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BRITISH HYPERTENSION SOCIETY GUIDELINES

Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004—BHS IV

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Summary of recommendations

- Provide advice on life-style modifications for all people with high blood pressure (BP) and those with borderline or high-normal BP. Advice on effective nonpharmacological interventions is provided (A).
- Initiate antihypertensive drug therapy in people with sustained systolic BP (SBP) $\geqslant$160 mmHg or sustained diastolic BP (DBP) $\geqslant$100 mmHg (A).
- Make treatment decisions in people with sustained SBP between 140 and 159 mmHg and/or sustained DBP between 90 and 99 mmHg according to the presence or absence of cardiovascular disease, other target organ damage, or an estimated cardiovascular disease (CVD) risk of $\geqslant$20% over 10 years, according to the Joint British Societies CVD risk assessment programme/risk chart (A).
- CVD risk replaces CHD risk estimation to reflect the importance of stroke prevention as well as CHD prevention. The new CVD risk threshold of $\geqslant$20% is equivalent to a CHD risk of approximately $\geqslant$15% over 10 years.
- In people with diabetes mellitus, initiate antihypertensive drug therapy if SBP is sustained $\geqslant$140 mmHg and/or DBP is sustained $\geqslant$90 mmHg (B).
- In nondiabetic people with hypertension, the optimal BP treatment goals are: SBP $<$140 mmHg and DBP $<$85 mmHg. The minimum acceptable level of control (Audit Standard) recommended is $<$150/$<$90 mmHg. Despite the best practice, these levels will be difficult to achieve in some hypertensive people (B).
- In people with diabetes and high BP, optimal BP goals are: SBP $<$130 mmHg and DBP $<$80 mmHg. The minimum acceptable level of control (Audit Standard) recommended is $<$140/$<$80 mmHg. Despite the best practice, these levels will be difficult to achieve in some people with diabetes and hypertension (B).
- Meta-analyses of BP-lowering trials have confirmed that, in general, the main determinant of benefit from BP-lowering drugs is the achieved BP, rather than choice of therapy. In some circumstances, there are compelling indications and contraindications for specific classes of antihypertensive drugs, and these are specified (A).
- Most people with high BP will require at least two BP-lowering drugs to achieve the recommended BP goals. A treatment algorithm (AB/CD) is provided to advise on the sequencing of drugs and logical drug combinations (C). When there are no cost disadvantages, fixed drug combinations

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are recommended to reduce the number of medications, which may enhance adherence to treatment (C).
- Other drugs that reduce CVD risk must also be considered, notably, low-dose aspirin and statin therapy (A).
- Unless contraindicated, low-dose aspirin (75 mg/day) is recommended for all people needing secondary prevention of ischaemic CVD, and primary prevention in people with hypertension over the age of 50 years who have a 10-year CVD risk $\geqslant 20\%$ and in whom BP is controlled to the audit standard (A).
- Statin therapy is recommended for all people with high BP complicated by CVD, irrespective of baseline total cholesterol or low-density lipoprotein (LDL)-cholesterol levels. Similarly, statin therapy is also recommended for primary prevention in people with high BP who have a 10-year CVD risk $\geqslant 20\%$, estimated from the Joint British Societies CVD risk-assessment programme/chart. Optimal cholesterol lowering should reduce the total cholesterol by 25% or LDL-cholesterol by 30% or achieve a total cholesterol of <4.0 mmol/l or LDL-cholesterol of <2.0 mmol/l, whichever is the greatest reduction (A).
- Glycaemic control should be optimised in people with diabetes, for example, HbA1c $<7\%$ (A).
- Advice is provided on the clinical management of hypertension in specific patient groups, that is, the elderly, ethnic minorities, people with diabetes mellitus, chronic renal disease, and in women (pregnancy, oral contraceptive use and hormone-replacement therapy).
- Suggestions for the improved implementation and audit of these guidelines in primary care are provided.

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Introduction

These guidelines update previous reports by working parties of the British Hypertension Society (BHS) in 1989,[1] 1993[2] and 1999.[3] Updating these guidelines is appropriate because, since 1999, there has been much new evidence in key areas that has allowed us to reinforce and extend previous recommendations.

Newly collated epidemiological data have strengthened the well-recognised relationship between blood pressure (BP) and cardiovascular disease (CVD) risk and have confirmed the overwhelming importance of systolic BP (SBP) as a determinant of risk.[4] The importance of BP as a risk factor was further underscored by the recent World Health Organisation (WHO) report which identified high BP as one of the most important preventable causes of premature morbidity and mortality in developed and developing countries.[5] New epidemiological data have also demonstrated the likelihood that in a majority of people high-normal BP will evolve to hypertension with ageing.[6] This observation prompted the US Joint National Committee 7 (JNC 7) report to introduce a new classification of BP; 'pre-hypertension', referring to those with high-normal BP.[7] The BHS has resisted the temptation to give such people a disease label, but acknowledge that lifestyle modification is appropriate for people with high-normal BP to reduce the likelihood of them developing 'hypertension' and the need for drug therapy.

There have also been new data on the safety and effectiveness of different classes of BP-lowering drugs, including much needed data on angiotensin-converting enzyme (ACE) inhibitors, dihydropyridine and non-dihydropyridine calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs).[8–21] These data have been subject to meta-analyses that have provided evidence that overall most classes of drugs are similarly safe and effective.[22–24] Moreover, these meta-analyses have confirmed that the benefits of BP-lowering therapy are primarily determined by the level of BP control rather than the class of drug used to achieve it. Another important conclusion drawn from analysis of these new trials is that prior concerns about the safety of dihydropyridine CCBs in people with hypertension[25] and/or diabetes[26] were unwarranted and are unfounded.

Additional new data included in this guideline relate to: the management of high BP in people with diabetes, especially type II diabetes;[13,21,26–32] the treatment of high BP among those with established cerebrovascular disease,[16] the treatment of people with target organ damage (TOD) such as left ventricular hypertrophy (LVH)[12] and chronic renal disease;[18–20,33] and the treatment of hypertension in ethnic groups, especially in the black population.[21] There are also much new data on the effectiveness of lifestyle measures in the prevention and treatment of hypertension and diabetes.[34–42] This new information adds to an already formidable body of evidence confirming the effectiveness of BP lowering in reducing the risk of CVD.

The BHS remains concerned that national and international surveys continue to reveal that there is a substantial under-diagnosis, under-treatment and poor rates of BP control in the UK.[43] The situation has improved in recent years, but, in general, the

management of hypertension in the UK remains suboptimal for the majority.[44] One of the key reasons for poor BP control in people with treated hypertension is the use of monotherapy by most doctors.[44] This contrasts with the evidence from clinical trials which have consistently shown that the majority of patients require two or more drugs to achieve current BP goals. Put simply, monotherapy for hypertension is usually inadequate therapy. To address this serious shortfall in treatment, the BHS has published a treatment algorithm based on the AB/CD rule.[45] This AB/CD algorithm is now formally incorporated into this guideline and underscores the need for at least two BP-lowering drugs for most people with hypertension. Moreover, it provides advice on rational drug selection and sequencing, based primarily on the age and ethnicity of the patient. Importantly, the AB/CD algorithm is not prescriptive or restrictive and offers therapeutic choice within a structured template.

The 1999 BHS guidelines[3] emphasised the fact that high BP should not be viewed as a risk factor in isolation. It is well recognised that people with hypertension frequently have a clustering of additional risk factors for CVD, including dyslipidaemia, impaired glucose tolerance, central obesity and hyperuricaemia—features of the metabolic syndrome.[46] Consequently, the treatment of BP in isolation will leave the patient at unacceptably high risk of cardiovascular complications and death, particularly from coronary heart disease (CHD) and stroke.[47] This guideline reinforces the view that the treatment of people with hypertension should not focus solely on BP but must also formally assess CVD risk and use multifactorial interventions to reduce total CVD risk. Hence, we provide detailed guidance on the assessment of CVD risk in people with hypertension and the management of associated CVD risk factors.

Statin therapy is a safe and effective therapy that reduces the risk of CHD and stroke. Many trials of statins have included patients with high BP and the relative risk reduction in people with hypertension treated with statins is similar to that observed for people without hypertension.[48] The Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) recently added to these data by confirming that statin therapy reduced the risk of CHD and stroke in people with treated hypertension even when BP was optimally controlled.[49] Moreover, this benefit was achieved in people with an average total cholesterol of only 5.5 mmol/l, a value typical of that seen in many people with hypertension. Consistent with national guidance at the time, the previous BHS guideline-recommended targeting statin therapy only at those with established CVD or at a very high risk of developing it ($\geqslant$40% CVD risk (equivalent to $\geqslant$30% CHD risk) over 10 years) and only then provided that baseline total cholesterol was $>$5 mmol/l. In the light of new evidence, this advice is no longer appropriate. In this new guideline, we effectively abolish the concept of a baseline cholesterol threshold for intervention with statins and reduce the risk threshold to $\geqslant$20% CVD risk over 10 years for primary prevention. Moreover, we adopt the lower total cholesterol and low-density lipoprotein (LDL)-cholesterol goals in keeping with the recent European Society of Hypertension/European Society of Cardiology guidelines.[50] Advice on the use of low-dose aspirin is unchanged from our previous 1999 guidelines.[3]

Consistent with the 1999 guidelines,[3] we endorse the continued use of the Framingham risk function, either as a computer programme or chart, to formally estimate the absolute risk to aid treatment decisions in people with stage 1 (mild) hypertension, and for the appropriate use of statins and aspirin for primary prevention. However, we have replaced CHD risk estimates with CVD risk estimates to reflect the treatment objective: to reduce all cardiovascular events, including stroke. This is consistent with forthcoming updated Joint British Society risk charts and computer programme.

Finally, we acknowledge that guidelines achieve nothing if they are not implemented. While awareness and familiarity with BHS guidelines in the UK is generally high, their implementation is inadequate. Adherence to these guidelines is key to improving BP and CVD risk management. The majority of BP management will take place in primary care and these guidelines are intended for general practitioners (GPs), practice nurses and generalists in hospital practice. We have tried to present the best currently available evidence on hypertension management and associated CVD risk factor management as clearly as possible. We have included an extended section on implementation, audit standards and the implications of this guideline for National Service Frameworks (NSFs) and the General Medical Services (GMS) contract for primary care. We also acknowledge the importance of involving patients in treatment decisions and clinical monitoring and welcome a contribution from the Blood Pressure Association, a patients' association for people with high BP.

These guidelines have been prepared by the BHS guidelines working party on behalf of the BHS. The working party reviewed new data published since the previous guideline and updated and amended the recommendations accordingly. The document was reviewed by members of the BHS and was sent out for review by a large number of National Stakeholder organisations (Appendix A). This ensured review by personnel with a broad range of expertise across the Health Care community, including patient organisations. The evidence supporting the recommendations contained in these new BHS guidelines is graded using the North of England Group Criteria[51] (Appendix B). These guidelines should be applied with due regard to local circumstances and policies, and with appropriate clinical

judgement as regards the needs of individual patients.

Blood pressure measurement

Blood pressure measurement

The BHS definition and classifications of BP levels have changed in line with recent European Guidelines and WHO/ISH (Box 1).[50,52]

Large variations in BP are normal in individuals. Hence, BP should be measured as accurately as possible using the BHS protocol (see Box 2). All adults should have their BP measured routinely at least every 5 years. Those with high-normal BP (SBP 130–139 mmHg or diastolic BP (DBP) 85–89 mmHg) and those who have had high BP readings at any time previously should have their BP re-measured annually.

BP measurement can be made in the clinic, home setting or using ambulatory blood pressure monitoring (ABPM).

Box 1 British Hypertension Society classification of blood pressure levels

Category	*Systolic blood pressure (mmHg)*	*Diastolic blood pressure (mmHg)*
Optimal blood pressure	<120	<80
Normal blood pressure	<130	<85
High-normal blood pressure	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	⩾180	⩾110
Isolated systolic hypertension (Grade 1)	140–159	<90
Isolated systolic hypertension (Grade 2)	⩾160	<90

This classification equates with that of the ESH[50] and that of WHO/ISH,[52] and is based on clinic blood pressure values. If systolic blood pressure and diastolic blood pressure fall into different categories, the higher value should be taken for classification.

Clinic measurement

BP should initially be measured in both arms as patients may have large differences (>10 mmHg) between arms. The arm with the higher values should be used for subsequent measurements. In patients with diabetes and in the elderly, measurements should also be made after at least 2 min standing, to determine whether there is significant orthostatic hypotension.

Cuffs of the appropriate size should be used (see Box 3) such that the bladder encircles at least 80% of the upper arm and it is important that the arm is supported at heart level during recordings. Using too large a cuff results in an underestimation of BP; similarly, too small a cuff will lead to overestimation. Although a universal cuff has been recommended,[53] the BHS recommends three different bladder sizes depending on arm circumference (see Box 3). It is important when purchasing any BP monitor to ensure that appropriate cuff sizes are available.

If the auscultatory method is being used, Korotkoff phase I and phase V sounds should be taken for SBP and DBP levels, respectively. If Phase V goes to zero, Phase IV should be used. At least two measurements (1–2 min apart) should be taken on each occasion, the initial measurement should be discarded and further measurements made if there are large (>10 mmHg) differences between initial readings. Timing of measurement should also be

Box 3 Blood pressure cuff sizes for mercury sphygmomanometer, semiautomatic and ambulatory monitors

Indication	*Bladder width × length (cm)*	*Arm circumference (cm)*
Small adult/child	12 × 18	<23
Standard adult	12 × 26	<33
Large adult	12 × 40	<50
Adult thigh cuff	20 × 42	<53

Alternative adult cuffs (width × length, 12 × 35 cm) have been recommended for all adult patients, but can result in problems with over- and under-cuffing. The British Hypertension Society recommends that cuff size be selected based on arm circumference.

Box 2 Blood pressure measurement by standard mercury sphygmomanometer or semiautomated device

- 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 tight clothing, support arm at heart level, ensure hand relaxed and avoid talking during the measurement procedure
- Use cuff of appropriate size (see Box 3)
- Lower mercury column slowly (2 mm/s)
- Read blood pressure to the nearest 2 mmHg
- 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

Full details of methods.[50] Download references from www.bhsoc.org.

considered in relation to the time of antihypertensive treatment.

Atrial fibrillation can make the measurement of BP particularly difficult due to marked beat-to-beat variability. This is a particularly important consideration when using semiautomatic or automated devices. In such patients, auscultatory measurements and multiple readings are recommended.

Home/self BP monitoring

There is an increasing use of home or self BP measurement. Some of the monitors used are inaccurate and many have not been formally validated. We strongly recommend the proper use of accurate, validated and well-maintained monitors, with an appropriate cuff size. Wrist monitors, in most instances, are not as accurate as upper arm devices and are not recommended. Measurements should be made under standardised conditions (Box 3).

The potential advantages of home monitoring include: the availability of multiple recordings throughout the waking period taken over many days, which may reduce white coat effect (see later) and misinterpretation of measurement variability. Importantly, home BP measurement also involves the patient more closely in the management of their own BP. Values from home measurements tend to be lower than clinic levels.[54] Consequently, thresholds and targets of treatment based on this technique should probably be adjusted downwards (eg by 10/5 mmHg), although evidence for true equivalence is lacking and will be variable. The disadvantages of this technique include reporting bias, and unsupervised alteration of medication. Newer BP monitors offer the advantages of built-in printers or internally storing all BP measurements, which can be subsequently downloaded via a telephone link to the physician. There is no uniform consensus about the frequency and timing of measurements, or about what levels should be regarded as abnormal, but patients with home BP levels of SBP <130 mmHg and DBP <85 mmHg can probably be regarded as having BP levels within the normal range.[53,54] It has been suggested that initial assessment or the assessment of treatment effects should be for a 7-day period, with recordings performed in the morning and evening, and excluding values for the first 24 h. The average of at least these 12 readings is then taken as the home BP level.[55]

The potential advantages of home BP monitoring notwithstanding, there is to date, little or no evidence of these recordings predicting CVD risk or outcomes more effectively than clinic readings.

Ambulatory monitoring

ABPM is increasingly used and guidelines from the BHS and Europe on the use and interpretation of this technique in clinical practice have been published.[53,56] Only validated well-maintained machines with appropriate cuff sizes should be used[56] (www.bhsoc.org). ABPM provides more information than either home or clinic measurements, for example, 24-h BP profile including mean daytime (usually 0700–2200 h) and night-time values, and BP variability. Like home BP measurements, there are no outcome trials based solely on ABPM values. Nevertheless, an increasing body of evidence suggests that ABPM values are a better predictor of CVD risk[57,58] and TOD[59,60] (for TOD definition, see Table 1), and is a better method of assessing treatment effects on BP. Most patients can tolerate measurements recorded at between 15- and 30-min intervals during the day, and 30- and 60-min intervals at night. ABPM thus provides multiple measurements taken over a 24–26-h period (to reduce white coat effect, the initial and last hours of measurement are sometimes ignored, though the value of doing this is unclear), and, therefore, more than 70 BP estimations can be made during a single 24-h period.

Table 1 Initial evaluation of the hypertensive patient

Causes of hypertension
Drugs (NSAID's, oral contraceptive, steroids, liquorice, sympathomimetics, ie some cold cures)
Renal disease (present, past or family history, proteinuria and/or haematuria: palpable kidney(s)—polycystic, hydronephrosis or neoplasm)
Renovascular disease (abdominal or loin bruit)
Phaeochromocytoma (paroxysmal symptoms)
Conn's syndrome (tetany, muscle weakness, polyuria, hypokalaemia)
Coarctation (radio-femoral delay or weak femoral pulses)
Cushings (general appearance)
Contributory factors
Overweight
Excess alcohol (>3 units/day)
Excess salt intake
Lack of exercise
Environmental stress
Complications of hypertension/TOD
Stroke, TIA, dementia, carotid bruits
LVH and/or LV strain on ECG, heart failure
Myocardial infarction, angina, CABG or angioplasty
Peripheral vascular disease
Fundal hemorrhages or exudates, papillodema
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
See Table 2

NSAIDs = nonsteroidal anti-inflammatory drugs; TOD = target organ damage; TIA = transient ischaemic attack; LVH = left-ventricular hypertrophy; CABG = coronary artery bypass graft; ECG = electrocardiogram.

Table 2 Compelling and possible indications, contraindications and cautions for the major classes of antihypertensive drugs

Class of drug	*Compelling indications*	*Possible indications*	*Caution*	*Compelling contraindications*
Alpha-blockers	Benign prostatic hypertrophy		Postural hypotension, heart failure[a]	Urinary incontinence
ACE inhibitors	Heart failure, LV dysfunction, post MI or established CHD, type I diabetic nephropathy, 2° stroke prevention[e]	Chronic renal disease,[b] type II diabetic nephropathy, proteinuric renal disease	Renal impairment[b] PVD[c]	Pregnancy, renovascular disease[d]
ARBs	ACE inhibitor intolerance, type II diabetic nephropathy, hypertension with LVH, heart failure in ACE-intolerant patients, post MI	LV dysfunction post MI, intolerance of other antihypertensive drugs, proteinuric renal disease, chronic renal disease, heart failure[b]	Renal impairment[b] PVD[c]	Pregnancy, renovascular disease[d]
Beta-blockers	MI, angina	Heart failure[f]	Heart failure[f], PVD, diabetes (except with CHD)	Asthma/COPD, heart block
CCBs (dihydropyridine)	Elderly, ISH	Elderly, Angina	—	—
CCBs (rate limiting)	Angina	MI	Combination with beta-blockade	Heart block, heart failure
Thiazide/thiazide-like diuretics	Elderly, ISH, heart failure, 2° stroke prevention			Gout[g]

COPD = chronic obstructive pulmonary disease; ISH = isolated systolic hypertension; PVD = peripheral vascular disease; LVH = left ventricular hypertrophy; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; MI = myocardial infarction.
[a]HF when used as monotherapy.
[b]ACE inhibitors or ARBs may be beneficial in chronic renal failure but should only be used with caution, close supervision and specialist advice when there is established and significant renal impairment.
[c]Caution with ACE inhibitors and ARBs in peripheral vascular disease because of association with renovascular disease.
[d]ACE inhibitors and ARBs are sometimes used in patients with renovascular disease under specialist supervision.
[e]In combination with a thiazide/thiazide-like diuretic.
[f]Beta-blockers are increasingly used to treat stable heart failure. However, beta-blockers may worsen heart failure.
[g]Thiazide/thiazide-like diuretics may sometimes be necessary to control BP in people with a histroy of gout, ideally used in combination with allopurinol.

Of the many measures available from 24-h ABPM, mean daytime and night-time values are usually used for assessment. As for home readings, ABPM values are usually lower than clinic measurements[61] and thresholds and targets should, therefore, be adjusted downwards (eg by 10/5 mmHg). However, we acknowledge that differences exist between the various guidelines as to what are normal and abnormal ABPM values.[50]

We do not recommend the use of ABPM for all patients, but it is helpful in specific circumstances (see Box 4).

Box 4 Potential indications for the use of 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
- Diagnoses and treatment of hypertension in pregnancy
- Evaluation of symptomatic hypotension

'White coat hypertension' and 'white coat' effect

Anticipation of measurement usually causes BP to rise due to an alerting reaction. If sufficiently exaggerated in the clinic setting, this may result in a truly normotensive person being diagnosed as hypertensive. This is often referred to as 'white coat hypertension' or isolated clinic hypertension. The same effect can occur among treated hypertensive patients when it is referred to as the 'white coat effect'. Spuriously high BP readings may also occasionally occur outside the clinic setting, when an exaggerated alerting response accompanies the application of the BP cuff.

Thus, white coat hypertension is used to describe the phenomenon of consistently elevated clinic BP levels but normal ABPM values. Its prevalence has been reported to range from 10–30% of people with high BP, and increases with age.[62] The prevalence of white coat hypertension is highly dependent on the threshold for hypertension and is much less than 10% in those with grade 2 or 3 hypertension based

on clinic readings. White coat hypertension may be the precursor of sustained hypertension,[63] and may confer an increased CVD risk,[64] although this has not been found in all studies.[65]

White coat hypertension should be considered when clinic BP is consistently elevated, or resistant to treatment in the absence of TOD.

BP-monitoring devices

The auscultatory method using the mercury sphygmomanometer has been the mainstay of clinical BP measurement for many years. However, with the anticipated withdrawal of environmental mercury for health and safety reasons, alternative measurement devices are required. Any such new device should be independently validated for its accuracy and the results published in a peer-reviewed journal. BP monitors recommended by the BHS (www.bhsoc.org and Appendix C) have been validated by protocols produced by the Association for the Advancement of Medical Instrumentation[66] and/or the BHS;[67] or the Association for the Advancement of Medical Instrumentation[66] and/or the more recent protocol from the European Society of Hypertension.[68] The mercury sphygmomanometer (still present in many clinics) is reliable and remains the gold standard, if properly maintained and used according to strict criteria (see Box 2). Aneroid devices are used widely, although these monitors are notoriously difficult to maintain in an accurate state over time, differ systematically from mercury devices, and are, therefore, not recommended for routine use.

Fortunately, an increasing number of well-validated, accurate and reasonably priced semi-automated devices are now available. A list of currently available monitors, validated to BHS standard, is available on the BHS Information Service website (www.bhsoc.org and Appendix C). However, many of these monitors have been developed for self-measurement of BP, and may not stand up to the rigours of daily clinic use, and their capacity to maintain accuracy over time is unknown.

ABPM devices remain relatively expensive and vary considerably in their accuracy, size, weight and noise level, as well as ease of use and information provided by the accompanying software. Currently available and validated ABPM devices can also be found on the BHS Information service website (www.bhsoc.org and Appendix C).

Patient evaluation/thresholds/targets

Assessment of hypertensive patients

All hypertensive patients should have a thorough history and physical examination, but need only a limited number of routine investigations. It is beyond the scope of these guidelines to discuss every detail of the clinical evaluation, but it is important to consider and document the following:

- the causes of secondary hypertension;
- contributory factors;
- complications of hypertension;
- CVD risk factors, to allow the assessment of CVD risk;
- contraindications to specific drugs.

Details are summarised in Table 1.
Routine investigation must include:

- urine strip test for protein and blood;
- serum creatinine and electrolytes;
- blood glucose—ideally fasted;
- lipid profile—ideally fasted;
- electrocardiogram (ECG).

Note that chest X-ray, urine microscopy and culture and echocardiography are not required routinely. An echocardiogram is valuable to confirm or refute the presence of LVH when the ECG shows 'high' left-ventricular voltage without T-wave abnormalities, as is often the case in young patients. When the clinical evaluation or results of these simple investigations suggest a need for further investigation, it may be best to refer for specialist advice, if the additional investigations needed are difficult to arrange from general practice. Indications for referral for specialist advice or treatment are suggested in Table 3.

Table 3 Suggested indications for specialist referral

Urgent treatment needed
Accelerated hypertension (severe hypertension with grade III–IV retinopathy)
Particularly severe hypertension (>220/120 mmHg)
Impending complications (eg transient ischaemic attack, left ventricular failure)
Possible underlying cause
Any clue in history or examination of a secondary cause, for example, 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 multi-drug regimen, that is, ⩾3 drugs
Young age (any hypertension <20 years; needing treatment <30 years)
Therapeutic problems
Multiple drug intolerance
Multiple drug contraindications
Persistent nonadherence or noncompliance
Special situations
Unusual blood pressure variability
Possible white-coat hypertension
Hypertension in pregnancy

Absolute CVD risk assessment

Increasing BP across the whole range has been shown to have a graded continuous relationship with increasing risk of both CHD and stroke.[4] However, the coexistence of other risk factors such as age, smoking and cholesterol have been shown to result in a dramatic increase in CVD risk associated with any BP stratum. Consequently, the absolute risk of a cardiovascular event occurring in hypertensive patients varies dramatically, perhaps over 20-fold, depending upon age, sex, level of BP and coexistence of other risk factors.[4,69]

Intuitive estimates of risk are crude and inaccurate.[70] Some guidelines have stratified risk based on the number of risk factors, the presence or absence of TOD and the presence of associated clinical conditions such as diabetes or renal disease.[52,71,72] The BHS believes that risk estimation is more accurate when major risk factors are evaluated and weighted using risk functions derived from epidemiological studies. The most commonly used is the Framingham risk function,[73] which has been shown to apply to Northern European populations including Britain.[74] One recent report suggests that the Framingham algorithm exaggerates CHD risk in the UK context.[75] This study, which was confined to men aged 40–59 years and which did not examine stroke risk, was none the less interesting because it suggested that it may in future be possible to adjust the Framingham equations to apply more accurately to the British population. More prospective data relating to CHD and stroke in British men and women will be required. In the same study,[75] using the thresholds of $>15\%$ CHD risk (equivalent to $>20\%$ CVD risk) over 10 years, the Framingham equation identifies 75% of those destined to have a CHD event and any overestimation of CHD risk was less apparent. In addition, it is likely that many of the people identified at $>15\%$ CHD risk by their risk factors, who do not then experience a CVD event in the next 10 years, will do so subsequently. The effect of changing from our earlier recommendations of $\geqslant 15\%$ 10-year CHD risk to $\geqslant 20\%$ 10-year CVD risk for the treatment of mild hypertension and for statin therapy will be to improve the identification of people who can benefit from such treatment although its full effect on sensitivity and specificity remains to be determined. For the present, we have chosen to continue to base risk prediction on the Framingham equation, because it remains the only method of estimating the risk of cardiovascular morbidity and mortality in both men and women, which includes most of the risk factors routinely available to the clinician.

In the 1999 guidelines,[3] the BHS endorsed the use of the Joint British Societies computer programme (the Cardiac Risk Assessor) and a CHD risk chart,[76] both of which were based on the Framingham risk function.[73] These were shown to be more user-friendly than other similar risk-assessment tools. Uptake of both the Joint British Societies chart and risk assessor was consequently very encouraging. However, the chart has two important inherent problems, in common with the others of its kind. Firstly, it predicts the 10-year absolute risk. This results in a propensity to undertreat young people at high relative risk and to overtreat older people at lower relative risk. For example, a 35-year-old woman, even if diabetic, a smoker, with a total cholesterol:HDL ratio of 9, and an SBP of 180 mmHg, does not reach the 10-year 30% risk of CHD threshold, the level at which intervention was previously recommended for some interventions.[3] In contrast, most elderly men would have qualified for intervention simply on account of their age and sex.

The second important problem of the first Joint British Societies prediction charts was the focus on CHD rather than CVD risk. In clinical practice, both the prescribing doctor and the patient are likely to be interested in all major cardiovascular events including stroke, rather than just fatal and nonfatal CHD, and certainly not just fatal events which a recent European approach has favoured.[77] In light of these two shortcomings, the latest Joint British Societies chart has been modified so that anyone below age 50 years will be assessed on the basis of their risk factors as if they were aged 49 years and all those aged 60 years and above will be assessed as if they were 69 years of age. This helps to improve the balance of emphasis between relative and short-term absolute risk. The chart now predicts 10-year CVD risk (combined fatal and nonfatal stroke and CHD) and, in view of the changing thresholds for intervention with statins (see later section), the only threshold emphasised in the charts is 20% 10-year CVD risk.

A further major change in the Joint British Societies risk charts is the lack of a separate chart for people with diabetes. This is based on the belief that the need for risk estimation among people with diabetes is rarely, if ever, required. The most recent Adult Treatment Program III (ATPIII) report[46] recommended that those with type II diabetes should be considered as 'coronary equivalents' (ie having the same CVD risk as a person who has established CHD), that is, 'secondary prevention', thereby obviating the need for formal risk assessment. This is based on one Finnish study[78] which conflicts with other epidemiological data.[79] However, the best current evidence strongly suggests that the CHD risk among people with diabetes aged >50 years, or those who have been diagnosed for at least 10 years, is equivalent to that to which those who have suffered a myocardial infarction (MI) are exposed. Furthermore, the short- and long-term case fatality rates following an MI among patients with diabetes are much higher than for those without. Hence for simplicity, given that most patients with type II diabetes are aged >50 years, it seems reasonable to treat all patients with diabetes as 'coronary equiva-

lents', thereby removing the need for total (often confusingly referred to as global) risk estimation. A risk scoring system ('engine') has been developed, based on the UK Prospective Diabetes Study (UKPDS), and this could be used for all patients with diabetes (including those with type I diabetes).[80] While this is undoubtedly the most accurate tool for assessing risk in people with diabetes, the threshold for intervention is exceeded by the substantial majority of these patients. There is a lack of evidence of the levels of cardiovascular risk and thresholds for intervention in patients with type I diabetes. Pending further evidence, it is reasonable to treat 'older' (>40 years) patients as type II diabetes, and to formally calculate the risk of younger type I diabetic patients using one of the dedicated risk assessors (Joint British Societies and the UKPDS risk engine), although these calculate risk for patients with type II diabetes.

The inadequacies of any risk-assessment system are acknowledged.[75] Nevertheless, the assessment of total risk is increasingly endorsed and encouraged as a guide to clinical practice, and strategies which do not incorporate such an approach are likely to be less cost-effective.

Improving accuracy at the expense of simplicity can only be realised by computerised systems, which incorporate many more variables, many of which are not routinely recorded. Moreover, the ideal system should predict major fatal and nonfatal cardiovascular (rather than coronary) events and incorporate some method of avoiding the shortcomings of predicting only short-term absolute risk. Despite more emphasis on simplicity than accuracy, the charts produced in these guidelines are the best available option. This tool, like all of the others available, should be used to guide rather than rule practice by clinicians who should be fully aware of the shortcomings of the system in use.

Blood pressure treatment thresholds (Box 5)

Previous BHS guidelines[2,3] advised early drug treatment of patients with more severe hypertension (⩾200/110 mmHg) and treatment of sustained BP ⩾160/100 mmHg. These recommendations remain sound and are not altered. It is recommended that all patients with grade I hypertension SBP: 140–159 and/or DBP: 90–99 mmHg) should be offered antihypertensive drug treatment if: (i) there is any complication of hypertension or TOD (for TOD definition see Table 1), or diabetes (Table 1) and/or (ii) the estimated 10-year CVD risk is ⩾20%, despite lifestyle advice.

Decisions on treatment at lower levels of CVD risk may also be influenced by the patient's attitude to treatment, and the benefit anticipated from treatment.

When a decision not to treat any patient with grade I (mild) hypertension is made, it is essential to continue observation and monitoring of BP, at least annually. BP will rise within 5 years to levels clearly requiring treatment in about 10–15% of patients. In addition, CVD risk will increase with age, and therefore risk should be reassessed accordingly. These patients should all be encouraged to continue with lifestyle measures to lower BP and CVD risk.

Thresholds for intervention are summarised below and in Figure 1.

- Accelerated (malignant) hypertension (papilloedema and/or fundal hemorrhages and exudates) or with acute cardiovascular complications, for example, aortic dissection; admit for immediate treatment.
- BP ⩾220/120 mmHg: treat immediately.
- BP >180–219/110–119 mmHg: confirm over 1–2 weeks, then treat.
- BP 160–179/100–109 mmHg:
  - cardiovascular complications/TOD (for TOD definition see Table 1) or diabetes (type I or II) present—confirm over 3–4 weeks, then treat;
  - cardiovascular complications/TOD (for TOD definition see Table 1) or diabetes (type I or II) absent: lifestyle measures, re-measure weekly initially, and treat if BP persists at these levels over 4–12 weeks.
- BP 140–159/90–99 mmHg:
  - cardiovascular complications/TOD (see Table 1) or diabetes (type I or II) present—confirm within 12 weeks, then treat;
  - cardiovascular complications/TOD or diabetes absent: recommend lifestyle measures, re-measure BP at monthly intervals;

Box 5 Thresholds and treatment targets for antihypertensive drug therapy

- Drug therapy should be started in all patients with sustained systolic blood pressures ⩾160 mmHg or sustained diastolic blood pressures ⩾100 mmHg despite nonpharmacological measures (A)
- Drug treatment is also indicated in patients with sustained systolic blood pressures 140–159 mmHg or diastolic blood pressures 90–99 mmHg if target organ damage is present, or there is evidence of established cardiovascular disease, or diabetes, or the 10-year cardiovascular disease risk is ⩾20% (B)
- For most patients a target of ⩽140 mmHg systolic blood pressure and ⩽85 mmHg diastolic blood pressure is recommended (A). For patients with diabetes renal impairment or established cardiovascular disease, a lower target of ⩽130/80 mmHg is recommended

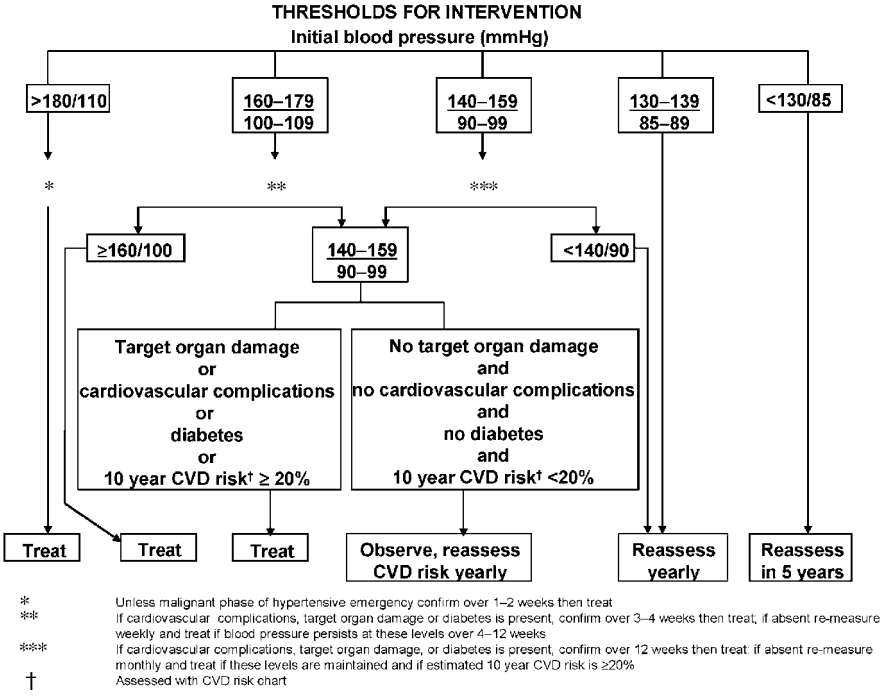

Figure 1 Blood pressure thresholds for intervention.

- if mild hypertension persists, estimate 10-year CVD risk formally using the Joint British Societies CVD risk chart computer programme[10] or the new CVD risk chart (Figure 2, see Appendix D for instructions on how to use the charts); treat if the estimated 10-year CVD risk is $\geqslant 20\%$.

BP treatment targets

Randomised controlled trial evidence on optimal targets for BP lowering is incomplete, with better evidence for DBP targets[81] than SBP targets, although for most patients above age 50 years, SBP is clearly a more important prognostic determinant of adverse CVD outcome.[82]

From all the intervention trials in hypertensive people, including those with and without diabetes, those at high CVD risk and those post stroke, the overwhelming evidence for an optimal DBP supports a 'lower the better' policy,[24] without any convincing evidence of a J-curve relationship. Despite limitations, the Hypertension Optimal Treatment (HOT) trial provides the best evidence to date on optimal targets during antihypertensive treatment of patients with a DBP of 100–115 mmHg.[81] Using an analysis based on achieved BP levels rather than an intention-to-treat approach, optimal target BP was reported to be 139/83 mmHg and reduction of BP below the optimal level caused no harm. Importantly, patients were little disadvantaged in the HOT trial provided BP was reduced below 150/90 mmHg. In light of these observations, in the 1999 BHS guidelines, we recommended a BP target of $<150/90$ mmHg as an '*Audit standard*', that is, the minimum target which all treated patients should attain. This recommendation remains unchanged.

In the HOT trial, an important practical finding was that the optimal DBP was attained by titrating treatment in a stepped-care fashion, aiming for DBP targets of either $\leqslant 90$, $\leqslant 85$ or $\leqslant 80$ mmHg. With this systematic method of treatment, the final DBP was above 90 mmHg in only 7% of patients.

For decades physicians have based their treatment on DBP targets. With increasing recognition of the importance of SBP as a risk predictor, several trials both completed and in progress, aim for both SBP and DBP targets of $<140/90$ mmHg. SBP targets are usually more difficult to achieve than DBP targets, but with adherence to a structured treatment algorithm, including dose titration of drugs and recommendations for add-on therapy, SBP targets of 140 mmHg can be achieved in the majority of patients.[49,83]

Among people with hypertension and diabetes in the HOT trial, there appeared to be a significant advantage, using an intention-to-treat analysis, of aiming for a DBP pressure $\leqslant 80$ mmHg, which halved the incidence of major cardiovascular events compared with treatment aiming for a DBP $\leqslant 90$ mmHg.

Considering prospective observational data and the findings of the HOT trial, recommendations for target BPs during treatment are shown in Box 6.

Lifestyle advice

Lifestyle measures

Lifestyle measures for BP reduction are given in Box 7 and Table 4.

Primary prevention of hypertension

Current approaches to the prevention of adverse cardiovascular sequelae due to hypertension are unsatisfactory since they require prolonged drug therapy for a large proportion of the adult population. Moreover, this strategy does not reduce the risk of treated hypertensive patients to that of the normotensive population.[47] A population strategy is therefore necessary: (1) to prevent the rise in BP with age, and therefore reduce the prevalence of hypertension, (2) to reduce the need for antihypertensive drug therapy and (3) to reduce CVD burden. The BHS proposes the following lifestyle modifications for the primary prevention of hypertension consistent with those recently outlined by the US National High BP Education Program:[84]

- maintain normal body weight for adults (eg body mass index 20–25 kg/m^2);
- reduce dietary sodium intake to <100 mmol/day (<6 g of sodium chloride or <2.4 g of sodium per day);
- engage in regular aerobic physical activity such as brisk walking ($\geqslant 30$ min per day, most days of the week);
- limit alcohol consumption to no more than 3 units/day in men and no more than 2 units/day in women.

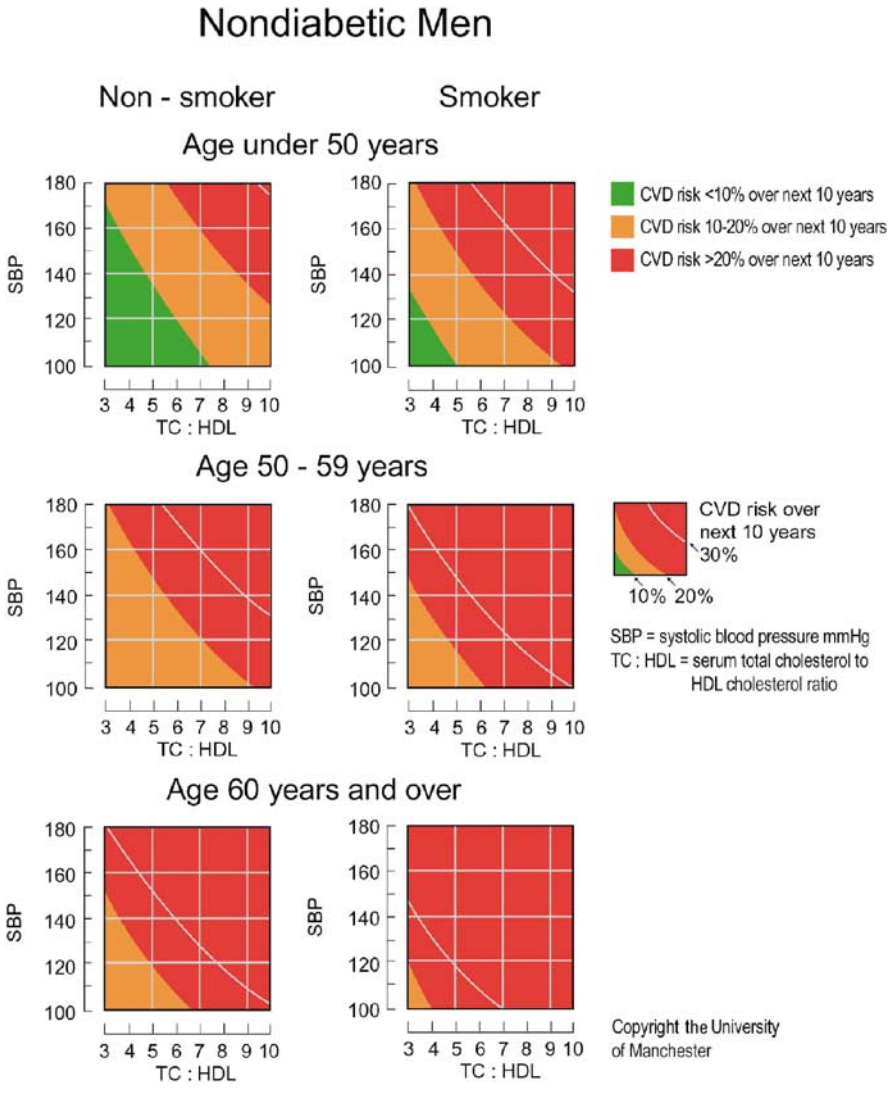

Figure 2 Joint British Societies CVD Risk Prediction Chart.

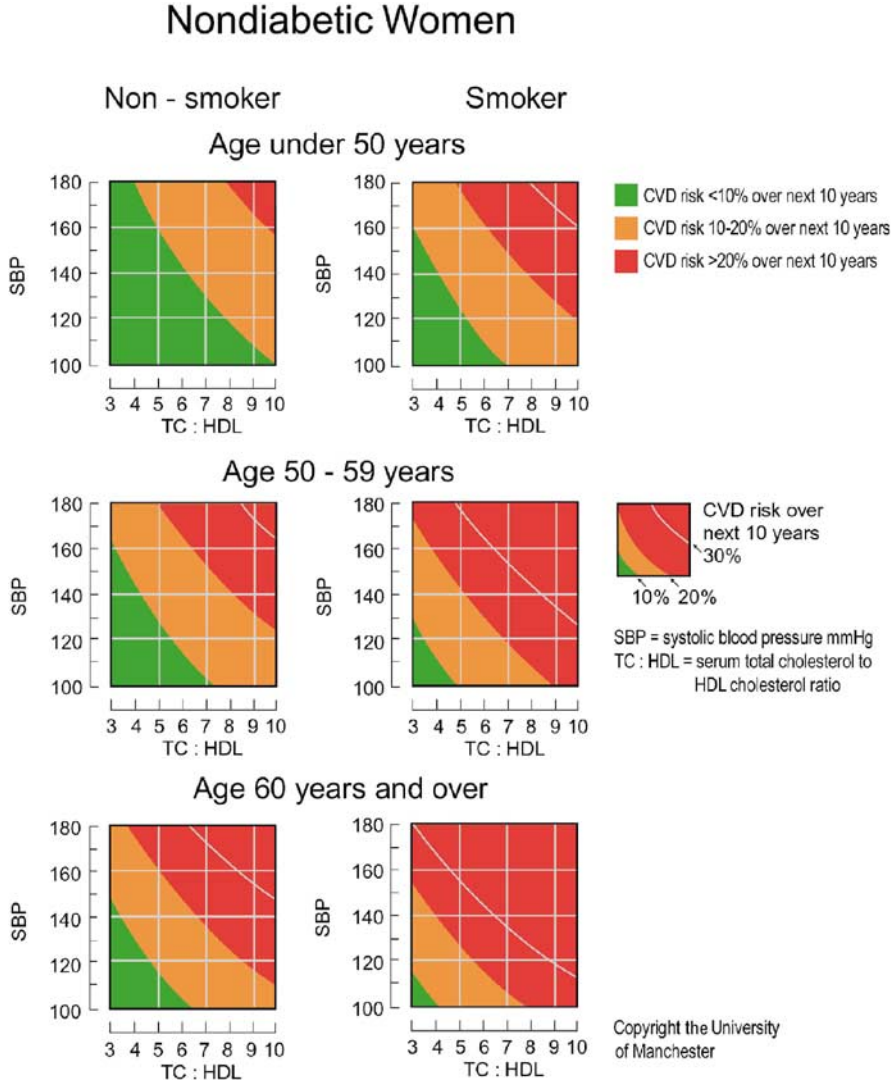

Figure 2 Continued

Box 6 Suggested target blood pressures during antihypertensive treatment. SBP and DBP should *both* be attained, for example, <140/85 mmHg means *less than* 140 mmHg for SBP and *less than* 85 mmHg for DBP

	Clinic BP (mmHg)	
	No diabetes	*Diabetes*
Optimal treated BP	<140/85	<130/80
Audit standard	<150/90	<140/80

Audit standard reflects the minimum recommended levels of BP control. Despite best practice, the Audit Standard will not be achievable in all treated hypertensives. For ambulatory (mean daytime) or home BP monitoring, reducing these targets by ~10/5 is recommended. BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure.

- consume a diet rich in fruit and vegetables (eg at least five portions per day);
- consume a diet with reduced content of saturated and total fat.

Lifestyle changes in established hypertension

Recent controlled trials[34–38,42,85–90] (clinical trials and trials included in reviews) have confirmed that lifestyle changes can lower BP (Table 4). These studies were not designed to quantify changes in deaths or cardiovascular events, but rely on the surrogate end point of reduced BP and its epidemiological link to reduced CVD, and it is therefore assumed that they will reduce CVD risk.

Clear verbal and written advice on lifestyle measures should be provided for all hypertensive patients and also those with high-normal BP or a strong family history. Effective lifestyle modification may lower BP as much as a single BP-lowering drug.[34] Combinations of two or more lifestyle modifications can achieve even better results.[34] Lifestyle interventions reduce the need for drug therapy, can enhance the antihypertensive effects of drugs, reduce the need for multiple drug regimens and can favourably influence overall CVD risk. Conversely, failure to adopt these measures may

Box 7 Lifestyle measures

- Lifestyle measures: weight reduction (A), reduced salt intake (A), limited alcohol consumption (A), aerobic exercise (A), reduced total fat and saturated fat intake (A) and increased fruit and vegetable consumption (A) are effective in lowering blood pressure
- Alone or in combination these interventions can reduce the need for drug therapy and enhance the effect of antihypertensive agents (A). A favourable effect on cardiovascular outcome is assumed, but not proven
- To reduce the overall cardiovascular disease risk, patients should stop smoking (B), reduce total fat and saturated fat intake and increase consumption of mono-unsaturated fats and oily fish (B)

Table 4 Lifestyle interventions for blood pressure reduction

Intervention	*Recommendation*	*Expected systolic blood pressure reduction (range)*
Weight reduction	Maintain ideal body mass index (20–25 kg/m^2)	5–10 mmHg per 10 kg weight loss[85,86]
DASH eating plan[a]	Consume diet rich in fruit, vegetables, low-fat dairy products with reduced content of saturated and total fat	8–14 mmHg[34,87]
Dietary sodium restriction	Reduce dietary sodium intake to <100 mmol/day (<2.4 g sodium or <6 g sodium chloride)	2–8 mmHg[84,87,88]
Physical activity	Engage in regular aerobic physical activity, for example, brisk walking for at least 30 min most days	4–9 mmHg[89,90]
Alcohol moderation	Men $\leqslant 21$ units per week Women $\leqslant 14$ units per week	2–4 mmHg[37]

DASH = Dietary Approaches to Stop Hypertension.
[a]Download the DASH eating plan from http://www.nhlbi.nih.gov/health/public/heart/hbp/dash.

attenuate the response to antihypertensive drugs. Lifestyle measures that lower BP and may reduce CVD risk in established hypertension are outlined in Table 4 and Box 8.

In patients with grade 1 (mild) hypertension, but no cardiovascular complications or TOD, the response to these measures should be observed during the first 4–6-month period of evaluation. When drug therapy has to be introduced more urgently, for example, in patients with grade 3 (severe) hypertension, lifestyle measures should be instituted alongside drug treatment. The initiation of drug treatment should never be delayed unnecessarily, especially in patients at higher levels of risk.

Weight reduction by calorie restriction is appropriate for the majority of hypertensive patients because most are overweight.[91] Low-calorie diets have a modest effect on BP in such individuals,[92–94] but nearly 50% can expect a reduction of 5/5 mmHg or better in the short term. Body mass index is frequently used as a measure of overweight but other measures of obesity, particularly central obesity, are better markers of adverse cardiovascular outcomes.[95] Weight reduction also has beneficial effects on associated risk factors such as insulin resistance, diabetes, dyslipidaemia and LVH.[96] The BP-lowering effect of weight reduction[97] may be enhanced by a simultaneous increase in physical exercise,[98] by alcohol moderation in heavy drinkers[99] and by reduction in sodium intake.[100]

Box 8 Lifestyle measures that lower blood pressure and cardiovascular disease

1. Lifestyle measures that 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

2. Measures to reduce cardiovascular disease risk
- Cessation of smoking
- Reduced total fat and saturated fat intake
- Replacement of saturated fats with mono-unsaturated fats
- Increased oily fish consumption

Salt reduction from an average of 10 to 5 g (5 g = ~1 teaspoon) daily lowers BP by about 5/2 mmHg[100–105] with larger BP falls in the elderly and in those with higher initial BP levels.[106] About one-third of people will achieve a reduction of 5/5 mmHg or more. These effects are additive to the BP-lowering effect of a healthy diet, for example, the Dietary Approaches to Stop Hypertension (DASH) diet.[34] All hypertensive patients should have clear verbal and written advice to reduce salt intake to

<6 g/day (<100 mmol/day). Many will already 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 of salt), some breakfast cereals, ready-prepared meals and flavour enhancers such as stock cubes or manufactured sauces. Patients, and those who cook for patients, should be provided with specific written advice (see Appendix E—Blood Pressure Association).

Alcohol intake above 21 units/week is associated with BP elevation[107–109] that is reversible by reducing the intake.[99,110] Binge drinking is associated with an increased risk of stroke.[111] Hypertensive patients should be advised to limit their alcohol intake to 21 units/week (men) and 14 units/week (women). Structured interventions to reduce alcohol consumption have on average a small effect on BP, reducing SBP (and possibly DBP) by about 2–3 mmHg.[99,110] Consumption of smaller amounts of alcohol, up to the recommended limit, may protect against CHD[108] and should not be discouraged.

Physical activity should be regular, aerobic (eg brisk walking) and tailored to the individual patient. For example, three vigorous training sessions per week may be appropriate for fit younger patients or brisk walking for 20 minutes/day in older patients.[112–114] Isometric exercise such as heavy weight lifting is not recommended for hypertensive patients due to the associated pressor effects on BP. Taking regular aerobic exercise has a small effect on BP, reducing SBP and DBP by about 2–3 mmHg.[115–118] Interventions which actively combine exercise and diet may reduce both SBP and DBP by 5–6 mmHg.[115–118,119] For patients with severe hypertension, or if hypertension is poorly controlled, heavy physical exercise should be discouraged and postponed until appropriate drug therapy has been instituted and found to be effective.

In observational studies, physical exercise appears to exert a strong protective effect against cardiovascular mortality.[120] Physical activity, either at work or in leisure time, is associated with a lower risk of CHD in men and women.[121–124] The largest reduction in risk is between sedentary and moderately active individuals with a more modest reduction between moderate and vigorous activity. Protection is lost when exercise is discontinued. Any activity appears to be of benefit but those that are more active appear to gain more protection. A reasonable strategy is regular aerobic exercise (eg brisk walking) for at least 30 min, ideally on most days but at least 3 days/week.

Increased fruit and vegetable consumption is supported by controlled-trial evidence that an increase from two to seven portions daily lowers BP by around 7/3 mmHg in hypertensive patients.[125] Hypertensive patients should be given clear advice to increase fruit and vegetable intake to at least five portions per day. When this is combined with an increase in low-fat dairy products and reduction of total and saturated fat, BP falls may be larger, averaging 11/6 mmHg in hypertensive patients.[125] The mechanism whereby fruit and vegetable consumption are thought to lower blood pressure is uncertain. However, this may be due to an associated increase in potassium intake, which is compatible with some supplementation studies.[126]

Lifestyle modifications NOT recommended for reducing BP: The best available evidence does not support the use of calcium, magnesium or potassium supplementation (ie tablets) individually or in combination to achieve a worthwhile reduction in BP.[39,40,127–136] Structured interventions to reduce stress (stress management, meditation, yoga, cognitive therapies, breathing exercises and biofeedback) have been shown to result in short term reductions in BP[137–141] but the interventions studied have been so varied, it is difficult to be prescriptive with regard to an effective strategy. Limited and inadequate evidence are available to support the use of garlic, herbal and other complimentary medicines to lower BP.

Cigarette smoking does not, except when chronic and heavy, appear to be associated with hypertension[142,143] but BP does rise acutely during smoking, and this results in the systematic underestimation of usual BP among regular smokers, since this is usually based on clinical readings when the patient is not smoking. Extensive observational data show that smoking has a graded adverse effect on risk of cardiovascular complications[144] and increases CVD risk more than mild hypertension. It is a major factor related to the persistent increase in coronary and stroke mortality in men with treated hypertension.[47] 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.[145–148] Hypertensive patients who smoke should be given advice and help to stop smoking. Physician advice and encouragement given repeatedly over time has been shown to reduce smoking by 21%.[149] The use of nicotine-replacement therapies is safe in hypertensives and approximately doubles smoking-cessation rates.[150] All forms of nicotine replacement therapy are effective particularly in those who seek help in stopping smoking.[149,151] Individuals need to recognise their increased risk due to smoking and also recognise the need to stop and be motivated to do so.

Dietary fat is a major determinant of the level of serum cholesterol, which with or without hypertension is an important predictor of CVD.[47] All patients should be advised to keep total dietary intake of fat to ⩽35% of total energy intake, to keep the intake of saturated fats to ⩽33% of total fat intake, to keep the intake of cholesterol to <300 mg per day, and to replace saturated fats by an increased intake of mono-unsaturated fats. These dietary changes can be very effective, but in clinical practice have been shown to reduce serum cholesterol by only about 6% on average,[152] because it is difficult to imple-

ment and sustain such measures.[153] Regular intake of fish and other sources of omega 3 fatty acids (at least two servings of fish per week) will further improve lipid profiles and has been shown to reduce BP,[154] as does the DASH diet.[125]

Effective implementation of these lifestyle measures requires enthusiasm, knowledge, patience and considerable time spent with patients and other family members. It is best undertaken by well-trained health professionals, for example, practice or clinic nurses, and should be supported by clear written information (see Appendix E—Blood Pressure Association). A common approach in successful lifestyle modification programmes is the use of group working. Healthcare teams and patient organisations could usefully provide information or organise local groups which promote healthy lifestyle changes.

Drug treatment

Introduction to drug treatment

Several classes of drugs have been used to lower BP, including thiazide/thiazide-like diuretics, beta-receptor-blocking drugs (beta-blockers), CCBs, ACE inhibitors, ARBs, alpha-adrenoceptor blockers (alpha-blockers) and older agents whose actions in general were sympatholytic, that is, they interfered at various sites with the activation of the sympathetic nervous system.

In unselected hypertensive populations, no one class of agents is any more effective at lowering BP than another. Overall, single drug therapy will reduce BP by, on average, no more than about 7–8%; however, there is substantial interindividual variation in response to single drugs with large absolute falls in some patients, contrasting with little or no response in others.[155]

These large variations in drug responses reflect marked heterogeneity in the pathogenesis of BP elevations in hypertension and the multiplicity of pathophysiological mechanisms responsible for higher levels of BP.[156]

There have been several attempts to profile subjects with regard to hypertensive phenotype in the hope that this would permit better selection for individual drug therapy. With one or two notable exceptions (age and ethnicity), this has been largely unsuccessful.[157,158]

The major drug classes are described below (for further reading see Kaplan[159] and Swales[160]):

Thiazide/thiazide-like diuretics

Thiazide/thiazide-like diuretics lower BP 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. Sustained actions of thiazide/thiazide-like diuretics on the kidney make them preferable to loop diuretics, with which short-term sodium and water loss may be compensated for by sodium retention during the latter part of the dosing interval and amelioration of their BP-lowering efficacy. Early blood volume loss with thiazide/thiazide-like diuretics may be accompanied by reflex activation of several vasoconstrictor mechanisms including the renin–angiotensin–aldosterone system, which may transiently raise peripheral vascular resistance and attenuate BP lowering. The lowering of BP following the introduction of thiazide/thiazide-like diuretic therapy over a period of days, results from gradual reduction in peripheral resistance.

Thiazide diuretics (bendroflumethiazide, hydrochlorthiazide) differ from thiazide-like diuretics (chlortalidone, indapamide) in several of their actions including ion channel-blocking activity, duration of action and carbonic anhydrase inhibitory activity, the implications of which are uncertain.

Thiazide/thiazide-like diuretic use in hypertension may be associated with hypokalaemia (drug and dose dependent), impaired glucose tolerance (worse when combined with a beta-blocker), small increments in blood levels of LDL cholesterol, triglycerides and urate.

Thiazide/thiazide-like diuretic use is associated in some patients with erectile dysfunction. Their efficacy is reduced in those receiving nonsteroidal anti-inflammatory drugs (NSAIDS), and they should usually be avoided in patients with a history of gout and those receiving lithium due to a high risk of lithium toxicity.

Potassium-retaining diuretics (eg amiloride, triamterene, spironolactone)

Potassium-retaining diuretics have two main roles in the treatment of hypertension. Firstly they may be used to limit potassium loss in patients treated with thiazide/thiazide-like diuretics. Secondly, spironolactone may play an important role in BP lowering in the increasingly recognised number of patients with 'resistant' hypertension in whom BP may be dependent on hyperaldosteronism.[161]

These potassium-retaining diuretics act by blocking sodium/potassium exchange in the renal distal tubules. They should not be used as first-line diuretic agents, except when the diagnosis of hyperaldosteronism has been made, but rather as add-on therapy to thiazide/thiazide-like diuretics. Care is needed in patients with impaired renal function due to the risk of hyperkalaemia. Also, when combined with an ACE inhibitor or an ARB, the risk of hyperkalaemia may be increased. One side effect of the aldosterone antagonist spironolactone, that is, gynaecomastia, is common due to their antiandrogen effects.

Loop diuretics have no place in the routine management of hypertension, except in patients with impaired renal function and/or heart failure.

Beta-adrenoceptor-blocking drugs (beta-blockers)
Beta-blockers were originally developed for their antianginal properties and were subsequently found to lower BP. Despite extensive investigations, their mode of action in lowering BP remains controversial and may differ according to the individual pharmacological and physico-chemical properties of drugs within the class. Most beta-blockers, with the exception of those with strong intrinsic sympathomimetic activity, reduce cardiac output by virtue of their negative chronotropic and inotropic effects. As with diuretics, short-term haemodynamic responses are offset by reflex activation of vasoconstrictor mechanisms, which may limit initial BP lowering. Longer term reduction in arterial pressure over days occurs due to restoration of vascular resistance to pretreatment levels. Partial blockade of renin release from the kidney may contribute to the later haemodynamic response.

Beta-blockers differ in their duration of action, their selectivity for beta-1 receptors, lipophilicity and partial agonist activity. Side effects include lethargy, aches in the limbs on exercise, impaired concentration and memory, erectile dysfunction, vivid dreams and exacerbation of symptoms of peripheral vascular disease and Raynaud's syndrome. They are contraindicated in asthma and cause adverse metabolic effects, including impairment of blood glucose control and worsening of dyslipidaemia—notably reduced HDL-cholesterol and raised triglycerides. There is accumulating evidence that beta-blockers increase the likelihood of new-onset diabetes, particularly when combined with thiazide/thiazide-like diuretics.

Calcium channel blockers (CCBs)
CCBs are used for their antianginal and antihypertensive properties. The dihydropyridine CCBs (eg nifedipine, amlodipine) are more selective at blocking L-type calcium channels in vascular smooth muscle cells and thereby inducing vascular relaxation with a fall in vascular resistance and arterial pressure. Nondihydropyridine CCBs (diltiazem and verapamil) at therapeutic doses block calcium channels in cardiac myocytes, thereby reducing cardiac output. Verapamil has an additional antiarrhythmic action through its effects on the atrioventricular node.

The earlier formulations of some dihydropyridines such as capsular nifedipine have a rapid onset of action, unpredictable effects on BP, and are accompanied by reflex sympathetic stimulation, tachycardia and activation of the renin–angiotensin–aldosterone system. In some cases, they can precipitate angina. These agents have no place in the management of hypertension even in the emergency setting. Longer acting dihydropyridines have been shown to lower BP very effectively by causing arterial vasodilatation with little or no neurohumoral activation.

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. Gum hypertrophy occurs, 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 extreme caution in combination with beta-blockers. Verapamil use is commonly accompanied by constipation.

Angiotensin-converting enzyme (ACE) inhibitors
These drugs block the conversion of angiotensin I to angiotensin II by inhibiting ACE. The resulting reduction in levels of angiotensin II leads to vasodilatation and a fall in BP. Angiotensin II has many additional actions that are potentially harmful to the cardiovascular system and has been implicated in the pathogenesis of structural changes in the heart, blood vessels and kidneys in hypertension and in other CVD.[162]

Acute falls in BP following the introduction of ACE inhibitors may occur when the renin–angiotensin system is activated, for example, in patients who are dehydrated, in heart failure, or in patients with accelerated hypertension. It is rarely seen, however, when therapy is initiated in uncomplicated hypertensive patients. Other physiological systems upon which angiotensin II may exert an important influence may contribute to the BP fall when the biosynthetic pathway is blocked by ACE inhibitors.

Side effects include the development of a persistent dry cough in 10–20% of users,[163] and rarely (circa 1%) angio-oedema. The latter is much more common in the black population (circa 4%). These drugs should be avoided in women of child-bearing potential because of the danger of foetal renal maldevelopment. They should not be used in patients with bilateral renal artery disease because they may precipitate deterioration in renal function and renal failure.

Angiotensin receptor blockers (ARBs)
These drugs block type I angiotensin II (AT1) receptors leading to vasodilatation and a fall in BP. In common with ACE inhibitors, they interfere with the actions of angiotensin II on the kidney. Owing to their receptor selectivity for the angiotensin receptor (AT1), and their lack of potentiation of bradykinin and possibly other vasoactive peptides, cough and angio-oedema are much less likely to occur than with ACE inhibitors. They are generally very well tolerated by patients intolerant of other therapies. Cautions and contraindications are similar to those outlined for ACE inhibitors.

Alpha-adrenoceptor blocking drugs (alpha blockers)
Early members of this class (eg prazosin) were short-acting drugs that blocked the activation of alpha-1 adrenoceptors in the vasculature, leading to vasodilatation. Postural hypotension was a recognised problem. Longer acting agents, for example, doxazosin and terazosin, lessen this problem. Additional properties include alleviation of some of the symptoms of benign prostatic hypertrophy. Stress incontinence may be exacerbated in women.

Sympatholytic agents and older drugs
Many of the earliest agents developed for BP control blocked the activation of the sympathetic nervous system at various levels including the cardiovascular regulatory nuclei in the brain stem, the peripheral autonomic ganglia and the postganglionic sympathetic neurone.

With one or two exceptions, few of these agents have any residual role to play in today's treatment of hypertension because side effects are common, often unpleasant and potentially harmful.

The use of methyldopa, which reduces sympathetic outflow from the brain stem will be discussed in more detail in relation to hypertension in pregnancy, which is its main indication. Other centrally acting sympatholytics include clonidine (now rarely used owing to its short duration of action and risks of withdrawal hypertension) and moxonidine a better tolerated drug, which acts as a central imidazoline receptor agonist, thereby reducing peripheral sympathetic activity.

Other vasodilators
Hydralazine—a short-acting nonselective vasodilator—has been replaced by better tolerated and more effective drugs. Minoxidil is a powerful vasodilator, the use of which is restricted to extreme resistant hypertension. It is potentially diabetogenic and stimulates body hair growth.

Intravenous nitrates, sodium nitroprusside and other intravenously administrated potent vasodilators such as fenoldopam, a dopamine agonist, are reserved for hospital use in hypertensive emergencies.

Importance of BP control

It is emphasised that optimal cardiovascular outcome is more consistently linked with BP control rather than with the drug class used to achieve it.[24] Although the evidence base on optimal target pressures for both SBP and DBP remains incomplete, in clinical practice, the majority of hypertensive patients on treatment remain well above currently recommended treatment targets for BP control.[44] Several individual trials and recent meta-analyses have shown beyond reasonable doubt that the lower the pressure the better, and that this should be the primary objective of any treatment strategy.[24]

Choice of antihypertensive drug

For each major class of antihypertensive drug, there are compelling indications for use in specific patient groups, and also compelling contraindications. There are also indications, contraindications and cautions that are less clear-cut, and which are given different weight by different doctors. These indications, contraindications and cautions for each of the drug classes are summarised in Table 2. When none of the special considerations listed in Table 2 apply, initial drug selection should follow step 1 of the AB/CD algorithm (see later).

Placebo-controlled trial evidence on 'older' BP-lowering drugs

Randomised placebo-controlled trials usually using diuretics and/or beta-blockers have shown significant reductions in stroke incidence of about 38%, coronary events of 16% and cardiovascular mortality of 21%.[164] The reduction in coronary events in these trials was less than the 20–25% risk reduction predicted from observational studies for a similar difference in BP.[165] The reduction in coronary events in two placebo-controlled trials using lower dose diuretics was larger at 28% than in earlier trials using higher doses of thiazide/thiazide-like diuretics.[166,167] These lower-dose thiazide/thiazide-like diuretic-based regimens also reduced cardiovascular and all-cause mortality significantly.

The larger benefit on coronary events observed in these trials with lower-dose thiazide/thiazide-like diuretics may be related to the different populations studied (older age, higher CVD risk or predominance of isolated systolic hypertension (ISH)), to the lower incidence of hypokalaemia, or to the play of chance.

The optimal dose of thiazide/thiazide-like diuretics is unclear, but higher doses, that is, >25 mg hydrochlorthiazide or >5 mg bendroflumethiazide, or >25 mg chlortalidone, should be avoided because such doses will further increase the risk of metabolic abnormalities with little if any additional BP lowering. Whether the very low doses commonly advocated (ie hydrochlorthiazide 12.5 mg, bendroflumethiazide 2.5 mg) are the most effective doses for BP lowering or preventing cardiovascular events remains uncertain[168] and requires further study.

Placebo-controlled trial evidence on 'newer' BP-lowering drugs

At the time of the last BHS guidelines, there was little evidence from randomised controlled trials on which to base recommendations regarding the effectiveness of newer agents such as ACE inhibitors

and CCBs with regard to CVD prevention. Since then, several placebo-controlled trials of ACE inhibitors have been performed, albeit not specifically in hypertensive populations. The Heart Outcomes Prevention Evaluation (HOPE),[30] Perindopril Protection Against Recurrent Stroke Study (PROGRESS),[16] EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)[17] and other trials have been carried out in patients at high CVD risk rather than high BP. In each of these trials, there were substantial reductions in CVD events in those allocated to an ACE inhibitor, accompanied by reductions in BP. It is the Committee's view that these cardiovascular benefits were most likely explained by better BP control in those allocated to the ACE inhibitor, but it is not possible to rule out other additional benefits. A single placebo-controlled trial with the dihydropyridine nitrendipine in patients with ISH resulted in convincing evidence of a reduction in CVD events in the active treatment group.[169]

Study on Cognition and Prognosis in the Elderly (SCOPE) recruited mostly patients with ISH, and set out to compare the ARB, candesartan with placebo.[170] The findings were confounded by the use of BP-lowering drugs in the placebo limb, such that the BP difference between limbs was less than expected and thus the study was underpowered. There were no significant differences in the primary outcome of combined CVD events or in stroke, but the nonsignificant reductions in both these end points were similar in size to those observed in the LIFE trial.

Active comparator trials comparing different BP-lowering drugs

Little, if any, differences in combined cardiovascular outcomes were observed in a series of trials comparing older regimes (usually diuretic/beta-blocker based) with newer regimens based on ACE inhibitors or CCBs (CAPtopril Prevention Project (CAPPP),[10] Nordic DlLiazem study (NORDIL),[9] International nifedipine once-daily study (INSIGHT),[8] Swedish Trial in Old Patients with hypertension 2 (STOP2).[11] This may have been the result of the inadequate power of each of these studies to show cause-specific differences in outcome. More recently, antihypertension and lipid-lowering treatment to prevent heart attack trial (ALLHAT), the largest hypertension trial ever conducted, reported its findings.[21] It was designed to compare the effect of four different first-line antihypertensive drugs on a combined primary end point of nonfatal MI and fatal CHD. In over 40 000 hypertensive patients, initial therapy with the reference drug, a thiazide-like diuretic, chlortalidone, was compared with the ACE inhibitor, lisinopril, the CCB amlodipine and the alpha-blocker' doxazosin. The ALLHAT population was recruited on the basis of higher CVD risk (many had established CHD or diabetes). The population was elderly and by design included a large proportion of women (47%) and African Americans (32%) (3% were Hispanic black).

The alpha-blocker limb was stopped prematurely after approximately 3 years due to an excess of combined CVD events compared with chlortalidone. This excess was largely due to a reported increase in heart failure, although there was no associated increase in mortality or in the primary endpoint—despite a 3 mmHg difference in SBP in favour of chlortalidone.

After an average of about 5 years, there was no difference in the primary outcome or all cause mortality in the remaining three limbs of the trial. For the secondary end point of stroke, there was a 15% excess in the lisinopril limb compared with chlortalidone ($P = 0.02$), which was compatible with less good BP control in the lisinopril limb of the trial. There was a reported 19% excess of heart failure in the lisinopril limb compared with the chlortalidone limb and in the amlodipine limb (38% excess compared with chlortalidone). Concerns have been raised about validation of this end point. ALLHAT was an important trial which had the potential to influence many guidelines, but the interpretation of the findings require detailed consideration before the unqualified conclusion and recommendations of the authors and the subsequent JNC 7 report[7] are accepted in clinical practice. A detailed critique of this study and an analysis of the results is beyond the scope of the guidelines and the reader is referred to the following commentaries.[171–173]

Following publication of ALLHAT, the second Australian National Blood Pressure study (ANBP2) trial, which for the first time compared a truly low dose of a thiazide diuretic (hydrochlorothiazide 12.5 mg once daily) with an ACE-inhibitor-based regimen, was reported.[168] This trial had several shortcomings, including poor compliance, and produced an equivocal result suggesting that the ACE inhibitor was of borderline superiority in protecting against cardiovascular events. The results appear to contradict those of ALLHAT and are of uncertain value.

In the Losartan Intervention for Endpoint reduction in hypertension (LIFE) study in which treatment with an ARB was compared with a beta-blocker,[12] the losartan-based regimen reduced cardiovascular events compared with the atenolol-based regimen. The difference was largely attributable to a risk reduction in stroke despite there being little difference in BP between groups. These data from the LIFE trial raise the possibility of stroke protection with ARB-based treatments that add to the benefit of BP lowering. However, controversy remains as to whether this reflects less effective stroke prevention afforded by beta-blockade, as suggested by some earlier trial evidence.[167]

Meta-analyses of BP-lowering trials

Since the 1999 BHS guideline, the Blood Pressure Lowering Trialists' Collaboration have conducted two major meta-analyses of BP-lowering drugs.[22,24] The first published in 2000 examined the effectiveness of 'newer therapies', that is, ACE inhibitor or CCB-based treatments *vs* conventional therapies (diuretic/beta-blocker-based) and concluded that 'newer therapies' were as effective, but no more effective than conventional therapy at reducing stroke, CHD morbidity or mortality, or all-cause mortality.[22] However, despite its size, this meta-analysis was still underpowered to demonstrate potentially important differences between drug classes with regard to cause specific outcomes. Nevertheless, this analysis confirmed the safety and efficacy of CCB-based therapy at a time when there was controversy about this issue. The 2000 meta-analysis has recently been updated in the second cycle of prospectively designed overviews from the Blood Pressure Lowering Treatment Trialists' Collaboration.[24] This new analysis of 29 trials and 162 341 participants with over 700 000 years of patient follow-up includes the more recent studies such as ALLHAT, ANBP-2, SCOPE and LIFE. Its findings are largely consistent with the 2000 meta-analysis, notably that, in general, the main driver of benefit from BP-lowering therapy is BP lowering *per* se, and that there is little evidence of additional drug class-specific benefits with regard to major cardiovascular outcomes overall. The caveats to this general conclusion are (1) that CCB-based therapy may be less protective than other agents against the development of heart failure; (2) there may be small benefits of CCB-based therapy, and even larger benefits of ARB-based therapy with regard to stroke prevention over and above the benefits of BP lowering; (3) there may be compelling indications for specific drug classes for target organ protection (see Table 2).

BP-lowering drugs and new-onset diabetes

People with hypertension experience a doubling in their lifetime risk of developing type II diabetes.[174] In several recent trials, different rates of the development of new-onset diabetes have been reported with different BP-lowering treatment strategies.[8,12,21]

In early trials using higher doses of thiazide/thiazide-like diuretics, impairment of glucose tolerance was observed.[167] Beta-blockers have also been shown to impair glucose tolerance and worsen other metabolic variables. In recent trials, when beta-blockers have been combined with thiazide/thiazide-like diuretics, new-onset diabetes occurred more frequently (by about 15%) than with regimens based on newer therapies such as ACE inhibitors, ARBs and CCBs.[8,12,21]

The longer-term consequences of these findings beyond the duration of the trials in which they have been observed are of concern because of the potential of impaired glucose tolerance and diabetes to increase CVD risk.

Recommendations for drug selection in practice—The BHS AB/CD algorithm

Hypertension control remains suboptimal in the UK.[43] Most people require more than one drug to control BP, and yet the majority of treated hypertensive patients continue to receive monotherapy.[43] Moreover, the UK has by far the lowest rate of fixed-dose combination therapy use in Europe and BP control rates lag substantially behind those of North America.[162] Hypertension guidelines hitherto have lacked the didactic treatment protocols common to other diseases such as asthma and heart failure, that have provided clear guidance on drug sequencing.

Since the 1999 BHS guidelines, clinical trials have clearly shown that treatment algorithms deliver better BP control than current clinical practice. The BHS has recently published a treatment algorithm (AB/CD)[45] designed to encourage improved BP control. Although randomised, controlled trials have yet to validate this specific algorithm, the recommended combinations are similar to those used in many randomised controlled trials of BP-lowering drugs, and involves extrapolation from an understanding of how different drugs work.

The treatment plan that we wish to endorse is modified from the original AB/CD rule.[45] Each letter refers to a BP-lowering drug class[175] and the AB/CD algorithm is illustrated in Figure 3.

It is important to note that the emphasis is on BP control. The AB/CD protocol is not restrictive and provides a template that allows the use of all classes of antihypertensive drugs. All things being equal and when there are no compelling indications for treatment with a specific class of drugs (see Table 2), then the cheapest available drugs should be used.

The theory underpinning the AB/CD algorithm is that hypertension can be broadly classified as 'high renin' or 'low renin', and is, therefore, best initially treated by one of two categories of antihypertensive drug, that is, those which inhibit (ACE inhibitors/ARBs or beta-blockers) and those which do not inhibit (CCBs or diuretics) the renin–angiotensin system. Renin-profiling studies have demonstrated that younger people <55 years and caucasians tend to have higher renin levels relative to older people ($\geqslant 55$ years) or the black population (of African descent). Thus, the A or B drugs which reduce BP at least in part by suppressing the renin–angiotensin system at one point or another are generally more effective as initial BP-lowering therapy in younger caucasian patients. In contrast, CCBs and diuretics

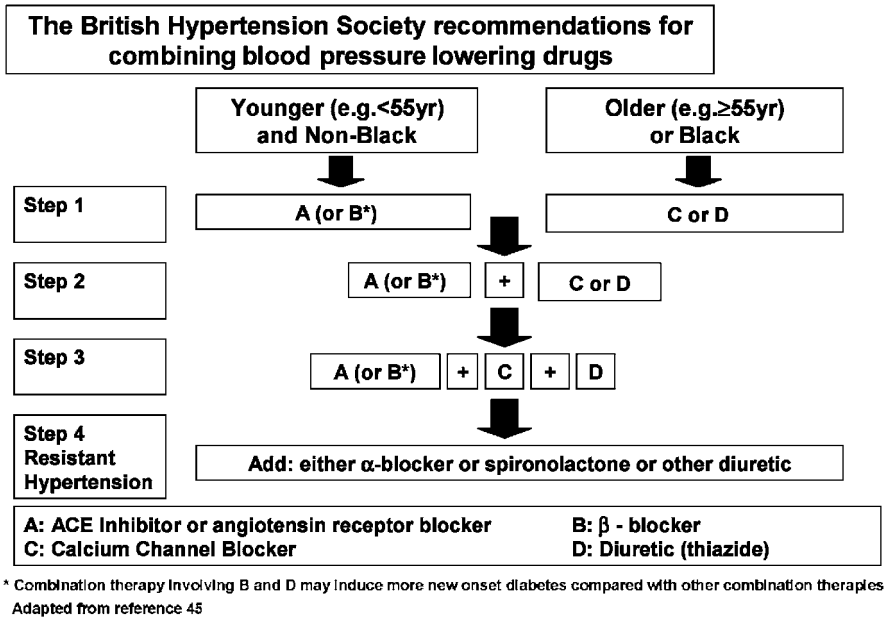

Figure 3 Recommendations for combining blood pressure lowering drugs/ABCD rule.[45]

are less effective as initial BP-lowering therapy in these patients, and are better used first-line in older caucasians or the black population of any age.[176–178]

Prospective evidence for the recommendations at step 1 arise from crossover studies in younger caucasian patients which found A or B to be almost twice as effective as C or D in reducing BP.[157,179] A randomised, parallel group study also reported D to be less effective in young caucasians, and that C was more effective (at all ages) than A or B in the black population.[158] The crossover studies permitted recognition of the two main categories of drug response, with correlation coefficients of 0.7 for the responses within each of the pairs, AB and CD, but no significant correlation between responses to drugs from opposite categories—for example, A and C. One other study, using ABPM, also reported a significant correlation between the BP-lowering response to A and B, but not between either of these and C.[155] The correlation data imply that there is little to be gained in efficacy from switching within each pair, for example, from A to B, whereas switching between pairs might enable a patient unresponsive to initial therapy to be controlled on a single drug. On the other hand, when a patient does respond to, but is intolerant of, a drug, it is logical to switch to the other member of the pair—for example, from B to A.

The evidence for recommending C or D in older patients derives from the ALLHAT study which showed that, in older patients, C and D lowered BP more than A (an ACE inhibitor), the difference being most marked in black patients.[21] Less direct evidence comes from a comparison of BP response to drugs in different trials. Outcome trials still in progress, Valsartan Antihypertensive Long-term Use Evaluation (VALUE) and ASCOT will provide direct comparisons within the same trial of the efficacy of C with A (an ARB) or B, respectively.

Turning to combination therapy—steps 2 and 3 in the AB/CD rule—the algorithm is less firmly scientifically based but supported by theory and clinical experience. The theory of combining one each of either A or B with either C or D derives from the respective effect of these categories on the renin–angiotensin system.[180,181] All four of the possible permutations of {A or B}+{C or D} have been approved by regulatory authorities as fixed-dose combinations. The most widely used combinations which are undoubtedly effective in terms of BP reduction are those of beta blockade and thiazide/thiazide-like diuretics, ACE inhibitor or ARB and thiazide/thiazide-like diuretics, and beta-blocker and CCB. When fixed-dose combinations replicate the desired treatment plan for a patient and when there is no cost disadvantage to their use, the BHS recommends the use of fixed-dose combinations as a sensible way of reducing the number of medications and thereby potentially improving adherence with therapy.

The AB/CD algorithm includes B in brackets. This is to emphasise the fact that each of the recent outcome trials that have reported the onset of new diabetes as a secondary end point has found a significant excess of new-onset diabetes in patients receiving an 'older' compared with a 'newer' class of drug (see above).[9,12] To what extent this is because older drugs enhance the already increased risk of developing type II diabetes in people with hypertension, and/or whether 'newer' drugs reduce that risk, is unclear. Retrospective studies of treated hypertensive cohorts have strongly implicated beta-

blocker therapy as potentiating the risk of developing new-onset diabetes. This is supported by the findings of the LIFE trial in which there was a significant 15% excess of new-onset diabetes over 5 years when beta-blocker-based therapy was directly compared to ARB-based therapy. All other treatments being equivalent, including the used of thiazide/thiazide-like diuretics in approximately 90% of patients in both arms of the trial. Whatever the mechanism, this is not cosmetic and the potential long-term effects of diabetes behove us to take the implication of this finding seriously. The ongoing ASCOT trial[182] will provide much-needed randomised controlled evidence as to whether these concerns are valid.

One *post hoc* analysis has suggested that the increased risk of new-onset diabetes is confined to patients with an elevated blood glucose at baseline, low HDL-cholesterol, obesity or genetic (family or ethnic) predisposition to diabetes.[183] Another suggested that the risk is confined to patients receiving the higher dose of older drug.[184] Thus, in patients at especially high risk of developing diabetes, that is, (1) strong family history of type II diabetes, (2) obesity, (3) impaired glucose tolerance and/or features of the metablic syndrome, or (4) specific ethnic groups, such as in the South Asian community, it is advisable to limit the dose of (B) and not to combine these drugs, particularly with a diuretic.

At step 3, we recommend combining A or (B) with C and D. This triple therapy combination has been used in many of the clinical outcome trials described earlier. Moreover, this triple therapy approach can be achieved by using only two tablets if fixed dose combinations are used, for example, BD + C, or AD + C.

In patients with more resistant hypertension, advice is even more anecdotal or theory-based A + B + C + D may be effective. Alternatively, it is at this stage that the addition of alpha blockade may be of particular use. Many patients with resistant hypertension may be helped by further elimination of sodium, and in particular, impressive BP lowering has been reported anecdotally with the use of the aldosterone antagonist spironolactone.[161,185,186]

Dosage

The drug formulation used should ideally be effective when taken as a single daily dose. An interval of at least 4 weeks should be allowed to observe the full response, unless it is necessary to lower BP more urgently. The dose of thiazide/thiazide-like diuretic should not be titrated up,[187] whereas other drug classes should be titrated according to the manufacturers' instructions. When the first drug is well tolerated but the response is insufficient, as is the case in over half of all hypertensive patients, the options are to substitute an alternative drug or to add a second drug. Substitution of an alternative drug is appropriate when hypertension is mild and uncomplicated and the response to the initial drug was small. In more severe or complicated hypertension, it is safer to add drugs stepwise until BP control is attained. Treatment can be stepped down later if the BP falls substantially below the optimal level.

Other routine medications for hypertension patients

Lipid-lowering agents

Two trials—ALLHAT[188] and ASCOT[49]—have recently reported cardiovascular outcomes associated with the use of statins, specifically among patients with hypertension. Prior to these two recent trials, other randomised controlled trial data were available from analyses of the hypertensive subgroups from lipid-lowering trials in secondary prevention,[189–192] primary prevention,[193,194] and a mixture of primary and secondary prevention.[48,194] The Heart Protection Study (HPS)[48] included over 20 000 patients, 41% of whom were hypertensive, and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial[195] included only elderly patients, 62% of whom were hypertensive. Like HPS, PROSPER mainly included patients with established vascular disease. Analyses of the hypertensive subgroups from all these trials show that the benefits of lipid lowering with statins in terms of preventing major coronary events are similar for hypertensive and normotensive patients.

Somewhat more surprising, and of special importance to the hypertensive population, is the finding that, in the statin trials, overall stroke risk was reduced by an average of 15 and 30% in primary and secondary prevention settings, respectively,[196] although no such benefit was observed in the PROSPER trial.[195]

The ALLHAT-LLT trial compared the impact of 40 mg pravastatin with usual care in over 10 000 hypertensive patients.[187] The differential effect of pravastatin on total and LDL-cholesterol of 9% and 17%, respectively, was smaller than expected, due to extensive statin use in the usual care group, and was associated with a nonsignificant 9% reduction in fatal CHD and non-fatal MI and a 9% reduction in fatal and nonfatal stroke. There was no apparent impact on all-cause mortality, which was the primary end point of the trial. By contrast, the results of the ASCOT-LLA trial,[49] which also included over 10 000 hypertensive patients at a modest background risk of cardiovascular disease, showed highly significant cardiovascular benefits (36% reduction in the primary end point of fatal CHD and nonfatal MI and 27% reduction in fatal and nonfatal stroke) associated with the use of atorvastatin 10 mg compared with placebo in patients with total cholesterol $\leqslant$6.5 mmol/l. These highly significant benefits were apparent despite exemplary BP control. The apparent difference in

effect seen in the ALLHAT and ASCOT trials probably reflects the greater relative difference in total and LDL-cholesterol achieved among the actively treated group in the ASCOT trial (24% and 35%, respectively).

Recommendations regarding the use of lipid-lowering therapy for patients with hypertension may be subdivided into those relating to secondary and to primary prevention.

Secondary prevention: Based on the results of the HPS[48] and other secondary prevention trials,[189–192] all patients up to the age of at least 80 with total cholesterol >3.5 mmol/l with active CHD, peripheral arterial disease or a history of ischaemic stroke should receive a statin. In light of the high coronary event rates observed among many patients with type II diabetes,[78] and the high long- and short-term fatality rates for such patients, it is recommended that patients with type II diabetes—diagnosed at least 10 years ago and/or aged 50 years or more—should be considered as CHD risk equivalents[197] as far as lipid lowering is concerned, and hence should be treated as for secondary prevention. Other patients with type II diabetes could be considered as for primary prevention on the basis of an estimated risk threshold,[80] but for simplicity regarding treatment threshold purposes, it is recommended to consider such patients as 'coronary equivalents'. Therapy should be titrated to lower total or LDL-cholesterol reduction of by 25% or 30%, respectively, or to <4.0 mmol/l or <2.0 mmol/l, respectively, whichever is the greater reduction. This should be regarded as the optimal therapeutic goal, but in view of current treatment practices we recommend an audit standard of total cholesterol <5.0 mmol/l or LDL-cholesterol <3.0 mmol/l with a total or LDL-cholesterol by 25% or 30%, respectively.

Primary prevention: Randomised placebo-controlled trial evidence has demonstrated significant benefits of statin therapy among normotensive and hypertensive adults with an estimated mean 10-year CHD risk of as low as 6%.[194] However, the majority of adults over the age of 40 in the UK are at or above a 6% 10-year CHD risk, and consequently it is not financially feasible nor conceptually ideal to treat all people at and above this level of risk. Only 1% of patients in the HPS[48] were hypertensive and did not have either a history of a cardiovascular event, active vascular disease and/or diabetes, and hence this trial does not supply a robust database on which to make recommendations for primary prevention of CVD in hypertensive patients. In view of the results of the ASCOT trial[49] and other currently-available trial data,[194] it seems reasonable, in the interests of simplicity, to treat with a statin all those patients at least up to the age of 80 years with a total cholesterol >3.5 mmol/l, who have an estimated 10-year CVD risk of 20% or more. In reality, this would mean considering statin therapy in most hypertensive patients (especially men) over the age of 50 years. As resources allow, a rationale for lowering this threshold could be made based on trial evidence.[49,194]

Target levels should be as for secondary prevention. The vast majority of patients will reach recommended total cholesterol or LDL-cholesterol targets using statin drugs at appropriate doses in combination with lifestyle measures.[198] For patients who do not reach targets or whose HDL-cholesterol or triglyceride levels remain abnormal (eg <1.0, >2.3 mmol/l, respectively) despite reaching LDL targets, referral to lipid specialists may be indicated for consideration of the addition of alternative lipid-lowering therapy. No trial data are currently available to advise whether in those patients, such as many type 2 diabetics, whose primary lipid abnormality is a low HDL-cholesterol and raised triglycerides, the use of a fibrate might be preferable to a statin. However, on currently available evidence, statins at suitable doses should be the drugs of choice.[43,156–169]

Aspirin

Since publication of the 1999 BHS guidelines, no new evidence to guide practice regarding the use of aspirin for hypertensive patients has been produced. Hence, the recommendations made at that time remain unchanged (see Box 9). In summary, all patients suitable for secondary preventive strategies, including those with type II diabetes of greater than 10-years duration, or over age 50, have a sufficient level of CVD risk to benefit from aspirin therapy, and should be considered for low-dose aspirin (75 mg/day) unless they have specific contraindications to aspirin use. For primary prevention, the balance of

Box 9 Other measures to reduce cardiovascular risk

Patients with established cardiovascular disease or at high risk according to the Joint British Societies cardiovascular disease-risk chart computer programme or cardiovascular disease risk chart should be considered for aspirin (A) and statin therapy (A) as follows:

- For primary prevention: 75 mg aspirin is recommended for hypertensive patients aged 50 years or more who have satisfactory control over their blood pressure and either target organ damage, diabetes or cardiovascular disease risk ⩾ 20%.
- For primary prevention: statin therapy is indicated when the 10-year cardiovascular disease risk is ⩾20%.
- For secondary prevention: statin therapy and aspirin therapy are indicated when there is evidence of cardiovascular disease, that is, angina/myocardial infarction, stroke, transient ischaemic attack, peripheral vascular disease, etc.

benefits *vs* harm mandate that patients need to be aged over 50 years and have a CVD risk level $\geqslant 20\%$ over 10 years to shift the balance in favour of benefit. Thus, for primary prevention, low-dose aspirin (75 mg/day) should only be offered to hypertensive patients aged over 50 years whose BP has been controlled to the audit standard ($<150/90$ mmHg) and who have a baseline CVD risk $\geqslant 20\%$ over 10 years and no contraindications to aspirin use.

Vitamins

Good laboratory-based evidence suggest that antioxidant vitamins may play an important role in providing protection against the atherosclerotic process.[199] However, to date, randomised trial data overall have shown no benefits in terms of cardiovascular morbidity and mortality associated with the use of vitamins A, C or E. Most recently, the HPS,[200] which included over 20 000 subjects, 41% of whom were hypertensive, showed no benefits whatsoever—cardiovascular or otherwise—associated with daily antioxidant supplementation of 600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene. Therefore, we do not recommend that vitamin supplementation should be used with any expectation of either reducing BP or CVD risk.

Special patient groups

Hypertension in the elderly

Hypertension the Historically, the elderly have been neglected in terms of appropriate risk factor assessment and hypertension management, although trial data show that older people have benefited as much if not more so from such interventions as younger individuals.[201] In the UK, CHD and stroke remain the major causes of death in people over the age of 65 years, with hypertension the commonest treatable risk factor. It is well recognised that ageing in Westernised societies is associated with a rise in SBP across the whole age range, while DBP increases up to the age of about 60 years, plateaus, and then falls, resulting in an age-related increase in pulse pressure and ISH.

It is important to note that older people show greater BP variability, and thus it is particularly important that multiple measurements are taken on several occasions to confirm the diagnosis of hypertension. Seated and standing measurements are important during the initial assessment and after initiating drug therapy, because of the high prevalence of orthostatic hypotension in this age group. In older people with significant orthostatic hypertension, that is, SBP, falls $\geqslant 20$ mmHg with postural symptoms, treatment may need to be titrated to the standing BP values.

Hypertension is common in older people and, even using the more conservative definition ($\geqslant 160/95$ mmHg), it is estimated that more than 50% of the 12 million people in the UK over 60 years are hypertensive. If hypertension is defined as $\geqslant 140/90$ mmHg, over 70% will be hypertensive, the majority of these patients having ISH.[43] It is obvious that with the very high prevalence of hypertension in this age group and the rapidly increasing numbers of older people in most populations, especially those in the 75+ age group, raised BP levels are an enormous public health problem.

Hypertension cannot be considered in isolation irrespective of age, and it is important that overall CVD risk is assessed when making decisions on treatment (see Figure 1). Lifestyle measures should be offered to all older people with hypertension and are just as effective as they are in younger people.[100]

The benefits of drug treatment for hypertension, including ISH, in those aged up to the age of 80 years, have been clearly demonstrated in randomised controlled trials. However, the absolute benefits of treatment are much greater in older people because of their increased absolute risk. Some studies have also suggested that the cognitive impairment associated with increasing age can also be reduced by treatment,[202] an important consideration in this age group.

Thiazide/thiazide-like diuretics are especially effective at lowering BP in older people, as are dihydropyridine CCBs.[169,203] Moreover, thiazide/thiazide-like diuretics and CCBs have been shown to be effective at reducing cardiovascular morbidity and mortality in older people with hypertension or ISH.[167,169] A recent meta-analysis has suggested that beta-blockers may not be as effective as thiazide/thiazide-like diuretics at reducing stroke deaths, CHD events or all-cause mortality in older people.[204] Consistent with this conclusion, ARB-based therapy (losartan) was recently shown to be substantially more effective than beta-blocker-based therapy (atenolol) at reducing the risk of stroke and cardiovascular mortality in older people with ISH.[205] The routine use of beta-blockers to treat high BP in older people should be limited unless there are specific indications, for example, post MI, angina or heart failure. Most older people will need more than one BP-lowering drug to control their BP and logical combinations are outlined in the AB/CD algorithm (Figure 3).

The benefits of BP-lowering therapy in people over the age of 80 years have not yet been established. A recent meta-analysis of intervention trials that included patients aged over 80 years concluded that active treatment reduced stroke and CHD events (both fatal and nonfatal), but no significant effect on overall mortality was apparent, although available data are too few as yet to evaluate this end point.[206] The ongoing HYpertension in the Very Elderly Trial (HYVET) has been designed to assess the safety and efficacy of antihypertensive therapy in the very elderly (80+ years).[207] Until such data become available, we recommend that those who reach 80 years of age while on treatment should probably remain on therapy, especially if

there is evidence of TOD or they have other significant CVD risk factors such as diabetes. For those aged over 80 years at the time of diagnosis of hypertension, no clear guidance can be given. However, in such circumstances, treatment decisions are best, based on consideration of the presence of other co-morbidities.

Hypertension in the young

There is little evidence to guide management of patients in 'younger patients with hypertension', that is, younger than the lowest age used in the Framingham-based risk calculator, namely 32 years. In those with stage 1 hypertension, that is, 140–159/90–99 mmHg, even up to the age of 49 years (the minimum age assigned by the risk tables in Figure 2), it is almost impossible for a nonsmoker to achieve an absolute CVD risk $\geqslant$20%/10 years, unless diabetic or markedly hyperlipidaemic (total cholesterol:HDL ratio $>$7.0). Precisely, because of this low absolute level of CVD risk, these patients will never be included within, or contribute many events to an outcome trial. Importantly, although these patients have a low *absolute* risk, they have a high risk of strokes and CHD relative to their peers.[82] Moreover, Framingham data show a steep rise in SBP and DBP over 10 years in 30-year old people within the top quartile of BP, and it can therefore be surmised that a young patient who is already hypertensive will, if left untreated, become more treatment resistant later in life. Although the hypertension in younger people may appear too mild to treat, it is not benign and it is worth reflecting on the fact that the underlying diathesis is sufficiently severe to have declared itself so young.

The profile of hypertension is also different in younger people. Diastolic hypertension is more common than it is in older people, and appears to be just as strong as a predictor of future cardiovascular events as SBP in this younger age group. With regard to SBP, when it is elevated in younger people, it heralds the onset of ISH with ageing, suggesting that large artery stiffening may be a consequence of untreated systolic hypertension in the young.[208] It is emphasised that, although treatment of stage 1 hypertension in younger people is often delayed because of their low absolute CVD risk over 10 years, it cannot be assumed that subtle and progressive vascular damage occurring in the untreated younger hypertensive patient is necessarily reversible.

One solution might be to calculate the lifetime, rather than 10-year, risks for younger patients. However, such actuarial tables, incorporating other risk factors, are not readily available. We therefore draw attention to the need to be circumspect about applying the thresholds in Figure 1 to treatment decisions in younger patients—particularly those in their early 30 s or younger, who will be exposed to more than a decade of increasing BP before their BP or absolute CVD risk reaches the recommended treatment thresholds for people with stage 1 hypertension. Given the lack of evidence from outcome trials at this younger age, and the unlikelihood that it will ever emerge, it is reasonable to reach a decision jointly with the patient, balancing the inconvenience and cost of treatment with their attitude to the potential benefits of treatment. Unlike their older counterparts, the younger patient can legitimately balance long-term risks against inconvenience of early treatment initiation. Whatever decision is reached, it is important that these patients are not lost to follow-up.

It is also important to note that secondary causes of hypertension are more common in younger people presenting with hypertension. For these reasons, referral for more specialised evaluation should be considered (see Table 3). Secondary hypertension should, in particular, be suspected if patients do not respond to the initial treatment recommendations for younger patients according to the AB/CD rule (Figure 3).

Hypertension and stroke

Stroke mortality has been falling in the UK for the past three decades and deaths from cerebral haemorrhage may have been falling for even longer.[209] This reduction probably results from a combination of a decrease in stroke incidence and severity, and in the case-fatality rate. However, increased survival rates and an ageing population has resulted in an increased burden of stroke in the UK population. In the UK, there are still over 120 000 strokes per annum, of which 20% are recurrent stroke. Approximately 80% of all strokes are due to cerebral infarction from large and small (lacunar) vessel disease as well as cardioembolic sources. In all, 10% of strokes result from cerebral haemorrhage, and the rest are related to subarachnoid haemorrhage and 'stroke of unknown causes'. Overall, 20% of people die within the first few months of a stroke, and up to 35% will be dependent at 1 year.[210] Although the majority of deaths within the first few months of stroke onset are directly related to the initial event, mortality after 1 year is often due to CVD other than stroke recurrence.[211]

Hypertension remains the most important treatable risk factor for the prevention of stroke and its recurrence, and antihypertensive therapy significantly reduces the risk. The relation between BP levels immediately poststroke and outcome (in terms of death and disability or stroke recurrence) is less clear, as is its clinical management. Half of all stroke patients will have a history of hypertension and up to 40% will be on antihypertensive treatment when their stroke occurs.[212] After acute cerebral haemorrhage or infarction, casual BP levels are usually increased, with more than 80% of patients having levels $\geqslant$160/95 mmHg within the

first 48 h of ictus. These values usually decrease spontaneously in the subsequent 10–14 days, the falls being most marked in those who continue their antihypertensive drugs.[213] The initial increase in BP after stroke may in part be simply due to the stress of hospitalisation, but other mechanisms may also be responsible.[214] Observational studies reporting post-stroke outcome in relation to initial casual BP levels are inconsistent.[215–217] However, using 24-h BP monitoring, and thus reducing the variability of BP measurement in the acute situation, it has been reported that for every 10 mmHg increase in 24-h SBP levels, the likelihood of death or dependency at 30 days post-ictus is almost doubled.[218] In contrast, the International Stroke Trial[219] reported a J-shape relation between initial BP and outcome, with early deaths increasing by 18% for every 10 mmHg of admission of SBP below 150 mmHg and by 4% for every 10 mmHg above 150 mmHg. It is not too surprising that low BP values are related to an adverse prognosis as they are often associated with large cerebral infarcts (total anterior cerebral artery occlusion) or concomitant severe cardiac disease.

There are potential pros and cons for both raising and lowering BP in the acute post-ictal situation. However, to date, there have been very few trials of either pressor or depressor interventions in the acute stroke period. Small studies of beta-blockers and CCBs used immediately post-stroke have shown no benefit, but these studies were too small to draw firm conclusions.[220] The recently reported Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) Trial[221] did suggest that the ARB candesartan may be of benefit in those with markedly elevated BP levels ($\geqslant$200/110 mmHg) within the first 48 h of cerebral infarction, but the findings of this small trial need confirmation. Whether antihypertensive treatment should be continued or stopped immediately post-stroke is also unclear and the subject of a major ongoing trial.[214] Presently, it is not possible to provide clear guidance on the clinical management of BP in the immediate ($<$48 h) post-stroke period. It has been suggested that treatment to lower BP is appropriate when BP is persistently elevated immediately post-stroke (SBP $>$ 220 mmHg or MAP $>$ 130 mmHg), although there are no clinical trial outcome data to support this view.[222] Agents such as labetalol, nitrates and sodium nitroprusside have been used to lower BP acutely in stroke patients, especially in situations where thrombolysis is being undertaken. These antihypertensives can be given by nonoral routes, an important consideration given that 30% of stroke patients are initially dysphagic. Other stroke patients for whom immediate BP reduction may be beneficial include patients with cerebral haemorrhage, those with cardiac and vascular emergencies such as hypertensive encephalopathy, aortic or carotid dissection, acute MI or angina.

Almost half of all stroke survivors will have a raised BP 1–6 months after stroke onset, and most observational studies have shown that higer BP levels at this stage are associated with an increased risk of stroke recurrence and the subsequent development of CHD events.[223] To date, only two small studies,[224,225] published more than 30 years ago, have assessed the benefit of pharmacological BP reduction in post-stroke subjects restricted to those who had hypertension, and they produced conflicting results. Although many of the large, placebo-controlled, BP-lowering trials in hypertension have included stroke patients, the evidence for benefit of treatment in these small subgroups has not been made available. There are, however, available data from seven randomised controlled intervention trials of BP reduction in stroke/transient ischaemic attack (TIA) patients who were not necessarily hypertensive.[16,224–229] Indeed, the majority of these studies included patients who were either normotensive or who had treated and controlled hypertension at entry. The majority of these studies were based on a diuretic and/or an ACE inhibitor as first-line agent with no particular BP target set, and the achieved BP reductions compared to placebo were quite modest (10/5 mmHg). Meta-analysis has shown that treatment significantly reduces the odds ratio for fatal and nonfatal stroke recurrence (0.74 95% CI 0.66–0.82), as well as for all major cardiovascular events (0.77, 0.70–0.84).[214] The PROGRESS Study is the largest study to show the benefits of BP reduction (using an ACE-inhibitor, perindopril with or without a thiazide-like diuretic indapamide) on stroke recurrence and major cardiovascular event rate in patients with a history of stroke or TIA irrespective of baseline BP level on entry to the study.[16] By inference, most patients with established CVD would benefit from BP lowering; hence conventional BP thresholds and targets do not apply (see Box 5), and the lowest BP tolerated is recommended. No firm recommendations can be given as to whether one class of antihypertensive agents is better than another in this situation, but the acute beta-blocker-based regimens seem to do poorly compared to those involving a thiazide/thiazide-like diuretic and/or ACE-inhibitor therapy.[214] When treatment should be started or restarted is also unclear, but practice is usually to initiate therapy a couple of weeks after the acute event. Whether a more aggressive stance should be adopted with regard to BP control in patients with primary intracerebral haemorrhage is also uncertain.

As with the general management of hypertension, other factors in stroke and TIA patients must also be considered. There is convincing evidence that patients who have had a TIA or cerebral infarct should receive an antiplatelet agent. Aspirin (75–300 mg daily) will reduce the risk of subsequent cardiovascular events by about 11% following acute stroke (irrespective of admission BP levels) and by 20% in those with a past history of ischaemic stroke.[230] For those stroke patients in atrial fibrillation, anticoagulation will reduce the incidence of a

further stroke by over 60% (paying careful attention to control of hypertension if present[231]), and statin therapy lowers risk of subsequent major vascular events by over 20% in those with TC levels >3.5 mmol/l.[48] In patients with symptomatic severe carotid artery stenosis ($\geqslant$70% but without near occlusion), carotid endarterectomy reduces subsequent stroke by 40%[232] (Box 10).

Hypertension in people with diabetes

When compared to people without diabetes, hypertension (defined as a BP $\geqslant$140/90 mmHg) is twice as common in people with diabetes. In type I diabetes, the excess prevalence of hypertension is strongly related to the presence of incipient or overt nephropathy. In type II diabetes, hypertension is very common with prevalence rates reaching 80% in many European countries.[233] Hypertension in diabetes is characterised by an earlier onset of systolic hypertension and a higher prevalence of ISH at any age when compared to people without diabetes. In type II diabetes, hypertension is more common in women than men and the age-related increase in SBP is steeper in women.[233]

In addition to being very common, hypertension greatly increases the already elevated CVD risk in people with diabetes. Diabetes increases the risk of coronary disease two-fold in men and four-fold in women.[27,81,234] The combination of hypertension and diabetes doubles the risk of developing microvascular and macrovascular complications, and doubles their risk of mortality when compared to nondiabetic people with hypertension.[27,81,234]

Benefits of BP lowering in people with diabetes

The impressive benefits of BP lowering in reducing or preventing an aggregate of major cardiovascular events, including heart failure, cardiovascular death and/or total mortality in people with diabetes, has been established in many clinical trials which have compared 'more' with 'less' intensive BP lowering.[27–30,235–237] In addition, 'more versus less' BP lowering has also been shown to significantly reduce the progression of retinopathy, albuminuria and the progression of nephropathy.[27–30,235–237]

Thresholds for intervention with BP-lowering therapy in people with diabetes

The previous BHS guidelines recommended that BP lowering with drug therapy is indicated in people with type I or type II diabetes when the SBP is $\geqslant$140 mmHg and/or the DBP is $\geqslant$90 mmHg.[3] This recommendation is endorsed by the present guideline and is consistent with International consensus.[7,238]

BP treatment goals in people with diabetes and hypertension

Population-based observational data suggest that, when compared to the nondiabetic population, CVD risk is elevated in people with diabetes at every level of BP and well into the conventional normotensive range.[239,240] Moreover, there appears to be no threshold below which risk substantially declines. Furthermore, from a pathophysiological perspective, people with diabetes exhibit disturbances to BP regulation and vascular function that increases their vulnerability to hypertensive injury.[241] These observations, allied to the clinical trial evidence that more intensive BP lowering is beneficial in reducing cardiovascular and diabetes-specific events in people with diabetes, have led to the recommendation that BP treatment targets should be lower in people with diabetes. International guidelines currently recommend a BP treatment target of $<$130/80 mmHg for people with hypertension and diabetes.[7,238] With regard to this target, three points should be emphasised:

(1) Hypertension, especially SBP, is more difficult to control to target in people with co-existing diabetes.[242]
(2) Most clinical trials have failed to achieve the recommended BP target, and it has been especially difficult to lower SBP to below 140 mmHg.[243]
(3) Control of DBP is less problematic and the main focus should be on SBP control, as many of these patients (especially with type II diabetes) will have ISH.

The recommendation that BP should be lowered to $<$130/80 mmHg in people with diabetes and

Box 10 Cerebrovascular disease

- Increasing blood pressure levels are a significant risk factor for primary stroke and recurrence even in the very elderly.
- Following acute stroke blood pressure levels are frequently raised and fall spontaneously over the next few days. Both high and low blood pressure levels immediately post-stroke are associated with an adverse prognosis.
- There is no evidence yet as to whether antihypertensive drugs should be started immediately after stroke or if current medication should be continued in the acute post-ictal phase.
- Thiazide/thiazide-like diuretics and/or angiotensin-converting enzyme inhibitors reduce the risk of stroke recurrence and major cardiovascular events by about 20–30% in those with a history of stroke or transient ischaemic attack whether normotensive or hypertensive at follow up. These benefits, irrespective of baseline BP, are more likely to be due to BP lowering.[16,228]
- To realize the full potential in both primary and secondary stroke prevention other cardiovascular disease risk factors must be treated.

hypertension is not yet firmly supported by clinical trial evidence. Nevertheless, there is no evidence from trials that have achieved lower BPs on treatment that such aggressive BP lowering would increase CVD risk or cause harm—on the contrary benefits appear to be the most likely outcome. Based on the available evidence, a first target for all patients with diabetes should be to reduce BP to below 140/80 mmHg.[3,81] Thereafter, further cardiovascular benefit would be expected if the BP could be lowered to an 'optimal target' of <130/80 mmHg.

Treatment of hypertension in people with diabetes: choice of therapy

This has been an area of great controversy, myths and misconceptions.[244] Most studies comparing drug classes for the treatment of hypertension in people with diabetes have been relatively small, often substudies within larger trials. There has been controversy about the safety and efficacy of CCBs at preventing cardiovascular events in people with diabetes.[26] There has also been a reluctance to use thiazide/thiazide-like diuretics because of perceived adverse effects on insulin sensitivity and metabolic parameters. Many of these concerns have been allayed by recent clinical trial results.[21]

International guidelines have uniformly recommended ACE inhibitors as first-line therapy for people with diabetes and hypertension.[7,238] However, it should be recognised that the evidence supporting this recommendation is limited. The recently reported ALLHAT study included over 12 000 people with hypertension and type II diabetes.[21] This study compared a thiazide-like diuretic (chlortalidone) with a CCB (amlodipine) or ACE inhibitor (lisinopril) as first-line therapy, and did not show superiority of the ACE inhibitor over the thiazide/thiazide-like diuretics at reducing coronary or cardiovascular events or mortality in people with type II diabetes. ALLHAT, added to other recent studies,[8,9,11] helps dismiss concerns about the safety and efficacy of CCBs and thiazide/thiazide-like diuretics for the treatment of hypertension in people with diabetes.[21]

The ARBs also represent an evidence-based strategy for renin–angiotensin system blockade in people with diabetes and hypertension, and the Losartan Intervention for Endpoint (LIFE) study demonstrated that losartan-based therapy was more effective than atenolol-based therapy at reducing cardiovascular events, cardiovascular death and total mortality in the cohort of people with type II diabetes.[13,245] Taken together with data demonstrating renoprotection with ARBs in people with type II diabetes,[18–20] the evidence for cardiorenal protection is marginally more substantial for ARBs than ACE inhibition in type II diabetes. In type I diabetes, there is more evidence for renoprotection with ACE inhibition, but there are no substantial data confirming cardiovascular protection with ACE inhibition, beyond the impact of improved BP control.[246]

Need for combination therapy

Good BP control is key to cardiovascular and renal protection in people with diabetes. Almost all patients with hypertension and diabetes will require a combination of BP-lowering drugs to achieve the recommended BP targets—with many requiring three or more drugs.[243,244] This combination is likely to include a thiazide/thiazide-like diuretic.[21] The evidence for renin–angiotensin system blockade especially for nephroprotection (and reduction in surrogates such as proteinuria) and cardiovascular protection strongly support the use of an ACE inhibitor or ARB[13,18–20,245,246] as part of the treatment cocktail, especially in those patients at higher CVD risk by virtue of established TOD. When there are no cost disadvantages, the combined drugs should be used as a fixed-dose combination to reduce the number of medications. Other drugs will be required to achieve BP targets in most people and longer acting CCBs, beta-blockers and alpha-blockers are all suitable therapies. In patients with renal impairment and/or oedema, a loop diuretic may be required as an alternative to, or in addition to, a thiazide/thiazide-like diuretics.

Diabetic nephropathy

Type 1 diabetes and diabetic nephropathy: BP reduction and ACE-inhibitor treatment slow the rate of decline of renal function in overt diabetic nephropathy[246] and delay progression from the microalbuminuric phase to overt nephropathy.[247–249] The ACE inhibitors may have a specific renoprotective action in patients with incipient or overt type I diabetic nephropathy, and are recommended as initial therapy. If ACE-inhibitor treatment has to be discontinued because of persistent cough, an ARB is the recommended alternative. The ACE inhibitor should be titrated to the maximum dose recommended and tolerated. Combinations of antihypertensive drugs are invariably required to achieve recommended BP targets. Low-dose thiazide/thiazide-like diuretics, CCBs, beta-blockers and alpha-blockers are all possible add-on drugs. Type I diabetic subjects with persistent microalbuminuria or proteinuria and any level of BPs are likely to benefit from ACE inhibition (or ARB) titrated to the recommended maximum dose.[246,247,250] It remains unclear whether this benefit accrues from blockade of the renin–angiotensin system *per se*, or the associated BP reduction.[251] The target BP is <130/80 mmHg.[81,247]

Type II diabetes and diabetic nephropathy: Since the previous BHS guidelines, there is now much more evidence on which to guide practice in people with type II diabetes and nephropathy. Hypertension accelerates the decline of renal function in type II diabetic patients with established nephropathy.[247,252] Moreover, antihypertensive therapy slows the progression of nephropathy in patients with type II diabetes.[247] ACE inhibitors have an antiproteinuric action and delay progression from microalbumi-

nuria to overt nephropathy,[247,249,253] but it is less clear whether they have a specific renoprotective action beyond BP reduction in overt nephropathy complicating type II diabetes. There is now good evidence that ARB-based antihypertensive therapy can delay the progression of microalbuminuria to overt nephropathy (proteinuria)[18] and the progression of overt nephropathy to end-stage renal disease.[19,20] This benefit of ARB-based therapy at delaying the progression of nephropathy in type II diabetes is complementary to the more substantial benefits achieved by improved BP control.[254]

Reducing cardiovascular disease risk in people with diabetes

The high CVD risk of people with diabetes and hypertension (especially type II diabetes), and the fact that many have established CVD at diagnosis means that people with type II diabetes and hypertension will also benefit from statin therapy, irrespective of their baseline cholesterol.[49,255] We recommend the routine use of statin therapy in people with type II diabetes complicated by hypertension. For people with type I diabetes, there is insufficient data to guide practice with regard to statins, but given the high rates of CVD among the population it seems reasonable to treat them as per type II diabetes. Low-dose aspirin is also indicated for primary prevention of CVD in patients aged over 50 years when BP is controlled to $<150/90$ mmHg and when 10-year CVD risk exceeds 20%. This multifactorial approach should be complemented by efforts to optimise glycaemic control and continued lifestyle measures because many diabetic patients, particularly those with type II diabetes, are overweight and would benefit substantially from weight reduction, increased exercise output and dietary sodium restriction.

Renal disease and hypertension

Renovascular disease (renal artery stenosis): this is relatively uncommon, but is a potentially curable cause of secondary hypertension. Routine investigation of all hypertensive patients is not justifiable, but doctors should be aware of important clues suggesting renovascular disease. These are:

- onset of hypertension before the age of 30;
- documented sudden onset of hypertension or sudden worsening of hypertension in middle age;
- accelerated (malignant) hypertension;
- resistant hypertension (to a $\geqslant$four drug regimen);
- renal impairment of unknown cause;
- large elevation of serum creatinine, especially with marked BP reduction by ACE inhibitor or ARB treatment ($\geqslant$30% increase of creatinine);[256]
- peripheral vascular disease or severe generalised atherosclerotic disease;
- recurrent 'flash' pulmonary oedema or heart failure with no obvious cause.

Where there is a high index of suspicion of renovascular disease, referral for expert advice should be considered.

Renal parenchymal disease: this accounts for hypertension in approximately 5% of people. Hypertensive patients with elevated serum creatinine or proteinuria at their initial assessment may have renal parenchymal or obstructive renal disease, and should be referred for specialist evaluation. Accelerated (malignant) hypertension may also be a consequence of renal parenchymal or vascular disease, and requires immediate hospital treatment because it causes rapid loss of renal function that can be irreversible if untreated. Apart from accelerated hypertension, hypertension *per se* is not a prominent cause of advanced renal disease, even though elevated BP is known to accelerate the age-related decline in glomerular filtration rate (GFR).

BP thresholds, targets and choice of therapy in people with renal disease and hypertension

BP is an important determinant of the rate of decline of GFR with age, and this becomes significant and important in people with evidence of renal impairment. Two factors are important in preserving residual renal function in people with diabetic and nondiabetic renal disease: (1) BP control and (2) blockade of the renin–angiotensin system.

The threshold for antihypertensive treatment in the previous guideline for patients with persistent proteinuria and/or renal impairment was $\geqslant$140 mmHg systolic, and/or $\geqslant$90 mmHg DBP.[3] This recommendation is unchanged.

Optimal BP control is defined as $<130/80$ mmHg,[257,258] and reducing BP to $<125/75$ mmHg may produce additional benefit in patients with chronic renal disease of any aetiology associated with proteinuria of $\geqslant$1 g per 24 h.[258,259] It is emphasised, however, that this concept that 'lower is better' for patients with renal disease and hypertension is based on limited evidence, and is largely extrapolated from retrospective analysis of clinical trial data.[258,259] Moreover, the African American Study of Kidney Disease (AASK) did not demonstrate that a lower target BP (128/78 mmHg) was better than less tight BP control (141/85 mmHg) at preserving renal function in African Americans with nondiabetic chronic renal disease.[33] The validity of this finding and its relevance to the UK population is unclear.

Choice of antihypertensive therapy: blockade of the renin–angiotensin system has been widely advocated as having 'renoprotective' benefits beyond that of BP control alone.[259,260–263] There are limited data on the renoprotective effects of ARBs in nondiabetic patients with chronic renal disease. In

the CO-OPERATE study, the combination of ARB and ACE inhibitor was more effective than the ARB or ACE inhibitor alone in protecting renal survival.[264] However, this was a small study and further work in this area is needed. Meta-analyses examining the renoprotective effect of ACE inhibitors in patients with nondiabetic renal disease have concluded that there is benefit of ACE inhibition beyond that attributable to BP lowering.[262,263] This is most notable in people with overt proteinuria.[33,260,262,263] Specific blockade of the renin–angiotensin system may be less important than BP control *per se* in preventing the development of renal impairment, in the progression of less advanced renal disease or in those without overt proteinuria.[21] ACE inhibitors may not be renoprotective beyond their BP-lowering effect in those with polycystic kidney disease.[262]

Blockade of the renin–angiotensin system (ACE inhibition or ARBs) as monotherapy will not be sufficiently effective in controlling BP in patients with renal disease and hypertension. Additional therapy should include a thiazide/thiazide-like diuretic. In patients with oedema or more advance renal impairment, for example, serum creatinine $>200\,\mu$mol/l, thiazide/thiazide-like diuretics may be ineffective and a loop diuretic (eg furosemide) may be required, often in higher doses than used conventionally. Most people will still require additional antihypertensive therapy. Dihydropyridine CCBs are an effective additional therapy and other classes of drug can be added as required.

Renal disease as a cardiovascular disease risk factor
It is now well recognised that even mild persistent elevations in urinary albumin excretion (even below the threshold currently used to define microalbuminuria) and/or mild elevations in serum creatinine, prior to initiation of antihypertensive therapy, are strong predictors of premature cardiovascular morbidity and mortality.[234,265–270] As such, most patients with renal disease and treated hypertension have established TOD (for TOD definition see Table 1), remain at substantial CVD risk, and would benefit from statin therapy and aspirin.

Oral contraceptives (OCs) and BP

Very little new evidence on this topic has emerged since the previous BHS guidelines were published, and hence recommendations made in 1999 remain essentially unchanged.

Combined OCs tend to increase BP by an average of 5/3 mmHg.[271] In a small proportion of women (eg 1%), severe hypertension may be induced.[272] The mechanisms whereby BP increases occur are not established and the effect appears to be idiosyncratic in that no subgroups of women have been identified as being particularly susceptible. Furthermore, BP may rise rapidly many months or even years after first using a combined OC. Since the current use of combined OCs is not only associated with an increase in BP but also in risk of stroke and MI,[273] BP should be measured prior to OC use and 6 monthly thereafter.

Observational data suggest that progestogen-only contraceptive pills (POPs) do not, on average, increase BP,[274,275] although virtually no trial evidence is available to confirm or refute this. However, POPs are currently recommended for women with hypertension induced by the combined OC, or women with hypertension wishing to use oral contraception.

While the combined OC is not absolutely contraindicated for women who are already hypertensive or even for those who develop hypertension on the combined OC, good BP control with antihypertensive medication is mandatory for such women who wish to remain on the combined OC. However, we recommend, pending further information, the use of the POP (with careful BP monitoring) for such women. It should be recognised that data on the impact of POPs on CVD risk are limited and that POPs are, in practice, less effective contraceptives than combined OCs. This is particularly important for younger women (<35 years), since they are more fertile, and therefore need safer contraception, and in whom the risks of cardiovascular events due to pregnancy outweigh likely risks due to use of the combined OC.

For women, particularly in those aged >35 years with other coexistent risk factors such as smoking and migraine (both of which are common in women of this age), we recommend that other nonhormonal forms of contraception should be sought. Greater protective effects against CVD are likely to accrue if the other risk factors—particularly smoking—could be effectively addressed.

Hormone replacement therapy (HRT) and BP

Observational data[276] and clinical trials evaluating various HRT formulations[277] suggest that, on average, the use of HRT does not cause BP to rise. On this basis, HRT is not contraindicated for women with hypertension, and women with hypertension should not be denied access to HRT as long as BP levels are effectively controlled to the latest optimal target levels (see earlier section). However, it is now clear that, contrary to the findings of extensive observational data,[278] several large randomised trials of commonly-used HRT formulations have established that 'opposed' HRT (containing oestrogen and progestogen) does not provide cardiovascular protection of any type in the context of primary prevention[279] or in those with established coronary disease.[280]

Similarly, in the Women's Estrogen for Stroke trial (WEST) trial,[281] 'unopposed' HRT (containing oestrogen only) did not prevent further stroke events in those with established cerebrovascular disease, and

in the large Women's Health Initiative (WHI) trial of women with no prior cardiovascular diseases, which is still in progress, the unopposed HRT has also produced, at best, no reduction in major cardiovascular events.

Overall, best evidence of the impact of HRT—whether unopposed or opposed—is that cardiovascular events, coronary, venous thromboembolic and stroke, are increased by the use of those formulations evaluated hither to in randomised trials.[282] Equally surprising is that, overall, health-related quality of life was not improved by HRT use[283] and on balance a global risk index—incorporating fatal and nonfatal coronary disease, invasive breast cancer, stroke, pulmonary embolus, endometrial carcinoma, colonic cancer, hip fracture and other death was significantly worsened in association with the use of opposed HRT in the largest trial of HRT to date.[279]

While it is possible that newer products such as the selective oestrogen receptor modulators or other formulations of opposed and unopposed oestrogen may not increase cardiovascular events or may even reduce them, current evidence dictates that HRT should not be prescribed to women with any expectation of reducing cardiovascular events. While the benefits of HRT for the treatment of severe menopausal symptoms are clear, users should be informed of the increased risks of cardiovascular and other serious disorders associated with their use.

Hypertension in pregnancy

Hypertension in pregnancy: This topic has been recently reviewed elsewhere.[284–287] For convenience, a list of definitions of hypertension and the related terms in pregnancy are given in Table 5. In pregnancy, DBP should be measured at the disappearance of sounds (phase V) and, unless phase V goes to zero, not at muffling (phase IV), as recommended in the past.[286,287] Automated and ABPM devices have been validated for use in pregnancy.[288,289] A note of caution is expressed about under-recording by automated devices in pre-eclampsia.[290]

Hypertension occurs in 8–10% of pregnancies, and may be the first sign of impending pre-eclampsia, a potentially more serious condition of the second half of pregnancy and the puerperium.[290,291]

The Working Group of the American National Heart, Lung and Blood Institute classifies hypertension in pregnancy as: chronic hypertension, pre-eclampsia, pre-eclampsia superimposed on chronic hypertension and gestational hypertension. The latter becomes transient hypertension of pregnancy if pre-eclampsia is not present at the time of delivery and BP returns to normal by 12 weeks post-partum or chronic hypertension if the elevation persists.[286] Commenting on the difficulties in categorising hypertension in pregnancy and the lack of precision in the definition of pre-eclampsia, the authors[288] conclude that 'any definition that is used clinically should be as loose as practical for patient safety, whereas research definitions should be stringent'.

Care must be taken to distinguish between chronic hypertension and pre-eclampsia. Elevated BP before 20 weeks' gestation usually means that hypertension preceded pregnancy. This will commonly be 'essential', but clinical evaluation is needed, recognising that secondary hypertension may present for the first time in pregnancy. An apparent onset of hypertension after 20 weeks' gestation may reflect hypertension that was undetected prior to pregnancy, and disguised by the BP fall of early-mid pregnancy.

Meta-analysis of trials of antihypertensive drugs in pregnancy shows a reduction in the risk of progression to severe hypertension and fewer hospital admissions.[292] Firm evidence is not available on the optimal threshold for treatment. However, there is consensus for initiating treatment at BP levels exceeding 150–160 mmHg SBP or 100–110 mmHg DBP or in the presence of TOD[286] (for TOD definition, see Table 1). Many initiate treatment at lower levels, but there is concern that excessive BP reduction may limit foetal growth.[293] The principal objective of antihypertensive treatment is protection for the mother who, when BP levels are only modestly elevated, is at low absolute risk of adverse cardiovascular outcomes. There is little evidence that treatment reduces the risk of developing pre-eclampsia or improves foetal outcome, although effective control of severe hypertension may buy more gestational time before delivery becomes necessary. Women with essential hypertension are at increased risk of pre-eclampsia and intrauterine growth restriction (IUGR). Management should therefore include frequent BP checks, preferably once a week, urinalysis and sequential assessment of foetal growth. Hospital referral should be made if there is poorly controlled hypertension, new onset proteinuria or suspicion of IUGR.

Pre-eclampsia and eclampsia: Criteria for the diagnosis of pre-eclampsia include a rise in BP of >15 mmHg DBP or >30 mmHg SBP from early pregnancy, or DBP of >90 mmHg on two occasions 4 h apart or >110 mmHg on one occasion and proteinuria ($1+$ is a indication for referral and >300 mg/24 h is the criterion for diagnosis). It is emphasised that 30% of eclamptic convulsions occur in the absence of either raised BP or proteinuria. Risk factors for pre-eclampsia include: first pregnancy, change of partner, previous pre-eclampsia, family history of pre-eclampsia, idiopathic hypertension, chronic renal disease, diabetes, systemic lupus erythematosus, multiple pregnancy and obesity. The increased risk of pre-eclampsia following change of partner[294] and the inverse association between risk and duration of sexual

Table 5 Definitions on hypertension related to pregnancy[290]

1. *Pre-eclampsia* is usually diagnosed on the basis of hypertension with proteinuria, as defined below:
   - Hypertension[a] defined as SBP >140 mmHg or DBP >90 mmHg *after* 20 weeks in a woman who was normotensive before 20 weeks' gestation
   - Proteinuria defined as 300 mg/l protein, or 30 mg/mmol creatinine in a random specimen, or an excretion or 300 mg per 24 h
2. *Chronic hypertension* is defined as BP ⩾140/90 *before* the 20th week of pregnancy, or if only measured after 20 weeks' gestation, persisting 6 weeks post partum.
3. *Pre-eclampsia superlimposed on chronic hypertension* is regarded as highly likely in women with known hypertension who develop new proteinuria, or in women with known hypertension and proteinuria who have sudden increases in BP or proteinuria, thrombocytopenia, or increases in hepatocelluar enzymes.
4. *Gestational hypertension* defined as the development of hypertension in pregnancy without other signs of pre-eclampsia

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Confirmed by at least two separate measurements.

cohabitation before conception[295] implicate an immunological basis of the condition.[296,297] In addition, immune reconstitution by antiretroviral treatment re-establishes a suppressed incidence of pre-eclampsia among women with human immunodeficiency virus to the rate expected in the normal population.[298]

Women with pre-eclampsia generally have no symptoms and can only be detected by routine screening. When present, the most frequent symptoms are headache, visual disturbance (often 'flashing lights'), vomiting, epigastric pain and oedema. These symptoms in conjunction with raised BP require urgent referral and treatment. Women rarely present with a convulsion, but a first seizure in the second half of pregnancy with no other known cause is highly suggestive of eclampsia. The Magpie trial has demonstrated the efficacy of magnesium sulphate in halving the risk of mothers with pre-eclampsia progressing to eclampsia.[299]

The role of low-dose aspirin in the prevention of pre-eclampsia has been controversial. Large trials have indicated no benefit,[300,301] but a recent systematic review has suggested a small protective effect.[302] Further trials of the potential protective effect of vitamins C and E, possibly via their antioxidant activity, are ongoing in women at risk of pre-eclampsia.[303,304]

Choice of antihypertensive therapy in pregnancy: Evidence underpinning the choice of antihypertensive therapy in pregnancy is inadequate to make firm recommendations. Methyldopa remains the antihypertensive drug of choice during pregnancy.[305,306] CCBs (especially long-acting formulations of nifedipine) and the vasodilator hydralazine are commonly used as second-line drugs. Labetalol (alpha- and beta-blocker) is also widely used as a second-line agent, particularly for resistant hypertension in the third trimester.[307] Other beta-blockers are used less often, because of evidence that they particularly inhibit foetal growth.[308,309] Meta-analysis of controlled trials of thiazide/thiazide-like diuretics has suggested a reduced incidence of pre-eclampsia.[310] In practice, thiazide/thiazide-like diuretics are used little for the management of hypertension, since on theoretical grounds they have the potential to further reduce the already decreased circulatory blood volume in women with pre-eclampsia.[311] However, there is no evidence that low-dose thiazide/thiazide-like diuretics in women with pre-existing hypertension are harmful and they may be continued through pregnancy. ACE inhibitors or ARBs should be avoided by women who wish to become pregnant and discontinued, ideally in the first trimster, if pregnancy occurs whilst taking these medications. This is necessary because in late pregnancy they may cause oligohydramnios, renal failure, hypotension and intrauterine death in the foetus.[312] It is frequently possible to withdraw antihypertensive medication altogether in the early stages while planning close follow-up. It is usual to switch from such agents back to the previous antihypertensive regimen after delivery.

The long-term prognostic implications of hypertensive disorders in pregnancy have become increasingly evident. It has previously been held that pre-eclampsia alone does not strongly predict future hypertension.[286,313] However, in so far as a mother with underlying previously undiagnosed chronic hypertension is at increased risk of pre-eclampsia, this will translate to postnatal hypertension and the diagnosis of the problem that occurred during pregnancy may only be made with hindsight. Furthermore, three large cohort studies in Norway and Scotland indicate future hypertension and important increase in long-term CVD risk consequent to both gestational hypertension and pre-eclampsia.[314–316] The converse is clear—ie that women with normotensive births have a reduced probability of later hypertension.[286] Pragmatically, all women with hypertension disorders in pregnancy should have their BP checked regularly thereafter.

BP in ethnic minority groups

Most UK-based surveys show that black people of African or African-Caribbean origin have higher levels of BP and rates of hypertension than their

white counterparts.[317–319] This is associated with higher rates of renal failure,[320] LVH[321] and stroke morbidity and mortality among the black population,[322] although CHD morbidity and mortality remain lower than in the white population.[322]

In general, hypertension among the black population is particularly sensitive to dietary salt restriction,[323] and if drug therapy is required BP levels respond better to thiazide/thiazide-like diuretics or CCBs than to beta-blockers,[324] ACE inhibitors[8,9] or angiotensin receptor blockers.[179] This presumably reflects the low renin status more frequently observed among the black population.[176]

These differential BP responses to drug classes were reflected in significantly different rates of cardiovascular end points—particularly stroke—associated with use of these agents in the ALLHAT trial.[21] This was the first hypertension trial to have included sufficient numbers of black subjects to allow an evaluation of drug effects on morbidity and mortality in this population. Among the black (but not white) population in ALLHAT, stroke and coronary events were significantly higher among those randomised to the ACE inhibitor compared with those randomised to chlortalidone.[21] No differences in these end points were observed between those randomised to the thiazide/thiazide-like diuretic and those randomised to the dihydropyridine CCB amlodipine.

These data are supportive of the AB/CD algorithm proposed for elderly or black patients (see earlier section). The AASK trial[33] in African-American patients with renal impairment compared the ACE inhibitor ramipril with amlodipine, and the beta-blocker metoprolol. The amlodipine limb was stopped prematurely, because of a perceived worsening of renal failure in a subgroup of those randomised to amlodipine. The decision was controversial[325] and has been misinterpreted to mean that dihydropyridine CCBs are unsuitable for black patients with renal insufficiency. We recommend that an agent which blocks the renin–angiotensin system should always be part of any antihypertensive regimen for patients of this type, but that very strict BP lowering—which will often require a CCB—is pivotal to management.

American guidance on BP management for black patients is available in an extensive consensus statement outlining recommendations for the Management of High BP in African-Americans, which has recently been published.[326]

Few new data relevant to hypertension management for British south Asians (from the Indian subcontinent) have been produced since the previous BHS guidelines, and hence recommendations relating to this group have not changed since 1999. It must be pointed out that essentially no morbidity/mortality data from hypertension trials relating to this population are available. What limited data are available suggest that this population in the UK has higher mean BPs and hypertension prevalence than the white population.[317,327] They also have high rates of type II diabetes,[328] tend to be insulin resistant,[328] and are at increased risk of stroke[322] and more particularly CHD[6] than whites in the UK.

No robust data are available to suggest that south Asians respond differently to antihypertensive agents than do white Europeans, but the high prevalence of glucose intolerance or diabetes, central obesity and dyslipidaemia may influence drug choice (Table 2). These frequently coexistent conditions certainly require an assertive multifactorial approach to CVD risk management.

Implementation and audit

The challenges for the future

The objectives highlighted and prioritised in the previous guideline[3] are reiterated below and remain relevant:

- to promote the primary prevention of hypertension and CVD by changes in the diet and lifestyle of the whole population;
- to increase the detection and treatment of undiagnosed hypertension by routine screening and increase awareness of hypertension among the public;
- to increase the proportion of patients on antihypertensive treatment who are controlled to optimal BP levels;
- to reduce the CVD risk of treated hypertensive patients by non pharmacological measures, and by appropriate use of aspirin and statin treatment;
- to increase the identification and treatment of patients with mild hypertension who are at high CVD risk, for example,
  - elderly patients;
  - those with ISH;
  - people with diabetes;
  - those with TOD or multiple risk factors;
  - to promote the continuation of drug treatment, and adherence to treatment, by optimising the choice and use of drugs, minimising side effects, and increasing information and choice for patients.

Implementation

The successful implementation of these guidelines in the community depends on the combined and coordinated efforts of patients, clinicians and support staff who work within primary care and the wider community health care system. These guidelines come at an opportune time. Primary Care Trusts (PCTs) across the country are actively involved in service redesign. To implement this guideline effectively, new systems of health-care delivery will need to be developed in primary care. Multidisci-

plinary teams will need to work in a systematic and structured way to advise, educate and support patients. This may involve the establishment of GPs with a Special Interest (GPSI) to lead clinical care in this area. This could result in a move away from rigid clinic-based care, towards a greater use of remote centres such as pharmacies, remote BP monitoring and diagnostic and treatment centres currently being developed, which would improve access and convenience for patients. Moreover, there is clearly a need for an extended role for nurse practitioners, pharmacists and other health-care professionals, to provide the foundation for the more widespread and effective detection, monitoring and treatment of BP and CVD risk.

The reduction of cardiovascular events in the population has been given a high priority by the Department of Health. This is illustrated by publication of the NSFs and by guidance issued by the National Institute for Clinical Excellence (NICE). Further support for the continued improvement in standards of care within primary and community care is provided by the new GMS contract for primary care.[329] These examples of emphasis and change in practice provide new opportunities to improve the clinical management of hypertension and CVD risk in the UK.

Supportive initiatives from the Department of Health

The NSFs were informed by the previous BHS guidelines[3] and those of the Joint British Societies.[76] These supportive initiatives have provided key drivers for improvements in care. Three NSFs are directly relevant to this guideline: the NSF for CHD, the NSF for older people and the NSF for diabetes.

National Service Framework for coronary heart disease (Department of Health—published March 2000)

This document was drafted by patients, clinicians, managers and government to be the blue print for the modernisation of CHD services in England over the next 10 years. It supports the government's commitment to reduce the death rate from CHD and stroke and related diseases in people under 75 by at least 40% by 2010. The NSF for CHD sets 12 standards for improved prevention, diagnosis, treatment and rehabilitation of CHD and goals to secure fair access to high-quality services over the next 10 years.

In Wales, a similar approach is being taken through 'Tackling CHD in Wales: Implementing Through Evidence'.[330] In Scotland, CHD and stroke have been combined and the equivalent document is CHD and stroke: Strategy for Scotland.[331]

The NSF was intended to be a practical, evidence-based and flexible approach to tackling CHD. It (a) sets national standards, (b) defines service models for preventing and treating CHD and (c) establishes milestones and goals as performance indicators by which progress would be measured. To date, it has been successful in many of its aims.

The detection and treatment of hypertension was recognised to be important in reducing CVD. In both secondary prevention and high-risk primary prevention, advice and treatment was to be given to maintain BP below 140/85. A BP of less than 150 mmHg SBP and less than 90 mmHg DBP was given as the audit standard, consistent with the previous BHS guideline.[3]

In contrast to these new BHS guidelines, the NSF defined 'high-risk primary prevention' as 'people without diagnosed CHD or other occlusive arterial disease but with a 10-year CHD risk $>30\%$'. This equates to a 10-year CVD risk of $>40\%$. This higher intervention threshold was set for valid pragmatic reasons. As new systems of care develop and mature, and when people at 'very high risk' have been successfully treated, the NSF suggests that primary-care physicians should intervene at lower levels of CVD risk.

The National Service Framework for older people (published by the Department of Health in March 2001)

This NSF set out a programme of action and reform to address problems faced by older people. Various standards were set and the standard most relevant to these guidelines is Standard 5, which stated that 'The NHS will take action to prevent strokes, working in partnership with other agencies where appropriate. People who are thought to have had a stroke have access to diagnostic services, are treated appropriately by a specialist stroke service, and subsequently, with their carers, participate in a multidisciplinary programme of secondary prevention and rehabilitation'.

General practices were urged to build on their CHD registers and use them to identify those at risk of stroke. PCTs were given a target that by April 2004 every general practice, should identify and treat patients identified at being at risk of stroke; that is, those with high BP, atrial fibrillation or other risk factors as detailed in the NSF for CHD. Practices were advised to put in place models of care which included a systematic approach for (a) identifying those at high risk of stroke, (b) identifying and recording modifiable risk factors for people at high risk of stroke, (c) providing and documenting the delivery of appropriate advice for treatment, (d) offering a regular review to those at risk of stroke. Hypertension was recognised as being an important risk factor and lifestyle and pharmaceutical interventions are recommended to maintain BP below 140/85, consistent with current BHS guidance.[3]

National Service Framework for diabetes: standards published in December 2001

This programme was to be implemented over the 10 years from April 2003. It recognised that there was an interdependence between the diabetes NSF, the

NSF for CHD and the stroke standard in the NSF for Older People. This is in addition to the planned NSF for renal services. Standard 4 states that 'all adults with diabetes shall receive high quality care throughout their lifetime, including support to optimise the control of their blood glucose, BP and other risk factors for developing the complications of diabetes'.

NICE guidance on essential hypertension
These guidelines are in development and are expected to be published in early 2004. They differ from the present guideline in two important respects: (1) The NICE guidance will focus solely on the treatment of 'essential hypertension' in uncomplicated patients. It will not provide guidance on BP management in the many important sub-groups outlined in this report from the BHS. (2) Unlike BHS guidance, NICE guidance will not provide advice on when to use aspirin and statin therapy to reduce the total CVD risk burden of people with high BP.

The BHS believes that a return to single risk factor management, as suggested by the remit of the NICE guidance on BP management, is a retrogressive step. BP is a routine measurement advocated for all adults in the UK. When BP is found to be elevated, a patient is identified who is at increased CVD risk, not only as a consequence of their elevated BP, but also due to the common aggregation of other risk factors such as dyslipidaemia, impaired glucose tolerance and concomitant TOD (for TOD definition see Table 1), or cardiovascular complications. Optimal management of BP must therefore involve assessment of these risk factors and multifactorial intervention to reduce not only BP, but also CVD risk.

The New General Medical Services Contract for primary care (2003)
This is seen by many as an important step forward in the development of British primary care services. When implemented throughout the UK, it will provide a major focus on quality of care and outcomes. The new quality framework is incenti-

Table 6 Hypertension quality indicators in new General Medical Service contract

	Points	*Maximum threshold*
Secondary prevention in CHD		
Ongoing management		
The percentage of patients with CHD whose notes have a record of blood pressure in the previous 15 months	7	90%
The percentage of patients with CHD, in whom the last blood pressure reading (measured in the last 15 months) is $\leqslant$150/90	19	70%
Stroke or transient ischaemic attacks		
Ongoing management		
The percentage of patients with TIA or stroke who have a record of blood pressure in the notes in the preceding 15 months	2	90%
The percentage with a history of TIA or stroke whom the last blood pressure reading (measured in the last 15 months) is 150/90 or less	5	70%
Hypertension		
Records		
The practice can produce a register of patients with established hypertension	9	
Diagnosis and management		
The percentage of patients with hypertension whose notes record smoking status at least once	10	90%
The percentage of patients with hypertension who smoke, whose notes contain a record that smoking cessation advice has been offered at least once	10	90%
Ongoing management		
The percentage of patients with hypertension in which there is a record of blood pressure in the past 9 months	20	90%
The percentage of patients with hypertension in whom the last blood pressure (measured in the last 9 months) is 150/90 or less	56	70%
Diabetes mellitus		
Ongoing management		
The percentage of patients with diabetes who have a record of blood pressure in the past 15 months	3	90%
The percentage of patients with diabetes in whom the last blood pressure is 145/85 or less	17	55%
Records and information about patients		
The blood pressure of patients age 45 and over is recorded in the preceding five years for at least 55% of patients	10	—
The blood pressure of patients age 45 and over is recorded in the preceding five years for at least 75% of patients	5	—

CHD = coronary heart disease; TIA = transient ischaemic attack.

vised and will reward practices for delivering quality care to encourage even higher standards. The quality framework has four main 'domains'. The one that is likely to attract most interest from clinicians, and which provides the greatest financial reward, is that related to clinical standards. Cardiovascular disease is covered with standards related to CHD, stroke or TIA, hypertension and diabetes. Each of the quality standards attracts points and points will result in financial rewards to practices which they can use to reward performance or develop services (see Table 6). Of the 550 Clinical Indicator points available, 158 relate directly to hypertension. There is a minimum threshold and, following achievement of this, funding increases in proportion to achievement until the maximum threshold is reached. As such, this new contract is likely to increase the focus on the detection and treatment of high BP and the quality of BP control.

Patient involvement

A vital aspect of the successful management and control of high BP is to obtain the participation and closer involvement of the individual affected. Where appropriate, people with high BP should be involved in the decision as to whether they should take lifestyle action or commence drug therapy, and in particular decisions about which individual drugs they should take, possible side-effects and the likelihood that they may need to take at least two, or even three, different drugs in order to get their BP controlled. Many are willing and keen to measure their own BP, and with professional advice and new technologies, this can save visits to a doctor or nurse when treatment is being changed or in those who are well controlled. At the same time, involvement of the individual makes it much more likely that good control of BP will be achieved. The AB/CD algorithm defines treatment plan for people with high BP and copies of individualised treatment plans could be made available to patients treated for high BP. Appropriate information for individuals with high BP in the UK can be obtained from the Blood Pressure Association, a charitable organisation specifically set up to provide information and support to individuals with high BP. Three booklets are available which cover the importance of BP, healthy eating and medicines in detail and there are a range of further leaflets covering other aspects of BP. Individuals can obtain these leaflets directly from the Blood Pressure Association or via their healthcare professional and can join the Association as members. Contact details are listed in Appendix E.

Conclusion

The evidence presented in these new guidelines strongly support the recommendation that the detection and treatment of high BP and its associated CVD risk should be a key focus of health-care policy in the UK. The ongoing reorganisation of health-care provision in primary care and the emphasis on audit, quality of care and improvement in the systems of care, provide an excellent opportunity to implement these new BHS recommendations, and, in so doing, deliver much improved hypertension management and thereby reduce the burden of CVD.

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References

1 Swales JD *et al.* Treating mild hypertension. *Br Med J* 1989; **298**: 694–698.
2 Sever P *et al.* Management guidelines in essential hypertension: report of the second working party of the British Hypertension Society. *Br Med J* 1993; **306**: 983–987.
3 Ramsay LE *et al.* Guidelines for management of Hypertension: report of the third working party of the British Hypertension Society. *J Human Hypertens* 1999; **13**: 569–592.
4 Prospective Studies Collaboration. Age-specific relevance of usual BP to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
5 Ezzati M *et al.* Selected major risk factors and global and regional burden of disease. *Lancet* 2002; **360**: 1347–1360.
6 Vasan RS *et al.* Impact of high-normal BP on the risk of cardiovascular disease. *New Engl J Med* 2001; **345**: 1291–1297.
7 Chobanian AV *et al.* The Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 2003; **289**: 2560–2572.
8 Brown MJ *et al.* Morbidity and mortality in patients randomised to double-blind treament with long-acting calcium channel blocker or diuretic in the International Nifedpine GITS study: intervention as a goal in hypertension treatment (INSIGHT). *Lancet* 2000; **356**: 366–372.
9 Hansson L *et al.* Randomised trial of effects of CCBs compared to diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diliazem (NORDIL) study. *Lancet* 2000; **356**: 359–365.

10 Hansson L *et al.* Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; **353**: 611–616.
11 Hansson L *et al.* Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; **354**: 1751–1756.
12 Dahlöf B *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
13 Lindholm LH *et al.* Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 1004–1010.
14 Hansson L *et al.* Study on COgnition and Prognosis in the Elderly (SCOPE). *Blood Press* 1999; **8**: 177–183.
15 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *New Engl J Med* 2000; **342**: 145–153.
16 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358**: 1033–1041.
17 EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; **362**: 782–788.
18 Parving HH *et al,* for the Irbesartan in Patients with type 2 Diabetes and Microalbuminuria Study Group. The effect of Irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *New Engl J Med* 2001; **345**: 870–880.
19 Brenner BM *et al*, for the RENAAL Study Investigators. Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *New Engl J Med* 2001; **345**: 861–869.
20 Lewis EJ *et al.* Renoprotective effect of the angiotensin-receptor antagonist Irbesartan in patients with nephropathy due to type 2 diabetes. *New Engl J Med* 2001; **345**: 851–860.
21 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *vs* diuretic: the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002; **288**: 2981–2997.
22 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000; **356**: 1955–1964.
23 Staessen JA, Wang J-G, Thijs L. Cardiovascular protection and BP reduction: a meta-analysis. *Lancet* 2001; **358**: 1305–1315.
24 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362**: 1527–1545.
25 Cutler JA. Calcium-channel blockers for hypertension—uncertainty continues. *N Engl J Med* 1998; **338**: 679–681.
26 Estacio RO *et al.* The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. *N Engl J Med* 1998; **338**: 645–652.
27 Tuomilehto J *et al.* Effects of calcium channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999; **340**: 677–684.
28 Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000; **23** (Suppl 2): B54–B64.
29 Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002; **61**: 1086–1097.
30 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355**: 253–259.
31 Lindholm L *et al.* Comparison of antihypertensive treatments in preventing cardiovascular event in elderly diabetic patients: results of the Swedish Trial in Old Patients with hypertension-2. *J Hypertens* 2000; **18**: 1671–1675.
32 Niskanen L *et al*, for the CAPPP study group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first line therapy with an ACE inhibitor compared with a diuretic/β-blocker-based treatment regimen. *Diabetes Care* 2001; **24**: 2091–2096.
33 Wright JT *et al*, for the African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease results from the AASK Trial. *JAMA* 2002; **288**: 2421–2431.
34 Sacks FM *et al.* Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; **344**: 3–10.
35 Stevens VJ *et al.* Long-term weight loss and changes in results of the Trials of Medicine Hypertension Prevention, phase II. *Annals Int Blood Pressure* 2001; **134**: 1–11.
36 Hagberg JM, Park JJ, Brown MD. The role of exercise training in the treatment of hypertension: an update. *Sports Med* 2000; **30**: 193–206.
37 Xin X *et al.* Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 2001; **38**: 1112–1117.
38 He J, Whelton PK. What is the role of dietary sodium and potassium in hypertension and target organ injury. *Am J Med Sci* 1999; **317**: 152–159.
39 Griffith LE *et al.* The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *Am J Hypertens* 1999; **12**: 84–92.

40 Kawano Y, Matsuoka H, Takishita S, Omae T. Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. *Hypertension* 1998; **32**: 260–265.
41 Jee SH *et al.* The effect of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. *Hypertension* 1999; **33**: 647–652.
42 Tuomilehto J *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001; **344**: 1343–1350.
43 Wolf-Maier K *et al.* Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 2004; **43**: 10–17.
44 Primatesta P, Brookes M, Poulter NR. Improved hypertension management and control: results from the health survey for England 1998. *Hypertension* 2001; **38**: 827–832.
45 Brown MJ *et al.* Better blood pressure control: how to combine drugs. *J Hum Hypertens* 2003; **17**: 81–86.
46 Anonymous. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143–3421.
47 Andersson OK *et al.* Survival in treated hypertension: follow up study after two decades. *Br Med J* 1998; **317**: 167–171.
48 Heart Protection Study Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
49 Sever PS *et al.* Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-then-average cholesterol concentrations, in the Anglo Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**: 1149–1158.
50 Guidelines Committee. 2003 European Society of Hypertension–European Society of Cardiology Guidelines for the Management of Arterial Hypertension. *J Hypertens* 2003; **21**: 1011–1053.
51 Eccles M *et al.* North of England evidence based guidelines development project. *Br Med J* 1998; **316**: 1303–1309.
52 Guidelines Subcommittee. 1999 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; **17**: 151–183.
53 O'Brien E *et al.* European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; **21**: 821–848.
54 Yarows SA, Julius S, Pickering TG. Home blood pressure monitoring. *Arch Intern Med* 2000; **160**: 1251–1257.
55 O'Brien E, Beevers G, Lip GYH. ABC of Hypertension. blood pressure measurement. Part IV—Automated sphygmomanometry: self blood pressure measurement. *Br Med J* 2001; **322**: 531–636.
56 O'Brien E *et al.* Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. *Br Med J* 2000; **320**: 1128–1134.
57 Clement DL *et al.* Prognostic value of ambulatory blood pressure recordings in patients with treated hypertension. *New Engl J Med* 2003; **348**: 2407–2415.
58 Ohkubo T *et al.* Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohsama study. *J Hypertens* 2002; **20**: 2183–2189.
59 Ohkubo T *et al.* Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens* 2000; **18**: 847–854.
60 Staessen JA *et al.* Predicting cardiovascular risk using conventional *vs* ambulatory blood pressure in older patients with systolic hypertension. *JAMA* 1999; **282**: 539–546.
61 Stergiou GS *et al.* Clinic, home and ambulatory pulse pressure: comparison and reproducibility. *J Hypertens* 2002; **20**: 1987–1993.
62 Owens P, Atkins N, O'Brien E. Diagnosis of white coat hypertension by ambulatory blood pressure monitoring. *Hypertension* 1999; **34**: 267–272.
63 Bidlingmeyer I *et al.* Isolated office hypertension: a prehypertensive state? *J Hypertens* 1996; **14**: 327–332.
64 Kuwajima I, Suzuki Y, Fujisawa A, Kuramoto K. Is white coat hypertension innocent? Structure and function of the heart in the elderly. *Hypertension* 1993; **22**: 826–831.
65 Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat hypertension *versus* sustained mild hypertension. *Circulation* 1998; **98**: 1892–1897.
66 Association for the Advancement of Medical Instrumentation. *American National Standard. Electronic or Automated Sphygmomanometers*. AAMI: Arlington, VA. 1993.
67 O'Brien E, Petrie J, Littler WA, de Swiet M, Padfield PL, Altman D, Bland M, Coats A, Atkins N. The British Hypertension Society Protocol for the evaluation of blood pressure measuring devices. *J Hypertens* 1993; **11** (Suppl 2): S43–S63.
68 O'Brien E *et al.* Working Group on blood pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Pressure Monitor* 2002; **7**: 3–17.
69 Stamler J. Established major coronary risk factors. In: Marmot M, Elliott P (eds). *CHD Epidemiology: From Aetiology to Public Health*. Oxford Medical Publications: Oxford. 1992.
70 Chatellier G, Blinowska A, Menard J, Degoulet P. Do physicians estimate reliably the CVD risk of hypertensive patients? *Medical Info* 1995; **8**: 876–879.
71 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
72 World Health Organization-International Society of Hypertension Writing Group. World Health Organization-International Society of Hypertension Statement on management of hypertension. *J Hypertens* 2003; **21**: 1983–1992.
73 Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. *Circulation* 1991; **83**: 356–362.
74 Haq IU *et al.* Is the Framingham risk function valid for northern European populations? A comparison of methods for estimating absolute coronary risk in high risk men. *Heart* 1999; **81**: 40–46.

75 Brindle P *et al.* Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *Br Med J* 2003; **327**: 1267–1270.
76 Wood D *et al*, for the British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, and British Diabetic Association. Joint British recommendations on prevention of CHD in clinical practice. *Heart* 1998; **80**: S1–S29.
77 Conroy RM *et al*, on behalf of the SCORE project group. Estimation of ten-year risk of fatal CVD in Europe: the SCORE project. *Eur Heart J* 2003; **24**: 987–1003.
78 Haffner SM *et al.* Mortality from CHD in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New Engl J Med* 1998; **339**: 229–234.
79 Evans JMM, Wang J, Morris AD. Comparison of CVD risk between patients with type 2 diabetes and those who had a myocardial infarction: cross sectional and cohort studies. *Br Med J* 2002; **324**: 939–943.
80 UKPDS Group. The UKPDS risk engine: a model for the risk of CHD in type 2 diabetes (UKPDS 56). *Clin Sci* 2001; **101**: 671–679.
81 Hansson L *et al*, for the HOT Study Group. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; **351**: 1755–1762.
82 Lewington S *et al.* Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
83 Julius S *et al*, for the VALUE Trial. For the VALUE trial: Long-term blood pressure trends in 13,449 patients with hypertension and high cardiovascular risk. *Am J Hypertens* 2003; **7**: 544–548.
84 Whelton PK *et al.* Primary prevention of hypertension. Clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA* 2002; **288**: 1882–1888.
85 The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. *Arch Intern Med* 1997; **157**: 657–667.
86 He J *et al.* Long-term effects of weight loss and dietary sodium restriction on incidence of hypertension. *Hypertension* 2000; **35**: 544–549.
87 Vollmer WM *et al.* Effects of diet and sodium intake on blood pressure. *Ann Intern Med* 2001; **135**: 1019–1028.
88 Chobanian AV, Hill M. National Heart, Lung, and Blood Institute Workshop on sodium and blood pressure: a critical review of current scientific evidence. *Hypertension* 2000; **35**: 858–863.
89 Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure. *Hypertension* 2000; **35**: 838–843.
90 Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure. *Ann Intern Med* 2002; **136**: 493–503.
91 Poulter NR *et al.* Concomitant risk factors in hypertensives: a survey of risk factors for cardiovascular disease amongst hypertensives in English general practices. *Blood Pressure* 1996; **5**: 209–215.
92 Conlin PR *et al.* The effect of dietary patterns on blood pressure control in hypertensive patients: results from the Dietary Approaches to Stop Hypertension (DASH) trial. *Am J Hypertens* 2000; **13**: 949–955.
93 Metz JA *et al.* A randomised trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on CVD risk reduction. *Arch Intern Med* 2000; **160**: 2150–2158.
94 Svetkey LP *et al.* Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomised clinical trial. *Arch Intern Med* 1999; **159**: 285–293.
95 Williams B. Insulin resistance: the shape of things to come. *Lancet* 1994; **344**: 521–524.
96 Neaton JD *et al.* Treatment of Mild Hypertension Study. Final results. *JAMA* 1993; **270**: 713–724.
97 Neter JE *et al.* Influence of weight reduction on blood pressure. A meta-analysis of randomized controlled trials. *Hypertension* 2003; **42**: 878–884.
98 Reid CM, Dart AM, Dewar EM, Jennings GL. Interactions between the effects of exercise and weight loss on risk factors, cardiovascular haemodynamics and left ventricular structure in overweight subjects. *J Hypertens* 1994; **12**: 291–301.
99 Puddey IB *et al.* Effects of alcohol and calorie restrictions on blood pressure and serum lipids in overweight men. *Hypertension* 1992; **20**: 533–541.
100 Whelton PK *et al.* Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of non-pharmacological intervention in the elderly (TONE). TONE Collaborative Research Group. *JAMA* 1998; **279**: 839–846.
101 Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Fall in blood pressure with modest reduction in dietary salt intake in mild hypertension. *Lancet* 1989; **1**: 399–402.
102 Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Effects of replacing sodium intake in subjects on a low sodium diet: a crossover study. *Clin Exp Hypertens A* 1989; **11**: 1011–1024.
103 Beard TC, Cooke HM, Gray WR, Barge R. Randomised controlled trial of a no-added-sodium diet for mild hypertension. *Lancet* 1982; **2**: 455–458.
104 Hooper L, Bartlett C, Davey Smith G, Ebrahini S. Systemic review of long term effects of advice to reduce dietary salt in adults. *Br Med J* 2002; **325**: 628–632.
105 Silman AJ, Locke C, Mitchell P, Humpherson P. Evaluation of the effectiveness of a low sodium diet in the treatment of mild to moderate hypertension. *Lancet* 1983; **1**: 1179–1182.
106 Midgley JP, Matthew AG, Greenwood CMT, Logan AG. Effect of reduced dietary sodium on blood pressure. A meta-analysis of randomized controlled trials. *JAMA* 1996; **275**: 1590–1597.
107 Hart CL, Smith D, Hole DJ, Hawthorne VM. Alcohol consumption and mortality from all causes, CHD, and stroke: results from a prospective cohort study of Scottish men with 21 years of follow-up. *Br Med J* 1999; **318**: 1725–1729.
108 Power C, Rodgers B, Hope S. U-shaped relation for alcohol consumption and health in early adulthood and implications for mortality. *Lancet* 1998; **352**: 877.

109 Thun MJ *et al.* Alcohol consumption and mortality among middle-aged and elderly US adults. *N Engl J Med* 1997; **337**: 1705–1714.
110 Matheswaran R, Beevers M, Beevers DG. Effectiveness of advice to reduce alcohol consumption in hypertensive patients. *Hypertension* 1992; **19**: 79–84.
111 Gill JS *et al.* Alcohol consumption—a risk factor for haemorrhagic and non-haemorrhagic stroke. *Am J Med* 1991; **90**: 481–497.
112 Braith RW *et al.* Moderate and high intensity exercise lowers blood pressure in normotensive subjects aged 60–79 years. *Am J Cardiol* 1994; **73**: 1124–1128.
113 Kokkinos PF *et al.* Effects of regular exercise on blood pressure and LV hypertrophy in African-American men with severe hypertension. *N Engl J Med* 1995; **333**: 1462–1467.
114 Arrol B, Beaglehole R. Exercise for hypertension. *Lancet* 1993; **341**: 1248–1249.
115 Anderssen S, Holme I, Urdal P, Hjermann I. Diet and exercise intervention have favourable effects on blood pressure in mild hypertensives: the Oslo Diet and Exercise Study (ODES). *Blood Pressure* 1995; **4**: 343–349.
116 Blomenthal JA *et al.* Exercise and weight loss reduce blood pressure in men and women with mild hypertension: effects on cardiovascular, metabolic and haemodynamic functioning. *Arch Intern Med* 2000; **169**: 1947–1958.
117 Gordon NF, Scott CB, Levine BD. Comparison of single venous multiple lifestyle interventions: are the antihypertensive effects of exercise training and diet-induced weight loss additive? *Am J Cardiol* 1997; **79**: 763–767.
118 Halbert JA *et al.* Physical activity and CVD risk factors: effect of advice from an exercise specialist in Australian general practice. *Med J Australia* 2000; **173**: 84–87.
119 Ebrahim S, Smith GD. Systematic review of randomised control trials of multiple risk factor interventions for preventing CHD. *Br Med J* 1997; **314**: 1666–1667.
120 Sandvik L *et al.* Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med* 1993; **328**: 533–537.
121 Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of CHD. *Am J Epidemiol* 1990; **132**: 612–628.
122 Lakka TA *et al.* Relation of leisure time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. *N Engl J Med* 1994; **330**: 1549–1554.
123 Morris JN *et al.* Exercise in leisure time: coronary attack and death rates. *Br Heart J* 1990; **63**: 325–334.
124 Paffenberger RS *et al.* The association of changes in physical activity in the prevention of CHD. *N Engl J Med* 1993; **329**: 538–545.
125 Appel LJ *et al*, for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997; **336**: 1117–1124.
126 Whelton PK *et al.* Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA* 1997; **277**: 1624–1632.
127 Chalmers J *et al.* Australian National Health and Medical Research Council dietary salt study in mild hypertension. *J Hypertens* 1986; **4** (Suppl 6): S629–S637.
128 Geleijnse JM, Witteman J, Bak AA den B, Grobbee DE. Reduction in blood pressure with a low sodium high potassium high magnesium salt in older subjects with mild hypertension. *Br Med J* 1994; **309**: 436–440.
129 Grobbee D, Hofman A. Effect of calcium supplementation on diastolic blood pressure in young people with mild hypertension. *Lancet* 1986; **2**: 703–706.
130 Henderson DG, Schierup J, Schodt T. Effect of magnesium supplementation on blood pressure and electrolyte concentration in hypertensive patients receiving long term diuretic treatment. *Br Med J* 1986; **293**: 664–665.
131 Lind L, Lithell H, Pollarc T, Ljunghall S. blood pressure response during long-term treatment with magnesium is dependent on magnesium status. *Am J Hypertens* 1991; **4**: 674–679.
132 Nowson C, Morgan T. Effect of calcium combination on blood pressure in normotensive and hypertensive people. *Hypertension* 1989; **13**: 630–639.
133 Sacks FM *et al.* Combinations of potassium, calcium and magnesium supplements in hypertension. *Hypertension* 1995; **26**: 950–956.
134 Siami A *et al.* Controlled trial of long term oral potassium supplements in patients with a mild hypertension. *Br Med J* 1987; **294**: 1453–1456.
135 Svetkey LP *et al.* Double-blind placebo-controlled trial of potassium chloride in the treatment of mild hypertension. *Hypertension* 1982; **9**: 444–450.
136 Witteman JCM *et al.* Reduction of blood pressure with oral magnesium supplementation in women with mild to moderate hypertension. *Am J Clin Nutr* 1994; **60**: 129–135.
137 Johnston DW *et al.* Effect of stress management on blood pressure in mild primary hypertension. *Br Med J* 1993; **306**: 963–966.
138 Patel C, Marmot M. Can general practitioners use training in relaxation and management of stress to reduce mild hypertension? *Br Med J* 1988; **296**: 21–24.
139 Patel C, Marmot MG, Terry DJ. Controlled trial of biofeedback-aided behavioural methods in reducing mild hypertension. *Br Med J* 1981; **282**: 2005–2008.
140 Patel C *et al.* Trial of relaxation in reducing coronary risk; four years follow up. *Br Med J* 1985; **290**: 1103–1106.
141 Schein MH *et al.* Treating hypertension with a device that slows and regularises breathing: a randomised double-blind controlled study. *J Hum Hypertens* 2001; **15**: 271–278.
142 Omvik P. How smoking affects blood pressure. *Blood Pressure* 1996; **5**: 71–77.
143 Primatesta P *et al.* Association between smoking and blood pressure: evidence from the health survey for England. *Hypertension* 2001; **37**: 187–193.
144 Doll R *et al.* Mortality in reation to smoking: 40 years' observational study on male British doctors. *Br Med J* 1994; **309**: 901–911.
145 Daly LE, Mulcahy R, Graham IM, Hickey N. Long term effect on mortality of stopping smoking after unstable angina and myocardial infarction. *Br Med J* 1983; **287**: 324–326.
146 Dobson AJ, Alexander HM, Heller RF, Lloyd DM. How soon after quitting smoking does risk of heart attack decline? *J Clin Epidemiol* 1991; **44**: 1247–1253.
147 Kawachi I *et al.* Smoking cessation and time course of increased risks of CHD in middle aged women. *Arch Intern Med* 1994; **154**: 169–175.

148 Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infraction after quitting smoking in men under 55 years of age. *N Engl J Med* 1985; **313**: 1512–1514.
149 Law M, Tang JL. An analysis of the effectiveness of interventions intended to help people stop smoking. *Arch Intern Med* 1995; **155**: 1933–1941.
150 Raw M, McNeill A, West R. Smoking correction: evidence based recommendations for the healthcare system. *Br Med J* 1999; **318**: 182–185.
151 Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis of efficacy of nicotine replacement therapies in smoking cessation. *Lancet* 1994; **343**: 139–142.
152 Tang JL *et al.* Systematic review of dietary intervention trails to lower blood total cholesterol in free-living subjects. *Br Med J* 1998; **316**: 1213–1220.
153 Imperial Cancer Research Fund OXCHECK Study Group. Effectiveness of health checks conducted by nurses in primary care: final results of the OXCHECK study. *Br Med J* 1995; **310**: 1099–1104.
154 Bao DQ *et al.* Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. *Hypertension* 1998; **32**: 710–717.
155 Attwood S *et al.* Within-patient correlation between the antihypertensive effects of atenolol, lisinopril and nifedipine. *J Hypertens* 1994; **12**: 1053–1060.
156 Sever P. The heterogeneity of hypertension. *Eur Soc Cardiol* 1999; **1**: L11–L13.
157 Dickerson JE *et al.* Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet* 1999; **353**: 2008–2013.
158 Materson BJ, Reda DJ, Cushman WC. Department of veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Am J Hypertens* 1995; **8**: 189–192.
159 Kaplan N. *Kaplan's Clinical Hypertension*, 8th edn. Williams and Williams: Lippincott. 2002.
160 Swales JD. *Textbook of Hypertension*. Blackwell Scientific Publications: UK. 1994.
161 Hood S *et al.* High prevalence of aldosterone-sensitive hypertension in unselected patients. *Q J Med* 2002; **95**: 621.
162 Luft FC. Mechanisms and cardiovascular damage in hypertension. *Hypertension* 2001; **37**: 594–598.
163 Lacourciere Y *et al.* Effects of modulators of the renin-angiotensin-aldosterone system on cough. Losartan Cough Study Group. *J Hypertens* 1994; **12**: 1387–1393.
164 Collins R, Peto R. Antihypertensive drug therapy: effects on Stroke and coronary heart disease. In: Swales JD (ed). *Textbook of Hypertension*. Blackwell Scientific Publications: UK. 1994, pp 1156–1164.
165 MacMahon S *et al.* Blood pressure, stroke and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**: 765–774.
166 SHEP Co-operative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *J Am Med Assoc* 1991; **265**: 3255–3264.
167 Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *Br Med J* 1992; **304**: 405–412.
168 Wing LMH *et al.* A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; **348**: 583–592.
169 Staessen JA *et al*, for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350**: 757–764.
170 Lithell H *et al*, for the SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Hypertension* 2003; **21**: 875–886.
171 Williams B. Drug treatment of hypertension. *Br Med J* 2003; **326**: 61–62.
172 McInnes GT. ALLHAT: a saga of missed opportunities. *J Hum Hypertens* 2003; **17**: 373–377.
173 Zanchetti A, Mancia G. The ALLHAT trial: a verdict or a challenge? *J Hypertens* 2003; **21**: 223.
174 Gress TW *et al*, for the Atherosclerosis Risk in Community (ARIC) Study. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000; **342**: 905–912.
175 Brown MJ. Matching the right drug to the right patient in essential hypertension. *Heart* 2001; **86**: 113–120.
176 Sagnella GA. Why is plasma renin activity lower in populations of African origin? *J Hum Hypertens* 2001; **15**: 17–25.
177 Gibbs CR, Beevers DG, Lip GY. The management of hypertensive disease in black patients. *Q J Med* 1999; **92**: 187–192.
178 He FJ, Markandu ND, Sagnella GA, MacGregor GA. Importance of the renin system in determining blood pressure fall with salt restriction in black and white hypertensives. *Hypertension* 1998; **32**: 820–824.
179 Deary A *et al.* Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. *J Hypertens* 2002; **20**: 771–777.
180 Laragh JH. Renin system analysis defines the special value of combination antihypertensive therapy using an antirenin agent (CEI) with a long-acting calcium channel blocker (CCB). *Am J Hypertens* 1998; **11**: 170S–174S.
181 Tsutamoto T *et al.* Effects of long-acting calcium channel antagonists on neurohumoral factors: comparison of nifedipine coat-core with amlodipine. *J Cardiovasc Pharmacol* 2003; **41** (Suppl 1): S77–S81.
182 Sever PS *et al.* Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. *J Hypertens* 2001; **19**: 1139–1147.
183 Lindholm LH *et al.* Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens* 2002; **20**: 1879–1886.
184 Brown MJ. Implications from hypertension outcome trials for the management of patients with hypertension and diabetes. *Br J Diabetes Vasc Dis* 2003; **3**: 245–251.
185 Taler SJ, Textor SC, Augustine JE. Resistant hypertension: comparing hemodynamic management to specialist care. *Hypertension* 2002; **39**: 982–988.
186 Lim PO, Jung RT, MacDonald TM. Raised aldosterone to renin ratio predicts antihypertensive efficacy of spironolactone: a prospective cohort follow-up study. *Br J Clin Pharmacol* 1999; **48**: 756–760.

187 Thijs L *et al.* A meta-analysis of outcomes trials in elderly hypertensives. *J Hypertens* 1992; **10**: 1103–1109.
188 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin *vs* usual care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; **288**: 2998–3007.
189 Randomised trial of cholesterol lowering in 4444 patients with CHD: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–1389.
190 Sacks FM *et al.* The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; **335**: 1001–1009.
191 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with CHD and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339**: 1349–1357.
192 Rubins HB *et al.* Gemfibrozil for the secondary prevention of CHD in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; **341**: 410–418.
193 Shepherd J *et al.* Prevention of CHD with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333**: 1301–1307.
194 Downs JR *et al.* Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/Tex-CAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; **279**: 1615–1622.
195 Shepherd J *et al.* Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**: 1623–1630.
196 Crouse JR, Byington RP, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. *Atherosclerosis* 1998; **138**: 11–24.
197 Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). *JAMA* 2001; **285**: 2486–2497.
198 Athyros VG *et al.* Treatment with atorvastatin to the National Cholesterol Educational Program goal *versus* 'usual' care in secondary CHD prevention. The Greek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin* 2002; **18**: 220–228.
199 Diaz MZ, Frei B, Vita JA, Keaney Jr JF. Antioxidants and atherosclerotic heart disease. *N Engl J Med* 1997; **337**: 408–416.
200 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 23–33.
201 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *Br Med J* 2003; **326**: 1419–1423.
202 Forette F *et al.* Prevention of dementia in randomised double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial. *Lancet* 1998; **352**: 1347–1351.
203 Ekbom T *et al.* Antihypertensive efficacy and side-effects of three beta-blockers and a diuretic in elderly hypertensives: a report from the STOP-Hypertension Study. *J Hypertens* 1992; **10**: 1525–1530.
204 Messerli FH, Grossman E, Goldbourt U. Are β-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. *JAMA* 1998; **279**: 1903–1907.
205 Kjeldsen SE *et al.* Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and LVH. A losartan intervention for endpoint reduction (LIFE) substudy. *JAMA* 2002; **288**: 1491–1498.
206 Gueyffier F *et al.* Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet* 1999; **353**: 793–796.
207 Bulpitt C *et al.* Hypertension in the very elderly trial (HYVET). Protocol for the main trial. *Drugs Aging* 2001; **18**: 151–164.
208 Franklin SS *et al.* Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. *Circulation* 1997; **96**: 308–315.
209 Lawlor DA *et al.* Secular trends in mortality by stroke subtype in the 20th century: a retrospective analysis. *Lancet* 2002; **360**: 1818–1823.
210 Wolfe CDA, Tilling K, Beech R, Rudd AG, for the European BIOMED Study of Stroke Care Group. Variations in case fatality and dependency from stroke in Western and Central Europe. *Stroke* 1999; **30**: 350–356.
211 Dennis MS *et al.* Long-term survival after first-ever stroke: The Oxfordshire Community Stroke Project. *Stroke* 1993; **24**: 796–800.
212 Gariballa SE, Robinson TG, Parker SG, Castleden CM. A prospective study of primary and secondary risk factor management in stroke patients. *J R Col Phys* 1995; **29**: 485–487.
213 Harper G, Castleden CM, Potter JF. Factors affecting changes in blood pressure after acute stroke. *Stroke* 1994; **25**: 1726–1729.
214 Robinson TG, Potter JF. Blood pressure in acute stroke. *Age Ageing* 2004; **33**: 6–12.
215 Britton M, Carlsson A. Very high blood pressure in acute stroke. *J Intern Med* 1990; **228**: 611–615.
216 Carlberg B, Asplund K, Hagg E. The prognostic value of admission blood pressure in patients with acute stroke. *Stroke* 1993; **24**: 1372–1375.
217 Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Effect of blood pressure and diabetes on stroke in progression. *Lancet* 1994; **344**: 156–159.
218 Robinson TG *et al.* The predictive role of 24-hour compared to casual blood pressure levels on outcome following acute stroke. *Cerebrovasc Dis* 1997; **7**: 264–272.
219 Leonardi-Bee J, Bath PMW, Phillips SJ, Sandercock PAG, for the IST Collaborative Group. Blood pressure and clinical outcomes in the international stroke trial. *Stroke* 2002; **33**: 1315–1320.
220 Blood pressure in acute stroke collaboration. Vasoactive drugs for acute stroke. *Cochrane Library* 2002; **4**.
221 Schrader J *et al.* The ACCESS study. Evaluation of acute candesartan cilexetil therapy in stroke survivors. *Stroke* 2003; **34**: 1699–1703.

222 Adams HP *et al.* Guidelines for the early management of patients with ischaemic stroke. A scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 2003; **34**: 1056–1083.
223 Carlsson A, Britton M. Blood pressure after stroke. A one-year follow-up study. *Stroke* 1993; **24**: 195–199.
224 Carter A. Hypotensive therapy in stroke survivors. *Lancet* 1970; **1**: 485–489.
225 Hypertension Stroke Co-operative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA* 1974; **229**: 409–418.
226 The Dutch TIA Trial Study Group. Trial of secondary prevention with atenolol after transient ischaemic attack or non-disabling ischaemic stroke. *Stroke* 1993; **24**: 543–548.
227 Eriksson S, Olofsson B, Wester P, for the TEST Study Group. Atenonol in secondary prevention after stroke. *Cerebrovasc Dis* 1995; **5**: 21–25.
228 PATS Collaborating Group. Post-stroke antihypertensive treatment study. A preliminary result. *Chin Med J* 1995; **108**: 710–717.
229 Bosch J *et al*, on behalf of the HOPE Investigators. Use of ramipril in preventing stroke: double blind randomised trial. *Br Med J* 2002; **324**: 699–702.
230 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002; **324**: 71–86.
231 European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; **342**: 1255–1262.
232 Rothwell PM *et al.* Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet* 2003; **361**: 107–116.
233 Williams B. Epidemiology and Pathogenesis of hypertension in diabetes. In: Williams B (ed). *Hypertension in Diabetes*. Martin Dunitz Ltd. London, 2003, pp 3–23.
234 Zanchetti A *et al.* Effects of individual risk factors on the incidence of cardiovascular events in the treated hypertensive patients in the Hypertension Optimal Treatment study. *J Hypertens* 2001; **19**: 1149–1159.
235 Curb JD *et al.* Effect of diuretic based antihypertensive treatment on CVD risk in people with diabetes. Systolic Hypertension in Elderly Program (SHEP) Cooperative research group. *JAMA* 1996; **276**: 1886–1892.
236 United Kingdom Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 1998; **317**: 703–713.
237 The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. *N Engl J Med* 2000; **342**: 145–153.
238 Zanchetti A *et al.* 2003 European Society of Hypertension–European Society of Cardiology Guidelines for the Management of Arterial Hypertension. *J Hypertens* 2003; **21**: 1011–1053.
239 Stamler J, Vaccaro A, Neaton JD, Wentworth D. Diabetes and other risk factors and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; **263**: 2335–2340.
240 Adler A *et al.* Association of systolic blood pressure with macrovascular and microvascular complications of type to diabetes (UKPDS 36): prospective observational study. *Br Med J* 2000; **321**: 412–419.
241 Williams B. The unique vulnerability of diabetic subjects to hypertensive injury. *J Human Hypertens* 1999; **13** (Suppl 2): S3–S8.
242 Brown MJ *et al.* Influence of diabetes and type of hypertension on response to antihypertensive therapy. *Hypertension* 2000; **35**: 1038–1042.
243 Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. *J Hypertens* 2002; **29**: 1461–1464.
244 Zanchetti A, Ruilope A. Antihypertensive treatment in patients with type 2 diabetes mellitus: what guidance from recent controlled randomised trials. *J Hypertens* 2002; **20**: 2099–2110.
245 Lindholm LH *et al.* Effects of losartan on sudden cardiac death in people with diabetes: date from the LIFE study. *Lancet* 2003; **362**: 619–620.
246 Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; **329**: 1456–1462.
247 Cooper ME. Pathogenesis, prevention, and treatment of diabetic nephropathy. *Lancet* 1998; **352**: 213–219.
248 Mogensen CE *et al.* Prevention of diabetic renal disease with special reference to microalbuminuria. *Lancet* 1995; **346**: 1080–1084.
249 Parving HH. Initiation and progression of diabetic nephropathy. *N Engl J Med* 1996; **335**: 1682–1683.
250 The Euclid Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normaoalbuminuria or microalbuminuria. *Lancet* 1997; **349**: 1787–1792.
251 Williams B. Lisinopril and albumin excretion in diabetes. *Lancet* 1997; **350**: 663–664.
252 Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *Br Med J* 1997; **314**: 783–788.
253 Ravid M, Leug R, Rachmanni R, Lisner M. Long-term renoprotecive effect of angiotensin converting enzyme inhibitors in non-insulin dependent diabetes: a seven year follow-up. *Arch Int Med* 1996; **156**: 286–289.
254 Bakris GL *et al.* Effect of blood pressure level on progression of diabetic nephropathy. *Arch Int Med* 2003; **163**: 1555–1565.
255 Collins R *et al.* MRC/BHF Heart Protection Study: cholesterol lowering with simvastatin in 5963 people with diabetes: A randomised controlled trial. *Lancet* 2003; **361**: 2005–2016.
256 Bakris GL *et al.* Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; **36**: 646–661.
257 Lazarus JM *et al*, for the Modification of Diet in Renal Disease Study Group. Achievement and safety of a low blood pressure goal in chronic renal disease. *Hypertension* 1997; **29**: 641–650.

258 Klahr S *et al*, for the Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 1994; **330**: 877–884.
259 Jafar TH *et al.* Progression of chronic kidney disease: the role of blood pressure and control of proteinuria, and angiotensin converting enzyme inhibition: a patient level meta-analysis. *Ann Intern Med* 2003; **139**: 244–252.
260 Gruppo Italiano di Studi Epidemiologici in Nefrologia. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet* 1997; **349**: 1857–1863.
261 Navis G, de Zeeuw D, de Jong PE. ACE-inhibitors: panacea for progressive renal disease? *Lancet* 1997; **349**: 1852–1853.
262 Giatras I, Lau J, Levey AS, for the Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: A meta-analysis of randomized trials. *Ann Intern Med* 1997; **127**: 337–345.
263 Jafar TH *et al.* Angiotensin converting enzyme inhibitors and progression of non-diabetic renal disease. A meta-analysis of patient level data. *Ann Intern Med* 2001; **135**: 73–87.
264 Nakao N *et al.* Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (CO-OPERATE): a randomised controlled trial. *Lancet* 2003; **361**: 117–124.
265 Jensen JS *et al.* Arterial hypertension, microalbuminuria, and risk of ischemic heart disease. *Hypertension* 2000; **35**: 898–903.
266 Gerstein HC *et al.* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**: 421–426.
267 Bigazzi R, Bianchi S, Baldari D, Campese VM. Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. *J Hypertens* 1998; **16**: 1325–1333.
268 Hillege HL *et al*, for the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106**: 1777–1782.
269 Redon J, Williams B. Microalbuminuria in essential hypertension: redefining the threshold. *J Hypertens* 2002; **20**: 353–355.
270 Ruilope LM *et al.* Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol* 2001; **12**: 218–225.
271 Weir RJ. Oral contraceptives, hormone replacement therapy and hypertension. In: Swales JD (ed). *Textbook of Hypertension*. Oxford Blackwell Scientific Publications: Oxford. 1994, pp 904–992.
272 Lim KG *et al.* Malignant hypertension in women of childbearing age and its relation to the contraceptive pill. *Br Med J* 1987; **294**: 1057–1059.
273 Farley TMM, Collins J, Schlesselman JJ. Hormonal contraception and risk of cardiovascular disease. *Contraception* 1998; **57**: 211–230.
274 Dong W, Colhoun HM, Poulter NR. blood pressure in women using oral contraceptives: results from the health survey for England 1994. *J Hypertens* 1998; **15**: 1063–1068.
275 Wilson ESB, Cruickshank J, McMaster M, Weir RJ. A prospective controlled study of the effect on blood pressure of contraceptive preparations containing different types of progestogen. *Br J Obstet Gynaecol* 1984; **91**: 1254–1260.
276 Nabulsi AA *et al.* Association of hormone replacement therapy with various CVD risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Investigators. *N Engl J Med* 1993; **328**: 1069–1075.
277 The writing group for the PEPI trial. Effect of oestrogen or oestrogen/progestin regimens on heart disease risk factors in post-menopausal women. *JAMA* 1995; **273**: 199–208.
278 Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. *Ann Rev Public Health* 1998; **19**: 55–72.
279 Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy menopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA* 2002; **288**: 321–333.
280 Hulley S *et al*, for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of CHD in postmenopausal women. *JAMA* 1998; **280**: 605–613.
281 Viscoli CM *et al.* A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; **345**: 1243–1249.
282 Barrett-Connor E. Clinical Review 162. Cardiovascular Endocrinology 3. An epidemiologist looks at hormones and heart disease in women. *J Clin Endocrin Metab* 2003; **88**: 4031–4402.
283 Hays J *et al*, for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on health-related quality of life. *New Engl J Med* 2003; **348**: 1839–1854.
284 Broughton Pipkin F. The hypertensive disorders of pregnancy. *Br Med J* 1995; **11**: 609–613.
285 Sibai BM. Treatment of hypertension in pregnant women. *New Engl J Med* 1996; **335**: 257–265.
286 Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; **183**: S1–S22.
287 Roberts JM, Pearson GD, Cutler JA, Lindheimer MD. Summary of the NHLBI working group on research on hypertension during pregnancy. *Hypertens Pregnancy* 2003; **22**: 109–127.
288 Higgins JR, de Swiet M. Blood pressure measurement and classification in pregnancy. *Lancet* 2001; **357**: 131–135.
289 Rubin P. Measuring diastolic blood pressure in pregnancy. Use the fifth Korotkoff sound. *Br Med J* 1996; **313**: 4–5.
290 Reinders A *et al.* Validation of the Welch Allyn 'Vital Signs' blood pressure measurement device in pregnancy and pre-eclampsia. *Br J Obstet Gynaecol* 2003; **110**: 134–138.
291 Shennan AH, Kissane J, de Swiet M. Validation of the Spacelabs 90207 ambulatory blood pressure monitor for use in pregnancy. *Br J Obstet Gynaecol* 1993; **100**: 904–908.

292 Wallenburg HCS. Prevention of pre-eclampsia: status and perspectives 2000. *Eur J Obstet Gynaecol Reprod Biol* 2001; **94**: 13–22.
293 von Dadelszen P *et al.* Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet* 2000; **355**: 87–92.
294 Trupin LS, Simon LP, Eskenazi B. Change in paternity: a risk factor for pre-eclampsia in multiparas. *Epidemiology* 1996; **7**: 240–244.
295 Robillard PY, Hulsey TC. Association of pregnancy-induced-hypertension, pre-eclampsia, and eclampsia with duration of sexual cohabitation before conception. *Lancet* 1996; **347**: 619.
296 Dekker G, Sibai B. Primary, secondary and tertiary prevention of pre-eclampsia. *Lancet* 2001; **357**: 209–215.
297 Roberts JM, Cooper DW. Pathogenesis and genetics of hypertension. *Lancet* 2001; **357**: 53–56.
298 Wimalasundera RC *et al.* Pre-eclampsia, antiretroviral therapy, and immune reconstitution. *Lancet* 2002; **360**: 1152–1254.
299 The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies benefit form magnesium sulphate? The Magpie trial: a randomised controlled trial. *Lancet* 2002; **359**: 1877–1890.
300 CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. *Lancet* 1994; **343**: 619–629.
301 Caritis S *et al.* Low-dose aspirin to prevent pre-eclampsia in women at high risk. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *N Engl J Med* 1998; **338**: 701–705.
302 Duley L, Henderson-Smart D, Knight M, King J. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. *Br Med J* 2001; **322**: 233–329.
303 Chappell LC *et al.* Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999; **354**: 810–816.
304 Chappell LC *et al.* Vitamin C and E supplementation in women at risk of pre-eclampsia is associated with changes in indices of oxidative stress and placental function. *Am J Obstet Gynecol* 2002; **187**: 777–784.
305 Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. *Lancet* 1982; **1**: 647–649.
306 Kyle PM, Redman CW. Comparative risk-benefit assessment of drugs used in the management of hypertension in pregnancy. *Drug Saf* 1992; **7**: 223–234.
307 Naden RP, Redman CW. Antihypertensive drugs in pregnancy. *Clinics Perinatol* 1985; **12**: 521–538.
308 Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *Br Med J* 1990; **301**: 587–589.
309 Lydakis C, Lip GY, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertension* 1999; **12**: 541–547.
310 Collins R, Yusuf S, Peto R. Overview of randomized trials of diuretics in pregnancy. *Br Med J* 1985; **290**: 17–23.
311 Sibai BM, Grossman RA, Grossman HG. Effects of diuretics on plasma volume in pregnancies with long-term hypertension. *Am J Obst Gynaecol* 1984; **150**: 831–835.
312 Hansenns M, Keirse MJ, Vankelecom F, Van Assche FA. Fetal and neonatal effects of treatment with angiotensin converting enzyme inhibitors. *Obst Gynecol* 1991; **78**: 128–135.
313 Chesley LC. Hypertension in pregnancy: definitions, familial factor and remote prognosis. *Kidney Int* 1980; **18**: 234–240.
314 Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *Br Med J* 2001; **323**: 1213–1217.
315 Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001; **357**: 2002–2006.
316 Wilson BJ *et al.* Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *Br Med J* 2003; **326**: 845–852.
317 Primatesta P, Bost L, Poulter NR. Blood pressure levels and hypertension status among ethnic groups in England. *J Human Hypertens* 2000; **14**: 143–148.
318 Lane D, Beevers DG, Lip GYH. Ethnic differences in blood pressure and prevalence of hypertension in England. *J Hum Hypertens* 2002; **16**: 267–273.
319 Cappuccio FP, Cooj DG, Atkinson RW, Wicks PD. The Wandsworth Heart and Stroke Study. A population-based study of CVD risk factors in different ethnic groups. Methods and baseline findings. *Nutr Metab Cardiovasc Dis* 1998; **8**: 371–385.
320 Shulman NB, Hall WD. Renal vascular disease in African-Americans and other racial minorities. *Circulation* 1991; **83**: 1477–1479.
321 Mayet J *et al.* Ethnic differences in the hypertensive heart and 24-hour blood pressure profile. *Hypertension* 1998; **31**: 1190–1194.
322 Cardiovascular Heart Disease statistics. British Heart Foundation Statistics Database 2003.
323 Luft FC *et al.* Salt sensitivity and resistance of blood pressure. *Hypertension* 1991; **17**: 102–108.
324 Materson BJ *et al*, for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *New Engl J Med* 1993; **328**: 914–921.
325 Williams B, Poulter N. AASK commentary. *Current Concepts in Hypertension* 2002; **4**: 2–6.
326 Douglas JG *et al*, the Hypertension in African Americans Working Group. Management of high blood pressure in African Americans. *Arch Intern Med* 2003; **163**: 525–541.
327 Williams B. Westernisd Asians and cardiovascular disease. Nature or nurture? *Lancet* 1995; **345**: 401–402.
328 McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with diabetes prevalence and CVD risk in south Asians. *Lancet* 1991; **337**: 382–386.
329 General Practitioners Committee and the NHS Confederation (2003). Investing in general practice: the new General Medical Services contract. www.doh.gov.uk/gmscontract/newgmscontract.pdf.
330 Wales: National Assembly (2001). Tackling coronary heart disease in Wales: implementing through evidence. Wales: National Assembly. www.wales.nhs.uk/publications/coronary-heart-disease-e.pdf.
331 Scotland. Health department (2002). Coronary Heart disease and stroke strategy for Scotland. Edinburgh: Scottish Executive. www.sctland.gov.uk/library5/health/chds.pdf.

Appendix A

Stakeholders who reviewed the guidelines

Blood Pressure Association
Nurses Hypertension Association
Diabetes UK
British Cardiac Association
Renal Association
Heart UK
Primary Care Cardiovascular Society
London Hypertension Society
British Heart Foundation
Royal College of General Practitioners
Friends of the British Hypertension Society
Department of Health

Appendix B

Categories of strength used in statements (based on North of England evidence-based guidelines, BMJ 1998) (51)

Strength of evidence

1a-Evidence from meta-analysis of randomised controlled trials.
1b-Evidence from at least one randomised controlled study.
IIa-Evidence from at least one controlled study without randomisation.
IIb-Evidence from at least one other type of quasi-experimental study.
III-Evidence from descriptive studies, such as comparative studies, correlation studies, and case-controlled studies.
IV-Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Strength of recommendation

A-Directly based on category I evidence.
B-Directly based on category II evidence or extrapolated recommendation from category I evidence.
C-Directly based on category III evidence or extrapolated recommendation from category I or II evidence.
D-Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.

Appendix C

Available from the British Hypertension Society Information Service

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- CD-ROM BP measurement available to download from the website www.abdn.ac.uk/medical/bhs
- Poster illustrating the ABCD drug treatment algorithm
- Poster illustrating guidance for measuring BP using a mercury sphygmomanometer
- Poster illustrating guidance for measuring BP using a digital BP monitor
- Lists of validated BP monitors
- Nurse distance learning pack available to download from the website www.bhsoc.org
- BHS live clinical trials feedback via live web casts
- Hypertension referral centres database
- Courses and conferences within the Hypertension field
- Healthcare Professionals factfile information

Appendix D

How to use the coronary risk-prediction charts for primary prevention

These charts are for estimating CVD risk (non-fatal MI and stroke, coronary and stroke death and new angina pectoris) for individuals who have *not* already developed CHD or other major atherosclerotic disease. They are an aid to making clinical decisions about how intensively to intervene on lifestyle and whether to use antihypertensive, lipid-lowering medication and aspirin.

- The use of these charts is not appropriate for the following patient groups. Those with:
  - CHD or other major atherosclerotic disease;
  - familial hypercholesterolaemia or other inherited dyslipidaemias;
  - chronic renal dysfunction;
  - type I and II diabetes mellitus.
- The charts should not be used to decide whether to introduce antihypertensive medication when BP is persistently at or above 160/100 or when TOD due to hypertension is present. In both cases, antihypertensive medication is recommended regardless of CVD risk. Similarly,

the charts should not be used to decide whether to introduce lipid-lowering medication when the ratio of serum total to HDL cholesterol exceeds 7. Such medication is generally then indicated, regardless of the estimated CVD risk.

- To estimate an individual's absolute 10-year of risk developing CVD, choose the table for his or her gender, smoking status (smoker/non-smoker) and age. Within this square, define the level of risk according to the point where the coordinates for SBP and the ratio of the total cholesterol to HDL-cholesterol to meet. If no HDL cholesterol result is available, then assume this is 1.00 mmol/l and the lipid scale can be used for total serum cholesterol alone.
- Higher risk individuals (red areas) are defined as those whose 10-year CVD risk exceeds 20%, which is approximately equivalent to the CHD risk of >15% over the same period, indicated by the previous version of these charts. As a minimum, those at highest CVD risk (greater than 30% shown by the line within the red area) should be targeted and treated now. When resources allow, others with a CVD risk of >20% should be progressively targeted.
- The chart also assists in the identification of individuals whose 10-year CVD risk moderately increased in the range 10–20% (orange area) and those in whom the risk is lower than 10% over 10 years (green area).
- Smoking status should reflect the lifetime exposure to tobacco and not simply tobacco use at the time of assessment. For example, those who have given up smoking within 5 years should be regarded as current smokers for the purposes of the charts.
- The initial BP and the first random (non-fasting) total cholesterol and HDL cholesterol can be used to estimate an individual's risk. However, the decision on using drug therapy should generally be based on repeat risk factor measurements over a period of time.
- Men and women do not reach the level of risk predicted by the charts for the three age bands until they reach the ages 49, 59 and 69 years, respectively. Everyone aged 70 years and over should be considered at higher risk. The charts will overestimate the current risk most in the under 40s. Clinical judgement must be exercised in deciding on treatment in younger patients. However, it should be recognised that BP and cholesterol tend to rise most and HDL cholesterol to decline most in younger people already possessing adverse levels. Thus untreated, their risk at the age 49 years is likely to be higher than the projected risk shown on the age-less-than 50 years chart.
- These charts (and all other currently available methods of CVD risk prediction) are based on groups of people with *untreated* levels of BP, total cholesterol and HDL cholesterol. In patients already receiving antihypertensive therapy in whom the decision is to be made about whether to introduce lipid-lowering medication or *vice-versa*, the charts can act as a guide, but unless recent pretreatment risk factor values are available it is generally safest to assume that CVD risk factor than that predicted by current levels of BP or lipids on treatment.
- CVD risk is also higher than indicated in the charts for:
  - those with a family history of premature CVD or stroke (male first-degree relatives aged <55 years and female first-degree relatives aged <65 years), which increases the risk by a factor approximately 1.5;
  - those with raised triglyceride levels;
  - women with premature menopause;
  - those who are not yet diabetic, but have impaired fasting glucose (6.1–6.9 mmol/l).
- In some ethnic minorities, the risk charts underestimate CVD risk, because they have not been validated in these populations. For example, in people originating from the Indian subcontinent, it is safest to assume that the CVD risk is higher than that predicted from the charts (1.5 times).
- These charts may be used to illustrate the direction of impact of risk factor intervention on the estimated level of CVD risk. However, such estimates are crude and are not based on randomised trial evidence. Nevertheless, this approach may be helpful in motivating appropriate intervention. The charts are primarily to assist in directing intervention to those who typically stand to benefit the most.

Appendix E

Blood Pressure Association

Contact details:
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Glossary

AASK	African American Study of Kidney Disease
AB/CD	British Hypertension Society recommendations for the treatment algorithm of the combination of antihypertensive treatments
ABPM	Ambulatory Blood Pressure Monitoring
ACCESS	Acute Candasartan Cilexetil Therapy in Stroke Survivors
ACE	Angiotensin-Converting Enzyme
ALLHAT	Antihypertension and Lipid Lowering treatment to prevent Heart Attack Trial
ANBP2	Australian National Blood Pressure study
ARBs	Angiotensin Receptor Blockers
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
ATPIII	Adult Treatment Program III
BHS	British Hypertension Society
BP	Blood Pressure
CAPPP	CAPtopril Prevention Project
CCBs	Calcium Channel Blockers
CHD	Coronary Heart Disease
CVD	Cerebrovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EUROPA	EUropean trial on Reductions Of cardiac events with Perindopril in stable coronary Artery disease
GFR	Glomerular Filtration Rate
GMS	General Medical Services
GP	General Practitioner
HDL	High-Density Lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
HPS	Heart Protection Study
HYVET	Hypertension in the Very Elderly Trial
INSIGHT	International nifendipine once-daily study
ISH	Isolated Systolic Hypertension
JNC 7	Seventh Joint National Committee
HRT	Hormone-replacement therapy
LIFE	Losartan Intervention for Endpoint reduction in hypertension
LDL	Low-Density Lipoprotein
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
NORDIL	NOrdic DILiazem study
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
NSFs	National Service Frameworks
OCs	Oral contraceptives
PCT	Primary Care Trust
POP	Progestogen-only pill
PROGRESS	Perindopril PROtection AGainst REcurrent Stroke Study
PROSPER	PROspective study of Pravostatin in the Elderly at Risk
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
SBP	Systolic Blood Pressure
SCOPE	Study on COgnition and Prognosis in the Elderly
STOP2	Swedish Trial I Old Patients with hypertension 2
TIA	Transient Ischaemic Attack
TOD	Target Organ Damage
UKPDS	United Kingdom Prospective Diabetes Study
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
WEST	Women's Estrogen for Stroke Trial
WHO	World Health Organisation