HYPERTENSION

Version 2 Final

Document control

Version history

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Changes since last version

1.1 Blood pressure 140/85

Introduction

Description

Hypertension is a major risk factor for cardiovascular disease.

There is a range of blood pressure seen in the population which may be considered as normal. [1]

The definition of "an elevation of systolic and or diastolic blood pressure, either primary or secondary" is rather vague and a more practical definition could be considered as

"the level of blood pressure where the benefits of treatment outweigh the risks".

Previous studies showed that the benefits of lowering blood pressure are significant and that there is a linear relationship between the level of blood pressure and cardiovascular risk. [2][3][4]

No evidence was found that a physiologically low blood pressure is harmful. [5]

The current NICE guidelines recommend treatment if there is a persistent rise in blood pressure to 160/100 mmHg or more. Where there is raised cardiovascular risk, existing cardiovascular disease or target organ (end-organ) damage treatment should be commenced at 140/90 mmHg. Isolated systolic hypertension (>160 mm Hg) should also trigger treatment. In all cases the target is to maintain blood pressure at or below 140/85 mmHg. [6]

Prevalence

The prevalence of hypertension, as defined above, rises from 4% in adults under 30, to 65% in those over 80 years old. [7] It is more common in some ethnic groups such as black and Japanese.

Aetiology

The kidneys and their renin-angiotensin-aldosterone system have a key role in controlling blood pressure. [7]

However, primary (essential) hypertension is of unknown aetiology. This accounts for over 90% of cases when no single cause is found.

Of the others (secondary hypertension) over 5% are due to bilateral parenchymal renal disease with only 2% secondary to a potentially curable condition such as phaeochromocytoma, Conn's syndrome, renal artery stenosis or para-thyroid disease. Within a hypertensive population secondary causes are found more often in younger patients.

It is estimated that genetic factors account for about 30% of the variation in blood pressure. [8]

Age, salt intake, obesity, and alcohol consumption are risk factors for hypertension. Excessive alcohol consumption occasionally causes a condition similar to Conn's syndrome. However of these, factors such as dietary salt, obesity and stress, seem to act only in genetically susceptible persons. There is no convincing evidence that "stress" causes non-labile hypertension (emphasising that white coat hypertension is not medically important).

Hypertension may develop during pregnancy (pre-eclampsia) and usually resolves following delivery. However, prenatal influences may promote hypertension in adult life. [9]

Diagnosis

Measurement of Blood Pressure

In 1896, Riva-Rocci developed a mercury sphygmomanometer capable of accurately recording blood pressure. Korotkov demonstrated his technique for auscultatory measurement in 1905.

The introduction of ambulatory blood pressure measurement techniques have demonstrated that not only is the measured blood pressure affected by the choice of equipment and technique, but also by factors such as activity, sleep, anxiety, and time of day. [10]

'White Coat Hypertension' is a well-known phenomenon where people with normal blood pressure become hypertensive during blood pressure measurement, but their blood pressure settles to normal when they are away from the medical environment. This group can be identified by ambulatory blood pressure measurement. Indeed, ambulatory measurement has been shown to be a more accurate predictor of cardiovascular outcome than the conventional technique.^[7]

In clinical practice, blood pressure should be measured on four occasions over several weeks to ensure that an accurate diagnosis is made before lifelong treatment is initiated.

The Recommended Technique for Measuring Blood Pressure is described in Appendix A.

Clinical Evaluation

The clinical evaluation of a hypertensive patient aims to identify possible secondary causes, complications of hypertension, and other risk factors for cardiovascular disease.

The patient's history may identify additional risk factors such as smoking, family history of cardiovascular disease, or pre-existing cardiovascular disease.

The history may also influence the eventual choice of treatment. For example, betablockers would be contraindicated in a patient with asthma, but ACE inhibitors might be first choice in a diabetic patient.

Presenting Features

In the absence of complications, hypertension is almost always asymptomatic. [8]

Most new cases are identified by screening or during the investigation of another condition. $^{[7]}$

Extreme or long-standing hypertension may cause damage to the cardiovascular and renal systems. Examples include retinopathy, left ventricular hypertrophy, peripheral vascular disease, and hypertensive nephropathy. These complications are known as: 'End-Organ Damage'.

Headache, dizziness, lethargy and epistaxis are popularly thought to be associated with high blood pressure. However, the available evidence shows that impression to be false.[7]

General Examination

General examination may identify risk factors for cardiovascular disease or secondary causes of hypertension. (See *Appendix B* for further details.)

The Key Findings On Examination:

"Examination of the fundi and clinical examination for evidence of left ventricular hypertrophy provide the best evidence of the severity of hypertension."[8]

Clinical signs which may be included within submitted medical reports of suggesting the presence of left ventricular hypertrophy include:

- Forceful apex beat.
- Apex beat displaced laterally. (Normal position is over the 5th intercostal space in the mid-clavicular line.)
- Accentuated aortic component of the 2nd heart sound and a 4th heart sound.

Clinical signs of hypertensive retinopathy may be described using the following grading and descriptive system.

A. Non-Malignant Hypertension.

Grade 1: silver wiring.

Grade 2: silver wiring and arteriovenous nipping.

B. Malignant Hypertension.

Grade 3: flame haemorrhages, hard exudates and cotton wool spots.

Grade 4: as grade 3, plus papilloedema.

Investigations

Routine investigations should include urinalysis, serum urea and electrolytes, cholesterol, glucose and full blood count. These are chosen for their ability to detect many of the secondary causes of hypertension and important cardiovascular risk factors.

The ECG may:

- demonstrate left ventricular hypertrophy, and / or strain.
- indicate underlying ischaemic heart disease.
- provide a baseline for monitoring the effectiveness of treatment.

Chest X-ray is only useful when there is a specific indication such as breathlessness.[7]

In complex or severe cases, renal ultrasound, echocardiography, serum hormone levels, urine catecholamines, renal angiography and immunological titres may be helpful in reaching a diagnosis.

Treatment

Targets for Treatment

- The target for treatment is a blood pressure of 140/85 mmHg or less.
- Diabetics and those with established cardiovascular disease need tight blood pressure control. In these cases, the target is 140/80 mmHg.^[11]

Non-Drug Treatment

Patients who stop smoking, reduce their alcohol and salt intake, and take regular exercise along with losing or reducing excess body weight are likely to achieve a useful reduction in blood pressure.

They will also improve their risk factors for cardiovascular disease.[7]

Thresholds for Drug Treatment

- The current NICE guidelines recommend treatment if there is a persistent rise in blood pressure to 160/100 mmHg or more.
- Where there is raised cardiovascular risk, existing cardiovascular disease or target organ damage treatment should be commenced at the lower level of 140/90 mmHg.
- Any reading of systolic hypertension (>160 mm Hg), in the absence of diastolic hypertension, should trigger treatment.
- In all cases the target is to maintain blood pressure at or below 140/85 mmHg. [12]

Drug Treatment

Most patients require lifelong treatment with a combination of antihypertensive drugs. As hypertension is usually asymptomatic, and most of the drugs have side effects, compliance with treatment is often sub-optimal.

With the publication of some large clinical outcome trials between July 2004 and December 2005, the National Institute for Health and Clinical Excellence (NICE) in collaboration with the British Hypertension Society (BHS) had a major review of the evidence and produced their recommendations for treatment options. They have drawn up recommendations and a treatment algorithm covering age, ethnicity and drug classes.

These are reproduced in Appendix B.

Diuretics

The thiazide diuretics have long term clinical trial evidence to confirm their effectiveness, are cheap, well tolerated, and can be taken once daily. Their effectiveness can be enhanced with the addition of an ACE inhibitor (see below).

Bendrofluazide is the most widely prescribed thiazide in the UK.

Other diuretics such as spironolactone or amiloride may be used as alternatives or additively but require additional monitoring of renal function and electrolytes.

Beta-Blockers

The beta-blockers inhibit the effect of catecholamines at beta-adrenoreceptors. Members of the class show differing affinities for beta₁ (mainly cardiac, 'cardioselective') and beta₂ (mainly vascular and bronchial) receptors. They are no longer a preferred initial therapy for hypertension alone and current recommendations are for their introduction if a combination of three other drugs has not achieved control.

The exception to this being in younger people with intolerance or contraindications to ACE inhibitors and angiotensin II receptor antagonists and in women with child-bearing potential.

Their main effect is to reduce sympathomimete activity thereby slowing the pulse and reducing the force of cardiac contractions. They are particularly suitable for the treatment of hypertensive patients who have concomitant symptomatic angina or a previous myocardial infarct.

Atenolol is the most widely prescribed beta-blocker in the UK.

Side effects of beta blockers include cold extremities and lethargy. They are contraindicated in subjects with reversible obstructive airways disease and in those with 2^{nd} or 3rd degree heart block.

Calcium Channel Blockers

These drugs inhibit the movement of calcium ions across cell membranes, and hence reduce intracellular calcium levels. In turn, this inhibits vascular smooth muscle contraction to produce vasodilatation, inhibits cardiac muscle contraction to reduce cardiac workload, and inhibits cardiac conducting tissues to slow the pulse.

 The dihydropyridine calcium channel blockers such as nifedipine and amlodipine are powerful vasodilators, but have little effect on the cardiac tissues.

- Verapamil has a strong effect on the atrioventricular node, giving it useful antiarrhythmic properties. (Verapamil and beta-blockers must not be prescribed together: they may induce heart block.)
- Diltiazem affects cardiac tissue to reduce heart rate and contractility, and vascular smooth muscle to cause vasodilatation.

The calcium channel blockers have been shown to be effective in several long-term studies.[13][14][15]

Side effects can be troublesome. They include ankle oedema, flushing, constipation and headache.

Angiotensin Converting Enzyme (ACE) Inhibitors.

The ACE inhibitors lower the blood pressure by blocking the conversion of angiotensin I to angiotensin II.

They are particularly appropriate for diabetics as they have a renal protective effect.

Ramipril reduces the rates of cardiovascular deaths and events, in addition to its effect on blood pressure. [16] Debate remains as to whether this is a class effect, however it appears that the dose at which Ramipril produces this effect is more acceptable than the dose which may be required with alternative preparations.

In December 2004, ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) was stopped early by the study's steering committee due to significant benefits observed in the amlodipine (calcium antagonist) plus perindopril (ACE inhibitor) arm of the study compared to the atenolol (beta blocker) plus bendroflumethiazide (diuretic) arm.

There is increasing evidence that in most circumstances ACE inhibitors have advantages over a beta blocker, diuretic combination.

ACE inhibitors also affect the metabolism of bradykinin. This causes a cough in about 15% of patients. It is a class effect and necessitates a change to a different class of drug rather than an alternative ACE inhibitor.

ACE inhibitors can impair renal function especially in patients with bilateral renal artery stenosis or pre-existing renal vascular disease, so this should be monitored regularly.

ACE inhibitors are contraindicated in pregnancy as they may adversely affect fetal and neonatal blood pressure control and renal function.

Angiotensin II receptor antagonists (angiotensin receptor blockers ARB)

This relatively new class of drugs blocks the angiotensin II type I receptors, which is a later stage than the ACE inhibitors. Thus, they have all the beneficial effects of the ACE inhibitors. [17] but do not induce the 'ACE inhibitor cough' side effect.

They are now considered a useful alternative where ACE inhibitors are not tolerated. ARBs are contraindicated in pregnancy for the same reasons as ACE inhibitors

Alpha-Blockers

The alpha₁-adrenoreceptor blockers inhibit the effects of noradrenaline at alpha₁ receptors in arteries and veins. This allows vasodilatation and a fall in blood pressure. Examples include doxazosin and terazosin. These drugs are often used as the third agent when a combination of two drugs has failed to control blood pressure. They may be particularly appropriate for men who also suffer symptoms of prostatism. Their main side effect is postural hypotension. Like beta-blockers their role is when the addition of a fourth line of therapy is required.

Aspirin

In therapeutic doses aspirin by itself is not a hypotensive agent. However, trials have shown that aspirin can reduce cardiovascular events in hypertensive patients, although it is associated with an increased number of gastro-intestinal and cerebral haemorrhages.[18] Aspirin is recommended for the primary prevention of cardiovascular disease in patients over 50 years old who have well controlled hypertension (<150/90 mmHg).^[6]

Treatment Considerations

Only 25% of hypertensive patients will achieve the current targets for blood pressure reduction with a single drug. [19] Most patients will require double or triple therapy. Because side effects are dose related, it is generally better to add a second drug, rather than increase the dose of a single agent to its maximum.

Poor control of blood pressure despite a triple combination of antihypertensive drugs is one of the indications for referral to a specialist clinic.

Other indications might include a suspected secondary cause, difficulties with tolerability of treatment, highly variable blood pressure, and the development of endorgan damage.

Some patients are symptomatic at time of diagnosis, or subsequently develop symptoms. The nature of these features may influence the choice of therapy. Subjects with angina may benefit from a beta blocker and/or a calcium channel antagonist.

Those with a significant reduction in cardiac output are best treated with a diuretic and either an ACE inhibitor or an ARB.

Prognosis

With untreated malignant hypertension, 88% of patients are dead after two years. [20]

Trials have shown that effective control of hypertension can reduce the incidence of stroke by 40% and heart attacks by 16%.[20][21]

Hypertension is one member in a group of important risk factors. Hypertension, hyperlipidaemia, diabetes and smoking synergistically increase the risk of cardiovascular disease.[22]

For example, in the case of a 50 year-old male smoker, each of these interventions could reduce his 10-year risk of heart attack from 30% to 20%:

- A 20 mmHg reduction of his systolic blood pressure.
- Stopping smoking.
- A 2 mmol/l reduction of his cholesterol.

Together, all three would halve his risk of heart attack to 15%.

Main Disabling Effects

The majority of hypertensives are asymptomatic.

They do not have a functional disability.

Assessing the claimant

Assessment should be made using all the information available. This includes information from the claimant's file, informal observations, medical history, 'Typical Day', and examination.

The Medical History

 A key point to obtain from the history is whether the claimant is under the care of a Consultant.

The vast majority of hypertension cases will be under the care of their General Practitioner. Referral to a Consultant suggests that the hypertension is difficult to control, a secondary cause of hypertension is suspected or that the claimant is intolerant of standard treatments. This information indicates something about the current severity of the condition and the likelihood of disabling side effects.

Many hypertensive subjects will have some side effects from their treatment.
 (Some common side effects are tabulated in *Appendix C*.) However, these will usually be of nuisance value – without causing functional disability.

Interpreting the Blood Pressure

A blood pressure measurement taken in the course of a disability examination is likely to be adversely affected by the circumstances. The measurement would not be useful for the formal diagnosis or assessment of hypertension, but it will provide some guidance as to the general level of the claimant's blood pressure. It is important that all the available information about the claimant's medical history, treatment, and the examination findings are used together to build up a picture of their condition.

Unexpected or Severe Hypertension

Unexpected or severe hypertension in a claimant unaware that they have hypertension must be addressed.

They should be advised to consult their GP within the next week so that their blood pressure can be monitored in a less stressful situation.

It is important to seek the claimant's informed consent to notify their GP, and complete an Unexpected Finding (UE1 (Rev)) form.[6]

Possible consequences of Uncontrolled Hypertension

Uncontrolled hypertension may lead to: heart attack, heart failure, stroke, multiinfarct dementia, peripheral vascular disease, renal failure and retinopathy, and thus may be associated with poor effort tolerance, immobility, visual loss and loss of independence.

The functional disability will be that of the secondary condition. (Details of expected disability are described in the protocols specific to the conditions, 'Ischaemic Heart Disease', 'Heart Failure' and 'Peripheral Vascular Disease'.)

In these cases, hypertension is not the most important condition to address. The focus of the assessment should be directed at the condition that is directly causing disability.

The IB-PCA assessment - use of a Non-Functional Descriptor(NFD)

Considering in the IB-PCA assessment the use of a Non-Functional Descriptor (NFD) the appropriate choice would be

• "A severe life-threatening disease, which is uncontrolled or uncontrollable by a recognised therapeutic procedure."

This NFD would be appropriate for hypertensive claimants whose blood pressure is at a level posing severe risk of causing end organ damage and remains poorly controlled despite evidence of compliance with maximum therapy or who are under the care of a hospital hypertension clinic.

There should be medical evidence on file to support this.

A claimant recently referred to a hospital hypertension clinic might be expected to have their blood pressure controlled within 6 to 12 months, so it would be appropriate to apply the NFD for this period.

However, a claimant whose blood pressure remains poorly controlled despite long-term attendance at a hospital hypertension clinic is unlikely to make rapid progress, and it would be appropriate to recommend the NFD for a longer period.

Psychological Effects

When a person is told that their blood pressure is high and they are at risk of cardiovascular complications, psychological problems may result. Emotions such as anxiety or denial may affect their ability to process, remember, or act upon the information they are given. This may hinder compliance with lifestyle advice and drug treatment.

Following a diagnosis of hypertension, some patients enter a heightened state of self-surveillance where they become aware of, and frightened by, normal physiological sensations.

'Dizziness', 'Headache' and 'Nose Bleed' are common symptoms that patients often associate with high blood pressure, although it has been shown that they are equally prevalent in moderately hypertensive and healthy populations.[7][9] Patients who have been told that they are hypertensive have a much higher incidence of headache than hypertensive patients who are unaware of their condition.[9]

In some studies, labelling a person as hypertensive has led to increased absenteeism from work.[9]

Indeed, a small number of hypertensive claimants may adopt an Illness behaviour or biopsychosocial pattern of disability.

Appendix A - Recommended Technique for Measuring Blood Pressure^[7]

- Use equipment that is well maintained and functions correctly. In examination centres, report worn-out or defective equipment to the MEA so that it can be replaced.
- The claimant should be comfortably seated.
- Record which arm is used for the measurement.
- (The blood pressure may differ and vary when measured in each arm.)
- The arm should be supported horizontally at the level of the heart (midsternum.)
- Use an appropriately sized cuff for the circumference of the arm. The bladder length should be at least 80% of the circumference of the arm: [23]

Person	Maximum Arm Circumference	Ideal Cuff Size
Small Child	17cm	4cm x 13cm
Children & Thin Adults	26cm	10cm x 18cm
Most Adults	33cm	12cm x 26cm
Large Adults	50cm	12cm x 40cm

- Place the manometer so that the scale can be easily read, and the mercury meniscus is close to eye level.
- Place the cuff so that the lower edge is 2-3 cm above the brachial artery pulsation. The bladder should lie over the brachial artery. The rubber tubes leading from the bladder <u>should exit proximally</u> so that the antecubital fossa is easily accessible. (NB It was traditional to have the tubes exiting distally. The recommendation has changed).
- Palpate the brachial artery and inflate the cuff to about 30 mmHg above the point where the pulse disappears. Then place the diaphragm of the stethoscope over the brachial artery, and slowly deflate the cuff by 2-3 mmHg per pulse beat.

Listen for the Korotkov sounds (Korotkov Phase Description)

Recommended Technique for Measuring Blood Pressure continued

Korotkov Phase	Description	Clinical Significance
Phase I	First appearance of tapping sounds.	Systolic Pressure.
Phase II	Brief period of softer swishing sounds	None
Phase III	Return of sharper sounds	None
Phase IV	Distinct muffling of sounds	Diastolic pressure *
Phase V	Disappearance of sounds	Diastolic Pressure

^{*}Phase IV is used only where phase V does not occur for example with hyperdynamic circulation in pregnancy

- Measure the blood pressure to the nearest 2 mmHg.
- When the sounds have disappeared, rapidly deflate the cuff.
- Record the blood pressure immediately, so that it is not forgotten.

Appendix B - The updated recommendation in the guidelines

The updated recommendations in the guidelines include the following:

 In hypertensive patients aged 55 and over, or Black patients* of any age, first choice of initial therapy should be either a calcium channel blocker or a thiazide-type diuretic.

- In hypertensive patients younger than 55, first choice initial therapy should be an ACE inhibitor (or an Angiotensin receptor blocker if an ACE inhibitor is not tolerated).
- If initial therapy was with a calcium channel blocker or thiazide-type diuretic and a second drug is required, add an ACE inhibitor (or an Angiotensin receptor blocker if an ACE inhibitor is not tolerated). If initial therapy was with an ACE inhibitor, add a calcium channel blocker or a thiazide-type diuretic.
- If treatment with three drugs is required, the combination of ACE inhibitor (or an Angiotensin receptor blocker if an ACE inhibitor is not tolerated), calcium channel blocker and thiazide-type diuretic should be used.

The decision not to recommend Beta-blockers for first line therapy is based on evidence that suggests that they perform less well than other drugs, particularly in the elderly, and the side effects associated with their use including increasing evidence that the most frequently used Beta-blockers at usual doses carry an unacceptable risk of provoking type 2 diabetes. The guidelines also make recommendations beyond a 3-drug combination, where, although the evidence is less certain, the Guideline Development Group took into account existing guidelines and constructed recommendations most compatible with current good practice.

^{*}Black patients are those of African or Caribbean descent, and not mixed race, Asian or Chinese patients

Appendix C - Common and Important Side Effects of Antihypertensive Drugs^[7]

Class of Drug	Side Effects
Alpha-Blockers	Postural Hypotension Stress incontinence
ACE Inhibitors	Cough
Beta-Blockers	Dyspnoea Lethargy Impotence Cold Peripheries
Calcium Channel Blockers	Headache Flushing
Thiazide Diuretics	Gout Impaired glucose tolerence

References

- 1. Hawthorne VM, Greaves DA, Beevers DG. Blood pressure in a Scottish town. *BMJ* 1974;**3**:600-3.
- Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. [Review] [77 refs]. Archives of Internal Medicine 1993; 153:598-615.
- He J, Whelton PK. Elevated systolic blood pressure as a risk factor for cardiovascular and renal disease. *Journal of Hypertension - Supplement* 1999; 17:S7-13.
- MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J 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. [see comments]. Lancet 1990; 335:765-74.
- Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. [see comments]. Lancet 1998; 351:1755-62.
- NICE clinical guideline 34 Hypertension: management of hypertension in adults in primary care (partial update of NICE clinical guideline 18) Published by the National Institute for Health and Clinical Excellence: June 2006
- 7. Beevers G, et al. ABC of Hypertension, fourth edition. BMJ Books, 2002.
- 8. The Oxford Textbook of Medicine on CD-ROM. Oxford University Press, 1996.
- 9. Baer DJ. Adult consequences of fetal growth restriction. Clin Obstet Gynecol. 2006; 49(2):270 283
- Basile JN, Lackland DT, Basile JM, Riehle JE, et al. A Statewide Primary Care Approach to Cardiovascular Risk Factor Control in High – Risk Diabetic and Nondiabetic Patients with Hypertension. Journal of Clinical Hypertension
- Thomas G. Pickering, John E. Hall, Lawrence J. Appel, Bonita E. et al Recommendations for Blood Pressure Measurement in Humans: An AHA Scientific Statement from the Council on High Blood Pressure Research Professional and Public Education Subcommittee J. lin. Hypertension 2005; 7(2): 102 - 109
- 12. NICE clinical guideline 18 Hypertension: management of hypertension in adults in primary care. Published by the National Institute for Health and Clinical Excellence: 2004
- Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. [see comments]. Lancet 2000; 356:359-65.

- 14. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). [see comments]. [erratum appears in Lancet 2000 Aug 5;356(9228):514]. Lancet 2000; 356:366-72.
- Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. [see comments]. Lancet 1997; 350:757-64.
- 16. Warner GT, Perry CM. Spotlight on Ramipril in the prevention of cardiovascular outcomes Am. J. Cardiovasc Drugs. 2003; 3(2);113 116
- 17. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I *et al.* Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). [see comments]. *Lancet* 1997; **349**:747-52.
- Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. [see comments]. Lancet 1998; 351:1755-62.
- 19. Beevers DG, et al. Hypertension in practice. Third edition. London: Martin Dunitz, 1999.
- 20. He J, Whelton PK. Elevated systolic blood pressure as a risk factor for cardiovascular and renal disease. *Journal of Hypertension Supplement* 1999; **17**:S7-13.
- Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. [see comments]. [Review] [84 refs]. Lancet 1990; 335:827-38.
- 22. Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. *Heart* 1998; **80 Suppl 2**:S1-29.
- 23. O'Brien E, Petrie J, LW, et al. Blood pressure measurement: recommendations of the British Hypertension Society. London: BMJ Books, 1997.