Evidence-based Clinical Practice Guideline

Essential hypertension:
managing adult patients in primary care

June 2006: The recommendations on prescribing have been updated, and sections of this document marked with a grey tint have been superseded. For details of the new recommendations on prescribing, see www.nice.org.uk/CG034

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⌘ Summary

Overview

This national guideline provides recommendations and supporting evidence for the care of patients with persistent raised blood pressure but no obvious underlying disease (essential hypertension). The guideline recognises that successfully reducing blood pressure, and (more broadly) cardiovascular risk, involves a partnership and good communication between patients and healthcare professionals. Its objective is to decrease subsequent cardiovascular morbidity and mortality due to stroke and coronary heart disease.

Guidance is provided on: establishing when a patient has persistent raised blood pressure; using cardiovascular risk assessments; providing lifestyle advice; managing the use of blood pressure lowering drugs; addressing adherence; and stopping treatment. The guideline has been developed for use by the National Health Service in England and Wales. NHS healthcare professionals, patient representatives and researchers developed this guideline, incorporating comments received from referees and from an extensive national stakeholder consultation.

Using a threshold of 140/90 mmHg, about 40% of the adult population have raised blood pressure although the proportion increases with age. In 2001, the NHS funded 90 million prescriptions for drugs that lower blood pressure at a cost of £840 million - nearly 15% of the total annual cost of all primary care drugs. This accepted, hypertension may often be inadequately treated and is a contributory factor in cardiovascular diseases which account for 30% of all deaths, and 4 million bed days annually: 8% of the total capacity of the NHS. A guideline on hypertension may thus be expected to impact on the healthcare received by a substantial proportion of the population and have major resource implications for the NHS.

This guideline emphasises the need for standardised measurement to establish the presence of persistent raised blood pressure (hypertension) in patients. Formal cardiovascular risk assessment is important for patients with hypertension who have not yet developed cardiovascular disease; it may identify underlying causes and important modifiable risk factors; it provides prognostic information; and it provides the clinician and patient with a context to discuss the value of blood pressure lowering drugs alongside other treatments for raised cardiovascular risk. In the long term a guideline integrating all aspects of cardiovascular protection is needed, including, for example, treatments for raised serum cholesterol and use of antiplatelet therapy.

Lifestyle advice should be an initial and periodically revisited aspect of care for patients with hypertension. This advice includes smoking cessation, healthy eating, restricting sodium salt intake, regular exercise, and avoiding excessive amounts of caffeine or alcohol. At the outset, patients may

achieve worthwhile changes in lifestyle which can remove or delay the need to use drugs. In certain patients treated for some time, lifestyle changes may help to reduce or stop drug therapy.

In most hypertensive patients, pharmacological intervention becomes necessary if blood pressure lowering is to be substantial and sustainable. Available evidence demonstrates firmly that a sustained reduction in blood pressure by drugs reduces the incidence of stroke, coronary heart disease and overall mortality. Trials indicate that drug therapy should be offered to patients with persistently raised blood pressure of 160/100 mmHg or more, or patients with blood pressure of 140/90 mmHg or more with either a raised risk of cardiovascular disease risk or target organ damage. Modelling the disease and the costs and consequences of treatment over the lifetime of patients suggests that this is a cost-effective use of NHS resources.

The guideline development group have had to interpret new evidence that indicates the use of a combination of older drugs (thiazide-type diuretics and beta-blockers) may lead to a small increased risk of new onset type-II diabetes. The unanimous consensus of the group was that it would be judicious to restrict the use of this combination of drugs when beginning treatment in patients at raised risk of developing diabetes, although the combination may become necessary if hypertension progresses or cardiovascular disease develops. As further evidence becomes available this position should be reviewed.

Using this guideline

This document is intended to be relevant to the primary care team, including general practitioners, practice nurses and other primary health care professionals who have direct contact with patients. It does not consider the hospital setting but provides criteria for referral to secondary care. To promote continuity of care, it is important that clinicians initiating treatment in secondary care are aware of the recommendations of this guideline. Inevitably, parts of this document are technical but we have tried as much as possible to make this document accessible to patients, carers of patients and the public.

The Summary (pages 1-17) can be used as a standalone document by those wanting to access the recommendations, supporting evidence and management charts. A table of contents for the full guideline is found on page 18. A description of the methods used to develop the guideline is found on page 25. The evidence review used in the guideline development process begins on page 40.

This full version of the guideline is available to download free-of-charge from the National Electronic Library for Health website (http://www.nelh.nhs.uk/). A printed copy of this document can be purchased from the Centre for Health Services Research, University of Newcastle. The Institute makes available three summary versions developed from this document on its website (http://www.nice.org.uk/): a patient version, a healthcare professional version and a quick reference guide.

Using recommendations and supporting evidence

The guideline development group have worked to understand and reflect the overall benefits, tolerability, harms, costs, feasibility and fairness of alternative patterns of care, as the evidence allows. However, healthcare professionals need to apply their general medical knowledge and clinical judgement when applying recommendations which may not be appropriate in all circumstances. Decisions to adopt any particular recommendation are made in the light of individual patients' views and circumstances as well as available resources. To enable patients to participate in the process of decision making to the extent that they are able and willing, clinicians need to be able to communicate information provided in this guideline. To this end, recommendations are often supported by evidence statements which provide summary information to help clinicians and patients discuss care options. Recommendations about drug treatment assume that clinicians will take account both of the response of individual patients and of the indications, contra-indications and cautions listed in the British National Formulary (BNF) or Summary of Product Characteristics (see www.medicines.org.uk).

Grading recommendations and evidence

There is a belief among the community of guideline developers that the way recommendations and evidence statements are graded needs to be improved. Consequently a new grading system has been evaluated and applied when developing this guideline.

Guideline Recommendation and Evidence Grading (GREG)	
Evidence Grade	**Interpretation of evidence**
I High	The described effect is plausible, precisely quantified and not vulnerable to bias.
II Intermediate	The described effect is plausible but is not quantified precisely or may be vulnerable to bias.
III Low	Concerns about plausibility or vulnerability to bias severely limit the value of the effect being described and quantified.
Recommendation Grade	**Interpretation of recommendation**
A Recommendation	There is robust evidence to recommend a pattern of care.
B Provisional Recommendation	On balance of evidence, a pattern of care is recommended with caution.
C Consensus Opinion	Evidence being inadequate, a pattern of care is recommended by consensus.

This new system grades evidence from 'I' (high) to 'III' (low) for each type of study (evaluation of treatment, diagnosis or prognosis) according to a series of quality criteria. It also provides a flexible framework for assessing studies that address the process of care (such as patient surveys) and economic analyses. Research provides robust evidence when it has been conducted to exclude bias, to include suitable populations in adequate numbers, and to measure suitable outcomes. Recommendations reflect the evidence, importance and feasibility of defined steps in the provision of healthcare. Grade A recommendations indicate a clear basis and conditions for providing (or not providing) a pattern of care. Grade B means there are important uncertainties that need more careful consideration. Grade C means that key information is unavailable but that the guideline group has reached a consensus recommendation based on its shared understanding of the issue. Full details of grading scheme are found on page 33.

Recommendation overview

- **Manage patients with existing coronary heart disease in line with current national guidance. Subsequently, patients with continuing hypertension should be offered lifestyle and pharmacological interventions in accordance with this guideline.**

  See: Prophylaxis for patients who have experienced a myocardial infarction: drug treatment, cardiac rehabilitation and dietary manipulation. NICE Inherited Guideline A, April 2001. http://www.nice.org.uk/

- **Manage patients with diabetes in line with current national guidance.**

  See: Management of Type 2 Diabetes - management of blood pressure and blood lipids. NICE Inherited Guideline H, October 2002. http://www.nice.org.uk/

- **Ask patients with a single raised blood pressure reading of more than 140/90 mmHg* to return for a minimum of two subsequent clinics where their blood pressure can be measured using the best conditions available.**

  See: Measuring blood pressure on page 9.

  * *Blood pressure is recorded as systolic/diastolic blood pressure measured in millimetres of mercury (mmHg). Raised blood pressure is noted when either systolic blood pressure exceeds 140 mmHg or diastolic blood pressure exceeds 90 mmHg.*

- **Offer lifestyle advice initially and then periodically to patients undergoing assessment or treatment for hypertension.**

  See: Lifestyle interventions on page 11.

- **Ask to conduct a formal cardiovascular risk assessment of patients with hypertension (persistent raised blood pressure more than 140/90 mmHg).**

  See: Estimating cardiovascular risk on page 13.

- **Consider the appropriate use of lipid-lowering and antiplatelet therapy alongside the use of antihypertensive therapy in patients at raised cardiovascular risk.**

- **Offer drug therapy beginning with a low-dose thiazide-type diuretic to (i) patients with persistent high blood pressure of 160/100 mmHg or more and (ii) patients at raised cardiovascular risk (ten year risk of CHD≥15% or CVD≥20% or existing cardiovascular disease or target organ damage) with persistent blood pressure of more than 140/90 mmHg.**

  See: Pharmacological interventions on page 15.

- **Consider the need for specialist investigation of patients with unusual signs and symptoms, where a secondary cause of hypertension is suspected, or in patients whose hypertension is resistant to drug treatment.**

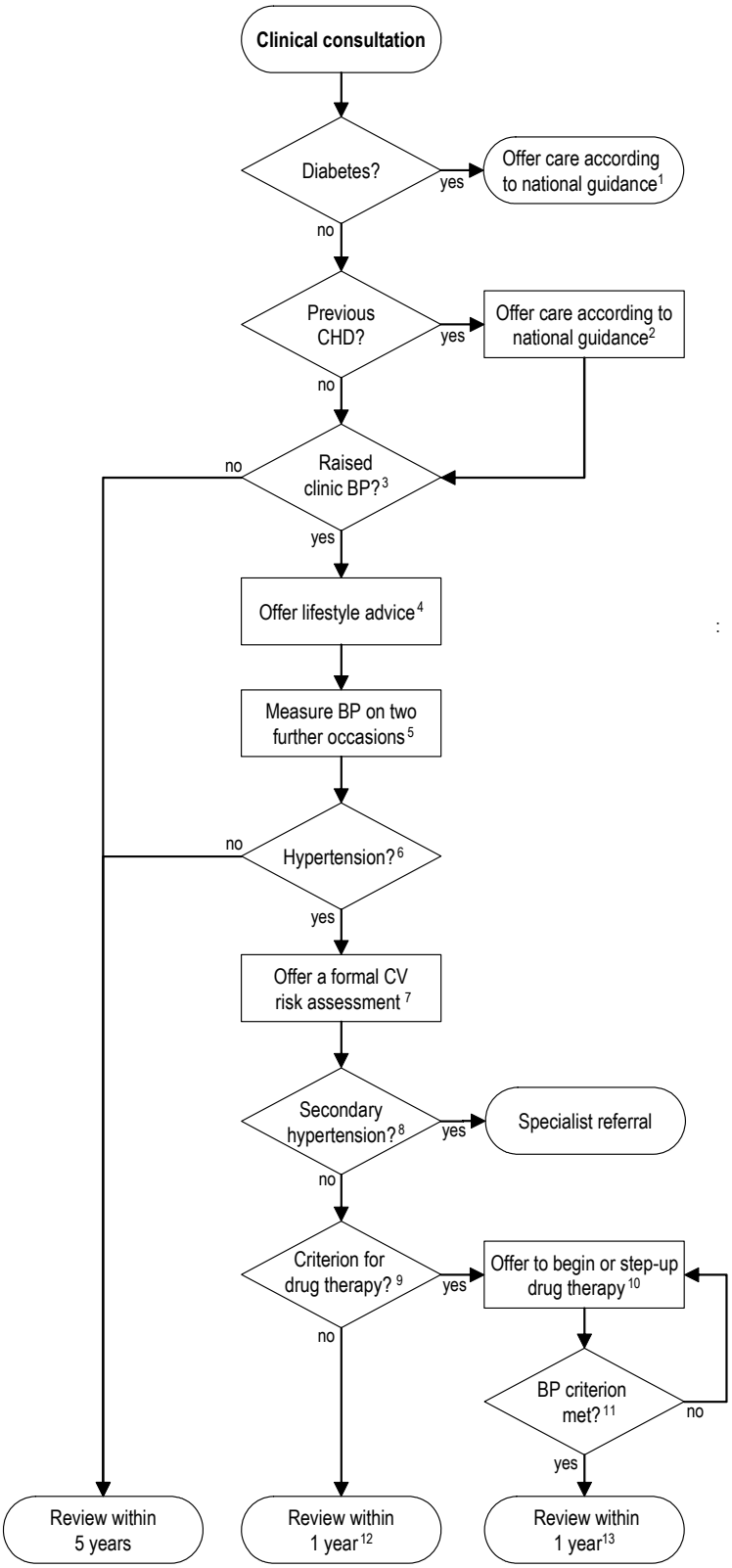
  See: Measuring blood pressure on page 9 and Pharmacological interventions on page 15 .

- **Once blood pressure is managed adequately, provide an annual review of care to monitor blood pressure, provide support and discuss lifestyle, symptoms and medication. More frequent review may be necessary in some patients.**

  See: Continuing treatment on page 17.

- **See also the management flowchart, overleaf**

*Management flowchart for raised blood pressure**



1 See the NICE Guideline 'Management of Type 2 Diabetes - management of blood pressure and blood lipids'.

2 See the NICE Guideline 'Prophylaxis for patients who have experienced a myocardial infarction: drug treatment, cardiac rehabilitation and dietary manipulation.'

3 Raised BP>140/90 mmHg. Take a second confirmatory reading at the end of the consultation. Take a standing reading in patients with symptoms of postural hypotension.

4 Explain the potential consequences of raised BP. Promote healthy diet, regular exercise and smoking cessation.

5 Ask the patient to return for at least two subsequent clinics at monthly intervals, assessing blood pressure under the best conditions available.

6 Hypertension: persistent raised BP>140/90 mmHg at the last two visits.

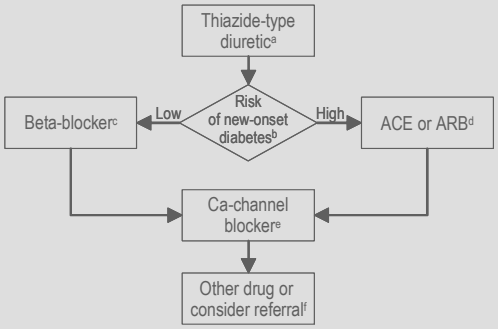
7 CV risk assessment may identify other modifiable risk factors and help explain the value of BP lowering and other treatment. Risk charts and calculators are less valid in patients with CVD or on treatment.

8 Refer patients with signs and symptoms of secondary hypertension to a specialist. Refer patients with malignant hypertension or suspected pheochromocytoma for immediate investigation.

9 Offer treatment for: (A) BP≥160/100 mmHg; or, (B) BP>140/90 mmHg and (10 year CHD risk≥15%, CVD risk≥20% or existing CVD or TOD).

Consider other treatments for raised cardiovascular risk including lipid lowering and antiplatelet therapies.

10 As needed, add drugs in the following order:*



* If a drug is not tolerated discontinue and proceed to the next line of therapy. If a drug is tolerated but target BP is not achieved add the next line of therapy. Drug cautions and contraindications are listed fully in the British National Formulary.

a In young patients (under 55) whose BP may be managed on monotherapy, consider starting with a beta-blocker.

b Patients at high risk have a strong family history of type II diabetes, have impaired glucose tolerance (FPG≥6.5mmol/l), are clinically obese (BMI≥30) or are of South-Asian or African-Caribbean ethnic origin.

c Beta-blocker contraindications include asthma, COPD and heart block.

d Offer an angiotensin receptor blocker (ARB) if an ACE inhibitor (ACE) is not tolerated because of cough. Contraindications include known or suspected renovascular disease and pregnancy.

e Only dihydropyridine calcium-channel blockers should be prescribed with a beta-blocker. Contraindications include heart failure.

f Consider offering a beta-blocker or ACE (if not yet used), another drug, or specialist referral. A beta-blocker and thiazide-type diuretic combination may become necessary in patients at high risk of developing diabetes if hypertension or cardiovascular disease progresses.

11 BP≤140/90 mmHg or further treatment is inappropriate or declined.

12 Check BP, reassess CV risk and discuss lifestyle.

13 Review patient care: medication, symptoms and lifestyle.

BP Blood pressure, systolic/diastolic
(BP>140/90 means either or both systolic and diastolic exceed threshold)
CHD Coronary heart disease
CVD Cardiovascular disease
TOD Target organ damage
<, > Less than, more than
≤, ≥ Less than or equal to, more than or equal to

* Flowcharts cannot capture all of the complexities affecting the clinical care of individuals. This flowchart is designed to help communicate the key steps, but is not intended for rigid use or as a protocol. Guidance on drug sequencing can provide a useful starting point but antihypertensive drug therapy will need adapting to individual patient response and experience.

Measuring blood pressure

• **Health care professionals taking blood pressure measurements need adequate initial training and periodic review of their performance.**	**C**
• **Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions.**	**C**
• **Where possible standardise the environment when measuring blood pressure: provide a relaxed, temperate setting, with the patient quiet and seated and with their arm outstretched and supported.[+]** + *See box overleaf: Estimating blood pressure by auscultation.*	**C**
• **If the first measurement exceeds 140/90 mmHg*, if practical, take a second confirmatory reading at the end of the consultation.** * *Blood pressure is recorded as systolic/diastolic blood pressure measured in millimetres of mercury (mmHg). Raised blood pressure is noted when either systolic blood pressure exceeds 140 mmHg or diastolic blood pressure exceeds 90 mmHg.*	**C**
• **Measure blood pressure on both of the patient's arms with the higher value identifying the reference arm for future measurement.**	**C**
• **In patients with symptoms of postural hypotension (falls or postural dizziness) measure blood pressure while standing. In patients with symptoms or documented postural hypotension (fall in systolic BP when standing of 20mmHg or more) consider referral to a specialist.**	**C**
• **Refer immediately patients with accelerated (malignant) hypertension (BP more than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage) or suspected pheochromocytoma (possible signs include labile or postural hypotension, headache, palpitations, pallor and diaphoresis).**	**C**
• **To identify hypertension (persistent raised blood pressure above 140/90 mmHg), ask the patient to return for at least two subsequent clinics where blood pressure is assessed from two readings under the best conditions available.**	**C**
• **Measurements should normally be made at monthly intervals. However patients with more severe hypertension should be re-evaluated more urgently.**	**C**

Measuring blood pressure (continued)

• **The value of routinely using automated ambulatory blood pressure monitoring or home monitoring devices as part of primary care has not been established: their appropriate use in primary care remains an issue for further research.**	**B**
- Readings from clinic and ambulatory blood pressure devices, when used side-by-side, may differ from one another and from true arterial pressure because they use different methods and assumptions.	II
- Average ambulatory readings from a series of patients, taken over 24 hours, are commonly lower than clinic readings by between 10/5 and 20/10 mmHg. However, an individual patient may have ambulatory readings higher or lower than clinic readings. Studies comparing clinic and ambulatory measurement vary in their design, setting, conduct of measurement and analysis: estimated differences between ambulatory and clinic values vary with these factors.	II
- Clinic and ambulatory readings may also differ due to a 'white coat' effect, a response to the setting or clinician.	II
- Epidemiological studies are inconsistent in demonstrating the additional prognostic value of ambulatory blood pressure monitoring to predict cardiovascular disease in unselected patients.	II
• **Consider the need for specialist investigation of patients with unusual signs and symptoms, or of those whose management depends critically on the accurate estimation of their blood pressure.**	**C**
• **To see the review of evidence go to 51.**	

Estimating blood pressure by auscultation

- Standardise the environment as much as possible:
  - Relaxed, temperate setting, with the patient seated
  - Arm out-stretched, in line with mid-sternum and supported
- Correctly wrap a cuff containing an appropriately sized bladder around the upper arm and connect to a manometer. Cuffs should be marked to indicate the range of permissible arm circumferences; these marks should be easily seen when the cuff is being applied to an arm.
- Palpate the brachial pulse in the antecubital fossa of that arm.
- Rapidly inflate the cuff to 20 mmHg above the point where the brachial pulse disappears.
- Deflate the cuff and note the pressure at which the pulse reappears: the approximate systolic pressure.
- Re-inflate the cuff to 20 mmHg above the point at which the brachial pulse disappears.
- Using one hand, place the stethoscope over the brachial artery ensuring complete skin contact with no clothing in between.
- Slowly deflate the cuff at 2-3 mmHg per second listening for the Korotkoff sounds.

Phase I:	The first appearance of faint repetitive clear tapping sounds gradually increasing in intensity and lasting for at least two consecutive beats: note the systolic pressure.
Phase II:	A brief period may follow when the sounds soften and or 'swish'.
Auscultatory Gap:	In some patients the sounds may disappear altogether.
Phase III:	The return of sharper sounds becoming crisper for a short time.
Phase IV:	The distinct, abrupt muffling of sounds, becoming soft and blowing in quality.
Phase V:	The point at which all sounds disappear completely: note the diastolic pressure.

- When the sounds have disappeared, quickly deflate the cuff completely if repeating the measurement.
- When possible, take readings at the beginning and end of consultations.

Lifestyle interventions

• **Ascertain patients' diet and exercise patterns as a healthy diet and regular exercise can reduce blood pressure. Offer appropriate guidance and written or audiovisual materials to promote lifestyle changes.**	**B**
- Education about lifestyle on its own is unlikely to be effective.	II
- Healthy, low calorie diets had a modest effect on blood pressure in overweight individuals with raised blood pressure, reducing systolic and diastolic blood pressure on average by about 5 to 6 mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 40% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Taking aerobic exercise (brisk walking, jogging or cycling) for 30-60 minutes, 3 to 5 times each week, had a small effect on blood pressure reducing systolic and diastolic blood pressure on average by about 2 to 3mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 30% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg or more in the short term, up to 1 year.	II
- Interventions actively combining exercise and diet were shown to reduce both systolic and diastolic blood pressure by about 4 to 5 mmHg in trials. About one quarter of patients receiving multiple lifestyle interventions were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- A healthier lifestyle, by lowering blood pressure and cardiovascular risk, may reduce, delay or remove the need for long term drug therapy in some patients.	III
• **Relaxation therapies* can reduce blood pressure and individual patients may wish to pursue these as part of their treatment. However routine provision by primary care teams is not currently recommended.**	**B**
* *Examples include: stress management, meditation, cognitive therapies, muscle relaxation and biofeedback.*	
- Overall, structured interventions to reduce stress and promote relaxation had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3 to 4 mmHg in trials. There is variation in the reduction in blood pressure achieved in trials and it is unclear why. About one third of patients receiving relaxation therapies were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- The current cost and feasibility of providing these interventions in primary care has not been assessed and they are unlikely to be routinely provided.	III
• **Ascertain patients' alcohol consumption and encourage a reduced intake where patients drink excessively as this can reduce blood pressure and has broader health benefits.**	**B**
- Excessive alcohol consumption (men: more than 21 units/week; women: more than 14 units/week) is associated with raised blood pressure and poorer cardiovascular and hepatic health.	I
- Structured interventions to reduce alcohol consumption, or substitute low alcohol alternatives, had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3 to 4 mmHg in trials. Thirty percent of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Brief interventions by clinicians of 10-15 minutes, assessing intake and providing information and advice as appropriate, have been reported to reduce alcohol consumption by a quarter in excessive drinkers with or without raised blood pressure, and to be as effective as more specialist interventions.	II
- Brief interventions have been estimated to cost between £40 and £60 per patient receiving intervention. The structured interventions used in trials of patients with hypertension have not been costed.	II
• **Discourage excessive consumption of coffee and other caffeine-rich products.**	**B**
- Excessive consumption of coffee (5 or more cups per day) is associated with a small increase in blood pressure (2/1 mmHg) in participants with or without raised blood pressure in studies of several months duration.	III

Lifestyle interventions (continued)

• **Encourage patients to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as this can reduce blood pressure.**	**B**
- Advice to reduce dietary sodium intake to less than 6g/day was shown to achieve a modest reduction in systolic and diastolic blood pressure of 2 to 3 mmHg in patients with hypertension, at up to 1 year in trials. About a quarter of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Long term evidence over 2 to 3 years from studies of normotensive patients shows that reductions in blood pressure tend to diminish over time.	II
- One trial suggests that reduced sodium salt, when used as a replacement in both cooking and seasoning, is as effective in reducing blood pressure as restricting the use of table salt.	III
• **Do not offer calcium, magnesium or potassium supplements as a method for reducing blood pressure.**	**B**
- The best current evidence does not show that calcium, magnesium or potassium supplements produce sustained reductions in blood pressure.	II
- The best current evidence does not show that combinations of potassium, magnesium and calcium supplements reduce blood pressure.	II
• **Offer advice and help to smokers to stop smoking.**	**A**
- There is no strong direct link between smoking and blood pressure. However, there is overwhelming evidence of the relationship between smoking and cardiovascular and pulmonary diseases, and evidence that smoking cessation strategies are cost-effective.	I
- *See: Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, NICE Technology Appraisal No. 39, March 2002. http://www.nice.org.uk/*	
• **A common aspect of studies for motivating lifestyle change is the use of group working. Inform patients about local initiatives by, for example, healthcare teams or patient organisations which provide support and promote healthy lifestyle change.**	**C**
• **To see the review of evidence go to page 78.**	

Estimating cardiovascular risk

- **If raised blood pressure persists and the patient does not have established cardiovascular disease, ask to formally assess the patient's cardiovascular risk. Tests may help identify diabetes, evidence of hypertensive damage to the heart and kidneys, and secondary causes of hypertension such as kidney disease.** **C**

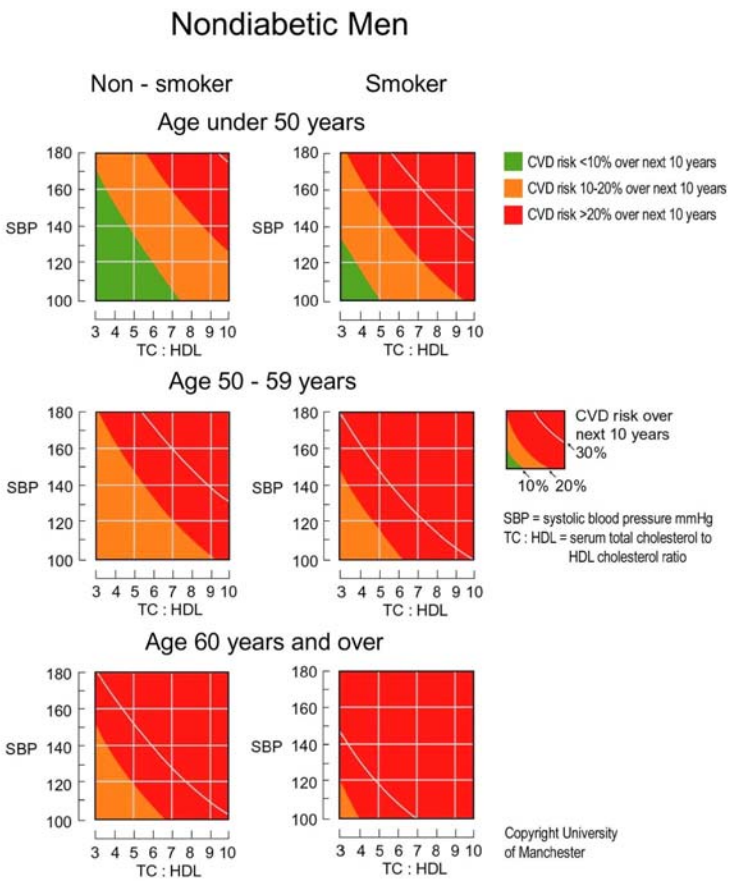
- **Test for the presence of protein in the patient's urine. Take a blood sample to assess plasma glucose, electrolytes, creatinine, serum total cholesterol and HDL cholesterol. Arrange for a 12 lead electrocardiograph to be performed.** **C**

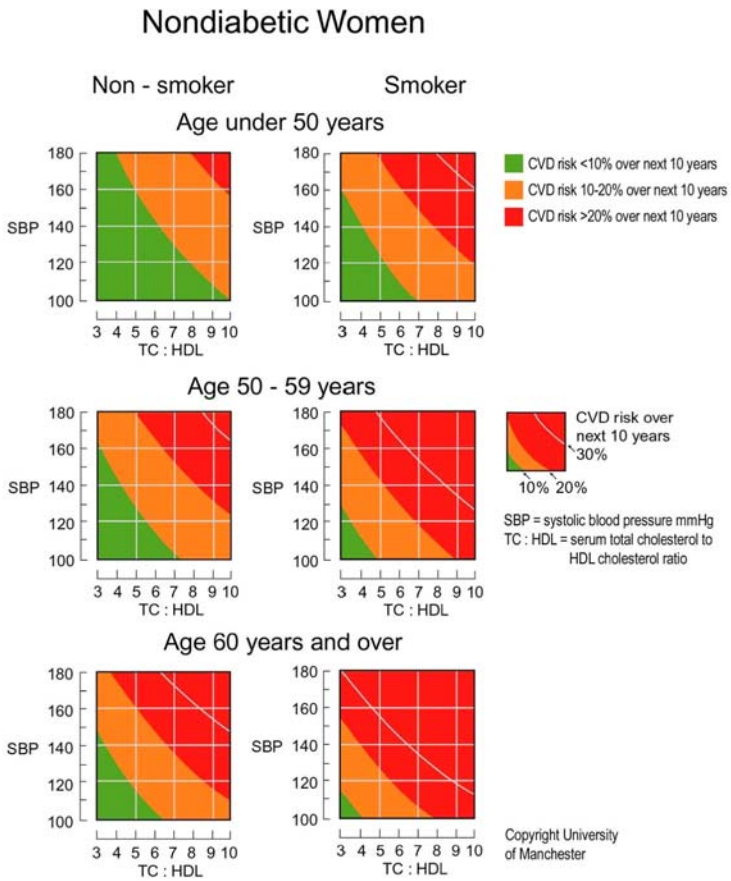
- **Consider the need for specialist investigation of patients with signs and symptoms suggesting a secondary cause of hypertension. Accelerated (malignant) hypertension and suspected pheochromocytoma require immediate referral.** **B**
  - An identifiable cause of hypertension is more likely when hypertension occurs in younger patients (less than 30 years of age), worsens suddenly, presents as accelerated (malignant) hypertension (BP more than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage) or responds poorly to treatment. III
  - An elevated creatinine level may indicate renal disease. Labile or postural hypotension, headache, palpitations, pallor and diaphoresis are potential signs of pheochromocytoma. Hypokalaemia, abdominal or flank bruits, or a significant rise in serum creatinine when starting an ACE inhibitor may indicate renovascular hypertension. Isolated hypokalaemia may be due to hyperaldosteronism. Potential signs of Cushing syndrome include osteoporosis, truncal obesity, moon face, purple striae, muscle weakness, easy bruising, hirsutism, hyperglycemia, hypokalaemia, and hyperlipidaemia. III

- **Use the cardiovascular risk assessment to discuss prognosis and healthcare options with patients, both for raised blood pressure and other modifiable risk factors.** **B**
  - Risk models provide a useful prognostic tool for clinicians and patients in primary care. They reinforce the need to offer treatment to patients based on their profile of cardiovascular risk rather than focusing on blood pressure in isolation. II
  - Most risk models derive from the Framingham Heart Study: a cohort of over 5,000 men and women aged 30 to 62 from Framingham, Massachusetts followed-up from 1971 to assess the determinants of cardiovascular disease. II
  - Limitations of commonly used risk models include poor validation in UK ethnic minorities and younger populations. II
  - Framingham risk calculator computer programmes currently provide the best assessment of risk of coronary heart disease and stroke over 10 years. The latest version developed by the Joint British Societies gives the risk of a cardiovascular event over 10 years (a combined score including the risk of coronary heart disease and stroke). II
  - Risk charts may be relatively imprecise, placing patients in bands of risks, although the visual presentation may be helpful to some patients. Evidence suggests that the Joint British Societies chart adheres most closely to Framingham risk calculators. III
  - When only the CHD risk score is known, CVD risk score can be approximated by multiplying by 4/3. When CHD and stroke risk are reported, the CVD risk can be approximated by adding these two scores together. III
  - + *See figure overleaf: Joint British Societies Cardiovascular Risk Charts for non-diabetic men and women.*

- **To see the review of evidence go to page 63.**

Ten Year Cardiovascular Risk Charts





Notes on use:

- These charts estimate cardiovascular disease (CVD) risk (non-fatal MI and stroke, coronary and stroke **death** and new angina pectoris) for individuals without vascular disease.
- In the broader context of this guideline the charts may help inform discussion about lifestyle and medic**ation** but **should not replace clinical judgment**.
- These charts are not appropriate for patients who have existing vascular disease or are at an age which already put them at higher risk (over 70).
- For each patient choose the table matching their gender, smoking status and age. If no HDL cholesterol result is available for the ratio TC/HDL, use the total serum cholesterol value (TC) as this assumes HDL is 1.00mmol/l
- If a patient has given up smoking within the last 5 years use the smokers' charts.
- Patients reach the level of risk predicted in each age bands when they reach the ages 49, 59, and 69 years respectively. The charts will overestimate current risk most in the under forties.
- These charts are based on groups of people with untreated blood pressure, total cholesterol and HDL cholesterol. They may still act as a guide when augmenting treatment.
- The charts will underestimate CV risk in patients with a family history of CVD, raised triglyceride levels, women with premature menopause, and those non-yet diabetic but with impaired fasting glucose (6.1-6.9mmol/l).
- In some ethnic minorities the risk charts may underestimate CHD risk and have not been validated in these populations.
- The chart can be used to indicate the amount that CV risk can be reduced by changes in smoking, blood pressure or cholesterol although this is approximate.

These charts were reproduced by the kind permission of the Joint British Societies.

June 2006: The recommendations on prescribing have been updated, and sections of this document marked with a grey tint have been superseded. For details of the how the new recommendations were developed, see www.nice.org.uk/CG034fullguideline

Pharmacological interventions

• **Drug therapy reduces the risk of cardiovascular disease and death. Offer drug therapy to (i) patients with persistent high blood pressure of 160/100 mmHg or more and (ii) patients at raised cardiovascular risk (ten year risk of CHD≥15% or CVD≥20% or existing cardiovascular disease or target organ damage) with persistent blood pressure of more than 140/90 mmHg.**	**A**
- In placebo-controlled trials, blood pressure management beginning with a low dose thiazide-type diuretic or beta-blocker has been shown to reduce mortality, myocardial infarction and stroke (relative risk reductions of 8%, 15% and 25% respectively).	I
• **Provide appropriate guidance and materials about the benefits of drugs and the unwanted side-effects sometimes experienced in order to help patients make informed choices.**	**C**
• **Offer drug therapy, adding different drugs if necessary, to achieve a target of 140/90 mmHg or until further treatment is inappropriate or declined. Titrate drug doses as described in the *British National Formulary* noting any cautions and contraindications.**	**A**
- In trials aiming to reduce blood pressure to below 140/90 mmHg using stepped medication regimes, between half and three-quarters of patients achieve target blood pressure.	I
- In these trials about one half of patients needed treatment with more than one drug.	I
• **Drug therapy should normally begin with a low dose thiazide-type diuretic+. If necessary, second line add a beta-blocker unless a patient is at raised risk of new-onset diabetes*, in which case add an ACE-inhibitor. Third line, add a dihydropyridine calcium-channel blocker.**	**A**
+ In younger patients, aged under 55, with moderately raised blood pressure and who may be managed on one drug, consider beginning with a beta-blocker.	
* Patients are considered at a raised risk of new-onset diabetes with a strong family history of type II diabetes, impaired glucose tolerance (FPG≥6.5mmol/l), if clinically obese (BMI≥30) or of South-Asian or African-Caribbean ethnic origin.	
- Findings from trials suggest that the onset of diabetes is greater in patients receiving a combination of a thiazide-type diuretic and beta-blocker when compared with other drug combinations. The combination may lead to a higher incidence of diabetes of 0.4% per year of treatment, i.e. one additional case of diabetes for 250 patients treated every year.	II
- From a model of lifetime costs and effects, based on the findings of trials, treatment using stepped care including thiazide diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers and calcium-channel blockers is estimated to be cost-effective.	II
• **Concern about increased new-onset diabetes among patients prescribed a thiazide-type diuretic with a beta-blocker means that this is not recommended as an initial combination for patients at raised risk of developing type II diabetes. However the combination may become appropriate to manage treatment resistant hypertension or if cardiovascular disease develops.**	**B**
• **If further blood pressure lowering is warranted, consider adding an ACE-inhibitor or beta-blocker (if not yet used), another antihypertensive drug, or referring to a specialist.**	**A**
- As a whole, head-to-head studies indicate similar benefits irrespective of whether blood pressure management begins with a low dose thiazide-type diuretic, beta-blocker, calcium-channel blocker, ACE-inhibitor, or angiotensin receptor blocker.	I
- Thiazide-type diuretics, beta-blockers, calcium-channel blockers, ACE-inhibitors and angiotensin receptor blockers appear similarly well tolerated as assessed by overall trial withdrawal rates. Withdrawal occurs typically at rates of 5% to 10% per year.	I
- Current evidence does not support the use of alpha blockers for initial treatment of raised blood pressure.	II
- There is no evidence from large-scale trials to support the use of centrally acting antihypertensive drugs for the initial treatment of raised blood pressure.	III

Pharmacological interventions (continued)

• **Consider substituting an angiotensin receptor blocker in patients who do not tolerate an ACE-inhibitor due to cough.**	**A**
- Trials of up to one year duration show reduced treatment-related cough in patients taking an angiotensin receptor blocker when compared with an ACE-inhibitor.	I
• **At review, consider modifying the medication of patients currently using only a thiazide-type diuretic and beta-blocker and at raised risk of diabetes, and those in whom concern about their treatment may affect adherence.**	**B**
- Concerns do not justify routinely changing the medication of patients treated currently with a thiazide-type diuretic and beta-blocker, and for whom continued blood pressure control is paramount. Changing therapy risks new side-effects and it may take time to re-establish adequate control of blood pressure. A change of therapy is unlikely to be appropriate in patients on three or more antihypertensive drugs.	II
• **Offer treatment as described to patients regardless of age and ethnicity. Be prepared to tailor drug therapy for individual patients who do not respond to the sequence of drugs indicated.**	**B**
- There is no compelling evidence in terms of reduced risk of cardiovascular disease to support the belief that different classes of drug work better in older or younger patients.	II
- There is evidence from short term studies of differential blood pressure lowering from certain drugs in the young and old and in certain ethnic groups. ACE-inhibitors and beta-blockers, whose mechanism of action is to suppress renin production, may not be effective in lowering blood pressure in patients of African descent, when used as monotherapy. However these agents may be effective in combination with a thiazide diuretic.	III
- One large randomised controlled trial (ALLHAT) found that ACE-inhibitors, used first line, may not prevent stroke in patients of African descent as effectively as low dose thiazide-type diuretics.	II
• **Offer patients with isolated systolic hypertension (systolic BP≥160 mmHg) the same treatment as patients with both raised systolic and diastolic blood pressure.**	**A**
- Patients with isolated systolic hypertension received similar benefits from treatment to other patients with raised blood pressure.	I
• **Offer patients over 80 years of age the same treatment as younger patients, taking account of any comorbidity and their existing burden of drug use.**	**B**
- Patients over 80 years of age are poorly represented in clinical trials and the effectiveness of treatment in this group is less certain. However, it is reasonable to assume that older patients will receive worthwhile benefits from drug treatment, particularly in terms of reduced risk of stroke.	II
• **Where possible recommend treatment with drugs taken only once a day.**	**A**
- A meta-analysis found that patients adhered to once daily blood pressure lowering regimens better than to regimens requiring two or more doses a day (91% vs. 83%). Similarly, once daily regimens were better adhered to than twice daily regimens (93% vs. 87%).	I
• **Prescribe non-proprietary drugs where these are appropriate and minimise cost.**	**B**
- Drug treatment, beginning with either a non-proprietary thiazide-type diuretic or beta-blocker minimizes cost.	II
- From a model of lifetime costs and effects, based on the findings of trials, treatment using stepped care including thiazide-type diuretics, beta-blockers, ACE-inhibitors/angiotensin receptor blockers and calcium-channel blockers is estimated to be cost-effective.	II
• **To see the review of evidence go to page 104.**	

Continuing treatment

• **The aim of medication is to reduce blood pressure to 140/90 mmHg or below. However, patients not achieving this target, or for whom further treatment is inappropriate or declined, will still receive worthwhile benefit from the drug(s) if these lower blood pressure.**	**B**
- In trials aiming to reduce blood pressure to below 140/90 mmHg using stepped medication regimes, between half and three-quarters of patients achieve target blood pressure.	I
- In these trials about one half of patients needed treatment with more than one drug.	I
• **Patients may become motivated to make lifestyle changes and want to reduce or stop using antihypertensive drugs. If at low cardiovascular risk and with well controlled blood pressure, these patients may be offered a trial reduction or withdrawal of therapy with appropriate lifestyle guidance and ongoing review.**	**B**
- When normal blood pressure has been established through drug therapy, the patients most likely to remain normotensive if they stop taking drugs are those who are relatively young, with lower on-treatment blood pressure, taking only one drug and who adopt lifestyle changes.	II
- Withdrawal of anti-hypertensive drugs has a much better chance of being successful when supported by structured interventions to encourage patients to restrict their salt intake and to lose weight if they are overweight.	I
• **Patients vary in their attitudes to their hypertension and their experience of treatment. It may be helpful to provide details of patient organisations that provide useful forums to share views and information.**	**C**
• **Provide an annual review of care to monitor blood pressure, provide patients with support and discuss their lifestyle, symptoms and medication.**	**C**
- Listening to patients' views about the pros and cons of treatment for hypertension, involving patients in each stage of the management of their condition, and providing clearly written supportive information are good clinical practice.	III
• **To see the review of evidence go to page 141.**	

Table of Contents

Glossary

Term	Definition
Aerobic exercise	Exercise requiring increased oxygen
Ambulatory blood pressure monitoring (ABPM)	A technique for measuring BP while an individual goes about their normal daily activities
Angina pectoris	A strangling pain in the chest due to reduced blood flowing to the heart muscles
Antihypertensive	Drug used to lower blood pressure
Arm(s) of a trial	The different interventions in a trial
Arrhythmia	A variation in the normal rhythm of the heart
Auscultation	Examination of the internal organs by listening to the sound produced
Biofeedback	Sight or sound information letting the individual know how an aspect of their body is functioning
Blinding	When the patient, the treatment provider or the person measuring the outcome (e.g. blood pressure) do not know what drug or treatment the patient is receiving
Blood pressure	Force exerted by blood against the walls of blood vessels
Caffeine	A substance which acts as a stimulant, found in coffee and tea
Calcium	An element necessary for normal body function; most of our calcium intake comes from milk and milk products
Calorie	A unit of heat, used as a measure of energy supplied by food
Cardiovascular Disease (CVD)	Disease affecting the heart or blood vessels.
Carry over effect	In cross-over trials the effect of treatment in the first period may persist during the second period, biasing the findings of the study.
Cerebrovascular accident (CVA)	Stroke (part of the brain is damaged due to lack of oxygen)
Cerebrovascular disease	Narrowing of the arteries supplying blood to the brain
Cognitive	Describing mental processes
Compliance	Patient's adherence to the advice and medication recommended by a clinician
Concealment of allocation	Neither the patient nor the person treating the patient knows in advance which arm of the trial the patient will be assigned to
Contra-indication	Reason why a person should not be prescribed a specific treatment
Coronary heart disease (CHD)	Heart disease due to narrowing of the arteries which provide the heart's blood supply; may manifest as angina or heart attack
Cross-over trial	A study where each individual receives 2 (or more) treatments, changing between them at a half-way point
Diastolic blood pressure DBP)	The lowest blood pressure during each heartbeat (e.g. 80 if blood pressure is 140/80 mmHg)
Dose titration	Change in the dose of a drug
Double blind	Describes a trial where neither the treatment provider nor the patient knows what treatment the patient is receiving – not usually possible for lifestyle studies
Drug trial	A study to investigate the effect of a drug(s) compared to a placebo(s) or another drug(s)
Endpoint	The outcome that is measured in a trial (e.g. blood pressure or death), assumed to respond to the treatment (same as Outcome)
Epidemiology	The study of who gets what disease

Term	Definition
Essential hypertension	High blood pressure which is not due to a known underlying disease
Evidence based medicine	Medical practice based on clear evidence
Excessive alcohol consumption	Over 21 units/week for men; over 14 units/week for women
Excessive coffee consumption	Over 5 cups/day
Guideline	A document which seeks to advise on the best treatment for specific conditions
Head-to-head trial	A trial comparing two or more active drugs or treatments
Heart failure	Reduction in the heart's pumping efficiency, leading to accumulation of fluid in the lungs and body, causing fatigue, breathlessness and leg swelling
Heterogeneity	Differences
Hypertension	High blood pressure
Intervention	The treatment given in a trial (e.g. a drug or lifestyle advice) which is thought to have an effect on the outcome
Intention-to-treat analysis	Statistical analysis of randomized controlled trial which analyzes the participants according to the treatment to which they were randomised and not the treatment they actually received
Ischaemic heart disease (IHD)	See Coronary heart disease
Lifestyle intervention	A measure to change a participant's behaviour in order to improve their health (e.g. exercise to reduce blood pressure)
Lipid lowering drugs	Drugs used to lower the level of fats in the blood
Loss to follow-up	Failure to measure the final outcome on a participant
Magnesium	An element necessary for normal body function; found in food
Markov model	A statistical model that models the transition of people between different states e.g. the transition from being healthy to having had a heart attack.
Mean	Average
Meta-analysis	A statistical method for combining the results from several different trials, that provides an overall more precise estimate of the effect of treatment that any of the individual trials could provide
Methodology	Methods used in a scientific study
Monotherapy	Use of only one drug (rather than two or more)
Morbidity	Disease and disability
Mortality	Death
Myocardial infarction (MI)	Heart attack (part of the heart is damaged due to lack of oxygen)
Negative predictive value	The probability that a person with a negative test does not have the disease
Normotension	Blood pressure that is within the normal range
Oscilllometry	The measurement of blood pressure using an electronic device rather than by listening to Korotkoff sounds (auscultation)
Outcome	Measurement in a trial (e.g. blood pressure or death) assumed to respond to the treatment (same as Endpoint)
Parallel trial	A study where two or more groups of individuals get different treatments at the same time
Peripheral vascular disease (PVD)	Narrowing of the arteries providing circulation to the legs
Placebo	A dummy pill
Placebo controlled trial	A drug trial where one group is given a placebo
Positive predictive value	The probability that a person with a positive test has the disease
Potassium	An element necessary for normal body function; found in food

Term	Definition
Probability	The likelihood of something happening; this can be anywhere between 0 (never happens) and 1 (always happens)
Primary care	Care by a general practitioner or his or her team
Randomisation	Assignments of participants to treatment groups at random, so that the distribution of participants within each group varies only by chance
Randomised controlled trial (RCT)	A scientific study where individuals are randomly assigned to receive one treatment or another (e.g. one drug or another, a lifestyle intervention or not).
Rapid atrial fibrillation	A rapid irregular heartbeat
Renin-Angiotensin System	Renin is an enzyme produced by the kidney and has an important role in hypertension. Renin converts a protein in the blood called angiotensinogen into angiotensin I. This is then turned into angiotensin II by angiotensin converting enzyme in the lungs. Angiotensin II reduces the size of the blood vessels (increasing blood pressure) and triggers the release of a hormone called aldosterone. Aldosterone is responsible for the retention of water and salt (which further increase blood pressure).
Risk factor	Something that puts an individual at increased risk of a specific disease
Secondary care	Care by a hospital-based team, following referral by a general practitioner
Sensitivity	The proportion of individuals with disease who are detected by a test
Sham treatment	A mock treatment that the treatment provider believes has no benefit to the patient
Single blind	Describes a trial where the treatment provider or the patient (usually the latter) does not know what treatment the patient is receiving
Sodium	An element necessary for normal body function; most of our sodium intake comes from common salt
Specificity	The proportion of individuals without disease who are classified appropriately by a test
Sphygmomanometer	A device used to measure blood pressure
Standard deviation (SD)	A measure of the average distance of observations from the mean
Statistical significance	The probability of something happening by chance. If this probability is less than 0.05 (1 in 20), it is often assumed that chance cannot explain the results and they are referred to as “statistically significant”
Stepped care	A drug intervention where the dose of the drugs can be increased and/or other drugs could be added
Systematic error	An error that tends to be always in a specific direction (i.e. always too high or always too low)
Systematic review	A scientific study which systematically identifies, reviews and analyzes specific evidence on a subject
Systolic blood pressure (SBP)	The peak blood pressure during each heartbeat (e.g. 140 if blood pressure is 140/80 mmHg)
Toxicity	The unwanted side-effects of drug treatment. These may vary from mild and/or self-limiting through to chronic and/or severe. Drugs are studied extensively before use in patients to understand (and avoid) the circumstances when they may become inappropriately toxic to patients.
Transient ischaemic attack (TIA)	Temporary paralysis, numbness, speech difficulty or other neurological symptoms that start suddenly and recover within 24 hours
Triple blind	Describes a trial where neither the patient, the treatment provider nor the person measuring the outcome (e.g. blood pressure), knows what treatment the patient is receiving – not usually possible for lifestyle studies
Withdrawal	Failure or refusal to take the assigned treatment (e.g. because of side effects or dislike of treatment)

⌘ Methods

Scope and Purpose

The National Guideline Research and Development Unit (NGRDU) was appointed by the National Institute for Clinical Excellence (the Institute) to develop an evidence-based clinical guideline for the management of essential hypertension in primary care. The Unit constituted the North of England Hypertension Guideline Development Group.

Guideline objectives

This guideline provides evidence-based recommendations for health care professionals, patients and carers to guide the appropriate primary care management of persistently raised blood pressure without primary cause (essential hypertension). A key aim is to promote the dialogue between professionals and patients on the relative benefits, risks, harms and costs of treatments. The guideline identifies effective and cost effective approaches to patient care and recognises that hypertension is one of a number of risk factors contributing to a range of cardiovascular diseases.

The guideline addresses the care of patients with essential hypertension, who may or may not have cardiovascular disease. It is cognisant of the National Service Frameworks (NSF) for Coronary Heart Disease and Older People [i,ii,iii], published national guidance on managing patients following myocardial infarction [iv] and on smoking cessation [v]. Where possible, it provides a firm evidence base for clinical actions and for the principles of relevant audit within the NSFs.

Areas not covered

This guideline does not address screening for or preventing hypertension, hypertension in pregnancy or the specialist management of secondary hypertension (where renal or pulmonary disease, endocrine complications or other disease provides an identifiable cause of raised blood pressure).

There are a number of lifestyle and disease markers that are strongly related to cardiovascular and other important diseases but only weakly related to raised blood pressure. Lines have had to be drawn as to the topics included in this guideline and those left to be addressed by others. Notable examples falling outside the scope of this work are cessation of smoking, treatment for raised serum cholesterol and drug therapies for obesity. However, the group felt it was important to include guidance on smoking cessation and felt confident of the established evidence for this.

Finally, this version does not make specific recommendations for the care of hypertension in patients with diabetes mellitus, which is addressed separately in a recent guideline [vi]. This anomaly may be addressed when both guidelines are revised.

Clinical questions addressed

The guideline group posed the following questions:

- How do I accurately assess and monitor BP?
- At what level of hypertension or cardiovascular risk do I offer treatment?
- What interventions do I offer, and in what order?
- What is the evidence for current targets for treating hypertension?
- What are the potential benefits, risks and harms for the patient in front of me?
- In which patients do I get most benefit with my limited resources?
- How do I communicate the risks and benefits of treatment to the patient?
- When should treatment be stopped?
- Who should do what, when organising care?
- What are the principles by which we judge success?
- What are achievable objectives for management?
- What routine sources of information are available for doctors and patients addressing hypertension?

In response to these questions the guideline sought to address the following aspects of patient care:

- Diagnosis.
- Conditions for beginning treatment for hypertension.
- The effectiveness and cost-effectiveness of non-pharmacological and pharmacological interventions.
- Evaluation of differences in particular groups of patients, for example in older patients and ethnic groups.
- Organisation (who does what, when and how) and delivery (communicating, educating, sequencing interventions, monitoring, assessing adherence and referral).
- Identifying appropriate standards of care and audit points to assess these.

Patients and clinicians covered by this guideline

This document is intended to be relevant to the primary care team, including General Practitioners, Practice Nurses and other primary health care professionals who have direct contact with patients. It does not consider the hospital setting but provides criteria for referral to secondary care. To promote continuity of care, it is important that clinicians initiating treatment in secondary care are aware of the recommendations of this guideline. Inevitably, parts of this document are technical but we have tried as much as possible to make this document accessible to patients, carers of patients and the public.

Other versions of this guideline

This full version of the guideline is made available to download free-of-charge from the National Electronic Library for Health website (http://www.nelh.nhs.uk/). A printed copy of this document can be purchased from the Centre for Health Services Research, University of Newcastle. The Institute produces three summary versions developed from this document: a patient version, a healthcare professional version and a quick reference guide (http://www.nice.org.uk/).

Disclaimer

The guideline development group assumes that health care professionals will use general medical knowledge and clinical judgement in applying the general principles and specific recommendations of this document to the management of individual patients. Recommendations may not be appropriate for use in all circumstances. Decisions to adopt any particular recommendation must be made by the practitioner in the light of circumstances presented by individual patients and available resources. Recommendations about drug treatment assume that clinicians will take account both of the response of individual patients and of the indications, contra-indications and cautions listed in the British National Formulary (BNF) or Summary of Product Characteristics. Clinicians will need to share appropriately the information within this guideline to enable patients to participate in the process of decision making to the extent they are able and willing [vii].

Contributors

The guideline development group

The guideline development group was composed of four types of members [viii]: relevant health care professionals, patient/carer representatives, a specialist resource and a specialist small-group leader.

The composition of the group was selected to ensure adequate relevant discussion of the evidence, of areas where there was no evidence, and of the subsequent recommendations in the guideline. The group leader had the role of ensuring that the group process worked effectively. The methodologist had the role of ensuring that guideline tasks were addressed and completed.

The members of the development group are (in alphabetical order):

- **Susan L Brent** Pharmacist
- **Paul Creighton** General Practitioner
- **Bill Cunningham** General Practitioner
- **Julie Eccles** Guideline Group Leader and General Practitioner
- **Gary Ford** Consultant Physician
- **John Harley** General Practitioner
- **Suzanne Laing** Nurse Practitioner
- **James Mason** Methodologist
- **Colin Penney** Patient Representative
- **Wendy Ross** General Practitioner
- **Jean Thurston** Patient Representative
- **Bryan Williams** Consultant Physician

Guideline support staff

The support staff were led by James Mason and provided the multidisciplinary skill base necessary to assess and present the evidence considered by the group. Support staff were responsible for reviewing and summarising the evidence on clinical effectiveness, safety, quality of life and health economics when available. Additionally they were responsible for drafting the guideline and providing resources for the guideline development group.

The members of the support staff were:

- **Beth Anderson** Project Administrator
- **Fiona Campbell** Systematic Reviewer
- **Julia Cooke** GP Registrar
- **Heather Dickinson** Statistician
- **Sylvia Hudson** Project Administrator
- **Sarah Hull** GP Registrar
- **Donald Nicolson** Systematic Reviewer
- **Dor Wilson** Information Specialist
- **Fiona Renton** Information Specialist
- **Andrew Yeates** GP Registrar

Involvement of stakeholders and referees

A substantial process of stakeholder involvement and refereeing surrounds the development of national guidelines developed for the Institute. Generic details of this process are found on the Institute web site (http://www.nice.org.uk/) in the document: The Guideline Development Process – An overview for stakeholders, the public and the NHS. In brief, the process involves identifying and registering relevant patient and professional organizations as stakeholders, obtaining their comments on the scope of the work; providing an opportunity for the submission of relevant evidence and commenting on two draft versions of the final document. Some stakeholder organizations are invited by the Institute to nominate individuals who, because of their knowledge or experience, may contribute as guideline development group members.

Eighty-two stakeholders registered with the Institute to contribute to the process of developing this guideline. These are shown, in alphabetical order, in Table 1

Table 1: Stakeholders registered for the guideline development process

Association of Welsh Community Health Councils	Health Development Agency
Abbott Laboratories Limited	Merck Pharmaceuticals
Action Heart*	Merck, Sharp and Dohme Ltd
Action on Pre-Eclampsia (APES)	National Heart Forum (UK)
Age Concern England*	National Kidney Research Fund
All Wales Medical and Pharmaceutical Advisers Forum	NCC for Acute Care+
Alliance Pharmaceuticals Ltd	NCC for Mental Health (British Psychological Society)+
Ambulance Service Association	NCC for Mental Health (Royal College of Psychiatrists)+
Association of British Clinical Diabetologists	NCC for Women's & Children's Health+
Association of the British Pharmaceuticals Industry (ABPI)	NHS Information Authority, (PHSMI Programme)
AstraZeneca UK Ltd	Novartis Pharmaceuticals UK Ltd
Aventis Pharma	Nursing & Supportive Care Collaborating Centre
BASF Pharmaceuticals	Patient Concern*
Bayer PLC	Patient Involvement Unit for NICE
Blood Pressure Association*	Pfizer Limited
Boehringer Ingelheim Ltd	Pharmacia Limited
Bristol-Myers Squibb Pharmaceuticals	Primary Care Cardiovascular Society
British Association for Nursing in Cardiac Care	Primary Care Pharmacists Association (PCPA)
British Association for Paediatric Nephrology	Sowerby Centre for Health Informatics at Newcastle
British Cardiac Patients Association*	Propriety Association of Great Britain (PAGB)
British Dietetic Association	Roche Products Limited
British Geriatrics Society	Royal College of Anaesthetists
British Geriatrics Society-Special Interest Group in Diabetes	Royal College of General Practitioners
British Heart Foundation*	Royal College of Midwives
British Hypertension Society*	Royal College of Nursing*
British In Vitro Diagnostics Association	Royal College of Obstetricians & Gynaecologists
British Lung Foundation	Royal College of Pathologists*
British Medical Association - Hospital Doctors Secretariat	Royal College of Psychiatrists
British Orthoptic Society	Royal College of Radiologists
British Psychological Society	Royal College of Speech and Language Therapists
BUPA	Royal Pharmaceutical Society of Great Britain
Chartered Society of Physiotherapy	Sankyo Pharma
Chronic Conditions Collaborating Centre	Sanofi-Synthelabo
College of Occupational Therapists	Servier Laboratories Limited
Community Practitioners' and Health Visitors' Association	Society of Chiropodists & Podiatrists
Consensus Action on Salt and Health	Solvay Healthcare Limited
Contact a Family	Stroke Association*
Department of Health NHS Executive	Takeda UK Ltd
Diabetes UK	Trinity Pharmaceuticals Limited
Diabetes UK Specialist Care Section Committee	UK & Overseas Heart Society 'Heart Link'*
Elan Pharmaceuticals Ltd	UK Advocacy Network*
	Wyeth Laboratories

* Organisations asked to offer nominations for guideline group membership
+ National Collaborating Centre

Additionally the guideline was reviewed by the following subject area experts:

- **Michael Alderman** Academic Consultant Physician
- **Brendan Delaney** Academic General Practitioner
- **Colin Johnston** Academic Consultant Physician
- **Peter Sever** Academic Consultant Physician
- **Simon Thomas** Academic Consultant Physician

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We are grateful to:

The **stakeholders** and **reviewers** who gave their time to review the guideline in draft form, and whose many helpful comments have helped to improve the final product.

Victoria Thomas (of the Patient Involvement Unit for NICE), who drafted a summary of patient experiences found on the DIPEx website.

David Simpson (of Primary Care Informatics) for helpful discussions about audit and for providing a standard enquiry for use with practice databases.

Stakeholders, **referees**, and **colleagues** who have provided the guideline development group with comments and suggestions as the work progressed.

Development Methods

Review methods

The aim of reviewing was to identify and synthesise relevant published and unpublished evidence to allow recommendations to be evidence-based wherever possible [ix]. The search was carried out using the electronic databases MEDLINE, EMBASE and CENTRAL, attempting to locate systematic reviews and meta-analyses, and original randomised trials using a combination of subject heading and free text searches. We made extensive use of high quality recent review articles and bibliographies, as well as contact with subject area experts. New searches were concentrated in areas of importance to the guideline development process, for which existing systematic reviews were unable to provide valid or up to date answers. The expert knowledge and experience of group members also backed up the search of the literature.

Electronic searches used a sensitive search strategy based on a combination of text and index terms to locate randomised controlled trials of treatments relevant to the guideline. If data necessary for our analyses were not reported, we wrote to authors or sponsoring agencies. We are grateful to investigators and sponsors who provided unpublished information to aid our work.

We assessed the quality of relevant studies retrieved and their ability to provide valid answers to the clinical questions addressed by the group. Assessment of study quality concentrated on internal validity (the extent to which the study measured what it intended to measure), external validity (the extent to which study findings could be generalised to other treatment settings) and construct validity (the extent to which measurement corresponded to theoretical understanding of a disease) [x]. Specific dimensions of quality examined in each study are reported in Table 2 [xi].

Table 2: Quality Criteria for Randomised Controlled Trials

Appropriateness of inclusion and exclusion criteria
Concealment of allocation
Blinding of patients
Blinding of health professionals
Blinding of data collectors/outcome assessors
Completeness and length of follow up
Appropriateness of outcome measures

Once data had been abstracted from individual papers and their quality assessed, the information was synthesised. Individual trials often have an insufficient sample size to identify significant outcomes with confidence [xii], so where appropriate, the results of randomised studies were combined using meta-analytic techniques [xiii]. Questions were answered using the best evidence available. When considering the effect of an intervention, if this could be addressed by the best study design then weaker designs were not reviewed. Where studies were of poor quality, or contained patient groups considered likely to have different responses, the effects of inclusion or exclusion were examined in sensitivity analyses. No trials that met our inclusion criteria were excluded from the primary analyses. However, where data on relevant outcomes were not available, these studies could not be included, thus leading to the potential for publication bias. A summary of methods used to describe the results of trials is provided in Appendix 1.

Review criteria

Scoping work revealed a vast number of trials of pharmaceutical interventions. Recent work suggests that study size is a useful proxy for study quality [xiv,xv]. Consequently to achieve the task in the timescale provided we reviewed only those pharmaceutical studies which enrolled 200 or more patients. Since the prime motivation for treatment in hypertension, an asymptomatic condition, is the prevention of mortality and morbidity, we reviewed those studies with a planned follow-up of at least a year since such studies are likely to have been designed to inform about these endpoints. Few non-pharmacological studies directly address cardiovascular endpoints or feature substantial durations of follow-up. Consequently in these areas we evaluated blood pressure reduction as a proxy endpoint and included trials with a follow-up of 8 weeks follow-up or more, which compared a group receiving a lifestyle intervention with a control group who received no treatment, usual treatment, sham therapy or a placebo.

Statistical methods

Pharmacological interventions

The outcomes analyzed were: all cause mortality, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke. We did not consider the following endpoints: renal disease (rare in non-diabetic patients); heart failure (inconsistently reported in trials); cardiovascular events (a concatenation of myocardial infarction and stroke). For each trial, the risk ratios comparing the risk of each outcome in the active treatment and control groups - or, for head-to-head trials, in the different treatment groups - were calculated. Results of trials were combined in a meta-analysis using the DerSimonian and Laird random effects model [xiii], to estimate an overall pooled risk ratio (RR) and its 95% confidence interval (95%CI). This model assumes that there are different effects of treatment in different populations, which are clustered about a mean effect; the pooled RR gives the best estimate of this mean effect. In the placebo-controlled trials reported in this guideline, a RR less than 1 favours treatment and a RR greater than 1 favours control. If the 95%CI include 1, there is no statistically significant difference between the treatments being compared.

Finally, we assessed the tolerability of the interventions by comparing the rate of overall withdrawal (percentage of patients who withdrew each year) in each treatment arm of a trial and calculating the difference in these rates (called the 'incident risk difference'). These incident risk differences were combined in a meta-analysis using the DerSimonian and Laird random effects model [xiii], to estimate an overall pooled incident risk difference and its 95% confidence interval.

We assessed heterogeneity between trials using a chi-squared statistic (Q). This assesses whether the trials are sufficiently similar to be validly combined. Although the test for heterogeneity is weak, it is usually assumed that if it gives p-values greater than 0.10, there is no significant heterogeneity and it is valid to discuss the combined findings.

We also assessed whether the effect in individual trials was related to the size of the trial; any such trend might indicate publication bias, e.g. where small trials were published only if they showed a positive effect. Again, this test for systematic variation in the magnitude of the estimated effect with the size of the trial is weak, but it is usually assumed that if it gives a p-value greater than 0.10, there is unlikely to be any such bias.

Lifestyle interventions

None of the studies identified were designed to quantify significant changes in rates of death or cardiovascular events, so we analysed the surrogate endpoint of reduced blood pressure. For each trial, the difference in the final value mean blood pressure in the treatment and control groups - or, for head-to-head trials, in the different treatment groups - was calculated. Change scores from baseline were used where complete data for final values was unavailable. These mean differences were weighted according to the precision of each trial (which depends largely on its size, with larger trials

getting more weight) and combined in a meta-analysis using the DerSimonian and Laird random effects model [xiii], to estimate an overall pooled weighted mean difference and its 95% confidence interval. While most of the trials were of parallel design (two or more groups received the various interventions at the same time), some were of crossover design (all participants received both active treatment and control interventions, but in a random order). Crossover trials have about four times greater precision than parallel trials of the same size, so we used methods have been developed recently to combine the parallel and crossover trials in the same meta-analysis [xvi,xvii]. Heterogeneity and the potential for publication bias were assessed in the same way as for pharmaceutical trials.

The mean percentage achieving a reduction of 10mmHg or more in systolic blood pressure was then estimated from the cumulative normal distribution [xviii] and confidence intervals were estimated using the delta method [xix].

Finally, we assessed the tolerability of the interventions by comparing the proportion of withdrawals (% of patients who withdrew) in each treatment arm of a trial and calculating the difference in these proportion (called the 'risk difference'). These risk differences were combined in a meta-analysis using the DerSimonian and Laird random effects model [xiii], to estimate an overall pooled risk difference and its 95% confidence interval.

Group process

The guideline development group was run using the principles of small group work and was led by a trained facilitator. The group underwent initial exercises to set its own rules to determine how it wanted to function and received brief training on reviewing methods, economic analysis and grading methodology. Additional training was provided in the group as the need arose in subsequent meetings. Findings, expressed as narratives, statements of evidence and recommendations, were reached by informal consensus. There was no obligation to force an agreement where none existed after discussion: dissensions were recorded in the guideline narrative [xx].

Evidence statements and recommendations

The guideline development group process produces summary statements of the evidence concerning available treatments and healthcare and from these makes its recommendations. Evidence statements and recommendations are commonly graded in guidelines reflecting the quality of the study designs on which they are based. An established scheme adapted from the Agency for Health Care Policy and Research (AHCPR) Classification is shown in Table 3 and Table 4 [xxi].

Table 3: AHCPR derived categories of evidence

Ia:	evidence from meta-analysis of randomised controlled trials
Ib:	evidence from at least one randomised controlled trial
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 non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV:	evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Table 4: AHCPR derived strengths 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

Two grading schemes were used when developing this guideline, the one above and a new scheme called GREG (Guideline Recommendation and Evidence Grading). [xxii] The new scheme seeks to address a number of problems, by extending grading from treatment to include diagnosis, prognosis and cost, and to handle the subtleties of clinical evidence more sensitively (Table 5).

Table 5: GREG scheme for assessing evidence and writing recommendations

EVIDENCE

Evidence statements provide information about disease, diagnosis and treatment, and are used to support recommendations. Each evidence statement is graded by scoring the study design and applying quality corrections.

Design	
Design Scores	
Treatment	
Randomised controlled trial	1
Non-randomised controlled study	2
Uncontrolled study	3
Diagnosis	
Blinded cohort study [i]	1
Unblinded cohort study	2
Other design	3
Prognosis	
Incident cohort study [ii]	1
Other cohort study	2
Descriptive data	
Population data	1
Representative sample	2
Convenience sample	3
Quality corrections	
Flawed design, conduct or analysis [iii]	+1
Imprecise findings [iv]	+1
Lack of consistency or independence [v]	+1
Inadequate relevance [vi]	+1
Very strong association [viii]	-1
Evidence Grade	**Score**
• I: High	≤1
• II: Intermediate	2
• III: Low	≥3

Notes

i. Blinding refers to independent interpretation of a test and reference standard.

ii. An incident cohort is identified and followed in time from a defined point in the progress of disease or care.

iii. Important flaws may be judged to occur when adequate standards of research are not followed or are unreported in published findings. Potential examples include failure to analyse by intention-to-treat, over-interpretation of secondary analyses, failure to adjust for potential confounding in non-randomised designs. For diagnostic studies this includes the need for an adequate reference standard and to apply different tests in an adequately short timescale.

iv. Sparse data (too few events or patients) are the most common reason for imprecision. A confidence interval including both no effect and a clinically important effect is an example of an imprecise finding.

v. Consistency in [1] design: involves methods, patients, outcome measures; and [2] findings: involves homogeneity of summary estimates. Independence refers to the availability of research from at least two independent sources. Evidence of publication bias also denotes lack of consistency.

vi. Adequate relevance requires [1] use in studies of a relevant patient-oriented health outcome or a strongly linked surrogate endpoint; and [2] a sufficiently representative and relevant patient group or mix.

vii. In comparative designs a very strong association can raise the quality score.

RECOMMENDATIONS

Recommendations provide guidance about appropriate care. Ideally, these should be based on clear evidence: a robust understanding of the benefits, tolerability, harms and costs of alternative patterns of care. They also need to be feasible in the healthcare setting addressed. There are 3 unique categories, and each recommendation may be positive or negative, conditional or unconditional reflecting current evidence and the understanding of the guideline group.

• A. Recommendation	There is robust evidence to recommend a pattern of care.
• B. Provisional Recommendation	On balance of evidence, a pattern of care is recommended with caution.
• C. Consensus Opinion	Evidence being inadequate, a pattern of care is recommended by consensus.

Use of the two schemes was evaluated in this and another guideline being developed contemporaneously. Both groups consistently favoured the new scheme and so the guideline is presented using the new grading scheme. The evaluation of the two schemes will be reported separately.

The key point of note is that any assessment of evidence quality is ultimately a subjective process. How bad does a trial have to be before it is flawed or how sparse do the findings have to be before we lose confidence in the findings? The purpose of an evidence grading scheme is to characterise the robustness of outcomes from studies, and the random and systematic biases that pertain to them.

Similarly recommendation grading must credibly assimilate evidence and health service context to credibly advise lines of care for *average* patients. Clinicians must use their judgement and awareness of patients' circumstances and values when considering recommendations from guidelines.

Costs and consequences

Approaches to cost-effectiveness have assisted in reaching recommendations in a series of primary care evidence-based guidelines [xxiii,xxiv]. This guideline involves a systematic appraisal of effectiveness, compliance, quality-of-life, safety and health service resource use and costs of a medical intervention provided in the British health care setting. Using the most current, pertinent and complete data available, the economic analysis attempts a robust presentation showing the possible bounds of cost-effectiveness that may result.

The guiding principle behind economic analysis is that it is desirable to use limited healthcare resources to maximise health improvements in the population. Well defined but narrow notions of health improvement may not reflect all aspects of value to patients, carers, clinicians or society. For example, evidence may lead the guideline group to recommend targeting additional resources to certain patient groups when unequal access to care is apparent. The group process allows discussion of what should be included in the definition of 'improved health' and more broadly of other concepts of value to society such as fairness, justice, dignity or minimum standards of care.

The range of values used to generate cost-effectiveness estimates reflects the available evidence and the concerns of the guideline development group. Recommendations are graded reflecting the certainty with which the costs and consequences of a medical intervention can be assessed. This practice reflects the desire of group members to have simple, understandable and robust information based on good data.

It is not generally helpful to present an additional systematic review of previous economic analyses that have adopted a variety of differing perspectives, analytic techniques and baseline data. However, the economic literature is reviewed to compare guideline findings with representative published economic analyses and to interpret any differences in findings when these occurred. A commentary is included when the group feel this aids understanding.

Scheduled review of this guideline

A provisional review date for this guideline is August 2008. The decision to update all or part of this guideline will be determined by the sponsor's monitoring and review policy.

Piloting and implementation

It is beyond the scope of the work to pilot the contents of this guideline or validate any approach to implementation. These limitations accepted, every effort has been made to maximise the relevance of recommendations to the intended audience through use of a guideline development group with relevant professional and patient involvement, by use of relevant expert reviewers and through the stakeholder process facilitated by the commissioning body.

Audit methods

It is beyond the scope of the work to validate an audit developed from the guideline recommendations. However, plausible audit points have been identified, consistent with assessing the quality of care received by patients. These audit points are based on information readily obtainable through the MIQUEST system (www.PrimaryCareInformatics.co.uk) which can be implemented on most General Practice patient database systems. Quality indicators from the new standard GMS contract are also discussed.

Declarations

Authorship and citation

Authorship of this full guideline document is attributed to members of the guideline development group and support staff under group authorship. Professor James Mason led the guideline development process, and can be contacted by email: jmason123@orange.net. Please cite this document as:

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Declarations of interest

The following people have declared no competing interests in relation to the guideline: Sue Brent, Paul Creighton, William Cunningham, Heather Dickinson, Julie Eccles, John Harley, Suzanne Laing, Colin Penney, Wendy Ross and Jean Thurston.

Gary Ford has received honoraria from a number of pharmaceutical companies for lectures and consultancy, and grant support for clinical trials from the pharmaceutical industry. He is deputy chair of the British Geriatrics Society Drugs and Prescribing Section, chair of the British Association of Stroke Physicians Training and Education Committee, and a member of the Stroke Association Research and Development Committee.

James Mason has previously received academic funding, fees and expenses for research and consultancy work from the UK Department of Health, medical charities and from the pharmaceutical industry who manufacture treatments discussed in this report.

Bryan Williams has received honoraria from a number of pharmaceutical companies for lectures and consultancy, and grant support for research projects and clinical trials from the pharmaceutical industry. He is ex-president of the British Hypertension Society; Trustee of the Blood Pressure Association; member of the Guidelines Committee of the European Society of Hypertension

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⌘ Evidence

Introduction

This guideline addresses the care of patients with essential hypertension (persistent raised blood pressure without primary cause) who may or may not have existing cardiovascular disease. Details of how this guideline was produced are found in the methods section (page 25).

The management of hypertension in primary care encompasses a number of interlocking themes. How should hypertension be defined and diagnosed? How important is hypertension in the context of other risk factors for cardiovascular disease? What are the potential benefits and harms of lifestyle and pharmacological interventions? How should the risks of disease and available treatments be discussed by clinicians and patients? How should the management of hypertension be organised in general practice to deliver appropriate patient care? Should limited healthcare resources be targeted at certain patients or certain treatments? The evidence sections of this guideline work through these issues and bring them together in summary management recommendations.

Recommendations for health care professionals, patients and carers are derived at relevant points in the evidence narrative together with supporting statements of evidence. These summary findings form the basis of shortened clinical and patient versions of the guideline.

Users of this document will vary in their understanding of medicine, clinical studies and statistics. Discussion of the clinical evidence found in published studies is sometimes very technical. We have endeavoured to minimise jargon throughout this guideline, adding background reading at points in the text and explanations of analytic techniques in appendices. Some sections can be omitted by more knowledgeable readers. Recommendations and supporting evidence statements are intended to be read and used by clinicians and patients to help inform healthcare decisions.

Why a new hypertension guideline?

A cursory glance at the world's medical literature reveals that there are many clinical guidelines available for the management of hypertension. A recent systematic review by the German Guideline Clearing House covering 1990 to 1999 identified 132 guidelines [1]. To this must be added regional and local guidelines and adaptations and manufacturers' guidance all vying for the attention of clinicians. Only 11 of the guidelines identified passed the review's quality criteria, and they varied widely when describing the development process; declaring competing interests; linking recommendations and evidence; and in their feasibility and implementation. A review of recent major guidelines is provided in Appendix 2.

The rationale for a new hypertension guideline comes from the need to update and systematize existing products. Reflecting the methodological aims of national guideline development in England and Wales, the steps involved are:

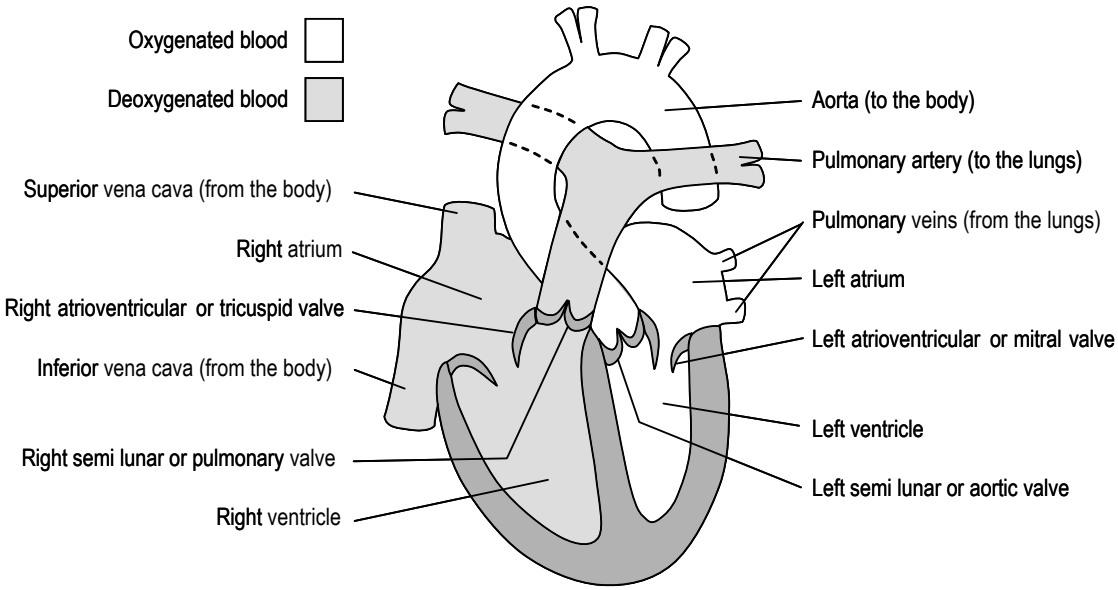
- To identify, present and systematically value evidence that usefully informs the long term management of raised blood pressure;
- To perform the evaluation of evidence using a transparent guideline development group process;
- To clearly link recommendations to supporting evidence;
- To develop clinical and patient-oriented versions as well as a full guideline document;
- To provide periodic updating of guidance as part of the sponsor's rolling programme of work; and
- To deliver a single, authoritative source of guidance to clinicians and patients in England and Wales.

Blood pressure explained

The heart

The heart pumps blood around the body. It is divided into right and left halves; each half contains an upper (atrium) and lower (ventricle) chamber (Figure 1). The low pressure right side receives deoxygenated blood returning from the body, pumping it through the right chambers into the pulmonary artery and the lungs. The high pressure left side of the heart receives oxygenated blood returning from the lungs via the pulmonary veins, pumping it through left chambers into the aorta and body.

Figure 1: Anatomy of the heart



When the heart is filling this is referred to as diastole and when the heart is pumping blood outward this is referred to as systole. During diastole the atria contract raising atrial pressures above

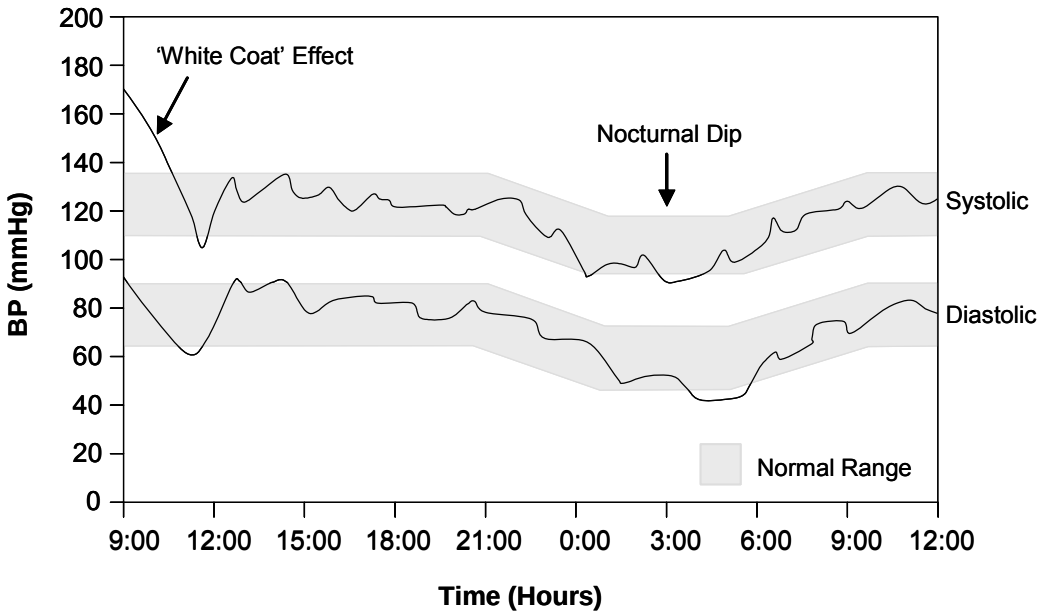
ventricular pressures. This opens the atrio-ventricular valves and allows the ventricles to fill. During systole the ventricles contract; as ventricular pressure exceeds atrial pressure the atrio-ventricular valves close. Ventricular pressures continue to rise until they exceed aortic (left) and pulmonary artery (right) pressure. At this point the semi-lunar valves open, allowing blood to be pumped out into the aorta and pulmonary artery.

Blood pressure

Blood pressure (BP), the pressure exerted on the walls of the arteries as blood flows through them, fluctuates with the cyclical pumping action of the heart. The highest and lowest readings are referred to as systolic and diastolic blood pressure. Blood pressure measurement is recorded in millimetres of mercury (mmHg), traditionally using a mercury manometer, as systolic over diastolic (e.g. 120/80 mmHg). The pulse pressure is the difference between the systolic and diastolic pressures.

Data from 24-hour ambulatory blood pressure monitoring shows a definite and reproducible daily pattern, similar in healthy volunteers and most hypertensive patients [2,3] (see Figure 2). Commonly, blood pressure readings are at their highest level when waking, flatten out during the day, and fall by 10- 20 % during the night [4]. Night workers demonstrate reversed patterns. Some patients exhibit unusual raised blood pressure during consultations with clinicians, which is called white coat hypertension.

Figure 2: An example of the pattern of daily variation in blood pressure



Since a number of factors can influence a blood pressure reading, a clinician will normally establish a pattern of raised blood pressure in a patient over time, rather than reacting to one measurement.

What is hypertension?

When blood pressure remains higher than normal over time (at least several months) it is called variously high blood pressure, raised blood pressure or hypertension. Hypertension occurs when the heart has to use more energy to pump against the greater resistance of the vascular system. If the heart is unable to meet this demand then over time the heart may thicken and stiffen (known as myocardial hypertrophy) and angina pectoris or myocardial infarction (heart attack) may develop.

A question often asked is what are normal and raised blood pressure? Our blood pressure tends to rise as we age: using a threshold of 140/90 mmHg about one third of individuals in middle age and two thirds in old age have raised blood pressure. Individuals vary and it seems arbitrary to label a proportion of the population as hypertensive. The important point is that hypertension is not a disease itself but one factor that may increase the chance of disease. On its own it may not be important enough to merit treatment. Beside hypertension, other important factors for cardiovascular disease are smoking, diabetes, family history, obesity, blood cholesterol level, physical inactivity and age. In some instances it may be appropriate to address one or more of these other factors first. When taken with these other risk factors it may be appropriate to offer treatment for raised blood pressure.

Hypertension is a risk factor in the development of diseases of the heart, vasculature and other organs such as the kidneys. Continued high blood pressure is cited as the commonest cause of stroke, which results from either blockage or, less commonly, haemorrhage of vulnerable blood vessels in the brain 5,6]. Hypertension may be present without symptoms although when these occur they can include chest pain, breathlessness, transient visual loss, headaches and wheeze [7,8]. Most individuals who suffer raised blood pressure (around 95%) have essential (or primary) hypertension with no identifiable cause [9]. Around 5% of individuals with raised blood pressure have secondary hypertension, where renal disease, pulmonary disease, endocrine complications, or other diseases underlie raised blood pressure [56]. These types of hypertension require specialist secondary care.

Measuring blood pressure

The gold standard for measuring blood pressure is direct recording of intra-arterial pressure using a catheter. However, this is a highly invasive and skilled procedure not practised in primary care [10]. Practically, measuring blood pressure relies on indirect measurement. The most common method is to close the artery in the arm with an inflatable cuff. The pressure is determined traditionally by listening with a stethoscope (called auscultation) or by electronic sensing (called oscillometry). Other methods not involving arterial occlusion exist (for example pulse-waveform analysis) but are not commonly used [10,11,53]. Blood pressure measurements can be taken in the practice setting, in an ambulatory mode (allowing the subject to continue normal activities) or by self or home measurement.

The Riva-Rocci/Korotkoff technique (RRK)

Measuring blood pressure by auscultation in the practice setting uses the RRK technique. This method has its origins more than a century ago. Riva-Rocci found that an air filled rubber bag could be inflated to block the brachial artery. Connected by tubing to a manometer, the systolic pressure was identified as the inflation pressure when the brachial pulse could no longer be palpated [12]. Soon afterwards the Russian military surgeon Korotkoff described the auscultatory sounds, now named after him, heard by listening to the brachial pulse with a stethoscope while deflating the cuff. The cuff is inflated to block the brachial pulse. The first sound occurring with the return of the brachial pulse is the systolic pressure (the point at which the heart pumping at its hardest overcomes the pressure exerted by the cuff to push blood past the obstruction). Intermediate sounds follow as the cuff pressure drops, with muffling and then the disappearance of sounds indicating the diastolic pressure (the point at which the heart is not pumping outward and the residual arterial pressure is sufficient to overcome the pressure exerted by the cuff). The interpretation of the sounds was later developed by Ettinger [13].

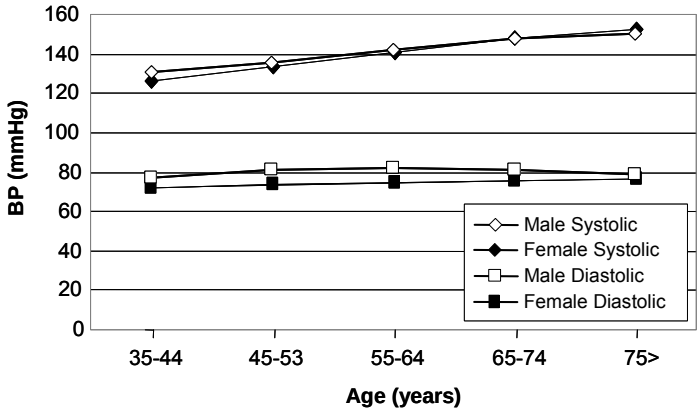
Some facts about raised blood pressure

- Defined as 140/90 mmHg, 40% of the adult population of England are hypertensive although the proportion increases with age.
- Epidemiological studies have studied large numbers of people with lower and higher blood pressure. Lowering diastolic blood pressure by 10 mmHg is associated with reductions in stroke of 56% and coronary heart disease of 37%.
- When blood pressure is lowered using drugs, all of the reduction in stroke and over half of the reduction in coronary heart disease seen in epidemiological studies are achieved.
- Differences in the physiology of ethnic populations may lead to variations in the prevalence of hypertension and other cardiovascular risk factors.
- In 2001, the NHS in England funded 90 million prescriptions for blood pressure lowering drugs at a cost of £840 million: nearly 15% of the total annual cost of all primary care drugs. These drugs are prescribed for a range of conditions including hypertension.
- Hypertension is a contributory factor in ischaemic heart disease and cerebrovascular disease which account respectively for 20% and 10% of all deaths
- Cardiovascular and cerebrovascular disease account for about 4 million bed days annually, 8% of the total capacity of the NHS.

The 1998 Health Survey for England obtained representative BP readings and data on hypertensive drug use from a sample of nearly 12,000 participants, by nurse interview. Average population systolic blood pressure increased with age, although diastolic remained roughly constant (Figure 3).

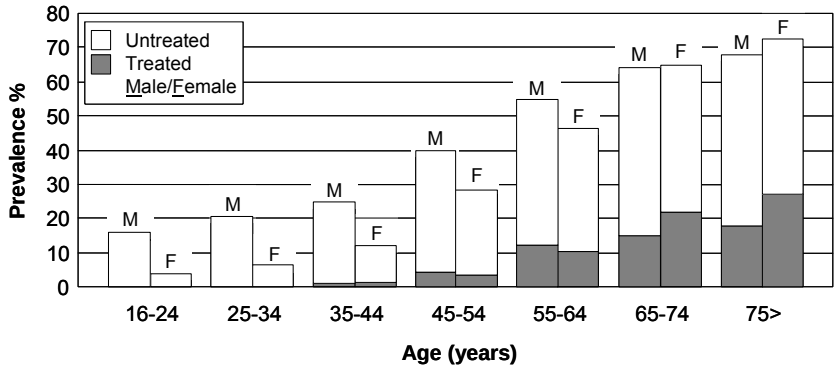
The threshold level for a diagnosis of hypertension is arbitrary and subject to dispute, partly because, at any specific age, blood pressure is normally distributed among the population [14]. A threshold of ≥140/90 mmHg is most commonly found in major published guidelines (see Appendix 2: A review of recent major guidelines, page 181).

Figure 3: Variation of mean blood pressure with age. (Data source: Health Survey for England [15])



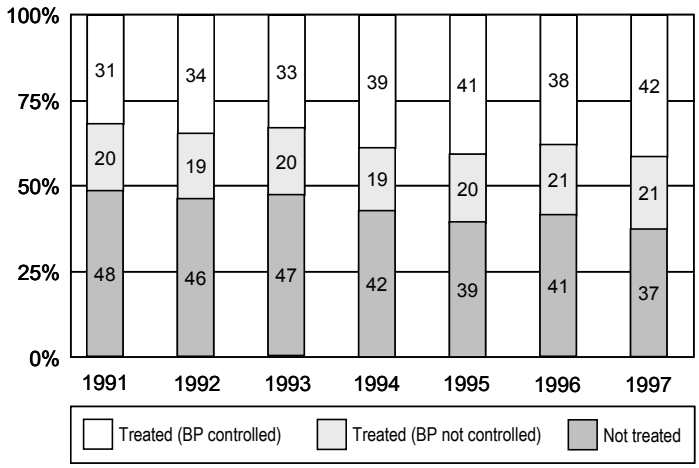
The Health Survey found little variation in the prevalence of high blood pressure among social classes as determined by the head of the household. Participants were asked if they were taking a drug specifically to treat their hypertension. Figure 4 shows the prevalence and use of drugs, for hypertension by age (although the findings do not differentiate between primary or secondary cause of hypertension or evaluate the adequacy of drugs used). Sixty percent of people on drugs took only one drug. Only 9% of people who were hypertensive had their blood pressure controlled so that it was below the target of 140/90 mmHg. Among those whose hypertension was controlled, 59% had received lifestyle advice from their doctors [16].

Figure 4: Prevalence of hypertension in England (≥140/≥90) by age and sex: 1998 (Data source: Health Survey for England [15])



Health Survey data from earlier years using a definition of hypertension of SBP≥160 mmHg and/or DBP≥95 mmHg suggest that adequate treatment of hypertension rose to about 40% of patients in 1997 (Figure 5).

Figure 5: Trend in treatment of adult hypertension (≥160/≥95 mmHg) in England (Data source: Saving Lives: Our Healthier Nation [48])



Hypertension and cardiovascular disease

A number of lifestyle and clinical factors may predispose people to develop cardiovascular disease. These include hypertension, smoking, diabetes mellitus, poor diet, obesity, sedentary lifestyle and aging [17,18]. The relationship between blood pressure and risk of cardiovascular disease has been studied extensively.

An analysis of 61 prospective observational studies, involving nearly one million individuals, explored the relationship between blood pressure level and 12,000 strokes and 34,000 ischaemic heart disease events over an average of 13.2 years follow-up [19]. Across age bands from 40 to 89, reduction in usual diastolic blood pressure of 20 mmHg systolic or 10 mmHg diastolic blood pressure was associated with reductions in death from stroke and ischemic heart disease of about one half, slightly more in the youngest and slightly less in the oldest. Findings were similar for men and women, for different types of stroke, and consistent across the range of blood pressure (down to 115/75 mmHg).

An earlier analysis of nine observational studies, involving 420,000 individuals explored the relationship between blood pressure level and 843 subsequent strokes and 4,856 coronary events over an average of 7 years follow-up [20]. Reductions in usual diastolic blood pressure of 5, 7.5 and 10 mmHg were associated with reductions in stroke of 34%, 46% and 56% and coronary heart disease of 21%, 29% and 37% respectively. The relationship between blood pressure and disease was constant over a wide range suggesting there is no clear threshold below which further reduction in blood pressure becomes unbeneficial or harmful.

The implication of these two studies is that some or all of the predicted benefits, found by comparing individuals with different usual blood pressure levels, could be obtained by one patient maintaining a similar reduction.

A systematic review of 14 antihypertensive randomised drug trials (diuretics or beta-blockers compared with placebo) included 37,000 patients [21]. A mean reduction in diastolic blood pressure of 5-6 mmHg over 5 years achieved a relative reduction in stroke of 42% (95% CI: 33-50%) and CHD of 14% (95%CI: 4-22%). The authors concluded that virtually all of the epidemiologically observed benefit from reduced stroke and over half of the reduction in coronary heart disease could be achieved by lowering blood pressure.

Hypertension, diabetes and ethnicity

There are ethnic differences in the prevalence of high blood pressure. In African American patients, the prevalence of hypertension and mortality arising from complications such as cardiovascular, cerebrovascular and renal disease is higher than other ethnic groups [22,23,24,25,26]. Mortality data from England and Wales (1988-92) shows similar trends, with mortality due to hypertensive complications 3.5 times higher than the national average in the African-Caribbean population [27]. British Asians also exhibit hypertension associated mortality rates 1.5 times higher than the national average [27].

The Whitehall II Study investigated a cohort of London-based civil servants aged 35-56 years, between 1985 and 1988 [28]. A 73% response rate provided a cohort including 8,973 white participants, 577 of South Asian origin and 360 of African-Caribbean origin. Participants were considered hypertensive if they had blood pressure above 160/95 mmHg or were receiving antihypertensive drugs. African-Caribbean (odds ratio: 4.0; 95%CI: 2.8 to 5.7) and South Asian (odds ratio: 2.3; 95%CI: 1.6 to 3.3) participants had a greater prevalence of hypertension than white participants, after findings were adjusted for age, service grade, sex and body mass index. Similarly, diabetes was more common in African-Caribbean (unadjusted odds ratio: 2.8; 95%CI: 1.7 to 4.6) and South Asian (unadjusted odds ratio: 4.2; 95%CI: 3.0 to 5.8) participants. Although both ethnic groups had lower total cholesterol scores that white participants, South Asian people tended to have a poorer lipid profile while African-Caribbean people tended to have a more favourable one.

A study conducted in nine practices in South London interviewed men and women aged 40-59 years of white, African and South Asian origin [29]. Random samples of each group were invited: 64% took some part in the study, although only about one half of these contributed blood pressure data. As with the Whitehall study, individuals were considered hypertensive if they had blood pressure above 160/95 mmHg or were receiving antihypertensive drugs. Age and sex adjusted prevalence ratios for hypertension were 2.6 (95% CI: 2.1 to 3.2) in people of African descent and 1.8 (95% CI: 1.4 to 2.3) in those of South Asian descent. Diabetes prevalence ratios were 2.7 (95% CI: 1.4 to 2.3) and 3.8 (95% CI: 2.6 to 5.6) for those of African and South Asian descent respectively. Differences in ethnic groups (West African vs. Caribbean and Hindu vs. Muslim) were not statistically significant. Similarly to the Whitehall study, people from these ethnic minority groups had lower total cholesterol scores than white participants although a lipid profile was not attempted.

A number of other studies of local populations have explored the relationship between ethnicity and cardiovascular risk factors. These studies raise methodological issues and do not provide a useful picture of hypertension because they did not seek to adjust for treatment. They demonstrate that varying patterns of risk factors may occur in different groups, although these may only be well understood with more definitive epidemiological research. A study comparing South Asian and European participants in Newcastle upon Tyne found that Bangladeshi participants had the poorest lipid profile while Indians had the best, similar to a European profile [30]. The age-adjusted prevalence of diabetes varied between Bangladeshi (23%), Pakistani (23%), Indian (13%) and European (4%) participants. A London based study drawing from factory worker and general practice populations confirmed the findings of the Whitehall II study, showing similar trends in lipid profile comparing European, South Asian and African-Caribbean participants [31]. Similarly a raised age-adjusted prevalence of diabetes was seen in Sikh (20%), Punjabi Hindu (19%), Gujarati Hindu (20%) and Muslim (19%) groups compared to white participants (5%). A survey of Bangladeshi participants in East London found a poor lipid profile and raised prevalence of diabetes compared to a non-Asian population [32].

The evidence thus shows that hypertension and diabetes are more common among certain ethnic groups in the UK. This greater prevalence of hypertension may lead to higher rates of cardiovascular disease and target organ damage [33,34,35,36,37,38]. Reasons for this greater prevalence may be environmental as well as physiological. A trend towards increased blood pressure and weight was observed with increasing urbanisation of rural black Africans [39], and with the migration of Punjabi participants from India to England [40].

Hypertension and NHS resources

It is estimated that a GP with a list of 2,000 patients will have about 400 consultations each year for essential hypertension; the corresponding workload for practice nurses is unclear [41]. Recent prescribing of drugs that affect blood pressure in England and Wales is shown in Table 6.

Table 6: Primary care use of blood-pressure lowering drugs: England 2001 (Data source: Department of Health [42,43])

BNF Chemical name	BNF heading	PXS ('000s)	PXS % change (2002-2001)	NIC (£'000s)	NIC/PXS (£)
• Thiazides and related diuretics	2.2.1	16,092	+13%	22,672	1.41
Loop diuretics	2.2.2	10,519	+5%	16,534	1.57
• Potassium sparing diuretics	2.2.3	1,482	+12%	6,055	4.09
• Potassium sparing diuretics with other diuretics	2.2.4	3,906	-10%	16,774	4.29
• Beta-andrenoceptor blocking drugs (Beta-blockers)	2.4	22,439	+10%	88,780	3.96
Vasodilator antihypertensive drugs	2.5.1	137	-3%	986	7.18
Centrally acting antihypertensive drugs	2.5.2	547	+9%	6,687	12.22
Adrenergic neurone blocking drugs	2.5.3	4	-29%	88	24.85
• Alpha adrenoceptor blocking drugs	2.5.4	3,952	+19%	98,218	24.85
• Angiotensin-converting enzyme inhibitors (ACE-inhibitors)	2.5.5.1	19,921	+14%	270,242	13.57
• Angiotensin receptor blockers (ARBs)	2.5.5.2	5,026	+39%	130,228	25.91
• Calcium-channel blockers	2.6.2	17,928	+6%	290,225	16.19
Total		101,953	+10%	947,489	9.29

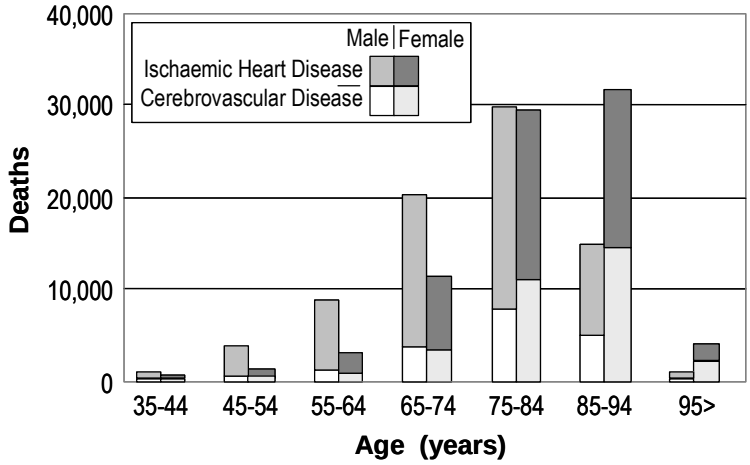
• Classes regularly used to treat essential hypertension

BNF British National Formulary [44]
PXS Prescription items dispensed;
OWC2 Class 2 drugs reimbursed at the proprietary price when generic unavailable;
NIC Net Ingredient Cost: cost of the drug before discounts and excluding dispensing costs; and
NIC/PXS: Cost per prescription.

A more detailed breakdown of drug use is found in Appendix 3. Thiazide-type diuretics, beta-blockers, ACE-inhibitors and calcium-channel blockers are used in similar quantities in primary care, although their costs vary by a factor of ten. These drugs are used for a range of conditions but their most common use is to treat raised blood pressure. Roughly, the NHS writes over 90 million scripts annually at a cost of £840 million, which is nearly 15% of the total annual cost of drugs in primary care.

Deaths directly following hypertensive disease are rare (3000 in the year 2000 or 0.5% of all deaths). However hypertension contributes to 100,000 deaths from coronary heart disease and 50,000 from cerebrovascular disease (respectively about 20% and 10% of all deaths in 2000). The age distribution of mortality is shown in Figure 6.

Figure 6: Deaths from coronary and cerebrovascular disease in England and Wales, 2000 (Data source: Office for National Statistics [45])



Stroke causes substantial disability, and may have long term negative impact upon quality of life. Annually 110,000 people in England and Wales experience a first stroke, and 30,000 people have further strokes [46]. Coronary and cerebrovascular diseases make considerable demands on secondary care. In terms of bed occupancy alone, these diseases account for about 4 million bed days, 8% of the total capacity of the NHS (Table 7).

Table 7: Annual hospital inpatient usage for treating cardiovascular diseases: England, 2000/1: (Data source: Hospital Episode Statistics [47]).

Condition	Finished Consultant Episodes	Average Length of Stay	Number of bed-days*
Hypertensive disease	17,953	7.3	84,730
Ischaemic heart disease	378,532	6.8	1,706,816
Cerebrovascular disease	144,661	26.4	2,368,443

* These data exclude bed-days falling outside the study period.

Because of its prevalence, the management of hypertension places great demands on health care providers. The successful management of hypertension is a priority for the NHS [48].

Measuring blood pressure

Recommendations and supporting statements

• **Health care professionals taking blood pressure measurements need adequate initial training and periodic review of their performance.**	**C**
• **Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions.**	**C**
• **Where possible standardise the environment when measuring blood pressure: provide a relaxed, temperate setting, with the patient quiet and seated and with their arm outstretched and supported.[+]** + *See Box 1: Estimating blood pressure by auscultation.*	**C**
• **If the first measurement exceeds 140/90 mmHg*, if practical, take a second confirmatory reading at the end of the consultation.** * *Blood pressure is recorded as systolic blood/diastolic blood pressure measured in millimetres of mercury (mmHg). Raised blood pressure is noted when either systolic blood pressure exceeds 140 mmHg or diastolic blood pressure exceeds 90 mmHg.*	**C**
• **Measure blood pressure on both of the patient's arms with the higher value identifying the reference arm for future measurement.**	**C**
• **In patients with symptoms of postural hypotension (falls or postural dizziness) measure blood pressure while standing. In patients with symptoms or documented postural hypotension (fall in systolic BP when standing of 20mmHg or more) consider referral to a specialist.**	**C**
• **Refer immediately patients with accelerated (malignant) hypertension (BP more than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage) or suspected pheochromocytoma (possible signs include labile or postural hypotension, headache, palpitations, pallor and diaphoresis).**	**C**
• **To identify hypertension (persistent raised blood pressure above 140/90 mmHg), ask the patient to return for at least two subsequent clinics where blood pressure is assessed from two readings under the best conditions available.**	**C**
• **Measurements should normally be made at monthly intervals. However patients with more severe hypertension should be re-evaluated more urgently.**	**C**

• **The value of routinely using automated ambulatory blood pressure monitoring or home monitoring devices as part of primary care has not been established: their appropriate use in primary care remains an issue for further research.**	**B**
- Readings from clinic and ambulatory blood pressure devices, when used side-by-side, may differ from one another and from true arterial pressure because they use different methods and assumptions.	II
- Average ambulatory readings from a series of patients, taken over 24 hours, are commonly lower than clinic readings by between 10/5 and 20/10 mmHg. However, an individual patient may have ambulatory readings higher or lower than clinic readings. Studies comparing clinic and ambulatory measurement vary in their design, setting, conduct of measurement and analysis: estimated differences between ambulatory and clinic values vary with these factors.	II
- Clinic and ambulatory readings may also differ due to a 'white coat' effect, a response to the setting or clinician.	II
- Epidemiological studies are inconsistent in demonstrating the additional prognostic value of ambulatory blood pressure monitoring to predict cardiovascular disease in unselected patients.	II
• **Consider the need for specialist investigation of patients with unusual signs and symptoms, or of those whose management depends critically on the accurate estimation of their blood pressure.**	**C**

Introduction

There is considerable guidance in the academic literature about how blood pressure should be measured. A comparison of the recommendations found in published guidelines (see Appendix 2) illustrates the range of opinion but fails to describe the pragmatism sometimes needed when measuring blood pressure in less than ideal circumstances. These limitations accepted, it is correct to aim to measure blood pressure in a standardised manner and thus measurement technique, equipment, setting and sources of error have to be considered.

Technique

Systolic pressure should be estimated by first palpating the brachial pulse with slow deflation of the cuff. The cuff is reinflated before listening for Korotkoff sounds. The first pass is important since sometimes the first sounds disappear as pressure is reduced (the auscultatory gap) leading to an underestimation of systolic pressure by auscultation alone. In a case series, 21% of 168 untreated hypertensive patients demonstrated an auscultatory gap [49]. A number of summaries are available highlighting good technique: an adaptation of these is shown in Box 1.

Box 1: Estimating blood pressure by auscultation

- Standardise the environment as much as possible:
  - Relaxed, temperate setting, with the patient seated
  - Arm out-stretched, in line with mid-sternum and supported
- Correctly wrap a cuff containing an appropriately sized bladder around the upper arm and connect to a manometer. Cuffs should be marked to indicate the range of permissible arm circumferences; these marks should be easily seen when the cuff is being applied to an arm.
- Palpate the brachial pulse in the antecubital fossa of that arm.
- Rapidly inflate the cuff to 20 mmHg above the point where the brachial pulse disappears.
- Deflate the cuff and note the pressure at which the pulse reappears: the approximate systolic pressure.
- Re-inflate the cuff to 20 mmHg above the point at which the brachial pulse disappears.
- Using one hand, place the stethoscope over the brachial artery ensuring complete skin contact with no clothing in between.
- Slowly deflate the cuff at 2-3 mmHg per second listening for the Korotkoff sounds.

Phase I:	The first appearance of faint repetitive clear tapping sounds gradually increasing in intensity and lasting for at least two consecutive beats: note the systolic pressure.
Phase II:	A brief period may follow when the sounds soften and or 'swish'.
Auscultatory Gap:	In some patients the sounds may disappear altogether.
Phase III:	The return of sharper sounds becoming crisper for a short time.
Phase IV:	The distinct, abrupt muffling of sounds, becoming soft and blowing in quality.
Phase V:	The point at which all sounds disappear completely: note the diastolic pressure.

- When the sounds have disappeared, quickly deflate the cuff completely if repeating the measurement.
- When possible, take readings at the beginning and end of consultations.

There has been some controversy as to whether phase IV or phase V sounds should be used to record diastolic blood pressure. Commonly, the difference in pressure between phase IV and V is less than 5 mmHg but occasionally can be substantial. Phase V can be absent with sounds audible to zero cuff pressure notably in some children, during pregnancy, with anaemia, aortic insufficiency and with elderly people. Phase V correlates better with direct measurement, is commonly used in clinical trials of antihypertensive therapies, and is more reproducible when assessed by different observers. There is now general consensus that phase V should be taken as the diastolic pressure except when absent [11,54,55].

Cuffs

Modern cuffs consist of an inflatable cloth-enclosed bladder which encircles the arm and is secured by Velcro or by tucking in the tapering end. The width of the bladder is recommended to be about 40%, and its length 80%, of the arm circumference. Manufacturers are now required to provide markings on the cuff indicating the arm circumference for which it is appropriate (BS EN 1060-1) [50]; these marks should be easily seen when the cuff is being applied to an arm. When the bladder is too small (under-cuffing) it is possible to overestimate blood pressure. The existence of over-cuffing and consequent underestimation is contentious although likely to be of smaller magnitude [10,51,52]. Research on adjustable cuffs is ongoing [55] although some guidelines recommend using large cuffs in all adults [54].

Setting

Blood pressure is maintained by a combination of mechanical, neuronal and endocrine self-regulating systems in the body. These systems can alter blood pressure in response to changes in environment. Individual readings are influenced (for example) by age, ethnicity, disease, the time of day, posture, emotions, exercise, meals, drugs, fullness of bladder, pain, shock, dehydration, acute changes in temperature and changes in altitude. These influences can be substantial, altering systolic readings by as much as 20 mmHg [53].

Standardising the environment in which blood pressure measurements are made reduces variation and enhances the interpretation of a series of readings taken over time [54,55]. A quiet, comfortable location at normal room temperature is optimal. Ideally, the patient should not need to pass urine, not recently have eaten, smoked or taken caffeine or exercise. Allowing the patient to rest at least five minutes before measurement is also advised [53,54,55].

Blood pressure readings tend to increase as patients move from the supine to standing position. The change may not be significant, but it is traditional for measurements to be taken whilst seated. Certain patients demonstrate a significant lowering of blood pressure when standing (postural hypotension) [53,54,55,56,57].

Blood pressure readings also tend to increase as the patient's arm is lowered below the horizontal and decrease when the arm is raised. Positioning the patient's arm out-stretched, level with their heart and in line with their mid sternum, supported by a table or some other means, prevents the patient exercising their arm [53,54,55,58,59]. The exercise effect is accentuated if the patient's arm remains outstretched for some time and also by certain drugs such as beta-blockers [XIV,53]. Differences in readings may occur according to the arm chosen in patients with narrowed arteries. Clinicians are commonly advised to take readings in both of the patient's arms initially, and subsequently use the arm that produces the higher reading. Consistent inter-arm differences of over 20/10 mmHg may suggest pathology warranting specialist referral [53,54,55].

Frequency of measurements

Given the range of factors that influence blood pressure and potential adverse consequences for the patient of misdiagnosis, guidelines recommend multiple visits to clinics before establishing a diagnosis and some guidelines further recommend multiple readings within each clinic visit. Before diagnosing mild hypertension the BHS guideline recommends two measurements per visit, repeated monthly over four to six months [IV]. The Joint National Committee (JNC VII) recommends two readings on each visit, separated by at least two minutes [XI]. Most randomised controlled trials investigating antihypertensive therapy have adopted similar approaches, measuring BP several times on two or more visits.

No evidence-based optimal pattern of measurement for assessing blood pressure in primary care was identified from the medical literature. The consensus of the guideline development group, when identifying hypertension opportunistically or during a planned health assessment, was to perform a sequence of confirmatory measurements. Patients with initial raised blood pressure (more than140/90 mmHg) should be invited to return to give second and third clinic readings under the most appropriate conditions available (see Box 1). A reading taken at the beginning and end of the consultation may help to determine the presence of a white coat effect (see page 56), in which case the lower reading should be taken. If raised blood pressure persists after the third clinic visit, a full assessment of the patient's cardiovascular risk should be used to inform discussions about care options, using the average of the recorded readings in the risk assessment (see: *Routine clinical investigations*, page 63).

Sources of error

Three types of error have been identified for the RRK technique. Failure to accurately identify the Korotkoff sounds can lead to over or under estimation. Digit preference refers to the tendency of clinicians to round readings up or down, often to the nearest zero. Observer prejudice occurs when clinicians alter readings toward their prior expectation, a particular concern when close to a threshold which changes management [10,11]. Supervised training and periodic reassessment may help minimise errors.

Devices

There is considerable guidance about the range of appropriate devices for measuring blood pressure [60,61,62] and about their maintenance and periodic recalibration [63]. Local medical physics and biomedical/clinical engineering departments can often give further advice.

The mercury manometer has been used traditionally for the measurement of blood pressure with the RRK technique. It is reliable and provides the reference standard for indirect measurement. However it is bulky, fragile and there are particular safety and economic concerns about the toxic effects of mercury. Environmental pressure has caused mercury manometers to be withdrawn from use in many countries and their use is decreasing in British primary and secondary care. The demise of the mercury manometer removes the compelling reason for retaining mmHg as the unit of pressure, and there is a debate as to whether to change to the kilopascal (SI unit) used by the scientific community [64].

Aneroid sphygmomanometers are more complex than mercury manometers, measuring pressure using a lever and bellows system. They are susceptible to knocks and may be less accurate than manometers, especially over time. Using the RRK technique they are subject to the same sources of observer error [11]. Automated devices are increasingly being used in hospitals and general practice.

All sphygmomanometers need regular maintenance. Rubber tubing can crack and leak making cuff deflation hard to control, underestimating systolic and overestimating diastolic readings. Faulty valves can cause similar problems [11].

White Coat Hypertension

The observation that clinicians (signified by their white coats) can cause spuriously high blood pressure readings in patients was first described in the 1940s [65]. Additionally, sympathetic symptoms such as sweating, tachycardia and palpitation sometimes occur. The effect is short-lived with blood pressure dropping to normality after or near the end of the consultation. Consequently, a patient may present as hypertensive in clinic (in a primary or secondary care setting) but be normotensive otherwise.

White Coat Hypertension (WCH) is estimated to occur in 15% to 30% of the population [3], although this may be inflated due to inadequate evaluation of patients. It is more common in pregnancy and with increasing age although poorly understood otherwise [66]. The size of white coat effect in individuals can vary over time and a small proportion (4%) may demonstrate atypical very high clinic readings [54]. There are no validated criteria currently available for diagnosing WCH. A definition of the presence of WCH might be if a patient's ambulatory – clinic pressure difference exceeds the norm or population average. However, available studies provide varying estimates of the norm.

Failing to identify WCH makes inappropriate treatment for hypertension in normotensive patients a possibility. Similarly, hypertensive individuals can also exhibit WCH and may receive inappropriate dose titrations or additional antihypertensive agents [67,68,69]. It is unclear whether WCH is a pre-hypertensive state or whether such patients are at increased risk of cardiovascular disease or target organ damage [70,71, 72,54]. Patients have historically been enrolled in trials using clinic BP values, and these trials will almost certainly have included a proportion of patients with WCH. It is unknown whether benefits of treatment differ substantially in those with or without WCH.

When blood pressure appears elevated during a clinic visit but not during ambulatory or home blood pressure monitoring this may indicate WCH, although a simple comparison of readings is problematic (see: *Interpreting ambulatory blood pressure* on *page 57*). WCH may also be captured by inconsistencies, for example: differences in doctor and nurse readings; differences at the start and end of consultations; and, discrepancies between readings in clinic and other healthcare settings [73].

Moving from clinic-based to ambulatory methods of measuring blood pressure has been proposed, since ambulatory methods can provide an average reading over 24 hours and a number of days.

Ambulatory and Home Blood Pressure Monitoring

Ambulatory blood pressure monitoring

Ambulatory Blood Pressure monitoring (ABPM) involves a cuff and bladder connected to electronic sensors which detect changes in cuff pressure and allow blood pressure to be measured oscillometrically. The cuff is inflated by a battery powered compressor and sensors within the cuff detect changes in pressure oscillations during cuff deflation. Systolic and diastolic pressure readings are deduced from the shape of these oscillometric pressure changes using an algorithm built into the measuring device. Developed as a research tool in the 1960s, these devices have considerably reduced in size and now can be described properly as ambulatory. Thus a patient's blood pressure can be automatically measured at repeated intervals (commonly every 30 minutes) throughout the day and night, while they continue routine activities. Systolic and diastolic pressure can be plotted over time, with most devices providing average day, night and 24 hour pressures [3] (see Figure 2, page 42).

An advantage of ABPM is the removal of observer error with automated reading. However, oscillometric measurement may be difficult in the presence of arrhythmias, particularly rapid atrial fibrillation, and in a subgroup of the general population in whom oscillometric readings are inaccurate for unknown reasons [3,64].

A number of ABPM devices are available varying in size, weight, noise level, data manipulation and cost [74,75]. Devices should be independently validated to one or both of two internationally accepted standards from the British Hypertension Society and the Association for the Advancement of Medical Instrumentation [76,77,78].

When using ABPM, patients need some understanding of how the device works and instruction about manual deflation, missed readings, arm position, and machine location: fitting takes 15-30 minutes. An appropriately sized cuff is necessary as with non-ambulatory monitoring and if one arm gives a higher reading at baseline then this should be used subsequently. Patients may be asked to make diary records of events that are known to affect blood pressure so that readings can be related to them, for example, periods of sleep. Sleeping times can be recorded or fixed times may be predefined, including preparing for sleep (e.g. 9pm - midnight) and waking up (e.g. 6am – 9 am) [3,75].

Interpreting ambulatory blood pressure

Oscillometry and auscultation are both indirect methods of measuring blood pressure. Different methods and assumptions mean these can vary in the readings they provide when both devices are used in identical conditions either in a clinic or community setting. When averaged over a day, ambulatory pressures measurements tend to be lower than their clinic readings with the result that some adjustment is necessary to compare the two methods. For example, the British Hypertension

Society recommends a downward correction of 12/7 mmHg when converting clinic to ambulatory values. Then WCH may be defined to exist in an individual when the clinic-ambulatory difference exceeds this correction value [71]. Studies have shown that while a lower average ambulatory value is typical, a minority of patients actually record higher ambulatory than clinic values [90,79,80]. Consequently, if only ambulatory values are taken, average corrections are useful in population studies but inappropriate to correct the readings of individuals.

Various methods have been used to determine normal ambulatory levels [67,71,81]. Most commonly, ambulatory pressures of patients recruited with normal clinic pressures are compared with normal clinic readings [72,82]. Distributions of office and ambulatory pressures have been correlated permitting an upper normal ambulatory value to be obtained by extrapolation from a defined upper normal clinic value [73,83]. Alternatively ambulatory and clinic values have been correlated with left ventricular hypertrophy (LVH) and other indices of target organ damage [84,85,86,87,88,89,90,91,92].

Recommended threshold ABPM values have been reported (Table 8) although a 'grey' area exists between normal and raised blood pressure [3,67,81,IV,X,XI,93]. A minority of studies have recommended even lower thresholds [VII,94].

Table 8: Recommended threshold levels for ambulatory blood pressure measurement [3]

	Normal	Abnormal
Daytime	≤135/85	>140/90
Night time	≤120/70	>125/75
24 Hour	≤130/80	>135/85

Home or self-monitoring blood pressure devices

Home monitoring devices are oscillometric, measuring BP on the upper arm, the wrist or the finger. Finger devices are not recommended as peripheral vasoconstriction, sensitivity of posture and the distal location may all lead to inaccuracy [97]. Potentially, wrist devices may have similar limitations but to a lesser degree. When used, measurement on the upper arm using an appropriately sized cuff, good technique and independently validated device is recommended.

Self measurement devices are popular with some patients. A range of automated, small and lightweight devices are available, typically costing £30-£300. As with ambulatory devices, home monitoring devices should be independently validated.

Home monitoring potentially offers some similar benefits to ABPM. Frequent measurement produces average values that may be more reproducible and reliable that traditional clinic measurement. Potentially, white coat hypertension, systematic error, terminal digit preference and observer prejudice can be removed [95,97,98]. Home monitoring allows patients to assess their own response to

antihypertensive medication, which may increase compliance with treatment. It has been argued that better evaluation provided by home monitoring may reduce unnecessary treatment, increase compliance and thus deliver cost savings [67,81]. The impact of home monitoring upon net treatment costs and cost-effectiveness needs to be evaluated by properly designed prospective studies. Home blood pressure devices are thought by some professionals to cause anxiety or obsessive self interest [96,97,98,74].

Potential disadvantages stem from the need for appropriate training to avoid biased measurement. Use of inappropriately sized cuffs, isometric exercise when not resting the arm, measurement after or during exercise and observer prejudice (for non-automated recording) are possible [54]. One study found that only 30% of patients using a manual home blood pressure monitor correctly adhered to the protocol. Further, less than 70% of the self-reported measurements were identical to those simultaneously recorded by the machine [99]. Observer bias was more apparent in those patients who were more hypertensive or whose readings showed more variation. As with ABPM, home monitoring devices are oscillometric and may have difficulty measuring pressure in cases of arrhythmias, and in certain patients for no apparent reason.

Self measurement may not be as effective in identifying white coat hypertension as ABPM. A study using ABPM as the reference test showed home BP monitoring to be highly specific (85%) but only moderately sensitive (57%) in detecting white coat hypertension [102]. An obvious limitation is the inability to measure sleeping pressures, and thus detect the extent of nocturnal dipping.

There is currently no consensus about the frequency, timing or number of measurements to be taken when calculating a home measurement mean value. The monitoring schedule employed may not be critical. One study reviewed schedules in 12 trials comparing home measurement with ambulatory and clinic measurements [100]. Although large differences were apparent between the schedules, no significant differences in the accuracy of mean home measurement values were demonstrated. Others have reported similar findings [101].

Interpreting self-measured blood pressure

As with ambulatory monitoring, the threshold values of self-monitored blood pressure which indicate hypertension need to be determined. The same methodologies used in ABPM have been used to try to establish threshold values for home monitoring. A synthesis of 17 studies attempted to determine normal home measurement values [102]. Home measured BP averaged 115/71 mmHg. Two standard deviations above the mean pressure of normotensive patients from these studies was 137/89 mmHg and the 95th percentile was 135/86 mmHg. Consequently the threshold most commonly recommended currently is 135/85 mmHg, identical to mean daytime ambulatory BP [XI,97]. The British Hypertension Society recommends a downward correction of 12/7 mmHg to clinic values when comparing with home monitoring values [93].

Predicting target organ damage and cardiovascular disease.

If clinic blood pressure measurements are inaccurate this may weaken the relationship between blood pressure and cardiovascular risk. Studies were systematically identified and retrieved that prospectively compared the ability of ambulatory, home and clinic measures of blood pressure to predict fatal or non-fatal cardiovascular events. Studies addressing markers of evolving disease, such as left ventricular mass or hypertrophy, were not included because of their uncertain relationship with patient outcome.

Details of six reports relating to four cohorts of patients were abstracted (Appendix 5). Studies were conducted in London, England [103], Ohasama, Japan [104,105], Umbria, Italy [106,107,108,109] and the final cohort was provided by European patients enrolled in a drug trial [110]. Two further studies are ongoing [111,112,113].

The four cohorts included about 4,500 participants; approximately 50% of participants were male and their mean age was nearly 55 years. Most participants were Caucasian or Japanese reflecting the location of the studies. The mean length of follow-up was 5 years.

The British study investigated ambulatory blood pressure using an intra-arterial cannula, and thus its findings may not generalise to indirect ambulatory measurement. This limitation accepted, 24 hour, day or night direct measurements predicted cardiovascular events whereas clinic measurement did not.

The Ohasama study compared self-measured home BP and clinic BP. Neither method demonstrated superior prediction of first stroke, although home measurement appeared to be a better predictor of cardiovascular mortality.

In the Italian cohort, ambulatory 24-hour systolic blood pressure was a better predictor than clinic assessment for cardiovascular morbidity and mortality. The analysis suggested that white coat hypertension and nocturnal dipping are independently associated with the risk of cardiovascular disease, the implication being that those not demonstrating a white coat effect or nocturnal dipping are at greater risk. It is plausible that a nocturnal reduction in blood pressure may protect target organs, although the definition of ‘non-dippers’ currently varies between studies (examples include a mean nocturnal pressure fall of less than 10% or an absolute reduction of less than10/5 mmHg). Varying definitions, as well as classification of day and night periods, may explain differences in the prevalence of non dippers seen in studies.

The SYST-EUR trial enrolled 4,695 patients into a trial comparing calcium-channel blocker initiated blood pressure control and placebo. A sub-study conducted in 46 of the 198 participating centres compared the prognostic value of ambulatory and clinic blood pressure readings. When treatment and placebo groups were taken together, this study provided no evidence that ambulatory values more accurately predicted cardiovascular morbidity or mortality than clinic readings.

Combining the evidence from these four cohorts, the difference in prognostic accuracy of home, ambulatory and clinic measures appears small and inconsistent. None of these studies adequately described their approach to analysing their data or the statistical robustness of models produced. A further potential confounder was the adequacy of clinic baseline measurements. It is possible that SYST-EUR, which had better baseline clinic assessment, minimised the 'regression to the mean' phenomenon and obtained more representative values. On the other hand, it is clear from large epidemiological studies that there is a very precise relationship between periodic clinic based blood pressure measurements and risk of cardiovascular disease [19,20].

Evidence is limited on the degree to which ambulatory and home monitoring blood pressure can be used to determine cardiovascular prognosis. Further adequately-designed, independent research is required on the additional cost and prognostic value of these approaches.

Using ambulatory and home monitoring appropriately

A number of guidelines and reviews provide indications for the appropriate use of ambulatory monitoring [54,IV,VI,X,XI]. ABPM's potential uses are to eliminate white coat hypertension as a source of misdiagnosis or mistreatment; to investigate treatment-resistant patients; to investigate patients with hypertensive clinic values but hypotensive symptoms; to identify nocturnal hypertension; and, to resolve unusual variability in patients' clinic readings. Use should be targeted to those patients where additional information obtained by ABPM may lead to a change in patient management, in terms of advice or interventions offered.

There is currently no consensus about the appropriate use of home monitoring. Protagonists argue that home monitoring mean results are not sensitive to the monitoring schedule used, are more reproducible and reliable than clinic readings and should be considered when more intensive monitoring is desirable, for example in cases of poor compliance [67,98,95]. Its usefulness as a tool in any context will depend upon good technique and validated equipment.

Ambulatory BP monitoring remains relatively expensive to deliver and requires trained staff. By comparison, home monitoring is much less expensive and devices are now available that are accurate and validated [97]. Both ambulatory and home measurement may plausibly reduce prescribing costs by curtailing antihypertensive prescriptions for patients who only exhibit white coat hypertension. Two randomised trials comparing the prognostic value of ambulatory and clinic measurements were retrieved [114,115] and these are described in Appendix 4: both have design limitations. Currently there are no adequate prospectively designed studies that demonstrate the effectiveness or cost effectiveness of home or ambulatory blood pressure monitoring.

Most hypertension is diagnosed and managed within primary care and it has not been demonstrated that excluding white coat hypertension by ABPM in all clinically diagnosed hypertensive patients is either practical or a good use of resources. Other parts of this guideline make clear that treatment

should not rest upon blood pressure alone but upon cardiovascular risk profile, and that clinic-based measurement requires a series of values taken in conditions designed to minimise contemporaneous influences. Currently ABPM is commonly conducted in specialist hypertension clinics. Restricting ABPM use to patients selected by referral may provide better value for money currently than widespread diffusion of this technology into primary care [93,54]. This approach may result in some patients with white coat hypertension receiving unnecessary treatment. However, if these patients are treated on the basis of substantially raised cardiovascular risk rather than hypertension in isolation, epidemiological and trial evidence indicates a favourable risk-benefit ratio [19,20,21].

Estimating cardiovascular risk

Recommendations and supporting statements

• **If raised blood pressure persists and the patient does not have established cardiovascular disease, ask to formally assess the patient's cardiovascular risk. Tests may help identify diabetes, evidence of hypertensive damage to the heart and kidneys, and secondary causes of hypertension such as kidney disease.**	**C**
• **Test for the presence of protein in the patient's urine. Take a blood sample to assess plasma glucose, electrolytes, creatinine, serum total cholesterol and HDL cholesterol. Arrange for a 12 lead electrocardiograph to be performed.**	**C**
• **Consider the need for specialist investigation of patients with signs and symptoms suggesting a secondary cause of hypertension. Accelerated (malignant) hypertension and suspected pheochromocytoma require immediate referral.**	**B**
- An identifiable cause of hypertension is more likely when hypertension occurs in younger patients (less than 30 years of age), worsens suddenly, presents as accelerated (malignant) hypertension (BP more than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage) or responds poorly to treatment.	III
- An elevated creatinine level may indicate renal disease. Labile or postural hypotension, headache, palpitations, pallor and diaphoresis are potential signs of pheochromocytoma. Hypokalaemia, abdominal or flank bruits, or a significant rise in serum creatinine when starting an ACE-inhibitor may indicate renovascular hypertension. Isolated hypokalaemia may be due to hyperaldosteronism. Potential signs of Cushing syndrome include osteoporosis, truncal obesity, moon face, purple striae, muscle weakness, easy bruising, hirsutism, hyperglycemia, hypokalaemia, and hyperlipidaemia.	III
• **Use the cardiovascular risk assessment to discuss prognosis and healthcare options with patients, both for raised blood pressure and other modifiable risk factors.**	**B**
- Risk models provide a useful prognostic tool for clinicians and patients in primary care. They reinforce the need to offer treatment to patients based on their profile of cardiovascular risk rather than focusing on blood pressure in isolation.	II
- Most risk models derive from the Framingham Heart Study: a cohort of over 5,000 men and women aged 30 to 62 from Framingham, Massachusetts followed-up from 1971 to assess the determinants of cardiovascular disease.	II
- Limitations of commonly used risk models include poor validation in UK ethnic minorities and younger populations.	II
- Framingham risk calculator computer programmes currently provide the best assessment of risk of coronary heart disease and stroke over 10 years. The latest version developed by the Joint British Societies gives the risk of a cardiovascular event over 10 years (a combined score including the risk of coronary heart disease and stroke).	II
- Risk charts may be relatively imprecise, placing patients in bands of risks, although the visual presentation may be helpful to some patients. Evidence suggests that the Joint British Societies chart adheres most closely to Framingham risk calculators.	III
- When only the CHD risk score is known, CVD risk score can be approximated by multiplying by 4/3. When CHD and stroke risk are reported, the CVD risk can be approximated by adding these two scores together.	III

Routine clinical investigations

A full cardiovascular assessment should be conducted in patients with persistently raised blood pressure who do not have established cardiovascular disease. There is no firm evidence from which to define the exact composition of assessment and recommendations are consensus-based. Medical history, physical examination, and limited diagnostic testing serve to identify an individual patient's

profile of cardiovascular risk factors including age and gender, smoking, hyperlipidaemia, diabetes, and family history of cardiovascular disease. Testing may detect diabetes and identify signs of developing target organ damage such as left ventricular hypertrophy and angina. It may also detect secondary causes of hypertension.

The guideline group identified the following tests as necessary to obtain an accurate profile of cardiovascular risk. These tests may help identify diabetes, evidence of hypertensive damage to the heart and kidneys, and secondary causes of hypertension such as kidney disease:

- Urine strip test for blood and protein
- Blood electrolytes and creatinine
- Blood glucose
- Serum total and HDL cholesterol
- 12 lead electrocardiogram.

Urine testing for proteinuria

The presence of protein in urine identifies patients with kidney damage, but does not distinguish between patients who have renal disease and secondary hypertension and those in whom kidney damage is due to essential hypertension. The test consists of dipping a test strip, which is impregnated with chemicals which react to protein, into a sample pot of urine. After 30-60 seconds (or according to manufacturer's instructions) the strip is read alongside a colour code provided. A test takes about 5 minutes; 100 urine testing strips cost about £25. A more sensitive test for urine protein is available by requesting the local chemical biochemistry laboratory to assay microalbumin in a random specimen of urine.

Blood electrolyte, urea, creatinine, glucose and total/HDL cholesterol levels.

These are measured in serum or plasma (glucose) using standard clinical biochemistry methods. Sodium and potassium levels are checked to exclude hypertension resulting from adrenal disease. Likewise, urea and creatinine measurements, which reflect kidney function, are measured to exclude kidney disease as a secondary cause of hypertension Glucose levels are tested to evaluate diabetes and cholesterol profiles are used to assess cardiovascular risk. A test takes about 5 minutes and pathology costs are about £10.

A blood test involves seating the patient comfortably, identifying a suitable vein, most commonly in the anterior cubital fossa, and using a tourniquet applied to the patient's upper arm. Blood is obtained using either a needle and syringe or a blood retrieval system.

12 lead electrocardiogram

An electrocardiogram (ECG) is recorded by placing electrodes at standard positions on the patient's arms and legs (limb leads) and on the chest wall (chest leads). The electrocardiograph amplifies the heart's electrical activity and produces a recording of 12 traces which reflects electrical activity corresponding to different positions around the heart. From this tracing, it is possible to determine heart rate, rhythm, conduction abnormalities, left ventricular size and damage to specific regions of the heart muscle. The presence of electrocardiographic left ventricular hypertrophy is a variable used in the Framingham risk calculator to assess cardiovascular risk. An echocardiogram might be considered, to confirm or refute the presence of LVH suggested by ECG findings. Currently there is insufficient evidence to recommend transthoracic echocardiogram as a routine investigation for all or selected patients in primary care.

A typical ECG requires time to adjust clothing, explanation, cleaning the skin, attaching electrodes to the appropriate positions on the patient's limbs and chest wall with red dots and performing the recording.

ECG machines commonly cost between £1000 and £2000: together with costs of servicing this is amortised over the useful life of the machine, making the cost per test small. More important is the cost of health service staff time taken to prepare and test patients. Allowing for preparation a test takes 15 to 20 minutes to conduct, costed at about £10 in 2002 [116].

Secondary Hypertension

- An identifiable cause of hypertension is more likely when hypertension occurs in younger patients (less than 30 years of age), worsens suddenly, presents as accelerated (malignant) hypertension (BP more than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage) or responds poorly to treatment. III
- An elevated creatinine level may indicate renal disease. Labile or postural hypotension, headache, palpitations, pallor and diaphoresis are potential signs of pheochromocytoma. Hypokalaemia, abdominal or flank bruits, or a significant rise in serum creatinine when starting an ACE-inhibitor may indicate renovascular hypertension. Isolated hypokalaemia may be due to hyperaldosteronism. Potential signs of Cushing syndrome include osteoporosis, truncal obesity, moon face, purple striae, muscle weakness, easy bruising, hirsutism, hyperglycemia, hypokalaemia, and hyperlipidaemia. III

Secondary hypertension refers to high blood pressure from an identifiable underlying cause. It may occur in up to 5% of hypertension cases, the most common cause being chronic renal disease. Other principal identifiable causes are renovascular hypertension, pheochromocytoma, Cushing syndrome, and primary aldosteronism. The prevalence of identifiable causes may be overestimated because of referral bias, where patients are included in studies only after being referred for resistant or difficult to control hypertension. Opinions differ about what causes should be classified as secondary hypertension: sometimes drug-induced hypertension and sleep apnoea are excluded [117].

Signs and symptoms of the main causes of secondary hypertension and available diagnostic tests are summarised, although many of these techniques are not provided in primary care but accessed through specialist referral. However, chronic renal disease may become evident from the findings of

blood urea, creatinine and urine analysis [56,118,119]. We retrieved no useful diagnostic studies which might establish primary care screening characteristics for secondary causes of hypertension as a basis for referral: current advice is simply to be aware of signs and symptoms and refer on the basis of a high index of suspicion and where the findings are likely to necessitate specialist management.

Renal and renovascular disease

Chronic renal disease is the most common identifiable cause of hypertension occurring in 2% to 5% of patients [117]. Renovascular disease includes a range of related conditions: renal artery stenosis, renovascular disease and renovascular hypertension, and may occur in 0.2% to 0.7% of patients. The constriction of renal blood flow and disorders that damage renal tissue may cause the kidneys to release excessive amounts of renin (an enzyme) into the blood. This promotes angiotensin II formation, having a powerful vasoconstrictor effect (raising blood pressure). In individual patients it may not be clear whether renal disease proceeds hypertension or vice-versa and the consequent clinical management may be similar. However, ACE-inhibitors are contra-indicated in patients with known or suspected renovascular disease, since in severe cases their use may lead to renal failure. In patients with renal impairment (plasma-creatinine concentration above 150 micromol/litre), ACE-inhibitors should be initiated under specialist supervision and with careful monitoring. The British National Formulary advises against routinely using ACE-inhibitors in patients with known or suspected renovascular disease [44].

Signs and symptoms indicating that hypertension may be associated with renal disease are: young onset of hypertension (before 30 years of age), sudden onset of hypertension or progressive deterioration in middle age, accelerated (malignant) hypertension (BP more than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage), oliguria (urine output <250 ml/day) or anuria (<50 ml/day), oedema, acidosis (acidic blood, <pH), abnormal serum urea or creatinine, systolic or diastolic 'bruit' (an unexpected audible swishing sound or murmur) [118], drug resistant hypertension or increased creatinine with ACE-inhibitor, hypertension onset > 60 years, DBP >110 mmHg, and anaemia (lowered red blood cell count) resulting in insufficient oxygen to tissues and organs. Although renal artery stenosis is suggested by the presence of an abdominal or flank bruit (sound heard by stethoscope), it is an insensitive test (sensitivity=65%; specificity=90%). When present it is a good marker (positive likelihood ratio=6.5) but when absent does not rule out renal artery stenosis (negative likelihood ratio=0.4) [117,120].

Renal disease may be diagnosed by elevated serum levels of urea or creatinine (found by a blood test) or reduced creatinine clearance (found by a blood and urine test). Specialist investigation includes magnetic resonance angiography for imaging of the kidneys, captopril (Capoten)-augmented radioisotopic renogram testing where an ACE-inhibitor is given and a scan taken to see if the drug reduces renal function in the ischaemic kidney, and duplex ultrasound scanning directly measuring the size of the kidneys [121, 122]. Test sensitivities have been reported for these investigations [117].

Pheochromocytoma

A pheochromocytoma is a tumour which produces and releases large amounts of adrenaline and noradrenaline (hormones) into the blood. It is rare and may occur in between 0.04% and 0.1% of patients; about 10% are malignant. Adrenaline causes an increase in heart rate and contractility, while noradrenaline increases systemic vascular resistance. Patients with signs and symptoms of pheochromocytoma need immediate specialist investigation given the seriousness of the condition and risk to the patient. The definitive treatment of pheochromocytoma is surgical removal of the tumour.

Signs and symptoms include a rapid heart rate, headache, high blood glucose levels, elevated basal metabolic rate, facial flushing, nervousness, sweating, decreased gastrointestinal movements and oedema.

Diagnostic techniques include plasma metanephrine (adrenaline metabolic waste product) screening and a 24 hour urine test for metanephrine and creatinine (protein metabolic waste product) [123,124]. Following positive findings two types of imaging study may be used to locate the tumour: metaiodobenzyl-guanidine (MIBG) scintigraphy and computed tomography (CT).

Hyperaldosteronism (primary aldosteronism)

Aldosterone is a compound which helps the kidneys to retain sodium and water. Hyperaldosteronism is the most likely common cause of mineralocorticoid hypertension and may occur in 0.01% to 0.03% of patients [125,117], although its prevalence is contested and may be much higher [126].

Signs and symptoms include sodium retention, heart rhythm irregularities and possibly muscle weakness as well as spontaneous or diuretic-induced hypokalaemia (low potassium levels in the blood) not explained by natural causes [118].

Many patients with hyperaldosteronism may not have hypokalaemia limiting the use of urine analysis to detect increased urinary excretion of potassium, a marker for hyperaldosteronism. Measurement of plasma aldosterone levels and plasma renin activity as the aldosterone:renin ratio may be used to detect primary aldosteronism [124]. As with any laboratory test, standardisation of laboratory assays is important.

Cushing's syndrome

Cortisol, a hormone produced in the adrenal glands above the kidneys, helps regulate blood sugar and water retention. An excess of cortisol can cause body tissues and organs to change: this is referred to as Cushing's Syndrome. It is caused either by excess cortisol production or by excessive use of certain steroids (glucocorticoids). Cortisol is itself regulated by adrenocorticotrophic hormone (ACTH), made in the pituitary gland below the brain.

Cushing's Disease refers specifically to over-production of ACTH by the pituitary gland and is the most common form of the syndrome. Over-production of cortisol can also be due to a tumour in the adrenal gland, either benign (an adenoma), or malignant (a carcinoma) and in this variant is not dependent on ACTH. Production of ACTH in an organ or gland other than the pituitary or adrenal gland (e.g. thymus gland, lung, pancreas) is called ectopic corticotrophin-releasing production [127]. Cushing's syndrome may occur in 0.1% to 0.6% of patients.

Signs and symptoms include hypertension, sudden onset of weight gain, central obesity, moon face, weakness, fatigue, backache, headache, glucose intolerance, oligomenorrhoea (infrequent menstruation), amenorrhoea (abnormal discontinuation of periods), increased thirst, increased urination, impotence, muscle atrophy, depression, insomnia thinning of the skin, cutaneous hyperpigmentation (darkening of the skin), osteoporosis [127].

Diagnosis of Cushing's syndrome begins with a single dose overnight dexamethasone-suppression test. A differential diagnosis is achieved by measuring plasma ACTH together with either a long dexamethasone suppression test or a corticotrophin-releasing hormone (CRH) stimulation test [128,129].

Other identifiable causes of hypertension

Hypothyroidism

Hypothyroidism is the under production of the hormone thyroxine (which controls metabolism) by the thyroid gland. Hypertension in hypothyroid patients may result from altered levels of renin, angiotensin and aldosterone. After thyroid replacement therapy diastolic blood pressure returns to normal in patients with hypothyroidism suggesting a cause-and-effect relationship [130,131,132]. Signs and symptoms include lethargy, fatigue, weight loss, hair loss, confusion, nausea, bone pain, muscle weakness, slow heart rate. Hypothyroidism is associated with increased diastolic blood pressure [133,134]. Hypothyroidism is diagnosed by measuring thyroid stimulating hormone levels [118].

Hyperthyroidism

Hyperthyroidism is the excessive secretion of thyroxine by the thyroid gland. Signs and symptoms include increased systolic blood pressure, increased metabolic rate, enlargement of the thyroid gland, tachycardia (increased heart rate), exophthalmia (abnormal protrusion of the eyeball in the orbit), oedema, dry hair and skin, weight gain, goitre (enlarged thyroid gland) [135]. Hyperthyroidism is diagnosed by measuring thyroid stimulating hormone levels [118].

Obstructive sleep apnoea

Obstructive sleep apnoea is caused by the upper airway becoming obstructed during sleep. It is more prevalent in men. Signs and symptoms include daytime somnolence (unnatural drowsiness and sleepiness), obesity, snoring, lower extremity oedema (abnormal amounts of fluid in the intercellular tissue spaces), nocturia (excessive nocturnal urination) and morning headaches. The main diagnostic technique is a polysomnograph to monitor normal and abnormal physiological activity during sleep [124,118].

Coarctation of aorta

Coarctation of aorta is a congenital condition where a segment of the aorta is too narrow, reducing oxygenated blood flow around the body. Signs and symptoms include high blood pressure, decreased or delayed femoral pulse, abnormal chest radiograph. Diagnostic techniques: doppler or CT imaging of the aorta [118].

Acromegaly

Acromegaly is a similar condition to Cushing's syndrome and follows from excess production of growth hormone in the anterior lobe of the pituitary gland. Signs and symptoms in addition to hypertension include cardiomegaly (overgrowth of heart), enlarged facial features, enlarged jaw, headache and arthralgia (joint pain), hypertrichosis (excessive hair growth), excessive sweating, tiredness, weakness, somnolence and impaired glucose tolerance [136]. Acromegaly is diagnosed by evidence of increased growth hormone secretion [136].

Drugs

A number of drugs are associated with raised blood pressure. Diagnosis is commonly made by a trial period not taking medication. Phenylpropanolamine (decongestant medication) found in inhaled cold remedies, may raise diastolic blood pressure [137,138]. Oral contraceptive pills containing oestrogen may cause small, and occasionally pronounced, rises in blood pressure. In rare cases malignant hypertension may occur [139]. Other drugs that may raise blood pressure include immunosuppressive agents, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, weight loss agents, stimulants, mineralocorticoids, antiparkinsonian agents, monoamine oxidase inhibitors, anabolic steroids, sympathomimetics [118].

Cardiovascular risk models

- Risk models provide a useful prognostic tool for clinicians and patients in primary care. They reinforce the need to offer treatment to patients based on their profile of cardiovascular risk rather than focusing on blood pressure in isolation.	II
- Most risk models derive from the Framingham Heart Study: a cohort of over 5000 men and women aged 30 to 62 from Framingham, Massachusetts followed-up from 1971 to assess the determinants of cardiovascular disease.	II
- Limitations of commonly used risk models include poor validation in UK ethnic minorities and younger populations.	II
- Framingham risk calculator computer programmes currently provide the best assessment of risk of coronary heart disease and stroke over 10 years. The latest version developed by the Joint British Societies gives the risk of a cardiovascular event over 10 years (a combined score including the risk of coronary heart disease and stroke).	II
- Risk charts may be relatively imprecise, placing patients in bands of risks, although the visual presentation may be helpful to some patients. Evidence suggests that the Joint British Societies chart adheres most closely to Framingham risk calculators.	III
- When only the CHD risk score is known, CVD risk score can be approximated by multiplying by 4/3. When CHD and stroke risk are reported, the CVD risk can be approximated by adding these two scores together.	III

Risk models have been developed (as charts, graphs or computer programmes) to allow clinicians to predict the likelihood of patients developing coronary or cardiovascular disease using lifestyle and clinical markers. Although they vary in detail, risk models may estimate an individual's risk of coronary heart disease and stroke over the next ten years using their gender, age, diabetic status, smoking status, total serum cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and blood pressure. An important aspect of risk models is that they lead the clinician to address a patient's overall profile of risk rather than treat one risk factor in isolation. Risk factors have a cumulative effect, and an individual with a number of modest risk factors may be at greater risk of developing cardiovascular disease than an individual with one high risk factor [18]. Since several risk factors are potentially modifiable, an important aspect is which of these to address and in what order. For example, it may be appropriate to address smoking or dietary habits before offering pharmacological treatment. Most risk models in common use are based upon the Framingham Heart Study.

The Framingham Heart Study

The National Heart Institute designed the Framingham Heart Study to identify the causes of cardiovascular disease by following a large cohort without manifest disease over a long period of time. In 1948, 5,209 men and women aged 30 to 62 from Framingham, Massachusetts were examined and interviewed about their lifestyle with further examination and tests occurring at two year intervals. In 1971, a second-generation group of 5,124 of the original participants' adult children and their spouses were enrolled and similarly examined. This latter cohort is used as the basis of current risk models.

Analyses of these cohorts identified the major risk factors for cardiovascular disease: high blood pressure and cholesterol, smoking, obesity, diabetes, and sedentary lifestyle; the impact of blood triglyceride and HDL cholesterol levels; and the effects of age, gender, and psychosocial issues.

The findings of this research are modelled in the Framingham chart, updated in 1998 [140], which estimates the risk of developing coronary heart disease (including angina, myocardial infarction or fatal coronary disease) over 10 years. Framingham equations predicting stroke [141] and total

cardiovascular disease [142] are available in the literature but not included in their own risk chart. Separate score sheets are provided for men and women and patient-specific factors used include blood cholesterol (either total or LDL cholesterol), HDL cholesterol, blood pressure, cigarette smoking, and diabetes mellitus.

Some general reservations apply to risk models derived from the Framingham data. The risk estimates apply only to those without known heart disease, and some versions predict the likelihood of coronary heart disease alone rather than other heart or vascular diseases such as stroke. The Framingham cohort is primarily white, and the estimation of levels of risk based upon its findings may not transfer reliably to other populations with different underlying risk of disease, or certain racial and ethnic groups [140]. The Framingham data are sparse for certain sex-age groups and estimates of risk for these groups may be imprecise. When a ten year window is modelled, potential longer term risks are excluded.

Whose risk model?

The Framingham data have been developed as statistical formulae, tables, charts and risk calculators by a range of authors (Table 9). Their use has been incorporated into the recommendations of major organisations including the Joint British recommendations [143,144], American Heart Association and American College of Cardiology [17], the British Hypertension Society [IV], and the Second Joint Task Force Recommendations of European and Other Societies [145].

Table 9: Risk models derived from Framingham data

Model	Age	Risk assessed	Risk factors measured
Framingham risk calculator	30-74	10 year CHD risk 10 year Stroke risk	Age, sex, smoking, BP, diabetes, HDL, TC, LVH
Framingham Chart	30-74	10 year CHD risk	Age, sex, smoking, BP, diabetes, HDL, TC
Modified Sheffield Table	M: 26-70 W: 34-70	10 year CHD risk bands: 15% or 30%	Age, sex, smoking, Hypertension (y/n), diabetes, TC:HDL ratio, LVH
Updated New Zealand Calculator	40-70	5 year CVD risk, Absolute Risk Reduction and NNT	Age, sex, smoking, systolic BP, diabetes, TC:HDL ratio, LVH
Canadian Graph	30-70	5 and 10 year CHD risk	Age, sex, smoking, systolic BP, diabetes, TC:HDL ratio, LVH
Revised British Joint Societies Graph	35-74	10 year CHD risk bands: <15%, 15-30%, >30%	Age, sex, smoking, systolic BP, diabetes, TC:HDL ratio
Joint European Guideline Chart	30-70	10 year CHD risk bands: <5%, 5-10%, 10-20%, 20-40%, >40%	Age, sex, smoking, diabetes, TC

CHD: Coronary Heart Disease
CVD: Cardiovascular Disease (CHD and stroke)
HDL: High density lipoprotein
LVH: Left ventricular hypertrophy
NNT: Number needed to treat
TC: Total cholesterol

The (modified) Sheffield Table, including a simple yes/no marker for hypertension, is used predominantly to guide statin therapy for raised cholesterol levels [146,147]. The New Zealand chart

estimates 5 year cardiovascular risk rather than the 10 year risk of coronary heart disease found in other models [148,149]. The Canadian graph estimates the 5 and 10 year risk of cardiovascular and cerebrovascular disease [150]. Tables provided by the Joint British Societies and European Societies estimate 10 year risk of coronary heart disease. The Joint British Societies provide a risk calculator as a spreadsheet and a computer programme, both of which calculate CHD and stroke risk over ten years [151]. These calculators, based on the Framingham Heart Study equations [152], are referred to collectively here as Framingham risk calculators. We identified no comparison of alternative software implementations, and have had to assume that these faithfully reproduce the predictions of the original risk equations. Three further risk models identified but not evaluated are the British Regional Heart Study Function [153], the Dundee risk disk [154] and the University College London computer programme CardioRisk Manager [155,156].

Besides the Framingham cohort, a number of other geographical and trial-based cohorts have been used to generate risk models (Table 10).

Table 10: Risk assessment models

Study (Country)	Sample characteristics	Participant selection criteria	Risk assessed	Risk factors measured	Assessment format
Framingham (USA)	5,145 participants M: 2,489; F: 2,856 30-74 years old	Excluded: overt CHD at baseline	10 year CHD risk 10 year CVA risk	Age, sex, smoking, height, weight, BMI, BP, diabetes, LDL, HDL, TC, and TG.	Charts, tables, and risk calculators by various authors
Menotti et al (Italy)	1,656 participants M: 100% 40-59 years old	Excluded: CHD at baseline	10 year CHD risk	Age, sex, systolic BP, serum cholesterol, smoking status	Chart and table
GISSI (Italy)	11,324 participants MI patients M: 9,601; F: 1,647	Excluded: allergy to fish oil, congenital defects, severe congestive heart failure	4 year risk of overall mortality	Age, sex, complications after MI, CV risk factors	Risk chart and graph
PROCAM (Germany)	4,639 participants M: 100% 40-65 years old	Excluded: prior history of MI or stroke	10 year MI risk	Age, sex, BP, blood sample analysed, resting ECG, personal and family case history	PROCAM risk calculator
Pocock et al 2001 (Europe and N. America)	47,088 participants (8 hypertension RCTs) M&F 30-84 years old	Trials had varying eligibility criteria	5 year CVD risk	Age, sex, smoking status, systolic BP, TC, height, creatinine concentration, MI, stroke, diabetes, LVH	Graph and Calculator
CVD Life expectancy (N. America)	Sample unclear (15% random sample from Lipid Research Clinics cohort) M: 52%; F: 48% ≥30 years old	Excluded: patients taking digitalis or anti-arrhythmic or lipid-altering medications; pregnant women	Years of life saved	Age, sex, BP, BMI, smoking status, alcohol consumption status, use of medication to reduce BP, presence of CVD/diabetes/LVH	Graph
SCORE (Europe)	205,178 participants M: 88,080; F: 117,098 19-80 years old	Excluded: prior history of MI	10 year CVD mortality risk	Age, sex, smoking, systolic BP, HDL and TC.	Charts for high risk and low risk populations

BMI: Body Mass Index; CHD: Coronary Heart Disease; CVA: Cerebrovascular Accident; CVD: Cardiovascular Disease; LDL: Low density lipoprotein; HDL: High density lipoprotein MI: Myocardial Infarction; TC: Total cholesterol; TG: Triglycerides

A study by Menotti and colleagues used data from an Italian rural cohort to derive an independent risk function to compare with the Framingham data [157]. The predictive model using the Italian cohort

found much lower levels of absolute risk than the Framingham data for the same profile of risk factors. This might be attributable to a 'Mediterranean diet' (high in fish and olive oil) or other factors. Consequently Framingham based risk models may overestimate the risk of coronary heart disease in Southern European populations.

The Italian-based GISSI model is based on predominantly male data and applies only to patients following myocardial infarction, providing estimates of 4 year risk of overall mortality [158].

The PROCAM study, conducted in Germany, examined only white males: the consequent model is available as a computer program [159].

Pocock et al [160] based their model on the findings of 8 randomised controlled trials (RCTs) of antihypertensive therapy, comprising treated and untreated European and North American participants. The model assesses risk of cardiovascular death rather than events. A major advantage is its ability to incorporate existing cardiovascular disease markers into its risk estimates. Height and creatinine concentration are optional parameters in the model. Risks for individuals are calculated from either a graph or a calculator. A limitation is the exclusion of non-fatal cardiovascular events from predictions.

The Cardiovascular Disease (CVD) Life Expectancy model, unlike other models reviewed, estimates years of life saved by modelling changes in the progression of coronary and cerebrovascular disease over an average patient's lifetime [161]. Its advantages are the removal of the 10 year threshold; provision of information on improved survival which may be helpful to patients; and, the combining of benefits of reduced stroke and coronary heart disease into one measure. Its predictions are based on the findings of 9 randomised controlled trials. The major limitation is that the long term consequences of treatment, beyond the follow-up of trials, are uncertain and long term models of survival cannot be easily validated. The assumptions are greatest in the youngest patients, in whom the model predicts greatest benefit. The findings are not published in an accessible form for use during consultation.

The SCORE model provides charts of the ten-year risk of fatal cardiovascular disease in high and low risk European populations based on cohort data from 12 countries [162]. The authors provide a good discussion of the problems of developing risk charts. They elect to estimate cardiovascular disease mortality since this is a hard endpoint in studies, while cardiovascular events are inconsistently defined across the cohort studies analysed. They identify the limitations of Framingham-derived diabetes charts, and do not provide separate charts for diabetes since this is inconsistently recorded in the cohort studies. Instead they offer a simple correction that the risk 'will be at least twice as high in diabetic men and at least four times as high in diabetic women'. Cardiovascular events as well as deaths are held to be important and this may limit the attraction of the SCORE product.

Evaluations of risk models

Jones and colleagues assessed the accuracy of cardiovascular risk models by comparing them with the original algorithms from the Framingham Heart Study [163], which they assumed accurately predicted the risk of cardiovascular disease. Data on 691 patients was supplied by 12 primary care practices in the Birmingham area, UK: according to the Framingham algorithm 8.5% and 42.1% of patients had projected 10 year CHD risks of ≥30% and ≥15% respectively. Sensitivity, specificity and positive/negative predictive values were assessed for the Modified Sheffield, Joint British Societies, Canadian, Framingham Table, Revised New Zealand and Joint European Societies models. Older versions of charts from the Sheffield, Joint British Societies and New Zealand groups were also evaluated, but were outperformed by the updated models. The findings are summarised in Table 11. Individual risk models predict risks over different periods of time and for different thresholds of risk.

Table 11: Comparison of the accuracy of risk models compared with the Framingham algorithm [163]

Model	Sensitivity	Specificity	Sensitivity	Specificity
Framingham Algorithm	100%	100%	100%	100%
	1 year CHD risk ≥3%		*1 year CHD risk ≥1.5%*	
Sheffield Modified	91.4% (81.3 to 96.9)	95.8% (93.8 to 97.3)	95.1% (91.6 to 97.4)	89.9% (86.4 to 92.7)
	10 year CHD risk ≥30%		*10 year CHD risk ≥15%*	
Joint British	84.7% (71.0 to 93.0)	98.7% (97.5 to 99.5)	89.4% (84.8 to 92.7)	99.5% (98.1 to 99.9)
Canadian	3.3% (0.4 to 11.7)	100% (99.4 to 100)	94.8% (91.3 to 97.2)	92.2% (89.0 to 94.6)
	10 year CHD risk ≥27%		*10 year CHD risk ≥15%*	
Framingham Chart	67.0% (53.7 to 77.3)	97.6% (96.0 to 98.7)	82.4% (77.0 to 86.9)	93.9% (91.0 to 96.1)
	5 year CVD risk ≥20%		*5 year CVD risk ≥10%*	
New Zealand Updated	75.3% (62.2 to 84.7)	92.2% (89.7 to 94.3)	83.2% (77.6 to 87.4)	78.8% (73.9 to 84.8)
	10 year CHD risk ≥20%			
Joint European	75.0% (66.5 to 81.8)	85.9% (82.3 to 89.0)		

Isles and colleagues assessed how accurately GPs and nurses from 37 practices in Dumfries and Galloway used the updated New Zealand chart, Joint British chart and an interim version of the Sheffield table [164,165]. Ten case histories were assessed and the correct use of charts was determined rather than accuracy of the chart against a reference standard. GPs could use all charts equally accurately, but nurses performed better with the New Zealand and Joint British charts than the Sheffield chart. Both groups found the former two easier to use and preferable to the latter.

McManus and colleagues compared the accuracy of GPs and nurses from 18 practices in central England, at calculating the risk of CHD [166]. Ten case histories were randomly selected in each practice: 2 each from 5 groups at differing risk of CHD. Seventy patients' records contained evidence of existing cardiovascular disease and were subsequently excluded leaving 110 patients to contribute to the analysis. Although the case notes contained most of the data required to perform a risk assessment, only 21% of records contained an estimate of HDL cholesterol. Clinicians apparently made assumptions when data were missing, since estimates were made for the majority of the 110 patients. Risk estimates were obtained using the modified Sheffield table, updated New Zealand

table, European Table and Joint British programme or chart. The Framingham algorithm provided standard reference values. Since either the Joint British programme or chart could be used a direct comparison of accuracy is of limited interpretation since those GPs using the programme were effectively using the standard reference tool. This accepted, the Joint British programme/chart combination achieved the best overall performance (Table 12). Regardless of method, nurses and GPs disagreed about risk status in about 20 to 25% of patients and the use of all methods tended to underestimate risk. Of concern are the 40% of patients in whom risk assessments were inappropriate because of existing cardiovascular disease.

Table 12: Comparison of GP and nurse use of risk models compared with the Framingham algorithm* [164]

	Sensitivity		Specificity	
Method	**Practice nurses**	**GPs**	**Practice nurses**	**GPs**
Subjective risk estimate	66% (56 to 76)	72% (63 to 82)	72% (63 to 81)	73% (64 to 82)
Modified Sheffield table	58% (47 to 69)	64% (53 to 75)	86% (76 to 96)	89% (81 to 97)
Updated New Zealand table	63% (52 to 73)	74% (65 to 84)	63% (52 to 73)	81% (71 to 92)
European table	65% (54 to 75)	61% (51 to 72)	74% (64 to 84)	72% (62 to 83)
Joint British program/chart	79% (70 to 89)	80% (71 to 89)	100%	83% (68 to 98)

* Missing values were replaced by population normal values.
GPs and nurses were assessing high (10 yr risk of CHD over 30%) or low risk.

Brindle and colleagues compared Framingham risk predictions with observed 10 year coronary disease event rates in 6,643 British men aged 40-59 years and free from cardiovascular disease at baseline during 1978 to 1980 [167]. The prospective study found that subsequent levels of cardiovascular disease were consistently lower than those predicted by the Framingham risk model: 2.8% died from coronary heart disease compared with 4.1% predicted (a relative overestimation of 47%); fatal or non-fatal coronary heart disease occurred in 10.2% of the men compared with 16.0% predicted (a relative overestimation of 57%). It is possible that differences in the Framingham population mean that risk estimates do not apply well to a British population. However there are a number of potential confounding influences that challenge this interpretation. These might include differing analytic approaches, accuracy of recording first coronary events and availability of primary and secondary care treatment. For example, by the mid 1980s aspirin, beta-blockers and ACE-inhibitors were being progressively more actively used to treat cardiovascular disease. It is possible that the original Framingham cohort provides a truer representation of the prognosis of untreated patients. The statistical tests employed in the study compare the (varying) British population with point estimates derived from the Framingham population. More meaningful tests would have compared the two (varying) populations with consequent probability values being less significant.

A retrospective study by *Ramachandran and colleagues* included a cohort of 1,700 men and women enrolled between 1972 and 1974, enrolled in an ischaemic heart disease study and followed up for 20 years [168]. This study found that predicted risk of a coronary heart disease event and observed event rates were similar in those at raised risk (>15% over ten years) although the predictions tended to underestimate observed disease in those at lower baseline risk.

Illustration of risk models

We devised 8 hypothetical patients of increasing risk without diabetes (Table 13) and applied these data to 5 commonly cited models (Table 14): the Framingham risk calculator, British, European and Canadian charts (all Framingham based) and the Italian risk model [157].

Table 13: Sample patient characteristics

Patient	Sex	Age	TC	HDL	Smoking	BP
1	Male	50	6	2.0	No	150/90
2	Male	60	6	2.0	Yes	160/100
3	Male	60	8	1.5	No	160/100
4	Male	70	8	1.5	Yes	180/105
5	Female	50	6	2.0	No	150/90
6	Female	60	6	2.0	Yes	160/100
7	Female	60	8	1.5	No	160/100
8	Female	70	8	1.5	Yes	180/105

HDL: High density lipoprotein MI: Myocardial Infarction; TC: Total cholesterol

Table 14: Comparison of 10 year CHD risk estimated by commonly cited risk models

Patient	Framingham Risk calculator (%)	British Joint Chart (%)	European Chart (%)	Italian (Menotti et al) (%)	Canadian (%)
1	5.4	<15	10-20	10-20	6
2	16.8	15-30	20-40	10-20	19
3	20.4	15-30	20-40	20-40	19
4	39.2	>30	>40	20-40	38
5	3.5	<15	5-10	N/A	4
6	11.0	<15	10-20	N/A	12
7	13.8	<15	10-20	N/A	13
8	25.3	15-30	20-40	N/A	25

Unlike the other models, the Italian risk model does not formally model diabetic status and applies only to males. The estimated levels of risk for each patient are generally consistent although some of the bands are wide. Different charts utilise differing numbers and ranges of risk bands. This can cause the same patient to be placed in a lower risk band with one chart, and a higher band with another. For example, the findings from the British and European charts for patients 2 and 3 estimate 10 year CHD risk to be anywhere from 15% to 40%, despite both charts being derived from the same Framingham data. The use of charts instead of a calculator introduces imprecision into risk estimation [163]. Comparisons with other risk models were not attempted because of differing requirements for input data or presentation of findings.

Limitations of Risk Models

As seen when comparing the GISSI, SCORE and Framingham models, algorithms based on one population may not perform well with different populations at different absolute risk of cardiovascular disease. The Framingham study sampled a white middle class population and is now several

decades old. Trends of disease over time and in different populations introduce uncertainty about the validity of findings in a UK general practice population today [169], and validation studies give conflicting answers. Predictive validity for high risk groups including African-American and South Asian people remains particularly unclear [170]. Research in the UK into the validity of risk prediction models for ethnic minority groups is needed. However, attempts to validate (or invalidate) the accuracy of risk predictions from Framingham data are problematic. Patient populations identified as being at risk will receive a variety of treatments either unavailable or used more aggressively than at the time of the Framingham study. The Framingham risk model may still provide our best estimate of what happens to untreated patients since more modern assessments will be confounded by recent advances in treatment.

A weakness inherent in most risk models is that they ignore the long term risk of disease beyond 10 years: this may be particularly important in younger patients for whom the long term benefits of prevention ultimately may be greatest [147]. It is unclear the extent to which patients understand and personalise long term risks and benefits [158]. A tendency to discount long term risks may limit individuals' willingness to participate in preventative strategies. Although prevention is often advocated in preference to cure [171] the attractiveness of treatment to patients without existing cardiovascular disease is uncertain.

The process of presenting risk algorithms (themselves estimated from statistical modelling) as charts, graphs and tables may introduce further imprecision by banding patients into categories of risk and by excluding some risk factors. Some charts estimate coronary heart disease: this excludes stroke which may be a particular concern in elderly patients. Multiplying the coronary heart disease risk level by 4/3 has been offered as a pragmatic solution (e.g. 30% coronary heart disease risk becomes 40% cardiovascular disease risk). However the balance of stroke and coronary heart disease changes with age, and this average correction may not work well in individual patients, particularly the elderly (see: Figure 6 page 49). Where both coronary heart disease and stroke risk are reported, the cardiovascular risk can be approximated by adding these two scores together.

There remains a debate about what constitutes a 'healthy norm'. A threshold for 10 year CHD risk of ≥15% implies 42% of patients (aged 30-70, without LVH) enrolled in the recent Birmingham study were 'at risk' [163]. Small changes in the threshold for commencing treatment may turn large numbers of people at intermediate risk into lifelong patients, while at the margin the additional patients derive the least benefit.

Lifestyle interventions

Recommendations and supporting statements

• **Ascertain patients' diet and exercise patterns as a healthy diet and regular exercise can reduce blood pressure. Offer appropriate guidance and written or audiovisual materials to promote lifestyle changes.**	**B**
- Education about lifestyle on its own is unlikely to be effective.	II
- Healthy, low calorie diets had a modest effect on blood pressure in overweight individuals with raised blood pressure, reducing systolic and diastolic blood pressure on average by about 5 to 6 mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 40% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Taking aerobic exercise (brisk walking, jogging or cycling) for 30-60 minutes, 3 to 5 times each week, had a small effect on blood pressure reducing systolic and diastolic blood pressure on average by about 2 to 3mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 30% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg or more in the short term, up to 1 year.	II
- Interventions actively combining exercise and diet were shown to reduce both systolic and diastolic blood pressure by about 4 to 5 mmHg in trials. About one quarter of patients receiving multiple lifestyle interventions were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- A healthier lifestyle, by lowering blood pressure and cardiovascular risk, may reduce, delay or remove the need for long term drug therapy in some patients.	III
• **Relaxation therapies* can reduce blood pressure and individual patients may wish to pursue these as part of their treatment. However routine provision by primary care teams is not currently recommended.**	**B**
* *Examples include: stress management, meditation, cognitive therapies, muscle relaxation and biofeedback.*	
- Overall, structured interventions to reduce stress and promote relaxation had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3 to 4 mmHg in trials. There is variation in the reduction in blood pressure achieved in trials and it is unclear why. About one third of patients receiving relaxation therapies were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- The current cost and feasibility of providing these interventions in primary care has not been assessed and they are unlikely to be routinely provided.	III
• **Ascertain patients' alcohol consumption and encourage a reduced intake where patients drink excessively as this can reduce blood pressure and has broader health benefits.**	**B**
- Excessive alcohol consumption (men: more than 21 units/week; women: more than 14 units/week) is associated with raised blood pressure and poorer cardiovascular and hepatic health.	I
- Structured interventions to reduce alcohol consumption, or substitute low alcohol alternatives, had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3 to 4 mmHg in trials. Thirty percent of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Brief interventions by clinicians of 10-15 minutes, assessing intake and providing information and advice as appropriate, have been reported to reduce alcohol consumption by a quarter in excessive drinkers with or without raised blood pressure, and to be as effective as more specialist interventions.	II
- Brief interventions have been estimated to cost between £40 and £60 per patient receiving intervention. The structured interventions used in trials of patients with hypertension have not been costed.	II
• **Discourage excessive consumption of coffee and other caffeine-rich products.**	**B**
- Excessive consumption of coffee (5 or more cups per day) is associated with a small increase in blood pressure (2/1 mmHg) in participants with or without raised blood pressure in studies of several months duration.	III

• **Encourage patients to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as this can reduce blood pressure.**	**B**
- Advice to reduce dietary sodium intake to less than 6g/day was shown to achieve a modest reduction in systolic and diastolic blood pressure of 2 to 3 mmHg in patients with hypertension, at up to 1 year in trials. About a quarter of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Long term evidence over 2 to 3 years from studies of normotensive patients shows that reductions in blood pressure tend to diminish over time.	II
- One trial suggests that reduced sodium salt, when used as a replacement in both cooking and seasoning, is as effective in reducing blood pressure as restricting the use of table salt.	III
• **Do not offer calcium, magnesium or potassium supplements as a method for reducing blood pressure.**	**B**
- The best current evidence does not show that calcium, magnesium or potassium supplements produce sustained reductions in blood pressure.	II
- The best current evidence does not show that combinations of potassium, magnesium and calcium supplements reduce blood pressure.	II
• **Offer advice and help to smokers to stop smoking.**	**A**
- There is no strong direct link between smoking and blood pressure. However, there is overwhelming evidence of the relationship between smoking and cardiovascular and pulmonary diseases, and evidence that smoking cessation strategies are cost-effective.	I
- *See: Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, NICE Technology Appraisal No. 39, March 2002. http://www.nice.org.uk/*	
• **A common strategy found in studies for motivating lifestyle change is the use of group working. Inform patients about local initiatives by, for example, healthcare teams or patient organisations which provide support and promote healthy lifestyle change.**	**C**

Overview

A vast epidemiological literature describes an apparent relationship between raised blood pressure and lifestyle choices and habits. For example, observational studies have shown that people with raised blood pressure tend also to have low dietary calcium [172]. Does inadequate intake of dietary calcium promote raised blood pressure or is the relationship a spurious one, arising from inadequate adjustment for other hard-to-measure influences (a common problem in observational studies). There is similar controversy about the role of diet, exercise, alcohol, caffeine, potassium and magnesium supplements, sodium (table) salt and relaxation therapies. Cause and effect can only be established by repeated and methodologically sound randomized controlled trials, supported by evidence of a plausible biological mechanism, particularly when the potential benefit is small.

Randomized controlled trials, enrolling patients who had raised average blood pressure defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥85 mmHg, analysing either blood pressure or major cardiovascular endpoints on an intention-to-treat basis, of 8 weeks or more follow-up, are included in this review. However, none of the studies identified were designed to quantify significant changes in rates of death or cardiovascular events due to lifestyle interventions: instead

they relied on the surrogate endpoint of reduced blood pressure with its epidemiological link to reduced rates of disease. Thus the evidence is less direct than for drug interventions which show reductions in morbidity directly. The requirement that trials have a follow-up of at least 8 weeks is arbitrary but it reflects the belief that shorter time frames cannot usefully inform us about enduring changes in blood pressure.

We searched electronic databases (Medline, Embase, CENTRAL) from 1998 to July 2003 for reports of relevant randomised controlled trials; articles published before 1998 were identified from hypertension guidelines, systematic reviews and meta-analyses [173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207]. Though there were a number of trials informing most of the areas of interest, the trials were commonly small and the intervention of short duration (several months) relative to the progression of raised blood pressure and cardiovascular disease. The quality of reporting of studies was commonly poor (see Table 15) and this may reflect poor methodological conduct, further weakening the strength of evidence and consequent recommendations for clinical care.

Table 15: Summary characteristics of trials of lifestyle interventions

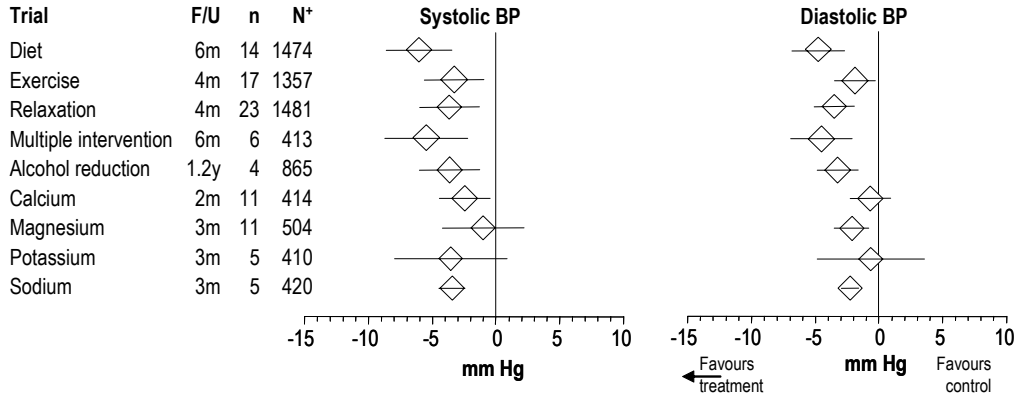
Type of intervention	Number of studies	Number of participants	Quality markers: Randomisation description	Concealment of allocation	Baseline comparability[a]	Blinding of: Participant[b]	Treatment provider	Outcome assessor
Diet	14	1,474	3 (21%)	2 (14%)	12 (86%)	-	-	4 (29%)
Exercise	17	1,357	1 (6%)	0 (0%)	13 (76%)	-	-	2 (12%)
Relaxation	23	1,481	6 (26%)	1 (4%)	5 (65%)	-	-	10 (43%)
Multiple intervention	6	413	2 (33%)	0 (0%)	5 (83%)	-	-	4 (67%)
Alcohol reduction	4	865	1 (33%)	0 (0%)	2 (67%)	-	-	2 (67%)
Coffee	0	0	-	-	-	-	-	-
Calcium	11	414	2 (18%)	1 (9%)	4 (36%)	9 (82%)	9 (82%)	1 (9%)
Magnesium	11	504	1 (9%)	0 (0%)	6 (55%)	9 (82%)	10 (91%)	0 (0%)
Potassium	5	410	3 (60%)	2 (40%)	2 (40%)	3 (60%)	3 (60%)	3 (60%)
Sodium	5	420	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)
Combined salts	2	240	1 (50%)	0 (0%)	2 (100%)	2 (100%)	2 (100%)	0 (0%)

a Confirmation of baseline comparability for parallel trials or of no carryover effect for crossover trials.
b Neither participant nor treatment provider could be blinded to behavioural interventions.

In overview, 98 trials including 7,993 participants were combined to provide principal findings on lifestyle interventions (see Figure 7), although these were augmented with a number of other trials and reviews. Statistically significant reductions in blood pressure were found, in the short term for improved diet and exercise, relaxation therapies, and sodium and alcohol reduction. For example, our best estimate is that a multiple intervention addressing diet and exercise can reduce systolic and diastolic blood pressure in a cohort of patients, on average, by about 5 mmHg. However this estimate is based on a limited number of patients and is uncertain. The 95% confidence interval shows that (19 times out of 20) the true average reduction may be anywhere between about 2 and 9 mmHg. Individual patients may achieve a greater or lesser reduction than the average and for a combined diet

and exercise intervention the best guess is that about one quarter of patients will achieve a reduction in systolic blood pressure of at least 10 mmHg.

Figure 7: Overview of lifestyle interventions: effect on systolic and diastolic blood pressure in randomised trials of patients with raised blood pressure (≥140/85 mmHg)



All estimates are DerSimonian-Laird Weighted Mean Differences, see individual meta-analyses for details

+ F/U: Median duration of follow up in months or years; n: number of studies; and, N: subjects randomised

Most areas featured considerable heterogeneity (i.e. study findings were inconsistent, some positive and some negative) over and above the variation expected by the normal play of chance. This heterogeneity tends to limit the strength of recommendation that can be made about any course of action.

Managing changes in lifestyle

See also: *Implementing lifestyle measures* on page *151.*

Our systolic (and to a lesser extent our diastolic) blood pressure tends to increase as we grow older. It is unhelpful to think of a single threshold above which we suddenly have problematically high blood pressure, although such thresholds can be useful to spur us into action. A review of our lifestyle helps us to identify changes we can make which may reduce our blood pressure and thus delay, reduce or remove the need for long term drug therapy as well as leading to a healthier life. The cumulative trial evidence suggests that individuals who develop improved habits of regular exercise, sensible diet and relaxation can reduce their blood pressure. Forming these habits will take determination and support. Health care professionals can provide advice, encouragement and materials but ultimately may have limited scope to influence poor dietary habits and inadequate exercise which result in part from the busy and stressful pace of life and in part from personal choice. Much of the research evidence for lifestyle change uses regular time spent together in groups for support and encouragement. Patient and healthcare organisations may be able to help provide patients with, or point them to local groups which encourage lifestyle change, particularly those promoting healthy eating and regular exercise.

Diet

- Healthy, low calorie diets had a modest effect on blood pressure in overweight individuals with raised blood pressure, reducing systolic and diastolic blood pressure on average by about 5 to 6 mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 40% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year. | II

Fourteen randomised controlled trials, including 1,474 participants, met the review inclusion criteria and are tabulated in Appendix 6 [208,209,210,211,212,213,214,215,216,217,218,219,220,221,222, 223,224,225,226]. Studies most commonly compared low calorie diets, aimed at overweight patients, with either the patients' usual diet or with a prescribed 'usual care' diet. In addition, one study compared fish oil capsules with olive oil capsules (as a control); one study compared diets supplemented with fibre from oats and wheat; one study compared soy milk with skimmed cows' milk; these studies are discussed separately [227, 228, 229].

The mean age of study participants was 48 years and 62% were male. Only 4 studies reported ethnicity and in these about 45% of the participants were white. The median duration of both treatment and follow-up was 26 weeks, ranging from 8 weeks to one year.

Randomisation could be confirmed as adequate in only 3 studies (21%) and concealment of allocation as adequate in only 1 (7%). Blinding was confirmed as adequate in 6 studies (43%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 12 studies (86%).

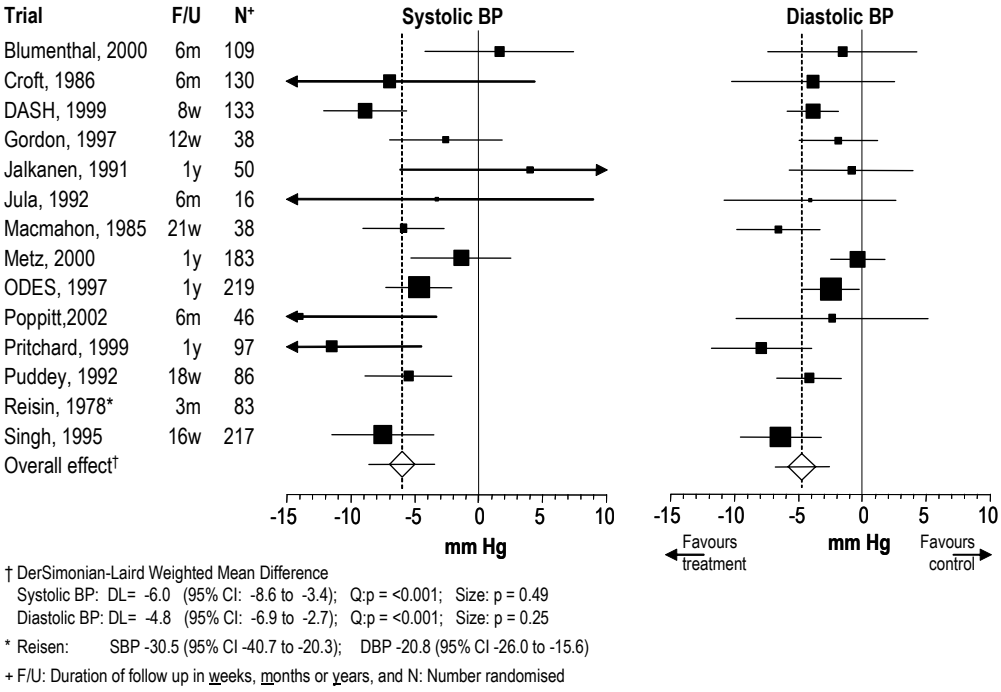
Studies varied in their methods and in definitions of diets prescribed. Some focussed primarily on low saturated fat, others primarily on weight reduction but in practice there was considerable overlap of content. Patients were sometimes given advice on other aspects of lifestyle, such as exercise. Dieticians, nurses or counsellors generally delivered interventions although in two studies doctors were primarily involved. Two of the studies provided meals for the participants [212,218]. Contact between participants and the treatment providers varied considerably from several times weekly through to occasionally. Crucially, we could identify no clear system for sub-grouping diet studies: there were too many confounding influences.

There was generally little change in the weight of people in the control groups, whereas average study losses in dietary intervention groups were between 2 and 9 kg.

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 8. Overall, with dietary intervention there was a significant reduction in both systolic (6.0 mmHg, 95% CI: 3.4 to 8.6) and diastolic (4.8 mmHg, 95%CI: 2.7 to 6.9) blood pressure. There was no evidence of reporting bias, but significant heterogeneity existed between studies. Forty percent (95%CI: 33% to 47%) of patients put on diets were likely to show at least a 10 mmHg reduction in systolic blood pressure. There was no overall difference in withdrawal when comparing diet and

control arms of studies (treatment vs. control, risk difference 3.6%, 95%CI: -0.1% to 7.2%), although studies varied.

Figure 8: Effect of diet on systolic and diastolic blood pressure in randomised trials of patients with raised blood pressure



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -6.0 (95% CI: -8.6 to -3.4); Q:p = <0.001; Size: p = 0.49
Diastolic BP: DL= -4.8 (95% CI: -6.9 to -2.7); Q:p = <0.001; Size: p = 0.25

* Reisen: SBP -30.5 (95% CI -40.7 to -20.3); DBP -20.8 (95% CI -26.0 to -15.6)

+ F/U: Duration of follow up in weeks, months or years, and N: Number randomised

Omission of a study which enrolled abnormally hypertensive patients (mean baseline BP: 170/110 mmHg) [221] resulted in a more modest estimate of reduced blood pressure due to diet: systolic 5.0 mmHg (95% CI: 3.1 to 7.0) and diastolic 3.7 mmHg (95%CI: 2.4 to 5.1).

While soy milk appeared to lower blood pressure when compared to skimmed cows' milk [229] and fish oil appeared to lower blood pressure when compared to olive oil [21], these findings were from single small short-term studies and require substantiation by other independent studies. In one small study, supplementing the diet with oats did not appear to lower blood pressure when compared to wheat [228].

The Cochrane Collaboration [230] carried out a review which had different inclusion criteria (it included simple interventions reported up to June 1998, had no restriction on length of follow up and also used weight loss as an end point) leaving only 4 studies common to both reviews. Nevertheless, its conclusions were similar. The recent Canadian guideline reviewed studies between 1966 and 1996 [231]. Although without a formal meta-analysis, it likewise concluded that overweight hypertensive patients should be advised to reduce their weight.

Exercise

- Taking aerobic exercise (brisk walking, jogging or cycling) for 30-60 minutes, 3 to 5 times each week, had a small effect on blood pressure reducing systolic and diastolic blood pressure on average by about 2 to 3mmHg in trials. However, there is variation in the reduction in blood pressure achieved in trials and it is unclear why. About 30% of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg or more in the short term, up to 1 year. | II

Seventeen randomised controlled trials of parallel design [232,208 ,233,234,215 ,235,236,237,238, 239,220,240,241,242,243,244,245,246] including 1,357 participants, met the review inclusion criteria and are tabulated in Appendix 7. Studies most commonly enrolled overweight patients and compared no intervention with a weekly schedule of three to five sessions of aerobic exercise. One study [236] offered advice to participants whereas all others provided facilities. Three further studies could not be included because of missing data [247,248,249].

The mean age of study participants was 53 years and 58% were male. Only 5 studies reported ethnicity and in these about 80% of the participants were white. The median duration of both intervention and follow-up was 17 weeks, ranging from 8 weeks to one year.

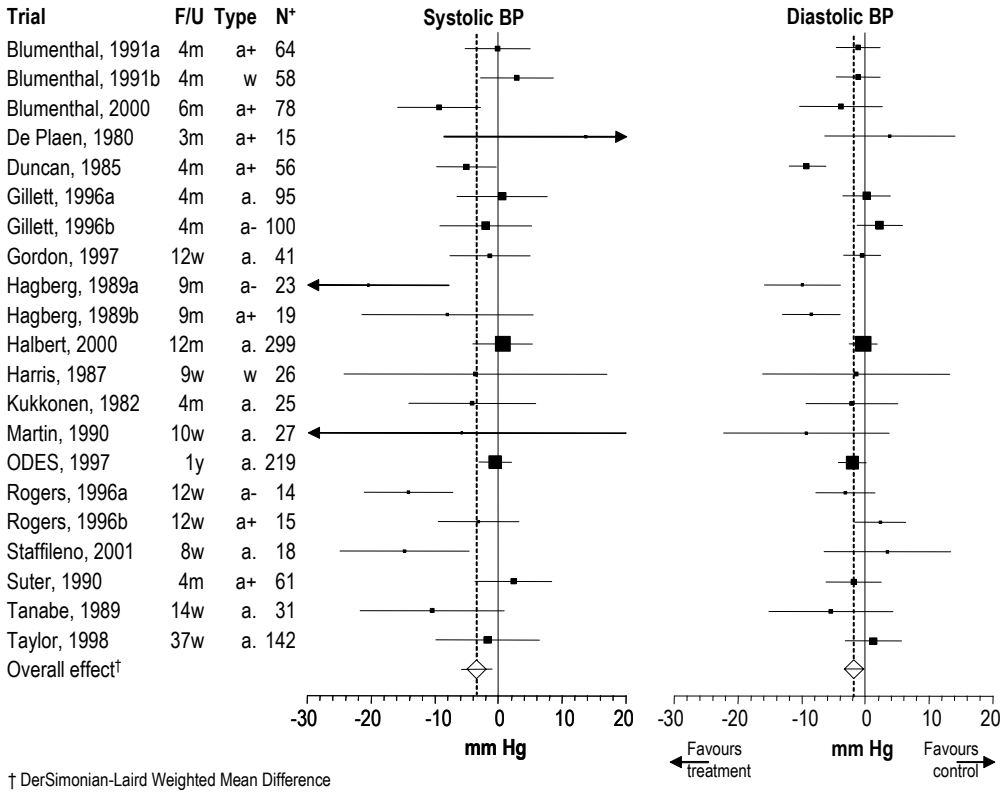
Randomisation could be confirmed as adequate in only one study (6%), and concealment of allocation as adequate in none (0%). Blinding was confirmed as adequate in 1 studies (6%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 13 studies (76%).

Overall, patients receiving exercise-promoting interventions achieved a modest reduction in both systolic (3.1 mmHg, 95%CI: 0.7 to 5.5) and diastolic (1.8 mmHg, 95% CI: 0.2 to 3.5) blood pressure compared to those in control groups (see Figure 9). There was no evidence of reporting bias. Significant heterogeneity existed between studies, although there was no obvious underlying cause for this. There were not enough studies to explore the relative merits of weight training compared to aerobics or differences between low and medium intensity aerobics. Thirty-one percent (95% CI: 23% to 38%) of patients receiving exercise interventions were likely to show at least 10 mmHg reduction in systolic blood pressure. People in the exercise arms were more likely to withdraw from the studies than those in the control arms (treatment vs. control, risk difference: 5.9%, 95%CI: 0.1% to 11.1%), although studies varied.

A recent systematic review of studies of the effect of exercise on blood pressure [179] included 7 studies between 1966 and 1995, all with at least 26 weeks follow-up, and including normotensive and hypertensive participants. The review found exercise had a small and statistically non-significant effect on blood pressure (-0.7/0.3 mmHg in 4 studies with hypertensive participants), but noted the poor quality of studies.

The recent Canadian guideline reviewed studies between 1966 and 1997[250]. Although without a formal meta-analysis, it reported short term reductions in blood pressure of 5 to 10 mmHg and recommended 50-60 minutes of moderate intensity exercise 3 or 4 times per week.

Figure 9: Effect of exercise on systolic and diastolic blood pressure in randomised trials of patients with raised blood pressure



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -3.1 (95% CI: -5.5 to -0.7); Q:p = 0.007; Size: p = 0.18
Diastolic BP: DL= -1.8 (95% CI: -3.5 to -0.2); Q:p = 0.001; Size: p = 0.48

Trials with multiple treatment arms (Blumenthal 1991, Hagberg 1989, ODES 1997 and Rogers 1996) were combined before the estimation of overall effect

+ F/U: Duration of follow up in weeks, months or years, N: Number randomised, and a: aerobic exercise, + moderate intensity, - low intensity, . unspecified; w: weight training

Relaxation therapies

- Overall, structured interventions to reduce stress and promote relaxation had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3 to 4 mmHg in trials. There is variation in the reduction in blood pressure achieved in trials and it is unclear why. About one third of patients receiving relaxation therapies were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year. II
- The current cost and feasibility of providing these interventions in primary care has not been assessed and they are unlikely to be routinely provided. III

Twenty-three randomised controlled trials of parallel design, including 1,481 participants, met the review inclusion criteria and are tabulated in Appendix 8: RCTs of relaxation interventions [251,252, 253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,178,271,272,273]. Twelve further trials could not be included because of missing data [274,275,276,277,278,279, 280,281,282,283,284,285].

The mean age of study participants was 49 years and 62% were male. Only 6 studies reported ethnicity and in these about 84% of the participants were white. The median duration of intervention was 8 weeks, ranging from 4 weeks to 6 months; the median duration of follow-up 17 weeks, ranging from 8 weeks to 4 years, reflecting that studies often assessed the longer term impact of interventions well after formal therapy had ceased.

Randomisation could be confirmed as adequate in only 7 studies (30%), and concealment of allocation as adequate in only 1 (4%). Blinding was confirmed as adequate in 7 studies (30%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 16 studies (70%).

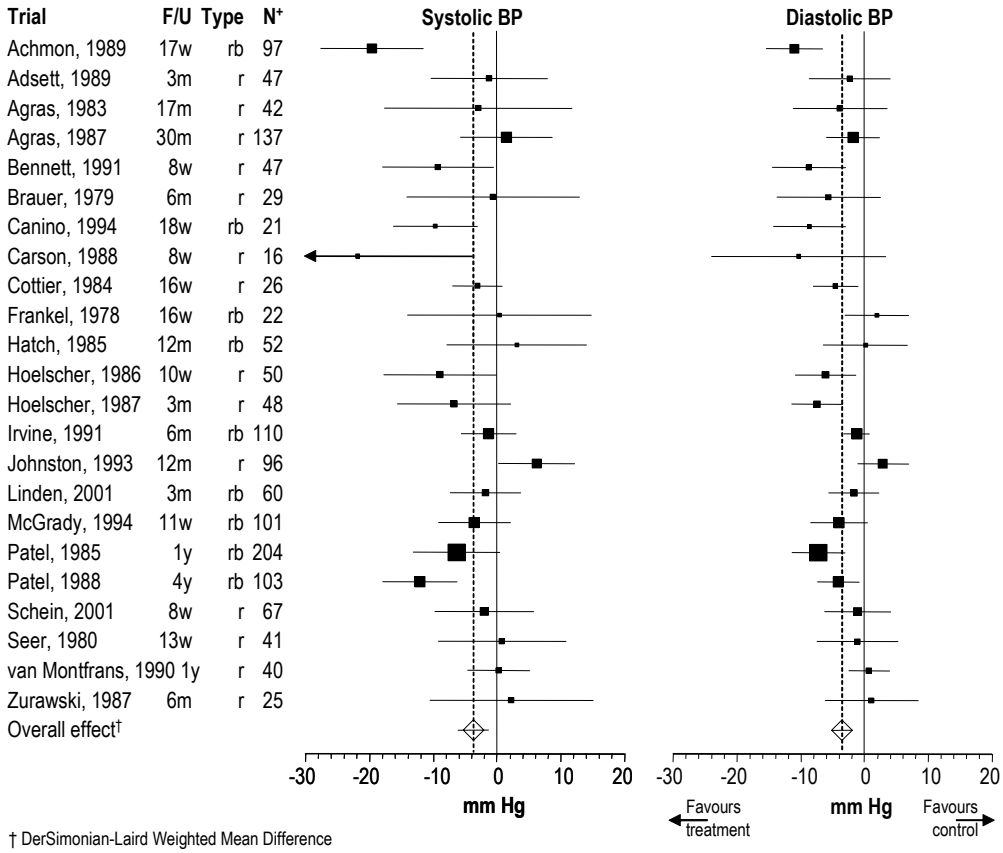
The common component in studies was a strategy to promote relaxation although this could be oriented through education, physical techniques (such as breathing or progressive muscle relaxation), talk therapies, stress management or some combination. Additionally some studies used biofeedback, where the participant received auditory or visual information about their heart rate, peripheral temperature or some other physical marker. There was variation in content, with individual studies incorporating (for example) forms of cognitive training, breathing management, meditation, yoga, behavioural contracts, assertiveness training and anger control techniques. Similarly, delivery varied, being provided by a range of health professionals, most commonly to groups but in a few studies to individuals. Most treatment sessions were about an hour in length (varying from 30 to 90 minutes) and were usually conducted once a week.

Control groups received care varying from no intervention to sham group therapy excluding components that investigators believed to be the effective aspects of therapy. Some studies included both types of control groups.

Overall relaxation interventions were associated with statistically significant reductions in systolic (3.7 mmHg, 95%CI: 1.3 to 6.0) and diastolic (3.5 mmHg, 95%CI: 1.9 to 5.1) blood pressure (see Figure 10). There was no evidence of reporting bias. However, significant heterogeneity existed between studies. Analysis of the additional value of biofeedback as a component of the intervention was inconclusive when comparing studies that did or didn't include it, or when comparing alternative interventions within trials. Thirty-three percent (95%CI: 25% to 40%) of patients receiving relaxation therapies were likely to show at least a 10 mmHg reduction in systolic blood pressure in the short term. Based on 12 of the studies, there was no significant difference in withdrawal when comparing treatment or control arms of studies (treatment vs. control, risk difference: 3.4%, 95%CI: 0.0% to 6.8%), although studies varied.

A recent systematic review of studies of the effect of stress reduction on blood pressure [179] included 7 studies between 1966 and 1995, all with at least 26 weeks follow-up, and including hypertensive participants. Although the inclusion criteria differed from ours, the review found a small and statistically non-significant effect on blood pressure (-1.0/-1.1 mmHg) consistent with longer follow-up studies reported here. The review similarly found considerable heterogeneity between studies.

Figure 10: Impact of relaxation interventions on blood pressure: findings from randomised controlled trials



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -3.7 (95% CI: -6.0 to -1.3); Q:p = <0.001; Size: p = 0.41
Diastolic BP: DL= -3.5 (95% CI: -5.1 to -1.9); Q:p = <0.001; Size: p = 0.38
Trials with multiple treatment arms were combined before the estimation of overall effect
+ F/U: Duration of follow up in weeks, months or years, N: Number randomised, and r: relaxation therapy; b: biofeedback

The recent Canadian guideline reviewed studies between 1966 and 1997 [286]. It concluded that multifaceted interventions to reduce stress were more likely to be effective than single component therapies and favoured the use of cognitive behavioural therapy, based on the findings of three meta-analyses [174,173,175]. For hypertensive patients in whom stress appears to be an important issue, they recommended that stress management including individualized cognitive behavioural therapy may be appropriate.

Multiple lifestyle interventions

- Education about lifestyle on its own is unlikely to be effective. II
- Interventions actively combining exercise and diet were shown to reduce both systolic and diastolic blood pressure by about 4 to 5 mmHg in trials. About one quarter of patients receiving multiple lifestyle interventions were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year. II

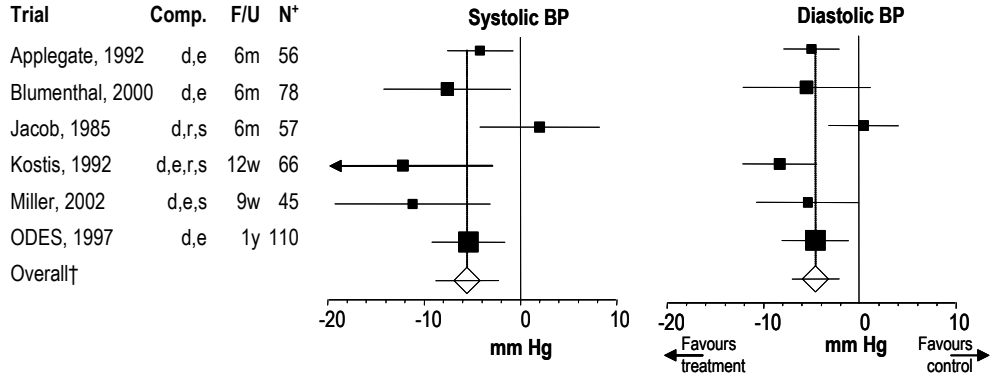
Six randomised controlled trials, including 413 participants, met the review inclusion criteria and are tabulated in Appendix 9: RCTs of multifaceted interventions [287,288,289,290,291,292,293]. Three of the studies essentially provided a therapeutic intervention combining group exercise and diet strategies similar to the lifestyle interventions found in the previous sections [287,288,290291]; one study also included relaxation and restriction of intake of common salt [289]; one study combined a weight loss diet, relaxation and salt restriction [292]; and one study combined a weight loss diet, exercise and salt restriction [293]. A further trial, which delivered a health education package to a British population with angina, did not meet our inclusion criteria for blood pressure and so was excluded from the meta-analysis and is considered separately [294]. Three further trials could not be included because of missing data [249,295,296]

The mean age of participants was 52 years, 66% were male and the median follow-up of studies was 6 months. Five studies reported ethnicity and in these about 75% of the participants were white.

Randomisation was confirmed as adequate in only 2 studies (33%). Concealment of allocation was inadequate or unclear in all six studies. Blinding was confirmed as adequate in 4 studies (67%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 5 studies (83%).

Overall, multifaceted interventions caused a modest reduction in both systolic (5.5, 95%CI: 2.3 to 8.8) and diastolic (4.5 mmHg, 95% CI: 2.0 to 6.9) blood pressure (see Figure 11). However heterogeneity existed between studies: the study of Jacob (1985) did not demonstrate a reduction in blood pressure. Twenty-six percent (95%CI: 2% to 49%) of patients receiving combined interventions were likely to show at least a 10 mmHg reduction in systolic blood pressure. Data from 5 studies found no statistically significant difference in withdrawal from treatment and control groups (treatment vs. control, risk difference: 4.9%, 95%CI: -2.6% to 12.4%).

Figure 11: Impact of combined lifestyle interventions on blood pressure: findings from randomised controlled trials



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -5.5 (95% CI: -8.8 to -2.3); Q:p = 0.07; Size: p = 0.41
Diastolic BP: DL= -4.5 (95% CI: -6.9 to -2.0); Q:p = 0.06; Size: p = 0.70

+ Comp: Components of intervention, d: diet, e: exercise, r: relaxation, s: salt restriction
F/U: Duration of follow up in weeks, months or years; and
N: Number randomised

It was not possible to assess from the available data whether the effects of diet and exercise were additive or whether the combination was no better than either diet or exercise on its own.

The large British health promotion study, of 688 participants, lasted longer (2 years) and was of older people (mean age 63 years) than the therapeutic studies. It did not show any reduction in blood pressure in response to health advice, but nevertheless reported fewer deaths among those receiving advice (29 in control group and 13 in treatment group), providing a relative reduction in mortality of 55%, an absolute reduction in mortality of 4.6% (95%CI: 1.0% to 8.4%) or a Number Needed to Treat of 22 to prevent a death during two years of follow-up. Patients in this trial, suffering from angina, were at higher risk than most other patients enrolled in lifestyle trials, leading to greater levels of morbidity and mortality. However, the benefit of health promotion in this trial does not appear mediated by reduced blood pressure or any other obvious prognostic marker (smoking, cholesterol or body mass index), and thus needs confirmation from further research.

A recent systematic review of studies of multiple interventions for preventing coronary heart disease; included 9 studies of normotensive and hypertensive participants, published between 1966 and 1995, and with at least 26 weeks follow-up [297]. The review found an overall reduction of 4.2/2.7mmHg, but no significant reductions in morbidity and mortality in studies not including drug interventions.

Alcohol

- Excessive alcohol consumption (men: more than 21 units/week; women: more than 14 units/week) is associated with raised blood pressure and poorer cardiovascular and hepatic health.	I
- Structured interventions to reduce alcohol consumption, or substitute low alcohol alternatives, had a modest effect on blood pressure, reducing systolic and diastolic blood pressure on average by about 3 to 4 mmHg in trials. Thirty percent of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Brief interventions by clinicians of 10-15 minutes, assessing intake and providing information and advice as appropriate, have been reported to reduce alcohol consumption by a quarter in excessive drinkers with or without raised blood pressure, and to be as effective as more specialist interventions.	II
- Brief interventions have been estimated to cost between £40 and £60 per patient receiving intervention. The structured interventions used in trials of patients with hypertension have not been costed.	II

The epidemiological link between alcohol consumption, blood pressure, cardiovascular disease and all-cause mortality has been studied extensively [298,299,300,301]. While moderate consumption may do no harm, the literature consistently finds that the move from moderate to excessive drinking (men: more than 21 units/week; women: more than 14 units/week) is associated both with raised blood pressure and a poorer prognosis. (Approximately: one half-pint of beer, glass of wine or a single measure of spirits equals one unit of alcohol or one standard drink and contains 8g or 10ml of alcohol [302]).

Three randomised controlled trials, including 397 participants, met the review inclusion criteria and examined the effect of changes in alcohol consumption on blood pressure (see Appendix 10) [303,304,226]. Interventions varied in their content but commonly featured a number of visits to a health care practitioner for advice on reducing intake of alcohol. At baseline, patients typically reported drinking 300 to 600 ml of alcohol, or 30-60 standard drinks, per week. Although alcoholism was not formally defined, very heavy drinkers were commonly excluded. A further cluster randomized trial with 93 participants was identified and included in a secondary analysis [305].

The mean age of study participants was 53 years; in the two studies that provided the details all participants were male and three quarters were white. The PATHS study [304], with 6 months treatment duration, two year follow-up and 59% of patients, differed in scale from the two other shorter and smaller trials.

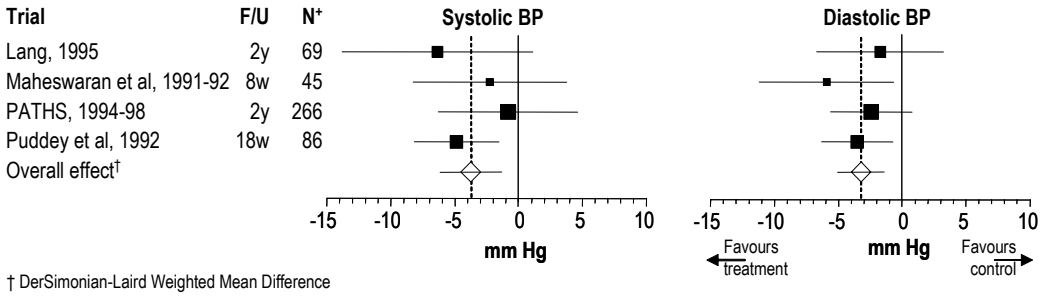
Randomisation could be confirmed as adequate only in the PATHS study, and concealment of allocation as adequate in none. Blinding was confirmed as adequate in 2 studies. Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in all 3 studies, with the possible exception of PATHS which did not report the proportions of men and women in the treatment and control groups. No studies were designed to assess the impact of alcohol reduction on cardiovascular endpoints.

Overall, interventions to reduce alcohol consumption caused small but statistically significant reductions in both systolic (3.4 mmHg, 95%CI: 0.9 to 6.0) and diastolic (3.4 mmHg, 95%CI: 1.5 to 5.4) blood pressure. Thirty percent (95%CI: 21% to 39%) of patients receiving a structured intervention to reduce alcohol consumption were likely to achieve a reduction of at least 10 mmHg in systolic blood

pressure. No harmful effects of intervention were reported in these trials; withdrawal rates were reported in only one small trial. Inclusion of the single cluster randomized study did not alter qualitatively the summary reduction in systolic (3.7 mmHg, 95% CI: 1.3 to 6.1) or diastolic (3.2 mmHg, 95%CI: 1.4 to 5.0) blood pressure, (see Figure 12).

The recent Canadian guideline reviewed studies between 1966 and 1996 [306]. Although without a formal meta-analysis, it recommended that alcohol consumption be limited in patients with hypertension to 2 or fewer standard drinks per day, with consumption not exceeding 14 standard drinks per week for men and 9 standard drinks per week for women.

Figure 12: Impact of alcohol reduction on blood pressure: findings from randomised controlled trials



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -3.7 (95% CI: -6.1 to -1.3); Q:p = 0.52; Size: p = 0.74
Diastolic BP: DL= -3.2 (95% CI: -5.0 to -1.4); Q:p = 0.65; Size: p = 0.78

+ F/U: Duration of follow up in weeks, months or years, and N: Number randomised

A number of reviews of brief interventions to reduce alcohol consumption in people with raised alcohol consumption have been published [307,308,309,310,311,312,313,314]. These found that brief opportunistic intervention (by a physician or nurse for 5-20 minute consultations) reduced self-reported alcohol consumption by about 25%. More specialist intervention did not appear to provide further benefits above brief intervention, although this latter comparison includes a greater proportion of participants with alcohol dependence and long term problems. A previous costing of a brief intervention for opportunistic screening [307] is reworked with current costs [116]. After initial assessment (2 minutes; £4) by a GP, intervention to reduced excessive alcohol consumption (15 minutes; £32) is necessary for 28% of men with and for 11% of women. Assuming that equal numbers of men and women are assessed and that materials cost £3 per intervention, the cost of brief intervention is £11 per patient screened or £60 per patient receiving intervention. If the screening and intervention are provided by a practice nurse this reduces to £7 per patient screened or £38 per patient receiving intervention.

Coffee

- Excessive consumption of coffee (5 or more cups per day) is associated with a small increase in blood pressure (2/1 mmHg) in participants with or without raised blood pressure in studies of several months duration. | III

Although coffee is a complex beverage containing many chemicals, only the effect of caffeine has been studied extensively [315]. According to personal taste and type of coffee, the amount of caffeine varies, but typically coffee contains 60 to 120 mg per 150ml cup. This can be compared with tea (20 to 40 mg per 150ml cup) and cola drinks (30 to 50 mg per 330ml can) [183, 316].

Caffeine consumption has long being associated with raised blood pressure and can demonstrate a dose-related increase of 5-15 mmHg systolic and 5-10 mmHg diastolic for several hours following consumption. The most likely mode of action of caffeine is as an adenosine receptor antagonist, which results in vasoconstriction and raises blood pressure. The half life of caffeine in the body is typically about 5 hours [317].

We identified no randomised controlled trials examining the impact of coffee or caffeine intake on patients with hypertension, which provided at least 8 weeks follow-up. A published systematic review included normotensive as well as hypertensive participants, and shorter durations of follow-up [184]. Eleven trials with a total of 522 participants and a median duration of 8 weeks (range 2 to 11 weeks) were included. Control groups drank a median of 5 caffeinated cups of coffee a day, with treatment groups receiving no, or decaffeinated, coffee. The reported overall effect of coffee was an increase in systolic (2.4 mmHg, 95%CI: 1.0 to 3.7) and diastolic (1.2 mmHg, 95%CI: 0.4 to 2.1) blood pressure.

Identifying the influence of coffee upon blood pressure, or identifying groups at particular risk, is problematic in the presence of confounding factors such as age, lifestyle, and cardiovascular disease. The small sample sizes and durations of existing trials do not provide an adequate evidence base to infer the long term effects of routine caffeine consumption.

Reducing sodium (salt) intake

- Advice to reduce dietary sodium intake to less than 6g/day was shown to achieve a modest reduction in systolic and diastolic blood pressure of 2 to 3 mmHg in patients with hypertension, at up to 1 year in trials. About a quarter of patients were estimated to achieve a reduction in systolic blood pressure of 10 mmHg systolic or more in the short term, up to 1 year.	II
- Long term evidence over 2 to 3 years from studies of normotensive patients shows that reductions in blood pressure tend to diminish over time.	II
- One trial suggests that reduced sodium salt, when used as a replacement in both cooking and seasoning, is as effective in reducing blood pressure as restricting the use of table salt.	III

Practical steps to reduce sodium intake include choosing low-salt foods (e.g. choosing fresh fruits and vegetables and avoiding processed foods) and reducing or substituting its use in cooking and seasoning. Much dietary salt comes from processed foods whose content should be labelled helping to monitor intake.

Five randomised controlled trials (4 of parallel design [318,319,320,321], 1 of crossover design [322,323]), examining the effect of sodium reduction on blood pressure, met the review inclusion criteria and included 420 patients (see Appendix 14). The findings of one Italian trial in young adults are considered separately [324]. A further trial could not be included because of missing data [325].

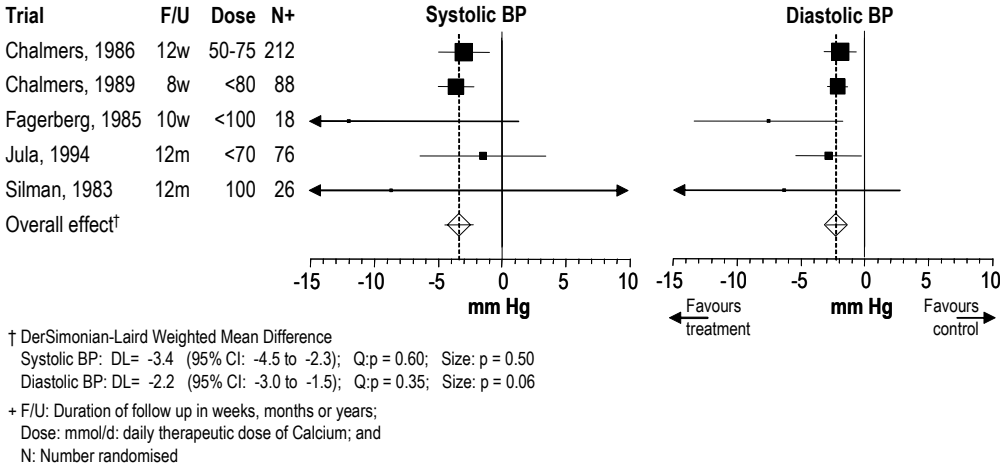
The mean age of study participants was 52 years and 81% were male. The ethnicity of participants was not reported in any of the studies. The median duration of both intervention and follow-up was 12 weeks.

One trial (17%) was double-blinded; blinding could not be confirmed in any of the other studies. Randomisation and concealment of allocation could not be confirmed to be adequate in any of the studies. Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 2 studies of parallel design (40%); the crossover study did not report on carryover effects.

The studies advised participants to change their diet so as to restrict their sodium intake to below 70-100 mmol/day (4.2 - 6.0g of salt). The Scientific Advisory Committee on Nutrition target for all adults is 6 grams/day [326].

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 13. Sodium reduction was associated with a statistically significant reductions in systolic (3.4 mmHg, 95%CI: 2.3 to 4.5) and diastolic (2.2 mmHg, 95%CI: 1.5 to 3.0) blood pressure. Twenty-three percent (95%CI: 17% to 30%) of patients who reduced their salt intake were likely to show at least a 10 mmHg reduction in systolic blood pressure. Based on 2 studies, there was no difference in withdrawal when comparing treatment and control arms of studies (treatment vs. control, risk difference: -0.6%, 95%CI: -6.5% to 5.4%).

Figure 13: Impact of sodium reduction on blood pressure: findings from randomised controlled trials



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -3.4 (95% CI: -4.5 to -2.3); Q:p = 0.60; Size: p = 0.50
Diastolic BP: DL= -2.2 (95% CI: -3.0 to -1.5); Q:p = 0.35; Size: p = 0.06

+ F/U: Duration of follow up in weeks, months or years;
Dose: mmol/d: daily therapeutic dose of Calcium; and
N: Number randomised

One Italian trial enrolled young, borderline hypertensive participants, aged 16-31 years. This trial found a dramatic reduction in systolic (18.4 mmHg, 95%CI: 10.1 to 26.7) blood pressure. The trial was poorly described and it is unclear whether the reduction in systolic blood pressure is due solely to the intervention. The authors note that the benefit was found mostly in participants less than 20 years of age. The inclusion of the trial in the meta-analysis increased the average benefit of salt reduction on systolic blood pressure (7.1 mmHg, 95%CI: 2.9 to 11.3), but introduced considerable statistical heterogeneity (Q: p=0.007).

Two recent systematic reviews have evaluated advice to reduce salt intake in normotensive and hypertensive adults, in trials with at least 6 months follow-up [201,179]. The inclusion criteria used in these reviews differ from ours, notably they included studies where the dose of antihypertensive drugs was allowed to vary. Regardless, both reviews found statistically significant reductions in blood pressure in studies with hypertensive participants, of 2.5/1.2 (up to 1 year follow-up) and 1.1/0.6 (1 to 6 years follow-up) [201] and 2.9/2.1 mmHg [179], suggesting that reductions in blood pressure tend to diminish over time.

The recent Canadian guideline [327], citing a previous systematic review, concluded that sodium restriction in adults over 44 years of age resulted in a reduction in blood pressure of 6.3/2.2 mmHg per 100 mmol/day reduction in sodium. Recommendations were made for clinicians to determine salt intake by interview; aim for a target range of 90–130 mmol per day (3–7 grams per day); provide advice on choosing low-salt foods (e.g. choosing fresh fruits and vegetables and avoiding pre-prepared foods) and reduce usage in cooking and seasoning.

Calcium supplements

See also: *Combined salt supplements,* page *100.*

Eleven randomised controlled trials (3 of parallel design [328,329,330], 8 of crossover design [331,332,333,334,335,336,172 ,337]), examining the effect of calcium supplementation on blood pressure, met the review inclusion criteria and included 414 patients (see Appendix 11). Another trial, carried out in patients who were undergoing dialysis, was excluded after consideration of their unusual calcium metabolism but its details are tabulated [338]. A further trial could not be included because of missing data [339].

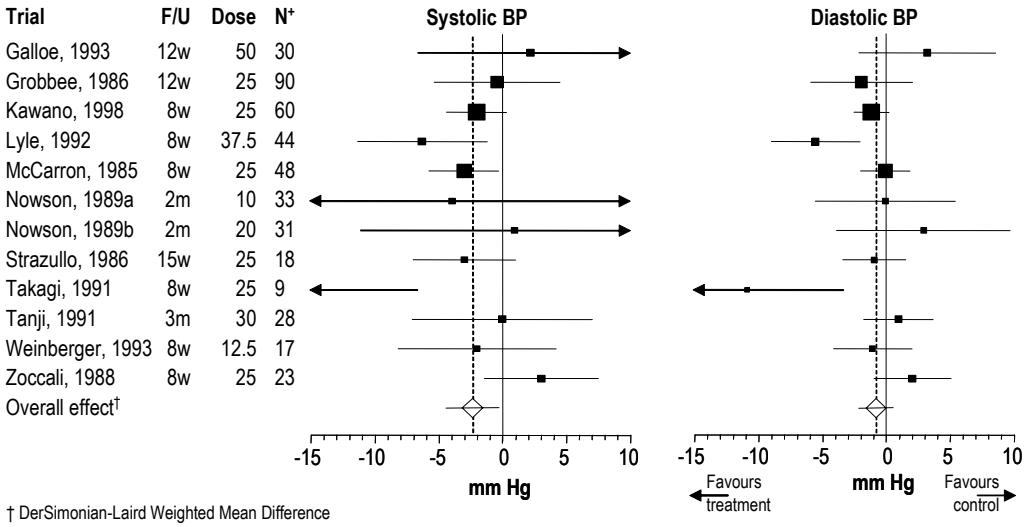
The mean age of study participants was 45 years and 68% were male. Only 4 studies reported ethnicity and in these 46% of the participants were white. The median duration of both intervention and follow-up was 8 weeks.

Randomisation could be confirmed as adequate in only 2 studies (18%) and concealment of allocation as adequate in only 1 (9%); 9 studies (82%) studies were double-blinded Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 1 study (33%) of parallel design; 3 studies (37%) of crossover design confirmed no carryover effect.

The intervention was provided as a simple oral supplement taken several times a day.

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 14. Calcium supplementation was associated with a small reduction in systolic blood pressure 2.3 mmHg, 95%CI: 0.3 to 4.4) which was statistically significant but not robust to minor changes in the reported blood pressure of the participants, and no difference in diastolic blood pressure (-0.8 mmHg, 95%CI: -2.1 to 0.6). No harmful effects of intervention were reported in these trials; withdrawal rates were on average around 10% in both treatment and control groups. The trials were unable to identify sub-groups of patients that might benefit from calcium.

Figure 14: Impact of calcium supplementation on blood pressure: findings from randomised controlled trials



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -2.3 (95% CI: -4.4 to -0.3); Q:p = 0.03; Size: p = 0.82
Diastolic BP: DL= -0.8 (95% CI: -2.1 to 0.6); Q:p = 0.01; Size: p = 0.68
Active treatment arms in Nowson et al, 1989 were combined before the estimation of overall effect

+ F/U: Duration of follow up in weeks, months or years;
Dose: mmol/d: daily therapeutic dose of Calcium; and
N: Number randomised

Magnesium supplements

See also: *Combined salt supplements,* page *100.*

Eleven randomised controlled trials (9 of parallel design [340,341,342, 343,344,345,346,347,348] 2 of crossover design [349,350]), examining the effect of magnesium supplementation on blood pressure, met the review inclusion criteria and included 504 patients (see Appendix 12).

The mean age of study participants was 55 years and 44% were male. Only 2 studies reported ethnicity and in these 11% of the participants were white. The median duration of both intervention and follow-up was 12 weeks.

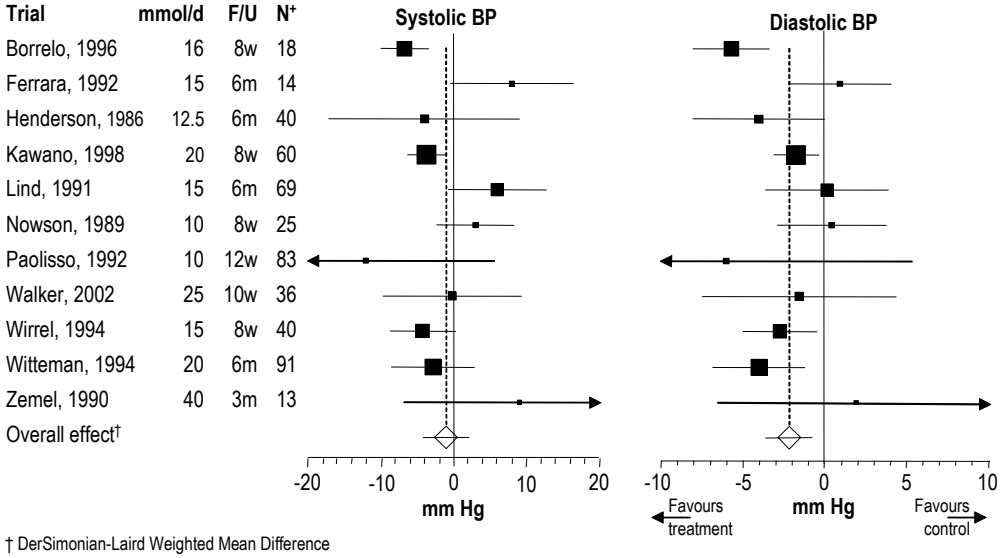
Ten studies (91%) studies were single- or double-blinded. Randomisation and concealment of allocation were confirmed to be adequate in one study (9%) and no studies respectively. Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 6 studies (67%) of parallel design; neither of the studies of crossover design reported on carryover effects.

The intervention was provided as a simple oral supplement taken several times a day.

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 15. Magnesium supplementation was associated with little change in systolic (-1.0 mmHg, 95%CI: -4.1 to 2.1) but a statistically significant reduction in diastolic (-2.1 mmHg, 95%CI: -3.5 to -0.7)

blood pressure. No harmful effects of intervention were reported in these trials; withdrawal rates were reported in only 8 studies, where these were on average around 7% in both treatment and control groups. The trials were unable to identify sub-groups of patients that might benefit from magnesium.

Figure 15: Impact of magnesium supplementation on blood pressure: findings from randomised controlled trials



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -1.0 (95% CI: -4.1 to 2.1); Q:p = 0.001; Size: p = 0.16
Diastolic BP: DL= -2.1 (95% CI: -3.5 to -0.7); Q:p = 0.02; Size: p = 0.78

+ mmol/d: daily therapeutic dose of Magnesium;
F/U: Duration of follow up in weeks, months or years; and
N: Number randomised

Potassium supplementation

See also: *Combined salt supplements,* page *100.*

Five randomised controlled trials (4 of parallel design [351,352,353, 354], 1 of crossover design [355]), examining the effect of potassium supplementation on blood pressure, met the review inclusion criteria and included 410 patients (see Appendix 13). The findings of one African trial are considered separately [356]. A further trial could not be included because of missing data [357].

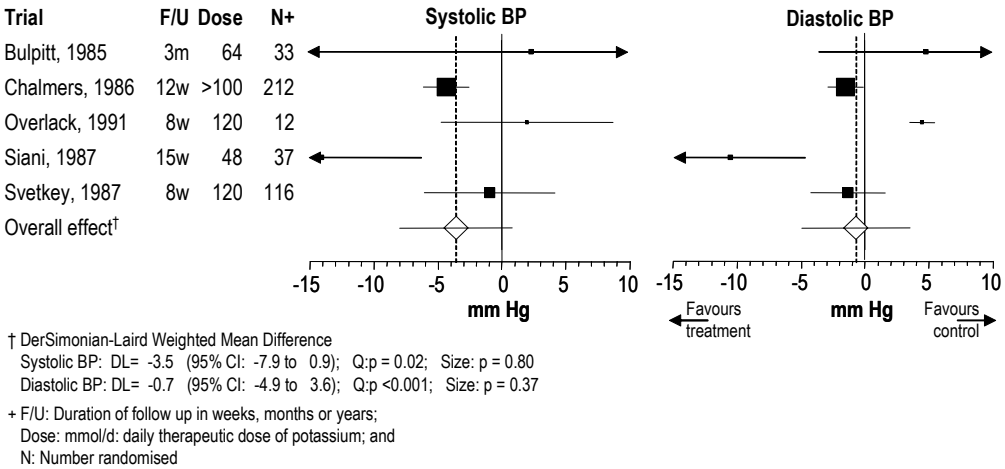
The mean age of study participants was 51 years and 76% were male. Only 1 study reported ethnicity and in this 86% of the participants were white. The median duration of both intervention and follow-up was 12 weeks.

Two studies were triple-blinded, two were assessment blinded and one was unclear. Randomisation and concealment of allocation were confirmed to be adequate in one (20%) and two (40%) studies respectively. Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 2 studies (50%) of parallel design; the crossover study did not report on carryover effects.

The intervention was provided as a simple oral supplement taken several times a day in all but one trial, where dietary advice was provided to increase intake of foods rich in potassium [352].

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 16. Potassium supplementation was not associated with any significant change in systolic (-3.5 mmHg, 95%CI: -7.9 to 0.9) or diastolic (-0.7 mmHg, 95%CI: -4.9 to 3.6) blood pressure. The findings of the studies were heterogeneous and there are no obvious reasons for this that can be deduced from the limited available evidence. No harmful effects of intervention were reported in these trials; average withdrawal rates of 6-8% were similar in both treatment and control groups.

Figure 16: Impact of potassium supplementation on blood pressure: findings from randomised controlled trials



† DerSimonian-Laird Weighted Mean Difference
Systolic BP: DL= -3.5 (95% CI: -7.9 to 0.9); Q:p = 0.02; Size: p = 0.80
Diastolic BP: DL= -0.7 (95% CI: -4.9 to 3.6); Q:p <0.001; Size: p = 0.37

+ F/U: Duration of follow up in weeks, months or years;
Dose: mmol/d: daily therapeutic dose of potassium; and
N: Number randomised

One trial, which enrolled treatment naïve and hypertensive Kenyan participants (DBP 90-109 mmHg and SBP>160 mmHg) reported an average reduction of 39/17 mmHg. Although the effect of various salts upon certain ethnic groups is known to vary, a reduction of this magnitude exceeds our understanding and requires confirmation from further independent research.

A meta-analysis by Whelton and colleagues found that oral potassium supplementation was associated with a significant reduction in both systolic blood pressure and diastolic blood pressure [197], based on 12 trials in normotensive people and 21 in hypertensive people, with a duration ranging from 4 days to 3 years (median 5 weeks). The review found that the blood pressure lowering effect was greater in hypertensive than normotensive people, although the statistical significance of findings in the hypertensive subgroup is not reported. The review also found that the effect was more pronounced in people eating a diet high in sodium chloride (common salt) and therefore recommended potassium supplementation for both prevention and treatment of hypertension, especially in people unable to reduce their intake of sodium.

In contrast, our restriction to trials of at least 8 weeks duration, enrolling only hypertensive patients, resulted in inclusion of only 5 trials with a median duration of 12 weeks and found that the blood pressure lowering effect of oral potassium supplementation was not statistically significant. The group concluded that there is not sufficient relevant evidence to recommend oral potassium supplementation for hypertension.

Combined salt supplements

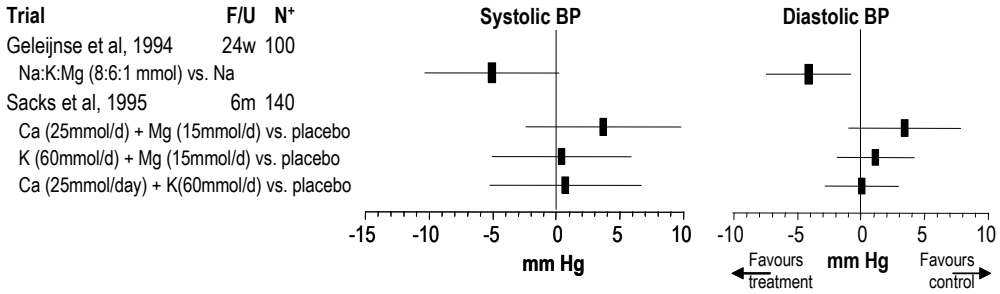
- The best current evidence does not show that calcium, magnesium or potassium supplements produce sustained reductions in blood pressure. II
- The best current evidence does not show that combinations of potassium, magnesium and calcium supplements reduce blood pressure. II

Two randomised controlled trials studied combinations of the potassium, magnesium, sodium and calcium salts considered individually in previous sections (see Appendix 15).

One study used paired supplements comparing two of calcium, potassium and magnesium with placebo [358]. None of the combined supplements reduced blood pressure when compared with placebo (see Figure 17). This was consistent with the findings for the individual supplements.

A second study compared a mineral (reduced sodium) salt containing sodium, potassium and magnesium with common sodium table salt. The mineral salt was used in prepared food as well as for seasoning [359]. The reduction of blood pressure by about 5/4 mmHg consistent with that found with strategies to reduce sodium salt intake.

Figure 17: Impact of combined supplements on blood pressure: findings from randomised controlled trials



+F/U: Duration of follow up in weeks, months or years; and N: Number randomised

Calcium (Ca), Magnesium (Mg), Potassium (K) and Sodium (Na) salts

Sodium is common table salt. Na:K:Mg is a reduced sodium mineral salt

The recent Canadian guideline reviewed studies between 1966 and 1996 [360]. Although without a formal meta-analysis, it recommended against supplementing calcium, magnesium or potassium intake amongst hypertensive participants above the recommended normal daily levels.

Drug therapy versus lifestyle change

- A healthier lifestyle, by lowering blood pressure and cardiovascular risk, may reduce, delay or remove the need for long term drug therapy in some patients. III

Five small randomised controlled trials enrolling 233 patients directly compared the effects of lifestyle interventions and drugs for the treatment of mild to moderate hypertension (see Appendix 16) [Goldstein et al 279, Murugesan et al 284, Kostis et al 289, MacMahon et al 361, 362, Koopman et al 363]. An additional quasi-randomised trial, which allocated participants to treatments on the basis of their birth date rather than at random, was also considered (Berglund et al [364]).

All trials were small (between 38 and 66 participants), of short duration (between 8 and 52 weeks) and were not designed to assess cardiovascular endpoints. Randomisation and concealment of allocation were either inadequate or not clearly reported in all trials. The outcome assessor was blinded to the treatment status of the participants in three trials [289,361,363]; blinding was not reported in two trials [279,284], and there was no blinding in one trial [364] . One trial was poorly reported and did not state the total number of participants [284]. In two trials the confidence intervals on the effects of treatment could not be estimated, as either the numbers in each treatment group [284] or the standard error of the treatment effects were not reported [279].

The populations studied in the trials differed in: (i) age – participants in one trial [363] were older, which probably accounted for their higher baseline blood pressure compared to participants in the other trials; (ii) treatment status at the point of recruitment – participants were currently untreated or treatment naïve in four trials [279,361,363,364], currently treated in one trial [289], or treatment status was not reported [284].

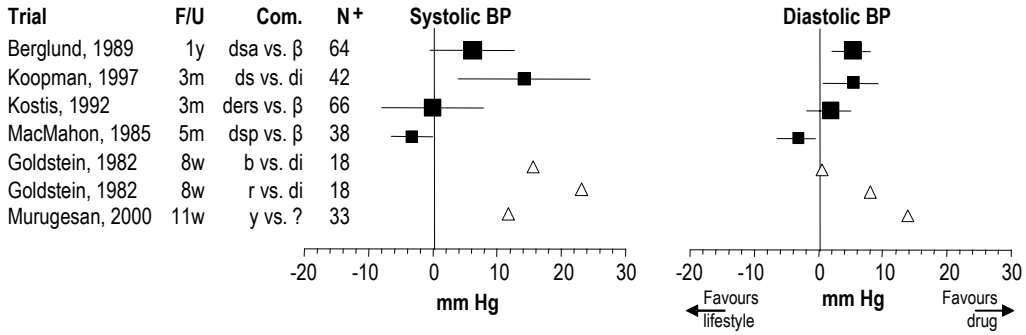
The trials compared different drugs with different lifestyle interventions. Typically either a diuretic or a beta-blocker was the class of drug used, although one trial allowed a choice of drugs. Four trials used a low calorie diet: one used diet alone; one combined a low calorie intake with a low sodium and high potassium diet; one used a multiple intervention combining weight loss, a low calorie and low sodium diet, exercise, and relaxation and one combined weight reduction with restricted sodium and alcohol intake. Two trials had relaxation interventions: one considered two separate relaxation interventions (biofeedback and muscular relaxation/breathing exercises); the other used yoga.

Five trials reported comparable blood pressure at baseline in both treatment groups and for one trial this was unclear. Within each study, findings for systolic and diastolic blood pressure were similar.

Trials comparing diet with drugs provided conflicting evidence (see Figure 18). In the trial of older participants (Koopman et al) who had not received treatment before and had a high baseline blood pressure, drug treatment appears more effective than diet in lowering blood pressure, whereas in a trial of younger participants (MacMahon et al) who were currently untreated and had a lower initial

blood pressure, diet appears significantly more effective than drug treatment in lowering blood pressure. The one trial (Kostis et al) comparing multiple lifestyle interventions with drugs found both treatments had similar effects on lowering blood pressure. Two trials found drugs to be more effective than relaxation although the confidence intervals on the treatment effects could not be determined (Murugesan et al, Goldstein et al).

Figure 18: Comparison of lifestyle and drug interventions: findings from randomised controlled trials



+ F/U: Duration of follow up in months, and N: Number randomised
Components: alcohol restriction; biofeedback; diet; exercise; potassium enhancement; relaxation; salt restriction; yoga vs. β-blocker; diurectic

Participants receiving dietary interventions improved their total cholesterol profiles in all four trials compared to participants receiving drugs. Cholesterol levels were not reported in either relaxation trial. Although it was a *post hoc* exercise, we combined cholesterol reductions found in the dietary trials by imputing missing standard deviations. Using a random effects model, the average reduction in cholesterol was 0.52 mmol/l (95% CI -0.34 to -0.7).

Withdrawals were reported in five trials: rates of withdrawal were similar for lifestyle and drug treatments.

The current evidence cannot determine whether a lifestyle intervention is generally better than drug treatment for reducing blood pressure. Although cholesterol levels were not a prespecified outcome, it was observed that, in all four trials with diet interventions, diets were better than antihypertensive drugs at reducing cholesterol. As reduced cholesterol levels are likely to lower the risk of cardiovascular morbidity or mortality irrespective of any change in blood pressure [140], a healthier diet may reduce, delay or remove the need for long-term drug therapy in some patients. Thus it seems important that patients are encouraged to try lifestyle changes before proceeding to or increasing drug therapy.

Smoking cessation

- There is no strong direct link between smoking and blood pressure. However, there is overwhelming evidence of the relationship between smoking and cardiovascular and pulmonary diseases, and evidence that smoking cessation strategies are cost-effective. I

A review of the health consequences of smoking and benefit of smoking cessation is not included in this guideline, since there is no direct link to raised blood pressure. However smoking reduces life expectancy and is associated with poor cardiovascular and pulmonary outcomes [365,366,367,368,369,370]. A NHS website: http://www.givingupsmoking.co.uk/ provides facts and information about giving up smoking.

The National Service Framework for Coronary Heart Disease [i] sets out the principle that those wishing to stop smoking will be helped by the NHS and identifies smoking cessation as one of the three areas that are an immediate priority. Primary Care Trusts are expected to establish a range of approaches to smoking cessation for smokers who wish to quit, and target disadvantaged communities, young people and pregnant women. Guidance is provided for members of primary health care teams to provide opportunistic advice to smokers [371,372,373]. NSF-CHD Standard 2 states '*The NHS and partner agencies should contribute to a reduction in the prevalence of smoking in the local population*'. NICE have issued guidance about prescribing nicotine replacement therapy and bupropion for people wanting to stop smoking [374].

Pharmacological interventions

Recommendations and supporting statements

- **Drug therapy reduces the risk of cardiovascular disease and death. Offer drug therapy to (i) patients with persistent high blood pressure of 160/100 mmHg or more and (ii) patients at raised cardiovascular risk (ten year risk of CHD≥15% or CVD≥20% or existing cardiovascular disease or target organ damage) with persistent blood pressure of more than 140/90 mmHg.** **A**
  - In placebo-controlled trials, blood pressure management beginning with a low dose thiazide-type diuretic or beta-blocker has been shown to reduce mortality, myocardial infarction and stroke (relative risk reductions of 8%, 15% and 25% respectively). I
- **Provide appropriate guidance and materials about the benefits of drugs and the unwanted side-effects sometimes experienced in order to help patients make informed choices.** **C**
- **Offer drug therapy, adding different drugs if necessary, to achieve a target of 140/90 mmHg or until further treatment is inappropriate or declined. Titrate drug doses as described in the *British National Formulary* noting any cautions and contraindications.** **A**
  - In trials aiming to reduce blood pressure to below 140/90 mmHg using stepped medication regimes, between half and three-quarters of patients achieve target blood pressure. I
  - In these trials about one half of patients needed treatment with more than one drug. I
- **Drug therapy should normally begin with a low dose thiazide-type diuretic[+]. If necessary, second line add a beta-blocker unless a patient is at raised risk of new-onset diabetes*, in which case add an ACE-inhibitor. Third line, add a dihydropyridine calcium-channel blocker.** **A**
  - + In younger patients, aged under 55, with moderately raised blood pressure and who may be managed on one drug, consider beginning with a beta-blocker.
  - * Patients are considered at a raised risk of new-onset diabetes with a strong family history of type II diabetes, impaired glucose tolerance (FPG≥6.5mmol/l), if clinically obese (BMI≥30) or of South-Asian or African-Caribbean ethnic origin.
  - Findings from trials suggest that the onset of diabetes is greater in patients receiving a combination of a thiazide-type diuretic and beta-blocker when compared with other drug combinations. The combination may lead to a higher incidence of diabetes of 0.4% per year of treatment, i.e. one additional case of diabetes for 250 patients treated every year. II
  - From a model of lifetime costs and effects, based on the findings of trials, treatment using stepped care including thiazide diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers and calcium-channel blockers is estimated to be cost-effective. II
- **Concern about increased new-onset diabetes among patients prescribed a thiazide-type diuretic with a beta-blocker means that this is not recommended as an initial combination for patients at raised risk of developing type II diabetes. However the combination may become appropriate to manage treatment resistant hypertension or if cardiovascular disease develops.** **B**

June 2006: The recommendations on prescribing have been updated, and sections of this document marked with a grey tint have been superseded. For details of the how the new recommendations were developed, see www.nice.org.uk/CG034fullguideline

• **If further blood pressure lowering is warranted, consider adding an ACE-inhibitor or beta-blocker (if not yet used), another antihypertensive drug, or referring to a specialist.**	**A**
- As a whole, head-to-head studies indicate similar benefits irrespective of whether blood pressure management begins with a low dose thiazide-type diuretic, beta-blocker, calcium-channel blocker, ACE-inhibitor or angiotensin receptor blocker.	I
- Thiazide-type diuretics, beta-blockers, calcium-channel blockers, ACE-inhibitors and angiotensin receptor blockers appear similarly well tolerated as assessed by overall trial withdrawal rates. Withdrawal occurs typically at rates of 5% to 10% per year.	I
- Current evidence does not support the use of alpha blockers for initial treatment of raised blood pressure.	II
- There is no evidence from large-scale trials to support the use of centrally acting antihypertensive drugs for the initial treatment of raised blood pressure.	III
• **Consider substituting an angiotensin receptor blocker in patients who do not tolerate an ACE-inhibitor due to cough.**	**A**
- Trials of up to one year duration show reduced treatment-related cough in patients taking an angiotensin receptor blocker when compared with an ACE-inhibitor.	I
• **At review, consider modifying the medication of patients currently using only a thiazide-type diuretic and beta-blocker and at raised risk of diabetes, and those in whom concern about their treatment may affect adherence.**	**B**
- Concerns do not justify routinely changing the medication of patients treated currently with a thiazide-type diuretic and beta-blocker, and for whom continued blood pressure control is paramount. Changing therapy risks new side-effects and it may take time to re-establish adequate control of blood pressure. A change of therapy is unlikely to be appropriate in patients on three or more antihypertensive drugs.	II
• **Offer treatment as described to patients regardless of age and ethnicity. Be prepared to tailor drug therapy for individual patients who do not respond to the sequence of drugs indicated.**	**B**
- There is no compelling evidence in terms of reduced risk of cardiovascular disease to support the belief that different classes of drug work better in older or younger patients.	II
- There is evidence from short term studies of differential blood pressure lowering from certain drugs in the young and old and in certain ethnic groups. ACE-inhibitors and beta-blockers, whose mechanism of action is to suppress renin production, may not be effective in lowering blood pressure in patients of African descent, when used as monotherapy. However these agents may be effective in combination with a thiazide diuretic.	III
- One large randomised controlled trial (ALLHAT) found that ACE-inhibitors, used first line, may not prevent stroke in patients of African descent as effectively as low dose thiazide-type diuretics.	II
• **Offer patients with isolated systolic hypertension (systolic BP≥160 mmHg) the same treatment as patients with both raised systolic and diastolic blood pressure.**	**A**
- Patients with isolated systolic hypertension received similar benefits from treatment to other patients with raised blood pressure.	I
• **Offer patients over 80 years of age the same treatment as younger patients, taking account of any comorbidity and their existing burden of drug use.**	**B**
- Patients over 80 years of age are poorly represented in clinical trials and the effectiveness of treatment in this group is less certain. However, it is reasonable to assume that older patients will receive worthwhile benefits from drug treatment, particularly in terms of reduced risk of stroke.	II
• **Where possible recommend treatment with drugs taken only once a day.**	**A**
- A meta-analysis found that patients adhered to once daily blood pressure lowering regimens better than to regimens requiring two or more doses a day (91% vs. 83%). Similarly, once daily regimens were better adhered to than twice daily regimens (93% vs. 87%).	I

- **Prescribe non-proprietary drugs where these are appropriate and minimise cost.** **B**
  - Drug treatment, beginning with either a non-proprietary thiazide-type diuretic or beta-blocker minimizes cost. II
  - From a model of lifetime costs and effects, based on the findings of trials, treatment using stepped care including thiazide-type diuretics, beta-blockers, ACE-inhibitors/angiotensin receptor blockers and calcium-channel blockers is estimated to be cost-effective. II

Introduction

In most hypertensive patients, pharmacological intervention becomes necessary if blood pressure lowering is to be substantial and sustainable. Published epidemiological studies and trials together conclusively demonstrate that a sustained reduction in blood pressure by drugs reduces the incidence of stroke, coronary heart disease and mortality. The size of benefit in any period (for example the next 10 years) generally depends on an individual's overall cardiovascular risk [375,376]. For an individual at any age, the greater the cardiovascular risk the greater the potential to benefit from treatment.

The Department of Heath National Service Framework for Coronary Heart Disease [i] standards 3 and 4 relate to patients at risk of cardiovascular disease. '*General practitioners and primary care teams should identify all people with established cardiovascular disease and offer them comprehensive advice and appropriate treatment to reduce their risks* (3)'. '*General practitioners and primary health care teams should identify all people at significant risk of cardiovascular disease but who have not developed symptoms and offer them appropriate advice and treatment to reduce their risks* (4).' Similarly, the Welsh National Service Framework for Coronary Heart Disease states, '*Everyone at high risk of developing coronary heart disease ... should have access to a multifactorial risk assessment and be offered an appropriate treatment plan'* [iii].

Based on the findings of trials, a range of drugs (some blood pressure lowering) are offered to patients with existing coronary heart disease. These patients are the subject of a previously published national guideline [377]. The recommendations include the use of aspirin, beta-blockers, statins and ace-inhibitors. Once patients are optimally treated to prevent further disease, persistent hypertension should be managed adapting the recommendations from this document.

Trials treating raised blood pressure, and described in this guideline, include patients both with and without cardiovascular disease and thus are relevant to the management of raised blood pressure in all of these patients after any disease specific care has been delivered.

Drugs for raised blood pressure are prescribed alone or in combination, and aim to control blood pressure while minimising side effects or toxicity. How the drugs work is not fully understood. A brief summary of drugs used for essential hypertension is provided in Table 16; further information can be found in the British National Formulary [44]. Drugs for hypertension rarely have serious side-effects when appropriately initiated and adequately monitored.

Table 16: Outline of drugs used for essential hypertension

Class	Common generic names[1]	Mode of action	Duration of action	Usage notes
Thiazide-type diuretics	bendroflumethiazide[2], indapamide	Vasodilation (widened blood vessels) and moderate diuresis (increased passing of sodium and water).	Commonly once daily morning use	Low dose thiazide-type diuretics produce (near) maximal BP lowering. Higher doses can cause side-effects. Generally well tolerated. Potassium changes in the blood can be corrected once identified.
Potassium-sparing diuretics	amiloride	Weakly diuretic, given additionally to, or combined with a thiazide (e.g. co-amilofruse) to retain potassium.	Once or twice daily	Few side-effects. Used to prevent or treat low levels of potassium in the blood. More effective than potassium supplements. Not to be used with potassium supplements. Use with an ACE-inhibitor can cause severely raised levels of potassium in the blood.
Beta-blockers	atenolol, bisoprolol, co-tenidone[3], metoprolol, propranolol, sotalol	Blocking beta receptors in the heart slows down and decreases the force of contraction of the heart.	Vary by drug from once to several times daily	Contraindicated with asthma, heart-block or a rate-limiting calcium-channel blocker. Cautions apply to patients with diabetes or peripheral vascular disease Reported side-effects include lethargy, depression and sleep disturbance.
Calcium-channel blockers	*'dihydropyridines'* amlodipine, felodipine, lacidipine nifedipine.	Reduced flow of calcium to vascular smooth muscle, reducing contraction efficiency and relaxing the vasculature.	Vary by drug from once to several times daily	Reported side-effects include initial headaches, palpitations and facial flushing; ankle swelling.
	'rate-limiting' diltiazem, verapamil	Additionally affect the conduction system, slowing the heart rate	Once or twice daily for longer acting forms	Caution against use in heart failure or use with a beta-blocker. Reported side-effects include constipation (verapamil) and skin rashes (diltiazem)
Angiotensin converting enzyme (ACE) inhibitors	captopril, enalapril, lisinopril, perindopril, ramipril, trandolapril	Prevent conversion of the protein angiotensin I to angiotensin II which raises blood pressure.	Vary by drug from once to several times daily	Dose titration and monitoring is necessary Contraindicated in pregnancy and some kidney diseases. Caution when initiating while on a diuretic or with renal failure. Adverse effects include a persistent dry cough, rash and loss of taste.
Angiotensin receptor blockers (ARBs) *or angiotensin II receptor antagonists*	candesartan, irbesartan, losartan, valsartan, telmisartan	Blocks the action of angiotensin II (which raises blood pressure) by directly blocking the receptor site.	Once daily	Contraindications and side effect profile similar to ACE-inhibitors but ARBs are not associated with the persistent dry cough sometimes attributed to ACE-inhibitor therapy.
Alpha receptor blockers	doxazosin, prazosin, terazosin	Block receptor sites in blood vessel walls, relaxing vessels.	Vary by drug from once to several times daily	These tend to be used as adjunctive treatment. Beneficial side-effect on blood lipid profile. Contraindications, cautions and side-effects vary by drug. Most common side-effects: initial dizziness, headache, flushing, nasal congestion, fluid retention and a rapid heart beat.

1 Accounting for 95% of prescriptions within each drug class in 2002.
2 Also named Bendrofluazide.
3 A combined beta-blocker and thiazide diuretic.

Studies included in the review

There are two major classes of randomised controlled trial (RCT) that describe the effects of available drug therapies: placebo controlled trials where patients receive either active or inactive pills and head-to-head studies where one active drug is compared with another. To capture major health outcome effects of reduced morbidity and mortality as well as major tolerability effects, long duration trials enrolling large numbers of patients are necessary. Consequently parallel-group RCTs, analysing major cardiovascular endpoints on an intention-to-treat basis, of 1 year or more duration and enrolling

200 or more patients are included in this review. Studies were included which enrolled patients who had raised average blood pressure defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥85 mmHg. We searched electronic databases (Medline, Embase, Central) from 1998 to July 2003 for reports of relevant randomised controlled trials; articles published before 1998 were identified from hypertension guidelines, systematic reviews and meta-analyses [378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,376,394,395,396,397,398,399,400,401,402].

Several of the drug classes reviewed are used to treat other medical conditions, for example ACE-inhibitors and beta-blockers are recommended in the treatment of patients following angina, myocardial infarction and heart failure. Following myocardial infarction, drugs are typically used at a fixed dose and the studies enrol patients both with and without raised blood pressure. In hypertension trials doses are typically titrated up and other drugs may be added to achieve a target blood pressure. Thus there is a clear rationale for analysing hypertension trials separately from trials of prophylaxis following heart disease. Most patients included in trials are without, or in the early stages of, cardiovascular disease. Consequently, recommendations for primary prevention in patients with raised blood pressure draw upon evidence from trials including patient populations with little or no existing cardiovascular disease. Several trials have addressed treatment for hypertension following stroke: these are included and similarities and differences are highlighted. Tabulated details of included and excluded trials discussed in this section are found in Appendix 17. All of the studies identified except one were designed to quantify significant changes in deaths or cardiovascular events due to pharmacological interventions. The Treatment of Mild Hypertension Study, which compared five types of drugs with placebo (all supplemented by the same lifestyle intervention), did not report deaths or cardiovascular events but rather relied on the surrogate endpoint of reduced blood pressure with its epidemiological link to reduced disease [403,404,405].

Placebo controlled trials

An overview of key design characteristics of the 20 placebo controlled trials identified is shown in Table 17 (22 trials are tabulated since two trials had additional treatment arms). Seldom was the method of randomisation or steps to conceal allocation from investigators or patients adequately described, although this reflects contemporary standards of reporting. Patients, clinicians and assessors were commonly blind to the treatment received although individual trials varied.

Many trials used stepped care regimes aiming to reduce blood pressure to a specified target by adding other drugs to first line therapy: most of these trials provided matching placebo stepped care to the control group (ANBPS, VA-NHLBI, EWPHE, SHEP, SHEP-P, SYST-EUR), but some provided no stepped care in the control group (MRC, MRC-O) and some provided the same active antihypertensive drugs as stepped care to both the active treatment and the control groups (IPPPSH, SCOPE).

Table 17: Summary characteristics of placebo controlled trials

	Thiazides (High Dose)	Thiazides (Low Dose)	Beta Blockers	Ca Channel Blockers	ACE-inhibitors	Angiotensin Receptor Blockers
Number of studies	7	5	7	1	1	1
Quality markers:						
Randomisation description	2 (29%)	0 (0%)	3 (43%)	1 (100%)	1 (100%)	1 (100%)
Concealment of allocation	0 (0%)	3 (60%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Blinding:						
Participant	6 (86%)	5 (100%)	6 (86%)	1 (100%)	1 (100%)	1 (100%)
Treatment provider	4 (57%)	4 (80%)	4 (57%)	1 (100%)	1 (100%)	1 (100%)
Outcome assessor	5 (71%)	4 (80%)	6 (86%)	1 (100%)	0 (0%)	1 (100%)
Baseline comparability	5 (71%)	5 (100%)	6 (86%)	1 (100%)	1 (100%)	1 (100%)

Thiazide-type diuretics

Thiazide-type diuretics (thiazides for short) include drugs classified by the British National Formulary (BNF) as a thiazide or thiazide related diuretic. Twelve trials were identified that met the review inclusion criteria, see Table 18. Seven trials, with 19,933 participants, starting from as early as 1964, studied high dose thiazides which are no longer used because of the risk of complications due to changed plasma potassium, uric acid, glucose, and lipids, with little additional blood pressure lowering effect compared to low dose thiazides [44]. The mean age of participants was 51, 59% were male and the mean duration of follow-up was 4.0 years.

Table 18: Description of individual placebo controlled trials of thiazide-type diuretics

Trial	Thiazide[1]	Dose category	Dose, mg	Country	Follow-up, yrs	Start year	Age in years Range	Age in years Mean	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
ANBPS [406]	Chlorothiazide	high[3]	500-1000	Australia	4.0	1973	30-69	50	157/101	3,931	5
HSCSG [407]	Methychlothiazide	high	10	US	2.1	1966	<75	59	167/100	452	53
MRC [408]	Bendroflumethiazide	high	10	UK	4.9	1977	35-64	52	161/98	12,951	7
Oslo [409]	Chlorothiazide	high	50	Norway	5.5	1972	40-49	45	156/97	785	4
USPHS [410]	Chlorothiazide	high	1000	US	>7	1965	<55	44	147/99	422	3
VAII [411]	Chlorothiazide	high	100	US	3.2	1964	-	51	164/104	380	39
VA-NHLBI [412]	Chlorthalidone	high	50-100	US	1.5	1978	21-50	38	-	1,012	0
EWPHE [413,414,415]	Hydrochlorothiazide	low[3]	25-50	Europe	4.7	1975	60+	72	183/101	840	77
MRC-O [416]	Hydrochlorothiazide	low	25-50	UK	5.8	1982	65-74	70	185/91	3,294	24
PATS [417]	Indapamide	low	2.5	China	2.0	1989	-	60	154/93	5,665	28
SHEP-P [418,419,420]	Chlorthalidone	low	25-50	US	2.8	1981	60+	72	172/75	551	23
SHEP [421,422,423,424]	Chlorthalidone	low	12.5-25	US	4.5	1985	60+	72	170/77	4,736	23

1 All trials featured co-treatment or stepped care except PATS: see the trial table for details.

2 Control Group death rate per 1000 patients per year.

3 High doses studies were defined as those using starting drugs and doses greater than or equal to chlorthalidone 50mg, hydrochlorothiazide 50mg, chlorothiazide 500mg, bendroflumethiazide 5mg, methychlothiazide 5mg [425].

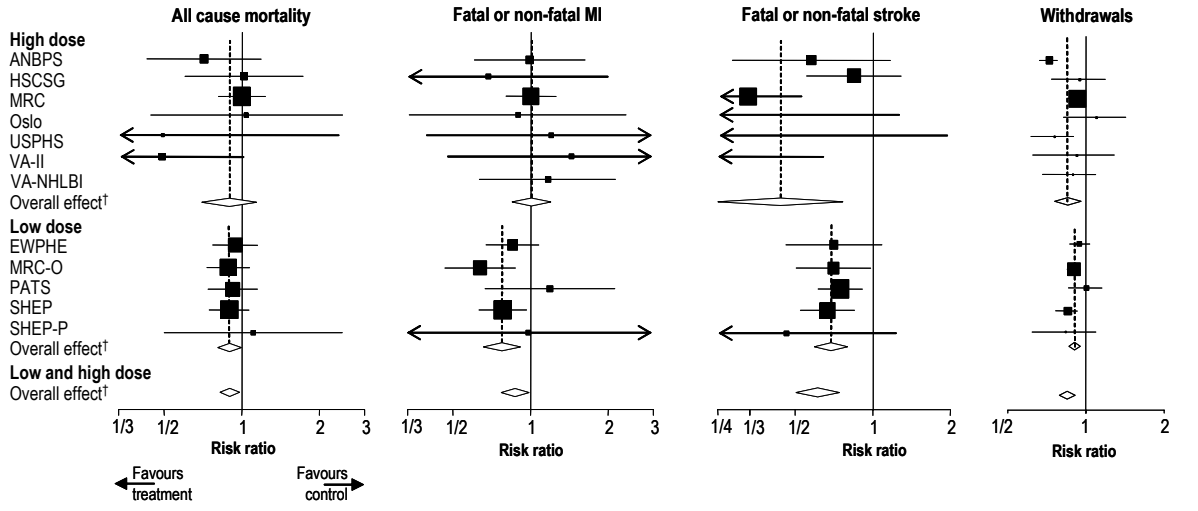
Five trials with 15,086 participants, starting between 1975 and 1989, studied low dose thiazides. Patients had a mean age of 67 years, 53% were male and the mean duration of follow-up was 4.0

years. Only two studies reported ethnicity and in these 86% of participants were Caucasian. 'Low dose' is taken pragmatically to mean the doses used in 'low dose' trials and now normally recommended by the BNF. Although the dichotomisation of low and high dose used in this guideline for placebo and head-to-head trials is the one commonly used by reviewers, individual thiazides may sometimes be used at even lower doses.

The underlying risk of disease in patients was proxied by the mortality rate in the control groups of the trials. HSCSG and PATS enrolled patients following a stroke, but it is interesting to note the apparent role of age. The underlying risk in PATS is similar to three other low dose thiazide trials in which patients are, on average, ten years older. It is unclear why the underlying risk in the EWPHE trial is so high, but this may be due to inclusion of patients with coronary heart disease. Two trials, SHEP and SHEP-P exclusively enrolled patients with isolated systolic hypertension (SBP 160-219 mmHg and DBP less than 90 mmHg).

A graphical presentation of pooled summary findings is shown in Figure 19 for all cause mortality, fatal or non-fatal myocardial infarction (MI) and fatal or non-fatal stroke. The high dose thiazide trials are of historical interest and, although the findings are more varied, the overall summary for each endpoint is consistent with the findings from the low-dose thiazide trials. The low dose trials show statistically significant reductions in mortality of 9%, in myocardial infarction of 22% and in stroke of 31%: a statistically consistent finding across the range of underlying risk.

Figure 19: Meta-analysis of placebo-controlled randomised controlled trials of high and low dose thiazide-type diuretics



† DerSimonian-Laird risk ratio (RR)

	All cause mortality				Fatal or non-fatal MI				Fatal or non-fatal stroke				Withdrawal			
	RR	95% CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p
H/D Thiazide	0.92	(0.77 to 1.10)	0.41	0.71	1.01	(0.84 to 1.21)	0.98	0.53	0.45	(0.27 to 0.78)	0.02	0.35	0.84	(0.75 to 0.95)	<0.001	0.92
L/D Thiazide	0.91	(0.83 to 1.00)	0.97	0.10	0.78	(0.67 to 0.90)	0.42	0.39	0.69	(0.60 to 0.78)	0.86	0.16	0.90	(0.86 to 0.95)	0.26	0.97
Combined	0.92	(0.84 to 1.00)	0.87	0.41	0.86	(0.77 to 0.97)	0.57	0.24	0.62	(0.52 to 0.74)	0.09	0.07	0.86	(0.80 to 0.92)	<0.001	0.96

Patients receiving placebo withdrew from treatment at an average rate of 10.7% per year. Overall,

withdrawal from active therapy was lower (Incident Risk Difference per year -1.2%, 95%CI: -1.9% to -0.6%) although there was variation between studies (Q, p<0.001). Individual studies varied from a 4% reduction in withdrawal per year to no difference. While rates of overall withdrawal are the most objective estimate of tolerability, they can conceal different problems: lack of efficacy, perceived side-effects, adverse events or disease progression. As the body of evidence increases in favour of new treatments some patients may be withdrawn from placebo-controlled trials because of symptoms or signs indicating the need for active therapy.

Beta-blockers

Seven trials with 27,433 participants were identified that met the review inclusion criteria (see Table 19). Trials started between 1977 and 1988; enrolled patients had a mean age of 57 years, 49% were male and the mean duration of follow-up was 4.3 years. It is unclear what proportion of participants was from ethnic minorities.

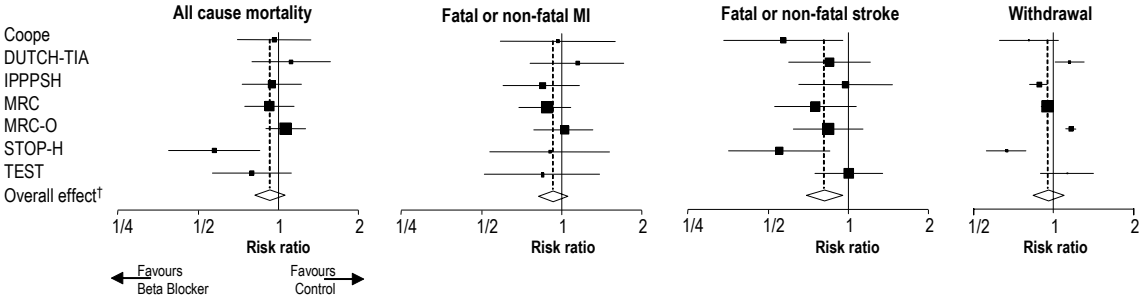
Table 19: Description of individual placebo controlled trials of beta-blockers

Trial	Beta-blocker[1]	Dose, mg	Country	Follow-up, yrs	Start year	Age in years Mean	Age in years Range	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
Coope [426]	Atenolol	100	UK	4.4	1978	69	60-79	196/99	884	34
DUTCH-TIA [427]	Atenolol	50	Netherlands	2.7	1986	-	-	158/91	1,473	29
IPPPSH [428]	Oxprenolol	160-320	International	3.4	1977	52	40-64	173/108	6,357	11
MRC [408]	Propranolol	240	UK	4.9	1977	52	35-64	161/98	13,057	6
MRC-O [416]	Atenolol	50-100	UK	5.8	1982	70	65-74	185/91	3,315	24
STOP-H [429]	Beta-blocker or Diuretic[3]		Sweden	2.1	1985	76	70-84	195/102	1,627	37
TEST [430]	Atenolol	50	Sweden	2.3	1988	70	40+	161/89	720	75

1 All trials featured stepped care, with additional drugs added if necessary
2 Control Group death rate per 1000 patients per year
3 Atenolol (50) or Metoprolol (100) or Pindodol (5)

A graphical presentation of pooled summary findings is shown in Figure 20 for all cause mortality, fatal or non-fatal myocardial infarction (MI) and fatal or non-fatal stroke. Overall, patients on beta-blockers had a statistically significant reduction in risk of stroke of 19%, and non-significant reductions in risk of death of 6% and of myocardial infarction of 8%.

Figure 20: Meta-analysis of placebo-controlled randomised controlled trials of beta-blockers



† DerSimonian-Laird risk ratio (RR)

	All cause mortality				Fatal or non-fatal MI				Fatal or non-fatal stroke				Withdrawal			
	RR	95% CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p
Beta Blocker	0.94	(0.83 to 1.06)	0.21	0.16	0.92	(0.81 to 1.05)	0.90	0.76	0.81	(0.69 to 0.95)	0.25	0.08	0.95	(0.83 to 1.09)	<0.001	0.59

Patients receiving placebo withdrew from treatment at an average rate of 10.6% per year. Withdrawal per year from active therapy and placebo was similar (Incident Risk Difference per year -0.4%, 95%CI: -1.6% to 0.8%) although there was variation between studies (Q, p<0.001). Individual studies varied from a 5% reduction in withdrawal per year to a 2% increase.

ACE-inhibitors

One trial, with 6,105 participants and a mean follow-up of 3.9 years was identified that met the review inclusion criteria (Table 20). The PROGRESS trial randomised patients following stroke to perindopril with the addition of a diuretic (indapamide) if necessary or placebo. Seventy percent of participants were male and 61% were Caucasian; 58% of patients assigned to the ACE–inhibitor also received the diuretic.

Table 20: Description of individual placebo controlled trials of ACE-inhibitors

Trial	ACE-inhibitor[1]	Dose, mg	Country	Follow-up, yrs	Start year	Age in years Range	Age in years Mean	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
PROGRESS [431]	Perindopril	4	International	3.9	1995	26-91	64	147/86	6,105	27

1 The PROGRESS trial allowed physicians to add a diuretic if they deemed it appropriate

2 Control Group death rate per 1000 patients per year

PROGRESS did not show an overall reduction in mortality (RR 0.96, 95%CI: 0.83 to 1.12), but statistically significant reductions in coronary events (RR 0.76, 95%CI: 0.60 to 0.96) and stroke (RR 0.73, 95%CI: 0.64 to 0.84).

Patients receiving placebo withdrew from treatment during the PROGRESS trial at an average rate of 8% per year. Withdrawal per year from active therapy was similar (Incident Risk Difference per year 0.6%, 95%CI: -0.2% to 1.3%).

The recent HOPE [432,433] study randomised patients with two or more cardiovascular risk factors to a fixed dose of ramipril or placebo. The trial was designed similarly to trials of secondary cardiovascular prevention rather than treatment of hypertension; the trial population were not hypertensive and the study is not included in this review.

Angiotensin receptor blockers

One trial, with 4,964 patients and a mean follow up of 3.7 years, was identified that met the review inclusion criteria (see Table 21). The SCOPE trial randomised elderly patients with mild to moderate hypertension and without cardiovascular disease in the preceding 6 months to candesartan or placebo; approximately one third were male and ethnicity was not reported.

Table 21: Description of individual placebo controlled trials of angiotensin receptor blockers

Trial	ARB[1]	Dose, mg	Country	Follow-up, yrs	Start year	Age in years Range	Age in years Mean	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
SCOPE [434]	Candesartan	8-16	Europe and N. America	3.7	1997	70-89	76	166/90	4,964	29

1 Physicians could add a diuretic and other antihypertensive agents to patients in treatment or control groups if they deemed it appropriate.
2 Control Group death rate per 1000 patients per year.

SCOPE did not show an overall reduction in mortality (RR 0.97, 95%CI: 0.83 to 1.14) or coronary events (RR 1.10, 95%CI: 0.79 to 1.55), but a borderline statistically significant reduction in stroke (RR 0.77, 95%CI: 0.59 to 1.01), primarily due to reduced non-fatal stroke.

Patients receiving placebo withdrew from treatment during the SCOPE trial at an average rate of 8% per year. Withdrawal per year from active therapy was similar (Incident Risk Difference per year -0.6%, 95%CI: -1.4% to 0.2%).

Two further placebo-controlled trials were identified (IDNT [435] and RENAAL [436]), but not considered adequately relevant to inform this guideline as both enrolled diabetic patients with mild renal impairment.

Calcium-channel blockers

One trial, with 4,695 participants and median follow-up of 2 years, was identified that met the review inclusion criteria (see Table 22). The SYST-EUR trial enrolled patients with isolated systolic hypertension, one third of whom were male; ethnicity was not reported.

Table 22: Description of individual placebo controlled trials of calcium-channel blockers

Trial	CCB[1]	Dose, mg	Country	Follow-up, yrs	Start year	Age in years Range	Age in years Mean	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
SYST-EUR [437,438,439,440,441]	Nitrendipine	10-40	Europe	2[3]	1989	60+	70	174/86	4,695	27

1 SYST-EUR featured stepped care, with additional drugs added if necessary.
2 Control Group death rate per 1000 patients per year.
3 Median follow-up.

SYST-EUR demonstrated no overall reduction in mortality (RR 1.06, 95%CI: 0.84 to 1.35), some indication of a possible reduction in coronary events (RR 0.71, 95%CI: 0.45 to 1.10) and a statistically significant reduction in stroke (RR 0.59, 95%CI: 0.41 to 0.84).

Patients receiving placebo withdrew from treatment at an average rate of 14% per year. Withdrawal from active therapy per year was greater (Incident Risk Difference per year 2.3%, 95%CI: 0.8% to 3.9%).

Two further placebo-controlled trials were excluded because of uncertainty about the validity of randomisation: SYST CHINA [442,443,444,445] and STONE [446].

Alpha blockers

No placebo-controlled trials of alpha blockers in this patient group were identified that met the review criteria.

Head-to-head trials

An overview of key design characteristics of the 15 head-to-head trials identified is shown in Table 23 (see also Appendix 17) and two further head-to-head trials with placebo arms (MRC, MRC-O). The method of randomisation and steps to conceal allocation from investigators or patients were inconsistently described. Similarly, blinding of the patient and the clinician providing treatment was variable although those who assessed the outcomes were commonly blind to the treatment received by patients. For a definition of thiazides see page *Thiazide-type diuretics* on page *109.*

Table 23: Summary characteristics of head-to-head drug trials

	Beta blockers vs. Thiazides	Calcium-channel blockers vs. Thiazides or Beta-blockers	ACE inhibitors vs. Thiazides or Beta-blockers	ACE inhibitors vs. Calcium-channel blockers	Angiotensin receptor blockers vs. Beta-blockers	Alpha blockers vs. Thiazides
Number of studies	4	10	4	2	1	1
Quality markers:						
Randomisation description	0 (0%)	5 (50%)	1 (25%)	1 (50%)	0 (0%)	1 (100%)
Concealment of allocation	0 (0%)	4 (40%)	1 (25%)	1 (50%)	0 (0%)	1 (100%)
Blinding:						
Participant	2 (50%)	7 (70%)	1 (25%)	1 (50%)	1 (100%)	1 (100%)
Treatment provider	1 (25%)	6 (60%)	1 (25%)	1 (50%)	1 (100%)	1 (100%)
Outcome assessor	4 (100%)	7 (70%)	3 (75%)	2 (100%)	1 (100%)	1 (100%)
Baseline comparability	4 (100%)	9 (90%)	3 (75%)	2 (100%)	1 (100%)	1 (100%)

Comparison of beta-blockers with thiazides

The review identified 4 trials with 20,686 participants (see Table 24). The mean age of participants was 54 years and 74% were male; the mean duration of follow-up was 4.9 years; in the one trial recording ethnicity (HAPPHY), all participants were Caucasian.

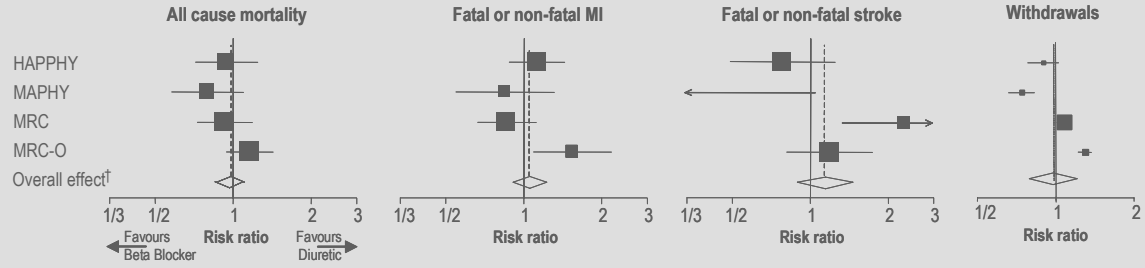
Table 24: Description of individual trials comparing beta-blockers with thiazides

Trial[1]	Drug	Comparator Drug	Country	Follow-up, yrs	Age in years Mean	Age in years Range	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
HAPPHY [447]	atenolol or metoprolol	hydrochlorothiazide or bendroflumethiazide	International	3.8	52	40-64	166/107	6,569	8
MAPHY [448]	metoprolol	hydrochlorothiazide or bendroflumethiazide	Europe	5.0	53	40-64	167/108	3,234	9
MRC [408]	propranolol	bendroflumethiazide	UK	4.9	52	35-64	161/99	8,700	7
MRC-O [416]	atenolol	hydrochlorothiazide	UK	5.8	70	65-74	185/91	2,183	25

1 All trials featured co-treatment or stepped care: see the trial table for details.
2 Pooled treatment groups death rate per 1000 patients per year.

A graphical presentation of pooled summary findings is shown in Figure 21 for all cause mortality, fatal or non-fatal myocardial infarction (MI) and fatal or non-fatal stroke. The trials provide evidence of similar effect upon overall mortality, stroke and myocardial infarction, although there is considerable heterogeneity in the latter two endpoints and it is unclear why the trials should differ in their findings. Overall, the results support the findings from the placebo-controlled trials of similar benefits for low dose thiazide diuretics and beta-blockers (see pages 109 and 111).

Figure 21: Meta-analysis of randomised controlled trials comparing beta-blockers with thiazides



† DerSimonian-Laird risk ratio (RR)

	All cause mortality				Fatal or non-fatal MI				Fatal or non-fatal stroke				Withdrawal			
	RR	95% CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p
BB vs. Th	0.98	(0.83 to 1.16)	0.17	0.09	1.07	(0.82 to 1.40)	0.03	0.83	1.06	(0.57 to 1.94)	0.004	0.91	0.98	(0.79 to 1.22)	<0.001	0.38

Patients who were managed initially with either thiazides or beta-blockers withdrew from treatment at an average rate of 7% per year: overall there was no difference in the rate of withdrawal (Incident Risk Difference per year 0.3%, 95%CI: -1.0% to 1.6%) although there was variation between studies (Q, p<0.001). Individual studies varied from a 2% reduction in withdrawal per year to a 3% increase when patients were treated with a diuretic.

Since the efficacy and tolerability of beta-blockers and thiazides appeared to be very similar, studies comparing other classes of drugs with beta-blockers or thiazides or both were combined.

Comparison of calcium-channel blockers with thiazides or beta-blockers

The review identified 10 trials with 90,441 participants (see Table 25). The mean age of participants was 66 years and 50% were male; the mean duration of follow-up was 3.8 years; in the 6 trials recording ethnicity, 60% were Caucasian.

Table 25: Description of individual trials comparing calcium-channel blockers with thiazides or beta-blockers

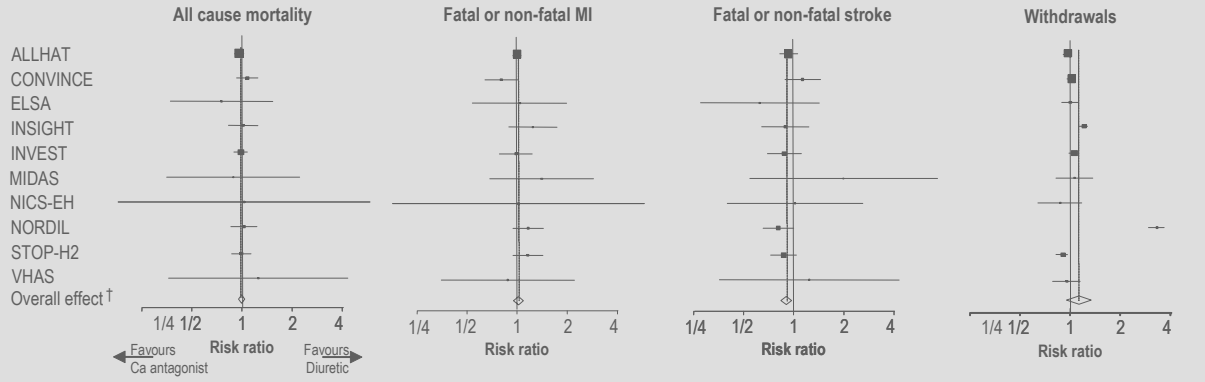
Trial[1]	Drug	Comparator Drug	Country	Follow-up, yrs[2]	Age in years Mean	Age in years Range	Baseline BP, mmHg	Number enrolled	Baseline Risk[3]
ALLHAT [449,450,451]	amlodipine	chlorthalidone	North & Central America	4.9	67	55+	146/84	24,303	29
CONVINCE [452,453]	verapamil	Atenolol or hydrochloro-thiazide	Americas, Europe, Middle East	3[4]	66	55+	150/87	16,602	13
ELSA [454]	lacidipine	Atenolol	International	3.2	56	45-75	164/101	2,334	4
INSIGHT [455,456]	nifedipine	co-amilozide	W. Europe, Israel	4	65	55-80	173/99	6,575	13
INVEST [457]	nifedipine	Hydrochloro-thiazide and amiloride	International	2.7	66	50+	151/87	22,576	29
MIDAS [458,459]	isradipine	Hydrochloro-thiazide	US	3	58	40+	150/97	883	6
NICS-EH [460,461]	nicardipine	Trichlor-methiazide	Japan	4.6	70	60+	172/94	429	3
NORDIL [462,463]	diltiazem	diuretic or beta-blocker	Norway, Sweden	4.5	60	50-74	173/106	10,916	9
STOP-H2 [464,465,466,467]	felodipine or isradipine	diuretic or beta-blocker	Sweden	5	76	70-84	194/98	4,409	33
VHAS [468,469]	verapamil	chlorthalidone	Italy	2	54	40-65	169/102	1,414	3

1 All trials featured co-treatment or stepped care: see the trial table for details.
2 Mean follow-up.
3 Pooled treatment groups death rate per 1000 patients per year.
4 Median follow-up.

A graphical presentation of pooled summary findings is shown in Figure 22 for all cause mortality, fatal or non-fatal myocardial infarction (MI) and fatal or non-fatal stroke. Calcium-channel blockers had a similar effect to thiazide diuretics or beta-blockers for overall mortality and coronary events although there was a borderline different of reduced stroke (RR 0.92, 95%CI: 0.85-1.00). A sensitivity analysis, excluding the dominant trial (ALLHAT) which provided nearly 50% of participants, found similar results.

Patients who were managed initially with thiazides or beta-blockers withdrew from treatment at an average rate of 7% per year. Withdrawal from initial calcium-channel blocker management was similar (Incident Risk Difference per year 0.4%, 95%CI: -0.8% to 1.7%) although there was variation between studies (Q, $p<0.001$). Individual studies varied from a 1% reduction in withdrawal per year to a 4% increase, when patients were treated with a calcium-channel blocker.

Figure 22: Meta-analysis of randomised controlled trials comparing calcium-channel blockers with thiazides or beta-blockers



† DerSimonian-Laird risk ratio (RR)

	All cause mortality				Fatal or non-fatal MI				Fatal or non-fatal stroke				Withdrawal			
	RR	95% CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p
Ca vs. Thi/BB	0.99	(0.94 to 1.03)	0.98	0.54	1.02	(0.97 to 1.08)	0.42	0.39	0.92	(0.85 to 1.00)	0.64	0.41	1.13	(0.95 to 1.34)	<0.001	0.42

Comparison of ACE-inhibitors with thiazides or beta-blockers

The review identified 4 trials with 45,795 participants (see Table 26). The mean age of participants was 65 years and 51% were male; the mean duration of follow-up was 5.0 years; in the two trials recording ethnicity, 67% were Caucasian.

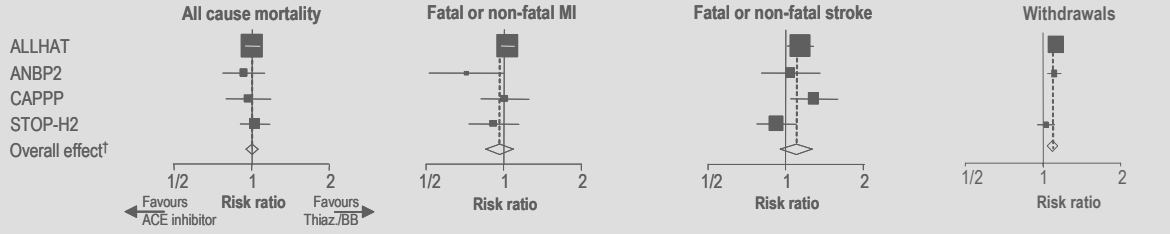
Table 26: Description of individual trials comparing ACE-inhibitors with thiazides or beta-blockers

Trial[1]	Drug	Comparator Drug	Country	Follow-up, yrs	Age in years Mean	Age in years Range	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
ALLHAT [449,450]	lisinopril	chlorthalidone	North & Central America	4.9	67	55+	146/84	24,309	30
ANBP2 [470]	enalapril	Hydrochloro-thiazide	Australia	4.1	72	65-84	168/91	6,083	16
CAPPP [471,472,473]	captopril	diuretic or beta-blocker	Sweden, Finland	6.1	53	25-66	161/99	10,985	6
STOP-H2 [464,465,466,467]	enalapril or lisinopril	diuretic or beta-blocker	Sweden	5.0	76	70-84	194/98	4,418	34

1 All trials featured co-treatment or stepped care: see the trial table for details.
2 Pooled treatment groups death rate per 1000 patients per year.

A graphical presentation of pooled summary findings is shown in Figure 23 for all cause mortality, fatal or non-fatal myocardial infarction (MI) and fatal or non-fatal stroke. Our current best understanding is that the trials provide evidence of similar effect on overall mortality, stroke and myocardial infarction.

Figure 23: Meta-analysis of randomised controlled trials comparing ACE-inhibitors with thiazides or beta-blockers



† DerSimonian-Laird risk ratio (RR)

	All cause mortality				Fatal or non-fatal MI				Fatal or non-fatal stroke				Withdrawal			
	RR	95% CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p
ACE vs. Th./BB	1.00	(0.95 to 1.06)	0.83	0.42	0.96	(0.85 to 1.09)	0.13	0.14	1.09	(0.95 to 1.25)	0.07	0.87	1.09	(1.04 to 1.15)	0.13	0.31

Patients managed initially with diuretics or beta-blockers withdrew from treatment at an average rate of 6% per year. Overall withdrawal from ACE-inhibitor was slightly greater (Incident Risk Difference per year 0.6%, 95%CI: 0.4% to 0.9%).

One further trial identified was excluded: UKPDS [474,475] enrolled only diabetic patients.

Comparison of ACE-inhibitors with calcium-channel blockers

The review identified 2 trials with 22,503 participants (see Table 27). The mean age of participants was 69 years and 49% percent were male; the mean duration of follow-up was 4.9 years; in the one trial recording ethnicity (ALLHAT), 60% were Caucasian.

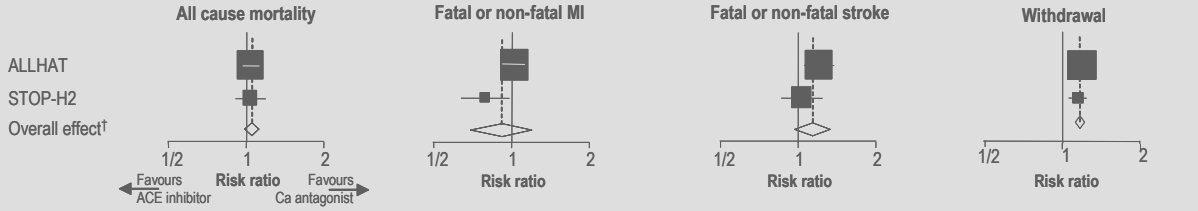
Table 27: Description of individual trials comparing ACE-inhibitors with calcium-channel blockers

Trial[1]	Drug	Comparator Drug	Country	Follow-up, yrs	Age in years Mean	Age in years Range	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
ALLHAT [449,450]	lisinopril	amlodipine	North & Central America	4.9	67	55+	146/84	18,102	30
STOP-H2 [464,465,466,467]	enalapril or lisinopril	felodipine or isradipine	Sweden	5.0	76	70-84	194/98	4,401	34

1 Trials featured co-treatment or stepped care: see the trial table for details.
2 Pooled treatment groups death rate per 1000 patients per year.

A graphical presentation of pooled summary findings is shown in Figure 24 for all cause mortality, fatal or non-fatal myocardial infarction (MI) and fatal or non-fatal stroke. Our current best interpretation is that the trials provide evidence of similar effect on overall mortality and stroke. However, the findings for coronary heart disease showed heterogeneity: ALLHAT showed no difference in efficacy of ACE-inhibitors and calcium-channel blockers, whereas the smaller STOP-H2 trial indicated that ACE-inhibitors were more effective.

Figure 24: Meta-analysis of randomised controlled trials comparing ACE-inhibitors with calcium-channel blockers



† DerSimonian-Laird risk ratio (RR)

	All cause mortality				Fatal or non-fatal MI				Fatal or non-fatal stroke				Withdrawal			
	RR	95% CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p	RR	95%CI	Q, p	Size, p
ACE vs. Ca	1.04	(0.98 to 1.11)	0.97	.	0.92	(0.71 to 1.18)	0.02	*	1.13	(0.97 to 1.32)	0.16	*	1.17	(1.12 to 1.21)	0.58	*

* Too few studies

Patients managed initially with calcium-channel blockers withdrew from treatment on average at 6% per year. Patients managed initially with ACE-inhibitors showed a slightly greater rate of withdrawal (Incident Risk Difference 0.9%, 95%CI: 0.6% to 1.2%).

Two further trials identified were excluded: ABCD [476] and FACET [477] enrolled only diabetic patients.

Comparison of angiotensin receptor blockers with beta-blockers

The review identified the LIFE trial which enrolled 9,222 patients. The mean age of participants was 67 years, 46% percent were male, and 92% were Caucasian.

Table 28: Description of the LIFE trial comparing an angiotensin receptor blocker and beta-blocker

Trial[1]	Drug	Comparator Drug	Country	Follow-up, yrs	Age in years Mean	Age in years Range	Baseline BP, mmHg	Number enrolled	Baseline Risk[2]
LIFE [477,478,479]	losartan	atenolol	International	4.8	67	55-80	174/98	9,222	19

1 LIFE featured stepped care: see the trial table for details.
2 Pooled treatment groups death rate per 1000 patients per year.

Compared with patients managed initially with a beta-blocker, those managed initially with an angiotensin receptor blocker demonstrated no overall reduction in coronary events (RR 1.05, 95%CI: 0.86 to 1.28) but a statistically borderline reduction in mortality (RR 0.89, 95%CI: 0.78 to 1.02) and a substantial reduction in stroke (RR 0.75, 95%CI: 0.64 to 0.88).

Patients managed initially with a beta-blocker withdrew from treatment at an average rate of 8% per year. The withdrawal rate for patients managed initially with an angiotensin receptor blocker was modestly lower (Incident Risk Difference per year -1.1%, 95%CI: -1.6% to -0.6%).

All patients enrolled had electrocardiographic signs of left ventricular hypertrophy, a sign of raised cardiovascular risk. Included were 1,195 patients with diabetes at enrolment and reduction in mortality appears to have occurred almost entirely in this subgroup. However, there persisted a reduction in stroke in non-diabetic patients. (RR: 0.74, 95%CI: 0.63 to 0.85). Mixed risk group trials such as LIFE can be difficult to interpret, and the findings of the LIFE trial need validation from further independent research.

Comparison of angiotensin receptor blockers with ACE-inhibitors

- Trials of up to one year duration show reduced treatment-related cough in patients taking an angiotensin receptor blocker when compared with an ACE-inhibitor.

We retrieved no randomised comparisons of angiotensin receptor blockers with ACE-inhibitors that reported primary endpoints used in our review. However, commonly noted aspect of angiotensin receptor blockers is their lower incidence of treatment-related cough when compared to an ACE-inhibitor. Although not systematically reviewed, several trials of up to one year duration were retrieved that show reduced treatment-related cough was reduced two to three fold in patients taking an angiotensin receptor blocker when compared with an ACE-inhibitor [480,481,482,483,484,485,486]. Consequently substitution with an angiotensin receptor blocker appears appropriate when an ACE-inhibitor is necessary but not tolerated due to cough.

Comparison of an alpha blocker with a thiazide

The review identified the ALLHAT study which enrolled 24,335 participants to initial management with an alpha blocker (doxazosin) or thiazide (chlorthalidone), as part of a four arm study. The mean age of participants was 67 years, 53% were male, and 59% were Caucasian. The alpha blocker arm of the ALLHAT study was discontinued after a median 3.3 years follow-up due its adverse cardiovascular event rate.

Alpha blocker initiated management demonstrated no overall change in mortality (RR 1.02, 95%CI: 0.92 to 1.14) or coronary events (RR 1.02, 95%CI: 0.89 to 1.15), but an increase in stroke relative to thiazide initiated management (RR 1.17 95%CI: 1.00 to 1.38). This difference may be due to the modest difference in blood pressure lowering achieved by the thiazide and alpha blocker treatment arms. There are methodological concerns about the early termination of trials and their subsequent interpretation.

Patients managed initially with thiazide withdrew from treatment at an average rate of 8% per year. Withdrawal following initial alpha blocker management per year was similar (Incident Risk Difference 0.4%, 95%CI: -0.1% to 0.6%).

Interpreting the evidence from drug trials

- In placebo-controlled trials, blood pressure management beginning with a low dose thiazide-type diuretic or beta-blocker has been shown to reduce mortality, myocardial infarction and stroke (relative risk reductions of 8%, 15% and 25% respectively).	I
- As a whole, head-to-head studies indicate similar benefits irrespective of whether blood pressure management begins with a low dose thiazide-type diuretic, beta-blocker, calcium-channel blocker, ACE-inhibitor or angiotensin receptor blocker.	I
- Thiazide-type diuretics, beta-blockers, calcium-channel blockers, ACE-inhibitors and angiotensin receptor blockers appear similarly well tolerated as assessed by overall trial withdrawal rates. Withdrawal occurs typically at rates of 5% to 10% per year.	I
- Current evidence does not support the use of alpha blockers for initial treatment of raised blood pressure.	II
- There is no evidence from large-scale trials to support the use of centrally acting antihypertensive drugs for the initial treatment of raised blood pressure.	
- Patients over 80 years of age are poorly represented in clinical trials and the effectiveness of treatment in this group is less certain. However, it is reasonable to assume that older patients will receive worthwhile benefits from drug treatment, particularly in terms of reduced risk of stroke.	II
- There is no compelling evidence in terms of reduced risk of cardiovascular disease to support the belief that different classes of drug work better in older or younger patients.	II

Substantial placebo-controlled evidence exists only for thiazide diuretics and beta-blockers. As these treatments have become established as beneficial, it has become less ethical to continue to include placebo arms in trials. Consequently newer drugs are compared with established drugs rather than placebo.

Given the strength of evidence from placebo controlled trials initiating blood pressure management with a thiazide and a beta-blocker it is useful to compare these. Statistically the findings for the two are similar (a finding supported by head-to-head trials comparing the two), and the best estimate of the value of treating raised blood pressure may be obtained by pooling the placebo-controlled results for low dose thiazide diuretics and beta-blockers. Combined, 11 trials including 37,687 participants and a mean follow-up of 4.0 years provide evidence of consistent and statistically significant reductions in overall mortality (RR: 0.92, 95%CI: 0.86 to 0.99, Q: p=0.59), fatal and non-fatal myocardial infarction (RR: 0.85, 95%CI: 0.77 to 0.94, Q: p=0.91) and fatal and non-fatal stroke (RR: 0.75, 95%CI: 0.67 to 0.83, Q: p=0.31).

Single large trials comparing management started with either an ACE-inhibitor (6,105 participants) or a calcium-channel blocker (4,695 participants) with placebo showed similar reductions in coronary disease and stroke to beta-blockers and diuretics. Neither demonstrated a reduction in overall mortality although confidence intervals around estimates are wide. However the two trials which directly compared ACE-inhibitors and calcium-channel blockers confirmed the similar efficacy of the drugs in preventing death, coronary heart disease and stroke.

The findings of head-to-head trials suggest remarkably similar benefits and tolerability, despite the varying modes of action of the different classes of drug. Although different starting drugs are compared, a substantial proportion of patients in trials go on to receive second or even third line therapy, potentially diluting any differences. Comparisons (direct and indirect) of management initiated with different therapies in 214,203 participants found no differences for overall mortality, coronary heart disease or stroke reaching statistical significance, except in a few instances. Individual

trials have favoured one agent over another on one or other endpoint, but these differences appear to be chance findings that disappear when several trial are available. For example the MRC trial may be largely responsible for the perception that beta-blockers do not prevent strokes as well as diuretics, although this impression is refuted by the evidence as a whole (see Figure 21). Hence it is inappropriate to over-interpret individual trials. The LIFE study provides the sole report demonstrating a lower incidence of stroke for an angiotensin receptor blocker when compared to a beta-blocker and needs validating with further independent research. As more and more comparisons are made between drugs, the risk of generating spurious positive findings increases. Currently, our best understanding is that beta-blockers, diuretics, calcium-channel blockers, ACE-inhibitors and angiotensin receptor blockers achieve similar benefits in patients achieving similar levels of blood pressure reduction. The value of alpha blockers on the basis of one trial terminated early remains unclear.

For the comparison of each drug class with placebo and for each head-to-head comparison of drug classes, we carried out a meta-regression to investigate whether the effect of treatment on the risk of death, coronary heart disease and stroke varied with age or baseline cardiovascular risk. In general, the findings did not appear to be sensitive to age or risk. The only association which was statistically robust was that ACE-inhibitors appeared to be more effective than thiazides or beta-blockers in preventing stroke in older people (over 70 years), whereas thiazides or beta-blockers appeared to be more effective in younger people. However, this trend was based on only four trials and may be due to chance; it cannot be regarded as evidence on which to base prescribing policy unless and until it is subsequently confirmed by independent findings from within randomised controlled trials.

It is reasonable to assume from the strong epidemiological evidence that benefits of treatment are related directly to the level of blood pressure reduction achieved [19,20,21]. This is consistent with analyses of trial-level data [391,518] although there are a number of potential confounding influences for such analyses. The trial evidence does not support one target blood pressure but validates the stepped approach, titrating up dose and adding additional drugs if necessary. Trials enrolling patients with substantially raised blood pressure (over 160/100 mmHg) consistently achieved average reductions of 20/10 to 30/15 mmHg in treatment arms, demonstrating that these kinds of reduction are achievable with a stepped approach.

Withdrawal rates on active therapy varied between trials from 6% to 16% per year, partly reflecting the varying conventions for stopping the treatment. Comparisons within trials revealed no clinically important differences in tolerability proxied by overall withdrawal. The LIFE trial found a small reduction in withdrawal (1.1% per year) for an angiotensin receptor blocker compared to a beta-blocker. Head-to-head trials found small increases in withdrawal for ACE-inhibitors when compared to other drugs, of the order of 1% per year.

The role of a single trial in four of the six head-to-head comparisons is notable. The ALLHAT study was a four arm trial comparing initial management with a thiazide, ACE-inhibitor, calcium-channel blocker and alpha blocker, with 41,135 participants contributing 38% of the total from all head-to-head

trials. Thus, this one trial has scope for disproportionate influence. Comparisons of either an ACE-inhibitor or a calcium-channel blocker with a diuretic yield findings that are typical of other trials. However, our understanding of head-to-head comparisons of ACE-inhibitors and calcium-channel blockers or of the value of alpha blockers may be unduly influenced by this one trial.

Relative benefits provide a powerful approach to describe the consistent effect of drugs across trials enrolling patients at very different levels of baseline risk, from the young and relatively healthy to older patients with existing cardiovascular disease. However, they are not helpful in communicating potential benefits of treatment to individuals. Describing the average absolute benefit from trials is unhelpful when baseline risk varies so dramatically within trials. Instead patients at a given level of cardiovascular risk may want to understand the value of treatment to them personally (See Patients' perspectives on page 141).

Isolated Systolic Hypertension

- Patients with isolated systolic hypertension received similar benefits from treatment as other patients with raised blood pressure. I

The review identified four trials enrolling patients with isolated systolic hypertension (ISH; systolic: 160-219 mmHg; diastolic less than 90 or 95 mmHg): these were SHEP, SHEP-P (diuretic-initiated therapy vs. placebo; see Thiazide-type diuretics on page 109), SYST-EUR (calcium-channel blocker-initiated therapy vs. placebo) and SYST-CHINA (either calcium-channel blocker, ACE-inhibitor or diuretic vs. placebo). These trials provide evidence that ISH should be treated in the same way as essential hypertension. They also provide evidence, consistent with a large population-based observational study [487] that raised systolic blood pressure is as important as raised diastolic blood pressure.

The group interpreted trials enrolling patients with ISH in the context of other published trials many of which have included patients both with and without ISH.

Ethnicity and pharmacological treatment

- There is evidence from short term studies of differential blood pressure lowering from certain drugs in the young and old and in certain ethnic groups. ACE-inhibitors and beta-blockers, whose mechanism of action is to suppress renin production, may not be effective in lowering blood pressure in patients of African descent, when used as monotherapy. However these agents may be effective in combination with a thiazide diuretic. III
- One large randomised controlled trial (ALLHAT) found that ACE-inhibitors, used first line, may not prevent stroke in patients of African descent as effectively as low dose thiazide-type diuretics. II

Ethnic groups also appear to differ in the underlying physiological mechanisms associated with high blood pressure and so may require different management strategies. Most studies comparing the mode of action of antihypertensive drugs in different ethnic groups have focused on the differences in renal physiology, salt sensitivity, and socioeconomic factors between Caucasians and people of

African origin [488,489]. Patients of African descent appear to have low renin profiles and may respond less well to ACE-inhibitors and beta-blockers whose mechanism of action is to suppress renin production [490]. This understanding is supported by subgroup analysis of the ALLHAT trial, which found these patients had reduced levels of stroke on a diuretic when compared to an ACE-inhibitor. Diuretics and calcium-channel blockers may be the most efficacious antihypertensive drugs in this patient group [490]. Some evidence suggests that Asian Americans also respond better to calcium-channel blockers than to ACE-inhibitors, but show similar responses to beta-blockers and diuretics [491]. Few studies have been carried out in other ethnic minorities.

It can not be assumed that ethnicity alone accurately predicts response to different classes of blood pressure lowering treatments: patients should be treated on the basis of individual needs.

See also Hypertension, diabetes and ethnicity on page 47.

Quality of life on hypertensive therapy

Outcomes summarized from trials include reductions in fatal and non-fatal cardiovascular events and likelihood of withdrawal from therapy: these are measured consistently in long term trials and they describe (in some sense) what patients might value from treatment. Quality of life has physical, social and psychological dimensions and varies from person to person. Health-related quality of life can be assessed by asking disease-specific questions or generic questions about aspects of health in general. Scores from generic questions are sometimes aggregated to give an overall health score between 0 (dead) and 1 (full health).

It is pertinent to ask if the act of taking antihypertensive therapy reduces quality of life, and then if different drugs are better of worse. A review of health-related quality of life, when using antihypertensive drugs in trials, retrieved papers published up until 2000 [492]. In 77 trials included in the review, many different kinds of measures of quality-of-life were used and thus it was not possible to make consistent comparisons between drugs about their effect on quality-of-life. Generic quality of life measures will need to be used consistently in long-term randomized controlled trials before the absolute and relative effects of antihypertensive treatment on health-related quality of life can be estimated.

Sequencing and combining drug therapy

- Findings from trials suggest that the onset of diabetes is greater in patients receiving a combination of a thiazide-type diuretic and beta-blocker than with other drug combinations. The combination may lead to a higher incidence of diabetes of 0.4% per year of treatment, i.e. one additional case of diabetes for 250 patients treated every year. | II

Drug trials suggest that the majority of patients are likely to end up on more than one drug sooner or later (Appendix 17). Each trial set out its own protocol for increasing dose or adding additional agents. The combinations utilised in trials were comprehensive (Table 29).

However, few studies have specifically evaluated which combination of antihypertensive drugs is most likely to provide optimal treatment. Current thought on drug sequencing is based on the principle that antihypertensive drugs can be separated into two groups; those which reduce blood pressure by suppressing the renin system (ACE-inhibitors/ARBs: class A; and beta-blockers: class B) and those which lead to reflex activation of the renin system but lower blood pressure by a different means (calcium-channel blockers: class C; and diuretics: class D) [493,494,495,496]. The modified Cambridge AB/CD rule has been promoted as a practical guide for blood pressure lowering drug therapy, and has been an important step forward in that it provides practical and workable advice on drug sequencing [496].

The AB/CD approach discriminates between the classes of drugs for use as monotherapy using several sources of evidence: trials comparing the blood pressure lowering effect of different classes of drug [497], drug rotation studies [495,498] and renin profiling [499,500,501,502]. Age and ethnicity are argued to have major roles in the blood pressure lowering efficacy of antihypertensive drugs. Younger Caucasians usually produce higher renin levels, have renin dependent hypertension, and thus should respond better to first line therapy with drugs which suppress the renin system - those belonging to the A or B class. Older participants and patients of African origin, with low renin hypertension, should respond better to drugs in class C or D [496]. Class C and D drugs activate the renin system making second line therapy with a drug which suppresses renin activity more effective. Hence, when dual drug therapy is required, it is plausible to combine drugs from classes A or B with C or D, which have a complementary action on the renin system [493,494,495,496].

Secondary analysis of the LIFE trial [478,479] generated concern that beta-blockers alone, or combined with diuretics, in elderly patients may lead to a greater incidence of diabetes mellitus than other drugs (although it is not strictly clear whether the combination increases the risk of diabetes or is less preventative than other drugs). Pharmacologically the effect is plausible since beta-blockers are observed to increase insulin resistance and thiazides reduce insulin output in some patients. A combination of the two agents could have a synergistic negative effect. This has led to a recommendation for dual therapy in elderly patients to be restricted to combining class A with an initial drug from class C or D [496]. Consequently, a combination of classes A, C and D has been recommended for triple therapy. Remaining licensed drugs for treatment resistant hypertension include spironolactone, α-blockers and centrally acting antihypertensives.

Table 29: Drug combinations used in trials reviewed in this guideline.

Trial	Diuretic	β-blocker	Calcium-channel blocker	α-blocker	ACE-inhibitor	ARB	Central acting antihyp.	Vaso-dilator antihyp.	Other
ALLHAT	x	x					x	x	
ALLHAT		x	x				x	x	
ALLHAT		x			x		x	x	
ALLHAT		x		X			x	x	
ANBP2	x	x	x			x			
ANBP2		x	x		x	x			
ANBPS	x	x					x	x	
CAPPP	x	x							
CAPPP					x				
CONVINCE	x		x						x
CONVINCE	x	x							x
CONVINCE	x	x							x
Coope	x	x	x				x		
DUTCH-TIA		x							
ELSA	x	x							
ELSA	x		x						
EWPHE	x						x		
HAPPHY		x						x	x
HAPPHY	x							x	x
HDFP	x						x	x	x
HSCSG	x						x		
INSIGHT	x	x			x				
INSIGHT		x	x		x				
IPPPSH		x							
INVEST									
INVEST									
LIFE	x	x							x
LIFE	x					x			x
MAPHY	x							x	
MAPHY		x						x	
MIDAS	x				x				
MIDAS			x		x				
MRC	x						x		x
MRC		x					x		
MRC-O	x		x						
MRC-O		x	x						
NICS-EH	x								
NICS-EH			x						
NORDIL	x	x		X	x	x	x	x	x
NORDIL	x		x	X	x				
Oslo	x	x					x		
PATS	x								
PROGRESS	x				x				
SCOPE	x					x			x
SHEP	x	x					x		
SHEP-pilot	x	x					x	x	
STONE	x		x		x				
STOP-H2	x	x							
STOP-H2					x				
STOP-H2			x						
SYST-CHINA	x		x		x				
SYST-EUR	x		x		x				
TEST		x							
TOMHS	x								
TOMHS		x							
TOMHS			x						
TOMHS				X					
TOMHS					x				
USPHS	x						x		
VA-II	x						x	x	
VA-NHLBI	x						x		
VHAS	x				x				
VHAS			x		x				

Black crossed cells show first line therapy, white crossed cells show drugs used subsequently in some patients.

To inform the concern about combining a thiazide-type diuretic and beta-blocker (the 'target' drugs), data on the incidence of diabetes were abstracted from drug trials using this combination. Seven trials reported this data (see Table 30). Treatment in intervention arms of trials involved initial treatment with a newer antihypertensive drug with subsequent addition of a thiazide, beta-blocker or other dugs if necessary. We estimated a pooled risk ratio for new onset diabetes using a random effects model.

The definition of new-onset diabetes used in most trial reports was unclear. The proportion of patients exposed to a combination of target drugs varied and was poorly reported: no estimation was possible for the CAPPP trial. Time exposed to drug combinations was unreported and we assumed that second line therapies were initiated without substantial delay.

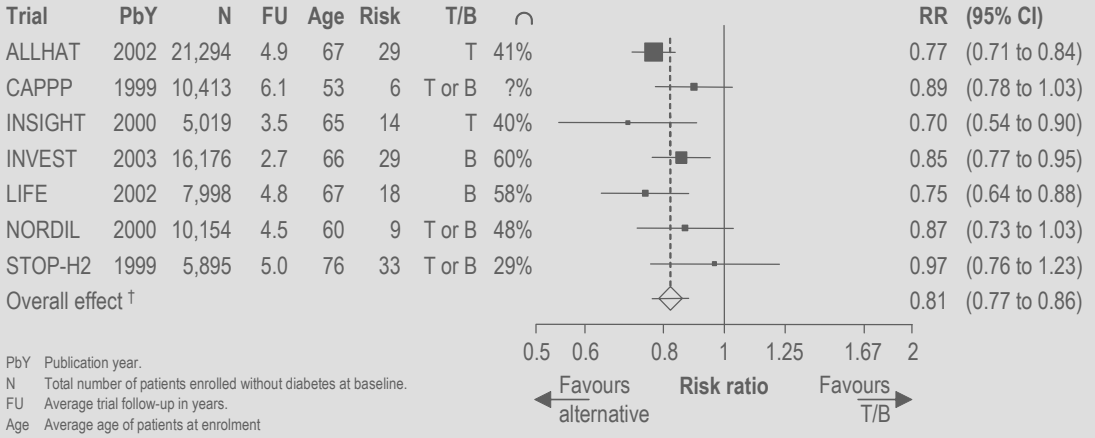
Overall there was a significantly higher incidence of diabetes in patients randomised to target drugs of whom about half received both agents: RR alternative(s) vs. target drug(s) = 0.81, 95%CI: 0.77 to 0.86 (see Figure 25). The summary finding was without substantial heterogeneity (Q, p=0.17) or variation of effect with study size (p=0.56). The finding was robust when using different methods of estimation. By visual inspection the findings provide no evidence to suggest that the relationship between target drug use and new onset diabetes changes with age, baseline risk, or the order in which the drugs are given.

Table 30: Trials using thiazide and beta-blocker combination therapy and reporting incidence of diabetes mellitus.

Trial	Treatment regimen †		+	*	Incidence of Diabetes¶	
	1st drug	*Further drugs added*	**TD ∩ BB**	**I(TD∪BB)**	*During trial*	*Per year*
ALLHAT	I1: CCB	BB or OD.	0%	Th: 17%	9.8% (561/5725)	2.0%
	I2: ACE		0%	Th: 16%	8.1% (473/5842)	1.7%
	C: TD		41%	-	11.6% (1128/9727)	2.4%
CAPPP	I: ACE	TD *then* CCB	0%	BB: ?	6.5% (337/5183)	1.1%
	C: TD or BB	TD and BB *then* CCB	?	-	7.3% (380/5230)	1.2%
INSIGHT	I: CCB	BB (or ACE‡) *then* OD	0%	BB: 38%	3.8% (96/2508)	1.1%
	C: TD		40%	-	5.5% (137/2511)	1.6%
INVEST	I: CCB	ACE *then* TD *then* OD	0%	Th: 41%	7.0% (569/8098)	2.6%
	C: BB	TD *then* ACE *then* OD	60%	-	8.2% (665/8078)	3.0%
LIFE	I: ARB	TD or OD	0%	Th: 62%	6.0% (241/4019)	1.3%
	C: BB		58%	-	8.0% (319/3979)	1.7%
NORDIL	I: CCB	ACE *then* TD or OD	0%	Th or BB: 30%	4.3% (216/5059)	0.9%
	C: TD or BB	TD and BB *then* ACE or OD	48%	-	4.9% (251/5095)	1.1%
STOP-H2	I1: ACE	TD	0%	Th: 28%	4.7% (93/1969)	1.0%
	I2: CCB	BB	0%	Th: 30%	4.8% (95/1965)	1.0%
	C: TD or BB	TD and BB	29%	-	4.9% (97/1961)	1.0%

† steps in dose are not shown.
ACE: Angiotensin Converting Enzyme inhibitor; ARB: angiotensin receptor blocker; BB: Beta-blocker; CCB: Calcium-channel blocker; TD: Thiazide or thiazide-like diuretic; OD: Other drug.
+ TD ∩ BB: approximate proportion taking TD and BB in combination.
* I(TD ∪ BB): in intervention arm, approximate proportion taking either a TD or BB second or third line.
¶ Patients enrolled in trials with diabetes at baseline are excluded from the numbers shown.
‡ if BB contraindicated.

Figure 25: Meta analysis of trials comparing thiazide and beta-blocker combination therapy with other combinations and reporting new onset diabetes mellitus.



PbY Publication year.
N Total number of patients enrolled without diabetes at baseline.
FU Average trial follow-up in years.
Age Average age of patients at enrolment
Risk Risk of all-cause mortality per 1000 patient years for all patients enrolled.
T/B Drug sequence in Thiazide diuretic (T)/Beta blocker (B) arm.
T (T, then B if necessary), B (B, then T if necessary), T or B (either, then both if necessary)
∩ Approximate percentage (T/B) receiving second drug;
† Heterogeneity, Q=9.04; p=0.17
Normalized effect vs. precision (Egger et al.), p=0.56

The incidence of diabetes varied across trials from 1% to 3% per year (i.e. 10 to 30 per 1,000 patient years of treatment). This may partly reflect baseline risk, but may also be due to different definitions of new onset diabetes. For example ALLHAT, the largest trial, which featured a high absolute rate, applied a very inclusive definition: one reading of fasting serum glucose ≥126mg/dL (≥7.0 mmol/L).

This guideline recommends treating raised blood pressure down to fairly low levels of cardiovascular risk. In these patients the absolute benefits of treatment are modest and thus the possible harms of drugs are particularly important. In England and Wales, the most commonly used antihypertensive agents are non-proprietary bendroflumethiazide (a thiazide-type diuretic) and atenolol (a beta-blocker), partly due to their low cost. Using a Framingham risk calculator, 60-year-old males with blood pressure 160/100 mmHg but without other risk factors may typically face a 20% risk of cardiovascular disease over the next ten years. Treatment for raised blood pressure in such (low risk) patients is predicted to reduce cardiovascular events by about 4 per 1,000 patient years of treatment. Assuming a 20% baseline risk of developing diabetes over the next ten years, the analysis implies that a combination of a thiazide diuretic and beta-blocker may lead to an additional 4 cases of diabetes per 1,000 patient years of treatment.

Our findings are vulnerable to confounding and reporting bias. However, the meta-analysis is based on findings in nearly 77,000 patients and its findings are pharmacologically plausible. The findings of one further trial of the effect of the combination of thiazides and beta-blockers on metabolic control (the ALPINE trial) [503] and an epidemiological study [504] are supportive. The ASCOT study, comparing the blood pressure lowering effects of an ACE-inhibitor and/or calcium-channel blocker and a beta-blocker and/or diuretic combination may further inform this issue [505]. The estimation of the proportion of patients receiving both drugs in the analysis (and their exposure time) is approximate. A patient level meta-analysis of these trials, providing data on exposure times to different agents, would

allow the medical community to better understand the diabetogenic potential of these drugs alone or in combination.

The analysis presented here cannot explore the increased risk of using either target drug (thiazide-type diuretic or beta-blocker) separately and this remains a research issue. Circumstantial evidence suggests that the increased risk may be attributable to the combination (rather than single target drugs) as there is a similar increased incidence of new onset diabetes regardless of starting drug. Another argument relates to the pattern of use of target drugs in intervention and control arms of the trials. In control (C) groups (see Table 30) about one half of patients remain on monotherapy of one target drug and about half progress to their combined use. In intervention (I) groups about one third of patients use one target drug (as part of second line therapy) and about two thirds use neither. Hence, patients on one target drug in both intervention and control groups partially balance one another as being at equal diabetogenic risk. This argument assumes no diabetogenic interaction between target and non-target drugs. Thus the analysis approximately compares those on both target drugs with those on none.

On the basis of costs and primary health outcomes alone, thiazide-type diuretics and beta-blockers would be suitable as initial and second line therapies to treat hypertension. If this combination is avoided, it is not straightforward to value the reduced risk of diabetes obtained against the increased cost of different drug combinations, although cost-effectiveness models could be constructed. The consensus view of the guideline development group was that many primary care physicians would be concerned about routinely prescribing a thiazide and beta-blocker combination to all patients in the early stages of treatment for hypertension, once appraised of the increased risk of developing diabetes.

The guideline development group had to decide what weight and interpretation to place on the evidence that use of the target drugs used alone or in combination may lead to a small increased risk of new onset type-II diabetes. The concern about the combination of a thiazide-type diuretic and beta-blocker created three possible interpretations: do not use the combination at all (at least as an initial combination); do not use the combination in patients who can be identified as being at high risk of developing type II diabetes; routinely use the combination, setting aside the analysis as being speculative and needing further research.

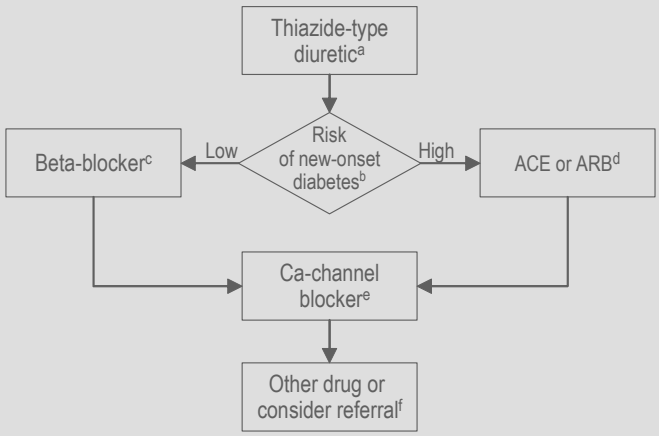
The final and unanimous consensus of the guideline group was that it would be judicious to restrict the use of a combination of thiazide-type diuretics and beta-blockers when beginning treatment in patients at raised risk of developing diabetes, although the group recognised that the combination may become necessary if hypertension progresses or cardiovascular disease develops. The group asserted that this position should be reviewed as new evidence becomes available.

The AB/CD rule has not been explicitly tested on a cardiovascular outcome, although a number of trials reflect its sequencing advice. As yet there is no evidence that AB/CD guided treatment results in better cardiovascular outcome than other approaches. Neither does current evidence addressing

health outcomes support first-line AB drugs for younger patients and CD for older patients: relative benefits appear consistent across age, although variable numbers of participants in trials have received additional second or third line therapy. Finally the AB/CD rule appears to have been derived without reference to cost or cost-effectiveness. Given the full evidence profile there seems no justification for routinely beginning a patient on an ACE-inhibitor or calcium-channel blocker: in routine care a low dose thiazide-type diuretic should be used as first line therapy. However the argument for choosing a drug that suppresses the renin system led the group to accept that in younger patients the sequence of giving a thiazide-type diuretic and then a beta-blocker could be reversed.

It was the view of the guideline development group that: the sequential use of drugs with different modes of action should be supported; current evidence justifies caution in the use of thiazide diuretics with beta-blockers at least in the early stages of treatment; and that it was helpful to provide simple guidance on drug sequencing. The following algorithm was developed to summarise the group's understanding of drug sequencing for hypertension and received unanimous consensus support from the group (Figure 26). This provides two paths based on thiazide-type diuretic initiated therapy. The definition of impaired glucose tolerance is a matter of judgement but was based on an overview of research findings [506,507,508].

Figure 26: Drug sequencing algorithm for essential hypertension



- If a drug is not tolerated discontinue and proceed to the next line of therapy. If a drug is tolerated but target BP is not achieved add the next line of therapy. Drug cautions and contraindications are listed fully in the *British National Formulary.*

a In young patients (under 55) whose BP may be managed on monotherapy, consider starting with a beta-blocker.

b Patients at high risk have a strong family history of type II diabetes, have impaired glucose tolerance (FPG≥6.5mmol/l), are clinically obese (BMI≥30) or are of South-Asian or African-Caribbean ethnic origin.

c Beta-blocker contraindications include asthma, COPD and heart block.

d Offer an angiotensin receptor blocker (ARB) if an ACE inhibitor (ACE) is not tolerated because of cough. Contraindications include known or suspected renovascular disease and pregnancy.

e Only dihydropyridine calcium-channel blockers should be prescribed with a beta-blocker. Contraindications include heart failure.

f Consider offering a beta-blocker or ACE (if not yet used), another drug, or specialist referral. A beta-blocker and thiazide-type diuretic combination may become necessary in patients at high risk of developing diabetes if hypertension or cardiovascular disease progresses.

Drug treatment and value-for-money

- Drug treatment, beginning with either a non-proprietary thiazide diuretic or beta-blocker minimizes cost. II
- From a model of lifetime costs and effects, based on the findings of trials, treatment using stepped care including thiazide diuretics, beta-blockers, ACE-inhibitors/angiotensin receptor blockers and calcium-channel blockers is estimated to be cost-effective. II

Two kinds of question can be asked about the cost-effectiveness of drug treatments for hypertension. The simpler (technical) question assumes that drug treatment for hypertension is worthwhile and asks about the most cost-effective way to treat patients. In what order and combination should drugs be offered to get best value-for-money? The harder (allocative) question asks whether drugs should be used at all or whether there are more important activities in the NHS to spend the money on instead. A simplifying assumption made in answering both of these questions is the understanding that the benefit will be the same, regardless of the drugs or sequence of drugs used. (In practice it is recognised that drugs are understood to have complimentary actions of working and in this respect some combinations may be preferable to others).

Cost-minimisation analysis

Therapeutic equivalence accepted, the technical question is addressed by cost-minimisation analysis: how can we treat patients as cheaply as possible leaving as much NHS resource as possible free to provide other healthcare? A simple comparison of drugs by cost per script (Table 6) is not valid since some drugs appear to be prescribed for shorter durations than others. Consequently the most commonly prescribed drugs have been costed for one year of use at a therapeutic dose (see Table 31). This provides a simple cost ranking for drugs of thiazides, beta-blockers, ACE-inhibitors, calcium-channel blockers and angiotensin receptor blockers. The ranking holds whether the average costs of each class, or the cheapest drugs within each class, are compared. Alpha-blockers, not recommended for initial use in hypertension, are typically similar in price to calcium-channel blockers.

Besides the acquisition cost of drugs, there are other resources involved when treating hypertension. GP and nurse visits and care for cardiovascular disease, when this occurs, all use healthcare resources. However, if drugs perform similarly then we can set these other costs aside in a cost-minimisation analysis: they are approximately the same for therapy beginning with any of the major antihypertensive drug classes. In practice, over the course of time many patients will receive more than one drug, potentially diluting cost differences. Initial use of non-proprietary once daily bendroflumethiazide or atenolol ensures cost-effective management of patients requiring only one drug. The combination of a thiazide diuretic and beta-blocker as an initial combination to treat hypertension is recommended in certain patients (e.g. judged at low risk of developing diabetes or without asthma) and as a combination currently costs, on average, £40 per year. In patients for whom this combination is contraindicated using two drugs will cost, on average, about £120 per year for a diuretic and ACE-inhibitor. Triple therapy may cost on average £300 per year.

Table 31: Annual ingredient cost of drugs for hypertension based on prescribing patterns in England in 2001.

Drug Class/Drug[1]	% of class[2]	Dose[3]	Cost (£)/year[4]
Thiazide-type diuretics			**12**
Bendroflumethiazide	93%	2.5mg OD	10
Indapamide	5%	1.5mg MR or 2.5mg OD	46
Potassium sparing diuretics			**20**
Amiloride Hydrochloride	33%	5mg BD or 10mg OD	20
Diuretics + Potassium sparing diuretics			**25**
Co-Amilozide (Amiloride HCl/Hydchlorothiazide)	17%	5mg/50mg OD	25
Beta-blockers			**29**
Atenolol	65%	50mg OD	14
Propranolol Hydrochloride	12%	160mg MR OD	84
Bisoprolol Fumarate	6%	10mg OD	115
Alpha blockers			**182**
Doxazosin Mesylate	87%	1-4mg OD	203
Prazosin Hydrochloride	7%	1-10mg BD	51
Terazosin Hydrochloride	5%	2mg OD	109
ACE-inhibitors			**107**
Lisinopril	34%	10-20mg OD	135
Ramipril	22%	2.5-5mg OD	117
Enalapril Maleate	20%	10-20mg OD	69
Angiotensin receptor blockers			**216**
Losartan Potassium	38%	50mg OD	225
Valsartan	19%	80mg OD	205
Candesartan Cilexetil	20%	8mg OD	195
Calcium-channel blockers			**181**
Amlodipine Besylate	37%	5-10mg OD	194
Felodipine	8%	5-10mg OD	120
Verapamil	5%	120-240mg BD	212

1 The most commonly used drugs in each class were identified from National Prescribing Data [42].
2 Although hypertension is the most common indication, drugs are used for other indications. Percentage in class refers to the proportion of scripts in the drug class.
3 The dose or range of dose for hypertension is found in the British National Formulary [44].
4 Calculated as 365.25 x number tablets per day x average tablet cost from National Prescribing Data, and rounded to the nearest one pound, in 2002 prices. Average costs per class are estimated by taking the weighted average of drugs shown and include generic and proprietary prescribing.

Cost-effectiveness analysis

The allocative question, whether hypertension is worth treating when compared with other competing demands on scarce resources, cannot be answered with certainty. Many NHS activities have not been adequately evaluated, making the value of alternative uses of resources hard to assess. To estimate the total benefit and cost of treatment for hypertension involves modelling the effect of treatment and cardiovascular disease processes over patients' remaining lives and involves a number of assumptions. A corollary of the allocation question is to ask whether only some patients should be offered treatment and not others. In the short term, those most at risk – for example older patients - can be shown to receive the most benefit in trials. However, the findings of trials and cardiovascular risk models truncate the value of long-term treatment most severely in the youngest patients. Models

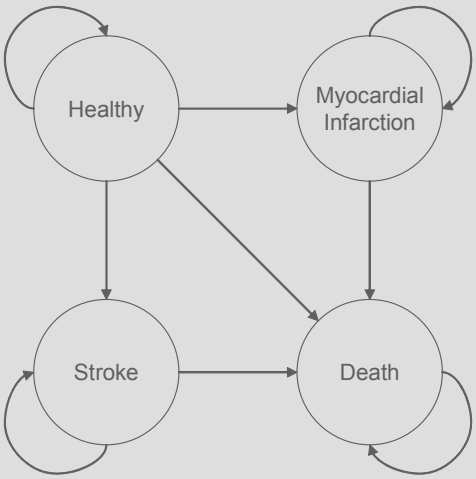
of lifetime costs and benefits are useful for exploring bounds of cost-effectiveness and exploring the influence of different risk and age thresholds for starting treatment, if it is accepted that to estimate costs and consequences after many years of treatment involves some educated guessing.

Disease modelling

A Markov model was constructed to provide a simplified representation of the long term consequences of hypertension. In the model patients begin in the 'healthy' state and as each year passes they can remain healthy, suffer a myocardial infarction (MI), stroke or die of other causes (see Figure 27). Patients who have an MI or stroke can never be healthy again; they can remain in that state or die. The model allows a cohort of people to grow old and die, recording the time spent in each state. The likelihood of morbidity and mortality can be adjusted for cohorts of people with different characteristics: age, initial blood pressure, gender and other risk factors. The consequence of drug treatment is to change the likelihood of disease and thus change the time spent in each of the health states. If time spent in each of the 'alive' health states is added up without weighting, the model predicts average survival or life-expectancy. If weights are applied (for example one year of healthy life scores 1, MI scores 0.88 and stroke scores 0.50 [513]), then the model can predict quality-adjusted survival, also called a QALY score (quality-adjusted life-years). Lifetime healthcare costs can also be estimated by including time spent on drugs, healthcare contacts and the costs of cardiovascular disease. The model is run with and without blood pressure lowering drugs to estimate the change in costs and life-expectancy attributable to drug therapy.

Many things can happen once a stroke or MI occurs - rapid decline, long term disability or remarkable recovery. These patients may then be treated in many different ways but this detail does not need to be reflected in the model provided we know what happens to these patients *on average*. The model will then still reasonably reflect the average value of treating hypertension. There are a number of key sources of data that are used to make calculations.

Figure 27: Transition state diagram for a model of hypertension and cardiovascular disease.



Sources of data and assumptions

National mortality statistics for England and Wales provide data on death by age and cause [509]. These are used to estimate the likelihood of dying each year from non cardiovascular causes.

Framingham risk equations are used to calculate the risk of healthy people suffering a stroke or MI each year according to their age, sex, blood pressure and other cardiovascular risk factors [140,141,142].

Framingham 30-year mortality data are used to calculate the risk of death each year for patients who have had a stroke or MI [510]. There is an initial high rate of death following these events and from then on the death rate is lower in survivors, although still above the population average. These rates vary by age and gender.

Costs of drugs are determined from Table 31, based on prescription pricing authority data [42]. Low, medium and high annual drug costs are modelled of £40 (a thiazide-type diuretic and a beta-blocker), £120 (a thiazide diuretic and ace-inhibitor) and £300 (a thiazide diuretic, ace-inhibitor and calcium-channel blocker). Acute care costs are modelled as £1,018 for myocardial infarction and £2,124 for stroke, from national data [511]. The published literature reveals widely ranging estimates for the long term costs associated with stroke reflecting, in part, the wide range of resulting disability. A stroke is assumed to cost the NHS £3,000 per year on average for the remaining lifetime of a survivor [512]. A myocardial infarction is assumed to cost £500 per year, primarily the cost of indicated drugs. These costs are conservative and do not reflect broader costs of care borne by society or loss of earnings.

The effect on the disease model of drug therapy is incorporated by applying the risk ratios from the meta-analyses of drug trials (see page 122) to the risk of stroke and MI in healthy people: risk ratios for myocardial infarction and stroke were RR=0.85 and RR=0.75 respectively. It is assumed that the costs and effect of treatment continue over each patient's remaining life.

Baseline life expectancies estimated by the model were for any starting age within one or two years of published national life table statistics (see E_o,Table 32). Rates of MI and stroke events and subsequent mortality were derived from the Framingham cohort, when morbidity and mortality were known to be higher than today. However, we are only interested in changes in survival within the model: small differences in overall life expectancy between the model and national data are unlikely to be important.

Discounting

We feel differently about having things now or in the future. Quite apart from inflation, if we have £100 we have decided to spend now on something we value we need an incentive to put off spending that money until tomorrow. Economists call this our marginal time preference and we vary in the level of incentive that we need. Social time preference (our individual values put together) means that the current value of healthcare policy costs and benefits is valued progressively less as these occur

further in the future. For example, if costs are discounted at 5% per annum: £1 spent this year is valued as £1, £1 committed for spending next year it is now valued at £1÷1.05 or about 95p, £1 spent in 10 years times it is currently valued at £1÷1.05^{10} or about 61p. Similarly disease prevented far off in the future is valued less than disease prevented now. When the cost-effectiveness of treatments is evaluated it is common to explore different discount rates and the most commonly used are 0% (no discounting) and a 5% discount rate on costs and benefits.

Dealing with uncertainty

Life is uncertain: the risk of disease, the benefit from taking drugs, the cost of healthcare. This uncertainty can be explored in two ways in a disease model. The first is called *deterministic*: the model is re-evaluated using, in turn, the highest and lowest credible value for each parameter in the model. (A parameter is a value such as the cost of caring for stroke, or the reduction in the risk of myocardial infarction when taking antihypertensive drugs). For example, the model explores different assumptions about the cost of antihypertensive drugs. Exploring uncertainty deterministically allows us to find the critical aspects of the model and assess how confident we are of overall predictions. If there are several critical aspects, these can be explored together to create 'best' and 'worst' scenarios. Exploring uncertainty in models is called sensitivity analysis.

The second approach to uncertainty is called *stochastic.* Instead of having one value for some parameters in the model, a random value can be chosen from a plausible range or distribution. These distributions can be put anywhere in the model where there is uncertainty. Then the model might be run a thousand times to predict the likely range of values of cost-effectiveness. The process of running the model many times is called a *Monte Carlo* analysis.

Findings

The model was used deterministically to evaluate blood pressure lowering in patients at age 50 and 70, male and female with initial blood pressure 140/85 mmHg and 180/110 mmHg, in non-smokers with total serum cholesterol and HDL of 5 and 1.5 mmol/l respectively. The low, medium and high cost scenarios assume antihypertensive drugs cost £40, £120 and £300 per year respectively.

Low cost scenario

Blood pressure lowering achieves an average survival gain of 0.73 to 0.90 years for men age 50 with blood pressure 140/85 mmHg and 180/110 mmHg respectively (see ΔE_1, Table 32). This falls to 0.34 and 0.41 years in 70 year old men. All other things equal women receive, on average, a smaller benefit reflecting a lower propensity to develop cardiovascular disease in middle age, however the difference is small when blood pressure is high (180/110mmHg). The total costs of care without treatment (C_0) are compared with the cost when antihyperytensive drugs are provided (at £40 per year, C_1). Savings due to prevented coronary heart disease and stroke in some instances exceed the cost of prescribing, (see ΔC_1 which equals C_1 minus C_0). Treatment using low cost drugs is highly

cost-effective for all scenarios modelled (see $\Delta C_{r1}/\Delta E_{r1}$) with discounted values ranging from cost-savings with health gains to £958 per life-year gained for 50 year old women with blood pressure 140/85 mmHg.

Table 32: Disease model findings by gender, age and initial blood pressure.

	MALE		FEMALE		MALE		FEMALE	
Age (years)	50	50	50	50	70	70	70	70
BP (mmHg)	140/85	180/110	140/85	180/110	140/85	180/110	140/85	180/110
Survival (years)*								
E_0	25.46	23.42	29.5	27.23	12.16	11.28	15.36	14.41
ΔE_1	0.73	0.90	0.66	0.94	0.34	0.42	0.26	0.40
Cost (£)*								
C_0	8,079	12,055	7,219	11,598	4,484	7,128	4,130	7,183
ΔC_1	63	-235	182	-124	-80	-370	23	-298
ΔC_2	1,704	861	2,264	1,263	656	93	1,046	565
ΔC_3	5,908	4,425	7,215	5,657	2,608	1,786	3,618	2,647
Cost-effectiveness (undiscounted)*								
Low $\Delta C_1/\Delta E_1$	-171+	-803+	97	-719+	-621	-1571+	-373+	-4163+
Medium $\Delta C_2/\Delta E_1$	2,334	957	3,430	1,344	1,929	221	4,023	1,413
High $\Delta C_3/\Delta E_1$	8,093	4,917	10,932	6,018	7,671	4,252	13,915	6,617
Cost-effectiveness (discounted)*								
Low $\Delta C_{r1}/\Delta E_{r1}$	300	-839+	958	-459+	-500+	-1682+	177	-1568+
Medium $\Delta C_{r2}/\Delta E_{r1}$	4,957	2,339	6,658	3,248	3,219	736	5,823	1,968
High $\Delta C_{r3}/\Delta E_{r1}$	13,071	9,500	19,479	11,581	11,581	6,182	18,546	9,984

* For an explanation see text.
\+ Cost saving with positive health gains

High cost scenario

Blood pressure tends to rise with age and a conservative assumption is that three drugs will be necessary to achieve the same benefit in patients. Consequently the net cost of care increases considerably (see ΔC_2, Table 32). Discounted cost-effectiveness values rise to: £6,182 per life-year gained for 70 year old men with blood pressure 180/110 mmHg to £19,479 per life-year gained for 50 year old women with blood pressure 140/85 mmHg.

The discounted cost-effectiveness ratio is commonly used in policy decisions. The National Institute for Clinical Excellence currently operates an approximate threshold for new technologies of about £30,000 per life-year gained or £30,000 per QALY. Treatment appears cost-effective for the range of drug costs modelled, both age groups and initial blood pressure levels, and either gender.

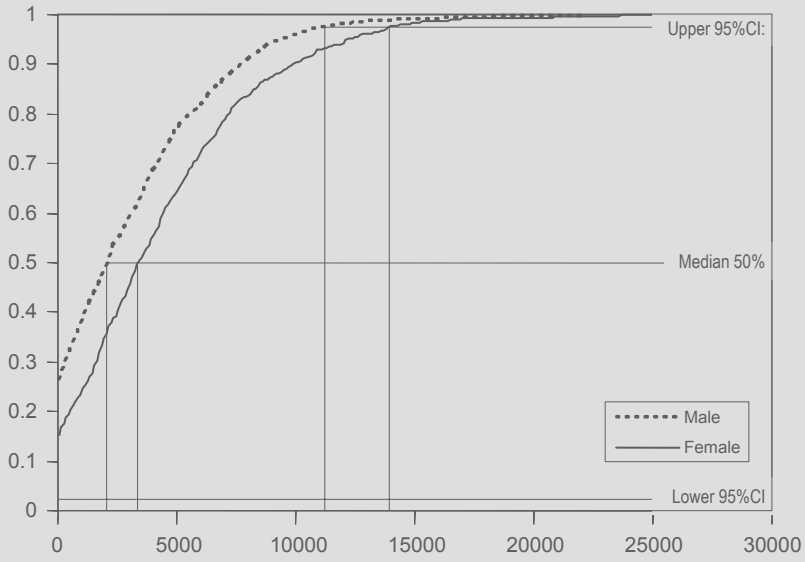
Sensitivity Analysis

Parameters in the model were systematically explored to determine which crucially affected the findings. The sensitivity to the cost of drugs is evident and as this cost falls the scenarios progressively become cost saving (costs of prevented cardiovascular disease exceed the cost of

prescribing drugs). The findings are sensitive to the size of reduction in risk of cardiovascular disease predicted from trials, and to the long term persistence of the blood-lowering effect of the drugs. Against this must be balanced the propensity of blood pressure to rise in individuals as they age, increasing the value of treatment. Exclusion of non-health service costs, particularly for the long term social care of disabling stroke suggests the analysis is conservative. The assumptions to some extent balance one another; their importance is greatest when estimating cost-effectiveness for the youngest patients where extrapolation over remaining life is the greatest. Drug treatment is modelled to be more cost-effective for smokers than non-smokers because of their greater cardiovascular risk.

Monte Carlo analyses were conducted for male and female patients aged 60 with blood pressure 160/100mmHg (non-smokers with total serum cholesterol and HDL of 5 and 1.5 mmol/l). Approximate gamma cost distributions were fitted to costs using low, published average and high values for acute MI and stroke; long term costs of MI and stroke (half to double the average values); and drug costs (average £120 from one-third to three times the average value). Log-normal distributions were fitted to relative risk reductions for MI and stroke using confidence intervals from trials to derive an estimate of variance. With future costs and benefits discounted at 5%, the median cost-effectiveness of therapy for men was estimated to be £2,200 per life year gained (95%CI: -3,500 to 11,200) and for women was estimated to be £3,400 per life year gained (95%CI: -3,000 to 14,000). These values are shown on a cost-effectiveness acceptability curve (Figure 28). The curve shows that there is a very high probability of treatment being cost-effective, accepting the assumptions made in the model.

Figure 28: Cost-effectiveness acceptability curve for antihypertensive drug therapy in non-smoking patients aged 60, BP: 160/100 mmHg



Quality-of-life weightings, drawn from the published literature were applied to time spent following MI (0.88) and stroke (0.5) [513]. Monte Carlo analyses were rerun for male and female patients aged 60 with blood pressure 160/100mmHg (non-smokers with total serum cholesterol and HDL of 5 and 1.5 mmol/l). Quality adjusted life years (QALYs) gained are slightly greater than life years gained. This

occurs because quality-of-life adjustment slightly steepens the survival curves, increasing the absolute separation between drug and no treatment curves. With future costs and benefits discounted at 5%, the median cost-effectiveness of therapy for men was estimated to be £1,700 per QALY gained (95%CI: -3,100 to 9,100) and for women was estimated to be £2,800 per QALY gained (95%CI: -2,000 to 11,500). In providing these estimates it has been assumed that drug therapy can be tailored for individuals such that it does not reduce quality-of-life.

Commentary

A recent review identified 10 pharmacoeconomic studies of antihypertensive therapy published between 1995 and 2000. Although costs per life-year gained were reported by the majority of studies, the review noted a lack of conformity in outcomes assessed, costs included, and populations studied [514]. Two studies used a similar approach to our model and produced similar findings indicating cost-effective care, which becomes more favourable with increasing age and blood pressure level [515,516].

It is worth emphasising that modelled findings are hypothetical: they cannot reflect the observed experiences of real patients. While potentially helpful to policy makers, a limitation of aggregating the various costs and consequences of treatment is that it removes any consideration of the physical reality of treatment. It is this reality that will guide patients' decisions and a patient at age 50 may find it helpful to know that treatment for the rest of their life may (on average) extend their life expectancy by 8-11 months. From a policy perspective drug treatment looks cost-effective; from a personal perspective some patients will decline treatment while others will accept and both decisions may be a rational weighing of informed personal values.

Describing the consequences of treatment

The consequences of treatment need to be personalized to reflect the level of cardiovascular risk faced by individual patients. The relative benefits found in trials have been applied to certain levels of cardiovascular risk as calculated by Framingham based risk calculators or charts commonly used in General Practice (see Table 33).

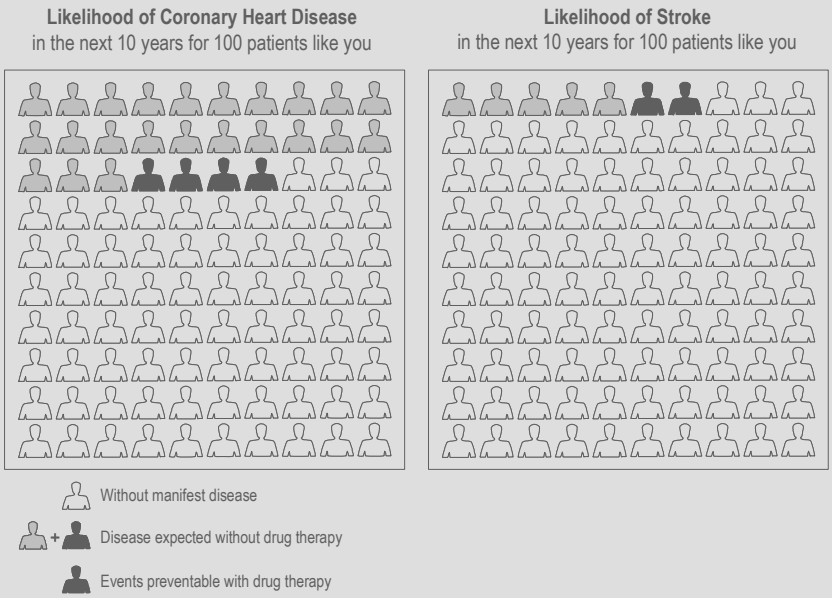
For example, a 65 year old male, non-smoking, without diabetes or evidence of left ventricular hypertrophy, with blood pressure 165/100 mmHg, total cholesterol 6 mmol/l and HDL cholesterol 1 mmol/l has a predicted 10 year risk for CHD of 27.1% and for stroke of 7.3% using the higher (systolic-based) values from a Framingham risk calculator. Treatment for raised blood pressure in this patient is predicted to reduce their 10 year risk of CHD down to about 23.0% and of stroke down to about 5.5%. This benefit can be shown pictorially (see Figure 29) and it would seem a sensible development of available risk calculator software to provide information to patients in this format.

Table 33: Absolute benefit of blood pressure reduction for essential hypertension, based on patient risk calculator score and evidence from trials

Coronary Heart Disease			Stroke		
10 year CHD risk	Reduction in CHD	(95%CI)	10 year Stroke risk	Reduction in Stroke	(95%CI)
5%	0.8%	(0.3% to 1.2%)	5%	1.3%	(0.9% to 1.7%)
10%	1.5%	(0.6% to 2.3%)	10%	2.5%	(1.7% to 3.3%)
15%	2.3%	(0.9% to 3.5%)	15%	3.8%	(2.6% to 5.0%)
20%	3.0%	(1.2% to 4.6%)	20%	5.0%	(3.4% to 6.6%)
25%	3.8%	(1.5% to 5.8%)	25%	6.3%	(4.3% to 8.3%)
30%	4.5%	(1.8% to 6.9%)	30%	7.5%	(5.1% to 9.9%)
35%	5.3%	(2.1% to 8.1%)	35%	8.8%	(6.0% to 11.6%)
40%	6.0%	(2.4% to 9.2%)	40%	10.0%	(6.8% to 13.2%)

Individual patients will value the benefits of treatment differently: some will choose treatment, others not and others defer to clinical opinion. The presentation of the risks and benefits of treatment for cardiovascular disease, and how patients understand and respond to these are important research issues [517].

Figure 29: Pictogram showing predicted 10-year risk of cardiovascular disease and predicted benefit from drug therapy



An approximate finding, on the basis of modelling work and conservative assumptions, is that patients aged 50 may extend their life-expectancy by between 8-11 months, and those aged 70 by between 3-5 months (see Table 32) if treated as aggressively as those participating in trials.

Continuing treatment

Recommendations

• **The aim of medication is to reduce blood pressure to 140/90 mmHg or below. However, patients not achieving this target, or for whom further treatment is inappropriate or declined, will still receive worthwhile benefit from the drug(s) if these lower blood pressure.**	**B**
- In trials aiming to reduce blood pressure to below 140/90 mmHg using stepped medication regimes, between half and three-quarters of patients achieve target blood pressure.	I
- In these trials about one half of patients needed treatment with more than one drug.	I
• **Patients may become motivated to make lifestyle changes and want to reduce or stop using antihypertensive drugs. If at low cardiovascular risk and with well controlled blood pressure, these patients may be offered a trial reduction or withdrawal of therapy with appropriate lifestyle guidance and ongoing review.**	**B**
- When normal blood pressure has been established through drug therapy, the patients most likely to remain normotensive if they stop taking drugs are those who are relatively young, with lower on-treatment blood pressure, taking only one drug and who adopt lifestyle changes.	II
- Withdrawal of anti-hypertensive drugs has a much better chance of being successful when supported by structured interventions to encourage patients to restrict their salt intake and to lose weight if they are overweight.	I
• **Patients vary in their attitudes to their hypertension and their experience of treatment. It may be helpful to provide details of patient organisations that provide useful forums to share views and information.**	**C**
• **Provide an annual review of care to monitor blood pressure, provide patients with support and discuss their lifestyle, symptoms and medication.**	**C**
- Listening to patients' views about the pros and cons of treatment for hypertension, involving patients in each stage of the management of their condition, and providing clearly written supportive information are good clinical practice.	III

Reviewing patient care

Antihypertensive medications are used extensively to manage hypertension; dose titrations, symptoms and blood pressure need to be managed and monitored. The guideline development group affirms the importance of fully involving patients in prescribing decisions and supporting them when starting, increasing, reducing or ceasing medicine to promote safety, a good health outcome and patient satisfaction. Periodic review of medicines, lifestyle and patient values and circumstances is thus an important aspect of good patient care. Although there is no evidence for the optimal period, the guideline development group felt that face-to-face medication review should occur once a year as a minimum to provide advice, review symptoms and revise medication when appropriate. For further discussion of the optimal review period see *Audit points* on page *153*.

The Medicines Partnership, an initiative supported by the Department of Health, offers a clinical concordance approach to medicines review, addressing the issues of patients' understanding and acceptance of the diagnosis, their agreement with the treatment proposed and their concerns about the medicines. A range of tools and examples of medication reviews are available from their website: http://www.medicines-partnership.org/medication-review/welcome.

Setting targets

- In trials aiming to reduce blood pressure to below 140/90 mmHg using stepped medication regimes, between half and three-quarters of patients' blood pressure reach target. I

Drug trials with a stepped care regime specify a target blood pressure. These targets, the proportion of patients achieving the target and the proportion of patients on monotherapy at the end of the trial are summarised in Table 34. In general, more recent trials had lower targets. Although a substantial proportion of patients achieved the target, this was usually achieved by using a combination of drugs.

Of the 29 drug trials which informed the guideline (excluding the early trials of high dose diuretics) 24 (83%) reported a target BP. The exceptions were: a trial comparing ACE-inhibitors with placebo in patients with high cardiovascular risk (PROGRESS), a study comparing low dose diuretics with placebo carried out in China in patients who had suffered a stroke (PATS); a study comparing calcium-channel blockers with low dose diuretics carried out in Japan (NICS-EH); two placebo-controlled studies evaluating beta-blockers in patients who had suffered a stroke on TIA (DUTCH-TIA, TEST). However, the proportion of patients achieving the target BP in each arm was reported in only 12/25 (48%) trials. Some trials (EWPHE, Coope et al., IPPPSH, STOP-H, HAPPHY, MAPHY, ALLHAT, CONVINCE, NORDIL, CAPPP, MRC, SCOPE, STOP-H2, LIFE) aimed at the same target blood pressure for all patients; these targets ranged from less than 140/90 mmHg in recent studies (ALLHAT, LIFE, INVEST, CONVINCE) to less than170/95 mmHg in an older study (Coope et al.). Other trials (SYST-EUR, MRC-O, INSIGHT, MIDAS, ANBP2, SHEP, SHEP-P, ELSA, VHAS) set targets for patients which depended on their baseline blood pressure or combined a target level with a target reduction, e.g. systolic blood pressure less than150 mmHg and a reduction $\geq$ 20 mmHg in SYST-EUR.

Between 21% (SYST-EUR) and 74% (IPPPSH) of the patients randomised to placebo achieved the target blood pressure (see Table 34). This may reflect initial diagnoses made on the basis of white coat hypertension; alternatively, some of these patients in the placebo group who achieved normotension may actually have been on active treatment.

Among patients randomised to active treatment, a higher percentage of the patients achieved the target blood pressure: the percentage ranged from 44% (SYST-EUR) to 80% (SHEP-P, IPPPSH) (see Figure 30). Differences in the proportion of patients achieving the target could be due to differences between trials in several aspects: the characteristics of the patients, e.g. age, baseline blood pressure; length of follow-up; treatment regime; and target blood pressure.

Table 34: Target blood pressures in drug trials

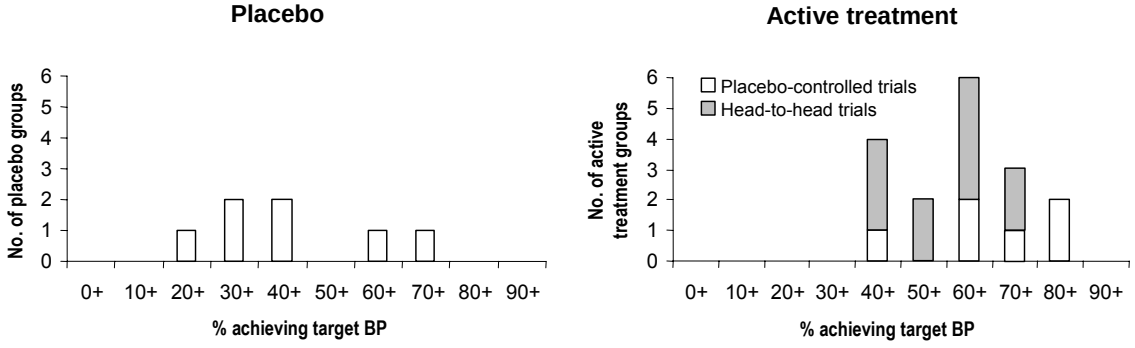
Target blood pressure (mmHg)					
Threshold		Reduction	Trials	% achieving target in active/*placebo* groups	% on monotherapy in active/*placebo* groups at end of trial
<140/90			ALLHAT	58%[2], 66%, 61%, 68%	62%[2], 60%, 57%, 59%
			CONVINCE	66%,66%	28%, 26%
			LIFE	48%,45%	11%, 11%
			INVEST	72%, 71%	23%, 22%
<140/90	and	≥ 20/10	INSIGHT	*	61%, 58%
DBP<90			NORDIL	*	50%, 45%
			MRC	73%/46%	78%/*
DBP≤90			CAPPP	*	*
SBP<150	and	≥ 20	SYST-EUR	44%/*21%*	36%/*17%*
SBP≤150 if baseline <180; SBP≤160 if baseline ≥ 180			MRC-O	*	48%, 62%
<160/90			EWPHE	*	65%, 37%
			SCOPE	*	25%/*16%*
<160/90 (or 140/80 if drug well tolerated)	and	≥ 20/10	ANBP2	*	65%, 67%
<160/95			STOP-H	*	33%/*
≤160/90			STOP-H2	*	*
SBP<160	or	≥ 20	SHEP-P	80%/*40%*	87%/*43%*
SBP<160 if baseline ≥ 180	and	>20 if baseline 160-179	SHEP	65-72%/*32-40%*	30%/*54%*
DBP≤ 90 or DBP≤ 95	and	>10%	VHAS	69%,67%	44%, 39%
DBP<95			HAPPHY	*	62%, 68%
			MAPHY	*	45%, 52%
DBP≤95			IPPPSH	80%/74%	30%/*15%*
DBP<95	and	>5	ELSA	54%, 48%	*
	and	≥ 10	MIDAS	*	56%, 54%
<170/105			Coope et al.	62%/*31%*	35%/*

1 Excluding early trials of high dose diuretics.

2 Alpha-blocker arm.

* Not reported.

Figure 30: Percentage of patients achieving target blood pressure in active treatment and placebo groups of randomised drug trials



In the HOT trial, 18,790 patients received stepped antihypertensive treatment starting with calcium-channel blocker, although the majority went on to receive at least one other drug [73]. Patients were randomised to one of three target diastolic blood pressures (≤ 90, ≤ 85, ≤ 80 mmHg), rather than to different drugs, and followed up for a mean of 3.8 years. Adjusted for multiple comparisons, there were no statistically significant differences in any outcome achieved by setting a lower target. The results are difficult to interpret, firstly because at the end of the trial the differences between the mean blood pressures in the different arms were very small and statistically non-significant (144/85, 141/83, 140/81 mmHg). Secondly, although the trial achieved remarkable reductions in blood pressure (26/20, 28/22, 30/24 mmHg) it had no placebo group, so it is unclear whether these reductions can be ascribed to the aggressive target-oriented treatment regimes.

A recent overview of regimes to lower blood pressure considered comparisons both of more intensive and less intensive regimes, comparisons between antihypertensive drugs and placebo and comparisons between different classes of drugs [518]. Although this review included studies of normotensive patients and those with diabetes and renal disease, its findings are consistent with those of trials restricted to patients with essential hypertension. On the basis of four studies (including HOT), it found that patients randomised to more intensive regimes had a non-significantly lower risk of death and coronary heart disease and a significantly lower risk of stroke. It also found that randomised groups which achieved a greater reduction in blood pressure tended to achieve a greater reduction in risk of death, coronary heart disease and stroke, consistent with evidence that, in every age group, people with lower blood pressure had a lower risk of these outcomes [19].

When to stop

- When normal blood pressure has been established through drug therapy, the patients most likely to remain normotensive if they stop taking drugs are those who are relatively young, with lower on-treatment blood pressure, taking only one drug and who adopt lifestyle changes.	II
- Withdrawal of anti-hypertensive drugs has a much better chance of being successful when supported by structured interventions to encourage patients to restrict their salt intake and to lose weight if they are overweight.	I

If a patient's blood pressure has been reduced to normal levels by antihypertensive drugs, both patient and doctor may want to know if medication can safely be stopped. Unnecessary drug treatment may put the patient at risk of adverse side effects and is a cost to society. While some patients may initially have been diagnosed as hypertensive on the basis of white coat hypertension and so may be able to safely stop their medication, other patients may risk serious cardiovascular events if they stop taking antihypertensive drugs. It would be useful to be able to identify patients who are likely to be able to stop medication without serious consequences.

In studies which have reported on withdrawal of antihypertensive medication [519,520,521,522,523, 524, 525,526,527,528,529,530,531,532,533], between 10% [531] and 60% [520] of patients remained normotensive for at least a year, although studies reporting better success rates were often

of highly selected patient populations. Further, the definition of normotension varied between studies, from blood pressure less than140/85mmHg [526] to diastolic blood pressure less than105mmHg [523] and the characteristics of the patients varied, e.g. mean age ranged from 51 [523,533] to 67 years [519], baseline blood pressure ranged from 126/80 mmHg [520,521] to 152/101mmHg [527], number of drugs ranged from one [519,522,532,533] to three or more [520].

There is consistent evidence, from a systematic review of 5,479 patients who stopped taking anti-hypertensive medication and who were followed up for at least a year [534], and from a subsequent study of 503 patients who were also followed up for a year [530], that patients are more likely to remain normotensive if they are younger, have lower blood pressure and have been treated with only one drug. Two studies, of 1,478 patients aged 60-84 years, found that on-treatment systolic blood pressure was the best measure of blood pressure to use in predicting success [530,532].

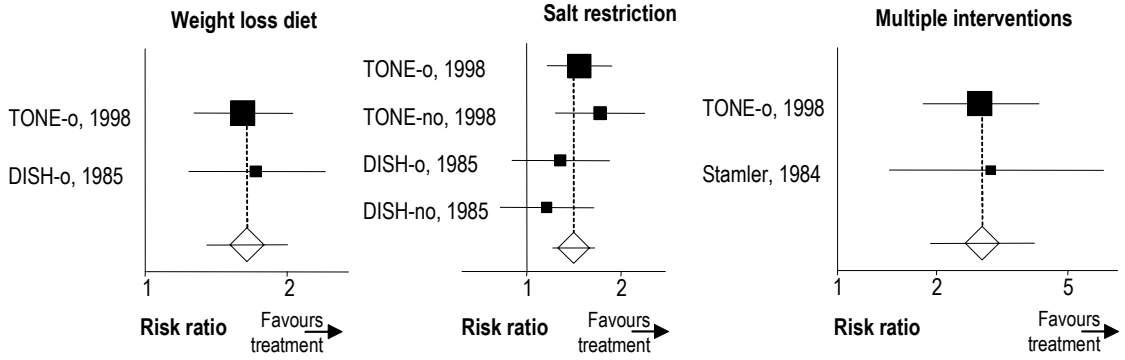
We identified three randomised controlled trials of interventions - weight loss and restriction of salt and alcohol - which might help patients to successfully stop taking anti-hypertensive medication [519,520,522] (summarised in Appendix 18: RCTs of lifestyle interventions to support withdrawal of anti-hypertensive drugs). The TONE [519] and DISH [520] studies were similar: they both evaluated the effects of a weight loss diet and restriction of salt; both randomised obese and non-obese patients independently; both had weekly group counselling sessions during the initial intensive phase of the intervention, followed by less frequent group sessions and individualised counselling during the later maintenance phase; patients in both studies had good blood pressure control (mean baseline blood pressure 129/72 mmHg in TONE and 127/80 mmHg in DISH). The TONE study enrolled patients who had been taking only one antihypertensive drug or a combination of a diuretic and a non-diuretic for a mean duration of 11.7 years. The DISH study enrolled patients who had been on treatment for at least 5 years and included some who were taking three or more antihypertensive drugs. The definitions of normotension - less than 150/90 mmHg in TONE and diastolic blood pressure less than 95 mmHg in DISH - might now be considered high. Meta-analysis of the results of these trials showed that obese patients who were put on a diet to lose weight were more likely to be successful in stopping medication than those who were not (RR = 1.6, 95%CI: 1.4 - 2.0). Likewise, patients who were encouraged to restrict their salt intake were more likely to remain normotensive (RR=1.4, 95%CI: 1.2 - 1.7), with little difference between obese and non-obese patients (see Figure 31). The smaller study by Stamler et al. compared the effects of a multiple intervention, which encouraged loss of weight and restriction of salt and alcohol, with no intervention to support drug withdrawal; it defined normotension as diastolic blood pressure less than 90 mmHg [522]. This study was combined in a meta-analysis with a similar comparison of two arms of the TONE study of obese patients: a comparison of the combination of weight loss and salt restriction with no intervention. Patients who received a multi-factorial intervention were more likely to successfully stop medication than those who were not (RR = 2.8, 95%CI: 1.9 - 4.0) and these interventions appeared to be more successful than those which addressed only diet or only salt restriction (see Figure 31). Combining all groups in these three studies [519,520,522], 42% of patients who received interventions remained normotensive for at least

a year, compared to only 25% in the control groups. This is consistent with the evidence (see Lifestyle interventions) that a healthy diet and reduced salt intake can lower blood pressure.

We found little evidence about whether patients became more likely to suffer severe cardiovascular events if antihypertensive medication was withdrawn. One study monitored cardiovascular events for 12-32 (average 24) months after withdrawal of medication from 975 patients who had a mean BP of 129/72 mmHg while on one antihypertensive medication [535]. It found no difference between the rate of cardiovascular events before and after withdrawal of medication, though the statistical power to detect a difference was low, largely because of the short period of monitoring while on medication. The best evidence on the possible effects of drug withdrawal is the epidemiological evidence from over a million adults, that any increase in blood pressure is associated with an increased risk of death from cardiovascular disease [19].

If patients become hypertensive after stopping drugs, this is most likely to happen in the first six months, although it can happen later [534]. To avoid this, patients should be carefully followed up and drugs should be withdrawn gradually following manufacturers' guidance.

Figure 31: Meta-analysis of RCTs of lifestyle interventions to support withdrawal of anti-hypertensive drugs



† DerSimonian-Laird risk ratio (RR) for the proportion remaining normotensive

o – obese, no – non obese

	Weight loss diet				Salt restriction				Multiple intervention			
	RR	95% CI	Heterogenity p	Report bias, p	RR	95%CI	Heterogenity p	Report bias, p	RR	95%CI	Heterogenity p	Report bias, p
	1.65	(1.36 to 2.00)	0.77	n/a	1.41	(1.21 to 1.65)	0.36	0.62	2.75	(1.92 to 3.97)	0.86	n/a

Patients' perspectives

- Listening to patients' views about the pros and cons of treatment for hypertension, involving patients in each stage of the management of their condition, and providing clearly written supportive information are good clinical practice. III

A recently published survey which examined the views of 452 hypertensive patients in one urban GP practice illustrates the complexity of feelings surrounding the taking of antihypertensive medications. There was a 77% response rate among patients invited to participate [536]. Four in every five people taking part in the study said they had reservations about taking antihypertensives. Over a third of patients reported experiencing current or previous side effects from blood pressure lowering medication and nearly 40% were concerned by the potential harm caused by the long term use of such drugs. Thirty-six percent of responders wondered if they still needed blood pressure lowering medication and two-thirds would prefer non-drug therapy. The most commonly cited reasons for taking antihypertensive medications were 'to achieve some good results' (92%), 'because of what happens at the doctors' (87%) and 'because it feels reassuring' (68%). Before starting on tablets to treat high blood pressure, patients often weighed the potential benefits against reservations in the context of a personal framework.

Information available on the DIPEx website (www.dipex.org) was summarised and discussed by the guideline development group. The DIPEx web site reflects patients' experiences of serious illness, aiming to share experiences, provide patient friendly information, answer common questions and provide information on relevant organisations and support groups to patients, family and friends, carers and health professionals.

The hypertension module contains transcribed interviews from 40-50 people who have experienced hypertension and can be viewed as transcripts, video or audio clips of individuals, or collated information on specific topics. The modules are produced by an advisory panel of patients, health professionals and social scientists with relevant expertise. Below is a summary of patients' accounts of discovery, treatment and living with hypertension.

Discovering hypertension

The route to diagnosis of hypertension was varied, with some patients detected during routine screening whilst others were identified after a specific event, for example a transient ischaemic attack (TIA), or following a consultation for a specific problem, for example dizziness or chest pain. Many patients perceived stress as a major causative factor, even to the extent that they would blame stresses in their lives of which they had previously been unaware. Other factors which they linked to hypertension were family history, genetic make-up, race, personality traits and specific habits such as alcohol consumption, smoking and salt intake. Patients reported a degree of frustration when they had eliminated factors they believed to contribute to their hypertension only to find that their blood pressure remained unchanged.

Many of those interviewed felt that they had not been given sufficient information regarding the cause of their hypertension. Attitudes were influenced by patients' background knowledge about hypertension and whether they were asymptomatic at diagnosis. Some patients exhibited a positive attitude, feeling that detection gave them the opportunity to modify their lifestyle and for their hypertension to be monitored and treated to prevent long term disease. Others felt that their hypertension might have been detected earlier if doctors had been more vigilant.

Treatment

Patients voiced a great deal of concern over the issue of long term medication, highlighting potential side effects and the cost and need for regular prescriptions as major worries. Many patients reported no problems with antihypertensive drugs, but others had experienced a variety of side effects. Patients were most concerned about taking beta-blockers and these were perceived as having a higher side effect profile. ACE-inhibitors and calcium-channel blockers were more favoured. Some patients found it difficult to accept side effects of blood pressure lowering medication when they were asymptomatic. In particular, drugs which led to impotence were considered unacceptable. Compliance to medication was also an issue, and many reported that they found it difficult to remember to take tablets. Some patients accepted that taking tablets was just part of everyday life, whilst others felt it to be a constant reminder of living with disease. Patients often felt under pressure from family members or health care professionals to be compliant and selecting the right combination of tablets often led to anxiety as patients were changed from one medication to another. In attempts to avoid or delay drug therapy, a proportion of patients wanted to try lifestyle measures or complementary therapies as an initial alternative to blood pressure lowering drugs.

Living with hypertension

Many patients were unsure of what it meant to have a diagnosis of hypertension - how serious was it? The increased risk of stroke and heart disease led some to focus on personal mortality, and to worry about dependants or financial issues if such events were to occur. Some patients reported that nothing really changed whilst others now viewed themselves as unhealthy or even experienced denial.

Patients were anxious as they found it difficult to regulate their behaviour, particularly as they did not have changing symptoms, so as not to further increase their risks of cardiovascular disease. Others reported symptoms that they thought were related to hypertension such as headache, dizziness and visual problems. Often side effects of tablets were attributed to disease.

Most patients made some attempt to incorporate lifestyle changes, such as restricting salt intake, increasing exercise and reducing stress. Patients often felt they wanted advice from health care professionals to avoid 'self-harm' and reported feelings of guilt and frustration if targets were not achieved. In general, patients welcomed information provided by general practitioners; some felt doctors did not provide enough information and looked for other sources such as the web, media or

medical magazines. Others felt doctors pitched information - both the amount and content - at just the right level. A minority of patients felt that the greater their understanding about high blood pressure, the more that they had to worry about. Other patients found that people's accounts of living with hypertension were a valuable source of reassurance; however, they acknowledged that speaking openly about this was often difficult. Some expressed the view that having hypertension was a very private issue, rarely discussed, but felt that talking did provide much needed support and welcomed sites such as DIPEx as a forum in which to share their experiences.

Education and adherence

Compliance with Prescribed Antihypertensive Medication

- A meta-analysis found that patients adhered to once daily blood pressure lowering regimens better than to regimens requiring two or more doses a day (91% vs. 83%). Similarly, once daily regimens were better adhered to than twice daily regimens (93% vs. 87%)	I
- Listening to patients' views about the pros and cons of treatment for hypertension, involving patients in each stage of the management of their condition, and providing clearly written supportive information are good clinical practice.	III

It is estimated that between 50-80% of patients with hypertension do not take all of their prescribed medication [537,538]. This has implications for the successful management of hypertension with poor adherence to medications linked to inadequately controlled blood pressure [539]. Understanding patient's reasons for not taking medications and implementing effective strategies to overcome barriers to taking prescribed medication is therefore a crucial aspect in the management of hypertension.

Compliance is used variably as a term within the literature, referring sometimes to the constant neglect of treatment [540, 541] and sometimes to a range of behaviours including delay in dosing, skipping a dose, longer lapses in dosing and over compliance when extra doses are taken [542]. It has been argued that recognizing these differences in compliance patterns is valuable in working with patients on improving their adherence to prescribed drug regimens [542]. Compliance has also been challenged as a concept because of its implied paternalism and failure to see patients as active, intentional and responsible participants in their health care management [540, 541]. Increasingly the term concordance is used within the literature, implying a more interactive and participatory approach to drug prescribing [538].

Not only is it important that drug regimens are adhered to in order to control blood pressure but it has also been suggested that partial compliance and erratic patterns of dosing may do more transient harm than any overall beneficial effect of treatment [543]. For example abrupt discontinuation of medications may lead to rebound hypertension with elevated blood pressure. Variability in blood pressure caused by abrupt changes in drug taking patterns has been linked to certain kinds of target organ damage such as pulmonary congestion and a consequent deterioration of congestive heart

failure [543]. Therefore strategies to improve adherence also need to address the need to maintain regular and consistent patterns of drug usage.

There are many factors that influence patients' decisions not to take their drugs as prescribed [544,545]. Factors most pertinent for patients suffering from hypertension include the asymptomatic nature of the disease. A condition without symptoms combined with the possibly unpleasant side effects of treatment may contribute to a patient's decision to stop or reduce their medication [546]. The long term nature of the treatment is also a factor that can lead to poorer compliance. Drug complexity, poor instructions, poor provider-patient relationships and patient's disagreement about their need for treatment may also serve as a reason for non-adherence to drug regimens [544].

A wide range of interventions have been developed to try and help patients follow their prescribed drug regimens. These have included simplified dosing, educational interventions, telephone and computer assisted monitoring, family interventions, increased convenience of care with provision of care at the work site, and a team approach with increased involvement of a community nurse and/or a community pharmacist [538,544].

Two systematic reviews have sought to assess the effectiveness of these interventions [544,547]. One looked specifically at the relationship between daily dose frequency and adherence to antihypertensive medication [547]. In a meta-analysis of data from 8 studies it was found that the average adherence rate was significantly higher for patients with once daily dosing compared taking those taking multiple daily doses (91% vs. 83%). Adherence rates were also significantly higher for patients taking once daily doses compared with twice daily doses (93% vs. 87%). The difference in adherence rates between twice daily and multiple daily dosing was not significant. Simplifying dosing regimens to once daily use appears to promote compliance. However it is insufficient on its own to result in adequate compliance and the medical consequences may be graver for patients failing to adhere to once daily regimens, since missing one dose will result in missing the total daily dose.

A narrative review of a wide range of interventions designed to increase compliance with prescribed drug regimens across a range of chronic disease entities found that half were associated with a statistically significant increase in medication adherence but that many were too small to show an effect. However they concluded that even the most effective interventions did not lead to large improvements in adherence and treatment outcomes [544].

Whilst they may not result in large improvements in adherence to prescribed drug treatments it would appear that improving patient education, providing counselling, involving families and other members of the health care team can all have a positive impact. Qualitative research methods have also contributed to an understanding of how patients weigh up their reservations about treatment against different reasons for taking treatment: this involves positive experiences with doctors, perceived benefits of medication and pragmatic considerations [545]. Patients will balance reservations and reasons differently. Greater adherence to drug treatment might be achieved if health care professionals asked patients how they perceived the advantages and disadvantages of taking

medication and listened to their reservations, their reasons for taking medication and the balance between the two.

Implementing lifestyle measures

Lifestyle interventions such as weight reducing diets, lowering salt intake, exercise, alcohol reduction and relaxation therapy can reduce blood pressure and it is recommended that patients are given advice to promote such lifestyle changes. However, it is recognised that lifestyle changes are difficult to adopt and their effectiveness is often limited. The concept of compliance has now evolved to encompass 'an active, intentional and responsible process whereby patients work to maintain their health in collaboration with health care personnel' rather than simply patients' adherence to instructions [541]. Many factors are thought to influence adherence including age, sex, education, understanding and disease perspectives, the mode of delivering advice and the type of health system [548]. Adherence may be improved by good communication between patients and health professionals addressing knowledge about disease, active involvement of patients in decisions, setting achievable goals and good family and community support [541,548,549].

Adherence with lifestyle modifications, especially dietary changes, is lower than with antihypertensive drug therapy by between 13% and 76% [550]. Few studies specifically address this issue and most research on adherence to lifestyle advice examines strategies to reduce cardiovascular risk. Important issues to consider are the characteristics of the 'information provider', the 'information receiver', the 'information itself' and the dissemination strategy.

Who should give it?

In many instances, lifestyle advice is given by nurses who manage clinics for the secondary prevention of coronary heart disease. These nurse-led initiatives have been shown to be effective at modifying lifestyle behaviours, reducing blood pressure, monitoring medication and ultimately in reducing mortality [551,552]. The regular follow-up provided by these clinics may help compliance [549]. The Department of Health has provided guidance for general practitioners and practice nurses who wish to refer patients to facilities such as leisure centres or gyms for supervised exercise programmes [553].

How should it be given?

Advice alone is less effective than specifically adapted programmes supported by written and audiovisual material [550,554]. Material tailored to meet the educational and cultural needs of the population it is targeting has also been shown to be effective [555].

Who should receive it?

Targeting of advice to higher risk populations is thought to be more clinically and cost effective. A systematic review of 18 trials examining the effects of multiple risk factor interventions (stopping smoking, exercise, dietary control, weight control, antihypertensive drugs and cholesterol lowering drugs) in the primary prevention of coronary heart disease in middle aged adults showed little overall effect on mortality. However, it was noted that hypertensive 'high risk' patients were more likely to benefit from counselling, education and effective drugs and thus targeting health education to this group might be of some value [556].

What are the most successful strategies for information delivery?

A review of 46 studies on compliance with drug therapy and lifestyle modifications in cardiovascular risk reduction identified the following effective strategies; behavioural skill training, self monitoring, telephone/mail contact, self-efficacy enhancement and external cognitive aids [549]. A review of compliance with low salt diets suggested that successful interventions require specific goals, delegation of responsibilities, in-depth patient assessment, behavioural motivation, implementation plans, repetitive education and extensive monitoring [557]. Delivering programmes through specific channels, for example community based projects may increase effectiveness [549].

Audit points

It is beyond the scope of the work of the guideline development group to develop and validate an audit template for the management of essential hypertension in primary care. There are two sets of criteria that may be helpful when developing an audit: terms developed by MIQUEST and quality criteria provided as part of the new GMS contract.

MIQUEST

Funded by the NHS Information Authority, MIQUEST is the recommended method of expressing queries and extracting data from different types of practice systems. The following series of audit questions are based on a MIQUEST enquiry routinely implemented by some general practices.

1. Number of patients with (and practice prevalence of) persistent raised blood pressure
2. Proportion of patients in (1) with a previously completed cardiovascular risk assessment
3. Proportion of patients in (1) given lifestyle advice in the last year including (as appropriate) smoking cessation, diet and exercise
4. Proportion of patients in (1) prescribed a thiazide in the last 6 months
5. Proportion of patients in (1) prescribed a beta-blocker in the last 6 months
6. Proportion of patients in (1) prescribed an ACE-inhibitor in the last 6 months
7. Proportion of patients in (1) prescribed a calcium-channel blocker in the last 6 months
8. Proportion of patients in (1) prescribed an angiotensin receptor blocker in the last 6 months
9. Proportion of patients in (1) prescribed another antihypertensive drug in the last 6 months
10. Proportion of patients in (1) prescribed no medication in the last 6 months
11. Proportion of patients in (10) recorded as declining medication
12. Proportion of patients in (1) prescribed aspirin in the last 6 months
13. Proportion of patients in (1) prescribed an alternative antiplatelet in the last 6 months
14. Proportion of patients in (1) prescribed a statin in the last 6 months
13. Proportion of patients in (1) prescribed an alternative lipid reducing agent in the last 6 months
14. Proportion of patients in (1) with latest systolic BP reading less than or equal to 140 mmHg
15. Proportion of patients in (1) with latest diastolic BP reading less than or equal to 80 mmHg
16. Proportion of patients in (1) with latest systolic BP reading less than or equal to 140 mmHg and diastolic BP reading less than or equal to 80 mmHg
17. Proportion of patients in (1) without a blood pressure reading in the last year.

GMS Contract Quality Indicators

The new GMS contract sets quality indicators for hypertension (See Table 35) [558]. These indicators provide targets for the management of patients but no rationale is provided for the thresholds. For example, research is needed to usefully inform whether 90% of patients with hypertension in primary care could appropriately achieve 150/90 mmHg or whether comorbidity, co-medication and informed choice are such that a lower threshold is necessary. The 9 month time window for assessing blood pressure implies that patients should be checked at six monthly intervals (the 9 month period presumably allowing for a margin of error). This is consistent with the advice for patients over 75 years of age receiving 4 or more medications found in the National Service Framework for Older People [ii]. The guideline group in discussing the review interval thought that there would be individual circumstances when six months was appropriate, but that the routine management of patients with controlled hypertension should involve annual review. This is consistent with National Service Framework advice for Coronary Heart Disease which requires annual audit data [i]. Curiously other GMS quality markers imply annual review (15 month window) for patients receiving care for the secondary prevention of coronary heart disease, stroke or heart failure. It is unclear why hypertension has been singled out for special attention in these linked GMS contract quality indicators.

Table 35: GMS contract quality indicators for hypertension

Indicator (All minimum thresholds are 25%)	**Points**	**Maximum threshold**
Records		
BP 1 The practice can produce a register of patients with established Hypertension	9	
Diagnosis and initial management		
BP 2 The percentage of patients with hypertension whose notes record smoking status at least once	10	90%
BP 3 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		
BP 4 The percentage of patients with hypertension in which there is a record of the blood pressure in the past 9 months	20	90%
BP 5 The percentage of patients with hypertension in whom the last blood pressure (measured in last 9 months) is 150/90 or less	56	70%

Research questions

- **The role of ambulatory and home blood pressure monitoring devices in improving patient care and health outcomes. The consequences for resource use (reflecting equipment purchase, maintenance, recalibration, staff, training and medication costs), patient participation in treatment and quality of life. The appropriate use of these devices either as a routine strategy or in self-selecting patients.**

- **The long-term value of table salt substitutes in lowering blood pressure.**

- **The long-term value of pragmatic multifaceted life-style interventions that could be supported by the NHS and other government agencies, including diet, exercise and relaxation.**

- **The validity of cardiovascular risk prediction models in British patient populations, particularly in young people and in ethnic minority groups.**

- **The presentation of individual benefits and risks of treatment to patients.**

- **The influence of class of drug on morbidity and mortality in different age and ethnic groups.**

- **The relationship between thiazide diuretic/beta-blocker co-treatment and new onset diabetes. Whether all patients are at increased risk or specific high risk groups.**

- **Determinants of current patterns of care and use of antihypertensive drugs. Methods to improve uptake where it is shown to be sub-optimal.**

References (Evidence)

- Methodological references are found on page 38
- References to previously published guidelines are found on page 196

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⌘ Appendices

Appendix 1: Describing the results of trials

Binary outcomes

A binary outcome provides two possibilities, for example: alive or dead; still on treatment or withdrawn from treatment. Binary data may be summarised in several ways in clinical studies. These are primarily odds ratios, risk ratios (also known as relative risks) and risk differences. Binary data from a comparative trial can be shown in a two by two table, e.g.

	Dead	Alive
Intervention Group	A	B
Control	C	D

Odds ratios are defined as: $\frac{A}{B} \Big/ \frac{C}{D}$

In other words, the odds ratio is the odds of death in the intervention group (number of deaths divided by the number of survivors) divided by the odds of death in the control group.

Risk Ratios are defined as: $\frac{A}{A+B} \Big/ \frac{C}{C+D}$

The risk ratio is the proportion of deaths in the intervention group (number of deaths in the intervention group divided by the total number allocated to the intervention) divided by the proportion of deaths in the control group. Trials sometimes refer to relative risk reductions (RRRs) which are calculated as one minus the Risk Ratio.

Risk Differences are defined as: $\frac{A}{A+B} - \frac{C}{C+D}$

The Risk Difference is the proportion of deaths in the intervention group (number of deaths in the intervention group divided by the total number allocated to the intervention) minus the proportion of deaths in the control group.

Worked Example:

In a trial of an ACE-inhibitor in patients with heart failure there were 452 deaths among 1285 patients randomised to receive enalapril, and 510 deaths among 1284 allocated to control after an average follow-up of 4.5 years [I]. Shown in a two by two table this is:

SOLVD trial	Dead	Alive
Intervention Group	452	833
Control	510	774

Using the formulae provides an odds ratio of 0.82, a risk ratio of 0.89, and a risk difference of -0.045 (or a 4.5% reduction in the risk of death).

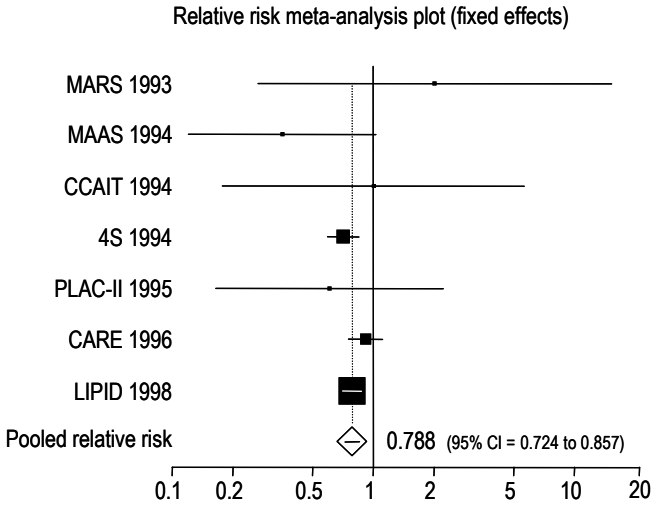
Each measure has advantages and disadvantages. The Odds Ratio is a statistically robust measure, but is hard to interpret clinically. The Risk Ratio is superficially easier to interpret, and both odds ratios and risk ratios may be particularly useful when attempting to combine studies which are estimating the same common underlying effect, but in which both severity of condition and length of follow up may vary. Neither measure is sufficient for clinical decision making alone: an odds ratio or risk ratio apparently showing a large effect from an intervention will not lead to large benefits in practice where the events are rare, and an apparently small relative effect may have a substantial impact where events are very common.

Risk Differences are not very helpful for exploring common underlying effects, but are very useful for describing the practical importance of the effects of treatment. Similarly, Number Needed to Treat (NNT) is used to describe absolute benefits (NNT is the inverse of the risk difference: 1/0.045 or 22 in our example). It expresses the number of patients who would have to receive the intervention for one patient to receive (or avoid) the outcome described in a trial. A main advantage of the risk difference is that it expresses the practical value of interventions. However, a standard problem for risk differences and numbers needed to treat is that they are often derived from trials that have different lengths of follow up. The risk difference tends to become bigger as follow-up increases. Thus the incidence risk difference is used to estimate treatment effects using a common time frame, for example the number of deaths avoided as a result of treating 100 patients for a year [II].

Trials enrol a sample from the population of all patients and estimate the effect of treatments. These estimates have a degree of uncertainty which becomes less the bigger the sample size. A Confidence Interval (CI) for a treatment effect estimated in a trial is the range in which the actual population treatment effect is assumed to lie, with a specified probability. The specified probability is arbitrary: 95% is the most commonly chosen value, meaning that the true underlying treatment effect is assumed to lie within the range 19 times out of 20. The smaller the confidence interval, the greater the precision of measurement in the study. More precise confidence intervals are achieved, all things being equal, by studies which enrol more patients. The best and most likely estimate of effect is the point estimate in the middle of the confidence interval range. For our example the best estimate was that after nearly 5 years of treatment, an ACE-inhibitor achieved a 4.5% reduction in the risk of death with a 95% confidence interval of 0.8% to 8.3%.

Meta-analysis of binary data

Commonly more than one trial exists to inform the value of a particular treatment. Where studies feature similar designs and use adequately similar outcomes it is possible to combine these to obtain an overall estimate of effect. This statistical process, called meta-analysis, involves taking a weighted average of the results of trials, where the most informative trials (biggest and with most events) contribute most to the overall result. Figures called forest plots are often used to display the findings of meta-analyses. The example below shows a meta-analysis of the results of trials of statin therapy following a myocardial infarction to reduce the risk of subsequent mortality. The finding from each trial is shown as a mark on a graph with a line showing its confidence interval. In this instance the mark used is a box, the size of which indicates how important the trial is to the combined, or pooled, result. The pooled finding is shown (in the example as a lozenge) after the individual studies and indicates a relative risk of death of 0.79 or 79% for patients receiving a statin when compared to those receiving placebo. Alternatively this may be expressed as a 21% relative reduction in the risk of death. The 95% confidence indicates, 19 times out of 20, that the true effect of the drug will lie between a relative risk of 72% and 86%: this range excludes the line of no effect or no change (one). The advantage of meta analysis is that it provides the most precise guess at the effect of treatment reflecting all available studies. However, if the studies themselves have limitations or differ in important ways, then meta analysis can be misleading.



Meta-analysis of continuous data

Many outcomes, such as blood pressure readings and pain or symptom scores, are not binary but continuous (or nearly so). With continuous data, the mean scores for treatment and control groups in each trial are subtracted to calculate a mean difference (for example a reduction in blood pressure) and confidence intervals for this change are calculated using standard formulae that reflect the spread of the data (referred to as the standard deviation). Where studies use a common continuous outcome

measure, meta-analysis can combine these to calculate a summary weighted mean difference comparing treatment and control groups.

For continuous data, either the final value of the outcome or the change between baseline and endpoint can be used in a meta-analysis. The analysis in this guideline uses blood pressure at the end of the treatment and control periods, rather than the change in blood pressure over the course of the trial. The final value - but not the change score - leads to an unbiased estimate of the treatment effect in parallel trials [III], and secondly because the final value is likely to yield a more precise estimate of the treatment effect in crossover trials [IV].

Dichotomising data that are naturally continuous (for example into treatment failures and successes) is not generally advisable. It is often arbitrary, may result in pooling scores based on different cut-offs in different studies or cut-offs that have been identified with knowledge of the data and thus show the data in a particular light. Dichotomisation may exaggerate small differences in effect and, more fundamentally, the approach removes much information from the original data.

Standardisation

When there are concerns that measurement between studies is not undertaken using a common metric, standardised mean differences can be calculated for each trial. Examples might be where different but related measures are used to estimate the same outcome in patients, or where it is likely that measures are used inconsistently by different investigators. Standardisation is achieved by dividing mean differences from studies by their standard deviation [V,VI]. Standardised weighted mean differences are difficult to interpret but can be worked back to a value on an original physical scale.

Studies examining different doses

Sometimes trials examine multiple dose regimens compared with a single control group. These trials are often conducted early during product development, are designed to determine the most appropriate dosage of a drug and may include groups receiving doses both within and outside the range ultimately licensed. It is important that such comparisons are not considered separately in the analyses, since they share a single control group and the resulting confidence intervals will be inappropriately narrow. In order to include all relevant information without undue statistical precision, an average effect is estimated for the range of therapeutic doses available.

Naturalistic studies

Double-blind randomised trials are occasionally criticised for inadequately representing treatment in the real world. In other words, trials that use a well defined population without co-morbidity, limit treatment options and make both the doctor and patient blind to the treatment received may provide

different results from those realised in practice. The evaluation of pharmaceuticals is best undertaken using a series of experimental studies. This is reflected in phase II and III studies (small-scale dose ranging through to larger trials, often for licensing). Studies in phase IV may relax some of the requirements of the earlier trials in order to better reflect the real world: these may include relaxation of blinding, allowing clinical strategies such as choice of drug after initial randomisation and co-morbidity. Such studies have been described as 'contaminated with the real world' [VII] and it may be difficult to work out what is being estimated (particularly with, say, strong patient or doctor preferences for one treatment). However, when examined with the earlier phase III trials, they may add useful information.

Meta-regression Analysis

Where a number of trials examine the same underlying question, more complex techniques may be used to understand trial evidence. Regression models can explore whether the size of benefit from treatments varies with certain factors such as age or the presence of other diseases [VIII].

References (Appendix 1)

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Appendix 2: A review of recent major guidelines

Important contributions come from a number of nationally and internationally recognised guidelines. Eight guidelines written in English and passing set methodological criteria identified by the German Guideline Clearing House [I], were included in this analysis. Two more recently published guidelines from the European Society of Hypertension and the Scottish Intercollegiate Guidelines Network have also been incorporated (see Table 36). In this section their content and methodology are described and similarities and differences are identified.

Table 36: Recent major guidelines for hypertension

Organisation	Publication Year	Acronym	Reference
New Zealand Guideline Group	1994	NZ	[II]
Veterans Health Administration (US)	1999	VHA	[III]
British Hypertension Society	1999	BHS	[IV]
Canadian Medical Association	1999	CMA	[V,VI]
World Health Organisation-International Society of Hypertension	1999	WHO	[VII]
Hypertension Society of South Africa	2000	SA	[VIII]
Scottish Intercollegiate Guidelines Network	2001	SIGN	[IX]
Institute for Clinical Systems Improvement (US)	2003	ICSI	[X]
Joint National Committee VII (US)	2003	JNC	[XI]
European Society of Hypertension	2003	ESH	[XII]

Patient assessment

All of the guidelines listed advocate undergoing a thorough initial medical history and physical examination, including weight, height and body mass index as well as questions about lifestyle. Blood pressure measurement alone is argued to be insufficient for diagnosis and subsequent treatment. A series of standardized blood pressure measurements taken over a number of visits is recommended, although there are differences in details (Table 37).

Table 37: Initial assessment of blood pressure in previously published guidelines

Guideline	Initial BP Measurement
NZ	2 per visit; 2 visits
VHA	2 per visit; 2 visits
BHS	2 per visit; 4 visits
CMA	2 per visit; 4 visits over 6 months.
WHO	Multiple measurements on several occasions
SA	2 per visit; 3 visits over 2 months.
SIGN	2 per visit; 3 visits. Also refers reader to BHS.
ICSI	2 per visit; 3 visits
JNC	2 or more measurements.
ESH	Multiple BP measurements on separate occasions

For example the BHS guideline recommends measurements over a 6 month period to establish a diagnosis in patients with mild hypertension, but JNC recommends confirmation over only 2 months.

Similarly, details on how to follow-up patients varied between guidelines (Table 38). Measurement standards and device calibration are recognized as essential: recommendations by the BHS, ESH and JNC guidelines.

Table 38: Follow-up assessment of blood pressure in previously published guidelines

Guideline	BP Threshold and Follow up periods					Frequency of follow-up once stabilised on drugs
NZ		2-5 years depending on CV risk/age				6 months
VHA		<130/<85: 2 years	130-139/85-89: 1 year	140-159/90-99: 2 months		1 month
BHS		<135/85: 5 years	135-159/85-99: 1 year	>160/100: 3 months		6 months
CMA		Non-drug treatment: 3-6 months	Drug treatment: monthly until stable			3-6 months
WHO		Low risk; 140-159/90: 6 months	Medium Risk; <160/179: 3 months	High risk; >180/110: treat		
SA		Lifestyle advice 6-12 months	Target organ damage/CVD/>140/90: 2 months			
SIGN	<130/85: 2-5 years	130-139/85-89: Lifestyle advice 1 year	140-159/90-99 Lifestyle advice 2 months	160-179/100-109 1 month	>180/110 1 day	3-6 months
ICSI		<130/<85: 2 years	130-139/85-89: 1 year	140-159/90-99: 2 months		1 month
JNC		<130/<85: 2 years	130-139/85-89: 1 year	140-159/90-99: 2 months		3-6 months
ESH		No guidance	130-139/85-89: follow up depends on other risk factors	140-179/90-109: 3-12 months		6 months (or more if necessary)

Definitions of hypertension and cardiovascular risk

All of the guidelines recognised that raised blood pressure is only one contributor to raised cardiovascular risk. Treatment advice should be influenced by overall cardiovascular risk and begin with the most appropriate risk factor. However, guidelines commonly had a higher threshold of blood pressure where treatment was recommended regardless of cardiovascular risk.

Thresholds for treating raised blood pressure are particularly important. As a threshold is lowered the proportion of the population identified as requiring treatment and subsequent cost increases dramatically while the size of benefits of treatment diminishes [XIII]. The issues are evident in the relative reluctance of clinicians to implement recommendations to treat borderline or mild hypertension [XIV]. Thresholds for defining hypertension found in guidelines are shown in Table 39.

Table 39: Categorisation of hypertension in previously published guidelines

	Optimal	Normal	High Normal	Border-line	Hypertension Stage or Grade		
					1 (Mild)	2 (Moderate)	3 (Severe)
NZ					150-170/90-100		
VHA	≤120/≤80	≤130/≤80	130-139/ 85-89		140-159/ 90-99	160-179/ 100-109	≥180/ ≥110
BHS		<135/85	135-139/85-89		140-159/ 90-99	160-199 100-109	≥200/ ≥110
CMA	<140/90				90-100 *	>100 *	
WHO	<120/80	<130/85	135-139/85-89	140-149/90-94	140-159/ 90-99	160-179/ 100-109	≥180/ ≥110
SA	<120/80	<130/85	135-139/85-89		140-159/ 90-99		≥180/ ≥110
SIGN		<140/90			140-159/ 90-99	160-179/ 100-109	≥ 180/ ≥110
ICSI	<120/<80	<130/<85	130-139/85-89		140-159/ 90-99	160-179/ 100-109	≥180/ ≥110
JNC	<120/80	<130/85	130-139/85-89		140-159/ 90-99	160-179 100-109	≥180/ ≥110
ESH	<120/80	120-129/ 80-84	130-139/85-89		140-159/ 90-99	160-179/ 100-109	≥ 180/ ≥110

*Diastolic value used only, patients over 60 have different values

The consensus from published guidelines is that hypertension is defined at a level of 140/90 mmHg or above. Each guideline used blood pressure level or grade variously with other factors to assess cardiovascular risk. These assessments varied in complexity but included the presence of existing cardiovascular disease, target organ damage, diabetes, age, smoking, gender, body mass index, serum lipid level, and family history. Different guidelines used different assessment methods and took different thresholds for treatment.

Special populations

Common conditions, for example coronary heart disease and diabetes, were generally covered by existing guidelines. However reference to less common conditions or patients with co-existing medical conditions, for example contraception, continuous obstructive pulmonary disease, elderly patients and children, was more variable (Table 40).

Table 40: Recommendations concerning special populations in previously published guidelines

	VHA 1999	BHS 1999	CMA 1999	WHO 1999	SA 2000	SIGN 2001	ICSI 2003	JNC 2003	ESH 2003
Coronary heart disease	*		*	*	*	*	*	*	*
Cardiac failure	*		*	*	*	*	*	*	*
Cerebrovascular disease				*	*	*		*	*
Peripheral vascular disease	*		*		*		*	*	
Isolated systolic hypertension	*				*				
Diabetes	*	*	*	*	*	*	*	*	*
Renal disease	*	*	*	*		*	*	*	*
Renovascular disease						*	*	*	
Asthma and COAD	*		*				*	*	
Dyslipidaemia	*		*				*	*	
Gout	*		*				*	*	
Depression	*						*		
Benign prostatic hyperplasia	*								
HRT		*						*	
Elderly	>60	>60	>80	>60		>80†	*	>60	*
Children and adolescents								*	
Pregnancy	*	*		*	*		*	*	*
Oral contraception								*	
Ethnic group	*	*		*				*	
Sleep apnoea								*	
Migraine							*		
Raynaud's disease							*		
Wolf-Parkinson-White syndrome							*		
Liver disease							*		

† The SIGN guideline applies only to people over 60 years of age and defines the over 80s as a special group.

Non-pharmacological recommendations

All of the guidelines addressed lifestyle modification as an integral part of the management of hypertension and as a first line treatment in some milder forms of the condition. Weight modification, limiting alcohol and sodium intake, regular exercise and smoking cessation were discussed by all guidelines (Table 41). There was less consistency about addressing other areas: dietary potassium, magnesium and calcium; dietary modification; and management of stress. The Canadian guideline suggested legislative changes that would enable healthier lifestyle choices to be easier.

Table 41: Recommendations for non-pharmacological interventions in previously published guidelines

	NZ 1994	VHA 1999	BHS 1999	CMA 1999	WHO 1999	SA 2000	SIGN 2001	ICSI 2003	JNC 2003	EHS 2003
Weight Reduction	*	*	*	*	*	*	*	*	*	*
Salt restriction	*	*	*	*	*	*	*	*	*	*
Alcohol restriction	*	*	*	*	*	*	*	*	*	*
Smoking cessation	*	*	*	*	*	*	*	*	*	*
Exercise	*	*	*	*	*	*	*	*	*	*
Diet	*	*	*		*	*	*	*	*	*
Calcium										
Potassium			*	*	*				*	*
Magnesium										
Relaxation/stress management				†	†				†	

† discussed, but no recommendation was made

However, the apparent similarity of coverage conceals differences in the advice given to help inform clinical decisions (Table 42).

Weight reduction

All of the guidelines recommended weight loss in the overweight as an effective strategy in reducing blood pressure. Three (NZ, BHS, SIGN) were non-prescriptive in the amount of weight loss they recommended. Three recommended an initial weight loss of around 5 kg (CMA, WHO, ICSI), while four gave targets based on individual body weight (US VHA, JNC, SA, SIGN). Two of the guidelines gave differing estimates of the benefit weight reduction may have upon blood pressure (BHS, JNC).

Salt Restriction

All of the guidelines recommended that hypertensive patients should limit salt intake. In seven of the guidelines (VHA, BHS, CMA, WHO, SIGN, ICSI, JNC,) specific recommendations were given regarding the maximum daily amount. While two simply recommended it be reduced (NZ, SA), eight guidelines gave practical suggestions on how this recommendation might be implemented (BHS, CMA, ISCI, WHO, SA, SIGN, JNC, ESH). Two offered no suggestions on how salt reduction might be achieved (NZ, VHA). Six guidelines (BHS, CMA, WHO, SIGN, ICSI) offered differing estimates, in the range 2-10/2.4-5 mm Hg, of the potential benefit salt reduction could have on blood pressure.

Alcohol restriction

Nine guidelines (JNC, VHA, BHS, CMA, WHO, SA, SIGN, ISCI, ESH) quantified the recommended daily or weekly intake of alcohol for hypertensive patients. In four this was expressed as an amount of ethanol. Three (SA, NZ, CMA) described ‘standard drinks’. These terms may be difficult to incorporate into the clinical setting without interpretation. The JNC guideline estimated that limiting alcohol consumption can lower systolic blood pressure by 2-4 mm Hg.

Table 42: Detailed recommendations for non-pharmacological interventions in previously published guidelines.

	Weight reduction	Salt restriction	Alcohol restriction	Smoking cessation	Exercise	Diet	Potassium	Relaxation/stress management
NZ '94	Excess weight loss advised	Restrict salt	Less than 3 standard drinks per day	yes	Regular moderate exercise	Reduce saturated fat and increase fruit, vegetable and cereal consumption		
VHA '99	Reduce weight to within 10% of their ideal body weight	Limit to 6g (2.4 g Na)/ day	1 oz/day for men, 0.5 oz/day for women and lighter men	yes	30-45 mins aerobic exercise 3-5 times/week	Adequate intake of K, Ca and Mg from fresh fruits and vegetables. Low saturated fats and increase in cereals		
BHS '99	Weight reduction advised Can reduce BP by 2.5/ 1.5 mmHg/ kg lost	Lower salt to 5g/day. Salt reduction from an average of 10 g to 5g/day lowers BP by about 5/3 mm Hg	Men: ≤ 21 units/week, women ≤14 units/week	yes	Dynamic exercise ≥3 times/week	Diet rich in fruit and veg: 2-7 portions daily lowers BP by 7/3 mmHg. Together with low saturated fat may lower BP by 11/6 mmHg	Referred to under diet	
CMA '99	Attain and maintain a BMI of 20-25	Restrict salt, e.g. 3-7g/ day. Decrease of 5 g/day lowers BP by 6/2 mmHg	Less than 3 standard drinks/day, less than 14/9 standard drinks per week for men/women	yes	50-60 mins moderately intense exercise, 3-4 times/week.	No specific recommend-ations	Potassium supplementation above dietary intake of 60 mmol/day not advised	Cognitive behavioural interventions advised for selected patients
WHO '99	Weight loss of at least 5 kg with further increments of 5 kg.	Limit to 6g (5.8 g Na)/ day. Reducing salt by 4.7-5.8 g/day from initial intake of 10.5 g/day reduces SBP by average of 4-6 mmHg	Ethanol: limit to 20-30 g/day for men and 10-20 g/day for women	yes	30-45 mins aerobic exercise 3-4 times/week may lower BP by 4-8 mmHg.	Diet rich in fruit and vegetables, fish and reduced fat intake. Cited trials where BP fell by 11/6 mmHg	Referred to under diet	May help but no evidence to support a recommendation
SA '00	Reduce weight to BMI less than 25.	Restrict salt	≤ 2 standard drinks per day	yes	30 mins moderate aerobic exercise 3-5 times/week.	Diet low in fat, high in fibre, unrefined carbohydrates with adequate fresh fruit and vegetables.		
SIGN '01	Patients with BMI≥25.0 should lose weight. 3-9% weight loss may reduce BP by ~3 mmHg	Limit to <5g/day. Decreasing NaCl intake from 10g to 5g can reduce BP by 5/3 mm Hg	Alcohol intake should be reduced when it exceeds 21 units/week for men and 14 units/week for women	yes	Increase physical activity by taking regular physical exercise. 30-45 mins walking most days can lower BP	Reduce saturated fat and increase fruit and vegetable consumption to 5 portions/day		
ICSI '03	10 pound reduction in weight can lower BP in the overweight	Limit to 2.3g daily. Salt restriction can reduce BP by 2.2-10/2.6-5 mm Hg	Ethanol. Men ≤ 1 oz/day, women and lighter men ≤ 0.5 oz/day	yes	30-45 mins aerobic exercise 3-5 times/week	Diet rich in fruit, vegetables, and low-fat dairy foods with reduced saturated and total fats	No evidence that supplementation lowers BP.	No demon-strable effect on BP reduction.
JNC VII '03	Maintain BMI 18.5-24.9. lowers SBP by 5-20 mm Hg/10-kg weight loss	Limit to 6g (2.4 g Na)/ day: lowers SBP by 2-8 mmHg	≤ 2/1 drinks/ day (1 oz or 30 ml ethanol) in most men/ women and lighter-weight men. Lowers SBP by 2-4 mmHg	Not discussed	Moderately intense exercise e.g. 30-45 mins brisk walking most days, may lower BP	Diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat lowers SBP by 2-8 mmHg	Adequate intake (~90 mmol/day) preferably from fresh fruits and vegetables.	Insufficient evidence to support use.
ESH '03	Weight reduction in overweight patients advised.	Reducing salt intake by 4.7-5.8 g/day from initial intake of 10.5 g/day reduces SBP by average of 4-6 mmHg	<20-30 g ethanol/day for men, <10 -20 g ethanol/day for women	yes	30–45 mins aerobic exercise 3-5 times/week. Reduces SBP by 4-8 mmHg.	Diet rich in fruit and vegetables with reduced saturated and total fats. Increase intake of fish.	Eat more potassium containing foods.	

Smoking cessation

The WHO and ESH guidelines described smoking cessation as perhaps the single most powerful lifestyle measure for the prevention of both cardiovascular and non-cardiovascular diseases in hypertensive patients. An exploration of various cessation strategies was made in four of the guidelines (BHS, WHO, VHA, ESH). The CMA guideline addressed smoking at the level of public policy rather than recommendations for individual behaviour change.

Exercise

There was considerable consistency in recommendations to use exercise to help control blood pressure. Most guidelines recommended aerobic exercise of 30-45 minutes 3-5 times a week, although the Canadian guidelines recommended a slightly longer period of exercise. Two guidelines (WHO, ESH) suggested that exercise may lower blood pressure by 4-8 mmHg.

Diet

Eight guidelines recommended a diet with increased fruit, vegetable and unrefined carbohydrate consumption and reduced saturated fats. Two guidelines (BHS, SIGN) attempted to quantify the number of portions of fruit and vegetables intended as an 'increase'. Six (WHO, VHA, BHS, SIGN, JNC, ESH) linked the possible benefits of a diet high in fruit, vegetables and fish with the consequent increase in dietary potassium, or potassium, calcium and magnesium. None of the guidelines recommended any additional supplementation of these minerals. Two guidelines (BHS, WHO) suggested that a suitable diet could achieve a reduction of up to 11/6 mmHg in blood pressure while the JNC estimated a lowering of systolic hypertension by 2-8 mmHg. The CMA guideline recommended that legislative changes be made, for example to improve food labelling, in order to provide a more supportive environment for choosing a healthy diet.

Relaxation/stress management

Three guidelines discussed interventions designed to reduce stress but made no recommendations because of a lack of research evidence to support their effectiveness in treating hypertension (JNC, WHO, ICSI). One recommended individualised cognitive behaviour interventions for patients in whom stress appears to be a factor (CMA).

Pharmacological recommendations

Five major classes of antihypertensive medication were consistently addressed by the guidelines: diuretics; beta-blockers; angiotensin converting enzyme inhibitors; calcium-channel blockers; and alpha-blockers. Recommendations for drug therapy were adjusted according to the presence or

absence of concomitant disease in all of the guidelines. Angiotensin receptor blockers were considered in all but the NZ Guideline.

Usual first line treatment recommendations were to use a low dose diuretic or beta-blocker. Guidance for titration of dose, and substitution or addition of agents was provided although the recommendations varied in content between guidelines, particularly for drug combinations.

Initiation of Drug Therapy

The threshold for initiating drug therapy for patients with less severe hypertension was determined by a range of factors in all of the guidelines. These included: blood pressure, the presence of concomitant disease, target organ damage or other cardiovascular risk factors, the costs of treatment, side effects, response of blood pressure to lifestyle changes and the patient's own personal preferences. Seven of the guidelines (JNC, VHA, ICSI, SA, WHO, ESH, SIGN) used a similar framework for beginning treatment (Table 43).

Table 43: Guidance on initiating drug treatment in previously published guidelines.

BP stages SBP/DBP in mmHg	Risk group A (no risk factors)	Risk Group B (at least 1 risk factor not including diabetes)	Risk Group C (Target organ damage, cardiovascular disease, diabetes)
High normal **130-139/85-89 mmHg**	Lifestyle modification	Lifestyle modification	Drug therapy
Stage 1 **140-159/90-99 mmHg**	Lifestyle modification – up to 12 months* (WHO, SIGN <15% CV risk)	Lifestyle modification – up to 6 months* (WHO: 15-20% CV risk)	Drug therapy (WHO: 20-30% CV risk) (SIGN: ≥20% CV risk)
Stages 2 and 3 **>160/>100 mmHg**	Drug therapy (WHO: 15-30 CV risk & 160-179/100-109: medium risk - monitor before using a drug	Drug therapy (WHO: 15-30%+ CV risk)	Drug therapy (WHO: 20-30%+ CV risk)

* SA guideline: Then drug therapy if needed and as resources permit

Patients with blood pressure readings below 160/100 mmHg were stratified into one of three risk groups based upon cardiovascular risk factors and target organ damage (Table 44). The WHO guideline differed slightly, offering a higher threshold for automatically beginning drug therapy on the basis of a threshold of 180/110 mmHg. It also used a more extensive list of factors that could influence prognosis, and gave absolute risks of major cardiovascular events for the different risk groups based upon data from the Framingham Study. It also described absolute treatment effects (cardiovascular events prevented per 10,000 patient-years) achieved with reductions in systolic/diastolic blood pressure. However, it gave no indication of how this information should be used by patients when making decisions about treatment. The SA guideline made an explicit reference to resource limitations in their recommendations on initiating drug therapy.

Table 44: Classification of risk factors in previously published guidelines

Major Risk Factors	Target Organ Damage / Clinical Cardiovascular Disease
Smoking Dyslipidaemia Diabetes mellitus Aged > 60 years Sex (men and postmenopausal women) Family history of cardiovascular disease (women < 65 years or men < 55 years)	Heart Disease: Left ventricular hypertrophy Angina or prior MI Prior heart failure Stroke or TIA Nephropathy Peripheral arterial disease Retinopathy

The NZ and BHS guidelines recommended the use of a 'Cardiac Risk Assessor', based on the Framingham risk function for estimating risk of coronary heart disease, to inform when to initiate drug treatment. The BHS guidelines recommended this particularly for those with blood pressure 140-159/90-99 mmHg who were at variable risk depending on other risk factors: patients in this range should be offered anti-hypertensive drug treatment if there was any complication of hypertension, target organ damage or diabetes mellitus or the 10-year risk of coronary heart disease was greater 15% despite lifestyle advice. The NZ guideline simply gave an acceptable level of absolute risk of cardiovascular disease (10% in five years) and it recommended that, if non-pharmacological treatment is unsuccessful in achieving this, then drug treatment should be considered. The CMA guideline provided a narrative on drug initiation but unlike other guidelines did not stratify patients into risk groups or assess their overall cardiovascular risk (Table 45).

Table 45: Summary of guidance for drug initiation in the Canadian Guideline

Patient categories				
<60 years DBP ≥90 mmHg	< 60 years DBP ≥100 mmHg	<60 Isolated systolic hypertension >160 mmHg particularly with target organ damage concomitant disease or other cardiovascular risk factor	<60 years BP above 140/90 mmHg Any of target organ damage, diabetes mellitus, renal or cardiovascular disease Other independent cardiovascular risk factors should be taken into account	>60 years ≥160/≥ 105mm Hg
Strongly consider drug therapy	Drug therapy	Drug therapy	Drug therapy	Drug therapy

Use and aim of pharmacological therapy

All guidelines gave recommendations for the therapeutic management of uncomplicated hypertension, describing a range of compelling indications and contraindications for different classes of antihypertensive drugs. Seven guidelines (ICSI, SA, BHS, VHA, SIGN, JNC, NZ) recommended initiating treatment with a low dose thiazide diuretic alone or in combination with a drug from another

class (JNC) or a β-blocker (VHA, SIGN). Two guidelines recommended the use of one drug from a broader range of drug classes for initial therapy; one recommending the use of a thiazide diuretic or β-blocker or ACE-inhibitor (CMA), and two described all major classes of drug as suitable for initial therapy (WHO, ESH) (Table 46). When made, recommendations about the length of time that initial therapy should be monitored before further change ranged from 1-3 months. All of the guidelines, except JNC, recommended that the lowest possible dose of any drug should be used initially and gave options for altering treatment regimes when initial drugs failed to reduce blood pressure to goal or caused intolerable side effects. All guidelines suggested substituting or adding another drug from a different class. Only four (DVA, WHO, ICSI, SIGN) recommended increasing the original drug dose. The BHS and NZ guidelines recommended that the dose of diuretic should not be increased.

Table 46: Use and aim of first-prescribed drugs in previously published guidelines

	Initial drug choice (Age<60, uncomplicated hypertension)	Aim of treatment BP mmHg	1. Initial therapy trial period 2. Action if goal BP not achieved	F/U once stabilized	Drug classes included in guidance
NZ	Low dose thiazide diuretic	120-140/70-80 or lower in the absence of side effects.	1. 3 months 2. Add or change to low dose beta-blocker	6 monthly	Diuretics, Beta-blockers Alpha-blockers ACE-inhibitors Calcium-channel blockers
DVA	Low dose diuretics and beta-blockers	≤140/90	1. No guidance 2. Increase original drug dose, substitute another drug or add another drug	3-6 months	Diuretics, Beta-blockers Alpha-blockers ACE-inhibitors Calcium-channel blockers
BHS	Low dose thiazide diuretic	<140/85	1. 4 weeks 2. Do not increase dose of diuretic. Inadequate response but well tolerated: substitute or add drug from a different class	3-6 months	Diuretics, Beta-blockers α-blockers ACE-inhibitors Calcium-channel blockers
CMA	Low dose thiazide diuretic, beta-blocker or ACE-inhibitor	<140/90	1. No guidance 2. Inadequate response and side effects: substitute drug from a different class Partial response: combination therapy with diuretic and beta-blocker or diuretic and ACE-inhibitor. BP still not controlled: try drugs from different classes	No guidance	Diuretics, Beta-blockers Alpha-blockers ACE-inhibitors Calcium-channel blockers ARBs
WHO	Low dose. All available drug classes are suitable for initial therapy.	<130/85 in young, middle aged or diabetic patients.	1. 3 months 2. No response: substitute drug from different class or a low dose combination, e.g. diuretic and β-blocker, diuretic and ACE-inhibitor; calcium-channel blocker and β-blocker or α-blocker and β-blocker Partial response: increase dose or add low dose of drug from different class or change to low dose combination, e.g. diuretic and β-blocker, diuretic and ACE-inhibitor; calcium-channel blocker and β-blocker or α-blocker and β-blocker	3-6 months	Diuretics, Beta-blockers Alpha-blockers ACE-inhibitors Calcium-channel blockers ARBs
SA	Low dose thiazide diuretic	<140/90	1. 2 months 2. Add low dose diuretic or reserpine (<0.1 mg/d), beta-blocker, ACE-inhibitor, long acting calcium-channel blocker or fixed dose combination	3-6 months.	Diuretics, Beta-blockers Alpha-blockers ACE-inhibitors Calcium-channel blockers ARBs
ICSI	Low dose thiazide diuretics	<140/90	1. No guidance 2. Increase dose of initial drug, substitute or add drug from a different class	At least annually	Diuretics, Beta-blockers ACE-inhibitors Calcium-channel blockers ARBs
JNC	Low dose thiazide diuretics either alone or in combination with 1 of the other classes (ACE-inhibitors, ARBs, β-blockers, CCBs)	< 140/90	1. 4 weeks 2. Add a second drug from a different class when use of a single drug in adequate doses fails to achieve the BP goal.	3-6 months	Diuretics, Beta-blockers, ACE-inhibitors Alpha-blockers Calcium-channel blockers Central alpha-agonists ARBs, Direct vasodilators
ESH	Low dose of a single agent or low dose combination of 2 agents	< 140/90	1. No guidance 2. Switch to a low dose of a different agent or increase dose of first compound or move to combination therapy.	6 months or more often if necessary	Diuretics, Beta-blockers Calcium-channel blockers ACE-inhibitors Alpha-blockers
SIGN	Low dose thiazide diuretics. β blockers may be used as alternative or supplementary to thiazide diuretics.	< 140/90	1. 3 months 2. No response: substitute a drug or low-dose combination from a different class. Partial response: increase dose or add a drug from a different class	3-6 months	Diuretics, Beta-blockers Calcium-channel blockers ACE-inhibitors Alpha-blockers ARBs

Patient education

Involving patients in their treatment was a stated priority within all guidelines, along with long-term follow-up. Ownership was encouraged variously by means of patient liaison and education, by recognition of preferences, and through lifestyle choices. A common problem identified was non-adherence or non-compliance with treatment. Recommended strategies were patient education, better-managed care programs, automatic follow-up of patients, and reducing complexity of tablet regimes.

Use of the published literature

The depth of information supporting the guideline recommendation varied as did the research evidence cited. Two guidelines did not cite any previously published work in the text (NZ, SA), whilst two gave references (VHA, WHO). Two gave references and classified the references according to their research design (ICSI, JNC). One guideline (BHS) supported their recommendation with references and graded the recommendation according to the research design of the evidence upon which they were based. One guideline (SIGN) performed a systematic literature review based on a Cochrane systematic review. None of the guidelines carried out their own meta-analyses of the research evidence available: estimations of benefit of lifestyle modifications were drawn from individual trials. However the CMA guideline tabulated summaries of each of the trials used to provide evidence for the recommendation.

Some of the trials, post-dating the guidelines, will not have been available to the guideline developers. However, checking against major placebo and head-to-head hypertension drug trials identified in this guideline reveals that guidelines have not made systematic use of the literature (Table 47). The evidence-base is evolving steadily with recent trials needing interpretation and inclusion in guidance.

Table 47: Selected hypertension trials and their reporting in guidelines

Trial[a]	Year[b]	NZ 1994	VHA 1999	BHS 1999	CMA 1999	WHO 1999	SA 2000	SIGN 2001	ICSI 2003	JNC 2003	ESH 2003
Trials included in the meta-analysis in the current guideline											
VA-II	1970										
HSCSG	1974										
USPHS	1977										
VA-NHLBI	1978										
ANBPS	1980										
EWPHE	1985							■			
IPPPSH	1985					■					■
MRC	1985					■					■
Coope	1986							■			
OSLO	1986										
SHEP-P	1986										
HAPPHY	1987					■					
MAPHY	1988										
CAPPP	1990			■		■	■	■			■
SHEP	1991	■			■	■		■	■	■	
STOP-H	1991					■		■	■		
SYST-EUR	1991				■	■		■	■		
MRC-O	1992					■		■	■		
STOP-H2	1993							■	■		
NICS-EH	1994										
PATS	1995									■	
ALLHAT	1996			■					■	■	■
MIDAS	1996								■		■
VHAS	1997					■					
HOPE	2000						■	■	■	■	■
INSIGHT	2000										■
NORDIL	2000										■
PROGRESS	2001					■[c]		■		■	■
LIFE	2002									■	■
ANBP2	2003									■	
SCOPE	2003										■
CONVINCE	2003									■	■
Trials referenced by the current guideline but not included in the meta-analysis											
HDFP[d]	1979								■		■
TOMHS[e]	1991	■	■					■			
HOT[d]	1995		■	■	■	■	■	■	■		■
ABCD[f]	1998								■		■
FACET[f]	1998										
UKPDS[f]	1998			■	■	■		■	■	■	■
RENAAL[f]	2001										
IDNT[f]	2001										

a Citation details of trials may be found in References (Evidence)
b Year of earliest publication
c Referred only to rationale and design
d Did not compare different drug classes
e Cardiovascular outcomes not reported by treatment group
f 100% diabetic

Cost effectiveness

Economic considerations were mentioned briefly in most guidelines. The South African guideline made an explicit recognition of the need to work within available resources. In no instance were concepts of cost-effectiveness applied systematically nor were they instrumental in the development of recommendations.

Methodology

Guidelines differed in their use and presentation of the research base upon which the recommendations were made. A summary of the use of the literature, evidence grading, use of groups to develop guidance and updating is provided in Table 48.

Commentary

Clinical guidelines can be developed with different (and non-exclusive) aims in mind: to inform funding agencies about reimbursement, as clinical or management directives or to promote a dialogue between clinicians and patients. While these aims have their place the brief of nationally commissioned guidelines for England and Wales is to inform the National Health Services, clinicians and patients about appropriate care. If there is to be a genuine dialogue between clinicians and patients then the way in which evidence is presented is paramount. Key steps include systematically identifying and valuing evidence, using a transparent valuation process, linking evidence to recommendations, finding the right presentation for clinicians and patients, and keeping recommendations up to date.

Current guidelines are inconsistent in their handing of these key domains. For example in no instance was the group or committee process or the level of patient involvement adequately described. Most clinicians and patients will never read the methodological details describing how a guideline is developed, but will access summary versions. For these summaries to be credible, it important that they are supported by an auditable trail of evidence collection, tabulation, valuation, summary and grading, and that this evidence supports recommendations.

Table 48: Methodological aspects of previously published guidelines

	Literature search	Grading of evidence	Development group	Updating
NZ	None described	Research evidence cited was not formally evaluated and recommendations were not graded. The type of evidence used to inform recommendations was not described	A 'Core Services Committee': roles not described	Revision expected as evidence becomes available.
DVA	MeSH terms covering key therapies, and study characteristics and design	Recommendations were rated: I usually indicated; always acceptable; useful and effective IIa acceptable, of uncertain effectiveness, and may be controversial. Weight of evidence in favour of usefulness/effectiveness IIb acceptable, of uncertain effectiveness and may be controversial. Not well established by evidence, can be helpful and probably not harmful Evidence was graded: A RCT B well-designed clinical studies C panel consensus	Thirty-eight individuals. Roles not always clear.	Revision expected as evidence becomes available.
BHS	Not described	Strength of evidence: Ia (meta analysis of RCTs) to IV expert opinion 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	No details given	No details given
Canada	MEDLINE and Cochrane Collaboration searches; reference lists in retrieved articles. Requests to experts and panel members.	Articles were classified according to study design and individually reviewed. Evidence from individual studies was graded I (RCT meeting certain criteria) to VI (small case report) Review articles were graded I (comprehensive search, avoidance of bias in study selection, assessment of validity of each article, conclusions supported by data) to V (meeting none of the 5 criteria in I) Recommendations were graded A Based on one or more studies at level 1 B Best evidence available was at level II C Best evidence was at level III D Best evidence was lower than level III and included expert opinion	A committee with a range of representatives from different bodies. Patient involvement unclear	No details given
WHO	None described	None described	Patient involvement unclear	No details given
SA	None described	Evidence not described or graded	Members' names and affiliation given. Patient involvement unclear	No details given
ICSI	None described	Research reports were graded as follows: Primary reports A (RCT) to D (case and cross sectional studies) Reviews M (Meta-analysis, systematic reviews, decision analysis, cost-benefit analysis, cost-effectiveness study) R: Narrative review, consensus statement or report X: Medical opinion In the 2002 update, some recommendations link to the evidence grade	No details	To be updated within 18 months
JNC	None described	Evidence supporting recommendations for prevention and treatment was classified: M meta-analysis Re retrospective analyses (case control) RA RCT F prospective follow-up – cohort study Pr previous review C clinical interventions (non-randomised) X cross-sectional population studies (prevalence)	Nine individuals. Contributions were sought from multidisciplinary experts. No mention of patient involvement	No details given
ESH	None described	Recommendations not classified upon strength of available evidence.	Members' names, affiliations, potential conflicts of interest given. Patient involvement unclear	No details given
SIGN	Systematic literature searches on MEDLINE, Healthstar, EMBASE, Cochrane Library. Based on a published Cochrane review	Evidence was graded when obtained from: Ia: meta-analysis of RCTs Ib: at least 1 RCT IIa: at least 1 well-designed controlled study without randomisation IIb: at least one other type of well-designed quasi-experimental study III: well-designed non-experimental descriptive studies IV: expert committee reports and/or respected clinical opinion Recommendations were rated: A Evidence levels Ia, Ib B Evidence levels IIa, IIb, III C Evidence level IV.	Members' names and affiliations listed and conflicts of interest available. Specialist reviewer names given. Age Concern represented.	Review expected in 2003 or earlier if more evidence becomes available.

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Appendix 3: Prescription cost analysis for cardiovascular drugs: England 2002, totals by chemical entities

BNF Chemical name [1]	PXS [2] (1,000s)	OWC2 [3] (1,000s)	NIC [4] (£ 1,000s)	NIC/PXS (£)
2.2.1.0 Thiazides And Related Diuretics				
Bendroflumethiazide	15,003.8	0.0	17,113.9	1.14
Chlorothiazide	1.3	0.3	53.3	42.19
Chlorthalidone	47.9	40.2	124.4	2.60
Cyclopenthiazide	38.5	27.5	82.8	2.15
Hydrochlorothiazide	4.0	3.7	14.2	3.52
Indapamide	904.9	420.7	4,826.5	5.33
Metolazone	65.8	62.7	298.4	4.54
Polythiazide	3.8	2.6	5.3	1.40
Xipamide	21.7	16.3	152.7	7.02
2.2.2.0 Loop Diuretics				
Bumetanide	1,113.7	0.0	4,082.8	3.67
Frusemide	9,377.3	4.3	12,184.9	1.30
Torasemide	27.6	23.9	266.3	9.64
2.2.3.0 Potassium-Sparing Diuretics				
Amiloride Hydrochloride	391.0	0.0	1,033.5	2.64
Spironolactone	1,087.4	0.0	4,910.0	4.52
Triamterene	3.6	3.3	111.9	30.91
2.2.4.0 Potassium Sparing Diuretics & Compounds				
Amiloride HCl With Loop Diuretics	133.6	61.2	660.8	4.95
Amiloride Hydrochloride With Thiazides	202.4	59.9	823.3	4.07
Co-Amilofruse (Amiloride HCl/Frusemide)	2,514.5	0.0	11,126.3	4.42
Co-Amilozide (Amiloride HCl/Hydchloroth)	674.5	0.0	2,262.1	3.35
Co-Flumactone (Hydroflumeth/Spironol)	35.4	13.0	489.4	13.81
Co-Triamterzide(Triamterene/Hydchloroth)	267.9	129.6	750.0	2.80
Spironolactone With Loop Diuretics	21.0	3.3	341.8	16.26
Spironolactone With Thiazides	0.3	0.0	27.6	110.06
Triamterene With Loop Diuretics	52.2	18.5	244.4	4.68
Triamterene With Thiazides	3.8	0.8	48.2	12.56
Bendroflumethiazide/Potassium	26.0	6.6	110.9	4.27
Bumetanide/Potassium	140.7	63.9	281.8	2.00
Frusemide/Potassium	20.4	2.7	120.9	5.92
2.4.0.0 Beta-Adrenoceptor Blocking Drugs				
Acebutolol Hydrochloride	55.0	44.5	1,465.4	26.67
Acebutolol Hydrochloride With Diuretic	5.0	0.7	186.0	37.13
Atenolol	14,720.6	27.7	21,762.0	1.48
Atenolol With Calcium-channel blocker	103.5	20.8	2,315.2	22.36
Atenolol With Diuretic	28.2	4.5	416.6	14.78
Atenolol with Thiazides	20.6	8.9	114.7	5.58
Betaxolol Hydrochloride	1.5	1.2	18.1	11.99

[1] Source: Prescription Pricing Authority [35]
[2] PXS: Prescription items dispensed
[3] OWC2: class 2 drugs reimbursed at the proprietary price when generic unavailable
[4] NIC: Net Ingredient Cost: cost of the drug before discounts and excluding dispensing costs

BNF Chemical name [1]	PXS [2] (1,000s)	OWC2 [3] (1,000s)	NIC [4] (£ 1,000s)	NIC/PXS (£)
Bisoprolol Fumarate	1,645.7	420.8	21,535.6	13.09
Bisoprolol Fumarate With Diuretic	0.1	0.0	1.6	20.44
Carvedilol	180.1	165.2	3,996.6	22.19
Celiprolol Hydrochloride	166.3	0.0	5,495.8	33.05
Co-Prenozide (Oxprenolol HCl/Cyclopenth)	36.0	15.5	651.7	18.08
Co-Tenidone (Atenolol/Chlorthalidone)	1,037.5	0.0	6,996.0	6.74
Labetalol Hydrochloride	126.0	9.3	1,317.9	10.46
Metoprolol Tartrate	713.1	19.6	2,258.6	3.17
Metoprolol Tartrate With Diuretic	11.6	1.6	123.4	10.64
Nadolol	11.6	10.0	99.3	8.58
Nadolol With Diuretic	3.0	0.7	37.5	12.51
Nebivolol	145.6	124.4	2,075.1	14.26
Oxprenolol Hydrochloride	130.9	35.4	1,236.9	9.45
Pindolol	17.1	0.0	130.6	7.64
Pindolol With Diuretic	12.2	2.5	161.5	13.25
Propranolol Hydrochloride	2,459.2	0.0	12,574.8	5.11
Propranolol Hydrochloride With Diuretic	20.8	4.2	191.0	9.16
Sotalol Hydrochloride	707.4	1.2	2,961.2	4.19
Timolol Maleate	52.1	49.7	269.5	5.17
Timolol Maleate With Diuretic	28.5	4.2	387.3	13.60
2.5.1 Vasodilator Antihypertensive Drugs				
Hydralazine Hydrochloride	111.5	0.0	385.6	3.46
Minoxidil	25.8	23.9	600.5	23.25
2.5.2 Centrally-Acting Antihypertensive Drugs				
Clonidine Hydrochloride	32.3	29.4	174.1	5.39
Methyldopa	211.9	0.0	801.0	3.78
Moxonidine	302.8	263.8	5,711.3	18.86
2.5.3 Adrenergic Neurone Blocking Drugs				
Debrisoquine Sulphate	3.4	0.0	83.4	24.34
Ketanserin	0.1	0.1	4.2	43.22
2.5.4 Alpha-Adrenoceptor Blocking Drugs				
Doxazosin Mesylate	3,528.0	1,838.8	92,964.3	26.35
Indoramin Hydrochloride	9.4	8.4	92.7	9.87
Phenoxybenzamine Hydrochloride	2.1	1.4	79.4	38.12
Phentolamine Mesylate	0.2	0.1	3.5	19.23
Prazosin Hydrochloride	227.2	0.8	1,315.2	5.79
Terazosin Hydrochloride	185.0	1.9	3,763.0	20.34
2.5.5.1 Angiotensin-Converting Enzyme Inhibitors				
Captopril	790.3	0.2	4,715.0	5.97
Cilazapril	38.0	32.8	586.8	15.46
Co-Zidocapt (Hydchloroth/Captopril)	58.7	0.0	1,697.6	28.94
Enalapril Maleate	3,484.3	0.0	32,866.5	9.43
Enalapril Maleate with Diuretic	38.6	9.2	1,028.3	26.65
Fosinopril Sodium	277.9	258.8	5,839.6	21.01
Imidapril Hydrochloride	34.8	32.4	335.9	9.65
Lisinopril	6,251.1	4,494.0	88,175.2	14.11
Lisinopril with Diuretic	236.7	63.3	4,900.6	20.71

BNF Chemical name [1]	PXS [2] (1,000s)	OWC2 [3] (1,000s)	NIC [4] (£ 1,000s)	NIC/PXS (£)
Moexipril Hydrochloride	1.5	1.4	22.9	15.28
Perindopril Erbumine	2,363.8	2,292.3	35,460.8	15.00
Quinapril Hydrochloride	280.8	268.4	3,806.1	13.56
Quinapril Hydrochloride with Diuretic	8.9	2.8	167.6	18.85
Ramipril	5,740.7	5,635.0	83,718.7	14.58
Ramipril with Calcium-channel blocker	5.2	4.3	195.9	37.46
Trandolapril	299.5	261.6	6,460.7	21.57
Trandolapril + Calcium-channel blocker	10.1	2.7	263.8	26.01
2.5.5.2 Angiotensin-II Receptor Antagonists				
Candesartan Cilexetil	976.1	904.9	21,326.1	21.85
Eprosartan	114.8	101.2	2,169.8	18.91
Irbesartan	836.7	756.9	22,540.6	26.94
Irbesartan with Diuretic	39.8	13.6	1,169.2	29.38
Losartan Potassium	1,776.8	1,706.4	52,988.8	29.82
Losartan Potassium With Diuretic	99.7	35.7	3,085.6	30.93
Telmisartan	239.0	207.3	4,445.8	18.60
Valsartan	943.4	859.1	22,501.9	23.85
2.6.2 Calcium-Channel Blockers				
Amlodipine Besylate	6,841.7	6,666.5	140,220.6	20.49
Diltiazem Hydrochloride	3,036.0	105.9	40,468.2	13.33
Felodipine	1,885.8	1,817.9	22,845.3	12.11
Isradipine	9.3	7.3	263.7	28.43
Lacidipine	582.8	547.9	11,726.0	20.12
Lercanidipine Hydrochloride	330.2	290.9	4,102.4	12.42
Nicardipine Hydrochloride	126.6	33.7	1,912.9	15.11
Nifedipine	4,188.3	322.3	57,716.0	13.78
Nimodipine	1.5	1.4	65.1	42.08
Nisoldipine	4.4	4.0	73.5	16.69
Verapamil Hydrochloride	921.7	140.2	10,830.8	11.75

Appendix 4: RCTs evaluating management based on home or ambulatory monitoring

Study	Comparison & analysis	Patient characteristicss	1. N 2. Male% 3. White% 4. Mean age 5. Diabetic% 6. Hypertensive%	1. Study design 2. Study duration 3. Loss to follow up 4. Mortality 5. CHD 6. Cerebrovascular	Outcome
SVATCH Vetter et al, 2000 **DN**	I: BP home measurement twice daily C: routine clinic BP measurement Both groups received losartan (ARB) 50 mg/day Wilcoxon paired samples test, and Wilcoxon-Mann-Whitney test	Switzerland. Adults (18-85) with mild-to-moderate hypertension (160-200/95-115), previously treated or untreated; without renal disease	1. 845 2. 49.2% 3. not reported 4. 57.9* 5. 7.1%* 6. 100%	1. PROBE multi-centre 2. 8 weeks 3. 223 not in per protocol analysis 4. 0 5. 0 6. 0	**Baseline BP** / **Endpoint BP** / **BP difference** I: 166.1/101.9 / 145.1(15.0)/88.7(8.3) / -21.0(SD)/-13.2(SD) C: 168.1/102.0 / 147.6((14.6)/90.1(7.8) / -20.5(SD)/-11.9(SD) **Responders (DBP ≤ 90) at 8 weeks** All patients: I: 196 (66.2%); C: 195 (59.8%); RD: 6.4% 0.05 <p< 0.1 Females: I: 109 (73.2%); C: 107 (64.1%); RD: 9.1% 0.005 <p< 0.01 Males: I: 87 (59.2%); C: 88 (55.3%); RD: 3.9% p <0.2
PLUR Schrader et al, 2000 **DN**	I: ambulatory BP measurement once a year C: casual clinic BP measurement Participants received ramipiril (ACE) 1.25 - 5 mg/day; and a calcium-channel blocker, or a diuretic, or a β-blocker could be administered additionally or alternatively Multiple *t*-test and students's *t*-test	Germany. Adults (35-65) with hypertension (SBP > 140 and/or DBP > 90) requiring treatment	1. 1,298 2. 45.7% 3. not reported 4. 54.3 5. 12.2% 6. 100%	1. PROBE multi-centre 2. 4.7 years 3. 195 4. n/a 5. n/a 6. n/a	**Baseline BP** / **Endpoint BP** / **BP difference** I: 143.7/89.3 / 130.4(11.9)/79.6(8.4) / -13.3(SD)/-9.7(SD) **Event** / **Intervention** / **Control** / **RD p** Protocol violation: 174 (26.7%) / 134 (20.7%) / 6.0% p=0.01 Drug-related adverse effects: 45 (6.9%) / 39 (6.0%) / 0.9% n/s Combined end point (CV events): 20 (3.1%) / 35 (5.4%) / 2.3% p=0.04

Appendix 5: Prognostic studies comparing ambulatory, home monitoring and clinic blood pressure

Study	Comparison	Patient characteristicss Analysis	1. N 2. Male% 3. White% 4. Mean age 5. Diabetic% 6. Hypertensive%	1. Study design 2. Study duration 3. Loss to follow up 4. Mortality 5. CHD 6. Cerebrovascular	Outcome
Khattar et al, 1999	Clinic: nurse or technician using traditional auscultatory technique after 5-10 minutes rest; average of 2 or more readings. 24 hour BP: measured by intra-arterial technique using a fine brachial artery cannula	England. Adults with persistently elevated clinic BP; excluding secondary hypertension Multivariate Cox regression	1. 723 2. 64.0%* 3. 76.7%* 4. 51* 5. 7.6% 6. 100% * those with f/u data	1. Prospective cohort 2. 9.2 years 3. 35 4. 73 5. 73 6. 30	*Clinic & ambulatory values added individually to an adjusted Cox regression mode lpredicting cardiovascular events* Model X^2 p — Model X^2 p 24-h systolic BP 11.07 <0.001 — night time systolic BP 10.57 0.001 day time systolic BP 10.33 0.001 — night time diastolic BP 9.87 0.004 24-h diastolic BP 7.58 0.008 — 24-h pulse pressure 6.12 0.01 day time diastolic BP 5.88 0.02 — 24-h (diastolic BP)² 12.59 0.002 clinic systolic BP 3.94 ns — clinic diastolic BP 0.22 ns *Adjusted Cox regression model with 24-hour BP as a predictor of time to a first event* Hazard ratio 95% CI p 24-hour systolic BP (per 10 increase) 1.14 1.06-1.23 0.001 *(clinic BP not reported)*
Ohasama study (Sakuma et al, 1997)	Home: semi-automated device; seated; < 1hr after waking over 4 weeks. (Mean number of readings was 23.0 (SD7.5)) Clinic: nurse or physician took 2 consecutive readings, using a fully automatic device (at baseline)	Japan. Adults, age> 40, without a history of stroke and not receiving antihypertensive treatment Multivariate Cox regression	1. 1,256 2. 39.3% 3. 100% 4. 61.7 5. not reported 6. not reported	1. Prospective cohort 2. 4.4 years 3. 2 4. 57 5. not reported 6. 39	*Adjusted relationship between home, clinic BP & first ever stroke* Measurement HR (95% CI) — Measurement HR (95% CI) *Home systolic quintile* — *Home diastolic quintile* 1st ≤ 109 5.71 (0.63-51.50) — 1st ≤ 65 1.13 (0.30-4.21) 2nd 110-116 5.86 (0.71-48.75) — 2nd 66-70 1.00 3rd 117-123 1.00 — 3rd 71-74 1.20 (0.32-4.48) 4th 124-132 8.35 (1.06-65.59) — 4th 75-80 1.34 (0.39-4.65 5th ≥ 133 14.63 (1.92-111.20) — 5th ≥ 81 3.52 (1.16-10.65) *Clinic systolic quintile* — *Clinic diastolic quintile* 1st ≤ 114 1.68 (0.34-8.40) — 1st ≤ 64 1.00 2nd 115-125 3.56 (0.96-13.17) — 2nd 65-70 2.89 (0.60-13.94) 3rd 126-132 2.24 (0.53-9.39) — 3rd 71-76 2.79 (0.58-13.44) 4th 133-143 1.00 — 4th 77-83 2.70 (0.56-13.03) 5th ≥ 144 6.04 (1.77-20.60) — 5th ≥ 84 6.12 (1.40-26.70)

Study	Comparison	Patient characteristicss Analysis	1. N 2. Male% 3. White% 4. Mean age 5. Diabetic% 6. Hypertensive%	1. Study design 2. Study duration 3. Loss to follow up 4. Mortality 5. CHD 6. Cerebrovascular	Outcome
Ohasama study (Ohkubo et al, 1998)	Home: using semi-automated device; seated; < 1hr after waking over 4 weeks. (Mean number of readings was 20.8 (SD8.3)) Clinic: nurse or physician took 2 consecutive readings, using a fully automatic device (at baseline)	Japan. Adults, age> 40, without a history of stroke and not receiving antihypertensive treatment Multivariate Cox regression	1. 1,913 2. 40% 3. 100% 4. 61 5. not reported 6. 33% taking antihypertensive drugs at baseline	1. Prospective cohort 2. 6.6 years 3. 124 4. 160 5. 17 deaths 6. 35 deaths	*Adjusted relationship between home, clinic BP & cardiovascular mortality* Measurement — HR (95% CI), p — HR (95% CI), p *Home Measurement* — *Clinic Measurement* *Systolic BP* 1.021 (1.000-1.042) p=0.048 — 1.000 (0.984-1.016) p=0.972 *Diastolic BP* 1.013 (0.982-1.044) p=0.414 — 1.005 (0.980-1.031) p=0.704 Hazard Ratio (HR) expressed as the increase in mortality risk per 1mmHg increase in BP. Data adjusted for age, sex, smoking, previous CVD, and antihypertensive medication
PIUMA study (Verdecchia et al, 1998; see also: Verdecchia et al, 1997; 2002)	Clinic: ≥3 sitting readings after 10 minute rest taken by a physician using a sphygmomanometer on ≥2 occasions. Ambulatory: 15 min/24 hours Electrocardiography: measured left ventricular mass	Italy. Adults with previously untreated essential hypertension (clinic BP ≥ 140/90); without CHD Multivariate Cox regression	1. 2010 2. 52% 3. 100% 4. 52 5. 7.6% 6. 79%	1. Prospective cohort 2. 3.8 years 3. not reported 4. 36 (cardiovascular) 5. 98 6. 79	*Adjusted Cox regression model with individually added variables* *Cardiovascular morbidity* — *Cardiovascular mortality* Variable — Comparison — HR (95% CI) — p — HR (95% CI) — p WCH — WCH vs. AH — 0.30 (0.09-0.95) — 0.007 NDS — no vs. yes — 1.46 (1.06-2.01) — 0.016 — 2.31 (1.06-5.03) — 0.026 Office SBP — 10 mmHg↑ — 1.12 (1.04-1.21) — 0.004 Office PP — 10 mmHg↑ — 1.20 (1.10-1.32) — 0.005 — 1.33 (1.10-1.61) — 0.01 24 SBP — 10 mmHg↑ — 1.23 (1.12-1.35) — 0.005 — 1.64 (1.28-2.09) — 0.01 24 PP — 10 mmHg↑ — 1.33 (1.17-1.51) — 0.006 — 1.37 (1.11-1.69) — 0.001 WCH: white coat hypertension; AH: ambulatory hypertension; NDS: Noctural dipping status (>10%); PP: pulse pressure. WCH and NDS were included in the base model.
PIUMA study Schillaci et al, 2000	Clinic: ≥3 sitting readings after 10 minute rest taken by a physician using a sphygmomanometer on ≥2 occasions. Ambulatory: 15 min/24 hours Electrocardiography: measured left ventricular mass	Italy. Adults with previously untreated essential hypertension (clinic BP ≥ 140/90); without CVD (Pooled data from 2 cohorts: Umbria and Cantanzaro) Multivariate Cox regression	1. 1925 2. 50% 3. 100% 4. 50 5. 6.4% 6. 100%	1. Prospective cohort 2. 4 years 3. not reported 4. 49 5. 96 6. 64	*Adjusted Cox regression model(per 1mmHg↑) for cardiovascular events* Variable — Adjusted hazard ratio (95% CI) — P-value Ambulatory systolic BP — 1.02(1.01-1.03) — <0.006 Clinic systolic, diastolic, and ambulatory diastolic BP were all analysed but were not found to be significant independent predictors of CVD mortality

Study	Comparison	Patient characteristicss Analysis	1. N 2. Male% 3. White% 4. Mean age 5. Diabetic% 6. Hypertensive%	1. Study design 2. Study duration 3. Loss to follow up 4. Mortality 5. CHD 6. Cerebrovascular	Outcome
Syst Eur (Staessen et al, 1999)	Clinic: 2 readings lying, sitting & standing 3 times over 1 month Ambulatory BP: ≤30min/24hrs	Europe. Adults, age≥ 60, with previously treated and untreated essential sitting systolic hypertension (160-219/≤ 95), or standing SBP > 140; without CVD (Participants were enrolled in the Syst-Eur trial) Multivariate Cox regression	1. 808 2. not reported 3. not reported 4. 69.6 years 5. not reported 6. 100%	1. Prospective cohort within RCT 2. 4.4 years 3. 272 4. 68 5. 69 6. 30	*Relationship between entry systolic BP (per 10 mmHg↑) and event in an adjusted Cox regression model* Fatal CVD: Clinic HR 1.24 (1.03-1.49) P-value ≤ 0.05; Ambulatory HR 1.16 (0.99-1.35) P-value *ns*; Daytime BP HR 1.07 (0.91-1.24) P-value ns; Night BP HR 1.17 (1.03-1.33) P-value ≤ 0.05 Fatal and non-fatal CVD: Clinic HR 1.13 (0.96-1.34) P-value *ns*; Ambulatory HR 1.18 (1.04-1.35) P-value ≤ 0.01; Daytime BP HR 1.11 (0.98-1.25) P-value ns; Night BP HR 1.21 (1.09-1.35) P-value ≤ 0.001 *Baseline and follow-up reduction in BP by specific measurements* Mean BP: Clinic / Ambulatory Baseline: 173.3/86.0 / 145.8/79.3 Follow up difference: -10.6/-4.2 / -8.5/-3.8

Appendix 6: RCTs of dietary interventions

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Blumenthal et al, 2000	C: Exercise: 1 hour schedule, 3-4 times weekly I: Exercise as above and weight management with aim of weight loss of 0.5 – 1.0 kg per week * A further control group maintained usual dietary and exercise habits	USA. Adults (> 29 years), currently untreated, essential hypertension SBP 130-180 and/or DBP 85–110, sedentary and obese (BMI 25-37), without CHD, renal disease or type I diabetes	1. unclear 2. unclear 3. unclear 4. 133 5. 6 months 6. 6 months	1. yes 2. 47.5 3. 44% 4. 75%	1. 141/94 C: 138.1/93.6 I: 142.7/93.2 2. 0 3. 0	1-4. Not reported 5. C: 133.7(13.9)/89.3(13.9), 44 I: 135.3(14.2)/87.6(14.2), 46	1/2. C: 10/54 (18.5%) I: 9/55 (16.4%)
Croft et al, 1986	I: Dietician advice on diet for weight reduction C: Not receiving weight reduction advice * All participants were given advice about modest restriction of salt use and reduction of excessive alcohol intake	U.K. Overweight patients, treatment naïve, aged 35–60 years. SBP: 140-200 mmHg and/or DBP: 90-114 mmHg. Excluded were MI, stroke in last 3 months, diabetes.	1. unclear 2. unclear 3. unclear 5. 130 4. 6 months 5. 6 months	1. Inadequately reported 2. not reported 3. 52.3% 4. not reported	1. 161/97 I: 161/98 C: 161/96 2. 0% 3. 0%	1.-4. not reported 5. I: 150(32.5)/91(17.9), 49 C: 157(28.0)/95(16.0), 61	1. I: 19/66(24.2%) C: 14/64(21.9%) 2. I: 17/66(25.8%) C: 3/64(4.7%)
DASH, 1994-99	I1: Fruit & veg diet provided (high red meat, fruit, medium veg, poultry, grain, nuts, fish, fats, sweets, low dairy) I2: Combination diet provided (high fruit, veg, fish, dairy, medium nuts, red meat, grain, poultry, low fat, sweets) C: control diet (high fats, sweets, poultry, grains, medium red meats, low nuts, veg, fish, dairy, fruit – resembling normal US diet) * Hypertensive sub-group analysed	USA. Adults; currently untreated SBP 140-160 & DBP 90-95, BMI ≤ 35; without CVD < 6 months, poorly controlled diabetes or renal failure. Sodium intake was similar across groups (3g/day); all participants were instructed to consume ≤ 3 caffeine & 2 alcohol drinks p/day.	1. blinded assessment 2. adequate 3. adequate 4. 133 5. 8 weeks 6. 8 weeks	1. yes 2. 49.2 3. 40.0% 4. 35.0%	1. 145/90 I1: 145.2/90.0 I2: 144.4/88.3 C: 144.7/90.1 2. 0% 3. 0%	1-4. not reported 5. I1: -6.6(9.2)/-2.4(5.7), 49 I2: -10.7(8.6)/-4.7(5.3), 37 C: +0.5(8.9)/+0.6(5.5), 47 I1+I2 vs. C	1/2. I1: 2/49(4%) I2: 0/37(0%) C: 3/47(6%)
Davy et al, 2002 *(not included in meta-analysis)*	I: dietary fibre oats 14g/day C: control wheat 14g/day	USA. Adults (50-75) with essential hypertension (SBP 130-159 and/or DBP 85-99), BMI 25-35 kg/m², sedentary or minimally physically active (< 2x30 mins p/wk aerobic exercise). Excluded if previous CVD, pulmonary disease, metabolic disease, or on medication affecting outcome variables, or dietary fibre intake > 30g p/day	1. blinded assessment 2. unclear 3. unclear 4. 36 5. 12 weeks 6. 12 weeks	1. unclear 2. 59.0 3. 100% 4. not reported	1. 140.3/89.5 I: 138.2/88.5 C: 142.3/90.4 2. 0% 3. 0%	1-4. not reported 5. I: 134.6(13.1)/87.6(8.5), 18 C: 140.3(10.6)/90.9(8.5), 18	1/2. I: 0/18 (0%) C: 0/18 (0%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Gordon et al, 1997	C: Supervised exercise training, 30–45 minutes; 3–5 days per week. Normal diet I: Exercise training plus dietary modification to restrict energy intake supervised by counsellors * A further dietary group were asked to avoid exercise	USA. Adults; sedentary, overweight, no cardiovascular disease, SBP 130-179 DBP 85–109, currently untreated, consuming <42 g/day ethanol	1. unclear 2. unclear 3 unclear 4. 55 5. 12 weeks 6. 12 weeks	1. yes 2. 48.4 R: 21-65 3. 30.9 % 4. not reported	1. 144/95 C: 145.0/96.0 I: 145.0/95.0 2. 0% 3. not reported	1-4. not reported 5. C: -9.9(6.4)/-5.9(4.6), 14 I: -12.5(6.3)/-7.9(4.3), 19	1/2. C: 0/14 (0.0%) I: 5/24 (20.8%)
Jalkanen, 1991	I: Energy restricted diet 1,000-1,500 kcal/day, 1.5 hour weekly sessions (every 3 weeks after 6 months) with discussions & lectures on behaviour modification, choice of food, physical exercise, and medical aspects of obesity & weight reduction C: No counselling/advice – 3 month nurse visit over one year	Finland. Adults (35-59); DBP≥95 and BMI 27-34 kg/m² currently treated and untreated hypertension. Doctors were asked to keep anti-hypertensive drugs at initial dosage.	1. unclear 2. unclear 3. unclear 4. 50 5. 12 months 6. 12 months	1. yes 2. 49 R: 35-59 3. 50% 4. not reported	1 154/102 I: 152.0/101.0 C: 155.0/102.0 2. 0% 3. 0%	1-4. not reported 5. I1: 144.0(20)/90.0(10), 24 C: 140.0(16)/91.0(7), 25	1/2 I: 1/25 (4.0%) C: 0/25 (0.0%)
Jula et al, 1992	I: Instruction to reduce sodium intake < 70 mmolp/day, change intake of polyunsaturated:saturated fatty acids in diet & lose weight (if necessary) C: No intervention * cluster randomised: subjects divided into 2 matching groups, which were randomised to treatment/control	Finland. Adults, both overweight and normal weight; currently untreated or treatment naive hypertensive; DBP 90-110 & SBP 160-200; without CVD	1. blinded assessment 2. unclear 3. unclear 4. 40 5. unclear 6. 6 months	1. yes 2. 43.7 R: 35-55 3. 45.0% 4. not reported	1. 148/97 I: 151.9/98.4 C: 143.9/96.1* 2. 0% 3. 0%	1-4. not reported 5. I: 133.3(11.8)/88.4(6.7), 7 C: 136.6(10.4)/92.6(5.4), 6 Sample size adjusted assuming ICC=0.1	1/2. I: 2/22 (9.1%) C: 1/18 (5.6%)
MacMahon et al, 1985	I: weight reduction – 3 weekly meetings for individually tailored diet aiming to reduce calorie intake by 1,000 p/day with 15% protein, 30% fat & 55% carbohydrates C: placebo tablets	Australia. Adults (20-55 years) with currently untreated hypertension (DBP 90-109 mm Hg), BMI > 26.0; without CHD, proteninuria	1. unclear 2. unclear 3. unclear 4. 56 5. 21 weeks 6. 21 weeks	1. yes 2. 41.8 3. 75.0% 4. not reported	1. 150.4/100.4 I: 149.8/101.2 C: 150.3/98.9 2. 0% 3. 0%	1-4. not measured 5. I: -13.3(5.0)/-9.8(4.9), 20 C: -7.4(5.0)/-3.1(5.2), 18	1. I: 3/20 (15.0%) C: 2/18 (11.1%) 2. I: 0/20(0%) C: 0/18(0%)
Metz et al, 2000	I: Prepared meal plan – 22% energy from fat, 58 % carbohydrate and 20 % protein. Diet adherence support received monthly C: Usual care diet: prescribed a macronutrient equivalent diet based on the American Dietetic Association	USA. Adults, sedentary, overweight, BMI 25–42, untreated hypertension, SDP/DBP140-180 and/or 90-105; currently treated hypertension DBP <100, without diabetes or any serious health problems	1. blinded assessment 2. adequate 3. adequate 4. 183 5. 1 year 6. 1 year	1. yes 2. 54.5 3. 45.3 % 4. 89.1 %	1. 145/90 I: 145.0/91.4 C: 145.0/90.3 2. 0% 3. 0%	1-4. not reported 5. I: -11.9(11.7)/-7.0(6.6), 79 C: -10.5(13.2)/-6.5(6.8), 79	1/2. I: 14/93 (15.1%) C: 11/90 (12.2%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
ODES 1993-97 Anderssen, 1995	I1: Dietary advice: increased intake of fish oil, veg, fibre-rich carbohydrates, reduced sugar & saturated fat intake; individualised program with follow-up at 3 & 9 months I2: Exercise: 3 weekly sessions (tailored aerobic, circuit training, jogging/fast walking) I3: I1+I2 C: No intervention * All participants advised to stop smoking	Norway. Adults, sedentary, overweight; 41-50, exercise ≤ once week; BMI>24, DBP 86-99; TC 5.2-7.7 mmol/L; HDL< 1.2 mmol/L; TG> 1.4 mmol/L, without CVD, diabetes; previous hypertension treatment unclear	1. open 2. unclear 3. inadequate 4. 219 5. 1 year 6. 1 year	1. yes 2. 44.9 3. 90.4% 4. not reported	1. 132/88 I1: 132.8/87.5 I2: 132.1/89.2 I3: 131.9/88.0 C: 128.7/87.0 * 2. 0% 3. 0%	1-4. not reported 5. I1: -6.4(10.4)/-3.4(7.4), 55 I2: -2.2(8.1)/-2.7(7.3), 54 I3: -5.9(9.0)/-5.2(7.4), 67 C: -0.5(11.1)/-0.7(11.1), 43 I1+I3 vs. I2+C	1. not reported 2. I1: 0/55 (0%) I2: 0/54 (0%) I3: 0/67 (0%) C: 0/43 (0%)
Poppitt et al, 2002	I1: low fat complex carbohydrate diet I2: low fat simple carbohydrate diet C: control diet	UK. Adults ≥ 3 risk factors for metabolic syndrome: >38 years, DBP 85-100, BMI 27-40 kg/m², central obesity, family history of type II diabetes, fasting plasma glucose 5.5-6.9 mmol/L, HDL cholesterol <1.0 mmol/L. triglycerol >2.0 mmol/L. Excluded if currently dieting or planning to begin a weight control program < 8 months	1. unclear 2. unclear 3. unclear 4. 46 5. 6 months 6. 6 months	1. yes 2. 46.4* 3. 30.8%* 4. not reported	1. 135.6/85.6 I1: 136/86 I2: 138/84 C: 132/87 2. not reported 3. 0%	1-4. not reported 5. I1: -7(-15.)/-1(-11.0), 14 I2: -5(11.0)/2(-11.0), 14 C: 8(-20)/3(10), 11	1. I1: 2/16 (12.5%) I2: 1/15 (6.7%) C: 4/15 (26.7%) 2. I1: 2/16 (12.5%) I2: 1/15 (6.7%) C: 4/15 (26.7%)
Prisco et al, 1998 *(not included in meta-analysis)*	I: EPA and DHA ethyl esters (4 g/day), 1g capsules taken with meals. C: Placebo (olive oil, 4 g/day) in 1 g capsules. * All participants followed a Mediterranean diet rich in olive oil.	Italy. Adults; essential hypertension (DBP 95-104), treatment naive, without diabetes, and cholesterol <5.5	1. double 2. unclear 3. unclear 4. 16 5. 4 months 6. 6 months	1. yes 2. 44.5 R: 33-56 3. 100 % 4. not reported	1. 152/97 I: 154.0/97.0 C: 150.0/97.0 2. 0 3. 0	1-4. not reported 5. I: 146.0(5.0)/91.0(6.0), 8 C: 150.0(4.0)/97.0(4.0), 8	1/2. I: 0/0 (0.0%) C: 0/0 (0.0%)
Pritchard et al, 1999	I1: Dietician group: individual counselling sessions on nutrition and exercise, restriction of alcohol, energy intake, advice to stop smoking I2: Doctor and dietician group: as I1 but 2 (5 min) doctor meetings for encouragement and monitoring C: Usual care	Australia. Adults, 25-65 yrs, overweight, existing diagnosis of hypertension > 140/90. Excluded if mentally unwell or if already participating in other programmes. Previous hypertension treatment unclear	1. blinded assessment 2. adequate 3. inadequate 4. 97 5. 1 year 6. 1 year	1. yes 2. not reported 3. not reported 4. not reported	1. 110 * I1: 109 I2: 112 C: 110 2. 0% 3. 0% mean BP reported: DBP+(SBP-DBP)/3	1-4. not reported 5. I1: 138(17)/87(11), 30 I2: 137(15)/85(9), 33 C: 149(18)/94(8), 34	1. I1: 16/30(53.3 %) I2: 9/33(27.3 %) C: 6/34(17.6 %) 2. I1: 0/30(0 %) I2: 0/33(0%) C: 0/34(0%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Puddey et al, 1992	I: hypocaloric diet – reduced calorie intake of 1,000-1,500 kcal/day (aggregated over low-alcohol and usual alcohol diet) C: normal diet – usual dietary intake (aggregated over low-alcohol and usual alcohol diet) * Factorial design: diet & alcohol	Australia. Overweight males (25-70); currently untreated SBP 130-160 and DBP 80-105, BMI > 25 kg/m², , alcohol consumption ≥ 3 standard drinks p/day, without CVA, renal disease, diabetes	1. unclear 2. unclear 3. unclear 4. 86 5. 18 weeks 6. 18 weeks	1. yes 2. 44.3 3. 100% 4. not reported	1. 137.4/85.0 I: 138.0/85.3 C: 136.8/84.6 2. 0% 3. 0%	1-4. not reported 5. I: -9.1(8.2)/-7.0(6.1, 45) C: -3.6(7.7)/-2.7(5.8), 41	1. I: 9/45 (20%) C: 4/41 (9.8%) 2. I: 0/45 (0%) C: 0/45 (0%)
Reisin et al, 1978	I: Weight reduction program & antihypertensive drug treatment C: Antihypertensive drug treatment only * All had fortnightly clinical meetings with dietician & physician. Anti-hypertensive medication was kept at the initial dose throughout study.	Israel. Overweight patients with uncomplicated currently treated essential hypertension. BP>140/90, weight >10% above ideal weight	1. unclear 2. unclear 3. unclear 4. 121 5. 3 months 6. 3 months	1. no 2. 44.6 3. 63.5% 4. not reported	1. 171/112 I: 171.7/112.9 C: 170.8/108.6 2. 0% 3. 0%	1-4. not reported 5. I2: -37.4(21.3)/-23.3(11.6), 57 C: -6.9(23.2)/-2.5(10.4), 26	1/2. not reported
Rivas et al, 2002 *(not included in meta-analysis)*	I: soy milk 1,000 ml/day C: skimmed cows milk 1,000 ml/day	Spain. Adults (18-70), mild to moderate essential hypertension (BP 140-179/90-109), 20 treatment naïve and 20 currentlyuntreated.	1. double 2. unclear 3. unclear 4. 40 5. 3 months 6. 3 months	1. yes 2. 48.5 3. 62.5% 4. not reported	1. 153.4/99.8 I: 155.0/100.3 C: 151.7/99.2 2. not reported 3. not reported	1-4. not reported 5. I: -18.4(10.7)/-15.9(9.8), 20 C: -1.4(7.2)/-3.7(5.0), 20	1/2. I: 0/20 (0%) C: 0/20 (0%)
Singh et al, 1995	I: Physician advised 1,600 Kcal/day diet including ≥400g/day fruit & veg, American Heart Association Step 1 C: Physician advised 2,100 kcal/day diet, American Heart Association Step 1 * Both diets replaced animal fats with vegetable fats. The dietician made weekly home-visits for promote dietary compliance and drug dosage.	India. Adults, overweight; currently treated and currently untreated BP >150/90, sedentary occupation India. All participants took a β-blocker or Ca channel blocker, aluminium hydroxide tablet, and were asked to decrease salt consumption to 5g/day.	1. blinded assessment 2. adequate 3. inadequate 4. 217 5. 16 weeks 6. 16 weeks	1. yes 2. 47.1 3. 77.8% 4. 0%?	1. 154/100 I: 152.5/99.6 C: 154.8/100.5 2. 0% 3. 17.5%	1-4. not reported 5. I: 10.5(14.1)/-8.0(11.1), 95 C: -3.0(14.1)/-1.5(11.1), 96	I. I: 0/108(0%) C: 0/109()%) 2. I: 13/108(12.0%) C: 13/109(11.9%)

Appendix 7: RCTs of interventions to increase exercise

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Blumenthal et al, 1991	I1: Aerobic exercise, walking or jogging, >70% max O_2 consumption: 50 minute schedule, 3 times weekly I2: Strength and flexibility training, flexibility and circuit weight training, 3 times weekly C: No intervention * All participants asked to maintain weight and to make no changes to their diet, especially sodium content	USA. Adults 29-59 years ; BP 140-180/90-105, 52/92 treatment naïve, 40/92 currently untreated, < 120% ideal body weight, history of essential hypertension, not currently performing regular aerobic exercise; without CHD, COPD, secondary hypertension	1. unclear 2. unclear 3. unclear 4. 99 5. 4 months 6. 4 months	1. yes 2. 45.2 3. 62.0% 4. 76.1%	1. 142/95* I1: 141.0/96.0* I2: 143.0/95.0* C: 142.0/96.0* 2. 0 3. not reported * completers	1-4. not reported 5. I1: 133.0(10.4)/89.0(6.8), 39 I2: 136.0(11.6)/89.0(6.4), 31 C: 133.0(8.6)/90.0(6.2), 22 I1+I2 vs. C	1. I1: 2/41 (4.9%) I2: 4/35 (11.4%) C: 1/23 (4.3%) 2. I1: 2/41 (4.9%) I2: 4/35 (11.4%) C: 1/23 (4.3%)
Blumenthal et al, 2000	I: Aerobic exercise: 1 hour schedule, 70 -85% of initial heart rate reserve: 3-4 times weekly cycling, walking and jogging C: No intervention * Further diet and exercise arm	USA. Adults (> 29 years), currently untreated, essential hypertension SBP 130-180 and/or DBP 85–110, sedentary and obese (BMI 25-37), without CHD, renal disease or type I diabetes	1. unclear 2. unclear 3. unclear 4. 133 5. 6 months 6. 6 months	1. yes 2. 47.5 3. 44% 4. 75%	1. 141/94 I: 138.1/93.6 C: 143.8/94.4 2. 0 3. 0	1-4. Not reported 5. I: 133.7(13.9)/89.3(13.9), 44 C: 142.9(9.8)/93.0(9.8), 22	1/2. I: 10/54 (18.5%) C: 2/24 (8.3%)
De Plaen et al, 1980	I: Exercise group: 1 hour schedule, >60-70% pre-training max O_2 consumption: 3 weekly supervised group sessions. Walking, jogging, bicycling, callisthenics, individually tailored C: Control group: not described	Belgium. Adults, DBP 100-120; without major cardiovascular or renal complications. All antihypertensive medication except thiazide diuretics stopped upon entry to trial: 4 I and 3 C continued to take drug	1. unclear 2. unclear 3. unclear 4. 15 5. 3 months 6. 3 months	1. unclear 2. 45.2* 3. 70.0%* 4. not reported * 10 completers	1. 159/107* I: 161.0/105.0* C: 156.0/110.0* 2. 0 3. not reported	1-4. not reported 5. I: 168.0(19.6)/111.0(9.8), 6 C: 154.0(14.0)/107.0(4.0), 4	1/2. I: 1/7(14.3%) C: 4/8(50%)
Duncan et al, 1985	I: Aerobic exercise, 70-80% intensity of maximal heart rate, walking or jogging: 1 hour schedule, 3 times weekly C: Control group	USA. Adults with mild essential hypertension; BP 140-160/90-104; without personal or family history of CHD or CVA	1. unclear 2. unclear 3. unclear 4. 56 5. 4 months 6. 4 months	1. yes 2. 30.4 3. 100% 4. 100%	1. 146/94 I: 146.3/94.3 C: 145.0/93.3 2. 0 3. not reported	1-4. not reported 5. I: 133.9(7.3)/87.2(4.0), 44 C: 138.8(7.3)/96.2(6.2), 12	1/2. I: 0/44(0%) C: 0/12(0%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Gillett et al, 1996	I1: health and fitness education – nurse led 1 hr/wk fitness education classes & instructed to exercise aerobically alone 10-30 minutes, 3 times weekly I2: health and fitness education and aerobic training – nurse led 1 hr/wk fitness education classes & low impact dance exercise, 60 minutes, 3 times weekly C: control – baseline & endpoint BP measured, no information about or instructions to exercise, and asked to continue normal daily activities	USA. Female adults, 60-70, non-smokers, non-exercisers (< 3/wk), obese (mean BMI = 32); excluding CVD, pulmonary, neurological, renal disease, untreated hypertension, musculoskeletal problems	1. unclear 2. unclear 3. unclear 4. 182 5. 4 months 6. 4 months	1 yes 2. 64.4 3. 0% 4. unclear	1. 140.6/81.5 I1: 142.7/81.9 I2: 139.1/81.3 C: 139.3/80.8 2. 0% 3. unclear	1-4. not reported 5. I1: 138.3(16.7)/79.6(9.5), 64 I2: 135.7(17.4)/81.7(9.1), 69 C: 137.6(16.2)/79.3(6.7), 31	1. I1: 7/71 (9.9%) I2: 6/75 (8.0%) C: 5/36 (13.9%) 2. unclear
Gordon et al, 1997	C: Dietary modification: restriction of energy intake I: Supervised exercise training, 30–45 minutes; 3–5 days per week plus dietary modification * Also 'exercise only' arm	USA. Adults; sedentary, overweight, no cardiovascular disease, SBP 130-179 DBP 85 – 109, not currently treated, consuming < 42 g p/day ethanol	1. unclear 2. unclear 3 unclear 4. 55 5. 12 weeks 6. 12 weeks	1. yes 2. 48.4 R: 21-65 3. 30.9 % 4. not reported	1. 144/95 C: 141.0/93.0 I: 145.0/95.0 2. 0% 3. not reported	1-4. not reported 5. C: -11.3(12.1)/-7.5(4.3), 15 I: -12.5(6.3)/-7.9(4.3), 19	1/2. C: 2/17 (11.8%) I: 5/24 (20.8%)
Hagberg et al, 1989	I1: Low intensity training group, 50% max O_2 consumption: 1 hour walking, 3 times weekly supervised during first month. I2: Moderate intensity training group, 70-85% max O_2 consumption: progressive from walking, jogging, cycle ergometry to treadmill exercise. 45-60 mins, 3 times weekly, supervised throughout. C: Control: not described.	USA. Adults (60-69 years), mean BP > 150/85, 13/33 currently treated, 20/33 currently untreated * Unclear whether anti-hypertensive medication was allowed to vary during the course of the study.	1. unclear 2. unclear 3. unclear 4. 33 5. 9 months 6. 9 months	1. unclear 2. 64.0 3. not reported 4. not reported	1. 158/94 I1: 164.0/94.0 I2: 157.0/99.0 C: 154.0/90.0 2. not reported 3. not reported	1-4. not reported 5. I1: -21.4(12.0)/-12.1(6.9), 11 I2: -9.2(13.6)/-10.7(2.8), 10 C: -1.3(16.3)/-2.3(6.7), 9 I1+I2 vs. C	1/2. I1: 3/14 (21.4%) I2: 0/10 (0%) C: 0/9 (0%)
Halbert et al, 2000	I: Tailored advice on physical activity: pamphlet with 3 month plan. Aerobic exercise for at least 20 minutes, 3 times weekly. Discussion on barriers to, and benefits of, exercise. C: Pamphlet promoting 'good nutrition' for older adults * Both groups had a 20 minute session with an exercise specialist	Australia. Sedentary adults, over 60 yrs.; without CVA, CHD, CVD or other life-threatening disease; not using β-blockers	1. unclear 2. unclear 3. inadequate 4. 299 5. 6 months 6. 12 months	1. yes 2. 67.3 3. not reported 4. not reported	1. 148.3/85.7 I: 148.6/85.6 C: 148.1/85.7 2. 0% 3. 0%	1-4. not reported 5. I: 147.4(19.0)/86.1(9.7), 123 C: 146.6(19.4)86.3(8.7), 141	1. unclear 2. I: 26/149 (17.4%) C: 9/150 (6.0%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Harris et al, 1987	I: Circuit weight training : workouts for arms, trunk & legs 3 times weekly C: Control group: not described	USA. Male adults; BP 140-160 and/or 90-95; non-smokers; had not participated in exercise programme at least one year before study	1. unclear 2. unclear 3. unclear 4. 26 5. 9 weeks 6. 9 weeks	1. yes 2. 31.9 R: 24-40 3. 100% 4. not reported	1. 144/95 I: 141.7/95.8 C: 146.1/94.6 2. 0% 3. 0%	1-4. not reported 5. I: 142.3(23.7)/91.3(25.3), 10 C: 145.8(27.6)/92.6(13.2), 16	1/2. I: 0/10(0%) C: 0/16(0%)
Kukkonen et al, 1982	I: Physical training group – supervised bicycle ergometer training 3 x 50 mins/wk C: No intervention * Data from 'borderline hypertensive' strata are reported.	Finland. Adults (35-50 years), BP > 141/91.	1. unclear 2. unclear 3. unclear 4. 25 5. 4 months 6. 4 months	1. unclear 2. 40.3 3. 100% 4. not reported	1. 143/98 I: 145.0/99.0 C: 140.0/97.0 2. not reported 3. not reported	1-4. not reported 5. I: 136.0(10.8)/88.0(10.8), 12 C: 140.0(13.9)/90.0(6.9), 12	1/2. I: 1/13(7%) C: 0/12(0%)
Martin et al, 1990	I: aerobic exercise regime – walking, jogging, stationary bicycling, heart rate 65-80% of max. C: placebo exercise regime -stretching, easy calisthenics, heart rate <60% of max. * Both interventions were 30 minutes, 4 times weekly (2 unsupervised and 2 supervised sessions)	USA. Male adults; 18-60, DBP 90-104 mm Hg; 13 treatment naïve, 12 currently untreated, excluding diabetes, renal disease, CHD, ≤ 60% overweight, no abnormal resting or exercising ECG	1. unclear 2. unclear 3. unclear 4. 27 5. 10 weeks 6. 10 weeks	1. yes 2. 43.5 R: 21-54 3. 100% 4. 74.1%	1. 137.4/94.5 I: 138.9/95.0 C: 136.1/94.1 2. 0% 3. 0%	1-4. not reported 5. I: 130.2(32.3)/85.2(15.8) 10 --6.4(28.8)/-9.6(14.9) C: 135.8(23.7)/94.4(12.9) 9 +0.9(29.1)/+0.8(18.6)	1. I: 3/13 (23.0%) C: 5/14 (35.7%) 2. I: 3/13 (23.0%) C: 5/14 (35.7%)
ODES 1993-97 Anderssen, 1995	I1: Dietary advice: increased intake of fish oil, veg, fibre-rich carbohydrates, reduced sugar & saturated fat intake; individualised program with follow-up at 3 & 9 months I2: Exercise: 3 weekly sessions (tailored aerobic, circuit training, jogging/fast walking) I3: I1+I2 C: No intervention * All participants advised to stop smoking	Norway. Adults, sedentary, overweight; 41-50, exercise ≤ once week; BMI>24, DBP 86-99; TC 5.2-7.7 mmol/L; HDL< 1.2 mmol/L; TG> 1.4 mmol/L, without CVD, diabetes; previous hypertension treatment unclear	1. open 2. unclear 3. inadequate 4. 219 5. 1 year 6. 1 year	1. yes 2. 44.9 3. 90.4% 4. not reported	1. 132/88 I1: 132.8/87.5 I2: 132.1/89.2 I3: 131.9/88.0 C: 128.7/87.0 * 2. 0% 3. 0%	1-4. not reported 5. I1: -6.4(10.4)/-3.4(7.4), 55 I2: -2.2(8.1)/-2.7(7.3), 54 I3: -5.9(9.0)/-5.2(7.4), 67 C: -0.5(11.1)/-0.7(11.1), 43 I2+I3 vs. I1+C	1. not reported 2. I1: 0/55 (0%) I2: 0/54 (0%) I3: 0/67 (0%) C: 0/43 (0%)

Rogers et al, 1996	I1: Low-intensity aerobic exercise, 50% max O_2 uptake: 45 minutes, 3 times weekly. Treadmill walking/jogging and heart rate self-monitoring
	I2: Moderate-intensity aerobic exercise, 70%-80% max O_2 uptake: 45 minutes, 3 times weekly. Treadmill walking/ jogging and heart rate self-monitoring
	C: No intervention
		USA. Adults; borderline hypertension 140-160 or 90-95; currently untreated, without CVA, CHD, CVD	1. blinded assessment
			2. unclear
			3. unclear
			4. 23
			5. 12 weeks
			6. 12 weeks
				1. yes
				2. 41.3
				3. not reported
				4. not reported
					1. 139/92
					I1: 140.0/93.0
					I2: 138.0/91.0
					C: 140.0/93.0
					2. 0%
					3. 0%
						1-4. not reported
						5.
						I1: -15.0(5.9)/-6.0(3.4), 6
						I2: -4.0(5.3)//-0.5(2.6), 7
						C: -1.0(5.8)//-3.0(4.5), 5
							1/2.
							I1: 2/8(25.0%)
							I2: 2/9(22.2%)
							C: 1/6(16.7%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Staffileno et al, 2001	I: Physical activity: asked to select pleasurable activities (eg walking) for 10 minute bouts 3 times daily, 5 days each week. Instructed to maintain usual diet during study C: No change in diet or activity during study period	USA. Post-menopausal females with currently untreated BP 130-179/85-109; less than 60 minutes physical activity weekly; willing to discontinue antihypertensive medication if currently treated	1. unclear 2. unclear 3. unclear 4. 18 5. 8 weeks 6. 8 weeks	1. not for BP 2. 59.7 3. 0% 4. 66.7%	1. 144/88 I: 141.0/91.7 C: 147.5/83.5 2. not reported 3. not reported	1-4. not reported 5. I: 134.1(11.7)/88.3(10.1), 9 C: 148.7(10.2)/84.7(11.5), 9	1/2. I: 0/9(0%) C: 0/9(0%)
Suter et al, 1990	I: Exercise: supervised jogging 2 hours, 4-6 sessions weekly, non-compulsory regular training sessions offered, self-monitoring of heart rate, running diaries maintained C: No intervention	Switzerland. Adults; non-medicated BP < 170/110; non-smokers; without CVD, ≤ 1 hour physical activity p/wk	1. unclear 2. unclear 3. unclear 4. 61 5. 4 months 6. 4 months	1. yes 2. 37.4 3. 100% 4. not reported	1. 133/88 I: 133.8/89.1 C: 132.3/86.2 2. 0% 3. 0%	1-4. not reported 5. I: -3.4(11.5)/-2.1(8.3), 39 C: -5.9(11.5)/-0.4(8.3), 22	1/2. I: 0/39(0%) C: 0/22(0%)
Tanabe et al, 1989	I: 60 minutes, 3 times weekly exercise on bicycle ergometer, 40-60% max O_2 take up C: observation weekly at outpatient clinic	Japan. Adults, 23-63, with essential hypertension (stage I-II WHO criteria)	1. unclear 2. unclear 3. unclear 4. 31 5. 10 weeks 6. 14 weeks	1 yes 2. 49.6 3. 48.4% 4. unclear	1. 154.6/100.1 I: 155.0/100.1 C: 153.7/100.0 2. unclear 3. unclear	1-4. not reported 5. I: 140.2(14.2)/93.5(14.2), 21 C: 150.5(16.8)/98.8(9.8), 10)	1. unclear I: C: 2. unclear I: C:
Taylor et al, 1998	I: Exercise referral programme: cost subsided, up to 20 sessions at a leisure centre, supervision available, advice to progressively increase duration and intensity C: No intervention * Both groups given Health Education Authority leaflet on preventing CHD	UK. Hypertensive adults (40-70); BP≥140/90, or BMI>25; without SBP≥200, CHD, diabetes, musculoskeletal condition that restricted exercise.	1. unclear 2. adequate 3. unclear 4. 142 5. 10 weeks 6. 37 weeks	1. yes 2. 54.2 3. 37.3% 4. not reported	1. 133/86 I: 132.2/86.1 C: 134.6/86.2 2. 0 3. 0	1-4. not reported 5. I: 129.7(17.1)/84.7(9.5) 40 C: 131.3(17.8)/83.3(9.4), 31	1/2. I: 57/97(58.8%) C: 14/45 (31.1%)

Appendix 8: RCTs of relaxation interventions

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Achmon et al, 1989	I1: Cognitive group therapy for anger control. Weekly 1½ hour therapist-led group sessions: exercises, role-play, assertive behaviour, instructed to practise methods in real life and keep a daily diary I2: Heart rate biofeedback. Weekly 1 hour group sessions led by psychology student and cognitive therapist: participants instructed on how to lower heart rate, pulse rate recorded C: Sham therapy. Attended 2 lectures aimed at stimulating anticipation of BP change, told that monthly BP readings could lower BP, physician available to answer medical questions, free discussion between participants allowed	Israel. Adults, treated or untreated essential hypertension, BP > 140/90, without heart or renal disease, not taking β-blocker, diuretic use allowed but with no dose alteration	1. unclear 2. unclear 3. unclear 4. 97 5. 17 weeks 6. 17 weeks	1. yes 2. 40.6; R: 25-60 3. 50.5 4. not reported	1. I1: 154.0/98.7 I2: 155.0/99.8 C: 155.4/96.1 2. 0 3. not reported	1– 4. not reported 5. I1: 136.9(13.8)/87.3(8.4), 30 I2: 128.4(12.3)/84.3(9.8), 27 C: 152.4(21.7)/96.9(7.1), 20	1/2. I1: 10/40 (25.0%) I2: 10/37 (27.0%) C: 0/20 (0%)
Adsett et al, 1989	I: Relaxation therapy. Weekly one hour therapist-led group sessions: progressive muscle relaxation, information about hypertension, lifestyle & stress C: Education program. Weekly one hour therapist-led group sessions: information about hypertension, lifestyle & stress * Factorial design 2x2 with β-blocker and placebo. I and C aggregated over β-blocker and placebo arms	Canada. Currently untreated mildly hypertensive blue-collar workers, mean DBP 90-105; without CVD, CVA, renal disease; researchers tried to ensure medication intake did not vary during study	1. blinded assessment 2. adequate 3. unclear 4. 47 5. 8 weeks 6. 3 months	1. yes 2. 46.6 3. 100% 4. not reported	1. 145/96 I1: 144.3/96.2 C: 146.5/96.4 2. 0% 3. 0%	1-4. not reported 5. I: -16.7(14.7)/-12.1(9.2), 21 C: -15.5(16.)/-9.8(11.9), 23	1/2. I: 2/23 (8.7%) C: 1/24 (4.2%)
Agras et al, 1983, Southam et al. 1982	I: Relaxation training. Weekly ½ hour therapist led group sessions: tailored instruction in progressive muscular relaxation C: Ambulatory/in clinic BP measurement only	USA. Adults; DBP > 90, essential hypertension 67% treated hypertensives; unclear whether medication was allowed to vary during study.	1. blinded assessment 2. unclear 3. unclear 4. 42 5. 8 weeks + bimonthly booster sessions 6. 17 months	1. unclear 2. 50.7 3. 66.7% 4. not reported	1. 141/95 I: 143.0/98.0 C: 139.9/93.0 2. 0% 3. 0%	1-4. not reported 5. I: 131.9(16.1)/83.0(10.7), 12 C: 134.8(22.2)/86.8(9.6), 18	1. I: 3/19 (15.8%) C: 2/23 (8.7%) 2. I: 7/19 (37%) C: 5/23 (22%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Agras et al, 1987	I: Relaxation training: 8 sessions (individual or group). Education about physiology of hypertension, contraction/ relaxation of muscles; provided with relaxation tapes; taught tension-relieving exercises during working day C: BP monitoring only	USA. Adults, currently treated essential hypertension DBP ≥ 90; unclear whether medication was allowed to vary during study	1. unclear 2. unclear 3. unclear 4. 137 5. 10 weeks 6 30 months	1. yes 2. 52.8 3. 81.8% 4. 89.0%	1. 145.8/97.9 I: 146.6/97.1 C: 145.0/98.8 2. 0% 3. 0%	1-4. not reported 5. I: -9.2(16.8)/-10.1(12.3), 47 C: -8.4(16.5)/-9.8(11.6), 49	1. I: 0/72 (0%) 2. 0/65 (0%) I: 25/72 (34.7%) C: 16/65 (24.6%)
Bennett et al, 1991	I1: Type-A management. Weekly 2 hour therapist-led sessions: education, relaxation, cognitive restructuring, meditation, time management, anger control, assertiveness training I2: Stress management. Weekly 2 hour therapist-led sessions; education, relaxation, cognitive restructuring, meditation; behavioural assignments & diary completion C: No intervention * All participants received handout based on British Heart Society booklet: guidance on BP, salt, exercise, stress before intervention	U.K. Adults; currently untreated mildly hypertensive Type A men DBP 90-104 Note. Type A personality: tendency to anger and hostility	1. unclear 2. unclear 3. unclear 4. 47 5. 8 weeks 6. 6 months	1. unclear 2. 46 3. 100% 4. not reported	1. 152/93 I1: 149.2/92.9 I2: 155.9/93.0 C: 151.2/93.5 2. 0% 3. 0%	1-4. not reported 5. I1: 137.0(12.4)/86.7(6.5), 15 I2: 145.9(14.7)/88.3(8.4), 15 C: 142.3(11.1)/87.9(4.4), 14	1/2. I1: 1/16 (6.3%) I2: 2/17 (11.8%) C: 0/14 (0%)
Brauer, et al, 1979	I1: Group relaxation therapy. Therapist-led weekly ½ hour sessions: muscle relaxation, breathing management, meditation; supplemented by 4 tape-recorded lessons I2: Relaxation therapy with minimal therapist interaction: muscle relaxation, 4 tape-recorded lessons C: Therapist-led sessions of non-specific psychotherapy for stress & tension * A behavioural psychiatrist, cardiologist & medical student acted as therapists treating all three groups	USA. Adults, essential hypertension, treated in previous 6 mths; ≥ 140/90; without CVD, renal disease; unclear whether medication was allowed to vary during study	1. blinded assessment 2. unclear 3. unclear 4. 35 5. 10 weeks 6. 6 months	1. unclear 2. 57.2 3. 86.2% 4. not reported	1. 150/93 I1: 153.0/92.7 I2: 150.0/94.8 C: 145.2/93.1 2. 0% 3. 0%	1-4. not reported 5. I1: -17.8(20.6)/-9.7(15.3), 10 I2: +0.7(15.6)/-4.3(6.1), 9 C: -1.6(15.0)/-1.1(8.7), 10	1. 6/35 (17.1%) 2. 6/35 (17.1%) Numbers by group not reported

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Canino et al, 1994	I1: Behavioural programme. Twice-weekly 1¼ hour therapist-led sessions: training in deep-muscle relaxation, biofeedback, anxiety management C1: placebo treatment – 15 x 75 mins therapist-led sessions; no coping skills strategies training, instructed to record 'stressful life events' & relaxation encouraged C2: No intervention (waiting list)	Venezuela. Adults; SBP > 140 and/or DBP > 90, currently untreated, excluding diabetes, heart/renal disease, 25-48 yrs	1. unclear 2. unclear 3. unclear 4. 21 5. 7½ weeks 6. 6 months	1. unclear 2. 35.4 R: 25-46 3. 66.7% 4. not reported	1. 148/97 I1: 147/96 C1: 156/100 C2: 145/97 2. 0% 3. 0%	1-4. not reported 5. I1: 136.6(6.2)/87.9(5.2), 7 C1: 149.5(3.3)/98.5(3.0), 4 C2: 144.8(8.8)/95.6(7.6), 9	1. not reported 2. I1: 1 C1: 0 C2: 0
Carson, et al, 1988	I: Group relaxation class weekly. Twice daily, ½ hour activity: listening to taped instructions on muscle relaxation C: Group relaxation class weekly. Twice daily, ½ hour activity: quiet reading of self- selected material * Both groups were nurse & dietician-led and received education on CHD & CHD risk management	USA. Adults; history of high blood pressure, elevated cholesterol; with CHD. Only 9 had a history of high BP; unclear whether medication was allowed to vary during study	1. unclear 2. unclear 3. unclear 4. 16 5. 8 weeks 6. 8 weeks	1. yes 2. 63.5 R: 49-73 3. 100% 4. not reported	1. 140/87 I: 137.0/86.0 C: 142.0/87.0 2. 100% 3. 50%?	1-4. not reported 5. I: -20.0(20.1)/-11.8(16.2), 8 C: +1.8(16.1)/-1.5(11.1), 8	1. not reported 2. 0
Cottier et al, 1984	I: Progressive muscle relaxation. 8x45 minute physician-led individual sessions; taught to practice relaxation during particular situations – telephone calls, at traffic lights, watching television, asked to practice twice daily at home for 20 minutes with the aid of a tape and to keep a diary C: Control. Blood pressure measured only and attended clinic for physical examination	USA. Adults, treated or untreated borderline-mild hypertension with no more than 2 drugs, untreated clinic BP 140-170/90-115 , home BP > 135/85	1. open 2. adequate 3. unclear 4. 30 5. 16 weeks 6. 16 weeks	1. yes 2. 34.7; R 18-50 3. 70.0 4. not reported	1. 130/90 I: 130/90 C: 130/90 2. unclear 3. unclear	1-4. not reported 5. I: 128(SD)/87.5(SD), 17 -2(4.9))/-2.5(4.1) C: 131(SD)/92(SD), 9 +1(4.5)/+2(4.8)	1. 4/30 (13.3%) 2. unclear
Frankel, et al, 1978	I1: Biofeedback. 20 therapist-led laboratory sessions of combined DBP & ECG feedback; autogenic training & progressive relaxation exercises; requested to practice exercises at home using tapes C1: Sham treatment. 20 therapist-led laboratory sessions of sham BP feedback conveying a 'sense of success' C2: No intervention	USA. Adults; currently treated & untreated hypertensive patients (mean DBP 90-105) uncomplicated essential hypertension; medication was held constant during the study	1. blinded assessment 2. adequate 3. unclear 4. 22 5. 16 weeks 6. 16 weeks	1. unclear 2. 45.8 R: 29-63 3. 54.5% 4. 63.6%	1. 148/95 I1: 148.0/95.0 C1: 150.0/95.0 C2: 147.0/94.0 2. 0% 3. 0%	1-4. not reported 5. I1: 151.0(16.9)/96.0(7.9), 7 C1: 149.0(18.0)/93.0(5.0), 7 C2: 152.0(13.0)/95.0(3.1), 8	1. not reported 2. 0

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Hatch, et al, 1985	I1: DBP biofeedback. Twelve 1½ hour therapist-led sessions with verbal praise when DBP was reduced I2: Progressive deep muscle relaxation. Twelve 1½ hour therapist-led sessions with instruction to tense & relax muscles C1:Self-directed relaxation Twelve 1½ hour therapist-led sessions; direction on the benefits of relaxation C2: No behavioural therapy	US adults; currently treated & currently untreated essential hypertensives 140/90 – 180/120; participants instructed to continue to take their medication as usual	1. unclear 2. adequate 3 unclear 4. 52 5. 3 months 6. 12 months	1. no, not SBP 2. 51.1 R: 21-70 3. 40.4% 4. 80.7%	1. 138/88* I1: 134.5/86.7 I2: 147.6/89.4 I3: 136.0/87.2 C: 136.0/87.7 2. 0% 3. 0%	1-4. not reported 5. I1: 134.6(9.2)/85.0(6.7), 5 I2: 129.3(14.4)/79.0(6.0), 7 I3: 133.7(8.5)/80.0(9.5), 3 C: 125.2(13.2)/82.2(8.1), 5	1. not reported 2. I1: 8/13 (62%) I2: 6/13 (46%) I3: 10/13 (77%) C: 8/13 (62%)
Hoelscher et al, 1986	I1: Individualised relaxation: therapist-led progressive muscle relaxation training sessions I2: Group relaxation: therapist-led progressive muscle relaxation training sessions I3: Group relaxation as I2 + behavioural contracts to practise relaxation C: No intervention (waiting list)	USA. Adults; currently untreated DBP 90-104; without CHD, CVA; participants instructed to continue to take their medication as usual	1. unclear 2. unclear 3. unclear 4. 50 5. 4 weeks 6. 10 weeks	1. unclear 2. 51.1 3. 52% 4. not reported	1. 149/96 I1: 152.7/97.3* I2: 150.3/95.3* I3: 150.0/95.2* C: 144.9/96.2* 2. 0% 3. 0%	1-4. not reported 5. I1: 138.1(13.6)/91.6(9.0), 11 I2: 135.7(9.4)/89.5(6.9), 12 I3: 140.3(10.6)/87.5(5.9), 12 C: 146.9(18.4)/95.6(6.7), 12	1. not reported 2. I1: 1/12 (8.3%) I2: 0/0 (0%) I3: 0/0 (0%) C: 2/14 (14.3%)
Hoelscher et al, 1987	I1: Live progressive relaxation with home relaxation tape. Weekly group sessions, taught muscle tensing & relaxing exercise, instructed to practice at home with a 16 minute recording of progressive relaxation on a tape-player I2: Live progressive relaxation without home relaxation tape. Weekly group sessions, taught muscle tensing & relaxing exercise, instructed to practice at home with cue cards C: Waiting list	USA. Adults, treated or untreated essential hypertension ≥ 1 year, BP ≥ 140/90, antihypertensive medication not altered in last 3 months	1. blinded assessment 2. unclear 3. unclear 4. 48 5. 4 weeks 6. 3 months	1. unclear 2. 51.9 3. not reported 4. not reported	1. 144.8/93.8 I1: 150.8/93.0 I2: 142.7/93.3 C: 141.0/95.0 2. not reported 3. not reported	1–4. not reported 5. I1: 137.5(11.8)/87.4(7.5), 16 I2: 135.8(13.9)/88.1(5.7), 16 C: 143.3(18.1)/95.2(6.6), 16	1/2. unclear
Irvine et al, 1991	I: Biofeedback and relaxation therapy. Behaviour therapist-led weekly ½ hour sessions on hypertension, risks, muscle relaxation, meditation & mental imagery, 'mini-relaxation' training, biofeedback C: Support therapy: behaviour therapist-led weekly sessions	U.K. Adults; mild primary hypertension, untreated in previous 6 mths, DBP 85-104 in age 18-34 or DBP 90-104 in age 35-59 ; without CHD	1. blinded assessment 2. unclear 3. unclear 4. 110 5. 12 weeks 6. 6 months	1. yes 2. 46.3 R: 25-64 3. 81.8% 4. not reported	1. 137/94 I: 137.3/94.1 C: 136.4/93.6 2. 0% 3. 0%	1-4. not reported 5. I: 129.9(10.6)/87.7(4.1) , 47 C: 131.2(10.6)/88.9(5.7) , 48	1. I: 5/55 (9.1%) C: 4/55 (7.3%) 2. I: 8/55 (14.5%) C: 7/55 (12.7%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Johnston et al, 1993	I: Stress management: ten ½ hour psychologist-led sessions on passive relaxation & meditation C: Mild exercise: ten ½ hour psychologist-led sessions on simple stretching exercises	USA. Adults; currently untreated mean DBP 95-105, treated BP < 110 without CHD, diabetes, BMI > 135	1. single 2. adequate 3. unclear 4. 96 5. 6 months 6. 12 months	1. yes 2. 46.6 R: 23-59 3. 47.9% 4. not reported	1. 138/91 I: 139.8/93.0 C: 140.1/91.9 2. 0% 3. 0%	1-4. not reported 5. I: 140.9(12.6)/92.9(7.6), 40 C: 134.7(13.0)/90.0(9.6), 32	1. I: 5/48(10.4%) C: 7/48(14.6%) 2. I: 8/48(12.5%) C: 16/48(33.3%)
Linden, et al, 2001	I: Mixed behavioural intervention. Weekly 1 hour sessions led by psychotherapists: autogenic training, thermal biofeedback, cognitive therapy, anxiety management, type-A hostile behaviour reduction, discussion of existential issues C: No intervention (waiting list)	Canada. Adults; BP > 140/90 currently treated and currently untreated, without CHD, diabetes; asked to maintain usual medication but physician could vary if necessary	1. unclear 2. unclear 3. unclear 4. 60 5. 10 weeks 6. 3 months	1. yes 2. 54.8 R: 28-75 3. 71.7% 4. 88.3%	1. 153/98 I: 152.0/97.9 C: 154.1/98.9 2. 0% 3. 0%	1-4. not reported 5. I: -6.9(12.3)/-5.4(8.9) , 23 C: -5.1(6.8)/-3.7(4.6) , 26	1/2. I: 4/27 (14.8%) C: 4/33 (12.1%)
McGrady, 1994	I: Group relaxation and feedback. Weekly 45 minute therapist-led sessions providing autogenic relaxation training & thermal biofeedback C: No intervention (waiting list)	USA. Adults; currently treated and currently untreated essential hypertension patients; medication varied in 37 participants during study (all excluded)	1. unclear 2. unclear 3. unclear 4. 138 5. 8 weeks 6. 11 week	1. unclear 2. 48.3 3. 38.6% 4. 75.2%	1. 132/86 I: 132.4/85.8 C: 130.9/85.6 2. 0% 3. 0%	1-4. not reported 5. I: 126.5(13.7)/82.6(10.4), 70 C: 130.0(12.3)/86.6(10.6), 31	1/2. 37/138 (26.8%) Withdrawal and loss to follow-up not reported by group. Numbers randomised to each group not reported
Patel, et al, 1981 Patel et al, 1985	I: Group biofeedback and relaxation. Weekly 1 hour sessions: stress education, breathing exercises, deep-muscle relaxation, meditation, biofeedback, provided with tape & requested to practice relaxation at home, health education literature on dietary fats & smoking C: Control: health education literature on dietary fats & smoking	UK. Adults; mild untreated hypertension: 2/3 of risk factors: mean BP > 140/90; plasma cholesterol >=6.3mmol/l) cigarette smokers	1. unclear 2. unclear 3. unclear 4. 204 5. 8 weeks 6. 4 years	1. yes 2. R: 35-64 3. 61.5% 4. not reported	1. 144.7/87.6 I: 145.2/87.4 C: 144.2/87.9 2. 0% 3. 0%	1. I: 2/107 (1.9%) C: 2/97 (2.1%) 3. not reported 2& 4. I: 2/88 (2.3%) C: 6/81 (27.4%) 5. I: 139.4(22.4)/85.2(13.6), 86 C: 145.7(21.0)/92.4(12.8), 75	1. I: 8/107 (7.5%) C: 4/97 (4.1%) 2. I: 21/107 (19.6%) C: 22/97(22.7%)
Patel et al, 1988	I: Group relaxation and biofeedback. Weekly physician & nurse-led 1 hour sessions: discussion; breathing exercise, deep muscle relaxation & simple meditation training provided; biofeedback provided; home practice encouraged C: No intervention * MRC mild hypertension trial (active drug vs. placebo) substudy: randomised to stop therapy, then further randomised into this trial.	UK. Adults; DBP 90-109, currently treated and currently untreated as determined by allocation in trial, mild hypertension 35-64 yrs	1. open 2. adequate 3. adequate 4. 134 5. 8 weeks 6. 1 year	1. no: not BP* 2. 53* 3. 50.5% * 4. not reported * Assessed in attenders after 1 year	1. 140.1/86.8 I: 144.9/88.6 C: 135.7/85.1 2. 0% 3. 0%	1. I: 1; C: 0 2: I: 0; C: 2 3: I: 1; C: 0 4: I: 1; C: 2 5. I: -4.9(15.0)/-1.5(8.4), 49 C: +7.1(15.0)/+2.6(8.4), 54	1. 23/134(17.2%) 2. 31/134 (23.1%) Withdrawal and loss to follow-up not reported by group

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Schein et al, 2001	I: BIM: 'breathe with interactive music' . Listening to sounds mimicking breathing patterns, using headphone and respiration sensor. C: Passive treatment. Listening to quiet synthesised music with non-identifiable rhythm * Both groups: 10 minutes every evening	Israel. Adults; essential hypertension (currently treated and stabilised and untreated), BP ≥ 140/90, home BP > 135/85; without CHD, CVD, renal disease, diabetes, BMI > 35 kg/m². It is unclear that drugs were kept constant during the study	1. triple 2. adequate 3. unclear 4. 61 5. 8 weeks 6. 8 weeks	1. yes 2. 57.1 3. 47.4% 4. not reported	1. 156/95 I: 156.6/96.7 C: 154.7/93.4 2. 0% 3. 0%	1-4. not reported 5. I: -15.2(13.4)/-10.0(6.5) , 31 C: -11.3(12.8)/-5.6(6.2), 24	1. I: 4/32(12%) C: 5/33(15%) 2. I: 1/32 (3%) C: 5/33 (15%)
Seer et al, 1980	I: Transcendental meditation. Psychiatrist-led sessions twice daily for 15-20 minutes with mantra recitation C1: Sham control: psychiatrist-led training twice daily 15-20 minutes without mantra recitation C2: No intervention (waiting list)	New Zealand. Adults; essential hypertension, currently untreated, without CHD, diabetes, renal disease	1. unclear 2. unclear 3. unclear 4. 41 5. 5 weeks 6. 13 weeks	1. unclear 2. 43.2 R: 22-62 3. 56.1% 4. not reported	1. 150/102 I: 152.4/103.6 C1: 147.4/100.1 C2: 149.8/102.2 2. 0% 3. 0%	1-4. not reported 5. I: -4.8(14.5)/-6.4(11.7), 14 C1: -5.1(9.5)/-7.6(9.6), 14 C2: +1.8(10.7)/+2.2(8.6), 13	1. not reported 2. I1: 0/14 (0%) I2: 0/14 (0%) C: 0/13 (0%)
van Montfrans et al, 1990	I: Relaxation therapy: 8, weekly, 1 hour therapist-led sessions on yoga, breathing, posture exercises, meditation & muscle relaxation C: Non-specific counselling: nurse led sessions encouraging passive relaxation & explaining role of stress in hypertension	Netherlands. Adults; currently untreated SBP 160-200 or DBP 95-110; mild uncomplicated HT, without diabetes, CHD, organ damage	1. unclear 2. inadequate 3. inadequate 4. 42 5. 8 weeks 6. 1 year	1. unclear 2. 41.5 R: 24-60 3. 51.4% 4. not reported	1. 154.7/99.8* I: 153.2/100.7* C: 156.2/98.9* 2. 0% 3. 0%	1-4. not reported 5. I: -2.2(7.7)/-2.4(4.7), 18 C: -2.5(6.8)/-3.1(4.9), 17	1/2. I: 3/23 (13.0%) C: 2/19 (10.5%)
Zurawski et al, 1987	I: Multi-modal stress management training. Weekly 1-11/2 hour therapist-led group sessions: progressive muscular relaxation, role of cognitions in stressful situations and coping strategies, learned cue controlled breathing and relaxation imagery C: Sham therapy. Weekly 1-11/2 hour therapist-led group sessions: biofeedback training control condition	USA. Adults, treated or untreated essential hypertension, but not excessively overweight, those on medication had their dosage stabilised for ≥ 3 months	1. unclear 2. unclear 3. unclear 4. 29 5. 8 weeks 6. 6 months	1. yes 2. 46.9*; R 18-60 3. 27.6* 4. 100	1. 137.5/86.3 I: 137.1/87.1 C: 137.9/85.3 2. unclear 3. unclear	1-4. not reported 5. I: 129.1(17.5)/80.3(9.5), 14 C: 126.8(14.0)/79.2(8.8), 11	1. 4/29(13.8%) 2. I: 0 C: 3/11(27.3%)

Appendix 9: RCTs of multifaceted interventions

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Applegate et al, 1992	I: Diet and exercise. Advice to increase physical activity to 2 hours each week. Eight dietician-led weekly group meetings & 2 individual meetings followed by 4 monthly group meetings. Weight loss goal of 4.5 kg; advice to reduce calorie intake & sodium to 1400mg per day C: No intervention	USA. Older adults 60-85yrs; currently untreated mild diastolic hypertension DBP 85-100; 115% ≥ ideal body weight; without CHD, stroke, diabetes	1. blinded assessment 2. unclear 3. unclear 4. 56 5. 6 months 6. 6 months	1. yes 2. 64.4 3. 44.7% 4. 61.7%	1. 144/88 I: 142.6/86.5 C: 144.5/88.4 2. 0% 3. 0%	1-4. not reported 5. I: -8.7(5.9)/-6.8(5.0), 21 C: 4.5(5.9)/-1.9(5.0), 26	1/2. I: 7/28 (25.0%) C: 2/30 (6.7%)
Blumenthal et al, 2000	I: Group diet and aerobic exercise: 1 hour schedule, 70 -85% of initial heart rate reserve: 3-4 times weekly cycling, walking and jogging. Weight management aimed at weight loss of 0.5–1.0 kg/week C: No intervention * Further exercise only arm	USA. Adults (> 29 years), currently untreated, essential hypertension SBP 130-180 and/or DBP 85–110, sedentary and obese (BMI 25-37), without CHD, renal disease or type I diabetes	1. unclear 2. unclear 3. unclear 4. 133 5. 6 months 6. 6 months	1. yes 2. 47.5 3. 44% 4. 75%	1. 141/94 I 142.7/93.2 C: 143.8/94.4 2. 0 3. 0	1-4. not reported 5. I: 135.3(14.2)/87.6(14.2), 46 C: 142.9(9.8)/93.0(9.8), 22	1/2. I: 9/54 (16.4%) C: 2/24 (8.3%)
Jacob et al, 1985	I: Combined behavioural treatment: relaxation therapy, salt and calorie restriction; 8 weekly group meetings of 90 mins with participant's spouse attendance; psychologist presented didactic material, followed by 20 min relaxation, relaxation tapes dispensed for home use C: BP measurement only	USA. Adults with untreated SBP 130-165 and DBP > 90 mm Hg; without CVD, no other serious illness	1. blinded assessment 2. unclear 3. unclear 4. 57 5. 6 months 6. 18 months	1. unclear 2. 54; R: 37-65 3. 54.0%* 4. 100%*	1. 143.8/85.6 I: 143.1/85.6 C: 144.5/85.5 2. 0 3. 0	1-4. not reported 5. I: -7.6(11.0)/-3.4(6.1), 26 C: -9.6(11.4)/-3.9(6.9), 24	1. I: 3/29 (10.3%) C: 4/28 (14.3%) 2. I: 3/29 (10.3%) C: 4/28 (14.3%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Kostis et al, 1992	I: Group non-pharmacological therapy. Weekly sessions (with spouse) focusing on weight loss (12-15 lbs) dietary change (reduced calorie, low salt), exercise (vigorous walking, swimming or exercise bike), & stress management (mental relaxation) C: Placebo medication * Further drug intervention (β-blocker) arm	USA. Adults; currently untreated mean DBP 95-105, treated BP < 110 without CHD, diabetes, BMI > 135	1. blinded assessment 2. unclear 3. unclear 4. 92 5. 12 weeks 6. unclear	1. yes 2. 57.4 3. 100% 4. 91.1%	1. 164/101 I: 162.3/100.7 C: 167.0/101.0 2. 0% 3. 0%	1-4. not reported 5. I: -12.4(14.6)/-8.0(6.2), 33 C: -4.9(18.9)/-0.1(9.7) , 23 (Beta-blocker arm: -12.2(15.2)/-9.5(7.0), 23)	1/2. I: 5/38 (13.2%) C: 5/28 (17.9%) (Beta-blocker arm: 3/26 (11.5%))
Miller et al, 2002	I: 'Lifestyle' intervention with 4 components; the DASH diet (fruits, vegetables, low fat dairy products, whole grains, poultry, fish, nuts, reduced red meat, sweets, sugar, total fat, saturated fat and cholesterol), a reduced sodium intake of 100 mmol/d, weight loss and 30-45 minutes of supervised moderate- intensity aerobic exercise on 3 days per week. Food was provided and exercise was supervised. C: Bimonthly data collection visit.	USA. Adults (22-70) with treated hypertension (SBP 130-170 mm Hg and DBP 80-100 mm Hg), BMI >25 kg/m². Exclusion criteria: active or prior CVA, medication treated diabetes, random glucose of 180 mg/dL, renal insufficiency.	1. blinded assessment 2. adequate 3. inadequate 4. 45 5. 9 weeks 6. 9 weeks	1. yes 2. 53.5 3. 38% 4. 38%	1. 136.3/83.6* I: 135.3/83.6* C: 137.1/83.6* 2. 0% 3. 0% * no's at end of follow-up	1-4. not reported 5. I: 124.8(14.5)/77.7(9.4), 20 C: 136.0(12.5)/83.0(8.4), 23 * 24-hour ambulatory BP	1/2. I: 2/22 (9.1%) C: 0/23 (0%)
ODES 1993-97 Anderssen, 1995	I: Diet and exercise. Advice to increase intake of fish oil, veg, fibre-rich carbohydrates, reduced sugar & saturated fat intake; individualised program with follow-up at 3 & 9 months. Exercise: 3 weekly group sessions (tailored aerobic, circuit training, jogging/fast walking) C: No intervention * All participants advised to stop smoking. Further separate diet and exercise arms	Norway. Adults, sedentary, overweight; 41-50, BMI>24, DBP 86-99; TC 5.2-7.7 mmol/L; HDL< 1.2 mmol/L; TG> 1.4 mmol/L, without CVD, diabetes; previous hypertension treatment unclear	1. open 2. unclear 3. inadequate 4. 219 5. 1 year 6. 1 year	1. yes 2. 44.9 3. 90.4% 4. not reported	1. 132/88 I: 131.9/88.0 C: 128.7/87.0 * 2. 0% 3. 0%	1-4. not reported 5. I: -5.9(9.0)/-5.2(7.4), 67 C: -0.5(11.1)/-0.7(11.1), 43	1. not reported 2. I: 0/67 (0%) C: 0/43 (0%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Cupples et al, 1994 *(not included in meta-analysis)*	I: Health education regarding cardiovascular risk factors given by trained health visitors. Review every 4 months and appropriate health education given C: No intervention	U.K. Adults < 75yrs; known angina for 6 months, no other serious illness	1. blinded assessment 2. adequate 3. inadequate 4. 688 5. 2 years 6. 2 years	1. yes 2. 63.2 3. 59.3% 4. not reported	1. 137/83 I: 137.2/83.1 C: 137.0/82.0 2. 100% 3. 0%	1. I: 13/342(3.8%) C: 29/346(8.4%) 2. I: 10/342(2.9%) C: 28/346(8.1%) 3-4. not reported 5. I: 136.5(21.3)/76.9(12.4), 317 C: 136.0(23.2)/77.0(13.7), 300	1. I: 25/342(3.8%) C: 46/346(8.3%) 2. I: 12/342 (7.3%) C: 17/346 13.3%)

Appendix 10: RCTs of interventions to reduce alcohol intake

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Maheswaran et al, 1992	I: Hospital clinic, individual tailored advice on reduction/substitution, fortnightly for 8 weeks. C: Usual care.	UK. Adult males attending hypertension clinic, >20 units alcohol p/wk, DBP≤105; without diabetes or secondary hypertension; not 'alcoholic'; treated or untreated with drugs.	1. blinded assessment 2. unclear 3. unclear 4. 45 5. 8 weeks 6. 8 weeks	1. yes 2. 45 3. 100% 4. 72.3%	1. 148/90 I: 144.2/90.1 C: 152.0/89.8 2. not reported 3. not reported	1-4. not reported 5. I: -6.3(10.1)/5.5(8.7), 21 C: -4.1(9.4)/0.4(8.5), 20	1. I: 1/22 (4.5%) C: 3/23 (13.0%) 2. I: 1/22 (4.5%) C: 3/23 (13.0%)
Puddey et al, 1992	I: Dietician advice to substitute with low-alcohol lager (0.9%), 3l provided per fortnight. C: Usual alcohol intake, 3l lager (5%) provided per fortnight. * Factorial design: diet and alcoholl	Australia. Overweight males (25-70); SBP 130-160 and DBP 80-105; BMI > 25 kg/m²; alcohol consumption ≥ 3 standard drinks/day; without CHD, CVA, renal disease, diabetes; currently untreated with drugs.	1. unclear 2. unclear 3. unclear 4. 86 5. 18 weeks 6. 18 weeks	1. yes 2. 44 3. 100% 4. not reported	1. 137/85 I: 136.4/85.2 C: 138.4/84.7 2. 0% 3. 0%	1-4. not reported 5. I: -8.8(7.7)/-6.7(6.8), 44 C: -4.0(8.0)/-3.2(6.4), 42	1. 13/86(15**%**) 2. not reported
PATHS, 1994-98	I: Individual cognitive behavioural intervention by trained female nurse, psychologist or social worker, 9 sessions. Advice to reduce alcohol to ≤14 drinks/week or 50% of normal. C: Usual care.	USA. Adults (21-79); ≥21 alcoholic drinks/week; DBP 90-99 or DBP 80-99 after withdrawal of antihypertensive medication and SBP<180; currently untreated with drugs.	1. blinded assessment 2. adequate 3. unclear 4. 266 5. 6 months 6. 2 years	1. unclear (gender not reported) 2. 59 3. not reported 4. 75%	1 146/89 I: 145.5/89.3 C: 147.7/89.7 2. not reported 3. not reported	1-4. not reported 5. I: -5.5(15.3)/-6.8(8.0), 53 C: -4.7 (11.3)/-4.4(8.0), 44	1. not reported 2. I: 85/138 (62%) C: 84/128 (66%)
Lang et al, 1995	I: Group worksite physician training at 1,3 & 6 months. Patient consultations at 1, 3, 6 & 18 months, advice on alcohol reduction. C: Routine worksite physician contact without alcohol intervention. * Cluster design: physicians were randomised, not patients.	France. Adults BP>140/90; excessive alcohol drinkers; GGT (gamma glutamyl transferase) >1.5 upper limit of normal range; without secondary hypertension or liver disease; treated or untreated with drugs.	1. unclear 2. unclear 3. unclear 4. 129 5.18 months 6. 2 years	1. yes 2. 43 3. 95% 4. not reported	1. 163/99 I: 164.5/99.9 C: 161.6/98.3 2. not reported 3. not reported	1-4. not reported 5. I: -13.8(17.4)/-7.3(11.9), 32 C: -7.5(14.2)/-5.6(9.2), 37 Sample size adjusted assuming ICC=0.1	1. 29 (22%) 2. 29 (22%)

Appendix 11: RCTs of interventions to increase calcium salt intake

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
RCTs of parallel design							
Grobbee et al, 1986	I: Calcium (25mmol/d) as citrate C: Matched placebo * Both in water soluble powdered form, 3 doses/day; no dietary advice was given	Adults (16-29); followed from earlier child CVD risk study; currently untreated; SBP > 140 and/or DBP>90; without secondary hypertension	1. double 2. unclear 3. unclear 4. 90 5. 12 weeks 6. 12 weeks	1. yes 2. 24.2 3. 85.6 4. not reported	1. 143/83 I: 143.2/83.3 C: 143.2/82.8 2. not reported 3. not reported	1-4. not reported 5. I: 138.9(13.5)/78.8(9.9), 46 C: 139.3(10.0)/80.7(9.5), 44	1. I 5/46 (10.9%) C 5/44 (11.4%) 2. I 0/46 (0%) C 0/44 (0%)
Lyle, 1992	I: Calcium (37.5 mmol/d) as carbonate C: Matched placebo * 3 doses/day	USA. Adults with untreated high normal-mildly hypertensive BP (DBP 85-104 mm Hg) free from renal dysfunction and not digesting > 1,000 mg/day dietary calcium	1. double 2. unclear 3. unclear 4. 44 5. 8 weeks 6. 8 weeks	1 no – sex 2. 34.1 3. 76.2% 4. unclear	1. 132.6/87.4 I: 132.4/88.2 C: 132.7/86.5 2. unclear 3. unclear	1-4. not reported 5. I: 124.5(5.8)/81.8(4.8), 21 C: 130.8(10.4)/87.3(6.7), 21	1. 2/44 (4.5%) not reported by arm 2. I: 1/22 (4.5%) C: 1/22 (4.5%)
Nowson et al, 1989	I1: Calcium (10 mmol/d) as carbonate I2: Calcium (20 mmol/d) as carbonate C: Placebo	Adults (22-77); DBP> 90, or mean arterial pressure >105.	1. double 2. unclear 3. unclear 4. 47 5. 2 months 6. 2 months	1. No 2. 57.0 3. 87.2% 4. not reported	1. 153/91 I1: not reported I2: not reported C: not reported 2. not reported 3. not reported	1-4. not reported 5. I1: -7.0(29.7)/-2(8.0), 16 I2: -2.0(21.0)/+1.0(11.2), 14 C: -3.0(13.2)/-2.0(8.2), 17	1. 3/47 (6.4%) not reported by arm 2. not reported
Petersen et al, 1994 *(excluded from meta-analysis as all patients were on haemodyalysis)*	I: Calcium (50 mmol/d) C: Matched placebo * 4 doses/day	Adults undergoing haemodialysis; currently treated and untreated for hypertension, SBP > 140 and DBP > 95; with renal complications; without diabetes; antihypertensive medication continued unchanged during the study	1. double 2. unclear 3. unclear 4. 23 5. 6 months 6. 6 months	1. yes 2. 55.0 R: 31-70 3. 60.9% 4. not reported	1. 145/81 I: 147.9/82.5 C: 142.9/80.0 2. not reported 3. not reported	1-4. not reported 5. I: 152.4(27.5)/75.6(8.5), 10 C: 147.9(31.3)/83.8(13.6), 10	1. I: 1/11 (9.1%) C: 2/12 (16.7%) 2. I: 1/11 (9.1%) C: 2/12 (16.7%)

Trial/	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration	1. Carryover effects 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Endpoint BP 2. Difference in endpoint BP in treatment and control groups	1. Withdrawal 2. Loss to follow-up
RCTs of crossover design							
Galloe et al, 1993	I: 50mmol (2g)/day calcium as gluconate (powdered form and sodium free) C: matching placebo * No washout period	Denmark. Adults attending outpatient chest clinic; mean arterial BP 110-130 mm Hg; SBP 160-220 and DBP 90-110 mm Hg; treatment naïve; without serious disease	1. double 2. adequate 3. unclear 4. 30 5. 12 weeks	1. no carry over 2. 62.8; R: 42-75 3. 66.7% 4. not reported	1. 168.8/96.5 2. not reported 3. not reported	1. I: not reported C: not reported 2. +2.2(20.1)/+3.3(12.3)	1. 10/30 (33%) 2. 10/30 (33%)
Kawano et al., 1998	I: 25mmol (1g)/day calcium as carbonate. C: No treatment. * No washout period	Japan. Adults, mild to moderate essential hypertension, currently treated (41 patients) and currently untrreated (19 patients), SBP≥140 and/or DBP≥90 mm Hg.. Anti-hypertensive medication did not change during course of study.	1. open 2. unclear 3. unclear 4. 60 5. 8 weeks.	1. not reported 2. 58; R:35-74 3. 58.3% 4. 0%	1. 149/90 2. not reported 3. not reported	1. I: not reported C: not reported 2. -2.0(9.3)/-1.1(5.4)	1. not reported 2. not reported
McCarron, 1985	I: 25mmol (1g)/day calcium C: matching placebo * 4 week washout period	USA. Adults, 21-70yrs, essential hypertension, MAP>105 mm Hg. 18 treatment naïve, 30 currently untreated, excluding MI<1yr., congestive heart failure, cerebrovascular accident, renal disease.	1. double 2. adequate 3. adequate 4. 48 5. 8 weeks	1. not reported 2. 51.8 3. 52.1% 4. 95.8%	1. 152/94 2. 0% 3. not reported	1. I: 149(16)/94(9) C: 152(17)/94(9) 2. -3.8(9.7)/0(S.D.)	1. 0/48 (0%) 2. 0/48 (0%)
Strazullo et al, 1986	I: 25mmol (1g)/day calcium (2x500 mg /day) C: matching placebo * 12 week washout period.	Italy. Adults; mild uncomplicated essential hypertension, DBP 90-105 mm Hg, currently treated and currently untreated, 9 patients treatment naïve.	1. triple 2. unclear 3. unclear 4. 18 5. 15 weeks	1. no carryover 2. 43.0 3. 61.1% 4. not reported	1. 145/91 2. not reported 3. not reported	1. I: 142(11.9)/91(7.1) C: 145(9.5)/92(6.0) 2. -3(SD)/-1(SD)	1. 1/18 (5.6%) 2. 1/18 (5.6%)
Takagi et al., 1991	I: 25mmol (1g)/day calcium C: No treatment. Both groups received a diet containing 500mg calcium, 2 sodium, & 3g potassium/day. * 4 week washout period	Japan. Mild to moderate essential hypertension.	1. unclear 2. unclear 3. unclear 4. 9 5. 8 weeks	1. not reported 2. 76.5; R:65-86 3. 33% 4. 0%	1. 145.5/77.5 2. not reported 3. not reported	1. I: 130(7.5)/70(5.7)* C: 145(16.4)/81(15.0)* 2. -15(SD)/-11(SD)* * mean 24-hr ambulatory BP	1. 0/9 (0%) 2. 0/9 (0%)
Tanji et al, 1991	I: 30mmol (1.2g)/day calcium as carbonate C: placebo * 1 week washout period	Adults (30-65); mild hypertension (DBP 90-104 mm Hg), currently untreated; excl.uding MI < 6 months, unstable angina, stable angina treated with calcium-channel blocker, unstable hypertensive end-organ damage, renal disease.	1. double 2. unclear 3. unclear 4. 28 5. 3 months	1. not reported 2. 47.5* 3. 33.3%* 4. 75%*	1. 146/95 2. not reported 3. not reported	1. I: 138(14)/88(8) C: 138(22)/87(8) 2. 0(SD)/1(SD)	1. 9/28 (32.1%) 2. 9/28 (32.1%)

Trial/	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration	1. Carryover effects 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Endpoint BP 2. Difference in endpoint BP in treatment and control groups	1. Withdrawal 2. Loss to follow-up
Weinberger et al, 1993	I: 12.5mmol (0.5g)/day calcium as carbonate C: matching placebo * 2 week washout period	Currently untreated mild essential hypertension	1. double 2. unclear 3. unclear 4. 17 5. 8 weeks	1. not reported 2. not reported 3. 58.8 4. not reported	1. 131/87 2. not reported 3. not reported	1. I: 134(15)/86(9) C: 136(18)/87(8) 2. -2(SD)/-1(SD)	1. 0/17 (0%) 2. 0/17 (0%)
Zoccali et al, 1986	I: 25mmol (1g)/day calcium as gluconate lactate and carbonate C: matching placebo * 2 week washout period	Italy. Adults; mild to moderate uncomplicated essential hypertension, SBP>140mm Hg, DBP>90mm Hg; 11 treatment naïve, 12 currently untreated,	1. double 2. unclear 3. unclear 4. 23 5. 8 weeks	1. no carryover 2. 42.6; R: 27-59 3. 69.6% 4. not reported	1. 142.0/87.0 2. not reported 3. not reported	1. I: 143(13.7)/88(9.2) C: 140(13.7)/86(9.2) 2. 3.0(SD)/2.0(SD)	1. 2/23 (8.7%) 2. 2/23 (8.7%)

Appendix 12: RCTs of interventions to increase magnesium salt intake

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
RCTs of parallel design							
Borrelo et al, 1996	I: Magnesium (10 mmol/d) as oxide C: Placebo	Italy. Adults with treatment naïve mild hypertension. Exclude renal/hepatic/ metabolic/hematologic dysfunction	1. triple 2. not reported 3. not reported 4. 83 5. 12 weeks 6. 12 weeks	1. yes 2. 50.0 3. 36.1% 4. not reported	1. 155.5/92.8 I: 155.0/93.0 C: 156.0/92.5 2: not reported 3: 0%	1. I: 0/9 (0%) C: 0/9 (0%) 2-4. not reported 5. I: 148.5(7.1)/87.5(6.3), 42 C: 155.2(8.2)/93.2(4.5), 41	1/2. I: 0/42 (0%) C: 0/41 (0%)
Ferrara et al, 1992	I: Magnesium (15 mmol/d) as pidolate C: Placebo	Italy. Adult (35-60); mild to moderate essential hypertension; BP<180/114; no ongoing chronic disease, renal failure or diabetes. Treated or untreated for hypertension.	1. double 2. unclear 3. unclear 4. 26 5. 6 months 6. 6 months	1. yes 2. 47.5 2. 57.1% 4. not reported	1. 157/95 I: 156.0/97.0 C: 158.0/93.0 2. 0% 3. 0%	1-4. not reported 5. I: 149.0(8.0)/90.0(3.0), 7 C: 141.0(8.0)/89.0(3.0), 7	1/2. I: 6/13 (46.2%) C: 6/13 (46.2%)
Henderson et al 1986	I: Magnesium (12.5mmol/d) as oxide 500mg C: Placebo	Denmark. Adult; DBP<105; hypertension treated with potassium depleting diuretics for more than 6 months; without heart disease.	1. double 2. unclear 3. unclear 4. 41 5. 6 months 6. 6 months	1. no. I: DBP lower 2. 62 3. not reported 4. not reported	1. 156/90 I: 154/87 C: 157/93 2. 0% 3. not reported	1-4. not reported 5. I: 150(20)/88(7), 20 C: 154(22)/92(6), 20	1/2. I: 1/21 (5%) C: 0/20 (0%)
Lind et al, 1991	I: Magnesium (15 mmol/d) as lactate and citrate C: Placebo	Sweden. Adult; mild essential hypertension; DBP≥95 or DBP 85–94 and SBP≥165; currently untreated; without cardiovascular disease, renal impairment or diabetes.	1. double 2. unclear 3. unclear 4. 71 5. 6 months 6. 6 months	1. unclear 2. 60.6 2. 52.1 % 4. not reported	1. 150/92 I: 151.0/91.8 C: 148.0/93.1 2. 0 3. 0	1-4. not reported 5. I: 152.0 (14.0)/89.1(7.4), 48 C: 146.0(11.0)/88.9(7.3), 21	1. I: 1/49 (2.0%) C: 1/22 (4.5%) 2. I: 1/49 (2.0%) C: 1/22 (4.5%)
Nowson et al, 1989	I: Magnesium (10 mmol/d) as aspartate C: Placebo * All participants followed a low sodium diet (50-70 mmol sodium/day)	Australia. Adult (50-77); mild essential hypertension, currently untreated.	1. double 2. unclear 3. unclear 4. 25 5. 8 weeks 6. 8 weeks	1. yes 2. 62.6 2. 68.0 % 4. not reported	1. 144.9/88.3 I: 144.3/86.4 C: 145.5/90.0 2. not reported 3. not reported	1-4. not reported 5. I: 146.0(6.5)/87.8(3.8), 12 C: -143.0(6.9)/87.3(4.7), 13	1/2. I: 0/12 (0%) C: 0/13 (0%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Paolisso et al, 1992	I: Magnesium (16 mmol/d) as pinolate C: Placebo * All subjects continued thiazide diuretic treatment during trial without any change in dosage	Italy. Adults with currently treated essential hypertension. Excluded if renal impaired or suffering papilloedema	1. triple 2. not reported 3. not reported 4. 18 5. 8 weeks 6. 8 weeks	1. yes 2. 64 3. 50% 4. not reported	1. 173/96 I: not reported C: not reported 2: not reported 3: 0%	1. I: 0/9 (0%) C: 0/9 (0%) 2-4. not reported 5. I: 159(12)/89(15), 9 C: 171(24)/95(9), 9	1/2. I: 0/9 (0%) C: 0/9 (0%)
Walker et al, 2002	I: Magnesium (25mmol/d) (600 mg/day aggregated over hawthorn and no hawthorn) C: No magnesium (aggregated over hawthorn and no hawthorn) * 2x2 factorial trial: Magnesium, hawthorne, placebo	UK. Adults with currently untreated hypertension (DBP 85-100) without coronary heart disease, diabetes or renal disease	1. double 2. adequate 3. inadequate 4. 36 5. 10 weeks 6. 10 weeks	1. unclear 2. 50.9 3. 50% 4. not reported	1. 150.1/96.7 I: 149.2/96.2 C: 151.1/97.2 2. 0% 3. not reported	1-4. not reported 5. I: 138.2(14.1)/88.9(9.1), 19 C: 138.4(15.0)/90.4(9.2), 17	1/2. I: 0/19 (0%) C: 0/17 (0%)
Witteman et al 1994	I: Magnesium (20 mmol/d) as aspartate hydrochloride C: Placebo	The Netherlands. Middle-aged and elderly women; mild to moderate essential hypertension; SBP≥140 and/or DBP≥90 but <185/105; currently untreated; without cardiovascular disease or type I diabetes.	1. single 2. unclear 3. unclear 4. 91 5. 6 months 6. 6 months	1. yes 2. 57.3 3. 0% 4. not reported	1. 146/90 I: 146.2/89.4 C: 146.4/90.0 2. 0% 3. 0%	1-4. not reported 5. I: 143.8(14.0)/86.1(7.0), 47 C: 146.6(13.5)/90.1(6.9), 44	1. I: 6/47 (12.8%) C: 7/44 (15.9%) 2. I: 0/47 (0%) C: 0/44 (0%)
Zemel et al 1990	I: Magnesium (40 mmol/d) as aspartate hydrochloride C: Placebo	USA. Adults (20-69); mild to moderate essential hypertension; currently untreated; SBP<180 and DBP 85-100 after withdrawal of medication for 3 months; without renal disease.	1. double 2. unclear 3. unclear 4. 13 5. 3 months 6. 3 months	1. yes 2. 49.8 3. 84.6% 4. ~60%	1. 143/90 I: 145/90 C: 140/89 2. 0% 3. 0%	1-4. not reported 5. I: 148(15.9)/92(5.3), 7 C: 139(12.5)/90(10), 6	1. not reported 2. I: 0/7 (0%) C: 0/6 (0%)

Trial/	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration	1. Carryover effects 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Endpoint BP 2. Difference in endpoint BP in treatment and control groups	1. Withdrawal 2. Loss to follow-up
RCTs of crossover design							
Kawano et al., 1998	I: Magnesium (20mmol/d) as oxide C: No treatment. * No washout period	Japan. Adults, SBP>140 and/or DBP>90 mm Hg. Anti-hypertensive medication did not change durting course of study.	1. open 2. unclear 3. unclear 4. 62 5. 8 weeks.	1. not reported 2. 58.1*; R: 35-74* 3. 56.7*% 4. 0%	1. not reported 2. not reported 3. not reported	1. I: 144.9(13.4)/88.3(7.1) C: 148.6(12.6)/90.0(7.1) 2. -3.7(10.1)/-1.7(5.4)	1. 2/62 (3.2%) 2. 2/62 (3.2%)
Wirrel et al 1994	I: Magnesium (15 mmol/d) as aspartate hydrochloride C: matching placebo * No washout period	Sweden. Moderate essential hypertension. All patients on beta-blockers. Medication unchanged during study.	1. double 2. unclear 3. unclear 4. 40 5. 8 weeks	1. not reported 2. 35.4*; R:26-69* 3. 76.9%* 4. not reported	1. 147.9/95.1 2. not reported 3. 0%	1. I: 145.1(18.2)/93.0(8.2) C: 149.3(18.6)/95.7(10.3) 2. -4.2(SD)/-2.7(SD)	1. 1/40 (2.5%) 2. 1/40 (2.5%)

Appendix 13: RCTs of interventions to increase potassium salt intake

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
RCTs of parallel design							
Bulpitt et al 1985	I: Potassium (64 mmol/d) as chloride C: No additional potassium * I: higher proportion given low salt dietary advice	UK. Adults; treatment including a potassium losing diuretic; without potassium sparing diuretic	1. blinded assessment 2. unclear 3. unclear 4. 33 5 3 months 6. 3 months	1. unclear 2. 55.0 3. 45.3 % 4. not reported	1. 151/96 I: 149.3/92.8 C: 151.5/97.5* 2. not reported 3. not reported	1. I: 0/14(0%); C: 1/19(7%) 2. I: 0/14(0%); C: 0/19(0%) 3. I: 0/14(0%); C: 1/19(7%) 4. I: 0/14(0%); C: 1/19(7%) 5. I: -5.2(22.7)/+0.5(9.7), 13 C: -7.5(27.5)/-4.3(13.1), 19	1. I: 1/14 (7.1%) C: 0/19(0%) 2. I: 1/14 (7.1%) C: 0/19(0%)
Chalmers et al, 1986	I: Advice to increase potassium in diet (>100 mmol/d) C: Usual diet * Factorial design: reduced sodium and increased potassium	Adults DBP 90 -100 currently untreated, no cardiovascular disease	1. unclear 2. unclear 3. unclear 4. 212 5. 12 weeks 6. 12 weeks	1. yes 2. 52.3 3. 85.4 % 4. not reported	I: 151/95 I: 151.5/94.5 C: 149.8/94.5 2. 0% 3. 0%	1-4. not reported 5. I: -7.6(6.5)/-4.6(5.0), 100 C: -3.3(6.4)/-3.1(5.0), 100	1/2. I: 5/105 (5%) C: 7/107 (7%)
Obel, 1988 *(not included in meta-analysis)*	I: Potassium (64 mmol/d) C: Matched placebo	Kenya. Adults (20-60); treatment naïve; DBP 90-109, SBP>160	1. double 2. unclear 3. unclear 4. 48 5. 16 weeks 6. 16 weeks	1. yes 2. 41 3. 43.8% 4. 0%	1. 174/100 I: 175.0/100.0 C: 173.0/100.0 2. not reported 3. not reported	1-4. not reported 5. I: 133.0(10)/83.0(4), 24 C: 172.0(7)/100.0(4), 24	1. not reported 2. I: 0/24 C: 0/24
Siani et al 1987	I: Potassium (48 mmol/d) C: Matched placebo	Italy. Adults (21-61); SBP>160 or DBP>90; without comorbidity; not taking diuretics; normal serum potassium.	1. triple 2. unclear 3. adequate 4. 37 5. 15 weeks 6. 15 weeks	1. yes 2. 45 3. 62.2% 4. not reported	1. 145/92 I: 144.8/91.6 C: 145.1/91.5 2. 0% 3. 0%	1-4. not reported 5. I: 131.8(12.7)/82.0(8.9), 18 C: 145.8(11.3)/92.5(9.2),19	1/2. I: 0/18(0%) C: 0/18(0%)
Svetkey et al 1987	I: Potassium (120 mmol/d) as chloride C: Matched placebo	USA. Adults; DBP 90 -105: currently untreated; without cardiac; renal disease or K > 5.0mEq/l.	1. triple 2. adequate 3. adequate 4. 116 5. 8 weeks 6. 8 weeks	1. not reported 2. 51.1 3. 74.0% 4. 86.1%	1.145/95 I: 147.5/95.2 C: 142.1/94.1 2. 0% 3. 0%	1-4. not reported 5. I: 141.1(13.0)/91.1(8.3), 54 C: 142.0(13.0)/92.4(6.3), 47	1. I: 5/59(8.5%) C: 10/57(17.5%) 2. I: 5/59(8.5%) C: 10/57(17.5%)

Trial/	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration	1. Carryover effects 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Endpoint BP 2. Difference in endpoint BP in treatment and control groups	1. Withdrawal 2. Loss to follow-up
RCTs of crossover design							
Overlack et al, 1991	I: Potassium (120 mmol day) as 50% potassium citrate and 50% potassium bicarbonate C: placebo * No washout period	Germany. Hypertensive adults not currently treated DBP 95-110mm Hg; excluding diabetes, cardiovascular or renal disease.	1. blinded assessment 2. unclear 3. unclear 4. 12 5. 8 weeks	1. not reported 2. 36.5; R 25-59 3. 66.7 % 4. not reported	1. 150.0/100.0 2. 0% 3. 0%	1. I: 153.5(13.6)/102.0(2.3) C: 151.5(2.8)/97.5(2.3) 2. +2(SD)/+4.5(SD)	1. 0/12 (0%) 2. 0/12 (0%)

Appendix 14: RCTs of interventions to reduce sodium salt intake

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
RCTs of parallel design							
Chalmers et al, 1986	I: Advice to reduce sodium in diet (50-75 mmol/d) C: Usual diet * Factorial design: reduced sodium and increased potassium	Adults DBP 90 -100 currently untreated, no cardiovascular disease	1. unclear 2. unclear 3. unclear 4. 212 5. 12 weeks 6. 12 weeks	1. yes 2. 52.3 3. 85.4 % 4. unclear	1. 151/95 I: 152.2/94.5 C: 149.5/94.5 2. 0% 3. 0%	1-4. not reported 5. I: -8.4(6.6)/-5.0(4.6), 99 C: -5.4(7.7)/-3.1(4.6),101	1/2. I: 6/105 (6%) C: 6/107 (6%)
Fagerberg et al 1985	I: energy restricted salt restricted (< 100mmol/d) diet C: energy restricted salt unrestricted diet * Adherence monitored by a dietician through interviews, body mass measurements and 24- hour urinary sodium excretion	Sweden. Adults with untreated essential hypertension, DBP 94-105, and BMI > 20-40% normal weight. Excluding CVD, renal disease or diabetes	1. unclear 2. unclear 3. unclear 4. 23 5. 9-11 weeks 6. 9-11 weeks	1. unclear 2. 51.3* 3. 100%* 4. not reported	1. 150.1/88.2 I: 147.6/85.9 C: 152.1/90.0 2. not reported 3. not reported	1-4. not reported 5. I: 132.6(11.6)/76.4(6.2), 8 C: 144.6(16.1)/83.9(6.3), 10	1/2. 5/23 (21.7%)
Jula et al, 1994	I: sodium restriction:< 70 mmol/d, advice on losing weight and reducing intake of saturated fats C: control: no advice * No antihypertensive medication used in either group	Finland. Adults 31-55 years, with treatment naive mild-moderate essential hypertension. Exclusion criteria oral contraceptives, any other regular medication or significant valvular disease.	1. unclear 2. unclear 3. unclear 4. 91 5. 12 months 6. 12 months	1. yes 2. 43.8* 3. 60.5%* 4. not reported	1. 146.7/97.1 I: 149.3/97.6 C: 144.1/96.6 2. not reported 3. not reported	1-4. not reported 5. I: 133.8(11.9)/88.8(6.1), 38 C: 135.3(9.9)/91.6(5.3), 38	1. 15/91 (16.5%) 2. not reported
Silman et al, 1983	I: Advice to reduce sodium to 100 mmol sodium per day C: Usual intake * All participants given general lifestyle advice	UK. Adults (50-64); untreated DBP 95-104; treatment naïve.	1. unclear 2. unclear 3. unclear 4. 28 5. 12 months 6. 12 months	1. unclear 2. range 50-64 3. unclear 4. unclear	1. 163/98 I: 165.3/98.8 C:160.5/98.3 2. 0% 3. 0%	1-4. not reported 5. I: -28.7(29.1)/-17.7(12.5), 10 C: -20.0(24.0)/-11.4(10.5), 15	1/2. I: 0/12 (0%) C: 1/16 (6.3%)
Costa et al, 1981 *(not included in meta-analysis)*	I Advised to take a low salt diet (130mmol/d) C Regular diet	Italy. Young adults age 16-31 years; treatment and disease history unclear	1. unclear 2. unclear 3. unclear 4. 41 5. 1 year 6. 1 year	1. unclear 2. ? R 16-31 3. unclear 4. unclear	1. 143/84 I: 143.4/84.1 C: 143.3/84.2 2. 0% 3. 0%	1-4. not reported 5. I: 129.3(12)/78.1(9), 21 C: 147.7(15)/83.9(11), 20	1/2. unclear

Trial/	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration	1. Carryover effects 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Endpoint BP 2. Difference in endpoint BP in treatment and control groups	1. Withdrawal 2. Loss to follow-up
RCTs of crossover design							
Chalmers, 1989	I: low sodium: advised to reduce dietary sodium intake to < 80 mmol/d + placebo tablets C: normal sodium: advised to reduce dietary sodium intake to < 80 mmol/d + slow release sodium chloride 80 mmol/d * No washout period	Australia. Adults attending outpatient clinics with mild untreated hypertension, DBP 90-100 mm Hg and without complications of hypertension or CVD	1. double 2. unclear 3. unclear 4. 88 5. 8 weeks	1. no carry-over 2. 58.6 3. 83.0% 4. not reported	1. 153.5/95.0 2. 0% 3. not reported	1. I: 148.5(SD)/91.9 (SD) C: 152.1(SD)/94.0(SD) 2. -3.6(6.7)/-2.1(3.8)	1. 9/88 (10.2%) 2. not reported

Appendix 15: RCTs of combined salt supplements

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. Baseline BP 2. CV disease% 3. Diabetes%	1. Total Mortality 2. CHD events 3. Cerebrovascular events 4. Cardiovascular events 5. Blood Pressure	1. Withdrawal 2. Loss to follow-up
Geleijnse, et al, 1994	I: Mineral salt and foods prepared with mineral salt (Na:K:Mg 8:6:1 mmol) C: Common salt diet (Na only) * All participants received prepared trial food	Netherlands. Adults aged 55 - 75; currently untreated SBP 140-200 or DBP 85-110; without CVD, renal disease, diabetes	1. double 2. adequate 3. unclear 4. 100 5. 24 weeks 6. 24 weeks	1. yes 2. 66.4 3. 51% 4. not reported	1. 158/90 I: 158.0/89.8 C: 157.5/90.8 2. 0% 3. 0%	1-4. not reported 5. I: 150.9(12.9)/86.8(8.1), 46 C: 156.0(13.6)/90.9(8.6), 51	1. I: 1/49 (2.0%) C: 2/51(3.9%) 2. I 3/49(6.1%) C: 0/51(0%)
Sacks et al, 1995	I1: Calcium (25 mmol/ day) and magnesium(15 mmol/d) I2: Potassium (60 mmol /day) and magnesium I3: Calcium and potassium C: Placebo group	USA. Currently untreated hypertensives, aged 21-70, DBP 85- 99; excluded cardiac disease, diabetes or renal failure. All except 2 patients treatment naïve.	1. double 2. inadequate 3. inadequate 4. 140 5. 6 months 6. 6 months	1. yes 2. 53.0 (R 25-66) 3. 65.6% 4. 64.8%	1. 139/90* I1: 139.1/89.5* I2: 140.1/89.6* !3: 136.0/90.4* C: 140.4/89.9* 2. 0% 3. 0% * based on 125 patients at mid-point of study	1-4. not reported 5. I1: -0.6(10.6)/-0.4(11.1), 31 I2: -3.9(6.5)/-2.7(6.5), 29 I3: -3.6(9.2)/-3.8(5.9), 29 C: -4.3(13.7)/-3.9(5.5), 30	1. I1:4/35(11.4%) I2:7/36(19.4%) I3:5/34(14.7%) C: 5/35(14.3%) 2. I1:4/35(11.4%) I2:7/36(19.4%) I3:5/34(14.7%) C:5/35(14.3%)

Appendix 16: RCTs comparing lifestyle and drug interventions

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. BP 2. CV disease% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up
Berglund et al, 1989	I1: Diet: Weight reduction by at least 5%, restriction of sodium (≤95 mmol/d) and decrease in excess alcohol intake (when ≥250 g/week). Individual goal set. Monthly then less frequent group meetings I2: Drug: Stepped care beginning with a beta-blocker (atenolol 50-100mg/day)	Sweden. Adults (40-69 years), treatment naïve or withdrawn from drug, DBP 90-104 after 3 readings; without CHD, diabetes or renal disease	1. open 2. inadequate: allocated by even/odd birth date 3. inadequate 4. 64 5. 1 year 6. 1 year	1. yes 2. 54 3. 100% 4. not reported	1. 153/96 I1: 152/96 I2: 155/97 2. 0% 3. 0%	1-4. not reported 5. I1: 147(14)/92(7), 31 I2: 141(12)/87(5), 30	1/2. I1: 3/34 (8.8%) I2: 0/30
Goldstein et al, 1982	I1: BP biofeedback – subjects instructed to reduce BP in relation to auditory & visual BP biofeedback by "whatever means proved successful", twice weekly 1 hour sessions I2: Relaxation - elicitation of the 'relaxation response' (muscular relaxation and passive counting of breaths while sitting with eyes closed), twice weekly 1 hour sessions I3: Drugs – dose & medication combinations varied until optimal BP control achieved by minimal required dose; (7 subjects received diuretics, one received propranolol, one received clonidine) C	USA. Adults (35-60 years) with untreated essential hypertension (SBP 150-165 and/or DBP 90-105); without obesity, CHD, alcoholism, history of drug abuse, or other serious disease.	1. unclear 2. unclear 3. unclear 4. 36 5. 8 weeks 6. 8 weeks	1. unclear 2. 51.5 3. 86.1% 4. unclear	1. 147.7/97.5 I1: 149.1/97.3 I2: 149.8/97.1 I3: 144.2/98.2 2. 0 3. 0	1-4. not reported 5. I1: 145(SD)/92.9(SD), 9 I2: 152.3(SD)/100.6(SD), 9 I3: 129.4(SD)/92.6(SD), 9	1/2. I1: 0/9 (0%) I2: 0/9 (0%) I3: 0/9 (0%)

Trial	Comparison	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Follow-up duration	1. Baseline comparability 2. Age 3. Male% 4. White%	1. BP 2. CV disease% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up
Koopman et al 1997	I1: Diet: Dietician led programme with monthly visits. Diet containing sodium <100mmol/24 hr (approx 6g table salt), potassium >75 mmol/24h, sodium/potassium ratio<1 and a low energy intake for those overweight (BMI >25) I2: Diuretic (chlorthalidone 25 mg/day). Visited a dietician monthly for a low profile standard advice for their diet	Netherlands. Adults (60-80 years), treatment naïve, DBP 95-110 and/or SBP 160-220 mmHg; without CHD or diabetes	1. blinded assessment 2. unclear 3. unclear 4. 42 5. 3 months 6. 3 months	1. yes 2. 67.7 3. not reported 4. not reported	1. 166/97* I1: 169/97* I2: 163/97* 2. 0% 3. 0%	1. I1/I2: 0 (0%) 2. I1: 0/20(0%) I2: 1/20(5%) 3. I1/I2: 0 (0%) 4. I1: 0/20(0%) I2: 1/20(5%) 5. I1: 161(16)/93(7), 20 I2: 147(17)/88(7), 20	1/2. I1: 0/20 (0%) I2: 2/22 (9.1%)
Kostis et al, 1992	I1: Group non-pharmacological therapy. Weekly sessions (with spouse) focusing on weight loss (12-15 lbs) dietary change (reduced calorie, low salt), exercise (vigorous walking, swimming or exercise bike), & stress management (mental relaxation) I2: β-blocker propanolol 80mg/day for 2 weeks, then 240mg/day	USA. Adults; currently untreated mean DBP 95-105, treated BP < 110 without CHD, diabetes, BMI > 135	1. blinded assessment 2. unclear 3. unclear 4. 66 5. 12 weeks 6. unclear	1. yes 2. 57 3. 100% 4. 92%	1. 163.3/100.5 I1: 162.3/100.7 I2: 164.8/100.2 2. 0% 3. 0%	1-4. not reported 5. I1: -12.4(14.6)/-8.0(6.2), 33 I2: -12.2(15.2)/-9.5(7.0), 23)	1/2. Ii: 5/38 (13.2%) I2: 3/26 (11.5%)
MacMahon et al 1985	I1: Weight reduction – 3 weekly meetings for individually tailored diet aiming to reduce calorie intake by 1,000 p/day with 15% protein, 30% fat & 55% carbohydrates I2: β-blocker (metoprolol 200 mg/day)	Australia. Adults (20-55 years), currently untreated, (DBP 90-109), BMI > 26.0; without CHD, proteninuria	1. blinded assessment 2. unclear 3. unclear 4. 56 5. 21 weeks 6. 21 weeks	1. yes 2. 41.8 3. 75.0% 4. not reported	1. 150.5/101.1 I1: 149.8/101.2 I2: 151.2/100.9 2. 0% 3. 0%	1-4. not reported 5. I1: -13.3(5.0)/-9.8(4.9), 20 I2 -9.9(5.2)/-6.2(4.7), 18	1/2. I1: 3/20 (15.0%) I2: 2/18 (11.1%))
Murugesan et al, 2000	I1: Yoga session in morning and evening for 1 hr/day, 6 days/wk I2: Antihypertensive medication prescribed by physician	Hypertensive adults (35-65 years), weight 53-81 kgs	1. unclear 2. unclear 3. unclear 4. 33 5. 11 weeks 6. 11 weeks	1. unclear 2. R: 35-65 3. not reported 4. not reported	1. 156.9/108.1 I1: 156.5/108.6 I2: 158.6/106.5 2. not reported 3. not reported	1-4. not reported 5. I1: 123.1(10.1)/82.4(9.1), n/a I2: 134.9(12.6)/96.5(8.3), n/a	1/2. not reported

Appendix 17: RCTs of pharmacological interventions

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
High dose diuretics vs. placebo							
ANBPS[1]	1. I: chlorothiazide 500-1000 mg/day C: placebo Step 2 methyldopa, propranolol or pindolol added; step 3 hydralazine or clonidine added in I; matching placebo stepped care in C. 2. Initially DBP<90, after 2 years DBP<80	Australia. Adults (30-69) with currently treated mild essential hypertension SBP < 200 mmHg,and DBP 95-110 mmHg; Exclusion criteria diabetes, CVA, angina, MI < 3 months, renal disease, other serious complications of hypertension or any potentially fatal disease.	1. participant – yes provider – no assessor – yes 2. unclear 3. unclear 4. 3,931* 5. 4 years *504 participants withdrawn after randomisation: ineligible for treatment	1. yes 2. 50.4 3. 63.3% 4. 100%	1. 157.4/100.5 I: 157.7/100.5 C: 157.1/100.4 2: 0.3% 3: 0%	1. I: 25/1,721 (1.5%) C: 35/1,706 (2.1%) 2. I: 33/1,721 (1.9%) C: 33/1,706 (1.9%) 3. I: 13/1,721 (0.8%) C: 22/1,706 (1.3%) 4. unclear 5. not reported	1. I: 612/1,721 (36%) C: 855/1,706 (50%) 2. I1: 0/1721 C: 0/1706 3. I1: 492/1,696 (29%) C: 903/1,671 (54%) 4. (DBP<90) I: 1,044/1,634 (64%) C: 407/1,617 (25%)
ANBPS > 60 *(subset - not included in meta-analysis)*	1. I: chlorothiazide 500-1000 mg/day C: placebo Step 2 methyldopa, propranolol or pindolol added; step 3 hydralazine or clonidine added. 2. Initially DBP<90, after 2 years DBP<80	Australia. Adults (60-69) with currently treated mild essential hypertension SBP < 200 mmHg,and DBP 95-110 mmHg; Exclusion criteria diabetes, CVA, angina, MI < 3 months, renal disease, other serious complications of hypertension or any potentially fatal disease.	1. participant – yes provider – no assessor – yes 2. unclear 3. unclear 4. 582 5. 3.9 years	1. no for SBP 2. 63.6; 3. 54.6% 4. not reported	1. 165.1/100.6 I: 166.3/100.7 C: 163.9/100.4 2: 0% 3: 0%	1. I: 7/293 (2.4%) C: 9/289 (3.2%) 2. I: 7/293 (2.4%) C: 9/289 (3.2%) 3. I: 7/293 (2.4%) C: 9/289 (3.2%) 4. not reported 5. unclear	1. I: 103/293 (35.2%) C: 109/289 (37.7%) 2. I: 0/293 (0%) C: 0/289 (0%) 3. I: 107/277 39%) C: 151/279 (54%) 4. (DBP<90) I: 70% C: 28%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
HSCSG	I: methychlothiazide 10mg/day and deserpidine 1 mg/day C: placebo 2. not reported	USA. Adults (< 75) with essential hypertension (BP 140-220/90-115) and a CVA and/or TIA < 1 year.	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 452 5. 2.1 years	1. unclear 2. 59 3. 58.6% 4. 19.5%	1. 167/100 I: 167/100 C: 167/100 2: 100% 3: unclear	1. I: 26/223 (11.7%) C: 24/215 (11.2%) 2. I: 5/223 (2.2%) C: 7/215 (3.3%) 3. I: 37/223 (15.9%) C: 42/215 (19.2%) 4. I: 42/223 (18.8%) C: 49/215 (22.8%) 5. I: 137(SD)/84(SD),44 -30(18.7)/-16(9.3) C: 167(SD)/98(SD),37 0(20.1)/-2(11.4)	1. I: 83/233 (35.6%) C: 84/219 (38.4%) 2. I: 10/233 (4.3%) C: 4/219 (1.8%) 3. not applicable 4. not applicable
MRC	I1: bendroflumethiazide 10 mg/day I2: β-blocker propranolol 240 mg/day C: placebo Step 2 methyldopa added to I1 and methyldopa or guanethidine added to I2; no stepped care in C. 2. DBP<90 within 6 months	UK. Adults (35-64) with untreated essential hypertension (SBP < 200 and DBP 90-109). Exclusion criteria MI/CVA < 3 months, angina or diabetes.	1. participant – yes provider – no assessor – yes 2. unclear 3. unclear 4. 17,354 5. 4.9 years	1. yes 2. 52.0 3. 52.1% 4. unclear	1. 161.4/98.2 I1: 161.4/98.5 I2: 161.4/98.5 C: 161.3/98.0 2: not reported 3: 0%	1. I1: 128/3,519 (3.6%) I2: 120/3,558 (3.4%) C: 253/6,941 (3.6%) 2. I1: 119/3,519(3.4%) !2: 103/3,558(2.9%) C: 234/6941(3.4%) 3. I1: 18/3,519 (0.5%) I2: 42/3,558 (1.2%) C: 109/6,941 (1.6%) 4. I1: 140/3,519 (4.0%) I2: 146/3,558 (4.1%) C: 352/6,941 (5.1%) 5. I1: 135.8(SD)/84.8(SD), n/a -25.6(SD)/-13.7(SD) I2: 139.2(SD)/85.8(SD), n/a -22.2(SD)/-12.7(SD) C: 148.7(SD)/90.8(SD), n/a -12.6(SD)/-7.2(SD)	1. I1: 1,770/4,297 (41.2%) I2: 1,925/4,403 (43.7%) C: 4,031/8,654 (46.6%) 2. I1: 778/4,297 (18.1%) I2: 845/4,403 (19.2%) C: 1,713/8,654 (19.8%) 3. I1: 70.8% I2: 77.9% C: not reported 4. I1: 75% I2: 73% C: 46%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
OSLO	I: hydrochlorothiazide 50 mg/day C: no treatment (treatment started if SBP ≥ 180 and/or DBP ≥ 110) Step 2 methyldopa 500-1000 mg/day or propranolol 80-320 mg/day added; step 3 other antihypertensive added. 2. <140/90	Norway. Adults (40-49) with essential hypertension (SBP 150-179, DBP < 110). Exclusion criteria CHD, CVD, drug-treatment for hypertension < 1 year, renal disease or diabetes.	1. participant – unclear provider – unclear assessor – yes 2. adequate 3. unclear 4. 785 5. 66 months	1. yes 2. 45.3 3. 100% 4. unclear	1. 155.8/96.8 I: 156.2/97.4 C: 155.3/96.2 2: 0% 3: 0%	1. I: 10/406 (2.5%) C: 9/379 (2.4%) 2. I: 8/406 (2.0%) C: 8/379 (2.1%) 3. I: 0/406 (0%) C: 3/379 (0.8%) 4. I: 20/406(4.9%) C: 20/379(5.3%) 5. I: 132.0(SD)/86.8(SD), 373 -24.2(SD)/-10.6(SD) C: 146.9(SD)/93.5(SD), 275 -8.4(SD)/-2.7(SD)	1. I: 85/406(18.5%) 15.7% other drug regimes 0.7% no drugs C: 74/379 (19.5%) 17.2% drug treatment started 2. I: 0/406(0%) C: 0/379(0%) 3. I: 140/395 (35.4%) C: not reported 4. not reported
USPHS	I: chlorothiazide 1 g/day and reserpine 200 mg/day. C: placebo 2. not reported	USA. Adults (< 55) with essential hypertension (home DBP 90-114 and clinic DBP ≥ 90), 59% treatment naive. Exclusion criteria diabetes, renal insufficiency, congestive heart failure or angina.	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 422* 5. 78-108 months 6. >7 years *33 participants were "misadmitted" and omitted leaving 389 for f/u and analysis	1. yes 2. 44.4 3. 80% 4. 72%	1. 146.8/99.0 I: 147.8/98.9 C: 145.9/99.0 2: 0% 3: 0%	1. I: 2/179 (1.0%) C: 4/184 (2.2%) 2. I: 7/179 (3.6%) C: 6/184 (3.1%) 3. I: 0/179 (0%) C: 2/184 (1.0%) 4. unclear 5. I: 128(SD)/80(SD), 40 -19.8(SD)/-18.9(SD) C: 142(SD)/94(SD), 20 -3.9(SD)/-5.0(SD)	1. I: 88/193(45.6%) 9.8% drug intolerance 2.1% morbid events 6.7% withdrew C: 121/196(61.7%) 2.0% drug intolerance 11.7% morbid events 9.0% withdrew 2. I: 14/193 (7.2%) C: 12/196 (6.1%) 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
VA-NHLBI	I: chlorthalidone 50-100 mg/day C: placebo Step 2 reserpine 0.25 mg/day added in I; matching placebo stepped care in C. 2. DBP<85	USA. Adults (21-50) with treated essential hypertension (DBP 85-105). Exclusion criteria CVD, renal disease or insulin dependent diabetes.	1. participant – yes provider – yes assessor – unclear 2. adequate 3. inadequate 4. 1,012 5. 1.5 years	1. unclear 2. 37.5 3. 81% 4. 74%	1. not reported 2: not reported 3: not reported	1. I: 2/410 (0.5%) C: 0/400 (0%) 2. I: 6/410 (1.5%) C: 5/400 (1.2%) 3. not reported 4. not reported 5. (at 8 months) I: not reported -11.8(SD) C: not reported -5.2(SD)	1. I: 100/508 (19.7%) C: 116/504 (23%) 2. I: 98/508 (19.3%) C: 104/504 (20.6%) 3. I: 47% C: 28% 4. I: 65% C: 35%
VA II	I: hydrochlorothiazide 100 mg/day, reserpine 0.2 mg/day and hydralazine 75-150 mg/day C: placebo 2. not reported	USA. Men with mild-moderate hypertension (DBP 90-129). Exclusion criteria CVA, hypertensive neuropathy, dissecting aneurysm, renal failure, surgically curable hypertension or unrelated fatal diseases.	1. participant – yes provider – yes assessor – unclear 2. unclear 3. unclear 4. 380 5. 3.2 years	1. yes 2. 51.2 3. 100% 4. 57.6%	1. 163.6/104.3 I: 162.1/103.8 C: 165.1/104.7 2: unclear 3: unclear	1. I: 10/157 (6.4%) C: 21/167 (12.6%) 2. I: 7/157 (4..5%) C: 5/167 (3.0%) 3. I: 5/157 (3.2%) C: 20/167 (12.0%) 4. unclear 5. (at 4 months) I: 134.9(SD)/86.4(SD), n/a -27.2(SD)/-17.4(SD) C: 169.3(SD)/106.9(SD), n/a +4.2(SD)/+1.2(SD)	1. I: 41/186 (22.0%) 1.1% drug intolerance 15.6% withdrew C: 48/194 (24.7%) 13.9% withdrew 2. I: 29/186 (15.6%) C: 27/194 (13.9%) 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
Low dose diuretics vs. placebo							
EWPHE	I: hydrochlorothiazide 25-50 mg/day and triamterene 50-100 mg/day C: placebo Step 2 methyldopa 250-2000 mg/day added in I; matching placebo stepped care in C. 2. <160/90	Western Europe. Adults (≥ 60) with hypertension (BP 160-239/90-119). Exclusion criteria congestive heart failure, CVA or insulin dependent diabetics.	1. participant – yes provider – yes assessor – yes 2. unclear 3. adequate 4. 840 5. 4.7 years	1. yes 2. 71.8 3. 30.2% 4. not reported	1. 182.5/101.0 I: 183/101 C: 182/101 2: 36% 3: excl. insulin dependent diabetes	1. I: 135/404 (33%) C: 149/412 (36%) 2. I: 48/404 (1.7%) C: 59/412 (3.8%) 3. I: 32/404 C: 48/412 4. unclear 5. (at 9 months) I: 151.5(SD)/88.2(SD), 351 -30.5(20.6)/-12.8(9.9) C: 174.6(SD)/96.5(SD), 339 -8.4(20.7)/-4.5(11.0)	1. I: 284/416 (68.3%) C: 306/424 (72.2%) 2. I: 12/416 (2.9%) C: 12/424 (2.8%) 3. I: 65% C: 37% 4. not reported
EWPHE-ISH *(subset - not included in meta-analysis)*	I: hydrochlorothiazide 25-50 mg/day and triamterene 50-100 mg/day C: placebo Step 2 methyldopa 250-2000 mg/day added. 2. <160/90	Western Europe. Adults (≥ 60) with isolated systolic hypertension SBP ≥160 & DBP ≤90). Exclusion criteria congestive heart failure, CVA or insulin dependent diabetics.	1. participant – yes provider – yes assessor– yes 2. adequate 3. adequate 4. 247 5. 6. 4.7 years	1. yes 2. 73.3 3. 26.3% 4. unclear	1. 178/93 I: 178/93 C: 178/93 2: unclear 3: excl. insulin dependent diabetes	1. I: 20/128 (15.6%) C: 23/119 (19/3%) 2. unclear I: 4/128 (3.1%) C: 0/119 (0.0%) 3. I: 3/128 (2.3%) C: 3/119 (2.5%) 4. I: 12/128 (9.4%) C: 14/119 (11.8%) 5. (total N = 62) I: 150(SD)/81(SD), n/a -28(SD)/-12(SD) C: 163(SD)/88(SD), n/a -15(SD)/-5(SD)	1. unclear I: C: 2. I: 0/128 C: 0/119 3. not reported 4. not reported

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
MRC-O	I1: β-blocker atenolol 50-100 mg/day I2: diuretic hydrochlorothiazide 25-50mg/day plus diuretic amiloride 2.5-5 mg/day C: placebo Step 2 other trial drug added; step 3 nifedipine 20 mg/day and/or other supplementary drugs added in I; no stepped care in C. 2. ≤ 150 if baseline SBP < 180 and SBP ≤ 160 if baseline SBP ≥ 180	UK. Adults (65-74) with currently untreated essential hypertension (SBP 160-209). Exclusion criteria MI/CVA < 3 months, impaired renal function or diabetes.	1. participant – yes provider – no assessor – yes 2. unclear 3. unclear 4. 4,396 5. 5.8 years	1. yes 2. 70.3 3. 41.8% 4. unclear	1. 184.7/90.6 I1: 184.7/90.8 I2: 184.8/91.0 C: 184.7/90.4 2: unclear 3: 0%	1. I1: 167/1,102 (15.2%) I2: 134/1,081 (12.4%) C: 315/2,213 (14.2%) 2. I1: 80/1,102 (7.3%) I2: 48/1,081 (4.4%) C: 159/2,213 (7.2%) 3. I1: 56/1,102 (5.1%) I2: 45/1,081 (4..2%) C: 134/2,213 (6.1%) 4. I1: 151/1,102(13.7%) I2: 107/1,081 (9.9%) C: 309/2,213 (14.0%) 5. unclear	1. I1: 861/1,102 (78.2%) I2: 653/1,081 (60.4%) C: 1,488/2,213 (67.2%) 2. I1: 349/1,102 (31.7%) I2: 358/1,081 (33.1%) C: 916/2,213 (41.4%) 3. I1: 48% I2: 62% C: not reported 4. not reported
PATS	I: indapamide 2.5 mg/day C: placebo 2. not reported	China. Adults with a history of CVA or TIA (> 4 weeks) irrespective of BP (BP <140/90 in 16% and BP ≥160/95 in 57%). Exclusion criteria secondary hypertension, type 1 diabetes or renal disease.	1. participant – yes provider – yes assessor – unclear 2. unclear 3. inadequate 4. 5,665 5. 2 years	1. yes 2. 60 3. 72% 4. not reported	1. 153.8/92.8 I: 154.0/93.0 C: 153.5/92.6 2: 100% 3: excl. type I diabetes	1. I: 146/2,841 (5.1%) C: 158/2,824 (5.6%) 2. I: 25/2,841 C: 21/2,824 3. I: 159/2,841 (5.6%) C: 217/2,824 (7.7%) 4. unclear I: 194/2,841 C: 247/2,824 5. I: 142.6(16.9)/85.7(8.7), n/a -11.4(SD)/-7.3(SD) C: 148.8(19.1)/88.6(10.1), n/a --4.7(SD)/-4.0(SD)	1. I: 308/2,841 (10.8%) 3.4% adverse effects C: 308/2,824 (10.9%) 3.6% adverse effects 2. I: 0/2,841 (0)%) C: 0/2,824 (0%) 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
SHEP-P	I: chlorthalidone 25-50 mg/day C: placebo Step 2 one of the following drugs assigned at random, reserpine 0.1-0.2 mg/day, metoprolol 100-200 mg/day, hydralazine 50-100 mg/day in I; matching stepped care in C. 2. SBP < 160 or ≥ 20 below baseline	USA. Adults (≥60) with systolic hypertension (SBP 160-219, DBP < 90), 47% previously treated. Exclusion criteria MI < 6 months, coronary bypass surgery < 2 years, uncontrolled congestive heart failure or insulin.	1. participant – yes provider – yes assessor – yes 2. inadequate 3. adequate 4. 551 5. 34 months	1 yes 2. 72 3. 36.8% 4. 81.6%	1. 172.4/75.4 I: 172/75 C: 174/77 2. 5% 3. excl. insulin-dependent diabetes	1. I: 32/443 (7.2%) C: 7/108 (6.5%) 2. I: 8/443(1.8%) C: 2/108(1.9%) 3. I: 11/443 (2.5%) C: 6/108 (5.6%) 4. unclear 5. I: 142(40)/68(8), 224 -30(SD)/-7(SD) C: 159(40)/73(8), 61 -15(SD)/-4(SD)	1. I: 115/315 (37%) C: 36/80 (45%) 2. I: 0/443 (0%) C: 0/108 (0%) 3. I: 87% C: 43% 4. After one yr: I: 80% C: 40%
SHEP	I: chlorthalidone 12.5-25 mg/day C: placebo Step 2 atenolol 25-50 mg/day or reserpine 0.05-0.10 mg/day added in I; matching stepped care in C. 2. SBP < 160 baseline SBP ≥ 180 and reduction > 20 if baseline SBP 160-179	USA. Adults (≥ 60) with isolated systolic hypertension (SBP 160-219 and DBP < 90), 33% currently treated. Exclusion criteria renal dysfunction.	1. participant – yes provider – yes assessor - yes 2. unclear 3. adequate 4. 4,736 5. 4.5 years	1. yes 2. 71.6 3. 43% 4. 86.1%	1. 170.3/76.6 I: 170.5/76.7 C: 170.1/76.4 2. 6.3% 3. 10.1%	1. I: 213/2,365 (9.0%) C: 242/2,371 (10.2%) 2. I: 140/2,365/ (5.9%) C: 184/2371 (7.8%) 3. I: 103/2,365 (4.4%) C: 159/2,371 (6.7%) 4. I: 199/2,365 (8.4%) C: 289/2,371 (12.2%) 2 & 4 are no. of events, 1 & 3 are no. of patients 5. I: 144.0(19.3)/67.7(10.2), 773 -26.5(SD)/-9.0(SD) C: 155.1(20.9)/71.1(12.8), 738 -15(SD)/-5.3(SD)	1. I: 448/1221 (36.7%) 3% received known active therapy as BP was too high 13% stopped medication because of side effects C: 570/1308 (43.6%) 44% received known active therapy as BP was too high 2. unclear 3. I: 30% C: 54% 4. I: 65-72% C: 32-40%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
TOMHS *(not included in meta-analysis as events not reported by treatment group)*	1. I1: lifestyle intervention + β-blocker (acebutolol 400 mg/d) I2: lifestyle intervention + calcium-channel blocker (amlodipine maleate 5 mg/d) I3: lifestyle intervention + diuretic (chlorthalidone 15 mg/d) I4: lifestyle intervention + α-antagonist (doxazosin mesylate 1 mg/d for 1 month then 2 mg/d) I5: lifestyle intervention + ACE-inhibitor (enalapril maleate 5 mg/d) C: lifestyle intervention + placebo 'lifestyle intervention' = aim to reduce weight, sodium, alcohol intake, increase physical activity Step 2: add chlorthalidone (15 mg/d) except in the chlorthalidone group where enalapril (2.5 mg/d was added 2. DBP < 95	USA. Adults (45-69); untreated DBP 90-99 or treated BP (on one drug) DBP 85-99; body weight 100-150% of ideal; without CHD, diabetes or renal disease	1. double 2. unclear 3. unclear 4. 902 5. 1 year 6. 4 years	1. yes 2. 54.8 3. 61.8% 4. 81.4%	1. 140.4/91.5 C: 141.1/90.5 I1: 140.2/90.7 I2: 138.1/90.9 I3: 140.5/90.4 I4: 140.8/90.6 I5: 140.8/90.2 2. 0% 3. 0%	1-4. not reported 5. I1: 120.3/77.6, 126 -20.1/-13.7 I2: 120.6/78.0, 120 -17.5/-12.9 I3: 118.7/77.3, 124 -21.8/-13.1 I4: 124.7/78.6, 129 -16.1/-12.0 I5: 123.2/78.0, 127 -17.6/-12.2 C: 130.5/82.4, 221 -10.6/-8.1	1. 153/902 (17%) 2. 55/902 (6.1%) I1: 6/132 (5%) I2: 11/131 (8%) I3: 12/136 (9%) I4: 5/134 (4%) I5: 8/135 (6%) C: 13/234 (6%) 3. I1: 77.8% I2: 82.5% I3: 67.5% I4: 66.1% I5: 68.1% C: 58.5% 4. 83%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
Beta-blockers vs. placebo (see also MRC and MRC-O)							
Coope et al.	I: atenolol 100 mg/day C: observation only Step 2 bendroflumethiazide 5 mg/day added (patients who could not tolerate 100 mg atenolol were given 50 mg atenolol or bendroflumethiazide alone.), step 3 methyldopa 500 mg/day added and step 4 other antihypertensive (usually nifedipine) added. 2. <170/105	UK. Adults (60-79) with untreated hypertension (SBP ≥ 170 or DBP ≥ 105). Exclusion criteria participants treated for hypertension < 3 months, with heart arrhythmias, treated diabetes or any other serious concomitant disease.	1. participant – no provider – no assessor – yes 2. adequate 3. inadequate 4. 884 5. 4.4 years	1. yes 2. 68.8 years 3. 30.9% 4. unclear	1. 196.4/98.8 I: 196.7/99.7 C: 196.1/98.0 2: unclear 3: 0% (excl. diabetes needing pharmacological treatment)	1. I: 60/419 (14.3%) C: 69/465 (14.8%) 2. I: 26/419 (4.8%) C: 30/465 (8.4%) 3. I: 20/419 C: 39/465 4. unclear 5. I: 161(SD)/73(SD), n/a -35.7(SD)/-26.7(SD) C: 180(SD)/86(SD), n/a -16.1(SD)/-12.0(SD)	1. I: 81/419 (19.3%) C: 111/465 (23.9%) 2. not reported 3. I: 35% C: ? 4. (in year 8) I: 62% C: 31%
DUTCH TIA	1. I: atenolol 50 mg/d β-blocker C: placebo 30 mg/day aspirin was taken at baseline by 48% subjects in both groups 2. not reported	The Netherlands. Adults with a TIA or non-disabling stroke < 3 months. Exclusion criteria: cerebral ischaemia, patients with contra-indications for β-blocker treatment or strict indication for β-blocker treatment	1. subject – adequate provider – adequate assessor – adequate 2. adequate 3. inadequate (telephone) 4. 1,473 5. 32 months	1. unclear 2. not reported 3. 64% 4. not reported	1. 157.5/91.0 I: 158/91 C: 157/91 2: 72% 3: 5.0%	1. I: 64/732 (13.3%) C: 58/741 (12.8%) 2. I: 45/732 (6.1%) C: 40/741 (5.4%) 3. I: 52/732 (7.1%) C: 62/741 (8.4%) 4. unclear 5. I: 148(SD)/86(SD) -10(SD)/-5(SD) C: 150(SD)/87(SD) -8(SD)/-4(SD)	1. I: 350/732 (48%) C: 316/741 (43%) 2. unclear 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
IPPPSH	I: oxprenolol 160-320 mg/day C: placebo Step 2 non-β-blocker antihypertensive added to both I & C. 2. DBP ≤ 95	International. Adults (40-64) with hypertension (DBP 100-125). Exclusion criteria MI or angina pectoris, heart failure, CVD, CVA, type I diabetes, renal disease or other serious diseases.	1. participant – yes provider – yes assessor – yes 2. unclear 3. inadequate 4. 6,357 5. 3.4 years	1. yes 2. 52.2 3. 50.2% 4. not reported	1. 173.0/107.8 I: 173.1/107.9 C: 172.8/107.6 2: not reported 3: 0%	1. I: 108/3,165 (3.4%) C: 114/3,155 (3.6%) 2. I: 61/3,165 (1.9%) C: 73/3,155 (2.3%) 3. I: 45/3,165 (1.4%) C: 46/3,155 (1.5%) 4. unclear 5. I: 140(SD)/85(SD), 573 -33.11(SD)/-22.9(SD) C: 145(SD)/90(SD), 520 -27.8(SD)/-17.6(SD)	1. I: 879/3,185(27.6%) C: 997/3,172(31.4%) 2. I: 20/3,185 (0.6%) C: 17/3,172 (0.5%) 3. I 943/3,185 (30%) C: 469/3,172 (15%) 4. SBP ≤ 160 and DBP ≤ 95: I: 80.0% C: 73.6%
STOP – H	I: β-blocker atenolol 50 mg/day or diuretic hydrochlorothiazide/ amiloride 25/2.5 mg/day, or β-blocker metropolol 100 mg/day or β-blocker pindolol 5 mg/day C: placebo Step 2 participants on diuretics given β-blocker and vice versa in I; no stepped care in C. Each centre was free to choose any of the four basic regimes, which then had to be maintained throughout the study. 2. <160/95	Sweden. Adults (70-84) with treated or untreated essential hypertension (BP ≥ 180-230/90-120 or DBP > 105 irrespective of SBP in untreated participants). Exclusion criteria MI or CVA ≤ 12 months.	1. participant – yes provider - yes assessor - yes 2. unclear 3. unclear 4. 1,627 5. 25 months	1. yes 2. 75.7 3. 37.0% 4. not reported	1. 195/102 I: 195/102 C: 195/102 2. not reported 3. not reported	1. I: 36/812 (4.4%) C: 63/815 (7.7%) 2. I: 25/812(3.1%) C: 28/815(3.4%) 3. I: 29/812(3.6%) C: 53/815(6.5%) 4. I: 58/812(7.1%) C: 94/815(11.5%) 5. I: 166(21)/85(10), 38 -29(SD)/-17(SD) C: 193(20)/95(11), 28 -2(SD)/-7(SD)	1. I: 166/812 (20.4%) C: 250/815 (30.7%) 2. I: 0/812 (0%) C: 0/815 (0%) 3. I: 33% C: not applicable 4. not reported

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
TEST	1. I: atenolol 50 mg/d β-blocker C: placebo 2. not reported	Sweden. Adults > 40 years with a TIA or non-disabling stroke <3 wks ago and hypertension >140/80 mm Hg. Exclusion criteria: CHD, life threatening disorders (subarachnoid haemorrhage, heart failure), patients with contra-indications for β-blocker treatment	1. subject – adequate provider – adequate assessor– unclear 2. adequate 3. unclear 4. 720 5. 2.3 yrs	1. yes 2. 70.4 3. 60.1% 4. unclear	1. 161.0/88.5 I: 161/88 C: 161/89 2: 90% 3: 12.5%	1. I: 51/372 (13.7%) C: 60/348 (17.2%) 2. I: 26/372 (7.0%) C: 29/348 (8.3%) 3. unclear I: 74/372 (19.9%) C: 69/348 (19.8%) 4. unclear I: /372 C: /348 5. I: 157(SD)/85(SD), 372 -4(SD)/-3(SD) C: 161(SD)/89(SD), 358 0(SD)/0(SD)	1. I: 114/372 (31%) C: 95/348 (27%) 2. I: 0/372 (0%) C: 0/348 (0%) 3. not applicable 4. not applicable
Calcium-channel blockers vs. placebo (see also TOMHS)							
IDNT *(not included in meta-analysis as 100% diabetic)*	I1: ARB irbesartan 75-300 mg/day I2: calcium-channel blocker amlodipine 2.5–10 mg/day C: placebo Step 2 other antihypertensive (apart from ACE II & calcium-channel blockers) added. 2. SBP ≤ 135, or ≥ 10 reduction if baseline SBP > 145, and DBP≤85	USA. Adults (30-70) with hypertension (SBP > 135 or DBP > 85 or documented treatment with antihypertensive) and mild renal impairment proteinuria (> 900 mg/day).due to type II diabetes.	1. participant – yes provider – yes assessor – unclear 2. adequate 3. unclear 4. 1,715 5. 2.6 years	1 age & BP – yes sex – no (lower proportion of women in placebo group) 2. 58.9 3. 66% 4. 72%	1. 159/87 I1: 160/87 I2: 159/87 C: 158/87 2. 28.7% 3. 100%	1. I1: 87/574 (15.0%) I2: 83/565 (14.6%) C: 93/565 (16.3%) 2. not reported 3. not reported 4. not reported 5. (at 48 months) I1: 138(SD)/74(SD), 99 -22(SD)/-13(SD) I2: 140(SD)/75(SD), 83 -19(SD)/-12(SD) C: 142(SD)/79(SD), 94 -16(SD)/-8(SD)	1. unclear 23.7% of patients withdrew from treatment (usually due to a cardiovascular event) and these were evenly distributed among the groups. . 2. I1: 5/579(0.9%) I2: 2/567(0.4%) C: 4/569(0.7%) 3. not reported (Patients in the placebo groups required an average of 3.3 nonstudy drugs compared with 3.0 in the intervention groups) 4. not reported

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
STONE *(not included in meta-analysis as not randomised)*	I: nifedipine 20-60 mg/day C: placebo Step 2 captopril 20-50 mg/day or dihydrochlorothiazide 25 mg/day added. 2. SBP140-159 and DBP≤90	China. Adults (60-79) with essential hypertension (SBP ≥ 160-219 or DBP ≥ 96-124). Exclusion criteria arrhythmia, CVA, congestive heart failure, angina, MI, renal disease or diabetes.	1. participant – yes provider –no assessor – yes 2. inadequate 3. inadequate 4. 1,797 5. 30 months	1. no - DBP lower in control group 2. 66.4 3. 46.9% 4. unclear	1. 168.5/97.7 I: 168.5/98.5 C: 168.6/96.9 2: 0% 3: 0%	1. I: 15/878 (1.7%) (2.0%) C: 26/885 (2.9%) (3.7%) 2. I: 2/878 (0.2%)751 (0.2%) C: 2/885 (0.2%) (0.3%) 3. I: 16/878 (1.8%)751 (2.1%) C: 36/885 (4.1%) (5.1%) 4. unclear 5. I: 143(SD)/84(SD), 166 -25.6(SD)/-12.9(SD) C: 152(SD)/88(SD), 88 -16.5(SD)/-10.5(SD)	1. I: 108/899 (12.0%) C: 98/898 (10.9%) 2. I: 21/899 (2.3%) C: 13/898 (1.4%) 3. not reported 4. I: 65% C: not reported
SYST-EUR	I: nitrendipine 10-40 mg/day C: placebo Step 2 enalapril 5-20 mg/day added and step 3 hydrochlorothiazide 12.5-25 mg/day added in I; matching stepped care in C. 2. SBP < 150 and reduction ≥ 20	Europe. Adults (≥60) with previously treated or untreated isolated systolic hypertension (sitting SBP 160-219 and DBP < 95 and standing SBP ≥ 140). Exclusion criteria renal disease, congestive heart failure, dissecting aortic aneurysm, CVA or MI < 1 year or any severe concomitant disease.	1. participant – yes provider – yes assessors — yes 2. adequate 3. unclear 4. 4,695 5. median 2 years	1 yes 2. 70.2 3. 33.1% 4. not reported	1. 173.8/85.5 I: 173.8/85.5 C: 173.9/85.5 2. 29.9% 3. 10.5%	1. I: 123/2,277 (5.4%) C: 137/2,181 (6.3%) 2. I: 33/2,277 (1.4%) C: 45/2,181 (2.1%) 3. I: 47/2,277 (2.1%) C: 77/2,181 (3.5%) 4. Incl. heart failure I: 186/2,277 (8.2%) C: 137/2,181 (6.3%) 5. I: 152.5(SD)/77.5(SD), 705 -21.3(17.6)/-2.0(9.0) C: 163.2(SD)/85(SD), 682 -10.6(17.6)/-1.5(9.0)	1. I: 626/2,398 (26.1%) C: 766/2,297 (33.3%) 2. I: 121/2,398 (5.0%) C: 116/2,297 (5.1%) 3. I: 216/601 (36%) C: 95/574 (17%) 4. at median 2 years: I: 43.5% C: 21.4%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
Syst-China *(not included in meta-analysis as not randomised)*	I: nitrendipine 10-40 mg/day C: placebo Step 2 ACE-inhibitor captopril 12.5-50 mg/day and/or hydrochlorothiazide 12.5-50 mg/day 2. SBP < 150 and reduction ≥ 20	China. Adults (≥ 60) with essential hypertension (SBP 160-219 and DBP < 95). Exclusion criteria CVD and renal impairment.	1. participant – unclear provider – unclear assessor – yes 2. inadequate 3. inadequate 4. 2,394 5. median:3.0 years	1. yes 2. 66.5 3. 64.4% 4. 0%	1. 170.5/86.0 I: not reported C: not reported 2. 11.2% 3. 4.1%	1. I: 61/1253(4.9%) C: 82/1141(7.2%) 2. I: 24/1253(2.0%) C: 31/1141(2.7%) 3. I: 45/1253(3.6%) C: 59/1141(5.2%) 4. I: 74/1253(6.0%) C: 94/1141(8.2%) 5. I: not reported -20.0(16.0)/-5.0(8.0), 1,253 C: not reported -11.0(17.0)/-2.0(8.0), 1,141	1. I: 346/1,253(27.6%) C: 480/1,141(42.1%) 2. I: 115/1,253 (9.2%) C: 122/1,141 (10.7%) 3. I: 584/795 (73.5%) C: 348/635 (54.8%) 4. not reported
ACE vs. placebo (see also TOMHS)							
HOPE *(not included in meta-analysis as high cardio-vascular risk)*	I: ramipril titrated to 10 mg/day C: placebo 2. not reported	North America, South America, Europe. Adults (> 55) with controlled hypertension and high cardiovascular risk (coronary artery disease, MI/CVA > 4 weeks, peripheral vascular disease, or diabetes plus one other risk factor). Exclusion criteria, heart failure, low-ejection fraction or overt nephropathy.	1. participant – yes provider – yes assessor – unclear 2. unclear 3. unclear 4. 9,297 5. median:4.5 years	1. yes 2. 66 3. 73.3% 4. unclear	1. 139/79 I: 139/79 C: 139/79 2: 87.8% 3: 38.5%	1. I: 482/4,645 (10.4%) C: 569/4,652 (12.2%) 2. I: 459/4,645(9.9%) C: 570/4,652 (12.3%) 3. I: 156/4,645 (3.4%) C: 226/4,652 (4.9%) 4. unclear 5. I: 136(SD)/76(SD), n/a -3(SD)/-3(SD) C: 139(SD)/77(SD), n/a 0(SD)/-2(SD)	1. I: 1,825/4,645(39.3%) C: 1,837/4,652(39.5%) 2. 6/9,541 (0.1%) unclear which group 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
HOPE (diabetic subset) *(not included in meta-analysis as 98% diabetic)*	I: ramipiril titrated to 10 mg/day C: placebo 2. not reported	North America, South America, Europe. Adults (. 55) with controlled hypertension and high cardiovascular risk (coronary artery disease, MI/CVA > 4 weeks, peripheral vascular disease, or diabetes plus one other risk factor). Exclusion criteria, heart failure, low-ejection fraction or overt nephropathy.	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 3,577 5. median:4.5 years	1. yes 2. 65.4 3. 63.0% 4. unclear	1. 142.0/79.7 I: 141.7/80.0 C: 142.3/79.3 2: 68.7% 3: 97.7% type II diabetes	1. I: 196/1,808 (10.8%) C: 248/1,769 (14.0%) 2. I: 185/1,808 (10.2%) C: 229/1,769 (12.9%) 3. I: 76/1,808 (4.2%) C: 108/1,769 (6.1%) 4. unclear 5. I: 139.8(SD)/76.7(SD), n/a -1.9(SD)/-3.3(SD) C: 142.9(SD)/77.0(SD), n/a +0.6(SD)/-2.3(SD)	1. I: 798/1,808 ((44.1%) C: 841/1,769 (47.5%) 2. unclear 3. not applicable 4. not applicable
PROGRESS	I: ACE-inhibitor perindopril 4 mg/day, combined with diuretic indapamide 2.5 mg/day (2.0 mg/day in Japan) if the treating physician deemed this appropriate C: placebo 2. none	Australia, New Zealand, China, Japan, Western Europe. Adults with a history of CVA or TIA < 5 years and with or without hypertension; Exclusion criteria no definite indication or contraindication for taking ACE-inhibitors.	1. participant – yes provider – yes assessor – no 2. adequate 3. unclear 4. 6,105 5. 3.9 years	1 yes 2. 64.0 3. 70.0% 4. 61.0%	1. 147/86 I: 147/86 C: 147/86 2. 100% 3. 12.5%	1. I: 306/3,049 (10.0%) C: 319/3,053 (10.4%) 2. I: 115/3,049 (3.9%) C: 154/3,053 (5.2%) 3. I: 307/3,049 (19.1%) C: 420/3,053 (26.2%) 4. Incl. "other vascular" deaths I: 458/3,049 (15%)3,049 C: 604/3,053 (19.8%)3,053 All the above are number of events. 5. I: 133(SD)/80(SD), 3049 -14(11.7)/-6(7.8) C: 142(SD)/84(SD), 3053 -5(11.7)/-2(7.8)	1. I: 1,020/3,051 (33.4%) 7.6% participants decision 2.2% cough 2.1% hypotension 2.2% heart failure C: 955/3,054 (31.3%) 8.2% participants decision 0.4% cough 0.9% hypotension 2.3% heart failure 2. I: 2/3,051 (0.07%) C: 1/3,054 (0.03%) 3. I: 1,281 (42%) C: 1,280 (42%) 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
ARB vs. placebo							
SCOPE	1. I: ARB candesartan 8-16 mg/day C: Placebo Step 2 diuretic HCT 12.5 mg/day added and step 3 other antihypertensive agents added except ACE/ARBs if BP > 160-90, in both I & C. 2. SBP < 160, DBP < 90	Europe & North America. Adults 70-89 with treated and untreated mild-to-moderately raised blood pressure, SBP 160-179 and/or DBP 90-99. Exclusion criteria; SBP ≥ 180, CVA or MI < 6 months, heart failure, liver or renal impairment, alcoholism, moderate dementia or serious concomitant disease	1. participant – yes provider – yes assessor – yes 2. adequate 3. unclear 4. 4,964 5. 44.6 months 6. 3.7 years	1. yes 2. 76.4* 3. 35.5* 4. not reported	1. 166.2/90.3 I: 166.0/90.3 C: 166.5/90.4 2: 4.6%-8.5% 3: 12.1%	1. I: 259/2,471 (10.5%) C: 266/2,458 (10.8%) 2. I: 70/2,471 (2.8%) C: 63/2,458 (2.6%) 3. I: 89/2,471 (3.6% C: 115/2,458 (4.7%) 4. I: 242/2471(9.8%) C: 268/2458(10.9%) 5. I: 145.2(16.1)/79.9(8.7), 2,468 -20.8(SD)/-10.4(SD) C: 148.5(16.8)/81.6(8.8), 2,455 -18.0(SD)/-8.8(SD)	1. I: 644.5/2490.5 (25.9%) 15% Adverse events C: 697.5/2473.5 (28.2%) 17% Adverse events 2. I: 6/2490.5 (0.2%) C: 2/2473.5 (0.1%) 3. I: 25% C: 16% 4. not reported
RENAAL *(not included in meta-analysis as 100% diabetic)*	I: ARB losartan 50-100 mg/day C: matching placebo Step 2 calcium blocker, diuretic, alpha blocker, β-blocker, and centrally acting antihypertensive added, titration of losartan to reach BP < 140/90 2. <140/90	Asia, Europe, North & South America, New Zealand. Adults (31-70) with type 2 diabetes and nephropathy. Exclusion criteria: type 1 DM, non diabetic renal disease, history of MI, CABG < 1 month, CVA, PCTA < 6 months TIA < 12 months, or heart failure.	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 1,513 5.. 3.4 years	1. yes 2. 60 3. 63.2% 4. 48.6%	1. 152.5/82.0 I: 152.0/82.0 C: 153.0/82.0 2: 11.4% 3: 100%	1. I: 158/748 (21.1%) C: 155/762 (20.3%) 2. I: 50/748 (6.7%) C: 68/762 (8.9%) 3. not reported 4. I: 247/748 (33.0%) C: 268/762 (35.1%) 5. I: 140.0(SD)/4.0(SD), n/a -12.0(SD)/-8.0(SD) C: 142.0(SD)/4.0(SD), n/a -11.0(SD)/-8.0(SD)	1. I: 507/751(67.5%) C: 559/762(73.4%) 2. I: 3/751 (0.4%) C: 0/762 (0.0%) 3. not reported 4. not reported
Alpha-blocker vs. placebo (see TOMHS)							

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
Beta-blockers vs. diuretics (also MRC, MRC-O, TOMHS)							
HAPPHY	I1: bendofluazide 5 mg/day or hydrochlorothiazide 50 mg/day I2: atenolol 100 mg/day or metoprolol 200 mg/day Step 2 hydralazine 75-150 mg/day added, step 3 spirinolactone 75-150 mg/day added and step 4 other antihypertensive added. 2. DBP < 95	Western Europe, Czechoslovakia, USA. Men (40-64) with untreated or currently treated (35%) mild to moderate essential hypertension (DBP 100-130). Exclusion criteria history of MI, angina, CVA or other serious disease.	1. participant – no provider – no assessor – yes 2. unclear 3. unclear 4. 6,569 5. 45.1 months	1. yes 2. 52.2 3. 100% 4. > 99%	1. 166/107 I1: 166/107 I2: 166/107 2: 0% 3: 0%	1. I1: 101/3,240 (3.1%) I2: 96/3,265 (2.9%) 2. I1: 116/3,240 (3.6%) I2: 132/3,265 (4.0%) 3. I1: 41/3,240 (1.3%) I2: 32/3,265 (1.0%) 4. I1: 157/3,240 (4.8%) I2: 164/3,265 (5.0%) 5. I1: 140(SD)/89(SD), 3,204 -26(SD)/-18(SD) I2: 140(SD)/88(SD), 3,218 -26(SD)/-19(SD)	1. I1: 389/3,272 (11.9%) I2: 351/3,297 (10.6%) 2. I1: 32/3,272 (1.0%) I2: 32/3,297 (1.0%) 3. I1: 61.9% I2: 68.0% 4. BP did not differ between 2 groups
MAPHY	I1: diuretic hydrochlorothiazide 50-100 mg/day or bendroflumethiazide 5-10 mg/day I2: β-blocker metoprolol 200-400 mg/day Step 2 hydralazine or other antihypertensive added. 2. DBP<95	Western Europe. Males (40-64) with treated or untreated essential hypertension (DBP 100-130). Exclusion criteria previous MI, CVA or angina.	1. participant – no provider – no assessor – yes 2. unclear 3. unclear 4. 3,234 5. 5 years	1. yes 2. 52.6 3. 100% 4. unclear	1. 166.8/107.5 I1: 166.8/107.5 I2: 166.9/107.6 2: 0% 3: 0%	1. I1: 83/1,624 (5.1%) I2: 65/1,609 (4.0%) 2. (mortality only) I1: 43/1,624 (2.6%) I2: 36/1,609 (2.2%) 3. (mortality only) I1: 9/1,624 (0.6%) I2: 2/1,609 (0.1%) 4. (mortality only) I1: 57/1,624 (3.5%) I2: 42/1,609 (2.6%) 5. I1: 142.7(16)/89.5(8), 1,624 -24.1(SD)/-18(SD) I2: 142.4(17)/88.7(8), 1,609 -24.5(SD)/-18.9(SD)	1. I1: 514/1625 (31.6%) I2: 376/1609 (23.3%) 2. I1: 1/1,625 (0.1%) I2: 0/1,609 (0%) 3. I1: 45.4% I2: 51.9% 4. not reported

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
Calcium-channel blockers vs. diuretics or beta-blockers (see also TOMHS)							
ALLHAT	I1: calcium-channel blocker amlodipine 2.5–10 mg/day I2: ACE-inhibitor lisinopril 10–40 mg/day I3: diuretic chlorthalidone 12.5–25 mg/day Step 2 atenolol 25-100 mg/day, reserpine 0.05-0.2 mg/day or clonidine 0.2-0.6 mg/day added and step 3 hydralazine 50-200 mg/day added. 2. < 140/90	USA, Canada, Puerto Rico and US Virgin Islands. Adults (≥ 55) with currently treated (90%) or untreated (10%) essential hypertension (BP < 180/110), and at least one risk factor for CHD. Exclusion criteria symptomatic heart failure, LV ejection fraction < 30%, or requiring more than 2 antihypertensive drugs for control of BP.	1. participant – yes provider – yes assessor – yes 2. adequate 3. adequate 4. 42,418 5. 4.9 years	1. yes 2. 66.9* 3. 53.2% 4. 59.7%	1. 146.3/84.0 I1: 146.2/83.9 I2: 146.4/84.1 I3: 146.2/84.0 2. 50.3 3. 36.2%	1. I1: 1,256/8,790 (13.9%) I2: 1,314/8,778 (14.5%) I3: 2,203/14,836 (14.4%) 2. I1: 1,466/8,790 (47.7%) I2: 1,505/8,778 (49.1%) I3: 2,451/14,836 (50.5%) 3. I1: 377/8,790 (20.8%) I2: 457/8,778 (25.0%) I3: 675/14,836 (21.0%) 4. I1: 2,432/8,790 (27.7%) I2: 2,514/8,778 (28.6%) I3: 3,941/14,836 (26.6%) 5. I1: 134.7(14.9)/74.6(9.9), 3,195 -11.5(SD)/-9.3(SD) I2: 135.9(17.9)/75.4(10.7), 2,963 -10.5(SD)/-8.7(SD) I3: 133.9(15.2)/75.4(9.8), 5,301 -12.3(SD)/-8.6(SD)	1. I1: 2,308/9,048 (25.5%) 2.0% adverse effects I2: 2,713/9,054 (30.0%) 2.9% adverse effects I3: 4,076/15,255 (26.7%) 1.8% adverse effects 2. I1: 258/9,048 (2.8%) I2: 276/9,054 (3.0%) I3: 419/15,255 (2.7%) 3. I!: 60.5% I2: 57.0% I3: 59.3% 4. I1: 2,118/9,048 (66.3%) I2: 1,813/9,054 (61.2%) I3: 3,615/15,255 (68.2%)
CONVINCE	I1: calcium-channel blocker verapamil 180-360 mg/day I2: β-blocker atenolol 50-100 mg/day or diuretic hydrochlorothiazide 12.5-25 mg/day (choice of drug determined by investigator) Step 2 hydrochlorothiazide 12.5-50 mg/day to verapamil or atenolol; or 50-100 mg/day atenolol to hydrochlorothiazide and step 3 other antihypertensive added. 2. SBP< 140 and/or DBP < 90	North America, Europe, Middle East, Central America, South America. Adults (≥55) with currently treated hypertension (BP < 175/100), untreated or treated < 2 months hypertension (SBP 140-190 & DBP 90-110), and at least one other CVD risk (cigarette smoking < 3 years, previous CVD, type II diabetes, obese)	1. participant – yes provider – no assessor – yes 2. adequate 3. unclear 4. 16,602 5. 2.2 years (median for blinded treatment) 6. 3 years (median)	1 yes 2. 65.6* 3. 44.0%* 4. 84.0%* * excluding 126 randomised participants because of data integrity concerns	1. 150.1/86.8 I1: 150.1/86.8 I2: 150.1/86.8 2. 12.3% 3. 19.7% (type II)	1. I1: 337/7,671 (4.4%) I2: 319/7,798 (4.1%) 2. I1: 133/7,671 (1.7%) I2: 166/7,798 (2.1%) 3. I1: 133/7,671 (1.7%) I2: 118/7,798 (1.5%) 4. I1: 262/7,671 (3.4%) I2: 243/7,798 /7,799 (3.1%) 5. I1: 136.5(SD)/79.0(SD), n/a -13.6(SD)/-7.8(SD) I2: 136.6(SD)/79.7(SD), n/a -13.5(SD)/-7.1(SD)	1. I1: 3,485/8,241 (42.3%) 3,086 stopped medication 62 excluded I2: 3,547/8,361 (42.4%) 3,164 stopped medication 64 excluded 2. I1: 570/8,241 (6.9%) I2: 563/8,361 (6.7%) 3. I1: 2,340/8,241 (28.4%) I2: 2,182/8,361 (26.1%) 4. I1: 65.5% I2: 65.9%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
ELSA	1. I1: β-blocker atenolol 50-100 mg/d I2: calcium antagonist lacidipine 4-6 mg/d Step two: diuretic hydrochlorothiazide 12.5-25 mg Nonrandomized cardiovascular treatment (antihypertensive or lipid-lowering agents) was given for 'variable time' to limited participants 2. DBP< 95 mm Hg and >5 mm Hg reduction	France, Germany, Greece, Italy, Spain, Sweden, UK. Adults (45-75) with previously treated and treatment naive hypertension SBP 150-210 and DBP 95-115 mm Hg. Exclude participants with no baseline or <1 follow up ultrasound carotid scan	1. subject – adequate provider – adequate assessor – unclear 2. adequate 3. unclear 4. 2,334 5. 3.8 years	1. yes 2. 56.0 3. 54.8% 4. 98.2%	1. 163.5/101.4 I1: 163.1/101.3 I2: 163.9/101.4 2: not reported 3: not reported	1. I1: 17/1,114 (1.5%) I2: 13/1,128 (1.2%) 2. I1: 17/1,114 (1.5%) I2: 18/1,128 (1.2%) 3. I1: 14/1,114 (1.2%) I2: 9/1,128 (0.8%) 4. I1: 73/1,114 I2: 69/1,128 5. I1: 141.5(SD)/85.7(SD) n -21.6(SD)/-15.6(SD) I2: 142.1(SD)/85.9(SD) n -21.8(SD)/-15.5(SD)	
INSIGHT	I1: calcium-channel blocker nifedipine 30-60 mg/day I2: co-amilozide (diuretics hydrochlorothiazide 25-50 mg/day and amiloride 2.5-5 mg/day) Step 2 β-blocker atenelol 25-50 mg/day or ACE-inhibitor enalapril 25-50 mg/day added; step 3 other antihypertensive (not calcium-channel blocker or diuretic) added. 2. <140/90 and reduction ≥20/10	Western Europe and Israel. Adults (55-80) with essential hypertension (BP ≥ 150/95, or SBP ≥ 160) and at least one cardiovascular risk factor.	1. participant – yes provider – yes assessors — yes 2. unclear 3. unclear 4. 6,575 5. 3.5 years	1. yes 2. 65 3. 46.4% 4. not reported	1. 173/99 I1: 173/99 I2: 173/99 2. unclear 3. 20.6%	1. I1: 176/3,223 I2: 172/3,203 2. I1: 77/3,223 (2.4%) I2: 61/3,203 (1.9%) 3. I1: 67/3,223 (2.1%) I2: 74/3,203 (2.3%) 4. unclear 5. I1: 139.9(SD)/81.0(SD), 831 -33.1(SD)/-18.0(SD) I2: 139.0(SD)/82.5(SD), 944 -34.0(SD)/-16.5(SD)	1. I1: 1,430/3,289 (43.5%) I2: 1,189/3,286 (36.2%) 2. I1: 198/3,289 (6.0%) I2: 205/3,286 (6.2%) 3. I1: 61% I2: 58% 4. not reported

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
INVEST	1. I1: verapamil sustained release, calcium-channel blocker 240 mg/d (+ trandolapril (ACE) 2 mg/d for patients with diabetes, renal impairment or heart failure) I2: atenolol, β-blocker 50 mg/d (+ trandolapril (ACE) 2 mg/d for patients with diabetes, renal impairment or heart failure) Step 2: add trandolapril 2 mg/d (I1) or hydrochlorothiazide 25 mg/d (I2); step 3 : increase dose of study drug; step 4: add hydrochlorothiazide 25 mg/d (I1) or trandolapril 2 mg/d (I2); step 5: maximum tolerated dose of study drug and non-study anti-hypertensive drugs except β-blocker (I1) or calcium-channel blocker (I2) 2. 140/90 mmHg 130/85 mmHg if diabetes or renal impairment	International. Adults (50 yrs >) with coronary artery disease and treated essential hypertension. Excluded if treated with β–blockers within 2 wks randomisation or in previous 12 months for MI	1. subject – no provider – no assessor – yes 2. adequate) 3. adequate 4. 22,576 5. 2.7 years	1. yes 2. 66.1 3. 47.9% 4. 48.4%	1. 150.9/87.1 I1: 150.8/87.2 I2: 150.9/87.1 2: 100% 3: 28.4%	1. I1: 873/10,967 (8.0%) I2: 893/11,041 (8.1%) 2. {non-fatal MI only} I1: 151/10,967 (1.4%) I2: 153/11,041 (1.4%) 3. [non-fatal stroke only] I1: 131/10,967 (1.2%) I2: 148/11,041 (1.3%) 4. unclear 5. I1: -18.7(22.2)/-10.0(12.4), 7,842 I2: 9.0(22.6)/-10.2(12.4), 7,850	1. I1: 1,969/11,267 17.5%) I2: 1,891/11,309 (16.7%) 2. I1: 300/11,267 (2.7%) I2: 268/11,309 (2.4%) 3. I1: 1,964/8,639 (22.7%) I2: 1,920/8,694 (22.1%) 4. I1: 5,625/7,842 (71.7%) I2: 5,553/7,850 (70.7%)

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
MIDAS	I1: calcium-channel blocker isradipine 2.5-5 mg/day I2: diuretic hydrochlorothiazide 25-50 mg/day Step 2 ACE-inhibitor enalapril 2.5-10 mg/day added. 2. DBP < 95 and reduction ≥10	USA. Adults (≥ 40) with essential hypertension (DBP 90-115) and confirmed carotid atherosclerosis. Exclusion criteria recent history of CVA, MI, renal disease, or type I diabetes.	1. participant – yes provider – yes assessors – yes 2. unclear 3. unclear 4. 883 5. 36 months	1 yes 2. 58.4 3. 78% 4. 72%	1. 149.7/96.5 I1: 150.6/96.7 I2: 148.9/96.2 2. 1.9% 3. 0	1. I1: 8/442 (1.8%) I2: 9/441 (2.0%) 2. I1: 17/442 (1.4%) I2: 12/441 (2.0%) 3. I1: 6/442 (1.4%) I2: 3/441 (0.7%) 4. (Includes angina, CHF, sudden death) I1: 25/442 (5.7%) I2: 14/441 (3.2%) 5. (SBP at 3 yrs, DBP at 6 mths) I1: 133.4(18.1)/83.7(SD), n/a -17.2(SD)/-13.0(SD) I2: 130.0(12.2)/83.2(SD), n/a -19.5(SD) /-13 (SD)	1. I1: 96/442 (21.7%) 9.3% adverse reaction I2: 90/441 (20.4%) 8.2% adverse reaction 2. not reported 3. I1: 55.5% I2: 54.2% 4. not reported
NICS-EH	I1: calcium-channel blocker nicardipine hydrochloride 40-80 mg/day I2: diuretic trichlormethiazide 2-4 mg/day 2. not reported	Japan. Adults (≥ 60) with currently treated (61%) or untreated (39%) essential hypertension (SBP 160-220 and DBP < 115). Exclusion criteria CVD.	1. participant – yes provider – yes assessor – unclear 2. unclear 3. adequate 4. 429 5. 4.6 years	1. no (greater % women in I1) 2. 69.8 3. 33.1% 4. 0%	1. 172.3/93.8 I1: 171.9/94.2 I2: 172.6/93.4 2: 0 3: 0	1. I1: 2/204 (1%) I2: 2/210 (1%) 2. I1: 2/204 (1%) I2: 2/210 (1%) 3. I1: 8/204 (4%) I2: 8/210 (4%) 4. I1: 10/204 (5%) I2: 10/210 (5%) 5. I1: 147.0(15)/81.0(8), 106 -24.9(SD)/-13.2(SD) I2: 147.0(16)/79.0(9), 94 -25.6(SD)/-14.4(SD)	1. I1: 57/215 (26.5%) 2.8% adverse reactions 3.7% BP too high 6.0% took other anti-Ht agents I2: 65/214 (30.4%) 4.2% adverse reactions 7.5% BP too high0 5.6% took other anti-Ht agents 2. I1: 11/215 (5.1%) I2: 4/214 (1.9%) 3. not applicable 4. not applicable

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
NORDIL	I1: calcium-channel blocker diltiazem 180-360 mg/day Step 2 ACE-inhibitor added, step 3 diuretic or α-blocker added and step 4 other antihypertensive added I2: diuretic and/or β-blocker Step 2 ACE-inhibitor or α -blocker added, step 3 other antihypertensive (not calcium-channel blocker) added 2. DBP<90	Norway and Sweden. Adults (50-74) with previously untreated essential hypertension (DBP ≥ 100).	1. participant – no provider – no assessors – yes 2. adequate* 3. adequate 4. 10,916 5. 4.5 years * 35 participants were excluded after randomistaion	1. yes 2. 60.4 3. 48.6% 4. not reported	1. 173.4/105.7 I1: 173.5/105.8 I2: 173.4/105.7 2. 2-7% 3. 6.7%	1. I1: 231/5,386 (4.3%) I2: 228/5,443 (4.2%) 2. I1: 183/5,386 (3.4%) I2: 157/5,443 (2.9%) 3. I1: 159/5,386 (3.0%) I2: 196/5,443 (3.6%) 4. I1: 403/5,386 (7.5%) I2: 400/5,443 (7.3%) 5. I1: 152.2(16.4)/87.6(7.6), n/a -21.3(SD)/-18.2(SD) I2: 149.1(16.7)/87.4(7.7), n/a -24.3(SD)/-18.3(SD)	1. I1: 1,244/5,410 (23.0%) I2: 383/5,471 (7.0%) 2. I1: 24/5,410 (0.4%) I2: 28/5,471 (0.5%) 3. I1: 50% I2: 45% 4. not reported
STOP-H2	I1: ACE-inhibitor enalapril or lisinopril 10 mg/day I2: calcium-channel blocker felodipine or isradipine 2.5 mg/day I3: β-blocker atenolol 50 mg/day, metoprolol 100 mg/day, pindolol 5 mg/day or diuretics hydrochlorothiazide 25 mg/day and amiloride 2.5 mg/day. Step 2 if started on ACE-inhibitor or β-blocker, hydrochlorothiazide and amiloride 25/2.5 mg/day added. if started on calcium-channel blocker or diuretic, atenolol 50mg/day, metroprolol 100mg/day, or pindolol 5mg/day added. 2. ≤ 160/95	Sweden. Adults (70-84) with treated or untreated essential hypertension (BP ≥ 180-230/90-120, and/or DBP > 105). Exclusion criteria MI or CVA ≤ 12 months.	1. participant – no provider – no assessor – yes 2. unclear 3. adequate 4. 6,614 5. 60 months	1. yes 2. 76.0 3. 33.2% 4. unclear	1. 194/98 I1: 194/98 I2: 194/98 I3: 194/98 2. 8--15% 3. 10.9%	1. I1: 380/2,205 (17.2%) I2: 362/2,196 (16.5%) I3: 369/2,213 (16.7%) 2. I1: 139/2,205 (6.3%) I2: 179/2,196 (8.2%) I3: 154/2,213 (7.0%) 3. I1: 215/2,205 (9.8%) I2: 207/2,196 (9.4%) I3: 237/2,213 (10.7%) 4. I1: 437/2,205 (41.9%) I2: 450/2,196 (43.6%) I3: 460/2,213 (44.1%) 5. (at 54 months) I1: 159(SD)/81(SD), n/a -35(SD)/-17(SD) I2: 159(SD)/80(SD), n/a -35(SD)/-18(SD) I3: 158(SD)/81(SD), n/a -36(SD)/-17(SD)	1. I1: 853/2,205 (38.7%) I2: 742/2,196 (33.8%) I3: 834/2,213 (37.7%) 2. I1: 0/2,205 (0%) I2: 0/2,196 (0%) I3: 0/2,213 (0%) 3. not reported 4. not reported

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
VHAS	I1: calcium-channel blocker verapamil 240 mg/day I2: diuretic chlorthalidone 25 mg/day Step 2 ACE-inhibitor captopril 25-50 mg/day added. 2. DBP ≤ 90 or ≤ 95 and > 10% reduction	Italy. Adults (40-65) with essential hypertension (BP ≥ 160/95). Exclusion criteria CVA, MI < 6 months, renal failure, type I diabetes mellitus or uncontrolled type II diabetes mellitus.	1. participant – yes provider – yes (Note double blind design for first 6 months only, then open design) assessor – yes 2. unclear 3. unclear 4. 1,414 5. 2 years	1. yes 2. 54.2 3. 48.9% 4. unclear	1. 169.0/102.3 I1: 169.1/102.2 I2: 168.8/102.3 2: 5.0 3: 3.6%	1. I1: 5/707 (0.7%) I2: 4/707 (0.6%) 2. I1: 8/707 (1.1%) I2: 9/707 (1.3%) 3. I1: 5/707 (0.7%) I2: 4/707 (0.6%) 4. unclear 5. I1: 140.2(SD)/85.7(SD), 166 -28.6(SD)/-16.6(SD) I2: 141.5(SD)/85.2(SD), 158 -27.6(SD)/-17(SD)	1. I1: 158/707 (23.5%) 2.5% adverse events I2: 166/707 (22.3%) 2.5% aderse events 2. I1: 0/707 (0%) I2: 0/707 (0%) 3. I1: 44.1% I2: 38.8% 4. I1: 69.3% I2: 66.9%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
ACE-inhibitors vs. diuretics or beta-blockers(see also STOP_H2, ALLHAT, TOMHS)							
ANBP2	I1: ACE-inhibitor enalapril I2: diuretic hydrochlorothiazide Step 2 β-blockers, calcium-channel blockers and ARBs added. 2. SBP <160 (or, if drug tolerated, <140) and reduction ≥ 20 DBP <90 (or, if drug tolerated <80) and reduction ≥10	Australia. Adults (65-84) with previously treated (62%) and untreated (38%) hypertension (SBP > 160 or BP > 140/90). Exclusion criteria recent CVD events < 6 months, life threatening illness or malignant hypertension.	1. participant – no provider – no assessor – yes 2. adequate 3. adequate 4. 6,083 5. 4.1 years	1 yes 2. 72.0 3. 49.0% 4. 95%	1. 167.5/91.0 I1: 167.0/91.0 I2: 168.0/91.0 2. 13.0% 3. 7.5%	1. I1: 195/3,044 (6.4%) I2: 210/3,037 (6.9%) 2. I1: 58/3,044 (1.9%) I2: 82/3,037 (2.7%) 3. I1: 112/3,044 (3.7%) I2: 107/3,0397(3.5%) 4. I1: 394/3,044 (12.9%) I2: 429/3,037 (14.1%) 5. I1: 141(SD)/79(SD), 1,183 -26(SD)/-12(SD) I2: 142(SD)/79(SD), 1,183 -26(SD)/-12(SD)	1. I1: 1,278/3,044 (42.0%) I2: 1,155/3,039 (38.0%) 2. I1: 0/3,044 (0%) I2: 2/3,039 (0.1%) 3. I1: 65% I2: 67% 4. not reported
CAPPP	I1: ACE-inhibitor captopril 50-100 mg/day I2: diuretic hydrochlorothiazide 25 mg/day or bendroflumethiazide 2.5 mg/day and/or β-blocker atenolol or metropolol 50-100 mg/day In I1, step 2 captopril 200mg/day, step 3 diuretic added and step 4 calcium-channel blocker added. In I2, step 2 optimum dose of β-blocker and diuretic and step 3 calcium-channel blocker added. 2. DBP ≤90	Sweden and Finland. Adults (25-66) with treated or untreated essential hypertension (DBP > 100). Exclusion criteria renal disorders.	1. participant – no provider – no assessor – yes 2. unclear 3. unclear 4. 10,985 5. 6.1 years	1 no - BP higher in captopril group 2. 52.6 3. 53.5% 4. not reported	1. 160.7/98.9 I1: 161.8/99.8 I2: 159.6/98.1 2. 4-7% 3. 5.2%	1. I1: 184/5,478 (3.4%) I2: 190/5,480 (3.5%) 2. I1: 162/5,478 (2.9%) I2: 161/5,480 (2.9%) 3. I1: 189/5,478 (3.5%) I2: 148/5,480 (2.7%) 4. (deaths only) I1: I2: 5. (at 5 years) I1: 150.0(SD)/90.0(SD) -10.7(SD)/-8.9(SD), n/a I2: 149.0(SD)/89.0 -10.6(SD)/-9.1(SD), n/a	1. I: not reported I2: not reported 2. I: 14/5,492 (0.25%) I2: 13/5,493 (0.24%) 3. not reported 4. not reported

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
UKPDS *(not included in meta-analysis as 100% diabetics)*	I1: ACE-inhibitor captopril 50-100 mg/day I2: β-blocker atenolol 50-100 mg/day Step 2 frusemide 20-80 mg/day, nifedipine 20-80 mg/day, methyldopa 500-1000 mg/day and prazosin 3 -15 mg/day could be added. 2. ≤ 150/85 (2/3 of patients randomly allocated to tight control), or ≤ 180/105 (1/3 of patients randomly allocated to less tight control)	UK. Adults (25-65) with type II diabetes and hypertension (untreated SBP ≥ 160 and/or DBP ≥ 90; treated SBP ≥ 150 and/or DBP ≥ 85). Exclusion criteria MI < 1 year, renal disease, angina, > 1 major vascular episode, malignant hypertension or severe concurrent illness.	1. participant – unclear provider – unclear assessor – yes 2. unclear 3. inadequate 4. 758 5. median: 8.4 years	1 yes 2. 56.2 3. 54% 4. 86%	1. 159.0/93.5 I1: 159/94 I2: 159/93 2. not reported 3. 100%	1. I1: 75/400 (18.8%) I2: 59/358 (16.5%) 2. I1: 61/400 (15.3%) I2: 46/358 (12.8%) 3. I1: 21/400 (5.3%) I2: 17/358 (4.7%) 4. unclear 5. I1: 144(14)/83(8), 145 -15.0(8.4).0/-11.0(4.2) I2: 143(14)/81(7), 129 -16.0(8.4)/-12.0(4.2)	1. I1: 163/400 (40.8%) I2: 184/358 (51.4%) 2. 47/758 (6.2%) (not reported by treatment group) 3. I1: 33% I2: 40% 4. not reported
Alpha blockers vs. diuretics (see also TOMHS)							
ALLHAT	I1: α-blocker doxazosin 2-8 mg/day I2: diuretic chlorthalidone 12.5-25 mg/day Step 2 atenolol 25-100 mg/day, reserpine 0.05-0.2 mg/day, or clonidine 0.2-0.6 mg/day added; step 3 hydralazine 50-200 mg/day added. 2. < 140/90	USA, Canada and Puerto Rico. Adults (≥ 55) with untreated (SBP ≥ 140 or DBP ≥ 90 and SBP = 180 and DBP ≤ 110), or treated essential hypertension (BP ≤ 180/110) and at least one additional risk factor for CHD.	1. participant – yes, provider – yes, assessor – yes 2. adequate 3. adequate 4. 24,335 5. median: 3.3 years	1. yes 2. 67 3. 53.2% 4. 59.5%	1. 145.0/83.4 I1: 145/84 I2: 145.83 2. 50.3 3. 35.6%	1. I1: 514/8,729 (5.7%) I2: 851/14,767 (5.6%) 2. I1: 365/8,729 (4.0%) I2: 608/14,767 (4.0%) 3. I1: 244/8,729 (2.7%) I2: 351/14,767 (2.3%) 4. unclear 5. I1: 137(SD)/76(SD), 1,487 -9(SD)/-8(SD) I2: 135(16)/76(10), 2,633 -11(SD)/-7(SD)	1. I1: 981/9,067 (10.8%) I2: 1455/15,268 (9.5%) 2. I1: 338/9,067 (3.7%) I2: 501/15,268 (3.3%) 3. I1: 62% I2: 83% 4. I1: 58% I2: 64%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
ACE-inhibitors vs. calcium-channel blockers (see also ALLHAT, STOP-H2, TOMHS)							
ABCD trial *(not included in meta-analysis as 100% diabetic)*	I1: ACE-inhibitor enalapril 5-40 mg/day and placebo nisoldipine I2: calcium-channel blocker nisoldipine 10-60 mg/day and placebo enalapril Step 2 metoprolol added; step 3 hydrochlorothiazide added. 2. Randomly allocated to DBP ≤ 75 (intensive treatment), or DBP 80-89 (moderate treatment)	USA. Adults (40-74) with non-insulin dependent diabetes and currently untreated hypertension (DBP ≥ 90). Exclusion criteria MI, CVA, or unstable angina < 6 months.	1. participants – yes providers – yes assessors – yes 2. unclear 3. unclear 4. 470 5. 5 years	1 yes 2. 57.4; 3. 67.4% 4. 66.8%	1. 155.5/98.0 I1: 156/98 I2: 155/98 2. 54.5% 3. 100%	1. I1: 14/235 (5.5%) I2: 18/235 (7.2%) 2. I1: 9/235 (2.1%) I2: 27/235 (10.6%) 3. I1: 7/235 (3.0%) I2: 11/235 (4.7%) 4. I1: 12/235 (5.1%) I2: 36/235 (15.3%) 5. unclear	1. I1: 129/235 (51.1%) I2: 142/235 (60.4%) 2. I1: 0/235 I2: 0/235 3. unclear 4. not reported
FACET *(not included in meta-analysis as 100% diabetic)*	I1: ACE-inhibitor fosinopril 20 mg/day I2: calcium-channel blocker amlodipine 10 mg/day Step 2 other study drug was added in each group. 2. SBP ≤140 and DBP ≤90, or reduction ≥ 20 if SBP >160 or DBP >110	Italy. Adults with non-insulin dependent diabetes and essential hypertension (SBP > 140 or DBP > 90). Exclusion criteria patients with renal disease, a history of CHD/ CVA or use of aspirin or antihypertensive agents other than diuretics and β-blockers.	1. participants – no providers – no assessors – yes 2. adequate 3. unclear 4. 380 5.. 2.7 years	1 yes 2. 63.1 3. 59.5% 4. not reported	1. 170.5/94.5 I1: 170/95 I2: 171/94 2. 0% 3. 100%	1. I1: 4/188 (2.1%), I2: 5/188 (2.7%) 2. I1: 10/188 (5.3%) I2: 13/188 (6.9%) 3. I1: 4/188 (2.1%), I2: 10/188 (5.3%) 4. I1: 14/188 (7.4%) I2: 23/188 (12.2%) 5. I1: 157(13.4)/88(13.4), 179 -13(20.5)/-7(10.3) I2: 153(13.3)/86(13.3), 178 -19(23.8)/-8(10.2)	1. I1: 40/189 (121.2%) I2: 57/191 (29.8%) 2. I1: 1/189 (0.5%) I2: 3/191 (1.6%) 3. I1: 131/188 (70%) I2: 141/188 (75%) 4. I1: 55.6% I2: 58.6%

Trial	1. Comparison 2. Target BP	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Mean duration of follow up	1. Baseline comparability 2. Age 3. Male% 4. White%	1: BP 2: CVD% 3. Diabetes%	1: Total Mortality 2: CHD events 3: Cerebrovascular events 4: Cardiovascular events 5: Blood Pressure	1. Withdrawal by treatment group and cause 2. Loss to follow-up 3. % on monotherapy at end of trial 4. % achieving target BP
Angiotensin receptor blockers vs. beta-blockers							
LIFE	I1: ARB losartan 50 mg/day I2: β-blocker atenolol 50 mg/day Step 2 hydrochlorothiazide 12.5 mg/day added, step 3 doubled dose of treatment drug, step 4 doubled dose of hydrochlorothiazide or other antihypertensive added. 2. <140/90	Denmark, Finland, Iceland, Norway, Sweden, UK and USA. Adults (55-80) with hypertension (BP 160-200/95-115) and ECG signs of LVH. Exclusion criteria MI or CVA < 6 months.	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 9,222 5. 4.8 years	1. yes 2. 66.9 3. 45.9% 4. 92.2%	1. 174.4/97.8 I1: 174.3/97.9 I2: 174.5/97.7 2: 23.8% 3: 13.0%	1. I1: 383/4,557(8.4%) I2: 431/4,546(9.5%) 2. I1: 198/4,557(4.3%) I2: 188/4,546(4.1%) 3. I1: 232/4,557(5.1%) I2: 309/4,546(6.8%) 4. I1: 508/4,557(11.1%) I2: 588/4,546(12.9%) 5. I1: 144.1(17.1)/81.3(9.6), n/a -30.2(18.5)/-16.6(10.1) I2: 145.4(16.4)/80.9(9.6), n/a -29.1(19.2)/-16.8(10.1)	1. I1: 1,545/4,605(33.6%) I2: 1,780/4,588(38.8%) 2. I1: 48/4,605 (1%) I2: 42/4,588 (0.9%) 3. I1: 11% I2: 11% 4. I1: 48% I2: 45%
LIFE (diabetic subset) *(not included in meta-analysis as 100% diabetic)*	I1: ARB losartan 50 mg/day I2: β-blocker atenolol 50 mg/day Step 2 hydrochlorothiazide 12.5 mg/day added, step 3 doubled dose of treatment drug, step 4 doubled dose of hydrochlorothiazide or other antihypertensive added. 2. <140/90	Denmark, Finland, Iceland, Norway, Sweden, UK and USA. Adults (55-80) with previously treated (80%) and untreated (20%) essential hypertension (BP 160-200/95-115), diabetes and ECG signs of LVH. Exclusion criteria MI or CVA< 6 months.	1. participant – yes provider – yes assessor – yes 2. unclear 3. unclear 4. 1,195 5. 4.7 years	1. yes 2. 67.4 3. 46.9% 4. 85.7%	1. 176.5/96.5 I1: 176.0/97.0 I2: 177.0/96.0 2: 35% 3: 100%	1. I1: 63/586 (10.8%) I2: 104/605 (17.1%) 2. I1: 41/586 (7.0%) I2: 50/605 (8.3%) 3. I1: 51/586(8.7%) I2: 65/605 (10.7%) 4. unclear I1: I2: 5. I1: 146.0(17)/79.0(11), 587 -31.0(19)/-17.0(11) I2: 148.0(19)/79.0(11), 606 -28.0(21)/-17.0(11)	1. I1: 254/586 (43.3%) I2: 334/609 (54.8%) 2. I1: 0/586 (0%) I2: 4/609 (0.7%) 3. I1: 9% I2: 6% 4. (SBP) I1: 38% I2: 34% (DBP) I1: 85% I2: 82%

Appendix 18: RCTs of lifestyle interventions to support withdrawal of anti-hypertensive drugs

Trial	1. Comparison 2. Definition of normotension	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Length of follow-up	1. Baseline comparability 2. Mean age 2. Male% 3. White%	1. BP 2. CV disease% 3. Diabetes%	% achieving successful drug withdrawal	1. Withdrawal 2. Loss to follow-up
TONE *(Obese participants only)*	1. I1: sodium reduction – weekly, nutritionist & exercise counsellor led sessions with aim < 80mmol sodium intake p/day I2: weight loss – weekly nutritionist & exercise counsellor led sessions with aim > 4.5 kg reduction I3: sodium reduction and weight loss - aim >4.5 kg & < 80 mmol sodium intake p/day C: usual lifestyle control group - no weight loss or reduced sodium intake Withdrawal of drug therapy was attempted in all participants after mean 90 (76-104) days 2. BP<150/90	Adults, 60-80yrs.; BP< 145/85, on one anti-hypertensive drug or a combination of a diuretic and a non-diuretic for a mean duration of 11.7 yrs., BMI > 27.8 kg/m²	1. single 2. unclear 3. adequate 4. 585 5. unclear 6. mean 29 (15-36) months	1. yes 2. 66 3. 47.5% 4. 71.8%	1. 129/72 2. 0% 3. 0%	I1: 49/144 (34%) I2: 54/147 (37%) I3: 65/147 (44%) C: 24/147 (16%)	1. unclear 2. I1: 9/340 (2.6%) I2: 3/147 (2.0%) I3: 2/147 (1.4%) C: 8/341 (2.3%)
TONE *(Non-obese participants only)*	1. I1: sodium reduction – weekly, nutritionist & exercise counsellor led sessions with aim < 80mmol sodium intake p/day C: usual lifestyle control group - no weight loss or reduced sodium intake Withdrawal of drug therapy was attempted in all participants after mean 90 (76-104) days 2. BP<150/90	Adults, 60-80yrs.; BP< 145/85, on one anti-hypertensive drug or a combination of a diuretic and a non-diuretic for a mean duration of 11.7 yrs., BMI < 27.8 kg/m²	1. single 2. unclear 3. adequate 4. 390 5. unclear 6. mean 29 (15-36) months	1. yes 2. 67 3. 59%% 4. 82%	1. 128.5/71.5 2. 0% 3. 0%	I1: 71/196 (36%) C: 41/194 (21%)	1. unclear 2. I1: 9/340 (2.6%) I2: 3/147 (2.0%) I3: 2/147 (1.4%) C: 8/341 (2.3%)

Trial	1. Comparison 2. Definition of normotension	Patient characteristics	1. Blinding 2. Randomisation 3. Concealment 4. N 5. Treatment duration 6. Length of follow-up	1. Baseline comparability 2. Mean age 2. Male% 3. White%	1. BP 2. CV disease% 3. Diabetes%	% achieving successful drug withdrawal	1. Withdrawal 2. Loss to follow-up
DISH *(Obese participants only)*	1. I1: Continue taking anti-hypertensive medication I2: Stop medication - restrict sodium and increase potassium I3: Stop medication - reduce weight C: Stop medication - no dietary interevention Groups I1 and I2 had 8 weekly group sessions, then monthly sessions with individual consultation as required. Drugs restarted if DBP 95-99 on 3 occasions in 3 months or 100-104 on 2 occasions in 1 month or ≥ 105 on 1 occasion 2. DBP <95	Adults; hypertensive, treated for at least 5 years, SBP ≤ 180 in past year; mean DBP < 95 in past year; mean last 2 DBP's ≤ 90; neither > 95; without CHD, stroke, ≥120% of ideal weight	1. single 2. unclear 3. unclear 4. 325 5. 8 weeks 6. 56 weeks	1. yes 2. 57.0 3. 35.7% 4. 23.2%	1. 128.3/80.3 2. 0% 3. 0%	I1: n/a I2: 45/101 (44.9%) I3: 52/87 (59.5%) C: 31/89 (35.3%)	1. 15% Refused to participate after randomisation 2. I1: 0/48 (0%) I2: 0/101 (0%) I3: 0/87 (0%) C: 0/89 (0%)
DISH *(Non-obese participants only)*	1. I1: Continue taking anti-hypertensive medication I2: Stop medication - restrict sodium and increase potassium; 8 weekly group sessions, then monthly sessions with individual consultation as required C: Stop medication - no dietary interevention Drugs restarted if DBP 95-99 on 3 occasions in 3 months or 100-104 on 2 occasions in 1 month or ≥ 105 on 1 occasion 2. DBP <95	Adults; hypertensive, treated for at least 5 years, SBP ≤ 180 in past year; mean DBP < 95 in past year; mean last 2 DBP's ≤ 90; neither > 95; without CHD, stroke, <120% of ideal weight	1. single 2. unclear 3. unclear 4. 171 5. 8 weeks 6. 56 weeks	1. yes, except lower proportion black participants in C 2. 61.6 3. 50.9% 4. 36.8%	1. 125.6/80.3 2. 0% 3. 0%	I1: n/a I2: 36/68 (53.4%) C: 32/70 (45.0%)	1. 15% Refused to participate after randomisation 2. I1: 0/33 (0%) I2: 0/68 (0%) C: 0/70 (0%)
Stamler	1. I1: Stay on drugs I2: Stop drugs 2 months after nutritional couselling began. Aimed at reduction of 10lb and sodium <1800mg/day and alcohol< 2 drinks/day C: Stop drugs, no dietary intervention 2. DBP<90	Adults, with currently treated hypertension and good BP control, 67% on diuretics only, mean weight 20% above ideal.	1. open 2. unclear 3. unclear 4. 189 5. mean 38 months 6. mean 38 months	1. yes 2. 56 3. 63%	1. ?/79	I1: n/a I2: 36/80 (45%) C:: 6/39 (15%)	1. I1: 3/48 (6%) I2: 14/97 (14%) C: 2/44 (4%) 2. I1: /48 I2: 17/97 (18%) C: 5/44 (11%)