NCGC National Clinical Guideline Centre

Update of clinical guidelines 18 and 34

Hypertension

The clinical management of primary hypertension in adults

Clinical Guideline 127

Methods, evidence, and recommendations

August 2011

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Contents

Rationale for update

This document is a partial update of Clinical Guideline 18 (2004) and Clinical Guideline 34 (2006) on Essential Hypertension in adults. The sections that have not been amended are integrated with the updated guidance in this document. Both guidelines are available in full in the appendices of the document.

Improvements in methodology since 2006 mean the way information is presented may, at times, be inconsistent (for example, the style of review write-up, and 2011 recommendations are not graded according to the strength of evidence, unlike those in the 2006).

New or amended sections of the guideline are indicated with an 'update' panel in the right hand margin.

Update 2011

Guideline development group members

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Update 2011

Acknowledgments

The development of this guideline was greatly assisted by the following people:

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Acronyms and abbreviations

ABPM	Ambulatory blood pressure measurement
ACEi	Angiotensin-converting enzyme inhibitors
ANOVA	Analysis of variance
ARB	Angiotensin receptor blocker
BNF	British National Formulary
CBPM	Clinic blood pressure measurement
CCA	Cost-consequences analysis
CCB	Calcium channel blocker
CEA	Cost-effectiveness analysis
c.f.	Confer (refer to)
CI / 95% CI	Confidence interval / 95% confidence interval
CUA	Cost-utility analysis
DH	Department of Health
DSA	Deterministic Sensitivity Analysis
ED	Emergency Department
EQ-5D	EuroQol-5D
GDG	Guideline Development Group
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBPM	Home blood pressure measurement
HES	Hospital Episode Statistics
HR	Hazard Ratio
HRQoL	Health-related quality of life
HT	Hypertensive / hypertension
HTA	Health technology assessment
ICD-10	International Classification of Diseases, 10th edition
ICER	Incremental cost-effectiveness ratio
ICH	Isolated clinic hypertension
ISH	Ischemia
IQR	Interquartile range

INMB	Incremental Net Monetary Benefit
IRR	Inter-rater reliability
ITT	Intention to treat
LOS	Length of Stay
LR+	Positive likelihood ratio
LY	Life-year
MD	Mean difference
NCGC	National Clinical Guideline Centre
NHS	National Health Service
NHSEED	The NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NPV	Negative predictive value
NS	Non-significant (not statistically significant)
NT	Normotensive
OR	Odds ratio
PICO	Framework incorporating patients, interventions, comparison and outcome
PPP	Purchasing Power Parity
PPV	Positive predictive value
p.r.n	Pro re nata
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QUADAS	Quality assessment tool for diagnostic accuracy studies
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
RRK	Riva-Rocci Korotkoff
RR	Relative risk
SD	Standard deviation
SE	Standard error
SPC	Summary of product characteristics
SR	Systematic review
SS	Statistically significant
WCH	White coat hypertension

1 Introduction

This guideline is for the clinical management of primary hypertension in adults (aged greater than 18 years). Hypertension (high blood pressure) is one of the most preventable causes of premature morbidity and mortality world-wide.

Hypertension is a major risk factor for stroke (ischaemic and haemorrhagic), myocardial infarction, heart failure, chronic kidney disease, peripheral vasculardisease, cognitive decline and premature death. Untreated hypertension is associated a progressive rise in blood pressure, often culminating in a treatment resistant state due to associated vascular and renal damage.

Blood pressure is quantified as diastolic and systolic pressures measured in millimetres of mercury (mmHg). The diastolic pressure represents the pressure during ventricular relaxation in diastole whereas the systolic pressure represents the peak pressure due to ventricular contraction during systole. Either or both pressures have specified upper limits of normal and elevation in either or both pressures are used to define hypertension.

Blood pressure is normally distributed in the population and there is no natural cut-point above which "hypertension" definitively exists and below which, it does not. Epidemiological studies demonstrate that the aforementioned disease risk associated with blood pressure is a continuous relationship and above blood pressures of 115/70mmHg, the risk of cardiovascular events doubles for every 20/10mmHg rise in blood pressure. The threshold blood pressure determining the presence of hypertension is defined as the level of blood pressure above which treatment has been shown to reduce the development or progression of disease. Primary hypertension was previously termed “essential hypertension” because of a long-standing view that high blood pressure was sometimes “essential” to perfuse diseased and sclerotic arteries. It is now recognised that the diseased and sclerotic arteries were most often the consequence of the hypertension and thus the term “essential hypertension” is redundant and the “primary hypertension” is preferred. Primary hypertension refers to the majority of people with sustained high blood pressure (approximately 90%) encountered in clinical practice, for which there is no obvious, identifiable cause. The remaining 10% are termed "secondary hypertension" for which specific causes for the blood pressure elevation can be determined (for example, Conn's adenoma, renovascular disease, or phaeochromocytoma).

Update 2011

Primary hypertension is remarkably common in the UK population and the prevalence is strongly influenced by age and lifestyle factors. Systolic and/or diastolic blood pressures may be elevated. Systolic pressure elevation is the more dominant feature of hypertension in older patients and diastolic pressure more commonly elevated in younger patients, (those less than 50 years of age). At least one quarter of the adult population of the UK have hypertension, (blood pressure ≥140/90mmHg) and more than half of those over the age of 60 years. As the demographics of the UK shifts towards an older, more sedentary and obese population, the prevalence of hypertension and its requirement for treatment will continue to rise.

Routine periodic screening for high blood pressure is now commonplace in the UK as part of National Service Frameworks for cardiovascular disease prevention. Consequently, the diagnosis, treatment and follow-up of patients with hypertension is one of the most common interventions in primary care, accounting for approximately 12% of Primary Care consultation episodes and approximately £1 billion in drug costs in 2006 .

NICE first issued guidance for the management of hypertension in primary care in 2004. This was followed by a rapid update of the pharmacological treatment chapter of the guideline in 2006. The current partial update of the hypertension guideline is in response to the regular five year review cycle of existing NICE guidance. It began with a scoping exercise which identified key areas of the existing guideline for which new evidence had emerged that was likely to influence or change existing guideline recommendations.

Sections of the guideline that have not been updated continue to stand, however, wherever NICE has subsequently issued new and related guidance relevant to existing recommendations, these have been identified and cross-referred to in this partial update, examples include interventions on lifestyle factors and public health policy recommendations such as smoking cessation, dietary salt restriction, alcohol intake and cardiovascular disease prevention and cardiovascular disease risk assessment. In addition, new NICE guidance developed in areas relevant to hypertension are also highlighted and cross referenced (for example, chronic kidney disease, stroke, diabetes and hypertension in pregnancy).

The recommendations that have been reviewed in this partial update of the guideline for the clinical management of primary hypertension in adults, include; blood pressure measurement for the diagnosis of hypertension; blood pressure thresholds for intervention with drug therapy and blood pressure targets for treatment; specific aspects of the recommendations for the pharmacological treatment of hypertension; the treatment of hypertension in the very elderly (people aged greater than 80 years); dilemmas surrounding decision making for treatment of hypertension in younger adults (less than 40 years); the treatment of drug resistant hypertension; and wherever appropriate, the impact of age and ethnicity on treatment recommendations.

Finally, despite the fact that the treatment of hypertension has a large clinical trial evidence base to inform recommendations, an important aspect of the evidence review for guideline development is to identify where gaps in knowledge remain. In so doing, research questions have been identified to prompt the gathering of further evidence to continue the evolution of guidance and clinical practice.

Update 2011

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC)
- The NCGC establishes a guideline development group
- A draft guideline is produced after the group assesses the available evidence and makes recommendations
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- The **full guideline** contains all the recommendations, plus details of the methods used and the underpinning evidence
- The **NICE guideline** lists the recommendations
- the **Quick Reference Guide (QRG)** presents recommendations in a suitable format for health professionals
- Information for the public - **'understanding NICE guidance' or UNG** - is written using suitable language for people without specialist medical knowledge
- **Clinical Pathway** – www.pathways.nice.org.uk/pathways/hypertension

This version is the full guideline. The other documents can be downloaded from NICE at www.nice.org.uk

Update 2011

2.2 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).

The National Institute for Health and Clinical Excellence funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Bryan Williams in accordance with guidance from the National Institute for Health and Clinical Excellence (NICE).

The group met every four weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded in Appendix B: Declarations of Interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B: Declarations of Interest.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta analysis and cost effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.3 What this guideline covers

Update 2011

- Adults with hypertension (18 years and older).
- Particular consideration will be given to the needs of black people of African and Caribbean descent and minority ethnic groups where these differ from the needs of the general population.
- People aged 80 years or older.
- Ambulatory monitoring.
- Home blood pressure monitoring.
- Blood pressure thresholds for intervention and targets for treatment.
- First-line therapy options, for example angiotensin-converting enzyme inhibitors versus angiotension receptors blockers.
- Calcium-channel blockers versus diuretics as preferred components in step two of the treatment algorithm, for example, combination therapy.
- Adherence to medication.
- Provision of appropriate information and support.
- Resistant hypertension (that is, fourth-line therapy).
- Response to blood pressure lowering drugs according to age and ethnicity.

For further details please refer to Appendix A: Scope and Appendix C: Review questions.

2.4 What this guideline does not cover

- People with diabetes.
- Children and young people (younger than 18 years).

- Pregnant women.
- Secondary causes of hypertension (for example, Conn's adenoma, phaeochromocytoma and renovascular hypertension).
- People with accelerated hypertension (that is, severe acute hypertension associated grade III retinopathy and encephalopathy).
- People with acute hypertension or high blood pressure in emergency care settings.
- Prevention of hypertension.
- Screening for hypertension.
- Specialist management of secondary hypertension (that is, hypertension arising from other medical conditions).
- Non-pharmacological interventions.

2.5 Relationships between the guideline and other NICE guidance

2.5.1 Related guidance

- Prevention of cardiovascular disease at the population level. NICE Public Health Guidance 25/ www.nice.org.uk/PH25
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Chronic kidney disease. NICE clinical guideline 73 (2008). Available from www.nice.org.uk/guidance/CG73
- Stroke. NICE clinical guideline 68 (2008). Available from www.nice.org.uk/guidance/CG68
- Lipid modification. NICE clinical guideline 67 (2008). Available from www.nice.org.uk/guidance/CG67
- Type II diabetes. NICE clinical guideline 66 (2008). Available from www.nice.org.uk/guidance/CG66
- Sleep apnoea – continuous positive airway pressure (CPAP). NICE technology appraisal guidance 139 (2008). Available from www.nice.org.uk/guidance/TA139
- MI: secondary prevention. NICE clinical guideline 48 (2007). Available from www.nice.org.uk/guidance/CG48
- Obesity. NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43
- Atrial fibrillation. NICE clinical guideline 36 (2006). Available from www.nice.org.uk/CG36
- Nutrition support in adults. NICE clinical guideline 32 (2006). Available from www.nice.org.uk/guidance/CG32
- Chronic heart failure. NICE clinical guideline 5 (2003). Available from www.nice.org.uk/guidance/CG5

Update 2011

3 2011 Methods

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009.[430]

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the guideline development group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A: Scope) and a list can be found in Appendix C: Review Questions. Further information on the outcome measures examined follows this section.

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual (2009).[430] Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. All searches were conducted on core databases, MEDLINE, Embase, Cinahl and The Cochrane Library. All searches were updated on 29th November 2010 and no papers were included beyond this date.

Update 2011

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix C: Literature search strategies.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and via organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

3.2.1.1 Call for evidence

The GDG decided to initiate a ‘call for evidence’ for meta-analyses, based on a systematic review, that include studies that use ambulatory blood pressure measurement as the reference standard and report sensitivity and specificity of home and/or clinic blood pressure measurement, as they believed that important evidence existed that would not be identified by the standard searches. The NCGC contacted all registered stakeholders and asked them to submit any relevant published or unpublished evidence.

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to the guideline population in the NHS economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases from 2003 onwards to find anything published since the original guideline. There were two questions not covered in either the original guideline or the previous rapid update, for which additional searches with no date restrictions were carried out. Additionally, the search was run on MEDLINE and Embase, with a specific economic filter, from 2009, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.The search strategies for health economics are included in Appendix D: Literature search strategies. All searches were updated on 29th November 2010. No papers published after this date were considered.

3.2.2.1 Call for evidence

The GDG decided to initiate a 'call for evidence' for cost-effectiveness analyses from a UK perspective, using methods in line with the NICE reference case, comparing ambulatory, home and clinic blood pressure measurement in the diagnosis of hypertension, as they believed that important evidence existed that would not be identified by the standard searches. The NCGC contacted all registered stakeholders and asked them to submit any relevant published or unpublished evidence.

3.2.3 Evidence of effectiveness

Update 2011

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix E:Review protocols).
- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual [430]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix D: Evidence tables – clinical studies and Appendix G: Evidence tables – health economic studies.
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta analysed, where appropriate and reported in GRADE profiles (for clinical studies) – see below for details
  - Observational studies: data has been presented for individual studies narratively or in summary tables (GRADE profiles have not been generated)
  - Diagnostic studies: data has been presented for individual studies narratively or in summary tables (GRADE profiles have not been generated)
  - Qualitative studies: each study summarised in a table where possible, otherwise presented in a narrative.

3.2.4 Inclusion/exclusion

See the review protocols in Appendix E: Review Protocols for full details.

3.2.5 Methods of combining clinical studies

Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel -Haenszel) techniques were used to calculate risk ratios (relative risk) for the following binary outcomes: angioedema. Where reported, time-to-event data was presented as a hazard ratio for the following binary outcomes: mortality, stroke, MI, heart failure, new onset diabetes, vascular procedures, angina requiring hospitalisation, study drug withdrawal. The continuous outcome blood pressure (mmHg)] was analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. No quality of life outcome data was reported by any of the studies included in the 2012 update reviews

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Where significant heterogeneity was present, we carried out sensitivity analysis based on the quality of studies, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, high loss to follow-up (≥ 20% missing data for studies ≤2 years follow-up and ≥30% for those with >2 years follow-up) or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was also explored to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as “less than”, a conservative approach was undertaken. For example, if the p value was reported as “p ≤0.001”, the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were un available then the methods described in section 16.1.3 of the Cochrane Handbook ‘Missing standard deviations’ were applied as the last resort.

Update 2011

3.2.6 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCT studies were evaluated and presented using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presentedas an ‘evidence profile,’ a single table that includes details of the quality assessment as well as pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in Table 1 and each graded using the quality levels listed in Table 2: The main criteria considered in the rating of these elements are discussed below (see 3.2.7 Grading of Evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

GRADE is currently designed only for randomised trials and observational studies.

Table 1: Description of quality elements in GRADE for intervention studies.

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 2: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by one level
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels

Table 3: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Update 2011

3.2.7 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW.
2. The rating for RCTs was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed below. Due to the wide diversity of study design, data reported and data analysis methods of the observational studies that were included in this guideline, it was very difficult to compare studies

for quality and therefore observational studies were not downgraded or upgraded in GRADE, and all remained as LOW quality evidence (please see below, section 3.2.12, for details of quality assessment of prognostic studies)..

3. The downgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality element are discussed further in the following sections 3.3.5 to 3.3.8/3.3.9 [if section for publication bias is relevant].

3.2.8 Study limitations

The main limitations for randomised controlled trials are listed in Table 4.

Table 4: Study limitations of randomised controlled trials

Limitation	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomised trials with allocation by day of week, birth date, chart number, etc)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up not accounted and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Carry-over effects in cross-over trials • Recruitment bias in cluster randomised trials

Update 2011

3.2.9 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (i.e. heterogeneity or variability in results), this suggests true differences in underlying treatment effect. When heterogeneity exists (Chi square p<0.1 or I- squared inconsistency statistic of >50%), but no plausible explanation can be found, the quality of evidence was downgraded by one or two levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results.

If inconsistency could be explained based on pre-specified subgroup analysis, the GDG took this into account and considered whether to make separate recommendations based on the identified explanatory factors, i.e. population and intervention. Where subgroup analysis gave a plausible explanation of heterogeneity, the quality of evidence was not downgraded.

3.2.10 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

3.2.11 Imprecision

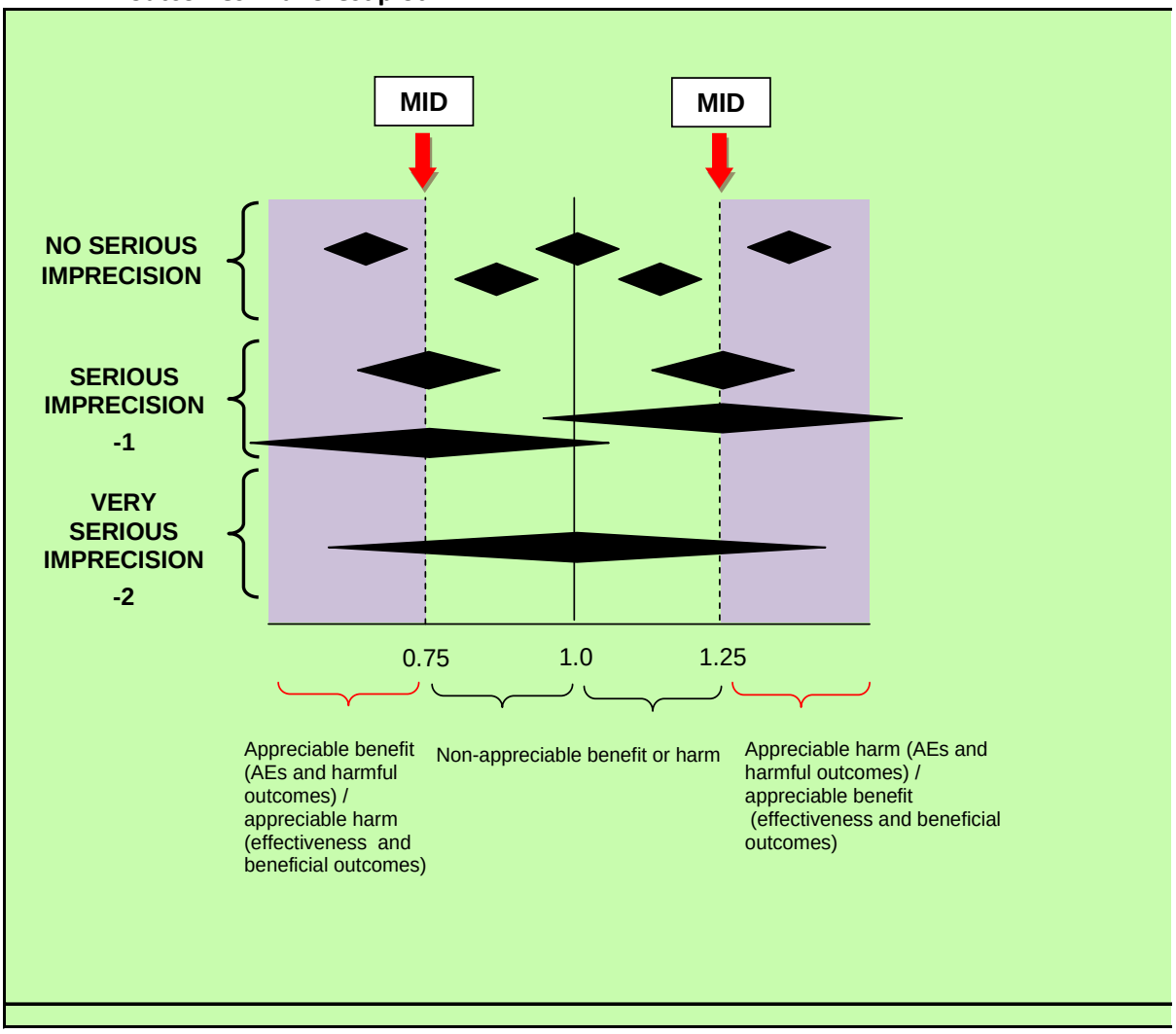
The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect as illustrated in Figure 1 and outlined in Table 5.

Table 5: Criteria applied to determine precision

Dichotomous and continuous outcomes
The 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect: 1. Does not cross either of the two minimal important difference (MID) thresholds (the threshold lines for appreciable benefit or harm); defined as precise Rating for precision: 'no serious imprecision' 2. Crosses one of the two MID thresholds (appreciable benefit or appreciable harm); defined as imprecise Rating for precision: 'serious' 3. Crosses both of the two MID thresholds (appreciable benefit and appreciable harm); defined as imprecise Rating for precision: 'very serious'

Update 2011

Figure 1: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



MID = minimal important difference determined for each outcome. The MIDs are the threshold for appreciable benefits and harms. The confidence intervals of the top five points of the diagram (within the green sector or within the purple sector) are considered precise because the upper and lower limits of the point estimate (diamond shapes) do not cross the pre-defined MID. Conversely, the bottom three points of the diagram are considered imprecise because the upper and lower limits of the point estimates (diamonds) for each of them cross the pre-defined MID and reduce the certainty of the result.

The following are the MID for the outcomes in this guideline (as agreed by the GDG).

Update 2011

Table 6: MIDs for the outcomes used in this guidance

Outcome	Relative risk reduction
Mortality from any cause	10%
Stroke (ischaemic or haemorrhagic)	10%
Myocardial infarction (MI) (including, where reported, silent MI)	10%

Outcome	Relative risk reduction
Heart failure	10%
New onset diabetes	10%
Vascular procedures (including both coronary and carotid artery procedures)	10%
Angina requiring hospitalisation	10%
Health-related quality of life (to use what is reported by trials)	As defined in literature for each specific QoL measure
Major adverse cardiac and cerebrovascular events (MAACE): fatal and non-fatal MI, fatal and non-fatal stroke, hospitalised angina, hospitalised heart failure, revascularisation (and different composites of this outcome)	15%
Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence	10%
Angioedema in black people of African and Caribbean descent	10%
Blood pressure	5 mmHg (mean difference, continuous outcome)

3.2.12 Prognostic studies

All prognostic study designs were included for the prognostic questions. The quality of the prognostic studies was assessed using the quality checklist in the NICE Guidelines Manual April 2009. The main criteria considered in assessing study quality were:

- The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results
- Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias
- The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias
- The outcome of interest is adequately measured in study participants, sufficient to limit bias
- Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results

The methodological flaws of the prognostic studies included in the guideline update, have been summarised in tables within appendix F, in order to give an overview of the quality of each individual study, since GRADE is not currently designed for prognostic studies. Odds ratios, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers. Data for selected outcomes has been summarised in tables within the relevant review chapter. Full data for all the outcomes has been reported in the evidence tables (see appendix F) for each individual prognostic study. Taking into consideration the advice on prognostic reviews in the NICE guidelines manual, meta-analysis was not undertaken for prognostic studies.

Update 2011

3.3 Evidence of cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist undertook:

- A systematic review of the economic literature
- New cost-effectiveness analysis in priority areas

3.3.1 Literature review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion / exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual.[430]
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G: Evidence tables – health economic studies.
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups) – see below for details.

Inclusion/exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies were excluded if they only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects. Abstracts, posters, reviews, letters/editorials, foreign language publications and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-OECD country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may have been excluded and this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix H [430] and the health economics research protocol in Appendix E: Review protocols.

When no relevant economic analyses were identified in the economic literature review, relevant UK NHS unit costs were presented to the GDG to inform consideration of cost effectiveness.

NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual, Appendix H.[430] It also shows incremental costs, incremental outcomes (for example, QALYs) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 7 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[468]

Update 2011

Table 7: Content of NICE economic profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Limitations	An assessment of methodological quality of the study(a): • Minor limitations – the study meets all quality criteria, or the study fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness • Very serious limitations – the study fails to meet one or more quality criteria and this is very likely to change the conclusions about cost effectiveness. Studies with very serious limitations would usually be excluded from the economic profile table.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making(a): • Directly applicable – the applicability criteria are met, or one or more criteria are not met but this is not likely to change the conclusions about cost effectiveness. • Partially applicable – one or more of the applicability criteria are not met, and this might possibly change the conclusions about cost effectiveness. • Not applicable – one or more of the applicability criteria are not met, and this is likely to change the conclusions about cost effectiveness.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
ICER	Incremental cost-effectiveness ratio: the incremental cost divided by the respective QALYs gained.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

a) Limitations and applicability were assessed using the economic evaluation checklist from The Guidelines Manual, Appendix H[430]

3.3.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new cost-effectiveness analysis was undertaken by the Health Economist in priority areas. Priority areas were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis were identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions. Results were presented in GDG meetings for discussion and interpretation.

The priority area identified for new economic analysis was diagnosis of hypertension – see 'Appendix J: Cost-effectiveness analysis – blood pressure monitoring for confirming a diagnosis of hypertension (new 2011)' for full methods. The 2006 cost-effectiveness analysis of drug treatment was also updated – see 'Appendix I: Cost-effectiveness analysis – pharmacological treatment (updated 2011)' for full methods.

Update 2011

3.3.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[429,430]

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a) The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.[429]

3.4 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix E: Evidence Tables – Clinical studies and Appendix G:Evidence tables – health economic studies.
- Summary of clinical and economic evidence and quality
- Forest plots and summary ROC curves
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline

The main considerations specific to each recommendation are outlined in the link from evidence to recommendation section preceding the recommendation section.

Update 2011

3.4.1 Research recommendations

When areas were identified for which good evidence was lacking, the guideline development group considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility

3.4.2 Validation process

The guidance is subject to a four week public consultation and feedback as part of the quality assurance and peer review the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

3.4.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will ask a National Collaborating Centre or the National Clinical Guideline Centre to advise NICE's Guidance executive whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.4.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

3.4.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Clinical Excellence to undertake the work on this guideline.

Update 2011

4 2004 Methods

4.1.1 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.[630] 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).[139]

Table 8: 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[81], so where appropriate, the results of randomised studies were combined using meta-analytic techniques [175]. 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.

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.[189,224] 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[175], 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[175], 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[175], 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.[147,193] 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[637] and confidence intervals were estimated using the delta method.[51]

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,[175] to estimate an overall pooled risk difference and its 95% confidence interval.

4.1.2 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.[471]

4.1.3 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 9 and Table 10.[14]

Table 9: AHCPR derived categories of evidence

	Level 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 10: AHCPR derived strengths of recommendations

	Strength of evidence
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).[392] 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 11).

Table 11: 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		**Notes**
Design scores		Notes
Treatment		i. Blinding refers to independent interpretation of a test and reference standard.
Randomised controlled trial	1	ii. An incident cohort is identified and followed in time from a defined point in the progress of disease or care.
Non-randomised controlled study	2	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.
Uncontrolled study	3	
Diagnosis		
Blinded cohort study	1	
Unblinded cohort study	2	
Other design	3	
Prognosis		
Incidence cohort study	1	
Other cohort study	2	
Descriptive data	3	
Population data	1	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.
Representative sample	2	
Convenience sample	3	
Quality corrections		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.
Flawed design, conduct or analysis	+1	
Imprecise findings	+1	
Lack of consistency or independence	+1 +1	
Inadequate relevance	+1	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.
Very strong association	-1	
Evidence Grade		
I: High	≤1	
II: Intermediate 2	2	
III: Low	≥3	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 three unique categories, and each recommendation may be positive or negative, conditional or unconditional reflecting current evidence and the understanding of the guideline group.		

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.**
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.

4.1.4 Costs and consequences

Approaches to cost-effectiveness have assisted in reaching recommendations in a series of primary care evidence-based guidelines.[188,393] 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.

4.2 2006 methods

4.2.1 Clinical evidence

4.2.1.1 Methodological introduction

Study inclusion and reporting criteria

A systematic search of the literature was performed on EMBASE and MEDLINE for randomised controlled trials comparing any combination of antihypertensive drugs from among the following five classes of drugs:

- ACE inhibitors (ACEi)
- angiotensin-II receptor antagonists (ARB)
- beta-receptor blockers (BB)
- calcium-channel blockers (CCB)
- thiazide-type diuretics (TD).

Placebo-controlled studies were not included because the main aim of this rapid partial update was to make recommendations regarding the optimal sequencing of drug treatment for hypertension, for which head-to-head studies are required, and because sufficient placebo-controlled studies of the main drug classes had been considered in the original NICE guideline. However, placebo-controlled studies were sought for isolated systolic hypertension because of a lack of comparator studies.

The cut-off date for evidence to be considered in the previous guideline was July 2004, so this update only searched for English-language titles published after that date. Papers published up to and including 19 December 2005 were considered – this constitutes the cut-off for evidence for this rapid update.

Studies were excluded due to:

- inadequate or no randomisation
- inadequate study power, defined as a sample size of less than 200 patients, or having a follow-up period of less than 12 months
- having an exclusive diabetic or paediatric patient population, unrepresentative of the general UK hypertensive population
- stroke, myocardial infarction, and mortality outcomes not being reported.

The following outcomes were recorded for each study, where available:

- mortality from any cause
- stroke (ischaemic or haemorrhagic)
- myocardial infarction (including, where reported, silent MI)
- heart failure
- new-onset diabetes mellitus
- vascular procedures (including both coronary and carotid artery procedures)
- incidence of unstable angina (or angina episodes requiring hospitalisation)
- study drug withdrawal.

Interpretation and analysis of results

All outcomes, with the exception of study drug withdrawal, vascular procedures and unstable angina, were entered into a meta-analysis for each drug combination using RevMan 4.2 software (©The Nordic Cochrane Centre). The overall effect size was reported as the relative risk (RR) with 95% confidence intervals in each case.

A p-value less than 0.05 was considered statistically significant for overall effect. Forest plots for each comparison are included in Appendix A.

In recording the outcomes, stroke was considered to be synonymous with 'cerebrovascular event'. Reports of 'cardiovascular events' or other composite outcomes other than those listed above were not considered.

Sensitivity analyses were performed based on the inclusion and exclusion of silent myocardial infarction and the inclusion and exclusion of secondary prevention studies. Additional subgroup analyses were performed to identify the source of any significant heterogeneity in study results (defined as an I2 statistic greater than 50%).

Where the heterogeneity has I^2 greater than 50%, the trials are reported individually in the evidence statements.

The following outcomes were not subject to meta-analysis due to potential variability or subjectivity in diagnosis or treatment protocols, and were reported as a narrative only:

- unstable angina
- revascularisation procedures
- study drug withdrawal.

Following consultation on the draft guideline, heart failure as an outcome was included in the meta-analysis. Because of inconsistency in definition of heart failure in the trials, this was analysed using a random effects model.

Secondary analyses

In addition to results in general hypertensive populations, the following subgroups were also considered separately:

- those patients with isolated systolic hypertension (ISH)
- black people of African and Caribbean descent younger patients (defined as under 55 years).

For ISH, due to the lack of evidence comparing different antihypertensive drugs, the results from placebo-controlled trials were also considered. These results included pre-defined subgroup analyses from trials in general hypertensive populations as well as one trial comprising only ISH patients. The results were entered into a meta-analysis according to the same procedure specified above. The definition of ISH varied slightly between studies: permitting a diastolic blood pressure up to 95 mmHg in one study (SYST-EUR[43,124,555]) and 90 mmHg in the others (SHEP[483,536,537,606], SHEP-P[281,484,485]).

No trials comprising only non-white patients were found, although two pre-defined subgroup analyses from trials in general hypertensive populations were found (ALLHAT[589-591], LIFE[154,176,222,369,370,507,618,619]). Results involving placebo comparisons in non-white populations were not considered.

Evidence on younger patients was extremely sparse, and evidence consideration was therefore extended to include papers pre-dating July 2004 and in which blood pressure lowering effect was the main outcome measure.

4.2.2 Cost-effectiveness evidence

The GDG drafted recommendations on the basis of the clinical evidence. A health economic analysis was then conducted to balance the clinical outcomes and to test the cost effectiveness of different initial antihypertensive medications.

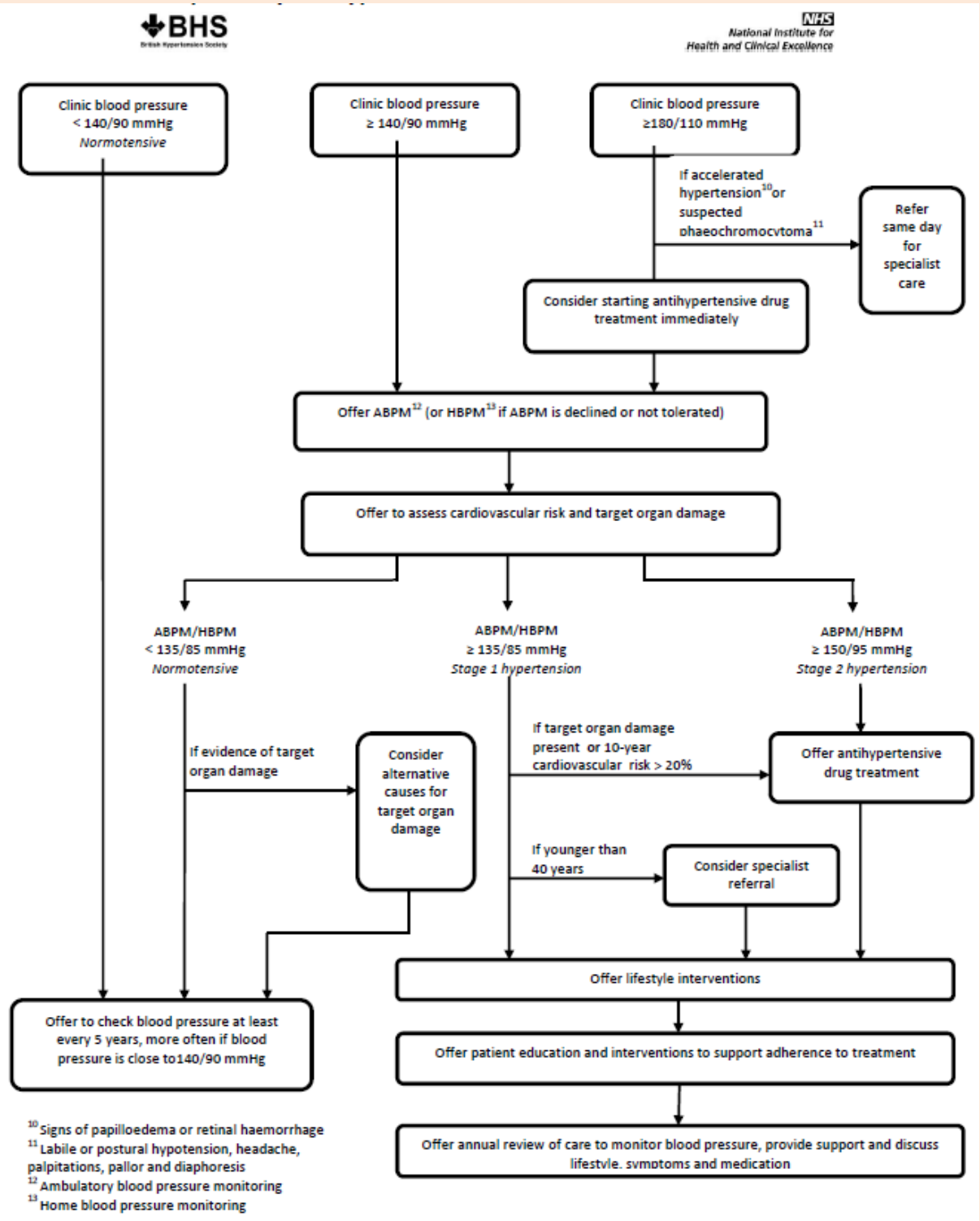
See 'Appendix I: Cost-effectiveness analysis – pharmacological treatment (updated 2011)' for full methods – note that analysis was updated as part of the 2011 update.

Update 2011

5 Guideline summary

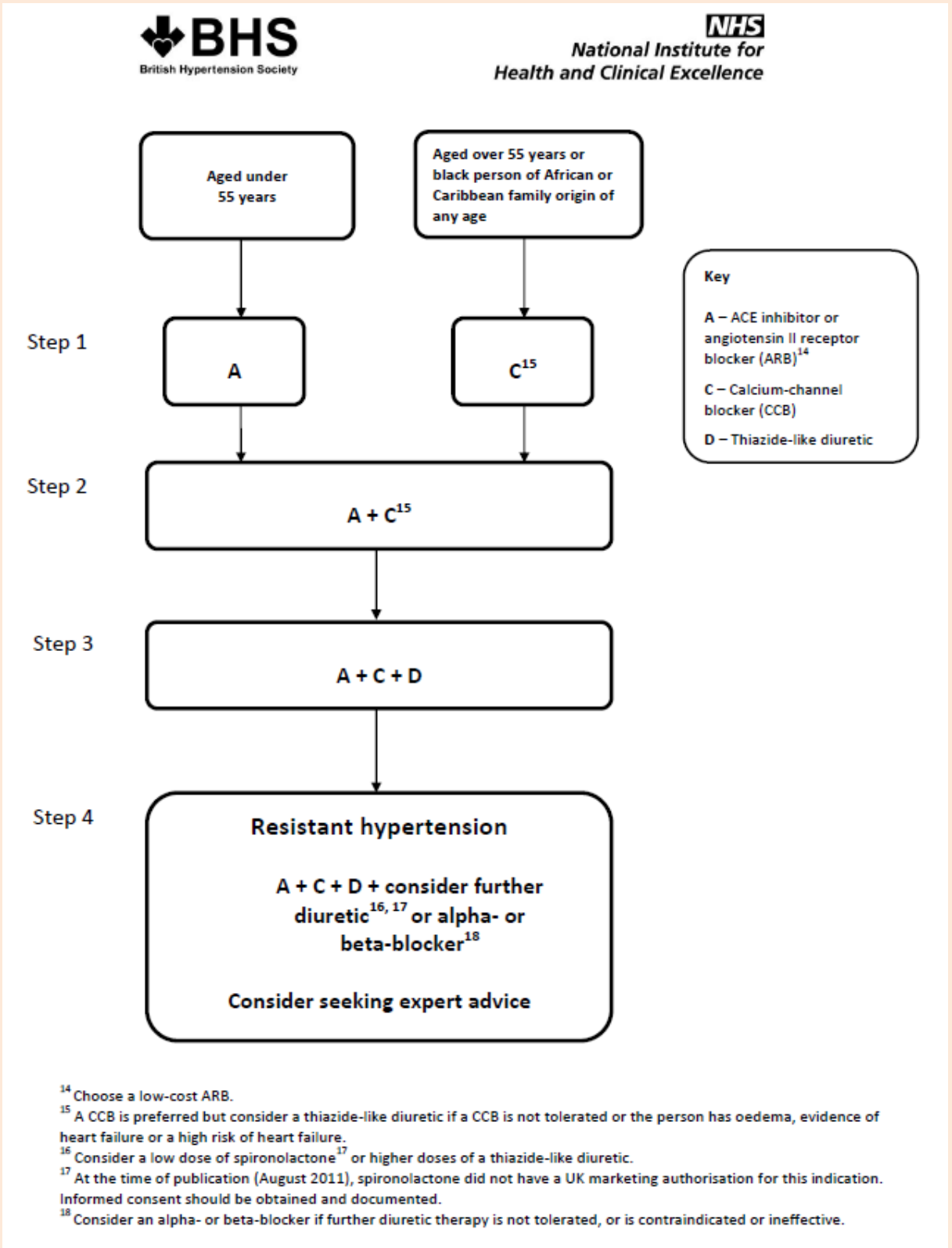
5.1 Algorithms

Figure 2: Diagnosis of Hypertension



Update 2011

Figure 3: Treatment of Hypertension



[14] Choose a low-cost ARB.
[15] A CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has oedema, evidence of heart failure or a high risk of heart failure.
[16] Consider a low dose of spironolactone[17] or higher doses of a thiazide-like diuretic.
[17] At the time of publication (August 2011), spironolactone did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.
[18] Consider an alpha- or beta-blocker if further diuretic therapy is not tolerated, or is contraindicated or ineffective.

Update 2011

5.2 Key priorities for implementation

From the full set of recommendations, the GDG selected ten key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The Guidelines Manual.[430] The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

Diagnosing hypertension

- If the clinic blood pressure is 140/90 mmHg or higher, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension. [new 2011]
- When using ABPM to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00).

  Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension. [new 2011]
- When using home blood pressure monitoring (HBPM) to confirm a diagnosis of hypertension, ensure that:
  - for each blood pressure recording, two consecutive measurements are taken, at least 1 minute apart and with the person seated and
  - blood pressure is recorded twice daily, ideally in the morning and evening and
  - blood pressure recording continues for at least 4 days, ideally for 7 days.

  Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of hypertension. [new 2011]

Initiating treatment

- Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:
  - target organ damage
  - established cardiovascular disease
  - renal disease
  - diabetes
  - a 10-year cardiovascular risk equivalent to 20% or greater. [new 2011]
- Offer antihypertensive drug treatment to people of any age with stage 2 hypertension. [new 2011]
- For people aged under 40 years with stage 1 hypertension and no evidence of target organ damage, cardiovascular disease, renal disease or diabetes, consider seeking specialist evaluation of secondary causes of hypertension and a more detailed assessment of potential target organ damage. This is because 10-year cardiovascular risk assessments can underestimate the lifetime risk of cardiovascular events in these people. [new 2011]

Monitoring treatment and blood pressure targets

- For people identified as having a 'white-coat effect', consider ABPM or HBPM as an adjunct to clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modification or drugs. [new 2011]

Choosing antihypertensive drug treatment

- Offer people aged 80 years and over the same antihypertensive drug treatment as people aged 55–80 years, taking into account any comorbidities. [new 2011]

Updte 2011

Step 1 treatment

- Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011]
- If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. [new 2011]
- For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide. [new 2011]

Step 4 treatment

- For treatment of resistant hypertension at step 4:
  - Consider further diuretic therapy with low-dose spironolactone (25 mg once daily) if the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalaemia.
  - Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l. [new 2011]

5.3 Full list of recommendations

1. Healthcare professionals taking blood pressure measurements need adequate initial training and periodic review of their performance. [2004]
2. Because automated devices may not measure blood pressure accurately if there is pulse irregularity (for example, due to atrial fibrillation), palpate the radial or brachial pulse before measuring blood pressure. If pulse irregularity is present, measure blood pressure manually using direct auscultation over the brachial artery. [new 2011]
3. Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions. [2004][a]
4. When measuring blood pressure in the clinic or in the home, standardise the environment and provide a relaxed, temperate setting, with the person quiet and seated, and their arm outstretched and supported. [new 2011]
5. If using an automated blood pressure monitoring device, ensure that the device is validated and an appropriate cuff size for the person's arm is used. [new 2011]
6. In people with symptoms of postural hypotension (falls or postural dizziness):
   - measure blood pressure with the person either supine or seated.
   - measure blood pressure again with the person standing for at least a minute prior to measurement. [2004, amended 2011]
7. If the systolic blood pressure falls by 20 mmHg or more when the person is standing:
   - review medication
   - measure subsequent blood pressures with the person standing

Update 2011

[a] A list of validated blood pressure monitoring devices is available on the British Hypertension Society's website (see www.bhsoc.org). The British Hypertension Society is an independent reviewer of published work. This does not imply any endorsement by NICE.

- consider referral to specialist care if symptoms of postural hypotension persist. [2004, amended 2011]

8. When considering a diagnosis of hypertension, measure blood pressure in both arms:
   - If the difference in readings between arms is more than 20 mmHg, repeat the measurements.
   - If the difference in readings between arms remains more than 20 mmHg on the second measurement, measure subsequent blood pressure in the arm with the higher reading. [new 2011]

9. If the clinic blood pressure is 140/90 mmHg or higher, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension. [new 2011]

10. If a person is unable to tolerate ABPM, home blood pressure monitoring (HBPM) is a suitable alternative to confirm the diagnosis of hypertension. [new 2011]

11. If the person has severe hypertension, consider starting antihypertensive drug treatment immediately, without waiting for the results of ABPM or HBPM. [new 2011]

12. While waiting for confirmation of a diagnosis of hypertension, carry out investigations for target organ damage (such as left ventricular hypertrophy, chronic kidney disease and hypertensive retinopathy) (see 21) and a formal assessment of cardiovascular risk using a cardiovascular risk assessment tool (see 20). [new 2011]

13. If hypertension is not diagnosed but there is evidence of target organ damage such as left ventricular hypertrophy, albuminuria or proteinuria, consider carrying out investigations for alternative causes of the target organ damage. [new 2011]

14. If hypertension is not diagnosed, measure the person's clinic blood pressure at least every 5 years subsequently, and consider measuring it more frequently if the person's clinic blood pressure is close to 140/90 mmHg. [new 2011]

15. When using ABPM to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00). Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension. [new 2011]

16. When using HBPM to confirm a diagnosis of hypertension, ensure that:
   - for each blood pressure recording, two consecutive measurements are taken, at least 1 minute apart and with the person seated and
   - blood pressure is recorded twice daily, ideally in the morning and evening and
   - blood pressure recording continues for at least 4 days, ideally for 7 days.

   Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of hypertension. [new 2011]

17. Refer the person to specialist care the same day if they have:
   - accelerated hypertension, that is, blood pressure usually higher than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage or
   - suspected phaeochromocytoma (labile or postural hypotension, headache, palpitations, pallor and diaphoresis). [2004, amended 2011]

18. Consider the need for specialist investigations in people with signs and symptoms suggesting a secondary cause of hypertension. [2004, amended 2011]

For NICE guidance on the early identification and management of chronic kidney disease see 'Chronic kidney disease' (NICE clinical guideline 73, 2008).

Update 2011

19. Use a formal estimation of cardiovascular risk to discuss prognosis and healthcare options with people with hypertension, both for raised blood pressure and other modifiable risk factors. [2004]

20. Estimate cardiovascular risk in line with the recommendations on Identification and assessment of CVD risk in 'Lipid modification' (NICE clinical guideline 67)[b]. [2008]

21. For all people with hypertension offer to:
    - test for the presence of protein in the urine by sending a urine sample for estimation of the albumin:creatinine ratio and test for haematuria using a reagent strip
    - take a blood sample to measure plasma glucose, electrolytes, creatinine, estimated glomerular filtration rate, serum total cholesterol and HDL cholesterol
    - examine the fundi for the presence of hypertensive retinopathy
    - arrange for a 12-lead electrocardiograph to be performed. [2004, amended 2011]

22. Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:
    - target organ damage
    - established cardiovascular disease
    - renal disease
    - diabetes
    - a 10-year cardiovascular risk equivalent to 20% or greater. [new 2011]

23. Offer antihypertensive drug treatment to people of any age with stage 2 hypertension. [new 2011]

24. For people aged under 40 years with stage 1 hypertension and no evidence of target organ damage, cardiovascular disease, renal disease or diabetes, consider seeking specialist evaluation of secondary causes of hypertension and a more detailed assessment of potential target organ damage. This is because 10-year cardiovascular risk assessments can underestimate the lifetime risk of cardiovascular events in these people. [new 2011]

25. Use clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modification or drugs. [new 2011]

26. For people identified as having a 'white-coat effect', consider ABPM or HBPM as an adjunct to clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modification or drugs. [new 2011]

27. Aim for a target clinic blood pressure below 140/90 mmHg in people aged under 80 years with treated hypertension. [new 2011]

28. Aim for a target clinic blood pressure below 150/90 mmHg in people aged 80 years and over with treated hypertension. [new 2011]

29. When using ABPM or HBPM to monitor the response to treatment (for example, in people identified as having a 'white-coat effect'[c] and people who choose to monitor their blood pressure at home) aim for a target average blood pressure during the person's usual waking hours of:
    - below 135/85 for people aged under 80 years
    - below 145/85 in people aged over 80 years and over. [new 2011]

Update 2011

[b] Clinic blood pressure measurements must be used in the calculation of cardiovascular risk.
[c] A discrepancy of more than 20/10 mmHg between clinic and average daytime ABPM or average HBPM blood pressure measurements at the time of diagnosis.

For NICE guidance on the prevention of obesity and cardiovascular disease see 'Obesity' (NICE clinical guideline 43, 2006) and 'Prevention of cardiovascular disease at population level' (NICE public health guidance 25, 2010).

30. Lifestyle advice should be offered initially and then periodically to people undergoing assessment or treatment for hypertension. [2004]

31. Ascertain people's diet and exercise patterns because a healthy diet and regular exercise can reduce blood pressure. Offer appropriate guidance and written or audiovisual materials to promote lifestyle changes. [2004]

32. Relaxation therapies can reduce blood pressure and people may wish to pursue these as part of their treatment. However, routine provision by primary care teams is not currently recommended. [2004]

33. Ascertain people's alcohol consumption and encourage a reduced intake if they drink excessively, because this can reduce blood pressure and has broader health benefits. [2004]

34. Discourage excessive consumption of coffee and other caffeine-rich products.

35. Encourage people to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as this can reduce blood pressure.[2004]

36. Do not offer calcium, magnesium or potassium supplements as a method for reducing blood pressure. [2004]

37. The best current evidence does not show that combinations of potassium, magnesium and calcium supplements reduce blood pressure. [2004]

38. Offer advice and help to smokers to stop smoking. [2004]

39. A common aspect of studies for motivating lifestyle change is the use of group working. Inform people about local initiatives by, for example, healthcare teams or patient organisations that provide support and promote healthy lifestyle change. [2004]

40. Where possible, recommend treatment with drugs taken only once a day. [2004]

41. Prescribe non-proprietary drugs where these are appropriate and minimise cost. [2004]

42. Offer people with isolated systolic hypertension (systolic BP 160 mmHg or more) the same treatment as people with both raised systolic and diastolic blood pressure. [2004]

43. Offer people aged 80 years and over the same antihypertensive drug treatment as people aged 55–80 years, taking into account any comorbidities. [new 2011]

44. Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). [2010]

45. Offer people aged under 55 years step 1 antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor or a low-cost angiotensin-II receptor blocker (ARB). If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB. [new 2011]

46. Do not combine an ACE inhibitor with an ARB to treat hypertension. [new 2011]

47. Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not

Update 2011

suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011]

48. If a diuretic is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5 mg–25.0 mg once daily) or indapamide (1.5mg slow release or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. [new 2011]

49. For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide. [new 2011]

50. Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly:
    - those with an intolerance or contraindication to ACE inhibitors and angiotensin-II receptor antagonists or
    - women of child-bearing potential or
    - people with evidence of increased sympathetic drive. [2006]

51. If therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-like diuretic to reduce the person's risk of developing diabetes. [2006]

52. If blood pressure is not controlled by Step 1 treatment, offer step 2 treatment with a CCB in combination with either an ACE inhibitor or an ARB[d]. [new 2011]

53. If a CCB is not suitable for step 2 treatment, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011]

54. For black people of African or Caribbean family origin, consider an ARB in preference to an ACE inhibitor, in combination with a CCB. [new 2011]

55. Before considering step 3 treatment, review medication to ensure step 2 treatment is at optimal or best tolerated doses. [new 2011]

56. If treatment with three drugs is required, the combination of ACE inhibitor or angiotensin-II receptor blocker, calcium-channel blocker and thiazide-like diuretic should be used. [2006]

57. Regard clinic blood pressure that remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice. [new 2011]

58. For treatment of resistant hypertension at step 4:
    - Consider further diuretic therapy with low-dose spironolactone (25 mg once daily)[e]. If the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkaelemia.
    - Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l. [new 2011]

59. When using further diuretic therapy for resistant hypertension at step 4, monitor blood sodium and potassium and renal function within 1 month and repeat as required thereafter. [new 2011]

Update 2011

[d] Choose a low-cost ARB.
[e] At the time of publication (August 2011), spironolactone did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

60. If further diuretic therapy for resistant hypertension at step 4 is not tolerated, or is contraindicated or ineffective, consider an alpha- or beta-blocker. [new 2011]

61. If blood pressure remains uncontrolled with the optimal or maximum tolerated doses of four drugs, seek expert advice if it has not yet been obtained. [new 2011]

62. Provide appropriate guidance and materials about the benefits of drugs and the unwanted side effects sometimes experienced in order to help people make informed choices. [2004]

63. People 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. [2004]

64. Provide an annual review of care to monitor blood pressure, provide people with support and discuss their lifestyle, symptoms and medication. [2004]

65. Because evidence supporting interventions to increase adherence is inconclusive, only use interventions to overcome practical problems associated with non-adherence if a specific need is identified. Target the intervention to the need. Interventions might include:
    - suggesting that patients record their medicine-taking
    - encouraging patients to monitor their condition
    - simplifying the dosing regimen
    - using alternative packaging for the medicine using a multi-compartment medicines system. (This recommendation is taken from 'Medicines adherence', NICE 408 clinical guideline 76). [new 2011]

Update 2011

5.4 Key research recommendations

1. Which automated blood pressure monitors are suitable for people with hypertension and atrial fibrillation?
2. In people aged under 40 with hypertension, what is the most accurate method of assessing the lifetime risk of cardiovascular events and the impact of therapeutic intervention on this risk?
3. In people aged under 40 with hypertension, what are the appropriate thresholds for intervention?
4. In adults with primary hypertension, does the use of out-of-office monitoring (HBPM or ABPM) improve response to treatment?
5. In people with treated hypertension, what is the optimal systolic blood pressure?
6. In adults with hypertension, which drug treatment (diuretic therapy versus other step 4 treatments) is the most clinically and cost effective for step 4 treatment?

6 Measuring blood pressure

For many years blood pressure has been measured using a brachial pressure cuff and auscultation of the brachial artery to identify the appearance and disappearance of Korotkoff sounds. Increasingly, automated devices for measuring blood pressure are now used in the clinic, hospitals and by people in their homes. In addition, ambulatory blood pressure measurement devices are available that are programmed to allow blood pressure to be measured repeatedly during the day and night. Blood pressure (BP) can be highly variable and this variability is due to the inherent variability in BP itself and the influence of factors such as posture, room temperature and pain/discomfort or stress. In addition there are factors related to the process of BP measurement itself that can contribute to BP variability such as the appropriateness of the cuff size, the rate of inflation and deflation of the cuff and the accuracy of the process of measurement or the automated BP monitor being used.

6.1 Techniques for measuring blood pressure

6.1.1 Manual blood pressure measurement

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.[579]

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.[64,482] Supervised training and reassessment may help minimise errors.

Systolic pressure is 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.[121] A number of summaries are available highlighting good technique: an adaptation of these is shown in Table 12.

Table 12: Estimating blood pressure by manual auscultation

Manual auscultation
Standardise the environment as much as possible: • Relaxed, temperate setting, with the patient seated and rested • 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.

Manual auscultation

- 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.[27,64,99]

6.2 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) [21]; 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.[482,553,636]

6.3 Conditions and environment

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.[65]

Standardising the environment in which blood pressure measurements are made reduces variation and enhances the interpretation of a series of readings taken over time.[27,99] 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.[27,65,99]

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).[27,65,66,99,452]

Blood pressure readings also tend to increase as the patient's arm is lowered below the horizontal and decrease when the arm is raised. When blood pressure is measured in the clinic setting, the patient's arm should be out-stretched, level with their heart and in line with their mid sternum, and supported by a table or some other means.[27,65,66,99,452] Blood pressure is usually measured in the non-dominant arm, especially when using home or ambulatory monitoring. Differences in readings may occur between arms. A BP difference of <10mmHg can be considered normal, however, a difference of more than 20mmHg between arms is unusual, occurring in <4% of people and is usually associated with underlying vascular disease. Clinicians are advised to take readings in both of the patient's arms initially, and use the arm with the higher reading for subsequent measurements of blood pressure. . Consistent inter-arm differences of over 20/10 mmHg may suggest pathology warranting specialist referral.[27,65,99]

6.4 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.[58] 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 reported to occur in as many as 15% to 30% of the population,[448] 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.[569] The size of white coat effect in individuals can vary over time and a small proportion (4%) may demonstrate atypical very high clinic readings.[27] 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.[490,506,635] 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.

"White Coat" Hypertension: A difference between clinic BP and home or ambulatory blood pressure averages is expected. This difference has been reported to average approximately 10/5mmHg but this will vary considerably and is usually greater in people with a higher baseline blood pressure and as people age. White coat hypertension is defined when a patient has a persistently elevated clinic BP and a normal home or ambulatory BP day time average, i.e. <135/85mmHg.

"White coat Effect" in people with hypertension: People with true hypertension, treated or untreated, can also exhibit a "White Coat Effect", for example a clinic BP reading that is disproportionately greater than their home or ambulatory BP averages, but their home or ambulatory BP averages are in a hypertensive range. Such patients are at risk of receiving more BP medication than they need and will require out of office measurement to monitor the efficacy of their BP treatment.

Update 2011

6.5 Blood pressure measurement devices

There is considerable guidance about the range of appropriate devices for measuring blood pressure.[100,171,446] and about their maintenance and periodic recalibration [[172] Local medical physics and biomedical/clinical engineering departments can often give further advice.

6.5.1 Mercury sphygmomanometer

The mercury sphygmomanometer has been used for the traditional measurement of blood pressure. 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. Mercury is being phased out of clinical use and mercury sphygmomanometers have already been removed from clinical areas in hospitals and primary care. Thus, alternatives to mercury sphygmomanometry are now required for routine clinical use.

Non-mercury devices that operate in a similar way to the traditional mercury column devices are available and provide a suitable alternative to mercury devices when manual auscultation is required to measure blood pressure.

6.5.2 Aneroid sphygmomanometers

Aneroid sphygmomanometers measure pressure using a lever and bellows system. They may be less accurate than mercury sphygmomanometers and their alternatives (see above), especially over time. Using the manual auscultation technique they are subject to the same sources of observer error.[64]

6.5.3 Automated devices

Automated devices are increasingly being used in hospitals and primary care. 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.[64]

6.6 Ambulatory blood pressure monitors

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.[448] (see Figure 2, page 41) 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.[445,448]

A number of ABPM devices are available varying in size, weight, noise level, data manipulation and cost.[450,452] 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

Update 2011

Instrumentation.[41,447,451] See British Hypertension Society website www.bhsoc.org for a list of validated monitors.

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).[448,450]

6.7 Home blood pressure monitors

Home monitoring devices are oscillometric, measuring BP on the upper arm, the wrist or the finger. 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.[104,449,556] 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.[490,556] Home blood pressure devices are thought by some professionals to cause anxiety or obsessive self interest.[449,452,556,569]

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.[27] 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.[303] 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.

See British Hypertension Society website www.bhsoc.org for a list of validated monitors.

Update 2011

6.8 Recommendations

1. Healthcare professionals taking blood pressure measurements need adequate initial training and periodic review of their performance. [2004]

2. Because automated devices may not measure blood pressure accurately if there is pulse irregularity (for example, due to atrial fibrillation), palpate the radial or brachial pulse before measuring blood pressure. If pulse irregularity is present, measure blood pressure manually using direct auscultation over the brachial artery. [new 2011]

3. Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions. [2004]

4. When measuring blood pressure in the clinic or in the home, standardise the environment and provide a relaxed, temperate setting, with the person quiet and seated, and their arm outstretched and supported. [new 2011]

5. If using an automated blood pressure monitoring device, ensure that the device is validated[f] and an appropriate cuff size for the person's arm is used. [new 2011]

6. In people with symptoms of postural hypotension (falls or postural dizziness):
   - measure blood pressure with the person either supine or seated.
   - measure blood pressure again with the person standing for at least a minute prior to measurement. [2004, amended 2011]

7. If the systolic blood pressure falls by 20 mmHg or more when the person is standing:
   - review medication
   - measure subsequent blood pressures with the person standing
   - consider referral to specialist care if symptoms of postural hypotension persist. [2004, amended 2011]

6.9 Research recommendation

Update 2011

1. Which automated blood pressure monitors are suitable for people with hypertension and atrial fibrillation?

Atrial fibrillation is common in older people and may prevent accurate blood pressure measurement with automated devices. It would be valuable to know if this can be overcome.

[f] A list of validated blood pressure monitoring devices is available on the British Hypertension Society's website (see www.bhsoc.org). The British Hypertension Society is an independent reviewer of published work. This does not imply an endorsement by NICE.

7 Diagnosis of Hypertension

Hypertension is diagnosed and subsequently treated to reduce the risk of developing stroke, ischaemic heart disease, heart failure, peripheral vascular disease, renal disease, dementia and premature death. A person's risk is not only determined by their blood pressure but also by the presence of target organ damage, established cardiovascular disease and other risk factors for cardiovascular disease such as lifestyle (e.g. diet, smoking, obesity and lack of exercise), diabetes and dyslipidaemia . The assessment of a person when contemplating a clinical diagnosis of hypertension must take account of these additional factors which are discussed in Chapter 8 of the guideline.

Blood pressure is highly variable and the 2004 guidance emphasised that hypertension should not be diagnosed nor treatment offered on the basis of a single BP measurement. Consequently, people with suspected hypertension have been required to undergo repeated measurements of their clinic BP on repeated clinic visits to confirm or refute the diagnosis of hypertension. The exception being the rarer occasions when patients present with severe elevations of BP, usually associated with evidence of target organ damage, when treatment is needed more urgently.

Update 2011

The emergence of automated BP monitoring, either for home use, or ambulatory BP monitoring devices, has revealed that there can be marked discrepancies between clinic BP measurement and home or ambulatory BP averages , which are known as either white coat hypertension (see 6.4) or masked hypertension (where clinic BP is normal but ABPM and/or HBPM measurements are elevated). The identification of these discrepancies has prompted consideration as to whether the conventional clinic blood pressure measurement method is still the most accurate at predicting the risk of future cardiovascular disease and establishing the diagnosis of hypertension.

7.1 Predicting outcome using clinic, home and ambulatory measurements

Review question: In adults with suspected primary hypertension, what is the best method to measure blood pressure (HBPM versus ABPM versus CBPM) to predict the development of cardiovascular events?

7.1.1 Clinical evidence 2004

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. Studies were conducted in London, England,[324] Ohasama, Japan,[465,523] Umbria, Italy,[526,613-615] and the final cohort was provided by European patients enrolled in a drug trial.[557] Two further studies are ongoing.[87,385,472]

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 five 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 than 10/5 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.[361,379]

7.1.2 Clinical evidence 2011

Three pooled analyses of prognostic studies[210,254,326] and 11 individual prognostic studies[77,86,159,178,211,253,284,404,438,564] were found that fulfilled the inclusion criteria and looked at the ability of clinic, home or ambulatory blood pressure measurements to predict outcomes. Outcomes of interest were mortality, stroke, MI, heart failure, diabetes, vascular procedures, hospitalisation for angina, and other major adverse cardiac and cerebrovascular events (MAACE).

The three pooled analyses[210,254,326] were meta-analyses of individual data from prospective studies. The individual studies included in these pooled analyses were excluded from our review in order to avoid duplication / double counting of data. Two of the pooled analyses[254,326] used data from four studies of random populations with longitudinal follow-up of fatal and non-fatal CV outcomes. They both included the same studies, however the people they included in the final analyses were different (one study[326] excluded people with no night-time data available, and the other study[254] excluded people with no daytime data available). The third pooled analysis[210] used data from three studies in the Belgian Ambulatory Blood Pressure Monitoring database (which contains individual data of HT patients from studies performed in Europe and coordinated by the university of Ghent or Leuven). Patients had a history of CV disease.

All prognostic studies were observational and were found to be methodologically sound / have a low risk of bias (see quality assessment summary tables in appendix F). Studies that were published before 2003 (the cut-off date of the original guideline, CG18[436]) were excluded.

- Studies were categorised into those which compared:
- Home versus clinic measurements (five studies)[86,211,438,534,564]
- ABPM versus clinic measurements (11 studies)[77,159,178,210,253,254,284,326,404]

Update 2011

- ABPM versus home versus clinic measurements (two studies)[211,534]

Four studies were conducted in people who were known or suspected to have hypertension[86,159,178,404] and the rest of the studies were in population samples which would have contained both hypertensive and non-hypertensive people. Mixed population studies are a better representation of how BP monitoring would be used in clinical practice and the prognostic ability of the blood pressure measurement methods to determine clinical outcome.

NOTE: The Hansen 2007 study[254] only assessesd daytime ABPM measurements; the Dawes 2006 study[159] only assessed 24h ABPM measurements; and the Fagard 2005 and Fagard 2008 studies[210,211] only assessed daytime and night-time ABPM, and not 24h measurements. All other studies assessed and compared separately all three types of ABPM measurements - 24h, daytime and night-time). The protocol used for measuring blood pressure (for example, the intervals between each ABPM reading and definitions of daytime and night-time periods) varied between studies.

Update 2011

7.1.3 Evidence statements – clinical

The table below (Table 13) summarises the overall results of the prognostic studies included for this review. Table 14summarises the numerical results for selected outcomes of the prognostic studies included for this review. The full data for all outcomes can be found in the evidence tables in the appendix.

NOTE: The 'best method' was chosen as the method of measuring BP that best predicted (ie. statistically significant predictors and higher HR values) clinical outcomes (after adjustment for covariates in multivariate analyses).

Table 13: Summary of included prognostic studies

Study	N	Follow-up time	Outcome	Best method	Representative of 'real life' home BP measurements?
Home vs clinic					
Bobrie 2004[86]	4939	Mean 3.2 years	CV events	Home	Yes – measurements over 4 days
Niiranen 2010[438]	2081	Mean 6.8 years	Mortality and CV events	Home	Yes – measurements over 7 days; but home BP threshold (for HT diagnosis) not given
Stergiou 2007[564]	665	Mean 8.2 years	CV events	NS difference	Yes – measurements over 3 days; but small study , and home BP threshold (for HT diagnosis) not given
ABPM vs clinic					
Bjorklund 2004[77]	872	Mean 6.6 years	CV morbidity	SBP: Office and ABPM (daytime SBP added more)	n/a
Dawes 2006[159]	10,129	Median 10 years	Mortality	ABPM (daytime)	n/a
Dolan 2005[178]	5292	Mean 7.9 years	CV mortality	ABPM (especially night-time)	n/a
Fagard 2008*[210]	302	Median 6.8 years	Mortality, CV mortality, CV events	ABPM (especially night-time)	n/a
Hansen 2005[253]	1700	Up to 9.5 years	Mortality and CV mortality	ABPM	n/a
Hansen 2007*[254]	7030	Median 9.5 years	CV death, stroke, cardiac events and CHD	ABPM (CV events); but no difference for mortality (total and CV)	n/a
Ingelsson 2006[284]	951	Up to 9.1 years	CHF	ABPM (night-time DBP)	n/a
Kikuya 2007*[326]	5682	Median 9.5 years	CV death, stroke, cardiac events	No difference	n/a

Study	N	Follow-up time	Outcome	Best method	Representative of 'real life' home BP measurements?
			and CHD		
Mesquita-Bastos 2010[404]	1200	Mean 8.2 years	CV events and stroke	ABPM (especially night-time)	n/a
Home vs ABPM vs clinic					
Fagard 2005[211]	391	Median 10.9 years	Major CV events	Home equal to ABPM and better than office	No – home BP measurement performed y investigator rather than patient.
USega 2005[534]	2051	Mean 10.9 years	Mortality	No difference	No – only measured home BP on 1 day; home BP threshold (for HT diagnosis) not given

Update 2011

Table 14: Summary of numerical results for prognostic studies (selected outcomes)

Study	Outcome	Best method	HR (95% CI) for SBP measurement
Home vs clinic			
Bobrie 2004[86]	CV events	Home	Home: 1.02 (1.01, 1.02) p=<0.001 Clinic: 1.01 (1.00, 1.01) p=0.09 Per 1mmHg rise in SBP
Niiranen 2010[438]	CV events	Home	Home: 1.22 (1.09, 1.37) p<0.001 Clinic: 1.01 (0.92, 1.12) p=0.80 per 10mmHg rise in SBP
Stergiou 2007[564]	CV events	No difference	Home: 1.00 (0.99, 1.02) p=0.68 Clinic: 1.01 (0.99, 1.03) p=0.08 Per 1mmHg rise in SBP
ABPM vs clinic			
Bjorklund 2004[77]	CV morbidity	SBP: Office and ABPM (daytime SBP added more)	ABPM (24h): 1.23 (1.07, 1.42) p<0.05 ABPM (daytime): 1.23 (1.07, 1.42) p<0.05 Clinic: 1.21 (1.04, 1.41) p<0.05 per 1SD rise in SBP
Dawes 2006[159]	Mortality	ABPM (daytime)	ABPM (daytime): 1.51 (1.25, 1.83); p<0.001 Clinic: 1.02 (0.84, 1.24); p=0.90 highest quartile of SBP compared to ?lowest
Dolan 2005[178]	CV mortality	ABPM (especially night-time)	ABPM (24h): 1.19 (1.14, 1.26) p<0.001 ABPM (night-time): 1.21 (1.16, 1.27) p<0.001 Clinic: 1.06 (1.02, 1.10) p<0.01 per 10mmHg rise in SBP
Fagard 2008*[210]	CV events	ABPM (especially night-time)	ABPM (24h): 1.20 (0.91-1.58) NS ABPM (daytime): 1.03 (0.77-1.36) NS ABPM (night-time): 1.34 (1.06-1.69) p<0.01 Per 1SD rise in SBP
Hansen 2005[253]	CV mortality	ABPM	ABPM (24h): 1.51 (1.28, 1.77) p<0.0001 ABPM (daytime):1.50 (1.27, 1.76) p<0.0001 Clinic: 1.25 (1.10, 1.42) p<0.001 per 10mmHg rise in SBP
Hansen 2007*[254]	Cardiac events / CV events	ABPM (CV events); but no difference for mortality (total and CV)	Cardiac events ABPM (daytime): 1.13 (1.04, 1.23) p<0.0001 Cardiac events Clinic: 1.06 (0.99, 1.13) p>0.05 CV events ABPM (daytime): 1.17 (1.10, 1.24) p<0.0001 CV events Clinic: 1.05 (1.00, 1.10) p>0.05 per 10mmHg rise in SBP
Ingelsson 2006[284]	CHF	ABPM (night-time)	ABPM (24h): 1.13 (0.91, 1.40) p>0.05 ABPM (night-time): 1.21 (0.98, 1.49) p>0.05 Clinic: 1.25 (0.98, 1.59) p>0.05 per 1SD rise in SBP
Kikuya 2007*[326]	Cardiac events	No difference	ABPM (24hrs): 1.20 (1.13, 1.27) p<0.0001 ABPM (daytime): 1.16 (1.09, 1.23) p<0.0001 Clinic: 1.09 (1.04, 1.15) p<0.001 per 10mmHg rise in SBP

Update 2011

Study	Outcome	Best method	HR (95% CI) for SBP measurement
Mesquita-Bastos 2007[404]	CV events	ABPM (esp. night-time)	ABPM (24h): 1.41 (1.20-1.65) <0.001 ABPM (daytime): 1.33 (1.10-1.60) <0.01 ABPM (night-time): 1.57 (1.32-1.86) p<0.001 Per 1SD rise in SBP
Home vs ABPM vs clinic			
Fagard 2005[211]	Major CV events	Home equal to ABPM and better than office	Home: 1.32 (1.06, 1.64) p=0.01 ABPM (daytime): 1.33 (1.07, 1.64) p<0.01 ABPM (night-time): 1.42 (1.16, 1.74) p<0.001 Clinic: 1.13 (0.88, 1.45) p=0.34 Per 1mmHg rise in SBP
Sega 2005[534]	Mortality	No difference	No HRs given, but all entry BP values had a direct exponential relationship with the risk of all-cause death or CV death Goodness of fit of the relationship of BP to risk of death (CV and all-cause) was not less for clinic, compared to home and ambulatory. β Coefficient ABPM (24h): 0.0557 ± 0.0008 p<0.0001 ABPM (daytime): 0.0479 ± 0.008 p<0.0001 ABPM (night-time): 0.0559 ± 0.007 p<0.0001 β Coefficient – the increase in risk per 1mm Hg increase in SBP

Summary

Studies showed that for predicting clinical outcomes:

ABPM versus CBPM (nine studies):

- ABPM was superior to CBPM (eight studies)
- There was no difference between ABPM and CBPM (one study)

HBPM versus CBPM (three studies):

- HBPM was superior to CBPM (two studies)
- There was no difference between HBPM and CBPM (one study)

HBPM versus ABPM versus CBPM (two studies):

- HBPM was similar to ABPM and both were superior to CBPM (one study)
- There was no difference between HBPM, ABPM and CBPM (one study)

Update 2011

7.2 Sensitivity and specificity of clinic, home and ambulatory measurements

Review question: In adults with suspected primary hypertension, what is the best method to measure blood pressure (HBPM versus ABPM versus CBPM) to establish the diagnosis of hypertension?

7.2.1 Clinical evidence

One systematic review/meta-analysis[275] was found that fulfilled the inclusion criteria and looked at the best method of measuring blood pressure for diagnosing hypertension. Studies were included in

the SR/MA if they were: RCTs, adult population (all ages), all settings except hospitalised (the main focus was to be on primary care). Studies were excluded from the SR/MA (unless these groups could be excluded from other data within a paper) if they: did not specify the diagnostic thresholds used, had spectrum bias (no normotensives or hypertensives in one measurement group), patients were pregnant, hospitalised, or were receiving treatment at the time of the comparison. The systematic review/meta-analysis included 20 studies (N=5863) and compared the sensitivity and specificity of CBPM and HBPM measurements (using ABPM as the reference standard – as ABPM has been shown to be the best blood pressure method for indicating prognosis). The systematic review/meta-analysis was of good quality, however the quality of the studies it included ranged from poor to good.

The population included in the 20 studies consisted of:

- primary care
- primary care at risk
- secondary care
- the general population
- general population at risk
- community volunteers

The 20 studies included in the SR/MA differed in terms of:

- Mean age (range <33 to 60 years)
- Gender: % male (range 16 to 69%)
- Sample size (range N=16 to N=2370)
- Mean baseline BP of population
- Sensitivity (Home vs ABPM range 0.48 to 0.91; clinic vs ABPM range 0.17 to 1.0)
- Specificity (Home vs ABPM range 0.34 to 0.92; clinic vs ABPM range 0 to 0.98)
- Number of measurements for ABPM (range: 24 to 111 in the daytime)
- Number of measurements for clinic BP (range: 2 to 18)
- Number of measurements for home BP (range: 18 to 56)
- Period of ambulatory measurement (range: 6 to 24 hours)
- BP thresholds used (range: ABPM SBP 91-144 mmHg; clinic SBP 90 to 160 mmHg; home SBP 127 to 140 mmHg))

Quality assessment (QUADAS criteria) of the included studies showed that they:

- had good reporting of attrition
- had good selection criteria of participants
- had reporting bias: all studies had lack of clarity of reporting
- avoided both partial and differential verification bias (i.e. all patients in the studies received the same comparison measurement tests, regardless of initial results)
- used validated devices for all strands of monitoring: 11/20 studies
- limited evidence of blinding to previous BP results from monitoring assessors

NOTE: only 10 of the 20 studies were ultimately included in the meta-analysis of data. Only studies with the same reference test threshold and same index test threshold were pooled and included in the meta analysis. Eight studies used a 135/85 mmHg ABPM threshold and a 140/90 mmHg clinic BPM threshold to diagnose hypertension, whilst three studies used a threshold of 135/85 mmHg for both ambulatory and home diagnosis. However, one of the clinic comparison studies used the full 24 hour mean ABPM rather than mean daytime readings and was therefore not comparable to the others and excluded from the analysis.

Update 2011

7.2.2 Evidence statements – clinical

One SR/MA[275] found the following sensitivities and specificities for CBPM and HBPM when using ABPM as the reference standard (Table 15):

Table 15: CBPM and HBPM for diagnosing Hypertension. The thresholds used in the SR/MA for diagnosis were: ABPM (daytime) 135/85 mmHg; clinic BP 140/90 mmHg; home BP 135/85 mmHg.

Parameter / BP test	Clinic / ABPM (7 studies)[219,461,540,566,567,602,603]	Home / ABPM (3 studies)[62,167,567]	Statistical significance (p-value)
Sensitivity,% % (95% CI)	74.62 (60.72, 84.83)	85.65 (77.95, 90.97)	NS (p-value not reported)
Specificity, % (95% CI)	74.61 (47.88, 90.38)	62.44 (47.98, 74.98)	NS (p-value not reported)

- Clinic versus Home BP (Table 15):
  - there was NS difference between the BP measurement methods for sensitivity or specificity

In a sensitivity analysis for CBPM which included only studies with mean BPs close to or above the diagnostic threshold (ie. a typical general practice screening population with no normotensives):

- CBPM sensitivity increased to 85.6% (CI 81.0 to 89.2) and specificity decreased to 45.9 (CI 33.0 to 59.3).
  - NOTE: The home BP studies already used a typical general practice screening population with no control group of normotensives and so the values remained the same.
- This made HBPM the same as CBPM for sensitivity but better for specificity

Clinic BP thresholds (140/90 mmHg vs 150/90 mmHg);Table 16:

- sensitivity decreased with increasing BP threshold, however, the change was NS.
- specificity increased with increasing BP threshold, however, the change was NS.

Home BP thresholds (135/85 mmHg vs 140/90 mmHg and 130/80 mmHg);Table 16:

- Sensitivity significantly decreased with increasing threshold
- Specificity significantly increased with increasing threshold

Summary:

- Home BP is a better measurement than clinic BP for diagnosing HT (in a typical general practice screening population), but is not as good as ABPM.
- A higher BP threshold (for clinic BP) resulted in worse sensitivity and better specificity for diagnosing HT (compared to the current standard threshold used for diagnosis: 140/90 mmHg), however the effect was NS.
- A higher BP threshold (for home BP) resulted in a significantly worse sensitivity and significantly better specificity for diagnosing HT (compared to the current standard threshold used for diagnosis: 135/85 mmHg)
- A lower BP threshold (for home BP) resulted in significantly better sensitivity and significantly worse specificity for diagnosing HT (compared to the current standard threshold used for diagnosis: 135/85 mmHg)

Update 2011

Table 16: CBPM and HBPM – sensitivity and specificity of different thresholds for diagnosing Hypertension. The thresholds used in the SR/MA for diagnosis by ABPM (daytime) was 135/85 mmHg.

Test threshold (referm=nces not provided in SR/MA)	Sensitivity, % (95% CI)	Relative sensitivity, % (95% CI)	Specificity, % (95% CI)	Relative specificity, % (95% CI)
Clinic BP thresholds				
140/90 (n=7)	74.73 (61.73 to 84.43)	1.00 (reference)	74.75 (49.82 to 89.82)	1.00 (reference)
150/90 (n=1)	66.34 (28.28 to 90.79)	0.89 (0.51 to 1.55), p=0.68	86.16 (24.80 to 99.16)	1.15 (0.71 to 1.88), p=0.57
Home BP thresholds				
140/90 (n=1)	52.56 (34.71 to 69.78)	0.63 (0.45 to 0.88), p=0.01	80.32 (67.88 to 88.74)	1.42 (1.20 to 1.68), p<.0001
135/85 (n=3)	83.15 (76.09 to 88.45)	1.00 (reference)	56.68 (46.42 to 66.40)	1.00 (reference)
130/80 (n=1)	91.75 (84.37 to 95.82)	1.10 (1.03 - 1.18), p=0.01	41.35 (30.13 to 53.53)	0.73 (0.57 to 0.93), p=0.01

7.3 Cost-effectiveness of clinic, home and ambulatory measurements

7.3.1 Economic evidence – literature review

Update 2011

An economic evaluation should ideally compare all relevant alternatives. No studies were identified comparing all of clinic blood pressure monitoring (CBPM), ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) at diagnosis.

One study (Krakoff 2006[338]) was identified that examined the cost effectiveness of ABPM compared with CBPM in the diagnosis of hypertension. This is summarised in the ABPM versus CBPM economic evidence profile below (Table 17, Table 18). A full evidence table is also provided in Appendix G: Evidence tables – health economic studies (2011 update).

One study was identified that examined HPBM and CBPM in the diagnosis of hypertension but was excluded as it was judged to have serious methodological limitations.[225]

Table 17: ABPM versus CBPM (diagnosis) – economic study characteristics

Study	Applicability	Limitations	Other Comments
Krakoff 2006[338] USA	Partially applicable(a)	Potentially serious(b)	• CBPM diagnosed population. • CBPM vs CBPM+ABPM at diagnosis. • Decision analytic model incorporating prevalence of white coat hypertension, rate of conversion to true hypertension and drop-out rate from treatment. • 5-year time horizon. • Costs: ABPM (diagnosis and annual follow-up) and hypertension treatment.

a) Does not incorporate all relevant comparators. Does not incorporate health effects (possibly conservative towards ABPM).Some uncertainty about the applicability of USA costs. Discounting not applied.

b) Source of prevalence of white coat hypertension unclear but varied in sensitivity analysis (15-20%). Limited sensitivity analysis.

Table 18: ABPM versus CBPM (diagnosis) – economic summary of findings (mean per person)

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Krakoff 2006[338] USA	-£80(a)	N/a	N/a	-£28 to -£132(b)

a) Converted from 2005 US dollars.

b) Two way sensitivity analysis varying white coat hypertension rate 15%-20% and the annual conversion rate of white coat hypertension to true hypertension 5%-20%.

7.3.2 Economic evidence - original economic analysis

The GDG considered the clinical evidence reviewed as part of the guideline update to suggest that ambulatory blood pressure monitoring (ABPM) may be more accurate at diagnosing patients with hypertension than clinic blood pressure monitoring (CBPM) or home blood pressure monitoring (HBPM); however it is also the most expensive option in terms of monitor costs. HBPM was found to be more specific than CBPM but was also associated with additional monitor costs. The use of ambulatory or home monitoring instead of clinic monitoring to confirm a diagnosis of hypertension was identified as the highest economic priority by the GDG due to it being a significant change in practice that would require considerable investment in new devices by primary care.

As described above, no cost-effectiveness analyses comparing all of ABPM, HBPM and CBPM were identified from the published literature. A protocol for a cost-effectiveness analysis in development was submitted, in response to the call for evidence in this area (see Methods), by a UK research group[g] who had also undertaken a systematic review and meta analysis of the sensitivity and specificity of CBPM and HBPM compared to ABPM that was included in the guideline as part of the clinical evidence review[275]. However, the cost-effectiveness analysis would not be completed within the timeframe of the guideline update and so a collaboration was agreed between the GDG and the research group.

Below is a summary of the analysis that was undertaken. For full details please see Appendix J: Cost-effectiveness analysis).

Update 2011

7.3.2.1 Methods

A cost-utility analysis was undertaken to look at different blood pressure monitoring methods for confirming a diagnosis of hypertension. A Markov model was used to estimate lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance[427]. Uncertainty was explored through probabilistic analysis and extensive sensitivity analyses.

The population used for the analysis was people with suspected hypertension – those with a screening clinic blood pressure measurement equal or above 140/90 mmHg. Analyses were run for ten gender and age (40, 50, 60, 70, 75 years) stratified subgroups.

The comparators selected for the model were confirmation of diagnosis with:

- Clinic blood pressure monitoring (CBPM)
- Home blood pressure monitoring (HBPM)

g Richard McManus, Professor of Primary Care Cardiovascular Research, University of Birmingham; Sue Jowett, Senior Lecturer in Health Economics, University of Birmingham; Pelham Barton, Reader in Mathematical Modelling, University of Birmingham; James Hodgkinson, Research Fellow, University of Birmingham; Jonathan Mant, Professor of Primary Care Research, University of Cambridge; Una Martin, Reader in Clinical Pharmacology, University of Birmingham; Carl Heneghan, Reader in Evidence-Based Medicine, University of Oxford; Richard Hobbs, Head of Primary Care Clinical Sciences, University of Birmingham.

- Ambulatory blood pressure monitoring (ABPM)

The population entering the model comprised people suspected of having hypertension based on a screening clinic blood pressure reading. This group therefore included both those that were truly hypertensive (true positive following screening) and those that were not (false positive following screening). The diagnosis process aimed to correctly confirm both true hypertensives (in order to reduce their cardiovascular risk via treatment) and true normotensives (in order to reduce unnecessary treatment). The key differences between diagnostic options were their ability to accurately diagnose both these groups. One of the key inputs in the model was therefore the sensitivity and specificity of the different diagnostic options and this was based on the meta analysis[275] included as clinical evidence in the guideline. In addition the comparators varied in terms of the time they took to confirm a diagnosis (and so receive treatment and the benefits of treatment in terms of cardiovascular risk reduction).

Key model assumptions (these are discussed in more detail in the full write-up in Appendix J: Cost-effectiveness analysis – blood pressure monitoring for confirmation of diagnosis of hypertension):

- People with hypertension have a higher risk of cardiovascular events than people without hypertension.
- Once a diagnosis of hypertension has been made (correctly and incorrectly; that is true positives and false positives) people receive treatment including antihypertensive drugs.
- Only people who are truly hypertensive (true positives receive benefit in terms of cardiovascular risk reduction from treatment.
  - People who are truly normotensive but are treated (false positives) do not receive any health benefits.
- People who are truly normotensive at entry to the model may develop hypertension over time.
- People diagnosed as not hypertensive (correctly or incorrectly; that is true negatives and false negative) will have a blood pressure check-up with CBPM every 5 years.
  - At this check-up, it is assumed that they will again screen positive and so be suspected of having hypertension again and their diagnosis is confirmed using the same method as previously (CBPM, HBPM or ABPM)
- People who have had a cardiovascular event experience reduced quality of life and have an increased risk of death.

Update 2011

Diagnosis confirmations using CBPM, HBPM or ABPM are associated with different initial costs. As they also vary in terms of their ability to correctly diagnose people with and without hypertension the downstream costs (including hypertension treatment, CVD costs and checkups in those diagnosed as not hypertensive) and QALYs also vary.

Model inputs were based on the clinical effectiveness review undertaken for the guideline, other published data and expert opinion where required. These are described in full in the technical report in Appendix J. All model inputs and assumptions were validated by the GDG and research group.

The cost of confirming a diagnosis with CBPM, HBPM and ABPM took into account device costs, maintenance and healthcare professional time. In the base-case analysis the cost per person was £38.00 for CBPM, £39.13 for HBPM and £53.40 for ABPM. This was based on the following assumptions:

- CBPM was assumed to require at least a further two sets of readings should be taken at monthly intervals. For costing purposes it was assumed in the base case that two sets of readings would be taken; the first with a practice nurse and the second with a GP (as this may involve a treatment consultation). A cost for the CBPM monitor was not included in the costing as GPs will still require clinic monitors even if HBPM or ABPM at diagnosis in instigated and so this cost will not vary dependant on the diagnosis strategy.
- HBPM was assumed to require measurements over 7 days. For costing purposes it was assumed that two healthcare consultations would be required; an initial appointment with a practice nurse

to explain to the patient how to use the monitor and a second once the monitoring was complete with a GP to review the results and provide treatment advice if necessary.

- ABPM was assumed to take place over a single 24 hour period. For costing purposes it was assumed that two healthcare consultations would be required: an initial appointment with a practice nurse to fit the monitor and a second with a GP to review the results and provide treatment advice if necessary. In addition time for a nurse to download the ABPM data was factored in.
- HBPM and ABPM device costs per person were calculated based on median published costs to the NHS and assuming a lifetime of 5 years, no resale value, a discount rate of 3.5% and uses per year per machine of 40 and 125 respectively.

Alternative diagnosis costs were used in a series of sensitivity analyses. This included scenarios with lower uses per year per machine and ABPM via direct access at hospital.

7.3.2.2 Results

This analysis of cost-effectiveness found that, confirming a diagnosis of hypertension with ABPM instead of CBPM or HBPM was the most cost-effective option in all age/gender subgroups (40, 50, 60, 70 and 75 years). In fact, ABPM was cost saving compared to CBPM when long term costs were taken into account. The key driver of cost savings with ABPM compared to CBPM was hypertension treatment costs avoided due to more accurate diagnosis (increased specificity). Results are summarised in Table 19.

In most subgroups ABPM was associated with higher QALYs, as well as lower costs, than CBPM and HBPM (that is ABPM was the dominant option). The exception was in the subgroups with starting age 40 years and the female subgroup with staring age 50 years, where ABPM still had lower costs but was associated with a small reduction in QALYs; however, ABPM was still the most cost effective option in these scenarios.

Update 2011

Table 19: Basecase analysis results (probabilistic analysis) – cost effectiveness (incremental costs and QALYS, and optimal strategy)

Subgroup	Incremental QALYs vs CBPM		Incremental costs vs CBPM		Most CE strategy	Probability CE
	HBPM	ABPM	HBPM	ABPM		
Male, 40 years	-0.001 (CI: -0.006, 0.004)	-0.004 (CI: -0.009, 0.005)	-£48 (CI: -£128, £17)	-£235 (CI: -£322, -£117)	ABPM	100%
Male, 50 years	0.001 (CI: -0.009, 0.009)	0.006 (CI: -0.003, 0.017)	-£34 (CI: -£89, £11)	-£156 (CI: -£233, -£62)	ABPM	100%
Male, 60 years	0.003 (CI: -0.010, 0.015)	0.017 (CI: 0.006, 0.029)	-£26 (CI: -£70, £7)	-£112 (CI: -£178, -£43)	ABPM	100%
Male, 70 years	0.005 (CI: -0.009, 0.017)	0.022 (CI: 0.012, 0.035)	-£23 (CI: -£65, £7)	-£89 (CI: -£150, -£30)	ABPM	100%
Male, 75 years	0.004 (CI: -0.007, 0.015)	0.021 (CI: 0.012, 0.030)	-£16 (CI: -£49, £6)	-£56 (CI: -£105, -£10)	ABPM	100%
Female, 40 years	-0.001 (CI: -0.004, 0.001)	-0.006 (CI: -0.008, -0.003)	-£68 (CI: -£167, £25)	-£323 (CI: -£389, -£222)	ABPM	100%
Female, 50 years	-0.001 (CI: -0.006, 0.004)	-0.001 (CI: -0.006, 0.007)	-£40 (CI: -£106, £15)	-£182 (CI: -£256, -£79)	ABPM	100%
Female, 60 years	0.001 (CI: -0.006, 0.008)	0.006 (CI: 0.000, 0.015)	-£32 (CI: -£83, £11)	-£146 (CI: -£220, -£55)	ABPM	100%
Female, 70 years	0.003 (CI: -0.005, 0.011)	0.014 (CI: 0.008, 0.021)	-£20 (CI: -£59, £8)	-£82 (CI: -£142, -£25)	ABPM	100%
Female, 75 years	0.002 (CI: -0.004, 0.007)	0.010 (CI: 0.006, 0.015)	-£17 (CI: -£52, £11)	-£63 (CI: -£121, -£8)	ABPM	100%

CE= cost effective at a £20,000 threshold; CI = 95% confidence interval; QALYs = quality-adjusted life years.

The conclusion that ABPM is cost-effective compared to CBPM and HBPM was robust to a wide range of sensitivity analyses including those varying the cost of ABPM. As might be expected, the conclusion was sensitive to changes to the accuracy of diagnosis with each method and in some scenarios HBPM became the most cost-effective option. The conclusion was somewhat sensitive to the assumption that check-ups for those diagnosed without hypertension are undertaken every 5 years; in the two lower age subgroups HBPM became cost-effective when check-ups were done annually. The conclusion was also sensitive to the assumption that people who were not hypertensive but were treated did not receive benefits from treatment; when non-hypertensive people also received a risk reduction from treatment CBPM became the most cost-effective option as there was now benefit to misdiagnosing people.

7.3.2.3 Interpretation & limitations

This analysis suggests that ABPM is the most cost-effective method of confirming a diagnosis of hypertension in a population suspected of having hypertension based a CBPM screening measurement $\geq$140/90 mmHg, compared with further CBPM or HBPM. This conclusion was consistent across a range of age/gender stratified subgroups. Uncertainties in the analysis were explored through extensive sensitive analysis which in most cases did not change conclusions. Where conclusions were impacted this was discussed by the GDG and it was felt that these should not change the overall conclusion.

It was noted that the analysis is most probably conservative in terms of ABPM in a number of places. For example, ABPM reduces treatment costs compared to CBPM and HBPM and the cost of these used in the basecase analysis is most likely on low side as it is based on most commonly used generic drug costs and a single clinic visit per year. In addition, the basecase does not incorporate any negative quality of life impacts of being on treatment and when even a 1% reduction in quality of life is incorporated into the analysis QALYs differences between options are considerably more favourable for ABPM. These effects were omitted from the basecase analysis because side effects of antihypertensive drugs are generally fairly mild and rare and patients can often change drugs if they experience side effects but also because no appropriate data was identified to quantify any effects. However, it is not implausible that there may be a small negative impact of being on pharmacological treatment due to side effects.

In was noted in GDG discussions that there were potentially some additional benefits of ABPM that were not captured by the model but that would be valued by patients. With ABPM less people are incorrectly diagnosed as having hypertension when they do not. These patients will therefore avoid unnecessarily drug treatment which will mean they won't experience side effects, incur prescription costs or be labelled as having a medical condition, with the potential psychological and practical impacts this can have[305]. With ABPM patients will also get a definitive diagnosis more quickly that with CBPM.

Sensitivity and specificity inputs

The relative sensitivity and specificity of CBPM, HBPM and ABPM is the key differentiator between treatments in the model and as such is an important input.

However, there were a number of limitations to the estimates of sensitivity and specificity used in the model.

A key assumption in the model, and the meta analysis used for sensitivity and specificity estimates, was that ABPM is the reference standard for diagnosing hypertension and so has 100% sensitivity and specificity. This is a potential limitation in that ABPM probably does not have 100% sensitivity and specificity. However, prognostic studies indicated that ABPM was most predictive of prognosis

Update 2011

and so this was considered a reasonable assumption for the analysis; without making this assumption it would not be possible to undertake the analysis.

Conclusions were however somewhat sensitive to variations in the sensitivity and specificity values, with HBPM becoming cost effective in some scenarios. However, while there is uncertainty around the assumption that ABPM is the gold standard with 100% sensitivity and specificity, the instances when conclusions were changed were generally quite extreme. For example, when the sensitivity and specificity of ABPM were set equal to that of HBPM or when the sensitivity of HBPM was increased to 100%.

In addition, while it is known that sensitivity and specificity vary with disease prevalence (and so age) data was not available to allow this to be incorporated into the basecase analysis. However, when examined in exploratory sensitivity analyses it seemed that it would probably not impact conclusions.

The GDG carefully considered the uncertainty around the estimates of sensitivity and specificity but given the currently available evidence felt that it should not impact the overall conclusion that ABPM was the preferred option.

Treating those who are not hypertensive

The basecase conclusion that ABPM was a more cost-effective option for confirming a diagnosis of hypertension than CBPM or HBPM was sensitive to the assumption that only people who were hypertensive received benefits (cardiovascular risk reduction) from treatment. When a risk reduction was also applied to people who were treated but who were not hypertensive (people incorrectly diagnosed as having hypertension), CBPM was the most cost effective option across all subgroups.

Update 2011

The basecase assumption was based on the clinical GDG members' opinion that there is currently insufficient evidence of benefit for initiating treatment below the currently recommended thresholds. While there is evidence of a continuous relationship between blood pressure and cardiovascular risk[361], it is not well established that initiating blood pressure treatment below 140/90 mmHg reduces that risk in people with uncomplicated hypertension. The meta analysis reported by Law and colleagues[351] was used to inform the cardiovascular risk reduction in the model for people with and without hypertension as results were stratified by pre-treatment blood pressure; people with hypertension therefore got a greater risk reduction than people without in the analysis. This meta analysis was reviewed as part of the guideline update in relation to the question of what the treatment initiation threshold should be (Chapter 9.1). This analysis asserts that cardiovascular risk reduction is obtained at all levels of pre-treatment blood pressure. However, the GDG noted that the analysis included studies with a range of populations and those that provided information for risk reduction where pre-treatment blood pressure was below 140/90 mmHg were generally in populations with a history of cardiovascular disease or other increased risk that are not necessarily representative of the more general hypertension population.

The sensitivity analysis results, with CBPM more cost-effective than ABPM or HBPM, suggests that misdiagnosing people as having hypertension when they do not is a good thing because the health benefits of doing so are worth the additional cost of treatment. This result is therefore more to do with what the diagnostic threshold should be rather than the method that should be used to confirm diagnosis. It should also be noted that potential negative effects of treatment (in terms of reducing people quality of life) were not considered in this sensitivity analysis.

The basecase analysis reflects the GDG's interpretation of the clinical data relating to treatment thresholds and as such was considered to reflect the most appropriate analysis for informing which method should be used to confirm a diagnosis of hypertension.

Differential treatment initiation threshold

In the model it is assumed for practical reasons that all people diagnosed with hypertension (CBPM 140/90 mmHg; HBPM/ABPM 135/85 mmHg) receive pharmacological treatment. However, this guideline recommends a differential treatment initiation threshold whereby people diagnosed with hypertension (by the above definition) generally receive pharmacological treatment if their blood pressure is ≥160/100 mmHg (HBPM/ABPM ≥150/95 mmHg), or they have an estimated 10-year cardiovascular risk equivalent to 20% or greater, target organ damage, pre-existing cardiovascular disease, renal disease or diabetes. In those with hypertension but not eligible for pharmacological treatment it is recommended they receive lifestyle advice and an annual check-up.

The implications of this simplification are likely to be that the analysis somewhat overestimates the costs of treating hypertension as some people won't need to be treated and somewhat overestimates the benefits of treatment (QALY gain), as some people won't get treated and so won't get the risk reduction from treatment. However, the cost implications will be mitigated by the fact that many people will eventually need drug treatment and that nearly half the cost of hypertension treatment in the model is the annual check-up which will still be required in those that have hypertension but not receiving drug treatment. The treatment costs used in the basecase analysis are also potentially conservative. In addition, the QALYs implications will be mitigated by the fact that the people who do not receive treatment will be at lower risk so the people who remain in the model will have higher risk and benefit more on average and lifestyle advice will provide some risk reduction in some patients at least.

In addition to the above considerations, the implication of the differential pharmacological treatment initiation threshold is effectively a reduction in the number of people eligible for treatment. This is therefore somewhat addressed by the sensitivity analysis where the prevalence of true hypertension in the model is varied through a wide range. The conclusion that ABPM was the most cost-effective option was maintained through a prevalence of true hypertension is the suspected hypertension population of 10-80%.

Update 2011

Check-up frequency

In the basecase analysis it was assumed that people who were diagnosed without hypertension were checked-up every 5 years. In a sensitivity analysis where this was change to an annual check-up, ABPM was no longer cost-effective in younger age groups. The GDG discussed the implications of this finding and felt that, while check-up frequency will vary between patients, on balance this should not impact the overall conclusion that ABPM should be used. It was however noted that in younger patients diagnosed as not hypertensive but in whom frequent follow-up is planned, it might be considered reasonable to use an alternative to ABPM to avoid high diagnosis costs.

Model input uncertainty

Throughout this report it has been highlighted where there have issues with model input uncertainty – this is a limitation of the analysis. In some places there was a lack of data to inform inputs; this included CVD event and post-event costs and the prevalence of true hypertension in a population of people with suspected hypertension. In other places there was variability between settings or patients, such as the cost of ABPM and the frequency of check-ups in those diagnosed without hypertension. The best available or more likely inputs were used for the basecase analysis and these were varied in sensitivity analyses.

7.3.3 Evidence statements – economic

- One partially applicable study with potentially serious limitations found that ABPM was cost saving compared to CBPM; the treatment costs avoided from not treating patients with WCH were greater than the additional costs of ABPM.

- New economic analysis from a current UK NHS and PSS perspective comparing CBPM, HBPM and ABPM for confirming a diagnosis of hypertension in a population with suspected hypertension found ABPM to be the most cost effective option across a range of age subgroups in both men and women. In most subgroups ABPM was found to both improve health (increased QALYs) and reduce costs overall. The conclusion was robust to the majority of sensitivity analyses undertaken including those varying the cost of ABPM.

7.4 Measurement protocols for diagnosing hypertension

7.4.1 Ambulatory blood pressure measurement

Review question: In adults with primary hypertension, what protocol should be used when measuring ambulatory blood pressure for treatment and diagnosis?

7.4.1.1 Clinical evidence

The literature was searched for all years (as this was not addressed in the previous guidelines)[425,436] and all study types were included. Studies were excluded if the population consisted of people who were exclusively diabetic or had CKD. Validation studies of ABPM machines were also excluded.

53 studies[77,88,111,151,178,190,200,210,211,237,253,271,272,284,325,326,363,387,405,416,456,491,534,562,563,573,622 46,52,56,114,131,133,150,196,353,386,389,390,420,473,527,530,531,538,541,557,576,595,600,608,609,654] were found that fulfilled the inclusion criteria and assessed what protocol should be used when measuring ambulatory BP for the treatment and diagnosis of adults with primary hypertension.

The studies addressing the question were categorised into two different types:

1. Prognostic studies (17studies;17 papers)[77,88,131,178,210,211,237,253,284,325,326,363,405,491,534,557,576] – those that assess the prognostic significance of ambulatory BP and the optimal schedule for measurement based on outcome data

2. Reliability / reproducibility studies (36 studies; 36 papers)[46,52,56,111,114,133,150,151,190,196,200,271,272,353,386,387,389,390,416,420,456,473,527,530,531,538,541,562,563,573,595,600,608,609,622,654] - those that assessed any of the following - the optimal ambulatory BP schedule based on:

a) the reproducibility of ABPM
b) its stability over time (variability of BP over time)
c) the relationship (correlation) between day and night values with mean 24h ABPM values
d) its ability to identify people diagnosed with HT / NT / ICH or dippers and non-dippers
e) changes in BP in response to treatment

Reliability /repeatability studies were deemed to be applicable to the question because they showed which aspects of the ABPM protocol (daytime, night-time, or 24h blood pressure measurements) were the most reliable, and therefore served as an indication of the 'best' / optimal ABP measurements to be taken.
Details of all the studies are included in Table 20and Table 26.

Update 2011

Table 21summarises the numerical results for selected outcomes of the prognostic studies included for this review. The full data for all outcomes can be found in the evidence tables in the appendix. A summary of the measurement intervals for BP readings used by each of the studies is summarised in Table 20, Table 22 and Table 23. All prognostic studies were found to be methodologically sound / have a low risk of bias (see quality assessment summary tables in appendix F) except for the Li 2008 study[363] which was rated as 'unclear' for a number of potential methodological flaws.

NOTE: For the prognostic studies, the 'best method' was chosen as the method of measuring BP that best predicted (ie. statistically significant predictors and higher HR values) clinical outcomes (after adjustment for covariates in multivariate analyses). For the 'reproducibilty/reliability studies' the 'best method' was chosen as the the method / protocol of measuring blood pressure that was the most reliable or repeatable.

Update 2011

Prognostic studies

Table 20: Study details and results for prognostic studies assessing the optimal ABPM protocol

Reference / study type	N	Population	Device	Follow-up time	Time and frequency of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
Bjorklund et al., 2004[77] within-group comparison	872	General population (HT and NT)	AUS	Mean 6.6 years	every 20 mins	CV mortality	24h, daytime and night-time are all predictors Use SBP not DBP
Boggia et al., 2007[88] Pooled analysis of other study data, within-group comparisons (IDACO)	7458 analysed	General population (HT and NT)	OSC or AUS	Median 9.6 years	D – range 15-30 mins N – range 30-60 mins	Total mortality, CV mortality, non-CV mortality, CV events, stroke, cardiac events	Both daytime and night-time BP (need to record ABPM throughout the whole day). NOTE: 24h BP was not measured.
Clement et al., 2003 [131] Within-group comparison	2232	HT	-	Median 5 years	D – 30 mins N – <60 mins	Total mortality, CV mortality, CV events, MI, stroke	24h and daytime (are better than night-time, especially SBP)
Dolan et al., 2005[178] within-group comparison	5292	HT	OSC	Mean 7.9 years	every 30 mins	All-cause mortality; Cardiac mortality; CV mortality	Night-time (better than daytime or 24h)
Fagard et al., 2005[211] within-group comparison	391	General population in primary care practice (HT and NT)	-	Median 10.9 years	D – 15 mins N – 30 mins	CV events	Night-time (better than daytime)

Reference / study type	N	Population	Device	Follow-up time	Time and frequency of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
Fagard et al., 2008[210] Pooled analysis of other study data ,within-group comparisons	302	HT (with history of CV disease)	not specified	Median 6.8 years	D –range 15-30 mins (10am – 6pm) N – range 30-60 mins (12am – 6am)	All-cause mortality; CV mortality; composite of major CV events	Night-time
Gosse et al., 2001[237] within-group comparison	256	HT	AUS	Mean Mean 84 months	D – 15 mins N – 15 or 30 mins	CV complications	24h, daytime, night-time and arising BP are all predictors (24h, daytime and arising slightly stronger predictors) Single BP value on rising in the morning (is as good as mean daytime or mean 24h measurements) Use SBP not DBP
Hansen et al., 2005[253] within-group comparison	1700	General population (HT and NT)	OSC	Up to 9.5 years	D – 15 mins N – 30 mins	All-cause mortality; CV mortality	Night, day and 24h SBPs and DBPs DBP better than SBP
Ingelsson et al., 2006[284] within-group comparison	951	General population (HT and NT)	AUS	Up to 9.1years (mean range 0.1 – 11.4 years)	D – 20 or 30 mins N – 20 or 60 mins	CHF	Night-time (better than daytime or 24h)
Khattar et al., 2001[325] within-group comparison	688	HT	Intra-arterial ABPM	Mean 9.2 years	Every hour	Non-CV death, coronary death, CeV death, peripheral vascular death, nonfatal MI, nonfatal stroke,	24h, daytime and night-time all predictors SBP and DBP in age <60 Only SBP in age >60

Reference / study type	N	Population	Device	Follow-up time	Time and frequency of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
						coronary revascularisation.	
Kikuya et al., 2007[326] Pooled analysis of other study data, within-group comparisons (IDACO)	5682	General population (HT and NT); <10% had underlying CV disease	-	Median 9.5 years	1 study: every 20 mins 1 study: every 30 mins 1 study: 15 mins day, 30 mins night 1 study: 20 mins day, 45 mins night	CV events; coronary events; cardiac events; fatal/non-fatal stroke	24h, daytime and night-time (SBP and DBP)
Li et al., 2008[363] Summary of prospective population studies (case series)	7458	General population (HT and NT)	not specified	Median 9.6 years	D – interval not specified N – interval not specified	CV mortality, non-CV mortality, CV events, stroke, cardiac events	Daytime and night-time (depending on which outcome) Night-time better for mortality outcomes Daytime better for non-CV mortality Both for CV events and stroke Need to record ABPM throughout the whole day
Metoki et al., 2006[405] within-group comparison	1542	General population (HT and NT)	OSC	Mean 10.6 years	30 mins over 24 hours Weekday average of 4 SBP = 2hr SBP value at different periods	Mortality risk from CeV and CV events	Night and early morning 2h SBP (CeV and CV mortality) Elevated daytime 2h SBP (Haem stroke mortality) elevated night-time 2h SBP (cerebral infarction and HD mortality) High BP at different times of day is associated with different subtypes of CeV and CV mortality risk.
Pickering et al., 2007[491] Summary of prospective	8945	1 study: general population (HT and NT) 6 studies: HT	OSC or AUS	Mean 5.8 years	15-30 mins over 24 hours	Cardiac events; stroke	Daytime for cardiac events, night-time for stroke One summary measure not enough to predict different clinical outcomes

Reference / study type	N	Population	Device	Follow-up time	Time and frequency of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
population studies (case series)		(NT controls)					
Sega et al., 2005[534] within-group comparison (PAMELA study)	2051	General population (HT and NT)	OSC	Mean 10.9 years	every 20 mins	All cause mortality; CV mortality	Nighttime better than daytime SBP better than DBP
Staessen et al., 1999[557] Within-group comparison: substudy ofSyst-Eur trial	837	HT (ISH)	OSC	Mean 4.4 years	D - ≤ 30 mins N - ≤ 30mins	Total mortality, CV mortality, CV events, stroke, cardiac events	Night-time (better than daytime) Excluding the first 2h does not improve accuracy
Suzuki et al., 2000[576] Within-group comparison	324	HT and NT	OSC	Mean 51.5 months	D – 30 mins N – 30 mins	CV events	Higher 24-h and nighttime BP (SBP and DBP) are associated with a higher incidence of CV events

NT = normotensives; HT = hypertensives; ISH = isolated sytolic HT; AUS = auscultatory device; OSC = oscillometric device; D = daytime; N = night-time

Table 21: Summary of numerical results for prognostic studies (for selected outcomes)

Study	Outcome	HR (95% CI) for SBP measurement
Bjorklund et al., 2004[77]	CV mortality	ABPM (24h): 1.23 (1.07, 1.42) p<0.05 ABPM (daytime): 1.23 (1.07, 1.42) p<0.05 ABPM (night-time): 1.18 (1.03, 1.34) p<0.05 per 1SD rise in SBP
Boggia et al., 2007[88]*	CV events	ABPM (24h): not given ABPM (daytime): 1.16 (1.07-1.26) p<0.001 ABPM (night-time): 1.21 (1.12-1.30) p<0.001 Per 1SD rise in SBP
Clement et al., 2003 [131]	CV events	No HRs given. Relative Risks: ABPM (24h): 1.34 (1.11-1.62) ABPM (daytime): 1.30 (1.08-1.58) ABPM (night-time): 1.27 (1.07-1.51) Per 1SD rise in SBP
Dolan et al., 2005[178]	CV mortality	ABPM (24h): 1.19 (1.14, 1.26) p<0.001 ABPM (daytime): 1.15 (1.10, 1.21) p<0.001 ABPM (night-time): 1.21 (1.16, 1.27) p<0.001 per 10mmHg rise in SBP
Fagard et al., 2005[211]	CV events	ABPM (24h): Not given ABPM (daytime): 1.33 (1.07, 1.64) p<0.01 ABPM (night-time): 1.42 (1.16, 1.74) p<0.001 Per 1mmHg rise in SBP
Fagard et al., 2008[210]*	Composite of major CV events	ABPM (24h): 1.20 (0.91-1.58) NS ABPM (daytime): 1.03 (0.77-1.36) NS ABPM (night-time): 1.34 (1.06-1.69) p<0.01 Per 1SD rise in SBP
Gosse et al., 2001[237]	CV complications	No HRs given,only characteristics of people with vs without complications and the statistical difference. ABPM (24h): 133 ± 16 vs. 143 ± 14 (p<0.001) ABPM (daytime): 138 ± 16 vs 149 ± 15 (p<0.01)

Study	Outcome	HR (95% CI) for SBP measurement
		ABPM (night-time): 121 ± 17 vs 129 ± 14 (p<0.05) SBP mm Hg without vs with complications Mean±SD
Hansen et al., 2005[253]	CV mortality	ABPM (24h): 1.51 (1.28, 1.77) p<0.0001 ABPM (daytime):1.50 (1.27, 1.76) p<0.0001 ABPM (night-time): 1.41 (1.23, 1.62) p<0.0001 per 10mmHg rise in SBP
Ingelsson et al., 2006[284]	CHF	ABPM (24h): 1.13 (0.91, 1.40) p>0.05 ABPM (day-time): 1.08 (0.85, 1.36) p>0.05 ABPM (night-time): 1.21 (0.98, 1.49) p>0.05 per 1SD rise in SBP
Khattar et al., 2001[325]	all cause mortality. (no results for cornonary death)	<60 yrs ABPM (24h): 1.01 (1.00, 1.02)p=0.04 < 60 yrsABPM (daytime): 1.01 (1.00, 1.02)p=0.04 <60 yrs ABPM (night-time): 1.01 (1.00, 1.02)p=0.04 >60 yrs ABPM (24h): 1.02 (1.00, 1.03) p=0.003 >60 yrsABPM (daytime): 1.02 (1.00, 1.03)p=0.004 >60 yrs ABPM (night-time): 1.02 (1.00, 1.03) p=0.007 No info on the reference rise of SBP, but likely per 1mmHg
Kikuya et al., 2007[326]	CV events – defined as CV endpoints in the evidence table (also used cardiac events in red)	ABPM (24hrs): 1.24 (1.19, 1.30) p<0.0001 ABPM (daytime): 1.20 (1.15, 1.25) p<0.0001 ABPM (night-time): 1.18 (1.14, 1.23) p<0.0001 ABPM (24hrs): 1.20 (1.13, 1.27) p<0.0001 ABPM (daytime): 1.16 (1.09, 1.23) p<0.0001 ABPM (night-time): 1.16 (1.10, 1.22) p<0.0001 per 10mmHg rise in SBP
Li et al., 2008[363]*	CV events	ABPM (24h): not given ABPM (daytime): 1.16 (1.07-1.26) <0.001 ABPM (night-time): 1.21 (1.12-1.30) <0.0001 per 1SD rise in SBP
Metoki et al., 2006[405]	Mortality risk from	ABPM (24h): 1.76 (1.39-2.25) p<0.002

Study	Outcome	HR (95% CI) for SBP measurement
	CeV and CV events	ABPM (daytime): 1.59 (1.25-2.01) p<0.002 ABPM (night-time): 1.78 (1.40-2.27)p<0.002 Per 1SD rise in SBP
Pickering et al., 2007[491]*	Cardiac events	ABPM (24h): not given ABPM (daytime): HR = 1.29(95% CI: 1.20-1.39); p < 0.0001 ABPM (night-time): HR = 1.22(95% CI: 1.14-1.30); p < 0.0002 per 10mmHg rise in SBP
Sega et al., 2005[534]	CV mortality	No HRs given, but all entry BP values had a direct exponential relationship with the risk of all-cause death or CV death Goodness of fit of the relationship of BP to risk of death (CV and all-cause) was not less for clinic, compared to home and ambulatory. β Coefficients: ABPM (24h): 0.0557 ± 0.0008 p<0.0001 ABPM (daytime): 0.0479 ± 0.008 p<0.0001 ABPM (night-time): 0.0559 ± 0.007 p<0.0001 β Coefficient – the increase in risk per 1mm Hg increase in SBP
Staessen et al., 1999[557]	CV events	ABPM (24h): 1.20 (0.98-1.49) NS ABPM (daytime): 1.17 (0.96-1.44) NS ABPM (night-time): 1.23 (1.03-1.46) ≤0.05 per 10mmHg rise in SBP
Suzuki et al., 2000[576]	CV events	ABPM (24h): 1.28 (1.05 to 1.54) p< 0.05 ABPM (daytime): No HR reported ABPM (night-time): 1.34 (1.13 to 1.58)p < 0.01 per 10mmHg rise in SBP

Reliability and reproducibility studies

Table 22: Study details and results for reliability/reproducibility studies assessing the optimal ABPM protocol

Reference / study type	Frequency of measurements							
	N	Population	Device	Follow-up	Consecutive readings	Time of measurement	Mathematical method	Proposed number of measurements (authors' conclusions)
Antivalle et al., 1990[46] case-series: RCT substudy	22	HT	AUS and OSC	4 weeks (3 measurements: baseline, 2 and 4 weeks)	24h	Daytime Night-time 24h intervals not given	Reproducibility of BP (between the 3 measurements over time)	Differences in BP measurements (3 measurements) was only significant during waking hours
Asagami et al., 1996[52] within-group comparison	64	Borderline HT	AUS and OSC	1-2 years on a work day	24h	Daytime (30 mins) Night-time (1 hr) 24h	Long-term reproducibility of BP (between the 2 measurements over time): SD	Daytime BPwas better (vs night-time and 24h)
Asmar et al., 2001[56] RCT	30	HT	-	1 month (2 measurements1 month apart)	24h	Daytime (15 mins) Night-time (30 mins) 24h	Reproducibility of BP (between the 2 measurements over time, after placebo treatment)	Placebo administration resulted in SS reductions between baseline and 1 month 24h ABPM (SBP), and daytime SBP/DBP. No treatment resulted in NS differences between baseline and 1 month for 24h, daytime and night-time SBP/ DBP. This suggests a placebo effect on

Reference / study type	Frequency of measurements							
								BP.
Calvo et al., 2003[111] Case-series	823	HT	OSC	48 h	48h	D – 20 mins (07.00-23.00) N – 30 mins (23.00-07.00) ABPM started on a weekday (Mon, Wed or Fri)	Comparison of day-to-day variations in BP	ABPM for 48 h revealed a statistically significant pressor response (this could largely be due to the novelty of wearing an ABPM device for the first time). The pressor effect remains statistically significant for the first 10 h of monitoring, independent of gender, day of the week of monitoring and number of a-HT drugs used. Nocturnal mean BP was similar between both days of sampling. The effect diminished, but was not eliminated, in extent and duration for successive sessions of ambulatory monitoring. ABPM for just 24 h may be insufficient for a proper diagnosis of HT, evaluation of treatment efficacy and identification of dipping status in relation to target-organ damage.
Campbell et al., 2010[114] within-group comparison	72	HT and NT	OSC	2 years (2 measurements 2 years apart)	24h	Daytime (15 mins) Night-time (30 mins) 24h	Reproducibility of BP (between the 2 measurements over time)	24h BP was more reproducible over time than daytime and night-time BP measurements.
Coats et al.,	100	HT	-	1 month	24h	Daytime only (30 mins)	Reproducibility	Average daytime ABPM DBP was

Reference / study type	Frequency of measurements							
1992[133] within-group comparison				(2 measurements1 month apart)			of BP (between the 2 measurements over time)	more reproducible than a single measuremnt from daytime. There was improved reproducibility with more measurements during the day
Cuspidi et al., 2002[150] case-series	208	HT	OSC	3 weeks (2 measurementswithin 3 weeks)	24h	Daytime (15 mins) Night-time (20 mins) 24h	Reproducibility of BP (between the 2 measurements over time)	There was no change in diurnal BP variations. This indicates that the short term reproducibility of diurnal changes in BP in the early phases of untreated essential HT, is overall satisfactory.
Cuspidi et al., 2007[151] Case-series	611	ICH	OSC	2 x 24h periods (1-4 weeks apart)	24h	D (working day) – 15 mins (07.00-23.00) N – 20 mins (23.00-07.00)	Correlation with clinical diagnosis of ICH Reproducibility of ICH diagnosis (repeated ABPM measurements)	Classification of ICH based on a single ABPM (using cut-offs suggested in major HT guidelines) has limited short-term reproducibility Repeated ABPM measurements at a short time interval should be used to ensure correct diagnosis of ICH and improve CV risk stratification, allowing a more appropriate treatment strategy
Eguchi et al., 2010[190] within-group comparison	43	HT	OSC	Measurements twice within a 2-week interval between measurements	24h	Every 30 mins	Reproducibility of ABP, BP variability and BP reduction	Reproducibility of ABP levels and BP varaiblity was fairly good. Reproducibility of BP reductions was fairly good for ABP levels, so a single ABPM before and during treatment is acceptable in a drug intervention trial.

Reference / study type	Frequency of measurements							
Enstrom et al., 1996[196] RCT	80	HT and NT	OSC	14 days (2 measurements: 1 work and 1 non-work day)	24h	Daytime Night-time 24h All: 20 min intervals	Reproducibility on work and non-work days: SD; reproducibility over time (2 measurements, 2 weeks apart)	BP was higher during the work day. Daytime and night-time: there was a SS difference in BP measurement between the 2 readings There was NS difference for night-time BP between the 2 readings There were no major differences in reporducibility if 1, 2 or 3 recordings / hour were used. Arbritrary dividing lines for day/night or according to patients' own statement did not have any major effect on the result. But it may be wise to perform recordings not less than every 30 mins for patients
Ernst et al., 2008[200] post-hoc analysis (DIDIMA study)	1004 ABPM sessions (529 studies)	Borderline HT, suspected WCH, suspected hypotension, MHT, Tx resistance, a-HT treatment	OSC	24h	3 readings /hr (daytime) 2 readings /hr (night-time)	D – 20 mins (6am – 6, 8 or 10pm) N – 30 mins (6, 8 or 10pm – 6am)	Correlation of shorter ABPM periods with 24h ABPM	After excluding the first hour, correlations for mean SBP the subsequent 3-, 5- and 7-hour periods demonstrated greatest improvement in correlation when session is increased from 4 to 6 hours. 6-hour ABPM can approximate the overall mean BP obtained from full 24-hour ABPM. Shortened sessions do not characterise the influence of circadian variation over the 24-hour mean BP and may

Reference / study type	Frequency of measurements							
								overestimate 24-hour BP levels.
Hermida et al., 2002[271] Case-series	538	HT	OSC	48 h	48h	D – 20 mins (07.00-23.00) N – 30 mins (23.00-07.00) ABPM started on a weekday (Mon, Wed or Fri)	Comparison of variations in BP	BP is significantly increased by the novelty of wearing an ABPM device for the first time (the 'ABPM effect'). Pressor effect remains statistically significant for the first 6-8h of monitoring, independent of gender, day of the week of monitoring and number of a-HT drugs used. Differences between successive days of ABPM are no longer significant when patients were evaluated for second or successive times. ABPM for just 24 h may be insufficient for a proper diagnosis of HT, evaluation of treatment efficacy and identification of dipping status in relation to target-organ damage.
Hernandez-del Rey et al., 2007[272] Historical case-series	611	HT	OSC	48h	24h / 48h	Night and day defined based on patient's diary; at least 14 measurements during period of activity and at least 7 during period of rest	Reproducibility of BP dipping pattern in 24-h vs 48-h ABPM	The percentages of patients classified as non-dipper for the first 24 h, the second 24 h and the 48 h average were 47, 50 and 48% respectively. When the first and second 24-h periods were compared, 147 (24%) subjects switched from dipper (D) to non-dipper (ND) or vice-versa.

Reference / study type	Frequency of measurements							
						Recording intervals (minutes between measurements) not given		When the first 24-h period was compared to the 48-h average, 66 (11%) subjects switched patterns. The proportions were similar separately for SBP and DBP, and between treated and untreated patients. In subjects with poor ABPM reproducibility, night-to-day ratios were of an intermediate value between those of subjects always classified as Dipper or non-dipper. Categorisation of D or non-dipper based on a single 24-h ABPM is moderately reproducible, since one out of every five patients change profile over the following 24 h. A more reliable classification of the BP circadian profile should be performed by repeating a second ABPM within a short period, but the use of 48-h ABPM in clinical practice should be assessed according to cost-effectiveness criteria.
Lede et al., 1997[353] case-series	49	Pregnant women with pre-eclampsia (DBP≥90mm	AUS	24h	24h	3 different frequencies of monitoring (FoM) readings/ hour: High FoM = 7/hr	Similarities in BP measurements between 3 FoMs	BP was similar in the three FoMs studied at daytime and night-time. There is therefore no strong argument to perform ABPM at high FoM

Reference / study type	Frequency of measurements							
		Hg and proteinuria >300mg).				Low FoM = 1/hr Medium FoM = 2/hr		BP measurement at a lower FoM may be better for the patient and reduce equipment deterioration whilst providing equivalent information as supplied by a high FoM
Mancia et al., 1992[386] case-series	29	HT	AUS	4 weeks (2 measurements4 weeks apart)	24h	Daytime (15 mins) Night-time (20 mins) 24h	Reproducibility of BP (between the 2 measurements over time; and hourly vs mean 24h, SDD)	The second ABPM recording was lower but was NS different from the first Reproducibility was lower for hourly rather than 24h average BP. This suggests that ABPM measurement loses its advantages for reproducibility if results are analysed over hourly periods
Mancia et al., 2004[387] SR / MA of 44 trials	6000	HT (treated)	AUS or OSC	1 week – 36 months	-	Daytime: not given Night-time: not given 24h: not given	Change in BP response by different measurement methods	Treatment-induced reduction in BP is smaller for the night-time than daytime average BP The effect of anti-HT treatment is unevenly distributed between day and night Results advocate a more systematic adoption of ABP monitoring in trials assessing CV protection by anti-HT drugs
Mansoor et al., 1994 [389]	25	HT	AUS and OSC	Mean 23 months	24h	Daytime Night-time	Reproducibility of BP (between 2 repeated studies and	24h and night-time BP had better reproducibility than daytime BP (between studies and between readings over time)

Reference / study type	Frequency of measurements							
within-group comparison						24h All: 15 min intervals	over time): SDD, co-efficient of variance and % of people within 10mm and 5mm SBP and DBP	
Mar et al., 1998[390] within-group comparison	138	HT (newly diagnosed)	OSC	Not given	24h	Daytime (20 mins) Night-time (1 hr) 24h	Diagnostic accuracy with varying number of measurements	Increasing the number of measurements led to a reduction in diagnostic error due to random variability of BP.
Murakami et al., 2004[416] within-group comparison	135	General population (HT and NT)	OSC	7 days	-	Fitted on Thursday between 10am – 2pm; D - every 30 mins (0700 to 2200 hours) N - 60 mins (2200 to 0700 hours).	Comparison of weekly variations in BP	Monday surge in BP was found in the awake and morning BP but not in the asleep BP Morning BP surge on Monday was higher than on the other days of the week except for Tuesday Morning BP surge on a Monday may be in accord with clinical evidence that CV events more frequently occur in the morning on Monday
Musso et al., 1997[420] case-series	40	NT	OSC	3 months (4 measurements each 28 days apart)	24h	Daytime (15 mins) Night-time (30 mins) 24h	Reproducibility of BP (between the 4 measurements over time)	There was high agreement between the 4 readings BP values were lower during the 4th reading (vs 1st) People should not be labelled as HT based on initial readings, since initial ABPM may yield higher

Reference / study type	Frequency of measurements								
									values than later monitoring
Octavio et al., 2010[456] within-group comparison	450	Suspected arterial HT	not specified	24h	24h	Group	BP reading interval		Reliability of conventional vs time-weighted quantification of 24-h ABP	Higher number of readings per hour during daytime leads to an overestimation of conventional 24-h average BP, particularly in individuals with preserved nocturnal BP dipping. This can be avoided either by scheduling the same number of readings/h throughout 24 h or by performing a time-weighted quantification of 24-h BP The clinical implications of these different approaches deserve further investigation.
							Day (0600 - 2300)	Night (2300 - 0600)		
						I	15 min	30 min		
						II	15 min	20 min		
						III	30 min	30 min		
Palatini et al., 1994[473] case-series	6461	ISH or high DBP	OSC	3 months	2 (3 months apart)	Daytime (10 mins) Night-time (30 mins) 24h			Reproducibility over time (2 measurements, 3 months apart)	Small but SS decreases in average daytime BP / no change in average nighttime BP occur when ABPM is performed twice 3 months apart. There was a SS increase in SBP when the period between midnight and 5 am was considered in nighttime analysis. ABPM shows better reproducibility than office BP, particularly for 24h BP. Nighttime BP was less reproducible than daytime BP,

Reference / study type	Frequency of measurements							
								probably due to sleep disturbance which was reported in 2/3 of patients.
Schillaci et al., 1994[527] case-series	24	HT	OSC	1 week (2 measurements1 week apart)	24h	Daytime (15 mins) Night-time (15 mins session 1, 1hr session 2) 24h	Reproducibility of BP (between the 2 measurements over time)	There was NS difference in daytime or night-time systolic or diastolic BP and heartrate between the two sessions A low number of cuff measurements of BP during the night (1 per hour) provides similar results to a high number of measurements in terms of sleep BP, and changes of BP from wake to sleep.
Schwartz et al., 2000[530] within-group comparison	143	NT	AUS	1 week	24h	Active period (daytime) Inactive period (night-time) All: 10 min intervals	Intraindividual BP variability (SDs), during the active (daytime) and inactive (nighttime) periods of the day	Men: had greater BP variation (SBP and DBP) during the inactive period (vs. active period) Women: SBP – there was NS difference in BP variation during the inactive period (vs. active period). DBP – as for men.
Schwartz et al., 2000[531] within-group comparison	240	NT	AUS	1 week	24h	Active period (daytime) Inactive period (night-time) All: 10 min intervals	Intraindividual BP variability (SDs), during active (daytime) and inactive (nighttime) periods of the day	Men and women: there was greater BP variation (SBP) during the inactive period (vs. active period) Women: DBP – there was NS difference in BP variation during the inactive period (vs. active period)

Reference / study type	Frequency of measurements							
Sheps et al., 1994[538] within-group comparison	294	HT and NT	AUS	2 months (2 measurements2 months apart)	24h	Daytime (7.5 mins) and other time frequencies	Reproducibility of BP (between the 2 measurements over time):	As few as six hours of monitoring with two to three readings/hour achieved most of the gain in precision obtainable by going from single BP readings toward continuous measurement during an entire awake period
Shinagawa et al., 2002[541] case-series	56	unclear	OSC	7 days	7 days of 24h recordings	Daytime (30 mins) Night-time (1 hour) 24h	BP variability on different days of the week	The average SBP (daytime) is higher on the first day of monitoring vs the other 6 days. Daytime BP was lowest on Sundays and the day-night ratio was optimal on weekends.
Stenehjem et al., 2004[562] within-group comparison	75	HT	AUS	4 weeks measurements before and after 4 week observation period (2 separate work days)	24h	D – 20 mins (0700 – 2200) N – 30 mins (2200 – 0700)	Reproducibility of BP variability, white coat effect and dipping pattern	Average ABPs are highly reproducible in patients with uncomplicated essential HT of limited duration. Nocturnal dipping pattern also reproduced satisfactorily. White coat effect and variability are greatly attenuated during repeated measurements, and these measures may thus be of less utility in clinical practice. ABP and pulse pressure and of nocturnal fall in BP have the most prognostic relevance and are of great value in clinical practice.
Stergiou et al., 2002[563]	133	HT (untreated)	OSC	2 work days	24h	Every 20 mins	Test-retest variability (correlations	Mean 24h (was better than awake or asleep BP)

Reference / study type	Frequency of measurements							
within-group comparison							and SDD)	
Suarez et al., 2003[573] retrospective diagnostic case-series	261	HT	OSC	24h	24h	D – 20 mins (0700-2400) N – 30 mins (2400 – 0700) Reference standard: mean 24h ABP (≤125/80) Index test: mean awake ABP (<135/85)	Agreement between ABP daytime average and 24-h average for diagnosing HT and assessing effects of anti-HT treatments (sensitivity / specificity)	In 90% of the records there was agreement between both criteria Daytime and 24 h average BP may carry similar information for diagnosing HT and assessing the effects of anti-HT treatment in clinical practice. ABPM used only during the daytime could be better tolerated and agreed to by patients than 24 h monitoring.
Thijs et al., 1992[595] within-group comparison: substudy of Syst-Eur trial	102	ISH	OSC	1 month (2 measurements – 1 month apart)	24h	Daytime Night-time 24h All intervals not <30 mins	Consistency (median differnce between the 2 recordings); repeatability (2 x SD of the changes between the 2 recordings)	24h and Daytime ABPM was better than night-time BP (all were better than clinic)
Trazzi et al., 1991[600] case-series	34	HT	AUS	4 weeks (2 measuremnts – 4 weeks apart)	24h	Daytime (10 mins) Night-time (20 mins) 24h	Reproducibility of BP (between the 2 measurements over time)	There WAS NS differnce in SBP / DBP measurements 4 weeks apart (24h ABPM) 24h ABPM was more reporducible than office BP due to a larger number of measurements.

Reference / study type	Frequency of measurements							
Van der Steen et al., 1999[608] within-group comparison	45	HT	AUS device may not be truly ABPM	2-3 weeks (2 measuremnts – 2-3 weeks apart)	24h	Daytime (15 mins) Night-time (30 mins) 24h	Reproducibility of BP (between the 2 measurements over time)	There was poor reproducibility. 24h and daytime BP were better than night-time measurements.
Van Ittersum et al., 1995[609] retrospective case-series	20	HT and WCH	OSC	24h	24h	Daytime (15 mins) Night-time (20 mins) long fixed sleep period: waking 7am-10pm and sleeping 10pm-7am short fixed sleep period: waking 10am to 11pm and sleeping 1am-7am pts diary sleep period: actual sleep times 24h	Differnce in BP using long and short sleep periods vs actual sleep period (pts diary)	A short sleeping period gives accurate measures of blood pressure during sleep. The long sleeping period method should be avoided as it can overestimate BP during sleep.
Wallace et al., 2005[622] Retrospective comparative study with historical control	31	HT	AUS	2 separate weekdays, 2-3 days apart SAME group: monitoring began at same time of day	24h	SAME group: first reading 177-1900; OPP group: sessions randomised to begin in morning (0700-0900) or evening (1700-1900). D - 15 ± 5 minutes (0600-2200)	Reproducibility of BP variables: averages, 24-h, day-time, night-time, crest, trough, trough:crest (Intra-class correlation)	For SBP the ABPM was only reproducible when monitoring began at the same time of day and not when variables were measured at opposite times of day TrBP and average 24-h SBP were significantly higher when the monitoring session began in the morning compared with the evening Reproducibility of DBP was similar

Reference / study type	Frequency of measurements							
				OPP group: sessions randomised to begin in morning or evening		N - 30-45 ± 5 minutes (2200-0600)		between SAME and OPP conditions. Ambulatory BP variables were consistently higher when monitoring session began in the morning
Zakopoulos et al., 2001[654] case-series	25	HT	OSC	4 months Four times (four(intervals of 1 week each)	24h	Daytime Night-time 24h All: 15 min intervals and 1 hr intervals	Reproducibility over time (2 measurements, 2 weeks apart)	There was no difference between the 4 readings (over time) for 1h, 24h daytime or night-time (SBP or DBP)

NT = normotensives; HT = hypertensives; ICH = isolated clinic HT; AUS = auscultatory device; OSC = oscillometric device; D = daytime; N = night-time; TrBP = trough BP.

Table 23: Day and night intervals and results for prognostic studies assessing the optimal ABPM protocol

Reference / study type	N	Follow-up time	Day protocol (mins)	Night protocol (mins)	Best: day (D), night (N) or 24h
DAY and NIGHT and 24h					
Hansen et al., 2005[253]	1700	Up to 9.5 years	15	30	D + N + 24h
Kikuya et al., 2007[326]	5682	Median 9.5 years	15, 20, 30	20, 30, 45	All intervals are the same. D + N + 24h
Khattar et al., 2001[325]	688	Mean 9.2 years	60	60	D + N + 24h
NIGHT and 24h					
Suzuki et al., 2000[576]	324	Mean 51.5 months	30	30	N + 24h
DAY and 24h					

Reference / study type	N	Follow-up time	Day protocol (mins)	Night protocol (mins)	Best: day (D), night (N) or 24h
Gosse et al., 2001[237]	256	Mean 84 months	15	15 or 30	Morning was as good as D + 24h
Clement et al., 2003 [131]	2232	Median 5 years	30	<60	D + 24h
DAY and NIGHT					
Boggia et al., 2007[88]	7458 analysed	Median 9.6 years	15-30	30-60	D + N
Cipriano and Gosse et al., 2001[237]	741	Mean 7.4 years	15	30	D + N
Pickering et al., 2007[491]	8945	Mean 5.8 years	15-30	15-30	D + N
Bjorklund et al., 2004[77]	872	Mean 6.6 years	20	20	D + N
Li et al., 2008[363]	7458	Median 9.6 years	-	-	D + N
Metoki et al., 2006[405]	1542	Mean 10.6 years	30	30	D + N
NIGHT					
Fagard et al., 2005[211]	391	Median 10.9 years	15	30	N
Fagard et al., 2008[210]	302	Median 6.8 years	15-30	30-60	N
Sega et al., 2005[534]	2051	Mean 10.9 years	20	20	N
Ingelsson et al., 2006[284]	951	Up to 9.1years (mean range 0.1 – 11.4 years)	20 or 30	30 or 60	N
Staessen et al., 1999[557]	837	Mean 4.4 years	≤30	≤30	N
Dolan et al., 2005[178]	5292	Mean 7.9 years	30	30	N

D = daytime; N = night-time

Table 24: Day and night intervals and results for reliability/reproducibility studies assessing the optimal ABPM protocol

Reference / study type	N	Follow-up time	Day protocol (mins)	Night protocol (mins)	Best: day, night or 24h
DAY and NIGHT and 24h					
Zakopoulos et al., 2001[654]	25	4 months	15	15	D + N + 24h
DAY + 24h					
Van der Steen et al., 1999[608]	45	2-3 weeks	15	30	D + 24h
Suarez et al., 2003[573]	261	24h	20	30	D + 24h
Thijs et al., 1992[595]	102	1 month	≥30	≥30	D + 24h
NIGHT + 24h					
Palatini et al., 1994[473]	6461	3 months	10	30	N + 24h
Mansoor et al., 1994 [389]	25	Mean 23 months	15	15	N + 24h
Antivalle et al., 1990[46]	22	4 weeks	-	-	N + 24h
DAY + NIGHT					
Schillaci et al., 1994[527]	24	1 week	15	15 or 60	D + N (60minswas fine for night)
DAY					
Schwartz et al., 2000[530]	143	1 week	10	10	D
Schwartz et al., 2000[531]	240	1 week	10	10	D
Asagami et al., 1996[52]	64	1-2 years	30	60	D
≤24h					
Campbell et al., 2010[114]	72	2 years	15	30	24h
Stergiou et al., 2002[563]	133	2 work days	20	20	24h
Ernst et al., 2008[200]	1004 sessions	24h	20	30	6h ≈ 24h
>24h					
Hermida et al., 2002[271]	538	48 h	20	30	>24h
Calvo et al., 2003[111]	823	48 h	20	30	>24h
OTHER – INTERVALS SPECIFIED					
Sheps et al., 1994[538]	294	2 months	7.5, 20 or 30	-	20 and 30 mins are almost as good (for D)

Reference / study type	N	Follow-up time	Day protocol (mins)	Night protocol (mins)	Best: day, night or 24h
Lede et al., 1997[353]	49	24h	7.5, 30 or 60	7.5, 30 or 60	All times are similar
Mancia et al., 1992[386]	29	4 weeks	15	20	24h was better than hourly
Octavio et al., 2010[456]	450	24h	15 or 30	20 or 30	D had lower readings,or perform the same number of readings for 24h
Enstrom et al., 1996[196]	80	14 days	20	20	20, 30 or 60 mins are fine
Mar et al., 1998[390]	138	Not given	20	60	Increased measurements are better
Coats et al., 1992[133]	100	1 month	30	-	More day measurements are better
NOT SPECIFIED					
Trazzi et al., 1991[600]	34	4 weeks	10	20	-
Van Ittersum et al., 1995[609]	20	24h	15	20	-
Cuspidi et al., 2002[150]	208	3 weeks	15	20	-
Cuspidi et al., 2007[151]	611	1-4 weeks	15	20	-
Asmar et al., 2001[56]	30	1 month	15	30	-
Wallace et al., 2005[622]	31	2-3 days	15	30-45	-
Stenehjem et al., 2004[562]	75	4 weeks	20	30	-
Eguchi et al., 2010[190]	43	2 weeks	30	30	-
Shinagawa et al., 2002[541]	56	7 days	30	60	-
Murakami et al., 2004[416]	135	7 days	30	60	-
Mancia et al., 2004[387]	6000	1 week – 36 months	-	-	-
Musso et al., 1997[420]	40	3 months	15	30	-
Hernandez-del Rey et al., 2007[272]	611	48h	-	-	-

+ = 'or' ; D= daytime; N = night-time

7.4.1.2 Health economic evidence

No relevant economic studies were identified relating to ABPM measurement protocols.

7.4.1.3 Evidence statements – clinical

The 17 prognostic studies recommend the following regimens (as the best predictors of CV events) :

- All day measurements are needed (11 studies):
  - day and night– day and night measurements predict different outcomes (four studies)[88,363,405,491]
  - 24h, day and night were all good predictors of outcome (five studies)[77,237,253,325,326]
  - 24h and day were the best predictors of outcome (one study)[131]
  - 24h and night were the best predictors of outcome (one study)[576]
- Night BP only is sufficient (a good predictor of outcome) (six studies)[178,210,211,284,557534]
- A single BP measurement on rising is sufficient – this is as good as using the 24h or daytime mean for predicting outcome (one study)[237]
- Excluding the first two hours does not improve accuracy (one study)[557]
- SBP is sufficeint (a good predictor of outcome) but DBP is not (four studies: one study - SBP in >60 years, DBP<60 years)[77,237,325,534]
- DBP is sufficient (a good predictor of outcome) but SBP is not (two studies: one study - SBP in >60 years, DBP<60 years)[253,325]

Update 2011

The 36 reliability/reproducibility studies showed the following:

1. The optimum interval between measurements:

- Repeat ABPM over a short time interval (one study)[151]
- A greater number of readings/hr leads to an overestimation of BP: use the same number readings over 24 hours or use a time-weighted calculation of 24h BP (one study)[456])
- One reading per hour for night-time is equivalent to a 15 min interval for night-time BP (one study)[527]
- A short sleep period (1-7am) is more accurate than using a long sleep (10pm – 7am) (one study)[609]
- Daytime BP: taking more measurements is better than just one measurement (one study)[133]
- More measurements taken lead to less diagnostic error (one study)[390]
- Taking 2-3 readings/hr for 6 hours is almost as good as continuous measuring every 7.5 mins for daytime ABPM (one study)[538]
- There is no difference between taking 1, 2 or 3 recordings per hour, but using an interval of <30 mins is probably not so good for the patient (one study)[196]
- There was no differnce between taking one, two or seven recordings per hr. However a lower number of recordings is probably better for the patient and for the longevity of the equipment (one study)[353]

2. When to begin measurements:

- SBP – take measurements at the same time of day, not at opposite times (one study)[622]
- Mean 24h BP is higher if measurements are started in the morning rather than the evening (one study)[622]
- DBP – readings are not affected by the time of day that measurements are taken (one study)[622]

3. The best time of day to take measurements

- All day measurements are needed (16 studies):
  - One hour (one study), 24h, day, night (two studies)[150,654]
  - Day and night are best (two studies)[387,527]
  - Day and 24h are best – one study showed 24 hour BP was slightly better but using 6 hour BP was sufficient if patients are not able to tolerate / comply with 24 hours of measuring (four studies)[473,573,595,608]
  - Night and 24 hour measurements gave greater reproducibility (two studies)[46,389]
  - Daytime measurements are best (especially for men in one study; three studies)[52,530,531]
  - Mean 24 hour measurements are best (two studies)[114,563]
  - 24h BP is similar to 6 hour BP: but 6 hour BP may overestimate the value as it does not account for 24 hour BP variation (one study)[200]

4. How often to repeat measurements (over time)

- Twice - four weeks apart: there was decreased variability and WCH (one study)[562]; similar measurements were found at both times (one study)[600]
- Twice - two weeks apart (one study)[190]
- Twice (second) or successive times, or 48 hours – this accounts for: circadian variation, the ABPM effect (higher BP the first time ABPM is used), the pressor effect (lower BP readings achieved with consecutive measurements) - three studies[111,271,272]
- Four times (four weeks apart): there was high agreement between the measuerments but the fourth measurement gave a lower BP reading – therefore don't label someone as being HT on the basis of an initial ABPM (1 study)[420]
- Twice (three months apart): BP was SS lower in the day but not at night or over 24h BP measurement (one study)[473]
- The first day of monitoring gave higher BP readings than measurements of the other six days (one study) [541]

5. What day of week to perform ABPM:

- Monday morning BP surge is greater than on other days (one study)[416]
- The day of the week does not affect the pressor effect ie. lower BP values are obtained with consecutive measurements (two studies)[111,271]
- Daytime BP is lowest on Sunday; the optimal day-night ratio occurs on weekends (one study)[541]
- BP is higher on a work day (one study)[196]

7.4.1.4 Evidence statements – economic

- No relevant cost-effectiveness evidence was identified.

Update 2011

7.4.2 Home blood pressure measurement

Review question: In adults with primary hypertension, what protocol should be used when measuring blood pressureat home for treatment and diagnosis?

7.4.2.1 Clinical evidence

The literature was searched for all years and studies published since the original guideline (2003 onwards) were included. All study types were included, if the population did not consist of people who were exclusively diabetic or had CKD. Validation studies of home blood pressure machines were excluded.

Eight studies[53,191,203,302,315,316,464,565,611,612] were found that fulfilled the inclusion criteria and assessed what protocol should be used when measuring home BP in for the treatment and diagnosis of adults with primary hypertension. Two of the studies (1 study;[53,464] one study[315,316]) were each published as two separate papers reporting different assessment methods or outcomes, so these studies have only been counted once, however results from both papers are reported and referenced here.

The studies addressing the question were categorised into two different types:

- Prognostic studies (two studies; three papers)[53,53,565] – those that assess the prognostic significance of home blood pressure and the optimal schedule for measurement based on outcome data
- Reliability / reproducibility studies (seven studies; eight papers)[191,203,302,315,316,565,611,612] - those that assess any of the following - the optimal home blood pressure schedule based on:
  - the reproducibility of home blood pressure
  - its stability over time
  - its relationship (correlation) with ABPM values
  - its ability to identify people diagnosed with Hypertension / Normotension
  - its ability to identify treatment responders

Reliability /repeatability studies were deemed to be applicable to the question because they showed which aspects of the HBPM protocol were the most reliable, and therefore served as an indication of the 'best' / optimal HBP measurements to be taken.

All prognostic studies were found to be methodologically sound / have a low risk of bias (see quality assessment summary tables in appendix F).

Details of all the studies are included in Table 25 and Table 26. NOTE: all home blood pressure measurements in the studies were taken when the patient was seated.

NOTE: For the prognostic studies, the 'best method' was chosen as the method of measuring BP that best predicted (ie. statistically significant predictors and higher HR values) clinical outcomes (after adjustment for covariates in multivariate analyses). For the 'reproducibility/reliability studies' the 'best method' was chosen as the the method / protocol of measuring blood pressure that was the most reliable or repeatable.

7.4.2.2 Economic evidence

No relevant economic studies were identified relating to HBPM measurement protocols.

7.4.2.3 Evidence statements – clinical

The studies showed the following:

Update 2011

The optimum number of readings to take (seated)

- Only one reading is sufficient (two studies)[123,283]
- Two or >two readings are needed: (two studies) [203,302]
- Three readings are needed: (two studies)[191,612]

The optimum interval between measurements

- Take a one minute interval, not every ten seconds (one study)[191]

Should any readings be discarded?

- The first and second reading are both fine (one study)[565]
- Discard the first reading (three studies, four papers) [315,316,565,568]
- Discard day one readings (one study)[565]
- Discard day one readings (two studies) [565,568]
- Keep day one readings (one study)[302]
- Discard day one and daytwo readings (one study)[612]

The best time of day to take measurements

- Morning and evening are best (two studies, three papers)[53,464,565]
- Morning only is sufficient (one study)[283]
- Morning and evening are best (one study) [302]

How many days to take measurements

- Three days (four studies)[123,228,283,568]
- Four or more days (one study)[302]
- Five or more days (two studies)[203,612]
- Seven days (one study, two papers) [315,316]

Update 2011

Table 25: Study details and overall results for prognostic studies assessing the optimal home blood pressure protocol

	Frequency of measurements							
Reference / study type	N	Population	Device	Consecutive readings	Days	Time of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
Stergiou et al., 2010[565] Within-group comparison (DIDIMA STUDY)	665	HT	AOD	2	3	M – seated, after 5 mins rest E – seated, after 5 mins rest	CV events (fatal / non-fatal)	more readings averaged (from 1-12) increased the prognostic ability. Take the 1st or 2nd readings; morning or evening are equally good; discard 1st day
Ohkubo ey al., 2004 and Asayama et al., 2006[53,464] Within-group comparison (OHASAMA STUDY)	1766	General population (HT and NT)	SOD	≥2	4 weeks	M – seated, within 1hr waking E – seated, just before going to bed	Stroke	Morning and evening are equally good; there is no threshold (1-14 measurements) – but take as many measurements as possible (preferably >14 measurements)

NT = normotensives; HT = hypertensives; AOD = automatic oscillometric device; SOD = semiautomatic oscillometric device; E = evening; M = morning; MS = mercury sphygmomanometer

Update 2011

Reliability / reproducibility studies

Table 26: Study details and results for reliability/reproducibility studies assessing the optimal home blood pressure protocol

	Frequency of measurements							
Reference / study type	N	Population	Device	Consecutive readings	Days	Time of measurement	Mathematical method	Proposed number of measurements (authors' conclusions)
Verberk et al., 2005[611]	MODERATE QUALITY systematic review of 4 within-group comparison observational studies (studies below)							
SR study 1: Celis et al., 1997[123] Within-group comparison	74	Elderly HT	MS	1	100	M – lying in bed M – after 10 mins standing E – standing before going to bed E – lying in bed for 10 mins	Variability (SD); t-test	Take one reading / day for 3 consecutive days
SR study 2: Stergiou et al., 1998[568] Within-group comparison	189	HT	AOD	2	3 workdays	M (6 – 10am) E (5 – 11am)	Test-retest variability (SD), correlation with ABPM	Take the average of the 2nd and 3rd working day
SR study 3: Garcia-Vera et al., 1999[228] Within-group comparison	48	HT	SOD	1	8	M E At work	Test-retest variability (SD), Generalisability theory	Take one reading at work and one at home for 3 consecutive days for reliable estimates for 2 months
SR study 4: Imai et al., 1993[283]	871	NT and HT	SOD	1	28	M - <1h after awakening	Variability (SD)	Take one reading/day in the morning for 3 consecutive days

	Frequency of measurements							
Within-group comparison								
Other studies								
Stergiou et al., 2010[565] Within-group comparison (DIDIMA STUDY)	665	HT	AOD	2	3	M – seated, after 5 mins rest E – seated, after 5 mins rest	Variability (SD)	More readings averaged reduced variability (from 1-12); discard the first day (as this gave unstable values)
Kawabe et al., 2005 and 2008[315,316] Within-group comparison	700	General population (HT and NT)	SOD	3	7	M – seated, within 1hr waking (before breakfast and medication, after urination) E – seated, before bed (not within 30 mins bathing)	Correlation with clinical diagnosis of HT / NT	Take 7 day measurements for diagnosis (more pronounced using 1st vs. mean 2nd and 3rd measurements or evening BP): this led to a diagnosis of HT more frequently, and NT less frequently
Eguchi et al., 2009[191] Cohort study	57	Known or suspected HT	AOD	3	8 weeks (4days/ week)	M – 10sec or 1 min intervals (randomised to eaither) E - 10sec or 1 min intervals (randomised to either)	Correlation with ABPM and Office BP	Take a 1 min interval of 3 measurements (this gave a better estimate of average daytime ABPM level; 10sec intervals gave higher readings than 1 min)
Johansson et al., 2010[302] Cohort study	464	HT	AOD	2	7	M – 1-2 min intervals E – 1-2 min intervals Mean number 27.5	Correlation with ABPM	Take duplicate measurements, at least 4 days (evening and morning); don't discard 1st day measurements (there was NS difference in

	Frequency of measurements							
								correlation with ABPM when the 1st day was excluded)
Ewald et al., 2006[203] Post-hoc analysis of RCT (OLMETEL STUDY): thus cohort	53	HT	AOD	≥1	12 weeks	M E	Identification of treatment responders (sensitivity/ specificity); response to Treatment	Take at least 2 measurements/day (this gives a better response to treatment); take at least 5 readings/week (this was the threshold for correctly predicting response to treatment)
Verberk et al., 2006[612] Post-hoc analysis of RCT (HOMERUS STUDY) thus cohort	216	HT	AOD	3	7	M – seated, after 5 mins rest (1 min interval between measurements) E – seated, after 5 mins rest (1 min interval between measurements)	Correlation with ABPM	Take a minimum of 5 days; 3 consecutive morning and evening measurements; discard 1st two days and 1st reading of each triplicate (for calculating mean values) – this is a time consuming protocol, so use it for a decision to start or change treatment, or for special patient groups

NT = normotensives; HT = hypertensives; AOD = automatic oscillometric device; SOD = semiautomatic oscillometric device; E = evening; M = morning; MS = mercury sphygmomanometer

7.4.2.4 Evidence statements – health economic

- No relevant cost-effectiveness evidence was identified.

7.5 Link from evidence to recommendations

Clinic blood pressure measurement (CBPM) on repeated clinic visits has long been the standard method for the diagnosis of hypertension and subsequent monitoring blood pressure control on treatment in clinical practice. The increased availability of automated blood pressure measuring devices has led to their increased use in clinical practice and clinical studies. Home blood pressure measurement (HBPM) or ambulatory blood pressure measurement (ABPM) both provide multiple measurements of blood pressure away from the clinic setting in a more usual environment.

This raised the question as to whether ABPM and/or HBPM may provide better prognostic information with regard to the relationship between blood pressure and clinical outcomes. The predictive value for clinical outcomes of blood pressure measurement based on clinic blood pressure measurement (CBPM), home blood pressure measurement (HBPM) and ambulatory blood pressure measurement (ABPM) were compared. Three pooled analyses were identified. [210,254,326] The clinical outcomes of interest were mortality, stroke, MI, heart failure, diabetes, vascular procedures, hospitalisation for angina, and other major adverse cardiac and cerebrovascular events (MACCE). All other studies identified were observational and comprised nine prognostic studies[77,159,178,210,253,254,284,326,404] that compared CBPM with ABPM, five studies[86,211,438,534,564] that compared CBPM with HBPM and two studies[211,534] that compared all three methods for blood pressure measurement. The studies included adult patients with normal blood pressure, suspected hypertension and known hypertension across a wide age range (30 to 71 years). All of the studies were deemed to have a low risk of bias.

The results of this analysis showed that when CBPM was compared to ABPM in 8 out ofthe 9 studies[77,159,178,210,253,254,284,404] ABPM was superior to CBPM at predicting clinical events there was no difference in one study. [326] ABPM can also provide data on the 24 hour average BP, daytime average BP and night-time average BP. The GDG noted that in some studies the daytime ABPM average was the most predictive of clinical outcomes, whereas in others the ABPM night-time average was the most predictive but there was no conclusive evidence suggesting a preference for day versus night-time averages. The GDG noted that from a practical perspective, when comparing different methods, ABPM daytime averages are preferred because they allow easier comparison with CBPM and HBPM averages which are also usually taken during the daytime.

There was less data comparing CBPM with HBPM in only three studies. [86,438,564] HBPM was superior to CBPM at predicting clinical outcomes in two of these studies[86,438] and no difference between the methods was noted in one small study. [564]

All three blood pressure measurement methods were compared with each other in only two studies in one of which there was no difference in their predictive value and in the other, ABPM and HBPM were similar to each other but superior to CBPM at predicting clinical outcomes.

Taken together, the GDG concluded that the analysis of these studies showed that CBPM was never superior to ABPM or HBPM at predicting clinical outcomes. Furthermore, ABPM was never inferior to other methods and was most often the best predictor of clinical outcomes. HBPM also appeared superior to CBPM at predicting clinical outcomes but there was less data with HBPM when compared ABPM. The GDG concluded that multiple blood pressure measurements away from the clinic setting are the best predictor of blood pressure-related clinical outcomes and that to date, studies with ABPM provided the most robust evidence. The GDG considered the reasons for this and noted that this in part, could relate to the fact that ABPM and HBPM are providing more measurements and more representative data of a person's usual blood pressure away from the clinic setting. It could

Update 2011

also relate to the fact that some people diagnosed as hypertensive based on their CBPM in reality have much lower blood pressures according to their ABPM or HBPM averages, i.e. white coat hypertension or a white coat effect, and consequently are at much lower risk of clinical outcomes than their CBPMs suggest.

That said, the GDG felt that more prospective data from epidemiological studies and clinical intervention trials, comparing the prognostic value of CBPM versus HBPM versus ABPM should be undertaken to better inform this prognostic relationship and better define treatment thresholds and targets according to daytime versus night-time averages and the optimal protocols for HBPM and ABPM measurement.

As well as looking at prognostic studies the GDG reviewed studies that compared the sensitivity and specificity of CBPM, HBPM and ABPM in order to address the important question of which is the best method to measure blood pressure to diagnose hypertension. A recent systematic review and meta-analysis [275] examined the relative effectiveness of CBPM or HBPM versus ABPM for establishing the diagnosis of hypertension. ABPM was used as the reference standard for this analysis on the basis that: i) it is a superior predictor of clinical outcomes (see above); and ii) ABPM is the test resorted to in clinical practice when there is uncertainty about the diagnosis of hypertension, thus, ABPM is the de facto reference standard for confirming the diagnosis of hypertension in clinical practice. Thus, the GDG agreed that it was appropriate to adopt ABPM as the reference standard for the analysis of the three different BP monitoring modalities to establish the diagnosis of hypertension. This systematic review included 20 studies (N=5863). For the purposes of the analysis, an ABPM daytime average of 135/85mmHg was taken as the threshold for the diagnosis of hypertension and the performance of CBPM or HBPM versus this reference standard was compared. The CBPM and HBPM thresholds for diagnosis of hypertension were 140/90mmHg and 135/85mmHg respectively. Nine studies that used these thresholds were meta-analysed.

Update 2011

The meta-analysis found that, compared with ABPM, CBPM had a mean sensitivity of 74.6% (95% CI, 60.7 to 84.8) and specificity of 74.6% (47.9 to 90.4) for the diagnosis of hypertension and HBPM had a mean sensitivity of 85.7% (78.0 to 91.0) and specificity of 62.4% (48.0 to 75.0). Neither differences in sensitivity or specificity between HBPM and CBPM were significant. In this context, “sensitivity” is the number of people who are diagnosed with hypertension according to CBPM or HBPM as a proportion of all those who actually have hypertension as defined by the ABPM reference standard. “Specificity” is the number who test negative for hypertension according to CBPM or HBPM as a proportion of all those that actually do not have hypertension as defined by ABPM. Thus based on the specificity results from the primary analysis of the meta-analysis CBPM will misdiagnose 25% of people who do not have hypertension as hypertensive; with HBPM this figure is 38%. In addition, based on sensitivity, with CBPM 25% of people with hypertension will mistakenly be diagnosed as not hypertensive; with HBPM that figure is 14%.

However, the studies included in the meta-analysis for CBPM were in a range of populations and a sensitivity analysis was also reported which included only studies with a mean BP close to or above the diagnostic threshold. This is relevant because sensitivity and specificity vary with disease prevalence – while it is often asserted that sensitivity and specificity are independent of disease prevalence it has been demonstrated that when categorisation is based on a continuous trait, as with hypertension, this is not the case. [98] In this analysis CBPM sensitivity increased to 85.6% (CI 81.0 to 89.2) and specificity decreased to 45.9 (CI 33.0 to 59.3). The HBPM studies were all in this restricted population and so the analysis for HBPM remained the same. With this restricted analysis CBPM and HBPM are virtually identical in terms of sensitivity, but HBPM was now more specific than CBPM. This sensitivity analysis was considered by the GDG to be more relevant to the guideline as screening the general population is outside of its scope.

The GDG also considered a sensitivity analysis looking at the impact of the diagnostic threshold on the performance of the different diagnostic methods. Perhaps not surprisingly, the specificity of

CBPM for diagnosing hypertension improved when the CBPM blood pressure threshold for diagnosis is increased, i.e. those defined as hypertensive when their CBPM is higher are more likely to be hypertensive according to ABPM. However, the corollary was also true, i.e. that the accuracy of diagnosis of hypertension when comparing CBPM with the ABPM reference standard is most uncertain in those who blood pressure is close to the CBPM diagnostic threshold of 140/90mmHg.

This detailed analysis suggested that the current practice of using CBPM to define hypertension will lead to drug treatment being offered to a substantial number of people who are normotensive according to ABPM. The GDG recognised that these data have profound implications for the diagnosis of hypertension. Firstly, they suggest that some patients randomised and treated in clinical outcome trials on the basis of their CBPM, may not have been hypertensive, potentially diluting and underestimating the true benefits of treatment in those who were hypertensive. Secondly and perhaps more importantly, these findings suggest that the current practice of using a series of CBPM alone for the diagnosis of hypertension can lead to inaccurate diagnosis.

Screening for hypertension was outside the scope of this guideline. However, the GDG agreed it is not practical to use ABPM or HBPM as a screening tool, despite them potentially offering greater accuracy than CBPM. The working assumption was that CBPM would still be used for screening patients and that the key decision that remained was how the diagnosis should be confirmed.

Taking into account the prognostic data and the meta-analysis of sensitivity and specificity, the GDG agreed that ABPM appeared to provide the best method of confirming a diagnosis of hypertension. The GDG also considered that a change in practice as profound as this required clear evidence that ABPM would not only be a more effective means of diagnosis but also, a more cost-effective means of establishing the diagnosis of hypertension.

Update 2011

The GDG agreed the most practical method to diagnose hypertension would be to use CBPM as a screening tool and that those people with a CBPM ≥140/90mmHg measured using the recommended standardised conditions, should then be offered ABPM to confirm or refute the diagnosis of hypertension based on a diagnostic threshold of an ABPM daytime average of ≥135/85mmHg.

The GDG reviewed the data regarding the number of measurements required to establish the ABPM daytime average blood pressure. The number of measurements taken during prognostic studies varied from every 15 minutes to every hour during the daytime. The GDG concluded that two measurements per hour should be taken during normal waking hours, e.g. 08.00hrs to 22.00hrs and that a minimum of 14 readings should be used to derive the daytime average blood pressure. This means that patients would not necessarily need to wear the ABPM monitor for a full 24hrs, depending on the time the monitoring session was initiated. For practical reasons and efficiency in use of the monitors, not every monitoring session will begin at 08.00hrs and some patients will start their session in the afternoon. In these patients continuation of monitoring for 24hrs will be required to capture the “normal waking hours” across a spread of 24hrs. Consideration would also need to be given to shift and night workers whose “normal waking hours” will differ.

When ABPM is poorly tolerated, inconvenient for the patient, or the patient does not want to undergo ABPM, HBPM should be offered to establish the diagnosis of hypertension. HBPM may also be preferred to monitor the control of blood pressure in treated patients with a significant white coat effect, or where this is the patient’s preference for monitoring their blood pressure control (see section 9.6 – monitoring blood pressure control). Regarding use of HBPM, the GDG noted that a range of strategies had been used in studies to establish the HBPM average blood pressure reading. The optimal timing of measurements and the number of measurements required was reviewed. The GDG concluded that a standardised approach was needed and recommended that patients should measure their blood pressure whilst seated and relaxed and that at each measurement session, two blood pressure measurements should be taken, at least one minute apart, in the morning and the evening. The recording should continue for at least 4 days and ideally 7 days. The readings on the

first day should be discarded and the readings for all remaining days should be used to establish the HBPM average.

The GDG discussed a number of caveats to recommendations regarding the use of ABPM to establish the diagnosis of hypertension. Some people may have severe hypertension at screening with CBPM (i.e. systolic BP ≥180mmHg and/or diastolic BP ≥110mmHg) and in such cases, clincians should not delay treatment whilst awaiting the results of ABPM – in these cases, the subsequent ABPM will serve to confirm the diagnosis and severity of the hypertension; ii) some people will have atrial fibrillation or other significant pulse irregularity that might render automated BP monitoring (ABPM and HBPM) inaccurate or impossible, in such cases manual auscultation of blood pressure in the clinic would be the only alternative; and iii) some people may not tolerate ABPM – in these people HBPM can be used an alternative on the grounds of better prognostic value and better specificity for hypertension. However, the GDG noted that based on current data, HBPM could not be considered equivalent to ABPM with regard to accuracy of diagnosis and emphasised that that ABPM is the preferred means of confirming or refuting the diagnosis of hypertension.

The GDG also discussed whether ABPM was necessary for confirmation of diagnosis in all patients, or whether it could be used more selectively, e.g. only in those close to the diagnostic threshold. The GDG noted that even in people with stages 2, or resistant hypertension, a significant white coat effect can occur, which would be important to document to facilitate decisions about the best strategy for subsequent monitoring of blood pressure control on treatment. The need for ABPM for people with evidence of target organ damage, e.g. LVH or albuminuria was also discussed by the GDG. It was noted that target organ damage may not always be due to hypertension, even when the two appear to co-exist. For example, the presence of ECG LVH in a patient subsequently shown not to be hypertensive on ABPM would prompt consideration of alternative causes for the ECG abnormality. Furthermore, some people have higher blood pressures away from the clinic (so called masked hypertension) and ABPM could reveal much worse blood pressure control levels than apparent in the clinic – this would be important to know. Finally, the GDG noted that people with target organ damage are a higher risk group and the best possible assessment of their blood pressure level when initiating treatment seemed appropriate, mindful of the better prognostic value of ABPM when compared to CBPM. Overall, the GDG could not identify a strong evidence-base or clinical argument against the use of ABPM to improve the accuracy of diagnosis of hypertension, which for many people results in exposure to life-long treatment. The residual concern in the GDG deliberations was not whether this was the right thing to do but rather, whether the strategy would be cost-effective (see below) and whether the practical challenges of implementing an ABPM-based strategy for diagnosis could be overcome.

The GDG were also mindful of the concerns about the accuracy of automated devices for measuring blood pressure in people with atrial fibrillation and considered this an important area for technology development to see if such problems can be overcome. The GDG noted that In some patients with chronic atrial fibrillation with good rate control, automated devices can function effectively but concluded that until automated devices, validated for routine clinical use are available for people with atrial fibrillation, manual auscultation over the brachial artery is the only practical alternative to measure blood pressure in people with significant cardiac rhythm irregularity.

As noted above, evaluation of the effectiveness of different methods for measuring blood pressure to establish the diagnosis of hypertension suggested that ABPM would be the most accurate method, avoiding clinical disease labelling and treatment of people who were not truly hypertensive according to their ABPM average blood pressure. The GDG noted, however, that despite the clear effectiveness of ABPM in improving the specificity and sensitivity of diagnosis for hypertension, ABPM devices are considerably more expensive than simple desk top blood pressure monitors and the GDG recognised the obvious potential cost implications of recommending the more widespread use of ABPM for the routine diagnosis of hypertension. The GDG thus identified modelling of the cost effectiveness of different methods for blood pressure measurement as the highest priority for economic analysis as a

prior literature search had identified no published work addressing this key question in sufficient detail.

The cost-effectiveness analysis compared CBPM, HBPM or ABPM for confirming a diagnosis in people with suspected hypertension. The GDG spent considerable time discussing the various factors that would potentially impact on the costs of using ABPM and also HPBM as an alternative to current standard practice of using a series of CBPM readings to confirm the diagnosis of hypertension. These included the number and type of healthcare appointments required to confirm a diagnosis with each method, the failure rate associated with ABPM and HBPM and the number of uses of the devices each year. As well as initial diagnosis costs, the analysis took into account downstream costs including hypertension treatment, checkups and development of cardiovascular disease. Health benefits were quantified in terms of QALYs. A summary of the cost-effectiveness analysis is provided in Section 7.3 with full details available in Appendix J: Cost-effectiveness analysis.

Contrary to what might have been expected and mindful of the higher costs of ABPM devices, the cost-effectiveness analysis found ABPM to be the most cost effective option for the diagnosis of hypertension across a range of age groups in both men and women. Remarkably, in most groups ABPM was found to actually improve health (increased QALYs) and reduce costs, suggesting that use of ABPM for the diagnosis of hypertension has the potential to be cost saving for the NHS. The GDG noted that this conclusion was robust to a wide range of sensitivity analyses including those varying the cost of ABPM, the failure rate for ABPM, the level of CVD risk and the prevalence of true hypertension in the population. Unsurprisingly, the conclusion was sensitive to assumptions regarding the accuracy of diagnosis with each method, e.g. when the other methods (CBPM or HBPM) were assumed to be as accurate as ABPM – which the effectiveness analysis suggests they are not. The conclusion was also sensitive to the assumption that people who were not hypertensive but were treated did not receive benefits from treatment, which they might. On the other hand, the analysis did not model the impact of unnecessarily treating people who are not hypertensive and the costs, inconvenience, adverse effects of treatment and impact disease labelling may have on individual patients incorrectly diagnosed as hypertensive.

Update 2011

The extensive GDG deliberations on the cost effectiveness analysis concluded that the use of ABPM for the routine diagnosis of hypertension, using a daytime average threshold of ≥135/85mmHg, in people who have previously been identified as potentially hypertensive at a threshold of ≥140/90mmHg using a CBPM, would be both cost-effective and in almost all cases, cost saving for the NHS, as well as improving the accuracy of diagnosis for patients. The GDG thus recommended that ABPM should be implemented for the routine diagnosis of hypertension in primary care.

The GDG also discussed other important aspects when considering the diagnosis of hypertension including: i) whether there might be an underlying secondary cause for the elevated blood pressure that might warrant referral for specialist evaluation; ii) whether the patient might have accelerated hypertension requiring emergency in-patient care; and iii) the need to assess for the presence of target organ damage and formally assess cardiovascular disease risk.

The GDG recognised and discussed the considerable challenges for implementation of this recommendation. Sufficient numbers of validated ABPM devices would need to be procured and adequately maintained. Staff would need to be trained in their use and the interpretation of data generated by the ABPM reports. The existing recommendations on use of appropriate cuff size (see section 6.2) and recognition that automated measurements may be unreliable or impossible in people with significant pulse irregularity (e.g. atrial fibrillation) (see section 6.5) still apply. Some people will not tolerate ABPM and in others the procedure will fail. The GDG modelled an anticipated failure rate of 5%, ranging to a more extreme failure rate of 10% in sensitivity analyses in the cost effective analysis and ABPM remained the most cost effective option for the diagnosis of hypertension. In those unable to tolerate or unwilling to undergo ABPM, the GDG recommended HBPM as an alternative means of confirming the diagnosis of hypertension with emphasis that ABPM

is the preferred method. For those with significant pulse irregularity, ABPM and HBPM are likely to be unreliable methods for blood pressure measurement and a series of CBPM readings via manual auscultation (see section 6.1.1) remains the only suitable option.

Finally, the GDG discussed the practicalities of implementing this strategy for the diagnosis of hypertension. That implementation of this strategy is a challenge is acknowledged. Presently, some but not all primary care practices have access to ABPM devices, others do not. Some practices access ABPM through referral to secondary care. Few practices presently have sufficient numbers of devices to increase their use as required by this guideline recommendation. The GDG discussed the fact that models of future care cannot just be based on what we do now and considered it likely that alternative models of service provision would emerge, reflecting first and foremost what was best and most convenient for patients and local demand. The GDG considered it inevitable that the costs of ABPM devices will fall as demand for their use increases and that different models of ABPM provision will evolve over time to meet local demand.

7.6 Recommendations

8. When considering a diagnosis of hypertension, measure blood pressure in both arms:
   - If the difference in readings between arms is more than 20 mmHg, repeat the measurements.
   - If the difference in readings between arms remains more than 20 mmHg on the second measurement, measure subsequent blood pressure in the arm with the higher reading. [new 2011]

9. If the clinic blood pressure is 140/90 mmHg or higher, offer ambulatory blood pressure monitoring (ABPM) to confirm the diagnosis of hypertension. [new 2011]

10. If a person is unable to tolerate ABPM, home blood pressure monitoring (HBPM) is a suitable alternative to confirm the diagnosis of hypertension. [new 2011]

11. If the person has severe hypertension, consider starting antihypertensive drug treatment immediately, without waiting for the results of ABPM or HBPM. [new 2011]

12. While waiting for confirmation of a diagnosis of hypertension, carry out investigations for target organ damage (such as left ventricular hypertrophy, chronic kidney disease and hypertensive retinopathy) (see 21) and a formal assessment of cardiovascular risk using a cardiovascular risk assessment tool (see 20). [new 2011]

13. If hypertension is not diagnosed but there is evidence of target organ damage such as left ventricular hypertrophy, albuminuria or proteinuria, consider carrying out investigations for alternative causes of the target organ damage. [new 2011]

14. If hypertension is not diagnosed, measure the person's clinic blood pressure at least every 5 years subsequently, and consider measuring it more frequently if the person's clinic blood pressure is close to 140/90 mmHg. [new 2011]

15. When using ABPM to confirm a diagnosis of hypertension, ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00). Use the average value of at least 14 measurements taken during the person's usual waking hours to confirm a diagnosis of hypertension. [new 2011]

16. When using HBPM to confirm a diagnosis of hypertension, ensure that:

Update 2011

- for each blood pressure recording, two consecutive measurements are taken, at least 1 minute apart and with the person seated **and**
- blood pressure is recorded twice daily, ideally in the morning and evening **and**
- blood pressure recording continues for at least 4 days, ideally for 7 days.

Discard the measurements taken on the first day and use the average value of all the remaining measurements to confirm a diagnosis of hypertension. [new 2011]

17. Refer the person to specialist care the same day if they have:
    - accelerated hypertension, that is, blood pressure usually higher than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage **or**
    - suspected phaeochromocytoma (labile or postural hypotension, headache, palpitations, pallor and diaphoresis). [2004, amended 2011]

18. Consider the need for specialist investigations in people with signs and symptoms suggesting a secondary cause of hypertension. [2004, amended 2011]

Update 2011

8 Assessing cardiovascular risk, target organ damage and secondary causes of hypertension

There are four key objectives in the assessment of a person with suspected hypertension; i) to confirm whether or not blood pressure is elevated (see section xxx); ii) to document the presence or absence of blood pressure related target organ damage damage (e.g. left ventricular hypertrophy, hypertensive retinopathy, increased albumin:creatinine ratio); iii) to evaluate the person's cardiovascular risk either due to established cardiovascular disease or high cardiovascular disease risk states (e.g. diabetes or CKD), or by calculation of their 10 year CVD risk estimate (ref section and NICE guidance), and iv) to consider whether their may be secondary causes for the hypertension.

The risk of clinical events associated with hypertension is not only determined by the level of blood pressure but also by; i) the presence of target organ damage; ii) the presence of established cardiovascular disease (iscahemic heart disease or heart failure, cerebrovascular disease, peripheral vascular disease) or concomitant disease associated with high cardiovascular disease risk, e.g. diabetes or CKD; or iii) the calculated cardiovascular risk (estimated from factors such as age, gender, smoking history, etc.). Therefore, routine assessment of simple markers of target organ damage, a clinical history and examination to identify associated cardiovascular disease and when indicated, cardiovascular risk calculation, all form part of the routine assessment of a patient with suspected or confirmed hypertension. This assessment will also help clinicians to decide the appropriate blood pressure threshold at which to consider drug therapy for the treatment of hypertension and whether any additional therapies to reduce cardiovascular disease risk (e.g. statins and antiplatelet therapy) should also be offered to the patient.

The clinical history, examination and routine blood and urine tests will also alert the clinician to possible secondary causes of hypertension, some of which are potentially life threatening (e.g. phaeochromocytoma), and others which might be amenable to potentially curative interventions (e.g. Conn's adenoma, fibromuscular dysplasia).

8.1.1 Hypertension and cardiovascular disease

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[361]. 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[379]. 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[135]. 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.

8.2 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, and eGFR
- Blood glucose
- Serum total and HDL cholesterol
- 12 lead electrocardiogram.

Update 2011

8.2.1 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 more sensitive test for urine protein is available by requesting the local chemical biochemistry laboratory to assay microalbumin in a random specimen of urine. For further information refer to NICE Clinical Guideline 73.

8.2.2 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. 12 lead electrocardiogram. Refer to NICE guidance on Diabetes (Clinical Guidelines 15 and 87).

From an ECG 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 cardiovascular risk calculators. An echocardiogram might be considered, to confirm or refute the presence of LVH suggested by ECG findings.

8.3 Cardiovascular Risk Assessment

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 (See NICE Lipids Modification, CG67). 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[23]. Since several risk factors are potentially modifiable, an important aspect is which of these to address and in what order.

8.4 Secondary Hypertension

- An identifiable cause of hypertension is more likely when hypertension occurs in younger patients (less than 40 years of age), worsens suddenly, presents as accelerated hypertension (BP more than 180/110 mmHg with signs of papilloedema and/or retinal haemorrhage) or responds poorly to treatment. [III]
- An elevated creatinine or reduced eGFR indicates 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 ACEi or ARB 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 10% of hypertension cases, the most common cause being chronic renal disease. Other principal identifiable causes are renovascular hypertension, pheochromocytoma, Cushing syndrome, and primary aldosteronism. Signs and symptoms of the main causes of secondary hypertension and available diagnostic tests are summarised below, although many of these techniques are not provided in primary care but accessed through specialist referral. 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.

8.4.1 Renal and renovascular disease

Chronic kidney disease is the most common identifiable cause of hypertension occurring in 2% to 5% of patients[182]. The British National Formulary advises against routinely using ACEi or ARBs in patients with known or suspected renovascular disease[26].

Signs and symptoms indicating that hypertension may be associated with renal disease are: young onset of hypertension (before 40 years of age), sudden onset of hypertension or progressive deterioration in middle age, accelerated 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 reduced eGFR, systolic or diastolic bruit[467], drug resistant hypertension or increased creatinine with ACEi or ARB, 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, 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)[182,505].

Renal disease may be diagnosed by elevated serum levels of urea or creatinine (found by a blood test) or reduced eGFR . Specialist investigation includes magnetic resonance angiography for imaging of the kidneys, and duplex ultrasound scanning directly measuring the size of the kidneys[467], [35]. Test sensitivities have been reported for these investigations[182].

8.4.2 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 or 24 hour urine collections for metadrenaline and normetadrenaline [22,250]. Following positive findings two types of imaging study may be used to locate the tumour: metaiodobenzyl-guanidine (MIBG) scintigraphy and computed tomography (CT).

8.4.3 Hyperaldosteronism (primary aldosteronism)

Aldosterone is a hormone that regulates sodium and water balance. Hyperaldosteronism can due to bilateral adrenal hyperplasia or Conn's adenoma occurring in 0.01% to 0.03% of patients[182,570]], although its prevalence is contested and may be much higher [[364].

Signs and symptoms include sodium retention, and hypokaelaemia leading to heart rhythm irregularities and possibly muscle weakness. The hypokaelaemia may only occur when diuretic-induced hypokalaemia is not explained by natural causes[467].

Measurement of plasma aldosterone levels and plasma renin activity as the aldosterone:renin ratio may be used to detect primary aldosteronism[250]. As with any laboratory test, standardisation of laboratory assays is important.

8.4.4 Cushing's syndrome

Cushing's syndrome is a syndrome generated by excess glucocorticoids. Cushing's Disease specifically refers 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[469]. 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[469].

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[217,437].

8.5 Other identifiable causes of hypertension

8.5.1 Hypothyroidism

Hypothyroidism is 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[185,329,509]. 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[75,572]. Hypothyroidism is diagnosed by measuring thyroid stimulating hormone levels[467].

8.5.2 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)[314]. Hyperthyroidism is diagnosed by measuring thyroid stimulating hormone levels[467].

8.5.3 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, nocturia and morning headaches. The main diagnostic technique is a polysomnograph to monitor normal and abnormal physiological activity during sleep [250,467]. Please refer to NICE Technology Appraisal 139 (www. http://guidance.nice.org.uk/TA139/Guidance/pdf/English) for guidance on continuous positive airway pressure (CPAP).

8.5.4 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[467].

8.5.5 Acromegaly

Acromegaly is due to excess production of growth hormone. Signs and symptoms of acromegaly include hypertension, cardiomegaly, enlarged facial features, enlarged jaw, headache and arthralgia, hypertrichosis, excessive sweating, tiredness, weakness, somnolence and impaired glucose tolerance[360]. Acromegaly is diagnosed by evidence of increased growth hormone secretion[360].

8.5.6 Drugs

A number of medications are known to cause raised blood pressure. These include decongestant found in inhaled cold remedies, may raise diastolic blood pressure[517,547]. Oral contraceptive pills containing oestrogen may cause small, and occasionally pronounced, rises in blood pressure. In rare cases accelerated hypertension may occur[535]. Other drugs that may raise blood pressure include immunosuppressive agents, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, weight loss agents, stimulants (for example, cocaine), mineralocorticoids, antiparkinsonian agents, monoamine oxidase inhibitors, anabolic steroids, sympathomimetics[467].

8.6 Recommendations

For NICE guidance on the early identification and management of chronic kidney disease see 'Chronic kidney disease' (NICE clinical guideline 73, 2008).

19. Use a formal estimation of cardiovascular risk to discuss prognosis and healthcare options with people with hypertension, both for raised blood pressure and other modifiable risk factors. [2004]

20. Estimate cardiovascular risk in line with the recommendations on Identification and assessment of CVD risk in 'Lipid modification' (NICE clinical guideline 67)[h]. [2008]

21. For all people with hypertension offer to:
    - test for the presence of protein in the urine by sending a urine sample for estimation of the albumin:creatinine ratio and test for haematuria using a reagent strip
    - take a blood sample to measure plasma glucose, electrolytes, creatinine, estimated glomerular filtration rate, serum total cholesterol and HDL cholesterol
    - examine the fundi for the presence of hypertensive retinopathy
    - arrange for a 12-lead electrocardiograph to be performed. [2004, amended 2011]

Update 2011

8.7 Research recommendations

2. In people aged under 40 with hypertension, what is the most accurate method of assessing the lifetime risk of cardiovascular events and the impact of therapeutic intervention on this risk?

Current short-term (over 10 years) risk estimates are likely to substantially underestimate the lifetime cardiovascular risk of younger people (aged under 40) with hypertension, because short-term risk assessment is powerfully influenced by age. Nevertheless, the lifetime risk associated with untreated stage 1 hypertension in this age group could be substantial. Lifetime risk assessments may be a better way to inform treatment decisions and evaluate the cost effectiveness of earlier intervention with pharmacological therapy.

[h] Clinic blood pressure measurements must be used in the calculation of cardiovascular risk.

9 Initiating and monitoring treatment, including blood pressure targets

The diagnostic threshold for defining hypertension has been progressively lowered over the past 50 years as treatment of hypertension has been shown to be beneficial at reducing cardiovascular morbidity and mortality when initiated at progressively lower blood pressure thresholds. During that time, the focus also shifted from hypertension diagnosed purely on the basis of diastolic pressure towards systolic pressure thresholds being the most common indication for treatment – this reflects the increased prevalence of hypertension with ageing and the usual progressive rise in systolic pressure with age. In the 2004 guideline, two different grades of hypertension were defined, Grade 1 hypertension (140-159/90-99mmHg) and Grade 2 hypertension (i.e ≥160/100mmHg).

The guideline recommended that patients with Grade 2 hypertension should be offered pharmacological treatment. The guideline was more cautious with regard to pharmacological treatment for uncomplicated Grade 1 hypertension (i.e. in those without evidence of target organ damage, cardiovascular disease, CKD or diabetes or at a calculated 10 year CVD risk <20%). This 2011 guideline partial update reviewed evidence published since the cut point of the last review (2003) to determine whether the existing recommendations for blood pressure thresholds for diagnosis and treatment of hypertension should be revised. Furthermore, in light of the recommendation in this guideline update that an ABPM daytime average blood pressure will hereafter be the preferred method for confirming the diagnosis of hypertension, the thresholds for diagnosis and grades of hypertension also needed to be reviewed with regard to ABPM daytime averages.

Once a decision has been made to initiate pharmacological treatment for hypertension, the next key question was “how low should blood pressure be lowered?” i.e. what is the recommended blood pressure target? The 2004 guideline noted that the evidence base to support a recommendation for an optimal treatment target for hypertensiion was less substantial than it should be. International consensus has specified an optimal treatment target for hypertension of <140/90 mmHg and in some cases even lower targets for people with established cardiovascular or renal disease or diabetes. There has also been concern but little evidence, as to the efficacy, safety and appropriate blood pressure target for the people at advanced age with hypertension (greater than 80 years). Consequently, studies examining optimal treatment targets have been reviewed.

Update 2011

9.1 Blood pressure thresholds for initiating pharmacological treatment

Review question: In adults with primary hypertension, at what blood pressure should treatment be initiated?

9.1.1 Clinical evidence

The literature was searched for studies published since the original guideline (2003 onwards). All study types were included, if the population did not consist of people who were exclusively diabetic or had CKD. Studies were excluded if they did not stratify results into more than one different BP value / threshold.

Thirty studies (31 papers)[49,50,54,57,60,61,68,89,101,119,136,165,206,208,213,243,244,247,269,285,291,313,331,332,340,351,454,466,521,546,629] were found that fulfilled the inclusion criteria and assessed at what BP should treatment be initiated (appropriate threshold for intervention). One of the studies[60,61] was published as two separate papers reporting different assessment outcomes, so this study has only been counted once, however results from both papers are reported and referenced here.

The studies addressing the question were categorised into three different types:

1. SRs / MAs (three studies)[54,206,351] . The SRs/MAs were of high quality however the studies they included were either low quality (observational)[54,206] or low to high (RCTs).[351].

2. Prognostic studies (27 studies; 28 papers)[49,50,57,60,61,68,89,101,119,136,165,208,213,243,244,247,285,291,313,331,332,340,454,466,521,546,629] - those that assess the risk of developing clinical outcomes (over time) at different BP values. Most of the prognostic studies were found to be methodologically sound (see quality assessment summary tables in appendix F) except for the following eight studies which had (or were rated as 'unclear' for) three or more of the six potential methodological flaws (Fagard 2007, Gudmundsson 2005, Obara 2007, Okayama 2006, Sleight 2009, Fagard 2004, Britton 2009, Conen 2007[101,136,206,208,243,454,466,546]).

Prognostic studies were divided into four categories: those that assessed BP measured by either clinic, home, ambulatory or self-reported / unknown methods.

3. Blood pressure equivalence studies (one study)[269]– those that calculate equivalent blood pressures using different measurement methods (home, ABPM or clinic), in order to set thresholds for the diagnosis and treatment of HT. All these studies were observational and therefore low quality.

Data from the included studies was not pooled into a meta-analysis. This was because for many studies only HRs were given rather than the number of patients with events, and data was often stratified differently in the studies (for example, by age, gender, treated/untreated or other population characteristics), making it not possible to pool together. Additionally, it was deemed inappropriate to pool the studies because the studies themselves differed considerably in their design and analysis, particularly regarding the following areas:

- blood pressure values, groups and thresholds used
- blood pressure measurement methods used
- outcome measures (and definitions of outcomes) used
- follow-up times used
- covariates taken into account in analyses

Details of all the studies are included in Table 27, Table 28 and Table 30. Table 29 summarises the numerical results for selected outcomes of the prognostic studies included for this review. The full data for all outcomes can be found in the evidence tables in the appendix.

Update 2011

Systematic reviews/Meta-analyses

Table 27: Study details and results for SRs/MAs assessing the risk of developing clinical outcomes at different BP thresholds.

Reference	N	Population	BP measurement method	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Asayama et al., 2009[54] MA of data from 4 cohort studies	4571	General population (HT and NT)	Clinic	Mean 9.5 years	Prognostic: Risk (HR) of developing clinical outcomes	Stroke; death from stroke	Optimal: <120/ <80 Normal: 120-129/80-84 High normal: 130-139/85-89 Grade 1 (mild) HT: 140-159/ 90-99 Grade 2 (moderate) HT: 160-179/ 100-109 Grade 3 (severe) HT: ≥180/110	Untreated groups: risk (HR) of first stroke increased linearly with BP. Treated people with optimal BP had higher risk of stroke than untreated people with optimal BP.
Law et al., 2009[351] SR/MA of 108 RCTs	248,445	HT and NT People of any age, disease status, pre-Treatment BP and use of other drugs	Clinic	Mean 3.5 years	BP difference trials designed to achieve a difference in BP between randomised groups	CHD events; stroke	10mm SBP increments from 120 – 180 mmHg	BP treatment reduced risk of CVD and stroke, regardless of patients' pre-treatment BP (as low as 110 SBP and 70 DBP; mmHg). Lowering BP by 10mmHg SBP or 5mmHg DBP reduced CVD events by around 25%, heart failure (by about 25%) and stroke (by about 33%). Authors concluded that BP lowering drugs should be offered to anyone at high risk (whatever the reason for high risk, e.g. age, cardiovascular disease event) not just to

Reference	N	Population	BP measurement method	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
								people with high BP, because a given BP reduction lowers the risk of coronary heart disease and stroke by a constant proportion irrespective of pre-treatment BP.
Fagard et al., 2007[206] SR/MA of 7 studies	11,502	General population, primary care and secondary care (HT and NT)	Clinic and ABPM (to give diagnoses)	Mean 8 years	Risk of developing events in people diagnosed as NT, WCH, MH or sustained HT	CV events	NT: normal BP clinic and ABPM; mean BP 121.8/75.6 and 119.7/72.6 respectively WCH: clinic HT, normal ABPM; mean BP 148.2/86.2 and 125.6/74.9 respectively MH: normal clinic, ABPM HT; mean BP 129.9/78.6 and 141.1/83.2 respectively Sustained HT: clinic HT and ABPM HT; mean BP 157.7/88.5 and 152.4/85.7 HT diagnosis - cut off BP Clinic: 140/90 mmHg ABPM: 135/85 mmHg (except 1 study 135/83mmHg)	NS difference between WCH and NT for incidence of CV events; worse CV events in MH and sustained HT

Prognostic studies

Table 28: Study details and results for prognostic studies assessing the risk of developing clinical outcomes at different BP thresholds

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Clinic BP measurements							
Arima et al., 2006[49] Sub-analysis of RCT (PROGRESS)	6105	HT and NT (Cerebrovascular disease)	Mean 3.9 years	Risk of developing events in people with different baseline BP values	Stroke, CV events	SBP values <120 (median 114) 120-139 (median 130) 140-159 (median 149) ≥160 (median 169)	The benefits of treatment were comparable for patients who were or were not HT at baseline, for baseline BP levels extending down to 115/75mmHg.
Arima et al., 2009[50] Cohort (HISAYAMA)	1621	General population (HT and NT)	32 years	Risk of developing events in people with different baseline BP values (grouped)	Stroke	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Grade 1 HT: 140-159 /90-99 Grade 2 HT: 160-179 /100-109 Grade 3 HT: ≥180 /110	Age-adjusted incidence of total stroke rose progressively with higher BP in both genders
Assmann et al., 2005[57] Cohort (PROCAM)	5389	General population (HT and NT)	10 years	Risk of developing events in people with different baseline BP values (grouped)	Major coronary event	NT: ≤140 /90 New HT: SBP >159 and/or DBP>94 Adequately treated HT: <160 /95 Inadequately treated HT: ≥160/95	In all HT men, including those receiving "adequate" antihypertensive Tx, the 10-year risk of CHD was at least doubled.
Barengo et al., 2009 and 2009[60,61] Cohort	41,895 (study 1) 47,610 (study 2)	General population (HT and NT)	Median 20 years	Risk of developing events in people with different baseline BP values (grouped)	Study 1: Mortality (all cause and CV) Study 2: stroke	NT:<160/95 and no Tx HT (≥160 SBP or 95 DBP or Tx in last 7 days); treated and controlled (<160/95mmHg) HT: Tx and not controlled HT and aware (HT diagnosis or current Tx) but untreated	In men, all-cause and cardiovascular mortality were significantly higher in all hypertensive groups compared with the normotensive group. In women, the mortality in those whose hypertension was controlled was not significantly

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
					(fatal or non-fatal)	HT but unaware	different from the normotensive group, suggesting that these women benefitted from achieving normal BP, although the uncontrolled, untreated and unaware groups had higher mortality. The risk of stroke was significantly higher in men and women in all hypertensive groups compared with the normotensive group. It may be higher in treated than untreated patients if they have had hypertension longer and it is more severe (also unaware were significantly younger so had lower risk).
Carlsson et al., 2009[119] Cohort study	2280	General population (HT and NT)	26 years	Risk of developing events in people with different baseline BP values (grouped)	Mortality; CV mortality	NT/optimal: <130 / <85 Pre-HT: 130-139 and/or 85- 89 DBP High: 140 - 159 and/or 90-94 DBP Very high: ≥160 and/or DBP ≥95	Risk of Events increased with increasing BP; Very high blood pressure (≥160/95mmHg) is an independent risk factor for all-cause and CV mortality in men and women.
Gudmundsson et al., 2005[243] Cohort study	3246	General population (HT and NT)	Up to 20 years (mean 13.6 for men and 14.4 for women)	Risk of developing events in people with different baseline BP values (grouped)	Mortality; CV mortality	NT/high-NT:<140 /<90 Mild-moderate HT: 140-179 /90-109 Severe HT: ≥180 /≥110	Patients treated for HT whose BP is not controlled have a higher risk of mortality than those whose BP is controlled. (Note: Tx target <160/<95mmHg; treatment not

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
							as aggressive as it would be today; number controlled to <140/90mmHg was less than half those labelled "controlled" in this study.)
Ishikawa et al., 2008[291] Cohort (JMS)	11,103	General population (HT and NT)	Mean 10.7 years	Risk of developing events in people with different baseline BP values (grouped)	Stroke	NT: <140/90, no treatment HT: treated (receiving Tx, irrespective of current BP) C: Controlled (<140/90) U: Uncontrolled (≥140 and/or DBP ≥90) HT: untreated (≥140 /90 without Tx) M: Mild (SBP 140-159 or DBP 90-99) MS: Moderate-severe (SBP ≥160 and/or DBP ≥100)	Risk of stroke higher among HT vs. NT patients, and treated vs. non-treated HT, even when BP controlled to <140/90mmHg Untreated HT might have had a shorter duration of HT (and therefore lower risk of stroke) or have WCH (also lower risk).
Kagiyama et al., 2008[313] Cohort	639	General population (HT and NT) but elderly (80 years)	4 years	Risk of developing events in people with different baseline BP values (grouped)	Mortality and CV mortality	SBP values NT: <140 Mild HT: 140-159 moderate-severe HT: >160	No association between total mortality and SBP in the very elderly overall (however increased risk with increase BP), but there was an association in those with CVD or on Tx.
Kokubo et al., 2008[331] Cohort (SUITA)	5494	General population (HT and NT)	Mean 11.7	Risk of developing events in people with different baseline BP values (grouped)	CV events (MI or Stroke)	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Stage 1 HT: 140-159 /90-99 Stage 2/3 HT: ≥160 /≥100 Very few people in stage 3 so combined into 'stage 2' values	Normal and high normal BP were a risk factor for the incidence of stroke and MI in men compared with optimal BP, as well as hypertension stage 1 or more. In women, the risk was seen at hypertension stages but not at normal/high normal BP (although numbers of events

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
							were lower in women).
Kono et al., 2005[332] Case-control	708	HT (with vs. without CV event)	n/a as case-control study	Risk of developing events in people with different baseline BP values (grouped)	CV events	SBP values NT: <140 Mild HT: 140-159 moderate-severe HT: >160	Positive relationship between BP status and risk of cardiovascular events
Kshirsagar et al., 2006[340] Cohort (ARIC)	8960	General population (HT and NT)	Mean 11.6 years	Risk of developing events in people with different baseline BP values (grouped)	CVD	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89	Normal BP and high normal BP were associated with a greater risk of incident cardiovascular disease compared with optimal BP. The risk was also higher for black people of African and Caribbean descent, older people (55-64 compared with 45-54), those with diabetes, high BMI, raised LDL cholesterol or renal insufficiency.
Obara et al., 2007[454] Post-hoc analysis (cohort)	1798	General population (HT and NT)	10,300 person-years	Risk of developing events in people with different baseline BP values (grouped)	Onset of or death due to circulatory disease (stroke, angina, MI, cardiac death)	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Grade 1 HT: 140-159 /90-99 Grade 2 HT: 160-179 /100-109 Grade 3 HT: ≥180 /110	In a relatively old cohort (mean age 60 years), risk of cardiovascular disease increased in higher BP groups
Okayama et al., 2006[466] Cohort (NIPPON DATA 80)	4244	General population (HT and NT)	19 years	Risk of developing events in people with different baseline BP values (grouped)	Mortality; CV mortality	SBP values Group 1: <120 Group 2: 120-139 Group 3: 140-159 Group 4: 160-179 Group 5: >179	Increased BP associated with cardiovascular disease mortality at all ages

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
						DBP values Group 1: <80 Group 2: 80-84 Group 3: 85-89 Group 4: 90-99 Group 5: >99	
Sairenchi et al., 2005[521] Cohort	97,153	General population (HT and NT)	Mean 8.7 years (men), 8.9 years (women)	Risk of developing events in people with different baseline BP values (grouped)	Mortality	Optimal: <120 /<80 Normal: 120-129 /80-84 High normal: 130-139 /85-89 Stage 1 HT: 140-159 /90-99 Stage 2/3 HT: ≥160 /≥100	Impact of SBP and DBP on cardiovascular disease around 2 times larger among middle-aged than elderly subjects (men and women); generally an increase in risk with increase BP values
Sleight et al., 2009[546] Post-hoc analysis of RCT (ONTARGET)	25,558	People with atherosclerotic disease or diabetes with end organ damage (High risk)	Mean 56 months	Risk of developing events in people classed into baseline BP quartiles	CV events (CV death, MI, Stroke, HF)	SBP values (quartiles) ≤130 mmHg 130-142 mmHg 142-154 mmHg >154 mmHg	No relationship found between SBP reduction and risk of MI, congestive heart failure and cardiovascular death. Avoid excessive SBP reduction (below 130mmHg) in older sicker high-risk patients For the primary outcome, there is a J-shaped pattern (nadir 130mmHg) in the relationship between on-treatment SBP (deciles) and adjusted risk of events; this was also true for cardiovascular mortality (nadir 130mmHg) and MI (126mmHg) but not for stroke.

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Haider et al., 2003[247] Cohort (Framingham heart study subset)	2040	General population	Mean 17.4 years	Risk of developing events in people classed into baseline BP groups	Congestive HF	SBP values 87-125 mmHg 126-141 mmHg ≥161 mmHg DBP values 49-74 mmHg 75-82 mmHg ≥83 mmHg	Both SBP and DBP were associated with CHF, but SBP conferred greater risk than DBP. Increased risk of events with increased BP value.
Benetos et al., 2003[68] Case-control	34,776	NT, HT and HT (Tx)	8-12 years	Risk of developing events in people iwth higher and lower BP values (and in Tx and un-Tx HT).	CVD, CHD and associated mortality	Treated (mean BP ~151/93 mmHg) Untreated (mean BP ~136/83 mmHg) High BP (≥140/90 mmHg) Lower BP(<140/90)	Treated HTs had higher SBP (+ 15 mmHg) and higher DBP (+ 9 mmHg), and a higher prevalence of associated risk factors and diseases. Treated HTs vs. untreated HTs presented a two-fold increase in the RR for CV mortality and CHD mortality. Adjustment for unmodifiable risk factors only slightly decreased the excess CV risk observed in treated people. After additional adjustment for modifiable associated risk factors, the increased mortality in treated people persisted. Only after additional adjustment for SBP were CV mortality and CHD mortality similar in the two groups of people. Therefore, the increased CV mortality in treated HT vs.

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
							untreated HT is mainly due to high SBP levels under treatment.
Weitzman et al., 2006[629] Cohort	9611	General population (HT and NT)	23 years	Risk of developing events in people classed into baseline BP groups	Mortality (stroke, CHD and all-cause)	SBP values 80-119 mmHg 120-129 mmHg 130-136 mmHg 137-149 mmHg 150-260 mmHg DBP values 40-77 mmHg 78-80 mmHg 81-85 mmHg 86-90 mmHg 91-150 mmHg	
Borghi et al., 2003[89] Cohort (Brisighella Heart Study)	2939	General population (HT and NT)	23 years	Risk of developing events in people classed into baseline BP groups	Mortality, CHD, MI, CeVD	SBP values <120 mmHg 120-139 mmHg 140-159 mmHg >159 mmHg DBP values <70 mmHg 70-79 mmHg 80-89 mmHg >89 mmHg	There is a consistent, strong, graded association between SBP (but not DBP) and cardiovascular events Increase in combined SHD and cerebrovascular disease risk was already evident with high-normal SBP
Fang et al., 2006[213]	26,587	General population (HT and NT)	Mean 9.5 years	Risk of developing events in people classed into	Stroke	ISH: ≥140 / <90 mmHg SDH: ≥140 / ≥90mmHg IDH: <140 / ≥90 mmHg (with or	Highest risk of stroke in people with ISH and SDH vs IDH and MHT.

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Cohort				baseline BP groups		without a-HT Tx) MHT: <140 / <90 (and controlled BP by a-HT Tx) NT: <140 / <90 (without history of HT)	People with SDH are at the highest risk of stroke and should be treated more aggressively.
Home BP measurements – no studies (one included in Fagard meta-analysis)							
Ambulatory BP measurements							
Fagard et al., 2004[208] Cohort sub-analysis of RCT (Syst-Eur)	295	HT (SBP)	Median 7.5 years	Risk of developing events in people classed as normal, abnormal or high BP	CV events	Normal ABP: <140mmHg Abnormal ABP: 140-159mmHg High ABP: ≥160mmHg	Baseline ABP predicts cardiovascular events. Increased events with increase in BP
Inoue et al., 2007[285] Cohort; sub-analysis of RCT (OHASAMA)	1,271	HT	Mean 11.2 years	Risk of developing events in people classed as HT (SBP-DBP; ISH, IDH) vs. NT	Stroke	NT: <135 / <80 mmHg SDH: ≥135 / ≥80 mmHg ISH: ≥135 / <80 mmHg IDH: <135 / ≥80 mmHg	ISH determined by ABPM was associated with a high risk of stroke, similar to that found for patients with combined systolic-diastolic HT.
Gustavsen et al., 2003 [244] Cohort	566	General population (NT, HT and WCH)	Mean 10.2 years	Risk of developing events in people classed as NT, WCH and HT	Death and CV events	NT: <140; mean = 129.1 mmHg HT: SBP >140; mean = 160.3 mmHg WCH: CBP>140, mean = 136.3; ABPM <135/90 mmHg	There is an increased cardiovascular risk in WCH compared to normotensive controls; the level of risk is the same as that seen with EHs (even though WCH had a lower average ABP than NT).
Self-reported / unknown BP measurement method							
Britton et al., 2009[101]	18,876	HT	Mean 20.7 years	Risk of developing events in people	HF	SBP values	Linear relationship between NT SBP (120-129mmHg and 130-

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Cohort				with different baseline BP values		NT (not on Tx) <120 mmHg 120-129 mmHg 130-139 mmHg HT (or on Tx) <130 mmHg 130-139 mmHg 140-149 mmHg 150-159 mmHg ≥160 mmHg	139mmHg) and risk of heart failure risk, as well as for HT SBP
Conen et al., 2007[136] Cohort (sub-analysis of RCT)	39,322	NT and HT women	Median 10.2 years	Risk of developing events in people with different baseline BP values	CV death, stroke or MI	Optimal: <120/ <75 Normal: 120-129/75-84 High normal: 130-139/85-89 HT: ≥140 /≥90	The CV risk of women with high normal BP is higher than those with normal BP; there was a strong and consistent increase in events down to the optimal BP category.
Deckers, 2006[165] Post-hoc analysis of RCT (EUROPA)	12,218	HT with CAD	Median 4.1 years	Risk of developing events in people with different baseline BP values	CV death, non-fatal MI	SBP values ≤130 mmHg >130-160 mmHg >160 mmHg	Higher baseline BP associated with increased risk.

Table 29: Summary of numerical results for prognostic studies (for selected outcomes)

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
Arima et al., 2006[49]	Stroke	SBP values (%, events/ person years) No HR values given 120 (median 114): 6.8% 120-139 (median 130) : 12.2% 140-159 (median 149): 12.5% ≥160 (median 169): 19.0%
Arima et al., 2009[50]	Stroke	Men Optimal: <120 /<80: Reference Men Normal: 120-129 /80-84: 1.64 (0.76-3.56) p>0.05 Men High normal: 130-139 /85-89: 1.52 (0.70-3.31) p>0.05 Men Grade 1 HT: 140-159 /90-99: 3.31 (1.73-6.32)p<0.05 Men Grade 2 HT: 160-179 /100-109: 4.22 (2.16-8.25)p<0.05 Men Grade 3 HT: ≥180 /110: 5.75 (2.93-11.30)p<0.05 Women Optimal: <120 /<80: Reference Women Normal: 120-129 /80-84: 1.53 (0.60-3.89)p>0.05 Women High normal: 130-139 /85-89: 2.19 (0.93-5.16)p>0.05 Women Grade 1 HT: 140-159 /90-99: 3.92 (1.84-8.35)p<0.05 Women Grade 2 HT: 160-179 /100-109: 4.89 (2.24-10.67)p<0.05 Women Grade 3 HT: ≥180 /110: 7.51 (3.39-16.64)p<0.05
Assmann et al., 2005[57]	Major coronary event	NT: ≤140 /90 New HT: SBP >159 and/or DBP>94 Adequately treated HT: <160 /95 Inadequately treated HT: ≥160/95 No HR values given
Barengo et al., 2009 and 2009[60,61]	CV mortality (MEN)	NT:<160/95 and no Tx : Reference HT (≥160 SBP or 95 DBP or Tx in last 7 days): No HR given HT treated and controlled (<160/95mmHg) 2.25 (1.70-2.99) HT: Tx and not controlled 2.41 (2.01-2.89)

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
		HT and aware (HT diagnosis or current Tx) but untreated 1.92 (1.65-2.23) HT but unaware 1.49 (1.33-1.68)
Benetos et al., 2003[68]	CVD, CHD and associated mortality	Treated (mean BP ~151/93 mmHg) Untreated (mean BP ~136/83 mmHg) High BP (≥140/90 mmHg) Lower BP(<140/90) No HRs given
Borghi et al., 2003[89]	Mortality	SBP values <120 mmHg Reference 120-139 mmHg 1.48 (1.04-2.10), p=0.0313 140-159 mmHg 1.92 (1.32-2.80), p=0.0006 >159 mmHg 2.38 (1.61-3.50), p<0.0001
Carlsson et al., 2009[119]	CV mortality	Men NT/optimal: <130 / <85 Reference Men Pre-HT: 130-139 and/or 85- 89 DBP 1.07 (0.58-1.97) Men High: 140 - 159 and/or 90-94 DBP 1.17 (0.66-2.09) Men Very high: ≥160 and/or DBP ≥95 3.12 (1.84-5.26) Women NT/optimal: <130 / <85 Reference Women Pre-HT: 130-139 and/or 85- 89 DBP 1.89 (0.76-4.68) Women High: 140 - 159 and/or 90-94 DBP 2.34 (1.01-5.45) Women Very high: ≥160 and/or DBP ≥95 3.84 (1.62-9.12)
Fang et al., 2006[213]	Stroke	NT: <140 / <90 (without history of HT) Reference ISH: ≥140 / <90 mmHg 2.35 (1.91-2.90) SDH: ≥140 / ≥90mmHg 2.96 (2.49-3.52) IDH: <140 / ≥90 mmHg (with or without a-HT Tx) 2.16 (1.69-2.76) MHT: <140 / <90 (and controlled BP by a-HT Tx) 1.33 (0.96-1.84)
Gudmundsson et al., 2005[243]	CV mortality	Men NT/high-NT:<140 /<90 Reference Men Mild-moderate HT: 140-179 /90-109 RR: 1.30 (0.79-2.14)

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
		Men Severe HT: ≥180 /≥110 RR: 1.23 (0.72-2.11) Women NT/high-NT:<140 /<90 Reference Women Mild-moderate HT: 140-179 /90-109 RR: 1.56 (0.85-2.86) Women Severe HT: ≥180 /≥110 RR: 2.57 (1.36-4.87) Only RRs given for above categories. However, per 1SD rise in SBP (22.4mmHg for men and 22.5 mmHg for women), HRs for Cv mortality are: 1.00 (0.87-1.15) for men and 1.34 (1.16-1.55),p<0.001 for women
Haider et al., 2003[247]	Congestive HF	SBP values 87-125 mmHg Reference 126-141 mmHg 1.48 (0.99-2.21), p=0.06 ≥161 mmHg 3.07 (2.10-4.49), p<0.001
Ishikawa et al., 2008[291]	Stroke	Men NT: <140/90, no treatment Reference Men HT: treated (receiving Tx, irrespective of current BP) RR:3.00 (2.00-4.51) Men C: Controlled (<140/90) RR 2.96 (1.66-5.26) Men U: Uncontrolled (≥140 and/or DBP ≥90) RR 3.05 (1.92-4.85) Men HT: untreated (≥140 /90 without Tx) RR 2.56 (1.83-3.57) Men M: Mild (SBP 140-159 or DBP 90-99) RR 2.34 (1.62-3.37) Men MS: Moderate-severe (SBP ≥160 and/or DBP ≥100) RR 3.17 (2.02-4.97) Women NT: <140/90, no treatment Reference Women HT: treated (receiving Tx, irrespective of current BP) RR 3.34 (2.29-4.87) Women C: Controlled (<140/90) RR 3.69 (2.20-6.17) Women U: Uncontrolled (≥140 and/or DBP ≥90) RR 3.16 (2.06-4.85) Women HT: untreated (≥140 /90 without Tx) RR 1.93 (1.35-2.76) Women M: Mild (SBP 140-159 or DBP 90-99) RR 1.95 (1.32-2.87)Women MS: Moderate-severe (SBP ≥160 and/or DBP ≥100) RR 1.87 (1.08-3.24) Only RRs given for above categories (but unclear). No HRs given
Kagiyama et al.,	CV mortality	SBP values

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
2008[313]		NT: <140: Reference Mild HT: 140-159: RR:1.71 (0.56-5.24) moderate-severe HT: >160: RR: 2.15 (0.51-8.97) Only RRs given for above categories. No HRs given
Kokubo et al., 2008[331]	CV events (MI or Stroke)	Men Optimal: <120 /<80 Reference Men Normal: 120-129 /80-84 2.04 (1.19-3.48) Men High normal: 130-139 /85-89 2.46 (1.46-4.14) Men Stage 1 HT: 140-159 /90-99 2.62 (1.59-4.32) Men Stage 2/3 HT: ≥160 /≥100 3.95 (2.37-6.58) Women Optimal: <120 /<80 Reference Women Normal: 120-129 /80-84 1.12 (0.59-2.13) Women High normal: 130-139 /85-89 1.54 (0.85-2.78) Women Stage 1 HT: 140-159 /90-99 1.35 (0.75-2.43) Women Stage 2/3 HT: ≥160 /≥100 2.86 (1.60-5.12) Overall Optimal: <120 /<80 Reference Overall Normal: 120-129 /80-84 1.62 (1.08-2.43) Overall High normal: 130-139 /85-89 2.08 (1.42-3.05) Overall Stage 1 HT: 140-159 /90-99 2.06 (1.42-2.98) Overall Stage 2/3 HT: ≥160 /≥100 3.53 (2.43-5.13)
Kono et al., 2005[332]	CV events	SBP values NT: <140 reference Mild HT: 140-159 Adjusted OR: 1.69 (1.10-2.60) moderate-severe HT: >160 Adjusted OR: 2.20 (1.08-4.45) Only adjusted ORs given. No HRs given
Kshirsagar et al., 2006[340]	CVD	Optimal: <120 /<80 Reference Normal: 120-129 /80-84 1.69 (1.37-2.09)

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
		High normal: 130-139 /85-89 2.33 (1.85-2.92)
Obara et al., 2007[454]	Onset of or death due to circulatory disease (stroke, angina, MI, cardiac death)	Optimal: <120 /<80 Normal: 120-129 /80-84 Reference High normal:130-139 /85-89 RR:1.19 (0.89-1.20), p=0.3 Grade 1-3 HT: 140->180 RR: 1.46 (1.00-1.17), p=0.011 Only adjusted RRs given. No HRs given
Okayama et al., 2006[466]	CV mortality	SBP values Group 1: <120 Reference Group 2: 120-139 Age adjusted RR: 2.36 (1.17-4.77) Group 3: 140-159 Age adjusted RR: 3.00 (1.51-5.94) Group 4: 160-179 Age adjusted RR: 3.46 (1.75-6.84) Group 5: >179 Age adjusted RR: 5.13 (2.59-10.16) No HRs given for categories above, but multivariate adjusted HRs for 1SD increase in SBP: 1.31 (1.17-1.47)
Sairenchi et al., 2005[521]	Mortality	Men Optimal: <120 /<80 Reference Men Normal: 120-129 /80-84 RR: 1.48 (0.50-4.44) Men High normal: 130-139 /85-89 RR:2.89 (1.07-7.86) Men Stage 1 HT: 140-159 /90-99 RR:3.06 (1.15-8.16) Men Stage 2/3 HT: ≥160 /≥100 RR:5.99 (2.13-16.8) Women Optimal: <120 /<80 Reference Women Normal: 120-129 /80-84 RR:0.86 (0.34-2.20) Women High normal: 130-139 /85-89 RR:1.19 (0.50-2.84) Women Stage 1 HT: 140-159 /90-99 RR:2.02 (0.93-4.38) Women Stage 2/3 HT: ≥160 /≥100 RR:4.09 (1.70-9.85) Only RRs for men and women aged 40-59 given above. No HRs given
Sleight et al., 2009[546]	CV events (CV death, MI, HF,	SBP values (quartiles) CV death

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
	Stroke)	≤130 mmHg Reference 130-142 mmHg 0.98 (0.86-1.12) 142-154 mmHg 0.93 (0.81-1.06) >154 mmHg 0.98 (0.86-1.11) MI ≤130 mmHg Reference 130-142 mmHg 0.87 (0.74-1.01) 142-154 mmHg 0.88 (0.75-1.02) >154 mmHg1.03 (0.88-1.20) CHF ≤130 mmHg Reference 130-142 mmHg 0.85 (0.71-1.01) 142-154 mmHg 0.87 (0.74-1.04) >154 mmHg0.84 (0.71-0.99) Stroke ≤130 mmHg Reference 130-142 mmHg 1.11 (0.92-1.33) 142-154 mmHg 1.32 (1.11-1.58) >154 mmHg1.51 (1.28-1.79)
Weitzman et al., 2006[629]	Mortality (stroke, CHD and all-cause)	SBP values 80-119 mmHg 120-129 mmHg 130-136 mmHg 137-149 mmHg 150-260 mmHg No HRs given, nor any other RRs or ORs relevant to the categories above.

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
Fagard et al., 2004[208]	CV events	Normal ABP: <140mmHg Reference Abnormal ABP: 140-159mmHg RR: 1.27 (0.64-2.52) High ABP: ≥160mmHg RR: 2.13 (1.09-4.13) No HRs given, but unadjusted RRs above calculated from data in outcome table.
Gustavsen et al., 2003 [244]	CV events	NT: <140; mean = 129.1 mmHg Reference HT: SBP >140; mean = 160.3 mmHg HR p<0.001 WCH: CBP>140, mean = 136.3; ABPM <135/90 mmHg HR 6.6 (p<0.001) HR p values given as shown, but no CIs and no HR value for HT were provided.
Inoue et al., 2007[285]	Stroke	NT: <135 / <80 mmHg Reference SDH: ≥135 / ≥80 mmHg 2.39 (1.48-3.87), p=0.0004 ISH: ≥135 / <80 mmHg 2.24 (1.33-3.76), p=0.0024 IDH: <135 / ≥80 mmHg excluded from model as number of subjects (n=37) and events (number not stated) were too low
Britton et al., 2009[101]	HF	SBP values NT (not on Tx) <120 mmHg Reference 120-129 mmHg 1.10 (0.89-1.37) 130-139 mmHg 1.35 (1.09-1.68) HT (or on Tx) <130 mmHg 1.91 (1.36-2.68) 130-139 mmHg 2.61 (2.04-3.34) 140-149 mmHg 2.04 (1.63-2.55) 150-159 mmHg 2.66 (1.99-3.55) ≥160 mmHg 3.42 (2.33-5.04)
Conen et al., 2007[136]	Major CV event	Optimal: <120/ <75 0.51 (0.40-0.64) Normal: 120-129/75-84 0.61 (0.48-0.76) High normal: 130-139/85-89 Reference HT: ≥140 /≥90 1.30 (1.08-1.57) Age adjusted HR used
Deckers, 2006[165]	CV death	SBP values ≤130 mmHg

Study	Outcome	HR (95% CI) for BP measurement (SBP/DBP) [HRs given unless indicated. Available RRs or ORs have been given if no HRs available]
		>130-160 mmHg >160 mmHg HRs not provided for above comparisons but multivariate HR for a 1mmHg increase in systolic BP: 1.01 (1.00-1.01)

Equiavlence studies

Table 30: Study details and results for equivalence studies determining thresholds for diagnosis and treatment using different blood pressure measurement methods.

Reference	N	Population	Follow-up	Study design	BP values at baseline (groups / thresholds); mmHg
Clinic and ABPM measurements					
Head et al., 2010[269] cross-sectional study	8575	NT and HT	Immediate	ABPM equivalents for clinic BPs	CLINIC MEASUREMENT CATEGORIES: lower limits of grade 3 (severe) HT(180/110 mm Hg) grade 2 (moderate) HT (160/100mmHg) grade 1 (mild) HT (140/90 mm Hg); for target upper limits for HT with associated conditions (130/80 mm Hg) HT with substantial proteinuria (125/75 mm Hg Upper limit of optimal normal (120/80 mm Hg).

Author's conclusions: equivalent thresholds

	Clinic BP threshold	ABPM predicted from staff measured seated clinic BP (n=5327)			ABPM predicted from doctor measured seated clinic BP (n=1490)		
		24h	Night	Day	24h	Night	Day
Grade 3 (severe) HT	>180/110	163/101	157/93	168/105	151/95	143/86	155/98
Grade 2 (moderate) HT	>160/100	148/93	139/84	152/96	138/86	128/78	142/90
Grade 1 (mild) HT	>140/90	133/84	121/76	136/87	126/78	113/69	129/81
Target BP + 1 condition	<130/80	125/76	112/67	128/78	119/70	106/61	123/73
Target BP + proteinuria	<125/75	121/71	107/63	124/74	116/66	102/57	120/69
Normal BP	<120/80	117/76	102/67	120/78	113/70	99/61	117/70

9.1.2 Evidence statements - clinical

Details of all the included studies are summarised in Table 31, Table 32 and Table 33.

- Most studies showed a continuous relationship between BP and risk of developing clinical outcomes (ie. an increased risk of outcome with increasing BP value)
- This was true regardless of BP measurement method (office, ABPM, self-reported/ not specified)
- The MA of Law et al.,[351] showed that BP treatment reduced CVD risk regardless of pre-treatment BP
- The Head 2010 study[269] provided equivalent threshold values for ABPM and clinic BP measurements for the diagnosis and treatment of HT.

9.1.3 Evidence statements – economic

No relevant cost-effectiveness evidence was identified.

9.2 Treatment of people aged 80 years and greater

Review question: in adults with primary hypertension, which is the most clinically and cost effective first-line anti-hypertensive treatment (drug classes) in elderly people (aged ≥80 years)?

9.2.1 Clinical evidence

Update 2011

The literature was reviewed from December 2005 onwards (the cut-off date of the previous guideline) for systematic reviews, RCTs and subgroup analyses of RCTs which addressed first-line ant-hypertensive treatment in elderly people (aged ≥80 years) with primary hypertension. Comparisons could be anti-hypertensive treatment or placebo. RCTs were included if there was: ≥12 months follow-up and N≥200 (in accordance with the 2006 guideline criteria) and the population did not consist of people who were exclusively diabetic or had CKD.

Two SR/MAs[67,419] were found that fulfilled the inclusion criteria and addressed the question. The first SR/MA (Musini et al 2009)[419] was a Cochrane review and included N=8 studies. The second SR/MA (Bejan-Angoulvant 2010)[67] was an update of a previous SR/MA and included additional data from the newer HYVET and HYVET-PILOT studies. , also consisted of 8 studies in total, and was an update of the Cochrane SR/MA.

The Bejan-Angoulvant SR/MA[67] was chosen to be included in this review instead of the Cochrane SR/MA becauseit provided data for more outcome measures than the Cochrane review, which pooled some outcomes together. Data was cross-checked between the two SR/MAs.

The Began-Angoulvant SR/MA[67] compared the development of clinical outcomes in patients who were ≥80 years old who had been randomised to treatment with either anti-hypertensive drugs or placebo. Data in the MA came from either sub-group analyses of RCTs (data from only the ≥80 year-old people in the trial), or from RCTs in which only people ≥80 years were enrolled. The mean follow-up time was 3.5 years (range 0 – 11.6) and the total number of patients included was N=6701. The 8 included studies differed in terms of sample size, mean SBP at baseline, follow-up time and the class of anti-hypertensive medication that patients were randomised to in the active treatment arm (D, CCB or BB). However they were similar in terms of the mean age of the study population (83 to 84 years old).

NOTE: The HYVET trial which was included in the MA, recruited people who were 'less ill' than those included in the other studies. Participants in HYVET were generally healthier than those in the

general population: they had low overall rates of stroke and death from any cause and at basline they were generally free of multiple comorbid conditions (low prevalence of previous cardiovascular disease, coronary artery disease and diabetes mellitus; inclusion criteria also excluded people with heart failure, dementia or those requiring nursing care).

The evidence profile below (Table 31) summarises the quality of the evidence and outcome data from the SR/MA included in this review,[67] comparing treatment vs placebo in people aged ≥80 years.

Update 2011

Table 31: Evidence profile comparing anti-hypertensive treatment versus placebo in people aged ≥80 years (systematic review/meta-analysis; Bejan-Angoulvant, 2010)[67]

NOTE: there was not enough data given in the study to calculate the HRs for these outcomes, so the RRs reported in the paper have been used in the GRADE profile.

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	anti-HT treatment	Placebo	Relative (95% CI)	Absolute	Quality
Mortality (all cause) (follow-up 0-11.6 years)											
1	SR/MA based on 8 RCTs*	no serious limitations	no serious inconsistency[1,2]	no serious indirectness	serious[3]	none	data not given in study		1.06 (0.89, 1.25)	not enough data given in study to calculate	MODERATE
Coronary events (follow-up 0-11.6 years)											
1	SR/MA based on 6 RCTs*	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	data not given in study		0.83 (0.56, 1.22)	not enough data given in study to calculate	LOW
Stroke (follow-up 0-11.6 years)											
1	SR/MA based on 7 RCTs*	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	data not given in study		0.65 (0.52, 0.83)	not enough data given in study to calculate	HIGH
CV events (follow-up 0-11.6 years)											
1	SR/MA based on 6 RCTs*	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	data not given in study		0.73 (0.62, 0.86)	not enough data given in study to calculate	HIGH
Heart failure (follow-up 0-11.6 years)											

1	SR/MA based on 6 RCTs*	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	data not given in study	0.50 (0.33, 0.76)	not enough data given in study to calculate	HIGH
coronary death (follow-up 0-11.6 years)										
1	SR/MA based on 7 RCTs*	no serious limitations	no serious inconsistency	no serious indirectness	very serious[4]	none	data not given in study	0.99 (0.69, 1.41)	not enough data given in study to calculate	LOW
Stroke death (follow-up 0-11.6 years)										
1	SR/MA based on 8 RCTs*	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	data not given in study	0.80 (0.80, 1.11)	not enough data given in study to calculate	MODERATE
CV death (follow-up 0-11.6 years)										
1	SR/MA based on 8 RCTs*	no serious limitations	serious[1]	no serious indirectness	very serious[4]	none	data not given in study	0.98 (0.83, 1.15)	not enough data given in study to calculate	VERY LOW

*moderate quality SR/MA based on moderate and high quality RCTs

[1] significant heterogeneity
[2] NS heterogenity when HYVET trial removed
[3] 95% confidence interval includes both 1) no effect and 2) the MID (appreciable benefit or appreciable harm); or only just crosses the MID
[4] 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm

9.2.2 Economic evidence

One study (Szucs 2010[580]) was identified from the update search that examined the cost-effectiveness of antihypertensive drug treatment in people over the age of 80 years. This is summarised in the economic evidence profile below (Table 32, Table 33). A full evidence table is also provided in Appendix G: Evidence tables – health economic studies (2011 update).

Table 32: Antihypertensive treatment versus no treatment in people aged over 80 years – economic study characteristics

Study	Applicability	Limitations	Other Comments
Szucs 2010[580]) Switzerland HYVET study	Partially applicable(a)	Potentially serious limitations(b)	• Model based on HYVET RCT[639] • Time horizon: 2 years • Health outcomes: life years gained • Costs: antihypertensive drugs, acute management and follow-up of MI, stroke and heart failure.

a) Some uncertainty about applicability of Swiss unit costs. QALYs not used. Discounting not in line with NICE reference case.

b) Based on single RCT analysis and so does not incorporate all available evidence for patients over 80 years. Some methodological issues about how health outcomes and costs are calculated and attributed in model.

Table 33: Antihypertensive treatment versus no treatment in people aged over 80 years – economic summary of findings (mean per person)

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Szucs 2010[580]) Switzerland HYVET study	-£14(a)	0.0457 life years gained	Treatment dominated no treated (lower costs and improved health outcomes)	One way sensitivity analyses of 20% variation in medication cost, cost of stroke, cost of HF, cost of MI, life expectancy. Medication cost and cost of stroke had the biggest impact. Results varied from treatment dominant to £1097 per life year gained.

a) Converted from 2007 Swiss Francs.

Update 2011

9.2.3 Evidence statements – Clinical

Study data has come from one moderate quality systematic review/meta-analysis[67] which included eight moderate and high quality RCTs.

In people aged ≥80 years old, anti-hypertensive treatment was significantly better than placebo for:

- stroke [high quality evidence]
- CV events [high quality evidence]
- heart failure [high quality evidence]

There was NS difference between anti-hypertensive treatment and placebo in people aged ≥80 years old for:

- total mortality [moderate quality evidence]
- coronary events [low quality evidence]

- coronary death [low quality evidence]
- stroke death [moderate quality evidence]
- CV death [very low quality evidence]

9.2.4 Evidence statements – Health economic

- One partially applicable study with potentially serious limitations found treating people over 80 years of age with hypertension was cost-effective compared to not treating them.

9.3 Link from evidence to recommendations

Two main sources of evidence informed the GDG discussion about blood pressure thresholds; i) observational data examining the relationship between blood pressure and clinical outcomes from normotensive and hypertensive people according to current threshold definitions, and ii) studies examining the impact of treatment of hypertension on clinical outcomes, taking account of the baseline and achieved blood pressure values in clinical trials. It was not possible to pool data from these studies because they included people across varying age ranges, at different levels of baseline cardiovascular risk and patients were either untreated or treated with a range of medications that could have influenced cardiovascular disease risk and clinical outcomes. Thus, studies were examined individually to determine the strength and consistency of evidence to support recommendations for pharmacological treatment thresholds and optimal blood pressure targets for people with treated hypertension.

A number of conclusions can be drawn from this analysis; i) there was a positive and continuous relationship between baseline blood pressure levels and the subsequent risk of clinical outcomes; ii) this relationship was consistent for the risk of stroke, ischaemic heart disease, heart failure and cardiovascular mortality; iii) this increased risk was most strongly related to systolic pressure, reflecting the fact that systolic pressure rises with ageing and most studies are conducted in older rather than younger people; iv) there was a paucity of data and no recent studies of the relationship between blood pressure and clinical events in younger people, i.e. <40 years.

Update 2011

The GDG noted that clinical trials invariably recruited older patients at high cardiovascular disease risk and that there were no trials that had been specifically designed to examine the appropriate blood pressure thresholds for initiating pharmacological treatment forhypertension. Nevertheless, the individual pharmacological treatment trials had usually randomised people into studies based on systolic blood pressure thresholds of 140 or 160mmHg and diastolic pressure thresholds of 90 or 100mmHg. The GDG also discussed whether recommending specific blood pressure treatment thresholds was justified. The GDG noted that the results of a meta-analysis and systematic review of 248,445 people in 108 randomised controlled trials (Law et al) had shown that blood pressure lowering reduced the risk of cardiovascular disease and stroke irrespective of the patients' pre-treatment blood pressure, even when pre-treatment pressures were as low as 110/70mmHg – suggesting that blood pressure lowering treatment could be offered to any person at high risk of cardiovascular disease, not just those with hypertension. The GDG concluded that such a hypothesis was consistent with the continuous relationship between blood pressure and clinical outcomes. However, it remainsl a hypothesis that requires prospective testing to properly define the balance between efficacy and safety, especially in people with low baseline blood pressure, as well as the cost-effectiveness of such a strategy.

With regard to treatment thresholds, the GDG agreed that the current grading of hypertension, i.e. Stage 1 Hypertension (CBPM ≥140/90mmHg) or Stage 2 hypertension (CBPM≥160-100) was useful to help stratify people for treatment and should be retained. Furthermore the GDG could see no point in any further grading of hypertension beyond Stage 2 as it would have no impact of treatment stratification or clinical decision making. In light of the fact that this guideline update recommends

using the ABPM daytime average BP to confirm the diagnosis of hypertension for initiating treatment, it was necessary to define the ABPM daytime average pressures that are equivalent to the thresholds for stages 1 and 2 hypertension, previously defined according to CBPM readings alone. A large study of 8,575 (Head et al., 2010) [269] examined the equivalent Clinic blood pressure and ABPM day time average pressure for normotensive and hypertensive people. Of interest, the difference between Clinic and ABPM was greatest when measured by doctors in the clinic rather than other clinical staff. Based on the clinic staff data, a mean daytime average ABPM of 136/76mmHg was equivalent to Stage 1 hypertension threshold defined according to a CBPM threshold of ≥140/90mmHg. The 136/76mmHg value was rounded to derive the threshold for defining stage 1 hypertension, i.e. ≥135/85mmHg according to the ABPM day time average. This ABPM diagnostic threshold is similar to that used as the reference standard in the systematic review of the specificity and sensitivity of the different blood pressure measurement methods for the diagnosis of hypertension. The GDG concluded that an ABPM day time average of ≥135/85mmHg should be used to define the threshold for Stage 1 hypertension.

In the study of Head et al,[269] the current CBPM threshold for the diagnosis of Stage 2 hypertension, i.e. ≥160/100mmHg, was equivalent to an ABPM daytime average of 152/96mmHg, which the GDG rounded to 150/95mmHg. Thus, the GDG concluded that a daytime ABPM average BP ≥150/95mmHg should be used to define the threshold for stage 2 hypertension.

In reviewing treatment thresholds, the GDG first reflected on the existing recommendation (2004) that pharmacological treatment should be offered for stage 2 hypertension, i.e. when the clinic blood pressure is ≥160-100mmHg (equivalent to an ABPM day time average of ≥150/95mmHg). This recommendation was based on the evidence review in 2004 which suggested that this level of blood pressure alone was sufficient to convey sufficient risk to benefit from pharmacological therapy for hypertension.The GDG reviewed this recommendation alongside the current evidence review which reinforced the message of the powerful effect of baseline blood pressure on clinical risk across a wide range of blood pressures and that pharmacologic treatment of blood pressure at or above the stage 2 hypertension threshold was associated with a clinical benefits and a reduction in risk. The GDG concluded that adults should be offered pharmacological treatment of hypertension at stage 2 hypertension (ABPM daytime average blood pressure ≥150/95mmHg).

Update 2011

The GDG then discussed whether pharmacologic treatment should be offered to all adults with Stage 1 hypertension, i.e. CBPM systolic pressure 140-159 and/or diastolic pressure 90-99mmHg, and ABPM daytime averages of ≥135/85mmHg but <150/95mmHg. The existing guidance from 2004 recognised the uncertainty about whether every adult with stage 1 hypertension should be offered treatment. The GDG noted that the current recommendation is to offer treatment to some but not all people with stage 1 hypertension (2004). The treatment being targeted at those with stage 1 hypertension and higher levels of cardiovascular disease risk as indicated by the presence of one or more of; target organ damage, established cardiovascular disease, the presence of concomitant disease that increases cardiovascular disease risk such as diabetes or CKD, or in those whose 10 year cardiovascular risk is estimated to be 20% or more (ref NICE CVD risk) [428].

The GDG discussed the fact that most of the people with stage 1 hypertension who would not be offered treatment according to this guidance will be younger (i.e. <40 years) because of their lower 10 year risk risk and lesser likelihood that they will have developed target organ damage or have established cardiovascular disease. Furthermore, there maybe greater uncertainty about the diagnosis of hypertension when blood pressure is close to the threshold for stage 1 hypertension. The GDG concluded that pharmacological treatment should be offered to people with stage 1 hypertension who also have higher levels of cardiovascular disease risk as indicated by the presence of one or more of; target organ damage, established cardiovascular disease, the presence of concomitant disease that increases cardiovascular disease risk such as diabetes or CKD, or in those whose 10 year cardiovascular risk is estimated to be 20% or more (ref NICE CVD risk)[428]. Moreover, those with stage 1 hypertension without any of these additional higher cardiovascular factors

indicators, i.e. uncomplicated stage 1 hypertension, would not usally be offered pharmacological therapy for hypertension but; i) would be recomended to undertake lifestyle modifications (see section x), and ii) should also be re-evaluated annually and pharmacological treatment offered if they develop more severe hypertension, i.e. stage 2 hypertension, or they develop target organ damage, diabetes, CKD, cardiovascular disease, or their estimated 10 year cardiovascular disease risk rises to 20% or more. In reality, this means that most people with stage 1 hypertension will be offered pharmacologic treatment because age is a major determinant of CVD risk and the majority of people with hypertension are older rather than younger. However, the GDG discussed the dilemma created by this recommendation about what to advise for younger people (i.e. <40 years) with "uncomplicated"stage 1 hypertension. This dilema is created by the fact that younger people with stage 1 hypertension are less likely to have overt evidence of target organ damage or vascular disease and assessment of their CVD risk over a relatively short duration of 10 years is unlikely to adequately reflect their lifetime risk of CVD. The GDG further discussed that this dilemma is compouned by the fact that when compared with older populations; i) in younger people, the time course over which clinical outcomes develop as a consequence of stage 1 hypertension are likely to be very long and much longer then those encountered in conventional clinical outcome trials and epidemiological studies. Thus, there is very much less epidemiological data linking uncomplicated stage 1 hypertension in younger people with adverse clinical outcomes; ii) younger people have not been included in clinical outcome trials in sufficient numbers to evaluate the impact of the pharmacological treatment of stage 1 hypertension on clinical outcomes and probably never will be as such trials would need to be unfeasibly large of too long a duration to be practical; iii) 10 year CVD risk estimates are strongly age dependent and as such, in younger people will rarely provide an indication for treatment of uncomplicated stage 1 hypertension. The GDG concluded that uncomplicated stage 1 hypertension in younger people is unlikely to be benign, blood pressure will most likely rise over time, and that there is uncertainty surrounding whether delayed pharmacological treatment will necessarily reverse any accumulated target organ or cardiovascular damage. The GDG also discussed the need to develop more accurate estimates of the lifetime risk of younger people with uncomplicated stage 1 hypertension and the cost-effectiveness of treatment. In this regard, the GDG recognised the importance of thorough assessment of target organ damage to exclude its presence before deciding not to offer pharmacological treatment of hypertension for younger people with seemingly uncomplicated stage 1 hypertension – the GDG thus recommended that evaluation of the potential benefit of treating uncomplicated stage 1 hypertension in younger people with regard to its impact on target organ structure and function should be a priority for future research. Meantime, the GDG recommended that for younger people (i.e. <40years) with uncomplicated stage 1 hypertension, specialist referral for exclusion of secondary causes of hypertension (see section xx) and detailed evaluation of target organ damage e.g. by echocardiography to exclude LVH and dysfunction, should be considered before concluding not to offer treatment. Moreover, when treatment is not offered, careful annual re-evaluation is necessary because blood pressure is likely to rise over time and target organ damage may develop.

Update 2011

9.4 Recommendations

22. Offer antihypertensive drug treatment to people aged under 80 years with stage 1 hypertension who have one or more of the following:
    - target organ damage
    - established cardiovascular disease
    - renal disease
    - diabetes
    - a 10-year cardiovascular risk equivalent to 20% or greater. [new 2011]

23. Offer antihypertensive drug treatment to people of any age with stage 2 hypertension. [new 2011]

24. For people aged under 40 years with stage 1 hypertension and no evidence of target organ damage, cardiovascular disease, renal disease or diabetes, consider seeking specialist evaluation of secondary causes of hypertension and a more detailed assessment of potential target organ damage. This is because 10-year cardiovascular risk assessments can underestimate the lifetime risk of cardiovascular events in these people. [new 2011]

9.5 Recommendations for research

3. In people aged under 40 with hypertension, what are the appropriate thresholds for intervention?

There is genuine uncertainty about how to assess the impact of blood pressure treatment in younger people (aged under 40) with stage 1 hypertension, and no overt target organ damage or CVD. In particular, whether those with untreated hypertension are more likely to develop target organ damage and, if so, whether such damage is reversible. Target organ damage and CVD as surrogate or intermediate disease markers are the only indicators that are likely to be feasible in younger people because traditional clinical outcomes are unlikely to occur in sufficient numbers over the time scale of a typical clinical trial. The data will be important to inform treatment decisions for younger people with stage 1 hypertension who do not have overt target organ damage.

9.6 Monitoring treatment efficacy

Update 2011

Review question: In adults with treated primary hypertension, what is the best method to measure blood pressure (home vs ambulatory vs office) for response to treatment?

9.6.1 Clinical evidence

The literature was searched for all years and studies published since the original guideline (2003 onwards) were included.

Two SRs/MAs[96,290] and 3 RCTs[137,439,554] were found that fulfilled the inclusion criteria and assessed which was the best BP measurement method for monitoring treatment in order to reach target BPs. All studies were of moderate to good quality. The first MA[96] compared the effects of home monitoring vs usual care on BP lowering and reaching BP targets. The second MA[290] compared BP measurements at end of treatment using office or home measurements. The 4 RCTs all assessed the effects of home monitoring vs office or ABPM monitoring on BP lowering and reaching BP targets.

NOTE: all RCTs were underpowered to detect a difference in BP. In order to detect a 5mm difference, a sample size of N≥500 is needed.

The evidence profiles below (Table 35,

Table 36, Table 37, Table 38 and Table 39) summarise the quality of the evidence and outcome data from the studies included in this review.[96,137,290,439,554].

Table 34: Evidence profile comparing self-monitoring vs. usual care (Bray 2010)[96]

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	self monitoring	usual care	Relative (95% CI)	Absolute	
Change in clinic systolic blood pressure (mm Hg) (Better indicated by lower values)											
1 [96]	randomised trials[1]	very serious[2]	serious[3]	no serious indirectness	serious[4]	none	0[5]	0[5]	-	3.82 lower (5.61 to 2.03 lower)[6]	VERY LOW
Change in clinic diastolic blood pressure (mm Hg) (Better indicated by lower values)											
1 [96]	randomised trials[7]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[8]	0[8]	-	1.45 lower (1.95 to 0.94 lower)[9]	LOW
Proportion of patients achieving clinic blood pressure target											
1 [96]	randomised trials[10]	very serious[2]	serious[3]	no serious indirectness	serious[4]	none	0/0 (0%)[11]	0/0 (0%)[11]	1.09 (1.02 to 1.16)[6]	Not estimable	VERY LOW
Change in daytime ABPM systolic blood pressure (mm Hg) (Better indicated by lower values)											
1 [96]	randomised trials[12]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[13]	0[13]	-	2.04 lower (4.35 lower to 0.27 higher)[14]	LOW
Change in daytime ABPM diastolic blood pressure (mm Hg) (Better indicated by lower values)											
1 [96]	randomised trials[12]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[13]	0[13]	-	0.79 lower (2.35 lower to 0.77 higher)[15]	LOW

[1] Meta-analysis of 20 RCTs
[2] Unclear randomisation process; unclear allocation concealment; unclear blinding; unclear ITT analysis; unclear drop-out rates
[3] I2 >50%
[4] 95% CI crosses MID
[5] Not stated. Total number of patients was 5,898
[6] p = 0.000
[7] Meta-analysis of 23 RCTs
[8] Not stated. Total number of patients was 6,038
[9] p = 0.015
[10] Meta-analysis of 12 RCTs
[11] Not stated. Total number of patients was 2,260
[12] Meta-analysis of 3 RCTs
[13] Not stated. Total number of patients was 572
[14] p = 0.89
[15] p = 0.96

Table 35: Evidence profile comparing reduction in blood pressure using clinic and home measurements (Ishikawa 2008)[290]

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Home blood pressure measurement	Clinic blood pressure measurement	Relative (95% CI)	Absolute	Quality
Change in systolic blood pressure (mm Hg) (Better indicated by lower values)											
1 [290]	randomised trials[1]	very serious[2]	serious[3]	no serious indirectness	serious[4]	none	0[5]	0[5]	-	MD 0 higher (0 to 0 higher)[6]	VERY LOW
Change in diastolic blood pressure (mm Hg) (Better indicated by lower values)											
1 [290]	randomised trials[1]	very serious[2]	serious[3]	no serious indirectness	serious[4]	none	0[5]	0[5]	-	MD 0 higher (0 to 0 higher)[7]	VERY LOW

[1] Meta-analysis of 22 RCTs. Data sets in which the methods of clinic BP measurements were not clearly described were excluded
[2] Unclear randomisation process; unclear allocation concealment; unclear blinding; unclear ITT analysis; unclear drop-out rates
[3] No details
[4] Difference in change not stated
[5] Not stated. Total number of patients was 6,322
[6] Reductions in clinic and home SBP were: -14.7±0.04 and -11.8±0.04 respectively; p<0.001
[7] Reductions in clinic and home DBP were: -10.7±0.03 and -8.1±0.05 respectively; p<0.001

Table 36: Evidence profile comparing reduction in blood pressure using home and ambulatory measurements (Ishikawa 2008)[290]

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Home blood pressure measuerement	Ambulatory blood pressure measurememnt	Relative (95% CI)	Absolute	Quality
Change in daytime systolic blood pressure (mm Hg) (Better indicated by higher values)											
1 [290]	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	MD 1.6 higher (1.1 to 2.2 higher)[4]	LOW
Change in daytime diastolic blood pressure (mm Hg) (Better indicated by higher values)											
1 [290]	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	MD 0.2 higher (0.4 lower to 0.8 higher)[5]	LOW

Change in nighttime systolic blood pressure (mm Hg) (Better indicated by higher values)											
1 [290]	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	MD 3.8 higher (3.3 to 4.4 higher)[4]	LOW
Change in nighttime diastolic blood pressure (mm Hg) (Better indicated by higher values)											
1 [290]	randomised trials[1]	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0[3]	0[3]	-	MD 1.2 higher (0.6 to 1.8 higher)[4]	LOW

[1] Meta-analysis of 5 RCTs.
[2] Unclear randomisation process; unclear allocation concealment; unclear blinding; unclear ITT analysis; unclear drop-out rates
[3] Not stated. Total number of patients was 801
[4] p<0.001
[5] p=0.55

Table 37: Evidence profile comparing treatment targeted to home DBP vs.treatment targeted to ambulatory DBP Niiranen 2006[439]

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Home blood pressure measurement	Ambulatory blood pressure measurement	Relative (95% CI)	Absolute	
Home systolic blood pressure (mm Hg) (follow-up 24 weeks; Better indicated by lower values)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	46	-	MD 2.6 higher (2.3 lower to 7.4 higher)[3]	VERY LOW
Home diastolic blood pressure (mm Hg) (follow-up 24 weeks; Better indicated by lower values)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	46	-	MD 2.6 higher (0.1 lower to 5.2 higher)[4]	VERY LOW
24-h systolic blood pressure (mm Hg) (follow-up 24 weeks; Better indicated by lower values)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52	46	-	MD 0.6 higher (3.0 lower to 4.3 higher)[5]	LOW
24-h diastolic blood pressure (mm Hg) (follow-up 24 weeks; Better indicated by lower values)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52	46	-	MD 1.5 higher (1.0 lower to 3.9 higher)[6]	LOW
Clinic systolic blood pressure (mm Hg) (follow-up 24 weeks; Better indicated by lower values)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	46	-	MD 1.1 higher (3.7 lower to 5.9 higher)[7]	VERY LOW
Clinic diastolic blood pressure (mm Hg) (Better indicated by lower values)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	46	-	MD 1.3 higher (5.0 lower to 2.3 higher)[8]	VERY LOW
Number of patients who reached target BP (follow-up 24 weeks)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	30/52 (57.7%)	20/46 (43.5%)	RR 1.33 (0.89 to 1.99)	143 more per 1000 (from 48 fewer to 430 more)	VERY LOW

Number of patients progressing to combination therapy (follow-up 24 weeks)											
1 [439]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	34/52 (65.4%)	31/46 (67.4%)	RR 0.97 (0.73 to 1.29)	20 fewer per 1000 (from 182 fewer to 195 more)	VERY LOW

[1] Unclear allocation concealment; unclear blinding; no ITT analysis
[2] 95% CI crosses MID
[3] p = 0.29
[4] p = 0.06
[5] p = 0.72
[6] p = 0.23
[7] p = 0.66
[8] p = 0.46
[9] 95% CI crosses both MIDs

Table 38: Evidence profile comparing treatment managed with ambulatory measurements vs.treatment managed with clinic measurements (Conen 2009)[137]

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ambulatopry blood pressure measurement	Clinic blood pressure measurement	Relative (95% CI)	Absolute	
Change in 24-h systolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [137]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70	66	-	mean 3.6 lower (7.0 to 0.3 lower)[3]	VERY LOW
Change in 24-h diastolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [137]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	66	-	MD 0.9 lower (3.0 lower to 1.1 higher)[4]	LOW
Change in clinic systolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [137]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70	66	-	MD 4.4 lower (10 lower to 1.1 higher)[5]	VERY LOW
Change in clinic diastolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [137]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	66	-	MD 0.4 lower (3.6 lower to 2.8 higher)[6]	LOW
Mean number of antihypertensive drugs used (follow-up 1 years; Better indicated by lower values)											
1 [137]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	70	66	-	mean 0.19 lower (0.53 lower to 0.15 higher)[8]	VERY LOW
Patients with controlled 24-h blood pressure (follow-up 1 years)											
1 [137]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42/70 (60%)	28/66 (42.4%)	RR 1.41 (1.01 to 1.99)[9]	174 more per 1000 (from 4 more to 420 more)	VERY LOW

Patients with controlled office blood pressure (follow-up 1 years)											
1 [137]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	29/70 (41.4%)	23/66 (34.8%)	RR 1.19 (0.77 to 1.83)[10]	66 more per 1000 (from 80 fewer to 289 more)	VERY LOW

[1] No details on allocation concealment; open label; no ITT analysis
[2] 95% CI crosses MID
[3] p = 0.03
[4] p = 0.37
[5] p = 0.12
[6] p = 0.81
[7] 95% CI crosses both MIDs
[8] p for difference = 0.49

[9] p = 0.04
[10] p = 0.4

Table 39: Evidence profile comparing treatment managed with home measurements vs.treatment managed with clinic measurements (Staessen 2004)[554]

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Home blood pressure measurement	Clinic blood pressure measurement	Relative (95% CI)	Absolute	
Patients able to permenantly stop antihypertensive drug treatment (follow-up 1 years)											
1 [554]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/203 (25.6%)	22/197 (11.2%)	RR 2.29 (1.45 to 3.63)[2]	144 more per 1000 (from 50 more to 294 more)	MODERATE
Clinic systolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [554]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	203	197	-	MD 6.8 higher (3.6 to 9.9 higher)[4]	LOW
Clinic diastolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [554]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	203	197	-	MD 3.5 higher (1.9 to 5.1 higher)[4]	LOW
Home systolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [554]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	203	197	-	MD 4.9 higher (2.5 to 7.4 higher)[4]	LOW
Home diastolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [554]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	203	197	-	MD 2.9 higher (1.5 to 4.3 higher)[4]	MODERATE
24-h systolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [554]	randomised	serious[1]	no serious	no serious	serious[3]	none	203	197	-	MD 4.9 higher (2.5 to 7.4	LOW

Update 2011

	trials		inconsistency	indirectness						higher)[4]	
24-h diastolic blood pressure (mm Hg) (follow-up 1 years; Better indicated by lower values)											
1 [554]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	203	197	-	MD 2.9 higher (1.4 to 4.4 higher)[4]	MODERATE

[1] Unclear allocation concealment
[2] log-rank p<0.001
[3] 95% CI crosses MID
[4] p <0.001

9.6.2 Economic evidence

An economic evaluation should ideally compare all relevant alternatives. No studies were identified in the update search comparing all of clinic blood pressure monitoring (CBPM), ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) for assessing blood pressure (BP) control in treated patients.

Two studies comparing CBPM and ABPM in treated patients were identified but were excluded as were judged to have serious methodological limitations[374,512].

One study (Staessen 2004[554]) was identified that examined the examined the cost effectiveness of HBPM compared with CBPM. This is summarised in the HBPM versus CBPM economic evidence profile below (Table 40, Table 41). A full evidence table is also provided in Appendix G: Evidence tables – health economic studies (2011 update). One other study of this comparison was also identified but was excluded in line with the review protocol as the HBPM included a telemonitoring component[476]. The Staessen 2004 study[554] was also included in the clinical review above. Note that this study is in a population diagnosed with CBPM and this may impact the applicability to a population diagnosed by another method. This is because if you are diagnosed by CBPM and then monitored by ABPM to some extent the result will be about the people who were incorrectly diagnosed in the first place not just differences in follow-up monitoring.

No cost-effectiveness studies were included in Clinical Guideline 18 relating to this topic.

Table 40: HBPM versus CBPM (assessing response to treatment) – economic study characteristics

Study	Applicability	Limitations	Other Comments
Staessen 2004[554] Belgium	Partially applicable(a)	Potentially serious(b)	• CBPM diagnosed population who are treated or not treated. • CPBM vs HBPM to assess BP control with treatment intensified if DBP >89mmHg, reduced if DBP <80mmHg. • Within-RCT analysis. • Costs: Antihypertensive drugs, physician visits, HBPM.

a) Some uncertainty about applicability of Belgian resource use and unit costs. Some uncertainty about applicability to a population not diagnosed with CBPM. QALYs not used (cost consequence analysis).

b) Given that blood pressure was significantly different, other clinical events and costs of these may be relevant and time horizon may be insufficient. Within trial analysis and so does not incorporate all available evidence on differences between options and results of this study inconsistent with meta analysis included in clinical review; clinical study considered to have methodological limitations.No analysis of uncertainty.

Table 41: HBPM versus CBPM (assessing response to treatment) – economic summary of findings (mean per person)

Study	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Staessen 2004[554] Belgium	-£256(a)	BP increased; medication discontinuation increased; no significant difference in left ventricular mass or symptoms	Lower costs with HBPM but worse BP control	NR

a) Converted from 2002 Belgium 2002 using purchasing power parities[468]

Update 2011

9.6.3 Evidence statements – clinical

One well-conducted meta-analysis[96] found that:

- Self-monitoring was significantly better than usual care for:
  - reducing clinic SBP and DBP (SBP: 20 RCTs, N=5898; DBP: 23 RCTs, N=6038) [very low and low quality evidence]
  - proportion of patients achieving target clinic blood pressure (12 RCTs, N=2260) [very low quality evidence]
  - There was NS difference between self-monitoring and usual care for reduction in mean daytime SBP and DBP ABPM (3 RCTs, N=572). [low quality evidence]
- When self-monitoring was accompanied by an additional co-intervention, participants were more likely to meet target blood pressure compared to when there was none.

One meta-analysis[290] found that:

- with anti-hypertensive treatment (regardless of drug class used for treatment):
  - clinic SBP and DBP fell significantly more than home blood pressure [very low quality evidence]
    - home blood pressure fell approximately 20% less than clinic blood pressure
    - changes in clinic blood pressure were linearly related to those of home blood pressure
    - the difference between clinic blood pressure and homeblood pressure was attributable to the difference in baseline blood pressure levels
  - home blood pressure fell significantly more than daytime ambulatory SBP and night-time ambulatory SBP and DBP [low quality evidence]
    - daytime ambulatory SBP fell 15% less and night-time ambulatory SBP fell 30% less than home blood pressure
  - the reduction in daytime ambulatory DBP was NS different than the reduction in home blood pressure [low quality evidence]
  - changes in home SBP were intermediate between clinic and ambulatory SBPs (for 24h, daytime and night-time measurements)

Update 2011

One RCT*[439] found that there was NS difference between treatment targeted to home DBP vs. targeted to ABPM DBP for:

- Home SBP and DBP blood pressure measurements (end of trial) [very low quality evidence]
- 24h ABPM SBP and DBP blood pressure measurements (end of trial) [low quality evidence]
- Clinic SBP and DBP blood pressure measurements (end of trial) [very low quality evidence]
- number of patients who reached target blood pressure [very low quality evidence]
- intensity of anti-hypertensive treatments (number of patients progressing to combination therapy) [very low quality evidence]

One RCT[137] found that:

- treatment managed with ABPM measurements was significantly better than treatment managed with CBPM for:
  - reductions in mean 24h ABPM SBP [very low quality evidence]
  - number of patients with controlled 24-hour blood pressure [very low quality evidence]
- there was NS difference between treatment managed with CBPM measurements versus measured with ABPM for:

- reductions in mean clinic SBP and DBP [low and very low quality evidence]
- reductions in mean 24h ABPM DBP [low quality evidence]
- number of patients with controlled clinic blood pressure measurements [very low quality evidence]
- number of antihypertensive drugs used [very low quality evidence]

One RCT*[554] found that:

- treatment managed with home blood pressure was significantly better than treatment managed with clinic blood pressure measurements for:
  - number of patients who could permanently stop a-HT treatment [moderate quality evidence]
- treatment managed with clinic blood pressure was significantly better than treatment managed with home blood pressure measurements for :
  - reduction in clinic SBP and DBP blood pressure [low quality evidence]
  - reduction in home SBP and DBP blood pressure [low and moderate quality evidence]
  - reduction in 24h ABPM SBP and DBP ABPM blood pressure [low and moderate quality evidence]

*NOTE: Both groups were given the same target BP for treatment, despite being measured by the two different methods, which would lead to a systematic under-treatment in one of the groups

9.6.4 Evidence statements – health economic

- No cost-effectiveness analyses were identified incorporating all of CBPM, ABPM and HBPM in the assessment of response to treatment.
- One partially applicable study with potentially serious limitations found that in a population diagnosed with hypertension using CBPM, monitoring response to treatment and adjusting treatment using HBPM was cost saving compared to CBPM; blood pressure control was however worse.

Update 2011

9.6.5 Link from evidence to recommendations

All clinical outcome trials have used CBPM to monitor treatment efficacy. Some of these trials have embedded substudies using HBPM or ABPM to monitor treatment effects but for the primary outcome measures, the blood pressure control was invariably monitored using CBPM. A meta-analysis by Bray et al., 2010 [96]showed that patients self monitoring their own blood pressure was associated with lower achieved CBPM and a greater liklihood of achieving the clinic blood pressure target. Interestingly another analysis (Ishikawa aet al., 2008)[290] also found that HBPM averages fell approximately 20% less than the corresponding CBPM but that the relationship between the two measures was linear. Two studies (Niiranen et al., 2006 and Conen et al., 2009)[137,439] examined whether monitoring blood pressure control with CBPM versus ABPM or HBPM impacted on blood pressure control and the number of treatements used to achieve the blood pressure targets and found no differences between blood pressure monitoring methods. The GDG noted that there was inadequate data comparing the use of HBPM or ABPM to monitor blood pressure control and whether they offer any important advantages over CBPM. Routine monitoring with HBPM or ABPM would also require considerable investment in additional monitors beyond that required for diagnosis of hypertension. The GDG recognised that patients may wish to monitor their own blood pressure using HBPM and the possibility that engaging patients in their own blood pressure monitoring process using HBPM could lead to better blood pressure control (NICE Medicine's Adherence Guideline, CG76)[426]. The GDG noted, however, that further data on self-monitoring and

self management of blood pressurewas required before this could be recommended as the preferred modality for monitoring blood pressure control in people with treated hypertension.

The GDG recommended that for people receiving antihypertensive medications, clinic blood pressure readings should usually be used to monitor their response to treatment.

The GDG discussed how to monitor blood pressure in people with significant discrepancies between their clinic blood pressure readings, recognising that CBPM may not provide an accurate representation of their blood pressure control. In people identified as having a white coat effect (people who are hypertensive according to their ABPM daytime average blood pressure but with a CBPM at diagnosis that exceeded their ABPM by ≥20 mmHg systolic, or ≥10mmHg diastolic) the GDG recommended that HBPM should be considered as an adjunct to CBPM to monitor the response to antihypertensive treatment and/or lifestyle modification.

9.6.6 Recommendations

25. Use clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modification or drugs. [new 2011]

26. For people identified as having a 'white-coat effect', consider ABPM or HBPM as an adjunct to clinic blood pressure measurements to monitor the response to antihypertensive treatment with lifestyle modification or drugs. [new 2011]

9.6.7 Research recommendations

4. In adults with primary hypertension, does the use of out-of-office monitoring (HBPM or ABPM) improve response to treatment?

There is likely to be increasing use of home and ambulatory blood pressure monitoring for the diagnosis of hypertension as a consequence of this guideline update. There are, however, very little data regarding the utility of HBPM or ABPM as means of monitoring blood pressure control or as indicators of clinical outcome in treated hypertension, compared with clinic blood pressure monitoring. Studies should incorporate HBPM and/or ABPM to monitor blood pressure responses to treatment and their usefulness as indicators of clinical outcomes.

Update 2011

9.7 Blood pressure targets for treatment

Review question: in adults with primary hypertension, what is the optimum BP that should be reached for once treatment has been initiated/ targeted for treatment?

9.7.1 Clinical evidence

The literature was searched for studies published since the original guideline (2003 onwards). All study types were included, if the population did not consist of people who were exclusively diabetic or had CKD. Studies were excluded if they did not stratify results into more than 1 different BP value / target.

Fifteen studies[29,49,82,134,168,209,280,282,298,462,463,539,549,616,623,655] were found that fulfilled the inclusion criteria and assessed what the optimum target blood pressure should be for treating people with primary hypertension. One of the studies ([29,298]) was published as two separate papers reporting different assessment methods or outcomes, so this study has only been counted once, however results from both papers are reported and referenced here.

The studies addressing the question were categorised into three different types:

1. More vs less intense treatment studies - (eight studies; eight papers)[29,82,280,282,298,463,549,616] – those that assess people who were randomised to more intense (strict or intense) BP lowering vs. less intense (mild or standard) BP lowering
2. Within-treatment BP studies (eight studies)[49,134,168,209,462,539,623,655] - those that assess within-treatment / achieved BP values and the associated risk of developing clinical outcomes.
3. Target BP studies(one study)[462] - those that target people to different specific blood pressure values (for example, according to age groups)

Details of all the included studies are summarised in Table 42 and Table 43 and Table 44.
NOTE: Data from the more vs less intense treatment studies was not pooled into meta-analysis because the studies varied widely in the following factors: treatment targets, interventions used to reach the target (type of anti-hypertensive drug), follow-up times, BP measurement method and outcome definitions. Therefore GRADE was performed on each individual RCT to give a quality rating for each outcome measure used in the study (see

Update 2011

Table 45).

More versus less intense treatment studies

Table 42: Study details and results for optimal blood pressure targets (trials comparing more vs. less intense blood pressure lowering treatment regimens were used to assess this)

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Target BP for Treatment (SBP / DBP, mmHg)	Outcomes	Final mean BP (SBP/DBP mmHg) and number people reaching target	Best Target BP (authors' conclusions)	QUALITY
BPLTTC, 2008[82] SR/MA	190,606 31 RCTs	HT not clear if underlying diabetes / CKD	Clinic	165/104 (<65 years) 173/104 (≥65 years)	Minimum of 1000 patient years in each trial	Not specified (just more vs. less intense)	CV events	not reported	NS difference between more vs. less intense BP lowering regimens; extent of risk reduction was directly related to the degree of BP lowering	LOW and VERY LOW (age <65 and >65 respectively); based on moderate quality SR/MA which included low to high quality RCTs)
Hosohata et al., 2007[280] RCT (HOMED-BP)	971	HT	Home	152/90 (more and less)	12 months	More intense <125/80 Less intense 125-134/80-84	BP changes/achievement of target BP	More: 132/80; 25% Less: 133/79; 45%	NS difference between more vs. less intense BP lowering regimens for change in BP; More people in less intense reached target BP.	MODERATE AND LOW
JATOS study group 2005 and	4320	HT	Clinic	172/89 (strict	12 months	Strict control	BP changes/ac	12 months: Strict: 139/76;	Strict treatment group was SS better for:	MODERATE

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Target BP for Treatment (SBP / DBP, mmHg)	Outcomes	Final mean BP (SBP/DBP mmHg) and number people reaching target	Best Target BP (authors' conclusions)	QUALITY
2008[29,298] RCT (JATOS)				and mild)	and 2 years	<140 SBP Mild control 140-160 SBP	hievement of target BP; morbidity (CVD and renal failure) and mortality	60% Mild: 147/79; 67% 2 years: Strict: 136/75 Mild: 146/78	lower final BP value (1 and 2 years) But was SS worse for number of people achieving target BP (1 year) There was NS difference for morbidity and mortality at 2 years	
Solomon et al., 2010[549] RCT (EXCEED)	228	HT	Clinic	161/90 (intensive) 162/94 (standard)	24 weeks	Intensive treatment <130 SBP Standard treatment <140 SBP	BP changes/achievement of target BP	Intensive: 131/75 Standard: 137/80 Intensive: 46% <130; 82% <140 Standard: 60% <140	More intense treatment was SS better for: lower final BP value More intense treatment increased chance of achieving SBP <140 mmHg	MODERATE AND LOW
Verdecchia et al., 2009[616] RCT (Cardio-Sis)	1111	HT	Clinic	163/90 (tight and usual control)	2 years	Tight control <130 SBP Usual	BP changes/achievement of target BP;	Tight: 132/77 Usual: 136/79 Achieved <140:	Tight control group was SS better for: reduction in CV events percentage achieving SBP (<130 and <140)	MODERATE

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Target BP for Treatment (SBP / DBP, mmHg)	Outcomes	Final mean BP (SBP/DBP mmHg) and number people reaching target	Best Target BP (authors' conclusions)	QUALITY
						control <140 SBP	CV endpoint	Tight 79% Usual 67% Achieved <130: Tight 72% Usual 27%	reduction in BP value	
Ichihara et al., 2003[282] RCT	140	HT	Clinic (pulse pressure analyser)	177/101 (mean)	12 months	Intense control <130/85 Moderate control <140/90	BP changes	Intense: 129/78 Moderate: 152/87	Intense control group was SS better for: reduction in BP value	LOW
Ogihara et al., 2003[463] RCT (VALISH)	3260	ISH	Clinic	169/81 (mean)	3.07 years (median)	Strict control <140 Moderate control ≥140 to <150 mmHg	BP changes/achievement of target BP; CV endpoint	Strict: 137/75 Moderate: 142/77 78% and 48% achieved target (strict and moderate groups respectively)	Strict control group was SS better for: percentage achieving target BPs (<140 and ≥140 to <150) reduction in BP value There was NS difference between the groups for:: reduction in CV events	MODERATE AND LOW

NT = normotensives; HT = hypertensives; ISH = isolated systolic hypertensives

Within-treatment blood pressure studies

Table 43: Study details and results for within-treatment / achieved blood pressure studies assessing the optimal blood pressure target for treatment

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Outcomes	In-treatment / achieved BPs	Best Target BP (authors' conclusions)	QUALITY
Wang et al., 2005623 SR/MA	12903 young (30-49 years ≥160/95mmHg) 3 trials; 14323 old (60-79 years ≥160mmHg / <95mmHg) 5 trials; 1209 very old patients (≥80 years ≥160mmHg / <95mmHg)	HT	Clinic	young: 154/100 old: 174/83 very old: 176/78	Median young: 5 years; old: 3.9 years; very old: 3.8 years	CV events; CV mortality	young: ≥160 / ≥95 old and very old: ≥160 / <95 (ISH)	Anti-hypertensive treatment improves outcomes mainly by lowering SBP; Patients with >median SBP reduction risk of outcome decreased regardless of decrease in DBP or achieved DBP. Active treatment tended to reduce the risk of any outcome to a similar extent (i.e. DBP did not lead to differences in cardiovascular outcome as long as SBP substantially decreased.	MODERATE quality SR/MA based on low quality observational studies
Zanchetti et al., 2009655 SR of different studies	a) low-risk patients (n=13 trials); b) elderly patients (n=11	HT (diabetic studies assessed by subgroup analysis)	Clinic	n/a	n/a	Total mortality; CV events; CV mortality	Risk groups (High, medium, low)	Achieved level of risk does not appear to correlate closely with the SBP values achieved. In high risk patients there is a 'ceiling effect' for treatment benefits. Delaying	MODERATE quality SR/MA based on low quality observational studies

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Outcomes	In-treatment / achieved BPs	Best Target BP (authors' conclusions)	QUALITY
	trials); c) diabetic patients (n=11 trials; these would be outside our inclusion criteria); d) high-risk patients (n=18 trials)							therapeutic correction of CV risk factors until a high level of risk is achieved,blunts the full benefits of interventions.	
Arima et al., 200649 RCT (PROGRESS) Treated as observational study as not using randomised groups	6105	Cerebrovascular disease (not necessarily HT)	Clinic	Stratified into: <120; 120-139; 140-159; ≥160	Median 3.9 years	Risk of Stroke	Stratified into: <120; 120-139; 140-159; ≥160	Patients with cerebrovascular disease would have lowest risk of recurrence of stroke with BP lowered to approximately 115/75mmHg	LOW
Coca et al., 2008134 Treated as observational study as not	22,576	HT	Clinic	Stratified into: SBP <140 vs. ≥140	61,836 patient years	Fatal/non-fatal stroke; Achieving target BP	SBP Stratified into: <140 vs. ≥140 DBP Stratified into: <90 vs. ≥90	Patients who achieved follow up SBP <140mmHg had lower risk of stroke than those with SBP ≥140mmHg; DBP <90mmHg	LOW

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Outcomes	In-treatment / achieved BPs	Best Target BP (authors' conclusions)	QUALITY
using randomised groups RCT (INVEST)				DBP: <90 vs. ≥90		<140/90		had lower risk than ≥90mmHg.	
Fagard et al., 2007209 Post-hoc analysis of RCT (Syst-Eur) Treated as observational study as not using randomised groups	4583	HT (systolic)	Clinic	Mean 174/86	median 2 years; further 4 years+ follow-up	Cerebrovascular events; CHD events; mortality; CV events; CV mortality	DBP Stratified into: ≥95; <9585; <85-75; <75-65; <65-55; <55	Antihypertensive treatment can be intensified to prevent cardiovascular events when systolic BP is not under control in older patients with systolic hypertension, at least until diastolic BP reaches 55mmHg, except in patients with coronary heart disease (MI/angina), in whom diastolic should not be lowered to <70mmHg.	LOW
Shimamoto et al., 2008539 Within-group comparison study (J-HEALTH)	26,512	HT	Clinic	Mean 166/95	Mean 3 years	Composite of CV events	SBP Stratified into: <130; 130-139; 140-149; 150-159; ≥160 DBP Stratified into: <75; 75-79; 80-84; 85-90; ≥90	Clear relationship between BP control and cardiovascular events; incidence of events increased in patients with SBP ≥140/85mmHg (≥140/90mmHg in very elderly) and in diabetic patients with BP ≥130/85mmHg during treatment. Results suggest	LOW

Reference / study type	N	Population	BP measurement method	Baseline mean BP (SBP/DBP mmHg)	Follow-up	Outcomes	In-treatment / achieved BPs			Best Target BP (authors' conclusions)	QUALITY
										that BP should be below 140/90 for reducing the risk of CV events. BP was controlled below 140.90 mmHg in the very elderly patients (≥85 years) and they also had a lower risk of CV events.	
Denardo et al., 2010168 A-priori subanalysis of RCT (INVEST) Treated as observational study as not using randomised groups	22,576	HT	Clinic	Overall mean: 149.5/86.3	24 months	Mortality, MI stroke	Stratified into age-groups and SBP / DBP nadirs.*			J-shaped relationship (among each age-group) with on-treatment SBP and DBP and clinical end-points / events. SBP at HR nadir increased with increasing age – highest for teh very old (140 mmHg). DBP at HR nadir was only slightly loer for the very old (70 mmHg). Therefore optimal management may involve a higher target SBP and lower target DBP for very old people (≥80 years) vs other age-groups.	LOW
							Age	BP nadirs			
								SBP	DBP		
							<60	110	75		
							60-<70	115	75		
							70-<80	135	75		
							≥80	140	70		

NT = normotensives; HT = hypertensives;

Target BP studies

Table 44: Study details and results for target blood pressure studies assessing the optimal blood pressure target for treatment

Reference / study type	N	Population	BP measurement method	Baseline mean blood pressure (SBP/DBP mmHg)	Follow-up	Outcomes	In-treatment / achieved blood pressure	Best Target blood pressure (authors' conclusions)	QUALITY
Ogihara et al., 2009[462] Sub-analysis of RCT (randomised to ARB vs ACEi) treated as observational study as not using randomised groups	4703	HT	Office	Overall: 163/92	Mean 3.2 years	CV events	All people: 136/78	Higher achieved blood pressure was associated with increased risk of CV events.	LOW

Table 45: GRADE profile for more versus less intense treatment studies

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	more intense BP lowering	less intense BP lowering	Relative (95% CI)	Absolute	Quality
CV events (aged <65 years): SR/MA - BPLTTC (follow-up 1000 patient-years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	212/5024 (4.2%)	365/9360 (3.9%)	RR 0.88 (0.75 to 1.04)	5 fewer per 1000 (from 10 fewer to 2 more)	LOW
CV events (aged >65 years): SR/MA - BPLTTC (follow-up 1000 patient-years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	156/2251 (6.9%)	260/4198 (6.2%)	RR 1.03 (0.85 to 1.24)	2 more per 1000 (from 9 fewer to 15 more)	VERY LOW
Final home SBP 12 months (Hosohata 2007 study) (follow-up 12 months; measured with: mmHg; Better indicated by lower values)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	817	870	-	MD 1 lower (2.2 lower to 0.2 higher)[6]	LOW
% reaching BP target (Hosohata 2007 study) (follow-up 12 months)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	163/817 (20%)	392/870 (45.1%)	RR 0.44 (0.38 to 0.52)[8]	252 fewer per 1000 (from 216 fewer to 279 fewer)	MODERATE
% reaching BP target (JATOS study group) (follow-up 1 years)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	1288/2165 (59.5%)	1453/2155 (67.4%)	RR 0.88 (0.84 to 0.92)[8]	81 fewer per 1000 (from 54 fewer to 108 fewer)	MODERATE
Change in SBP (JATOS study group) (follow-up 1 years; measured with: mmHg; Better indicated by lower values)											

1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	2165	2155	-	MD 7.20 lower (8.05 to 6.35 lower)[10]	MODERATE
Mortality (JATOS study group) . (follow-up 2 years)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	9/2165 (0.4%)	8/2155 (0.4%)	RR 1.12 (0.43 to 2.9)[11]	0 more per 1000 (from 2 fewer to 7 more)	MODERATE
Morbidity (JATOS study group) (follow-up 2 years)											
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	86/2165 (4%)	86/2155 (4%)	RR 1.0 (0.74 to 1.33)[11]	0 fewer per 1000 (from 10 fewer to 13 more)[11]	MODERATE
Change in SBP (Solomon 2010) (follow-up 2 years; measured with: mmHg[12]; Better indicated by lower values)											
1	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	serious[5]	none	114	114	-	MD 5.30 lower (0 to 0 higher)	LOW
% reaching target (Solomon 2010) (follow-up 2 years)											
1	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	94/114 (82.5%)	68/114 (59.6%)	RR 1.38 (1.16 to 1.64)[14]	227 more per 1000 (from 95 more to 382 more)	MODERATE
% reaching target (Verdecchia 2009) (follow-up 2 years)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	399/507 (78.7%)	334/499 (66.9%)	RR 1.18 (1.09 to 1.27)[10]	120 more per 1000 (from 60 more to 181 more)	MODERATE
CV events (Verdecchia 2009) (follow-up 2 years)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	27/507 (5.3%)	52/499 (10.4%)	HR 0.50 (0.31 to 0.79)[16]	51 fewer per 1000 (from 21 fewer to 71 fewer)	MODERATE

Change in SBP (Verdecchia 2009) (follow-up 2 years)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	399/507 (78.7%)	334/499 (66.9%)	RR 1.18 (1.09 to 1.27)[17]	120 more per 1000 (from 60 more to 181 more)	MODERATE
Final SBP (Ichihara 2003) (follow-up 2 years; measured with: mmHg; Better indicated by lower values)											
1	randomised trials	very serious[18]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	71	-	MD 23 lower (0 to 0 higher)[19]	LOW
Change in SBP (Ogihara 2010) (follow-up 2 years; measured with: mmHg; Better indicated by lower values)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	serious[5]	none	1545	1534	-	MD 5.40 lower (6.31 to 4.49 lower)[10]	LOW
% reaching target (Ogihara 2010) (follow-up 2 years)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	0/1545 (0%)	0/1534 (0%)	RR 1.41 (1.33 to 1.5)[10]		MODERATE
CV events (Ogihara 2010) (follow-up 2 years)											
1	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	47/1545 (3%)	52/1534 (3.4%)	HR 0.89 (0.6 to 1.31)[11]	4 fewer per 1000 (from 13 fewer to 10 more)	MODERATE

[1] RCTs included were of low to high quality; the SR/MA itself was of moderate quality
[2] 95% CI crosses both no effect and the lower MID (appreciable benefit/harm)
[3] 95% CI crosses both MIDs (appreciable benefit and appreciable harm)
[4] randomised, ITT, but underpowered and attrition bias
[5] 95% CI crosses the lower MID
[6] NS difference between groups
[7] 95% CI does not cross either MID
[8] Favours less intense (p<0.00001)
[9] Unclear allocation concealment
[10] Favours Intense (p<0.00001)
[11] p>0.05 (NS)
[12] Favours intense (p=0.03)
[13] open label, not true ITT
[14] Favours intense (p=0.0002)
[15] Inadequate allocation concealment and blinding
[16] Favours intense (p=0.03)
[17] Favours intense (p<0.001)
[18] single blind, inadequate allocation concealment, ITT unclear
[19] Favours intense (p<0.05)

9.7.2 Health economic evidence

One study (Jonsson 2003[308]) was identified from the update search that compared different blood pressure targets. This is summarised in the economic evidence profile below (Table 46, Table 47). A full evidence table is also provided in Appendix G: Evidence tables – health economic studies (2011 update). No cost-effectiveness studies were included in Clinical Guideline 18 relating to this topic.

Table 46: Treatment targets – economic study characteristics

Study	Comparators	Applicability	Limitations	Other Comments
Jonsson 2003 Sweden HOT study	Target DBP <90mmHg Target DBP <85mmHg Target DBP <80mmHg	Partially applicable(a)	Potentially serious(b)	• Within RCT analysis (HOT[260]). • Population: Hypertension and DBP110-115mmHg • Follow-up: mean 3.8year. • Costs: antihypertensive drugs, healthcare visits, side effects, cardiovascular hospitalisations.

a) Some uncertainty about applicability of international resource use and Swedish unit costs. QALYs not used (clinical outcomes reported as not significantly different). Discounting not applied.

b) Within RCT analysis and so does not incorporate all available evidence on differences between targets; issues raised with interpretation of clinical trial as achieved BPs very similar despite different targets.

Table 47: Treatment targets – economic summary of findings (mean per person)

Study	Comparators	Incremental cost (£)	Incremental effects	ICER	Uncertainty
Jonsson 2003 Sweden HOT study	Target DBP <90mmHg Target DBP <85mmHg Target DBP <80mmHg	Reference £82(a) £181 (a)	Clinical outcomes were reported as not significantly different between groups – see clinical evidence review for details[260].	N/a	Differences in cost were statistically significant (p<0.01). A sensitivity analysis including non-CV hospitalisations increased total costs but differences between groups were similar.

a) Converted from 1995 Swedish Kroner.

9.7.3 Evidence statements – clinical

More vs. less intense treatment studies (moderate and low quality evidence) showed:

- NS difference for:
  - CV events (2 studies)[82,463] – RRR was related to degree of blood pressure lowering
  - Change in blood pressure (1 study)[280]
  - Morbidity and mortality (1 study)[29,298]
- Less intense was better for:
  - More people reaching target (2 studies)[29,280,298]
- More intense was better for:
  - Lower final blood pressure value (5 studies)[29,282,298,463,549,616]
  - Reduction in CV events (1 study)[616]
  - Percentage reaching target SBP <130 (1 study)[616]
  - Percentage reaching target SBP <140 (3 studies)[463,549,616])

Update 2011

In-treatment / achieved blood pressure studies showed that:

- Higher achieved blood pressure was associated with increased risk CV events (2 studies and 1 SR/MA)[168,539,623]
- Achieved SBP did not correlate with risk CV events (1 SR/MA)[655]
- Blood pressure <140/90 had a lower risk of CV events (2 studies)[134,539]
- Lowest risk of stroke was at blood pressure 115/75 mmHg (1 study)[49]
- DBP did not lead to risk differences as long as SBP substantially decreased (1 SR/MA)[655]
- DBP <90 had a lower risk of stroke (1 study)[134]
- Up to DBP 55 (had lower risk of stroke) when SBP was controlled; except for MI/angina patients where DBP should not be <70 (1 study)[209]
- Optimal management may involve a higher target SBP and lower target DBP for very old people (≥80 years) vs other age-groups (1 study)[168])

Target blood pressure studies showed that:

- Higher achieved blood pressure was associated with increased risk CV events (1 study)[462]

9.7.4 Evidence statements – economic

- One partially applicable within RCT analysis (HOT) with potentially serious limitations found that lower blood pressure targets were associated with higher costs and no significant difference in clinical outcomes.

9.7.5 Link from evidence to recommendations: blood pressure treatment targets.

Update 2011

The GDG assessed a series of studies to define optimal treatment targets for people receiving antihypertensive therapy. The studies addressing this question were categorised into three different types; i) meta-analyses/systematic reviews of trials that had examined “more versus less” blood pressure lowering on treatment, i.e. people randomised to more intense versus less intense blood pressure lowering; ii) analyses of the relationship between achieved blood pressure on treatment versus clinical outcomes; iii) studies targeting patients to specific blood pressure values.

The more versus less studies studies provided more robust evidence for treatment targets because they are randomised controlled trials whereas the studies using post-hoc stratifaction of on-treatment achieved blood pressures versus outcomes are not randomised and are potentially confounded by the fact that the blood pressure response to treatment may reflect underlying vascular damage, i.e. those responding less well to treatment may have more underlying vascular damage and by inference a higher risk of clinical outcomes. Moreover, such studies did not usually adjust the results according to baseline blood pressure, age and other key variables. The results of the more versus less treatment studies failed to show a consistent benefit of the lower blood pressure target on clinical outcomes[82,463] but the relative risk reduction did appear to be related to the extent of blood pressure lowering across the range. One study [29,298] did show a benefit of more intensive lowering on cardiovascular morbidity and mortality. More intensive blood pressure lowering, not surprisingly, was associated with more patients reaching a lower final blood pressue value. One smaller study (Verdechia etal., 2009)[616] did show better regression of LVH with more intensive BP lowering and also as a secondary analysis, a reduction in a composite of cardiovascular outcomes. In studies randomising patients to less intensive blood pressure lowering, more patients achieved the less intensive blood pressure target[29,280,298] reflecting the fact that lower blood pressure targets are more diifuclt to achieve and generally required more medications.

In two studies (one a systematic review) examining the impact of achieved blood pressure on treatment versus clinical oucomes, a higher achieved blood pressure was associated with a higher risk of cardiovascular events [168,539,623] and a blood pressure on treatment of <140/90mmHg

associated with a lower risk of cardiovascular events in two studies[134,539]. Similarly, in one study, a higher achieved blood pressure was associated with a increased risk cardiovascular events [462]. In constrast, in one systematic review, the achieved systolic blood pressure did not correlate with the risk of cardiovascular events (1 SR/MA)[655]. The risk of stroke appeared particularly sensitive to achieved blood pressure on treatment with the lowest risk in those with the lowest on-treatment blood pressure, down to a value of 115/75 mmHg [49]. Similar findings were observed for on-treatment stroke risk in the analysis of Sleight et al (2009). This latter study also stratified on treatment outcomes according to baseline blood pressure and showed that those in patients with a baseline systolic blood pressure <130mmHg, further blood pressure lowering appeared to be associated with an increased risk of cardiovascular events. This latter finding from a large clinical trial of patients at high cardiovascular risk does not support the uncritical adoption of lowering blood pressure in all patients at high risk of cardiovascular disease, irrespective of their baseline blood pressure.

A Cochrane analysis of prospective studies of more versus less blood pressure treatment identified only studies randomised on the basis of lowering diastolic pressure and showed no evidence of more versus less blood pressure lowering on clinical outcomes (add ref – we did discuss). The same analysis noted an absence of any studies designed to prospectively examine the optinal systolic treatment target.

A formal cost effectiveness analysis of more versus less blood pressure lowering was not prioritised as there was no clear evidence of effectivenss. From this perspective, one potentially applicable study was identified (HOT study)[260] with potentially serious limitations. This study found that lower blood pressure targets were associated with higher costs, due to the requirement for more treatment and no significant difference in clinical outcomes.

Based on these analyses, the GDG concluded that most clinical trials had adopted a treatment target of <140/90 mmHg and that there was no convincing evidence supporting a lower treatment target for the pharmacological treatment of hypertension. That said, the evidence specifically examining optimal treatment targets for hypertension is inadequate and consequently the optimal treatment target could not be clearly defined with certainty. The GDG recommended that the target blood pressure for people treated for hypertension should be <140/90 mmHg (consistent with the usual target bloodpressure in clinical outcome trials), based on clinic blood pressure readings. For those with a white coat effect and thus requiring HBPM to monitor their blood pressure control, or those patients preferring to use HBPM to monitor their blood pressure control, the recommended target should be a HBPM average of <135/85mmHg (based on the equivalent values for CBPM versus HBPM used for diagnosis of hypertension). The GDG also noted the need for further studies prospectively randomising people to more versus less systolic blood pressue lowering to determine the optimal systolic pressure treatment target for people with treated hypertension.

Update 2011

Blood pressure thresholds and targets for people over the age of 80 years:

Previous guidelines in 2004 and 2006 noted the considerable uncertainty surrounding the balance of benefits and risk when considering initiating blood pressure lowering treatment for people over the age of 80 years. The uncertainty reflected tha fact that people over the age of 80 years had largely been excluded from recruitment into blood pressure treatment trials and thus, the evidence of benefit of treatment in this age group had not been established. Whilst it seemed likely that these people would accrue benefits from blood pressure lowering, it was also conceivable that treatment coud lead to more adverse effects such as syncope and falls, that might have offset any benefits of treatment.

The GDG considered one systematic review (Bejan-Angoulvant, 2010)[67] which compared the development of clinical outcomes in people aged ≥80 years who had been randomised to antihypertensive treatment versus placebo. This meta-analysis included data from 8 studies, including subgroups aged ≥80 years who had been randomized into treatment trials as well as one large study (HYVET study) (Beckett, et al 2009)[63] which included only hypertensive people aged

≥80years. The total sample size was 6,701 and the mean follow-up was 3.5 years. The baseline blood pressure and initial therapy differed between studies. The results of the analysis showed that in hypertensive people ≥80 years, pharmacological treatment was significantly better than placebo for reducing the risk of stroke, cardiovascular events and heart failure. The HYVET study provided the most robust and highest quality evidence and had randomised people at a clinic systolic blood pressure threshold of ≥160mmHg and treated blood pressure to a clinic blood pressure target of <150/90mmHg. The GDG noted that the population randomised into the HYVET study were generally healthier, with lower comorbidity than typically seen in this age group.

The GDG recommended that people aged ≥80 years, should be offered pharmacological treatment for hypertension when they have stage 2 hypertension, i.e. when their ABPM daytime average blood pressure is ≥150/95mmHg and should be treated to a clinic blood pressure target of <150/90mmHg. If HBPM is being used to monitor blood pressure control in people over the age of 80 years, then the blood pressure target equivakent to the recommended CBPM target of <150/90mmHg, using a HBPM average would be ~140/85mmHg.

This recommendation regarding the treatment of people over the age of 80 years applies to people who have stage 2 hypertension but are not currently treated when they reach the age of 80 years. It does not mean that people reaching this age who have been previously treated at lower levels of blood pressure and/or to a lower treatment target of <140/90mmHg should have their treatment back-titrated. There is an important distinction between continuing long-term and well-tolerated treatment in people over the age of 80 years and the initiation of blood pressure lowering therapy at that age. For the latter, the evidence supports initiation of treatment at stage 2 hypertension, treating to a CBPM target of <150/90mmHg. It is conceivable lower thresholds and targets for this age group might be appropriate, however, the balance if safety and efficacy for a more aggressive treatment strategy has not been established. Indeed, before the emergence of the recent evidence (see above), there was genuine uncertainty about the balance of efficacy versus harm with regard to initiating blood pressure treatment in people aged 80 years or over. In this regard, the GDG also noted that the key studies supporting this recommendation generally included older people who were fit and active and had low levels of comorbidities. The GDG recommended that treatment decisions in those aged ≥80 years should be based on the realistic expectations of clinical benefit from treatment in the context of other comorbidities which might limit life expectancy. Furthermore, the GDG recommended that for older patients who are already receiving antihypertensive treatment when they reach the age of 80 years, the aforementioned evidence supports continuation of treatment.

Update 2011

9.8 Recommendations

27. Aim for a target clinic blood pressure below 140/90 mmHg in people aged under 80 years with treated hypertension. [new 2011]

28. Aim for a target clinic blood pressure below 150/90 mmHg in people aged 80 years and over with treated hypertension. [new 2011]

29. When using ABPM or HBPM to monitor the response to treatment (for example, in people identified as having a 'white-coat effect' and people who choose to monitor their blood pressure at home) aim for a target average blood pressure during the person's usual waking hours of:
    - below 135/85 for people aged under 80 years
    - below 145/85 in people aged over 80 years and over. [new 2011]

9.9 Research Recommendation

5. In people with treated hypertension, what is the optimal systolic blood pressure?

Data on optimal blood pressure treatment targets, particularly for systolic blood pressure, are inadequate. Current guidance is largely based on the blood pressure targets adopted in clinical trials but there have been no large trials that have randomised people with hypertension to different systolic blood pressure targets and that have had sufficient power to examine clinical outcomes.

9.10 Frequency of review

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.

Update 2011

10 Integrating the assessment of blood pressure, target organ damage and cardiovascular risk assessment and clinical decision making regarding treatment initiation, treatment and targets

The algorithms found in Section 5.1 illustrate the recommended schema for the assessment of blood pressure, clinical decision making regarding initation of treatment and review. Clinic blood pressure is usually measured at scheduled reviews in primary care or on occasions opportunistically during health screening. When clinic blood pressure is <140/90mmHg, further investigation is not usually indicated and clinic blood pressure should be re-measured at least every five years. More frequent review should be considered in people whose clinic blood pressure is close to the 140/90mmHg threshold or in those in whom there is evidence of cardiovascular disease or when their estimated 10 year cardiovascular disease risk is close to, or exceeds 20%.

People with a clinic blood pressure ≥140/90mmHg should be offered ABPM to determine whether their daytime ABPM average is ≥135/95mmHg. If a person's ABPM daytime average is <135/85mmHg they should be offered annual review. If the ABPM daytime average is ≥135/85mmHg (i.e. stage 1 hypertension), they should be offered lifestyle advice and considered for pharmacological treatment. If their ABPM day time average is ≥150/95mmHg (i.e. stage 2 hypertension), they should be offered lifestyle advice and pharmacological treatment.

Update 2011

All people considered hypertensive should undergo routine clinical evaluation to determine the presence of target organ damage, cardiovascular disease, diabetes or CKD and have their 10 year cardiovascular disease risk estimated. A review of lifestyle factors that may contribute to the development of hypertension and/or increase a patient's cardiovascular disease risk should also be undertaken. If the initial clinical evaluation suggests the possibility of secondary hypertension, the patient should be referred for specialist review.

If the patient has stage 1 hypertension and evidence of TOD, cardiovascular disease, diabetes, CKD, or their estimated 10 year CVD risk is ≥20%, they should be offered treatment. If not, they should be offered lifestyle advice and annual review as their blood pressure and cardiovascular disease risk will increase over time. For younger people i.e. aged <40 years, special consideration should be given to the possibility of secondary hypertension and the exclusion of target organ damage before deciding not to initatite therapy for stage 1 hypertension and specialist review should be considered. If not offered pharmacological treatment, they should be offered lifestyle advice and annual review.

If the initial clinic blood pressure is ≥180/110mmHg and there is evidence of target organ damage and/or cardiovascular disease, the initiation of pharmacological therapy should not be delayed whilst awaiting the results of ABPM. If the initial evaluation suggests the possibility of accelerated hypertension or phaechromocytoma, the patient should be referred immediately (same day) for specialist care.

When pharmacological treatment is considered, all patients should be offered lifestyle advice (see section 11). People at higher risk, i.e. with target organ damage, established CV disease, diabetes, CKD or an estimated 10 year CVD risk ≥20%, should be considered for additional therapy to reduce their cardiovascular disease risk (e.g. statins and antiplatelet therapy) if not already initiated (see NICE guidance on CVD risk, statins and antiplatelet therapy).

When pharmacological treatment is offered, clinic blood pressure should usually be used to monitor the response to treatment and the target blood pressure is <140/90mmHg in people aged <80 years and <150/90mmHg in people aged ≥80 years.

For people with white coat hypertension (see section 6.4), home blood pressure monitoring (section 9.6) should be considered to monitor the response to treatment - the target blood pressure for optimal treatment is a HPBM average of <135/85mmHg.

Update 2011

11 Lifestyle interventions

11.1 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[627]. 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 eight 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 eight 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[31,118,187,192,214,293,366,388,37,117,153,204,205,238,239,248,251,268,279,299,300,319-323,444,489,632-634,152,241,350,407]. 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 (Table 48) and this may reflect poor methodological conduct, further weakening the strength of evidence and consequent recommendations for clinical care.

Table 48: Summary characteristics of trials of lifestyle interventions

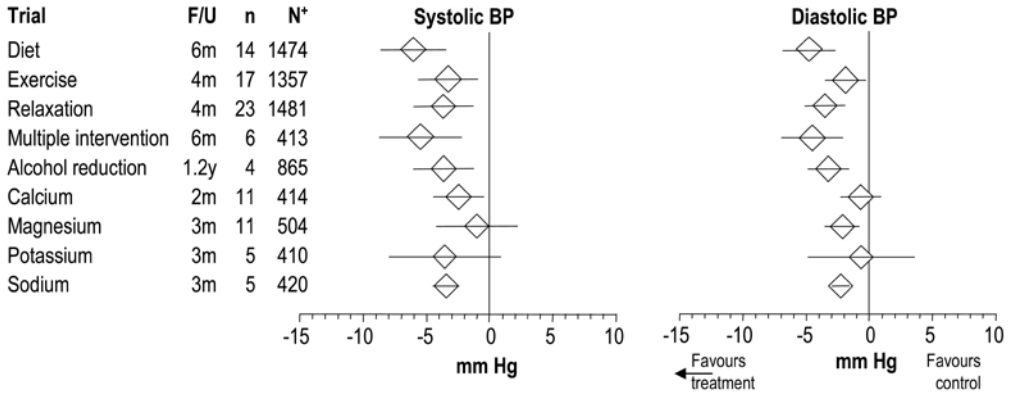
Type of intervention	Number of studies	Number of participants	Quality markers:		Baseline comparability a	Blinding of:		
			Randomisation description	Concealment of allocation		Participant b	Treatment provider	Outcome assessor
Diet	14	1,474	3 (21%)	2 (14%)	12 (86%)	-	-	4 (29%)
Exercise	17	1,357	1 (6%)	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 4) 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 4: Overview of lifestyle interventions: effect on systolic and diastolic blood pressure in randomised trials of patients with raised blood pressure (≥140/85mmHg)



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.

11.1.1 Managing changes in lifestyle

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.

11.1.2 Diet

Fourteen randomised controlled trials, including 1,474 participants, met the review inclusion criteria.[18,45,84,138,144,235,262,295,310,406,508,520,545,577,617], [380,495,499,502]. 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[498], [158], [510].

The mean age of study participants was 48 years and 62% were male. Only four 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 eight weeks to one year.

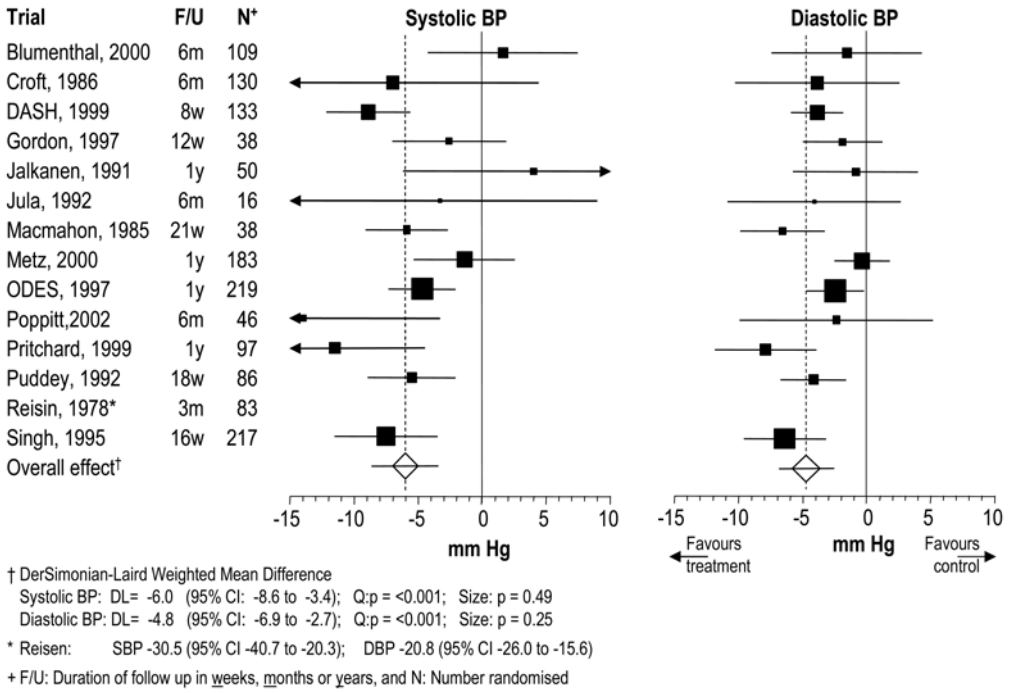
Randomisation could be confirmed as adequate in only three studies (21%) and concealment of allocation as adequate in only one (7%). Blinding was confirmed as adequate in six studies (43%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood 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[406,520]. 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 two and nine kilograms.

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 5. 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 5: Effect of diet on systolic and diastolic blood pressure in randomised trials of patients with raised blood pressure



Omission of a study which enrolled abnormally hypertensive patients (mean baseline BP: 170/110 mmHg)[508] 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[510] and fish oil appeared to lower blood pressure when compared to olive oil[135], 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[158].

The Cochrane Collaboration[415] 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 four studies common to both reviews. Nevertheless, its conclusions were similar. The recent Canadian guideline reviewed studies between 1966 and 1996[355]. Although without a formal meta-analysis, it likewise concluded that overweight hypertensive patients should be advised to reduce their weight.

11.1.3 Exercise

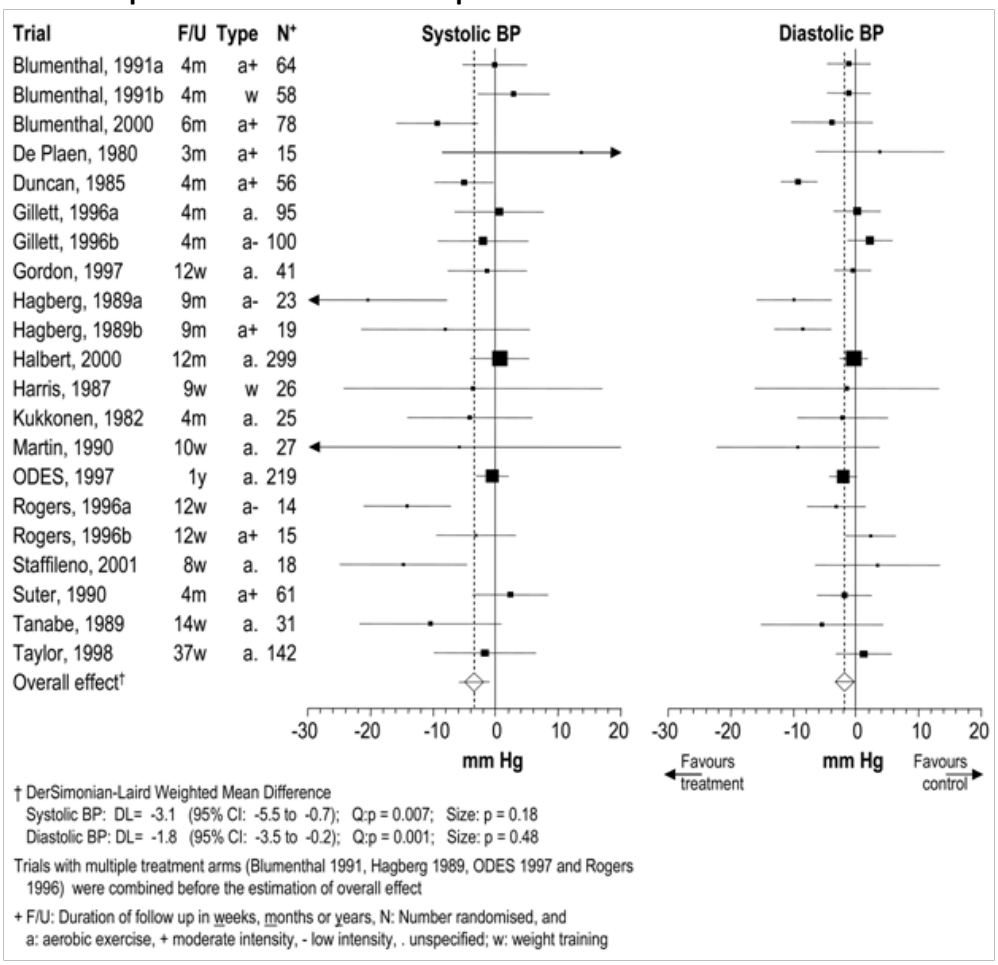
Seventeen randomised controlled trials of parallel design[84,85,162,184,235,246,249,261,341], [18,45,231,391,513,559,575,583,585] including 1,357 participants, met the review inclusion criteria. Studies most commonly enrolled overweight patients and compared no intervention with a weekly schedule of three to five sessions of aerobic exercise. One study[249] offered advice to participants whereas all others provided facilities. Three further studies could not be included because of missing data[274,327,604].

The mean age of study participants was 53 years and 58% were male. Only five 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 eight 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 one study (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 6). 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.

Figure 6: Effect of exercise on systolic and diastolic blood pressure in randomised trials of patients with raised blood pressure



A recent systematic review of studies of the effect of exercise on blood pressure[187] included seven 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[132]. 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 three or four times per week.

11.1.4 Relaxation therapies

Twenty-three randomised controlled trials of parallel design, including 1,481 participants, met the review inclusion criteria. RCTs of relaxation interventions[32,33], [31,34,69,95,115,120,142,221,265,276,277,289,304,367,397,477-479,525,533,610,661]. Twelve further trials could not be included because of missing data[128,232,245,345,398,586], [36,80,92,288,418].

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

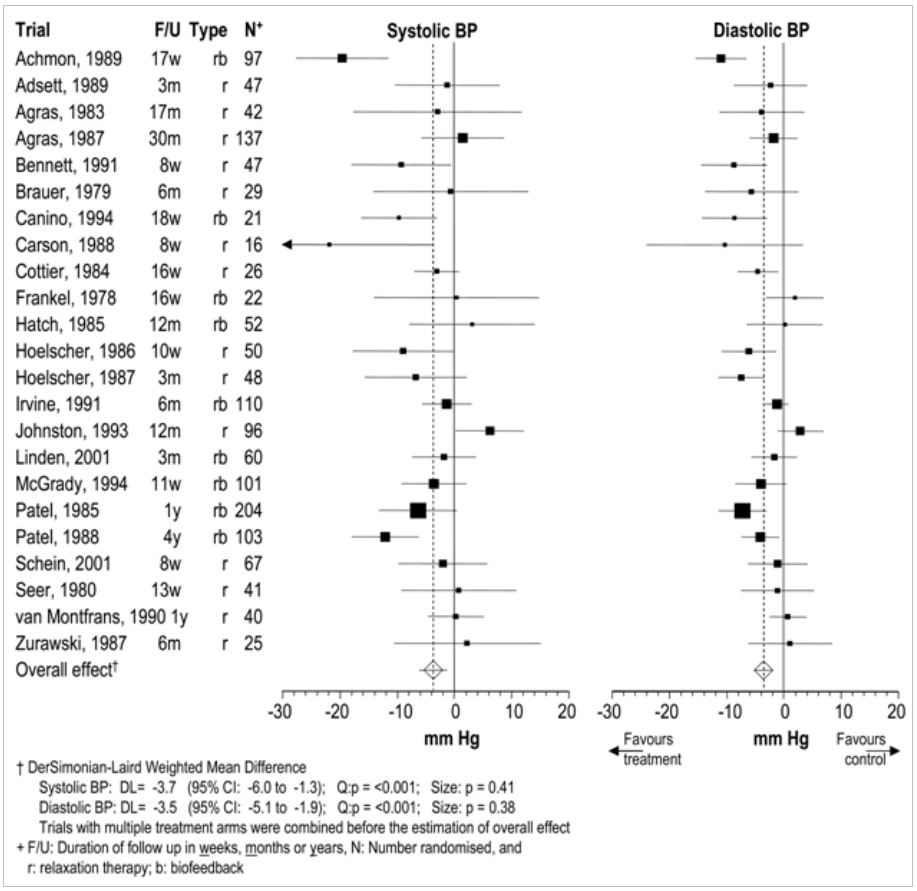
Randomisation could be confirmed as adequate in only seven studies (30%), and concealment of allocation as adequate in only one (4%). Blinding was confirmed as adequate in seven studies (30%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood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

Figure 7: Impact of relaxation interventions on blood pressure: findings from randomised controlled trials



A recent systematic review of studies of the effect of stress reduction on blood pressure[187] included seven 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.

The recent Canadian guideline reviewed studies between 1966 and 1997[550]. 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[192,293,366]. 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.

11.1.5 Multiple lifestyle interventions

Six randomised controlled trials, including 413 participants, met the review inclusion criteria. RCTs of multifaceted interventions[45,47,84,294,337,337,408,599]. 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[45,47,84,337], [599]; one study also included relaxation and restriction of intake of common salt[337]; one study combined a weight loss diet, relaxation and salt restriction[294]; and one study combined a weight loss diet, exercise and salt restriction[408]. A further trial, which delivered a health education package to a British population with angina, did not meet

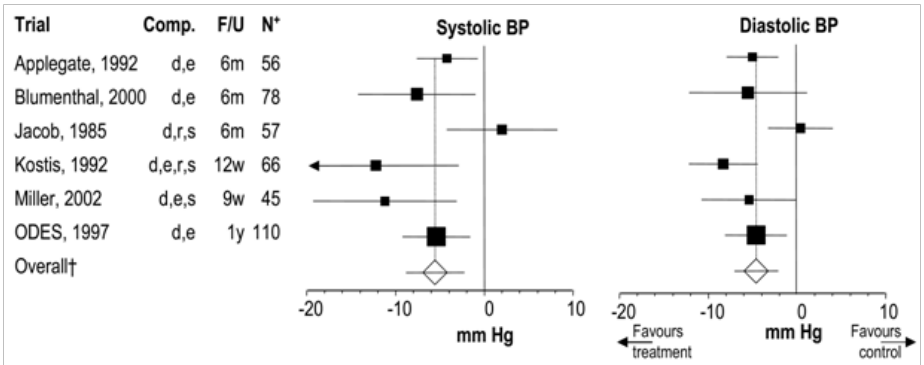
our inclusion criteria for blood pressure and so was excluded from the meta-analysis and is considered separately[146]. Three further trials could not be included because of missing data[274,309,334].

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

Randomisation was confirmed as adequate in only two studies (33%). Concealment of allocation was inadequate or unclear in all six studies. Blinding was confirmed as adequate in four studies (67%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in five 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 8). 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 five studies found no statistically significant difference in withdrawal from treatment and control groups (treatment versus control, risk difference: 4.9%, 95%CI: −2.6% to 12.4%).

Figure 8: Impact of combined lifestyle interventions on blood pressure: findings from randomised controlled trials



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 (two 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 nine studies of normotensive and hypertensive participants, published between 1966 and 1995, and with at least 26 weeks follow-up[186]. 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.

11.1.6 Alcohol

The epidemiological link between alcohol consumption, blood pressure, cardiovascular disease and all-cause mortality has been studied extensively[181,263,497,596]. 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[287]).

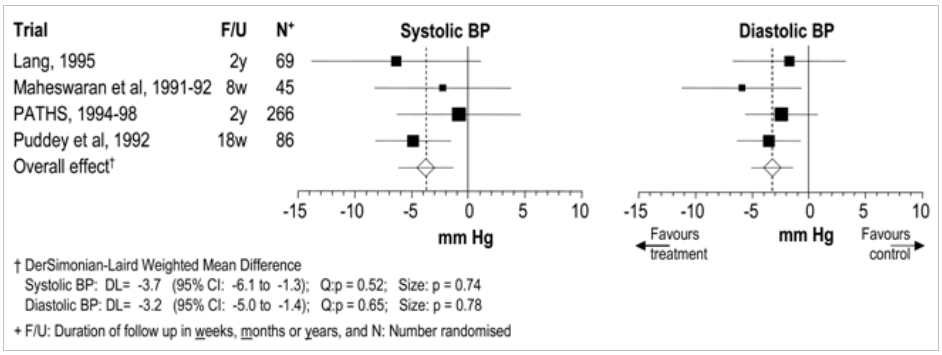
Three randomised controlled trials, including 397 participants, met the review inclusion criteria and examined the effect of changes in alcohol consumption on blood pressure[148,382,502]. Interventions varied in their content but commonly featured a number of visits to a health care practitioner for 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[348].

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[148], 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 two studies. Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in all three 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 9).

Figure 9: Impact of alcohol reduction on blood pressure: findings from randomised controlled trials



The recent Canadian guideline reviewed studies between 1966 and 1996[113]. Although without a formal meta-analysis, it recommended that alcohol consumption be limited in patients with hypertension to two or fewer standard drinks per day, with consumption not exceeding 14 standard drinks per week for men and nine standard drinks per week for women.

For recommendations on preventing the development of hazardous and harmful drinking, see NICE Public Health guidance 24 (http://guidance.nice.org.uk/PH24).

11.1.7 Coffee

Although coffee is a complex beverage containing many chemicals, only the effect of caffeine has been studied extensively[516]. 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)[444], [130].

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 five hours[297].

We identified no randomised controlled trials examining the impact of coffee or caffeine intake on patients with hypertension, which provided at least eight weeks follow-up. A published systematic review included normotensive as well as hypertensive participants, and shorter durations of follow-up[299]. Eleven trials with a total of 522 participants and a median duration of eight weeks (range 2 to 11 weeks) were included. Control groups drank a median of five 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.

11.1.8 Reducing sodium (salt) intake

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 (four of parallel design[125,212,311,544], one of crossover design[10,11]), examining the effect of sodium reduction on blood pressure, met the review inclusion criteria and included 420 patients. The findings of one Italian trial in young adults are considered separately[141]. A further trial could not be included because of missing data[395].

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.

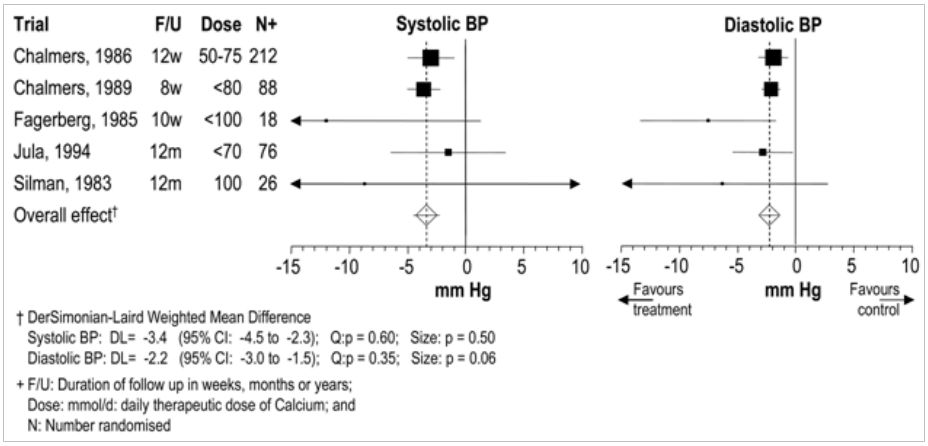
One trial (17%) was double-blinded; blinding could not be confirmed in any of the other studies. Randomisation and concealment of allocation could not be confirmed to be adequate in any of the

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[532] and NICE public health guidance on the prevention of cardiovascular diseases recommends people aim for a maximum intake of 6 grams per day per adult by 2015 and 3 grams by 2025.

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 10. 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 two studies, there was no difference in withdrawal when comparing treatment and control arms of studies (treatment versus control, risk difference: −0.6%, 95%CI: −6.5% to 5.4%).

Figure 10: Impact of sodium reduction on blood pressure: findings from randomised controlled trials



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[187,279]. 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 one year follow-up) and 1.1/0.6 (one to six years follow-up)[279] and 2.9/2.1 mmHg[187], suggesting that reductions in blood pressure tend to diminish over time.

The recent Canadian guideline[220], 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.

11.1.9 Calcium supplements

Eleven randomised controlled trials (three of parallel design[242,378,442], eight of crossover design[227,318,396,571,581,584,627,660]), examining the effect of calcium supplementation on blood pressure, met the review inclusion criteria and included 414 patients. Another trial, carried out in patients who were undergoing dialysis, was excluded after consideration of their unusual calcium metabolism but its details are tabulated[487]. A further trial could not be included because of missing data[414].

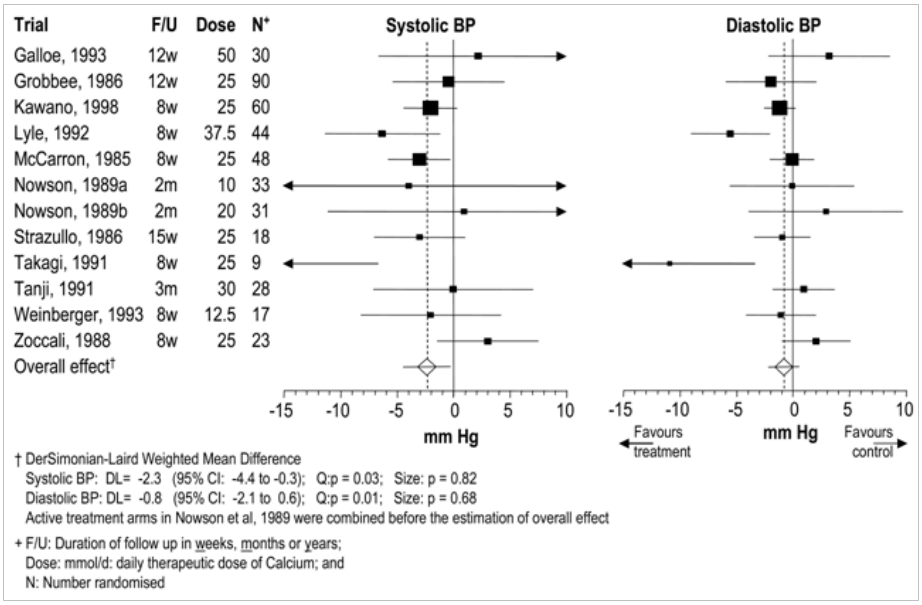
The mean age of study participants was 45 years and 68% were male. Only four studies reported ethnicity and in these 46% of the participants were white. The median duration of both intervention and follow-up was eight weeks.

Randomisation could be confirmed as adequate in only two studies (18%) and concealment of allocation as adequate in only one (9%); nine 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 one study (33%) of parallel design; three 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 11. 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 11: Impact of calcium supplementation on blood pressure: findings from randomised controlled trials



11.1.10 Magnesium supplements

Eleven randomised controlled trials (nine of parallel design[215,270,365], [91,443,475,621,646,659]] 2 of crossover design [[317,645]), examining the effect of magnesium supplementation on blood pressure, met the review inclusion criteria and included 504 patients.

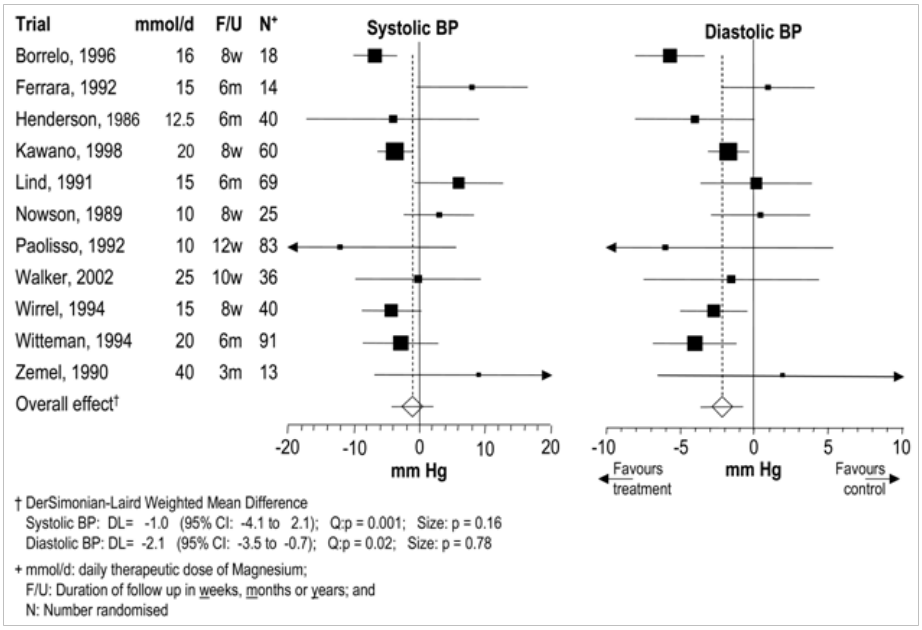
The mean age of study participants was 55 years and 44% were male. Only two studies reported ethnicity and in these 11% of the participants were white. The median duration of both intervention and follow-up was 12 weeks.

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 six 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 12. 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 eight 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 12: Impact of magnesium supplementation on blood pressure: findings from randomised controlled trials



11.1.11 Potassium supplementation

Five randomised controlled trials (four of parallel design[107,543,543], [578], one of crossover design[470]), examining the effect of potassium supplementation on blood pressure, met the review inclusion

criteria and included 410 patients. The findings of one African trial are considered separately[455]. A further trial could not be included because of missing data[149].

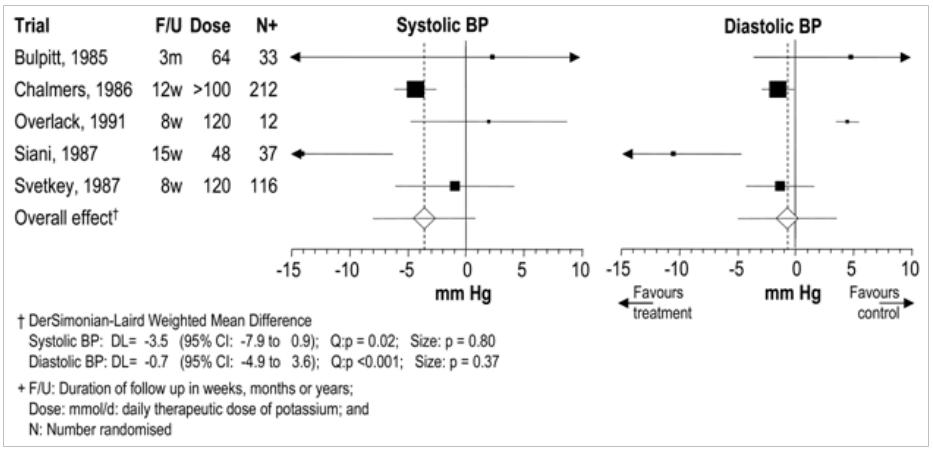
The mean age of study participants was 51 years and 76% were male. Only one study reported ethnicity and in this 86% of the participants were white. The median duration of both intervention and follow-up was 12 weeks.

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 two 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[125].

Average changes in blood pressure, when comparing treatment and control groups, are shown in Figure 13. 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 13: Impact of potassium supplementation on blood pressure: findings from randomised controlled trials



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[633], based on 12 trials in normotensive people and 21 in hypertensive people, with a duration ranging from four days to three years (median five 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.

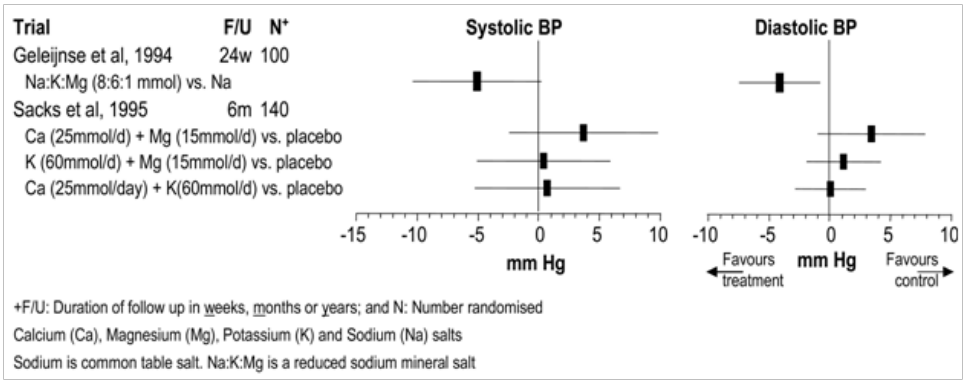
In contrast, our restriction to trials of at least 8 weeks duration, enrolling only hypertensive patients, resulted in inclusion of only 5 trials with a median duration of 12 weeks and found that the blood pressure lowering effect of oral potassium supplementation was not statistically significant. The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

11.1.12 Combined salt supplements

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

One study used paired supplements comparing two of calcium, potassium and magnesium with placebo[519]. None of the combined supplements reduced blood pressure when compared with placebo (see Figure 14). This was consistent with the findings for the individual supplements.

Figure 14: Impact of combined supplements on blood pressure: findings from randomised controlled trials



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[229]. The reduction of blood pressure by about 5/4 mmHg consistent with that found with strategies to reduce sodium salt intake.

The recent Canadian guideline reviewed studies between 1966 and 1996[108]. Although without a formal meta-analysis, it recommended against supplementing calcium, magnesium or potassium intake amongst hypertensive participants above the recommended normal daily levels.

11.1.13 Drug therapy versus lifestyle change

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. Goldstein et al [232], Murugesan et al [418], Kostis et al [337], MacMahon et al [380], [381], Koopman et al [333]. 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[72]).

All trials were small (between 38 and 66 participants), of short duration (between eight 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[333,337,380]; blinding was not reported in two trials[232,418], and there was no blinding in one trial[72]. One trial was poorly reported and did not state the total number of participants[418]. In two trials the confidence intervals on the effects of

treatment could not be estimated, as either the numbers in each treatment group[418] or the standard error of the treatment effects were not reported[232].

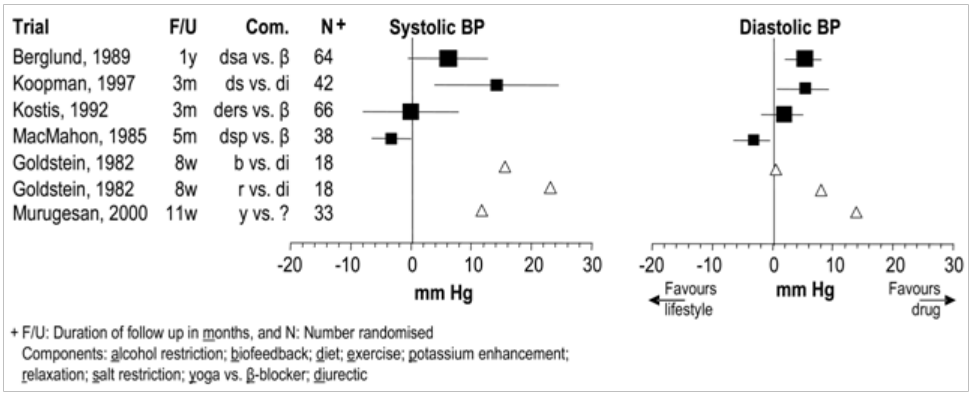
The populations studied in the trials differed in: (i) age – participants in one trial[333] were older, which probably accounted for their higher baseline blood pressure compared to participants in the other trials; (ii) treatment status at the point of recruitment – participants were currently untreated or treatment naïve in four trials[72,232,333,380], currently treated in one trial[337], or treatment status was not reported[418].

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 15). In the trial of older participants[333] 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[381] 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[337] 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[418].

Figure 15: Comparison of lifestyle and drug interventions: findings from randomised controlled trials



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[643], 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.

11.1.14 Smoking cessation

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[179,180,357,410,488,648]. The NHS website www.smokefree.nhs.uk has facts and information about giving up smoking.

Refer to NICE's public health guidance on smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities for more information (www.guidance.nice.org.uk/PH10).

11.1.15 Recommendations

For NICE guidance on the prevention of obesity and cardiovascular disease see 'Obesity' (NICE clinical guideline 43, 2006) and 'Prevention of cardiovascular disease at population level' (NICE public health guidance 25, 2010).

30. Lifestyle advice should be offered initially and then periodically to people undergoing assessment or treatment for hypertension. [2004]

31. Ascertain people's diet and exercise patterns because a healthy diet and regular exercise can reduce blood pressure. Offer appropriate guidance and written or audiovisual materials to promote lifestyle changes. [2004]

32. Relaxation therapies can reduce blood pressure and people may wish to pursue these as part of their treatment. However, routine provision by primary care teams is not currently recommended. [2004]

33. Ascertain people's alcohol consumption and encourage a reduced intake if they drink excessively, because this can reduce blood pressure and has broader health benefits. [2004]

34. Discourage excessive consumption of coffee and other caffeine-rich products.

35. Encourage people to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as this can reduce blood pressure.[2004]

36. Do not offer calcium, magnesium or potassium supplements as a method for reducing blood pressure. [2004]

37. The best current evidence does not show that combinations of potassium, magnesium and calcium supplements reduce blood pressure. [2004]

38. Offer advice and help to smokers to stop smoking. [2004]

39. A common aspect of studies for motivating lifestyle change is the use of group working. Inform people about local initiatives by, for example, healthcare teams or patient organisations that provide support and promote healthy lifestyle change. [2004]

12 Pharmacological interventions

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, heart failure and mortality. The size of benefit in any period (for example the next 10 years) generally depends on an individual's overall cardiovascular risk. [135,379] 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 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*'. '*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*.' 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*'.

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. [440] The recommendations include the use of aspirin, beta-blockers, statins and ACEi. 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 always fully understood. A brief summary of drugs used for essential hypertension is provided in Table 49; further information can be found in the British National Formulary. [306] Drugs for hypertension rarely have serious side-effects when appropriately initiated and adequately monitored.

Update 2011

Table 49: Outline of drugs used for essential hypertension

Commonly used Classes of Antihypertensive Drug Therapies in the United Kingdom (This is intended as a guide and reference to the product label and British National Formulary is recommended for detailed prescribing information)				
Class	Common generic names	Mode of action	Duration of action	Usage notes
Thiazide diuretics	bendroflumethiazide, hydrochlorthiazide	Vasodilation and moderate diuresis (increased excretion of sodium, potassium and water).	Commonly once daily morning use	Can cause gout and hypokalaemia and rarely hyponatraemia. Can increase the risk of developing type 2 diabetes
Thiazide – like diuretics	Chlortalidone, indapamide	Vasodilation and moderate diuresis (increased excretion of sodium,	Commonly once daily morning use	Can cause gout and hypokalaemia and rarely hyponatraemia. Can increase the risk of

Commonly used Classes of Antihypertensive Drug Therapies in the United Kingdom (This is intended as a guide and reference to the product label and British National Formulary is recommended for detailed prescribing information)				
		potassium and water).		developing type 2 diabetes
Potassium-sparing diuretics	Spironolactone amiloride	Vasodilation and moderate diuresis (increased excretion of sodium, potassium and water).	Once or twice daily	Used for resistant hypertension. Spironolactone can cause gynaecomastia in males. Not to be used with potassium supplements. Can cause hyperkalaemia, especially in patients with impaired renal function. Should be avoided in primary care patients with a baseline potassium >4.5mmol/L and used with caution in people with renal impairment. Careful monitoring of potassium and renal function is required..
Beta-blockers	atenolol, bisoprolol, metoprolol, propranolol, sotalol	Suppress plasma renin production. Negative inotropic and chrontropic effects on the heart. Beta-blockers with alpha receptor activity also produce vasodilatation	Vary by drug from once to several times daily	Not recommended as a preferred therapy for hypertension. Can be considered for resistant hypertension or as an initial therapy for women of child bearing potential. Also used for patients with angina, post myocardial infarction and chronic heart failure. Contraindicated with asthma, heart-block or in combination with a rate-limiting calcium-channel blocker. Reported side-effects include lethargy, depression and sleep disturbance. Increased risk of type 2 diabetes, especially when combined with thiazide or thiazide-like diuretics.
Calcium-channel blockers	'dihydropyridines' amlodipine, felodipine, lacidipine nifedipine.	Vasodilatation and natiuresis vasculature.	Vary by drug from once to twice daily. Note only modified release formulation of nifedipine should be	Reported side-effects include initial headaches, palpitations, facial flushing and ankle swelling.

Commonly used Classes of Antihypertensive Drug Therapies in the United Kingdom (This is intended as a guide and reference to the product label and British National Formulary is recommended for detailed prescribing information)				
			used to treat hypertension	
	'rate-limiting CCBs' diltiazem, verapamil	Heart rate slowing, vasodilatation and natiuresis	Once or twice daily for longer acting forms	Caution against use in heart failure or use with a beta-blocker. Reported side-effects similar to dihydropyridines but also include constipation (verapamil) and skin rashes (diltiazem)
Angiotensin converting enzyme (ACEi) inhibitors	captopril, enalapril, lisinopril, perindopril, ramipril, trandolapril	Inhibition of angiotensin coverting enzyme and reduced angiotensin II production.	Vary by drug from once to several times daily	Contraindicated in pregnancy. .Careful monitoring of potassium levels and renal function required in people with renal impairment. Adverse effects include a persistent dry cough, rash and loss of taste. Rarely angioedema which is more common in black people of African or Caribean origin
Angiotensin receptor blockers (ARBs)	candesartan, irbesartan, losartan, olmersartan, valsartan, telmisartan	Selective inhibition of the angiotensin AT-1 receptor.	Once daily	Contraindicated in pregnancy. Careful monitoring of potassium levels and renal function required in people with renal impairment. Generally well tolerated and unlike ACEi, do not cause cough
Alpha receptor blockers	doxazosin, prazosin, terazosin	Antagonists of the Alpha 1 receptor.	Vary by drug from once to several times daily	Consider for the treatment of resistant hypertension. Beneficial side-effect on blood lipid profile. May also be considered for men with symptoms of prostatic outflow obstruction. Caution in women in whom they may cause or worsen symptoms of stress incontinence. Contraindications, cautions and side-effects vary by drug. Most common side-effects: initial dizziness, postural hypotension,

Commonly used Classes of Antihypertensive Drug Therapies in the United Kingdom (This is intended as a guide and reference to the product label and British National Formulary is recommended for detailed prescribing information)				
				headache, flushing, nasal congestion, fluid retention, ankle swelling and tachycardia.

12.1 2004 guidance: pharmacological interventions

12.1.1 Placebo controlled trials

An overview of key design characteristics of the 20 placebo controlled trials identified is shown in Table 50 (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.

Table 50: Summary of characteristics of placebo controlled trials

	Thiazides (High Dose)	Thiazides (Low Dose)	Beta Blockers	Ca Channel Blockers	ACEi	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%)

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).

12.1.1.1 Thiazide-type diuretics

Thiazide-type diuretics (thiazides for short) include drugs classified by the British National Formulary (BNF) as a thiazide or thiazide like diuretic. Twelve trials were identified that met the review inclusion criteria, see Table 51. 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. [26] The mean age of participants was 51, 59% were male and the mean duration of follow-up was 4.0 years.

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).

Table 51: Description of individual placebo controlled trials of thiazide-type diuretics

Trial	Thiazide1	Dose category	Dose, mg	Country	Follow-up, yrs	Start year	Age in years		Baseline BP, mmHg	Number enrolled	Baseline Risk2
							Range	Mean			
ANBPS[4]	Chlorothiazide	high3	500–1000	Australia	4.0	1973	30–69	50	157/101	3,931	5
HSCSG[2]	Methychlothiazide	high	10	US	2.1	1966	<75	59	167/100	452	53
MRC[402]	Bendroflumethiazide	high	10	UK	4.9	1977	35–64	52	161/98	12,951	7
Oslo[356]	Chlorothiazide	high	50	Norway	5.5	1972	40–49	45	156/97	785	4
USPHS[548]	Chlorothiazide	high	1000	US	>7	1965	<55	44	147/99	422	3
VAII[1]	Chlorothiazide	high	100	US	3.2	1964	-	51	164/104	380	39
VA-NHLBI[3]	Chlorthalidone	high	50–100	US	1.5	1978	21–50	38	-	1,012	0
EWPHE[6,42,453]	Hydrochlorothiazide	low3	25–50	Europe	4.7	1975	60+	72	183/101	840	77
MRC-O[15]	Hydrochlorothiazide	low	25–50	UK	5.8	1982	65–74	70	185/91	3,294	24
PATS[20]	Indapamide	low	2.5	China	2.0	1989	-	60	154/93	5,665	28
SHEP-P[281,484,485]	Chlorthalidone	low	25–50	US	2.8	1981	60+	72	172/75	551	23
SHEP[13,483,536,606]	Chlorthalidone	low	12.5–25	US	4.5	1985	60+	72	170/77	4,736	23

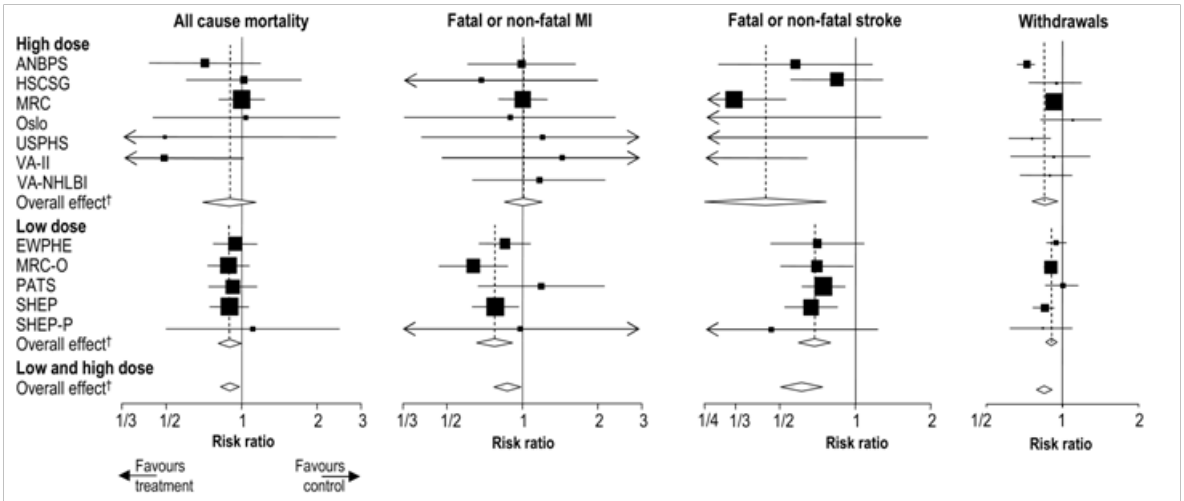
All trials featured co-treatment or stepped care except PATS: see the trial table for details.

Control Group death rate per 1000 patients per year.

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 [501].

A graphical presentation of pooled summary findings is shown in Figure 16 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 16: Meta-analysis of placebo-controlled randomised controlled trials of high and low dose thiazide 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.

12.1.1.2 Beta-blockers

Seven trials with 27,433 participants were identified that met the review inclusion criteria (see Table 52). 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 52: Description of individual placebo controlled trials of beta-blockers

Trial	Beta-blocker1	Dose, mg	Country	Follow-up, yrs	Start year	Age in years		Baseline BP, mmHg	Number enrolled	Baseline Risk2
						Mean	Range			
Coope [140]	Atenolol	100	UK	4.4	1978	69	60–79	196/99	884	34
DUTCH-TIA [19]	Atenolol	50	Netherlands	2.7	1986	-	-	158/91	1,473	29
IPPPSH [7]	Oxprenolol	160–320	International	3.4	1977	52	40–64	173/108	6,357	11
MRC [402]	Propranolol	240	UK	4.9	1977	52	35–64	161/98	13,057	6
MRC-O [15]	Atenolol	50–100	UK	5.8	1982	70	65–74	185/91	3,315	24
STOP-H [156]	Beta-blocker or Diuretic3		Sweden	2.1	1985	76	70–84	195/102	1,627	37
TEST [197]	Atenolol	50	Sweden	2.3	1988	70	40+	161/89	720	75

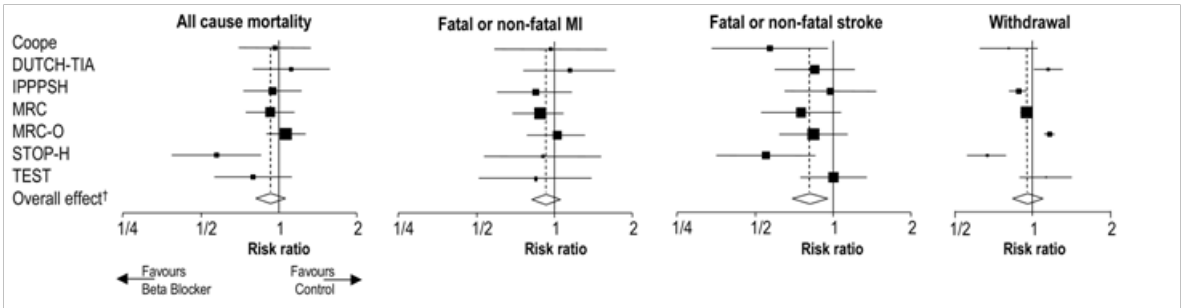
All trials featured stepped care, with additional drugs added if necessary

Control Group death rate per 1000 patients per year

Atenolol (50) or Metoprolol (100) or Pindodol (5)

A graphical presentation of pooled summary findings is shown in Figure 17 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 17: Meta-analysis of placebo-controlled randomised controlled trials of beta-blockers



† DerSimonian-Laird risk ratio (RR)

	All cause mortality RR 95% CI	Q, p Size, p	Fatal or non-fatal MI RR 95%CI	Q, p Size, p	Fatal or non-fatal stroke RR 95%CI	Q, p Size, p	Withdrawal 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.

12.1.1.3 ACE inhibitors (ACEi)

One trial, with 6,105 participants and a mean follow-up of 3.9 years was identified that met the review inclusion criteria (Table 53). 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 ACEi also received the diuretic.

Table 53: Description of individual placebo controlled trials of ACEi

Trial	ACEi 1	Dose, mg	Country	Follow-up, yrs	Start year	Age in years		Baseline BP, mmHg	Number enrolled	Baseline Risk2
						Range	Mean			
PROGRESS [500]	Perindopril	4	International	3.9	1995	26–91	64	147/86	6,105	27
The PROGRESS trial allowed physicians to add a diuretic if they deemed it appropriate 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[25,652] 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.

12.1.1.4 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 54). 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 54: Description of individual placebo controlled trials of angiotensin receptor blockers

Trial	ARB1	Dose, mg	Country	Follow-up, yrs	Start year	Age in years		Baseline BP, mmHg	Number enrolled	Baseline Risk2
						Range	Mean			
SCOPE [371]	Candesartan	8–16	Europe and N. America	3.7	1997	70–89	76	166/90	4,964	29
Physicians could add a diuretic and other antihypertensive agents to patients in treatment or control groups if they deemed it appropriate. 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[362] and RENAAL[97]), but not considered adequately relevant to inform this guideline as both enrolled diabetic patients with mild renal impairment.

12.1.1.5 Calcium-channel blockers

One trial, with 4,695 participants and median follow-up of two years, was identified that met the review inclusion criteria (see Table 55). The SYST-EUR trial enrolled patients with isolated systolic hypertension, one third of whom were male; ethnicity was not reported.

Table 55: Description of individual placebo controlled trials of calcium-channel blaockers

Trial	CCB1	Dose, mg	Country	Follow-up, yrs	Start year	Age in years		Baseline BP, mmHg	Number enrolled	Baseline Risk2
						Range	Mean			
SYST-EUR[43,124,207,555,558]	Nitrendipine	10–40	Europe	23	1989	60+	70	174/86	4,695	27

SYST-EUR featured stepped care, with additional drugs added if necessary.
Control Group death rate per 1000 patients per year.
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[16,17,373,624]] and STONE [[233].

12.1.1.6 Alpha blockers

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

12.2 2006 rapid pharmacological update: head to head trials

Most studies reported comparisons involving two or more drug classes in each treatment arm administered according to a stepped administration protocol. In such cases, an initial antihypertensive drug would be administered, followed by either:

- an increase in the dosage of the first drug, and/or
- the addition of a second drug if blood pressure targets were not reached using the first drug alone.

All results should therefore be interpreted as demonstrating the efficacy and tolerability of each drug only when used as the initial step in a wider antihypertensive drug treatment regimen.

Many studies permitted a third drug to be added in patients unresponsive to both primary and secondary antihypertensive drugs. Such drugs typically included alpha-blocking drugs such as doxazosin or centrally acting antihypertensive drugs such as clonidine.

The update search found no new studies comparing ACEi or angiotensin-II receptor antagonists with beta-blockers, or comparing ACEi with ARBs.

Three studies (CONVINCE[78,79], NORDIL[257,594] and CAPPP[256,259,592]) included in the original guideline were excluded due to the confounded use of either beta-blocker or thiazide diuretic as first-line antihypertensive therapy within the same treatment arm. A fourth study (MAPHY)[640] was a post-hoc follow-up of a subgroup of patients already included in the HAPPHY study[641], and so was excluded from the update.

One new study (MOSES)[528] identified by the update search was excluded as it reported the primary end-point as a composite of all-cause mortality, cardiovascular, and cerebrovascular events, including all recurrent events, rather than as the first event only.

12.2.1 Clinical evidence statements: head-to-head drug comparisons

ACE inhibitors versus calcium-channel blockers	
A meta-analysis of three studies (ALLHAT[589-591], JMIC-B[650,651], STOP-H2[155,255,258,368]) comparing ACE inhibitors with calcium-channel blockers (CCBs) showed that ACE inhibitors were associated with a higher incidence of stroke (RR 1.14, 95% CI 1.02 to 1.28) but a lower incidence of new-onset diabetes (RR 0.85, 95% CI 0.75 to 0.98) and heart failure (RR 0.85, 95% CI 0.78 to 0.93). No significant difference was found for mortality.	I
For MI there was substantial heterogeneity among the studies (I2 = 69%). Two studies (ALLHAT[589-591], JMIC-B[650,651]) found no significant difference between study drugs in terms of MI incidence, while a third study (STOP-H2[155,255,258,368]) found that ACE inhibitors were associated with a reduced incidence of MI (RR 0.77, 95% CI 0.62 to 0.96). Of the two studies (ALLHAT[589-591], JMIC-B[650,651]) reporting the outcomes of unstable angina and revascularisation procedures, neither found any significant difference. The two studies (ALLHAT[589-591], STOP-H2[155,255,258,368]) that reported the frequency of study drug withdrawals each found ACE inhibitors to be associated with more withdrawals than CCBs (respectively: RR 1.17, 95% CI 1.12 to 1.23; RR 1.14, 95% CI 1.06 to 1.24).	II
ARBs versus calcium-channel blockers	
One study (VALUE)[312] was found comparing ARBs with CCBs when used as first-line antihypertensive therapy. ARBs were associated with a higher incidence of MI compared to CCBs (RR 1.17, 95% CI 1.01 to 1.36). There was no significant difference in stroke reduction, mortality or incidence of heart failure. The study also reported frequencies of adverse events for each drug class and showed several differences, but overall these did not particularly favour either drug. Pre-specified adverse events for ARBs versus CCBs included peripheral oedema (14.9% versus 32.9%, p<0.0001), dizziness (16.5% versus 14.3%, p<0.0001) and headache (14.7% versus 12.5%, p<0.0001). Additional adverse events identified included diarrhoea (8.8% versus 6.8%, p<0.0001), serious cases of angina (4.4% versus 3.1%, p<0.0001) and syncope (1.7% versus 1.0 %, p<0.0001).	II
ACE inhibitors versus thiazide-type diuretics	
A meta-analysis of three studies (ANBP2[644], ALLHAT[589-591], PHYLLIS[657]) comparing ACE inhibitors with thiazide-type diuretics showed that ACE inhibitors are associated with a higher incidence of stroke than thiazide-type diuretics (RR 1.13, 95% CI 1.02 to 1.25). However, no difference was found for mortality.	I
For MI, the studies are heterogeneous (I2 = 66.5%). One study based in a relatively elderly and predominantly white population (ANBP2)[644] reported a lower incidence of MI for ACE inhibitors (RR 0.71, 95% CI 0.51 to 0.98), but the remaining studies (ALLHAT[589-591], PHYLLIS[657]) found no significant difference. For heart failure, a meta-analysis of two studies (ALLHAT[589-591], ANBP2[644]) also demonstrated heterogeneity (I2 = 67.1%). ALLHAT[589-591] reported a higher incidence with ACE inhibitors than thiazide-type diuretics (RR 1.19, 95% CI 1.08 to 1.31), but in ANBP2[644] there was no significant difference. One study (ALLHAT)[589-591] reported no significant difference in unstable angina but a higher incidence of revascularisation procedures (RR 1.10, 95% CI 1.00 to 1.21) with ACE inhibitors.	II

Both studies (ALLHAT[589-591] and ANBP2[644]) found ACE inhibitors to be associated with a higher incidence of withdrawal compared to thiazide-type diuretics (RR 1.12, 95% CI 1.08 to 1.17; RR 1.10, 95% CI 1.04 to 1.17). One study (ALLHAT)[589-591] reported new-onset diabetes as an outcome, and found that the incidence of diabetes after four years of follow-up was significantly higher for thiazide-type diuretics compared to ACE inhibitors (p<0.001).	
Calcium-channel blockers versus thiazide-type diuretics	
A meta-analysis of five studies (ALLHAT[589-591], INSIGHT[105,106], MIDAS[90], NICS-EH[343], VHAS[514,658]) comparing calcium-channel blockers with thiazide-type diuretics found no significant differences for mortality, MI or stroke. There was a statistically significantly higher incidence of heart failure with CCBs (RR 1.38, 95% CI 1.25 to 1.53). Conversely, based on the results of three studies (ALLHAT[589-591], INSIGHT[105,106], NICS-EH[343]), CCBs are associated with a reduced incidence of new-onset diabetes (RR 0.78, 95% CI 0.64 to 0.96).	I
Only the ALLHAT[589-591] study reported unstable angina as an outcome and found no significant difference between the drug classes. For revascularisation procedures, neither ALLHAT[589-591] nor MIDAS[90] found a significant difference. In terms of study drug withdrawal, one study (INSIGHT)[105,106] found thiazide-type diuretics to be associated with more withdrawals than CCBs (RR 1.20, 95% CI 1.13 to 1.28), although the other studies (ALLHAT[589-591], MIDAS[90], VHAS[514,658]) did not find a significant difference between the two drug classes.	II
Outcomes in those with isolated systolic hypertension (ISH)	
A meta-analysis of three randomised controlled trials (SHEP[483,536,537,606], SHEP-P,[281,484,485] SYST-EUR[43,122,555]) compared active antihypertensive drug therapy using either thiazide-based diuretics or a calcium-channel blocker with placebo in patients with isolated systolic hypertension. Antihypertensive drug therapy was associated with a reduced incidence of stroke (OR 0.62, 95% CI 0.51 to 0.77) and myocardial infarction (OR 0.74, 95% CI 0.61 to 0.91), although there was no statistically significant difference in mortality rate.	I
Based on the results of a subgroup analysis from one randomised controlled trial (INSIGHT)[105,106], initial antihypertensive therapy with the CCB nifedipine was comparable to the thiazide-type diuretic hydrochlorothiazide plus amiloride in terms of mortality. Based on the results of another subgroup analysis of patients with ISH from a randomised-controlled trial involving patients with hypertensive LVH (LIFE)[328], initial therapy with an ARB is associated with a reduced incidence of stroke (RR 0.60, 95% CI 0.38 to 0.92) and a lower mortality rate (RR 0.54, 95% CI 0.34 to 0.87) compared to initial antihypertensive therapy with a beta-blocker. The two drugs were comparable in terms of the incidence of myocardial infarction.	II
Beta-blockers versus thiazide-type diuretics	**Level**
Three studies (HAPPHY[641], MRC[402], MRC-0[15]) were found comparing the efficacy of beta-blockers and thiazide-type diuretics. One study (HAPPHY) included only male patients. A meta-analysis of these three studies showed no significant difference between the two drug classes in terms of mortality.	I
Heterogeneity in the study results (I2 >75%) suggested that a meta-analysis would be inappropriate for the outcomes of myocardial infarction and stroke. Sensitivity analyses were performed for variation between the studies in terms of age (by including/excluding MRC-0[15], in which the average age of participants was 70) and gender (by including/excluding HAPPHY)[641], but these were unable to account for the observed heterogeneity. One study (MRC-0)[15] found beta-blockers to be associated with a higher incidence of myocardial infarction compared to thiazide-type diuretics (RR 1.63, 95% CI 1.15 to 2.32). No association was	II

found in the other two studies[402,641], which considered younger patients. One study (MRC)[402] in a relatively young population (average age 52 years) found beta-blockers to be associated with a higher incidence of stroke compared to thiazide-type diuretics (RR 2.31, 95% CI 1.33 to 4.00). However, no association was found in the other two studies[15,641]. In terms of the frequency of withdrawal of the study drug, two studies (MRC[402], MRC-0[15]) found beta-blockers to be associated with more withdrawals (RR 1.06, 95% CI 1.01 to 1.11; RR 1.29, 95% CI 1.22 to 1.37) while the remaining study[641] reported a non-significant result.	
Angiotensin-II receptor antagonists versus beta-blockers	
One study (LIFE)[176,222,507,618,619] was found comparing the angiotensin-II receptor antagonist (ARB) losartan with the beta-blocker atenolol as first-line antihypertensive therapy. The study found no significant difference between the two treatments in terms of myocardial infarction, revascularisation procedures, heart failure or angina. However, the study did find ARBs to be associated with a reduced incidence of stroke (RR 0.75, 95% CI 0.63 to 0.88), new-onset diabetes (RR 0.75, 95% CI 0.64 to 0.88) and fewer study drug withdrawals (RR 0.86, 95% CI 0.82 to 0.91). Although mortality was lower in the ARB treatment group, this result was not statistically significant.	I
Calcium-channel blockers versus beta-blockers	
A meta-analysis of three studies (ASCOT[157], ELSA[656], INVEST[481]) compared calcium-channel blockers (CCBs) with beta-blockers. There was no statistically significant difference in mortality or myocardial infarction. Based on the results of the two studies reporting stroke as an outcome (ASCOT[157], ELSA[656]), CCBs were associated with a reduced incidence of stroke (RR 0.77, 95% CI 0.67 to 0.88).	I
For heart failure, a meta-analysis of two studies (ASCOT[157], INVEST[481]) showed substantial heterogeneity (I2 = 67.4%), but neither study alone found a statistically significant difference between CCBs and beta-blockers. Based on the results of one study (ASCOT)[157], CCBs are associated with a reduced incidence of new-onset diabetes (RR 0.71, 95% CI 0.64 to 0.78). ASCOT[157] also found CCBs to be associated with a lower incidence of unstable angina (HR 0.68, 95% CI 0.51 to 0.92) and fewer revascularisation procedures (HR 0.86, 95% CI 0.77 to 0.96) than BBs, but the INVEST[481] study found the association between both classes of drugs to be non-significant for these outcomes. Study withdrawal was reported in two studies. In ASCOT[157] there were fewer withdrawals associated with CCBs (RR 0.64, 95% CI 0.52 to 0.77), but in INVEST[481] there was no significant difference.	II

12.2.2 Meta-analysis results summary

Table 56 summarises the results from the meta-analysis comparing different drug classes in general antihypertensive populations. Included are comparisons and outcomes in which inter-study heterogeneity was considered too great to include the pooled effect size in the evidence statements above and hence these should be treated with caution.

Table 56: Summary of effect sizes for each comparison included in the meta-analysis

Comparison	Studies	Total n	Effect size RR [95% CI]	I2 (%)
01 Beta-blockers versus thiazides				

Comparison	Studies	Total n	Effect size RR [95% CI]	I2 (%)
01 Mortality	3	15,765	1.04 [0.91, 1.20]	44.1
02 Myocardial infarction	3	15,765	1.15 [0.82, 1.60]	76.8
03 Stroke	3	15,765	1.27 [0.73, 2.23]	77.6
03 ARBs versus beta-blockers				
01 Mortality	1	9,103	0.89 [0.78, 1.01]	N/A
02 Myocardial infarction	1	9,103	1.05 [0.86, 1.28]	N/A
03 Stroke	1	9,103	0.75 [0.63, 0.88]	N/A
04 Heart failure	1	9,103	0.95 [0.76, 1.18]	N/A
05 Diabetes	1	7,998	0.75 [0.64, 0.88]	N/A
06 Calcium-channel blockers versus beta-blockers				
01 Mortality	3	44,075	0.94 [0.88, 1.00]	5.7
02 Myocardial infarction (inc. silent MI)	3	44,075	0.93 [0.83, 1.03]	0
03 Myocardial infarction (exc. silent MI)	3	44,075	0.91 [0.81, 1.02]	0
04 Stroke	2	21,499	0.77 [0.67, 0.88]	0
05 Heart failure	2	41,833	0.96 [0.74, 1.26]	67.4
06 Diabetes	1	14,112	0.71 [0.64, 0.78]	N/A
04 ACE inhibitors versus calcium-channel blockers				
01 Mortality	3	23,625	1.04 [0.98, 1.11]	0
02 Myocardial infarction	3	23,619	0.94 [0.74, 1.19]	69.3
03 Stroke	3	23,619	1.15 [1.03, 1.27]	5.2
04 Heart failure	3	23,619	0.85 [0.78, 0.93]	0
05 Diabetes	2	15,501	0.85 [0.76, 0.94]	15.2
02 ARBs versus calcium-channel blockers				
01 Mortality	1	15,313	1.02 [0.93, 1.12]	N/A
02 Myocardial infarction	1	15,313	1.17 [1.01, 1.36]	N/A
02 Stroke	1	15,313	1.14 [0.97, 1.33]	N/A
03 Heart failure	1	15,313	0.88 [0.76, 1.01]	N/A
05 ACE inhibitors versus thiazides				
01 Mortality	2	29,697	1.00 [0.94, 1.06]	0%
02 Myocardial infarction	3	30,204	0.87 [0.60, 1.24]	66.5
03 Stroke	3	30,204	1.13 [1.02, 1.25]	0
04 Heart failure	2	29,697	1.07 [0.81, 1.41]	67.1
07 Calcium-channel blockers versus thiazides				
01 Mortality	5	32,195	0.97 [0.93, 1.02]	0
02 Myocardial infarction	5	32,195	1.02 [0.96, 1.08]	0
03 Stroke	5	32,195	0.93 [0.84, 1.04]	0
04 Heart failure	5	32,195	1.38 [1.25, 1.53]	0.2
05 Diabetes	3	20,885	0.82 [0.75, 0.90]	43.8
08 Antihypertensive therapy versus placebo (ISH population)				
01 Mortality	3	9,745	0.88 [0.77, 1.01]	0
02 Myocardial infarction	3	9,745	0.75 [0.62, 0.91]	0
03 Stroke	3	9,745	0.64 [0.52, 0.78]	0

12.3 2011 update: Pharmacological therapy for hypertension

Following the rapid pharmacological update of the guideline in 2006 the use of an algorithm-based approach to treatment was recommended, based on an A,C,D, where A represented an ACEi (or ARB when an ACEi was not tolerated), C respresented a CCB, and D represented a thiazide-type diuretic. The guideline also recommended that initial therapy for primary hypertension (step 1) should be stratified according to age and ethnicity. Specifically, the guideline recommended that for older people aged ≥55years, treatment should be initiated with a CCB (C) or thiazide-type diuretic (D). For people under the age of 55 years, an ACEi (or ARB id ACEi was not tolerated)(A) was recommended for initial (step 1) therapy. In the absence of clinical outcomes data in younger people, this recommendation was based on data suggesting that an ACEi (or ARB) was likely to produce the most effective blood pressure lowering as initial therapy in younger patients. However, due a lack of head-to-head comparison trials, it was unclear in 2006 whether an ARB could be considered equivalent to an ACEi as intial therapy for younger people. The evidence review in 2006 had also suggested that for black people of African and Caribbean descent at any age, a CCB or thiazide type diuretic was the preferred initial therapy at any age.

Since 2006, important new data has become available in a number of areas; i) comparison of ACEi with ARB – to determine if treatment with an ARB is equivalent at preventing clinical outcomes when compared to treatment with an ACEi; ii) for step 2 therapy, comparison between a a combination of A+C versus A+D on clinical outcomes – this is important because if one of these combinations is preferred then it would impact on the preferred step 1 therapy for people aged ≥55 years, or black people of African and Caribbean descent at any age; iii) new data showing differential effects of antihypertensive treatments on blood pressure variability, suggesting that blood pressure variability *per se* is an independent predictor of clinical outcomes; iv) a review of diuretic therapy, specifically addressing whether the predominant use of low dose bendroflumethiazide as the preferred diuretic for the treatment of hypertension in the UK is justified when the majority of clinical trials have used different thiazide-type diuretics; and v) new data on antihypertensive therapy options for resistant hypertension (step 4 treatment). Finally, since 2006, the cost of antihypertensive therapies has decreased significantly, some more than others (e.g. CCBs and ARBs) due to generics becoming available. Consequently, this update of hypertension guideline dealing with pharmacological treatment for primary hypertension reviewed recommendations with regard to; i) the equivalence of ACEi versus ARBs on clinical outcomes; ii) the appropriate choice of diuretic therapy for the treatment of hypertension and their place in the hierarchy of treatment; iii) the preferred combination of therapies for step 2 and step 3 treatment; and iv) the treatment of resistant hypertension, i.e. step 4 treatment. This review of pharmacological treatment strategies was supported by an updated cost-effectiveness analysis comparing different treatments with updated costings.

Update 2011

12.3.1 Angiotensin-converting enzyme inhibitors (ACEi) versus Angiotensin Receptor Blockers (ARB)

Forest plots found in Appendix H: Forest plots.

12.3.1.1 Clinical evidence

The literature was reviewed from December 2005 onwards (this was the cut-off date of the previous NICE guidance on pharmacological treatment of hypertension, CG34) for systematic reviews and RCTs comparing ACEi vs ARB for first-line treatment in adults with primary hypertension. RCTs were included if there was: ≥12 months follow-up, N≥200 and the population did not consist of people who were exclusively diabetic or had CKD.

Three RCTs[552,587,653] were found which fulfilled the inclusion criteria and addressed the question and were included in the review.

- The first RCT[653] (the ONTARGET trial) compared treatment with the ACEi ramipril (5 mg/day) vs. the ARB telmisartan (50 mg/day) and vs. a combination of the two (ACEi+ARB) in N=25,620 people with hypertension, and had a median follow-up time of 56 months. Treatment followed a stepped add-on therapy protocol (stepped up to double or triple therapy) for non-responders in each arm.
- The second RCT[587] compared treatment with the ACEi enalapril (20 mg/day) vs. the ARB losartan (50 mg/day) in N=560 people with hypertension, and had a follow-up time of 24 months. Treatment followed a one-step dose adjustment protocol for the ACEi arm.
- The third RCT[552] (CORD IB trial) compared treatment with the ACEi ramipril (5 mg/day) vs. the ARB losartan (50 mg/day) in N=3860 people with hypertension, and had a follow-up time of 12 months. Treatment followed a stepped dose adjustment and add-on therapy protocol (increased dose then if needed added on additional antihypertensive) for non-responders in each arm.

NOTE: no quality of life data was found, or data assessing the effects of ACEi vs ARB in people aged 80+ or black people of African and Caribbean descent.

NOTE: we additionally looked for outcomes relating to sexual dysfuntion in men, for ACE vs ARB (as this is thought to be an important ussue particulary for erectile dysfunction sufferers). However,no outcomes relating to this were reported in any of the studies.

12.3.1.2 Evidence statements - clinical

The evidence profile below (Table 57) summarises the quality of the evidence and outcome data from the three RCTs[552,587,653] included in this review, comparing ACEi versus ARB.

Update 2011

ARB was significantly better than ACEi for:

- less study drug withdrawals* [moderate quality evidence]

There was NS difference between ACEi and ARB for:

- mortality (all cause) [high quality evidence]
- MI (fatal and non-fatal) [moderate quality evidence]
- stroke (fatal and non-fatal) [moderate quality evidence]
- angina requiring hospitalisation [moderate quality evidence]
- coronary revascularisation [high quality evidence]
- new onset diabetes [moderate quality evidence]
- heart failure [moderate quality evidence]

*There was significant heterogeneity for this outcome when the data from the three trials were pooled together. Heterogeneity could be explained by the fact that both low and high quality trials had been pooled together (details of sensitivity analysis by methodological quality can be found in the forest plot for this outcome). Low quality trials were defined as those which had no blinding or allocation concealment. Data included in GRADE for this outcome was therefore based on the high quality trial alone. However the overall quality rating given by GRADE for this outcome was 'moderate' due to imprecision (reasons outlined in the evidence profile).

Table 57: Evidence profile comparing ACEi versus ARBs

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	ACEi	Relative (95% CI)	Absolute	Quality
Mortality (all cause) (follow-up 12 - median 56 months)											
2 CORDIB[55] 2 ONTARGET[653]	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	995/10443 (9.5%)	1018/10535 (9.7%)	HR 0.98 (0.9 to 1.07)	2 fewer per 1000 (from 9 fewer to 6 more)	HIGH
MI (fatal and non-fatal) (follow-up 12-56 months)											
2 CORDIB[55] 2 ONTARGET[653]	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	443/10443 (4.2%)	417/10535 (4%)	HR 1.07 (0.94 to 1.22)	3 more per 1000 (from 2 fewer to 8 more)	MODERATE
Stroke (fatal and non-fatal) (follow-up 12 - median 56 months)											
2 CORDIB[55] 2 ONTARGET[653]	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	378/10443 (3.6%)	413/10535 (3.9%)	HR 0.92 (0.8 to 1.06)	3 fewer per 1000 (from 8 fewer to 2 more)	MODERATE
Hospitalisation for angina (follow-up median 56 months)											
1 ONTARGET[653]	randomised trials	no serious limitations[3]	no serious inconsistency	no serious indirectness	serious[2]	none	954/8542 (11.2%)	925/8576 (10.8%)	HR 1.04 (0.95 to 1.14)	4 more per 1000 (from 5 fewer to 14 more)	MODERATE
Coronary revascularisation (follow-up median 56 months)											
1 ONTARGET[653]	randomised trials	no serious limitations[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1290/8542 (15.1%)	1269/8576 (14.8%)	HR 1.02 (0.95 to 1.1)	3 more per 1000 (from 7 fewer to 14 more)	HIGH
New onset diabetes (follow-up 12-56 months)											

2 CORDIB[55] [2] ONTARGET[653]	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	404/7195 (5.6%)	372/7386 (5%)	HR 1.12 (0.97 to 1.29)	6 more per 1000 (from 1 fewer to 14 more)	MODERATE
Heart failure (follow-up median 56 months)											
1 ONTARGET[653]	randomised trials	no serious limitations[3]	no serious inconsistency	no serious indirectness	serious[2]	none	537/8542 (6.3%)	514/8576 (6%)	HR 1.05 (0.93 to 1.19)	3 more per 1000 (from 4 fewer to 11 more)	MODERATE
Study drug withdrawal (follow-up 12 - median 56 months)											
1 ONTARGET[653]	randomised trials	serious[3,4]	no serious inconsistency[5]	no serious indirectness[3]	serious[6]	none	1812/10572 (17.1%)	2067/10665 (19.4%)	HR 0.87 (0.81 to 0.92)[7]	23 fewer per 1000 (from 14 fewer to 34 fewer)	LOW

[1] 1/2 studies (CORD IB): no blinding, no allocation concealment; but this trial was small compared to the other included one (ONTARGET) so overall weighted as no serious limitations.
[2] 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
[3] Random, double blind, allocation concealment, powered, ITT analysis. However unclear final dropouts (but treatment withdrawal was <30% for median 56 months follow-up) so acceptable.
[4] Patients who entered the trial had already been 'filtered' at run-in to exclude those with poor compliance or who did not perform well.
[5] 3 studies originally included and pooled but there was significant heterogeneity (p<0.1 and I2 >50%). Low quality trials removed based on sensitivity analysis, and result reported here is from the high quality trial data.
[6] 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm
[7] p<0.0001; favours ARB

12.3.1.3 Economic evidence

Three studies were identified in the update search that included ACEi and ARB in the comparators but all were excluded due to being judged to have serious methodological limitations[202,529,560].

In the absence of a published cost effectiveness analysis, current UK drugs costs were presented to the GDG to inform decision making. It was noted that losartan has recently come off patent and other ARBs are also due to come off patent over the next few years.

12.3.1.4 Evidence statements – Clinical

ARB was significantly better than ACEi for:

- less study drug withdrawals* [low quality evidence]

There was a non-significant difference between ACEi and ARB for:

- mortality (all cause) [high quality evidence]
- MI (fatal and non-fatal) [moderate quality evidence]
- stroke (fatal and non-fatal) [moderate quality evidence]
- angina requiring hospitalisation [moderate quality evidence]
- coronary revascularisation [high quality evidence]
- new onset diabetes [moderate quality evidence]
- heart failure [moderate quality evidence]

*There was significant heterogeneity for this outcome when the data from the three trials were pooled together. Heterogeneity could be explained by the fact that both low and high quality trials had been pooled together (details of sensitivity analysis by methodological quality can be found in the forest plot for this outcome). Low quality trials were defined as those which had no blinding or allocation concealment. Data included in GRADE for this outcome was therefore based on the high quality trial alone. However the overall quality rating given by GRADE for this outcome was still 'low' for reasons outlined in the evidence profile.

12.3.1.5 Evidence statements – Health economics

- No relevant evidence of cost-effectiveness was available.
- In terms of drug acquisition costs alone, in December 2010 based on BNF 60 the lowest cost ARB was £25.94 per year (losartan [100mg used for costing]) and the lowest cost ACEi was £20.73 per year (ramipril [10mg used for costing]).

12.3.2 Diuretics

In adults with primary hypertension, which is the most clinically and cost effective thiazide type diuretic (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first line treatment, and does this vary with age and ethnicity?

12.3.2.1 Clinical evidence

Thiazide-type diuretics versus placebo or other antihypertensive drug class

The literature was searched for all years (as this was not addressed in the previous guidelines)[425,436]. SRs/MAs and RCTs were included that compared the following TDs

Update 2011

(bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) with either placebo or other classess of a-HT drugs for 1st-line therapy. Studies were excluded if they had sample sizes of N<200, follow-up of <1 year or populations which were exclusively diabetic or had chronic kidney disease. Pre-specified outcomes of interest were only clinical outcomes (e.g. stroke, MI etc.) and not BP measurements.

NOTE: in the previous NICE hypertension guidelines [425,436] a lot of the evidence for diuretics was on Chlorthiazide, which is no longer used in the UK and is why many of the studies have not been included in this review.

14 RCTs (21 papers) were identified which fulfilled the inclusion criteria and addressed the question, and were included in the review {1995 6420 /id;Sareli, 2001 489 /id;1978 6415 /id;Beckett, 2008 387 /id;The ALLHAT Officers and Co-ordinators for the ALLHAT Collaborative Research Group, 2000 6139 /id;Weir, 2003 2500 /id;The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), 2002 752 /id;Wing, 2003 6558 /id;Borhani, 1996 6140 /id;1985 1144 /id;Zanchetti, 2004 80 /id;Zanchetti, 1998 785 /id;Rosei, 1997 786 /id;Perry, 2000 417 /id;SHEP Cooperative Research Group, 1991 470 /id;SHEP Cooperative Research Group, 1988 471 /id;Kostis, 1997 654 /id;Vaccarino, 2001 545 /id;Perry, 1986 418 /id;Hulley, 1985 6137 /id;Perry, 1989 6142 /id;Malacco, 2003 16093 /id;Tresukosol, 2005 1971 /id}. NOTE: several of the studies were published as multiple papers (SHEP: three papers;[335,483,606] SHEP-P: three papers;[281,484,485] VHAS: two papers;[514,658] and ALLHAT: three papers[589,591,628]) reporting different outcomes, so these studies have only been counted once, however results from all the papers are reported and referenced here[483].

The table below (Table 58) summarises the studies included in the review. {1995 6420 /id;Sareli, 2001 489 /id;1978 6415 /id;Beckett, 2008 387 /id;The ALLHAT Officers and Co-ordinators for the ALLHAT Collaborative Research Group, 2000 6139 /id;Weir, 2003 2500 /id;The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), 2002 752 /id;Wing, 2003 6558 /id;Borhani, 1996 6140 /id;1985 1144 /id;Zanchetti, 2004 80 /id;Zanchetti, 1998 785 /id;Rosei, 1997 786 /id;Perry, 2000 417 /id;SHEP Cooperative Research Group, 1991 470 /id;SHEP Cooperative Research Group, 1988 471 /id;Vaccarino, 2001 545 /id;Perry, 1986 418 /id;Hulley, 1985 6137 /id;Perry, 1989 6142 /id;Malacco, 2003 16093 /id;Tresukosol, 2005 1971 /id}. Table 59 summarises the diuretics used in each trial and their doses.

Update 2011

Data was categorised into those diuretics that were classed as:

- thiazide diuretics (TDs): bendrofluazide / bendroflumethiazide (BDZ) and hydrochlorothiazide (HCTZ)
- 'thiazide-like' diuretics (TDLs): chlorthalidone (CTD) and indapamide (IND)

Table 58: Summary of included studies

Study	N	Intervention	Comparison	Follow-up	Results
TDs – BDZ					
MRC[8]	17,354	BDZ (10mg/day)	Propanolol (240mg/day) or placebo	Mean 4.9 years	NS difference in overall mortality, CHD events or cardiovascular events between BDZ and propanolol. BDZ better than propanolol for reduced cerebrovascular events. NS difference in overall mortality or CHD events between BDZ and placebo. BDZ better than placebo for reduced

Study	N	Intervention	Comparison	Follow-up	Results
					cardiovascular, and cerebro-vascular events
TDs – HCTZ					
THAI elderly{Tresukosol, 2005 1971 /id}	200	HCTZ (25-50 mg/day)	CCB (amlodipine) (5-10 mg/day)	18 months	No difference between HCTZ and CCB for mortality
MIDAS[90]	883	HCTZ (25 – 50 mg/day)	CCB (isradipine) (2.5- 5mg/daily)	36 months	NS differences between HCTZ and isradipine for overall mortality, CHD events, cardiovascular, and cerebro-vascular events
Sareli et al. 2001 [524]	409	HCTZ (12.5 mg/day)	CCB (nifedipine SR) (30 mg/day) or CCB (verapamil hydrochloride SR) (240 mg/day) or ACEi (enalapril maleate) (10 mg/day)	13 months in total but 2 months for monotherapy data	NS differences between groups
PHYLLIS[657]	508	HCTZ (25 mg qid) pravastatin in 50% of patients.	ACEi (fosinopril) (25mg qid) pravastatin in 50% of patients.	Mean 2.6 years	NS differences in CHD events, cerebrovascular events or cardiovascular events
TDLs – CTD					
VA-NHLBI[3]	1012	CTD (50 mg/day initially)	Placebo	2 years	NS differences between groups
SHEP[335,483,536,537,606]	4736	CTD (12.5-25 mg/day)	Placebo	4.5 years	CTD better than placebo for reduced CHD events, reduced stroke and reduced cardiovascular events. NS difference for HF (fatal and non-fatal).
SHEP- P[281,484,485]	441	CTD (25-50 mg/day)	Placebo	34 months	NS differences between groups
VHAS[514,658]	1414	CTD (25mg/day)	CCB (verapamil) (240mg/day)	2 years	NS differences in overall mortality, CHD events, or cerebrovascular
SHELL[384]	1882	CTD (12.5-25 mg/day)	CCB (lacidipine) (4-6 mg/day)	Median 32 months	No difference between CTD and CCB for mortality, stroke, MI and HF

Study	N	Intervention	Comparison	Follow-up	Results
ALLHAT [589,591,628]	42,418	CTD (12.5-25mg/day)	CCB (amlodipine) (2.5- 10mg/day) or ACEi (Iisinopril) (10-40mg/day)	Mean 4.9 years	NS difference between CTD and ACEi I for overall mortality and CHD events. CTD better for cardiovascular and cerebro-vascular events NS difference between CTD vs. CCB for all cause mortality and CHD events, cardiovascular events, and cerebrovascular events
ANBP2[644]	6083	CTD (GP's choice of dose)	ACEi (enalapril) (GP's choice of dose)	Mean 4.1 years	CTD worse than enalapril for CHD events. NS difference for overall mortality, cardiovascular and cerebro-vascular events
TDLs – IND					
PATS[20]	5665	IND (2.5 mg/day)	Placebo	Mean 2 years	IND better for reduced stroke (fatal and non-fatal), total mortality, CV deaths and coronary deaths
HYVET[63]	3845	IND SR (1.5 mg/day)	Placebo	Mean 2.1 years	IND better for reduced MI (fatal and non-fatal), HF (fatal and non-fatal) and mortality. NS difference between groups for stroke

Table 59: Diuretic and dosage used in trial

Diuretic used	Number of trials	Doses used
TDs		
HCTZ	5 Sareli[524] ANBP2[644] PHYLLIS[657] MIDAS[90] THAI elderly{Tresukosol, 2005 1971 /id}	 12.5mg/day At GPs discretion 25mg qid 25-50mg/day 25-50 mg/day
BDZ	1 MRC[8]	 10mg/day
TDLs		
IND	2 PATS[20] HYVET[63]	 2.5mg/day 1.5mg/day (SR)
CTD	6 ALLHAT[591,628] SHEP[335,483,536,537] SHELL[384]	 12.5 – 25mg/day 12.5 – 25mg/day 12.5-25 mg/day

Diuretic used	Number of trials	Doses used
	VHAS[514,658] SHEP-P[484,485] VA-NHLBI[3]	25mg/day 25-50mg/day 50-100mg/day

The evidence profiles below (Table 60 to

Table 67) summarise the evidence and outcome data from the 14 RCTs{1995 6420 /id;Sareli, 2001 489 /id;1978 6415 /id;Beckett, 2008 387 /id;The ALLHAT Officers and Co-ordinators for the ALLHAT Collaborative Research Group, 2000 6139 /id;Weir, 2003 2500 /id;The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), 2002 752 /id;Wing, 2003 6558 /id;Borhani, 1996 6140 /id;1985 1144 /id;Zanchetti, 2004 80 /id;Zanchetti, 1998 785 /id;Rosei, 1997 786 /id;Perry, 2000 417 /id;SHEP Cooperative Research Group, 1991 470 /id;SHEP Cooperative Research Group, 1988 471 /id;Kostis, 1997 654 /id;Vaccarino, 2001 545 /id;Perry, 1986 418 /id;Hulley, 1985 6137 /id;Perry, 1989 6142 /id;Malacco, 2003 16093 /id;Tresukosol, 2005 1971 /id} included in this review comparing diureticsvs. placebo or other a-HT drug classes. Data are presented for each diuretic.

NOTE: cerebrovascular events in some trials was cited and was synonymous with stroke.

Table 60: Bendroflumethazide versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bendroflumethiazide versus placebo	control	Relative (95% CI)	Absolute	Quality
Overall mortality (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	128/3519 (3.6%)	253/6941 (3.6%)	HR 1 (0.81 to 1.24)	0 fewer per 1000 (from 7 fewer to 9 more)	LOW
CHD event (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	119/3519 (3.4%)	234/6941 (3.4%)	HR 1 (0.8 to 1.25)	0 fewer per 1000 (from 7 fewer to 8 more)	LOW
Stroke (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	18/3519 (0.5%)	109/6941 (1.6%)	HR 0.44 (0.30 to 0.63)	9 fewer per 1000 (from 6 fewer to 11 fewer)	LOW
Cardiovascular event (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	140/3519 (4%)	352/6941 (5.1%)	HR 0.78 (0.65 to 0.94)	11 fewer per 1000 (from 3 fewer to 17 fewer)	LOW

[1] Allocation concealment unclear and attrition high
[2] 95% CI includes no effect and appreciable benefit or appreciable harm
[3] 95%CI does not include no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm

Table 61: Indapamide versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide versus placebo	control	Relative (95% CI)	Absolute	Quality
Overall mortality (follow-up mean 2.05 years)											
2 PATS[20] HYVET[63]	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	342/4774 (7.2%)	393/4736 (8.3%) 8.90%	HR 0.85 (0.74 to 0.99)	12 fewer per 1000 (from 1 fewer to 21 fewer) 13 fewer per 1000 (from 1 fewer to 22	MODERATE

										fewer)	
CHD event (follow-up mean 2.05 years)											
2 PATS[20] HYVET[63]	randomised trials	no serious limitations[1]	serious[3]	no serious indirectness	serious[2]	none	50/4774 (1%)	78/4736 (1.6%) 1.90%	HR 0.53 (0.36 to 0.77)	8 fewer per 1000 (from 4 fewer to 11 fewer) 9 fewer per 1000 (from 4 fewer to 12 fewer)	LOW
Stroke (follow-up mean 2.05 years)											
2 PATS[20] HYVET[63]	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	210/4774 (4.4%)	286/4736 (6%) 5.70%	HR 0.72 (0.61 to 0.87)	17 fewer per 1000 (from 8 fewer to 23 fewer) 16 fewer per 1000 (from 7 fewer to 22 fewer)	MODERATE
Cardiovascular event (follow-up mean 2.05 years)											
2 PATS[20] HYVET[63]	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	203/4774 (4.3%)	259/4736 (5.5%) 4.70%	HR 0.77 (0.64 to 0.93)	12 fewer per 1000 (from 4 fewer to 19 fewer) 11 fewer per 1000 (from 3 fewer to 17 fewer)	MODERATE
Quality of life - no limitations in daily activities (follow-up mean 2 years)											
1 PATS[20]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	2125/2841 (74.8%)	2019/2824 (71.5%)	HR 1.09 (1.03 to 1.16)	30 more per 1000 (from 11 more to 52 more)	MODERATE

[1] Both had allocation concealment; attrition was >20% in one trial and no data provided in the other trial
[2] 95%CI does not cross the line of no effect but crosses both appreciable benefit or harm and non-appreciable benefit or harm
[3] Heterogeneity was 77%. This could be due to different populations. One trial recruited adults aged 80 years+ and the other trial recruited patients with a recent TIA or stroke.

Table 62: Chlorthalidone versus placebo

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorthalidone versus placebo	control	Relative (95% CI)	Absolute	
Overall mortality (follow-up mean 2 years)											
3 SHEP[335,483,536,537] SHEP-P[484,485] VA-NHLBI[3]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/508 (1.6%)	5/504 (1%)	HR 0.87 (0.73 to 1.04)	1 fewer per 1000 (from 3 fewer to 0 more)	LOW
CHD events (follow-up mean 2 years)											
3 SHEP[335,483,536,537] SHEP-P[484,485] VA-NHLBI[3]	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[4]	none	16/508 (3.1%)	8/504 (1.6%)	HR 2.0 (0.86 to 4.67)	16 more per 1000 (from 2 fewer to 56 more) 16 more per 1000 (from 2 fewer to 57 more)	VERY LOW
Stroke											
2 SHEP[335,483,536,537] SHEP-P[484,485]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	114/2808 (4.1%)	165/2479 (6.7%)	HR 0.63 (0.49 to 0.80)	24 fewer per 1000 (from 13 fewer to 33 fewer) 24 fewer per 1000 (from 13 fewer to 34 fewer)	MODERATE
Cardiovascular event (follow-up mean 2 years)											
2 SHEP[335,483,536,537] VA-NHLBI[3]	randomised trials	serious[1,6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/508 (0.4%)	0/504 (0%)	HR 4.31 (0.27 to 68.84)	0 more per 1000 (from 0 fewer to 0 more)	MODERATE

[1] No ITT analysis conducted on data in one study, attrition >20% in two studies
[2] 95%CI crosses both no effect and appreciable harm or benefit
[3] Heterogeneity 59%
[4] 95%CI does not cross no effect but includes both appreciable benefit or harm and non-appreciable benefit or harm
[5] Attrition >20%
[6] ITT analysis not conducted in one study and attrition > 20% in the other study

Table 63: Chlorthalidone versus calcium channel blocker.

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorthalidone versus CCB	control	Relative (95% CI)	Absolute	
Overall mortality (follow-up 2 to 4.9 years)											
3 ALLHAT[591,628] SHELL[384] VHAS[514,658]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2329/16483 (14.1%)	1406/10439 (13.5%) 7.50%	HR 1.03 (0.97 to 1.10)	4 more per 1000 (from 4 fewer to 12 more) 2 more per 1000 (from 2 fewer to 7 more)	MODERATE
CHD events (follow-up 2 to 4.9 years)											
2 ALLHAT[591,628] VHAS[514,658]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2460/15543 (15.8%)	1474/9497 (15.5%) 8.90%	HR 0.94 (0.88 to 1.0)	1 more per 1000 (from 7 fewer to 11 more) 1 more per 1000 (from 4 fewer to 7 more)	MODERATE
Stroke (follow-up 2 to 4.9 years)											
3 ALLHAT[591,628] SHELL[384] VHAS[514,658]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	717/16483 (4.3%)	419/10439 (4%)	HR 0.94 (0.83 to 1.06)	2 more per 1000 (from 2 fewer to 8 more)	LOW
Cardiovascular events (follow-up mean 4.9 years)											
1 ALLHAT[591,628]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3941/14836 (26.6%)	2432/8790 (27.7%)	HR 0.96 (0.91 to 1.01)	12 more per 1000 (from 0 more to 23 more)	MODERATE
Heart failure (follow-up mean 32 months)											
1 SHELL[384]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2,5]	none	19/940 (2%)	23/942 (2.4%)	HR 0.83 (0.46 to 1.62)	4 fewer per 1000 (from 13 fewer to 15 more)	VERY LOW
MI (follow-up mean 32 months)											
1 SHELL[384]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2,5]	none	14/940 (1.5%)	12/942 (1.3%)	HR 1.17 (0.54 to 2.53)	2 more per 1000 (from 6 fewer to 19 more)	VERY LOW

[1] Attrition was >20% in both trials. There was inadequate explanantion of allocation concealment in one trial
[2] 95%CI includes both no effect and appreciable benefit or harm
[3] Attirtion >20%
[4] Unclear allocation concealment and open blind
[5] 95%CI includes both no effect and both appreciable benefit and appreciable harm

Table 64: Chlorthalidone versus ACEi Inhibitor

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorthalidone versus ACEi	control	Relative (95% CI)	Absolute	
Overall mortality (follow-up 4.1 to 4.9 years)											
2 ALLHAT[591,628] ANBP2[644]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2413/17873 (13.5%)	1509/11822 (12.8%) 10.70%	HR 1.00 (0.94 to 1.07)	2 more per 1000 (from 6 fewer to 9 more) 2 more per 1000 (from 5 fewer to 8 more)	MODERATE
CHD events (follow-up 4.1 to 4.9 years)											
2 ALLHAT[591,628] ANBP2[644]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2533/17873 (14.2%)	1563/11822 (13.2%) 9.50%	HR 0.97 (0.91 to 1.03)	40 more per 1000 (from 6 more to 81 more) 29 more per 1000 (from 5 more to 60 more)	MODERATE
Stroke (follow-up 4.1 to 4.9 years)											
2 ALLHAT[591,628] ANBP2[644]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	107/3037 (3.5%)	112/3044 (3.7%) 4.40%	HR 0.88 (0.79 to 0.98)	4 fewer per 1000 (from 1 fewer to 8 fewer) 5 fewer per 1000 (from 1 fewer to 9 fewer)	LOW
Cardiovascular events (follow-up 4.1 to 4.9 years)											
2 ALLHAT[591,628] ANBP2[644]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	429/3037 (14.1%)	394/3044 (12.9%) 20.80%	HR 0.91 (0.86 to 0.96)	11 fewer per 1000 (from 5 fewer to 17 fewer) 17 fewer per 1000 (from 7 fewer to 26 fewer)	LOW

Table 65: Hydrochlorthiazide versus calcium channel blockers

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HCTZ versus CCB	control	Relative (95% CI)	Absolute	Quality
Overall mortality (follow-up 2 to 36 months)											
3 Sareli, MIDAS, THAI{Sareli, 2001 489 /id;Borhani, 1996 6140 /id;Tresukosol, 2005 1971 /id}	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/599 (1.7%)	10/833 (1.2%)	HR 1.18 (0.48 to 2.90)	2 more per 1000 (from 6 fewer to 22 more)	VERY LOW
CHD events (follow-up 2 to 36 months)											
2 Sareli, MIDAS[90,524]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/499 (2.6%)	19/733 (2.6%) 2.30%	HR 0.77 (0.37 to 1.57)	12 more per 1000 (from 7 fewer to 51 more) 11 more per 1000 (from 6 fewer to 46 more)	VERY LOW
Stroke (follow-up mean 36 months)											
1 MIDAS[90]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/441 (0.7%)	6/442 (1.4%) 1.40%	HR 1.99 (0.5 to 7.97)	13 more per 1000 (from 7 fewer to 90 more) 14 more per 1000 (from 7 fewer to 92 more)	VERY LOW
Cardiovascular events (follow-up 2 to 36 months)											
2 Sareli, MIDAS[90,524]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	14/499 (2.8%)	26/733 (3.5%) 3%	HR 1.8 (0.94 to 3.44)	27 more per 1000 (from 2 fewer to 81 more) 23 more per 1000 (from 2 fewer to 69 more)	LOW

[1] None of the trials provide adequate information on allocation concealment. One of the trials had attrition >20% and ITT analysis was not conducted on the data in the other trial
[2] 95%CI includes no effect and appreciable benefit and appreciable harm
[3] Trial did not provide adequate information on allocation concealment and attrition > 20%
[4] 95% CI includes both no effect and appreciable benefit or appreciable harm

Table 66: Hydrochlorthiazide versus ACEi Inhibitor

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HCTZ versus ACEi	control	Relative (95% CI)	Absolute	Quality
Overall mortality (follow-up mean 2 months)											
1 Sareli [524]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/58 (1.7%)	0/60 (0%)	HR 4.06 (0.08 to 204.37)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW
CHD events (follow-up mean 2.6 years)											
1 PHYLLIS[657]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/253 (1.2%)	1/254 (0.4%)	HR 3.02 (0.31 to 29.07)	8 more per 1000 (from 3 fewer to 104 more)	VERY LOW
Stroke (follow-up mean 2.6 years)											
1 PHYLLIS[657]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/253 (0%)	1/254 (0.4%)	HR 3.90 (0.08 to 196.36)	11 more per 1000 (from 4 fewer to 535 more) 12 more per 1000 (from 4 fewer to 541 more)	VERY LOW
Cardiovascular event (follow-up mean 2.6 years)											
1 PHYLLIS[657]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/253 (0%)	1/254 (0.4%)	HR 3.90 (0.08 to 196.36)	11 more per 1000 (from 4 fewer to 535 more) 12 more per 1000 (from 4 fewer to 541 more)	VERY LOW

[1] No information on allocation concealment and attrition >20%
[2] 95%CI includes both no effect and appreciable benefit and appreciable harm
[3] No information on allocation concealment and unclear on attrition

Table 67: Bendroflumethiazide versus Beta blocker

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bendroflumethiazide versus Beta blocker	control	Relative (95% CI)	Absolute	
Overall mortality (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	128/3519 (3.6%)	120/3558 (3.4%)	HR 1.08 (0.84 to 1.39)	3 more per 1000 (from 5 fewer to 13 more)	VERY LOW
CHD events (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	119/3519 (3.4%)	103/3558 (2.9%)	HR 1.17 (0.9 to 1.52)	5 more per 1000 (from 3 fewer to 15 more)	LOW
Stroke (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	18/3519 (0.5%)	42/3558 (1.2%)	HR 0.43 (0.25 to 0.75)	7 fewer per 1000 (from 3 fewer to 9 fewer)	LOW
Cardiovascular events (follow-up mean 4.9 years)											
1 MRC[8]	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	140/3519 (4%)	146/3558 (4.1%)	HR 1.03 (0.82 to 1.3)	1 more per 1000 (from 7 fewer to 12 more)	VERY LOW

[1] Allocation concealment unclear and attrition > 20%
[2] 95%CI includes both no effect and appreciable benefit and appreciable harm
[3] 95%CI does not include no effect but does cross appreciable and non-appreciable benefit and harm
[4] 95%CI includes no effect and appreciable benefit or appreciable harm

Head to head comparisons

The literature was searched for all years (as this was not addressed in the previous guidelines)[425,436]. SRs/MAs and RCTs were included that compared the fllowing TDs with each other: bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide for 1st-line therapy. There was no restriction placed on sample size or follow-up time. Populations which were exclusively diabetic or had chronic kidney disease were excluded. Outcomes of interest were only BP measurements. All studies included in this review measured BP in the office. However two studies[94,199] used both office and ABPM or just ABPM measurements.

A total of 15 RCTs were found that fulfilled the inclusion criteria. The different comparisons are detailed in the table (Table 1) below.

- Six RCTs [94,194,339,493,494,551] Emeriau, 2001[195] were found which compared Indapamide (IND) vs. Hydrochlorothiazide (HCTZ).
- Two RCTs [39,76] were found which compared Indapamide (IND) vs. bendrofluazide/bendroflumethiazide (BDZ).
- Two RCTs [266,503] were found which compared Indapamide (IND) vs. chlorthalidone (CTD).
- Three RCTs[93 198 216] were found which compared Chlorthalidone (CTD) vs. hydrochlorothiazide (HCTZ).
- One RCT[5] was found which compared Hydrochlorthiazide (HCTZ) vs. bendroflumethiazide (BDZ).

NOTE: several studies[194,195,503] assessed additional arms treating people with other classes of a-HT drugs. These were not included because they did not answer this part of the question (TDs vs. TDs) and were not included in the first part of the question (TDs vs. placebo / other a-HT classes) because they did not meet inclusion criteria (ie. were N<200 and/or had <1 year follow-up time).

NOTE: all RCTs were underpowered to detect a difference in BP. In order to detect a 5mm difference, a sample size of N≥500 is needed.

NOTE: five studies were cross-over trials: Bowlus 1964, Ernst 2006, Elliott 1991, Hatt 1975, Kreeft 1984[93,194,198,266,339]

The table below (Table 1) summarises the studies included in this review and the results[5,39,76,93,94,194,195,198,216,266,339,493,494,503,551]

Data was categorised into those diuretics that were classed as:

- thiazide diuretics (TDs): bendrofluazide / bendroflumethiazide (BDZ) and hydrochlorothiazide (HCTZ)
- 'thiazide-like' diuretics (TDLs): chlorthalidone (CTD) and indapamide (IND)

Table 68: Summary of included studies

Study	N	Intervention	Control	Follow-up	Results
TDL vs TD					
Bowlus 1964[93]	29	CTD (50mg/day)	HCTZ (100 mg/day	6 weeks treatment, 2 weeks washout	NS difference in BP between groups.
Ernst, 2006[198]	30	CTD (12.5mg/day) force titrated to 25mg/day	HCTZ (25mg/day) force titrated to 50mg/day	8 weeks treatment, 4 weeks washout, 8 weeks treatment	NS difference (office BP and 24hr ABPM) between groups.

Update 2011

Study	N	Intervention	Control	Follow-up	Results
Finnerty, 1976[216]	54	CTD (50mg/day plus placebo)	HCTZ (100mg/day)	2 weeks no treatment, followed by 4 weeks of treatment in either arm.	NS difference in BP between groups.
Kreeft, 1984[339]	17	IND (2.5mg/day)	HCTZ (50mg/day)	2 months placebo run-in, 12 weeks TD drug, 2 months placebo washout, 12 weeks alternate TD drug.	NS difference in BP between groups.
Plante, 1988[493]	47	IND (2.5mg/day)	HCTZ (50 mg/day)	48 weeks	IND better for reduced BP (no P value reported) and was less likely to be associated with hypokalaemia.
Plante, 1983[494]	24	IND (2.5mg/day)	HCTZ (50 mg/day)	4-6 washout placebo period, followed by 12 weeks active therapy.	IND better for reduction in DBP in the recumbent position
Spence, 2000[551]	39	IND (2.5mg/day)	HCTZ (25 mg/day)	6 months	NS difference in BP between groups
Brandao, 2010[94]	94	IND (1.5 mg/day)	HCTZ (25 mg/day)	12 weeks Previously untreated patients. Addition of ACEi at 6 weeks if target BP not met.	NS difference in BP (office or ABPM) between groups
Emeriau, 2001[195]	524	IND (SR) (1.5 mg/day)	HCTZ (25 mg/day) Amlodipine (5 mg/day)	4 week washout placebo period; 12 weeks treatment	Similar reduction in BP between groups (equivalence test)
Elliot, 1991[194]	11	IND (2.5mg/day) or HCTZ (25 mg/day)	Placebo (lactose)	28 days	NS difference in BP between groups.
Alem, 2008[39]	26	IND (2.5mg/day)	BDZ (2.5 mg/day)	28 days	Both IND and BDZ reduced BP to a significant degree.
Bing, 1981[76]	20	IND	BDZ	22 weeks	Equivalent fall in BP in both groups

Study	N	Intervention	Control	Follow-up	Results
		(2.5mg/day)	(5 mg/day)		
TDL vs TDL					
Rakić, 2002[503]	80	IND (2.5mg/day)	CTD (25mg/day) NIC (60mg/day) PPL (120mg/day)	6 months	Significant decreases in BP in all groups
Hatt, 1975[266]	36	IND (5mg/day)	CTD (100mg/day)	10 days washout, followed by 90 day crossover	IND better % reduction in DBP.
TD vs TD					
Anonymous, 1984[5]	44	HCTZ (12.5mg/day)	BDZ (12.5mg/day)	12 months	NS difference in BP between groups.

Table 69: Thiazide drug and dosages used in trials

TD name	Number of trials	Doses used
CTD	5 Bowlus, 1964[93] Ernst, 2006[198] Finnerty, 1976[216] Hatt, 1975[266] Rakić, 2002[503]	 50mg/day 12.5mg/day force titrated to 25mg/day 50mg/day plus placebo 100mg/day 25mg/day
HTCZ	11 Anonymous, 1984[5] Elliot, 1991[194] Bowlus, 1964[93] Ernst, 2006[198] Finnerty, 1976[216] Kreeft, 1984[339] Plante, 1988[493] Plante, 1983[494] Spence, 2000[551] Brandao, 2010[94] Emeriau, 2001[195]	 12.5mg/day 25 mg/day 100mg/day 25mg/day force titrated to 50mg/day 100mg/day 50mg/day 50mg/day 50mg/day 25 mg/day 25 mg/day 25 mg/day
Indapamide	11 Brandao, 2010[94] Emeriau, 2001[195] Alem, 2008[39] Bing, 1981[76] Elliot, 1991[194] Hatt, 1975[266]	NOTE: ALL (except one) OF THESE TRIALS STATED THAT THE PREPARATION WAS SR. ALL JUST STATED INDAPMIDE AND THE DOSE. 1.5 mg/day 1.5 mg/day (SR) 2.5mg/day 2.5mg/day 2.5mg/day

TD name	Number of trials	Doses used
	Kreeft, 1984[339] Plante, 1988[493] Plante, 1983[494] Rakić, 2002[503] Spence, 2000[551]	5mg/day 2.5mg/day 2.5mg/day 2.5mg/day 2.5mg/day 2.5mg/day
BDZ	3 Alem, 2008[39] Bing, 1981[76] Anonymous, 1984[5]	 2.5 mg/day 5 mg/day 12.5mg/day

Table 70 to Table 75 below summarise the quality of the evidence and outcome data from the studies included in the review [39,76,93,94,194,195,198,216,266,339,493,503,551]Figure 1: TDL vs TD (CTD vs HCTZ)

Table 70: Thiazide-like diuretics versus thiazide diuretics (chlorthalidone versus hydrochlorthiazide)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorthalidone	HCTZ	Relative (95% CI)	Absolute	Quality
SBP seated (change from baseline) BOWLUS (follow-up 6 weeks; measured with: mmHg; Better indicated by lower values)											
1[93]	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	29	-	MD 7 lower (to lower)[1]	MODERATE
DBP seated (change from baseline) BOWLUS (follow-up 6 weeks; measured with: mmHg; Better indicated by lower values)											
1[93]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	29	29	-	MD 2.1 lower (to lower)[1]	MODERATE
SBP seated (change from baseline) ERNST (follow-up 8 weeks; measured with: mmHg; Better indicated by lower values)											
1[198]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 6.3 higher (to lower)[1]	MODERATE
DBP seated (change from baseline) ERNST (follow-up 8 weeks; measured with: mmHg; Better indicated by lower values)											
1[198]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 1.2 lower (to lower)[1]	MODERATE
SBP: 24h ABPM (change from baseline) ERNST (follow-up 8 weeks; measured with: mmHg; Better indicated by lower values)											
1[198]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 5 lower (to lower)[1]	MODERATE
SBP unknown method (change from baseline) FINNERTY (follow-up 4 weeks; measured with: mmHg; Better indicated by lower values)											
1[216]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	28	-	MD 4 higher (to lower)[1]	MODERATE
DBP unknown method (change from baseline) FINNERTY (follow-up 4 weeks; measured with: mmHg; Better indicated by lower values)											
1[216]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26	28	-	MD 1.3 higher (to lower)[1]	MODERATE

[1] NS differnce between groups
[2] High dropout rates; no ITT analysis
[3] unclear allocation concealment

Table 71: Thiazide-like diuretics versus thiazide-like diuretics (indapimide versus chlorthalidone)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide versus Chlorthalidone	control	Relative (95% CI)	Absolute	Quality
SBP supine (end of follow-up) HATT (Better indicated by lower values)											
1[266]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	38	38	-	MD 0 higher (10.14 lower to 10.14 higher)	VERY LOW
DBP supine (end of follow-up) HATT (Better indicated by lower values)											
1[266]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	38	38	-	MD 4 lower (9.94 lower to 1.94 higher)	VERY LOW
SBP supine (end of follow-up) RAKIC (follow-up 6 months; measured with: mmHg; Better indicated by lower values)											
1[503]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 3.10 higher (3.08 lower to 9.28 higher)[4]	MODERATE
DBP supine (end of follow-up) RAKIC (follow-up 6 months; measured with: mmHg; Better indicated by lower values)											
1[503]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	20	20	-	MD 3.50 higher (0.22 lower to 7.22 higher)[4]	MODERATE

[1] Although the trial was single blinded, randomisation and allocation concealment was not described and there was no ITT analysis
[2] 95%CI includes no effect and both appreciable benefit and appreciable harm
[3] 95%CI include no effect and appreciable benefit or harm
[4] NS difference between groups

Table 72: Thiazide-like diuretics vs Thiazide diuretics (Indapamide versus hydrochlorthiazide)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide versus HCTZ	control	Relative (95% CI)	Absolute	Quality
SBP supine (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)											
5[194,339,493,494,551]	randomised trials	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	77	74	-	MD 8.36 lower (10.92 to 5.8 lower)	VERY LOW
DBP supine (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)											
5[194,339,493,494,551]	randomised trials	very serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	77	74	-	MD 4.2 lower (5.48 to 2.92 lower)	VERY LOW
SBP upright (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)											
4[194,339,494,551]	randomised trials	no serious limitations	very serious[4]	no serious indirectness	no serious imprecision	none	54	55	-	MD 8.74 lower (11.75 to 5.73 lower)	LOW

DBP upright (end of follow-up) (follow-up 28 days to 48 weeks; Better indicated by lower values)											
4[194,339,494,551]	randomised trials	no serious limitations	very serious[5]	no serious indirectness	no serious imprecision	none	54	55	-	MD 3.85 lower (5.41 to 2.28 lower)	LOW
SBP supine (change from baseline) (follow-up 3-6 months; measured with: mmHg; Better indicated by lower values)											
2[195,551]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	196	192	-	MD 3.95 lower (7.03 to 0.87 lower)	MODERATE
DBP supine (change from baseline) (follow-up mean 3-6 months; measured with: mmHg; Better indicated by lower values)											
2[195,551]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	196	192	-	MD 0.76 lower (2.5 lower to 0.98 higher)	MODERATE
SBP upright (change from baseline) (follow-up mean 6 months; Better indicated by lower values)											
1[551]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	18	21	-	MD 12.55 lower (17.11 to 7.99 lower)	HIGH
DBP upright (change from baseline) (follow-up mean 6 months; Better indicated by lower values)											
1[551]	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[7]	none	18	21	-	MD 2.07 lower (7.2 lower to 3.06 higher)	MODERATE
SBP seated (change from baseline) (follow-up 12 weeks; Better indicated by lower values)											
1[94]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	33	-	MD 5.5 higher (0 to 0 higher)[9]	MODERATE
DBP seated (change from baseline) (follow-up 12 weeks; Better indicated by lower values)											
1[94]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	33	-	MD 5.9 higher (0 to 0 higher)[9]	MODERATE
SBP: 24h ABPM (change from baseline) (follow-up 12 weeks; Better indicated by lower values)											
1[94]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	33	-	MD 7.5 higher (0 to 0 higher)[9]	MODERATE
DBP: 24h ABPM (change from baseline) (follow-up 12 weeks; Better indicated by lower values)											
1[94]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32	33	-	MD 2.0 higher (0 to 0 higher)[9]	MODERATE

[1] There were inadequate methodological information in two of the three trials
[2] Heterogeneity was 78%
[3] Heterogeneity was 76%
[4] Heterogeneity was 72%
[5] Heterogeneity 68%
[6] 1/2 studies unclear for allocation concealment
[7] 95%CI includes no effect and appreciable harm or benefit

[8] unclear allocation concealment
[9] There was NS differnce between groups

Table 73: Thiazode-like diuretic versus thiazide diuretic (Indapamide vs benroflumethiazide)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide versus Bendrofluazide/Bendroflumethiazide	control	Relative (95% CI)	Absolute	Quality
SBP supine (end of follow-up) (follow-up mean 22 weeks; Better indicated by lower values)											
1[76]	randomised trials	very serious	no serious inconsistency	no serious indirectness	serious	none	10	10	-	MD 32 lower (72.34 lower to 8.34 higher)	VERY LOW
SBP upright (end of follow-up) (follow-up mean 22 weeks; Better indicated by lower values)											
1[76]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 2 lower (32.58 lower to 28.58 higher)	LOW
DBP supine (end of follow-up) (follow-up mean 22 weeks; Better indicated by lower values)											
1[76]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10	10	-	MD 5 lower (18.85 lower to 8.85 higher)	VERY LOW
DBP Upright (end of follow-up) (follow-up mean 22 weeks; Better indicated by lower values)											
1[76]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10	10	-	MD 0 higher (30.97 lower to 30.97 higher)	LOW
SBP (absolute change) (follow-up mean 22 weeks; Better indicated by lower values)											
1[39]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	13	10	-	MD 5.6 higher (8.35 lower to 19.55 higher)	VERY LOW
DBP (absolute change) (follow-up mean 22 weeks; Better indicated by lower values)											
1[39]	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	13	10	-	MD 3.2 higher (1.85 lower to 8.25 higher)	VERY LOW

[1] Lacked most methodological information
[2] 95%CI includes no effect and appreciable benefit and appreciable harm
[3] 95%CI includes no effect and appreciable and non-appreciable harm or benefit

Table 74: Thiazide diuretic vs thiazide diuretic (hydrochlorthiazide vs bendroflumethiazide)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HCTZ	BDZ	Relative (95% CI)	Absolute	Quality
SBP supine (change from baseline) (follow-up 12 months; measured with: mmHg; Better indicated by lower values)											
15	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	15	-	MD 1 lower (0 to 0 higher)[2]	MODERATE
DBP supine (change from baseline) (follow-up 12 months; measured with: mmHg; Better indicated by lower values)											
15	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	15	-	MD 3 higher (0 to 0 higher)[2]	MODERATE
SBP upright (change from baseline) (follow-up 12 months; measured with: mmHg; Better indicated by lower values)											
15	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	15	-	MD 1 higher (0 to 0 higher)[2]	MODERATE
DBP upright (change from baseline) (follow-up 12 months; measured with: mmHg; Better indicated by lower values)											
15	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	15	-	MD 4 higher (0 to 0 higher)[2]	MODERATE

12.3.2.2 Economic evidence

No relevant economic studies were included that compared different types of diuretic. Economic studies were considered relevant to the question if they compared one diuretic with another or examine the impact of cost and effectiveness differences between different diuretics on the overall decision about which drug to treat people with. Economic studies that included only one type of diuretic were not considered helpful to decision making and were excluded.

In the absence of a published cost effectiveness analysis, current UK drugs costs were presented to the GDG to help inform decision making.

12.3.2.3 Evidence statements - Clinical

Diuretics versus placebo or other anti-hypertensive drugs

Table 75: Results of studies / meta-analysis

Class of diuretic	Diuretic name	Outcome measure and statistical significance (arm favoured)							Studies / references
		MI	CV event	Stroke	Mortality	CHD event	HF	ADL	
Diuretics versus placebo									
TDs	BDZ		SS (BDZ)	SS (BDZ)	NS	NS			MRC
TDLs	CTD		SS (CTD)	SS (CTD)	NS	SS (CTD)			SHEP, SHEP-P, VA-NHLBI
	IND		SS (IND)	SS (IND)	SS (IND)	SS (IND)		SS (IND)	HYVET, PATS
Diuretics versus other anti-hypertensive classes									
TDs	BDZ vs BB		NS	SS (BDZ)	NS	NS			MRC
	HCTZ vs ACEi		NS	NS	NS	NS			PHYLIIS, Sareli
	HCTZ vs CCB		NS	NS	NS	NS			Sareli, MIDAS, THAI elderly
TDLs	CTD vs ACEi		SS (CTD)	SS (CTD)	NS	SS (CTD)			ALLHAT, ANBP2
	CTD vs CCB	NS	NS	NS	NS	NS	NS		ALLHAT, SHELL, VHAS

Head to head comparisons

NOTE: The results of the meta-analyses comparing IND vs HCTZ for SBP and DBP (supine and upright) should be interpreted with extreme caution due to the observed significant heterogeneity. This appears to be attributed to one of the RCTs[494] which reports an effect size in the opposite direction to the other studies and because it has much smaller SDs than the other trials, it has therefore been weighted more highly. If this trial is removed from the MA then heterogeneity is reduced to more acceptable levels of 0% and the effect becomes NS. Removing the two lower quality trials (Plante, 1988 and Kreeft, 1984)[339,493] from the analysis did not result in removing the observed heterogeneity. If a random effects model is applied to the pooled estimate, then the effect size also becomes NS.

Update 2011

NOTE: Some data were not provided in a usable format for inclusion in meta-analysis or were unable to be pooled; data from each of these studies has been summarised individually in Table 68 (and in the evidence profiles), along with pooled data where meta-analysis was possible.[5,93,94,198,216,503]

NOTE: all data given are for between-group differences

Table 76: Results of studies / meta-analysis

Diuretic name (intervention)	Diuretic name (comparison)	Outcome measure and statistical significance (arm favoured)														Studies / references
		Change from baseline								End of follow-up				Absolute change		
		Supine		Upright		Seated		24h ABPM		Supine		Upright		unclear method		
		SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	SBP	SBP	SBP	
Thiazide-like diuretic vs Thiazide diuretic																
CTD	HCTZ	NS (unclear BP method)				NS	NS	NS								93,198,216
IND	HCTZ	SS (IND)	NS	SS (IND)	NS	NS	NS	NS	NS	SS* (IND)	SS* (IND)	SS* (IND)	SS* (IND)			94,194,195,339,493,494,551
IND	BDZ									NS	NS	NS	NS	NS	NS	39,76
Thiazide-like diuretic vs thiazide-like diuretic																
IND	CTD	NS	NS							NS	NS					266,503
TD vs TD																
HCTZ	BDZ	NS	NS	NS	NS											5

*significant heterogeneity. Hetereogenity is removed if the Plante 2003 trial[494] is excluded from the analysis, and the overall effect becomes NS. If a random effects model is applied to the pooled estimate, then the effect size also becomes NS.

NOTE: there were no studies found that compared:

- CTD vs BDZ
- IND vs BDZ

Update 2011

12.3.2.4 Evidence statements – Health economic

Update 2011

- No evidence comparing the cost-effectiveness of different diuretics was identified.
- In terms of drug acquisition costs alone, in December 2010 based on BNF 60: bendroflumethiazide (2.5mg) cost £11.86 per year; chlortalidone (50mg[i]) cost £19.81 per year; indapamide (2.5mg non-proprietary) cost £16.03 per year.

12.4 Cost-effectiveness analysis

Update 2011

This model was developed as part of the 2006 pharmacological update (CG34) to balance clinical outcomes and to test the cost effectiveness of different classes of initial antihypertensive medications. As part of the 2011 update this analysis was rerun with updated costs. The relative risks for ARBs were also updated based on new ACEi vs ARB data.

A summary of the analysis methods and results are provided below. Full methods and results including an overiew of the overall impact of the update compared to the previous analysis is available in 'Appendix I: Cost-effectiveness analysis – pharmacological treatment'.

12.4.1 Methodological introduction

12.4.1.1 Economic question

The aim of the model was to estimate the cost effectiveness of the various blood pressure-lowering drug classes for the management of hypertension in primary care.

12.4.1.2 Population and subgroups

The model considered patients with essential hypertension seen in primary care, excluding those with pre-existing cardiovascular disease (CVD), heart failure (HF) or diabetes. It was designed to be run separately for different cohorts, defined by age (55, 65, 75 and 85) and sex. In addition, the model classified these cohorts by baseline CVD risk (0.5%–5% per year), by heart failure risk (0–5% per year) and by diabetes risk (0–5% per year). A base case analysis was performed for 65-year-old men and women with 2% CVD risk, 1% HF risk and 1.1% diabetes risk, and a sensitivity analysis considered the effect of varying these risk levels.

The trial evidence that the model is based on included relatively few younger (under 55) or black people of African and Caribbean descent, so the results may not be reliable for these groups. However, we did conduct sensitivity analyses to explore how different assumptions about treatment effects might impact on the cost-effectiveness results for younger (45) and black people of African and Caribbean descent.

12.4.1.3 Interventions compared

The analysis assessed the costs and effects of the various classes of blood pressure-lowering drugs alongside a 'do nothing' comparator. Inclusion of no treatment as an option is important for economic evaluations as it allows us to identify low-risk groups for whom treatment is not likely to be cost effective.

The interventions compared were thus:

- no intervention (NI)

i Note that 25mg was considered the optimal dose but only 50mg tablets were listed in the BNF.

- thiazide-type diuretics (D)
- calcium-channel blockers (C)
- beta-blockers (B)
- ACEi/angiotensin-II receptor antagonists (ARBs) (A).

At basecase, it was assumed that 80% of patients starting on ACEi would continue with these, but that 20% would switch to ARBs due to an inability to tolerate ACEi (expert opinion). ACEi/ARBs were combined as a strategy as they were considered to have equivalent effectiveness. The costs and effects of the drugs were weighted to take account of this.

For simplicity only first-line drugs were considered. However, it should be noted that the relative treatment effects from the meta-analysis include additional benefits from various second and third line treatments offered in the trials.

12.4.1.4 Outcomes

The treatment effects were measured in terms of prevention of CVD events (non-fatal unstable angina, MI, heart failure and stroke) and CVD-related deaths. The only adverse effects modelled were onset of HF and diabetes, although we did examine the possible impact of other adverse reactions to the drugs in sensitivity analyses.

It should also be noted that the model does not explicitly include cost impacts of withdrawals, non-concordance or transfers between treatments. The impact of such changes on effectiveness is implicitly included through the use of intention-to-treat trial data.

Health outcomes for the cost-effectiveness analysis are summarised in the form of quality adjusted life-years (QALYs), where one QALY represents one year of healthy life.

12.4.1.5 Cost effectiveness

The results of cost-effectiveness analysis are usually presented as incremental cost-effectiveness ratios (ICERs), which determine the additional cost of using one drug (X) per additional QALY gained, compared with no intervention or another drug (Y):

$$ICERs = \frac{Cost\ of\ X - Cost\ of\ Y}{QALY\ of\ X - QALY\ of\ Y}$$

Where more than two interventions are being compared, the ICERs are calculated using the following process.

- The drugs are ranked in terms of cost, from the cheapest to the most expensive (cheapest indicated by LC (lowest cost) in the results table below).
- If a drug is more expensive and less effective than the previous one, then it is said to be ruled out by 'simple dominated' and is excluded from further analysis (indicated by '-' in the results table below).
- ICERs are then calculated for each drug compared with the next most expensive non-dominated option. If the ICER for a drug is higher than that of the next most effective strategy, then it is ruled out by 'extended dominance' (indicated by '-' in the results table below).
- ICERs are recalculated excluding any drugs subject to extended dominance (these ICERs are given in the results table below).

It is important to bear in mind that comparison between the crude cost-effectiveness ratios for two drugs each compared with 'no intervention' can be highly misleading. To illustrate, the incremental cost of starting antihypertensive therapy with the cheapest drug is relatively low, while the

incremental benefit is high, and thus the ICER is small. A more expensive but more effective drug may also appear to have a relatively small cost-effectiveness ratio when compared with 'no treatment'. However, the more expensive drug may have a larger ICER when it is compared with the cheaper drug – the incremental cost of switching from the cheaper drug to the more expensive one may be quite large in relation to the incremental health gain. Nevertheless, the more expensive drug may still be a *cost-effective* alternative to the cheaper drug if its ICER is less than the maximum amount that we are prepared to pay for a QALY, which is considered to be around £20,000 to £30,000 for NICE decisions. In this situation the most cost-effective option is the more expensive drug, despite its larger ICER. However, if the ICER for the more expensive drug were to exceed the threshold of £20,000 to 30,000 per QALY, then it would not be cost effective and the cheaper option should be preferred.

12.4.2 Results of the health economic model

12.4.2.1 Base case results

The base case results are presented in Table 3 for 65-year-old men and women with an annual CVD risk of 2%, HF risk of 1% and diabetes risk of 1.1%. This analysis suggests that antihypertensive treatment is cost effective for this population and that the most cost-effective initial drug in this group is calcium-channel blockers (C). The ICER of C compared with thiazide-type diuretics (D) is £1,520 to £1,960 per QALY gained, which is below the level usually considered to be affordable in the NHS (about £20,000 to £30,000 per QALY).

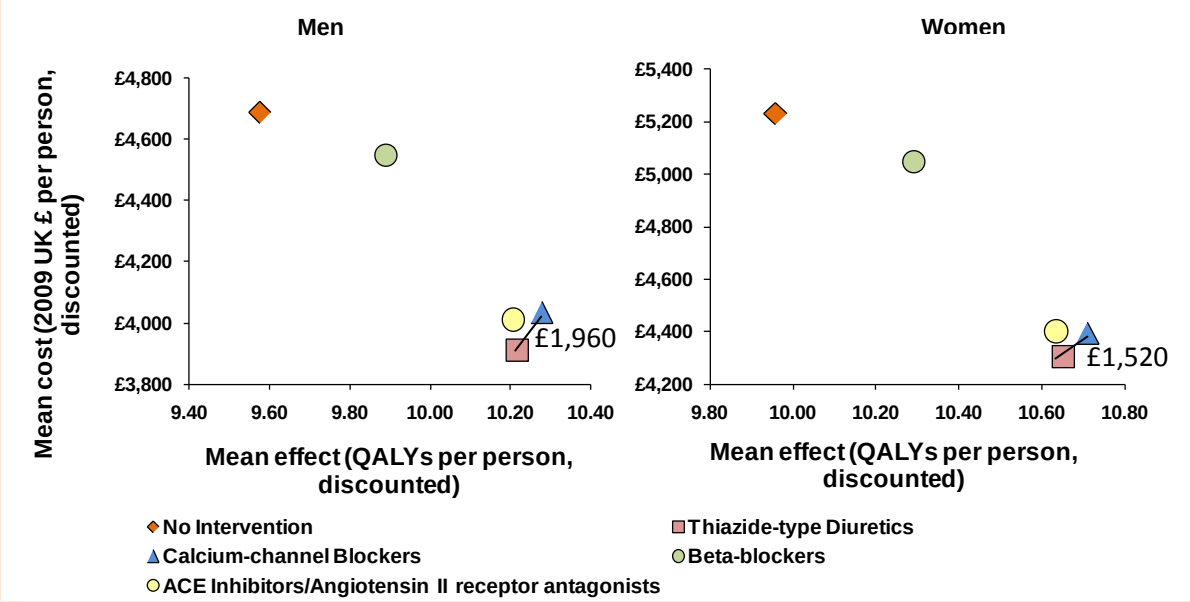
Table 12.77: Base case results (65-year-old, 2% risk, 1.1% diabetes risk, 1% HF risk)

Men			
	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£3,910	10.22	LC
A	£4,010	10.21	-
C	£4,030	10.28	£1,960
B	£4,550	9.89	-
NI	£4,690	9.57	-
Women			
	Cost (£)	Effect (QALYs)	ICER (£/QALY)
D	£4,310	10.65	LC
C	£4,390	10.71	£1,520
A	£4,400	10.63	-
B	£5,050	10.29	-
NI	£5,230	9.96	-

Update 2011

Beta-blockers (B) are ruled out by simple dominance, since D, A and C are estimated to be cheaper and more effective. This can be seen in Figure 1, since B lies to the northwest of D, A and C. The ACEi/ARB option (A) is also ruled out by extended dominance, since treating some patients with D and the remainder with C would be cheaper and more effective than A; in Figure 18, A lies to the northwest of a straight line joining points D and C. However, it should be noted that the absolute differences between A, C and D are small.

Figure 18: Base case results (65-year-old, 2% cardiovascular risk, 1.1% diabetes risk, 1% HF risk)



QALYs = quality-adjusted life years

Update 2011

The results of this analysis are set out in more detail, together with the sensitivity analyses, in 'Appendix I: Cost-effectiveness analysis – pharmacological treatment (updated 2011)'.

12.4.3 Conclusions

This analysis found that treating hypertension is highly cost-effective. Treatment resulted in improved health outcomes (higher QALYs) with all of the drug classes in the model and actually resulted in overall cost savings compared to no treatment as the reduction in cardiovascular events led to savings that offset the relatively low cost of antihypertensive medication; although it should be noted that this is based on low cost generic drugs. In most people CCBs were found to be the most cost-effective treatment option for initial treatment of essential hypertension.

In terms of how the analysis has changed in 2011 since 2006, the most significant change in the model inputs in the 2011 update was the reduction in drugs costs; in particular the cost of CCBs, ACEs and ARBs. CCBs remained the most cost effective option, meaning no change from 2006 in the interpretation of the base-case result in terms of overall cost effectiveness. The ICER for CCBs did however reduce considerably (from £12,250 to £1,960) making CCBs more cost effective than they were in 2006. CCBs are also no longer the most expensive option, both B and NI being more expensive, meaning that CCBs are now cost saving compared to NI; this was not the case in the 2006 guideline. Another key difference is that the absolute difference between ACEs/ARBs, CCBs and TDs is now much smaller than it was in 2006 with BBs even less cost effective. The results of the subgroup analysis remain largely unchanged apart from that in both men and women, CCBs are cost effective a greater percentage of the time compared with TDs in higher CVD risk and older age groups; however this difference is not very large. Both old and new analyses show similar trends of cost effectiveness but the new analysis has ACE/ARB cost effective in fewer scenarios than before with the heart failure risk where this is the case moving to intermediate/high risk.

Update 2011

The considerations that were highlighted in the 2006 guideline are still relevant and are described below.

The trials on which the cost-effectiveness calculations are based did not, in general, show large differences in clinical outcomes between drug classes. Some of the outcomes have point estimates of effect that are not statistically significant. In these situations the point estimate is used as the best

estimate of effect and so effects that are not statistically significant have a bearing on the relative cost effectiveness. Where the outcomes have a large effect on quality of life or cost (for example, stroke or death) the effect on overall cost effectiveness may be relatively important. The GDG considered the effect of this uncertainty about important outcomes in reaching their conclusions. The relative cost effectiveness of the agents also depends on the propensity of patients treated with them to develop new-onset diabetes or heart failure. The GDG were aware that both of these adverse outcomes should be treated with some caution in this context. It is not clear that an elevated blood glucose developing as a consequence of drug treatment has the same long-term health impact as in other circumstances, and the same applies to heart failure diagnoses, particularly since the definition of this outcome in some studies would not satisfy currently accepted criteria.

The applicability of the model to people under the age of 55 is uncertain, since it is based on trial data from mostly older people. However, sensitivity analysis showed that the drugs that affect the renin-angiotensin system are likely to be the most cost-effective option in this group if they are even slightly more effective in the young than is suggested from the overall trial data.

These results are sensitive to the cost of CCBs. The more expensive brands are not likely to be cost effective for use in the NHS. For example, the model estimates that for 65-year-olds at 2% annual CVD risk, 1.1% diabetes risk and 1% heart failure risk CCBs are only cost effective if they cost less than £94 per patient per year.

Finally, it should be emphasised that there is still considerable uncertainty about the size of some treatment effects, which translates into uncertainty about the relative cost-effectiveness of the drugs. The evidence base is also difficult to interpret because of the complex nature of some of the treatment protocols and also because of differences in some of the trial populations.

12.5 Step two therapy

12.5.1.1 Clinical evidence

The literature was reviewed from December 2005 onwards for systematic reviews and RCTs comparing A+C versus A+D for second-line treatment in adults with primary hypertension. RCTs were included if there was: ≥12 months follow-up, N≥200 and the population did not consist of people who were exclusively diabetic or had CKD.

One RCT[296] was found that fulfilled the inclusion criteria and addressed the question, and was included in the review.

- The RCT[296] (the ACCOMPLISH trial) compared treatment with the ACEi benazepril (20 then 40mg/day) + the CCB amlodipine (5 mg/day) vs. the ACEi benazepril (20 then 40mg/day) + the diuretic hydrochlorothiazide (12.5 mg/day) in N=11,506 people with hypertension, and had a follow-up time of 24 months. Treatment followed a dose-adjustment protocol for non-responders in each arm.

NOTE: no quality of life data was found, or data assessing the effects of ACEi vs ARB in people aged 80+ or black people of African and Caribbean descent.

The evidence profile below (Table 78) summarises the quality of the evidence and outcome data from the one RCT[296] included in this review, comparing ACEi + CCB vs. ACE + D.

Update 2011

Table 78: ACEi + CCB versus ACEi +Diuretic for second line therapy – quality assessment

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	A+C	A+D	Relative (95% CI)	Absolute	
Mortality (all cause): ACCOMPLISH trial (follow-up mean 36 months)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	236/5744 (4.1%)	262/5762 (4.5%)	HR 0.90 (0.76 to 1.07)	4 fewer per 1000 (from 11 fewer to 3 more)	MODERATE
MI (fatal and non-fatal): ACCOMPLISH trial (follow-up mean 36 months)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	none	125/5744 (2.2%)	159/5762 (2.8%)	HR 0.78 (0.62 to 0.99)[4]	6 fewer per 1000 (from 0 fewer to 10 fewer)	MODERATE
Stroke (fatal and non-fatal): ACCOMPLISH trial (follow-up mean 36 months)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	112/5744 (1.9%)	133/5762 (2.3%)	HR 0.84 (0.65 to 1.08)	4 fewer per 1000 (from 8 fewer to 2 more)	MODERATE
Hospitalisation for unstable angina: ACCOMPLISH trial (follow-up mean 36 months)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44/5744 (0.8%)	59/5762 (1%)	HR 0.75 (0.5 to 1.1)	3 fewer per 1000 (from 5 fewer to 1 more)	MODERATE
Coronary revascularisation: ACCOMPLISH trial (follow-up mean 36 months)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	334/5744 (5.8%)	386/5762 (6.7%)	HR 0.86 (0.74 to 1)	9 fewer per 1000 (from 17 fewer to 0 more)	MODERATE
Study drug withdrawal: ACCOMPLISH trial (follow-up mean 36 months)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	1684/5744 (29.3%)	1756/5762 (30.5%)	HR 0.93 (0.88 to 0.98)[5]	18 fewer per 1000 (from 5 fewer to 31 fewer)	MODERATE

[1] Random, double blind, allocation concealment, powered, ITT analysis. However no washout / run-in and <20% drop-outs (but Tx withdrawal was >30% for median 36 months follow-up).
[2] 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
[3] 95% confidence interval includes both 1) appreciable benefit or harm and 2) non-appreciable benefit or harm
[4] p=0.04; favours A+C
[5] p=0.01; favours A+C

12.5.2.1 Economic evidence

One study was identified in the update search that included A+C and A+D as comparators but was excluded due to being judged to have serious methodological limitations[522].

12.5.2.2 Evidence statements - clinical

ACEi + CCB was significantly better than ACEi + D for:

- MI (fatal and non-fatal) [moderate quality evidence]
- less study drug withdrawals [moderate quality evidence]

There was NS difference between A+C and A+D for:

- mortality (all cause) [moderate quality evidence]
- stroke (fatal and non-fatal) [moderate quality evidence]
- hospitalisation for unstable angina [moderate quality evidence]
- coronary revascularisation [moderate quality evidence]
- new onset diabetes [moderate quality evidence]

12.5.2.3 Evidence statements – health economic

- No relevant cost-effectiveness evidence was identified.

Update 2011

12.6 Resistant hypertension

The GDG agreed to define the term 'resistant hypertension' in the guideline as someone whose blood pressure is not controlled to <140/90mmHg, despite optimal or best tolerated doses of third line treatment.

12.6.1.1 Clinical evidence

The literature was searched for all years (as this was not addressed in the previous guidelines)(Newcastle Guideline Development and Research Unit;National Collaborating Centre for Chronic Conditions) and all study types were included. Studies were included that compared 4th-line antihypertensive drugs with placebo,head to head comparisons or gave before-and after data, in people with resistant hypertension (defined as: people whose blood pressure remains uncontrolled, despite taking optimal doses of 3 anti-hypertensive drugs). Populations which were exclusively diabetic or had chronic kidney disease were excluded.

Six cohort studies [126,163,226,347,383,511] were found which fulfilled the inclusion criteria and addressed the question, and were included in the review.

- The first cohort study [163] identifed and categorised people with resistant hypertension receiving treatment with spironolactone ('true resistant hypertension), from people with controlled ('white coat reisistant' hypertension). For those with 'true resistant hypertension' the study then compared data from before to after the introduction of spironolactone. The study had a total of N=236 participants and had a median follow-up time of 15 months. Treatment began with an initial dose of 25mg, and was titrated to 50-100mg/d as required.
- The second cohort study [347] assessed N=133 participants with resistant hypertension and measured their blood pressure before and after spironolactone 25-50mg/d, with a 3-month and 6-month follow up period.
- The third cohort study [383] compared two groups of people with hypertension (total of N=69 participants). Group A were untreated hypertensives and Group B were drawn from a hypertension clinic with treatment resistant hypertension. Group A was randomised to receive either spironolactone 50 mg/d or bendroflumethiazide 2.5 mg/d in a crossover design. All people in group B received 50mg/d of spironolactone. Group A received four weeks treatment, four weeks washout, four weeks treatment, and group B had a mean follow up time of 3.7 months.
- The fourth cohort study [226] assessed N=12 people with resistant hypertension before and after receiving spironolactone (25mg/d and force-titrated to 50mg/d at 4 weeks), and had a follow up time of eight weeks treatment. Other anti-hypertensive treatment was discontinued, if necessary for a low blood pressure.
- The fifth cohort study [126] reviewed participants with uncontrolled hypertension in the ASCOT-BPLA open-label RCT. All participants N=1411 received an anti-hypertensive regimen based on either Atenolol or Amlodopine. The comparison was between those who were prescribed additional spironolactone vs. those who were not prescribed spironolactone. The median follow up time was 5.5 years.
- The sixth cohort study [511] compared Spironolactone with Doxazosin in N = 198 patients with resistant hypertension. There was no mean follow-up time reported. Participants were followed up until treatment was changed with the addition of a new drug/change in dosage to control blood pressure or when blood pressure was controlled within a pre-specified target.

No evidence profile was generated as GRADE was not performed in this guideline on observational studies. However GRADE automatically assigns a quality rating of 'low' to observational studies.

Update 2011

The table below (Table 79) summarises the quality of the evidence and the outcome data from the six cohort studies [126,163,226,347,383,511] included in this review of the effectiveness of 4th line antihypertensive treatment in resistant hypertension in adults.

Table 79: Summary table of studies examining the role of fourth line antihypertensives in resistant hypertension

Study	Intervention	Comparison	Follow-up	Results	Evidence Quality
Rodilla et al. 2009{Rodilla, 2009 16014 /id}	Spironolactone	Doxazosin	Until change of treatment/ target blood pressure maintained	Spironolactone best (decreased home or ambulatory SBP and DBP)	Low
Mahmud et al. 2005{Mahmud, 2005 15968 /id}	Previously untreated-spironolactone/bendroflumethiazide	4th line Spironolactone	3-4 months	Spironolactone effective in reducing BP when used as a 4th line drug	Low
Chapman et al. 2007{Chapman, 2007 373 /id}	ASCOT trial patients an a-HT regimen based on either Atenolol or Amlodopine Plus addition of Spironolactone	ASCOT trial patients on a-HT regimen based on either Atenolol or Amlodopine	Median 5.5 years	Addition of spironolactone effective in reducing BP	Low
De Souza et al. 2010{de Souza F., 2010 15965 /id}	Spironolactone	Before vs. after Spironolactone	12 months (Median 15 months, IQR 13-20 months)	Spironolactone effective in reducing 'office' and ambulatory blood pressure.	Low
Lane et al. 2007{Lane, 2007 802 /id}	Spironolactone	Before vs. after Spironolactone	6 months	Spironolactone effective in reducing SBP and DBP	Low
Gaddam et al. 2010{Gaddam, 2010 15967 /id}	Spironolactone	Before vs. after Spironolactone	8 weeks	Addition of spironolactone effective in reducing SBP and DBP	Low

Update 2011

12.6.1.2 Economic evidence

No relevant economic studies were identified that examined drugs in patients with resistant hypertension.

In the absence of a published cost effectiveness analysis, current UK drugs costs for agents that might be considered for use in resistant hypertension were presented to the GDG to help inform decision making.

12.6.1.3 Evidence statements – clinical

Six studies found that blood pressure was reduced in people with resistant hypertension who were treated with 4th-line spironolactone.

One study [511] found that 4th line therapy with spironolactone was better than doxazosin for reduction in SBP and DBP [low quality]

Three studies[163,347 226] found that SBP and DBP was reduced after 4th line spironolactone treatment (vs. before treatment). [low quality].

One study [383] found BP reduced in those treated with spironolactone compared with those previously untreated and reported drop out rates of 10% due to adverse effects [low quality].

One study [126] found the addition of spironolactone (as 4th line therapy) was effective in reducing BP, and an adverse event rate of 13% was reported [low quality].Evidence statements – health economic

Update 2011

12.6.1.4 Evidence statements – economic

- No relevant cost-effectiveness evidence was identified.
- In terms of drug acquisition costs alone, in December 2010 based on BNF 60: spironolactone (25mg) cost £23.73 per year.

12.7 Special groups for consideration

12.7.1 People aged over 80 years

See section 9 on page 115.

12.7.2 Younger people

Outcomes in younger patients	
The literature search found no evidence for the clinical outcomes summarised above, therefore blood pressure response to drug therapy was used as a surrogate. Three studies[164,177,394] and an age-stratified analysis from a fourth study[55] compared blood pressure response across various drug classes and identified ACE inhibitors and beta-blockers as more effective at lowering blood pressure in younger people, when compared to calcium channel-blockers or thiazide-type diuretics. In older people, initial treatment with calcium channel-blockers or thiazide-type diuretics has been shown to be more effective at blood pressure lowering than ACE inhibitors, angiotensin-II receptor antagonists or beta-blockers[157,312,589-591].	

12.7.3 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. [40,110,127,145,542] 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. [504] British Asians also exhibit hypertension associated mortality rates 1.5 times higher than the national average. [504]

The Whitehall II Study investigated a cohort of London-based civil servants aged 35–56 years, between 1985 and 1988.[638] 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.[116] 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.[74,286] 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. [400] 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.[399]

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.[145,230,236,252,409,542] 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[496], and with the migration of Punjabi participants from India to England.[73]

12.7.3.1 Clinical evidence

The literature was reviewed from December 2005 onwards (the cut-off date of the previous guideline, CG34,[425] where this was covered previously) for systematic reviews, RCTs, sub-group analyses of RCTs and cohort studies looking at first-line anti-hypertensive treatment of black people of African or Caribbean descent who have primary hypertension. Studies were included if there was: N≥1000 and the population did not consist of people who were exclusively diabetic or had CKD.

Two subgroup analyses[354,492] of an RCT (ALLHAT) were found which fulfilled the inclusion criteria and addressed the question, and were included in the review. The ALLHAT study was originally included in the previous NICE guidelines.[425,441] ALLHAT compared ACEi vs TD vs. CCB vs. alpha-blocker and 1/3 of the population were black people (NOTE: the term 'black' was that used in the ALLHAT trial). However, the studies included in the previous guidelines did not give data for the ACEi vs. CCB arms in black people and did not give the incidences of angioedema, which these newer subgroup analyses have looked at. Both the subgroup analyses were planned a-priori as part of the design of the ALLHAT trial.

- The first subgroup analysis of the ALLHAT RCT[492] assessed the incidence of angioedema in people treated within each arm of trial (ACEi vs. TD vs. CCB vs. alpha-blocker) and the incidence of the outcome in different subgroups of people (including different ethnic groups: black people vs. non-black people). The study follow-up time was mean 4.9 years and the number of people who developed angioedema was N=53 out of the total study group of N=42,418. Because the data we are interested in is the incidence of agioedema in black people vs. non-black people (ie. has come from the subgroup analysis), this study data has been classed as 'observational' (see section below entitled 'evidence profile').
- The second sub-group analysis of the ALLHAT RCT[354] assessed the incidence of clinical endpoints that occurred in subgroups of patients, including black people vs. non-black people who were randomised to the ACEi and CCB arms of the ALLHAT trial. The study follow-up time was mean 4.9 years and the number of people who developed angioedema was N=53 out of the total study group of N=42,418. This study has been classified as 'observational' because it is a subgroup analysis of an RCT.

Update 2011

The evidence profiles below (Figure 1 and Figure 2) summarises the quality of the evidence and outcome data from the two RCT (ALLHAT) subgroup analyses[354,492] included in this review, comparing outcomes in black people and non-black people. Where data was unable to be put into GRADE, it has been written up narratively in the evidence statements.

Update 2011

Table 80: Evidence profile comparing ACEi versus other antihypertensive classes (TD, CCB or alpha) in black people and non-black people (data from Piller et al., 2006)[492]

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi	other a-HT classes (TD, CCB or alpha)	Relative (95% CI)	Absolute	Quality
Angioedema (black people) out of total randomised (follow-up mean 4.9 years)											
1	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/3210 (0.7%)	6/10196 (0.1%)	RR 12.18 (4.96 to 29.88)	7 more per 1000 (from 2 more to 17 more)	HIGH
Angioedema (non-black people) out of total randomised (follow-up mean 4.9 years)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/3210 (0.7%)	6/10196 (0.1%)	RR 0 (2.47 to 0)[3]	1 fewer per 1000 (from 1 more to 1 fewer)	MODERATE
Angioedema (black people) out of those who developed angioedema (follow-up mean 4.9 years)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/37 (62.2%)	6/16 (37.5%)	inappropriate to calculate (loss of randomisation)	375 fewer per 1000 (from 375 fewer to 375 fewer)	MODERATE
Angioedema (non-black people) out of those who developed angioedema (follow-up mean 4.9 years)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/37 (37.8%)	10/16 (62.5%)	inappropriate to calculate (loss of randomisation)	625 fewer per 1000 (from 625 fewer to 625 fewer)	MODERATE

[1] Subgroup analysis of RCT: but pre-specified and the trial deliberately recruited a specific number of black people to be able to do this analysis
[2] 95% confidence interval excludes no effect, but the CI includes appreciable benefit and non-appreciable benefit or appreciable harm and non-appreciable harm
[3] SS - favours other a-HT classes (p<0.0001)
[4] Loss of randomisation in groups (incidence of angioedema in black people and non-black people, out of those who developed angioedema in the trial, rather than all participants randomised in the trial)

Table 81: Evidence profile comparing ACEi vs CCB in black people and non-black people (data from Leenan et al., 2006)[354]

NOTE: there was not enough data given in the study to calculate the HRs for these outcomes, so the RRs reported in the paper have been used in the GRADE profile

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi	CCB	Relative (95% CI)	Absolute	Quality
CHD (black people) (follow-up mean 4.9 years)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	data not given in study		1.09 (0.92, 1.03)	not enough data given in study to calculate	HIGH
CHD (non-black people) (follow-up mean 4.9 years)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	data not given in study		0.97 (0.86, 1.10)	not enough data given in study to calculate	MODERATE
Stroke (black people) (follow-up mean 4.9 years)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	none	data not given in study		1.51 (1.22, 1.86) [5]	not enough data given in study to calculate	MODERATE
Stroke (non-black people) (follow-up mean 4.9 years)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	data not given in study		1.07 (0.89, 1.28)	not enough data given in study to calculate	LOW
Combined CVD (black people) (follow-up mean 4.9 years)											
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	none	data not given in study		1.13 (1.02, 1.24)[5]	not enough data given in study to calculate	MODERATE
Combined CVD (non-black people) (follow-up mean 4.9 years)											

1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	none	data not given in study	1.03 (0.96, 1.10)	not enough data given in study to calculate	MODERATE
Heart Failure (black people) (follow-up mean 4.9 years)										
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[2]	none	data not given in study	0.89 (0.75, 1.06)	not enough data given in study to calculate	MODERATE
Heart Failure (non-black people) (follow-up mean 4.9 years)										
1	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	none	data not given in study	0.85 (0.75, 0.97)[6]	not enough data given in study to calculate	MODERATE

[1] Subgroup analysis of RCT: but pre-spcified and the trial deliberately recruited a specific number of black people to be able to do this anlysis
[2] 95% confidence interval includes both 1) no effect and 2) appreciable benefit or appreciable harm
[3] 95% confidence interval excludes no effect, but the CI includes appreciable benefit and non-appreciable benefit or appreciable harm and non-appreciable harm
[4] 95% confidence interval crosses both 1) no effect and 2) appreciable benefit or harm and non-appreciable benefit or harm
[5] SS - favours CCB (p-value not given)
[6] SS - favours ACEi (p-value not given)

12.7.3.2 Economic evidence

No relevant economic studies were identified.

12.7.3.3 Evidence statements

One RCT (subgroup analysis)[492] found that:

- Over half (55%) of people who developed angioedema were black people
- The incidence of angioedema (out of all the people who developed angioedema in the trial) was:
  - in black people: higher in the ACEi group versus other a-HT classes (TD, CCB or alpha) combined (62% vs. 38%)
  - in non-black people: lower in the ACEi group versus other a-HT classes (TD, CCB or alpha) combined (38% vs. 63%)

[moderate quality evidence]

The risk of angioedema in both black people and non-black people was:

- significantly higher in the ACEi group vs. other a-HT classes (TD, CCB or alpha) combined (as a proportion of the total randomised, see the forest plot in section H.1.4)

[high and moderate quality evidence]

One RCT (subgroup analysis)[354] found that:

- In black people:
  - CCB was significantly better than ACEi for risk of:
  - Combined CVD [moderate quality evidence]
  - Stroke [moderate quality evidence]
  - There was NS difference between ACEi and CCB for risk of:
  - CHD [high quality evidence]
  - HF [moderate quality evidence]
  - In non-black people:
  - ACEi was significantly better than CCB for risk of:
  - HF [moderate quality evidence]

There was NS difference between ACEi and CCB for risk of:

- CHD [moderate quality evidence]
- Combined CVD [moderate quality evidence]
- Stroke [low quality evidence]

- No relevant cost-effectiveness evidence was identified.

Update 2011

12.7.4 Chronic kidney disease

For guidance pertaining to people with hypertension and chronic kidney disease refer to NICE Clinical Guideline 73.

12.7.5 Type 1 and Type 2 diabetes

For guidance pertaining to people with hypertension and Type 1 diabetes refer to NICE Clinical Guideline 15.

For guidance pertaining to people with hypertension and Type 2 diabetes refer to NICE Clinical Guideline 66.

12.7.6 Women who are pregnant or breast-feeding

For guidance on women who are pregnant or breast-feeding, refer to NICE Clinical Guideline 107 http://guidance.nice.org.uk/CG107.

12.8 Stopping treatment

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. Some patients may be at risk of 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.

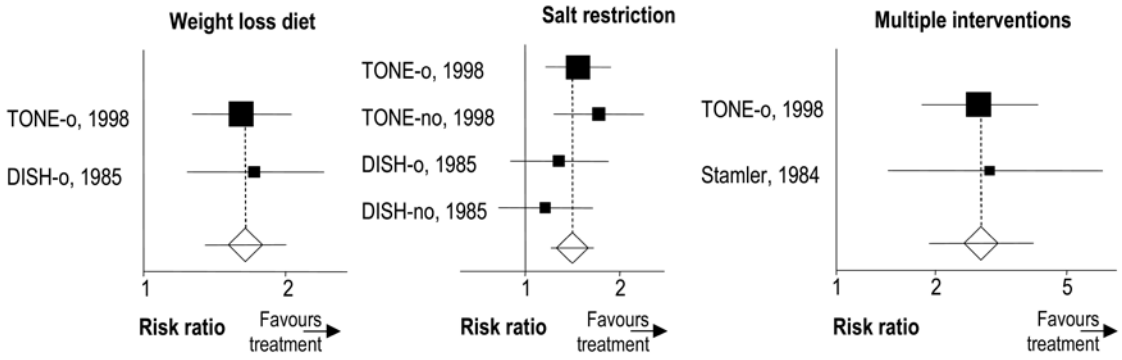
In studies which have reported on withdrawal of antihypertensive medication[240,349,411,561,631], [421], [9,38,201,359,413,433,435,582,597], between 10%[433] and 60%[349] of patients remained normotensive for at least a year, although studies reporting better success rates were often of highly selected patient populations. Further, the definition of normotension varied between studies, from blood pressure less than 140/85mmHg[38] to diastolic blood pressure less than 105mmHg[411] and the characteristics of the patients varied, e.g. mean age ranged from 51[9,411] to 67 years[631], baseline blood pressure ranged from 126/80 mmHg[240,349] to 152/101mmHg[359], number of drugs ranged from one[9,201,561,631] to three or more[349].

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[434], and from a subsequent study of 503 patients who were also followed up for a year[435], 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[201,435].

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 [349,561,631]. The TONE[631] and DISH[349] 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 19). 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[561]. 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[349,561,631], 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.

Figure 19: 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

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 blood pressure of 129/72 mmHg while on one antihypertensive medication[336]. 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[361].

If patients become hypertensive after stopping drugs, this is most likely to happen in the first six months, although it can happen later[434]. To avoid this, patients should be carefully followed up and drugs should be withdrawn gradually following manufacturers' guidance.

12.9 Link from evidence to recommendations- Pharmacological treatment of hypertension

The pharmacological update of this guideline in 2006 recommended a stepped care approach to treatment. The recommendation for initial treatment (step 1) was stratified by age and ethnicity reflecting data from clinical trials showing differential effects of the different classes of blood pressure lowering drugs on blood pressure lowering and clinical outcomes in younger (<55years) versus older people and in black people of African and Caribbean descent. Antihypertensive therapies were designated "A" drugs (ACEi or ARBs), "C" drugs (calcium channel blockers) and "D" drugs (thiazide-type diuretics). The recommendation for step 1 treatment for younger people was an "A" drug. At that timethe GDG felt that the benefit from ACEi and ARBs were closely correlated (although lacked head to head evidence) and that they should be treated as equal in terms of efficacy; however, due to cost differences, felt ACE inhibitors should be initiated first and an ARB considered an alternative for when an ACEi was poorly tolerated, usually due to an ACE-inhibitor-induced cough.

ACE-inhibitors versus ARBs for step 1 treatment:

For this update, the GDG considered evidence from 3 RCTS published since December 2005 comparing ACEi versus ARB for step 1 treatment for adults with primary hypertension. The first RCT[653] (the ONTARGET trial) compared treatment with the ACEi ramipril (10 mg/day) versus the ARB telmisartan (80 mg/day) and versus a combination of the two (ACEi+ARB) in 25,620 people considered to be at high cardiovascular disease risk. Many (approximately 70%), but not all of these patients had treated hypertension. The study had a median follow-up time of 56 months. A second RCT[587] compared treatment with the ACEi enalapril (20 mg/day) versus the ARB losartan (50 mg/day) in N=560 people with hypertension, for a follow-up time of 24 months. The third study[552] (CORD IB trial) compared treatment with the ACEi ramipril (5 mg/day) versus the ARB losartan (50 mg/day) in N=3860 people with hypertension, and had a follow-up time of 12 months. The evidence showed no significant differences between ACEi and ARBs on major clinical outcomes including death, cardiovascular events, stroke and diabetes. There was no consistent trend favouring one drug class over the other. Study drug withdrawal was significantly lower with ARB compared with ACEi. The GDG considered that this most likely reflected better tolerability of the ARB as ACEis are known to cause cough in some patients whereas ARBs do not. There was heterogeneity in the analysis for this latter finding but the lower withdrawal from ARB therapy was a robust finding in the largest trial (ONTARGET). Moreover, the GDG noted that there was an eight week run-in to ONTARGET when patients were prescribed the ACEi to see if they could tolerate the drug, thus, pre-selecting a group with short-term tolerability of the drugs. The results are therefore likely to underestimate the true withdrawal rate from ACEi. The GDG noted that side-effects of a drug are an important consideration in making treatment decisions for the management of a symptomless condition.

The ONTARGET study also compared the combination of ACEi + ARB versus ACEi alone and found that there was no advantage of the ACEi + ARB combination on clinical outcomes and a more adverse effects associated with the combination of ACEi + ARB. The GDG concluded that there was no evidence to support the use of ACEi + ARB for the treatment of hypertension and that this combination should not be used for the treatment of primary hypertension.

The largest study in the analysis comparing ACEi versus ARB was ONTARGET and the GDG discussed the fact that this study was not a trial designed to specifically examine the treatment of hypertension with initial therapy, but rather looked at the use of an ACEi or ARB for prevention of cardiovascular events. In this regard, the participants in ONTARGET were selected to be at high cardiovascular risk, although 70% of patients in ONTARGET had a history of hypertension and were receiving antihypertensive therapy/s or had discontinued their treatment prior to randomisation to the study drugs. The GDG debated whether ACEi and ARBs could be considered equivalent, based on data

Update 2011

primarily from one large study that was not specifically a hypertensive population. It was noted that ONTARGET was designed to test non-inferiority of the ARB versus the most commonly used ACEi (Ramipril) with regard to clinical outcomes and that further large trials addressing the same question are unlikely to happen - this may, therefore, be the best evidence ever available for a hypertensive population. It was reassuring that the other studies in the analysis, albeit much smaller but studying a more typical hypertensive population, were consistent with the findings of ONTARGET.

No relevant cost effectiveness analyses comparing ACEi versus ARBs were identified. However, the difference between the lowest cost ARB and the lowest cost ACEi has reduced considerably due to the recent availability of generic losartan; generic losartan (100mg) is now only about £5 more per year than generic ramipril (10mg). Patent expiry is imminent for many other ARBs too and the GDG considered it likely that the cost of ACEi and ARBs are likely to become similar over the lifetime of this guideline update.

The ethnicity of participants was not reported for all of the trials but the GDG did not consider this prevented extrapolation of the findings to a UK population. Finally, the GDG could not identify any quality of life data comparing ACEi versus ARBs.

The GDG concluded that the drug classes ACE iand ARBs should be considered equivalent with regard to their effect on clinical outcomes and recommended that people aged <55 years should be offered step one treatment with an ACEi or a low cost ARB. For patients intolerant of ACEi, an ARB should be offered. The GDG also recommended that an ACEi and an ARB should not be combined for the treatment of hypertension. The GDG noted that in women aged <55years and of child bearing potential, the use of ACEi or ARB has been reported to increase the risk of foetal malformation if taken during pregnancy. Women taking these medications should be advised that if they become pregnant, they should discontinue treatment and inform their doctor. In women planning conception, ACEi and ARBs should be avoided during this time and alternative treatments considered if required – see clinical Clinical Guideline 97 on Hypertension in Pregnancy.

Update 2011

Choice of thiazide-type diuretic therapy for hypertension:

The 2006 pharmacological update recommended thiazide-type diuretics as a step 1 treatment option for people aged ≥55 years or black people of African and Caribbean descent of any age – the other step 1 option for this group of people being a CCB. There are many different drugs labelled as thiazide-type diuretics. The predominant thiazide-type diuretic used in the UK for the treatment of hypertension is low dose (2.5mg o.d.) bendroflumethiazide (BFZ). This is somewhat unusual because this thiazide-type diuretic is rarely used anywhere else in the world as the preferred diuretic for the treatment of hypertension. This may be unimportant if the clinical outcomes data with low dose BFZ is equivalent to that with the other, more commonly used thiazide-type diuretics elsewhere in the world.

This issue of comparability of different thiazide-type diuretics has been brought into sharper focus by recognition of the fact that, although often grouped together as thiazide-type diuretics, from a pharmacological perspective, there are two broad groups; i) classical thiazide diuretics (e.g. BFZ and hydrochlorthiazide; HCTZ) i.e. the name ends in thiazide, and ii) thiazide-like diuretics (e.g. chlorthalidone; CTD and indapamide; IND). The thiazide-like diuretics retain the main action of thiazide diuretics, i.e. inhibition of the sodium chloride co-transporter in the distal nephrons of the kidney. However, the thiazide and thiazide-like drugs have differential effects on other enzyme effects in the kidney, e.g. carbonic anhydrase inhibition, which can differ by up to 10,000-fold. Differential effects on platelet aggregation and regulation of angiogenesis have also been reported. The relevance of these actions beyond the characteristic thiazide action of inhibition of the sodium chloride cotransporter with regard to blood pressure control and the prevention of clinical outcomes is unknown. Nevertheless, the GDG considered it important to examine the evidence base supporting the use of classical thiazides (BFZ or HCTZ) when compared to the thiazide-like diuretics such as CTD and IND.

Another important element of the data review for thiazide-type diuretic therapy was to examine the doses of diuretics used in the various clinical outcome trials. The trials evaluating clinical outcomes with thiazide-type diuretics have usually been evaluated by grouping all of these various drugs used at various doses altogether. The early diuretic trials used much higher doses than commonly used today. The reduction in dose to what is now known as "low dose" diuretic therapy resulted from concern about the development of electrolyte disturbances (usually hypokalaemia) and metabolic disturbances (hyperglycaemia) with higher dose diuretic therapy. Consequently, the GDG reviewed the important question as to what is the most clinically and cost effective thiazide-type diuretic for the treatment of adults with primary hypertension?

The analysis examined data for the four most commonly used thiazide-type diuretics; i) classical thiazide diuretics (e.g. Bendroflumethiazide (BDZ) and hydrochlorthiazide(HCTZ), and ii) thiazide-like diuretics (e.g. chlorthalidone (CTD) and indapamide (IND). The analysis was complex and the GDG noted that there were no direct comparisons between the different diuretics with regard to clinical outcomes. Where head-to-head comparisons had been undertaken, they were usually based on blood pressure changes as the main outcome. These studies were often of short duration and too small to provide robust data. The GDG considered all of them to be underpowered to detect a significant blood pressure difference between diuretic treatments. There was also considerable variation in the doses of diuretics used in the various studies – some early studies using four times the doses used routinely in today's clinical practice making it impossible to pool data for analysis. Consequently, the GDG found it difficult to reach firm conclusions regarding the comparative efficacy of different thiazide-type diuretics with regard to blood pressure lowering.

The GDG then reviewed the clinical outcome studies with thiazide-type diuretics and found no direct comparator studies between different diuretics. Furthermore, interpretation of data from head-to-head trials comparing diuretics with placebo or other antihypertensive drugs was complicated by the markedly different diuretic doses used across studies. The GDG noted that the data demonstrating benefits of BFZ on clinical outcomes came from older studies (MRC) in which the dose of BFZ (10mg o.d.) was four times the usual dose of BFZ i.e. 2.5mg o.d., used in clinical practice today. The GDG also noted that there was no study evaluating and confirming the benefit of low dose BFZ on clinical outcomes – the only data coming from older studies with much higher doses of BFZ, i.e. 10mg od. This concerned the GDG, mindful of the fact that low dose BFZ (2.5mg o.d.) has been the preferred thiazide-type diuretic for the treatment of hypertension in the UK. The GDG also noted that there was limited evidence confirming benefit of initial therapy on clinical outcomes with low doses of hydrochlorthiazide (12.5-25mg o.d.), the other commonly used thiazide-type diuretic world-wide.

The GDG next discussed the evidence for the thiazide-like diuretics, i.e. IND or CTD and noted that the there was evidence showing benefits of low dose IND or low dose CTD on a range of clinical outcomes. The GDG noted that the evidence for IND and CTD was derived from more contemporary studies that had more consistently used lower doses across studies, typically; IND 1.5mg SR or 2.5mg o.d., or CTD 12.5mg or 25mg o.d. Some of the IND studies used an SR formulation, others did not. The GDG concluded that the consistency of the data suggested that the SR formulation was unlikely to have influenced the clinical outcomes in studies with IND.

No relevant cost-effectiveness studies were found that compared different types of diuretic. Current UK drugs costs were considered by GDG and it was noted that the aforementioned thiazide-type diuretics were all available as generics.

Considering all of the data cited above, the GDG were concerned that there was no evidence confirming a beneficial effect of low dose bendroflumethiazide, i.e. 2.5mg o.d., on clinical outcomes in people with hypertension. This observation is important because bendroflumethiazide 2.5mg od. is the most commonly used thiazide-type diuretic for the treatment of hypertension in the U.K. This does not mean that bendroflumethiazide 2.5mg o.d. is ineffective but it does make it difficult to assess whether it is as effective at preventing clinical outcomes as other thiazide-like diuretics, e.g.

chlortalidone and indapamide for which evidence confirming benefits on clinical outcomes does exist. Having undertaken this analysis it was difficult for the GDG to recommend treatment with low dose thiazide-type diuretics, e.g. bendroflumethiazide or hydrochlorthoazide for which there was no evidence of a benefit on clinical outcomes.

Consequently, the GDG recommended that when thiazide-type diuretics are used for the treatment for primary hypertension, thiazide-like diuretics, e.g. chlortalidone (12.5mg -25mg od) or indapamide (1.5mg SR or 2.5mg o.d.) should be preferred to conventional thiazide diuretics, e.g. bendroflumethiazide or hydrochlorthiazide. The GDG did not consider it necessary to recommend that those people already treated with low dose BFZ and in whom blood pressure is controlled, should be switched to CTD or IND. However, when new diuretic therapy was to be initiated, then CTD or IND should be preferred.

The cost-effectiveness of pharmacological treatment of hypertension:

As part of the 2006 pharmacological update of this guideline (CG34), the cost effectiveness of different classes of antihypertensive medications as initial therapy for hypertension was evaluated. The analysis assessed the costs and effects of the major antihypertensive drug classes; (A), i.e. ACE-I / ARB, (B) beta blockers, (C) CCBs and (D) thiazide-type diuretics. No intervention (NI) was also included as a comparator. Details of this analysis are shown in appendix x.

Since 2006 the cost of antihypertensive drugs has decreased; in particular the cost of CCBs and ARBs. The GDG decided that it would be informative to rerun the cost-effectiveness analysis as part of the 2011 update with updated costs. The base case analysis modelled the results for 65-year-old men and women with 2% CVD risk, 1% HF risk and 1.1% diabetes risk. Sensitivity analysis undertaken in 2006 were also rerun to evaluate whether and how the results varied by age, sex, and by varying the risks of CVD, HF and diabetes. The GDG noted that the clinical trial evidence on which the model is based included relatively few younger (under 55) people, so speculative sensitivity analyses were conducted to explore how different assumptions about treatment effects might impact on the cost-effectiveness results for younger (under 45) people.

Update 2011

The top line conclusion from this analysis is that treating hypertension is highly cost-effective. Treatment resulted in improved health outcomes (higher QALYs) and remarkably, with most of the drug classes in the model, actually resulted in overall cost savings when compared to no treatment. This cost saving is due to the fact that the reduction in cardiovascular events led to savings that offset the relatively low cost of antihypertensive medication. The GDG noted that this conclusion is based on the use of low cost generic drugs.

Another important conclusion is that for most people, CCBs were found to be the most cost-effective treatment option for initial treatment of primary hypertension. Indeed, unlike the analysis in 2006, CCBs are now cost saving when compared to no intervention.

The GDG noted another key difference from the 2006 analysis is that the absolute difference in costs between ACE/ARB, CCBs and thiazide-type diuretics is now much smaller than it was in 2006. The difference is QALYs between these drugs is also fairly small. Just as in 2006, beta-blockers are ruled out by simple dominance, however now all other treatments are estimated to be both cheaper and more effective – further justifying the decision not to recommend beta-blockers as a preferred initial therapy for primary hypertension.

The GDG then reviewed the cost-effectiveness analysis in various sub-groups and noted that when compared to the 2006 analysis, CCBs are most cost effective in a greater number of scenarios. The GDG noted that the sub-group analysis of cost-effectiveness was particularly sensitive to the relative effects of drug therapy on the prevention of diabetes and heart failure. The model predicts that for people at low to intermediate risk of heart failure, CCBs are the most cost-effective option because

they are associated with a low risk of developing diabetes, especially when compared to thiazide type diuretics, and they also have a good effectiveness profile across the range of other CVD risks.

Conversely, when people are judged to be at a high risk of developing heart failure, thiazide-type diuretics were estimated to be the most cost-effective option, provided that they do not also have a high risk of diabetes. For people with a high risk of both heart failure and diabetes, ACE inhibitors or ARBs may be the most cost-effective option. The GDG noted that the applicability of this data to people under the age of 55 is uncertain, since it is based on trial data from mostly older people. Furthermore, although the model was robust to a variety of sensitivity analyses, there remains uncertainty about the size of some treatment effects, which translates into uncertainty about the relative cost-effectiveness of the drugs.

The GDG considered the implications of the cost-effectiveness analysis with regard to the preferred treatment strategy for hypertension. Most people with primary hypertension are a low-to intermediate risk of heart failure and have an increased risk of developing diabetes, this suggests that CCBs would be the most cost-effective step 1 therapy for most people aged over 55 years. The caveat to this conclusion is that the risk of heart failure increases with increasing age, especially in the elderly (i.e. ≥80 years) in whom a thiazide-like diuretic would be a more cost effective treatment. Moreover, some people might not tolerate a CCB or may have evidence of oedema that might benefit from the preferred used of a thiazide-type diuretic.

The GDG concluded that the cost-effectiveness analysis demonstrated that CCBs are the most cost-effective initial therapy for most people aged >55 years with primary hypertension, and indeed, cost saving when compared to no intervention. It was considered that the evidence supporting this conclusion was stronger than in 2006. In addition the GDG discussions around this recommendation highlighted new data demonstrating; i) that CCBs appear to be the most effective treatment option to suppress blood pressure variability, which in turn appears to be an independent predictor of cardiovascular disease risk in people with treated hypertension (see below); and ii) that new evidence suggests that for treatment at step 2, the combination of A + C will usually be preferred to A + D, thereby impacting on the preferred choice of therapy for step 1 treatment (see section below – step 2 treatment). Consequently, the GDG recommended that a CCB should be the preferred initial therapy for people with primary hypertension and aged >55 years. A thiazide-like diuretic (i.e. chlortalidone or inadapamide) are considered a suitable alternative for those who cannot tolerate a CCB or who have developed, or are at high risk of developing heart failure.

Update 2011

Blood Pressure Variability and the impact of Antihypertensive therapy:

Just after the scope for this guideline update had been finalised, a series of analyses were published showing that excessive variability in blood pressure is an independent risk factor for cardiovascular events, over and above the effect of the level of blood pressure itself. Furthermore, a systematic review of previous trials suggested that different classes of antihypertensive medications varied in their capacity to influence blood pressure variability. The GDG decided to review this data as part of this update (see Appendix F.1). The GDG noted that blood pressure variability can be measured in a number of ways but is perhaps most easily understood when expressed at the standard deviation (SD) around the mean of a number of blood pressure readings. The series of blood pressure readings may have been taken repeatedly at a single clinic visit, or an analysis of the variation between clinic visits, or across a series of measurements recorded by ABPM. Put simply, two people could have the same mean blood pressure but a different SD value for multiple readings, reflecting differences in blood pressure variability. This can be expressed as systolic or diastolic pressure variability. The studies reviewed by the GDG involved a series of retrospective analyses of clinical trial data (see appendix x). Review or these studies showed that variability in systolic blood pressure when measured visit-to-visit was a strong predictor of stroke, independent of mean systolic blood pressure. Moreover, in people with treated hypertension, a higher residual blood pressure variability is associated with a higher risk of vascular events. The GDG noted that it was unclear if blood

pressure variability was causally related to clinical outcomes, or a marker of more severe underlying vascular disease. Furthermore, blood pressure is highly variable and although less so when measured under standardised conditions, it is unclear what the boundaries of normal versus abnormal variability would be in usual clinical practice. The GDG agreed that whatever the underlying mechanisms, systolic blood pressure variability appears to be an important independent predictor of clinical outcomes.

The GDG also reviewed data from a systematic review and meta-analysis which examined the effect of different classes of blood pressure treatment on blood pressure variability in trials. This analysis revealed that blood pressure variability was most effectively reduced by CCBs, closely followed by thiazide-type diuretics. The analysis also showed that beta-blockers were the least effective and may actually increase blood pressure variability.

Having considered these findings on blood pressure variability the GDG concluded that those most at risk of having increased systolic blood pressure variability, i.e. older hypertensive people, will already be treated with the most effective drug classes to suppress systolic blood pressure variability, i.e. a CCB (or a thiazide-like diuretic if a CCB is not indicated or tolerated) as step 1 therapy, according to the recommendations in this guideline update. The GDG concluded that the updated guidance recommends the best available evidence-based treatment options to suppress blood pressure variability in people with hypertension.

Step two therapy:

Many people with treated hypertension will require more than one drug to control their blood pressure. For people whose blood pressure is not controlled by step 1 treatment, i.e. A in younger adults (≤55years) or C or D in people aged >55yrs, the 2006 pharmacological update of this guideline recommended that step 2 therapy should be a combination of A + C or A + D. the choice of which combination was solely dictated by whether the patient was commenced on treatment with C or D at step 1. This reflected the fact that at the time of the 2006 update, there was no published data to better inform the discussion about whether there was a preferred combination for most people at step 2.

Update 2011

For this 2011 update of the guideline, one RCT [296] was found which prospectively examined the effect of A + C versus A + D on clinical outcomes in the ACCOMPLISH trial. This study compared treatment with the ACE-i benazepril + the CCB amlodipine vs. the ACE-i benazepril + the thiazide diuretic hydrochlorothiazide in 11,506 people with hypertension, for a follow-up of 24 months.

The GDG discussed the evidence which showed that ACE+CCB was significantly more effective at preventing MI when compared to ACEi + diuretic. Study withdrawal was also significantly lower in patients randomised to treatment with the combination of ACEi+CCB. The other clinical outcomes were not significantly different between groups but all numerically favoured the ACEi + CCB combination. The GDG noted that the ACCOMPLISH trial was stopped earlier than planned because the primary composite outcome was significantly in favour of the ACEi + CCB. Thus, the study had inadequate power to address individual cardiovascular outcomes. There was no quality of life data identified.

The GDG concluded that the combination of ACEi+CCB had a treatment advantage over ACEi+diuretic. However, the GDG noted that this conclusion is based on a single large study. The GDG also noted that the ACEi used in this study, i.e.benazepril, is not used in the UK but concluded that there was unlikely to be an important difference between benazepril and other ACEi. Likewise, the GDG considered it likely that the results with the ACEi + CCB would be replicated with an ARB + CCB. The GDG also considered the black people of African or Caribean origin, ACEi are associated with an increased risk of developing angioedema which can be life threatening. Although the incidence of this adverse of ACEi in back people of African or Caribean origin is low, the GDG suggested that an ARB in preference to an ACEi should be considered for such patients when step 2

treatment in required. The GDG concluded that this data from the ACCOMPLISH trial, taken together with the updated cost-effectiveness analysis and the data on blood pressure variability, all favour the combination of A + C versus A +D – with the caveat that the differences between C and D in each of these areas of analysis, whilst usually favouring C, was not large. The GDG emphasised that whilst a CCB should usually be preferred versus thiazide-like diuretic as step 1 and step 2 therapy for most people, a thiazide-like diuretic is a highly effective alternative and is preferred in people with evidence or, or at high risk of developing heart failure.

The GDG recommended that A + C should be the preferred step 2 therapy for most patients. A+D is an alternative step 2 treatment in those intolerant of a CCB or in those with a high risk of heart failure.

Step 3 Treatment for Hypertension:

The GDG did not formally review new evidence for step 3 treatment for the 2011 update. However, the GDG discussed the implications of the recommendations for step 1 and 2 treatments with regard to step 3 treatment. The GDG concluded that it follows from the evidence reviews cited above that the recommended step 3 treatment should be; A (ACEi or ARB) + CCB + D (thiazide-like diuretic, i.e. chlothalidone or indapamide).

Resistant hypertension: (step 4 treatment)

The GDG decided that the term 'resistant hypertension' should be applied to people requiring step 4 treatment and defined resistant hypertension as follows;

Definition of Resistant Hypertension: A person with resistant hypertension is someone who has confirmed hypertension and in whom clinic blood pressure is not controlled (<140/90mmHg) despite treatment with a rational combination of optimum or best tolerated doses of three antihypertensive drugs (usually A+C+D).

Update 2011

The GDG noted that poor compliance with therapy and white coat hypertension could each manifest as apparent resistance to drug treatment and should be considered. Secondary causes for hypertension should also be reconsidered in people with resistant hypertension and discussion with a specialist may be required to address some of these issues.

Based on health survey for England data, the GDG estimated that resistant hypertension is likely to affect approximately 500,000 people with treated hypertension in the U.K. and thus represents an important clinical problem. These people will be older and often have established cardiovascular disease, diabetes or CKD and thus, be at high cardiovascular risk. From a cardiovascular risk perspective, such people potentially have much to gain in terms of absolute benefit from further blood pressure lowering.
The GDG noted that the treatment of resistant hypertension has not been studied in detail, in part because few drugs are developed that are specifically targeted at resistant hypertension. There is as a consequence, a paucity of data upon which to base guidance for the treatment of resistant hypertension. For the 2006 pharmacological update of this guideline, there was no formal evidence review for step 4 treatment and the GDG cautiously recommended a range of options that included; "further diuretic therapy", alpha blockers or beta blockers. For this 2011 update the literature was searched for all years and all study types were included. Populations which were exclusively diabetic or had chronic kidney disease were excluded.

The data search failed to indentify a single head-to-head RCT that met our search criteria. Six studies did meet the search criteria, however, these were all retrospective cohort studies – i.e. post-hoc analyses of studies in which patients had been treated with four or more antihypertensive therapies. The GDG noted that all of these studies evaluated the use of low doses of spironolactone (an aldosterone antagonist), usually 25mg o.d. Together, the review of this data suggested that low dose spironolactone was effective in resistant hypertension based on the surrogate outcome of blood

pressure lowering. There was no data on other clinical outcomes. It is unclear from this very limited data whether spironolactone is always the most effective treatment option for every patient with resistant hypertension. Furthermore, the GDG noted that spironolactone is not licensed for the treatment of hypertension in the U.K. but this does not preclude its use. Not all people are able to tolerate spironolactone, the main adverse effect being the development of nipple tenderness and/or gynaecomastia in males. Another important consideration is that spironolactone is a potassium sparing diuretic and may cause hyperkalaemia, especially when combined with an ACE-inhibitor or ARB, as will be the case for most people with resistant hypertension treated according to the algorithm recommended by this guideline. The GDG considered this to be a very important safety issue. Where reported, the studies that have used spironolactone for the treatment of resistant hypertension have not used it when the baseline potassium level exceeded 5.00mol/L, and spironolcatone was used with caution in people with a reduced eGFR. The GDG discussed these safety aspects and recommended that in primary care, low dose spironolactone should only be considered for the treatment of resistant hypertension when the blood potassium level is <4.5mmol/L. Particular caution is advised in people with a reduced GFR as they are at increased risk of hyperkaelemia and renal function should be monitored closely in all patients receiving sprinolactone. Blood potassium, sodium and creatinine values should be checked approximately 2 weeks after treatment initiation and perdiodically thereafter.

The GDG also highlighted that patients should be advised to discontinue spironolactone treatment if they become significantly dehydrated due to illness such as vomiting and/or diaorrhea. The GDG recognised that the emphasis of too many caveats and concerns might limit the use of what can be a very effective drug in the setting of resistant hypertension. Nevertheless, care is needed to monitor patients when treatment regimens become increasingly complex.

The GDG discussed the potential use of other drug classes for resistant hypertension and noted that treatments such as higher doses of thiazide type diuretics, alpha blockers and beta blockers have been used as add-on therapy in clinical trials at step 2 and 3 but not necessarily at step 4. The GDG concluded that this provides some evidence for the potential effectiveness of these other treatment options as “add-on” therapy. The GDG also considered alternative “further diuretic therapy” to spironolactone if this was deemed inappropriate treatment because of an elevated baseline potassium level or concerns about renal function. The GDG concluded that If blood potassium levels are higher than 4.5 mmol/l, then higher-dose thiazide-like diuretic treatment may be considered as an alternative. The GDG also discussed newer therapies such as the direct renin inhibitor aliskiren but concluded that there was insufficient evidence of its effectiveness to determine its suitability for use in resistant hypertension.

Update 2011

In summary, the GDG concluded that resistant hypertension is an important clinical problem that has been poorly studied with regard to the underlying causes and the most effective treatment options. Clinicians should consider referral of people with resistant hypertension for specialist advice/evaluation – especially those who are younger and those with complex comorbidities. The best evidence, albeit weak evidence, suggests that low dose spironolactone (e.g. 25mg o.d.), when safe to use and when tolerated, can be an effective means of further lowering blood pressure. It is unclear if this is the optimal treatment for most people with resistant hypertension or whether other treatment options would be more effective in most or some cases. When use of spironolactone is not possible or not tolerated, then higher dose thiazide-like diuretic, alpha blockers or beta blockers are suitable alternatives for step 4 treatment, with the caveat that the evidence base is very limited and careful monitoring of electrolytes and renal function is essential. The GDG recognised the need of more research in this area.

12.10 Recommendations

40.Where possible, recommend treatment with drugs taken only once a day. [2004]

41. Prescribe non-proprietary drugs where these are appropriate and minimise cost. [2004]

42. Offer people with isolated systolic hypertension (systolic BP 160 mmHg or more) the same treatment as people with both raised systolic and diastolic blood pressure. [2004]

43. Offer people aged 80 years and over the same antihypertensive drug treatment as people aged 55–80 years, taking into account any comorbidities. [new 2011]

44. Offer antihypertensive drug treatment to women of child-bearing potential in line with the recommendations on Management of pregnancy with chronic hypertension and Breastfeeding in 'Hypertension in pregnancy' (NICE clinical guideline 107). [2010]

Step 1 treatment

45. Offer people aged under 55 years step 1 antihypertensive treatment with an angiotensin-converting enzyme (ACE) inhibitor or a low-cost angiotensin-II receptor blocker (ARB). If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), offer a low-cost ARB. [new 2011]

46. Do not combine an ACE inhibitor with an ARB to treat hypertension. [new 2011]

47. Offer step 1 antihypertensive treatment with a calcium-channel blocker (CCB) to people aged over 55 years and to black people of African or Caribbean family origin of any age. If a CCB is not suitable, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011]

48. If a diuretic is to be initiated or changed, offer a thiazide-like diuretic, such as chlortalidone (12.5 mg–25.0 mg once daily) or indapamide (1.5mg slow release or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. [new 2011]

49. For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide. [new 2011]

50. Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly:
    - those with an intolerance or contraindication to ACE inhibitors and angiotensin-II receptor antagonists **or**
    - women of child-bearing potential **or**
    - people with evidence of increased sympathetic drive. [2006]

51. If therapy is initiated with a beta-blocker and a second drug is required, add a calcium-channel blocker rather than a thiazide-like diuretic to reduce the person's risk of developing diabetes. [2006]

Step 2 treatment

52. If blood pressure is not controlled by Step 1 treatment, offer step 2 treatment with a CCB in combination with either an ACE inhibitor or an ARB[j]. [new 2011]

[j] Choose a low-cost ARB.

Update 2011CCC

53. If a CCB is not suitable for step 2 treatment, for example because of oedema or intolerance, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. [new 2011]

54. For black people of African or Caribbean family origin, consider an ARB[k] in preference to an ACE inhibitor, in combination with a CCB. [new 2011]

Step 3 treatment

55. Before considering step 3 treatment, review medication to ensure step 2 treatment is at optimal or best tolerated doses. [new 2011]

56. If treatment with three drugs is required, the combination of ACE inhibitor or angiotensin-II receptor blocker, calcium-channel blocker and thiazide-like diuretic should be used. [2006]

Step 4 treatment

57. Regard clinic blood pressure that remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice. [new 2011]

58. For treatment of resistant hypertension at step 4:
    - Consider further diuretic therapy with low-dose spironolactone (25 mg once daily)[l]. If the blood potassium level is 4.5 mmol/l or lower. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkaelemia.
    - Consider higher-dose thiazide-like diuretic treatment if the blood potassium level is higher than 4.5 mmol/l. [new 2011]

59. When using further diuretic therapy for resistant hypertension at step 4, monitor blood sodium and potassium and renal function within 1 month and repeat as required thereafter. [new 2011]

60. If further diuretic therapy for resistant hypertension at step 4 is not tolerated, or is contraindicated or ineffective, consider an alpha- or beta-blocker. [new 2011]

61. If blood pressure remains uncontrolled with the optimal or maximum tolerated doses of four drugs, seek expert advice if it has not yet been obtained. [new 2011]

Update 2011

12.11 Research recommendations

6. In adults with hypertension, which drug treatment (diuretic therapy versus other step 4 treatments) is the most clinically and cost effective for step 4 treatment?

Although this guideline provides recommendations on the use of further diuretic therapy for treatment at step 4 (resistant hypertension), they are largely based on post-hoc observational data from clinical trials. More data are needed to compare further diuretic therapies, for example a potassium-sparing diuretic with a higher-dose thiazide-like diuretic, and to compare diuretic therapy with alternative treatment options at step 4 to define whether further diuretic therapy is the best option.

[k] Choose a low-cost ARB.

[l] At the time of publication (August 2011), spironolactone did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

13 Patients' perspectives

13.1 Introduction

A published survey that examined the views of 452 hypertensive patients in one urban GP practice illustrated the range of feelings surrounding the taking of antihypertensive medications. There was a 77% response rate among patients invited to participate[71]. 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.

13.2 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.

13.3 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. ACEi 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.

13.4 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.

13.5 Education and adherence

13.5.1 Compliance with Prescribed Antihypertensive Medication

It is estimated that between 50–80% of patients with hypertension do not take all of their prescribed medication[377,518]. This has implications for the successful management of hypertension with poor adherence to medications linked to inadequately controlled blood pressure[273]. 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[346], [344] 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[620]. 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[620]. 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[346], [344]. Increasingly the term concordance is used within the literature, implying a more interactive and participatory approach to drug prescribing[518].

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[143]. 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[143]. 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[70,267]. 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[83]. 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[267].

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[267,518].

Two systematic reviews have sought to assess the effectiveness of these interventions[267,292]. One looked specifically at the relationship between daily dose frequency and adherence to antihypertensive medication[292]. In a meta-analysis of data from eight 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[267].

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[70]. 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.

13.5.2 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[344]. 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[647]. 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[344,358,647].

Adherence with lifestyle modifications, especially dietary changes, is lower than with antihypertensive drug therapy by between 13% and 76%[109]. 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[112,417]. The regular follow-up provided by these clinics may help compliance[358]. 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[173].

How should it be given?

Advice alone is less effective than specifically adapted programmes supported by written and audiovisual material[109,605]. Material tailored to meet the educational and cultural needs of the population it is targeting has also been shown to be effective[342].

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[186].

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[358]. 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[376]. Delivering programmes through specific channels, for example community based projects may increase effectiveness[358].

13.5.3 Recommendations

62. Provide appropriate guidance and materials about the benefits of drugs and the unwanted side effects sometimes experienced in order to help people make informed choices. [2004]

63. People 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. [2004]

64. Provide an annual review of care to monitor blood pressure, provide people with support and discuss their lifestyle, symptoms and medication. [2004]

65. Because evidence supporting interventions to increase adherence is inconclusive, only use interventions to overcome practical problems associated with non-adherence if a specific need is identified. Target the intervention to the need. Interventions might include:
    - suggesting that patients record their medicine-taking
    - encouraging patients to monitor their condition
    - simplifying the dosing regimen
    - using alternative packaging for the medicine using a multi-compartment medicines system. (This recommendation is taken from 'Medicines adherence', NICE 408 clinical guideline 76). [new 2011]

Update 2011

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15 Glossary

Term	Definition
Ambulatory blood pressure monitoring (ABPM)	A technique for measuring BP while an individual goes about their normal daily activities
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Aerobic exercise	Exercise requiring increased oxygen
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Angina pectoris:	A strangling pain in the chest due to reduced blood flowing to the heart muscles
Antihypertensive	Drug used to lower blood pressure
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm
Arrhythmia	A variation in the normal rhythm of the heart
Association	Statistical relationship between two or more events, characteristics or other variables. The relationship may or may not be causal.
Auscultation	Examination of the internal organs by listening to the sound produced
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Biofeedback	Sight or sound information letting the individual know how an aspect of their body is functioning
Blinding	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
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	Disease affecting the heart or blood vessels
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Term	Definition
Case-series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Cerebrovascular accident	Stroke (part of the brain is damaged due to lack of oxygen)
Cerebrovascular disease	Narrowing of the arteries supplying blood to the brain
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cognitive	Describing mental processes
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.
Comorbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Consensus methods may used when there is a lack of strong evidence on a particular topic.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Coronary heart disease	Heart disease due to narrowing of the arteries which provide the heart's blood supply; may manifest as angina or heart attack
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare

Term	Definition
	treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life-years (QALYs).
Credible Interval	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Diastolic blood pressure	The lowest blood pressure during each heartbeat (e.g. 80 if blood pressure is 140/80 mmHg)
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.
Dose titration	Change in the dose of a drug
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.
Effectiveness	See 'Clinical effectiveness'.
Efficacy	See 'Clinical efficacy'.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.
EQ-5D (EuroQol-5D)	A standardise instrument used to measure a health outcome. It provides a single index value for health status.
Essential hypertension	High blood pressure which is not due to a known underlying disease
Excessive alcohol consumption	Over 21 units/week for men; over 14 units/week for women
Excessive coffee consumption	Over 5 cups/day
Evidence	Information on which a decision or guidance is based. Evidence is obtained

Term	Definition
	from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals and/or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more efficient and should be preferred, other things remaining equal.
Extrapolation	In data analysis, predicting the value of a parameter outside the range of observed values.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study based on measurement in a particular patient population and/or a specific context hold true for another population and/or in a different context. In this instance, this is the degree to which the guideline recommendation is applicable across both geographical and contextual settings. For instance, guidelines that suggest substituting one form of labour for another should acknowledge that these costs might vary across the country.
Gold standard See 'Reference standard'.	GRADE / GRADE profile A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Health-related quality of life (HRQoL)	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
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 Or lack of homogeneity.	The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Hypertension	High blood pressure
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.

Term	Definition
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention to treat analysis (ITT)	A strategy for analysing data from a randomised controlled trial. All participants are included in the arm to which they were allocated, whether or not they received (or completed) the intervention given to that arm. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by randomisation and which may reflect non-adherence to the protocol.
Intervention	Healthcare action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Intraoperative	The period of time during a surgical procedure.
Ischaemic heart disease	See Coronary heart disease
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Lifestyle intervention	A measure to change a participant's behaviour in order to improve their health (e.g. exercise to reduce blood pressure)
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by 1- specificity.
Lipid lowering drugs	Drugs used to lower the level of fats in the blood
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Loss to follow-up	The loss of participants during the course of a study.
Magnesium	An element necessary for normal body function; found in food
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Monotherapy	Use of only one drug (rather than two or more)
Multivariate model	A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

Term	Definition
Negative predictive value (NPV) [In screening/diagnostic tests:]	A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
Normotension	Blood pressure that is within the normal range
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Oscilllometry	The measurement of blood pressure using an electronic device rather than by listening to Korotkoff sounds (auscultation)
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P-value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Peripheral vascular disease	Narrowing of the arteries providing circulation to the legs
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening/diagnostic tests: A measure of the usefulness of a screening/diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	For diagnostic tests. The proportion of patients with that particular test result who have the target disorder.
Potassium	An element necessary for normal body function; found in food
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	For diagnostic tests. The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by general practitioners, nurses, dentists, pharmacists,

Term	Definition
	opticians and other healthcare professionals.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are retrospective.
Publication bias	Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Rapid atrial fibrillation	A rapid irregular heartbeat
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity Is plotted against 1-specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
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

Term	Definition
	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).
Reporting bias	See publication bias.
Resistant hypertension	Someone whose blood pressure is not controlled to <140/90mmHg, despite optimal or best tolerated doses of third line treatment
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are prospective.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Sensitivity	Sensitivity or recall rate is the proportion of true positives which are correctly identified as such. For example in diagnostic testing it is the proportion of true cases that the test detects. See the related term 'Specificity'
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): two or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (For example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).
Specificity	The proportion of true negatives that a correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Sphygmomanometer	A device used to measure blood pressure
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.

Term	Definition
Stepped care	A drug intervention where the dose of the drugs can be increased and/or other drugs could be added
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.
Systolic blood pressure	The peak blood pressure during each heartbeat (e.g. 140 if blood pressure is 140/80 mmHg)
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
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	Temporary paralysis, numbness, speech difficulty or other neurological symptoms that start suddenly and recover within 24 hours
Treatment allocation	Assigning a participant to a particular arm of the trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
Withdrawal	Failure or refusal to take the assigned treatment (e.g. because of side effects or dislike of treatment)