BP persists at these levels over 4–12 weeks Grade I hypertension: BP 140–159/90–99 mm Hg Cardiovascular disease, diabetes, or target organ damage: either confirm or refute diagnosis by (a) ABPM) or HBPM, or (b) repeat clinic measurement within weeks, then treat if diagnosis confirmed No clinical cardiovascular disease, diabetes or target organ damage: lifestyle advice and either confirm or refute diagnosis by (a) ABPM or HBPM, or (b) re-measure clinic BP at monthly intervals for 3–6 months. If mild hypertension persists, estimate 10-year cardiovascular diseases risk and treat if this is ≥20% (if <20%, keep under annual review) ABPM, ambulatory blood pressure measurement; BP, blood pressure; HBPM, home blood pressure measurement. Modified and updated from Williams B, et al. (2004). BMJ, 328, 364–40. Table 16.17.2.4 Blood pressure reductions associated with lifestyle interventions for patients with hypertension Intervention Recommendation Expected SBP reduction (range) Weight reduction Maintain ideal BMI (20–25 kg/m2) 5–10 mm Hg per 10 kg weight loss DASH eating plan Consume diet rich in fruit, vegetables, low-fat dairy products with reduced content of saturated and total fat 8–14 mm Hg Dietary sodium restriction Reduce dietary sodium intake to <100 mmol/day (<2.4 g sodium or <6 g sodium chloride) 2–8 mm Hg Physical activity Engage in regular aerobic physical activity, e.g. brisk walking for at least 30 min most days 4–9 mm Hg Alcohol moderation Men ≤21 units/week 2–4 mm Hg Women ≤14 units/week BMI, body mass index; DASH, Dietary Approaches

to Stop Hypertension; SBP, systolic blood pressure.

section 16 Cardiovascular disorders 3764 lifestyle interventions to reduce blood pressure and/or cardiovas- cular disease risk are shown in Box 16.17.2.4. Patients are often enthusiastic to try lifestyle changes rather than take drug therapy. This is a reasonable initial option in pa- tients with grade I hypertension who do not have associated target organ damage or high cardiovascular disease risk. In patients with more severe hypertension or those at high risk, lifestyle measures should be recommended alongside drug therapy. This is important because these measures may improve the effectiveness of drug therapy and also contribute to a reduction in overall cardiovas- cular risk. Note, however, that effective implementation of lifestyle measures requires enthusiasm, knowledge, patience, and consid- erable time spent with patients and other family members. It is best undertaken by well-trained health professionals (e.g. prac- tice or clinic nurses), and should be supported by clear written information. Weight reduction Many patients with hypertension are overweight, and weight re- duction by calorie restriction is an appropriate recommendation. The blood pressure lowering effect of weight reduction may be en- hanced by increased regular aerobic physical exercise, by alcohol moderation in heavy drinkers, and by a reduction in sodium intake. On average, blood pressure may fall by as much as 1 mm Hg per kg weight loss, although results vary in studies and the maximum overall effect of combined lifestyle interventions is an average of 10 mm Hg fall in SBP. Body mass index (BMI) is frequently used as a measure of overweight, but other measures of obesity—particularly central obesity—are better markers of adverse cardiovascular out- comes in people with hypertension. In this regard, weight reduction also has beneficial effects on associated risk factors such as insulin resistance, risk of developing diabetes, and dyslipidaemia. Dietary salt reduction Sodium intake influences blood pressure and all international guidelines recommend dietary sodium restriction. Dietary salt re- duction from an average of 10 to 5 g/day (5 g = 1 teaspoon) lowers blood pressure by about 5/2 mm Hg, with larger blood pressure falls in elderly people, blacks, and those with higher initial blood pres- sure levels. About one-third of people will achieve a reduction of 5/ 5 mm Hg or more. These effects are additive to the blood pressure lowering effect of a healthy diet (e.g. the Dietary Approaches to Stop Hypertension (DASH) diet; http://www.nhlbi.nih.gov/health/ public/heart/hbp/dash/). Many patients will already be aware of the relationship between salt and blood pressure and will have discontinued adding salt at the table and even when cooking, but few are aware of the large amount of salt in processed foods, such as bread (one slice contains 0.5 g salt), some breakfast cereals, ready-prepared meals, and flavour en- hancers such as stock cubes or manufactured sauces. Patients, and those who cook for patients, should be provided with specific written advice, such as that from http://www.bpassoc.org.uk. Increased fruit and vegetable consumption Using the DASH diet, which increased vegetable consumption from two to seven portions per day, blood pressure was lowered by around 7/3 mm Hg in hypertensive patients. Hypertensive pa- tients should therefore be given clear advice to increase fruit and vegetable intake to at least five portions per day. When this is com- bined with an increased use of low-fat dairy products and reduc- tion of total and saturated fat, then blood pressure falls averaging 11/6 mm Hg are seen. The mechanism whereby fruit and vegetable consumption lowers blood pressure is uncertain, but it may be due to an associated increase in potassium intake, as suggested by some supplementation studies. Physical activity Regular physical activity, especially when combined with dietary measures, can be particularly effective at reducing blood pressure (Table 16.17.2.4). The activity should be regular, aerobic (e.g. brisk walking), and tailored to the individual. For example, three vigorous training sessions per week may be appropriate for fit younger pa- tients, or brisk walking

for 20 min/day in older patients. This activity will be expected to reduce SBP and DBP by about 2–3 mm Hg, with the combination of exercise and diet reducing both by 5–6 mm Hg. Heavy physical exercise should be discouraged in people with severe hypertension or those in whom hypertension is poorly controlled. Exercise can be recommenced once drug therapy has been started and blood pressure is better controlled. In addition to its effects on blood pressure, physical exercise ap- pears to exert a strong protective effect against cardiovascular mor- tality and is associated with a lower risk of coronary heart disease in men and women. Protection is lost when exercise is discontinued. Any activity appears to be of benefit, but people who are more active appear to gain more protection. A reasonable strategy is regular aer- obic exercise (e.g. brisk walking) for at least 30 min, ideally on most days, but at least 3 days per week. Alcohol intake An alcohol intake of above 21 units per week is associated with blood pressure elevation, and binge drinking is associated with an increased risk of stroke. Hypertensive patients should be ad- vised to limit their alcohol intake to 21 units per week (men) and 14 units per week (women). On average, structured interventions to reduce alcohol consumption have a small effect on blood pres- sure, reducing SBP (and possibly DBP) by about 2–3 mm Hg. Consumption of smaller amounts of alcohol, up to the recom- mended limit, may protect against cardiovascular disease and should not be discouraged. Box 16.17.2.4 Lifestyle measures that lower blood pressure and reduce cardiovascular disease risk Measures to lower blood pressure • Weight reduction • Reduced salt intake • Limitation of alcohol consumption • Increased physical activity • Increased fruit and vegetable consumption • Reduced total fat and saturated fat intake Measures to reduce cardiovascular disease risk • Cessation of smoking • Reduced total fat and saturated fat intake • Replacement of saturated fats with monounsaturated fats • Increased consumption of oily fish

 Caffeine consumption Following caffeine consumption there is a dose-related increase in SBP of 5–15 mm Hg and of DBP of 5–10 mm Hg that persists for several hours. A systematic review of studies of median duration 8 weeks showed that people drinking an average of five cups of caf- feinated coffee a day had blood pressure 2.4 mm Hg (systolic) and 1.2 mm Hg (diastolic) higher than controls (no coffee, or decaffein- ated coffee). There is no good data on the effect of withdrawing or limiting caffeine intake in patients with hypertension. Sleep and blood pressure Blood pressure characteristically falls during sleep, and sleep duration impacts on the risk of developing hypertension. The risk of developing hypertension in one survey was increased by about twofold in adults in middle age who sleep 5 h or less each night. This may simply re- flect a higher 24 h average blood pressure load and longer duration of sympathetic nervous system activation as a consequence of less time asleep, which in turn would give rise to a higher risk of longer-term cardiovascular structural damage, leading to sustained hypertension. Whatever the mechanism, sleep deprivation should be considered in the assessment of people developing hypertension. Consistent with the association between sleep deprivation and hypertension, high blood pressure is more common in patients with obstructive sleep apnoea. Although this could be explained by the fact that both conditions are commoner in males and in obese individuals, a few studies indicate that continuous positive airways pressure can reduce blood pressure, particularly nocturnal pressures, implying a causal relationship. Lifestyle strategies to reduce cardiovascular risk in hypertensive patients Cigarette smoking Patients with hypertension should be encouraged and given support to stop smoking. Nicotine replacement therapy and other strategies are safe and effective in people with hypertension and double the chance of quitting smoking. Those who fail on their first attempt to quit should be encouraged to continue trying: the chance of success increases with the number of

quit attempts. Although smoking is not a major contributor to an elevated blood pressure, it does signifi- cantly amplify the cardiovascular risk associated with hypertension. Smoking is a major factor related to the persistent increase in cor- onary and stroke mortality in men with treated hypertension. Those who stop smoking experience a rapid decline in risk, by as much as 50% after 1 year, but up to 10 years may be needed to reach the risk level of those who have never smoked. Smoking an e-cigarette causes an acute rise in blood pressure of about 10/7 mm Hg that lasts for about 30 minutes, which is comparable to the effect of smoking a conventional (tobacco) cigarette, but overall vaping poses only a small fraction of the risks of smoking and switching com- pletely from smoking to vaping conveys substantial health benefits. Reduced dietary saturated fat intake Reducing dietary fat intake can reduce serum cholesterol values, which can reduce the risk of cardiovascular disease. All patients should be advised to keep total dietary intake of fat to less than one- third of their total energy intake, to keep the intake of saturated fats to less than one-third of their total fat intake, and to replace saturated fats by an increased intake of monounsaturated fats. These dietary changes can be very effective, but reduce serum cholesterol by only about 6% on average, in part because of difficulty in sustaining such dietary discipline. A regular intake of fish and other sources of n-3 fatty acids (at least two servings of fish per week) will further improve lipid profiles and has been shown to reduce blood pressure. Lifestyle modifications that are ineffective at lowering
blood pressure Dietary supplements The best available evidence does not support the use of calcium, magnesium, or potassium supplementation (i.e. tablets), individu- ally or in combination, to achieve a worthwhile reduction in blood pressure. Inadequate information is available from randomized con- trolled trials to support any recommendation for garlic, herbal, or other complementary medicines. Psychological stress reduction Structured interventions to reduce stress (e.g. stress management programmes, meditation, yoga, cognitive therapies, breathing exer- cises, biofeedback, and acupuncture) have been shown to modestly reduce blood pressure in some but not all studies. However, many of these interventions are time consuming and have been short term, and it is difficult to know whether they would be an effective inter- vention for adequate blood pressure control over the longer term. Pharmacological treatments The treatment of hypertension has been subjected to many large randomized controlled trials that have compared active treatments with placebo, and different treatment strategies with each other. Hypertension has the most impressive evidence base in medicine to guide treatment decisions, and analysis of this has provided im- portant guiding principles with regard to treatment strategies: • Effective blood pressure lowering is overwhelmingly important in reducing the risk of major cardiovascular events in people with hypertension, thus the first priority in treatment is to control blood pressure. • Many patients will require more than one drug to control blood pressure; monotherapy is rarely sufficient. • Although early studies focused primarily on DBP as the treatment target, SBP is invariably more difficult to control and should now be the main focus of treatment. • The blood pressure response to an individual class of blood pres- sure lowering medication is heterogeneous, hence there is no ‘per- fect drug’ for every patient. • Some trials have indicated that certain comorbidities or target organ damage provide compelling indications for inclusion of specific classes of drug therapy in the treatment regimen. • There is inadequate clinical outcome data for treatment studies of younger patients as most of the studies, especially the more recent ones, have been conducted in patients over the age of 55 years, and typically with a mean age over 65 years. Blood pressure lowering therapy is effective at reducing the risk of stroke, myocardial infarction, heart failure, chronic kidney dis- ease, peripheral vascular disease, and death. It may also be effective at reducing the risk of vascular dementia. On average, lowering blood pressure by

20/10 mm Hg will reduce the risk of major cardiovascular

section 16 Cardiovascular disorders 3766 events by one-half, with the reduction in stroke risk appearing to follow the predicted reduction in risk based on the epidemiological association between stroke and blood pressure. There appears to be a shortfall in the reduction in risk of ischaemic heart disease with blood pressure lowering when compared to epidemiological predic- tions, which is best addressed by attention to concomitant risk fac- tors. Importantly, the risk reduction associated with blood pressure lowering appears to be continuous across a wide range of blood pres- sures, thus the absolute benefit from treatment is greatest in those with the highest absolute cardiovascular disease risk. This provides the rationale for advocating the use of complementary strategies to re- duce cardiovascular disease risk (e.g. statins and antiplatelet therapy) in those with established vascular disease, target organ damage, or at high calculated cardiovascular disease risk (i.e. a calculated cardio- vascular disease risk of 20% or more over 10 years). The main classes of blood pressure lowering therapies are sum- marized in this section. Those that have been used in clinical trials are shown in Table 16.17.2.5. The overriding treatment priority is to control blood pressure, but there is general consensus among international guidelines about indications and contraindications for the use of specific classes of blood pressure lowering therapy in specific clinical situations, and these are detailed in Tables 16.17.2.6 and 16.17.2.7. It is important to note that these lists are not compre- hensive and are subject to change as new evidence emerges, and the reader is directed towards the information sheets for each specific drug for more detailed prescribing information. Diuretics Thiazides Thiazide-type diuretics (TTDs) were the first major class of drug used to treat hypertension on a large scale and they remain one of the main therapeutic options for the treatment of essential hypertension. Commonly used examples include chlortalidone, hydrochlorothiazide, and bendroflumethiazide. TTDs lower blood pressure by a complex series of mechanisms. Urinary loss of sodium resulting from a blockade of renal tubular reabsorption of sodium is integral to the antihypertensive effect. The early changes in salt and water balance are often accompanied by counteractivation of sev- eral vasoconstrictor mechanisms, including the renin–angiotensin– aldosterone system, which may transiently raise peripheral vascular resistance and attenuate blood pressure lowering. There is subse- quently a gradual reduction in peripheral vascular resistance and a new steady state of reduced total body sodium and blood pressure. The sustained actions of thiazide/thiazide-like diuretics on the kidney make them preferable to loop diuretics for the control of blood pressure. This is because loop diuretics are shorter acting, and the short-term sodium and water loss is usually compen- sated for by sodium retention during the latter part of the dosing interval and reduced blood pressure lowering efficacy. There is really no place for loop diuretics in the routine management of essential hypertension, but TTDs become ineffective in patients with a glomerular filtration rate below 30 ml/min and in such Table 16.17.2.5 Drugs used in clinical trials of treatment of hypertension Class of drug Drug Target dose (mg) ACE inhibitors Captopril 150–200 Enalapril 20 Lisinopril 40 Angiotensin receptor blockers Eprosartan 600–800 Candesartan 12–32 Losartan 100 Valsartan 160–320 Irbesartan 300 β-blockers Atenolol 100 Metoprolol 100–200 Calcium channel blockers Amlodipine 10 Diltiazem extended release 360 Nitrendipine 20 Thiazide-type diuretics Bendroflumethiazide 10 Chlortalidone 12.5–25 Hydrochlorothiazide 25–100 Indapamide 1.25–2.5 Table 16.17.2.6 Indications favouring the use of specific classes of blood pressure lowering drugs Thiazide diuretics Isolated systolic hypertension (elderly) Heart failure Hypertension in blacks ACE inhibitors Heart failure LV dysfunction Postmyocardial infarction Diabetic nephropathy Nondiabetic nephropathy LV hypertrophy Carotid atherosclerosis Proteinuria/microalbuminuria Atrial fibrillation

Metabolic syndrome Angiotensin receptor blockers Heart failure Post-myocardial infarction Diabetic nephropathy Proteinuria/microalbuminuria LV hypertrophy Atrial fibrillation Metabolic syndrome ACEi-induced cough β-Blockers Angina pectoris Post-myocardial infarction Heart failure Tachyarrhythmias Glaucoma Pregnancy Calcium antagonists (dihydropyridines) Isolated systolic hypertension (elderly) Angina pectoris LV hypertrophy Carotid/coronary atherosclerosis Pregnancy Hypertension in blacks Diuretics (antialdosterone) Heart failure Post-myocardial infarction Calcium antagonist (verapamil/diltiazem) Angina pectoris Carotid atherosclerosis Supraventricular tachycardia Loop diuretics Stage 4 and 5 chronic kidney renal disease Heart failure

16.17.2 Essential hypertension: Diagnosis, assessment, and treatment 3767 patients loop diuretics are often required for effective blood pres- sure lowering, especially when there is clinical evidence of sodium and water retention. The main adverse effects of TTDs are hypokalaemia, hyponatraemia (less commonly), impaired glucose tolerance, and small increments in blood levels of LDL cholesterol and triglycerides. TTDs elevate serum uric acid levels and should be avoided in patients predisposed to gout. They should also be avoided in those receiving lithium because of a high risk of lithium toxicity. An incidental advantage of thiazides may be re- duction in osteoporosis as a result of calcium retention. To minimize the adverse effects of TTDs, low doses of these drugs have been recommended by guidelines for the treatment of essen- tial hypertension, and these are well tolerated. On the basis of some small studies it has been assumed that the dose response to TTDs is generally flat (unlike the adverse effect profile), and this has been used to further justify the low-dose strategy for TTDs, but it should be emphasized that some patients do respond to and tolerate higher doses. Moreover, when thiazides are combined with drugs that block the renin–angiotensin system (e.g. ACE inhibition), then the dose response is steeper and higher doses may be used in patients with more resistant hypertension. Potassium-retaining diuretics Potassium-retaining diuretics (e.g. spironolactone or amiloride), are effective blood pressure lowering agents that are much less commonly used for the routine treatment of hypertension. They can be very effective in combination with TTDs, and are increas- ingly used as part of a multidrug strategy for the treatment of re- sistant hypertension. They are used and effective in large doses in the treatment of primary aldosteronism. They have the advan- tage over TTDs in not causing hypokalaemia or hyperuricaemia and do not impair glucose tolerance, but spironolactone causes nipple tenderness and gynaecomastia in some patients, which is dose-dependent and can limit its use. Eplerenone, which was de- veloped to bind selectively to mineralocorticoid receptors with minimized binding to progesterone and androgen receptors, does not have such sexual adverse effects. As would be antici- pated from their mode of action, if potassium-sparing diuretics are used in combination with drugs that block the activity of the renin–angiotensin system or in patients with renal impairment, then monitoring of serum potassium is required because of the increased risk of hyperkalaemia. β-Adrenoceptor blocking drugs (β-blockers) β-Blockers reduce blood pressure and cardiovascular events in patients with hypertension. Most β-blockers, with the exception of those with strong intrinsic sympathomimetic activity, reduce cardiac output due to their negative chronotropic and inotropic effects. As with diuretics, short-term haemodynamic responses can be off-set by counteractivation of vasoconstrictor mechanisms, which may limit initial blood pressure lowering. Longer-term reduction in arterial pressure, which occurs over days, is due to restoration of vascular re- sistance to pretreatment levels. Partial blockade of renin release from the kidney may contribute to the later haemodynamic response. β-Blockers differ in their duration of action, their selectivity for β1-receptors, lipophilicity, and partial agonist activity. Side effects include lethargy, aches in the limbs on exercise, impaired concen- tration and memory, erectile

dysfunction, vivid dreams, and exacer- bation of symptoms of peripheral vascular disease and Raynaud's syndrome. They are contraindicated in asthma and can cause adverse metabolic effects, including impaired glucose tolerance and worsening of dyslipidaemia—notably reduced HDL-cholesterol and raised triglycerides. There is accumulating evidence that β-blockers increase the likelihood of new-onset diabetes, particularly when combined with TTDs. Moreover, meta-analyses suggest that there is a shortfall in cardiovascular protection with β-blocker-based treat-ment for hypertension (especially in stroke reduction) when com- pared to treatment with other main drug classes. As a consequence, British and American guidelines do not recommend β-blockers as an initial therapy for uncomplicated hypertension, and they should only be used when there is a compelling indication other than blood pressure control (e.g. in patients with hypertension and angina or chronic heart failure). One exception is in younger women of child-bearing potential, in whom β-blockers are often very effective at lowering blood pressure, perhaps due to higher-renin levels of younger people, and safer than ACE inhibition or angiotensin re-ceptor blockers (ARBs) in those anticipating pregnancy. Calcium channel blockers This class of drug has been extensively used in treating hypertension since the 1970s: they are very effective at reducing blood pressure and have an extensive evidence base supporting their use. In add- ition to their blood pressure lowering properties, they are also ef- fective antianginal agents.
Table 16.17.2.7 Compelling and possible contraindications to specific classes of blood pressure lowering therapies Compelling Possible Thiazide diuretics Gout Metabolic syndrome Glucose intolerance Pregnancy β-Blockers Asthma AV block (grade 2 or 3) Peripheral artery disease Metabolic syndrome Glucose intolerance Athletes and physically active patients Chronic obstructive pulmonary disease Calcium antagonists (dihydropyridines) Tachyarrhythmias Heart failure Calcium antagonists
(verapamil, diltiazem) AV block (grade 2 or 3) Heart failure ACE inhibitors Pregnancy Angioneurotic oedema Hyperkalaemia Bilateral renal artery stenosis Angiotensin receptor antagonists Pregnancy Hyperkalaemia Bilateral renal artery stenosis Diuretics (antialdosterone) Renal failure Hyperkalaemia ACE, angiotensin converting enzyme; AV, atrioventricular. Data from Williams, et al. BHS Guidelines 2004. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV.

 There are two main groups of calcium channel blocker (CCB), the dihydropyridines (e.g. amlodipine, nifedipine) and the nondihydropyridines (e.g. diltiazem, verapamil). The dihydropyrid ine CCBs act mainly by inducing relaxation of arterial smooth muscle by blocking L-type calcium channels, thereby inducing peripheral vascular relaxation with a fall in vascular resistance and arterial pressure. Nondihydropyridine CCBs also block calcium channels in cardiac muscle and reduce cardiac output. Verapamil has an additional antiarrhythmic action through its effects on the atrioventricular node. The earlier formulations of some dihydropyridines, such as cap- sular nifedipine, had a rapid onset of action, unpredictable effects on blood pressure, and were accompanied by reflex sympathetic stimulation and tachycardia. With the availability of longer-acting formulations of dihydropyridine CCBs, these shorter-acting CCBs have no place in the management of hypertension, even (and espe- cially) in the emergency setting (see Chapter 16.17.5). Side effects of dihydropyridine CCBs include dose-dependent peripheral oedema, which is not due to fluid retention but results from transudation of fluid from the vascular compartments into the dependent tissues due to precapillary arteriolar dilatation. This oedema does not respond to diuretic therapy but is alleviated by limb elevation, and there is some evidence that it may be reduced by coadministration of an ACE inhibitor or ARB

because of their effects on venous capacitance. Gum hypertrophy can occur with dihydropyridine CCBs, but is rarely seen with nondihydropyridine CCBs. Nondihydropyridine CCBs cause less peripheral oedema but are negatively inotropic and negatively chronotropic and should therefore be avoided in patients with compromised left ventricular function, and used with caution in combination with β-blockers. Verapamil use is commonly accompanied by constipation. Blockade of the renin–angiotensin system The renin–angiotensin system has been a very popular target for drug development to treat hypertension. Inhibition of the renin–angiotensin system is predictably effective at lowering blood pressure by inhibiting the various central and peripheral pressor effects of angiotensin II, and blockade may also lower blood pressure by other mechanisms involving improvements in endothelial function, vagal tone, and baro- receptor function, and via inhibition of the renal tubular reabsorption of sodium. In addition, inhibition of the renin–angiotensin system has been promoted by clinical trial evidence showing reduced morbidity and mortality with these treatments in patients with heart failure, delay in the progression of renal disease, and reduction in cardiovascular events in patients at high cardiovascular risk. ACE inhibitors The ACE inhibitors, which block the conversion of angiotensin I to angiotensin II, were the first effective drugs to inhibit the renin– angiotensin system and have been used to treat hypertension since the late 1970s. The resulting reduction in levels of angiotensin II leads to vasodilatation and a fall in blood pressure. Angiotensin II has many additional actions that are potentially harmful to the cardiovascular system and have been implicated in the pathogenesis of structural changes in the heart, blood vessels, and kidneys in hypertension. Sharp falls in blood pressure following the introduction of ACE inhibitors may occur when the renin–angiotensin system is acti- vated (e.g. in patients who are dehydrated, in heart failure, or have accelerated hypertension). This is rarely a problem when therapy is initiated in uncomplicated hypertensive patients. Side effects of ACE inhibitors include the development of a persistent dry cough in about 20% of users. This is more common in women and in people from Asia, and only disappears after discontinuation of the drug. Another rare but important complication is angio-oedema, which occurs in around 1% but is much more common in the black popu- lation (c.4%). ACE inhibitors should be avoided in women of child- bearing potential because of the danger of fetal renal malformation. They should not be used in patients with known bilateral renal artery disease because they may precipitate deterioration in renal function and renal failure. It should be routine practice to check the serum creatinine 10–14 days after initiation of ACE inhibition, and to stop the drug if this has risen by more than 30%: lesser elevations can be tolerated. Particularly careful monitoring of renal function and serum potassium is required in patients with more advanced renal impairment of any cause because of the risk of hyperkalaemia. Angiotensin receptor blockers (ARBs) In the 1990s, the ARBs, which are highly selective inhibitors of the angiotensin II type 1 receptor (AT-1), emerged as an alternative to ACE inhibition. In general, they are as effective as ACE inhibitors at reducing blood pressure, but appear to have a longer duration of action, and in common with ACE inhibitors they inhibit the actions of angiotensin II on the cardiovascular system and kidney. They are very well tolerated by patients, with a placebo-like adverse effect profile. Cough and angio-oedema are much less likely to occur than with ACE inhibitors and most guidelines recommend switching pa- tients to an ARB when an ACE-induced cough occurs. Cautions and contraindications are similar to those outlined for ACE inhibitors. Direct renin inhibition A third strategy to inhibit the renin–angiotensin system for the treat- ment of hypertension is direct renin inhibition, the first nonpeptide, orally active, direct renin inhibitor being aliskiren. This has high specifi- city for renin and is a potent renin inhibitor with a long half-life (c.24 h). It inhibits the rate-limiting step in angiotensin production, notably the renin-dependent conversion of angiotensinogen to angiotensin I, and in initial studies appeared to have similar blood

pressure lowering effi- cacy to other means of inhibiting the renin system (i.e. ACE inhibition or ARBs), but with less side effects than ACE inhibition. However, the combination of aliskiren with ACE inhibitor or ARBs was found to have serious adverse cardiovascular and renal outcomes in a large clinical trial (ALTITUDE) that was stopped following interim data analysis, as a result of which some regulatory authorities have stated that the com- bination of these drugs is contraindicated (in patients with diabetes) or not recommended (in other patients), and recommended that aliskiren should not be used in those with eGFR less than 30 ml/min (CKD4). α-Adrenergic blocking drugs The original members of this class (e.g. prazosin) were short acting drugs that blocked the activation of α1 adrenoceptors in the vas- culature, leading to vasodilatation. The dosages that were initially recommended were too high, and postural hypotension and syn- cope proved serious problems that retarded the acceptance of this class of drugs, although the use of lower doses and the development of longer-acting agents (e.g. doxazosin) has largely overcome this problem. Blockade of sphincteric receptors improves symptoms in

 patients with benign prostatic hypertrophy, and occasionally these same sphincteric effects can worsen symptoms of stress incontin- ence in women. Uniquely among antihypertensive drugs, the α1- antagonists produce modest favourable changes in plasma lipids, with a reduction in total and LDL cholesterol and triglycerides, and an increase in high-density lipoprotein (HDL) cholesterol. Centrally acting sympatholytic drugs Some of the earliest drugs developed to treat hypertension targeted the activation of the sympathetic nervous system at various levels, including the cardiovascular regulatory nuclei in the brainstem, the peripheral autonomic ganglia, and the post-ganglionic sympathetic neuron. With one or two exceptions, few of these agents have any re- sidual role to play in the modern treatment of hypertension because side effects are common, often unpleasant, and potentially harmful. Methyldopa Methyldopa reduces sympathetic outflow from the brainstem. It was originally developed in the late 1950s and for many years it was one of the mainstays of antihypertensive therapy. However, it frequently causes sedation, impaired psychomotor performance, dry mouth, and erectile dysfunction. This unfavourable impact upon quality of life led to it being replaced by more effective drugs, although it is still used extensively in the management of hypertension of pregnancy, which is now its main indication. Clonidine Clonidine is now rarely used because of its short duration of action and risk of a withdrawal syndrome after discontinuing the drug: sudden dis- continuation results in a rebound rise in catecholamines with features that may resemble phaeochromocytoma, such as severe hypertension, tachycardia, and sweating. This is exacerbated when patients are also receiving nonselective β-blockers such as propranolol. The syndrome is treated by readministering the drug and then gradually discontinuing it, or the intravenous infusion of labetalol in an emergency. Moxonidine Moxonidine is a newer centrally acting agent that is an imidazoline receptor agonist, acting to reduce sympathetic outflow and blood pressure. It has a lower incidence of side effects and is better toler- ated than other centrally acting agents. Direct vasodilators Hydralazine Hydralazine was previously extensively used as part of a stepped care regimen. However, its main disadvantages were sympathetic activation and the development of a lupus-like syndrome, particularly in patients with the slow acetylator genotype, which together with the need for multiple daily dosage have resulted in its replacement by other agents, except for occasional use in severe hypertension and hypertension as- sociated with pregnancy. No end-point trials have been carried out. Minoxidil Minoxidil is a very potent vasodilator. Its use is confined to specialist practise for the treatment of severe and resistant hypertension because of its side effects, which include stimulation of body hair growth,

tachycardia, and severe fluid retention. For this reason, combination with a potent loop diuretic and a β-blocker is almost always necessary. Other therapies Hypertension is common, as are the side effects of its treatment, which continue to drive the search for new drugs that might be safer, more effective, better tolerated and/or have additional benefits (e.g. on endothelial function). Drugs under investigation include endothelin receptor antagonists and phosphodiesterase type 5 inhibitors. Pharmacological treatment strategies Initial drug therapy After a suitable period of observation and after assessment of con- comitant risk factors, comorbid disease, and overall cardiovascular disease risk, a decision may be reached to treat the patient with drug therapy. However, even when this is contemplated it is important to continue to emphasize the importance of lifestyle changes to re- duce cardiovascular risk and enhance the efficiency of blood pres- sure lowering medications, and it is also important to view the patient's blood pressure in the context of their overall cardiovascular risk burden and decide whether other therapies such as statins and antiplatelet therapy might also be appropriate. Once a decision has been made to initiate drug therapy, it is usual to commence treatment with a single drug. Monotherapy will on average reduce systolic pressure by 7 to 13 mm Hg and diastolic pressure by 4– 8 mm Hg. This will give some indication as to whether monotherapy is likely to be effective at achieving the recommended blood pressure goal, but there is marked heterogeneity in response among individ- uals to particular drugs. Treatment should normally commence with a low dose of the drug selected. If an adequate response is not obtained, the dose of the initial drug can be increased. However, if there has not been much response to the starting dose and the patient's blood pressure remains well short of the target blood pressure, then a more appropriate action would be to add a second drug, either separately or as a combination tablet, mindful of the fact that most people with hypertension require two or more drugs to adequately control their blood pressure. Alternatively, if the initial drug produced a weak re- sponse, or none at all, and the patient could conceivably get to their blood pressure goal on monotherapy, then the first drug could be dis- continued and replaced with another class of antihypertensive agent. Initial therapy with a two-drug combination The heterogeneity of blood pressure responses to different classes of blood pressure lowering drugs and the likelihood that most people will be uncontrolled by monotherapy, and that up-titration in people at high risk may be too slow and leave them at risk for too long, has led to the suggestion that more people should be initiated on treatment with low-dose combination therapy. Low-dose two-drug combination therapy has long been recommended in European and American hypertension guidelines for the treatment of patients whose blood pressure is greater than 20/10 mm Hg above their goal blood pressure and therefore unlikely to achieve their goal blood pressure with monotherapy, and the 2018 European guideline has gone further than this by recommending that, with the exception of frail older patients and those at low risk and with Grade 1 hyper- tension (and particularly if SBP is <150 mm Hg), all patients should start treatment with a two drug combination, preferably in a single pill. It remains to be seen whether this recommendation will get traction in routine practice. The European guidelines are shown in Fig. 16.17.2.7 and the American guidelines in Fig. 16.17.2.8.

section 16 Cardiovascular disorders 3770 Fig. 16.17.2.7 2018 European Society of Hypertension/European Society of Cardiology guideline recommendations for uncomplicated hypertension (Panel A), hypertension in patients with coronary artery disease (Panel B), and hypertension in patients with chronic kidney disease (Panel C). ACEi, angiotensin coverting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; MI, myocardial infarction; o.d., once daily. a CKD is defined

as eGFR <60 ml/min/1.73 m2. b Use loop diuretic when eGFR <30 ml/min/1.73 m2. c Beware of the risk of hyperkalaemia. Reproduced from Williams B, et al. (2018). 2018 ESC/ESH guidelines for the management of arterial hypertension. J Hypertens, 36, 1953–2041, with permission from Wolters Kluwer.

16.17.2 Essential hypertension: Diagnosis, assessment, and treatment 3771 Adult aged ≥ 18 years with hypertension Implement lifestyle interventions (continue throughout management) Set blood pressure goal and initiate blood pressure lowering-medication based on age, diabetes, and chronic kidney disease (CKD) General population (no diabetes or CKD) Age ≥60 years Age <60 years All ages Diabetes present No CKD All ages CKD present with or without diabetes Blood pressure goal SBP <140 mm Hg DBP <90 mm Hg Blood pressure goal SBP <140 mm Hg DBP <90 mm Hg Blood pressure goal SBP <140 mm Hg DBP <90 mm Hg Blood pressure goal SBP <150 mm Hg DBP <90 mm Hg Nonblack Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combinationa Select a drug treatment titration strategy A. Maximize first medication before adding second or B. Add second medication before reaching maximum dose of first medication or C. Start with 2 medication classes separately or as fixed-dose combination Reinforce medication and lifestyle adherence. For strategies A and B, add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB). For strategy C, titrate doses of initial medications to maximum. Reinforce medication and lifestyle adherence. Add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB). Reinforce medication and lifestyle adherence. Add additional medication class (eg. β-blocker, aldosterone antagonist, or others) and/or refer to physician with expertise in hypertension management. Continue current treatment and monitoring.b Yes Yes Yes Yes No No No At goal blood pressure? At goal blood pressure? At goal blood pressure? No Initiate thiazide-type diuretic or CCB, alone or in combination Initiate ACEI or ARB, alone or in combination with other drug classa Black All races Diabetes or CKD present At goal blood pressure? Fig. 16.17.2.8 JNC8 hypertension guideline management algorithm. Note: (a) ACE inhibitor and ARBs should not be used in combination; (b) if blood pressure fails to be maintained at goal, re-enter the algorithm where appropriate based on the current individual therapeutic plan. From James PA, et al. (2014). 2014 Evidence-based guidelines for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC8). JAMA, 311, 507–20.

section 16 Cardiovascular disorders 3772 Choice of initial therapy There is some variation in the international guidelines with re- gard to the preferred initial therapy for essential hypertension. In the United States of America, the Joint National Committee 8 (JNC8) guideline recommends initial drug treatment with an ACE inhibitor, ARB, CCB, or TTD in nonblack hypertensive patients, with a CCB or TTD preferred in black patients (Fig. 16.17.2.8 and Table 16.17.2.8). The 2018 European guideline makes recommendations based on the patient’s comorbidities, in particular coronary artery disease and chronic kidney disease, but for uncomplicated hypertension the recommendation is for an ACEi or ARB in combination with a CCB or TTD in a single pill combination (Table 16.17.2.7 and Fig. 16.17.2.7). The British Hypertension Society/NICE guideline suggests that the most appropriate initial blood pressure lowering agent (1) for people 55 years or older (without type 2 diabetes), and for black people of African or Caribbean family origin of any age (without type 2 diabetes), is a CCB, with a thiazide-like diuretic (e.g. indapamide) preferred if a CCB is not suitable; and (b) for people aged under 55 years, and any person with type 2 diabetes, an ACE

inhibitor or a low-cost ARB is preferred initial therapy (Fig. 16.17.2.9). The ra- tionale for this recommendation was founded on the observation that plasma renin levels fall as people age and are lower in blacks at any age. Therefore drugs that target the renin system are more likely to be more effective initial therapy in higher-renin younger patients, whereas the converse is true with ageing. The argument against the use of β-blockers as a preferred initial therapy (especially for older patients), unless there are compelling other indications (Table 16.17.2.7), is because they appear less effective at reducing the risk of stroke than the alternatives, are associated with an in- creased risk of developing diabetes, and are the least cost-effective treatment option for essential hypertension. Combination therapy for controlling blood pressure All guidelines recognize that combinations of blood pressure lowering drugs are often required to achieve recommended blood pressure goals. If two drugs in a single pill combination are inad- equate the 2018 European guidelines recommend the use of a renin angiotensin system blocker, a calcium channel blocker and a diuretic in a single pill combination, followed if necessary by the intro- duction of spironolactone. The American JNC8 guidelines (Fig. 16.17.2.8 and Table 16.17.2.8) recommend selecting any two of the medications recommended as suitable for the particular patient as initial therapy. The British guideline (Fig. 16.17.2.9) provides ex- plicit guidance on preferred combinations of treatment as follows: • Step 2—a CCB (C) combined with either an ACE inhibitor or ARB (A); • Step 3—add a thiazide-like diuretic (D); • Step 4—add higher-dose thiazide-like diuretic, spironolactone, an α-blocker or a β-blocker. The preference for the combination of A + C at step 2 is based on data (e.g. the ACCOMPLISH study), suggesting that A + C may be more effective than A + D at preventing cardiovascular events, despite similarities in blood pressure control. Resistant hypertension Drug-resistant hypertension can be defined as blood pressure that is not controlled despite treatment with an appropriate combination of three drug therapies (e.g. A + C + D—see Fig. 16.17.2.9) prescribed at their maximum recommended and tolerated doses. In the ab- sence of evidence of target organ damage, white coat hypertension should be excluded by 24 h ambulatory monitoring if this has not already been done. Other causes for resistant hypertension include (1) secondary hypertension (e.g. renovascular or endocrine); (2) in- gestion of drugs that may raise blood pressure (e.g. nonsteroidal anti-inflammatory agents); (3) heavy alcohol intake; (4) sleep ap- noea; (5) sodium and fluid retention as a result of inadequate diur- etic therapy; and (6) poor patient adherence to treatment. Poor adherence to therapy is often difficult to detect in hyperten- sive patients and can lead to expensive investigations for secondary causes. One way of detecting effectiveness of treatment is to use ABPM to monitor blood pressure after directly observed consump- tion of medication. Although this may not resolve the problem of adherence to treatment, it will identify whether the treatment is effective if adhered to, thus avoiding the need for further investi- gations. Where adherence is obviously poor, certain manoeuvres can help to improve it. The treatment should be made as simple as possible, using once-daily drugs and combination tablets, and a Table 16.17.2.8 Three strategies for the drug treatment of hypertension Strategy Description First step Second step Third (final) step A Start one drug, titrate to maximum dose, and then add a second drug Titrate the initial drug up to its maximum recommended dose to achieve goal BP. Move to second step if BP goal not achieved Add a second drug (ACE inhibitor, ARB, CCB, or thiazide-type diuretic) and titrate this up to its maximum recommended dose to achieve goal BP. Move to third step if BP goal not achieved Add a third drug (ACE inhibitor, ARB, CCB or thiazide-type diuretic), avoiding the combined use of an ACE inhibitor and ARB, and titrate this up to its maximum recommended dose to achieve goal BP. B Start one drug and then add a second drug before achieving maximum dose of the initial drug Start with one drug, then add a second drug before achieving the maximum recommended dose of the initial drug, then titrate

both drugs up to their maximum recommended doses to achieve goal BP. Move to final step if BP goal not achieved C Start with two drugs at the same time, either as separate pills or a combination pill Start with two drugs simultaneously, either as two separate drugs or as a combination pill. Move to final step if BP goal not achieved

16.17.2 Essential hypertension: Diagnosis, assessment, and treatment 3773 carer needs to be involved in administering medication to those who are confused. Whenever possible, effective communication with full information and involvement of the patient in his or her treatment is essential. Nurses, pharmacists, and other health professionals can play a vital role in this process. Most patients with truly drug-resistant hypertension (i.e. those who are taking their medications as prescribed) are likely to be re- taining sodium and will respond to further diuretic therapy. A sup- pressed plasma renin despite treatment with A + C + D would be indicative of sodium retention because these treatments would be expected to elevate plasma renin, hence the preferred initial ap- proach to treatment in this situation is further diuretic therapy, either with increased dosage of the thiazide diuretic, or using low- dose spironolactone (e.g. 25 mg/day), or amiloride (10–20 mg/day), with careful monitoring of electrolytes. A recent randomized cross- over trial found the addition of spironolactone to be more effective than that of bisoprolol or doxazosin in this context. For some pa- tients with very severe drug-resistant hypertension it may be neces- sary to use a combination of minoxidil, loop diuretic, and β-blocker to improve blood pressure control. Follow-up It is essential that patients are monitored regularly and it is im- portant that this message is conveyed to the patient. In the early stages of treatment, the frequency of monitoring will be deter- mined by the response to therapy, comorbidities, and the com- plexity of the treatment regimen required to control the blood pressure. Once blood pressure is controlled, patients should be re- viewed at least annually, and most will be reviewed every 6 months. Patients are increasingly monitoring their own blood pressure in the intervening period. Withdrawal of therapy Most patients with hypertension require lifelong therapy. Some with grade I hypertension who make substantial adjustments to their lifestyle may obtain sufficient fall in their blood pressure to warrant withdrawal of monotherapy. However, patients with target organ damage or those at high cardiovascular disease risk should not usually have their therapy withdrawn, unless there is a compelling clinical reason to do so. It is also important to note that in patients with previously severe hypertension that has subsequently been well Adult under 55 years, and any patient with type 2 diabetes Adult over 55 years or black person of African or Caribbean family origin of any age (who do not have type 2 diabetes) Key A–ACE inhibitor or angiotensin II receptor blocker (ARB)1 C–Calcium-channel blocker (CCB) D–Thiazide-like diuretic, e.g. indapamide C2 A Step 1 Step 2 Step 3 Step 4 A + C2 A + C + D Resistant hypertension A + C + D consider further diuretic3, 4 or α- or β-blocker5 Consider seeking expert advice 1 Choose a low-cost ARB. 2 A CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure. 3 Consider a low close of spironolactone4 or higher doses of a thiazide-like diuretic. 4 At the time of NICE consultation (March 2019) not all forms of spironolactone had a marketing authorisation for this indication. Informed consent should be obtained and documented. 5 Consider an α- or β-blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective. Fig. 16.17.2.9 British Hypertension Society/NICE treatment algorithm for the treatment of essential hypertension. From National Institute for Health and Care Excellence (2011) CG 127 Hypertension: management of hypertension in adults in primary care. Available from https://www.nice.org.uk/CG127, with modification from National Clinical Guideline Centre (2019) CG 136 Hypertension in adults: diagnosis and management. Available from

https://www.nice.org.uk/ng136.

section 16 Cardiovascular disorders 3774 controlled, treatment withdrawal may not always result in an im- mediate increase in blood pressure. This can sometimes convey the false impression that treatment may no longer be required because blood pressure can sometimes take many months to progressively rise back to dangerously high pretreatment values. Thus, any patient who discontinues therapy must remain under review with regular monitoring of their blood pressure, and all but a very few will re- quire treatment again. Other issues Nonadherence with therapy Nonadherence to antihypertensive medication is common: after ex- clusion of white coat and secondary hypertension, 50% of patients with apparent resistance to antihypertensive drugs are partially or completely nonadherent to prescribed treatment. Indirect tests of adherence include asking patients to complete a structured, self-reported medication adherence measure (e.g. Morisky), patient interview, pill counts, and prescription refill counts. Another approach is supervised administration of medi- cations and monitoring of blood pressure, but this requires appro- priate clinical staff and facilities and is therefore expensive, as well as being inconvenient for patients. An objective test is therapeutic drug monitoring in blood or urine. The latter has the advantages of being noninvasive, that sampling time is not important, and that a single assay can detect multiple drugs/metabolites, the concen- trations of which are typically higher than in the blood. It is not, however, a panacea: it is difficult to develop an analytic method suitable for extraction and concentration of all drugs; the complex metabolism of some drugs means that the parent compound may not be present (particularly ACE inhibitors); and it does not allow judgement about when a patient took any drug that is found in their urine. A survey of UK hypertension specialists in 2016 reported that about 60% did not routinely check adherence, but awareness of the importance of this issue is increasing, and urinary testing is being more widely adopted. Factors responsible for nonadherence are shown in Table 16.17.2.9. To deal with the matter requires the physician to engage in an open and honest discussion with the patient to explore the reasons underlying their failure to take their medication as prescribed. It may be that an asymptomatic patient is unaware of the risks of per- sistent high blood pressure and the possible harmful consequences of it remaining so, and discussion may be helped by visual repre- sentations of risk. It will almost certainly be important to find out how the patient is managing their drugs, in particular the number of different drugs, their dosing frequency, and perceived side effects. Complicated dosing regimens are associated with lower adherence, hence use of single pill combination drugs may improve matters, and it may be appropriate to negotiate a reduction in the number of pills in the hope of achieving a higher but more realistic blood pressure target. Use of motivational interviewing techniques, which can be beneficial in encouraging lifestyle changes and managing substance abuse, has also been shown to improve medication adherence.
Table 16.17.2.9 Factors contributing to nonadherence with antihypertensive drugs and possible solutions Factors Possible solutions Socioeconomic Poor socioeconomic status Illiteracy Unemployment Limited drug supply Cost of drugs Make patients aware of support from governmental and voluntary agencies such as the Citizens Advice Bureau in the UK Issue repeat prescriptions to cover a longer duration—such as three months Healthcare system Clinician-patient relationship Lack of knowledge and training for healthcare providers Inadequate time for consultation Book longer appointments Training of healthcare assistants, nurses, doctors, and pharmacists to discuss adherence Condition Lack of symptoms Chronic or incurable disease No immediate consequences of stopping the drugs Education through written and verbal information—shared decision making Patient support groups Peer support and education Treatment

Complex treatment regimens Duration of treatment Low drug tolerability and adverse effects of treatment such as dry cough with angiotensin converting enzyme inhibitors, ankle swelling with calcium channel blockers, and electrolyte disturbances and gout with diuretics Simplify the regimen and minimize side effects through use of monotherapy, single pill combination drugs, lower doses to prevent side effects, slow release formulations to reduce dose frequency, trying other drugs in the same class or changing the class Patient Patient's knowledge of the disease Patient's perception of risk and awareness of costs and benefits of treatment Nonacceptance of monitoring Psychiatric illness Patient education through written and verbal information Motivational interviewing Promoting self-care through home monitoring Using smart phone applications to set medication reminders and record their home blood pressure, which could be shared electronically with their doctor Reproduced from Hammed MA, Dasgupta I, Gill P (2016). Poor adherence to antihypertensive drugs. BMJ, 354, i3268, with permission from BMJ Publishing Group Ltd. Adapted from WHO report on adherence to long term therapies (http://apps.who.int/medicinedocs/fr/d/Js4883e/)

16.17.2 Essential hypertension: Diagnosis, assessment, and treatment 3775 Indications for specialist referral There are circumstances when referral to a specialist centre is in- dicated for the management of hypertension. These include uncer- tainty about the decision to treat, investigations to exclude secondary hypertension, severe and complicated hypertension, and resistant hypertension, among others as detailed in Box 16.17.2.5. Medication to reduce cardiovascular risk Blood pressure should not be treated in isolation and should be considered as part of a comprehensive strategy to reduce cardiovas- cular disease risk. In this regard, patients at high risk, that is, those with established cardiovascular disease, target organ damage, and/ or diabetes, or those with a calculated cardiovascular disease risk which is elevated (e.g. ≥10% over 10 years), should be offered add- itional interventions to reduce risk. These include reinforcement of lifestyle advice, especially smoking cessation, and treatment with statin therapy to further reduce their risk of stroke and coronary disease. The routine use of statins to reduce total cholesterol values by 1 mmol/litre has been associated with a reduction in the risk of is- chaemic heart disease events by about one-third and stroke by about one-fifth, over and above the benefit already accrued from blood pressure lowering. Moreover, the relative risk reduction associated with statin therapy in higher-risk hypertensive patients is not de- pendent on a high baseline cholesterol value. Once blood pressure has been controlled, higher-risk hyperten- sive patients should also be considered for treatment with low-dose aspirin (75 mg/day). This has been shown to reduce the incidence of myocardial infarction in higher-risk patients over 50 years old and should be offered routinely to patients who come into this category and who do not have contraindications. In view of the increased in- cidence of haemorrhage, it is not indicated in lower-risk hyperten- sive patients. Intercurrent illness Patients who develop intercurrent illness that is likely to lead to volume depletion (e.g. diarrhoea, vomiting, high fever) should be told to stop taking their antihypertensive medications (particu- larly diuretics, ACEi, and ARBs) until they are able to eat and drink normally. This is very important if they develop postural dizziness, which is a marker of significant intravascular volume depletion in this clinical context. Other treatments for hypertension Device-based therapies Renal denervation Initial uncontrolled and unblinded studies reported impressive re- duction in blood pressure in patients with resistant hypertension, but a subsequent blinded randomized trial (SIMPLICITY HTN-3) failed to show benefit. A total of 535 patients were randomized in a 2:1 (active: sham) ratio: the mean reduction in office SBP at 6 months in the denervation group was 14 mm Hg, compared with 12 mm Hg in the controls, with

24 hr ambulatory SBP reduced by 7 mm Hg and 5 mm Hg, respectively. Following these findings several ongoing trials were stopped, but there has subsequently been a resurgence of interest. This treatment should not be offered to patients with hyper- tension in routine clinical practice. Baroreflex stimulation, carotid bulb expansion, and carotid body ablation In the Rheos Pivotal Trial 265 patients had a baroreflex activation therapy device implanted. One month after implantation they were randomized to receive baroreflex activation therapy immediately, or to have device activation delayed for 6 months. At 6 months, 42% of those whose device had been activated at 1 month had achieved SBP below 140 mm Hg, compared to 24% of those whose device had not been switched on; by 12 months over 50% of both groups had achieved this blood pressure target. Follow-up over 22–53 months suggested that the effect on blood pressure was maintained, and this persists at six years. However, the place of baroreflex activation therapy in the management of hypertension is not yet clear, and it should only be offered in the context of clinical trials. First-in-man studies of carotid bulb expansion using a dedicated carotid stent and of carotid body ablation using a transvenous cath- eter are ongoing. Arteriovenous anastomosis creation with a coupler In the ROX CONTROL HTN study patients were randomized to ar- teriovenous coupler therapy, which via an endovascular procedure created an arteriovenous anastomosis between an iliac artery and iliac vein, or to normal care. At 12 months office based SBP was re- duced by 25 mm Hg, DBP by 21 mm Hg and mean 24-hour ABPM by 13 mm Hg in 39 treated patients. This difference is clearly sub-stantial, but it is notable that the controls did not undergo any sham procedure (the importance of which has been well demonstrated in trials of renal denervation in hypertension), also that 30% of pa- tients in the intervention group required stenting or venoplasty for late ipsilateral venous stenosis. A randomized trial including a sham treated group (ROX CONTROL HTN-2) was due to complete in May 2019, but as of September 2019 no results had been posted on Box 16.17.2.5 Recommended and possible indications for specialist referral for patients with hypertension • Urgent treatment needed: − Accelerated hypertension (severe hypertension with grade III—IV retinopathy) − Particularly severe hypertension (>220/120 mm Hg) − Impending complications (e.g. TIA, left ventricular failure) • Possible underlying cause: − Any clue in history or examination of a secondary cause, e.g. hypokalaemia with increased or high-normal plasma sodium (Conn's syndrome) − Elevated serum creatinine − Proteinuria or haematuria − Sudden-onset or worsening of hypertension − Resistance to multidrug regimen, i.e. ≥3 drugs − Young age (any hypertension <20 years; needing treatment <30 years) • Therapeutic problems: − Multiple drug intolerance − Multiple drug contraindications − Persistent nonadherence • Special situations: − Unusual blood pressure variability − Possible white coat hypertension − Hypertension in pregnancy

 ClinicalTrials.gov. This treatment should only be offered in the con- text of clinical trials. Hypertension in specific groups of patients People of black African origin Hypertension is more prevalent in blacks, is associated with more target organ damage, and consequently carries a worse prognosis, with a particularly high risk of stroke. Black patients as a group tend to respond better to diuretics, CCBs, and dietary salt restriction than white patients. ACE inhibitors, ARBs, and β-blockers are generally less effective as initial therapy, but become more effective when com- bined with diuretics and/or CCBs. Older people Most people with hypertension are elderly, and elderly people have much higher absolute risk of cardiovascular events than younger people with hypertension. If a blood pressure of 140/90 mm Hg or more is used to define hypertension, then over 70% of people over the age of 60 years will be hypertensive, with most of these having isolated systolic hypertension. Studies in patients aged more than 80 years confirm that treatment can be well tolerated and associated with impressive

reductions in the risk of stroke, heart failure, and mortality. Surveys suggest that doctors consistently underestimate the risks and undertreat hypertension in older people, largely because of con- cerns about significant potential side effects, notably falls due to postural hypotension, and the belief that older patients recruited into trials are not representative of the patients that they care for. These concerns are real: analysis of a large database of individuals aged 70–90 years showed a significant increase in hospitalizations for hip fracture in the 30 days after initiation of antihypertensive drug treatment. Other considerations when treating older people include eGFR declines with age and renal conservation of sodium and fluid in the face of depletion is impaired, thus elderly patients are more prone to dehydration as a result of diuretic therapy; clear- ance of drugs and their active metabolites is decreased as a result of declining hepatic and renal function; comorbidity is much more common; and communication and adherence with therapy may be more difficult with decline in cognitive function (and there is vari- able data from clinical trials as to whether this decline may be re- tarded or accelerated by antihypertensive treatment). With regard to very old and frail people, a European Society of Hypertension and European Union Geriatric Medicine Society working group have stated that: • Elderly patients should be monitored for the development of frailty using a validated tool, because change in treatment strategy may be needed if they become frail. • There is particular concern about polypharmacy in the very old and frail, hence combination of two antihypertensive drugs (whether or not they are in a single pill combination) should be considered if monotherapy fails to control BP, but only if the po- tential benefit of BP reduction is considered to outweigh the risk of hypotension, and use of more than three antihypertensive drugs should not be recommended in general. As a general rule, drug regimens should be as simple as possible and dosages increased gradually, the greatest danger resulting from lowering pressure too much and too rapidly. The low risk of fall injuries reported in clinical trials of healthy older adults may not reflect the risk in older adults with multiple chronic conditions. Physicians working in medical admission units will be all too fa- miliar with the scenario of the older patient, taking a plethora of antihypertensives, who is admitted after a collapse. Biological rather than chronological age should be the deciding factor in initiating antihypertensive treatment, but there is never any substitute for clin- ical common sense—the elderly man with mild cognitive impair- ment, prone to falls, and with occasional dizziness on standing up, is not likely to be well served by the doctor who advocates medication to reduce marginally elevated blood pressure. Children Although secondary hypertension is more common in children than in adults, no specific cause is found for hypertension in most adoles- cents. The criteria for drug treatment, however, have to be modified because of the lower normal blood pressure range. The JNC guide- lines recommend that blood pressures above the 95th percentile— taking into account age, height, and sex—should be considered elevated. In principle, treatment regimens are the same as those re- commended for adults, with appropriate dose adjustment. FURTHER READING Blood pressure measurement Agabiti-Rosei E, et al. (2007). Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension, 50, 1–7. European Society of Hypertension (2008). Guidelines for blood pressure monitoring at home: a summary report of the Second International Consensus Conference on Home Blood Pressure Monitoring. J Hypertens, 26, 1505–26. Hodgkinson J, et al. (2011). Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pres- sure monitoring in diagnosis of hypertension: systematic review. Br Med J, 342, d3621. Kikuya M, et al. (2007). Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. Circulation, 115, 2145–52. O’Brien E, et al. (2003). European Society of Hypertension recom- mendations for conventional, ambulatory and home blood pressure measurement. J Hypertens, 21,

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