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

August 2019: NICE's original guidance on hypertension in adults was published in 2004. It was updated in 2006, 2011 and 2019. See the NICE website for the guideline recommendations and the evidence reviews for the 2019 update. This document preserves evidence reviews and committee discussions for the 2011 guideline.

Commissioned by the National Institute for Health and Clinical Excellence

Royal College of Physicians · Royal College of Nursing · RCS Advancing Surgical Standards · Royal College of General Practitioners · NHS Evidence accredited provider · BHS British Hypertension Society

Published by the National Clinical Guideline Centre at
The Royal College of Physicians, 11 St Andrews Place, Regents Park, London, NW1 4BT
First published 2004, republished 2006

Update information

August 2019: The guideline was updated and evidence sections affected and recommendations were removed from this full guideline.

November 2016: A footnote was added to recommendations 46, 47, 53, 55, 57 and 58 covering angiotensin-converting enzyme (ACE) inhibitors about 2 MHRA drug safety alerts. These alerts cover ACE inhibitor use during pregnancy and breastfeeding.

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

Name	Role
Bernard Higgins	Clinical Director, National Clinical Guideline Centre
Bryan Williams	Professor of Medicine, Guideline Development Group Chair
Helen Williams	Consultant Pharmacist for cardiovascular disease, Southwark Health and Social Care
Jane Northedge	Patient and care representative
John Crimmins	General Practitioner, Vale of Glamorgan
Kate Lovibond	Senior Health Economist, National Clinical Guideline Centre
Mark Caulfield	Professor of Clinical Pharmacology, Barts and the London School of Medicine
Michaela Watts	Hypertension Nurse Specialist, Addenbrooke's Hospital, Cambridge
Naomi Stetson	Primary Care Nurse, Watling Medical Centre, Burnt Oak
Paul Miller	Senior Information Scientist, National Clinical Guideline Centre
Rachel O'Mahony	Senior Research Fellow, National Clinical Guideline Centre
Richard McManus	Professor of Primary Care Cardiovascular Research, University of Birmingham
Shelley Mason	Patient and carer representative
Terry McCormack	General Practitioner, Spring Vale Medical Centre, North Yorkshire, Primary Care Cardiovascular Society
Taryn Krause	Senior Project Manager/Research Fellow, National Clinical Guideline Centre

Update 2011

Acknowledgments

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

- Jill Cobb, Information Scientist, National Clinical Guideline Centre
- Ralph Hughes, Health Economist, National Clinical Guideline Centre
- Fatema Limbada, Project Coordinator, National Clinical Guideline Centre
- Jill Parnham, Director of Operations, National Clinical Guideline Centre
- David Wondering, Health Economic Lead, National Clinical Guideline Centre
- Jacoby Patterson, Systematic Reviewer
- Julie Brown, Systematic Reviewer
- Sue Jowett, Senior Lecturer in Health Economics, 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.

Update 2011

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).

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

Update 2011

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.

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

- 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).

Update 2011

- 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.

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.

Upda

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

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

Update 2011

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.

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

Update 2011

Quality element	Description
	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

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 0, 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].

Study limitations

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

Update 2011

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

Limitation	Explanation
	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

3.2.8 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.

Update 2011

3.2.9 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.

3.2.10 Imprecision

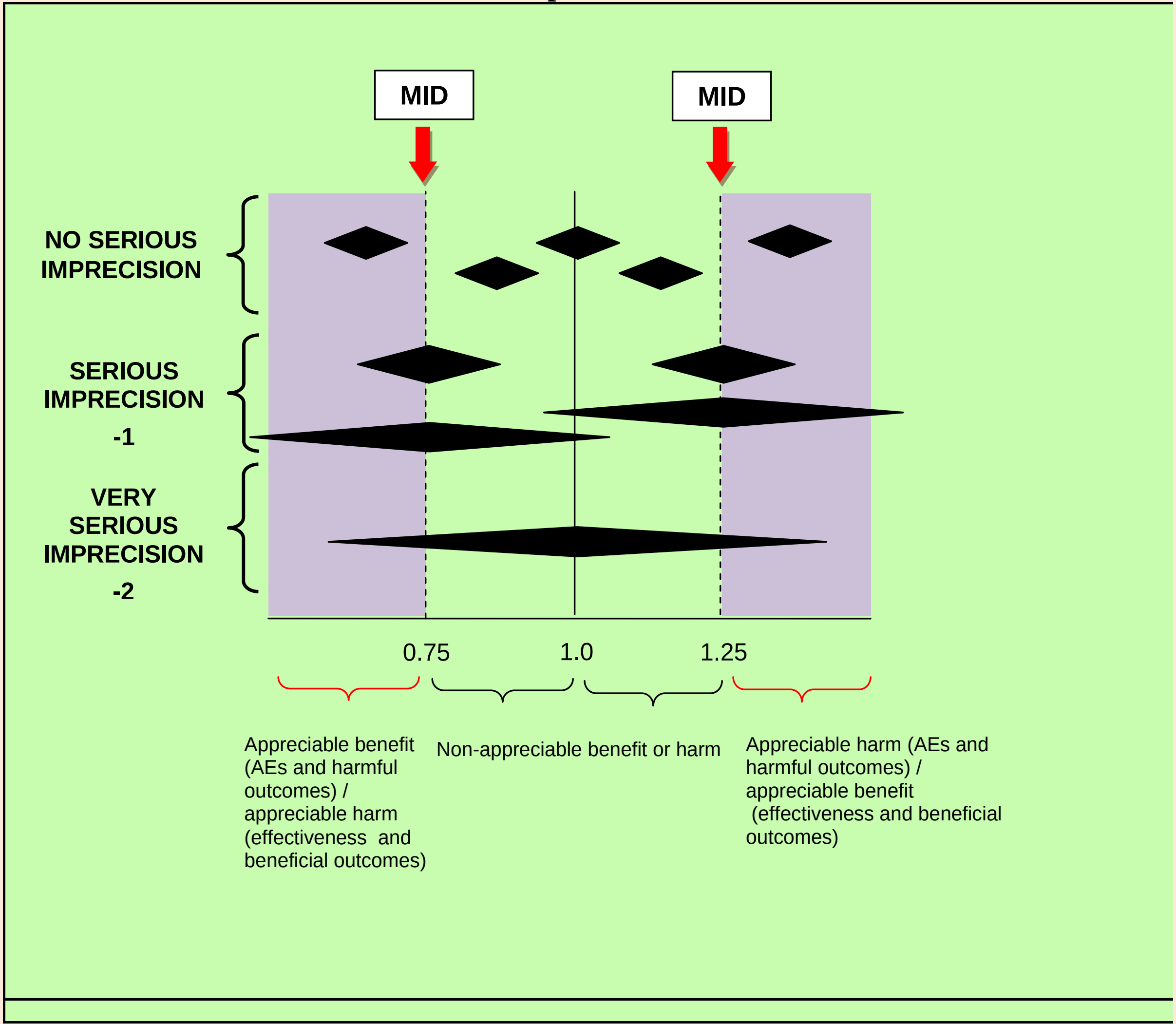
The criteria applied for imprecision are based on the confidence intervals for pooled or the best estimate of effect as illustrated in Figure 1 and outlined in Table 5.

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).

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%
Heart failure	10%

Update 2011

Outcome	Relative risk reduction
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)

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.

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]

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

Update 2

Item	Description
	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.

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

Update 2011

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.

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.

Update 2011

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

	Strength of 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 i. Blinding refers to independent interpretation of a test and reference standard. ii. An incident cohort is identified and followed in time from a defined point in the progress of disease or care. iii. Important flaws may be judged to occur when adequate standards of research are not followed or are unreported in published findings. Potential examples include failure to analyse by intention-to-treat, over-interpretation of secondary analyses, failure to adjust for potential confounding in non- randomised designs. For diagnostic studies this includes the need for an adequate reference standard and to apply different tests in an adequately short timescale. iv. Sparse data (too few events or patients) are the most common reason for imprecision. A confidence interval including both no effect and a clinically important effect is an example of an imprecise finding. v. Consistency in [1] design: involves methods, patients, outcome measures; and [2] findings: involves homogeneity of summary estimates. Independence refers to the availability of research from at least two independent sources. Evidence of publication bias also denotes lack of consistency. vi. Adequate relevance requires [1] use in studies of a relevant patient-oriented health outcome or a strongly linked surrogate endpoint; and [2] a sufficiently representative and relevant patient group or mix. vii. In comparative designs a very strong association can raise the quality score.
Treatment		
Randomised controlled trial	1	
Non-randomised controlled study	2	
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	
Representative sample	2	
Convenience sample	3	
Quality corrections		
Flawed design, conduct or analysis	+1	
Imprecise findings	+1	
Lack of consistency or independence	+1	
Inadequate relevance	+1	
Very strong association	+1	
	-1	
Evidence Grade		
I: High		
II: Intermediate 2	≤1	
III: Low	2	
	≥3	
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		

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.**
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. 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.

2006 methods

Clinical evidence

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.

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

The algorithms were replaced in the 2019 update. See www.nice.org.uk/guidance/ng136 for the updated visual summary.

5.2 Key priorities for implementation

The current recommendations can be found at www.nice.org.uk/guidance/ng136.

Full list of recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136

5.3 Key research recommendations

The current research recommendations can be found at www.nice.org.uk/guidance/ng136

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.

5.4 *Techniques for measuring blood pressure*

5.4.1 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:

Manual auscultation
• 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. • 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]

5.5 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]

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]

5.6 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.

Update 2011

"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.

5.7 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.

5.7.1 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.

Update 2011

5.7.2 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]

5.7.3 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]

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 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

Update

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]

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.

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136

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 an endorsement by NICE.

Research recommendation

The current research recommendations can be found at www.nice.org.uk/guidance/ng136.

This section has been updated and replaced except section 6.4 Measurement protocols for diagnosing hypertension. See the NICE website for the updated guideline recommendations and evidence review.

6 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 7 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.

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 5.6) 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.

Update 2011

6.1 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?

6.1.1 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]

6.1.2 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).

Update 2011

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]
- 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.

6.1.3 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).

Update 2011

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 and CHD	No difference	n/a
Mesquita-Bastos 2010[404]	1200	Mean 8.2 years	CV events and stroke	ABPM (especially night-time)	n/a

Update

Study	N	Follow-up time	Outcome	Best method	Representative of 'real life' home BP measurements?
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

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
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

Update 2011

Study	Outcome	Best method	HR (95% CI) for SBP measurement
			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)

6.2 *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?

6.2.1 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-

Update 2011

Update 2011

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.

6.2.2 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):

Update 2011

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

6.3 *Cost-effectiveness of clinic, home and ambulatory measurements*

6.3.1 Economic evidence – literature review

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]

Update 2011

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

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%.

6.3.2 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[b] 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).

6.3.2.1 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)
- 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

Update 2011

b 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.

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.

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.

Update 2011

6.3.2.2 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.

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.

Update 2011

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

Update 2011

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.

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 0). 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.

Update 2011

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%.

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.

Update 2011

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.

6.3.3 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.

6.4 *Measurement protocols for diagnosing hypertension*

6.4.1 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?

6.4.1.1 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.

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)
Fagard et al., 2008[210]	302	HT (with history of CV	not specified	Median 6.8 years	D –range 15-30 mins (10am – 6pm)		

Reference / study type	N	Population	Device	Follow-up time	Time and frequency of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
Pooled analysis of other study data ,within-group comparisons		disease)			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, coronary revascularisation.	24h, daytime and night-time all predictors SBP and DBP in age <60 Only SBP in age >60
Kikuya et al., 2007[326]	5682	General population	-	Median 9.5 years	1 study: every 20 mins 1 study: every 30 mins	CV events; coronary events;	24h, daytime and night-time (SBP and DBP)

Reference / study type	N	Population	Device	Follow-up time	Time and frequency of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
Pooled analysis of other study data, within-group comparisons (IDACO)		(HT and NT); <10% had underlying CV disease			1 study: 15 mins day, 30 mins night 1 study: 20 mins day, 45 mins night	cardiac events; fatal/non-fatal stroke	
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 population studies (case series)	8945	1 study: general population (HT and NT) 6 studies: HT (NT controls)	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
Sega et al., 2005[534]	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

Reference / study type	N	Population	Device	Follow-up time	Time and frequency of measurement	Outcomes	Proposed protocol (authors' conclusions) – best prognostic ability
within-group comparison (PAMELA study)							
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) ABPM (night-time): 121 ± 17 vs 129 ± 14 (p<0.05) SBP mm Hg without vs with complications Mean±SD

Study	Outcome	HR (95% CI) for SBP measurement
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 CeV and CV events	ABPM (24h): 1.76 (1.39-2.25) p<0.002 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

Study	Outcome	HR (95% CI) for SBP measurement
		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 BP.
Calvo et al.,	823	HT	OSC	48 h	48h	D – 20 mins (07.00-	Comparison of	ABPM for 48 h revealed a

Reference / study type	Frequency of measurements							
2003[111] Case-series						23.00) N – 30 mins (23.00-07.00) ABPM started on a weekday (Mon, Wed or Fri)	day-to-day variations in BP	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 measurement s 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., 1992[133] within-group comparison	100	HT	-	1 month (2 measurement s1 month apart)	24h	Daytime only (30 mins)	Reproducibility of BP (between the 2 measurements over time)	Average daytime ABPM DBP was more reproducible than a single measuremnt from daytime. There was improved reproducibility with more measurements during the day

Reference / study type	Frequency of measurements							
Cuspidi et al., 2002[150] case-series	208	HT	OSC	3 weeks (2 measurement swithin 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.
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	Reproducibility on work and non-work days: SD; reproducibility over time (2 measurements,	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-

Reference / study type	Frequency of measurements							
						All: 20 min intervals	2 weeks apart)	time BP between the 2 readings There were no major differences in reporducibility if 1, 2 or 3 recordings / hour were used. Arbitrary 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 sessio ns (529 studies)	Borderline HT, suspected WCH, suspected hypotension, MHT, Tx resistance, a-HT treatment	OSC	24h	3 readings /hr (daytim e) 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 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	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,

Reference / study type	Frequency of measurements							
						weekday (Mon, Wed or Fri)		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 Recording intervals (minutes between measurements) not given	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. 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

Reference / study type	Frequency of measurements							
								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 Hg and proteinuria >300mg).	AUS	24h	24h	3 different frequencies of monitoring (FoM) readings/ hour: High FoM = 7/hr Low FoM = 1/hr Medium FoM = 2/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 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 measurements 4 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

Reference / study type	Frequency of measurements							
								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] within-group comparison	25	HT	AUS and OSC	Mean 23 months	24h	Daytime Night-time 24h All: 15 min intervals	Reproducibility of BP (between 2 repeated studies and over time): SDD, co-efficient of variance and % of people within 10mm and 5mm SBP and DBP	24h and night-time BP had better reproducibility than daytime BP (between studies and between readings over time)
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	135	General population (HT and NT)	OSC	7 days	-	Fitted on Thursday between 10am – 2pm; D - every 30 mins (0700 to 2200 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

Reference / study type	Frequency of measurements									
comparison						N - 60 mins (2200 to 0700 hours).				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 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		

Reference / study type	Frequency of measurements							
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, 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 measurement s1 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	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.

Reference / study type	Frequency of measurements							
							day	
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)
Sheps et al., 1994[538] within-group comparison	294	HT and NT	AUS	2 months (2 measurements 2 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.

Reference / study type	Frequency of measurements							
								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] within-group comparison	133	HT (untreated)	OSC	2 work days	24h	Every 20 mins	Test-retest variability (correlations and SDD)	Mean 24h (was better than awake or asleep BP)
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.,	34	HT	AUS	4 weeks	24h	Daytime (10 mins)	Reproducibility	There WAS NS differnce in SBP /

Reference / study type	Frequency of measurements							
1991[600] case-series				(2 measuremnts – 4 weeks apart)		Night-time (20 mins) 24h	of BP (between the 2 measurements over time)	DBP measurements 4 weeks apart (24h ABPM) 24h ABPM was more reporducible than office BP due to a larger number 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	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	Reproducibility of BP variables: averages, 24-h, day-time, night-time, crest, trough, trough:crest (Intra-class	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

Reference / study type	Frequency of measurements							
				same time of day OPP group: sessions randomised to begin in morning or evening		(0600-2200) N - 30-45 ± 5 minutes (2200-0600)	correlation)	morning compared with the evening Reproducibility of DBP was similar 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.

Update 2011

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)
Lede et al., 1997[353]	49	24h	7.5, 30 or 60	7.5, 30 or 60	All times are similar

Reference / study type	N	Follow-up time	Day protocol (mins)	Night protocol (mins)	Best: day, night or 24h
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

6.4.1.2 Health economic evidence

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

6.4.1.3 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]

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]

Update 2011

3. The best time of day to take measurements

- All day measurements are needed (16 studies):
  - o One hour (one study), 24h, day, night (two studies)[150,654]
  - o Day and night are best (two studies)[387,527]
  - o 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]
  - o Night and 24 hour measurements gave greater reproducibility (two studies)[46,389]
  - o Daytime measurements are best (especially for men in one study; three studies)[52,530,531]
  - o Mean 24 hour measurements are best (two studies)[114,563]
  - o 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]

6.4.1.4 Evidence statements – economic

- No relevant cost-effectiveness evidence was identified.

Update 2011

6.4.2 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?

6.4.2.1 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.

6.4.2.2 Economic evidence

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

6.4.2.3 Evidence statements – clinical

The studies showed the following:

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]

Update 2011

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

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] Within-group	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							
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 correlation with ABPM when the 1st day was excluded)
Ewald et al., 2006[203]	53	HT	AOD	≥1	12 weeks	M	Identification of	Take at least 2

	Frequency of measurements							
Post-hoc analysis of RCT (OLMETEL STUDY): thus cohort						E	treatment responders (sensitivity/ specificity); response to Treatment	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

6.4.2.4 Evidence statements – health economic

- No relevant cost-effectiveness evidence was identified.

6.5 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 also relate to the fact that

Update 2011

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.

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.

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 8.2 – 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.

Upda

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 6.3 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.

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

Update 2011

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 5.5) and recognition that automated measurements may be unreliable or impossible in people with significant pulse irregularity (e.g. atrial fibrillation) (see section 5.7) 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 5.4.1) 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.

6.6 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136.

7 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).

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.

7.1 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

7.1.1 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.

7.1.2 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.

7.2 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.

7.3 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.

7.3.1 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].

7.3.2 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).

7.3.3 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.

7.3.4 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].

7.4 Other identifiable causes of hypertension

7.4.1 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].

7.4.2 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].

7.4.3 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).

7.4.4 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].

7.4.5 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].

Update 2011

7.4.6 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].

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136

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

Research recommendations

The current research recommendations can be found at www.nice.org.uk/guidance/ng136

8 Initiating and monitoring treatment, including blood pressure targets

This section has been updated and replaced. See the NICE website for the updated guideline recommendations and evidence review.

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

Blood pressure thresholds for initiating pharmacological treatment

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

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

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 people with high BP, because a given BP reduction lowers the risk of

Reference	N	Population	BP measurement method	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
								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 (fatal or non-fatal)	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 HT but unaware	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 different from the normotensive group, suggesting that these

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
							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 as aggressive as it would be today; number controlled to <140/90mmHg was less than

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
							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 were lower in women).
Kono et al., 2005[332]	708	HT (with vs. without CV event)	n/a as case-control study	Risk of developing events in people with different baseline BP values	CV events	SBP values NT: <140 Mild HT: 140-159	Positive relationship between BP status and risk of cardiovascular events

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
Case-control				(grouped)		moderate-severe HT: >160	
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 DBP values Group 1: <80 Group 2: 80-84 Group 3: 85-89 Group 4: 90-99 Group 5: >99	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)
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.
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	Both SBP and DBP were associated with CHF, but SBP conferred greater risk than DBP. Increased risk of events with increased BP value.

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
						≥83 mmHg	
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. 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	

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
						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] Cohort	26,587	General population (HT and NT)	Mean 9.5 years	Risk of developing events in people classed into baseline BP groups	Stroke	ISH: ≥140 / <90 mmHg SDH: ≥140 / ≥90mmHg IDH: <140 / ≥90 mmHg (with or without a-HT Tx) MHT: <140 / <90 (and controlled BP by a-HT Tx) NT: <140 / <90 (without history of HT)	Highest risk of stroke in people with ISH and SDH vs IDH and MHT. 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	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

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
RCT (Syst-Eur)							
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] Cohort	18,876	HT	Mean 20.7 years	Risk of developing events in people with different baseline BP values	HF	SBP 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	Linear relationship between NT SBP (120-129mmHg and 130-139mmHg) and risk of heart failure risk, as well as for HT SBP
Conen et al.,	39,322	NT and HT	Median 10.2	Risk of developing	CV death,	Optimal: <120/ <75	The CV risk of women with high

Reference	N	Population	Follow-up	Study design	Outcomes	BP values at baseline (groups / thresholds); mmHg	Best BP threshold (authors' conclusions)
2007[136] Cohort (sub-analysis of RCT)		women	years	events in people with different baseline BP values	stroke or MI	Normal: 120-129/75-84 High normal: 130-139/85-89 HT: ≥140 /≥90	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) 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)

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]
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) 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)

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]
		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., 2008[313]	CV mortality	SBP values 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.,	CV events (MI	Men Optimal: <120 /<80 Reference

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[331]	or Stroke)	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) 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

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]
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, Stroke)	SBP values (quartiles) CV death ≤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)

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]
		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.
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.,	Stroke	NT: <135 / <80 mmHg Reference

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]
2007[285]		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 >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]					CLINIC MEASUREMENT CATEGORIES: lower limits of grade 3 (severe) HT(180/110 mm Hg)

Reference	N	Population	Follow-up	Study design	BP values at baseline (groups / thresholds); mmHg
cross-sectional study	8575	NT and HT	Immediate	ABPM equivalents for clinic BPs	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

8.1.1 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.

Evidence statements – economic

No relevant cost-effectiveness evidence was identified.

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)?

Clinical evidence

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

Update 2011

Update 2011

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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	anti-HT treatment	Placebo	Relative (95% CI)	Absolute	
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

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

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]

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.

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.

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).

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.

Update 2011

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.

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136

Recommendations for research

The current research recommendations can be found at www.nice.org.uk/guidance/ng136.

8.2 *Monitoring treatment efficacy*

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?

8.2.1 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]

Update 2011

Quality assessment							Summary of findings				
							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**	
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		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Home blood pressure measurement**	**Ambulatory blood pressure measurememnt**	**Relative (95% CI)**	**Absolute**	
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

Update 20

[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

Update 2011

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 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
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

8.2.2 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]

Evidence statements – clinical

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

Update 2011

- 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)

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

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.

8.2.3 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

Update 2011

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.

Update 2011

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136.

Research recommendations

The current research recommendations can be found at www.nice.org.uk/guidance/ng136.

8.3 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?

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

Table 45).

Update 2011

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 2008[29,298]	4320	HT	Clinic	172/89 (strict and	12 months and 2	Strict control	BP changes/achievement	12 months: Strict: 139/76;	Strict treatment group was SS better for: lower final BP value (1	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
RCT (JATOS)				mild)	years	<140 SBP Mild control 140-160 SBP	of target BP; morbidity (CVD and renal failure) and mortality	60% Mild: 147/79; 67% 2 years: Strict: 136/75 Mild: 146/78	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 control <140 SBP	BP changes/achievement of target BP; CV endpoint	Tight: 132/77 Usual: 136/79 Achieved <140: Tight 79% Usual 67%	Tight control group was SS better for: reduction in CV events percentage achieving SBP (<130 and <140) reduction in BP value	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
								Achieved <130: Tight 72% Usual 27%		
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 trials);	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 therapeutic correction of CV	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
	c) diabetic patients (n=11 trials; these would be outside our inclusion criteria); d) high-risk patients (n=18 trials)							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 using randomised groups	22,576	HT	Clinic	Stratified into: SBP <140 vs. ≥140 DBP:	61,836 patient years	Fatal/non-fatal stroke; Achieving target BP <140/90	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 had lower risk than ≥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
RCT (INVEST)				<90 vs. ≥90					
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 that BP should be below 140/90 for reducing the risk of CV events. BP was	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
								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.* Age – BP nadirs (SBP / DBP): <60: 110 / 75 60-<70: 115 / 75 70-<80: 135 / 75 ≥80: 140 / 70	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

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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	more intense BP lowering	less intense BP lowering	Relative (95% CI)	Absolute	
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 ($p<0.05$)

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	Reference	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.
	Target DBP <85mmHg	£82(a)			
	Target DBP <80mmHg	£181 (a)			

a) Converted from 1995 Swedish Kroner.

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])

In-treatment / achieved blood pressure studies showed that:

Update 2011

- 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]

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.

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

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.

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

Update 2011

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.

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136

Update 2011

Research Recommendation

The current recommendations can be found at www.nice.org.uk/guidance/ng136

8.4 *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

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.

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

Update 2011

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 9). 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 5.6), home blood pressure monitoring (section 8.2) 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

9 Lifestyle interventions

9.1 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.

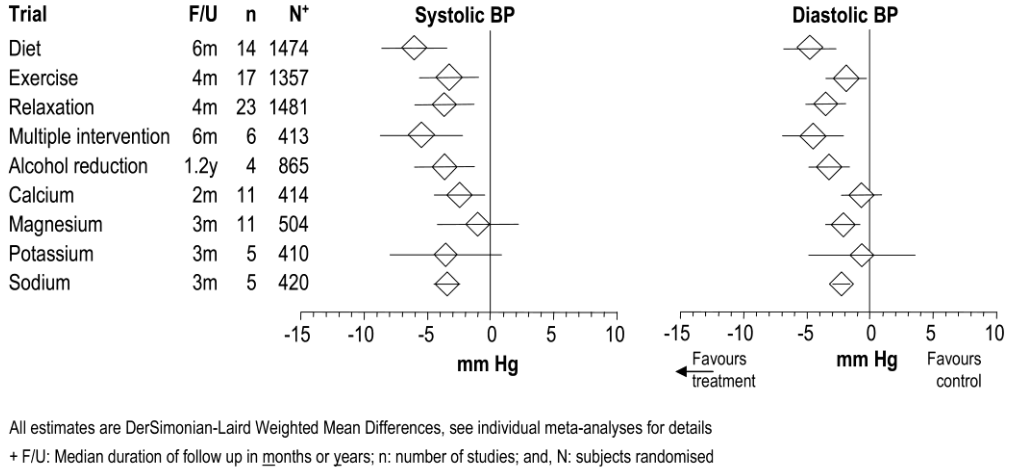
Table 48: Summary characteristics of trials of lifestyle interventions

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)



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.

9.1.1 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.

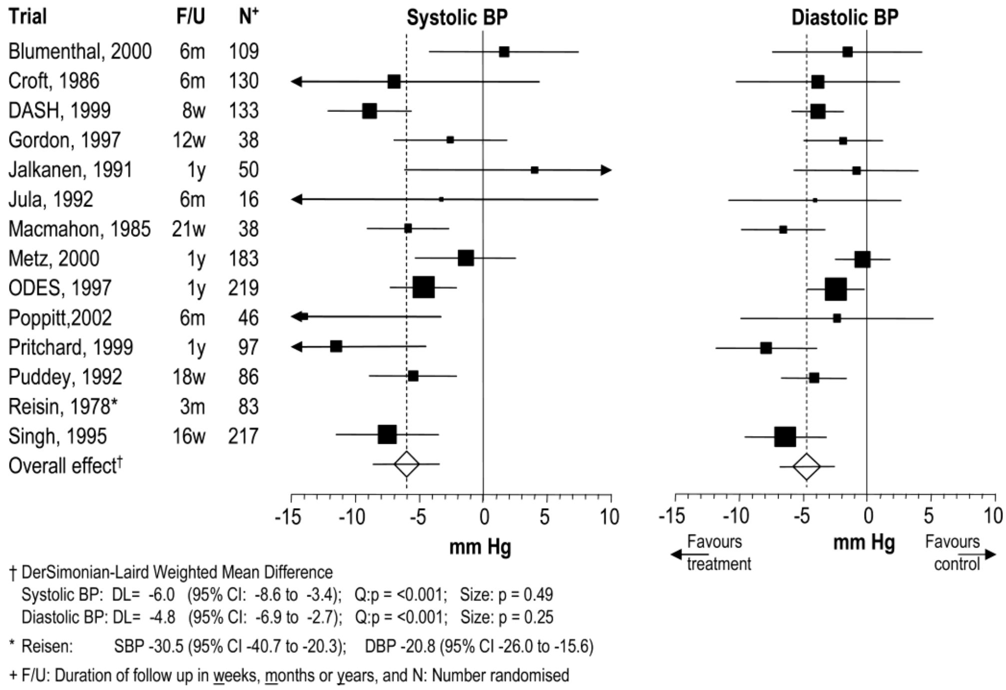
9.1.2 Diet

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.

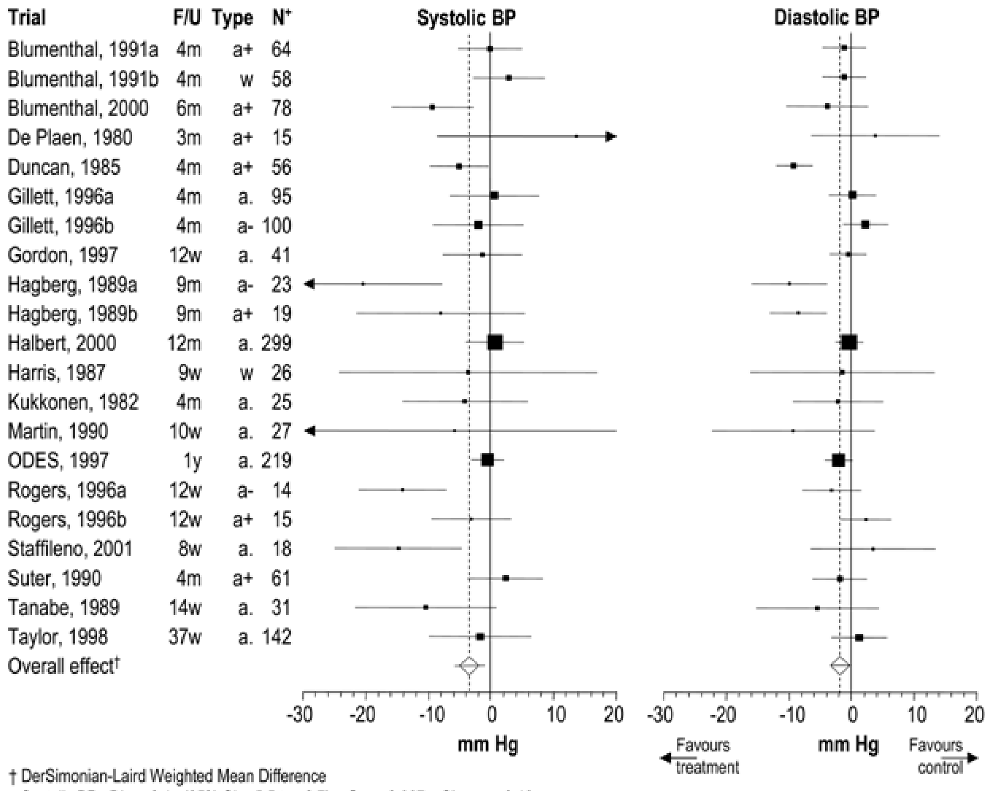
9.1.3 Exercise

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



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

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

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

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.

9.1.4 Relaxation therapies

This section on relaxation therapies has been updated and replaced. See the NICE website for the updated guideline recommendations and evidence review.

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 data128,232,245,345,398,586, 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

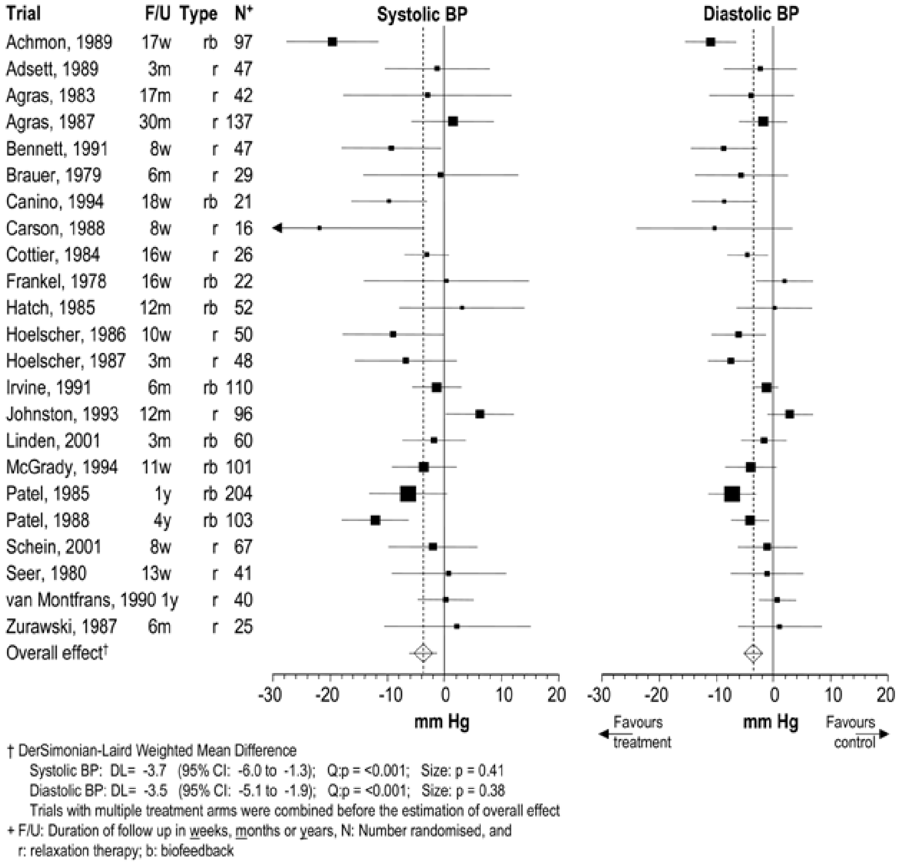
studies (30%). Treatment and control groups were confirmed as comparable at baseline, with regard to age, sex and initial blood pressure in 16 studies (70%).

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.

9.1.5 Multiple lifestyle interventions

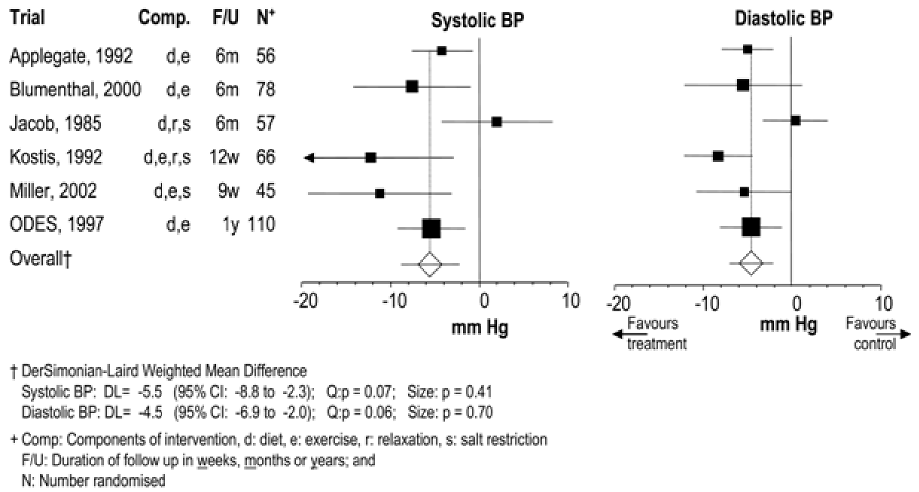
Six randomised controlled trials, including 413 participants, met the review inclusion criteria. RCTs of multifaceted interventions[45,47,84,294,337,337,408,599]. Three of the studies essentially provided a therapeutic intervention combining group exercise and diet strategies similar to the lifestyle 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.

9.1.6 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]).

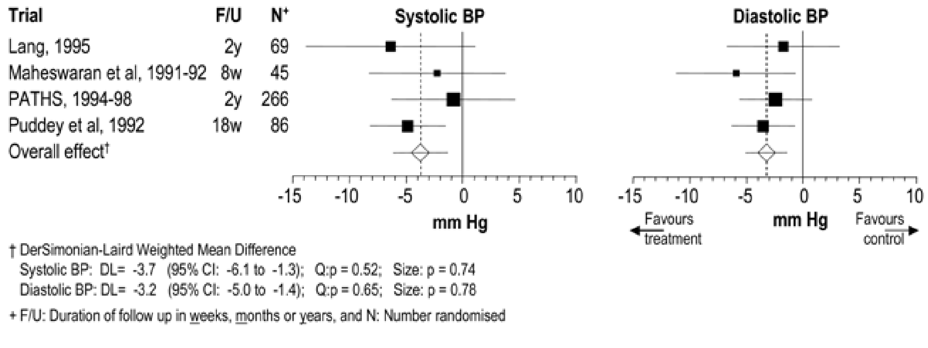
Three randomised controlled trials, including 397 participants, met the review inclusion criteria and examined the effect of changes in alcohol consumption on blood pressure[148,382,502]. Interventions varied in their content but commonly featured a number of visits to a health care practitioner for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

9.1.7 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.

9.1.8 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.

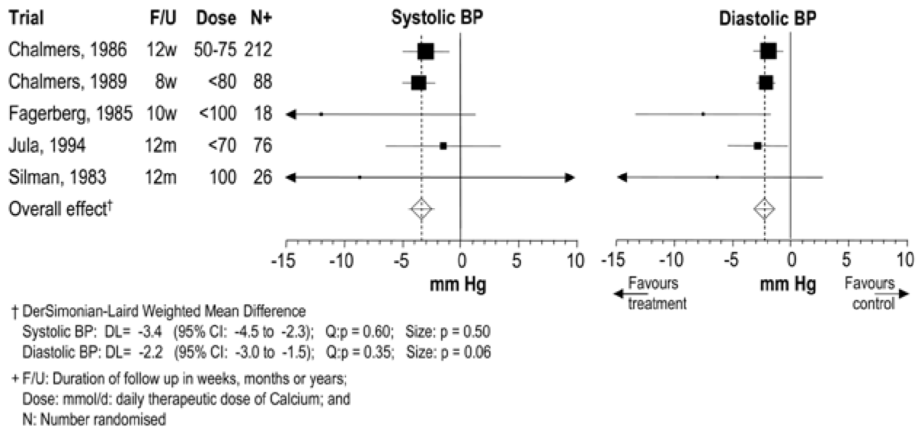
Five randomised controlled trials (four of parallel design[125,212,311,544], one of crossover design[10,11]), examining the effect of sodium reduction on blood pressure, met the review inclusion criteria and included 420 patients. The findings of one Italian trial in young adults are considered separately[141]. 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.

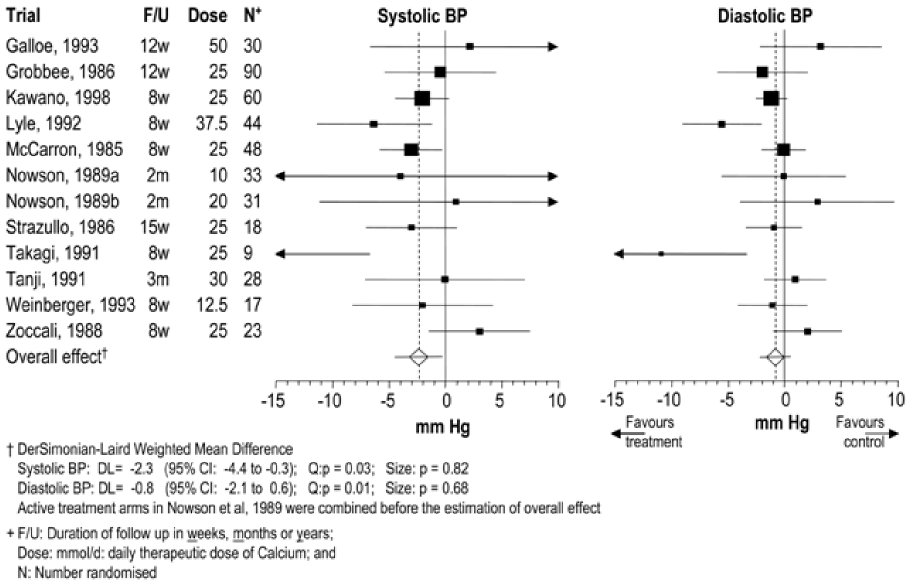
The recent Canadian guideline[220], citing a previous systematic review, concluded that sodium restriction in adults over 44 years of age resulted in a reduction in blood pressure of 6.3/2.2 mmHg per 100 mmol/day reduction in sodium. Recommendations were made for clinicians to determine salt intake by 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.

9.1.9 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

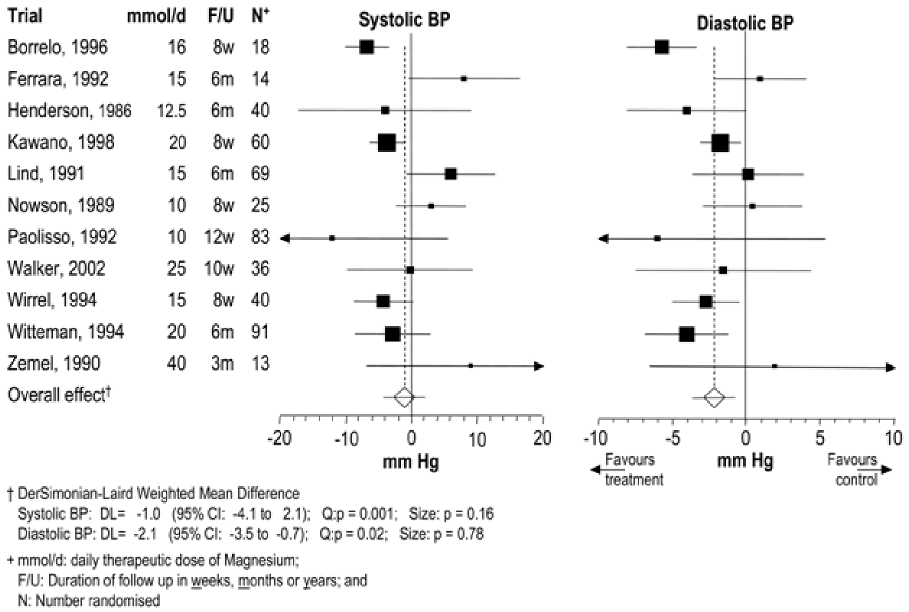


9.1.10 Magnesium supplements

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

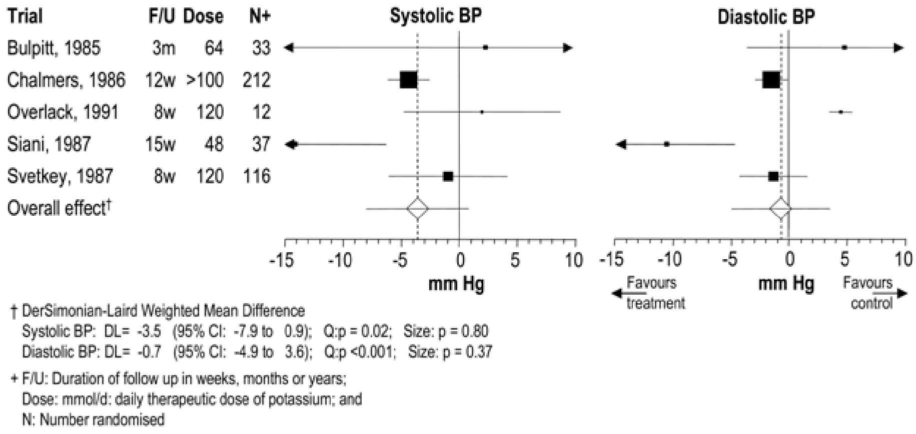


9.1.11 Potassium supplementation

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.

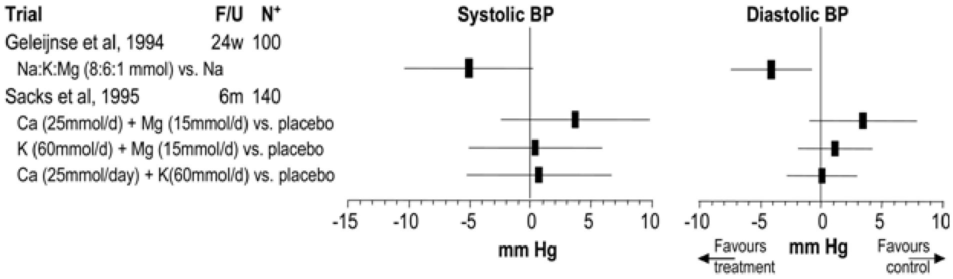
In contrast, our restriction to trials of at least 8 weeks duration, enrolling only hypertensive patients, resulted in inclusion of only 5 trials with a median duration of 12 weeks and found that the blood pressure lowering effect of oral potassium supplementation was not statistically significant. The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

9.1.12 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



+F/U: Duration of follow up in weeks, months or years; and N: Number randomised
Calcium (Ca), Magnesium (Mg), Potassium (K) and Sodium (Na) salts
Sodium is common table salt. Na:K:Mg is a reduced sodium mineral salt

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.

9.1.13 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].

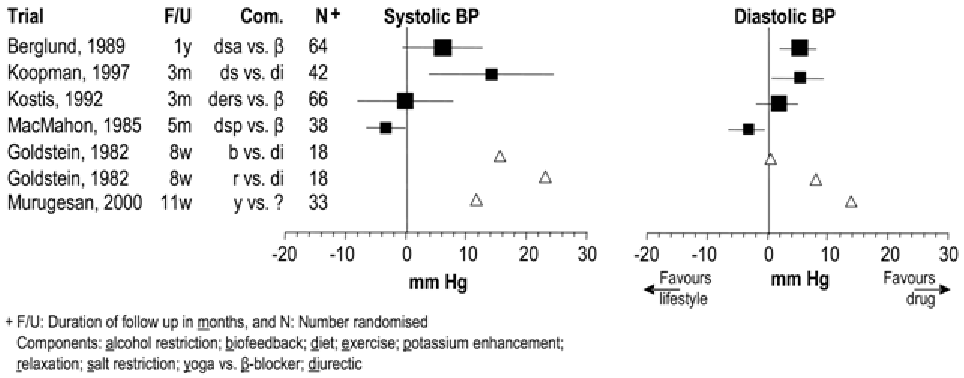
The populations studied in the trials differed in: (i) age – participants in one trial[333] were older, which probably accounted for their higher baseline blood pressure compared to participants in the other trials; (ii) treatment status at the point of recruitment – participants were currently untreated 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.

9.1.14 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).

9.1.15 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136.

10 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.

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, 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
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

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)				
				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 used to treat hypertension	Reported side-effects include initial headaches, palpitations, facial flushing and ankle swelling.
	'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

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)				
				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, headache, flushing, nasal congestion, fluid retention, ankle swelling and tachycardia.

10.1 *2004 guidance: pharmacological interventions*

10.1.1 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%)

	Thiazides (High Dose)	Thiazides (Low Dose)	Beta Blockers	Ca Channel Blockers	ACEi	Angiotensin Receptor Blockers
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).

10.1.1.1 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

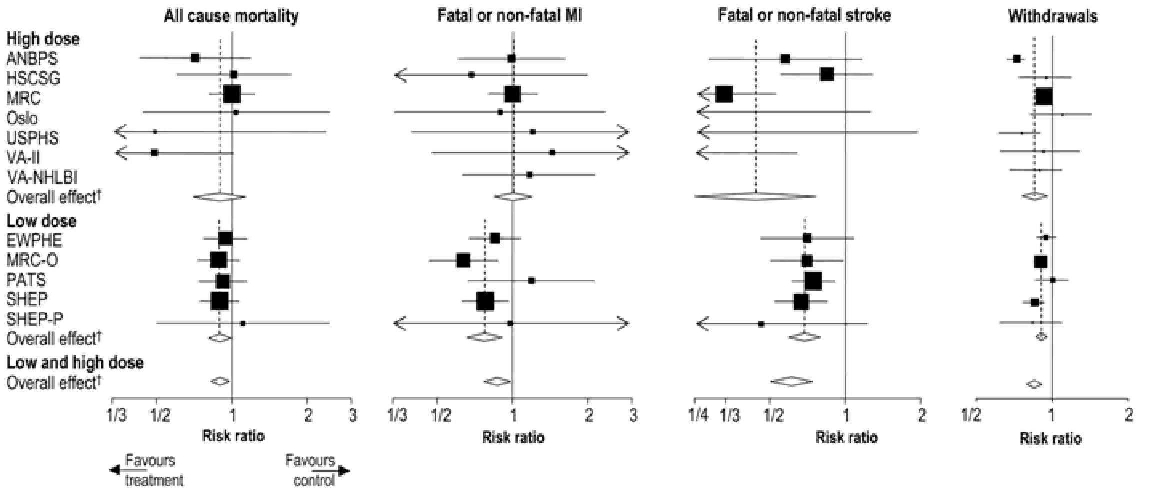
All trials featured co-treatment or stepped care except PATS: see the trial table for details.

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.

10.1.1.2 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.

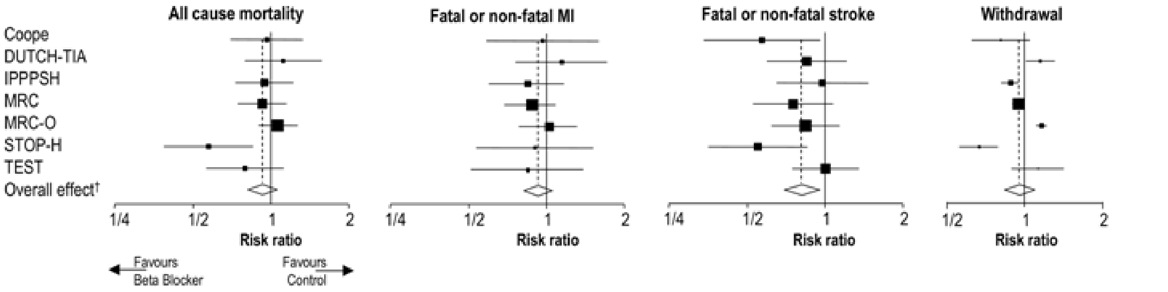
Table 52: Description of individual placebo controlled trials of beta-blockers

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.

10.1.1.3 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.

10.1.1.4 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.

10.1.1.5 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].

10.1.1.6 Alpha blockers

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

10.2 *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.

10.2.1 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	I

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.	
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. 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).	II
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 significant higher incidence of	I

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).	
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 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.	II
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	I

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.	
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

10.2.2 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				
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

Comparison	Studies	Total n	Effect size RR [95% CI]	I2 (%)
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

10.3 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.

10.3.1 Angiotensin-converting enzyme inhibitors (ACEi) versus Angiotensin Receptor Blockers (ARB)

Forest plots found in Appendix H: Forest plots.

10.3.1.1 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.

Update 2011

- 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.

10.3.1.2 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.
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).

Update 2011

Table 57: Evidence profile comparing ACEi versus ARBs

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	ACEi	Relative (95% CI)	Absolute	
Mortality (all cause) (follow-up 12 - median 56 months)											
2 CORDIB[552] 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[552] 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[552] 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[552] 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

10.3.1.3 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.

10.3.1.4 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.

Update 2011

10.3.1.5 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]).

10.3.2 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?

10.3.2.1 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 (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.

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 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

Study	N	Intervention	Comparison	Follow-up	Results
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
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

Study	N	Intervention	Comparison	Follow-up	Results
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] VHAS[514,658] SHEP-P[484,485] VA-NHLBI[3]	 12.5 – 25mg/day 12.5 – 25mg/day 12.5-25 mg/day 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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Bendroflumethiazide versus placebo	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	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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide versus placebo	control	Relative (95% CI)	Absolute	
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%)	HR 0.85 (0.74 to 0.99)	12 fewer per 1000 (from 1 fewer to 21 fewer)	MODERATE
								8.90%		13 fewer per 1000 (from 1 fewer to 22 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		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorthalidone versus ACEi	control	Relative (95% CI)	Absolute	Quality
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%)	HR 1.00 (0.94 to 1.07)	2 more per 1000 (from 6 fewer to 9 more)	MODERATE
								10.70%		2 more per 1000 (from 5 fewer to 8 more)	
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%)	HR 0.97 (0.91 to 1.03)	40 more per 1000 (from 6 more to 81 more)	MODERATE
								9.50%		29 more per 1000 (from 5 more to 60 more)	
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%)	HR 0.88 (0.79 to 0.98)	4 fewer per 1000 (from 1 fewer to 8 fewer)	LOW
								4.40%		5 fewer per 1000 (from 1 fewer to 9 fewer)	
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%)	HR 0.91 (0.86 to 0.96)	11 fewer per 1000 (from 5 fewer to 17 fewer)	LOW
								20.80%		17 fewer per 1000 (from 7 fewer to 26 fewer)	

Table 65: **Hydrochlorthiazide versus calcium channel blockers**

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HCTZ versus CCB	control	Relative (95% CI)	Absolute	
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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HCTZ versus ACEi	control	Relative (95% CI)	Absolute	
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)

Update 2011

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.

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 (2.5mg/day)	BDZ (5 mg/day)	22 weeks	Equivalent fall in BP in both groups

Study	N	Intervention	Control	Follow-up	Results
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] Kreeft, 1984[339] Plante, 1988[493] Plante, 1983[494] Rakić, 2002[503]	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 5mg/day 2.5mg/day 2.5mg/day 2.5mg/day 2.5mg/day

TD name	Number of trials	Doses used
	Spence, 2000[551]	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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorthalidone	HCTZ	Relative (95% CI)	Absolute	
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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide versus Chlorthalidone	control	Relative (95% CI)	Absolute	
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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indapamide versus HCTZ	control	Relative (95% CI)	Absolute	
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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	HCTZ	BDZ	Relative (95% CI)	Absolute	
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

10.3.2.2 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.

10.3.2.3 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.

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

Update 2011

Update 2011

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

10.3.2.4 Evidence statements – Health economic

- 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[d]) cost £19.81 per year; indapamide (2.5mg non-proprietary) cost £16.03 per year.

Update 2011

10.4 *Cost-effectiveness analysis*

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'.

Update 2011

10.4.1 Methodological introduction

10.4.1.1 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.

10.4.1.2 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.

10.4.1.3 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)
- 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).

---

d Note that 25mg was considered the optimal dose but only 50mg tablets were listed in the BNF.

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.

10.4.1.4 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.

10.4.1.5 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.

10.4.2 Results of the health economic model

10.4.2.1 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).

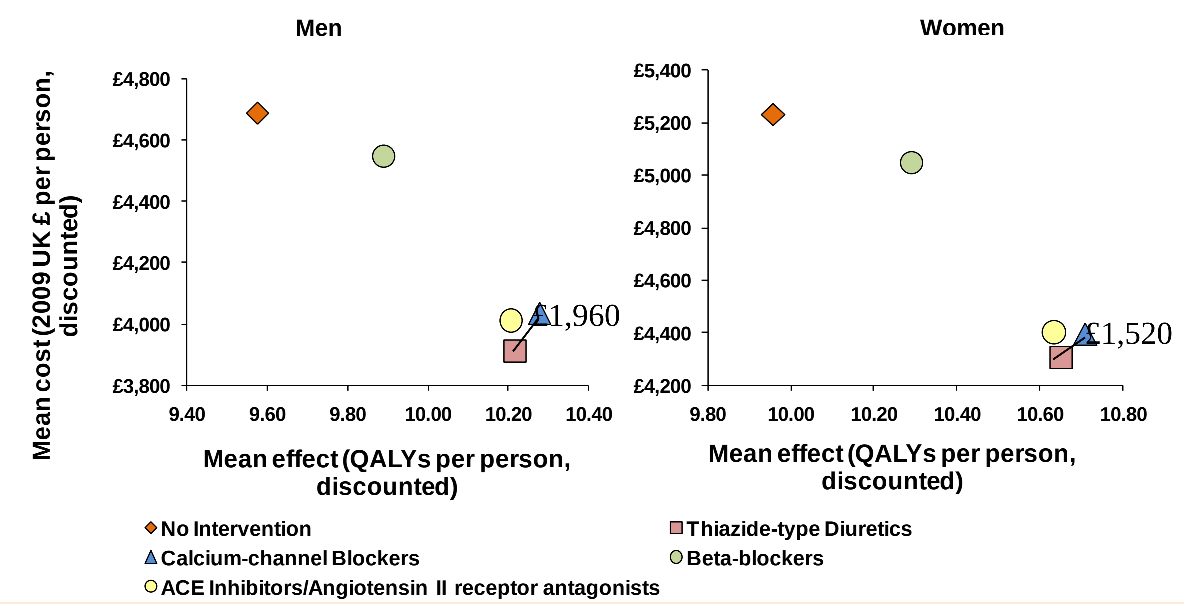
Table 10.77: Base case results (65-year-old, 2% risk, 1.1% diabetes risk, 1% HF risk)

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	-

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.

Update 2011

Figure 18: Base case results (65-year-old, 2% cardiovascular risk, 1.1% diabetes risk, 1% HF risk)



QALYs = quality-adjusted life years

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)'.

10.4.3 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.

The considerations that were highlighted in the 2006 guideline are still relevant and are described below.

Update 2011

Update 2011

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.

10.5 *Step two therapy*

This section has been updated and replaced. See the NICE website for the updated guideline recommendations and evidence review.

10.5.1.1 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

10.5.2.1 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].

10.5.2.2 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]

10.5.2.3 Evidence statements – health economic

- No relevant cost-effectiveness evidence was identified.

Update 2011

10.6 Resistant hypertension

This section has been updated and replaced. See the NICE website for the updated guideline recommendations and evidence review.

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.

10.6.1.1 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.

Update 2011

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.

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

10.6.1.2 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.

10.6.1.3 Evidence statements – clinical

Six studies found that blood pressure was reduced in people with resistant hypertension who were treated with 4th-line spironolactone.

Update 2011

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

10.6.1.4 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.

10.7 Special groups for consideration

This section has been updated and replaced. See the NICE website for the updated guideline recommendations and evidence review.

10.7.1 People aged over 80 years

See section 8 on page 106.

10.7.2 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].	

10.7.3 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]

10.7.3.1 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.

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

Update 2011

Update 2011

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.

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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi	other a-HT classes (TD, CCB or alpha)	Relative (95% CI)	Absolute	
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		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACEi	CCB	Relative (95% CI)	Absolute	
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)

10.7.3.2 Economic evidence

No relevant economic studies were identified.

10.7.3.3 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.

10.7.4 Chronic kidney disease

For guidance pertaining to people with hypertension and chronic kidney disease refer to NICE Clinical Guideline 73.

10.7.5 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.

Update 2011

10.7.6 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.

10.8 *Stopping treatment*

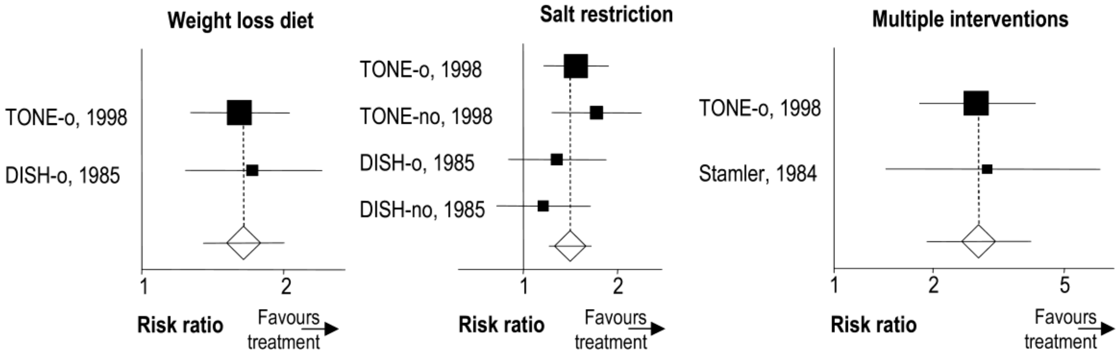
If a patient's blood pressure has been reduced to normal levels by antihypertensive drugs, both patient and doctor may want to know if medication can safely be stopped. Unnecessary drug treatment may put the patient at risk of adverse side effects and is a cost to society. Some patients may be at risk 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.

10.9 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

Update 2011

their treatment prior to randomisation to the study drugs. The GDG debated whether ACEi and ARBs could be considered equivalent, based on data 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?

Update 2011

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.

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.

Update 2011

Update 2011

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.

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.

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).

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.

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

Update 2011

electrolytes and renal function is essential. The GDG recognised the need of more research in this area.

Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136

Research recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng136

11 Patients' perspectives

This section has been updated and replaced. See the NICE website for the updated guideline recommendations and evidence review.

11.1 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.

11.2 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.

11.3 *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.

11.4 *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.

11.5 Education and adherence

11.5.1 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.

11.5.2 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].

11.5.3 Recommendations

12 Reference list

1 Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA.* 1970; 213(7):1143-1152.
2 Effect of antihypertensive treatment on stroke recurrence. Hypertension-Stroke Cooperative Study Group. *JAMA.* 1974; 229(4):409-418.
3 Evaluation of drug treatment in mild hypertension: VA-NHLBI feasibility trial. Plan and preliminary results of a two-year feasibility trial for a multicenter intervention study to evaluate the benefits versus the disadvantages of treating mild hypertension. Prepared for the Veterans Administration-National Heart, Lung, and Blood Institute Study Group for

Evaluating Treatment in Mild Hypertension. *Annals of the New York Academy of Sciences.* 1978; 304:267-292.
4 The Australian therapeutic trial in mild hypertension. Report by the Management Committee. *Lancet.* 1980; 1(8181):1261-1267.
5 Hydrochlorothiazide and bendroflumethiazide in low doses--a comparative trial. *Acta Pharmacologica Et Toxicologica.* 1984; 54 Suppl 1:47-51.
6 An international trial of antihypertensive therapy in elderly patients. Objectives, protocol and organization. European Working Party on High Blood Pressure in the Elderly (EWPHE). *Archives Internationales De Pharmacodynamie Et De Therapie.* 1985; 275(2):300-334.
7 Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH). The IPPPSH Collaborative Group. *Journal of Hypertension.* 1985; 3(4):379-392.
8 MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. *BMJ.* 1985; 291(6488):97-104.
9 Course of blood pressure in mild hypertensives after withdrawal of long term antihypertensive treatment. Medical Research Council Working Party on Mild Hypertension. *BMJ.* 1986; 293(6553):988-992.
10 Effects of replacing sodium intake in subjects on a low sodium diet: a crossover study. Australian National Health & Medical Research Council Dietary Salt Study Management Committee. *Clinical and Experimental Hypertension Part A: Theory and Practice.* 1989; 11(5-6):1011-1024.
11 Fall in blood pressure with modest reduction in dietary salt intake in mild hypertension. Australian National Health and Medical Research Council Dietary Salt Study Management Committee. *Lancet.* 1989; 1(8635):399-402.
12 Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *New England Journal of Medicine.* 1991; 325(5):293-302.
13 Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA.* 1991; 265(24):3255-3264.
14 *Acute Pain Management: Operative or Medical Procedures and Trauma*. Rockville, MD: Agency for Health Care Policy and Research Publications; 1992
15 Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ.* 1992; 304(6824):405-412.
16 Systolic hypertension in the elderly: Chinese trial (syst-China). Interim report. *Zhonghua Xin Xue Guan Bing Za Zhi.* 1992; 20(5):270-5, 323.
17 Systolic hypertension in the elderly: Chinese trial (Syst-China)--second interim report. *Zhonghua Xin Xue Guan Bing Za Zhi.* 1993; 21(3):135-7, 185.
18 The Oslo Diet and Exercise Study (ODES): design and objectives. *Controlled Clinical Trials.* 1993; 14(3):229-243.
19 Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. The Dutch TIA Trial Study Group. *Stroke.* 1993; 24(4):543-548.
20 Post-stroke antihypertensive treatment study. A preliminary result. PATS Collaborating Group. *Chinese Medical Journal.* 1995; 108(9):710-717.
21 *BS EN 1060-1: 1996 Specification for Non-Invasive Sphygmomanometers. General Requirements.* 15-6-1996.
22 *Clinical and Experimental Pheochromocytoma*. Cambridge, MA.: Blackwell; 1996

23 Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on coronary prevention. *European Heart Journal.* 1998; 19(10):1434-1503.
24 *Health Survey for England: Cardiovascular Disease*. The Stationary Office; 1999
25 Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet.* 2000; 355(9200):253-259.
26 *British National Formulary, Issue 44, March 2003*. BMJ Books and Pharmaceutical Press; 2001
27 Mulrow CD (editors). *Evidence Based Hypertension*. London: BMJ; 2001
28 Craig R, Mindell J (editors). *Health Survey for England 2006. Volume 1: Cardiovascular Disease and Risk Factors in Adults.* Leeds: The Information Centre; 2008. Available from: http://www.ic.nhs.uk/webfiles/publications/HSE06/HSE%2006%20report%20VOL%201%20v2.pdf
29 Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertension Research.* 2008; 31(12):2115-2127.
30 *NHS Supply Chain catalogue*. Available from: http://www.supplychain.nhs.uk/portal/page/portal/Public/NHS-CAT Last accessed on: 17 February 2010.
31 Achmon J, Granek M, Golomb M, Hart J. Behavioral treatment of essential hypertension: a comparison between cognitive therapy and biofeedback of heart rate. *Psychosomatic Medicine.* 1989; 51(2):152-164.
32 Adsett CA, Bellissimo A, Mitchell A, Wilczynski N, Haynes RB. Behavioral and physiological effects of a beta blocker and relaxation therapy on mild hypertensives. *Psychosomatic Medicine.* 1989; 51(5):523-536.
33 Agras WS, Southam MA, Taylor CB. Long-term persistence of relaxation-induced blood pressure lowering during the working day. *Journal of Consulting and Clinical Psychology.* 1983; 51(5):792-794.
34 Agras WS, Taylor CB, Kraemer HC, Southam MA, Schneider JA. Relaxation training for essential hypertension at the worksite: II. The poorly controlled hypertensive. *Psychosomatic Medicine.* 1987; 49(3):264-273.
35 Aitchison F, Page A. Diagnostic imaging of renal artery stenosis. *Journal of Human Hypertension.* 1999; 13(9):595-603.
36 Aivazyan TA, Zaitsev VP, Salenko BB, Yurenev AP, Patrusheva IF. Efficacy of relaxation techniques in hypertensive patients. *Health Psychology.* 1988; 7 Suppl:193-200.
37 Alam S, Johnson AG. A meta-analysis of randomised controlled trials (RCT) among healthy normotensive and essential hypertensive elderly patients to determine the effect of high salt (NaCl) diet of blood pressure. *Journal of Human Hypertension.* 1999; 13(6):367-374.
38 Alderman MH, Davis TK, Gerber LM, Robb M. Antihypertensive drug therapy withdrawal in a general population. *Archives of Internal Medicine.* 1986; 146(7):1309-1311.
39 Alem M, Milia P, Muir S, Lees K, Walters M. Comparison of the effects of diuretics on blood pressure and arterial stiffness in patients with stroke. *Journal of Stroke and Cerebrovascular Diseases.* 2008; 17(6):373-377.
40 American Heart Association. *2000 Heart and Stroke Statistical Update.* American Heart Association, 1999.
41 American National Standard for Electronic or Automated Sphymomanometers. *ANSI/AAMI SP10 1987.* Arlington, VA: Association for the Advancement of Medical Instrumentation, 1983.

42 Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, De SA, Dollery C, Fagard R, Forette F, . Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. *Lancet.* 1985; 1(8442):1349-1354.
43 Amery A, Birkenhager W, Bulpitt CJ, Clement D, De Leeuw P, Dollery CT. Syst-Eur: a multicenter trial on the treatment of isolated systolic hypertension in the elderly objectives, protocol, and organisation. *Ageing.* 1991; 3:287-302.
44 Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *American Heart Journal.* 1991; 121(1 Pt 2):293-298.
45 Anderssen S, Holme I, Urdal P, Hjermann I. Diet and exercise intervention have favourable effects on blood pressure in mild hypertensives: the Oslo Diet and Exercise Study (ODES). *Blood Pressure.* 1995; 4(6):343-349.
46 Antivalle M, Lattuada S, Salvaggio A, Paravicini M, Rindi M, Libretti A. Placebo effect and adaptation to noninvasive monitoring of BP. *Journal of Human Hypertension.* 1990; 4(6):633-637.
47 Applegate WB, Miller ST, Elam JT, Cushman WC, el Derwi D., Brewer A, Graney MJ. Nonpharmacologic intervention to reduce blood pressure in older patients with mild hypertension. *Archives of Internal Medicine.* 1992; 152(6):1162-1166.
48 Ara, R and Brennan, A. *Economic Evaluation of Sibutramine for the Treatment of Obesity in Adults Without Other Co-Morbidities in the UK.* School of Health and Related Research (ScHARR), University of Sheffield, 2004.
49 Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S, Macmahon S, Neal B. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: The PROGRESS trial. *Journal of Hypertension.* 2006; 24(6):1201-1208.
50 Arima H, Tanizaki Y, Yonemoto K, Doi Y, Ninomiya T, Hata J, Fukuhara M, Matsumura K, Iida M, Kiyohara Y. Impact of blood pressure levels on different types of stroke: the Hisayama study. *Journal of Hypertension.* 2009; 27(12):2437-2443.
51 Armitage P, Berry G, Matthews JNS.*Statistical Methods in Medical Research*. 4th ed. Oxford: Blackwell Science; 2002
52 Asagami T, Kushiro T, Inoue J, Kanmatsuse K. Long-term reproducibility and usefulness of daytime recording of noninvasive 24-hour ambulatory blood pressure monitoring in borderline hypertension: a two-year follow-up study. *Clinical and Experimental Hypertension (New York).* 1996; 18(5):637-657.
53 Asayama K, Ohkubo T, Kikuya M, Obara T, Metoki H, Inoue R, Hara A, Hirose T, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Prediction of stroke by home "morning" versus "evening" blood pressure values: the Ohasama study. *Hypertension.* 2006; 48(4):737-743.
54 Asayama K, Ohkubo T, Yoshida S, Suzuki K, Metoki H, Harada A, Murakami Y, Ohashi Y, Ueshima H, Imai Y, Japan Arteriosclerosis Longitudinal Study (JALS) group. Stroke risk and antihypertensive drug treatment in the general population: the Japan arteriosclerosis longitudinal study. *Journal of Hypertension.* 2009; 27(2):357-364.
55 ASCOT Steering Committee. Age-Stratified Analysis of Blood Pressure Responses. Personal communication: 06
56 Asmar R, Safar M, Queneau P. Evaluation of the placebo effect and reproducibility of blood pressure measurement in hypertension. *American Journal of Hypertension.* 2001; 14(6 I):546-552.
57 Assmann G, Cullen P, Evers T, Petzinna D, Schulte H. Importance of arterial pulse pressure as a predictor of coronary heart disease risk in PROCAM. *European Heart Journal.* 2005; 26(20):2120-2126.
58 Ayman D, Goldshine AD. Blood pressure determination by patients with essential hypertension: the difference between clinic and home readings before treatment. *American Journal of the Medical Sciences.* 1940; 200(4):465-474.

59 Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, Vessey M, Fowler G, Molyneux A, Hughes T. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. *Journal of Neurology, Neurosurgery & Psychiatry.* 1988; 51(11):1373-1380.
60 Barengo NC, Hu G, Kastarinen M, Antikainen R, Tuomilehto J. The effects of awareness, treatment and control of hypertension on future stroke incidence in a community-based population study in Finland. *Journal of Hypertension.* 2009; 27(7):1459-1465.
61 Barengo NC, Kastarinen M, Antikainen R, Nissinen A, Tuomilehto J. The effects of awareness, treatment and control of hypertension on cardiovascular and all-cause mortality in a community-based population. *Journal of Human Hypertension.* 2009; 23(12):808-816.
62 Bayo J, Cos FX, Roca C, Dalfo A, Martin-Baranera MM, Albert B. Home blood pressure self-monitoring: Diagnostic performance in white-coat hypertension. *Blood Pressure Monitoring.* 2006; 11(2):47-52.
63 Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine.* 2008; 358(18):1887-1898.
64 Beevers G, Lip G, O'Brien E. ABC of hypertension: Blood pressure measurement. Part II. *BMJ.* 2001; 322(7293):1043-1047.
65 Beevers G, Lip GY, O'Brien E. ABC of hypertension. Blood pressure measurement. Part I-sphygmomanometry: factors common to all techniques. *BMJ.* 2001; 322(7292):981-985.
66 Beevers G, Lip GY, O'Brien E. ABC of hypertension: The pathophysiology of hypertension. *BMJ.* 2001; 322(7291):912-916.
67 Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, Staessen JA, Gueyffier F. Treatment of hypertension in patients 80 years and older: The lower the better? A meta-analysis of randomized controlled trials. *Journal of Hypertension.* 2010; 28(7):1366-1372.
68 Benetos A, Thomas F, Bean KE, Guize L. Why cardiovascular mortality is higher in treated hypertensives versus subjects of the same age, in the general population. *Journal of Hypertension.* 2003; 21(9):1635-1640.
69 Bennett P, Wallace L, Carroll D, Smith N. Treating Type A behaviours and mild hypertension in middle-aged men. *Journal of Psychosomatic Research.* 1991; 35(2-3):209-223.
70 Benson J, Britten N. Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. *BMJ.* 2002; 325(7369):873.
71 Benson J, Britten N. Patients' views about taking antihypertensive drugs: questionnaire study. *BMJ.* 2003; 326(7402):1314-1315.
72 Berglund A, Andersson OK, Berglund G, Fagerberg B. Antihypertensive effect of diet compared with drug treatment in obese men with mild hypertension. *BMJ.* 1989; 299(6697):480-485.
73 Bhatnagar D, Anand IS, Durrington PN, Patel DJ, Wander GS, Mackness MI, Creed F, Tomenson B, Chandrashekhar Y, Winterbotham M, others. Coronary risk factors in people from the Indian subcontinent living in west London and their siblings in India. *Lancet.* 1995; 345(8947):405-409.
74 Bhopal R, Unwin N, White M, Yallop J, Walker L, Alberti KG, Harland J, Patel S, Ahmad N, Turner C, Watson B, Kaur D, Kulkarni A, Laker M, Tavridou A. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. *BMJ.* 1999; 319(7204):215-220.

75 Bing RF, Briggs RS, Burden AC, Russell GI, Swales JD, Thurston H. Reversible hypertension and hypothyroidism. *Clinical Endocrinology.* 1980; 13(4):339-342.
76 Bing RF, Russell GI, Swales JD, Thurston H. Indapamide and bendrofluazide: A comparison in the management of essential hypertension. *British Journal of Clinical Pharmacology.* 1981; 12(6):883-886.
77 Bjorklund K, Lind L, Zethelius B, Berglund L, Lithell H. Prognostic significance of 24-h ambulatory blood pressure characteristics for cardiovascular morbidity in a population of elderly men. *Journal of Hypertension.* 2004; 22(9):1691-1697.
78 Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm RH, Jr., Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, Williams G, Wittes J, Zanchetti A, Anders RJ, CONVINCE Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA.* 2003; 289(16):2073-2082.
79 Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH, Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, White WB, Williams G, Wittes J, Zanchetti A, Fakouhi TD. Rationale and design for the controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Trial. *Controlled Clinical Trials.* 1998; 19:370-390.
80 Blanchard EB, Miller ST, Abel GG, Haynes MR, Wicker R. Evaluation of biofeedback in the treatment of borderline essential hypertension. *Journal of Applied Behavior Analysis.* 1979; 12(1):99-109.
81 Bland JM, Jones DR, Bennett S, Haines AP, MacFarlane AJ. Is the clinical trial evidence about new drugs statistically adequate? *British Journal of Clinical Pharmacology.* 1985; 19:155-160.
82 Blood Pressure Lowering Treatment Trialists' Collaboration, Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, Bulpitt C, Chalmers J, Fagard R, Gleason A, Heritier S, Li N, Perkovic V, Woodward M, Macmahon S. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ.* 2008; 336(7653):1121-1123.
83 Bloom BS. Daily regimen and compliance with treatment. *BMJ.* 2001; 323(7314):647.
84 Blumenthal JA, Sherwood A, Gullette EC, Babyak M, Waugh R, Georgiades A, Craighead LW, Tweedy D, Feinglos M, Appelbaum M, Hayano J, Hinderliter A. Exercise and weight loss reduce blood pressure in men and women with mild hypertension: effects on cardiovascular, metabolic, and hemodynamic functioning. *Archives of Internal Medicine.* 2000; 160(13):1947-1958.
85 Blumenthal JA, Siegel WC, Appelbaum M. Failure of exercise to reduce blood pressure in patients with mild hypertension. Results of a randomized controlled trial. *JAMA.* 1991; 266(15):2098-2104.
86 Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, Menard J, Mallion JM. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA.* 2004; 291(11):1342-1349.
87 Bobrie G, Genes N, Vaur L, Clerson P, Vaisse B, Mallion JM, Chatellier G. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? *Archives of Internal Medicine.* 2001; 161(18):2205-2211.
88 Boggia J, Li Y, Thijs L, Hansen TW, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Kuznetsova T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Wang J, Sandoya E, O'Brien E, Staessen JA, International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet.* 2007; 370(9594):1219-1229.
89 Borghi C, Dormi A, L'Italien G, Lapuerta P, Franklin SS, Collatina S, Gaddi A. The relationship between systolic blood pressure and cardiovascular risk--results of the Brisighella Heart Study. *Journal of Clinical Hypertension.* 2003; 5(1):47-52.

90 Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA, Kappagoda MD, Rocco MV, Schnaper HW, Sowers JR, Bond MG. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). *JAMA.* 1996; 276(10):785-791.
91 Borrello G, Mastroroberto P, Curcio F, Chello M, Zofrea S, Mazza ML. The effects of magnesium oxide on mild essential hypertension and quality of life. *Current Therapeutic Research.* 1996; 57(10):767-774.
92 Bosley F, Allen TW. Stress management training for hypertensives: cognitive and physiological effects. *Journal of Behavioral Medicine.* 1989; 12(1):77-89.
93 Bowlus WE, Langford HG. A comparison of the antihypertensive effect of chlorthalidone and hydrochlorthiazide. *Clinical Pharmacology and Therapeutics.* 1964; 5:708-711.
94 Brandao SA, Izar CO, Fischer SM, Santos AO, Monteiro CM, Povoa RM, Helfenstein T, Carvalho AC, Monteiro AM, Ramos E, Gidlund M, Figueiredo Neto AM, Fonseca FA. Early increase in autoantibodies against human oxidized low-density lipoprotein in hypertensive patients after blood pressure control. *American Journal of Hypertension.* 2010; 23(2):208-214.
95 Brauer AP, Horlick L, Nelson E, Farquhar JW, Agras WS. Relaxation therapy for essential hypertension: a Veterans Administration Outpatient study. *Journal of Behavioral Medicine.* 1979; 2(1):21-29.
96 Bray EP, Holder R, Mant J, McManus RJ. Does self-monitoring reduce blood pressure? Meta-analysis with meta-regression of randomized controlled trials. *Annals of Medicine.* 2010; 42(5):371-386.
97 Brenner BM, Cooper ME, de ZD, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *New England Journal of Medicine.* 2001; 345(12):861-869.
98 Brenner H, Gefeller O. Variation of sensitivity, specificity, likelihood ratios and predictive values with disease prevalence. *Stat Med.* 1997; 16(9):981-991.
99 British Hypertension Society.*Blood Pressure Measurement CD-ROM*. BMJ; 1999
100 British Hypertension Society. *Validated devices suitable for home use*. Available from: http://www.bhsoc.org/blood_pressure_list.stm Last accessed on: 11 November 2010.
101 Britton KA, Gaziano JM, Djousse L. Normal systolic blood pressure and risk of heart failure in US male physicians. *European Journal of Heart Failure.* 2009; 11(12):1129-1134.
102 Bronnum-Hansen H, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. *Stroke.* 2001; 32(9):2131-2136.
103 Bronnum-Hansen H, Jorgensen T, Davidsen M, Madsen M, Osler M, Gerdes LU, Schroll M. Survival and cause of death after myocardial infarction: the Danish MONICA study. *Journal of Clinical Epidemiology.* 2001; 54(12):1244-1250.
104 Brook RD. Home blood pressure: accuracy is independent of monitoring schedules. *American Journal of Hypertension.* 2000; 13(6 Pt 1):625-631.
105 Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet.* 2000; 356(5):366-372.
106 Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T. Principal results from the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *European Heart Journal.* 2001; 3(Suppl B):B20-B26.
107 Bulpitt CJ, Ferrier G, Lewis PJ, Daymond M, Bulpitt PF, Dollery CT. Potassium supplementation fails to lower blood pressure in hypertensive patients receiving a potassium losing diuretic. *Annals of Clinical Research.* 1985; 17(4):126-130.

108 Burgess E, Lewanczuk R, Bolli P, Chockalingam A, Cutler H, Taylor G, Hamet P. Lifestyle modifications to prevent and control hypertension. 6. Recommendations on potassium, magnesium and calcium. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *Canadian Medical Association Journal.* 1999; 160(9 Suppl):S35-S45.
109 Burke LE, Dunbar-Jacob JM, Hill MN. Compliance with cardiovascular disease prevention strategies: a review of the research. *Annals of Behavioral Medicine.* 1997; 19(3):239-263.
110 Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension.* 1995; 25(3):305-313.
111 Calvo C, Hermida RC, Ayala DE, Lopez JE, Fernandez JR, Dominguez MJ, Mojon A, Covelo M. The 'ABPM effect' gradually decreases but does not disappear in successive sessions of ambulatory monitoring. *Journal of Hypertension.* 2003; 21(12):2265-2273.
112 Campbell NC, Ritchie LD, Thain J, Deans HG, Rawles JM, Squair JL. Secondary prevention in coronary heart disease: a randomised trial of nurse led clinics in primary care. *Heart.* 1998; 80(5):447-452.
113 Campbell NR, Burgess E, Choi BC, Taylor G, Wilson E, Cleroux J, Fodor JG, Leiter LA, Spence D. Lifestyle modifications to prevent and control hypertension. 1. Methods and an overview of the Canadian recommendations. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *Canadian Medical Association Journal.* 1999; 160(9 Suppl):S1-S6.
114 Campbell P, Ghuman N, Wakefield D, Wolfson L, White WB. Long-term reproducibility of ambulatory blood pressure is superior to office blood pressure in the very elderly. *Journal of Human Hypertension.* 2010; 24(11):749-754.
115 Canino E, Cardona R, Monsalve P, Perez AF, Lopez B, Fragachan F. A behavioral treatment program as a therapy in the control of primary hypertension. *Acta Cientifica Venezolana.* 1994; 45(1):23-30.
116 Cappuccio FP, Cook DG, Atkinson RW, Strazzullo P. Prevalence, detection, and management of cardiovascular risk factors in different ethnic groups in south London. *Heart.* 1997; 78(6):555-563.
117 Cappuccio FP, MacGregor GA. Does potassium supplementation lower blood pressure? A meta-analysis of published trials. *Journal of Hypertension.* 1991; 9(5):465-473.
118 Cappuccio FP, Siani A, Strazzullo P. Oral calcium supplementation and blood pressure: an overview of randomized controlled trials. *Journal of Hypertension.* 1989; 7(12):941-946.
119 Carlsson AC, Theobald H, Hellénius M, Wändell PE. Cardiovascular and total mortality in men and women with different blood pressure levels -A 26year followup. *Blood Pressure.* 2009; 18(3):105-110.
120 Carson MA, Hathaway A, Tuohey JP, McKay BM. The effect of a relaxation technique on coronary risk factors. *Behavioral Medicine.* 1988; 14(2):71-77.
121 Cavallini MC, Roman MJ, Blank SG, Pini R, Pickering TG, Devereux RB. Association of the auscultatory gap with vascular disease in hypertensive patients. *Annals of Internal Medicine.* 1996; 124(10):877-883.
122 Celentano A, Galderisi M, Tammaro P, Mureddu GF, Garofalo M, de Divitiis O. Effects on casual and 24-h ambulatory blood pressure of slow-release nicardipine and chlorthalidone in arterial essential hypertension: double-blind, crossover study. *International Journal of Clinical Pharmacology, Therapy, and Toxicology.* 1990; 28(5):190-196.

123 Celis H, De CP, Fagard R, Thijs L, Staessen JA. For how many days should blood pressure be measured at home in older patients before steady levels are obtained? *Journal of Human Hypertension.* 1997; 11(10):673-677.
124 Celis H, Yodfat Y, Thijs L, Clement D, Cozic J, de Cort P, Forette F, Grégoire M, Heyrman J, Stibbe G, van den Haute M, Staessen J, Fagard R, The Syst-Eur Investigators. Antihypertensive therapy in older patients with isolated systolic hypertension: the Syst-Eur experience in general practice. *Family Practice.* 1996; 13(2):138-143.
125 Chalmers J, Morgan T, Doyle A, Dickson B, Hopper J, Mathews J, Matthews G, Moulds R, Myers J, Nowson C, others. Australian National Health and Medical Research Council dietary salt study in mild hypertension. *Journal of Hypertension - Supplement.* 1986; 4(6):S629-S637.
126 Chapman N, Dobson J, Wilson S, Dahlof B, Sever PS, Wedel H, Poulter NR, Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension.* 2007; 49(4):839-845.
127 Chaturvedi N, McKeigue PM, Marmot MG. Resting and ambulatory blood pressure differences in Afro-Caribbeans and Europeans. *Hypertension.* 1993; 22(1):90-96.
128 Chesney MA, Black GW, Swan GE, Ward MM. Relaxation training for essential hypertension at the worksite: I. The untreated mild hypertensive. *Psychosomatic Medicine.* 1987; 49(3):250-263.
129 Chien KL, Huang PJ, Chen MF, Chiang FT, Lai LP, Lee YT. Assessment of quality of life in a double-blind, randomized clinical trial of imidapril and captopril for hypertensive Chinese in Taiwan. *Cardiovascular Drugs and Therapy.* 2002; 16(3):221-226.
130 Chou T. Wake up and smell the coffee. Caffeine, coffee, and the medical consequences. *Western Journal of Medicine.* 1992; 157(5):544-553.
131 Clement DL, De Buyzere ML, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E, Office versus Ambulatory Pressure Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *New England Journal of Medicine.* 2003; 348(24):2407-2415.
132 Cleroux J, Feldman RD, Petrella RJ. Lifestyle modifications to prevent and control hypertension. 4. Recommendations on physical exercise training. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *Canadian Medical Association Journal.* 1999; 160(9 Suppl):S21-S28.
133 Coats AJS, Radaelli A, Clark SJ, Conway J, Sleight P. The influence of ambulatory blood pressure monitoring on the design and interpretation of trials in hypertension. *Journal of Hypertension.* 1992; 10(4):385-391.
134 Coca A, Messerli FH, Benetos A, Zhou Q, Champion A, Cooper-DeHoff RM, Pepine CJ. Predicting stroke risk in hypertensive patients with coronary artery disease: a report from the INVEST. *Stroke.* 2008; 39(2):343-348.
135 Collins R, Peto R, Macmahon S, Hebert P, Fiebach NH, Eberlein KA, Godwin J, Qizilbash N, Taylor JO, Hennekens CH. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet.* 1990; 335(8693):827-838.
136 Conen D, Ridker PM, Buring JE, Glynn RJ. Risk of cardiovascular events among women with high normal blood pressure or blood pressure progression: prospective cohort study. *BMJ.* 2007; 335(7617):432.
137 Conen D, Tschudi P, Martina B. Twenty-four hour ambulatory blood pressure for the management of antihypertensive treatment: a randomized controlled trial. *Journal of Human Hypertension.* 2009; 23(2):122-129.

138 Conlin PR, Chow D, Miller ER, III, Svetkey LP, Lin PH, Harsha DW, Moore TJ, Sacks FM, Appel LJ. The effect of dietary patterns on blood pressure control in hypertensive patients: results from the Dietary Approaches to Stop Hypertension (DASH) trial. *American Journal of Hypertension.* 2000; 13(9):949-955.
139 Cook TD, Campbell DT.*Quasi-Experimentation: Design and Analysis Issues for Field Settings*. Chicago: Rand McNally; 1979
140 Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *BMJ.* 1986; 293(6555):1145-1151.
141 Costa FV, Ambrosioni E, Montebugnoli L, Paccaloni L, Vasconi L, Magnani B. Effects of a low-salt diet and of acute salt loading on blood pressure and intralymphocytic sodium concentration in young subjects with borderline hypertension. *Clinical Science.* 1981; 61 Suppl 7:21s-23s.
142 Cottier C, Shapiro K, Julius S. Treatment of mild hypertension with progressive muscle relaxation. Predictive value of indexes of sympathetic tone. *Archives of Internal Medicine.* 1984; 144(10):1954-1958.
143 Cramer JA. Consequences of intermittent treatment for hypertension: the case for medication compliance and persistence. *American Journal of Managed Care.* 1998; 4(11):1563-1568.
144 Croft PR, Brigg D, Smith S, Harrison CB, Branthwaite A, Collins MF. How useful is weight reduction in the management of hypertension? *Journal of the Royal College of General Practitioners.* 1986; 36(291):445-448.
145 Cruickshank JK, Beevers DG, Osbourne VL, Haynes RA, Corlett JC, Selby S. Heart attack, stroke, diabetes, and hypertension in West Indians, Asians, and whites in Birmingham, England. *BMJ.* 1980; 281(6248):1108.
146 Cupples ME, McKnight A. Randomised controlled trial of health promotion in general practice for patients at high cardiovascular risk. *BMJ.* 1994; 309(6960):993-996.
147 Curtin F, Altman DG, Elbourne D. Meta-analysis combining parallel and cross-over clinical trials. *Statistics in Medicine.* 2002; 21(15):2131-2144.
148 Cushman WC, Cutler JA, Hanna E, Bingham SF, Follmann D, Harford T, Dubbert P, Allender PS, Dufour M, Collins JF, Walsh SM, Kirk GF, Burg M, Felicetta JV, Hamilton BP, Katz LA, Perry HM, Jr., Willenbring ML, Lakshman R, Hamburger RJ. Prevention and Treatment of Hypertension Study (PATHS): effects of an alcohol treatment program on blood pressure. *Archives of Internal Medicine.* 1998; 158(11):1197-1207.
149 Cushman WC, Langford HG. Randomised controlled trial of potassium chloride versus placebo in mildly hypertensive blacks and whites. *Circulation.* 1988; 78:Suppl II-370.
150 Cuspidi C, Macca G, Michev I, Salerno M, Fusi V, Severgnini B, Corti C, Meani S, Valerio C, Magrini F, Zanchetti A. Short-term reproducibility of nocturnal non-dipping pattern in recently diagnosed essential hypertensives. *Blood Pressure.* 2002; 11(2):79-83.
151 Cuspidi C, Meani S, Sala C, Valerio C, Fusi V, Zanchetti A, Mancia G. How reliable is isolated clinical hypertension defined by a single 24-h ambulatory blood pressure monitoring? *Journal of Hypertension.* 2007; 25(2):315-320.
152 Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *American Journal of Clinical Nutrition.* 1997; 65(2 Suppl):643S-651S.
153 Cutler JA, Follmann D, Elliott P, Suh I. An overview of randomized trials of sodium reduction and blood pressure. *Hypertension.* 1991; 17(1 Suppl):I27-I33.
154 Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen M, Omvik S, Wedel H. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002; 359:995-1003.

155 Dahlöf B, Hansson L, Lindholm LH, Schersten B, Wester PO, Ekbom T, Hedner T, de Faire U. STOP-Hypertension-2: a prospective intervention trial of newer versus older treatment alternatives in old patients with hypertension. *Blood Pressure.* 1993; 2:136-141.
156 Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet.* 1991; 338(8778):1281-1285.
157 Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* 2005; 366(9489):895-906.
158 Davy BM, Melby CL, Beske SD, Ho RC, Davrath LR, Davy KP. Oat consumption does not affect resting casual and ambulatory 24-h arterial blood pressure in men with high-normal blood pressure to stage I hypertension. *Journal of Nutrition.* 2002; 132(3):394-398.
159 Dawes MG, Coats AJ, Juszczak E. Daytime ambulatory systolic blood pressure is more effective at predicting mortality than clinic blood pressure. *Blood Pressure Monitoring.* 2006; 11(3):111-118.
160 de Hoon JN, Vanmolkot FH, van den Ven LL, Van Bortel LM. Quality of life comparison between bisoprolol and nifedipine retard in hypertension. *Cardiovascular Drugs and Therapy.* 1997; 11(3):465-471.
161 de Lame PA, Droussin AM, Thomson M, Verhaest L, Wallace S. The effects of enalapril on hypertension and quality of life. A large multicenter study in Belgium. *Acta Cardiologica.* 1989; 44(4):289-302.
162 De Plaen JF, Detry JM. Hemodynamic effects of physical training in established arterial hypertension. *Acta Cardiologica.* 1980; 35(3):179-188.
163 de Souza F., Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension.* 2010; 55(1):147-152.
164 Deary AJ, Schumann AL, Murfet H, Haydock SF, Foo RS, Brown MJ. Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. *Journal of Hypertension.* 2002; 20(4):771-777.
165 Deckers JW, Goedhart DM, Boersma E, Briggs A, Bertrand M, Ferrari R, Remme WJ, Fox K, Simoons ML. Treatment benefit by perindopril in patients with stable coronary artery disease at different levels of risk. *European Heart Journal.* 2006; 27(7):796-801.
166 Degl'innocenti A, Elmfeldt D, Hofman A, Lithell H, Olofsson B, Skoog I, Trenkwalder P, Zanchetti A, Wiklund I. Health-related quality of life during treatment of elderly patients with hypertension: results from the Study on COgnition and Prognosis in the Elderly (SCOPE). *Journal of Human Hypertension.* 2004; 18(4):239-245.
167 Den Hond E, Celis H, Fagard R, Keary L, Leeman M, O'Brien E, Vandenhoven G, Staessen JA. Self-measured versus ambulatory blood pressure in the diagnosis of hypertension. *Journal of Hypertension.* 2003; 21(4):717-722.
168 Denardo SJ, Gong Y, Nichols WW, Messerli FH, Bavry AA, Cooper-DeHoff RM, Handberg EM, Champion A, Pepine CJ. Blood pressure and outcomes in very old hypertensive coronary artery disease patients: an INVEST substudy. *American Journal of Medicine.* 2010; 123(8):719-726.
169 Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke.* 1990; 21(6):848-853.
170 Dennis MS, Bamford JM, Sandercock PA, Warlow CP. Incidence of transient ischemic attacks in Oxfordshire, England. *Stroke.* 1989; 20(3):333-339.

171 Department of Health. *Blood Pressure Measurement Devices - Mercury and Non-Mercury.* (MDA DB2000(03)). London: Department of Health, 2000.
172 Department of Health. *Medical Devices and Equipment Management: Repair and Maintenance Provision.* (MDA DB2000(02)). London: Department of Health, 2000.
173 Department of Health. *Exercise Referral Systems: a National Quality Assessment Framework.* London: 2001.
174 Department of Health. *NHS reference costs 2008-09*. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591
175 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials.* 1986; 7(3):177-188.
176 Devereux RB, Dahlof B, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris KE, Edelman JM, Wachtell K. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. *Circulation.* 2004; 110(11):1456-1462.
177 Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. *Lancet.* 1999; 353(9169):2008-2013.
178 Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension.* 2005; 46(1):156-161.
179 Dolfgoff S, SCHREK R, BALLARD GP, BAKER LA. Tobacco smoking as an etiologic factor in disease. 2. Coronary disease and hypertension. *Angiology.* 1952; 3(4):323-334.
180 Doll R, HILL AB. Smoking and carcinoma of the lung; preliminary report. *BMJ.* 1950; 2(4682):739-748.
181 Doll R, Peto R, Hall E, Wheatley K, Gray R. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *BMJ.* 1994; 309(6959):911-918.
182 Dosh SA. The diagnosis of essential and secondary hypertension in adults. *Journal of Family Practice.* 2001; 50(8):707-712.
183 Drummond MF, Sculpher M, Torrance G, O'Brien B, Stoddart G.*Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. Oxford: OUP; 2005. Available from: http://www.oup.com/us/catalog/general/subject/Medicine/PublicHealth/?view=usa&ci=9780198529453
184 Duncan JJ, Farr JE, Upton SJ, Hagan RD, Oglesby ME, Blair SN. The effects of aerobic exercise on plasma catecholamines and blood pressure in patients with mild essential hypertension. *JAMA.* 1985; 254(18):2609-2613.
185 Dzau VJ, Herrmann HC. Hormonal control of angiotensinogen production. *Life Sciences.* 1982; 30(7-8):577-584.
186 Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. *BMJ.* 1997; 314(7095):1666-1674.
187 Ebrahim S, Smith GD. Lowering blood pressure: a systematic review of sustained effects of non-pharmacological interventions. *Journal of Public Health Medicine.* 1998; 20(4):441-448.
188 Eccles M, Mason J. How to develop cost-conscious guidelines. *Health Technology Assessment.* 2001; 5(16)

189 Egger M, Jüni P, Bartlett C, Holenstein F, Stern J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technology Assessment.* 2003; 7(1)

190 Eguchi K, Hoshide S, Hoshide Y, Ishikawa S, Shimada K, Kario K. Reproducibility of ambulatory blood pressure in treated and untreated hypertensive patients. *Journal of Hypertension.* 2010; 28(5):918-924.

191 Eguchi K, Kuruvilla S, Ogedegbe G, Gerin W, Schwartz JE, Pickering TG. What is the optimal interval between successive home blood pressure readings using an automated oscillometric device? *Journal of Hypertension.* 2009; 27(6):1172-1177.

192 Eisenberg DM, Delbanco TL, Berkey CS, Kaptchuk TJ, Kupelnick B, Kuhl J, Chalmers TC. Cognitive behavioral techniques for hypertension: are they effective? *Annals of Internal Medicine.* 1993; 118(12):964-972.

193 Elbourne D, Altman DG, Higgins JPT, Curtin F, Worthington HV, vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology.* 2002; 31(1):140-149.

194 Elliott WJ, Weber RR, Murphy MB. A double-blind, randomized, placebo-controlled comparison of the metabolic effects of low-dose hydrochlorothiazide and indapamide. *Journal of Clinical Pharmacology.* 1991; 31(8):751-757.

195 Emeriau JP, Knauf H, Pujadas JO, Calvo-Gomez C, Abate G, Leonetti G, Chastang C, European S, I. A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study. *Journal of Hypertension.* 2001; 19(2):343-350.

196 Enstrom I, Pennert K. Does it matter whether ambulatory blood pressure is recorded during a work day or a non-work day? *Journal of Hypertension.* 1996; 14(5):565-569.

197 Eriksson S, Olofsson B, Wester P. Atenolol in Secondary Prevention after Stroke. *Cerebrovascular Diseases.* 1995; 5(1):21-25.

198 Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJG, Phillips BB, Zimmerman MB, Bergus GR. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension.* 2006; 47(3):352-358.

199 Ernst ME, Carter BL, Zheng S, Grimm RH, Jr. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *American Journal of Hypertension.* 2010; 23(4):440-446.

200 Ernst ME, Weber CA, Dawson JD, O'Connor MA, Lin W, Carter BL, Bergus GR. How well does a shortened time interval characterize results of a full ambulatory blood pressure monitoring session? *Journal of Clinical Hypertension.* 2008; 10(6):431-435.

201 Espeland MA, Whelton PK, Kostis JB, Bahnson JL, Ettinger WH, Cutler JA, Appel LJ, Kumanyika S, Farmer D, Elam J, Wilson AC, Applegate WB. Predictors and mediators of successful long-term withdrawal from antihypertensive medications. TONE Cooperative Research Group. Trial of Nonpharmacologic Interventions in the Elderly. *Archives of Family Medicine.* 1999; 8(3):228-236.

202 Esposti LD, Di Martino M., Saragoni S, Sgreccia A, Capone A, Buda S, Esposti ED. Pharmacoeconomics of antihypertensive drug treatment: an analysis of how long patients remain on various antihypertensive therapies. *Journal of Clinical Hypertension.* 2004; 6:76-84.

203 Ewald S, vor dem EJ, Uen S, Neikes F, Vetter H, Mengden T. Relationship between the frequency of blood pressure self-measurement and blood pressure reduction with antihypertensive therapy : results of the OLMETEL (OLMEsartan TELemonitoring blood pressure) study. *Clinical Drug Investigation.* 2006; 26(8):439-446.

204 Fagard RH. The role of exercise in blood pressure control: supportive evidence. *Journal of Hypertension.* 1995; 13(11):1223-1227.

205 Fagard RH. Physical activity in the prevention and treatment of hypertension in the obese. *Medicine and Science in Sports and Exercise.* 1999; 31(11 Suppl):S624-S630.
206 Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: A meta-analysis. *Journal of Hypertension.* 2007; 25(11):2193-2198.
207 Fagard RH, Staessen JA. Treatment of isolated systolic hypertension in the elderly: the Syst-Eur trial. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Clinical and Experimental Hypertension.* 1999; 21(5&6):491-497.
208 Fagard RH, Staessen JA, Thijs L, Bulpitt CJ, Clement D, de Leeuw PW, Jaaskivi M, Mancia G, O'Brien E, Palatini P, Tuomilehto J, Webster J, Systolic Hypertension in Europe Trial Investigators. Relationship between ambulatory blood pressure and follow-up clinic blood pressure in elderly patients with systolic hypertension. *Journal of Hypertension.* 2004; 22(1):81-87.
209 Fagard RH, Staessen JA, Thijs L, Celis H, Bulpitt CJ, de Leeuw PW, Leonetti G, Tuomilehto J, Yodfat Y. On-treatment diastolic blood pressure and prognosis in systolic hypertension. *Archives of Internal Medicine.* 2007; 167(17):1884-1891.
210 Fagard RH, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Prognostic significance of ambulatory blood pressure in hypertensive patients with history of cardiovascular disease. *Blood Pressure Monitoring.* 2008; 13(6):325-332.
211 Fagard RH, Van Den Broeke C, de Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. *Journal of Human Hypertension.* 2005; 19(10):801-807.
212 Fagerberg B, Andersson OK, Persson B, Hedner T. Reactivity to norepinephrine and effect of sodium on blood pressure during weight loss. *Hypertension.* 1985; 7(4):586-592.
213 Fang X-H, Zhang X-H, Yang Q-D, Dai X-Y, Su F-Z, Rao M-L, Wu S-P, Du X-L, Wang W-Z, Li S-C. Subtype hypertension and risk of stroke in middle-aged and older chinese: A 10-year follow-up study. *Stroke.* 2006; 37(1):38-43.
214 Feldman RD, Campbell N, Larochelle P, Bolli P, Burgess E, Carruthers G, Floras J, Haynes B, Honos G, Leenen F, Leiter LA, Logan AG, Myers J, Spence D, Zarnke KB. Lifestyle modifications to prevent and control hypertension. *Canadian Medical Association Journal.* 1999; 161(Supplement):S1-S22.
215 Ferrara LA, Iannuzzi R, Castaldo A, Iannuzzi A, Dello RA, Mancini M. Long-term magnesium supplementation in essential hypertension. *Cardiology.* 1992; 81(1):25-33.
216 Finnerty FA, Jr. A double-blind study of chlorthalidone and hydrochlorothiazide in an outpatient population of moderate hypertensives. *Angiology.* 1976; 27(12):738-744.
217 Fitzgerald PA. Endocrinology. *Current Medical Diagnosis and Treatment*, 40th edn. New York: Lange/McGraw-Hill, 2001: 1088-1160.
218 Fletcher AE, Bulpitt CJ, Chase DM, Collins WC, Furberg CD, Goggin TK, Hewett AJ, Neiss AM. Quality of life with three antihypertensive treatments. Cilazapril, atenolol, nifedipine. *Hypertension.* 1992; 19(6 Pt 1):499-507.
219 Flores L, Recasens M, Gomis R, Esmatjes E. White coat hypertension in type 1 diabetic patients without nephropathy. *American Journal of Hypertension.* 2000; 13(5 Pt 1):560-563.
220 Fodor JG, Whitmore B, Leenen F, Larochelle P. Lifestyle modifications to prevent and control hypertension. 5. Recommendations on dietary salt. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *Canadian Medical Association Journal.* 1999; 160(9 Suppl):S29-S34.
221 Frankel BL, Patel DJ, Horwitz D, Friedewald WT, Gaarder KR. Treatment of hypertension with biofeedback and relaxation techniques. *Psychosomatic Medicine.* 1978; 40(4):276-293.

222 Franklin SS, Wachtell K, Papademetriou V, Olsen MH, Devereux RB, Fyhrquist F, Ibsen H, Kjeldsen SE, Dahlof B. Cardiovascular morbidity and mortality in hypertensive patients with lower versus higher risk: a LIFE substudy. *Hypertension.* 2005; 46(3):492-499.
223 Fravel MA, Ernst ME, Weber CA, Dawson JD, Carter BL, Bergus GR. Influence of patient characteristics on success of ambulatory blood pressure monitoring. *Pharmacotherapy.* 2008; 28(11):1341-1347.
224 Freemantle N, Urdahl H, Eastaugh J, Hobbs FD. What is the place of beta-blockade in patients who have experienced a myocardial infarction with preserved left ventricular function? Evidence and (mis)interpretation. *Progress in Cardiovascular Diseases.* 2002; 44(4):243-250.
225 Fukunaga H, Ohkubo T, Kobayashi M, Tamaki Y, Kikuya M, Obara T, Nakagawa M, Hara A, Asayama K, Metoki H, Inoue R, Hashimoto J, K, Imai Y. Cost-effectiveness of the introduction of home blood pressure measurement in patients with office hypertension. *Journal of Hypertension.* 2008; 26(4):685-690.
226 Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM, Calhoun DA. Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *Journal of Human Hypertension.* 2010; 24(8):532-537.
227 Galloe AM, Graudal N, Moller J, Bro H, Jorgensen M, Christensen HR. Effect of oral calcium supplementation on blood pressure in patients with previously untreated hypertension: a randomised, double-blind, placebo-controlled, crossover study. *Journal of Human Hypertension.* 1993; 7(1):43-45.
228 Garcia-Vera MP, Sanz J. How many self-measured blood pressure readings are needed to estimate hypertensive patients' "true" blood pressure? *Journal of Behavioral Medicine.* 1999; 22(1):93-113.
229 Geleijnse JM, Witteman JC, Bak AA, den Breeijen JH, Grobbee DE. Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. *BMJ.* 1994; 309(6952):436-440.
230 Gibbs CR, Beevers DG, Lip GY. The management of hypertensive disease in black patients. *QJM.* 1999; 92(4):187-192.
231 Gillett PA, White AT, Caserta MS. Effect of exercise and/or fitness education on fitness in older, sedentary, obese women. *Journal of Aging and Physical Activity.* 1996; 4:42-45.
232 Goldstein IB, Shapiro D, Thananopavarn C, Sambhi MP. Comparison of drug and behavioral treatments of essential hypertension. *Health Psychology.* 1982; 1(1):7-26.
233 Gong L, Zhang W, Zhu Y, Zhu J, Kong D, Page V, Ghadirian P, LeLorier J, Hamet P. Shanghai trial of nifedipine in the elderly (STONE). *Journal of Hypertension.* 1996; 14(10):1237-1245.
234 Goodacre S, Nicholl J, Dixon S, Cross E, Angelini K, Arnold J, Revill S, Locker T, Capewell SJ, Quinney D, Campbell S, Morris F. Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *British Medical Journal.* 2004; 328(7434):254.
235 Gordon NF, Scott CB, Levine BD. Comparison of single versus multiple lifestyle interventions: are the antihypertensive effects of exercise training and diet-induced weight loss additive? *American Journal of Cardiology.* 1997; 79(6):763-767.
236 Gorton T. Blood pressure of adults by age and sex, United States. *Vital and Health Statistics Series 11, Data From the National Health Survey.* 1964; 11:1-40.
237 Gosse P, Cipriano C, Bemurat L, Mas D, Lemetayer P, N'Tela G, Clementy J. Prognostic significance of blood pressure measured on rising. *Journal of Human Hypertension.* 2001; 15(6):413-417.

238 Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. *JAMA.* 1998; 279(17):1383-1391.
239 Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *American Journal of Hypertension.* 1999; 12(1 Pt 1):84-92.
240 Grimm RH, Jr., Neaton JD, Elmer PJ, Svendsen KH, Levin J, Segal M, Holland L, Witte LJ, Clearman DR, Kofron P, . The influence of oral potassium chloride on blood pressure in hypertensive men on a low-sodium diet. *New England Journal of Medicine.* 1990; 322(9):569-574.
241 Grobbee DE, Hofman A. Does sodium restriction lower blood pressure? *BMJ.* 1986; 293(6538):27-29.
242 Grobbee DE, Hofman A. Effect of calcium supplementation on diastolic blood pressure in young people with mild hypertension. *Lancet.* 1986; 2(8509):703-707.
243 Gudmundsson LS, Johannsson M, Thorgeirsson G, Sigfusson N, Sigvaldason H, Witteman JCM. Hypertension control as predictor of mortality in treated men and women, followed for up to 30 years. *Cardiovascular Drugs and Therapy.* 2005; 19(3):227-235.
244 Gustavsen PH, Hoegholm A, Bang LE, Kristensen KS. White coat hypertension is a cardiovascular risk factor: A 10-year follow-up study. *Journal of Human Hypertension.* 2003; 17(12):811-817.
245 Hafner RJ. Psychological treatment of essential hypertension: a controlled comparison of meditation and meditation plus biofeedback. *Biofeedback and Self Regulation.* 1982; 7(3):305-316.
246 Hagberg JM, Montain SJ, Martin WH, III, Ehsani AA. Effect of exercise training in 60- to 69-year-old persons with essential hypertension. *American Journal of Cardiology.* 1989; 64(5):348-353.
247 Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. *Annals of Internal Medicine.* 2003; 138(1):10-16.
248 Halbert JA, Silagy CA, Finucane P, Withers RT, Hamdorf PA, Andrews GR. The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomised controlled trials of 4 weeks or longer. *Journal of Human Hypertension.* 1997; 11(10):641-649.
249 Halbert JA, Silagy CA, Finucane PM, Withers RT, Hamdorf PA. Physical activity and cardiovascular risk factors: effect of advice from an exercise specialist in Australian general practice. *Medical Journal of Australia.* 2000; 173(2):84-87.
250 Hall WD. Resistant hypertension, secondary hypertension, and hypertensive crises. *Cardiology Clinics.* 2002; 20(2):281-289.
251 Hamet P. The evaluation of the scientific evidence for a relationship between calcium and hypertension. *Journal of Nutrition.* 1995; 125(2 Suppl):311S-400S.
252 Hammond IW, Devereux RB, Alderman MH, Lutas EM, Spitzer MC, Crowley JS, Laragh JH. The prevalence and correlates of echocardiographic left ventricular hypertrophy among employed patients with uncomplicated hypertension. *Journal of the American College of Cardiology.* 1986; 7(3):639-650.
253 Hansen TW, Jeppesen J, Rasmussen S, Ibsen H, Torp-Pedersen C. Ambulatory blood pressure and mortality: a population-based study. *Hypertension.* 2005; 45(4):499-504.
254 Hansen TW, Kikuya M, Thijs L, Bjorklund-Bodegard K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Jeppesen J, Ibsen H, Imai Y, Staessen JA, IDACO I. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. *Journal of Hypertension.* 2007; 25(8):1554-1564.

255 Hansson L. Results of the STOP-Hypertension-2 trial. *Blood Pressure.* 2000; 9(Suppl 2):17-20.
256 Hansson L, Hedner T, Lindholm L, et al. The Captopril Prevention Project (CAPPP) in Hypertension: baseline data and current status. *Blood Pressure.* 1997; 6:365-367.
257 Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlöf B, Karlberg BE. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet.* 2000; 356:359-365.
258 Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Schersten B, Wester PO, Hedner T. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet.* 1999; 354:1751-1756.
259 Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de FU, Morlin C, Karlberg BE, Wester PO, Bjorck JE. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet.* 1999; 353(9153):611-616.
260 Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet.* 1998; 351(9118):1755-1762.
261 Harris KA, Holly RG. Physiological response to circuit weight training in borderline hypertensive subjects. *Medicine and Science in Sports and Exercise.* 1987; 19(3):246-252.
262 Harsha DW, Lin PH, Obarzanek E, Karanja NM, Moore TJ, Caballero B. Dietary Approaches to Stop Hypertension: a summary of study results. DASH Collaborative Research Group. *Journal of the American Dietetic Association.* 1999; 99(8 Suppl):S35-S39.
263 Hart CL, Smith GD, Hole DJ, Hawthorne VM. Alcohol consumption and mortality from all causes, coronary heart disease, and stroke: results from a prospective cohort study of scottish men with 21 years of follow up. *BMJ.* 1999; 318(7200):1725-1729.
264 Harvard CEA Registry. *Cost Effectiveness Analysis (CEA) Registry*. 1997. Tufts-New England Medical Center. https://research.tufts-nemc.org/cear4/Default.aspx
265 Hatch JP, Klatt KD, Supik JD, Rios N, Fisher JG, Bauer RL, Shimotsu GW. Combined behavioral and pharmacological treatment of essential hypertension. *Biofeedback and Self Regulation.* 1985; 10(2):119-138.
266 Hatt PY, Leblond JB. A comparative study of the activity of a new agent, indapamide, in essential arterial hypertension. *Current Medical Research and Opinion.* 1975; 3(3):138-144.
267 Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. *Cochrane Database of Systematic Reviews.* 2002;(2):CD000011.
268 He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *Journal of Human Hypertension.* 2002; 16(11):761-770.
269 Head GA, Mihailidou AS, Duggan KA, Beilin LJ, Berry N, Brown MA, Bune AJ, Cowley D, Chalmers JP, Howe PRC, Hodgson J, Ludbrook J, Mangoni AA, McGrath BP, Nelson MR, Sharman JE, Stowasser M. Definition of ambulatory blood pressure targets for diagnosis and treatment of hypertension in relation to clinic blood pressure: Prospective cohort study. *BMJ.* 2010; 340(7751):849.

270 Henderson DG, Schierup J, Schodt T. Effect of magnesium supplementation on blood pressure and electrolyte concentrations in hypertensive patients receiving long term diuretic treatment. *BMJ.* 1986; 293(6548):664-665.
271 Hermida RC, Calvo C, Ayala DE, Fernandez JR, Ruilope LM, Lopez JE. Evaluation of the extent and duration of the "ABPM effect" in hypertensive patients. *Journal of the American College of Cardiology.* 2002; 40(4):710-717.
272 Hernandez-del RR, Martin-Baranera M, Sobrino J, Gorostidi M, Vinyoles E, Sierra C, Segura J, Coca A, Ruilope LM, Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry Investigators. Reproducibility of the circadian blood pressure pattern in 24-h versus 48-h recordings: the Spanish Ambulatory Blood Pressure Monitoring Registry. *Journal of Hypertension.* 2007; 25(12):2406-2412.
273 Hershey JC, Morton BG, Davis JB, Reichgott MJ. Patient compliance with antihypertensive medication. *American Journal of Public Health.* 1980; 70(10):1081-1089.
274 Hinderliter A, Sherwood A, Gullette EC, Babyak M, Waugh R, Georgiades A, Blumenthal JA. Reduction of left ventricular hypertrophy after exercise and weight loss in overweight patients with mild hypertension. *Archives of Internal Medicine.* 2002; 162(12):1333-1339.
275 Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FDR, Deeks JJ, Heneghan C, Roberts N, McManus RJ. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. *BMJ.* 2011; 342:d3621
276 Hoelscher TJ, Lichstein KL, Fischer SM, Hegarty TB. Relaxation treatment of hypertension: Do home relaxation tapes enhance treatment outcome? *Behavior Therapy.* 1987; 18(1):33-37.
277 Hoelscher TJ, Lichstein KL, Rosenthal TL. Home relaxation practice in hypertension treatment: objective assessment and compliance induction. *Journal of Consulting and Clinical Psychology.* 1986; 54(2):217-221.
278 Hollenberg NK, Williams GH, Anderson R, Akhras KS, Bittman RM, Krause SL. Symptoms and the distress they cause: comparison of an aldosterone antagonist and a calcium channel blocking agent in patients with systolic hypertension. *Archives of Internal Medicine.* 2003; 163(13):1543-1548.
279 Hooper L, Bartlett C, Davey SG, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. *BMJ.* 2002; 325(7365):628.
280 Hosohata K, Saito S, Ohkubo T, Kikuya M, Obara T, Kato T, Totsune K, Miura Y, Arakawa K, Fujishima M, Fujii J, Fukiyama K, Hisamichi S, Iimura O, Ishii M, Omae T, Saruta T, Yoshinaga K, Abe I, Abukawa T, Ashida T, Dohba N, Etoh T, Fujimura A, Gotoh T, Hama H, Hano T, Hayashi H, Hayashida N, Hayashi M, Hiramori K, Hirai Y, Hirata Y, Hiwada K, Hora K, Ichikawa S, Imaizumi T, Ishikawa K, Ito I, Iwaoka D, Kanamasa K, Katagiri T, Katayama S, Kawano Y, Kida H, Kimura G, Kitaoka H, Kobayashi S, Kohara K, Kojima S, Komuro I, Kumagai H, Kusano E, Kushiro T, Kuwajima I, Maruyama Y, Masani F, Matsubara H, Matsubara T, Matsumoto M, Matsuoka H, Matsuura H, Mishima Y, Miura M, Miyamori I, Murakami H, Muratani H, Nakao K, Naruse M, Nishio I, Ogihara T, Ohta M, Ohtsuka K, Ohuchi Y, Oikawa S, Okabe M, Okumura K, Saitoh I, Saitoh H, Sakata T, Saku K, Sasaki H, Senda S, Shimada K, Shimamoto K, Shiomi T, Shirato K, Takada M, Takeda K, Takeda N, Takeshita A, Takishita S, Toba K, Tochikubo O, Tomoike H, Ueno Y, Umemura S, Urata H, Yamada K, Yamaguchi T, Yamashina A, Yoshimura M, Satoh H, Oka Y, Katagiri H, Kondo Y, Shishido H, Kohinata A, Kanno Y, Ikeda H, Takahashi T, Kimura A, Funahashi J, Takada N, Hanazawa T, Osugi M, Hashimoto J, Miyamura T, Masuda Y, Tanaka S, Koizumi M, Ando T, Tsuchida A, Nanba M, Yonekura S, Shiroishi M, Nakagawa M, Oda K, Kanahara I, Hirota N, Tsutsui M, Anzai J, Hosoda S, Shiiki M, Takagawa Y, Iida M, Tada M, Noto T, Tanaka H, Tajima G, Kawamorita K, Komai K, Seki H, Omoto A, Takahashi H,

Kitabayashi A, Kimura M, Kimura Y, Takahashi K, Kawamorita Y, Emura Y, Ishikawa Y, Nagai K, Nagai S, Ito T, Nihei K, Yamada S, Yamamoto N, Suzuki Y, Ito H, Ito M, Fujita T, Tominaga S, Suzuki K, Ishibashi K, Ando Y, Sato S, Morikawa H, Kashima S, Nakayama D, Hayashi Y, Ohta K, Metoki H, Fukami K, Hayashi T, Kishi M, Tajima J, Seino J, Hoshi H, Imai Y, Kimura H, Mori R, Matsuo K, Tanno Y, Shibasaki A, Yamagishi T, Ohtomo E, Ohtsuka Y, Sasaki S, Seino M, Kurosawa K, Kyogoku S, Ito K, Ono Y, Watanabe S, Hiwatashi N, Yagi C, Unakami H, Asayama K, Mouri T, Watanabe T, Kikuchi K, Maruyama N, Sone M, Iwamoto M, Naganuma S, Mashiko H, Ishii H, Takaya Y, Kamimoto M, Shirai A, Watanabe R, Tohyama Y, Araki F, Sakuma H, Amada Y, Sato E, Techigawara M, Nakamura K, Nakayama T, Hasegawa K, Minami J, Kumagai Y, Cho T, Okamoto K, Iguchi T, Honzawa T, Koitabashi T, Horikoshi H, Nagao T, Yoshimatsu H, Seki K, Akiyama N, Suga H, Matsunaga R, Sinozaki T, Ishimaru Y, Yagi N, Takikawa H, Hukutome T, Nakajima C, Sato H, Simizu J, Arai M, Koide H, Takada H, Umezu T, Aoki H, Nakamoto H, Komahashi K, Sekiya S, Sugimoto H, Arai T, Inokuma S, Funazaki T. Progress report on the Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) study: Status at February 2004. *Clinical and Experimental Hypertension.* 2007; 29(1):69-81.

281 Hulley SB, Furberg CD, Gurland B, McDonald R, Perry HM, Schnaper HW. Systolic Hypertension in the Elderly Program (SHEP): antihypertensive efficacy of chlorthalidone. *American Journal of Cardiology.* 1985; 56(15):913-920.

282 Ichihara A, Hayashi M, Koura Y, Tada Y, Hirota N, Saruta T. Long-term effects of intensive blood-pressure lowering on arterial wall stiffness in hypertensive patients. *American Journal of Hypertension.* 2003; 16(11 Pt 1):959-965.

283 Imai Y, Satoh H, Nagai K, Sakuma M, Sakuma H, Minami N, Munakata M, Hashimoto J, Yamagishi T, Watanabe N, . Characteristics of a community-based distribution of home blood pressure in Ohasama in northern Japan. *Journal of Hypertension.* 1993; 11(12):1441-1449.

284 Ingelsson E, Bjorklund-Bodegard K, Lind L, Arnlov J, Sundstrom J. Diurnal blood pressure pattern and risk of congestive heart failure. *JAMA.* 2006; 295(24):2859-2866.

285 Inoue R, Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hirose T, Hara A, Hoshi H, Hashimoto J, Totsune K, Satoh H, Kondo Y, Imai Y. Stroke risk in systolic and combined systolic and diastolic hypertension determined using ambulatory blood pressure. The Ohasama study. *American Journal of Hypertension.* 2007; 20(10):1125-1131.

286 Institute for Clinical Systems Improvement. *Hypertension Diagnosis and Treatment.* Bloomington, MN: Institute for Clinical Systems Improvement, 2000.

287 International Centre for Alcohol Policies. *What Is a "Standard Drink"?* (5). Washington, DC: International Centre for Alcohol Policies, 1998.

288 Irvine MJ, Johnston DW, Jenner DA, Marie GV. Relaxation and stress management in the treatment of essential hypertension. *Journal of Psychosomatic Research.* 1986; 30(4):437-450.

289 Irvine MJ, Logan AG. Relaxation behavior therapy as sole treatment for mild hypertension. *Psychosomatic Medicine.* 1991; 53(6):587-597.

290 Ishikawa J, Carroll DJ, Kuruvilla S, Schwartz JE, Pickering TG. Changes in home versus clinic blood pressure with antihypertensive treatments: a meta-analysis. *Hypertension.* 2008; 52:856-864.

291 Ishikawa S, Kario K, Kayaba K, Gotoh T, Nago N, Nakamura Y, Tsutsumi A, Kajii E. Continued high risk of stroke in treated hypertensives in a general population: The Jichi medical school cohort study. *Hypertension Research.* 2008; 31(6):1125-1133.

292 Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, Ilersich AL. Relationship between daily dose frequency and adherence to antihypertensive

pharmacotherapy: evidence from a meta-analysis. *Clinical Therapeutics.* 2002; 24(2):302-316.
293 Jacob RG, Chesney MA, Williams DM, Ding Y, Shapiro AP. Relaxation therapy for hypertension: design effects and treatment effects. *Annals of Behavioral Medicine.* 1991; 13(1):5-17.
294 Jacob RG, Fortmann SP, Kraemer HC, Farquhar JW, Agras WS. Combining behavioral treatments to reduce blood pressure. A controlled outcome study. *Behavior Modification.* 1985; 9(1):32-53.
295 Jalkanen L. The effect of a weight reduction program on cardiovascular risk factors among overweight hypertensives in primary health care. *Scandinavian Journal of Social Medicine.* 1991; 19(1):66-71.
296 Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ, ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *New England Journal of Medicine.* 2008; 359(23):2417-2428.
297 James JE. Is habitual caffeine use a preventable cardiovascular risk factor? *Lancet.* 1997; 349(9047):279-281.
298 JATOS Study Group. The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS): protocol, patient characteristics, and blood pressure during the first 12 months. *Hypertension Research.* 2005; 28(6):513-520.
299 Jee SH, He J, Whelton PK, Suh I, Klag MJ. The effect of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. *Hypertension.* 1999; 33(2):647-652.
300 Jee SH, Miller ER, III, Guallar E, Singh VK, Appel LJ, Klag MJ. The effect of magnesium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *American Journal of Hypertension.* 2002; 15(8):691-696.
301 Johannesson M. The cost-effectiveness of th switch towards more expensive antihypertensive drugs. *Health Policy.* 1994; 28(1):1-13.
302 Johansson JK, Niiranen TJ, Puukka PJ, Jula AM. Optimal schedule for home blood pressure monitoring based on a clinical approach. *Journal of Hypertension.* 2010; 28(2):259-264.
303 Johnson KA, Partsch DJ, Rippole LL, McVey DM. Reliability of self-reported blood pressure measurements. *Archives of Internal Medicine.* 1999; 159(22):2689-2693.
304 Johnston DW, Gold A, Kentish J, Smith D, Vallance P, Shah D, Leach G, Robinson B. Effect of stress management on blood pressure in mild primary hypertension. *BMJ.* 1993; 306(6883):963-966.
305 Johnston ME, Gibson ES, Terry CW, Haynes RB, Taylor DW, Gafni A, Sicurella JI, Sackett DL. Effects of labelling on income, work and social function among hypertensive employees. *Journal of Chronic Diseases.* 1984; 37(6):417-423.
306 Joint Formulary Committee.*British National Formulary: BNF 60*. 60th ed. London: UK: BMJ Group and Pharmaceutical Press; 2010. Available from: http://www.bnf.org.uk
307 Jonsson B, Carides GW, Burke TA, Dasbach EJ, Lindholm LH, Dahlof B. Cost effectiveness of losartan in patients with hypertension and LVH: an economic evaluation for Sweden of the LIFE trial. *Journal of Hypertension.* 2005; 23(7):1425-1431.
308 Jonsson B, Hansson L, Stalhammar NO. Health economics in the hypertension optimal treatment (HOT) study: costs and cost-effectiveness of intensive blood pressure lowering and low-dose aspirin in patients with hypertension. *Journal of Internal Medicine.* 2003; 253:472-480.
309 Jula A, Ronnemaa T, Rastas M, Karvetti RL, Maki J. Long-term nopharmacological treatment for mild to moderate hypertension. *Journal of Internal Medicine.* 1990; 227(6):413-421.

310 Jula A, Ronnemaa T, Tikkanen I, Karanko H. Responses of atrial natriuretic factor to long-term sodium restriction in mild to moderate hypertension. *Journal of Internal Medicine.* 1992; 231(5):521-529.
311 Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term nonpharmacological treatment with sodium restriction in mild-to-moderate essential hypertension. *Circulation.* 1994; 89(3):1023-1031.
312 Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A, VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet.* 2004; 363(9426):2022-2031.
313 Kagiyama S, Fukuhara M, Ansai T, Matsumura K, Soh I, Takata Y, Sonoki K, Awano S, Takehara T, Iida M. Association between blood pressure and mortality in 80-year-old subjects from a population- based prospective study in Japan. *Hypertension Research.* 2008; 31(2):265-270.
314 Kaplan NM. Other Forms of Secondary Hypertension. In: Kaplan NM, Lieberman E (eds), *Clinical Hypertension*, 7th edition edn. Baltimore: Williams & Wilkins, 1998:
315 Kawabe H, Saito I. Correlation of repeated measurements of home blood pressure on one occasion and diagnosis of hypertension: study by measurement over seven consecutive days. *Clinical and Experimental Hypertension.* 2008; 30(1):79-85.
316 Kawabe H, Saito I, Saruta T. Influence of repeated measurement on one occasion, on successive days, and on workdays on home blood pressure values. *Clinical and Experimental Hypertension.* 2005; 27(2-3):215-222.
317 Kawano Y, Matsuoka H, Takishita S, Omae T. Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures. *Hypertension.* 1998; 32(2):260-265.
318 Kawano Y, Yoshimi H, Matsuoka H, Takishita S, Omae T. Calcium supplementation in patients with essential hypertension: assessment by office, home and ambulatory blood pressure. *Journal of Hypertension.* 1998; 16(11):1693-1699.
319 Kelley GA. Aerobic exercise and resting blood pressure among women: a meta-analysis. *Preventive Medicine.* 1999; 28(3):264-275.
320 Kelley GA, Kelley KS. Aerobic exercise and resting blood pressure in women: a meta-analytic review of controlled clinical trials. *Journal of Women's Health & Gender-Based Medicine.* 1999; 8(6):787-803.
321 Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure : A meta-analysis of randomized controlled trials. *Hypertension.* 2000; 35(3):838-843.
322 Kelley GA, Kelley KS, Tran ZV. Walking and resting blood pressure in adults: a meta-analysis. *Preventive Medicine.* 2001; 33(2 Pt 1):120-127.
323 Kelley GA, Sharpe KK. Aerobic exercise and resting blood pressure in older adults: a meta-analytic review of randomized controlled trials. *Journals of Gerontology Series A, Biological Sciences and Medical Sciences.* 2001; 56(5):M298-M303.
324 Khattar RS, Swales JD, Banfield A, Dore C, Senior R, Lahiri A. Prediction of coronary and cerebrovascular morbidity and mortality by direct continuous ambulatory blood pressure monitoring in essential hypertension. *Circulation.* 1999; 100(10):1071-1076.
325 Khattar RS, Swales JD, Dore C, Senior R, Lahiri A. Effect of aging on the prognostic significance of ambulatory systolic, diastolic, and pulse pressure in essential hypertension. *Circulation.* 2001; 104(7):783-789.
326 Kikuya M, Hansen TW, Thijs L, Bjorklund-Bodegard K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Staessen JA, International Database on Ambulatory Blood Pressure Monitoring in relation to Cardiovascular Outcomes Investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation.* 2007; 115(16):2145-2152.

327 Kinoshita A, Urata H, Tanabe Y, Ikeda M, Tanaka H, Shindo M, Arakawa K. What types of hypertensives respond better to mild exercise therapy? *Journal of Hypertension - Supplement.* 1988; 6(4):S631-S633.
328 Kjeldsen SE, Lyle PA, Kizer JR, Dahlof B, Devereux RB, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristianson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Snapinn SM, Harris KE, Wedel H, LIFE Study Group. The effects of losartan compared to atenolol on stroke in patients with isolated systolic hypertension and left ventricular hypertrophy. The LIFE study. *Journal of Clinical Hypertension.* 2005; 7(3):152-158.
329 Klein A. Thyroid Hormone and High Blood Pressure. In: Laragh JH, Brener BM, Kaplan NM (eds), *Endocrine Mechanism in Hypertension*, New York: Raven Press, 1989: 61-79.
330 Koehler E, Brown E, Haneuse J-PA. On the Assessment of Monte Carlo Error in Simulation-Based Statistical Analyses. *The American Statistician.* 2009; 63(2):155-162.
331 Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. *Hypertension.* 2008; 52(4):652-659.
332 Kono S, Kushiro T, Hirata Y, Hamada C, Takahashi A, Yoshida Y. Class of antihypertensive drugs, blood pressure status, and risk of cardiovascular disease in hypertensive patients: A case-control study in Japan. *Hypertension Research.* 2005; 28(10):811-817.
333 Koopman H, Deville W, van Eijk JT, Donker AJ, Spreeuwenberg C. Diet or diuretic? Treatment of newly diagnosed mild to moderate hypertension in the elderly. *Journal of Human Hypertension.* 1997; 11(12):807-812.
334 Korhonen M, Kastarinen M, Uusitupa M, Puska P, Nissinen A. The effect of intensified diet counseling on the diet of hypertensive subjects in primary health care: a 2-year open randomized controlled trial of lifestyle intervention against hypertension in eastern Finland. *Preventive Medicine.* 2003; 36(1):8-16.
335 Kostis JB, Davis BR, Cutler J, Grimm RH, Jr., Berge KG, Cohen JD, Lacy CR, Perry HM, Jr., Blaufox MD, Wassertheil-Smoller S, Black HR, Schron E, Berkson DM, Curb JD, Smith WM, McDonald R, Applegate WB. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. *JAMA.* 1997; 278(3):212-216.
336 Kostis JB, Espeland MA, Appel L, Johnson KC, Pierce J, Wofford JL. Does withdrawal of antihypertensive medication increase the risk of cardiovascular events? Trial of Nonpharmacologic Interventions in the Elderly (TONE) Cooperative Research Group. *American Journal of Cardiology.* 1998; 82(12):1501-1508.
337 Kostis JB, Rosen RC, Brondolo E, Taska L, Smith DE, Wilson AC. Superiority of nonpharmacologic therapy compared to propranolol and placebo in men with mild hypertension: a randomized, prospective trial. *American Heart Journal.* 1992; 123(2):466-474.
338 Krakoff LR. Cost-effectiveness of ambulatory blood pressure: a reanalysis. *Hypertension.* 2006; 47(1):29-34.
339 Kreeft JH, Langlois S, Ogilvie RI. Comparative trial of indapamide and hydrochlorothiazide in essential hypertension, with forearm plethysmography. *Journal of Cardiovascular Pharmacology.* 1984; 6(4):622-626.
340 Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *American Journal of Medicine.* 2006; 119(2):133-141.

341 Kukkonen K, Rauramaa R, Voutilainen E, Lansimies E. Physical training of middle-aged men with borderline hypertension. *Annals of Clinical Research.* 1982; 14 Suppl 34:139-145.
342 Kumanyika SK, Adams-Campbell L, Van HB, Ten Have TR, Treu JA, Askov E, Williams J, Achterberg C, Zaghloul S, Monsegu D, Bright M, Stoy DB, Malone-Jackson M, Mooney D, Deiling S, Caulfield J. Outcomes of a cardiovascular nutrition counseling program in African-Americans with elevated blood pressure or cholesterol level. *Journal of the American Dietetic Association.* 1999; 99(11):1380-1391.
343 Kuwajima I, Kuramoto K, Ogihara T, Iimura O, Abe K, Saruta T, et al. Tolerability and safety of a calcium channel blocker in comparison with a diuretic in the treatment of elderly patients with hypertension: Secondary analysis of the NICS-EH. *Hypertension Research.* 2001; 24:475-480.
344 Kyngas H, Lahdenpera T. Compliance of patients with hypertension and associated factors. *Journal of Advanced Nursing.* 1999; 29(4):832-839.
345 LaGrone R, Jeffrey TB, Ferguson CL. Effects of education and relaxation training with essential hypertension patients. *Journal of Clinical Psychology.* 1988; 44(2):271-276.
346 Lahdenpera T, Kyngas H. Compliance and its evaluation in patients with hypertension. *Journal of Clinical Nursing.* 2000; 9:826-833.
347 Lane DA, Shah S, Beevers DG. Low-dose spironolactone in the management of resistant hypertension: A surveillance study. *Journal of Hypertension.* 2007; 25(4):891-894.
348 Lang T, Nicaud V, Darne B, Rueff B. Improving hypertension control among exssive alcohol drinkers: a randomised controlled trial in France. The Walpa Group. *Journal of Epidemiology and Community Health.* 1995; 49(610):616.
349 Langford HG, Blaufox MD, Oberman A, Hawkins CM, Curb JD, Cutter GR, Wassertheil-Smoller S, Pressel S, Babcock C, Abernethy JD, . Dietary therapy slows the return of hypertension after stopping prolonged medication. *JAMA.* 1985; 253(5):657-664.
350 Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III--Analysis of data from trials of salt reduction. *BMJ.* 1991; 302(6780):819-824.
351 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009; 338(7705):1245.
352 Law MR, Morris JK and Wald NJ. Unpublished Data From the Published Study: *Law MR, Morris JK, Wald NJ. Use of Blood Pressure Lowering Drugs in the Prevention of Cardiovascular Disease: Meta-Analysis of 147 Randomised Trials in the Context of Expectations From Prospective Epidemiological Studies. BMJ. 2009; 338(7705):1245.* Personal communication: 22/11/10
353 Lede RL, Voto LS, Orti J, Margulies M. Agreement between different frequencies of measurements in ambulatory blood pressure monitoring. *Journal of Obstetrics and Gynaecology*. 1997; 17(4):337-339.
354 Leenen FH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, Alderman MH, Atlas SA, Basile JN, Cuyjet AB, Dart R, Felicetta JV, Grimm RH, Haywood LJ, Jafri SZ, Proschan MA, Thadani U, Whelton PK, Wright JT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension.* 2006; 48(3):374-384.
355 Leiter LA, Abbott D, Campbell NR, Mendelson R, Ogilvie RI, Chockalingam A. Lifestyle modifications to prevent and control hypertension. 2. Recommendations on obesity and weight loss. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and

Stroke Foundation of Canada. *Canadian Medical Association Journal.* 1999; 160(9 Suppl):S7-12.
356 Leren P, Helgeland A. Oslo Hypertension Study. *Drugs.* 1986; 31 Suppl 1:41-45.
357 Levin ML, Goldstein H, Gerhardt PR. Cancer and tobacco smoking; a preliminary report. *JAMA.* 1950; 143(4):336-338.
358 Levine DM, Cohen JD, Dustan HP, Falkner B, Flora JA, Lefebvre RC, Morisky DE, Oberman A, Pickering TG, Roccella EJ, . Behavior changes and the prevention of high blood pressure. Workshop II. AHA Prevention Conference III. Behavior change and compliance: keys to improving cardiovascular health. *Circulation.* 1993; 88(3):1387-1390.
359 Levinson PD, Khatri IM, Freis ED. Persistence of normal BP after withdrawal of drug treatment in mild hypertension. *Archives of Internal Medicine.* 1982; 142(13):2265-2268.
360 Levy A, Lightman SL. Diagnosis and management of pituitary tumours. *BMJ.* 1994; 308(6936):1087-1091.
361 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002; 360(9349):1903-1913.
362 Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *New England Journal of Medicine.* 2001; 345(12):851-860.
363 Li Y, Boggia J, Thijs L, Hansen TW, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Kuznetsova T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Wang J, Sandoya E, O'Brien E, Staessen JA, International Database on Ambulatory Blood Pressure Monitoring in relation to Cardiovascular Outcomes Investigators. Is blood pressure during the night more predictive of cardiovascular outcome than during the day? *Blood Pressure Monitoring.* 2008; 13(3):145-147.
364 Lim PO, Rodgers P, Cardale K, Watson AD, MacDonald TM. Potentially high prevalence of primary aldosteronism in a primary-care population. *Lancet.* 1999; 353(9146):40.
365 Lind L, Lithell H, Pollare T, Ljunghall S. Blood pressure response during long-term treatment with magnesium is dependent on magnesium status. A double-blind, placebo-controlled study in essential hypertension and in subjects with high-normal blood pressure. *American Journal of Hypertension.* 1991; 4(8):674-679.
366 Linden W, Chambers L. Clinical effectiveness of non-drug treatment for hypertension: a meta-analysis. *Annals of Behavioral Medicine.* 1994; 16:35-45.
367 Linden W, Lenz JW, Con AH. Individualized stress management for primary hypertension: a randomized trial. *Archives of Internal Medicine.* 2001; 161(8):1071-1080.
368 Lindholm LH, Hansson L, Ekbom T, Dahlöf B, Lanke J, Linjer E, et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish trial in old patients with hypertension -2. *Journal of Hypertension.* 2000; 18:1671-1675.
369 Lindholm LH, Ibsen H, Borch-Johnsen K, Olsen MH, Wachtell K, Dahlof B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman JM, Snapinn S, For the LIFE study group. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. *Journal of Hypertension.* 2002; 20(9):1879-1886.
370 Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against Atenolol. *Lancet.* 2002; 359:1004-1010.

371 Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Journal of Hypertension.* 2003; 21(5):875-886.
372 Little P, Barnett J, Barnsley L, Marjoram J, Fitzgerald-Barron A, Mant D. Comparison of agreement between different measures of blood pressure in primary care and daytime ambulatory blood pressure. *BMJ.* 2002; 325(7358):254.
373 Liu L, Wang JG, Gong L, Liu G, Staessen JA. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. *Journal of Hypertension.* 1998; 16(12 Pt 1):1823-1829.
374 Lorgelly P, Siatis I, Brooks A, Slinn B, Millar-Craig MW, Donnelly R, Manning G. Is ambulatory blood pressure monitoring cost-effective in the routine surveillance of treated hypertension patients in primary care? *British Journal of General Practice.* 2003; 53:794-796.
375 Luengo-Fernandez R, Gray AM, Rothwell PM. Costs of stroke using patient-level data: a critical review of the literature. *Stroke.* 2009; 40(2):e18-e23.
376 Luft FC, Morris CD, Weinburger MH. Compliance to a low sodium diet. *American Journal of Clinical Nutrition.* 1997; 65:S698-S703.
377 Luscher TF, Vetter H, Siegenthaler W, Vetter W. Compliance in hypertension: facts and concepts. *Journal of Hypertension - Supplement.* 1985; 3(1):S3-S9.
378 Lyle RM. Does baseline serum total calcium level influence the blood pressure response to calcium supplementation? A double-blind study. *Netherlands Journal of Medicine.* 1992; 41(1-2):48-55.
379 Macmahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990; 335(8692):765-774.
380 MacMahon SW, Macdonald GJ, Bernstein L, Andrews G, Blacket RB. A randomized controlled trial of weight reduction and metoprolol in the treatment of hypertension in young overweight patients. *Clinical and Experimental Pharmacology and Physiology.* 1985; 12(3):267-271.
381 MacMahon SW, Macdonald GJ, Bernstein L, Andrews G, Blacket RB. Comparison of weight reduction with metoprolol in treatment of hypertension in young overweight patients. *Lancet.* 1985; 1(8440):1233-1236.
382 Maheswaran R, Beevers M, Beevers DG. Effectiveness of advice to reduce alcohol consumption in hypertensive patients. *Hypertension.* 1992; 19(1):79-84.
383 Mahmud A, Mahgoub M, Hall M, Feely J. Does aldosterone-to-renin ratio predict the antihypertensive effect of the aldosterone antagonist spironolactone? *American Journal of Hypertension.* 2005; 18(12):1631-1635.
384 Malacco E, Mancia G, Rappelli A, Menotti A, Zuccaro MS, Coppini A, Shell I. Treatment of isolated systolic hypertension: the SHELL study results. *Blood Pressure.* 2003; 12(3):160-167.
385 Mallion JM, Genes N, Vaur L, Clerson P, Vaisse B, Bobrie G, Chatellier G. Blood pressure levels, risk factors and antihypertensive treatments: lessons from the SHEAF study. *Journal of Human Hypertension.* 2001; 15(12):841-848.
386 Mancia G, Omboni S, Parati G, Trazzi S, Mutti E. Limited reproducibility of hourly blood pressure values obtained by ambulatory blood pressure monitoring: Implications for studies on antihypertensive drugs. *Journal of Hypertension.* 1992; 10(12):1531-1535.
387 Mancia G, Parati G. Office compared with ambulatory blood pressure in assessing response to anti hypertensive treatment: a meta-analysis. *Journal of Hypertension.* 2004; 22(3):435-445.

388 Mandle CL, Jacobs SC, Arcari PM, Domar AD. The efficacy of relaxation response interventions with adult patients: a review of the literature. *Journal of Cardiovascular Nursing.* 1996; 10(3):4-26.
389 Mansoor GA, McCabe EJ, White WB. Long-term reproducibility of ambulatory blood pressure. *Journal of Hypertension.* 1994; 12(6):703-708.
390 Mar J, Pastor R, Abasolo R, Ruiz de GR. Ambulatory blood pressure monitoring and diagnostic errors in hypertension: a Bayesian approach. *Medical Decision Making.* 1998; 18(4):429-435.
391 Martin JE, Dubbert PM, Cushman WC. Controlled trial of aerobic exercise in hypertension. *Circulation.* 1990; 81(5):1560-1567.
392 Mason, J. and Eccles, M. *Guideline Recommendation an Evidence Grading (GREG): a New Grading Method for Clinical Guideline Development Groups. Volume Report 109.* Newcastle upon Tyne: Centre for Health Services Research, University of Newcastle upon Tyne, 2003.
393 Mason J, Eccles M, Freemantle N, Drummond M. A framework for incorporating cost-effectiveness in evidence-based clinical practice guidelines. *Health Policy.* 1999; 47(1):37-52.
394 Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, Hamburger RJ, Fye C, Lakshman R, Gottdiener J. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *New England Journal of Medicine.* 1993; 328(13):914-921.
395 Maxwell MH, Kushiro T, Dornfeld LP, Tuck ML, Waks AU. BP changes in obese hypertensive subjects during rapid weight loss. Comparison of restricted v unchanged salt intake. *Archives of Internal Medicine.* 1984; 144(8):1581-1584.
396 McCarron DA, Morris CD. Blood pressure response to oral calcium in persons with mild to moderate hypertension. A randomized, double-blind, placebo-controlled, crossover trial. *Annals of Internal Medicine.* 1985; 103(6 (Pt 1)):825-831.
397 McGrady A. Effects of group relaxation training and thermal biofeedback on blood pressure and related physiological and psychological variables in essential hypertension. *Biofeedback and Self Regulation.* 1994; 19(1):51-66.
398 McGrady AV, Yonker R, Tan SY, Fine TH, Woerner M. The effect of biofeedback-assisted relaxation training on blood pressure and selected biochemical parameters in patients with essential hypertension. *Biofeedback and Self Regulation.* 1981; 6(3):343-353.
399 McKeigue PM, Marmot MG, Syndercombe Court YD, Cottier DE, Rahman S, Riemersma RA. Diabetes, hyperinsulinaemia, and coronary risk factors in Bangladeshis in east London. *British Heart Journal.* 1988; 60(5):390-396.
400 McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. *Lancet.* 1991; 337(8738):382-386.
401 McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, Kaambwa B, Banting M, Bryan S, Little P, Williams B, Hobbs FD. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet.* 2010; 376(9736):163-172.
402 Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *BMJ.* 1985; 291(6488):97-104.
403 Melsop KA, Boothroyd DB, Hlatky MA. Quality of life and time trade-off utility measures in patients with coronary artery disease. *American Heart Journal.* 2003; 145(1):36-41.

404 Mesquita-Bastos J, Bertoquini S, Polonia J. Cardiovascular prognostic value of ambulatory blood pressure monitoring in a Portuguese hypertensive population followed up for 8.2 years. *Blood Pressure Monitoring.* 2010; 15(5):240-246.
405 Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hara A, Hirose T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognostic significance of night-time, early morning, and daytime blood pressures on the risk of cerebrovascular and cardiovascular mortality: the Ohasama Study. *Journal of Hypertension.* 2006; 24(9):1841-1848.
406 Metz JA, Stern JS, Kris-Etherton P, Reusser ME, Morris CD, Hatton DC, Oparil S, Haynes RB, Resnick LM, Pi-Sunyer FX, Clark S, Chester L, McMahon M, Snyder GW, McCarron DA. A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on cardiovascular risk reduction. *Archives of Internal Medicine.* 2000; 160(14):2150-2158.
407 Midgley JP, Matthew AG, Greenwood CM, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA.* 1996; 275(20):1590-1597.
408 Miller ER, III, Erlinger TP, Young DR, Jehn M, Charleston J, Rhodes D, Wasan SK, Appel LJ. Results of the Diet, Exercise, and Weight Loss Intervention Trial (DEW-IT). *Hypertension.* 2002; 40(5):612-618.
409 Miller JM, Miller JM. Diabetes mellitus and hypertension in black and white populations. *Southern Medical Journal.* 1986; 79(10):1229.
410 Mills CA, Porter MM. Tobacco smoking habits and cancer of the mouth and respiratory system. *Cancer Research.* 1950; 10(9):539-542.
411 Mitchell A, Haynes RB, Adsett CA, Bellissimo A, Wilczynski N. The likelihood of remaining normotensive following antihypertensive drug withdrawal. *Journal of General Internal Medicine.* 1989; 4(3):221-225.
412 Montgomery AA, Fahey T, Ben-Shlomo Y, Harding J. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: a Markov decision analysis. *Journal of Hypertension.* 2003; 21(9):1753-1759.
413 Morgan T, Hopper J, Anderson A, Carricks L, Jones E, Johns J. Can drug therapy be stopped in elderly hypertensive patients? *Cardiology in the Elderly.* 1994; 2:119-125.
414 Morris CD, Karanja N, McCarron DA. Dietary versus supplemental calcium to reduce blood pressure. *Clinical Research.* 1988; 36:A139.
415 Mulrow CD, Chiquette E, Angel L, Cornell J, Summerbell C, Anagnostelis B, Grimm R, Jr., Brand MB. Dieting to reduce body weight for controlling hypertension in adults. *Cochrane Database of Systematic Reviews.* 2000;(2):CD000484.
416 Murakami S, Otsuka K, Kubo Y, Shinagawa M, Yamanaka T, Ohkawa S-I, Kitaura Y. Repeated ambulatory monitoring reveals a Monday morning surge in blood pressure in a community-dwelling population. *American Journal of Hypertension.* 2004; 17(12):1179-1183.
417 Murchie P, Campbell NC, Ritchie LD, Simpson JA, Thain J. Secondary prevention clinics for coronary heart disease: four year follow up of a randomised controlled trial in primary care. *BMJ.* 2003; 326(7380):84.
418 Murugesan R, Govindarajulu N, Bera TK. Effect of selected yogic practices on the management of hypertension. *Indian Journal of Physiology and Pharmacology.* 2000; 44(2):207-210.
419 Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. *Cochrane Database of Systematic Reviews.* 2009; Issue 4:CD000028.
420 Musso NR, Vergassola C, Barone C, Lotti G. Ambulatory blood pressure monitoring: how reproducible is it? *American Journal of Hypertension.* 1997; 10(8):936-939.
421 Myers MG, Reeves RA, Oh PI, Joyner CD. Overtreatment of hypertension in the community? *American Journal of Hypertension.* 1996; 9(5):419-425.

422 National Centre for Social Research and University College London.Department of Epidemiology and Public Health.*Health Survey for England, 2006 [Computer File]*. 3rd ed. Colchester: Essex: UK Data Archive [distributor]; 2010
423 National Clinical Guideline Centre. *Unstable Angina and NSTEMI: the Early Management of Unstable Angina and Non-ST-Segment-Elevation Myocardial Infarction.* (CG94). London: Royal College of Physicians, 2010.
424 National Clinical Guideline Centre for Acute and Chronic Conditions. *Management of Stable Angina: NICE Guideline: Draft for Consultation, December 2010*. 2010. London, National Clinical Guideline Centre for Acute and Chronic Conditions. http://www.nice.org.uk/nicemedia/live/11878/52141/52141.pdf
425 National Collaborating Centre for Chronic Conditions.*Hypertension: Management in Adults in Primary Care: Pharmacological Update*. London: Royal College of Physicians; 2006. Available from: http://guidance.nice.org.uk/CG34
426 National Collaborating Centre for Primary Care.*Medicines Adherence - Involving Patients in Decisions About Prescribed Medicines and Supporting Adherence. National Clinical Guideline Number 76*. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2009. Available from: http://guidance.nice.org.uk/CG76
427 National Institute for Health and Clinical Excellence. *Guide to the Methods of Technology Appraisal.* London: National Institute for Health and Clinical Excellence, 2008.
428 National Institute for Health and Clinical Excellence. *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease.* London: National Institute for Health and Clinical Excellence, 2008.
429 National Institute for Health and Clinical Excellence. *Social Value Judgements. Principles for the development of NICE guidance. Second edition.* Available from: http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf Last accessed on: 15 November 2010.
430 National Institute for Health and Clinical Excellence.*The Guidelines Manual*. London: National Institute for Health and Clinical Excellence; 2009. Available from: http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf
431 National Institute for Health and Clinical Excellence. *Chest Pain of Recent Onset: Assessment and Diagnosis of Recent Onset Chest Pain or Discomfort of Suspected Cardiac Origin.* London: National Institute for Health and Clinical Excellence, 2010.
432 National Institute for Health and Clinical Excellence. *Clopidogrel and Modified-Release Dipyridamole for the Prevention of Occlusive Vascular Events: Review of NICE Technology Appraisal Guidance 90.* London: National Institute for Health and Clinical Excellence, 2010.
433 Nelson M. Author's reply to two responses. *BMJ.* 2002;
434 Nelson M, Reid C, Krum H, McNeil J. A systematic review of predictors of maintenance of normotension after withdrawal of antihypertensive drugs. *American Journal of Hypertension.* 2001; 14(2):98-105.
435 Nelson MR, Reid CM, Krum H, Muir T, Ryan P, McNeil JJ. Predictors of normotension on withdrawal of antihypertensive drugs in elderly patients: prospective study in second Australian national blood pressure study cohort. *BMJ.* 2002; 325(7368):815.
436 Newcastle Guideline Development and Research Unit. *Hypertension: Management of Hypertension in Adults in Primary Care.* London: National Institute for Clinical Excellence, 2004.
437 Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocrinology Review.* 1998; 19(5):647-672.

438 Niiranen TJ, Hanninen MR, Johansson J, Reunanen A, Jula AM. Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure: the Finn-Home study. *Hypertension.* 2010; 55(6):1346-1351.
439 Niiranen TJ, Kantola IM, Vesalainen R, Johansson J, Ruuska MJ. A comparison of home measurement and ambulatory monitoring of blood pressure in the adjustment of antihypertensive treatment. *American Journal of Hypertension.* 2006; 19(5):468-474.
440 North of England Evidence-based Guidelines Development Project. *Primary Care Management of Secondary Prophylaxis for Patients Who Have Experienced a Myocardial Infarction: Drug Treatment, Cardiac Rehabilitation and Dietary Manipulation.* Newcastle: University of Newcastle, Centre for Health Services Research, 2001.
441 North of England Hypertension Guideline Development Group. *Essential Hypertension: Managing Adult Patients in Primary Care.* Newcastle upon Tyne: Cetnre for Health Services Research, 2004.
442 Nowson C, Morgan T. Effect of calcium carbonate on blood pressure in normotensive and hypertensive people. *Hypertension.* 1989; 13(6 Pt 1):630-639.
443 Nowson CA, Morgan TO. Magnesium supplementation in mild hypertensive patients on a moderately low sodium diet. *Clinical and Experimental Pharmacology and Physiology.* 1989; 16(4):299-302.
444 Nurminen ML, Niittynen L, Korpela R, Vapaatalo H. Coffee, caffeine and blood pressure: a critical review. *European Journal of Clinical Nutrition.* 1999; 53(11):831-839.
445 O'Brien E. Replacing the mercury sphygmomanometer. Requires clinicians to demand better automated devices. *BMJ.* 2000; 320(7238):815-816.
446 O'Brien E. State of the market for devices for blood pressure measurement. *Blood Pressure Monitoring.* 2001; 6(6):281-286.
447 O'Brien E, Atkins N. A comparison of the British Hypertension Society and Association for the Advancement of Medical Instrumentation protocols for validating blood pressure measuring devices: can the two be reconciled? *Journal of Hypertension.* 1994; 12(9):1089-1094.
448 O'Brien E, Beevers G, Lip G. ABC of hypertension: Blood pressure measurement. Part III. *BMJ.* 2001; 322(7294):1110-1114.
449 O'Brien E, Beevers G, Lip GY. ABC of hypertension: Blood pressure measurement. Part IV-automated sphygmomanometry: self blood pressure measurement. *BMJ.* 2001; 322(7295):1167-1170.
450 O'Brien E, Coats A, Owens P, Petrie J, Padfield PL, Littler WA, de SM, Mee F. Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British hypertension society. *BMJ.* 2000; 320(7242):1128-1134.
451 O'Brien E, Petrie J, Littler W, de SM, Padfield PL, Altman DG, Bland M, Coats A, Atkins N. An outline of the revised British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *Journal of Hypertension.* 1993; 11(6):677-679.
452 O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *BMJ.* 2001; 322(7285):531-536.
453 O'Malley K, McCormack P, O'Brien ET. Isolated systolic hypertension: data from the European Working Party on High Blood Pressure in the Elderly. *Journal of Hypertension - Supplement.* 1988; 6(1):S105-S108.
454 Obara F, Saitoh S, Takagi S, Shimamoto K. Influence of hypertension on the incidence of cardiovascular disease in two rural communities in Japan: the Tanno-Sobetsu [corrected] study. *Hypertension Research - Clinical and Experimental.* 2007; 30(8):677-682.
455 Obel AO. Placebo-controlled trial of potassium supplements in black patients with mild essential hypertension. *Journal of Cardiovascular Pharmacology.* 1989; 14(2):294-296.

456 Octavio JA, Contreras J, Amair P, Octavio B, Fabiano D, Moleiro F, Omboni S, Groppelli A, Bilo G, Mancia G, Parati G. Time-weighted vs. conventional quantification of 24-h average systolic and diastolic ambulatory blood pressures. *Journal of Hypertension.* 2010; 28(3):459-464.
457 Office for National Statistics. *Mortality Statistcs: Cause: Review of the Registrar General on Deaths by Cause, Sex and Age in England and Wales, 2000.* London: Office of National Statistics, 2001.
458 Office for National Statistics. *Life Tables (Online Edition).* 2011. London, Office for National Statistics.
459 Office for National Statistics (ONS). *England and Wales, Interim Life Tables, 1980-82 to 2007-09*. Available from: http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=14459 Last accessed on: 21 October 2010.
460 Office for National Statistics (ONS). *Mortality statistics: deaths registered in 2008.* Available from: http://www.statistics.gov.uk/statbase/product.asp?vlnk=15096 Last accessed on: 21 October 2010.
461 Ogedegbe G, Pickering TG, Clemow L, Chaplin W, Spruill TM, Albanese GM, Eguchi K, Burg M, Gerin W. The misdiagnosis of hypertension: The role of patient anxiety. *Archives of Internal Medicine.* 2008; 168(22):2459-2465.
462 Ogihara T, Saruta T, Rakugi H, Fujimoto A, Ueshima K, Yasuno S, Oba K, Takeda K, Higaki J, Nakao K. Relationship between the achieved blood pressure and the incidence of cardiovascular events in Japanese hypertensive patients with complications: A sub-analysis of the CASE-J trial. *Hypertension Research.* 2009; 32(4):248-254.
463 Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, Imai Y, Kikuchi K, Ito S, Eto T, Kimura G, Imaizumi T, Takishita S, Ueshima H, Valsartan in Elderly Isolated Systolic Hypertension Study Group. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension.* 2010; 56(2):196-202.
464 Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y, Ohasama S. How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *Journal of Hypertension.* 2004; 22(6):1099-1104.
465 Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Itoh O, Bando T, Sakuma M, Fukao A, Satoh H, Hisamichi S, Abe K. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *Journal of Hypertension.* 1997; 15(4):357-364.
466 Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H, NIPPON DATA. Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). *Journal of Hypertension.* 2006; 24(3):459-462.
467 Onusko E. Diagnosing secondary hypertension. *American Family Physician.* 2003; 67(1):67-74.
468 Organisation for Economic Co-operation and Development (OECD). *OECD Stat Extracts: purchasing power parities for GDP*. Available from: http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4 Last accessed on: 10 November 2010.
469 Orth DN. Cushing's syndrome. *New England Journal of Medicine.* 1995; 332(12):791-803.
470 Overlack A, Conrad H, Stumpe KO. The influence of oral potassium citrate/bicarbonate on blood pressure in essential hypertension during unrestricted salt intake. *Klinische Wochenschrift.* 1991; 69 Suppl 25:79-83.

471 Pagliari CP, Grimshaw JM, Eccles M. The potential influence of small group processes on guideline development. *Journal of Evaluation in Clinical Practice.* 2001; 7(2):165-173.
472 Palatini P, Julius S, Collatina S, Rappelli S, Staessen J, Pessina AC. Optimizing the assessment of the elderly patient with borderline hypertension: the Hypertension and Ambulatory Recording in the OLD (HAROLD) study. *Aging.* 1997; 9(5):365-371.
473 Palatini P, Mormino P, Canali C, Santonastaso M, De VG, Zanata G, Pessina AC. Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST Trial. Hypertension and Ambulatory Recording Venetia Study. *Hypertension.* 1994; 23(2):211-216.
474 Palmer, S, Sculpher, M, Philips, Z, Robinson, M, and et al. *A Cost Effectiveness Model Comparing Alternative Management Strategies for the Use of Glycoprotein IIB/IIIA Anatagonists in Non-ST-Elevation Acute Conorary Syndrome.* York: Center for Health Economics, 2002.
475 Paolisso G, Di MG, Cozzolino D, Salvatore T, D'Amore A, Lama D, Varricchio M, D'Onofrio F. Chronic magnesium administration enhances oxidative glucose metabolism in thiazide treated hypertensive patients. *American Journal of Hypertension.* 1992; 5(10):681-686.
476 Parati G, Omboni S, Albini F, Piantoni L, Giuliano A, Revera M, Illyes M, Mancia G, TeleBPCare Study Group. Home blood pressure telemonitoring improves hypertension control in general practice. The TeleBPCare study. *Journal of Hypertension.* 2009; 27(1):198-203.
477 Patel C, Marmot M. Can general practitioners use training in relaxation and management of stress to reduce mild hypertension? *BMJ.* 1988; 296(6614):21-24.
478 Patel C, Marmot MG, Terry DJ. Controlled trial of biofeedback-aided behavioural methods in reducing mild hypertension. *BMJ.* 1981; 282(6281):2005-2008.
479 Patel C, Marmot MG, Terry DJ, Carruthers M, Hunt B, Patel M. Trial of relaxation in reducing coronary risk: four year follow up. *BMJ.* 1985; 290(6475):1103-1106.
480 Payne R. *Excel worksheet for calculating cardiovascular risk*. Available from: http://cvrisk.mvm.ed.ac.uk/calculator/excelcalc.htm
481 Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA.* 2003; 290(21):2805-2816.
482 Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZ. Human blood pressure determination by sphygmomanometry. *Circulation.* 1993; 88(5 Pt 1):2460-2470.
483 Perry HM, Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, Kuller L, Pressel S, Stamler J, Probsfieldt JL. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 2000; 284:465-471.
484 Perry HM, McDonald RH, Hulley SB, Smith WM, Furberg CD, Greenlick MR. Systolic Hypertension in the Elderly Program. Pilot Study (SHEP-PS): morbidity and mortality experience. *Journal of Hypertension.* 1986; 4(6):S21-S23.
485 Perry HM, Jr., Smith WM, McDonald RH, Black D, Cutler JA, Furberg CD, Greenlick MR, Kuller LH, Schnaper HW, Schoenberger JA, . Morbidity and mortality in the Systolic Hypertension in the Elderly Program (SHEP) pilot study. *Stroke.* 1989; 20(1):4-13.
486 Personal Social Services Research Unit. *Unit costs of health and social care 2010*. Available from: http://www.pssru.ac.uk/uc/uc2010contents.htm Last accessed on: 23 December 10 A.D.

487 Petersen LJ, Rudnicki M, Hojsted J. Long-term oral calcium supplementation reduces diastolic blood pressure in end stage renal disease. A randomized, double-blind, placebo controlled study. *International Journal of Artificial Organs.* 1994; 17(1):37-40.
488 Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ.* 2000; 321(7257):323-329.
489 Petrella RJ. How effective is exercise training for the treatment of hypertension? *Clinical Journal of Sport Medicine.* 1998; 8(3):224-231.
490 Pickering T. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. *American Journal of Hypertension.* 1996; 9(1):1-11.
491 Pickering T, Schwartz J, Verdecchia P, Imai Y, Kario K, Eguchi K, Pierdomenico S, Ohkubo T, Wing L. Prediction of strokes versus cardiac events by ambulatory monitoring of blood pressure: results from an international database. *Blood Pressure Monitoring.* 2007; 12(6):397-399.
492 Piller LB, Ford CE, Davis BR, Nwachuku C, Black HR, Oparil S, Retta TM, Probstfield JL, ALLHAT Collaborative Research Group. Incidence and predictors of angioedema in elderly hypertensive patients at high risk for cardiovascular disease: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Journal of Clinical Hypertension.* 2006; 8(9):649-656.
493 Plante GE, Dessurault DL. Hypertension in elderly patients. A comparative study between indapamide and hydrochlorothiazide. *American Journal of Medicine.* 1988; 84(1B):98-103.
494 Plante GE, Robillard C. Indapamide in the treatment of essential arterial hypertension: results of a controlled study. *Current Medical Research and Opinion.* 1983; 8 Suppl 3:59-66.
495 Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, Robinson E, Wareham NJ. Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. *American Journal of Clinical Nutrition.* 2002; 75(1):11-20.
496 Poulter NR, Khaw KT, Hopwood BE, Mugambi M, Peart WS, Rose G, Sever PS. The Kenyan Luo migration study: observations on the initiation of a rise in blood pressure. *BMJ.* 1990; 300(6730):967-972.
497 Power C, Rodgers B, Hope S. U-shaped relation for alcohol consumption and health in early adulthood and implications for mortality. *Lancet.* 1998; 352(9131):877.
498 Prisco D, Paniccia R, Bandinelli B, Filippini M, Francalanci I, Giusti B, Giurlani L, Gensini GF, Abbate R, Neri Serneri GG. Effect of medium-term supplementation with a moderate dose of n-3 polyunsaturated fatty acids on blood pressure in mild hypertensive patients. *Thrombosis Research.* 1998; 91(3):105-112.
499 Pritchard DA, Hyndman J, Taba F. Nutritional counselling in general practice: a cost effective analysis. *Journal of Epidemiology and Community Health.* 1999; 53(5):311-316.
500 PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet.* 2001; 358(9287):1033-1041.
501 Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA.* 1997; 277(9):739-745.
502 Puddey IB, Parker M, Beilin LJ, Vandongen R, Masarei JR. Effects of alcohol and caloric restrictions on blood pressure and serum lipids in overweight men. *Hypertension.* 1992; 20(4):533-541.

503 Rakic D, Rumboldt Z, Bagatin J, Polic S. Effects of four antihypertensive monotherapies on cardiac mass and function in hypertensive patients with left ventricular hypertrophy: randomized prospective study. *Croatian Medical Journal.* 2002; 43(6):672-679.
504 Raleigh VS. Diabetes and hypertension in britain's ethnic minorities: implications for the future of renal services. *BMJ.* 1997; 314(7075):209.
505 Ramsay L, Williams B, Johnston G, MacGregor G, Poston L, Potter J, Poulter N, Russell G. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *Journal of Human Hypertension.* 1999; 13(9):569-592.
506 Redon J, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension.* 1998; 31(2):712-718.
507 Reims HM, Oparil S, Kjeldsen SE, Devereux RB, Julius S, Brady WE, Fyhrquist F, Ibsen H, Lindholm LH, Omvik P, Wedel H, Beevers G, de Faire U, Kristianson K, Lederballe-Pedersen O, Nieminen MS, Dahlof B, LIFE Study Group. Losartan benefits over atenolol in non-smoking hypertensive patients with left ventricular hypertrophy: the LIFE study. *Blood Pressure.* 2004; 13(6):376-384.
508 Reisin E, Abel R, Modan M, Silverberg DS, Eliahou HE, Modan B. Effect of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. *New England Journal of Medicine.* 1978; 298(1):1-6.
509 Richards AM, Nicholls MG, Espiner EA, Ikram H, Turner JG, Brownlie BE. Hypertension in hypothyroidism: arterial pressure and hormone relationships. *Clinical and Experimental Hypertension Part A: Theory and Practice.* 1985; 7(11):1499-1514.
510 Rivas M, Garay RP, Escanero JF, Cia P, Jr., Cia P, Alda JO. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *Journal of Nutrition.* 2002; 132(7):1900-1902.
511 Rodilla E, Costa JA, Perez-Lahiguera F, Baldo E, Gonzalez C, Pascual JM. Spironolactone and doxazosin treatment in patients with resistant hypertension. *Revista Espanola De Cardiologia.* 2009; 62(2):158-166.
512 Rodriguez Roca GC, onso Moreno FJ, Garcia JA, Vega A, Llisterri Caro JL, Barrios A, V, Segura FA, Clemente = Lirola E et al. Cost-effectiveness of ambulatory blood pressure monitoring in the follow-up of hypertension. *Blood Pressure.* 2006; 15(1):27-36.
513 Rogers MW, Probst MM, Gruber JJ, Berger R, Boone JB, Jr. Differential effects of exercise training intensity on blood pressure and cardiovascular responses to stress in borderline hypertensive humans. *Journal of Hypertension.* 1996; 14(11):1369-1375.
514 Rosei EA, Dal Palú C, Leonetti G, Magnani B, Pessina A, Zanchetti A. Clinical results of the Verapamil in Hypertension and Atherosclerosis Study. *Journal of Hypertension.* 1997; 15:1337-1344.
515 Rosengren A, Wilhelmsen L, Hagman M, Wedel H. Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16-year follow-up of the Primary Prevention Study, Goteborg, Sweden. *Journal of Internal Medicine.* 1998; 244(6):495-505.
516 Rosmarin PC. Coffee and coronary heart disease: a review. *Progress in Cardiovascular Diseases.* 1989; 32(3):239-245.
517 Roth RP, Cantekin EI, Bluestone CD, Welch RM, Cho YW. Nasal decongestant activity of pseudoephedrine. *Annals of Otology, Rhinology and Laryngology.* 1977; 86(2 pt. 1):235-242.
518 Royal Pharmaceutical Society of Great Britian Working Party. *Partnership in Medicine Taking: a Consultative Document.* London: Royal Pharmaceutical Society of Great Britain and Mercke Sharpe and Dohme, 1996.

519 Sacks FM, Brown LE, Appel L, Borhani NO, Evans D, Whelton P. Combinations of potassium, calcium, and magnesium supplements in hypertension. *Hypertension.* 1995; 26(6 Pt 1):950-956.
520 Sacks FM, Obarzanek E, Windhauser MM, Svetkey LP, Vollmer WM, McCullough M, Karanja N, Lin PH, Steele P, Proschan MA, . Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH). A multicenter controlled-feeding study of dietary patterns to lower blood pressure. *Annals of Epidemiology.* 1995; 5(2):108-118.
521 Sairenchi T, Iso H, Irie F, Fukasawa N, Yamagishi K, Kanashiki M, Saito Y, Ota H, Nose T. Age-specific relationship between blood pressure and the risk of total and cardiovascular mortality in Japanese men and women. *Hypertension Research - Clinical and Experimental.* 2005; 28(11):901-909.
522 Saito I, Kobayashi M, Matsushita Y, Saruta T. Pharmacoeconomical evaluation of combination therapy for lifetime hypertension treatment in Japan. *Journal of the Medical Association of Japan.* 2005; 48(12):574-585.
523 Sakuma M, Imai Y, Tsuji I, Nagai K, Ohkubo T, Watanabe N, Sakuma H, Satoh H, Hisamichi S. Predictive value of home blood pressure measurement in relation to stroke morbidity: a population-based pilot study in Ohasama, Japan. *Hypertension Research.* 1997; 20(3):167-174.
524 Sareli P, Radevski IV, Valtchanova ZP, Libhaber E, Candy GP, Den HE, Libhaber C, Skudicky D, Wang JG, Staessen JA. Efficacy of different drug classes used to initiate antihypertensive treatment in black subjects: results of a randomized trial in Johannesburg, South Africa. *Archives of Internal Medicine.* 2001; 161(7):965-971.
525 Schein MH, Gavish B, Herz M, Rosner-Kahana D, Naveh P, Knishkowy B, Zlotnikov E, Ben-Zvi N, Melmed RN. Treating hypertension with a device that slows and regularises breathing: a randomised, double-blind controlled study. *Journal of Human Hypertension.* 2001; 15(4):271-278.
526 Schillaci G, Verdecchia P, Porcellati C, Cuccurullo O, Cosco C, Perticone F. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. *Hypertension.* 2000; 35(2):580-586.
527 Schillaci G, Verdecchia P, Zampi I, Battistelli M, Bartoccini C, Porcellati C. Non-invasive ambulatory BP monitoring during the night: Randomised comparison of different reading intervals. *Journal of Human Hypertension.* 1994; 8(1):23-27.
528 Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K, Berger J, Zidek W, Dominiak P, Diener HC. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke.* 2005; 36(6):1218-1226.
529 Schwander B, Gradl B, Zollner Y, Lindgren P, Diener HC, Luders S, Schrader J, Villar FA, Greiner W, Jonsson B. Cost-utility analysis of eprosartan compared to enalapril in primary prevention and nitrendipine in secondary prevention in Europe--the HEALTH model. *Value in Health.* 2009; 12(6):857-871.
530 Schwartz GL, Turner ST, Moore JH, Sing CF. Effect of time of day on intraindividual variability in ambulatory blood pressure. *American Journal of Hypertension.* 2000; 13(11):1203-1209.
531 Schwartz GL, Turner ST, Moore JH, Sing CF. Predictors of interindividual variation in ambulatory blood pressure and their time or activity dependence. *American Journal of Hypertension.* 2000; 13(1 I):52-60.
532 Scientific AdvisoryCommittee on Nutrition. *Salt and Health.* Norwich: The Stationery Office, 2003.
533 Seer P, Raeburn JM. Meditation training and essential hypertension: a methodological study. *Journal of Behavioral Medicine.* 1980; 3(1):59-71.

534 Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation.* 2005; 111(14):1777-1783.
535 Semple PF. Investigation. *ABC of Hypertension: Articles From the British Medical Journal,* London: British Medical Asssociation, 1981: 38-41.
536 SHEP Cooperative Research Group. Rationale and design of a randomized clinical trial on prevention of stroke in isolated systolic hypertension. *Journal of Clinical Epidemiology.* 1988; 41(12):1197-1208.
537 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA.* 1991; 265(24):3255-3264.
538 Sheps SG, Bailey KR, Zachariah PK. Short-term (six hour), ambulatory blood pressure monitoring. *Journal of Human Hypertension.* 1994; 8(12):873-878.
539 Shimamoto K, Fujita T, Ito S, Naritomi H, Ogihara T, Shimada K, Tanaka H, Yoshiike N, -HEALTH Study Committee. Impact of blood pressure control on cardiovascular events in 26,512 Japanese hypertensive patients: the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study, a prospective nationwide observational study. *Hypertension Research - Clinical and Experimental.* 2008; 31(3):469-478.
540 Shimbo D, Kuruvilla S, Haas D, Pickering TG, Schwartz JE, Gerin W. Preventing misdiagnosis of ambulatory hypertension: algorithm using office and home blood pressures. *Journal of Hypertension.* 2009; 27(9):1775-1783.
541 Shinagawa M, Otsuka K, Murakami S, Kubo Y, Cornelissen G, Matsubayashi K, Yano S, Mitsutake G, Yasaka K, Halberg F. Seven-day (24-h) ambulatory blood pressure monitoring, self-reported depression and quality of life scores. *Blood Pressure Monitoring.* 2002; 7(1):69-76.
542 Shulman NB, Hall WD. Renal vascular disease in African-Americans and other racial minorities. *Circulation.* 1991; 83(4):1477-1479.
543 Siani A, Strazzullo P, Russo L, Guglielmi S, Iacoviello L, Ferrara LA, Mancini M. Controlled trial of long term oral potassium supplements in patients with mild hypertension. *BMJ.* 1987; 294(6585):1453-1456.
544 Silman AJ, Locke C, Mitchell P, Humpherson P. Evaluation of the effectiveness of a low sodium diet in the treatment of mild to moderate hypertension. *Lancet.* 1983; 1(8335):1179-1182.
545 Singh RB, Niaz MA, Bishnoi I, Singh U, Begum R, Rastogi SS. Effect of low energy diet and weight loss on major risk factors, central obesity and associated disturbances in patients with essential hypertension. *Journal of Human Hypertension.* 1995; 9(5):355-362.
546 Sleight P, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R, Schumacher H, Weber M, Böhm M, Williams B, Pogue J, Koon T, Yusuf S, ONTARGET i. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. *Journal of Hypertension.* 2009; 27(7):1360-1369.
547 Smith MB, Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. *JAMA.* 1993; 269(17):2258-2263.
548 Smith WM. Treatment of mild hypertension: results of a ten-year intervention trial. *Circulation Research.* 1977; 40(5 Suppl 1):I98-105.
549 Solomon SD, Verma A, Desai A, Hassanein A, Izzo J, Oparil S, Lacourciere Y, Lee J, Seifu Y, Hilkert RJ, Rocha R, Pitt B, Exforge Intensive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction Investigators. Effect of intensive versus standard blood

pressure lowering on diastolic function in patients with uncontrolled hypertension and diastolic dysfunction. *Hypertension.* 2010; 55(2):241-248.
550 Spence JD, Barnett PA, Linden W, Ramsden V, Taenzer P. Lifestyle modifications to prevent and control hypertension. 7. Recommendations on stress management. Canadian Hypertension Society, Canadian Coalition for High Blood Pressure Prevention and Control, Laboratory Centre for Disease Control at Health Canada, Heart and Stroke Foundation of Canada. *Canadian Medical Association Journal.* 1999; 160(9 Suppl):S46-S50.
551 Spence JD, Huff M, Barnett PA. Effects of indapamide versus hydrochlorothiazide on plasma lipids and lipoproteins in hypertensive patients: a direct comparison. *Canadian Journal of Clinical Pharmacology.* 2000; 7(1):32-37.
552 Spinar J, Vitovec J, Soucek M, Dusek L, Pavlik T, Invesigators CORD. CORD: COmparsion of Recommended Doses of ACE inhibitors and angiotensin II receptor blockers. *Vnitrni Lekarstvi.* 2009; 55(5):481-488.
553 Sprafka JM, Strickland D, Gomez-Marin O, Prineas RJ. The effect of cuff size on blood pressure measurement in adults. *Epidemiology.* 1991; 2(3):214-217.
554 Staessen JA, Den HE, Celis H, Fagard R, Keary L, G, O'Brien ET. Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. *JAMA.* 2004; 291(8):955-964.
555 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, Bulpitt CJ, De Leeuw P, Dollery CT, Fletcher AE, Forette F, Leonetti G, Nachev C, O'Brien ET, Rosenfeld J, Rodicio JL, Tuomilehto J, Zanchetti A. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet.* 1997; 350(9080):757-764.
556 Staessen JA, Thijs L. Development of diagnostic thresholds for automated self-measurement of blood pressure in adults. First International Consensus Conference on Blood Pressure Self-Measurement. *Blood Pressure Monitoring.* 2000; 5(2):101-109.
557 Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA.* 1999; 282(6):539-546.
558 Staessen JA, Wang JG, Thijs L, Celis H, Gasowski J, Fagard RH. Use of dihydropyridines for antihypertensive treatment in older patients: Evidence from the systolic hypertension in Europe trial. *Journal of Clinical & Basic Cardiology.* 2000; 3:15-21.
559 Staffileno BA, Braun LT, Rosenson RS. The accumulative effects of physical activity in hypertensive post-menopausal women. *Journal of Cardiovascular Risk.* 2001; 8(5):283-290.
560 Stafilas PC, Sarafidis PA, Lasaridis AN, Aletras VH, Niakas D. An economic evaluation of the 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of mild-to-moderate hypertension in Greece. *American Journal of Hypertension.* 2005; 18(9):1233-1240.
561 Stamler R, Stamler J, Grimm R, Gosch F, Dyer A, Berman R, Civinelli J, Elmer P, Fishman J, Van HN, . Trial on control of hypertension by nutritional means: three-year results. *Journal of Hypertension - Supplement.* 1984; 2(3):S167-S170.
562 Stenehjem AE, Os I. Reproducibility of blood pressure variability, white-coat effect and dipping pattern in untreated, uncomplicated and newly diagnosed essential hypertension. *Blood Pressure.* 2004; 13(4):214-224.
563 Stergiou GS, Baibas NM, Gantzarou AP, Skeva II, Kalkana CB, Roussias LG, Mountokalakis TD. Reproducibility of home, ambulatory, and clinic blood pressure: implications for the design of trials for the assessment of antihypertensive drug efficacy. *American Journal of Hypertension.* 2002; 15(2 Pt 1):101-104.

564 Stergiou GS, Baibas NM, Kalogeropoulos PG. Cardiovascular risk prediction based on home blood pressure measurement: the Didima study. *Journal of Hypertension.* 2007; 25(8):1590-1596.
565 Stergiou GS, Nasothimiou EG, Kalogeropoulos PG, Pantazis N, Baibas NM. The optimal home blood pressure monitoring schedule based on the Didima outcome study. *Journal of Human Hypertension.* 2010; 24(3):158-164.
566 Stergiou GS, Salgami EV, Tzamouranis DG, Roussias LG. Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: is it the same phenomenon? *American Journal of Hypertension.* 2005; 18(6):772-778.
567 Stergiou GS, Skeva II, Baibas NM, Kalkana CB, Roussias LG, Mountokalakis TD. Diagnosis of hypertension using home or ambulatory blood pressure monitoring: comparison with the conventional strategy based on repeated clinic blood pressure measurements. *Journal of Hypertension.* 2000; 18(12):1745-1751.
568 Stergiou GS, Skeva II, Zourbaki AS, Mountokalakis TD. Self-monitoring of blood pressure at home: how many measurements are needed? *Journal of Hypertension.* 1998; 16(6):725-731.
569 Stergiou GS, Zourbaki AS, Skeva II, Mountokalakis TD. White coat effect detected using self-monitoring of blood pressure at home: comparison with ambulatory blood pressure. *American Journal of Hypertension.* 1998; 11(7):820-827.
570 Stewart PM. Mineralocorticoid hypertension. *Lancet.* 1999; 353(9161):1341-1347.
571 Strazzullo P, Siani A, Gugliemi S, Di CA, Galletti F, Cirillo M, Mancini M. Controlled trial of long-term oral calcium supplementation in essential hypertension. *Hypertension.* 1986; 8(11):1084-1088.
572 Streeten DH, Anderson GH, Jr., Howland T, Chiang R, Smulyan H. Effects of thyroid function on blood pressure. Recognition of hypothyroid hypertension. *Hypertension.* 1988; 11(1):78-83.
573 Suarez C, Del AC, Garcia-Polo I. Ambulatory blood pressure monitoring: is the daytime period enough for making clinical decisions? *Blood Pressure Monitoring.* 2003; 8(6):267-270.
574 Sutcliffe SJ, Fox KF, Wood DA, Sutcliffe A, Stock K, Wright M, Akhras F, Langford E. Incidence of coronary heart disease in a health authority in London: review of a community register. *British Medical Journal.* 2003; 326(7379):20.
575 Suter E, Marti B, Tschopp A, Wanner HU, Wenk C, Gutzwiller F. Effects of self-monitored jogging on physical fitness, blood pressure and serum lipids: a controlled study in sedentary middle-aged men. *International Journal of Sports Medicine.* 1990; 11(6):425-432.
576 Suzuki Y, Kuwajima I, Aono T, Kanemaru A, Nishinaga M, Shibata H, Ozawa T. Prognostic value of nighttime blood pressure in the elderly: a prospective study of 24-hour blood pressure. *Hypertension Research - Clinical and Experimental.* 2000; 23(4):323-330.
577 Svetkey LP, Simons-Morton D, Vollmer WM, Appel LJ, Conlin PR, Ryan DH, Ard J, Kennedy BM. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Archives of Internal Medicine.* 1999; 159(3):285-293.
578 Svetkey LP, Yarger WE, Feussner JR, DeLong E, Klotman PE. Double-blind, placebo-controlled trial of potassium chloride in the treatment of mild hypertension. *Hypertension.* 1987; 9(5):444-450.
579 Swales JD.*Manual of Hypertension*. Blackwell Science; 1995
580 Szucs TD, Waeber B, Tomonaga Y. Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: an analysis of the HYVET study from a Swiss perspective. *Journal of Human Hypertension.* 2010; 24(2):117-123.

581 Takagi Y, Fukase M, Takata S, Fujimi T, Fujita T. Calcium treatment of essential hypertension in elderly patients evaluated by 24 H monitoring. *American Journal of Hypertension.* 1991; 4(10 Pt 1):836-839.
582 Takata Y, Yoshizumi T, Ito Y, Ueno M, Tsukashima A, Iwase M, Kobayashi K, Fujishima M. Comparison of withdrawing antihypertensive therapy between diuretics and angiotensin converting enzyme inhibitors in essential hypertensives. *American Heart Journal.* 1992; 124(6):1574-1580.
583 Tanabe Y, Urata H, Kiyonaga A, Ikeda M, Tanaka H, Shindo M, Arakawa K. Changes in serum concentrations of taurine and other amino acids in clinical antihypertensive exercise therapy. *Clinical and Experimental Hypertension Part A: Theory and Practice.* 1989; 11(1):149-165.
584 Tanji JL, Lew EY, Wong GY, Treguboff C, Ward JA, Amsterdam EA. Dietary calcium supplementation as a treatment for mild hypertension. *Journal of the American Board of Family Practice.* 1991; 4(3):145-150.
585 Taylor AH, Doust J, Webborn N. Randomised controlled trial to examine the effects of a GP exercise referral programme in Hailsham, East Sussex, on modifiable coronary heart disease risk factors. *Journal of Epidemiology and Community Health.* 1998; 52(9):595-601.
586 Taylor CB, Farquhar JW, Nelson E, Agras S. Relaxation therapy and high blood pressure. *Archives of General Psychiatry.* 1977; 34(3):339-342.
587 Tedesco MA, Natale F, Calabro R. Effects of monotherapy and combination therapy on blood pressure control and target organ damage: a randomized prospective intervention study in a large population of hypertensive patients. *Journal of Clinical Hypertension.* 2006; 8(9):634-641.
588 Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics.* 2003; 21(3):191-200.
589 The ALLHAT Officers and Co-ordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA.* 2000; 283:1967-1975.
590 The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA.* 2002; 288(23):2981-2997.
591 The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to Pravastatin vs usual care. *JAMA.* 2002; 288(23):2998-3007.
592 The CAPPP group. The Captopril Prevention Project: a prospective intervention trial of angiotensin converting enzyme inhibition in the treatment of hypertension. *Journal of Hypertension.* 1990; 8:985-990.
593 The NHS Information Centre Prescribing Support Unit. *NHS Prescription Cost Analysis 2009.* The Health and Social Care Information Centre, 2009.
594 The Nordic Diltiazem Study Group. A prospective intervention trials of calcium antagonist therapy in hypertension. *Blood Pressure.* 1993; 2(4):312-321.
595 Thijs L, Amery A, Clement D, Cox J, De CP, Fagard R, Fowler G, Guo C, Mancia G, Marin R, O'Brien E, O'Malley K, Palatini P, Parati G, Petrie J, Ravogli A, Rosenfeld J, Staessen J, Webster J. Ambulatory blood pressure monitoring in elderly patients with isolated systolic hypertension. *Journal of Hypertension.* 1992; 10(7):693-699.
596 Thun MJ, Peto R, Lopez AD, Monaco JH, Henley SJ, Heath CW, Jr., Doll R. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *New England Journal of Medicine.* 1997; 337(24):1705-1714.

597 Thurm RH, Smith WM. On restting of "Barostats" in hypertensive patients. *JAMA.* 1967; 201:301-304.
598 Toal CB, Mahon WA, Barnes C, Burelle D. Nifedipine gastrointestinal therapeutic system (GITS) for hypertensive patients in a primary care setting: results of the Extended Release Adalat Canadian Trial (EXACT). *Clinical Therapeutics.* 1997; 19(5):924-935.
599 Torjesen PA, Birkeland KI, Anderssen SA, Hjermann I, Holme I, Urdal P. Lifestyle changes may reverse development of the insulin resistance syndrome. The Oslo Diet and Exercise Study: a randomized trial. *Diabetes Care.* 1997; 20(1):26-31.
600 Trazzi S, Mutti E, Frattola A, Imholz B, Parati G, Mancia G. Reproducibility of non-invasive and intra-arterial blood pressure monitoring: implications for studies on antihypertensive treatment. *Journal of Hypertension.* 1991; 9(2):115-119.
601 Tresukosol D, Sriyudhasak O. Amlodipine and hydrochlorothiazide for isolated systolic hypertension in the Thai elderly. *Siriraj Medical Journal.* 2005; 57(9):374-379.
602 Trudel X, Brisson C, Larocque B, Milot A. Masked hypertension: different blood pressure measurement methodology and risk factors in a working population. *Journal of Hypertension.* 2009; 27(8):1560-1567.
603 Ungar A, Pepe G, Monami M, Lambertucci L, Torrini M, Baldasseroni S, Tarantini F, Marchionni N, Masotti G. Isolated ambulatory hypertension is common in outpatients referred to a hypertension centre. *Journal of Human Hypertension.* 2004; 18(12):897-903.
604 Urata H, Tanabe Y, Kiyonaga A, Ikeda M, Tanaka H, Shindo M, Arakawa K. Antihypertensive and volume-depleting effects of mild exercise on essential hypertension. *Hypertension.* 1987; 9(3):245-252.
605 Uusitupa M, Louheranta A, Lindstrom J, Valle T, Sundvall J, Eriksson J, Tuomilehto J. The Finnish Diabetes Prevention Study. *British Journal of Nutrition.* 2000; 83 Suppl 1:S137-S142.
606 Vaccarino V, Berger AK, Abramson J, Black HR, Setaro JF, Davey JA, Krumholz HM. Pulse pressure and risk of cardiovascular events in the systolic hypertension in the elderly program. *American Journal of Cardiology.* 2001; 88(9):980-986.
607 Van Bortel LM, Bulpitt CJ, Fici F. Quality of life and antihypertensive effect with nebivolol and losartan. *American Journal of Hypertension.* 2005; 18(8):1060-1066.
608 van der Steen MS, Lenders JW, Graafsma SJ, den AJ, Thien T. Reproducibility of ambulatory blood pressure monitoring in daily practice. *Journal of Human Hypertension.* 1999; 13(5):303-308.
609 van Ittersum FJ, Ijzerman RG, Stehouwer CD, Donker AJ. Analysis of twenty-four-hour ambulatory blood pressure monitoring: what time period to assess blood pressures during waking and sleeping? *Journal of Hypertension.* 1995; 13(9):1053-1058.
610 Van Montfrans GA, Karemaker JM, Wieling W, Dunning AJ. Relaxation therapy and continuous ambulatory blood pressure in mild hypertension: a controlled study. *BMJ.* 1990; 300(6736):1368-1372.
611 Verberk WJ, Kroon AA, Kessels AG, de Leeuw PW. Home blood pressure measurement: a systematic review. *Journal of the American College of Cardiology.* 2005; 46:743-751.
612 Verberk WJ, Kroon AA, Kessels AG, Lenders JW, Thien T, Van Montfrans GA, Smit AJ, de Leeuw PW. The optimal scheme of self blood pressure measurement as determined from ambulatory blood pressure recordings. *Journal of Hypertension.* 2006; 24(8):1541-1548.
613 Verdecchia P, Reboldi G, Porcellati C, Schillaci G, Pede S, Bentivoglio M, Angeli F, Norgiolini S, Ambrosio G. Risk of cardiovascular disease in relation to achieved office and ambulatory blood pressure control in treated hypertensive subjects. *Journal of the American College of Cardiology.* 2002; 39(5):878-885.

614 Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Pede S, Porcellati C. Ambulatory pulse pressure: a potent predictor of total cardiovascular risk in hypertension. *Hypertension.* 1998; 32(6):983-988.
615 Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Porcellati C. Prognostic significance of the white coat effect. *Hypertension.* 1997; 29(6):1218-1224.
616 Verdecchia P, Staessen JA, Angeli F, de SG, Achilli A, Ganau A, Mureddu G, Pede S, Maggioni AP, Lucci D, Reboldi G, Cardio-Sis i. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet.* 2009; 374(9689):525-533.
617 Vogt TM, Appel LJ, Obarzanek E, Moore TJ, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Cutler JA, Windhauser MM, Lin PH, Karanja NM. Dietary Approaches to Stop Hypertension: rationale, design, and methods. DASH Collaborative Research Group. *Journal of the American Dietetic Association.* 1999; 99(8 Suppl):S12-S18.
618 Wachtell K, Hornestam B, Lehto M, Slotwiner DJ, Gerdts E, Olsen MH, Aurup P, Dahlof B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Rokkedal J, Devereux RB. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *Journal of the American College of Cardiology.* 2005; 45(5):705-711.
619 Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlof B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *Journal of the American College of Cardiology.* 2005; 45(5):712-719.
620 Waeber B, Brunner HR, Metry JM. Compliance with antihypertensive treatment: implications for practice. *Blood Pressure.* 1997; 6(6):326-331.
621 Walker AF, Marakis G, Morris AP, Robinson PA. Promising hypotensive effect of hawthorn extract: a randomized double-blind pilot study of mild, essential hypertension. *Phytotherapy Research.* 2002; 16(1):48-54.
622 Wallace JP, Park S, Zakutansky DW, Lehmkuhl LA, Jastremski CA. Time of day to monitor ambulatory blood pressure affects the outcome. *Blood Pressure Monitoring.* 2005; 10(1):43-50.
623 Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. *Hypertension.* 2005; 45(5):907-913.
624 Wang JG, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. *Archives of Internal Medicine.* 2000; 160(2):211-220.
625 Ward, S. *Statins for the Prevention of Coronary Events.* London: National Insititute for Clinical Excellence, 2005.
626 Ward S, Lloyd JM, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technology Assessment.* 2007; 11(14):1-iv.
627 Weinberger MH, Wagner UL, Fineberg NS. The blood pressure effects of calcium supplementation in humans of known sodium responsiveness. *American Journal of Hypertension.* 1993; 6(9):799-805.
628 Weir MR. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or CCB vs diuretic: the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Current Hypertension Reports.* 2003; 5(5):405-407.

629 Weitzman D, Goldbourt U. The significance of various blood pressure indices for long-term stroke, coronary heart disease, and all-cause mortality in men: the Israeli Ischemic Heart Disease study. *Stroke.* 2006; 37(2):358-363.
630 West R. Assessment of evidence versus consensus or prejudice. *Journal of Epidemiology and Community Health.* 1992; 46(4):321-322.
631 Whelton PK, Appel LJ, Espeland MA, Applegate WB, Ettinger WH, Jr., Kostis JB, Kumanyika S, Lacy CR, Johnson KC, Folmar S, Cutler JA. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *JAMA.* 1998; 279(11):839-846.
632 Whelton PK, He J. Potassium in preventing and treating high blood pressure. *Seminars in Nephrology.* 1999; 19(5):494-499.
633 Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA.* 1997; 277(20):1624-1632.
634 Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Annals of Internal Medicine.* 2002; 136(7):493-503.
635 White WB. Ambulatory blood pressure as a predictor of target organ disease and outcome in the hypertensive patient. *Blood Pressure Monitoring.* 1999; 4(3-4):181-184.
636 White WB, Dey HM, Schulman P. Assessment of the daily blood pressure load as a determinant of cardiac function in patients with mild-to-moderate hypertension. *American Heart Journal.* 1989; 118(4):782-795.
637 Whitehead A. Meta-Analysis of Controlled Clinical Trials. Chichester, UK: Wiley, 2002: 192.
638 Whitty CJ, Brunner EJ, Shipley MJ, Hemingway H, Marmot MG. Differences in biological risk factors for cardiovascular disease between three ethnic groups in the Whitehall II study. *Atherosclerosis.* 1999; 142(2):279-286.
639 Widimsky J. Treatment of very elderly hypertensives significantly reduces total mortality and the risk of death from stroke. Results of the HYVET trial. *Cor Et Vasa.* 2008; 50(9):354-357.
640 Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G. Primary prevention with Metoprolol in patients with hypertension: mortality results from the MAPHY study. *JAMA.* 1988; 259(13):1976-1982.
641 Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, Hörnkvist PE, Pennert K, Tuomilehto J, Wedel H. Beta Blockers versus diuretics in hypertensive men: main results from the HAPPHY Trial. *Journal of Hypertension.* 1987; 5(5):561-572.
642 Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *Journal of Human Hypertension.* 2004; 18(3):139-185.
643 Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation.* 1998; 97(18):1837-1847.
644 Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. *New England Journal of Medicine.* 2003; 348(7):583-592.

645 Wirell MP, Wester PO, Stegmayr BG. Nutritional dose of magnesium in hypertensive patients on beta blockers lowers systolic blood pressure: a double-blind, cross-over study. *Journal of Internal Medicine.* 1994; 236(2):189-195.
646 Witteman JC, Grobbee DE, Derkx FH, Bouillon R, de Bruijn AM, Hofman A. Reduction of blood pressure with oral magnesium supplementation in women with mild to moderate hypertension. *American Journal of Clinical Nutrition.* 1994; 60(1):129-135.
647 World Health Organisation. *Adherence to Long Term Therapies: Evidence for Action.* WHO, 2003.
648 Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. *JAMA.* 1950; 143(4):329-336.
649 Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics.* 2003; 21 Suppl 1:43-50.
650 Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura O, Ishii M, Saruta T, Arakawa K, Hosoda S, Kawai C. Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) subgroup analysis. *Hypertension Research - Clinical and Experimental.* 2004; 27(7):449-456.
651 Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura O, Ishii M, Saruta T, Arakawa K, Hosoda S, Kawai C, Japan Multicenter Investigation for Cardiovascular Diseases-. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertension Research - Clinical and Experimental.* 2004; 27(3):181-191.
652 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *New England Journal of Medicine.* 2000; 342(3):145-153.
653 Yusuf S, Teo K, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *New England Journal of Medicine.* 2008; 358(15):1547-1559.
654 Zakopoulos NA, Nanas SN, Lekakis JP, Vemmos KN, Kotsis VT, Pitiriga VC, Stamatelopoulos SF, Moulopoulos SD. Reproducibility of ambulatory blood pressure measurements in essential hypertension. *Blood Pressure Monitoring.* 2001; 6(1):41-45.
655 Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? how far can cardiovascular risk be reduced? *Journal of Hypertension.* 2009; 27(8):1509-1520.
656 Zanchetti A, Bond MG, Hennig M, Neiss A, Mancia G, Dal Palu C, Hansson L, Magnani B, Rahn KH, Reid JL, Rodicio J, Safar M, Eckes L, Rizzini P, European Lacidipine Study on Atherosclerosis investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation.* 2002; 106(19):2422-2427.
657 Zanchetti A, Crepaldi G, Bond MG, Gallus G, Veglia F, Mancia G, Ventura A, Baggio G, Sampieri L, Rubba P, Sperti G, Magni A, PHYLLIS I. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: principal results of PHYLLIS--a randomized double-blind trial. *Stroke.* 2004; 35(12):2807-2812.
658 Zanchetti A, Rosei EA, et al. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. *Journal of Hypertension.* 1998; 16:1667-1676.

659 Zemel PC, Zemel MB, Urberg M, Douglas FL, Geiser R, Sowers JR. Metabolic and hemodynamic effects of magnesium supplementation in patients with essential hypertension. *American Journal of Clinical Nutrition.* 1990; 51(4):665-669.
660 Zoccali C, Mallamaci F, Delfino D, Ciccarelli M, Parlongo S, Iellamo D, Moscato D, Maggiore Q. Double-blind randomized, crossover trial of calcium supplementation in essential hypertension. *Journal of Hypertension.* 1988; 6(6):451-455.
661 Zurawski RM, Smith TW, Houston BK. Stress management for essential hypertension: comparison with a minimally effective treatment, predictors of response to treatment, and effects on reactivity. *Journal of Psychosomatic Research.* 1987; 31(4):453-462.
662 Zyczynski TM, Leidy NK, Kong BW, Helaszek CT, Michelson EL. Effects of candesartan cilexetil on health-related quality of life in black patients with systemic hypertension in the ABC Trial. *Heart Disease.* 2000; 2(6):400-406.

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

Term	Definition
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.
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.

Term	Definition
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 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

Term	Definition
Excessive coffee consumption	Over 5 cups/day
Evidence	Information on which a decision or guidance is based. Evidence is obtained 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.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Term	Definition
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.
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

Term	Definition
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, 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

Term	Definition
	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 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.

Term	Definition
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.
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.

Term	Definition
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)

Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Hypertension: clinical management of primary hypertension in adults

1.1 Short title

Hypertension (partial update)

2 The remit

This is a partial update of 'Hypertension (persistently high blood pressure) in adults' (2004) and 'Hypertension: management of hypertension in adults in primary care', NICE clinical guideline 34 (2006).

This guideline update is 6 years from publication of the 2004 NICE hypertension guideline, and is being undertaken as part of the guideline review cycle.

3 Clinical need for the guideline.

3.1 Epidemiology

a) High blood pressure (hypertension) is one of the most important preventable causes of premature morbidity and mortality in the UK. Hypertension is a major risk factor for stroke (ischaemic and haemorrhagic), myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. Untreated hypertension is usually associated with a progressive rise in blood pressure. The vascular and renal damage that this may cause can potentially culminate in a treatment-resistant state.

b) Blood pressure is normally distributed in the population and there is no natural cut-off point above which 'hypertension' definitively exists and below which it does not. The risk associated with increasing blood pressure is continuous, with each 2 mmHg rise in systolic blood pressure associated with a 7% increased risk of mortality from ischaemic heart disease and a 10% increased risk of mortality from stroke. Hypertension is remarkably common in the UK and the prevalence is strongly influenced by age. In any individual person, systolic and/or diastolic blood pressures may be elevated. Diastolic pressure is more commonly elevated in younger people, that is, those younger than 50 years. With ageing, systolic hypertension becomes a more significant problem, as a result of progressive stiffening and loss of compliance of larger arteries. At least one quarter of adults (and more than half of those older than 60) have high blood pressure.

c) The clinical management of hypertension is one of the most common interventions in primary care, accounting for approximately £1 billion in drug costs alone in 2006.

3.2 Current practice

a) NICE issued guidance for the management of hypertension in adults in primary care in 2004 ('Hypertension [persistently high blood pressure] in adults', NICE clinical guideline 18). The pharmacological section of this guideline was subsequently updated in 2006 ('Hypertension: management of hypertension in adults in primary care', NICE clinical guideline 34).

b) Hypertension is usually detected by opportunistic measurement, or during scheduled screening in primary care. The diagnosis of hypertension has traditionally been based on the use of seated measurements of blood pressure in the GP's surgery. However, there is increasing use of 24-hour ambulatory measurements of blood pressure, as well as patient self-measurement using automated devices in the home. Guidance is needed on the use and interpretation of data from these alternative blood pressure measurements.

c) Once the diagnosis of hypertension has been confirmed, a simple set of routine clinical tests is currently recommended. NICE has also advocated formal estimation of cardiovascular risk to determine whether people with treated hypertension might benefit from other risk-reducing treatments (that is, statins and anti-platelet therapy) to optimally reduce their cardiovascular disease risk.

d) The treatment of hypertension involves both lifestyle advice and drug therapy. Successful adoption of lifestyle advice may be sufficient to manage mild hypertension in people at low cardiovascular risk, and without evidence of cardiovascular disease or organ damage. However, for most people drug therapy will also be needed to lower blood pressure to recommended targets.

e) A wide range of classes of drugs is available for the treatment of hypertension. Individual patients' blood pressures respond differently to specific classes of drug therapy – there is no perfect drug for every patient. This variation is, in part, determined by age and ethnicity. At the time of drafting the 2006 recommendations, there was inadequate data to inform best treatment options for hypertension that was resistant to treatment with three drugs.

f) Substantial clinical trial data have been published since the original guideline in 2004 and the rapid update in 2006. These data needs to be reviewed in the context of existing guidance; it consolidates and strengthens the evidence for some existing recommendations and fills important evidence gaps where guidance is needed.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider.

The areas that will be addressed by the guideline are described in the following sections.

Important aspects regarding the detection and clinical management of high blood pressure that have not been prioritised for review in this update will remain unchanged from the 2004 guidance.

4.1 Population

Adults with hypertension who may, or may not, have pre-existing cardiovascular disease.

4.1.1 Groups that will be covered

a) Adults with hypertension (18 years and older).

b) 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.

c) People aged 80 years or older.

4.1.2 Groups that will not be covered

a) People with diabetes.

b) Children and young people (younger than 18 years).

c) Pregnant women.

d) Secondary causes of hypertension (for example, Conn's adenoma, phaeochromocytoma and renovascular hypertension).

e) People with accelerated hypertension (that is, severe acute hypertension associated grade III retinopathy and encephalopathy).

f) People with acute hypertension or high blood pressure in emergency care settings.

4.2 Healthcare setting

a) Primary care.

b) Secondary care (excluding emergency care).

c) Community settings in which NHS care is received.

4.3 Clinical management

4.3.1 Key clinical issues that will be reviewed

a) Ambulatory monitoring.

b) Home blood pressure monitoring.

c) Blood pressure thresholds for intervention and targets for treatment.

d) First-line therapy options, for example ACE inhibitors versus angiotension receptors blockers.

e) Calcium-channel blockers versus diuretics as preferred components in step two of the treatment algorithm, for example, combination therapy.

f) Adherence to medication.

g) Provision of appropriate information and support.

h) Resistant hypertension (that is, fourth-line therapy).

i) Response to blood pressure lowering drugs according to age and ethnicity.

4.3.2 Clinical issues that will not be reviewed

a) Prevention of hypertension.

b) Screening for hypertension.

c) Specialist management of secondary hypertension (that is, hypertension arising from other medical conditions).

d) Non-pharmacological interventions.

4.4 Main outcomes

a) Mortality from any cause.

b) Stroke (ischaemic or haemorrhagic).

c) Myocardial infarction (MI) (including, where reported, silent MI).

d) Heart failure.

e) New-onset diabetes mellitus.

f) Vascular procedures (including both coronary and carotid artery procedures).

g) Angina requiring hospitalisation.

h) Trial withdrawal rates as a surrogate for adverse effects of drug treatment.

i) Major adverse cardiac and cerebrovascular events (MAACE): fatal and non-fatal MI, fatal and non-fatal stroke, hospitalised angina, hospitalised heart failure, revascularisation.

j) Health-related quality of life.

k) Blood pressure response to treatment.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in May 2010.

4.7 Related NICE guidance

- 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

4.8 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website).

- Prevention of cardiovascular disease. NICE public health guidance. Publication date to be confirmed.

5 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B: Declarations of Interest

GDG meeting	Declaration	Action
Bryan Williams		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• None made.	None required.
Declared 13th August 2009	• I have received travel expenses and speaker honoraria for invited lectures, workshops and small group meetings on hypertension at national and international conferences. ln most cases the funds for this (as for most congresses) are via the pharmaceutical industry, although usually paid via the conference agency. The travel and subsistence costs are in accordance with the ABPI code. ln this context, the hypertension guideline does not deal with specific products unlike specific appraisals, instead, it deals with classes of drug treatments all of which are now generically available, or will be by the time the guideline deliberates. • My University and hospital trust has received investigator initiated research grants from pharmaceuticals, usually in the context of my participation as a member of the scientific steering committee of large-scale clinical trials in hypertension and NIHR adopted studies which provide the evidence base for guideline development. The funds follow the usual institutional and NIHR formulae to meet the costs and overheads of conducting these studies and related meetings. ln the past year, these have been from Servier,Pfizer and Novartis. My department also receives funding from government bodies such as MRC and NIHR on the same basis. • I am a past-president and member of the British Hypertension Society. I am a member of the European and lnternational Societies of Hypertension. I am founding Trustee (pro-bono) of the Patient's charity and lnformation service; the Blood Pressure Association (BPA). I have lead authored previous national guidelines from the British Hyperlension Society (BMJ 2004) and was previously clinical advisor to the NICE hypertension GDG in 2004 and 2006. I have been the author of many reports from major clinical trials in hypertension.	
Helen Williams		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• I have received speaker honoraria or attended advisory boards for the following companies: Boehringer-Ingelheim, Pfizer, Servier, Sanofi-Aventis, Solvay, Takeda, but none during the development of the guideline that are related to hypertension. • Non-specific funding has been received to support a project to improve prescribing in cardiac rehabilitation services for South London Cardiac and Stroke Network from: Boehringer-Ingelheim,	None required.

GDG meeting	Declaration	Action
	Pfizer, Servier, Sanofi-Aventis, Solvay	
Declared on 20th January, 2011	• April 2010: received an honorarium from Bayer for participation in an expert panel meeting for a drug unrelated to hypertension • June 2010: Received an honorarium from Sanofi Aventis for presenting at a meeting focusing on the treatment of atrial fibrillation • July and Nov 2010: Attended and presented at an expert panel meeting supported by Servier focusing on the management on angina • Sept 2010: presented at the Primary Care Cardiovascular Society at a satellite meeting focusing on Acute Coronary Syndromes supported by Lilly / Daiichi Sankyo • Nov 2010: Received an honorarium payment from Sanofi-Aventis for providing training on the management of atrial fibrillation	
Jane Northedge		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• None made.	None required.
John Crimmins		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• None made.	None required.
Mark Caulfield		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• Clinical Directorship paid by London Genetics 2009-2010. This is a company designed to harness genetic research talents across London to enable new drug discovery and prediction of medicine response- but with no direct interest in any drug therapies and in particular no interests in licensed or generic antihypertensives currently available. I represent seven London Universities on how to draw genetic research opportunities into London. Renumeration is up to £18,000 per year based on work done. • My clinical trials unit has undertaken the following study on anti-hypertensives: The Accelerate Trial - sponsored by Novartis. Phase 3 study of efficacy of amlodipine and aliskerin combination therapy - to my knowledge this combo is not available in the UK. • President of the British Hypertension Society 2009-2010 • Member of the European Society of Hypertension Council. Co-author on recent ESH Guideline re-appraisal. • I have no shares or interests in companies marketing, or who have marketed therapies that might be covered in this guidance.	None required.
Michaela Watts		
1st GDG meeting (7th June 2010) until submission	• None made.	None required.

GDG meeting	Declaration	Action
of guidance (21 January 2011)		
Naomi Stetson		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• None made.	None required.
Shelley Mason		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• None made.	None required.
Terry McCormack		
1st GDG meeting (7th June 2010) until submission of guidance (21 January 2011)	• I have received speaker honoraria or attended advisory boards for the following companies: Boehringer-Ingelheim, Pfizer, Servier, Sanofi-Aventis, Solvay, Takeda I have not had any further pecuniary interests since that time and I will not have any further hypertension-related pecuniary interests in the 18 months of the GDG membership.	None required.
3rd GDG meeting	• I am an investigator for Siguity which is a phase 3 study of Ivabradine, a Servier drug, which has no relationship with hypertension. I received sponsorship from merck, Sharpe and Dohne to attend the European Society of Cardiology meeting.	
4th GDG meeting	• I have received speaker fees from Merck to give talks on lipids. I received an educational grant from Boehringer Ingelheim to attend the annual scientific meeting of the Primary Care Cardiovascular Society.	
6th GDG meeting Declared on 8th January, 2011	• In relation to hypertension I have received speaker's fees for two talks given at Pulse Magazine hypertension seminars sponsored by Daiichi Sankyo. • Not related to hypertension - I have received advisory board honoraria, research grants, speaker's fees and educational grants from Astra Zeneca, Boehringer Ingelheim, Merck Sharpe and Dohme, Pfizer, Roche, and Servier. • I was an investigator and steering committee member for the HYVET study • I am a member of the Primary Care Cardiovascular Society Council. • I am a member of the Executive Committee of the British Hypertension Society. • I am an Editor of the British Journal of Cardiology.	
Richard McManus		
2nd GDG meeting (5 July 2010) until submission of guidance (21 January 2011)	• None received	None required.

GDG meeting	Declaration	Action
Declared on 11th January, 2011	• I hold an NIHR Career Development Fellowship which pays 75% of my salary. I run a research group which holds several grants investigating different methods of blood pressure monitoring and the management of hypertension. • I am a member of the NICE expert panel for the Quality and Outcomes Framework for hypertension and was previously a member of the same panel prior to NICE taking over the QOF contract. • I am a member of the British Hypertension Society and sit on its monitoring working group (Chair from January 2011).	

Appendix C: Review questions

Review questions
1. In adults with suspected primary hypertension, what is the best method to measure blood pressure (home vs ambulatory vs office) to establish the diagnosis and predict the development of CV events?
2. In adults with treated primary hypertension, what is the best method to measure blood pressure (home vs ambulatory vs office) for response to treatment and to predict the development of CV events?
3. In adults with primary hypertension, what protocol should be used when measuring ambulatory BP for treatment and diagnosis?
4. In adults with primary hypertension, what protocol should be used when measuring BP at home for treatment and diagnosis?
5. In adults with primary hypertension, at what BP should treatment be initiated?
6. In adults with primary hypertension, what is the optimum BP that should be reached for once treatment has been initiated/ targeted for treatment?
7. If used, should ambulatory or home blood pressure readings be interpreted differently to office measurements? i.e. are different thresholds for intervention/targets for treatment required, or should adjustment be made to readings.
8. In adults with primary hypertension, which is the most clinically and cost effective anti-hypertensive monotherapy (ACEi vs ARB) for first-line treatment, and does this vary with age and ethnicity?
9. In adults with primary hypertension, which is the most clinically and cost effective thiazide diuretic (bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first-line treatment, and does this vary with age and ethnicity?
10. In adults with primary hypertension, which is the most clinically and cost effective combination of anti-hypertensives (A+C or A+D) for second line treatment, and does this vary with age and ethnicity?
11. In adults with resistant hypertension, which is the most clinically and cost effective fourth-line pharmacological treatment, and does this vary with age and ethnicity?
12. In adults with primary hypertension, what is the most clinically and cost effective first-line anti-hypertensive treatment (drug classes) in elderly people (aged ≥80 years)?
13. In adults with primary hypertension, what is the most clinically and cost effective first-line anti-hypertensive treatment (drug classes) in black people of African or Caribbean descent)?

Appendix D: Literature search strategies

Search strategies used for the Hypertension guideline (partial update) are outlined below and were run as per the NICE Guidelines Manual 2009 http://www.nice.org.uk/media/5F2/44/The_guidelines_manual_2009_-_All_chapters.pdf .

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID), the Cochrane Library (Wiley) and Cinahl (EBSCO). Usually, searches were constructed in the following way:

A PICO format was used for **intervention** searches where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search Filters were also added to the search where appropriate.

All search results retrieved on Cinahl were restricted to exclude Medline records. The majority of searches were run from the final search date in either the original hypertension guideline (CG18), i.e. 2003 or the rapid update (CG34), i.e. 2005. Searches run for all available dates followed the dates in the table below. Full date parameters for each search are given by question in section 1.3 of this appendix.

Database	Date available from
Medline	1950
Embase	1980
Cinahl	1982
The Cochrane Library (to 2010 Issue 4)	1996 for Cochrane Reviews 1995 for DARE 1898 for CENTRAL 1904 for Methods Studies 1995 for HTA and NHSEED

Searches for the **health economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Appraisals database (HTA) and the Health Economic Evaluation Database (HEED). HTA and NHSEED searches were carried out via the interface provided by the Centre for Reviews and Dissemination (CRD). Searches of HTA, NHS EED and HEED were constructed using basic population terms only. The economics databases were searched 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, For Medline and Embase an economic filter (instead of a study type filter) was added to the same population terms used for the clinical searches.

The final search date for all searches was 29th November 2010. Any studies added to the databases after this date were not included unless specifically stated in the text.

The search strategies are presented below in the following order:

Section 1.1	Population terms by database. The same searches were used for all questions and for both clinical and health economic searches.
Section 1.2	Study filter terms by database. These include filters for epidemiological study designs, health economic studies and exclusions.
1.2.1	Systematic reviews
1.2.2	Randomised controlled trials (RCTs)
1.2.3	Combined RCT and Observational studies

1.2.4	Health economics
1.2.5	Excluded study designs and publication types
1.2.6	Excluded population
Section 1.3	Searches run for specific questions with the intervention or exposure terms by database.
1.3.1	Measuring blood pressure • AMB1 • AMB2 • AMB3 • AMB4 • AMB12
1.3.2	Thresholds for intervention • THRESHOLD5
1.3.3	Targets for treatment • OPTIMUM6
1.3.4	Pharmacological interventions • ACEi vs ARB7 • DIURETICS8 • COMBI9 • RESISTANT10 • OVER80s11 • ETHNICITY13

D.1 Population search strategies

Medline

1	exp Hypertension/
2	hypertens*.ti,ab.
3	(essential adj3 hypertension).ti,ab.
4	(isolat* adj3 hypertension).ti,ab.
5	(elevat* adj3 blood adj pressur*).ti,ab.
6	(high adj3 blood adj pressur*).ti,ab.
7	(increase* adj3 blood pressur*).ti,ab.
8	((systolic or diastolic or arterial) adj3 pressur*).ti,ab.
9	or/1-8
10	exp pregnancy/
11	exp Hypertension, Pregnancy-Induced/
12	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
13	exp Hypertension, Malignant/
14	exp Hypertension, Portal/
15	exp Hypertension, Pulmonary/
16	exp Hypertension, Renal/
17	exp Intracranial Hypertension/
18	exp Ocular Hypertension/
19	exp diabetes mellitus/
20	or/10-19

	9 not 20

Embase

	exp Hypertension/
1	hypertens*.ti,ab.
2	(essential adj3 hypertension).ti,ab.
3	(isolat* adj3 hypertension).ti,ab.
4	(elevat* adj3 blood adj pressur*).ti,ab.
5	(high adj3 blood adj pressur*).ti,ab.
6	(increase* adj3 blood pressur*).ti,ab.
7	((systolic or diastolic or arterial) adj3 pressur*).ti,ab.
8	or/1-8
9	exp pregnancy/
10	exp Hypertension, Pregnancy-Induced/
11	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
12	exp Hypertension, Malignant/
13	exp Hypertension, Portal/
14	exp Hypertension, Pulmonary/
15	exp Hypertension, Renal/
16	exp Intracranial Hypertension/
17	exp Ocular Hypertension/
18	exp diabetes mellitus/
19	or/10-19
20	9 not 20

Cinahl

S1	S6 not S17
S17	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16
S16	pregnancy n1 hypertension or malignant n1 hypertension or portal n1 hypertension or pulmonary n1 hypertension or renal n1 hypertension or intracranial n1 hypertension or ocular n1 hypertension
S15	pre eclampsia or pre-eclampsia or preeclampsia
S14	MH "ocular hypertension"
S13	MH "Intracranial hypertension"
S12	MH "Hypertension, Renal"
S11	MH "Hypertension, Portal"
S10	MH "Hypertension, Malignant"
S9	MH "Pregnancy-Induced Hypertension"
S8	(MH "Diabetes Mellitus+")
S7	MH "Pregnancy"
S6	S1 or S2 or S3 or S4 or S5
S5	essential n3 hypertension or isolat* n3 hypertension
S4	systolic n3 pressur* or diastolic n3 pressur* or arterial n3 pressur*
S3	high n3 blood n1 pressur* or increas* n3 blood n1 pressur* or elevat* n3 blood n1 pressur*
S2	hypertens*
S1	MH "hypertension"

Cochrane

#1	MeSH descriptor Hypertension explode all trees
#2	hypertens*:ti,ab,kw
#3	(essential or isolat*) near/3 hypertension:ti,kw,ab
#4	(elevat* or high or increase*) near/3 (blood near/1 pressur*):ti,ab,kw
#5	(systolic or diastolic or arterial) near/3 pressur*:ti,ab,kw
#6	(#1 OR #2 OR #3 OR #4 OR #5)
#7	MeSH descriptor Pregnancy explode all trees
#8	MeSH descriptor Hypertension, Pregnancy-Induced explode all trees
#9	MeSH descriptor Hypertension, Malignant explode all trees
#10	MeSH descriptor Hypertension, Portal explode all trees
#11	MeSH descriptor Hypertension, Pulmonary explode all trees
#12	MeSH descriptor Hypertension, Renal explode all trees
#13	MeSH descriptor Intracranial Hypertension explode all trees
#14	MeSH descriptor Ocular Hypertension explode all trees
#15	Pre eclampsia or pre-eclampsia or preeclampsia:ti.ab.kw
#16	(Pregnancy or malignant or portal or pulmonary or renal or intracranial or ocular) near/1 hypertension:ti,ab,kw
#17	MeSH descriptor Diabetes Mellitus explode all trees
#18	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19	(#6 AND NOT #18)

HTA / NHS EED – Centre for Reviews and Dissemination

#1	hypertens*

HEED (Health Economic Evaluations Database

#1	hypertens* in Article Title, Abstract or Keywords

D.2 Study design search terms

D.2.1 Systematic review search terms

Medline

1	review.pt. or review.ti. or "review"/
2	(systematic$ or evidence$ or methodol$ or quantitativ$ or analys$ or assessment$).ti,sh,ab.
3	1 and 2
4	meta-analysis.pt.
5	meta-analysis/
6	meta-analysis as topic/
7	"systematic review"/
8	(meta-analy$ or metanaly$ or metaanaly$ or meta analy$).ti,ab.
9	((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh.
10	((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
11	or/3-10

Embase

1	review.pt. or review.ti. or "review"/
2	(systematic$ or evidence$ or methodol$ or quantitativ$ or analys$ or assessment$).ti,sh,ab.
3	1 and 2
4	meta-analysis.pt.
5	meta-analysis/
6	meta-analysis as topic/
7	"systematic review"/
8	(meta-analy$ or metanaly$ or metaanaly$ or meta analy$).ti,ab.
9	((systematic$ or evidence$ or methodol$ or quantitativ$) adj5 (review$ or survey$ or overview$)).ti,ab,sh.
10	((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
11	or/45-52

D.2.2 Randomised controlled trial (RCTs) search terms

Medline

1	randomized controlled trial$.pt,sh.
2	clinical trial$.pt,sh.
3	random allocation/
4	double blind method/
5	single blind method/
6	((clin$ or control$) adj5 trial$).ti,ab.
7	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
8	placebos/
9	placebo$.ti,ab.
10	random$.ti,ab.
11	(volunteer$ or "control group" or controls or prospective$).ti,ab.
12	research design/
13	or/1-12
14	animals/ not humans/
15	13 not 14

Embase

1	exp randomized controlled trial/
2	(random$ or placebo$).ti,ab.
3	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
4	double blind method/
5	exp comparative study/
6	exp evaluation/
7	exp follow up/
8	exp prospective study/
9	placebos/
10	or/1-9
11	exp human/
12	10 and 11

D.2.3 Combined RCT and Observational studies search terms

Medline

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	double-blind method/ or random allocation/ or single-blind method/
4	exp Clinical Trial/
5	exp Clinical Trials as Topic/
6	clinical trial.pt.
7	random.ti,ab.
8	(clin$ adj25 trial$).ti,ab.
9	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

10	Placebos/ or placebo$.ti,ab.
11	Research Design/ or Comparative Study/
12	exp Evaluation Studies/ or follow-up studies/ or prospective studies/
13	(volunteer$ or "control group" or controls or prospectiv$).ti,ab.
14	exp epidemiological studies/
15	cohort stud$.ti,ab.
16	case control stud$.ti,ab.
17	((crossover or cross-over or cross over) adj2 (design$ or stud$ or procedure$ or trial$)).ti,ab.
18	or/1-17

Embase

1	controlled study/ or randomized controlled trial/
2	Clinical Trial/
3	clinical study/ or major clinical study/ or clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/
4	Placebo/
5	"Double Blind Procedure"/
6	Randomization/
7	((clinical$ or control$ or compar$) adj3 (trial$ or study or studies)).mp.
8	or/1-7
9	compar$.tw.
10	control$.tw.
11	9 and 10
12	placebo.tw.
13	randomi$.tw.
14	(blind$ or mask$).tw.
15	crossover procedure/
16	(cross adj2 over adj2 (study or design)).ti,ab.
17	exp Cohort Analysis/
18	exp Longitudinal Study/
19	exp Prospective Study/
20	Observational Study/
21	exp follow up/
22	cohort studies.ti,ab.
23	exp Case Control Study/
24	case control stud$.ti,ab.
25	or/8,11,12-24

D.2.4 Health economics search terms

Medline

1	exp "Costs and Cost Analysis"/
2	economics/
3	exp Economics, Hospital/
4	exp Economics, Medical/
5	exp Economics, Nursing/

6	exp Economics, Pharmaceutical/
7	exp "Fees and Charges"/
8	exp Budgets/
9	ec.fs.
10	(economic$ or pharmacoeconomic$ or price$ or pricing$ or cost$ or budget$).ti,ab.
11	(value adj2 (money or monetary)).ti,ab.
12	(expenditure not energy).ti,ab.
13	or/1-12
14	((metabolic or energy or oxygen) adj1 cost$).ti,ab.
15	13 not 14

Embase

1	health economics/
2	exp economic evaluation/
3	exp health care cost/
4	exp pharmacoeconomics/
5	exp fee/
6	budget/
7	(economic$ or pharmacoeconomic$ or cost$ or price$ or pricing$ or budget$).ti,ab.
8	(value adj2 (money or monetary$)).ti,ab.
9	(expenditure not energy).ti,ab.
10	or/1-9
11	((metabolic or energy or oxygen) adj1 cost$).ti,ab.
12	10 not 11

D.2.5 Excluded study designs search terms

The following study designs and publication types were removed from the retrieved results using the NOT operator.

Medline & Embase

1	letter$/
2	editorial.pt.
3	historical article.pt.
4	anecdote.pt.
5	commentary.pt.
6	note.pt.
7	case report/
8	case report$.pt.
9	case study/
10	case study.pt.
11	exp animal/ not human/
12	nonhuman/
13	exp animal studies/
14	animals, laboratory/

15	exp experimental animal/
16	exp animal experiment/
17	exp animal model/
18	exp rodentia/
19	exp rodents/
20	exp rodent/
21	or/1-20

D.2.6 Excluded population search terms

The following populations were removed from the retrieved results using the NOT operator.

Medline

1	exp child/
2	child$.tw.
3	exp infant/
4	infan$.tw.
5	(baby or babies).tw.
6	"adolescent"/
7	(pediatric$1 or paediatric$1).tw.
8	or/1-7
9	exp adult/
10	8 not 9

Embase

1	exp child/
2	child*.tw.
3	childhood/
4	infancy/
5	infan*.tw.
6	(baby or babies).tw.
7	exp adolescent/
8	(pediatric$1 or paediatric$1).tw.
9	or/1-8
10	adult/
11	aged/
12	or/10-11
13	9 not 12

D.3 Searches by specific question

D.3.1 Measuring blood pressure

AMB1
In adults with suspected primary hypertension, what is the best method to measure blood pressure (home vs ambulatory vs office) to establish the diagnosis and predict the development of CV events?

AMB2
In adults with treated primary hypertension, what is the best method to measure blood pressure (home vs ambulatory vs office) for response to treatment and to predict the development of CV events?
Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	Home or ambulatory or office blood pressure measurement	None	SRs / Combined RCT and Observational filter (Medline and Embase only)	2003-29/11/10

Medline

1	ambulatory blood pressure monitoring.ti,ab.
2	ambulat*.ti,ab.
3	((home or self or office) adj2 "'blood monitor*").ti,ab.
4	blood pressure monitor*.ti,ab.
5	24-hour.ti,ab.
6	24 hour monitor*.ti,ab.
7	or/1-6
8	exp "Sensitivity and Specificity"/
9	(sensitivity or specificity).ti.
10	(predictive adj3 value*).tw.
11	exp diagnostic errors/
12	((False adj positive*) or (false adj negative*)).ti.
13	(observer adj variations*).ti.
14	(roc adj curve*).ti.
15	(likelihood adj ratio*).ti.
16	Likelihood function/
17	or/8-16
18	exp *prognosis/
19	prognos*.ti.
20	prevalence/
21	incidence/
22	(prevalence or incidence).ti.
23	or/18-22

24	7 and (17 or 23)

Embase

1	ambulatory blood pressure monitoring.ti,ab.
2	ambulat*.ti,ab.
3	((home or self or office) adj2 "'blood monitor*'').ti,ab.
4	blood pressure monitor*.ti,ab.
5	24-hour.ti,ab.
6	24 hour monitor*.ti,ab.
7	or/1-6
8	exp "Sensitivity and Specificity"/
9	(sensitivity or specificity).ti.
10	(predictive adj3 value*).tw.
11	exp diagnostic errors/
12	((False adj positive*) or (false adj negative*)).ti.
13	(observer adj variations*).ti.
14	(roc adj curve*).ti.
15	(likelihood adj ratio*).ti.
16	Likelihood function/
17	or/8-16
18	exp *prognosis/
19	prognos*.ti.
20	prevalence/
21	incidence/
22	(prevalence or incidence).ti.
23	or/18-22
24	7 and (17 or 23)

Cinahl

S28	S10 and S27
S27	S20 or S26
S26	S21 or S22 or S23 or S24 or S25
S25	prevalence or incidence
S24	(MH "Incidence")
S23	(MH "Prevalence")
S22	prognos*
S21	(MH "Prognosis")
S20	S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19
S19	"likelihood function*"
S18	likelihood n3 ratio*
S17	roc n1 curve*
S16	observer n1 variation*
S15	false n1 positive* or false n1 negative*
S14	(MH "Diagnostic Errors")
S13	predictive n3 value*

S12	sensitivity or specificity
S11	(MH "Sensitivity and Specificity")
S10	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9	24 hour monitor*
S8	24-hour
S7	self and blood and monitor*
S6	office and blood and monitor*
S5	home and blood and monitor*
S4	blood pressure monitor*
S3	ambulat*
S2	ambulatory blood pressure monitoring
S1	MH "Blood Pressure Monitoring, Ambulatory"

Cochrane

#1	MeSH descriptor Blood Pressure Monitoring, Ambulatory explode all trees
#2	ambulatory blood pressure monitoring:ti,kw,ab
#3	ambulat*:ti,kw,ab
#4	blood pressure monitor*:ti,kw,ab
#5	(home or self or office) near/2 (blood near/1 monitor*):ti,kw,ab
#6	24-hour:ti,kw,ab
#7	24 hour monitor*:ti,kw,ab
#8	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9	MeSH descriptor Sensitivity and Specificity explode all trees
#10	sensitivity:ti or specificity:ti,kw,ab
#11	predictive near/3 value*:ti,kw,ab
#12	MeSH descriptor Diagnostic Errors explode all trees
#13	(false near/1 positive*) or (false near/1 negative*):ti,kw,ab
#14	observer near/1 variation*:ti,kw,ab
#15	roc near/1 curve*:ti,ab,kw
#16	(likelihood near/3 ratio*):ti,ab,kw
#17	MeSH descriptor Likelihood Functions explode all trees
#18	(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 or #17)
#19	MeSH descriptor Prognosis explode all trees
#20	prognos*:ti,ab,kw
#21	MeSH descriptor Prevalence explode all trees
#22	MeSH descriptor Incidence explode all trees
#23	(prevalence or incidence):ti,ab,kw
#24	(#19 OR #20 OR #21 OR #22 OR #23)
#25	(#18 OR #24)
#26	(#8 AND #25)

AMB3
In adults with primary hypertension, if used, should ambulatory or home blood pressure readings be interpreted differently to office measurements? i.e. are different thresholds for intervention/targets for treatment required, or should adjustment be made to readings.

AMB4

In adults with primary hypertension, what protocol should be used when measuring BP at home for treatment and diagnosis?

Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	Home or ambulatory blood pressure monitoring	None	None	2003-29/11/10

Medline

1	*Blood Pressure Monitoring, Ambulatory/
2	((blood pressure* or BP) adj3 ambulatory).ti,ab.
3	((blood pressure* or BP) adj3 home).ti,ab.
4	((blood pressure* or BP) adj3 self).ti,ab.
5	HBPM.ti,ab.
6	or/1-5

Embase

	((blood pressure* or BP) adj3 home).ti,ab.
	((blood pressure* or BP) adj3 ambulatory).ti,ab.
	((blood pressure* or BP) adj3 self).ti,ab.
	HBPM.ti,ab.
	*blood pressure monitoring/
	or/1-5

Cinahl

S6	S1 or S2 or S3 or S4 or S5
S5	HBPM
S4	((blood pressure* or BP) and self)
S3	((blood pressure* or BP) and ambulatory)
S2	((blood pressure* or BP) and home)
S1	MM "Blood Pressure Monitoring, Ambulatory"

Cochrane

#1	MeSH descriptor Blood Pressure Monitoring, Ambulatory, this term only
#2	Ambulatory blood pressure monitoring:ti,kw,ab
#3	((blood pressure* or BP) near/3 home):ti,kw,ab
#4	((blood pressure* or BP) near/3 self):ti,kw,ab
#5	((blood pressure* or BP) near/3 ambulatory):ti,kw,ab
#6	HBPM:ti,kw,ab
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)

AMB12
In adults with primary hypertension, what protocol should be used when measuring ambulatory blood pressure for treatment and diagnosis?
Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	Ambulatory blood pressure monitoring	None	None	All dates-29/11/10

Medline

1	*Blood Pressure Monitoring, Ambulatory/
2	((blood pressure* or BP) adj ambulatory).ti,ab.
3	ABPM.ti,ab.
4	or/1-3

Embase

1	((blood pressure* or BP) adj ambulatory).ti,ab.
2	ABPM.ti,ab.
3	*blood pressure monitoring/
4	or/1-3

Cinahl

S4	S1 or S2 or S3
S3	ABPM
S2	((blood pressure* or BP) and ambulatory)
S1	MM "Blood Pressure Monitoring, Ambulatory"

Cochrane

#1	MeSH descriptor Blood Pressure Monitoring, Ambulatory, this term only
#2	(ambulatory near (blood pressure or BP)):ti,kw,ab
#3	ABPM:ti,kw,ab
#4	(#1 OR #2 OR #3)

D.3.2 Thresholds for intervention

THRESHOLD5
In adults with primary hypertension, at what BP should treatment be initiated?
Search constructed by combining the columns in the following table using the AND Boolean operator

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	Any treatment	None	None	2003-29/11/10

Medline

1	exp antihypertensive agents/
2	(anti-hypertens* or antihypertens* or anti hypertens*).ti,ab.
3	or/1-2
4	risk factors/
5	risk assessment/
6	or/4-5
7	3 and 6

Embase

1	exp antihypertensive agent/
2	exp antihypertensive therapy/
3	(anti-hypertens* or antihypertens* or anti hypertens*).ti,ab.
4	or/1-3
5	risk factor/
6	risk assessment/
7	or/5-6
8	exp blood pressure/
9	blood pressure monitoring/
10	or/8-9
11	4 and 7 and 10

Cinahl

S7	S3 and S6
S6	S4 or S5
S5	(MH "Risk Assessment")
S4	(MH "Risk Factors+")
S3	S1 or S2
S2	(MH "Antihypertensive Agents+")
S1	anti-hypertens* or antihypertens* or anti hypertens*

Cochrane

#1	(anti-hypertens* or antihypertens* or anti hypertens*):ti,ab,kw
#2	risk*:ti,ab,kw
#3	(#1 AND #2)

D.3.3 Targets for treatment

OPTIMUM6

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

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary	Any treatment	None	None	2003-29/11/10

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
hypertension				

Medline

1	((target* or level* or optimum or optimal) adj3 blood pressure).ti,ab.
2	(intensive adj3 (blood pressure or anti?hypertens* or control or treatment)).ti,ab.
3	((tight* or strict*) adj3 (blood pressure or control*)).ti,ab.
4	(normotensive* or normotension).ti,ab.
5	or/1-4
6	*blood pressure/
7	5 and 6

Embase

1	((target* or level* or optimum or optimal) adj3 blood pressure).ti,ab.
2	(intensive adj3 (blood pressure or anti?hypertens* or control or treatment)).ti,ab.
3	((tight* or strict*) adj3 (blood pressure or control*)).ti,ab.
4	(normotensive* or normotension).ti,ab.
5	or/1-4
6	exp blood pressure/
7	5 and 6

Cinahl

S7	S5 and S6
S6	(anti-hypertens* or antihypertens* or anti hypertens*)
S5	S1 or S2 or S3 or S4
S4	(normotensive* or normotension)
S3	((tight* or strict*) and (blood pressure or control*))
S2	(intensive and (blood pressure or antihypertens* or anti-hypertens* or anti hypertens* or control or treatment))
S1	((target* or level* or optimum or optimal) and blood pressure)

Cochrane

#1	((target* or level* or optimum or optimal) near/3 blood pressure):ti,ab,kw
#2	(intensive near/3 (blood pressure or anti hypertens* or anti-hypertens* or antihypertens* or control or treatment)):ti,ab,kw
#3	((tight* or strict*) near/3 (blood pressure or control*)):ti,ab,kw
#4	(normotensive* or normotension):ti,ab,kw
#5	(#1 OR #2 OR #3 OR #4)
#6	(anti-hypertens* or antihypertens* or anti hypertens*):ti,ab,kw
#7	(#5 AND #6)

D.3.4 Pharmacological interventions

ACEivsARB7: In adults with primary hypertension, which is the most clinically and cost effective anti-hypertensive monotherapy (ACEi vs ARB) for first-line treatment and does this vary by age and ethnicity?

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	ACE inhibitor	ARB	SRs / RCTs Medline and Embase only	2005-29/11/10

Medline

1	*angiotensin converting enzyme inhibitors/
2	ace inhibitor*.ti,ab.
3	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
4	or/1-3
5	*Angiotensin II Type 1 Receptor blockers/
6	*Angiotensin 2 receptor antagonist/
7	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
8	or/5-7
9	4 and 8

Embase

1	*Angiotensin II Type 1 Receptor blockers/
2	*Angiotensin 2 receptor antagonist/
3	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
4	or/1-3
5	*angiotensin converting enzyme inhibitors/
6	ace inhibitor*.ti,ab.
7	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
8	or/5-7
9	4 and 8

Cinahl

S7	S3 and S6
S6	S4 or S5
S5	captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril
S4	MH "Angiotensin-Converting Enzyme Inhibitors"
S3	S1 or S2
S2	candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan
S1	MH "Angiotensin II Type I Receptor Blockers"

Cochrane

#1	MeSH descriptor Angiotensin II Type 1 Receptor Blockers explode all trees
#2	candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan:ti,ab,kw
#3	(#1 OR #2)
#4	MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees

#5	captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril:ti,ab,kw
#6	(#4 OR #5)
#7	(#3 AND #6)

DIURETICS8: In adults with primary hypertension, which is the most clinically and cost effective thiazide diuretic (bendrofluazide/bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first line treatment and does this vary by age and ethnicity?

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	Thiazide diuretic	None	SRs / RCTs Medline and Embase only	All dates-29/11/10

Medline

1	bendroflumethiazide/
2	chlorthalidone/
3	indapamide/
4	metolazone/
5	xipamide/
6	hydrochlorothiazide/
7	exp Sodium Chloride Symporter Inhibitors/
8	diuretics/
9	7 and 8
10	thiazide diuretic*.ti,ab.
11	or/1-6,9-10

Embase

1	*bendroflumethiazide/
2	*chlortalidone/
3	*indapamide/
4	*metolazone/
5	*xipamide/
6	*hydrochlorothiazide/
7	*thiazide diuretic agent/
8	thiazide diuretic*.ti,ab.
9	or/1-8

Cinahl

S4	S1 or S2 or S3
S3	bendroflumethiazide or chlorthalidone or indapamide or metolazone or xipamide or hydrochlorothiazide
S2	thiazide diuretic*
S1	(MH "Diuretics, Thiazide+")

Cochrane

#1	(bendroflumethiazide or chlorthalidone or indapamide or metolazone or xipamide or hydrochlorothiazide):ti,ab,kw

#2	thiazide diuretic*:ti,ab,kw
#3	MeSH descriptor Sodium Chloride Symporter Inhibitors explode all trees
#4	(#1 OR #2)
#5	MeSH descriptor Diuretics, this term only
#6	(#3 AND #5)
#7	(#4 OR #6)

COMBI9: In adults with primary hypertension, which is the most clinically and cost effective combination of anti-hypertensives (A+C or A+D) for second line treatment and does this vary by age and ethnicity?

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	ACE inhibitor + Calcium Channel Blocker (CCB) or ARB + CCB in second line treatment	None	SRs / RCTs Medline and Embase only	2005-29/11/10

Medline

1	*angiotensin converting enzyme inhibitors/
2	ace inhibitor*.ti,ab.
3	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
4	or/1-3
5	*Angiotensin II Type 1 Receptor blockers/
6	*Angiotensin 2 receptor antagonist/
7	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
8	or/5-7
9	4 or 8
10	*calcium channel blockers/
11	(amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil).ti,ab.
12	10 or 11
13	9 and 12

Embase

1	*angiotensin converting enzyme inhibitors/
2	ace inhibitor*.ti,ab.
3	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
4	or/1-3
5	*Angiotensin II Type 1 Receptor blockers/
6	*Angiotensin 2 receptor antagonist/
7	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
8	or/5-7
9	4 or 8

10	*calcium channel blockers/
11	(amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil).ti,ab.
12	10 or 11
13	9 and 12

Cinahl

S11	S17 and S10
S10	S8 or S9
S9	amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil
S8	MH "calcium channel blockers"
S7	S3 or S6
S6	S4 or S5
S5	captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril
S4	MH "Angiotensin-Converting Enzyme Inhibitors"
S3	S1 or S2
S2	candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan
S1	MH "Angiotensin II Type I Receptor Blockers"

Cochrane

#1	MeSH descriptor Angiotensin II Type 1 Receptor Blockers explode all trees
#2	candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan:ti,ab,kw
#3	(#1 OR #2)
#4	MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees
#5	captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril:ti,ab,kw
#6	(#4 OR #5)
#7	(#3 OR #6)
#8	MeSH descriptor Calcium Channel Blockers explode all trees
#9	(amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil):ti,ab,kw
#10	(#8 OR #9)
#11	(#7 AND #10)

RESISTANT10: In adults with resistant hypertension, which is the most clinically and cost effective fourth-line pharmacological treatment and does this vary by age and ethnicity?

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults with primary hypertension	Any fourth line pharmacological treatment	None	SRs / RCTs Medline and Embase only	2005-29/11/10

Medline

1	((difficult* or hard or poor*) adj2 control*).ti,ab.
2	(uncontrolled adj2 hypertens*).ti,ab.
3	(fourth line or fourth-line).ti,ab.

4	drug resistance/
5	((resistant or resistance) adj3 hypertens*).ti,ab.
6	or/1-5

Embase

1	((difficult* or hard or poor*) adj2 control*).ti,ab.
2	(uncontrolled adj2 hypertens*).ti,ab.
3	(fourth line or fourth-line).ti,ab.
4	((resistant or resistance) adj3 hypertens*).ti,ab.
5	drug resistance/
6	or/1-5

Cinahl

S6	S1 or S2 or S3 or S4 or S5
S5	(MH "Drug Resistance")
S4	((resistant or resistance) and hypertens*)
S3	(fourth line or fourth-line)
S2	(uncontrolled and hypertens*)
S1	((difficult* or hard or poor*) and control*)

Cochrane

#1	((difficult* or hard or poor*) near/2 control*):ti,ab,kw
#2	(uncontrolled near/2 hypertens*):ti,ab,kw
#3	(fourth line or fourth-line):ti,ab,kw
#4	((resistant or resistance) near/3 hypertens*):ti,ab,kw
#5	MeSH descriptor Drug Resistance, this term only
#6	(#1 OR #2 OR #3 OR #4 OR #5)

OVER80s11: Does the treatment of hypertension in people aged ≥ 80 years reduce the risk of major adverse outcomes?

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Adults (≥80 years old) with primary hypertension	Any pharmacological treatment	None	SRs / RCTs Medline and Embase only	2005-29/11/10

Medline

1	*diuretics, thiazide/
2	(chlortalidone or indapamide or metolazone or xipamide or amiloride or triamterene).ti,ab.
3	1 or 2
4	*adrenergic alpha-antagonists/
5	(doxazosin or indoramin or prazosin or terazosin).ti,ab.
6	4 or 5
7	*adrenergic beta-antagonists/
8	(Oxprenolol or pindolol or acebutolol or celiprolol or atenolol or nadolol or sotalol or carvedilol or bisoprolol or metoprolol or nebivolol or timolol or propranolol or betaxalol or esmolol or labetalol).ti,ab.

9	7 or 8
10	*calcium channel blockers/
11	(amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil).ti,ab.
12	10 or 11
13	*angiotensin converting enzyme inhibitors/
14	ace inhibitor*.ti,ab.
15	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
16	or/13-15
17	*Angiotensin II Type 1 Receptor blockers/
18	*Angiotensin 2 receptor antagonist/
19	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
20	or/17-19
21	3 or 6 or 9 or 12 or 16 or 20
22	(80 years or aged 80 or centenarian* or nonagenarian* or octogenarian* or elderly or older).ti,ab.
23	exp aged/
24	22 or 23
25	21 and 24

Embase

1	*Angiotensin II Type 1 Receptor blockers/
2	*Angiotensin 2 receptor antagonist/
3	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
4	or/1-3
5	*angiotensin converting enzyme inhibitors/
6	ace inhibitor*.ti,ab.
7	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
8	or/5-7
9	*adrenergic alpha-antagonists/
10	(doxazosin or indoramin or prazosin or terazosin).ti,ab.
11	or/9-10
12	*adrenergic beta-antagonists/
13	(Oxprenolol or pindolol or acebutolol or celiprolol or atenolol or nadolol or sotalol or carvedilol or bisoprolol or metoprolol or nebivolol or timolol or propranolol or betaxalol or esmolol or labetalol).ti,ab.
14	12 or 13
15	*calcium channel blockers/
16	(amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil).ti,ab.
17	15 or 16
18	*diuretics, thiazide/
19	(chlortalidone or indapamide or metolazone or xipamide or amiloride or triamterene).ti,ab.
20	or/18-19

21	4 or 8 or 11 or 14 or 17 or 20
22	(80 years or aged 80 or centenarian* or nonagenarian* or octogenarian* or elderly or older).ti,ab.
23	exp aged/
24	22 or 23
25	21 and 24

Cinahl

S19	S3 and S18
S18	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S17	(MH "Adrenergic Beta-Antagonist+")
S16	(MH "Adrenergic Alpha-Antagonists+")
S15	oxprenolol or pindolol or acebutolol or celiprolol or atenolol or nadolol or sotalol or carvedilol or bisoprolol or metoprolol or nebivolol or timolol or propranolol or betaxalol or esmolol or labetalol
S14	doxazosin or indoramin or prazosin or terazosin
S13	chlortalidone or indapamide or metolazone or xipamide or amiloride or triamterene
S12	bendroflumethiazide or chlorthalidone or indapamide or metolazone or xipamide
S11	(MH "Diuretics+")
S10	(MH "Diuretics, Thiazide+")
S9	amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil
S8	MH "calcium channel blockers"
S7	captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril
S6	MH "Angiotensin-Converting Enzyme Inhibitors"
S5	candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan
S4	MH "Angiotensin II Type I Receptor Blockers"
S3	S1 or S2
S2	80 years or aged 80 or centenarian* or nonagenarian* or octogenarian* or elderly or older
S1	(MH "Aged, 80 and Over")

Cochrane

#1	(80 years or aged 80 or centenarian* or nonagenarian* or octogenarian* or elderly or older):ti,ab,kw
#2	MeSH descriptor Aged, 80 and over, this term only
#3	(#1 OR #2)
#4	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan or captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or amlodipine or felodipine or isradipine or lacidipine or lercanidipine or nicardipine or nifedipine or nimodipine or diltiazem or verapamil):ti,ab,kw
#5	(chlortalidone or indapamide or metolazone or xipamide or amiloride or triamterene or doxazosin or indoramin or prazosin or terazosin or oxprenolol or pindolol or acebutolol or celiprolol or atenolol or nadolol or sotalol or carvedilol or bisoprolol or metoprolol or nebivolol or timolol or propranolol or betaxalol or esmolol or labetalol):ti,ab,kw
#6	(#4 OR #5)
#7	(#3 AND #6)

ETHNICITY13: In adults with primary hypertension, what is the most clinically and cost effective first-line anti-hypertensive treatment (drug classes) in black people of African or Caribbean descent)?

Population	Intervention / exposure	Comparison	Study filter used	Date parameters
Black adults (≥18 years old) of African or Caribbean descent with primary hypertension	ACE inhibitors / ARBs	None	SRs / RCTs Medline and Embase only	2005-29/11/10

Medline

1	*angiotensin converting enzyme inhibitors/
2	ace inhibitor*.ti,ab.
3	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
4	or/1-3
5	*Angiotensin II Type 1 Receptor blockers/
6	*Angiotensin 2 receptor antagonist/
7	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
8	or/5-7
9	4 or 8
10	(black* or afro* or african*).ti,ab,hw.
11	exp population groups/
12	10 or 11
13	9 and 12

Embase

1	*Angiotensin II Type 1 Receptor blockers/
2	*Angiotensin 2 receptor antagonist/
3	(candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan).ti,ab.
4	or/1-3
5	*angiotensin converting enzyme inhibitors/
6	ace inhibitor*.ti,ab.
7	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril).ti,ab.
8	or/5-7
9	4 or 8
10	(black* or afro* or african*).ti,ab,hw.
11	exp "ethnic or racial aspects"/
12	exp "ethnic and racial groups"/
13	or/10-12
14	9 and 13

Cinahl

S11	S5 and S10

S10	S6 or S7 or S8 or S9
S9	black* or afro* or african*
S8	(MH "Race Factors")
S7	(MH "Minority Groups")
S6	(MH "Ethnic Groups+")
S5	S1 or S2 or S3 or S4
S4	candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan
S3	MH "Angiotensin II Type I Receptor Blockers"
S2	captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril
S1	MH "Angiotensin-Converting Enzyme Inhibitors"

Cochrane

#1	MeSH descriptor Angiotensin II Type 1 Receptor Blockers explode all trees
#2	candesartan or eprosartan or ibesartan or telmisartan or valsartan or losartan or olmesartan:ti,ab,kw
#3	(#1 OR #2)
#4	MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees
#5	captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril:ti,ab,kw
#6	(#4 OR #5)
#7	(#3 OR #6)
#8	MeSH descriptor Population Groups explode all trees
#9	(black* or afro* or african*):ti,ab,kw
#10	(#8 OR #9)
#11	(#7 AND #10)

Appendix E: Review protocols

E.1 Review protocol for the diagnosis of hypertension and monitoring treatment efficacy

- Predicting outcome using clinic, home and ambulatory measurements
- Sensitivity and specificity of clinic, home and ambulatory measurements
- Measuring response to treatment using clinic, home and ambulatory measurements

Review questions	**AMB1: In adults with suspected primary hypertension, what is the best method to measure blood pressure (home vs ambulatory vs office) to establish the diagnosis and predict the development of CV events?** **AMB2: In adults with treated primary hypertension, what is the best method to measure blood pressure (home vs ambulatory vs office) for response to treatment and to predict the development of CV events?**
Objectives	This aim of this review is to estimate the accuracy and cost-effectiveness of BP measurements (home vs ambulatory vs. office) for establishing the diagnosis of and prognosis in adults ≥18 years old with suspected primary hypertension; and for establishing response to treatment in adults ≥18 years old with treated primary

	hypertension.
Criteria	**Population(s):** AMB1: Adults ≥18 years old with suspected primary hypertension who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes AMB2: Adults ≥18 years old with treated primary hypertension who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention(s):** Home; ambulatory (and home vs. ambulatory) Studies looking at home telemonitoring BP will be excluded, as this not common in clinical practice **Comparison(s):** Gold standard (office) **Outcome(s):** • Sensitivity • Specificity • Risk of developing clinical outcomes: • Mortality • Stroke • MI Vascular procedures (including both coronary and arotid artery procedures) • Angina requiring hospitalisation 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) Studies will be excluded if they: • have no comparative BP measurement arm • are validation studies • are RCTs for treatment that have not monitored Tx throughout trial by ≥two different BP measurement methods (office or home or ABPM) and use two methods only at end of stu • assess the prediction of future BP (rather than the specified clinical outcomes)
Search Strategy	See Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG18, however the studies included within the SR/MA may have been published pre- and post- 2003); RCTs; non-RCTs: mainly diagnostic, prognostic and cohort studies Taking into consideration the advice on prognostic reviews in the NICE guidelines manual, meta-analysis or GRADE will not be undertaken for prognostic studies as well as for other non-RCTs.

E.2 Review protocols for the diagnosis of hypertension: measurement protocols for diagnosing hypertension

- Ambulatory blood pressure measurement
- Home blood pressure measurement

Review questions	**AMBU PROTOCOL: In adults with primary hypertension, what protocol should be used when measuring ambulatory BP for treatment and diagnosis?** **HOME PROTOCOL: In adults with primary hypertension, what protocol should be used when measuring BP at home for treatment and diagnosis?**
Objectives	This aim of this review is to establish the best protocols for measuring ambulatory BP and home BP for diagnosis of hypertension and for monitoring treatment (in adults ≥18 years old).
Criteria	**Population (s):** Adults ≥18 years old with suspected primary hypertension (diagnosis) or hypertension (treatment) who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s) and comparison(s):** Home vs Home; ABPM vs ABPM Studies looking at home telemonitoring BP will be excluded, as this not common in clinical practice Studies will be selected from abstract lists if they mention more than 1 method or protocol of measuring home BP or if they directly assess what the optimum HBP protocol should be; otherwise they will be excluded at the abstracting stage. **Outcome(s):** • Sensitivity • Specificity • Reliability / reproducibility • Risk of developing clinical outcomes: • Mortality • Stroke • MI • Vascular procedures (including both coronary and arotid artery procedures) • Angina requiring hospitalisation • Major adverse cardiac and cerebrovascular events (MAACE): fatal and non-fatal MI, fat and non-fatal stroke, hospitalised angina, hospitalised heart failure, revascularisation (A DIFFERENT COMPOSITES OF THIS OUTCOME) Studies will be excluded if they: • are validation studies • are prognostic studies that only give one of the following ABPM: day, night, 24hours. N to compare all of them for which is best predictor • assess the prediction of future BP (rather than the specified clinical outcomes)

Search Strategy	See appendix Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG18, however the studies included within the SR/MA may have been published pre- and post- 2003); RCTs; non-RCTs: mainly diagnostic, prognostic and cohort studies, reliability / reproducibility studies Taking into consideration the advice on prognostic reviews in the NICE guidelines manual, meta-analysis or GRADE will not be undertaken for prognostic studies as well as for other non-RCTs.

E.3 Review protocol for initiating and monitoring treatment, including blood pressure targets

- Blood pressure thresholds for initiating treatment
- Blood pressure targets for treatment
- Monitoring treatment (covered in AMB1 and AMB2 protocol, xxx)
- Equivalent thresholds for intervention / treatment targets

Blood pressure thresholds for initiating treatment and blood pressure targets for treatment

Review questions	**INITIATION: In adults with primary hypertension, at what BP should treatment be initiated?** **OPTIMUM: In adults with primary hypertension, what is the optimum BP that should be reached for once treatment has been initiated/ targeted for treatment?**
Objectives	This aim of this review is to determine the appropriate level (threshold) of BP that a person must have in order for treatment to be initiated, and to determine the appropriate BP that treatment should be targeted to in order to gain an appropriate reduction in risk of CV events.
Criteria	**Population (s):** Adults ≥18 years old with suspected primary hypertension (diagnosis) or hypertension (treatment) who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s) and comparisons:** Home, ABPM and clinic **Outcome(s):** FOR INITIATION • Risk of developing clinical outcomes (at different BPs; studies will be excluded if they do not assess results by stratifying into different BP thresholds / values (thresholds or treatment targets) • Mortality • Stroke • MI

	• Vascular procedures (including both coronary and arotid artery procedures) • Angina requiring hospitalisation • 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) FOR OPTIMUM Same outcomes as above plus: • Number of patients with controlled BP • Number of patients reaching target • Final BP values Studies will be excluded if they: • do not stratify results by different BP thresholds / values • compare treated vs. untreated patients (for OPTIMUM)
Search Strategy	See appendix Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG18, however the studies included within the SR/MA may have been published pre- and post- 2003); RCTs; non-RCTs: mainly diagnostic, prognostic and cohort studies. Taking into consideration the advice on prognostic reviews in the NICE guidelines manual, meta-analysis or GRADE will not be undertaken for prognostic studies as well as for other non-RCTs.

Equivalent thresholds for intervention / treatment targets

Review question	**ADJUST (AMB3): if used, should ambulatory or home blood pressure readings be interpreted differently to office measurements? i.e. are different thresholds for intervention/targets for treatment required, or should adjustment be made to readings.**
Objectives	To establish the adjustment factor required for ambulatory, home and office BP measurements in order to give the same (in adults ≥18 years old).
Criteria	See ‘review strategy’
Search Strategy	See ‘review strategy’
Review Strategy	For this question data from the reviews comparing all three BP measurement methods (ABPM, home and clinic) were used to determine equivalent thresholds for intervention and targets for treatment based on outcome measures showing equivalent prognosis.

E.4 Review protocol for pharmacological interventions

- Step one therapy: Angiotensin-converting enzyme inhibitors (ACEi) versus Angiotensin Receptor Blockers (ARB); Diuretics
- Step two therapy: A+C vs A+D
- Resistant hypertension
- Special groups for consideration: people aged over 80 years and ethnicity

Step-one therapy: ACEi vs ARBs

Review	**In adults with primary hypertension, which is the most clinically and cost effective**

question	anti-hypertensive monotherapy (ACEi vs ARB) for first-line treatment, and does this vary with age and ethnicity?
Objectives	Since the publication of the earlier HT guidelines, a major outstanding issue for first line therapy was A vs A (as there was no evidence for these comparisons). Recent evidence has now emerged directly comparing ACEi and ARB. Therefore the aim of this review is to estimate the efficacy, safety and cost-effectiveness of ACEi vs ARB for first-line treatment of adults ≥18 years old with primary hypertension.
Criteria	**Population (s):** Adults ≥18 years old with primary hypertension who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s):** ACEi* **Comparison(s):** ARB* *In accordance with the 2006 guideline, all drugs in these classes will be assessed (licensed and unlicensed) as we are assuming a class effect **Outcome(s):** Effectiveness 10% • Mortality from any cause • Stroke (ischaemic or haemorrhagic) 10% • Myocardial infarction (MI) (including, where reported, silent MI) • Heart failure • New onset diabetes • Vascular procedures (including both coronary and carotid artery procedures) • Angina requiring hospitalisation • Health-related quality of life (to use what is reported by trials) • 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) 10% Safety • Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence) • Angioodema in black people of African and Caribbean descent
Search Strategy	See appendix Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG34, however the studies included within the SR/MA may have been published pre- and post- 2006); RCTs. Where appropriate, meta-analysis will be undertaken. Subgroup analyses will be done for age >80 years (vs <80 years) and for black people of African and Caribbean descent (vs. white people)

	Sensitivity analysis will be carried out based on methodological quality if significant heterogeneity exists. Overall assessment of the quality (for each outcome) will be undertaken using GRADE. Studies will be excluded if they: • have sample size of N<200 (in accordance with the 2006 guideline exclusion criteria) • have follow-up time of <12 months (in accordance with the 2006 guideline exclusion criteria)

Step-one therapy: diuretics

Review question	**In adults with primary hypertension, which is the most clinically and cost effective thiazide diuretic (bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first-line treatment, and does this vary with age and ethnicity?**
Objectives	A major issue for first line therapy is which diuretic is most effective because in the UK we use bendrofluazide for which there is very little evidence and the rest of the world do not use this drug. Is there a better diuretic to use? This was not looked at in the previous guidelines and so we have searched all dates. Therefore the aim of this review is to to estimate the efficacy, safety and cost-effectiveness of specific diuretics (bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) for first-line treatment of adults ≥18 years old with primary hypertension.
Criteria	**Population (s):** Adults ≥18 years old with primary hypertension who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s):** TD / TDLs (bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide) **Comparison(s):** TD/TDLs (head-to head – using the four named drugs above), placebo, other a-HT drug classes (BB, CCB, ACEi, ARBs: all drugs – licensed and unlicensed as we are assuming a class effect) **Outcome(s):** Effectiveness — 10% • Mortality from any cause • Stroke (ischaemic or haemorrhagic) — 10% • Myocardial infarction (MI) (including, where reported, silent MI) • Heart failure • New onset diabetes • Vascular procedures (including both coronary and carotid artery procedures) • Angina requiring hospitalisation • Health-related quality of life (to use what is reported by trials) • 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) • BP lowering (for part 2 of the question only – see review strategy section) Safety • Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence) • Angioodema in black people of African and Caribbean descent	10%
Search Strategy	See appendix Appendix D:Search Strategies.	
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG34, however the studies included within the SR/MA may have been published pre- and post- 2006); RCTs. Where appropriate, meta-analysis will be undertaken. Subgroup analyses will be done for age >80 years (vs <80 years) and for black people of African and Caribbean descent (vs. white people) Sensitivity analysis will be carried out based on methodological quality if significant heterogeneity exists. Overall assessment of the quality (for each outcome) will be undertaken using GRADE. Review strategy for part 1 and 2 of the question: **PART 1: TDs/TDLs vs placebo or other a-HT drug classes** TDs/TDLs must be: bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide Sample size must be N>200 (in accordance with the 2006 guideline exclusion criteria Follow up must be ≥1 year (in accordance with the 2006 guideline exclusion criteria Outcomes must be clinical only (not BP) Exclude studies if they report AEs / withdrawals but not our pre-specified clinical outcomes **PART 2: Head-to-head - TDs/TDLs vs other TDs/TDLs** TDs/TDLs must be: bendrofluazide / bendroflumethiazide, chlorthalidone, indapamide, hydrochlorothiazide Sample size: any Follow up: any Outcomes: BP only (only use clinical if reported ≥1 year results)	

Step-two therapy

Review question	**COMBI: In adults with primary hypertension, which is the most clinically and cost effective combination of anti-hypertensives (A+C or A+D) for second line treatment, and does this vary with age and ethnicity?**
Objectives	The earlier HT guideline recommended the use of adding in either CCBs or D for second-line therapy (ie. A+C or A+D). Recent evidence has now emerged directly comparing these combinations. The aim of this review is therefore to estimate the efficacy, safety and cost-effectiveness of ACEi + CCB or ARB + CCB vs. ACE + Diuretic or ARB + Diuretic) for second-line treatment of adults ≥18 years old with primary hypertension.
Criteria	**Population (s):** Adults ≥18 years old with primary hypertension who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes

	Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s):** A (ACEi or ARB)* + CCB* in second line treatment **Comparison(s):** A (ACEi or ARB)* + D* in second line treatment *In accordance with the 2006 guideline, all drugs in these classes will be assessed (licensed and unlicensed) as we are assuming a class effect **Outcome(s):** Effectiveness 10% • Mortality from any cause • Stroke (ischaemic or haemorrhagic) 10% • Myocardial infarction (MI) (including, where reported, silent MI) • Heart failure • New onset diabetes • Vascular procedures (including both coronary and carotid artery procedures) • Angina requiring hospitalisation • Health-related quality of life (to use what is reported by trials) • 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) 10% Safety • Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence) • Angioodema in black people
Search Strategy	See appendix Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG18, however the studies included within the SR/MA may have been published pre- and post- 2003); RCTs. Where appropriate, meta-analysis will be undertaken. Subgroup analyses will be done for age >80 years (vs <80 years) and for black people of African and Caribbean descent (vs. white people) Sensitivity analysis will be carried out based on methodological quality if significant heterogeneity exists. Overall assessment of the quality (for each outcome) will be undertaken using GRADE. Studies will be excluded if they: • have sample size of N<200 (in accordance with the 2004 guideline exclusion criteria) • have follow-up time of <12 months (in accordance with the 2004 guideline exclusion criteria)

Resistant hypertension

Review question	**In adults with resistant hypertension, which is the most clinically and cost effective fourth-line pharmacological treatment, and does this vary with age and ethnicity?**
Objectives	Resistant hypertension has not been covered in the previous guidelines. The aim of this review is therefore to estimate the efficacy, safety and cost-effectiveness of fourth-line therapy in adults ≥18 years old with resistant hypertension.
Criteria	**Population (s):** Adults (≥18 years old) with resistant hypertension (people whose BP is still uncontrolled despite treatment with optimal doses of three a-HT drugs) who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s):** 4th line drugs (MOST WIDELY USED OPTIONS: including alpha-blockers; beta-blockers; other/further diuretics such as amiloride and spironolactone; aliskerin; aldosterin antagonists; moxonidine) **Comparison(s):** Any comparison (placebo or each other) **Outcome(s):** Effectiveness 10% • Mortality from any cause • Stroke (ischaemic or haemorrhagic) 10% • Myocardial infarction (MI) (including, where reported, silent MI) • Heart failure • New onset diabetes • Vascular procedures (including both coronary and carotid artery procedures) • Angina requiring hospitalisation • Health-related quality of life (to use what is reported by trials) • 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) 10% Safety • Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence) • Angioodema in black people
Search Strategy	See appendix Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG18, however the studies included within the SR/MA may

	have been published pre- and post- 2003); RCTs; cohort studies. Where appropriate, meta-analysis will be undertaken. Subgroup analyses will be done for age >80 years (vs <80 years) and for black people of African and Caribbean descent (vs. white people) Sensitivity analysis will be carried out based on methodological quality if significant heterogeneity exists. Overall assessment of the quality (for each outcome) will be undertaken using GRADE. Studies will be excluded if they: • are RCTs with a sample size of N<200 (in accordance with the 2004 guideline exclusion criteria); unless evidence is sparse • are RCTs with a follow-up time of <12 months (in accordance with the 2004 guideline exclusion criteria); unless evidence is sparse

Special groups for consideration: people aged over 80 years

Review question	**In adults with primary hypertension, what is the most clinically and cost effective first-line anti-hypertensive treatment (drug classes) in elderly people (aged ≥80 years)?**
Objectives	In the previous guidelines (CG18 and CG34) there was no evidence available showing whether there were differences in treatment effects in elderly people (80+). However data has since then emerged on drug treatment in this age-group. Therefore the aim of this review is to to estimate the efficacy, safety and cost-effectiveness of anti-hypertensive drugs for the first-line treatment of adults ≥80 years old with primary hypertension.
Criteria	**Population (s):** Adults ≥80 years old with primary hypertension who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s):** All a-HT drug classes (BB, CCB, ACEi, ARBs)* Comparison(s): all a-HT drug classes (BB, CCB, ACEi, ARBs)* *In accordance with the 2006 guideline, all drugs in these classes will be assessed (licensed and unlicensed) as we are assuming a class effect **Outcome(s):** Effectiveness 10% • Mortality from any cause • Stroke (ischaemic or haemorrhagic) 10% • Myocardial infarction (MI) (including, where reported, silent MI) • Heart failure • New onset diabetes • Vascular procedures (including both coronary and carotid artery procedures) • Angina requiring hospitalisation • Health-related quality of life (to use what is reported by trials) • 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) 10% Safety • Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence) • Angioodema in black people of African and Caribbean descent
Search Strategy	See appendix Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG34, however the studies included within the SR/MA may

	have been published pre- and post- 2006); RCTs. Where appropriate, meta-analysis will be undertaken. Sensitivity analysis will be carried out based on methodological quality if significant heterogeneity exists. Overall assessment of the quality (for each outcome) will be undertaken using GRADE. Studies will be excluded if they: • have sample size of N<200 (in accordance with the 2006 guideline exclusion criteria) • have follow-up time of <12 months (in accordance with the 2006 guideline exclusion criteria)

Special groups for consideration: ethnicity

Review question	**In adults with primary hypertension, what is the most clinically and cost effective first-line anti-hypertensive treatment (drug classes) in black people of African or Caribbean descent)?**
Objectives	In the previous guideline there was little evidence available showing whether there were differences in treatment effects in elderly people (80+). However data has since then emerged on drug treatment in this age-group. Therefore the aim of this review is to to estimate the efficacy, safety and cost-effectiveness of anti-hypertensive drugs for the first-line treatment of adults ≥80 years old with primary hypertension.
Criteria	**Population (s):** Black adults (of African or Caribbean descent) ≥18 years old with primary hypertension who may or may not have pre-existing cardiovascular disease, chronic kidney disease and diabetes Studies in indirect populations will not be considered (ocular HT, pulmonary HT, HT during pregnancy, acute HT, malignant HT, portal HT, renal HT and intercranial HT) Studies in adult women of conception age will be considered (in accordance with BNF). Studies with an exclusive diabetic or CKD population will be excluded (in accordance with the 2006 guideline exclusion criteria) **Intervention (s):** ACEi* **Comparison(s):** ARB* *In accordance with the 2006 guideline, all drugs in these classes will be assessed (licensed and unlicensed) as we are assuming a class effect **Outcome(s):** Effectiveness 10% • Mortality from any cause • Stroke (ischaemic or haemorrhagic) 10% • Myocardial infarction (MI) (including, where reported, silent MI) • Heart failure • New onset diabetes • Vascular procedures (including both coronary and carotid artery procedures) • Angina requiring hospitalisation • Health-related quality of life (to use what is reported by trials) • 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) 10% Safety • Study drug withdrawal rates (surrogate for adverse effects of drug treatment and for adherence) • Angioodema
Search Strategy	See appendix Appendix D:Search Strategies.
Review Strategy	Study design: SRs / meta-analyses (will be included if they are published after the cut-off date of the previous guideline CG34, however the studies included within the SR/MA may have been published pre- and post- 2006); RCTs; sub-group analyses of RCTs, cohort studies. Where appropriate, meta-analysis will be undertaken. Sensitivity analysis will be carried out based on methodological quality if significant heterogeneity exists. Overall assessment of the quality (for each outcome) will be undertaken using GRADE. Studies will be excluded if they have a: • sample size of N<1000 in each arm (as a very large study, ALLHAT, has been published with a sample size of 42,418) • follow-up time of <12 months (in accordance with the 2006 guideline exclusion criteria)

E.4.1 Health economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify economic studies relevant to the review questions set out above.
Criteria	Populations, interventions and comparators, and date cut-offs as specified in the question-specific review protocols. Must be a relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis).
Search strategy	See Appendix D:.
Review strategy	Each study is assessed using the NICE economic evaluation checklist – NICE (2009) Guidelines Manual, Appendix H. **Inclusion/exclusion criteria** • If a study is rated as both 'Directly applicable' and 'Minor limitations' (using the NICE economic evaluation checklist) then it should be included in the guideline. An evidence table should be completed and it should be included in the economic profile. • If a study is rated as either 'Not applicable' or 'Very serious limitations' then it should be excluded from the guideline. It should not be included in the economic profile and there is no need to include an evidence table. • If a study is rated as 'Partially applicable' and/or 'Potentially serious limitations' then there is discretion over whether it should be included. The health economist should make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim being to include studies that are helpful for decision making in the context of the guideline. Where exclusions occur on this basis, this should be noted in the relevant section of the guideline with references. Also exclude: • unpublished reports unless submitted as part of the call for evidence

Review question	All questions – health economic evidence
	• abstract-only studies • letters • editorials • reviews of economic evaluations(a) • foreign language articles **Where there is discretion** The health economist should be guided by the following hierarchies. Setting: 1. UK NHS 2. OECD countries with predominantly public health insurance systems (e.g. France, Germany, Sweden) 3. OECD countries with predominantly private health insurance systems (e.g. USA, Switzerland) 4. Non-OECD settings (always 'Not applicable') Economic study type: 1. Cost-utility analysis 2. Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis) 3. Comparative cost analysis 4. Non-comparative cost analyses including cost of illness studies (always 'Not applicable') Year of analysis: • The more recent the study, the more applicable it is Quality and relevance of effectiveness data used in the economic analysis: • The more closely the effectiveness data used in the economic analysis matches with the studies included for the clinical review the more useful the analysis will be to decision making for the guideline.

(a) Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.

Appendix F: Clinical evidence tables

F.1 Blood pressure variability

STUDY 1								
P. M. Rothwell, S. C. Howard, E. Dolan, E. O'Brien, J. E. Dobson, B. Dahlof, N. R. Poulter, and P. S. Sever. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 9 (5):469-480, 2010. ID 15883	1) RCT Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) Country not stated Selection, randomisation, allocation concealment, power calculation, attrition not described (referenced to another paper) Participants in two treatment groups well matched Intention to treat analysis Medications added in to patients in either group Interpretation of apparent correlates with treatment effects in trials on the basis of data collected after randomisation potentially subject to bias No differences between groups in loss to follow up 2) Medical Research Council trial Country not stated	1) whole study 19257; used in this analysis 18530 (96.2%) who had at least 2 scheduled follow up visits from 6 months onwards 2) 4396	1) Inclusion: Patients with hypertension aged 40-79 years and had at least 3 other cardiovascular risk factors but no previous history of coronary heart disease. Clinic BPs (CBP) 6-monthly using validated semi-automatic oscillometric device, seated and rested for 5 minutes; measured 3 times at 5 minute intervals and mean of last 2 measurements used. Participants at 4 centres had repeated annual ambulatory BPs using validated monitors giving daytime (0900-2100) and night-time (0100-0600) and 24-hour readings. 2) Hypertensive patients (mean SBP 160-209mmHg and mean DBP <115mmHg) aged	1) amlodipine-perindopril to achieve CBP target ≤140/90mmHg without diabetes or ≤130/80mmHg with diabetes, plus other antihypertensives as needed 2) atenolol 50mg daily or a diuretic combination (hydrochlorothiazide 25mg plus amiloride 2.5mg daily), titrated to achieve clinic SBP <150mmHg (if mean run-in SBP 160-179mmHg) or <160mmHg (if mean run-in SBP ≥180mmHg)	1) atenolol-thiazide to achieve CBP target ≤140/90mmHg without diabetes or ≤130/80mmHg with diabetes plus other antihypertensives as needed 2) placebo	1) Median 5.5 years	Primary endpoint: 1) Risk of stroke and coronary events 2) Stroke risk Visit-to-visit variability in BP was a strong predictor of long-term risk of stroke; this was increased by atenolol	none

STUDY 1								
	No data for individual patients on add-on treatments with other drugs; use of other drugs was particularly high in atenolol group (52% vs. 38% in diuretic group at 5 years) with drugs (e.g. nifedipine) that would have reduced variability		65-74 years. Clinic BP measured 3 times sitting using random zero sphygmomanometer; mean of 2nd 2 readings used.					

Baseline characteristics:

1) ASCOT-BPLA:

	Atenolol-based regimen	Amlodipine-based regimen	Difference
Systolic BP:			
Mean	141.8 (13.0)	139.1 (11.1)	2.68 (2.58-2.78), p<0.0001
Maximum	164.2 (18.9)	157.4 (16.1)	6.80 (6.68-6.92), p<0.0001
Minimum	122.6 (13.5)	123.0 (11.8)	-0.40 (-0.50 to +0.30)
Within-individual visit-to-visit variability:			
Standard deviation	13.42 (5.77)	10.99 (4.79)	2.43 (2.36-2.50), p<0.0001
Coefficient of variation (SD/mean)	9.41 (3.78)	7.87 (3.23)	1.54 (1.49-1.59)
Within-visit variability:			
Standard deviation	5.91 (0.02)	5.42 (0.02)	0.49 (0.44-0.54)
Range of 3 readings	5.16 (0.04)	4.85 (0.04)	0.31 (0.20-0.42)
Diastolic BP:			
Mean	82.1 (7.6)	80.2 (7.4)	1.98 (1.90-2.06)
Maximum	93.5 (9.6)	90.4 (9.0)	3.10 (3.00-3.20)
Minimum	71.8 (8.4)	70.8 (8.1)	1.00 (0.90 to 1.10)
Within-individual visit-to-visit variability:			
Standard deviation	6.98 (2.72)	6.26 (2.42)	0.72 (0.67-0.77)
Coefficient of variation (SD/mean)	8.54 (3.30)	7.86 (3.04)	0.68 (0.63-0.73)

2) MRC trial:

STUDY 1
No treatment-group differences in group SD and coefficient of variation of SBP at baseline. Outcomes: 1) ASCOT-BPLA: Hazard ratio for stroke with randomised treatment (amlodipine versus atenolol, 0.78, 0.67-0.90, p=0.001) diminished less after adjustment for mean SBP during follow up (0.84, 0.72-0.98, p=0.025) than after adjustment for visit-to-visit variability using standard deviation of SBP (0.94, 0.81-1.10, p=0.47). Similarly for risk of coronary events (0.85, 0.77-0.94, p=0.002 changed to 0.88, 0.80-0.98, p=0.019 after adjusting for mean SBP and to 1.00, 0.90-1.11, p=0.96 after adjusting for SD of SBP). Adjustment for variability in DBP had less effect. Group SD of SBP decreased on treatment with amlodipine and increased in the atenolol group, independent of effects on mean BP. The reduced event rates in the amlodipine group could not be fully accounted for by changes in mean BP or other risk factors but were explained by variability. Patients with good control of BP but high residual variability in SBP had a 5 times higher risk of stroke than those with low residual SBP variability. 2) MRC trial: Atenolol increased visit-to-visit variability in SBP compared to placebo, whereas the diuretic combination did not. Mean SBP was higher in atenolol group than diuretic group (156.6 (12.1) mmHg vs. 151.2 (12.1) mmHg) in the first 18 months of the trial, mainly due to a higher maximum SBP (178.2 (16.1)mmHg vs. 168.8 (15.7)mmHg) as a consequence of increased variability, with little difference in minimum SBP (135.9 (13.5)mmHg vs. 134.2 (12.7)mmHg). The risk of stroke in the atenolol group was higher than placebo for the first 2 years (HR 1.31, 0.81-2.10) when variability was also higher than with placebo (SD 14.38 (5.34) vs. 12.12 (4.48), p<0.001) despite substantially lower mean BP (156.6 (12.1)mmHg vs. 167.4 (12.0)mmHg, p<0.001). The risk of stroke was lower on atenolol than placebo after 2 years of follow up (HR 0.62, 0.40-0.94), by which time the difference in mean BP was still large 151.8 (13.0)mmHg vs. 166.3 (14.2)mmHg, p<0.001) but variability no longer differed (SD 12.30 (6.24) vs. 12.68 (6.21), p=0.12).

STUDY 2								
P. M. Rothwell, S. C. Howard, E. Dolan, E. O'Brien, J. E. Dobson, B. Dahlof, P. S. Sever, and N. R. Poulter. Prognostic significance	1a) RCT UK-TIA aspirin trial and 3 similar validation cohorts: 1b) RCT European Stroke Prevention Study (ESPS-1) placebo group only 1c) RCT Dutch TIA trial 1d) Subgroup of RCT	1a) total 2435 with Recent TIA or ischaemic stroke; this analysis: 2006 TIA only 1b) 2500 1c) 3150	1a) Recent TIA Sitting BP measured once every 4 months with mercury sphygmomanometer and patient rested. 4 categories: stable normotension (maximum ≤140mmHg); episodic moderate hypertension (minimum ≤140mmHg and maximum 140-179mmHg); episodic severe hypertension (minimum ≤140mmHg and maximum	1a) Aspirin 1200mg or 300mg 1b) dipyridamole 75mg + aspirin 325mg three times daily 1c) aspirin 283mg or atenolol 50mg 1d and 2)	1a) Placebo 1b) Placebo 1c) aspirin 30mg or placebo 1d and 2) atenolol-thiazide to achieve CBP target ≤140/90mmHg without diabetes	1a) median 10 (range 1-20) follow ups at 4-monthly intervals 1b) 2 years	1a) Vascular events and deaths 1b-d) Stroke 2) Risk of stroke and total coronary events Visit-to-visit variability in	none

STUDY 1								
of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 375 (9718):895-905, 2010. ID 6157	Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) Variability in BP measurements could be due to non-adherence to guidelines for measurement or inadequate calibration of measuring devices BP measured only once in 1a and 1c No data on use of, or compliance with, antihypertensive drugs during follow up in older TIA cohorts Findings cannot be generalised to healthy cohorts 2) RCT Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA)	1d) 2011 2) 18530 (96% of total in study) had 2 or more visits from 6 months onwards (median 10, IQR 9-11)	≥180mmHg); and stable hypertension (minimum >140mmHg) 1b) mean of left and right arm sitting after rest, mercury sphygmomanometer every 3 months 1c) Sitting BP measured once every 4 months with mercury sphygmomanometer and patient rested 1d) Previous TIA or stroke 2) Patients with hypertension aged 40-79 years and had at least 3 other cardiovascular risk factors but no previous history of coronary heart disease. Clinic BPs (CBP) 6-monthly using validated semi-automatic oscillometric device, seated and rested for 5 minutes; measured 3 times at 5 minute intervals and mean of last 2 measurements used. Participants at 4 centres had repeated annual ambulatory BPs using validated monitors giving daytime (0900-2100) and night-time (0100-0600) and 24-hour readings. For all: Visit-to-visit variability defined as Standard deviation (SD) and Coefficient of variation (SD/mean) or SD and range of 3 readings at 1 visit	amlodipine-perindopril to achieve CBP target ≤140/90mmHg without diabetes or ≤130/80mmHg with diabetes, plus other antihypertensives as needed	or ≤130/80mmHg with diabetes plus other antihypertensives as needed	1c) mean 2.6 years 2) Median 5 years	SBP was a strong predictor of subsequent stroke independent of mean SBP; maximum SBP reached was also a strong predictor of subsequent stroke independent of mean SBP. Increased residual variability in SBP in patients with treated hypertension is associated with a high risk of vascular events.	

STUDY 1

			Covariates: age, gender, baseline vascular risk factors					

Rothwell 6157

Baseline characteristics:

1a-d) UK-TIA aspirin trial: 2006 patients, 1438 men, mean age 60.3 (9.1) years; age and gender not specified for other cohorts. Available data:

		ASCOT-BPLA subgroup with previous TIA			
	UK-TIA aspirin trial	Atenolol group	Amlodipine group	ESPS-1 placebo group	Dutch TIA trial
n	1324	1012	999	1247	3150
Mean baseline SBP (mmHg)	150.2 (25.3)	163.7 (18.7)	164.4 (17.9)	156.3 (22.7)	157.9 (26.3)
Mean 1 year SBP (mmHg)	146.6 (23.4)	148.3 (19.7)	143.3 (17.4)	154.8 (22.3)	151.7 (22.5)
Mean Visit-to-visit variability:					
SD	14.2 (6.6)	14.4 (6.1)	11.4 (4.9)	14.6 (6.8)	14.9 (6.4)
Coefficient of variation (SD/mean)	9.6 (3.9)	10.00 (4.0)	8.2 (3.3)	9.3 (4.1)	9.7 (3.9)

Outcomes:

1a) UK-TIA aspirin trial: 1324 (66%) patients reached visit 7, of whom 270 had a stroke or coronary event. Mean SBP over visits 1-7 predicted stroke: adjusted HR 1.43 (1.18-1.74) per 20mmHg, p<0.0001. Visit-to-visit variability in SBP was a stronger predictor: adjusted HR 4.37 (2.73-6.99) independent of mean SBP in patients receiving (HR 3.67, 2.34-5.75) and not receiving (HR 2.27, 1.41-3.67) antihypertensives at baseline. The effect was similar for men and women but decreased with age: 9.43 (1.96-45.5) at <56 years; 3.01 (0.97-9.36) at 56-64 years and 1.71 (0.74-3.98) at ≥65 years. Maximum SBP was more predictive than mean SBP, and was most predictive at lower values of mean SBP: HR for maximum SBP adjusted for mean SBP: 4.95 (1.28-22.4, p=0.007) at mean SBP <130mmHg; 3.19 (1.65-6.23, p=0.0001) at 130-159mmHg and 1.13 (0.50-2.53, p=0.75) at ≥160mmHg. Patients with episodic severe hypertension (minimum ≤140mmHg and maximum ≥180mmHg) had a higher risk of stroke than those with stable hypertension (13.7% vs. 4.5%, p=0.003; age and gender-adjusted HR 3.58, 1.58-8.10) despite a lower mean SBP (157.9 (8.7)mmHg vs. 167.3 (7.2)mmHg, p=0.001.

1a-d): Hazard ratios for stroke (top versus bottom decile of each measure):

		ASCOT-BPLA subgroup with previous TIA			
	UK-TIA aspirin trial	Atenolol group	Amlodipine group	ESPS-1 placebo group	Dutch TIA trial

STUDY 1

Mean SBP (unadjusted)	3.63 (2.41-5.48)	1.81 (0.89-3.67)	0.94 (0.36-2.42)	1.89 (0.96-3.71)	2.34 (1.41-3.89)
SD SBP adjusted for mean SBP	4.84 (3.03-7.74)	4.29 (1.78-10.36)	4.39 (1.68-11.50)	1.78 (1.21-2.62)	3.35 (1.63-6.87)
Coefficient of variation SBP adjusted for mean SBP	3.82 (2.54-5.73)	3.51 (1.56-7.93)	3.25 (1.32-8.00)	2.22 (1.52-3.22)	3.41 (1.62-7.19)

2) Patients with episodic severe hypertension (minimum ≤140mmHg and maximum ≥180mmHg) had a higher risk of stroke than those with stable hypertension (4.0% vs. 2.7%, p=0.03 despite a lower mean SBP (142.1 (14.8)mmHg vs. 147.3 (13.8)mmHg, p<0.0001). Maximum SBP predicted stroke (e.g. top decile Hazard ratio for risk of stroke in atenolol group 2.51, 1.69-3.73, p=0.0008).

Variability was related to factors that correlate with arterial stiffness including age, female gender, smoking, diabetes and peripheral vascular disease (data not given).

STUDY 3

A. J. Webb, U. Fischer, Z. Mehta, and P. M. Rothwell. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. Lancet 375 (9718):906-	Meta-analysis Country not applicable From published systematic reviews from Medline and Cochrane databases, reference lists of reviews, no language restrictions Not individual patient data, so not possible to exclude from analysis people who had a non-fatal event during early follow up but whose BP data contributed to group means thereafter (but potential bias assessed as small by authors) Low rate of reporting of BP variability in trials (assessed as unlikely to introduce bias	389 RCTs for outcome of BP variability; 21 for clinical outcomes DRUGS vs DRUGS	Inclusion criteria referenced to web appendix: briefly, trials of the drug classes listed Exclusion: no valid comparison group, lasted <2 weeks, ineligible patient group, BP or group variation in BP not reported Covariates: age, gender, ethnic	8 main drug classes: thiazide and thiazide-like diuretics; β blockers; ACE inhibitors; angiotensin-2-receptor blockers; dihydropyridine calcium channel blockers; non-dihydropyridine calcium channel blockers; α1 blockers; placebo	1) versus all of the other of the 8 drug classes or placebo 2) versus each of the other of the 8 drug classes or placebo one at a time	2 weeks for BP variability ; 1 year for clinical outcomes	For trials with >100 patients per treatment group with at least 1 year of follow up: risk of stroke, MI, heart failure, cardiovascular mortality Calcium channel blockers, non-dihydropyridine calcium channel blockers and diuretics reduced variability, whereas angiotensin-receptor blockers, ACE inhibitors and β blockers increased it. Effects of treatment on variation in SBP were correlated with effects on risk of stroke (but not MI or heart failure) independently of differences in mean SBP.	none

STUDY 3								
915, 2010. ID 15886	on the basis of funnel plots referenced to web appendix)		origin, diabetes, renal failure					

Webb 15886

Baseline characteristics:

Changes in inter-individual variance (SD2) in BP (a surrogate for within-individual variability) expressed as the ratio of the variances follow up versus baseline (VR) and as the percentage differences in coefficient of variation follow up versus baseline (CV) both within trial (between treatment groups) and across trials (for each drug class). SD and CV correlated with each other but not with mean SBP. Significant heterogeneity among the 682 treatment groups ($p<0.001$), 24.7% of which explained by drug class after adjustment for age, gender, ethnic origin, diabetes, renal failure, baseline SBP and DBP.

SD of SBP at follow up and variance ratio

	Patients	**Trials**	**SD (95% CI)**	**Ratio of variances follow up versus baseline: VR (95% CI)**
Calcium channel blockers	34221	134	14.97 (14.74-15.46)	0.89 (0.82-0.97)
Non-dihydropyridine calcium channel blockers	6777	33	15.92 (15.31-16.76)	0.96 (0.84-1.10)
Non-loop diuretics	30090	58	15.65 (15.24-16.17)	1.17 (1.01-1.35)
Angiotensin-2-receptor blockers	20748	61	16.74 (16.35-17.07)	1.20 (1.04-1.39)
ACE inhibitors	19235	160	16.95 (16.49-17.43)	1.00 (0.91-1.10)
β blockers	20255	96	17.25 (16.83-17.70)	1.15 (1.02-1.28)
α1 blockers	9540	13	17.00 (16.52-17.64)	1.33 (1.08-1.63)
Placebo	14514	119	17.29 (16.79-17.75)	1.26 (1.09-1.47)

Outcomes:

Within trial comparisons between drug classes on inter-individual variability of SBP at follow up:

	Drug class versus placebo			**Drug class versus all other drug classes (or placebo)**		
	Patients	Trials	Ratio of variances follow up versus baseline: VR (95% CI), p value	Patients	Trials	Ratio of variances follow up versus baseline: VR (95% CI), p value

STUDY 3						
Calcium channel blockers	11294	34	0.76 (0.67-0.85), p<0.0001	106697	94	0.81 (0.76-0.86), p<0.0001
Non-dihydropyridine calcium channel blockers	736	6	0.76 (0.51-1.12), p=0.17	2753	39	0.81 (0.66-0.98), p=0.035
Non-loop diuretics	12187	20	0.91 (0.80-1.03), p=0.15	81772	69	0.87 (0.79-0.96), p=0.007
Angiotensin-receptor blockers	6756	13	0.93 (0.87-1.00), p=0.044	39447	47	1.16 (1.07-1.25), p=0.0002
ACE inhibitors	7074	43	0.94 (0.82-1.08), p=0.39	76064	125	1.08 (1.02-1.15), p=0.008
β blockers	1210	19	1.04 (0.88-1.23), p=0.65	39392	78	1.17 (1.07-1.28), p=0.0007

Calcium channel blockers, non-dihydropyridine calcium channel blockers and diuretics reduced variability, whereas angiotensin-receptor blockers, ACE inhibitors and β blockers increased it.

Clinical outcomes: odds ratio (OR) of outcome during follow up in treatment group with lower SD of SBP (lower variability):

	Risk of stroke	Risk of MI	Risk of heart failure
VR <1.00	OR 0.87 (0.77-0.97), p=0.12	1.01 (0.91-1.08), p=0.45	NS
VR ≤0.80	OR 0.79 (0.71-0.87), p<0.0001	not stated	not stated
Calcium channel blockers vs. all other drugs	OR 0.88 (0.83-0.94), p=0.0002	NS	not stated
β blockers vs. all other drugs	OR 1.19 (1.01-1.42), p=0.0394	NS	not stated

In a model including mean SBP and VR SBP, each variable was independently related to stroke risk (mean SBP p=0.038; VR p=0.014).

Appendix G: Evidence tables – health economic studies (2011 update)

G.1 Diagnosis of hypertension

<table>
<tr><td colspan="5">L. R. Krakoff. Cost-effectiveness of ambulatory blood pressure: a reanalysis. Hypertension 47 (1):29-34, 2006.</td></tr>
<tr><td>Study details</td><td>Population & interventions</td><td>Health outcomes</td><td>Costs</td><td>Cost effectiveness</td></tr>
<tr>
<td>Economic analysis: Cost analysis

Study design: Decision analytic model
Approach to modelling: Model calculates the different numbers of treated patients taking into account prevalence of white coat hypertension, annual incidence of new true hypertension in those with white coat hypertension and annual loss to follow-up and treatment.

Perspective: USA, healthcare payer
Time horizon: 5 years
Discounting: Costs: none; Outcomes: n/a</td>
<td>Population:
People identified as hypertensive based on CBPM

Intervention 1:
No further tests to confirm diagnosis, annual follow-up with CBPM
Intervention 2:
ABPM to confirm diagnosis and at annual follow-up</td>
<td>None</td>
<td>Total costs (mean per patient):
Intvn 1: £984
<table>
<tr><td>Intvn 2:</td><td>Total costs</td><td>Incremental (2-1)</td><td>CI/p</td></tr>
<tr><td>15%WCH/conv 5%</td><td>£922</td><td>-£61</td><td>NR</td></tr>
<tr><td>15%WCH/conv 10%</td><td>£935</td><td>-£49</td><td>NR</td></tr>
<tr><td>15%WCH/conv 20%</td><td>£955</td><td>-£29</td><td>NR</td></tr>
<tr><td>20%WCH/conv 5%</td><td>£886</td><td>-£97</td><td>NR</td></tr>
<tr><td>20%WCH/conv 10%</td><td>£903</td><td>-£81</td><td>NR</td></tr>
<tr><td>20%WCH/conv 20%</td><td>£929</td><td>-£54</td><td>NR</td></tr>
<tr><td>25%WCH/conv 5%</td><td>£850</td><td>-£134</td><td>NR</td></tr>
<tr><td>25%WCH/conv 10%</td><td>£870</td><td>-£113</td><td>NR</td></tr>
<tr><td>25%WCH/conv 20%</td><td>£904</td><td>-£80</td><td>NR</td></tr>
</table>
WCH = baseline prevalence of white coat hypertension; Conv = annual conversion rate of white coat hypertension to true hypertension

Currency & cost year: USA dollars, cost year unclear assumed to be 2005† (presented here as 2005 UK pounds‡)

Cost components incorporated: ABPM; hypertension treatment (visits, diagnostic tests, pharmacotherapy).</td>
<td>None</td>
</tr>
<tr><td colspan="5">Data sources</td></tr>
<tr><td colspan="5">Health outcomes: Prevalence white coat hypertension: source not stated but rate varied in analysis 15%-20%. Incidence of new hypertension in those with white coat hypertension: based on review of literature and varied in analysis. Annual loss to follow-up and treatment: assumed 5% (limited evidence but considered conservative).</td></tr>
</table>

Quality-of-life weights: n/a. **Cost sources:** Cost per ABPM use: Centre for Medicare and Medicaid Services of the United States (£47). Annual treatment cost: estimated based on 5-year survey from US MCO and report that if followed guidelines for using diuretics would reduce by 40% (£212).
Comments
Source of funding: NR. **Limitations:** 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. Source of prevalence of WCH unclear but varied in sensitivity analysis. Limited sensitivity analysis. **Other:** none
Overall quality*: Potentially serious limitations **Overall applicability**:** Partially applicable

Abbreviations: ABPM = ambulatory blood pressure monitoring; CBPM = clinic blood pressure monitoring; CI = confidence interval; NR = not reported; MCO = managed care organisation; NR = not reported.
† Year paper accepted for publication; ‡ Converted using 2005 Purchasing Power Parities[468]
**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable*

G.2

G.3 Initiating and monitoring treatment, including blood pressure targets

G.3.1 Monitoring treatment effect

J. A. Staessen, Hond E. Den, H. Celis, R. Fagard, L. Keary, G, and E. T. O'Brien. Antihypertensive treatment based on blood pressure measurement at = home or in the physician's office: a randomized controlled trial. Journal of the American Medical Association 291 (8):955-964, 2004.

Study details	Population & interventions	Health outcomes	Costs	Cost effectiveness
Economic analysis: CCA **Study design:** Within RCT analysis **Perspective:** Belgium health insurance system **Follow-up:** 1 year **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Patients with hypertension (office DBP >95mmHg) • N = 400 • Mean age = 53 years • M = 48% • Belgian 93.2%; Irish 6.8% **Intervention 1:** Monitoring and treatment adjustment based on CBPM (average of 3). N=203 **Intervention 2:** Monitoring and treatment adjustment based on average of HBPM (average of 6 per day over 1 week). N=197	Blood pressure: BP was significantly lower in the office than the home group. Antihypertensive medications: Significantly more home than office group patients discontinued antihypertensive drug treatment. Left ventricular mass and reported symptoms: No significant differences.	**Total costs (mean per patient):** Intvn 1: £2811 Intvn 2: £2555 Incremental (2-1):-£256 (CI:NR, p=0.04) **Currency & cost year:** 2002 Belgium Euros (presented here as 2002 UK pounds†) **Cost components**	**Basecase ICER (Intvn 2 vs Intvn 1):** N/a. Costs were lower in the HBPM group but outcomes blood pressure control was worse. **Other:** n/a **Subgroup analyses:** None **Analysis of uncertainty:** n/a

	Treatment intensified if DBP >89mmHg; treatment reduced if DBP <80mmHg		**incorporated:** Antihypertensive drugs, physician visits, HBPM	

Data sources
Health outcomes: Within RCT analysis; **Quality-of-life weights:** n/a. **Cost sources:** Resource use from within RCT; Belgian units costs from health insurance system for drugs and physician costs. HBPM from manufacturer.
Comments
Source of funding: AstraZeneca and Pfizer **Limitations:** Some uncertainty about applicability of Belgian resource use and unit costs. QALYs not used (cost consequence analysis). In terms of health effects looks at BP, hypertensive drug use, and LV mass/symptom. 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 (need to confirm if study included in clinical review and if other evidence exists. **Other:** Physician fees and drug costs significantly lower for home monitoring but partially offset by increased cost of home monitoring.
Overall quality*: Potentially serious limitations **Overall applicability**:** Partially applicable

Abbreviations: BP = blood pressure; CBPM = clinic blood pressure monitoring; CCA = cost-consequence analysis; CI = confidence interval; DBP = diastolic blood pressure; HBPM = home blood pressure monitoring; ICER = incremental cost-effectiveness ratio; NR = not reported; RCT = randomised clinical trial.
† Converted using 2002 Purchasing Power Parities[468].
**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable.*

G.3.2 Blood pressure targets for treatment

B. Jonsson, L. Hansson, and N. O. Stalhammar. Health economics in the hypertension optimal treatment (HOT) study: costs and cost-effectiveness of intensive blood pressure lowering and low-dose aspirin in patients with hypertension. J.Intern.Med. 253:472-480, 2003.

Study details	Population & interventions	Health outcomes	Costs	Cost effectiveness
Economic analysis: Cost analysis/CCA **Study design:** Within RCT analysis **Perspective:** International resource use,	**Population:** Patients with hypertension and DBP110-115mmHg • N = 18,790 • Countries = 26 • Male = NR • Mean age = 61.5years **Intervention 1:** Treatment to target DBP <90mmHg	None reported in paper for whole population (only diabetes subgroup). Paper states that differences in events were non-significant in the overall population. See clinical evidence review for more details.	**Total costs – all patients (mean per patient):** Intvn 1: £2200 Intvn 2: £2282 Intvn3: £2381 Incremental (2-1):£82 (CI: NR , p<0.01) Incremental (3-2):£99 (CI: NR , p<0.01) Incremental (3-1):£181	**Basecase ICER:** Costs significantly increased as the target was lowered and there was no significant difference in cv events. **Subgroup analyses:** Diabetes subgroup – out of scope of guideline. **Analysis of uncertainty:** Cost of non-cv

Swedish costs, healthcare payer **Followup:** mean 3.8 years **Discounting:** Costs: NR; Outcomes: NR	**Intervention 2:** Treatment to target DBP <85mmHg **Intervention 3:** Treatment to target DBP <80mmHg All patients received felodipine (CCB). Additional therapy and dose increments in four further steps were prescribed to reach the randomised target. 50% of patients were also randomised to aspirin (75mg daily).		(CI: NR , p<0.01) **Currency & cost year:** 1995 Swedish Kroner (presented here as 1995 UK pounds†) **Cost components incorporated:** Antihypertensive drugs, physician visits, hospitalisations, side effects.	hospitalisations included – increased total costs, differences remained similar. Swedish patients only used – not considered relevant to guideline.
Data sources				
Health outcomes: Within RCT analysis; **Quality-of-life weights:** N/a; **Cost sources:** Resource use collected within RCT; units costs were from Swedish national data sources or published studies.				
Comments				
Source of funding: AstraZeneca; **Limitations:** Some uncertainty about applicability of International resource use and Swedish unit costs. QALYs not used (although clinical outcomes reported as not significantly different). Discounting not applied. 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. **Other:** n/a				
Overall quality*: Potentially serious limitations	**Overall applicability**:** Partially applicable			

Abbreviations: BP = blood pressure; CCA = cost-consequence analysis; CI = confidence interval; cv = cardiovascular; DBP = diastolic blood pressure; ICER = incremental cost-effectiveness ratio; NR = not reported; RCT = randomised clinical trial; QALYs = quality-adjusted life years.
† Converted using 1995 Purchasing Power Parities[468].
**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable.*

G.4 Pharmacological interventions

G.4.1 People aged over 80 years

T. D. Szucs, B. Waeber, and Y. Tomonaga. Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: an analysis of the HYVET study from a Swiss perspective. Journal of Human Hypertension 24 (2):117-123, 2010.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: CEA **Study design:** Decision analytic model based on	**Population:** Patients with hypertension and aged >80 years.	**Primary outcome measure:** Life-years (mean per patient)	**Total costs – all patients (mean per patient):** Intvn 1: £1021 (undiscounted) Intvn 2: £1006 (undiscounted)	**Basecase ICER:** Treatment dominated no treated (lower costs and improved health outcomes)

single RCT (HYVET[639]). **Approach to modelling:** Estimated costs based on drug doses and usage in HYVET and key clinical events. Life-years gained were calculated by applying the estimated life expectancy for the population to deaths avoided with treatment. **Perspective:** Switzerland, healthcare payer **Time horizon:** 2 years **Discounting:** Costs: 5%; Outcomes: None	**Intervention 1:** No antihypertensive treatment **Intervention 2:** Antihypertensive treatment • 25.8% 1.5mg indapamide SR alone • 23.9% 1.5mg indapamide SR and 2mg perindopril • 49.5% 1.5mg indapamide SR and 4mg perindopril 100% compliance assumed for all patients.	Intvn 1: 1.6216 Intvn 2: 1.6672 Incremental (1-2): 0.0457 (CI: NR) **Other outcome measures (mean per patient):** None	Incremental (2-1):-£14 (discounted) (CI: NR , p=NR) **Currency & cost year:** 2007 Swiss Francs (presented here as 2007 UK pounds†) **Cost components incorporated:** Antihypertensive drugs, acute management and follow-up of MI, stroke and heart failure (medication, interventions, hospitalisation, outpatient treatment, rehabilitation).	**Other:** None **Subgroup analyses:** None **Analysis of uncertainty:** 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 dominant to £1097 per life year gained.
Data sources				
Health outcomes: Swiss population mortality data and HYVET RCT[639]; **Quality-of-life weights:** N/a; **Cost sources:** Resource use for drugs based on HYVET with units costs from Swiss pharmacy retail prices. MI, stoke and HF costs based on published studies – each event includes acute costs and 2 years of follow-up.				
Comments				
Source of funding: None; **Limitations:** Some uncertainty about applicability of Swiss unit costs. QALYs not used. Discounting not in line with NICE reference case. Based on single RCT and so does not incorporate all available clinical evidence for patients over 80. Some methodological issues about how health outcomes and costs are calculated and attributed in model. **Other:** n/a				
Overall quality*: Potentially serious limitations **Overall applicability**:** Partially applicable				

Abbreviations: BP = blood pressure; CEA = cost effectiveness analysis; CI = confidence interval; DBP = diastolic blood pressure; HF = heart failure; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; NR = not reported; RCT = randomised clinical trial; QALYs = quality-adjusted life years.
† Converted using 2007 Purchasing Power Parities[468].
**Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable.*

Appendix H: Forest plots

H.1 Head to head comparisons, see section 10.2

The final cut-off date for all searches was 19 December 2005.
The following abbreviations were used: ACEi = angiotensin-converting inhibitors; ARB = angiotensin-II receptor antagonists; BB = beta-blockers; CCB = calcium-channel blockers; CI = confidence interval; MI = myocardial infarction; RR = relative risk.

Figure 20: ACE Inhibitors versus Calcium Channel Blockers - Mortality

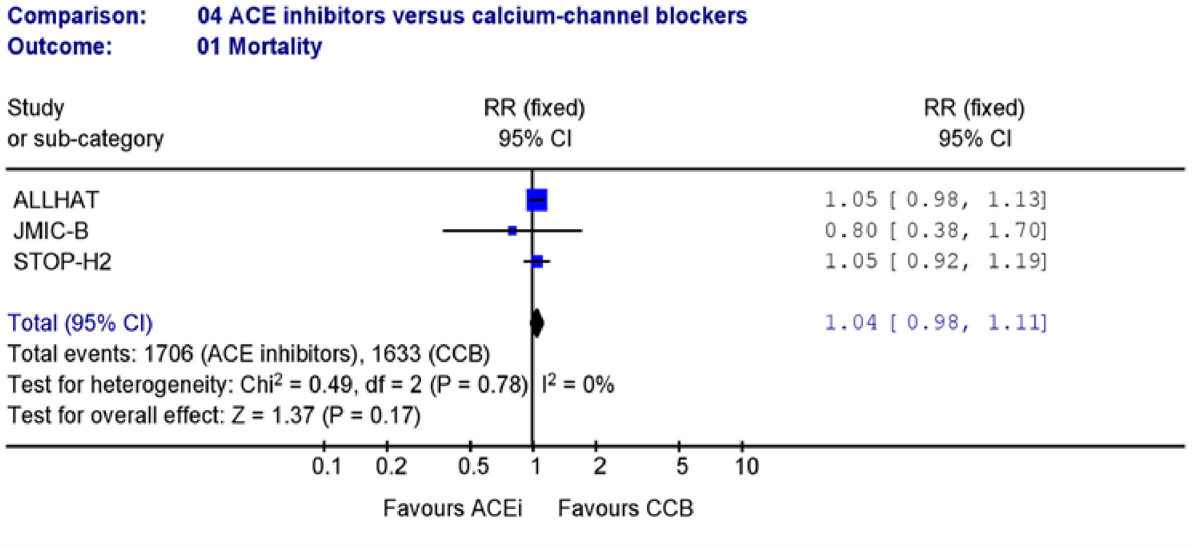


Figure 21: ACE Inhibitors versus Calcium Channel Blockers – Myocardial Infarction

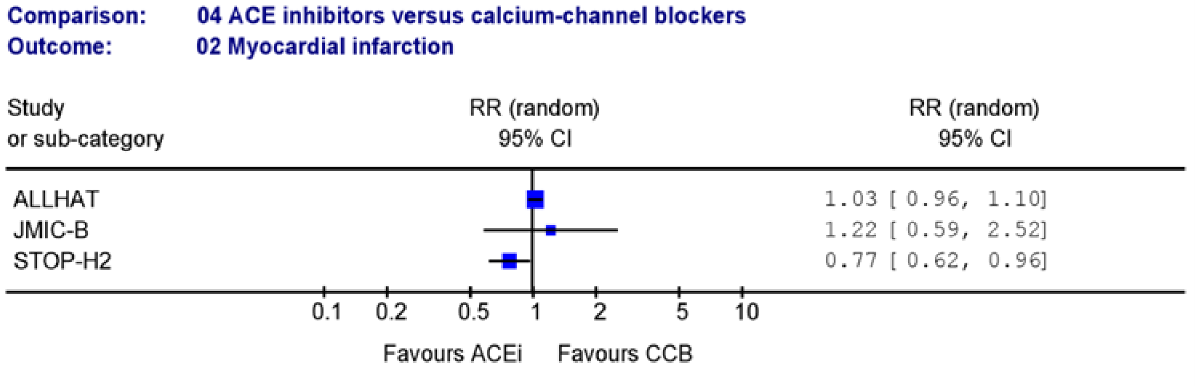


Figure 22: ACE Inhibitors versus Calcium Channel Blockers - Stroke

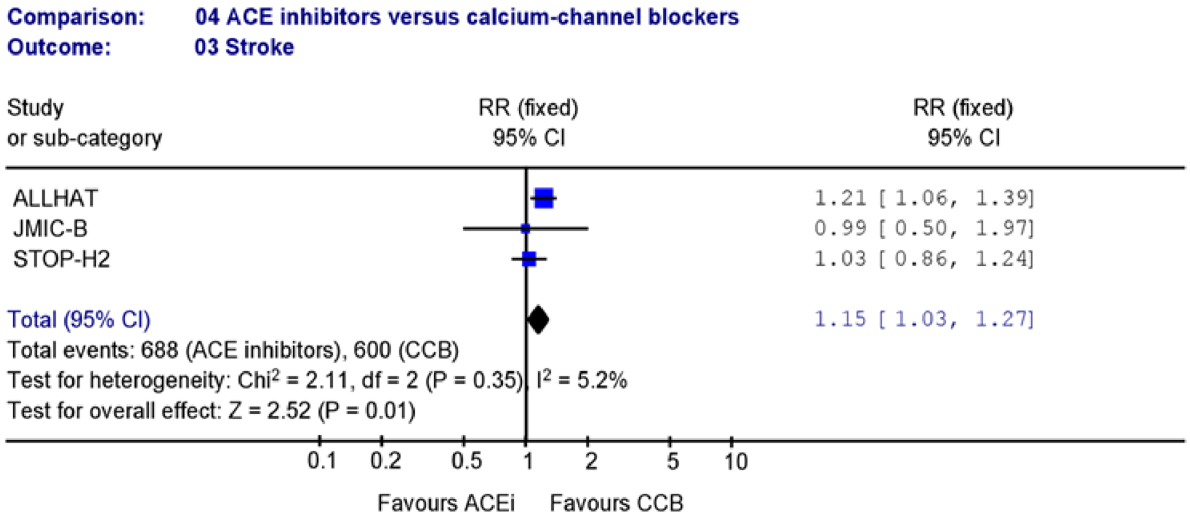


Figure 23: ACE Inhibitors versus Calcium Channel Blockers – Heart Failure

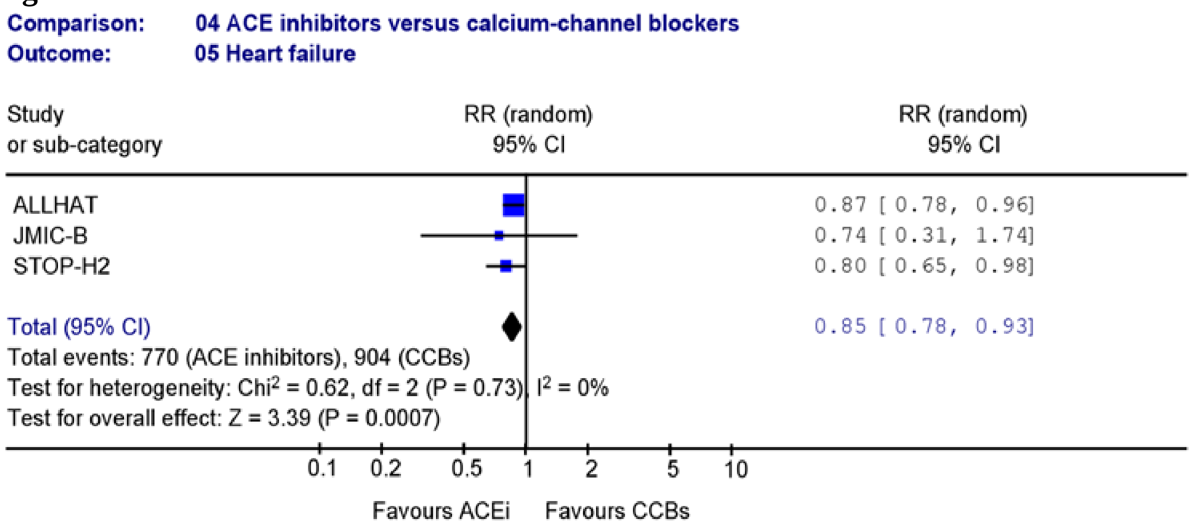


Figure 24: ACE Inhibitors versus Calcium Channel Blockers - Diabetes

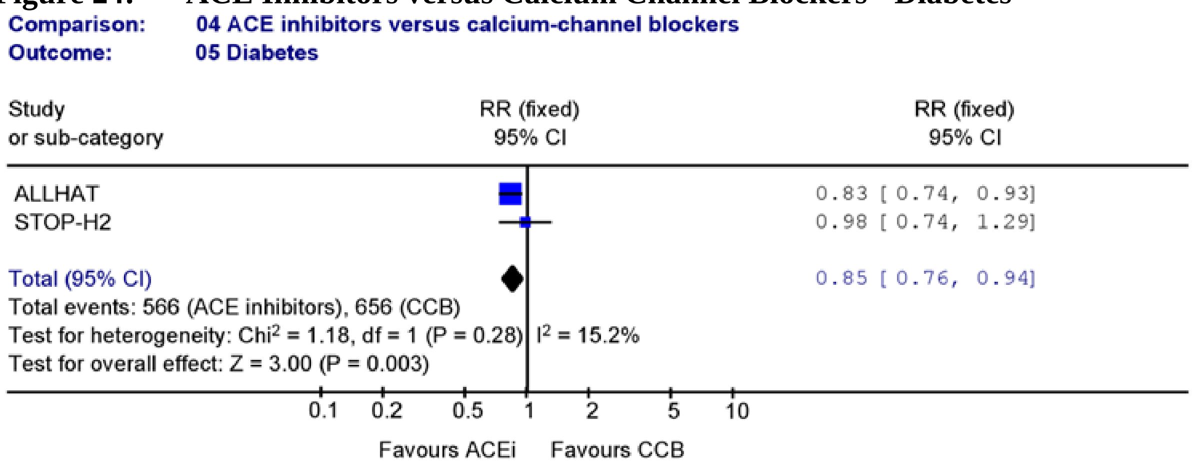


Figure 25: ARBs versus Beta-Blockers - Mortality

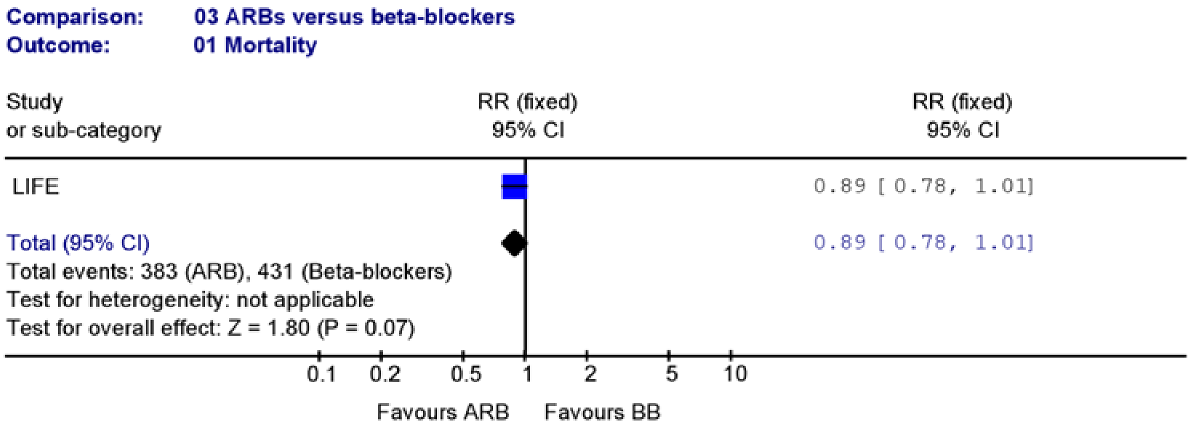


Figure 26: ARBs versus Beta-Blockers – Myocardial Infarction

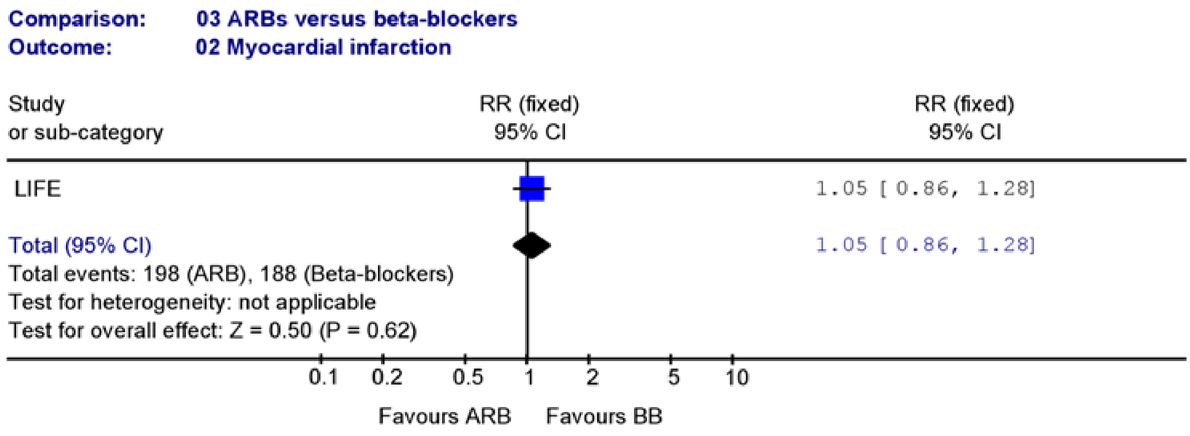


Figure 27: ARBs versus Beta-Blockers - Stroke

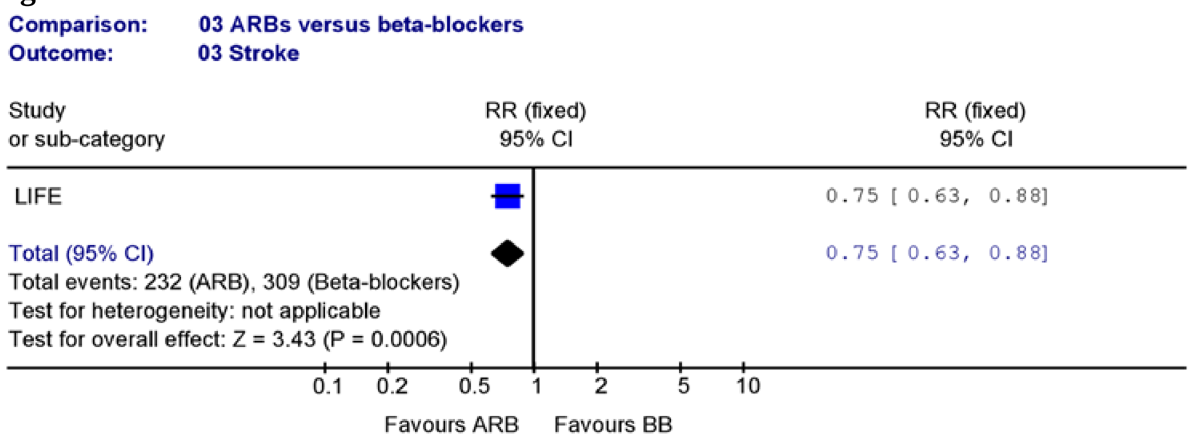


Figure 28: ARBs versus Beta Blockers – Heart Failure

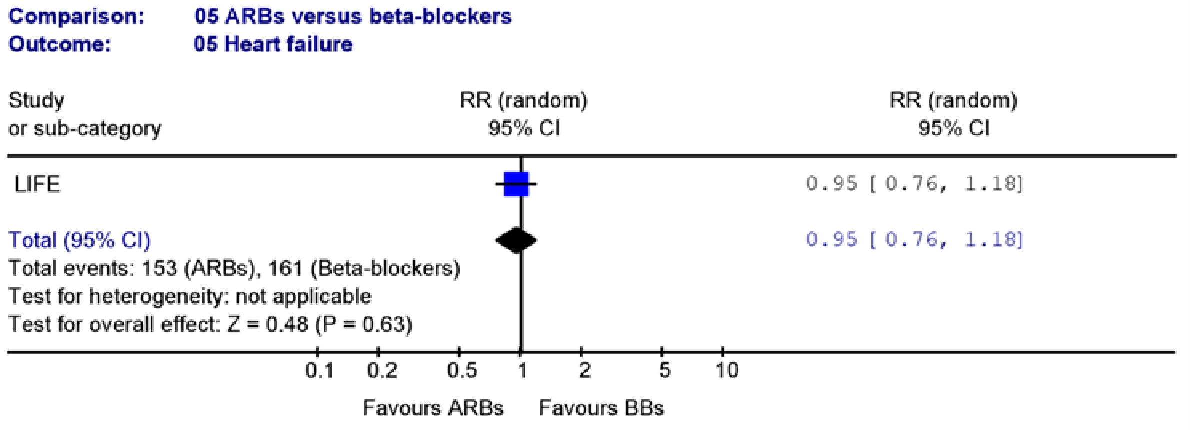


Figure 29: ARBs versus Beta-Blockers - Diabetes

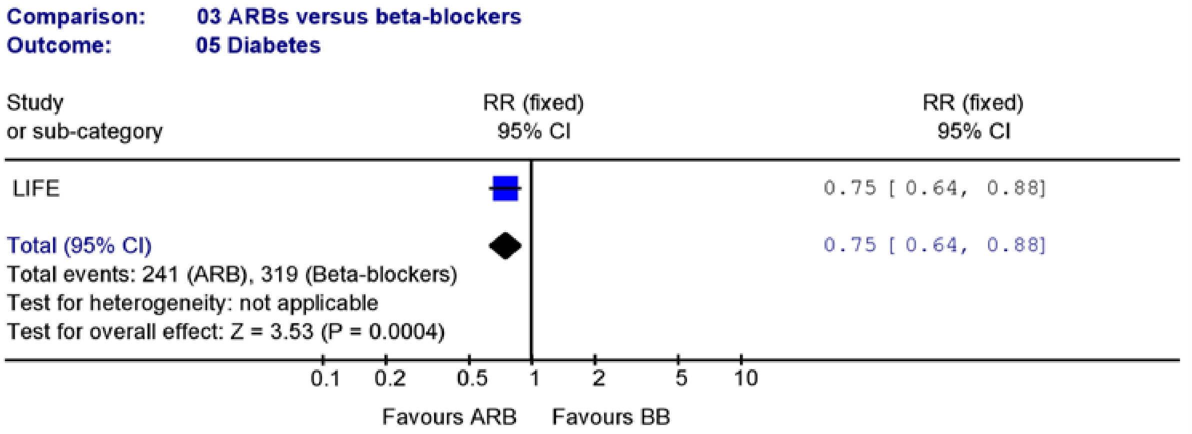


Figure 30: ARBs versus Calcium Channel Blockers - Mortality

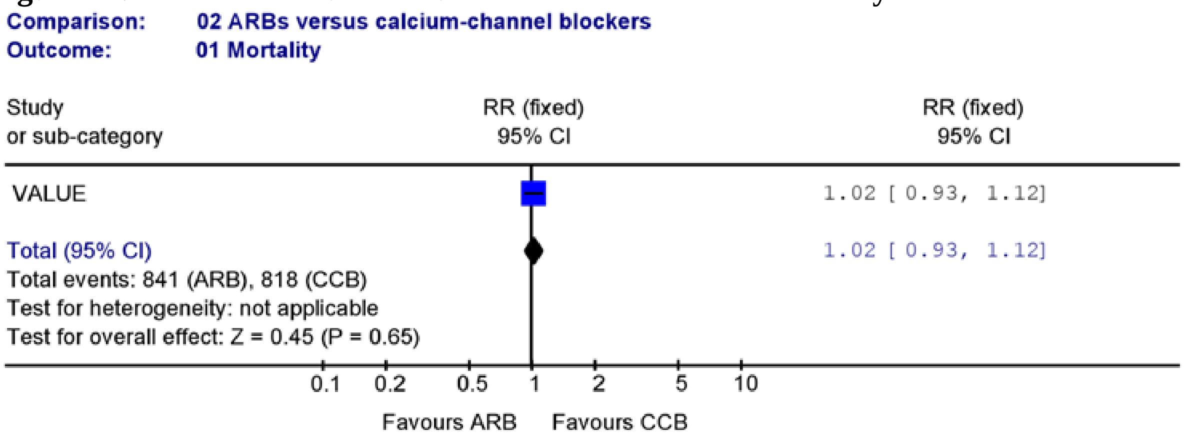


Figure 31: ARBs versus Calcium Channel Blockers – Myocardial Infarction

Comparison: 07 ARBs versus calcium-channel blockers
Outcome: 02 Myocardial infarction

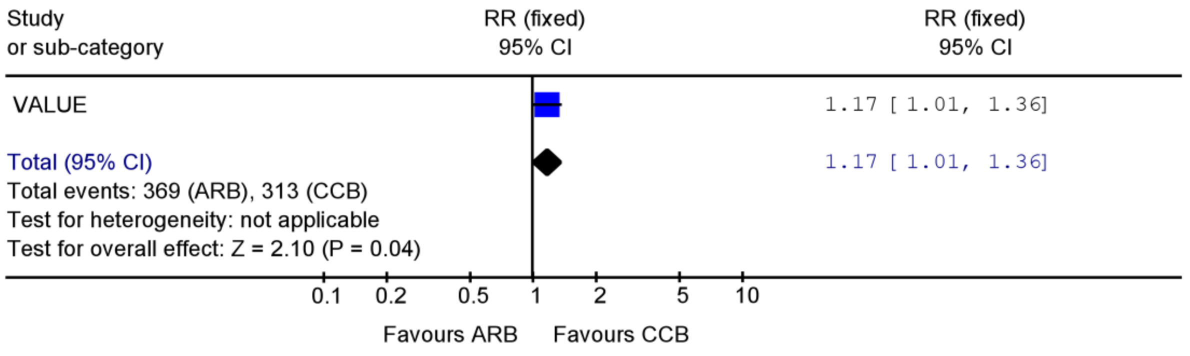


Figure 32: ARBs versus Calcium Channel Blockers - Stroke

Comparison: 02 ARBs versus calcium-channel blockers
Outcome: 02 Stroke

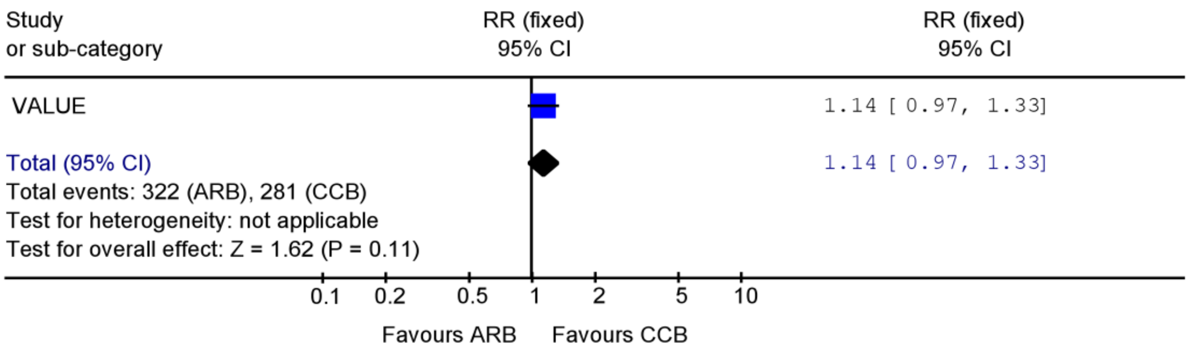


Figure 33: ARBs versus Calcium Channel Blockers – Heart Failure

Comparison: 07 ARBs versus calcium-channel blockers
Outcome: 04 Heart failure

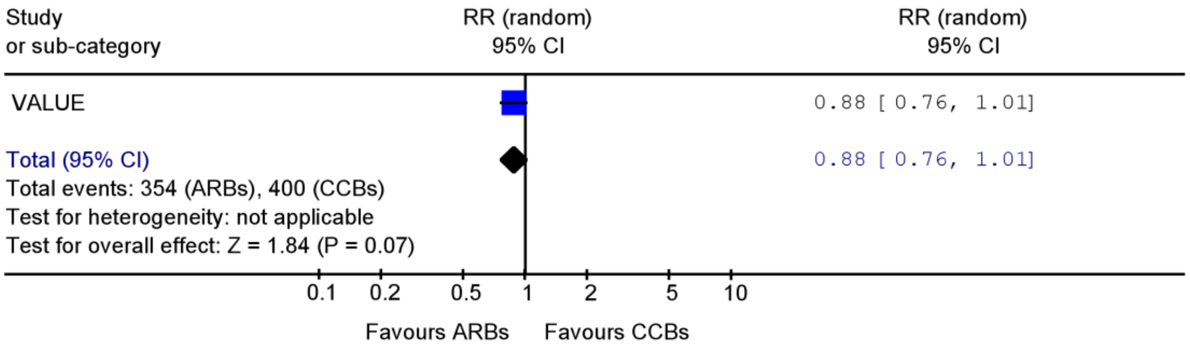


Figure 34: ACE Inhibitors versus Thiazides - Mortality

Comparison: 05 ACE inhibitors versus thiazides
Outcome: 01 Mortality

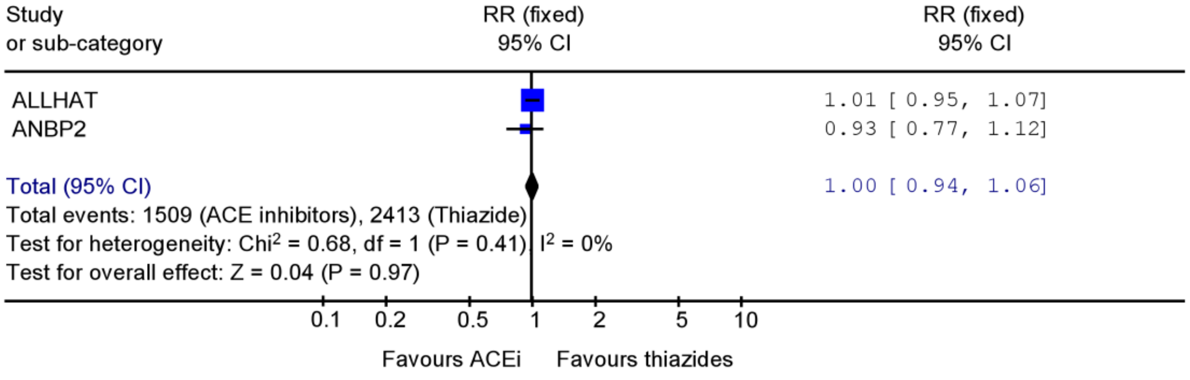


Figure 35: ACE Inhibitors versus Thiazides – Myocardial Infarction

Comparison: 05 ACE inhibitors versus thiazides
Outcome: 02 Myocardial infarction

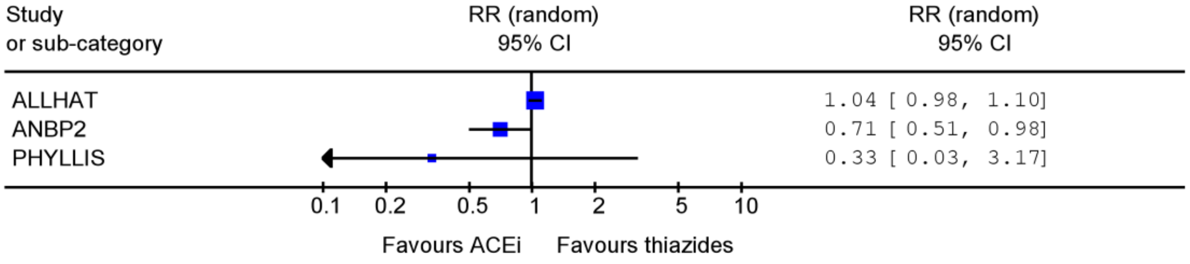


Figure 36: ACE Inhibitors versus Thiazides - Stroke

Comparison: 05 ACE inhibitors versus thiazides
Outcome: 03 Stroke

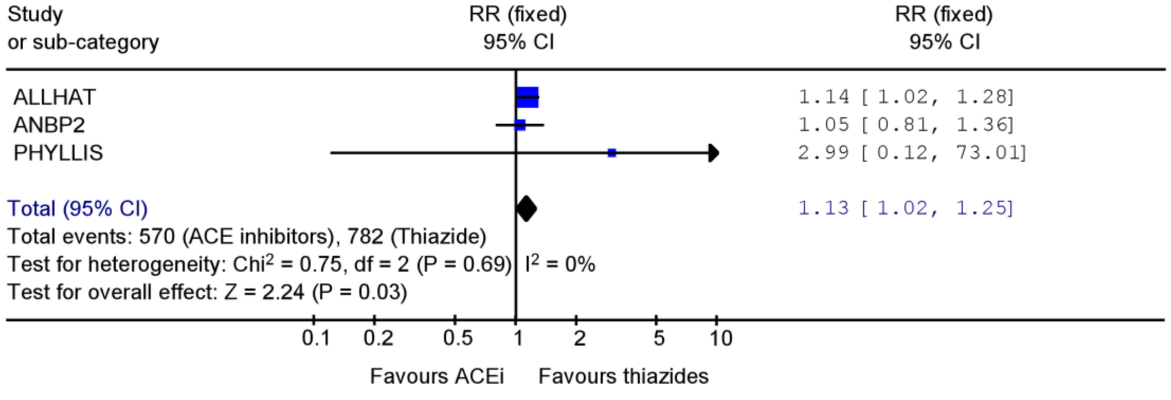


Figure 37: ACE Inhibitors versus Thiazides – Heart Failure

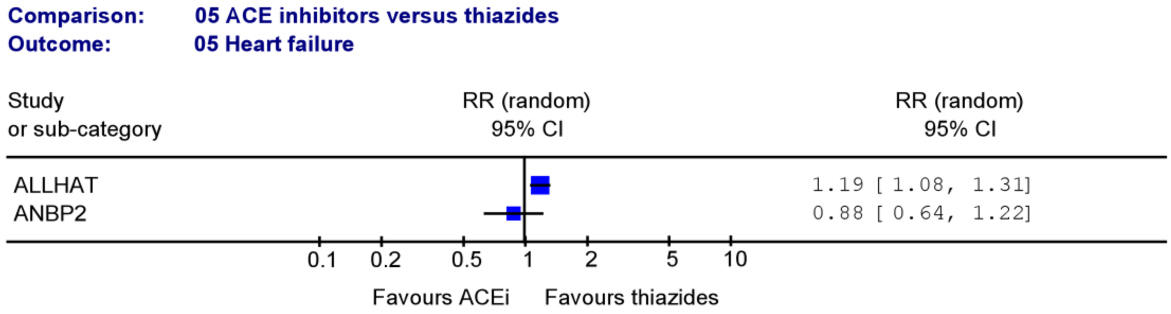


Figure 38: Calcium Channel Blockers versus Beta-Blockers - Mortality

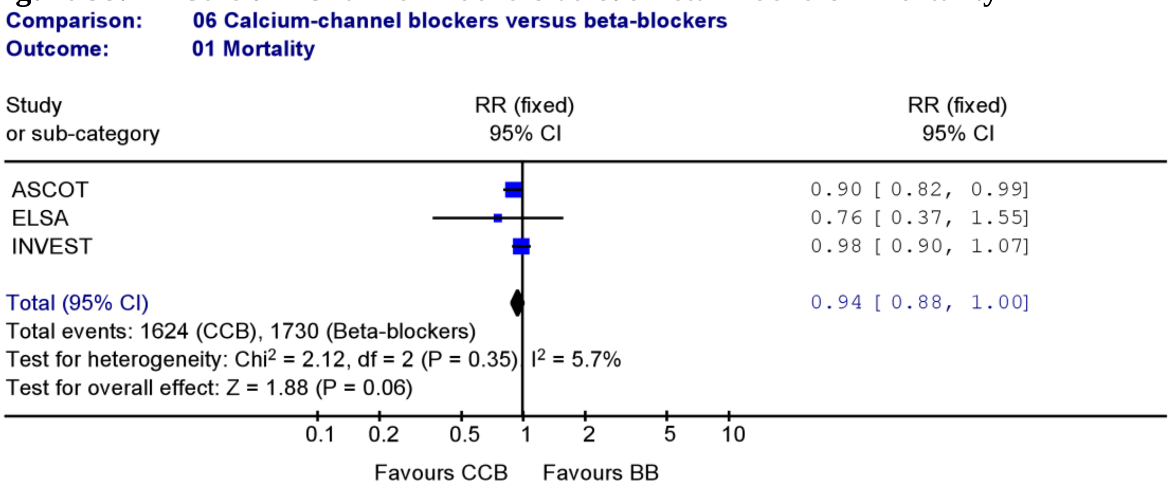


Figure 39: Calcium Channel Blockers versus Beta-Blockers – Myocardial Infarction

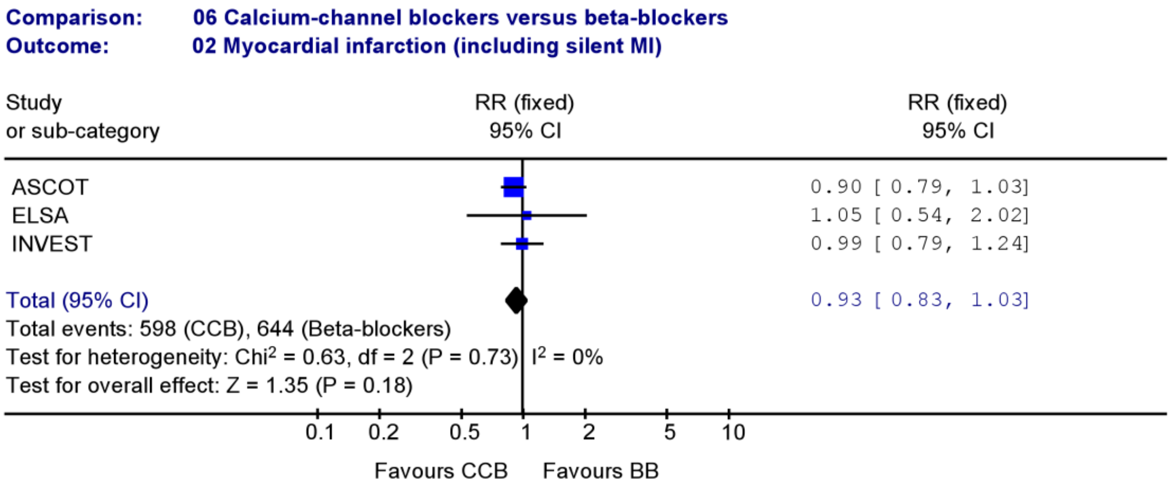


Figure 40: Calcium Channel Blockers versus Beta-Blockers – Myocardial Infarction

Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 03 Myocardial infarction (excluding silent MI)

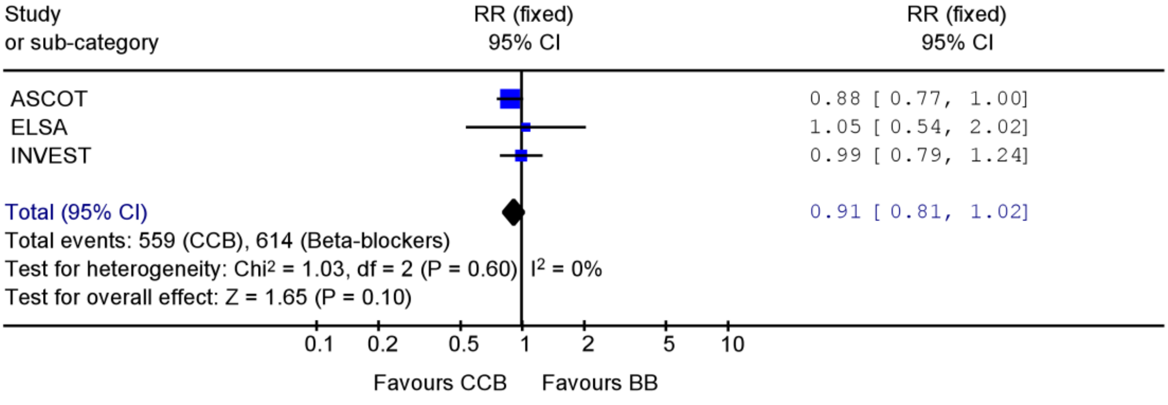


Figure 41: Calcium Channel Blockers versus Beta-Blockers - Stroke

Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 04 Stroke

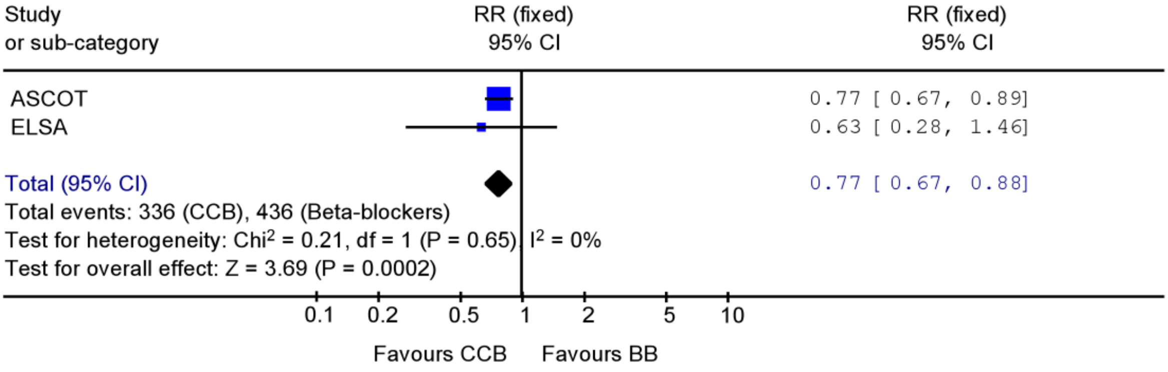


Figure 42: Calcium Channel Blockers versus Beta-Blockers – Heart Failure

Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 06 Heart failure

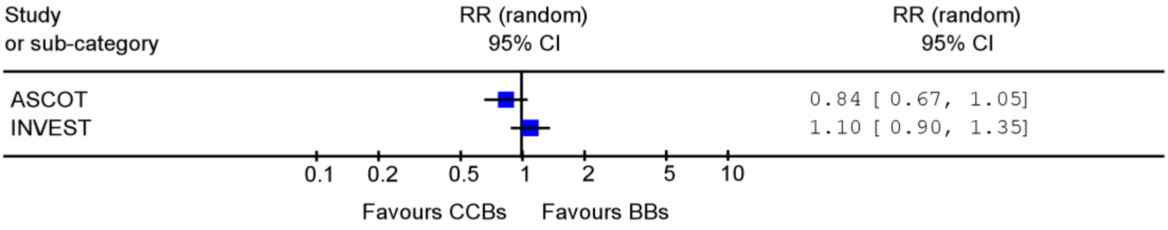


Figure 43: Calcium Channel Blockers versus Beta-Blockers - Diabetes

Comparison: 06 Calcium-channel blockers versus beta-blockers
Outcome: 06 Diabetes

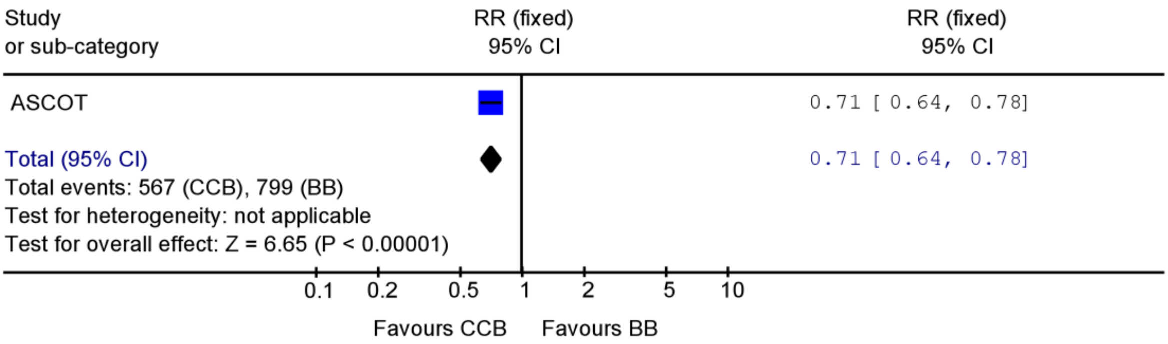


Figure 44: Calcium Channel Blockers versus Thiazides - Mortality

Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 01 Mortality

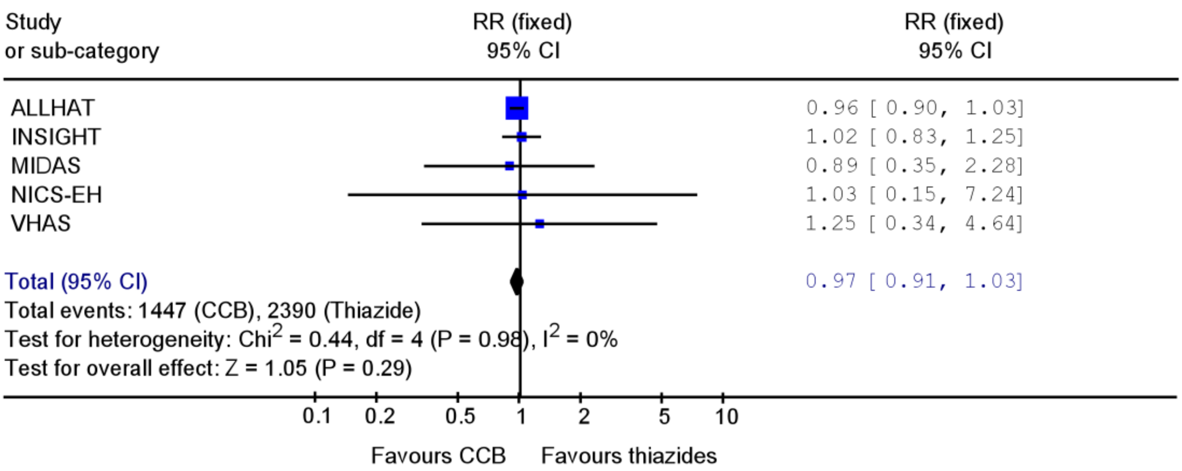


Figure 45: Calcium Channel Blockers versus Thiazides – Myocardial Infarction

Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 02 Myocardial infarction

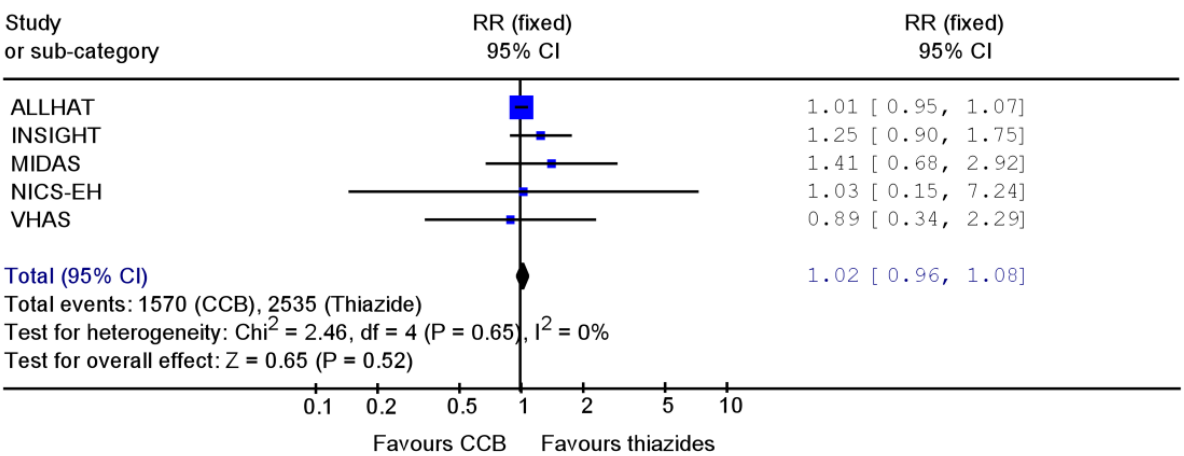


Figure 46: Calcium Channel Blockers versus Thiazides - Stroke

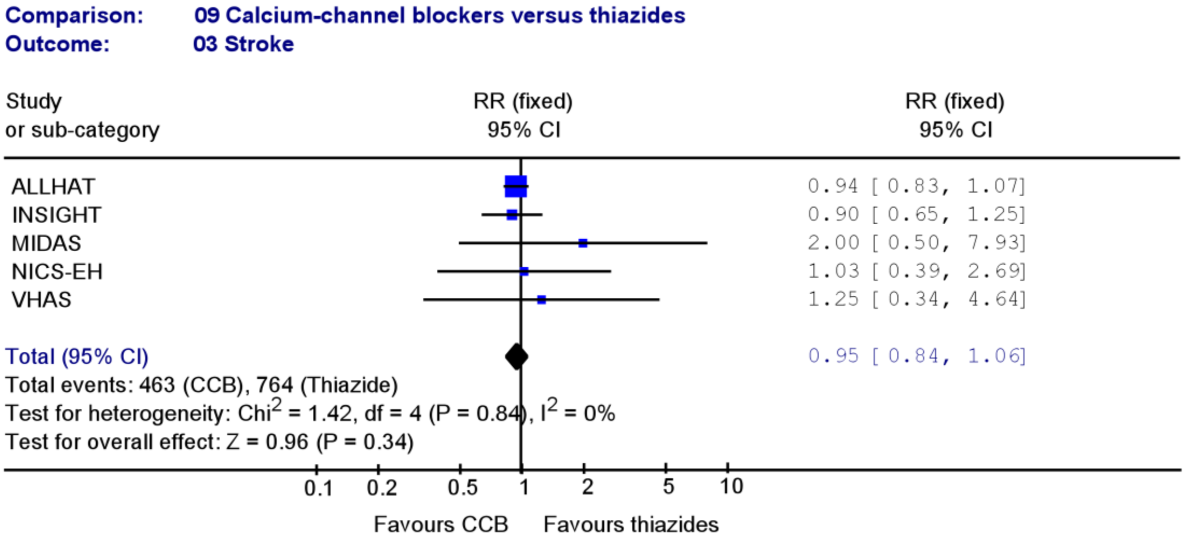


Figure 47: Calcium Channel Blockers versus Thiazdies – Heart Failure

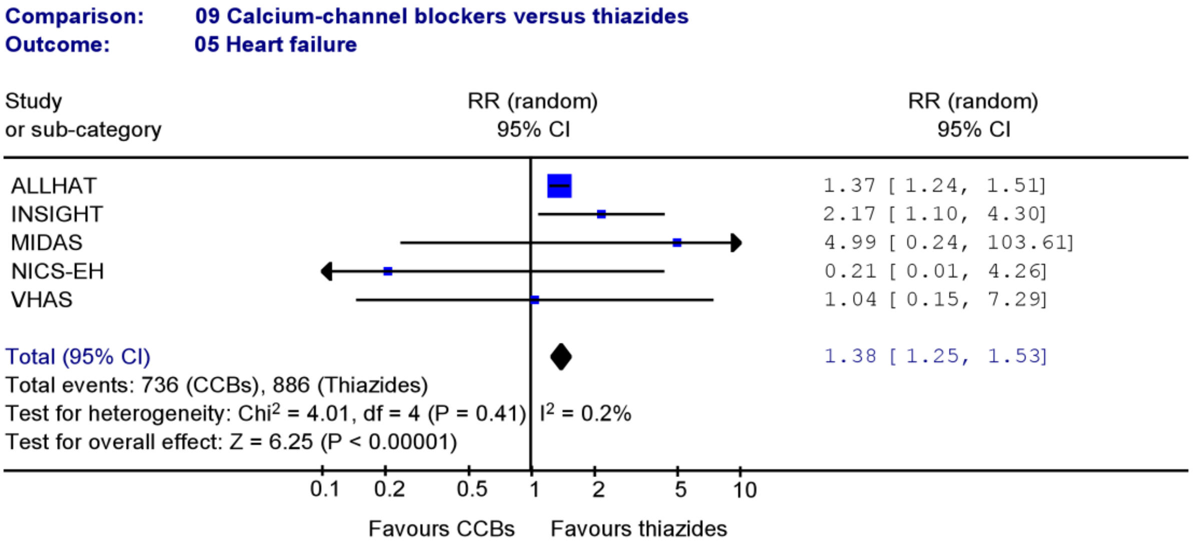


Figure 48: Calcium Channel Blockers versus Thiazides - Diabetes

Comparison: 09 Calcium-channel blockers versus thiazides
Outcome: 05 Diabetes

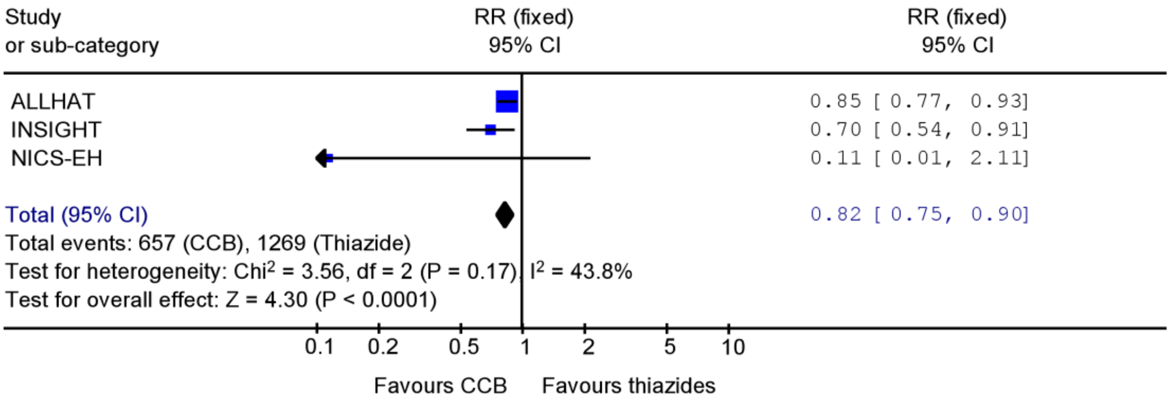


Figure 49: Antihypertensive drug therapy versus placebo - Mortality

Comparison: 01 Antihypertensive drug therapy versus placebo
Outcome: 01 Mortality

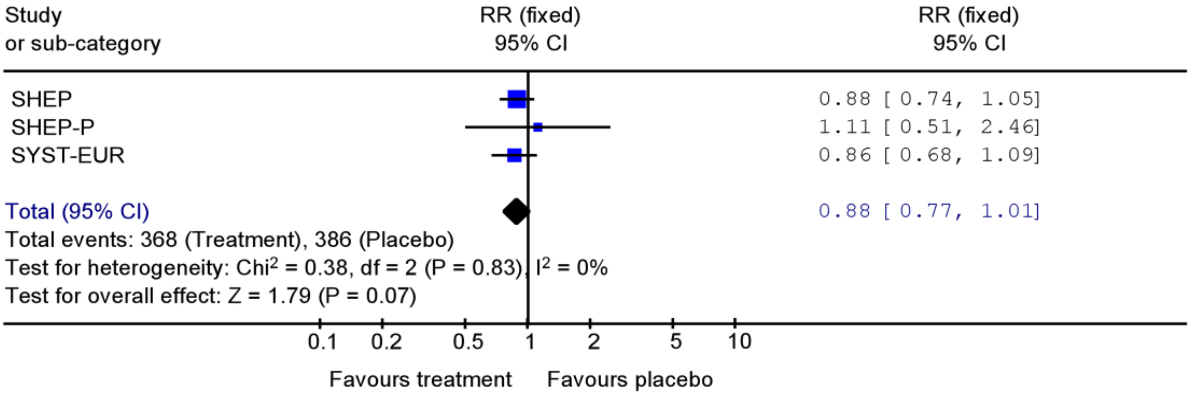


Figure 50: Anti-hypertensive drug therapy versus placebo – Myocardial Infarction

Comparison: 01 Antihypertensive drug therapy versus placebo
Outcome: 02 Myocardial infarction

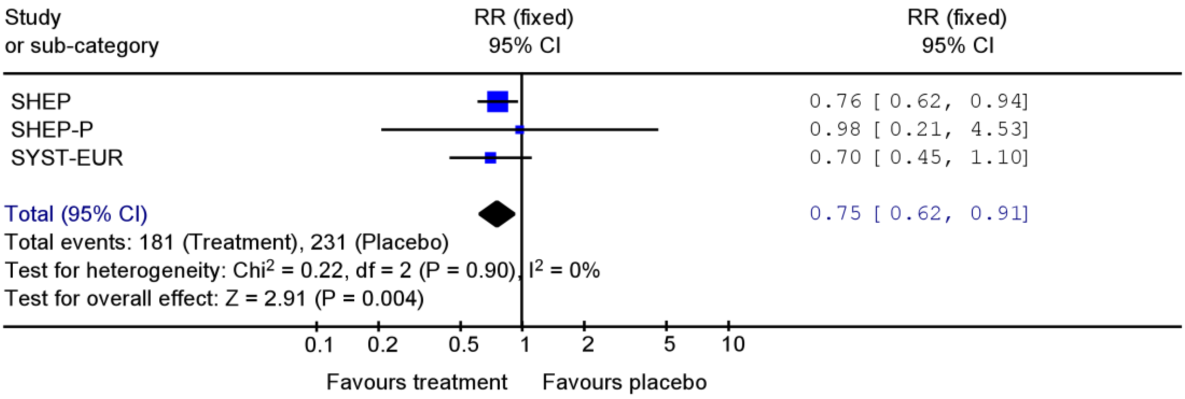
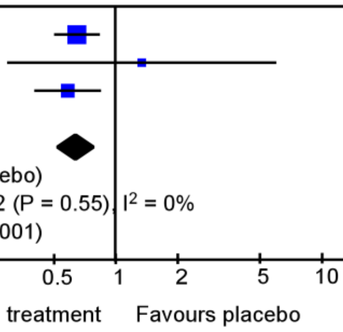


Figure 51: Antihypertensive drug therapy versus placebo - Stroke

Comparison: 01 Antihypertensive drug therapy versus placebo
Outcome: 03 Stroke

Study or sub-category	RR (fixed) 95% CI
SHEP	0.65 [0.51, 0.83]
SHEP-P	1.34 [0.30, 5.96]
SYST-EUR	0.58 [0.41, 0.84]
Total (95% CI)	0.64 [0.52, 0.78]

Total events: 161 (Treatment), 238 (Placebo)
Test for heterogeneity: $Chi^2 = 1.20$, df = 2 (P = 0.55), $I^2 = 0\%$
Test for overall effect: Z = 4.46 (P < 0.00001)



H.1.1 First line therapy, ACEi versus ARBs, see section 0

Figure 52: Mortality

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	6	1901	4	1959	1.01	2.22	0.4%	1.58 [0.42, 5.87]
ONTARGET 2008	989	8542	1014	8576	-11.9	500.67	99.6%	0.98 [0.89, 1.07]
Total (95% CI)		**10443**		**10535**			**100.0%**	**0.98 [0.90, 1.07]**
Total events	995		1018					

Heterogeneity: $Chi^2 = 0.51$, df = 1 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 0.49 (P = 0.63)

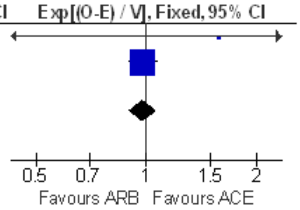


Figure 53: Myocardial infarction

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	3	1901	4	1959	-0.43	1.71	0.8%	0.78 [0.17, 3.48]
ONTARGET 2008	440	8542	413	8576	14.82	213.04	99.2%	1.07 [0.94, 1.23]
Total (95% CI)		**10443**		**10535**			**100.0%**	**1.07 [0.94, 1.22]**
Total events	443		417					

Heterogeneity: $Chi^2 = 0.17$, df = 1 (P = 0.68); $I^2 = 0\%$
Test for overall effect: Z = 0.98 (P = 0.33)

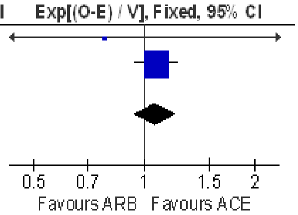


Figure 54: Stroke

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	9	1901	8	1959	0.63	4.24	2.1%	1.16 [0.45, 3.01]
ONTARGET 2008	369	8542	405	8576	-17.42	193.08	97.9%	0.91 [0.79, 1.05]
Total (95% CI)		**10443**		**10535**			**100.0%**	**0.92 [0.80, 1.06]**
Total events	378		413					

Heterogeneity: $Chi^2 = 0.24$, df = 1 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 1.20 (P = 0.23)

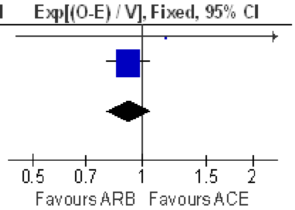


Figure 55: Hospitalisation for angina

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ONTARGET 2008	954	8542	925	8576	17.34	462.25	100.0%	1.04 [0.95, 1.14]
Total (95% CI)		**8542**		**8576**			**100.0%**	**1.04 [0.95, 1.14]**
Total events	954		925					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								

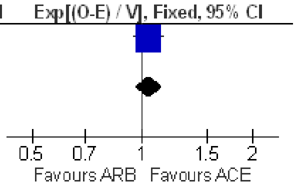


Figure 56: Coronary revascularisation

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ONTARGET 2008	1290	8542	1269	8576	14	639.71	100.0%	1.02 [0.95, 1.10]
Total (95% CI)		**8542**		**8576**			**100.0%**	**1.02 [0.95, 1.10]**
Total events	1290		1269					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.58)								

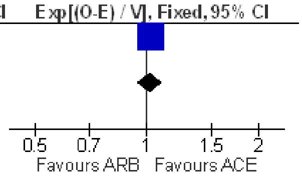


Figure 57: New onset diabetes

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	5	1901	6	1959	-0.42	2.73	1.4%	0.86 [0.26, 2.81]
ONTARGET 2008	399	5294	366	5427	22.08	190.89	98.6%	1.12 [0.97, 1.29]
Total (95% CI)		**7195**		**7386**			**100.0%**	**1.12 [0.97, 1.29]**
Total events	404		372					
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.66); I² = 0%								
Test for overall effect: Z = 1.56 (P = 0.12)								

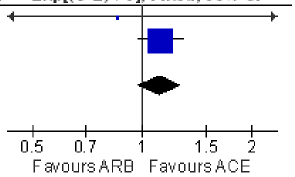


Figure 58: Heart Failure

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ONTARGET 2008	537	8542	514	8576	13.07	262.62	100.0%	1.05 [0.93, 1.19]
Total (95% CI)		**8542**		**8576**			**100.0%**	**1.05 [0.93, 1.19]**
Total events	537		514					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.81 (P = 0.42)								

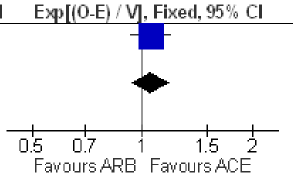
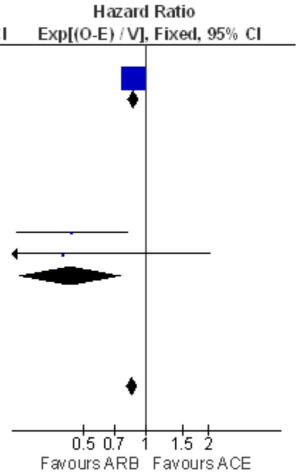


Figure 59: Study drug withdrawals

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.11.2 High quality trials								
ONTARGET 2008	1796	8542	2029	8576	-136.34	952.7	98.8%	0.87 [0.81, 0.92]
Subtotal (95% CI)		**8542**		**8576**			**98.8%**	**0.87 [0.81, 0.92]**
Total events	1796		2029					
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.42 (P < 0.00001)								
2.11.3 Low quality trials								
CORD IB 2009	14	1901	33	1959	-8.19	9.83	1.0%	0.43 [0.23, 0.81]
Tedesco 2006	2	129	5	130	-1.32	1.43	0.1%	0.40 [0.08, 2.05]
Subtotal (95% CI)		**2030**		**2089**			**1.2%**	**0.43 [0.24, 0.77]**
Total events	16		38					
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 2.83 (P = 0.005)								
Total (95% CI)		**10572**		**10665**			**100.0%**	**0.86 [0.81, 0.92]**
Total events	1812		2067					
Heterogeneity: Chi² = 5.49, df = 2 (P = 0.06); I² = 64%								
Test for overall effect: Z = 4.70 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.48, df = 1 (P = 0.02), I² = 81.7%								



H.1.2 ACEi versus ARBs, see section 10.3.1

Figure 60: Mortality

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	6	1901	4	1959	1.01	2.22	0.4%	1.58 [0.42, 5.87]
ONTARGET 2008	989	8542	1014	8576	-11.9	500.67	99.6%	0.98 [0.89, 1.07]
Total (95% CI)		**10443**		**10535**			**100.0%**	**0.98 [0.90, 1.07]**
Total events	995		1018					
Heterogeneity: Chi² = 0.51, df = 1 (P = 0.48); I² = 0%								
Test for overall effect: Z = 0.49 (P = 0.63)								

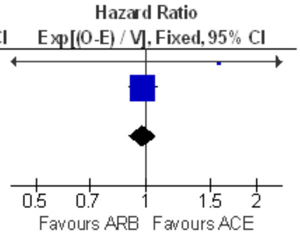


Figure 61: Myocardial Infarction

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	3	1901	4	1959	-0.43	1.71	0.8%	0.78 [0.17, 3.48]
ONTARGET 2008	440	8542	413	8576	14.82	213.04	99.2%	1.07 [0.94, 1.23]
Total (95% CI)		**10443**		**10535**			**100.0%**	**1.07 [0.94, 1.22]**
Total events	443		417					
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 0.98 (P = 0.33)								

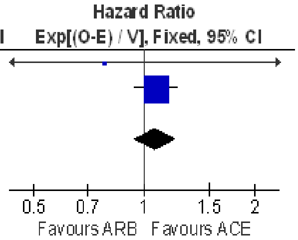


Figure 62: Stroke

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	9	1901	8	1959	0.63	4.24	2.1%	1.16 [0.45, 3.01]
ONTARGET 2008	369	8542	405	8576	-17.42	193.08	97.9%	0.91 [0.79, 1.05]
Total (95% CI)		**10443**		**10535**			**100.0%**	**0.92 [0.80, 1.06]**
Total events	378		413					
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%								
Test for overall effect: Z = 1.20 (P = 0.23)								

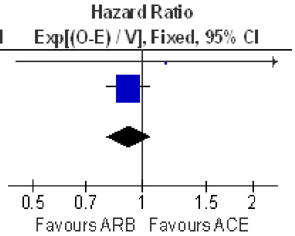


Figure 63: Hospitalisation for Angina

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ONTARGET 2008	954	8542	925	8576	17.34	462.25	100.0%	1.04 [0.95, 1.14]
Total (95% CI)		**8542**		**8576**			**100.0%**	**1.04 [0.95, 1.14]**
Total events	954		925					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)

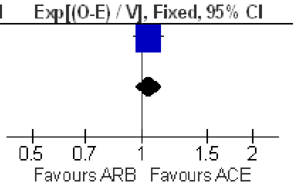


Figure 64: Coronary revascularisation

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ONTARGET 2008	1290	8542	1269	8576	14	639.71	100.0%	1.02 [0.95, 1.10]
Total (95% CI)		**8542**		**8576**			**100.0%**	**1.02 [0.95, 1.10]**
Total events	1290		1269					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)

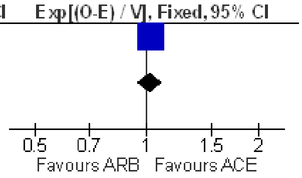


Figure 65: New onset diabetes

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
CORD IB 2009	5	1901	6	1959	-0.42	2.73	1.4%	0.86 [0.26, 2.81]
ONTARGET 2008	399	5294	366	5427	22.08	190.89	98.6%	1.12 [0.97, 1.29]
Total (95% CI)		**7195**		**7386**			**100.0%**	**1.12 [0.97, 1.29]**
Total events	404		372					

Heterogeneity: $Chi^2 = 0.20$, df = 1 (P = 0.66); $I^2 = 0\%$
Test for overall effect: Z = 1.56 (P = 0.12)

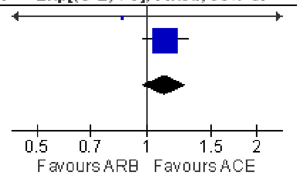


Figure 66: Heart failure

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ONTARGET 2008	537	8542	514	8576	13.07	262.62	100.0%	1.05 [0.93, 1.19]
Total (95% CI)		**8542**		**8576**			**100.0%**	**1.05 [0.93, 1.19]**
Total events	537		514					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)

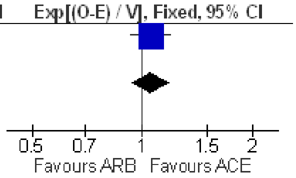
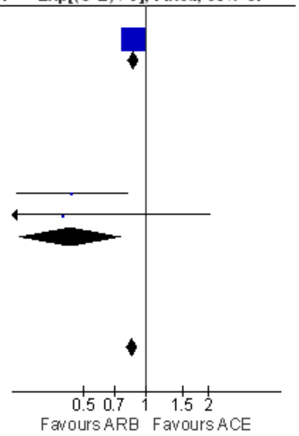


Figure 67: Study drug withdrawal

Study or Subgroup	ARB Events	ARB Total	ACE Events	ACE Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.11.2 High quality trials								
ONTARGET 2008	1796	8542	2029	8576	-136.34	952.7	98.8%	0.87 [0.81, 0.92]
Subtotal (95% CI)		**8542**		**8576**			**98.8%**	**0.87 [0.81, 0.92]**
Total events	1796		2029					
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.42 (P < 0.00001)								
2.11.3 Low quality trials								
CORD IB 2009	14	1901	33	1959	-8.19	9.83	1.0%	0.43 [0.23, 0.81]
Tedesco 2006	2	129	5	130	-1.32	1.43	0.1%	0.40 [0.08, 2.05]
Subtotal (95% CI)		**2030**		**2089**			**1.2%**	**0.43 [0.24, 0.77]**
Total events	16		38					
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 2.83 (P = 0.005)								
Total (95% CI)		**10572**		**10665**			**100.0%**	**0.86 [0.81, 0.92]**
Total events	1812		2067					
Heterogeneity: Chi² = 5.49, df = 2 (P = 0.06); I² = 64%								
Test for overall effect: Z = 4.70 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.48, df = 1 (P = 0.02), I² = 81.7%								



H.1.3 Diuretics

H.1.3.1 Indapamide versus placebo

Figure 68: Overall mortality

Study or Subgroup	Indapamide Events	Indapamide Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
HYVET	196	1933	235	1912	-22.43	106.87	58.5%	0.81 [0.67, 0.98]
PATS	146	2841	158	2824	-6.58	75.88	41.5%	0.92 [0.73, 1.15]
Total (95% CI)		**4774**		**4736**			**100.0%**	**0.85 [0.74, 0.99]**
Total events	342		393					
Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%								
Test for overall effect: Z = 2.15 (P = 0.03)								

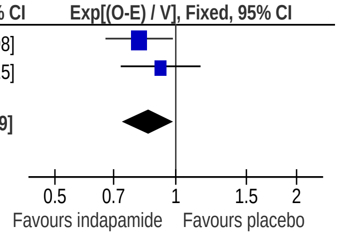


Figure 69: CHD event

Study or Subgroup	Indapamide Events	Indapamide Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
HYVET	22	1933	57	1912	-15.5	15.87	58.2%	0.38 [0.23, 0.62]
PATS	25	2841	21	2824	-1.92	11.41	41.8%	0.85 [0.47, 1.51]
Total (95% CI)		**4774**		**4736**			**100.0%**	**0.53 [0.36, 0.77]**
Total events	47		78					
Heterogeneity: Chi² = 4.34, df = 1 (P = 0.04); I² = 77%								
Test for overall effect: Z = 3.34 (P = 0.0009)								

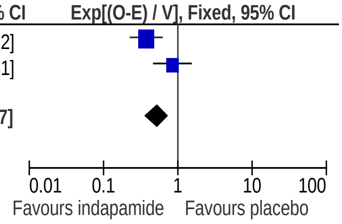


Figure 70: Stroke

Study or Subgroup	indapamide Events	indapamide Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
HYVET	51	1933	69	1912	-9.48	29.33	24.2%	0.72 [0.50, 1.04]
PATS	159	2841	217	2824	-29.6	91.76	75.8%	0.72 [0.59, 0.89]
Total (95% CI)		**4774**		**4736**			**100.0%**	**0.72 [0.61, 0.87]**
Total events	210		286					

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 3.55 (P = 0.0004)

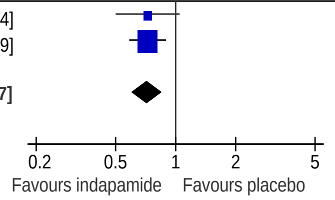


Figure 71: Cardiovascular event

Study or Subgroup	Indapamide Events	Indapamide Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
HYVET	9	1933	12	1912	-1.53	5.14	4.5%	0.74 [0.31, 1.76]
PATS	194	2841	247	2824	-28.11	108.66	95.5%	0.77 [0.64, 0.93]
Total (95% CI)		**4774**		**4736**			**100.0%**	**0.77 [0.64, 0.93]**
Total events	203		259					

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)

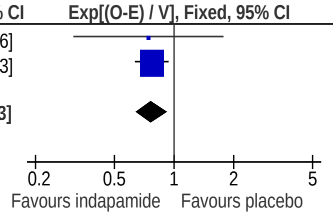
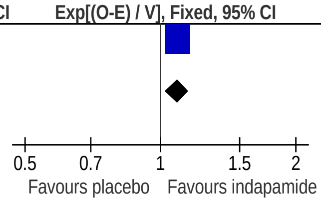


Figure 72: Quality of life

Study or Subgroup	indapamide Events	indapamide Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
PATS	2125	2841	2019	2824	90.32	1,035.32	100.0%	1.09 [1.03, 1.16]
Total (95% CI)		**2841**		**2824**			**100.0%**	**1.09 [1.03, 1.16]**
Total events	2125		2019					

Heterogeneity: Not applicable
Test for overall effect: Z = 2.81 (P = 0.005)



H.1.3.2 Chlorthalidone versus placebo

Figure 73: Overall mortality

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
SHEP	213	2365	242	2371	-14.96	113.29	92.5%	0.88 [0.73, 1.05]
SHEP-P	32	443	7	108	-0.66	6.15	5.0%	0.90 [0.41, 1.98]
VA-NHLBI	8	508	5	504	-1.45	3.08	2.5%	0.62 [0.20, 1.91]
Total (95% CI)		**3316**		**2983**			**100.0%**	**0.87 [0.73, 1.04]**
Total events	253		254					

Heterogeneity: Chi² = 0.35, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)

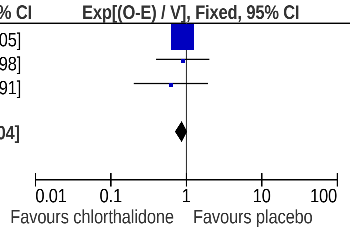


Figure 74: CHD events

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
SHEP	140	2365	184	2371	-23.18	79.51	92.0%	0.75 [0.60, 0.93]
SHEP-P	8	443	2	108	-0.05	1.58	1.8%	0.97 [0.20, 4.61]
VA-NHLBI	16	508	8	504	3.69	5.33	6.2%	2.00 [0.86, 4.67]
Total (95% CI)		**3316**		**2983**			**100.0%**	**0.80 [0.65, 0.98]**
Total events	164		194					

Heterogeneity: Chi² = 4.90, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 2.10 (P = 0.04)

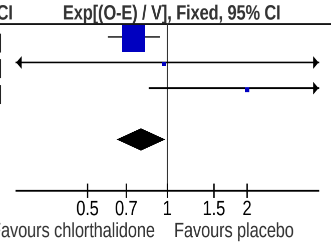


Figure 75: Stroke

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
SHEP	103	2365	159	2371	-27.52	62.51	95.9%	0.64 [0.50, 0.83]
SHEP-P	11	443	6	108	-2.69	2.68	4.1%	0.37 [0.11, 1.21]
Total (95% CI)		**2808**		**2479**			**100.0%**	**0.63 [0.49, 0.80]**
Total events	114		165					

Heterogeneity: Chi² = 0.82, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 3.74 (P = 0.0002)

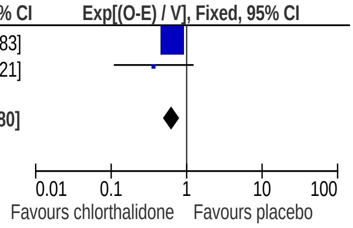
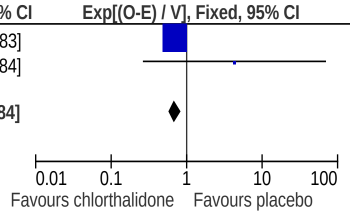


Figure 76: Cardiovascular events

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	placebo Events	placebo Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
SHEP	199	2365	289	2371	-42.97	117.85	99.6%	0.69 [0.58, 0.83]
VA-NHLBI	2	508	0	504	0.73	0.5	0.4%	4.31 [0.27, 68.84]
Total (95% CI)		**2873**		**2875**			**100.0%**	**0.70 [0.58, 0.84]**
Total events	201		289					

Heterogeneity: Chi² = 1.66, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 3.88 (P = 0.0001)



H.1.3.3 Chlorthalidone versus calcium channel blockers

Figure 77: Overall mortality

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	2203	14836	1256	8790	33.4	808.12	92.2%	1.04 [0.97, 1.12]
SHELL	122	940	145	942	-4.5	66.25	7.6%	0.93 [0.73, 1.19]
VHAS	4	707	5	707	0.49	2.22	0.3%	1.25 [0.33, 4.65]
Total (95% CI)		**16483**		**10439**			**100.0%**	**1.03 [0.97, 1.10]**
Total events	2329		1406					

Heterogeneity: Chi² = 0.81, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)

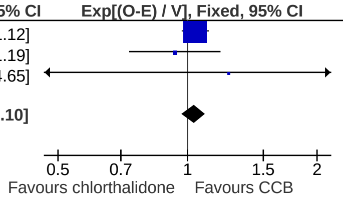


Figure 78: CHD events

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	2451	14836	1466	8790	-62.2	917.33	99.5%	0.93 [0.88, 1.00]
VHAS	9	707	8	707	4.23	4.24	0.5%	2.71 [1.05, 7.03]
Total (95% CI)		**15543**		**9497**			**100.0%**	**0.94 [0.88, 1.00]**
Total events	2460		1474					

Heterogeneity: Chi² = 4.79, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.91 (P = 0.06)

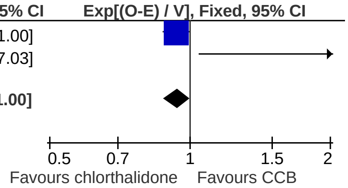


Figure 79: Stroke

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	675	14836	377	8790	-16.8	241.9	92.0%	0.93 [0.82, 1.06]
SHELL	38	940	37	942	0.54	18.75	7.1%	1.03 [0.65, 1.62]
VHAS	4	707	5	707	-0.49	2.22	0.8%	0.80 [0.22, 2.99]
Total (95% CI)		**16483**		**10439**			**100.0%**	**0.94 [0.83, 1.06]**
Total events	717		419					

Heterogeneity: Chi² = 0.22, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)

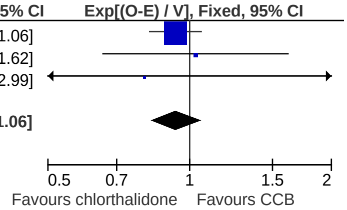


Figure 80: Cardiovascular events

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	3941	14836	2432	8790	-60.29	1,503.92	100.0%	0.96 [0.91, 1.01]
Total (95% CI)		**14836**		**8790**			**100.0%**	**0.96 [0.91, 1.01]**
Total events	3941		2432					

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

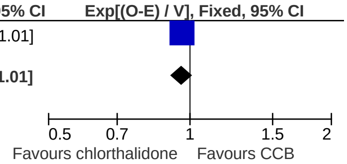


Figure 81: Heart failure (fatal and non-fatal)

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
SHELL	19	940	23	942	-1.98	10.4	100.0%	0.83 [0.45, 1.52]
Total (95% CI)		**940**		**942**			**100.0%**	**0.83 [0.45, 1.52]**
Total events	19		23					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

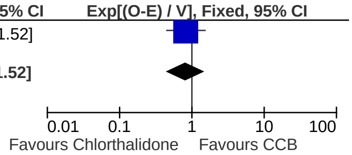
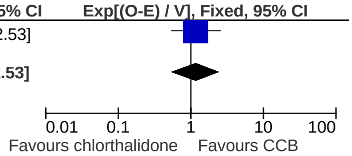


Figure 82: Myocardial infarction

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
SHELL	14	940	12	942	1.01	6.46	100.0%	1.17 [0.54, 2.53]
Total (95% CI)		**940**		**942**			**100.0%**	**1.17 [0.54, 2.53]**
Total events	14		12					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.40 (P = 0.69)



H.1.3.4 Chlorthalidone versus ACE Inhibitors

Figure 83: Overall mortality

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	2203	14836	1314	8778	-3.61	823.07	89.1%	1.00 [0.93, 1.07]
ANBP2	210	3037	195	3044	7.94	101.11	10.9%	1.08 [0.89, 1.31]
Total (95% CI)		**17873**		**11822**			**100.0%**	**1.00 [0.94, 1.07]**
Total events	2413		1509					

Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)

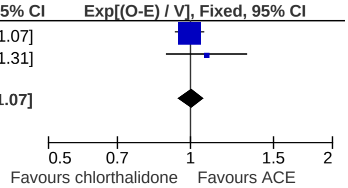


Figure 84: CHD events

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	2451	14836	1505	8778	-40.94	932.45	96.5%	0.96 [0.90, 1.02]
ANBP2	82	3037	58	3044	11.97	33.97	3.5%	1.42 [1.02, 1.99]
Total (95% CI)		**17873**		**11822**			**100.0%**	**0.97 [0.91, 1.03]**
Total events	2533		1563					

Heterogeneity: Chi² = 5.15, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.93 (P = 0.35)

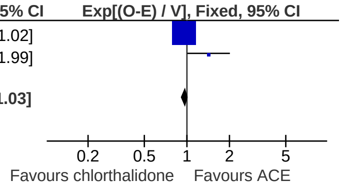


Figure 85: Stroke

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	675	14836	457	8778	-37.83	264.37	82.9%	0.87 [0.77, 0.98]
ANBP2	107	3037	112	3044	-2.45	54.72	17.1%	0.96 [0.73, 1.25]
Total (95% CI)		**17873**		**11822**			**100.0%**	**0.88 [0.79, 0.98]**
Total events	782		569					

Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)

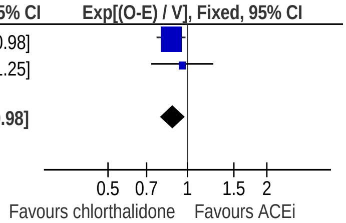
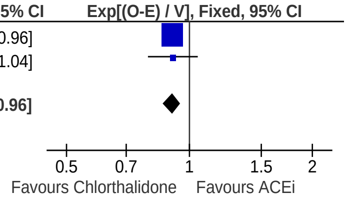


Figure 86: Cardiovascular events

Study or Subgroup	Chlorthalidone Events	Chlorthalidone Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ALLHAT	3941	14836	2514	8778	-124.24	1,274	86.1%	0.91 [0.86, 0.96]
ANBP2	429	3037	394	3044	-19.21	205.38	13.9%	0.91 [0.79, 1.04]
Total (95% CI)		**17873**		**11822**			**100.0%**	**0.91 [0.86, 0.96]**
Total events	4370		2908					

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)



H.1.3.5 Hydrochlorthiazide versus calcium channel blockers

Figure 87: Overall mortality

Study or Subgroup	HCTZ Events	HCTZ Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MIDAS	9	441	8	442	0.52	4.24	88.9%	1.13 [0.44, 2.93]
Sareli 2001	1	58	1	291	0.61	0.28	5.9%	8.83 [0.22, 358.72]
THAI elderly	0	100	1	100	-0.34	0.25	5.2%	0.26 [0.01, 12.93]
Total (95% CI)		**599**		**833**			**100.0%**	**1.18 [0.48, 2.90]**
Total events	10		10					

Heterogeneity: Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

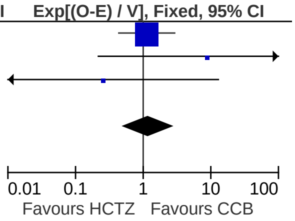


Figure 88: CHD events

Study or Subgroup	HCTZ Events	HCTZ Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MIDAS	12	441	17	442	-2.48	7.03	94.4%	0.70 [0.34, 1.47]
Sareli 2001	1	58	2	291	0.49	0.42	5.6%	3.21 [0.16, 66.09]
Total (95% CI)		**499**		**733**			**100.0%**	**0.77 [0.37, 1.57]**
Total events	13		19					

Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)

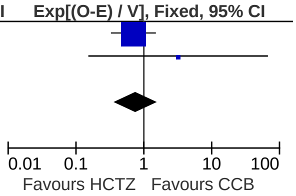


Figure 89: Stroke

Study or Subgroup	CCB Events	CCB Total	HCTZ Events	HCTZ Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MIDAS	6	442	3	441	-1.38	2	100.0%	0.50 [0.13, 2.01]
Total (95% CI)		**442**		**441**			**100.0%**	**0.50 [0.13, 2.01]**
Total events	6		3					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

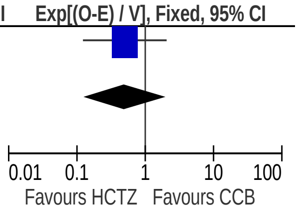
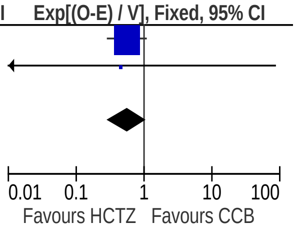


Figure 90: Cardiovascular events

Study or Subgroup	HCTZ Events	HCTZ Total	CCB Events	CCB Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MIDAS	14	441	25	442	-5.24	8.97	98.5%	0.56 [0.29, 1.07]
Sareli 2001	0	58	1	291	-0.11	0.14	1.5%	0.46 [0.00, 85.84]
Total (95% CI)		**499**		**733**			**100.0%**	**0.56 [0.29, 1.06]**
Total events	14		26					

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)



H.1.3.6 Hydrochlorthiazide verus ACE Inhibitor

Figure 91: Overall mortality

Study or Subgroup	HCTZ Events	HCTZ Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Sareli 2001	1	58	0	60	0.35	0.25	100.0%	4.06 [0.08, 204.37]
Total (95% CI)		**58**		**60**			**100.0%**	**4.06 [0.08, 204.37]**
Total events	1		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

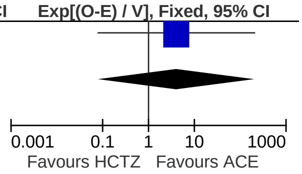


Figure 92: CHD events

Study or Subgroup	HCTZ Events	HCTZ Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
PHYLLIS	3	253	1	254	0.83	0.75	100.0%	3.02 [0.31, 29.07]
Total (95% CI)		**253**		**254**			**100.0%**	**3.02 [0.31, 29.07]**
Total events	3		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.96 (P = 0.34)								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

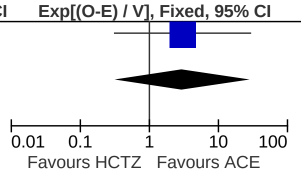


Figure 93: Stroke

Study or Subgroup	HCTZ Events	HCTZ Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
PHYLLIS	0	253	1	254	-0.34	0.25	100.0%	0.26 [0.01, 12.93]
Total (95% CI)		**253**		**254**			**100.0%**	**0.26 [0.01, 12.93]**
Total events	0		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

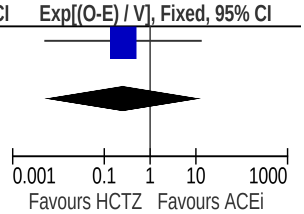
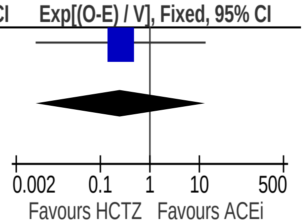


Figure 94: Cardiovascular events

Study or Subgroup	HCTZ Events	HCTZ Total	ACEi Events	ACEi Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
PHYLLIS	0	253	1	254	-0.34	0.25	100.0%	0.26 [0.01, 12.93]
Total (95% CI)		**253**		**254**			**100.0%**	**0.26 [0.01, 12.93]**
Total events	0		1					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI



H.1.3.7 Bendroflumethazide versus beta blockers

Figure 95: Overall mortality

Study or Subgroup	Bendroflumethiazide Events	Bendroflumethiazide Total	Beta blocker Events	Beta blocker Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MRC	128	3519	120	3558	4.82	61.94	100.0%	1.08 [0.84, 1.39]
Total (95% CI)		**3519**		**3558**			**100.0%**	**1.08 [0.84, 1.39]**
Total events	128		120					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

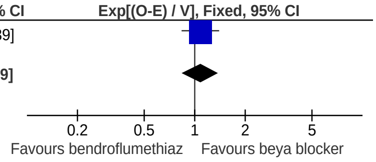


Figure 96: CHD events

Study or Subgroup	Bendroflumethiazide Events	Bendroflumethiazide Total	Beta blocker Events	Beta blocker Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MRC	119	3519	103	3558	8.73	55.21	100.0%	1.17 [0.90, 1.52]
Total (95% CI)		**3519**		**3558**			**100.0%**	**1.17 [0.90, 1.52]**
Total events	119		103					

Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)

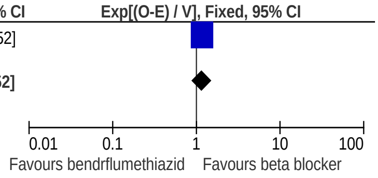


Figure 97: Stroke

Study or Subgroup	Bendroflumethiazide Events	Bendroflumethiazide Total	Beta blocker Events	Beta blocker Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MRC	18	3519	42	3558	-10.53	12.6	100.0%	0.43 [0.25, 0.75]
Total (95% CI)		**3519**		**3558**			**100.0%**	**0.43 [0.25, 0.75]**
Total events	18		42					

Heterogeneity: Not applicable
Test for overall effect: Z = 2.97 (P = 0.003)

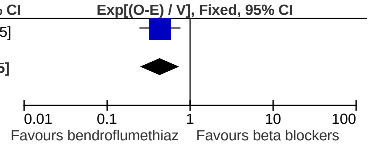
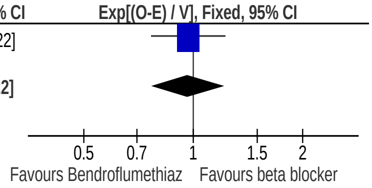


Figure 98: Cardiovascular events

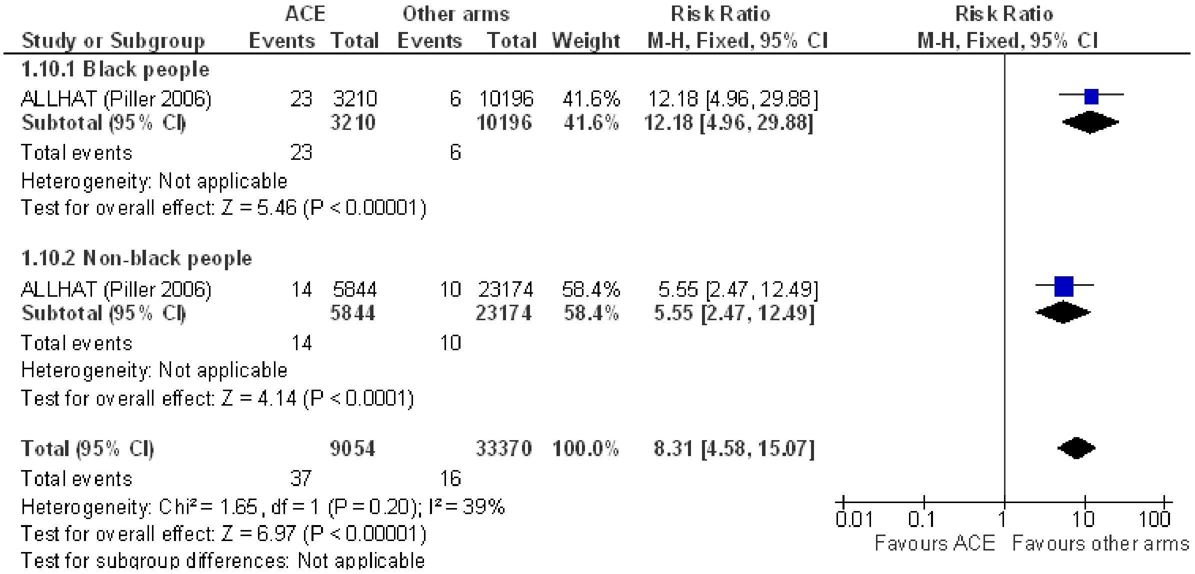
Study or Subgroup	Bendroflumethiazide Events	Bendroflumethiazide Total	Beta blocker Events	Beta blocker Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
MRC	140	3519	146	3558	-2.25	71.47	100.0%	0.97 [0.77, 1.22]
Total (95% CI)		**3519**		**3558**			**100.0%**	**0.97 [0.77, 1.22]**
Total events	140		146					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)



H.1.4 Ethnicity, see section 10.7.2

Figure 99: Angioedema



H.1.5 Diuretics

H.1.5.1 Indapamide versus cholrthalidone

Figure 100: Systolic blood pressure (end of follow-up)

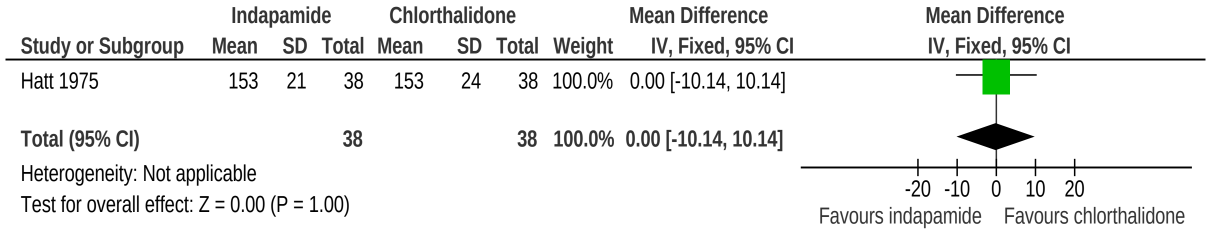


Figure 101: Diastolic blood pressure (end of follow-up)

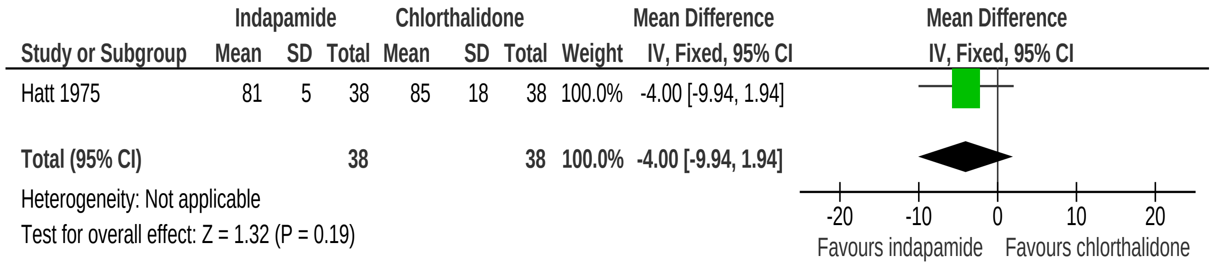


Figure 102: Systolic blood pressure (change from baseline)

Study or Subgroup	Indapamide Mean	Indapamide SD	Indapamide Total	Chlorthalidone Mean	Chlorthalidone SD	Chlorthalidone Total	Weight	Mean Difference IV, Fixed, 95% CI
Rakic 2002	-21.5	11.64	20	-24.6	7.97	20	100.0%	3.10 [-3.08, 9.28]
Total (95% CI)			**20**			**20**	**100.0%**	**3.10 [-3.08, 9.28]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

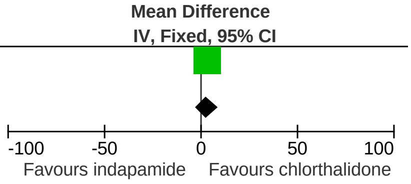
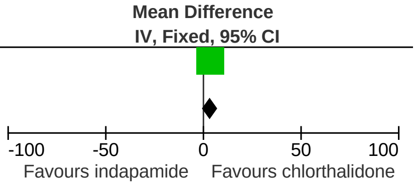


Figure 103: Diastolic blood pressure (change from baseline)

Study or Subgroup	Indapamide Mean	Indapamide SD	Indapamide Total	Chlorthalidone Mean	Chlorthalidone SD	Chlorthalidone Total	Weight	Mean Difference IV, Fixed, 95% CI
Rakic 2002	-10.1	5.82	20	-13.6	6.17	20	100.0%	3.50 [-0.22, 7.22]
Total (95% CI)			**20**			**20**	**100.0%**	**3.50 [-0.22, 7.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)



H.1.5.2 Indapamide versus hydrochlorthiazide

Figure 104: Systolic blood pressure supine (end of follow-up)

Study or Subgroup	Indapamide Mean	Indapamide SD	Indapamide Total	HCTZ Mean	HCTZ SD	HCTZ Total	Weight	Mean Difference IV, Fixed, 95% CI
Elliot 1991	153	9.8	6	155	9.8	6	5.3%	-2.00 [-13.09, 9.09]
Kreeft 1984	142	11	17	138	15	17	8.4%	4.00 [-4.84, 12.84]
Plante 1983	127	4	13	139	4	11	63.5%	-12.00 [-15.21, -8.79]
Plante 1988	162	14.37	23	170	8.72	19	13.1%	-8.00 [-15.06, -0.94]
Spence 2000	136.1	14.9	18	135.2	10.6	21	9.6%	0.90 [-7.34, 9.14]
Total (95% CI)			**77**			**74**	**100.0%**	**-8.36 [-10.92, -5.80]**

Heterogeneity: Chi² = 18.56, df = 4 (P = 0.0010); I² = 78%
Test for overall effect: Z = 6.40 (P < 0.00001)

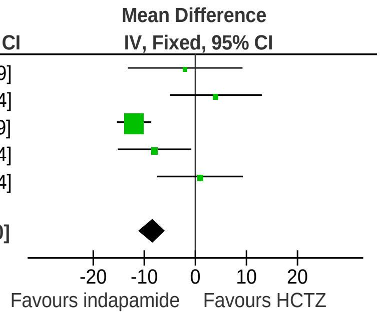


Figure 105: Diastolic blood pressure supine (end of follow-up)

Study or Subgroup	Indapamide Mean	Indapamide SD	Indapamide Total	HCTZ Mean	HCTZ SD	HCTZ Total	Weight	Mean Difference IV, Fixed, 95% CI
Elliot 1991	93	4.9	6	94	4.9	6	5.3%	-1.00 [-6.54, 4.54]
Kreeft 1984	88	7	17	86	7	17	7.4%	2.00 [-2.71, 6.71]
Plante 1983	83	2	13	89	2	11	63.4%	-6.00 [-7.61, -4.39]
Plante 1988	89	9.58	23	94	8.72	19	5.3%	-5.00 [-10.54, 0.54]
Spence 2000	87.1	5.32	18	88.3	3.9	21	18.5%	-1.20 [-4.17, 1.77]
Total (95% CI)			**77**			**74**	**100.0%**	**-4.20 [-5.48, -2.92]**

Heterogeneity: Chi² = 16.77, df = 4 (P = 0.002); I² = 76%
Test for overall effect: Z = 6.44 (P < 0.00001)

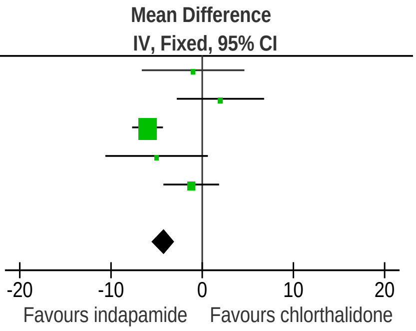


Figure 106: Systolic blood pressure upright (end of follow-up)

	Indapamide			HCTZ				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Elliot 1991	156	12.25	6	157	9.8	6	5.8%	-1.00 [-13.55, 11.55]
Kreeft 1984	137	16	17	137	17	17	7.4%	0.00 [-11.10, 11.10]
Plante 1983	127	5	13	139	4	11	69.9%	-12.00 [-15.60, -8.40]
Spence 2000	136.3	15.8	18	138	1.4	21	16.9%	-1.70 [-9.02, 5.62]
Total (95% CI)			**54**			**55**	**100.0%**	**-8.74 [-11.75, -5.73]**

Heterogeneity: Chi² = 10.54, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 5.69 (P < 0.00001)

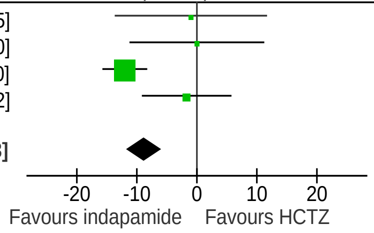


Figure 107: Diastolic blood pressure upright (end of follow-up)

	Indapamide			HCTZ				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Elliot 1991	93	4.9	6	94	4.9	6	7.9%	-1.00 [-6.54, 4.54]
Kreeft 1984	90	7	17	91	7	17	11.0%	-1.00 [-5.71, 3.71]
Plante 1983	84	2	13	90	3	11	56.5%	-6.00 [-8.08, -3.92]
Spence 2000	98.6	5.9	18	99.7	3.7	21	24.6%	-1.10 [-4.25, 2.05]
Total (95% CI)			**54**			**55**	**100.0%**	**-3.85 [-5.41, -2.28]**

Heterogeneity: Chi² = 9.45, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 4.83 (P < 0.00001)

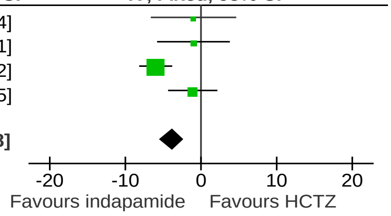


Figure 108: Systolic blood pressure supine (change from baseline)

	Indapamide			HCTZ				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Emeriau 2001	-22.7	15.4	178	-19.4	15.5	171	90.4%	-3.30 [-6.54, -0.06]
Spence 2000	-19.1	18.7	18	-9.05	11.5	21	9.6%	-10.05 [-19.99, -0.11]
Total (95% CI)			**196**			**192**	**100.0%**	**-3.95 [-7.03, -0.87]**

Heterogeneity: Chi² = 1.60, df = 1 (P = 0.21); I² = 38%
Test for overall effect: Z = 2.51 (P = 0.01)

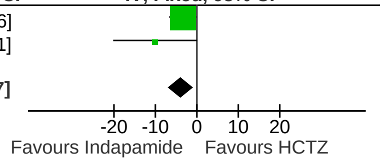


Figure 109: Diastolic blood pressure supine (change from baseline)

	Indapamide			HCTZ				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Emeriau 2001	-11.8	9.7	178	-10.8	8.5	171	82.8%	-1.00 [-2.91, 0.91]
Spence 2000	-9.4	7.7	18	-9.8	5.2	21	17.2%	0.40 [-3.80, 4.60]
Total (95% CI)			**196**			**192**	**100.0%**	**-0.76 [-2.50, 0.98]**

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)

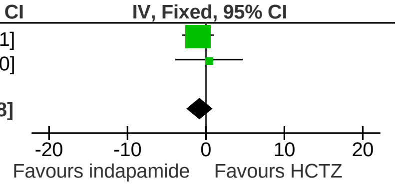


Figure 110: Systolic blood pressure upright (change from baseline)

	Indapamide			HCTZ				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Spence 2000	-18.5	1.1	18	-5.95	10.6	21	100.0%	-12.55 [-17.11, -7.99]
Total (95% CI)			**18**			**21**	**100.0%**	**-12.55 [-17.11, -7.99]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.39 (P < 0.00001)

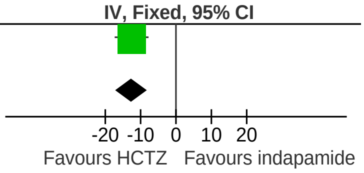
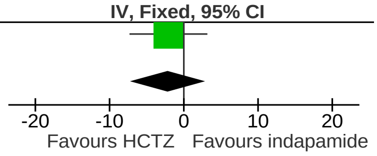


Figure 111: Diastolic upright (change from baseline)

	Indapamide			HCTZ				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Spence 2000	-7.23	9.4	18	-5.16	6.4	21	100.0%	-2.07 [-7.20, 3.06]
Total (95% CI)			**18**			**21**	**100.0%**	**-2.07 [-7.20, 3.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)



H.1.5.3 Indapamide versus Bendrofluazide/Bendroflumethiazide

Figure 112: Systolic blood pressure supine (end of follow-up)

	Indapamide			Bendrofluazide				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bing 1981	130	56.9	10	162	31.6	10	100.0%	-32.00 [-72.34, 8.34]
Total (95% CI)			**10**			**10**	**100.0%**	**-32.00 [-72.34, 8.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

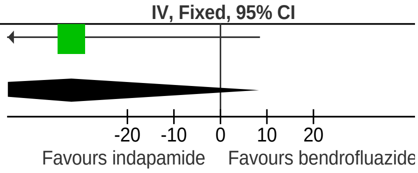


Figure 113: Systolic blood pressure upright (end of follow-up)

	Indapamide			Bendrofluazide				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bing 1981	148	37.9	10	150	31.6	10	100.0%	-2.00 [-32.58, 28.58]
Total (95% CI)			**10**			**10**	**100.0%**	**-2.00 [-32.58, 28.58]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.90)

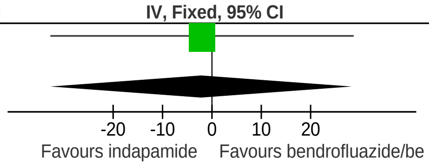


Figure 114: Diastolic blood pressure supine (end of follow-up)

	Indapamide			Bendrofluazide				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bing 1981	85	15.8	10	90	15.8	10	100.0%	-5.00 [-18.85, 8.85]
Total (95% CI)			**10**			**10**	**100.0%**	**-5.00 [-18.85, 8.85]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

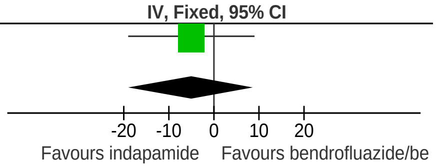


Figure 115: Diastolic blood pressure upright (end of follow-up)

	Indapamide			Bendrofluazide				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Bing 1981	100	47.4	10	100	15.8	10	100.0%	0.00 [-30.97, 30.97]	
Total (95% CI)			**10**			**10**	**100.0%**	**0.00 [-30.97, 30.97]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									

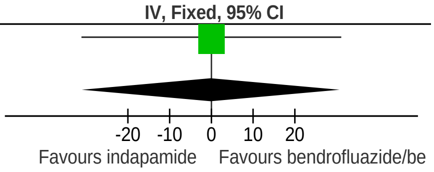


Figure 116: Systolic blood pressure (absolute change)

	Indapamide			Bendrofluazide				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Alem 2008	18.8	14.1	13	13.2	18.8	10	100.0%	5.60 [-8.35, 19.55]	
Total (95% CI)			**13**			**10**	**100.0%**	**5.60 [-8.35, 19.55]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.79 (P = 0.43)									

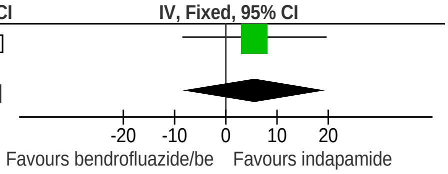
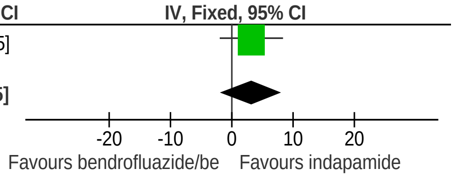


Figure 117: Diastolic blood pressure (absolute change)

	Indapamide			Bendrofluazide				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Alem 2008	8.6	6.4	13	5.4	5.9	10	100.0%	3.20 [-1.85, 8.25]	
Total (95% CI)			**13**			**10**	**100.0%**	**3.20 [-1.85, 8.25]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.24 (P = 0.21)									



Appendix I: Cost-effectiveness analysis – pharmacological treatment (updated 2011)

Update 2011

I.1 Introduction

This model was developed as part of the 2006 pharmacological update (CG34) to balance clinical outcomes and to test the cost effectiveness of different 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. The methods and results below have been updated to reflect the revisions to the analysis. A summary of the overall impact of the update compared to the previous analysis is given after the results section.

I.2 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.

I.3 Methods

I.3.1 Population and subgroups

The model considered patients with essential hypertension seen in primary care, excluding those with pre-existing cardiovascular disease (CVD), heart failure 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).

The basecase analysis presented below shows the results for 65-year-old men and women with 2% CVD risk, 1% heart failure risk and 1.1% diabetes risk. Sensitivity analysis are also presented showing whether and how the results vary by age, sex, CVD, heart failure and diabetes risk.

The model is based on trial evidence that 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, speculative sensitivity analyses were conducted to explore how different assumptions about treatment effects might impact on the cost-effectiveness results for younger people (under 45).

I.3.2 Interventions compared

The analysis assessed the costs and effects of alternative drugs alongside a 'do nothing' comparator. Inclusion of no treatment as an option is important for economic evaluations as it allows identification of low-risk groups for whom treatment is not likely to be cost effective. The interventions compared were thus:

- no intervention (NI)
- thiazide-type diuretics (D)
- calcium-channel blockers (C)
- beta-blockers (B)
- angiotensin-converting enzyme inhibitors (ACEis) / angiotensin-II receptor blockers (ARBs) (A).

At basecase, it was assumed that 80% of patients will be on ACEis and 20% will be on ARBs, because of some people's inability to tolerate ACEis (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.

I.3.3 Outcomes

The treatment effects were measured in terms of prevention of CVD events: non-fatal unstable angina, myocardial infarction (MI), heart failure and stroke, and CVD-related deaths. Other CVD events, including onset of stable angina, peripheral vascular disease and transient ischaemic attacks were not modelled, because data on them are not consistently reported in the trials.

The only side effects modelled were onset of heart failure and diabetes. Other side effects were not modelled in the basecase analysis, although the possible impact of adverse reactions to the drugs in sensitivity analyses was examined. 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.

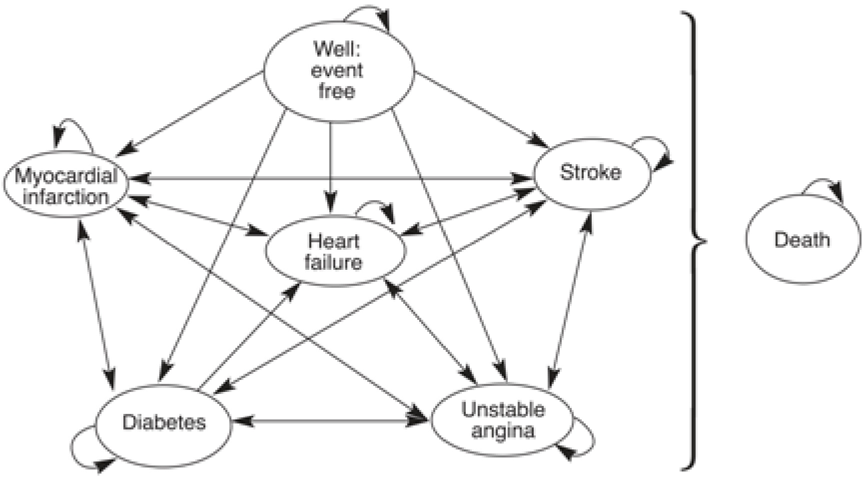
Health outcomes for the cost-effectiveness analysis are summarised in the form of quality-adjusted life-years (QALYs), where one QALY represents one year of healthy life.

I.3.4 Model structure and assumptions

A Markov model was developed to evaluate the incremental costs and effects of lifetime treatment with alternative drugs for the management of hypertension in primary care from a UK NHS perspective.

In a Markov model there are a finite number of health states. It is assumed that at any point in time, all patients must be in one and only one of the states. The model then replicates how a hypothetical cohort of people move between the states. Figure 118 shows a schematic representation of the patients' pathways. All patients start in the event-free health state. During each six-month cycle of the model, a proportion of patients enter one of the qualifying event health states (MI, unstable angina, stroke, diabetes, heart failure or death) while the remainder stay in the event-free state. Patients can experience more than one non-fatal event in subsequent periods of the model. Ultimately, all patients end up in the death state.

Figure 118: Model structure for hypertension(a)



a) Arrows represent the possible transitions between each of the health states

The rate at which people move through the model is regulated by transition probabilities, which describe the likelihood of moving between states over each model cycle (6 months). These transition probabilities are adjusted for each subgroup by age, sex, ethnicity, baseline CVD, heart failure risk and diabetes risk. For illustration, the equivalent annual transition probabilities for untreated 65-year-old men and women with 2% CVD, 1% heart failure risk and 1.1% diabetes risk are shown in Table 82 and Table 83. Unless better data for a hypertensive population were available, the probabilities were based on those used in an analysis of the cost effectiveness of statins developed by the University of Sheffield's School of Health and Related Research (ScHARR) for the NICE technology appraisal[625]. The GDG advised on this and other data used in the model.

Table 82: Probabilities for a 65-year-old untreated man with 2% annual CVD risk

Parameter	Annual probability (%)	Source
Well to unstable angina	0.0017	Statins model[625]
Well to MI	0.0035	Statins model[625]
Well to diabetes	0.0110	ASCOT trial[157]
Well to stroke	0.0054	Statins model[625]
Well to heart failure	0.0098	SHEP[483]
Well to death	0.0180	Statins model and population life tables[625]
Unstable angina to MI	0.0300	Statins model[625]
Unstable angina to diabetes	0.0067	Assumed to be the same as MI to diabetes
Unstable angina to stroke	0.0095	Assumed to be the same as MI to stroke
Unstable angina to heart failure	0.0230	Assumed to be the same as MI to heart failure
Unstable angina to death	0.0348	Statins model and population life tables[625]
MI to unstable angina	0.0078	HOPE[25]
MI to MI	0.0721	Statins model[625]
MI to diabetes	0.0067	HOPE[25]
MI to stroke	0.0095	Statins model[625]
MI to heart failure	0.0230	HOPE[25]
MI to death	0.0258	Statins model and population life tables[625]
Diabetes to unstable angina	0.0033	Double the risk of the well population

Parameter	Annual probability (%)	Source
Diabetes to MI	0.0069	Double the risk of the well population
Diabetes to stroke	0.0108	Double the risk of the well population
Diabetes to heart failure	0.0197	Double the risk of the well population
Diabetes to death	0.0359	Double the risk of the well population
Stroke to unstable angina	0.0016	Assumed to be the same as stroke to MI
Stroke to MI	0.0016	Statins model[625]
Stroke to diabetes	0.0067	Assumed to be the same as MI to diabetes
Stroke to stroke	0.2875	Statins model[625]
Stroke to heart failure	0.0115	Assumed to be half of MI to heart failure
Stroke to death	0.3548	Statins model and population life tables[625]
Heart failure to unstable angina	0.0230	Assumed to be the same as heart failure to MI
Heart failure to MI	0.0230	SOLVD[12]
Heart failure to stroke	0.0103	SOLVD[12]
heart failure to heart failure	0.0545	SOLVD[12]
Heart failure to death	0.0768	SOLVD and population life tables[12]

Table 83: Probabilities for a 65-year-old untreated woman with 2% annual CVD risk

Parameter	Annual probability (%)	Source
Well to unstable angina	0.0010	Statins model[625]
Well to MI	0.0024	Statins model[625]
Well to diabetes	0.0110	ASCOT trial[157]
Well to stroke	0.0076	Statins model[625]
Well to heart failure	0.0098	SHEP[483]
Well to death	0.0141	Statins model and population life tables[625]
Unstable angina to diabetes	0.0067	Assumed to be the same as MI to diabetes
Unstable angina to stroke	0.0095	Assumed to be the same as MI to stroke
Unstable angina to heart failure	0.0230	Assumed to be the same as MI to heart failure
Unstable angina to death	0.0307	Statins model and population life tables[625]
MI to unstable angina	0.0078	HOPE[25]
MI to MI	0.0721	Statins model[625]
MI to diabetes	0.0067	HOPE[25]
MI to stroke	0.0095	Statins model[625]
MI to HF	0.0230	HOPE[25]
MI to death	0.0217	Statins model and population life tables[625]
Diabetes to unstable angina	0.0021	Double the risk of the well population
Diabetes to MI	0.0048	Double the risk of the well population
Diabetes to stroke	0.0153	Double the risk of the well population
Diabetes to heart failure	0.0196	Double risk of well
Diabetes to death	0.0283	Double the risk of the well population
Stroke to unstable angina	0.0016	Assumed to be the same as stroke to MI
Stroke to MI	0.0016	Statins model[625]
Stroke to diabetes	0.0067	Assumed to be the same as MI to diabetes
Stroke to stroke	0.2875	Statins model[625]
Stroke to heart failure	0.0115	Assumed to be half of heart failure to MI

Parameter	Annual probability (%)	Source
Stroke to death	0.3507	Statins model and population life tables[625]
Heart failure to unstable angina	0.023	Same as MI to heart failure
Heart failure to MI	0.023	SOLVD[12]
Heart failure to stroke	0.0103	SOLVD[12]
Heart failure to heart failure	0.0545	SOLVD[12]
Heart failure to death	0.0727	SOLVD and population life tables[12]

The model is run first assuming that the cohort was to receive no intervention (NI). The model is then re-run for each active treatment (A, B, C and D) with transition probabilities adjusted to reflect the expected reduction in CVD events and diabetes and heart failure incidence from the clinical meta-analysis. Healthcare costs and QALYs are then estimated for each option (NI, A, B, C and D) by weighting the time spent in the various states by mean costs and 'utilities' (health-related quality of life) of the health states. The cost and utility data used in the model are described below.

The time horizon modelled is a lifetime, with an assumed upper age of 100, by which time most of the cohort have died.

I.3.5 Baseline risks

The probabilities of primary CVD events by age for a 45-year-old cohort with initial CVD risk of 2% are shown in Table 84. CVD risk was assumed to rise at the rate of 0.03% per annum for men and 0.008% per annum for women (estimated from the Health Survey for England data 1998 by ScHARR[24]). The proportion of first CVD events that were unstable angina, MI, stroke or death were taken from the age-specific UK incidence rates used in the ScHARR statins model. In the statins model they obtained their data from the Bromley Coronary Heart Disease Register and Oxfordshire Community Stroke Project. The risk of new-onset diabetes in the baseline model (1.1%) was taken from the metabolically neutral arm of the ASCOT trial[157]. The incidence of heart failure in the baseline model (0.98%) was taken from the placebo arm of the SHEP trial[483].

Table 84: Baseline incidences of primary events in untreated population

Distribution of primary cardiovascular disease events					
Men					
Age	UA %	MI %	Stroke %	CVD death %	Other* %
45	10.7	29.5	12.9	10.1	36.8
55	7.1	17.2	20.6	13.4	41.7
65	8.3	17.3	27.0	16.0	31.4
75	8.1	16.1	34.3	14.3	27.2
85	9.6	18.6	35.1	13.7	23.0
Source: ScHARR statins model[625].					
Women					
Age	UA %	MI %	Stroke %	CVD death %	Other* %
45	11.7	8.0	22.9	9.1	48.3
55	7.3	9.2	28.8	10.6	44.1
65	5.2	12.1	38.2	17.1	27.4
75	3.4	10.2	46.4	15.2	24.8
85	2.9	10.0	50.1	14.7	22.3
Annual probability of primary cardiovascular disease events					
Men					

Age	UA %	MI %	Stroke %	CVD death %	Total risk %
45	0.21	0.59	0.26	0.20	2.00
55	0.16	0.40	0.47	0.31	2.30
65	0.22	0.45	0.70	0.42	2.60
75	0.23	0.47	0.99	0.41	2.90
85	0.31	0.60	1.12	0.44	3.20
Women					
Age	UA %	MI %	Stroke %	CVD death %	Total risk %
45	0.23	0.16	0.46	0.18	2.00
55	0.15	0.19	0.60	0.22	2.08
65	0.11	0.26	0.83	0.37	2.16
75	0.08	0.23	1.04	0.34	2.24
85	0.07	0.23	1.16	0.34	2.32
* Stable angina and TIA. UA = unstable angina; MI = myocardial infarction					

The risk of CVD-related mortality was estimated from CVD incidence in the cohort, and the proportion of CVD events estimated to be fatal (from the ScHARR model). Non-CVD related mortality by age and sex (Table 85) was taken from life tables for England and Wales prepared by the Government Actuaries Department (GAD) and from data on the proportion of deaths due to CVD-related causes from the Office for National Statistics[457]. In the base-case model it was assumed that the hypertensive cohort was not at increased risk of non-CVD death compared with the general population. However, this assumption was tested in a sensitivity analysis LC = lowest cost option; '-' = option ruled out by simple or extended dominance

* *1 = A and B dominated: C versus D*

** *Relative risk of CVD event following stroke compared with CVD event risks for people who have not had a CVD event*

Risk of non-CVD death

As shown in Table 105, conclusions are not sensitive to changes in the assumptions about the relative risk of death from non-CVD in the hypertensive cohort compared with the general population. Hypertensive treatment remains highly cost-effective, and CCBs remain the preferred option (holding all other variables at their base-case values).
Table 105, raising the cohort's relative risk from 1 to 8.

Table 85: Baseline non-cardiovascular disease related death

Deaths by age, sex and underlying cause, 2004 registrations, England and Wales						
Age	**All cause ICD10: A00–R99**		**Circulatory ICD: I00–I99**		**Non-circulatory as proportion of all deaths**	
	Men	Women	Men	Women	Men %	Women %
45	12,417	8,139	3,930	1,362	0.68	0.83
55	27,117	17,649	9,330	3,541	0.66	0.80
65	52,709	37,041	19,783	11,304	0.62	0.69
75	87,367	88,404	35,607	35,958	0.59	0.59
85	51,329	109,488	20,816	46,470	0.59	0.58
Source: Office for National Statistics[457]						

All cause mortality, estimated from life tables, 2002–04, England and Wales		
Age	**Annual probability of death in age band**	
	Men %	Women %
45	0.0037	0.0025
55	0.0093	0.0059
65	0.0236	0.0154
75	0.0537	0.0406
85	0.0870	0.0807

Source: Government Actuary's Department[458]		
Estimated non-circulatory deaths for hypertensive cohort		
Age	**Annual probability of death in age band**	
	Men %	Women %
45	0.25%	0.20%
55	0.61%	0.47%
65	1.48%	1.07%
75	3.18%	2.41%
85	5.17%	4.65%

The risk of secondary or subsequent events, following unstable angina, MI, stroke or heart failure are shown in Table 86. The increased risks of mortality and other CVD events for patients who develop diabetes were assumed to be twice those seen in non-diabetic patients. The British Hypertension Society guideline (2004)[642] noted that the increase in CVD risk in men is twice, while in women it is four-fold. This assumption was tested in a sensitivity analysis. Probabilities of having unstable angina, heart failure and diabetes after an MI were taken from HOPE[25], which was a secondary prevention trial. The probability of having diabetes after a stroke was assumed to be the same as that of having diabetes from MI. The probabilities of unstable angina (UA), MI, stroke, heart failure and CVD death following onset of heart failure were taken from the placebo arm of the SOLVD trial[12]. Because of a lack of data, it was also assumed that transitions from UA to diabetes, heart failure and stroke and from stroke to unstable angina were the same as those seen in the MI population (expert opinion). It was also assumed that the risk of heart failure following a stroke is half that following MI.

Table 86: Baseline incidences of secondary events in untreated population

After	Transition to	Annual risk	Source
Unstable angina (UA)	UA	No recurrence	Expert opinion
	MI	0.03000	Statins model[625]
	Diabetes	0.00667	Assumed same as MI to diabetes
	Stroke	0.00950	Assumed same as MI to stroke
	Heart failure	0.02300	Assumed same as MI to heart failure
	CVD death	0.02000	Statins model[625]
MI	UA	0.00775	HOPE[25]
	MI	0.07210	Statins model[625]
	Diabetes	0.00667	HOPE[25]
	Stroke	0.00950	Statins model[625]
	Heart failure	0.02300	HOPE[25]
	CVD death	0.01100	Statins model[625]
Stroke	UA	0.00160	Assumed same as for stroke to MI
	MI	0.00160	Statins model[625]
	Diabetes	0.00667	Assumed same as MI to diabetes
	Stroke	0.28750	Statins model[625]
	Heart failure	0.01150	Assumed half rate for MI to heart failure
	CVD death	0.34000	Statins model[625]
Heart failure	UA	0.02300	SOLVD[12]
	MI	0.02300	SOLVD[12]
	Stroke	0.01025	SOLVD[12]
	Heart failure	0.05450	SOLVD[12]

After	Transition to	Annual risk	Source
	CVD death	0.06200	SOLVD[12]

I.3.6 Treatment effects

The relative treatment effects of these interventions were taken from the meta-analysis of head-to-head studies done for the 2006 guideline update (except for the ACEi versus ARB data that was taken from a meta analysis of studies in the 2011 update[552,587,653]. Comparisons including data from large recent studies were chosen to estimate the treatment effects for the economic evaluation: D versus NI, C versus D, C versus B, C versus ACEi, and ACEi versus ARB (Table 87). Sensitivity analyses were conducted for two other scenarios: firstly by replacing the estimate for B with a comparison with D (Table 88) and secondly by replacing the estimate for ACEis with a comparison with D (Table 89).

Table 87: Relative risks of drugs versus no treatment (basecase analysis)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
UA	0.893	0.881	0.984	1.01
MI	0.780	0.796	0.855	0.85
Diabetes	0.985	0.808	1.137	0.77
Stroke	0.690	0.656	0.851	0.69
Heart failure	0.530	0.731	0.761	0.65
Death	0.910	0.883	0.939	0.90

Table 88: Relative risks of drugs versus no treatment (scenario 1: B versus D)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
UA	0.893	0.881	0.984 *	1.01
MI	0.780	0.796	0.835	0.85
Diabetes	0.985	0.808	1.138 *	0.77
Stroke	0.690	0.656	0.794	0.69
Heart failure	0.530	0.731	0.762 *	0.65
Death	0.910	0.883	0.901	0.90
* Based on B versus C comparison, since B versus D were not available for this outcome.				

Table 89: Relative risks of drugs versus no treatment (scenario 2: ACEi versus D)

Outcome	Thiazide-type diuretics (D)	Calcium-channel blockers (C)	Beta-blockers (B)	ACEi/ARB (A)
UA	0.893	0.881	0.984	1.01
MI	0.780	0.796	0.855	0.90
Diabetes	0.985	0.808	1.138	0.85
Stroke	0.690	0.656	0.851	0.64
Heart failure	0.530	0.731	0.762	0.72
Death	0.910	0.883	0.939	0.84

I.3.7 Cost data

The NICE reference case[430] specifies that costs should be measured from an NHS and personal social services perspective. These should include the direct cost of drug treatment and also potential savings from avoided treatments due to reduced incidence of CVD and/or metabolic disease. Costs were calculated using cost weights for each of the states of the model, multiplied by the time spent in each state. As per current NICE guidance[430], an annual discount rate of 3.5% was used for both costs and health benefits.

The costs of health states used in the model are shown in Table 90. Event costs reviewed as part of the diagnosis model undertaken for the 2011 update were updated on the same basis (stroke, MI, unstable angina) adjusted for the 6-month cycle length of this model (see 'Appendix J: Cost-effectiveness analysis – blood pressure monitoring for confirming a diagnosis of hypertension (new 2011)' for details). Other event costs were simply inflated to 2009/10 costs (diabetes, heart failure).

Costs for stroke and post-stroke were based on Youman et al.[649] (these were also used in the NICE Statins health technology assessment (HTA)[625]). Costs of diabetes were based on estimates from a NICE submission done by ScHARR when they evaluated the use of sibutramine for the treatment of obesity[48]. Acute MI costs are based on those reported by Palmer et al. (also utilised in the Statins HTA) this included costs for revascularisation. Post-MI costs are based on an estimate made by the 2004 GDG for the hypertension guideline. Initital and subsequent costs for unstable angina were assumed to be 60% of the costs for MI. Heart failure costs were taken from NHS reference costs. It was assumed that people with no event had an annual GP check-up (as recommended in the guideline). A check-up was estimated to cost £28 based on the average UK cost of a GP appointment[486].

Costs were inflated to 2009/10 prices using the Personal Social Services Research Unit (PSSRU), Unit Costs of Health and Social Care 2010 inflation indices[486].

Table 90: Costs of health states

Health state	Cost per 6-month cycle	Source
MI	£4,933	Palmer 2004[474] inflated to 2009/10[486]
Post-MI costs	£282	NICE Hypertension guideline 2004[441] inflated to 2009/10[486]
Unstable angina	£2,960	Assumed 60% of MI cost.
Subsequent unstable angina costs	£169	Assumed 60% of post-MI cost.
Diabetes	£455	Ara 2004[48] inflated to 2009/10[486]
Stroke	£10,190	Youman et al.[649] inflated to 2009/10[486]
Post-stroke costs	£1,119	Youman et al.[649] inflated to 2009/10[486]
Heart failure	£2,649	NHS reference costs 2005/06 inflated to 2009/10[486]
Post-heart failure costs	£282	Assumed to be same as post MI
Death	£0	
No event	£28	

Drug costs were calculated based on the prices quoted in the British National Formulary 60 (September 2010) based on the optimal dose for hypertension[306]. Optimal doses were provided by clinical members of the GDG. In the base-case analysis, the non-proprietary cost for the most commonly used drug in each class (as based on the 2008 NHS Prescription Cost Analysis[593]) was used. The exception was for ARBs where losartan was used in the base-case analysis as it has recently come off patent and so is now considerably cheaper than other drugs in the class and therefore likely to be more commonly prescribed in the future than historically. The impact of using the cheapest and most expensive drug in each class was also tested in sensitivity analyses. Drug costs used are summarised in Table 91.

Update 2011

Table 91: Drug costs per year

	Used in basecase analysis	Cheapest drug	Most expensive drug
ACEi	Ramipril (10mg): £20.73	Ramipril (10mg): £20.71	Cilaipril (5mg): £163.08

	Used in basecase analysis	Cheapest drug	Most expensive drug
ARB	Losartan (100mg): £25.94	Losartan (100mg): £25.94	Valsartan (320mg): £263.71
B	Atenolol (100mg): £13.17	Atenolol (100mg): £13.17	Acebutolol (800mg): £485.45
C	Amlodipine (10mg): £18.64	Amlodipine (10mg): 18.64	Isradipine (10mg): £431.22
D	Bendroflumethiazide (2.5mg): £11.86	Bendroflumethiazide (2.5mg): £11.86	Xipamide (20mg): £50.74
The cost of diuretics are also analysed in a further sensitivity analysis using the cost for: chlortalidone (50mg(a)): £19.81; indapamide (2.5mg): £16.03.			

a) 25mg was considered the optimal dose but a cost for this tablet size was not listed in the BNF.

Source: British National Formulary 60, September 2010[306]

Update 2011

I.3.8 Quality of life (utility)

In the NICE reference case, the value of health outcomes – including beneficial and harmful impacts of treatment on mortality and morbidity – is estimated using the QALY approach. This requires estimates of survival and quality of life associated with each health state included in the model.

The utility values used in the model are shown in Table 92 and Table 93. An extensive literature search was conducted during the development of the statins HTA model to identify the best available utility estimates for the various health states[625]. Thus estimates for MI, unstable angina and stroke were taken from the statins HTA. Diabetes and heart failure estimates were taken from the Cost-Effectiveness Analysis (CEA) Registry[264]. For MI and unstable angina a higher utility was applied after the initial 6 months. For diabetes, stroke and heart failure a constant utility from onset of the condition was assumed.

Table 92: Health state utility weights

Health state	Utility weight	Source
MI (first 6 months)	0.76	Statins model[625]
Post MI	0.88	Harvard CE Registry[264]
Unstable angina (first 6 months)	0.77	Statins model[625]
Post unstable angina	0.80	Assumption
Stroke	0.63	Statins model[625]
Diabetes	0.90	Harvard CE Registry[264]
Heart failure	0.71	Harvard CE Registry[264]
Death	0.00	Statins model[625]

Table 93: Utility weight by age

Age group	Age utility weight	Source
45–54	0.85	DH Health Survey for England 1996[24]
55–64	0.79	DH Health Survey for England 1996[24]
65–74	0.78	DH Health Survey for England 1996[24]
75+	0.73	DH Health Survey for England 1996[24]

DH = Department of Health.

As in the Statins model[625], utilities were adjusted to reflect the fact that health-related quality of life in the general population decreases with age (that is, multiply the disease utility weight by age utility weight). Age utility weights were taken from the Department of Health, Health Survey for England (1996)[24].

Antihypertensive medication may be expected to have two opposing effects on quality of life: improvements through the reduced incidence of CVD events (as discussed above) and reductions through the impact of treatment-related adverse effects. The latter could potentially be important in assessing the balance between benefits and harms, particularly for low-risk individuals. Differences in adverse effects between the drugs could also have an influence on their relative cost effectiveness. A Medline search was done to identify utility estimates that could be used to reflect the latter for the included drug classes. Some studies were identified that estimated the incidence of drug-related adverse events and quality of life[129,160,161,218,278,598,607,662]. However, none of these included data in a form suitable for estimation of utilities. Most published cost-effectiveness studies have assumed zero, or minimal (0.01), loss of quality of life due to treatment-related side effects (Harvard CEA Registry[264]). Where these have compared different antihypertensive medications, they have generally assumed equal utility loss from adverse effects of treatment[301,307]. Few studies have directly measured treatment utilities from patients. The economic analysis of the SCOPE trial included direct assessment of utility using the EuroQoL health status measurement instrument[166]. This estimated a mean change in utility of minus 0.03 for the candesartan group and minus 0.05 for the mixed hypertensive treatment control group over a mean follow-up of 3.7 years. However, it is not possible to separate out the impact of treatment side effects, or to attribute utility losses to individual drugs. Another cost-effectiveness study[412] estimated utilities from 148 hypertensive patients using the standard gamble technique. They found a net loss in utility of 0.027, but did not report any difference by drug.

Given this paucity of information, we assumed no loss of utility due to adverse effects of the drugs in the basecase model. However, we did a sensitivity analysis to investigate how large any such effects would have to be to change the results.

I.4 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).

$$\text{ICERs} = \frac{\text{Cost of X} - \text{Cost of Y}}{\text{QALY of X} - \text{QALY of Y}}$$

Where more than two interventions are being compared, the ICERs are calculated using the following process:

1. The drugs are ranked in terms of cost, from the cheapest to the most expensive (cheapest indicated by LC (lowest cost) in the results tables below).
2. If a drug is more expensive and less effective than the previous one, then it is said to be ruled out by 'simple dominance' and is excluded from further analysis (indicated by a dash '-' in the results tables below).
3. 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 a dash '-' in the results tables below).
4. ICERs are recalculated excluding any drugs subject to dominance or extended dominance (these ICERs are given in the results tables below).

I.5 Sensitivity analysis

The model includes a base-case analysis supplemented with univariate and multivariate deterministic sensitivity analyses to test the impact of uncertainty over various model parameters and assumptions.

I.6 Results

I.6.1 Base-case results

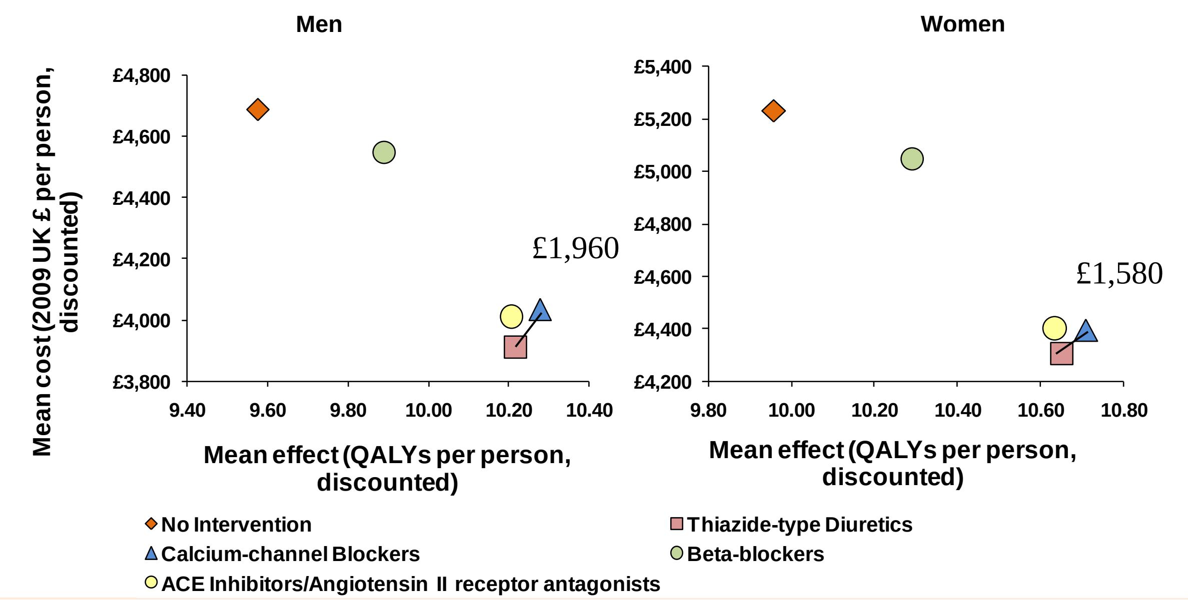
The base-case results are presented in Table 94 for 65-year-old men and women with an annual CVD risk of 2%, heart failure risk of 1% and diabetes risk of 1.1%. This suggests that antihypertensive treatment is cost effective for this population and that the most cost-effective initial drug class in this 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). Beta-blockers (B) are ruled out by simple dominance, since D, A and C are estimated to be cheaper and more effective. This is illustrated in Figure C2, 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 119, 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.

Table 94: 2011 base-case results (65-year-old, 2% risk, 1.1% diabetes risk, 1% heart failure risk)

Men			
	Cost (£)	**Effect (QALYs)**	**ICER (cost per 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 (cost per 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	-

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

Figure 119: 2011 base-case results (65-year-old, 2% cardiovascular risk, 1.1% diabetes risk, 1% heart failure risk)



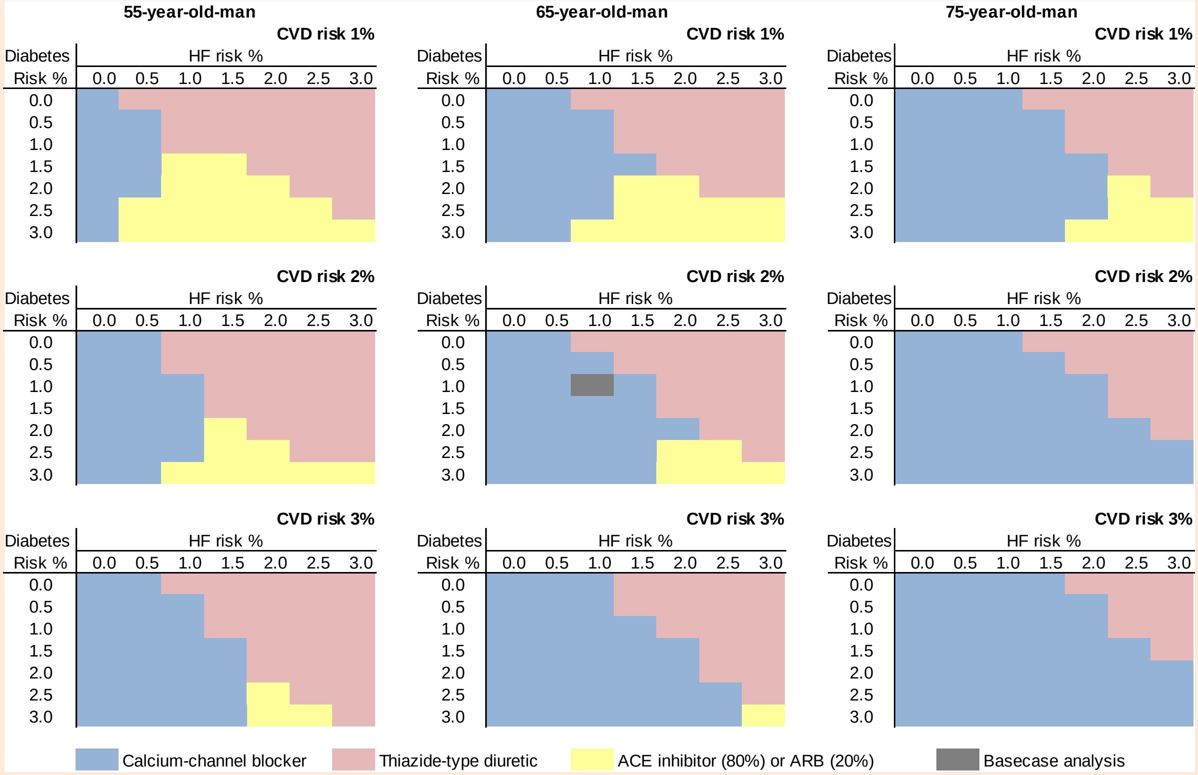
Update 2011

I.6.2 Results for patient subgroups

Figure 120 and Figure 121 show how cost effectiveness varies with age, sex, annual CVD risk, annual diabetes risk and annual heart failure risk, based on a cost-effectiveness threshold of £20,000 per QALY. The meta-analysis found that thiazide-type diuretics and CCBs have similar effects on the incidence of MI, stroke and death (Chapter 10). However, CCBs are associated with significantly higher rates of heart failure but lower rates of diabetes. Thus, CCBs appear to be a more cost-effective option for people over 55 years of age at relatively low risk of heart failure and for those at relatively high risk of diabetes. The GDG noted that in a 55 year old the upper rates of heart failure and diabetes explored in the analysis were extremely unlikely.

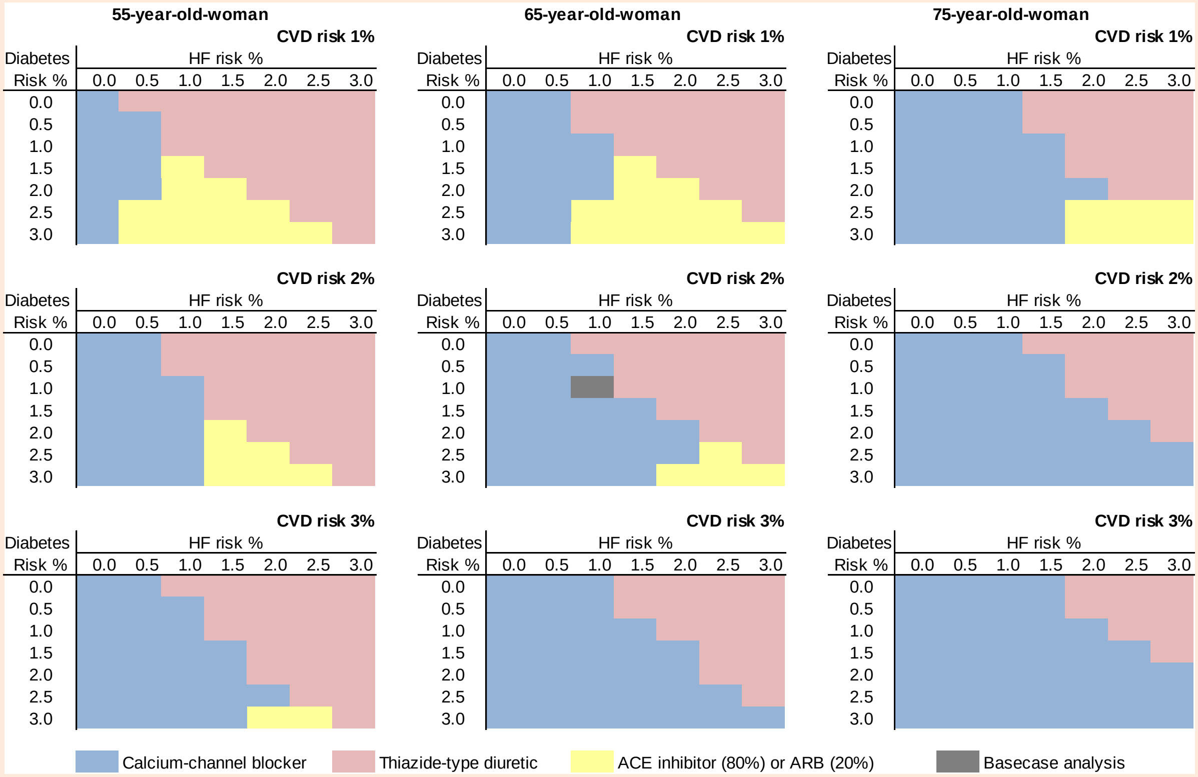
A appear to be a cost-effective alternative to C at high levels of diabetes risk and intermediate levels of heart failure risk. This is because they are associated with lower rates of heart failure and diabetes, but higher rates of stroke.

Figure 120: Four-way sensitivity analysis: most cost-effective (represented by colour) first-line drug for men by age, annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year



ARB = angiotensin-II receptor blocker; CVD = cardiovascular disease; HF = heart failure;

Figure 121: Four-way sensitivity analysis: most cost-effective first-line drug for women by age, annual risk of cardiovascular disease, diabetes and heart failure, based on a cost-effectiveness threshold of £20,000 per quality-adjusted life-year.



ARB = angiotensin-II receptor blocker; CVD = cardiovascular disease; HF = heart failure;

Update 2011

In addition, as Table 95 shows, when CVD is 0.5% (holding all other variables constant at their base-case values, for men and women age 55 A becomes the preferred option. This suggests that A could be cost effective in in the young/low risk people.

Table 95: Sensitivity analysis for annual CVD risk and age (1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios of most effective (highest QALYs) option								
	MEN				WOMEN			
Annual CVD risk	Age							
	55	65	75	85	55	65	75	85
0.5%	A dominant	£5,370	£2,350	£2,240	A dominant	£12,440	£2,800	£2,330
1.0%	£16,860	£2,950	£2,000	£1,970	£3,750*	£3,490	£2,090	£1,860
2.0%	£4,000	£1,960	£1,510	£1,530	£3,200	£1,520	£1,210	£1,170
3.0%	£2,210	£1,430	£1,170	£1,190	£1,050	£800	£700	£680
5.0%	£1,180	£900	£740	£730	£260	£230	£160	£70

*All ICERs above are for C apart from * where ICER is for D*

Update 2011

I.6.3 Younger people

The model is not designed to estimate cost effectiveness for a younger population, since most of the evidence about treatment effects derives from studies in older people. However, we can use the model to test the possible impact of improved performance of ACEis, ARBs and BBs in a younger, non-black group . Taking the predicted baseline effects of a 45-year-old cohort (at 2% annual CVD risk, 1% annual heart failure risk and 1.1% annual diabetes risk), cost effectiveness was estimated for given percentage improvements in treatment effects for ACEi/ARB and BB compared with the meta-analysis figures.

Diuretics appear to be the most cost-effective option for this age group in the base-case analysis, as shown in Table 96. However, if the relative risks for ACEi/ARBs were only 1% (men)/1.2% (women) or better than the meta-analysis estimates, then they would be cost effective (cost per QALY less than £20,000). Beta-blockers continued to be dominated even at higher percentage improvements, assuming an equal percentage improvement of ACEi/ARBs and BBs for the younger population. This analysis does lend some support to the hypothesis that ACEi/ARBs may be cost effective in younger non-black patients.

Table 96: Sensitivity analysis for increased effectiveness of A/B for younger patients (45-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
% improvement in effects of A/B	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
0%	LC	-	-	-	3	£610	-	LC	-	2
1%	-	-	LC	-	1	£5,730	-	LC	-	2
2%	-	-	LC	-	1	-	-	LC	-	1
3%	-	-	LC	-	1	-	-	LC	-	1
4%	-	-	LC	-	1	-	-	LC	-	1
10%	-	-	LC	-	1	-	-	LC	-	1
12%	-	-	LC	-	1	-	-	LC	-	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A dominates all*
2 = B and C dominated: D versus A
3 = D dominates all

Update 2011

I.6.4 Other sensitivity analyses

A range of sensitivity analyses were conducted to assess the impact of different input parameters on the base-case results. In these analyses we held all other parameters fixed at their base-case values. The results are interpreted using a cost-effectiveness threshold of £20,000 per QALY. Table 97 summarises the results for those parameters that led to a change of conclusion from the base case. These results are discussed further in the sections that follow this table.

Table 97: List of sensitivity analyses results that altered base-case conclusions

Parameters changed	Most cost-effective option
Base case men age 65 (2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)	C
Treatment effects	
Upper limits for effects of C vs D	D
Lower limits for effects of ACEi vs C	A
Lower limits for effects of ARB vs ACEi	A
Alternative treatment effect data scenario 1: lower limits for effects of B vs D	B
Alternative treatment effect data scenario 2: lower limits for effects of ACEi vs D	A
Event risks	
RR of CVD events with diabetes of 4, when risk of diabetes is 4%	A
RR of CVD events with heart failure >11 (base case heart failure risk) and any RR ≥1 when when heart failure risk is 2% and 4%.	D
Quality of life	
Reduction in quality of life from drug side effects 3.6% or more	NI
Reduction in quality of life of 0.27% or more due to side effects of C	D
Costs	
Cost of CCBs more than £94 per annum	D
Highest cost drug in each class used	D

Update 2011

I.6.4.1 Uncertainty over treatment effects

The results are sensitive to uncertainty over the magnitude of treatment effects estimated from the meta-analyses (Table 98, Table 99 and Table 100).

The conclusion that CCBs were the most cost-effective option was robust to variations in the treatment effects, except in the following scenarios:

- Diuretics dominate all other options when the effects of CCBs compared with diuretics are increased to their upper 95% confidence limits.
- ACEi/ARB are the most cost-effective option in three tested scenarios:
  - Lower limits for effects of ACEi versus C (A dominates all interventions).
  - Lower limits for effects of ACEi versus D (£620 per QALY for A versus D).
  - Lower limits for effects of ARB vs ACEi (£840 per QALY for A versus D, C versus A > £20,000 per QALY gained)
- Beta-blockers are the most cost-effective option if we take the lower limits for the effects of B versus D (£2,010 per QALY for B versus D).

These extreme results may be relatively unlikely, however, since the relative risks for all outcomes would all have to be simultaneously at their lower 95% limits.

Table 98: Sensitivity analysis for efficacy of treatment (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
Comparison	Lower limit of treatment effect					Upper limit of treatment effect				
	D	B	A	C	*	D	B	A	C	*
D vs NI	LC	-	-	£970	1	LC	-	-	£4,470	1
C vs D	-	-	LC	£360	2	LC	-	-	-	3
B vs C	LC	-	-	£1,960	1	LC	-	-	£1,960	1
ACEi vs C	-	-	LC	-	4	LC	-	-	£1,960	1
ARB vs ACEi	LC	-	£840	£55,420	5	LC	-	-	£1,960	1

LC = lowest cost option; ’-‘ = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = Band D dominated: C versus A
3 = D dominates all
4 = A dominates all
5 = B dominated: A versus D, C versus A

Update 2011

Table 99 shows how results do not change if the treatment effects for BB are taken from the mean relative risks in comparison with diuretics (rather than compared with CCB as in the base-case model). BBs remain dominated and CCBs are the most cost-effective option in this case. If the lower limits of the confidence intervals for BB compared with diuretics are used, BB appear to be the most cost-effective option with an estimated ICER of £2,010.

Table 99: Sensitivity analysis for treatment effects (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk) (Alternative treatment effect data scenario 1: BB versus DD)

Incremental cost-effectiveness ratios (cost per QALY)															
Comparison	Lower limit of treatment effect					Basecase treatment effect					Upper limit of treatment effect				
	D	B	A	C	*	D	B	A	C		D	B	A	C	*
B vs D	LC	£2,010	-	£1,960	1	LC	-	-	£1,960	2	LC	-	-	£1,960	2

LC = lowest cost option; ’-‘ = option ruled out by simple or extended dominance
** 1 = A dominated: C vs D, B versus C*
2 = A and B dominated by C: C versus D

Update 2011

Table 100 shows how the results also do not change if the treatment effects of ACEi are based on their mean relative risks compared with diuretics, rather than with CCBs as in the base-case model. However, the ACEi/ARB combination appears to be the most cost-effective option if the lower confidence intervals for the effects of ACEi versus diuretics are used.

Table 100: Sensitivity analysis for treatment effects (65-year-old men with 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk) (Alternative treatment effect data scenario 2: ACEi versus DD)

Incremental cost-effectiveness ratios (cost per QALY)															
Comparison	Lower limit of treatment effect					Base-case treatment effect					Upper limit of treatment effect				
	D	B	A	C	*	D	B	A	C		D	B	A	C	*
ACEi vs D	LC	-	£620	-	1	LC	-	-	1,760	2	LC	-	-	£1,760	2

LC = lowest cost option; ’-‘ = option ruled out by simple or extended dominance
** 1 = B and C dominated: A versus D*
2 = A and B dominated: C versus D

Update 2011

I.6.4.2 Use of ARBs

The percentage of ARBs used in conjunction with ACEi in the base-case model was assumed to be 20%. The model is not sensitive to assumptions about the number of patients who cannot tolerate ACEis and switch to ARBs. Varying this percentage up to 100% did not impact conclusions; CCBs remained cost effective (Table 101).

Table 101: Sensitivity analysis, percentage of ARBs used in conjunction with ACEi (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)								
% of ARBs	MEN				WOMEN			
	D	B	A	C	D	B	A	C
0%	LC	-	-	£1,960	LC	-	-	£1,520
10%	LC	-	-	£1,960	LC	-	-	£1,520
15%	LC	-	-	£1,960	LC	-	-	£1,520
20%	LC	-	-	£1,960	LC	-	-	£1,520
25%	LC	-	-	£1,960	LC	-	-	£1,520
50%	LC	-	-	£1,960	LC	-	-	£1,520
60%	LC	-	-	£1,960	LC	-	-	£1,520
70%	LC	-	-	£1,960	LC	-	-	£1,520
80%	LC	-	-	£1,960	LC	-	-	£1,520
90%	LC	-	-	£1,960	LC	-	-	£1,520
100%	LC	-	-	£1,960	LC	-	-	£1,520

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

Update 2011

I.6.4.3 Event risk assumptions

Risk of CVD events for people with diabetes

In the base-case analysis it is assumed that the relative risk of CVD event for people with diabetes is 2 (that is the risk of CVD events is doubled). At all levels of diabetes risk, CCBs remained the most cost effective option in most scenarios regarding the relative risks of CVD events; even if the relative risk of CVD events with diabetes was set to 1 (that is, no increase in risk of CVD events in people with diabetes). It is more cost-effective to treat with ACEi/ARB at a high level of diabetes risk (4%) if the relative risk of CVD events is also high (RR = 4).

Table 102: Sensitivity analysis for relative risk of CVD events and diabetes (65-year-old men 2% CVD risk, 1.1% diabetes risk)

Incremental cost-effectiveness ratios (cost per QALY)															
RR **	Annual risk of diabetes = 1.1%					Annual risk of diabetes = 2%					Annual risk of diabetes = 4%				
	D	B	A	C	*	D	B	A	C	*	D	B	A	C	*
1	LC	-	-	£3,760	1	-	-	LC	£1,490	2	-	-	LC	£3,360	2
2	LC	-	-	£1,960	1	-	-	LC	£1,690	2	-	-	LC	£8,620	2
4	LC	-	-	£1,640	1	LC	-	£310	£2,510	3	-	-	LC	-	4

LC = lowest cost; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = D and B dominated: C versus A
3 = B dominated: A versus D, C versus A
4 = D, B and C dominated by A

Update 2011

*** Relative risk of CVD events following heart failure compared with CVD event risks for people who have not had a CVD event*

Risk of CVD events for people with heart failure

The results are sensitive to the relative risk of CVD events for people with heart failure (Table 103). For a given level of heart failure risk, the cost effectiveness of CCBs worsens as the relative risk of CVD events for people with heart failure increases. This may be explained by the fact that D does better in preventing heart failure than CCBs. At 1% annual risk of heart failure (as in the base-case analysis, CCBs are no longer cost-effective compared with diuretics only if the risks of CVD events with heart failure are more than 11 times higher than in the base case.

Table 103: Sensitivity analysis for relative risk and incidence of CVD events following heart failure (65-year-old men 2% CVD risk, 1.1% diabetes risk)

Incremental cost-effectiveness ratios (cost per QALY)															
RR **	Annual risk of heart failure = 1%					Annual risk of heart failure = 2%					Annual risk of heart failure = 4%				
	D	B	A	C	*	D	B	A	C	*	D	B	A	C	*
1	LC	-	-	£1,960	1	LC	-	-	-	2	LC	-	-	-	2
2	LC	-	-	£2,960	1	LC	-	-	-	2	LC	-	-	-	2
4	LC	-	-	£4,990	1	LC	-	-	-	2	LC	-	-	-	2

LC = lowest cost; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = D dominates all other options
*** Relative risk of CVD events following heart failure compared with CVD event risks for people who have not had a CVD event*

Update 2011

Risk of CVD events for people with stroke

As shown in Table 104, conclusions are not sensitive to the relative risk of CVD events following a stroke; CCB remains the most cost-effective option.

Table 104: Sensitivity analysis for relative risk of CVD events following a stroke (65-year-old 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
RR**	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
1	LC	-	-	£1,960	1	LC	-	-	£1,520	1
2	LC	-	-	£1,970	1	LC	-	-	£1,580	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
*** Relative risk of CVD event following stroke compared with CVD event risks for people who have not had a CVD event*

Update 2011

Risk of non-CVD death

As shown in Table 105, conclusions are not sensitive to changes in the assumptions about the relative risk of death from non-CVD in the hypertensive cohort compared with the general population. Hypertensive treatment remains highly cost-effective, and CCBs remain the preferred option (holding all other variables at their base-case values).

Table 105: Sensitivity analysis for relative risk of non-CVD death (65-year-old 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)		
RR**	MEN	WOMEN

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)										
	D	B	A	C	*	D	B	A	C	*
1	LC	-	-	£1,960	1	LC	-	-	£1,520	1
2	LC	-	-	£1,500	1	LC	-	-	£1,310	1
4	LC	-	-	£1,250	1	LC	-	-	£1,160	1
8	LC	-	-	£1,030	2	LC	-	-	£1,000	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 =A and B dominated: C versus D*
2= A and B dominated: C versus D and D versus NI
*** Relative risk of non-CVD death for population in model (people with hypertension) compared to general population*

I.6.4.4 Quality of life

Quality of life due to drug side effects

The base-case model assumes there is no loss in quality of life due to hypertensive treatment side effects. If the loss of quality of life due to the side effects of hypertensive treatment is assumed to be 3.6% or greater, then treatment may not be cost effective. This assumes equal quality of life loss for all drugs, which is unlikely given that we know that there are differing rates of adverse events and withdrawals.

Update 2011

Table 106: Sensitivity analysis for quality of life loss from hypertensive treatment (65-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
QoL reduction	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*
0%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
1%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
2%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
3%	LC	-	-	£1,960	1	LC	-	-	£1,520	1
4%	LC	-	-	£1,960	2	LC	-	-	£1,520	2
5%	LC	-	-	-	3	LC	-	-	£1,520	2

LC = lowest cost; QoL = quality of life; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = A and B dominated by NI: NI versus C (NI ICER not shown – NI cost effective)
3 = A, B and C dominated by NI: NI versus D (NI ICER not shown – NI cost effective)

Small differences in adverse effects of the different drugs may change their relative cost effectiveness. Holding all other parameters constant at their base-case values, CCBs remain the most cost-effective option provided that their impact on quality of life due to adverse effects does not exceed about 0.27% (Table 107). For comparison, the quality of life impact of chronic lower-extremity oedema has been estimated at 10% (Harvard CEA registry). Thus, if an individual experiences even minor or infrequent side effects with CCBs, then alternative antihypertensive treatment may be more cost effective.

Update 2011

Table 107: Sensitivity analysis for quality of life with CCBs and ACEi/ARBs (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)																
Reduction with C	0% reduction with A				0.2% reduction with A				0.4% reduction with A				0.6% reduction with A			
	D	A	C	*	D	A	C	*	D	A	C		D	A	C	*
0.1%	LC	-	£2,940	1	LC	-	£2,940	1	LC	-	£2,940	1	LC	-	£2,940	1

Incremental cost-effectiveness ratios (cost per QALY)																
0.2%	LC	-	£5,890	1	LC	-	£5,890	1	LC	-	£5,890	1	LC	-	£5,890	1
0.4%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2
0.8%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2
1.0%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2
2.0%	LC	-	-	2	LC	-	-	2	LC	-	-	2	LC	-	-	2

LC = lowest cost; '-' = option ruled out by simple or extended dominance
** 1 = B and A dominated: C versus D*
2 = D dominated all

Quality of life due to events

Table 108 interpretation: The results are not sensitive to changes in the assumed quality of life change due to CVD events or the onset of diabetes. C remained the most cost-effective option under all scenarios tested.

Table 108: Sensitivity analysis for quality of life loss from CVD events and diabetes (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Incremental cost-effectiveness ratios (cost per QALY)										
	Lower limit					Upper limit				
Quality of life loss	D	B	A	C	*	D	B	A	C	*
Unstable angina (0.7-0.9)	LC	-	-	£1,960	1	LC	-	-	£1,950	1
MI (0.7-0.9)	LC	-	-	£1,960	1	LC	-	-	£1,950	1
Diabetes (0.8-1)	LC	-	-	£1,930	1	LC	-	-	£1,990	1
Stroke (0.5-0.7)	LC	-	-	£1,930	1	LC	-	-	£1,960	1
Heart failure (0.6-0.8)	LC	-	-	£2,010	1	LC	-	-	£1,920	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*

Update 2011

I.6.4.5 Costs

Drug costs

In the base-case model, CCBs were assumed to cost £18.64 per patient per annum (based on the BNF 60, September 2010, price of amlodipine). If this is increased to £94 or more, then CCBs were no longer cost effective compared with diuretics.

As shown in table Table 109, the model is sensitive to assumptions about the cost of drugs. CCBs remained the most cost-effective option when the cheapest drugs are used. When the most expensive drugs are used, the ICERs increase to a level above what is usually considered affordable by the NHS, between £20,000–£30,000 per QALY, making D the optimal choice. However, this is an unlikely scenario.

Table 109: Sensitivity analysis for cost of drugs (65-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk) (cheapest and most expensive)

Incremental cost-effectiveness ratios (cost per QALY)										
Cost of drugs	MEN					WOMEN				
	D	B	A	C	*	D	B	A	C	*

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)										
Cheapest	LC	-	-	£1,960	1	LC	-	-	£1,520	2
Most expensive	LC	-	-	£85,160	1	LC	-	-	£95,660	1

LC = lowest cost option; '-' = option ruled out by simple or extended dominance
** 1 = A and B dominated: C versus D*
2 = B dominated: C versus A

As shown in Table 110, the conclusion that CCBs are the most cost effective option is not sensitive to the cost of the diuretics used in the analysis. When chlortalidone is used for costing purposes diuretics are dominated and A becomes the lowest cost option, but CCBs remain the most cost-effective option.

Table 110: Sensitivity analysis on the cost of diuretics (65-year-old, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)								
Thiazide-type diuretic	MEN				WOMEN			
	D	B	A	C	D	B	A	C
Chlortalidone	-	-	LC	£310	-	-	-	LC
Indapamide	LC	-	-	£1,040	LC	-	-	£480

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

Health state costs

As shown in Table 111, CCBs remained the most cost-effective option when assumptions about the costs of events are changed. When the costs of events are reduced by 50% one at a time holding other events constant, CCB remained cost effective when compared with the next most cost effective alternative (D). When costs of events were doubled, CCB remained the optimal choice.

Table 111: Sensitivity analysis for costs of events (65-year-old men, 2% CVD risk, 1.1% diabetes risk, 1% heart failure risk)

Update 2011

Incremental cost-effectiveness ratios (cost per QALY)								
	Lower limit of costs (50% reduction)				Upper limit of costs (50% reduction)			
	D	B	A	C	D	B	A	C
No event	LC	-	-	£1,940	LC	-	-	£2,000
Unstable angina	LC	-	-	£1,890	LC	-	-	£2,090
Unstable angina sub.	LC	-	-	£1,920	LC	-	-	£2,030
MI	LC	-	-	£1,740	LC	-	-	£2,400
Post-MI	LC	-	-	£1,870	LC	-	-	£2,140
Diabetes	LC	-	-	£2,040	LC	-	-	£1,800
Stroke	LC	-	-	£2,440	LC	-	-	£1,010
Post-stroke	LC	-	-	£1,980	LC	-	-	£1,910
Heart failure	LC	-	-	£1,090	LC	-	-	£3,690
Post heart failure	LC	-	-	£1,260	LC	-	-	£3,370

LC = lowest cost option; '-' = option ruled out by simple or extended dominance

I.7 Impact of the 2011 update

I.7.1 Model inputs

The most significant change in the model inputs in the 2011 update was the reduction in drugs costs; in particular the cost of CCBs, ACEis and ARBs.

I.7.2 Base case results

CCBs remained the most cost effective option in the updated base-case analysis, meaning no change from 2006 in the interpretation 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.

Due to reductions in drug costs since 2006 overall costs for all drug classes in the updated analysis were cost saving compared with no intervention (based on low cost generic options); in 2006 this was only the case for diuretics. As cost reductions for drugs were relatively greater for CCBs, ACEis and ARBs than other classes CCBs were also no longer the most expensive option, both B and NI being more expensive. In addition the overall costs of the ACEi/ARB or CCBs options were much similar to those for diuretics in the updated analysis; in the 2006 analysis ACEi/ARB and CCBs had considerably higher costs than diuretics.

I.7.3 Subgroup and sensitivity analysis results

The results of the subgroup analysis (by age, annual CVD, diabetes and heart failure risk) remain largely unchanged although, in both men and women, CCBs are the most cost effective option in a greater number of scenarios; however, this difference is not great. Both old and new analyses show similar trends of cost effectiveness but in the new analysis A is the most cost effective option in fewer scenarios than before with the heart failure risk where this is the case moving to intermediate/high risk.

Table 112 summarises how the other sensitivity analysis results have changed in the 2011 update from the 2006 analysis.

Table 112: Changes to the interpretation of sensitivity analyses from 2006 update

Sensitivity analysis	Interpretation changes
Younger people	**No change.**
Treatment effects	**Minor changes:** C cost effective in women with upper limits of B vs C – differs from 2006 where A is the cost effective option and C is dominated.
Use of ARBs	**Minor changes:** conclusion nolonger sensitive to this input.
Relative risk of CVD events with diabetes	**Minor changes:** C now remains cost effective even when no increase in risk of CVD events for people with diabetes (RR = 1).
Relative risk of CVD events following heart failure	**Minor changes:** C remains cost effective to a higher increase in risk of CVD event for people with heart failure.
Relative risk of CVD events following a stroke	**No change.**
Non-CVD death	**No change.**
Quality of life loss from hypertensive treatment	**No change.**
Quality of life loss with CCBs and ACE/ARBs	**Minor changes:** quality of life loss required for C to nolonger be cost effective has increased slightly.
Quality of life loss from CVD events and diabetes	**No change.**
Cost of drugs	**No change.**
Cost of diuretics	**New analysis:** no change in base case interpretation.

Update 2011

Sensitivity analysis	Interpretation changes
Costs of events	**No change.**

I.8 Limitations of the model

The model was based on various assumptions that could possibly bias the results.

Firstly, it was assumed that treatment effects from the meta-analysis were attributable to the first-line drug. However, the percentage of patients remaining on monotherapy in the trials varied widely: from about 60% in ALLHAT to about 10% in ASCOT, for example. The above results will therefore tend to overestimate the effectiveness and cost effectiveness of hypertensive treatment compared with no intervention. However, this is unlikely to change the overall conclusions. If we assume that 90% of patients receive a second drug at the price of £60 per annum, the ICER for CCBs versus diuretics increases to about £2000 per QALY. There might be a more serious problem if some trials used more or less effective protocols following failure to achieve blood pressure targets on the first drug, introducing bias to the estimates of relative effectiveness between the first-line drugs. This issue also applies to the interpretation of the clinical evidence from the meta-analysis of trials.

Secondly, the data for diuretics in the model was based on the meta-analysis undertaken for the 2006 pharmacological update (CG34) that pooled data for thiazide and thiazide-like diuretics together (referred to collectively as thiazide-type diuretics). The 2011 update reviewed the evidence for the different types of diuretics and concluded that there was limited data for thiazide diuretics at appropriate doses and so recommended that a thiazide-like diuretic (chlortalidone or indapamide) was a more evidenced-based therapy option. However, the data used for diuretic treatment effect in the model was heavily weighted by the very large ALLHAT study which used chlortalidone; therefore it was considered that this was unlikely to significantly impact conclusions.

Update 2011

A third limitation of the model derives from the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only on their current health state (there is no 'memory' in the model). Thus the probability of new-onset diabetes for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient's health outcome and healthcare costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost effective than they may be in reality. So the model is conservative in this respect.

A forth potentially important limitation of the model is the lack of utility data for the side effects of the different drugs. The relative ranking of CCBs, ACEi/ARBs and thiazide-type diuretics is quite sensitive to assumptions about their relative side effects. Further research in this area is likely to be worthwhile.

Fifth, the lack of data on relative treatment effects for under-45s and black people means that it is difficult to predict the relative cost effectiveness of the different drugs in these subgroups. Evidence exists on differences in blood pressure response by age and ethnicity. However, extrapolating this evidence to longer-term outcomes (CVD events and incidence of diabetes) is more difficult.

A sixth limitation of the model relates to the treatment of withdrawals and non-concordance with treatment. Since the treatment effects are based on 'intention-to-treat' analyses, the impact of withdrawals and non-concordance from the trials is already included in the model. However, the model continues to attribute drug costs for all patients throughout their lifetime. This is a conservative assumption that will tend to underestimate the cost effectiveness of treatment. On the other hand, concordance and continuation of treatment may well differ between the trial context and routine practice.

Because of the short timescales for the guideline update and the other priorities for new analysis it was not possible to conduct a probabilistic sensitivity analysis with the model. This further analysis may be useful, particularly given the sensitivity of the results to extreme assumptions about the relative treatment effects.

Update 2011

I.9 Conclusions

This analysis found that treating hypertension is highly cost-effective. Treatment resulted in improved health outcomes (higher QALYs) and with allof the drug classes in the model actually resulted in overall cost savings compared to no treatment as the reduction in cardiovascular events led to savings that offsets 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.

This analysis suggests that which of the drug classes is most cost-effective depends on their relative effects 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 diabetes and they also have a good effectiveness profile across the range of other CVD risks.

For people at high risk of heart failure, however, CCBs do not appear to be cost-effective. Thiazide-type diuretics are estimated to be the most cost-effective alternative for those at high risk of heart failure, provided that they do not also have a high risk of diabetes. For people with a high risk of both heart failure and diabetes, ACEis or ARBs may be the most cost-effective option. However, 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.

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. The results are also sensitive to the possible impact of drug side effects. For groups or individuals expected to have significant side effects from CCBs, thiazide-type diuretics might prove to be more cost effective. There is also considerable uncertainty about the size of some treatment effects, which translates into uncertainty about the relative cost effectiveness of the drugs.

Finally the model results are robust to changes in the estimated treatment costs and quality of life impacts of diabetes, heart failure and other CVD events. They are also robust to changes in the relative risks of secondary CVD events following unstable angina, MI or stroke and also to assumptions about rates of non-CVD-related deaths in this hypertensive cohort.

Appendix J: Cost-effectiveness analysis – blood pressure monitoring for confirming a diagnosis of hypertension (new 2011)

J.1 Introduction

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.

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 a call for evidence in this area (see Methods), by a UK research group[i] 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:

- The analysis was conceptualised by the research group.
- The research protocol including draft model structure, key assumptions and data sources was developed by the research group.
- The analysis was undertaken by the guideline health economist with input from the research group, the GDG (in particular the health economic subgroup) and senior NCGC health economic support. This included finalising the model structure, key assumptions and data sources, identifying and analysing data where necessary, programming the model and drafting this report.
- Both the GDG and research group were consulted on and agreed the final model structure, assumptions and inputs and had the opportunity to review this report.
- The GDG made recommendations for this guideline taking into account the results of the analysis.

Update 2011

i 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.

J.2 Methods

J.2.1 Model overview

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].

J.2.1.1 Population

The population included for the analysis was people with suspected hypertension – those with a screening clinic blood pressure measurement equal or above 140/90 mmHg.

J.2.1.2 Comparators

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

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

J.2.2 Approach to modelling

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 subsequent sections of this report):

- 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 negatives) will have a blood pressure check-up with CBPM every 5 years.

Update 2011

  - 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.

Confirmation of diagnosis using CBPM, HBPM or ABPM is associated with different initial costs. As the different methods of monitoring 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.

Uncertainty was explored through probabilistic analysis and extensive sensitivity analyses.

J.2.2.1 Model structure

A Markov model was constructed to calculate lifetime costs and QALYs for each comparator. In a Markov model a set of mutually exclusive health states are defined that describe what can happen to the population of interest over time. People in the model can only exist in one of these health states at a time. Possible transitions are defined between each of the health states and the probability of each transition occurring within a defined period of time (a cycle) is assigned to each possible transition.

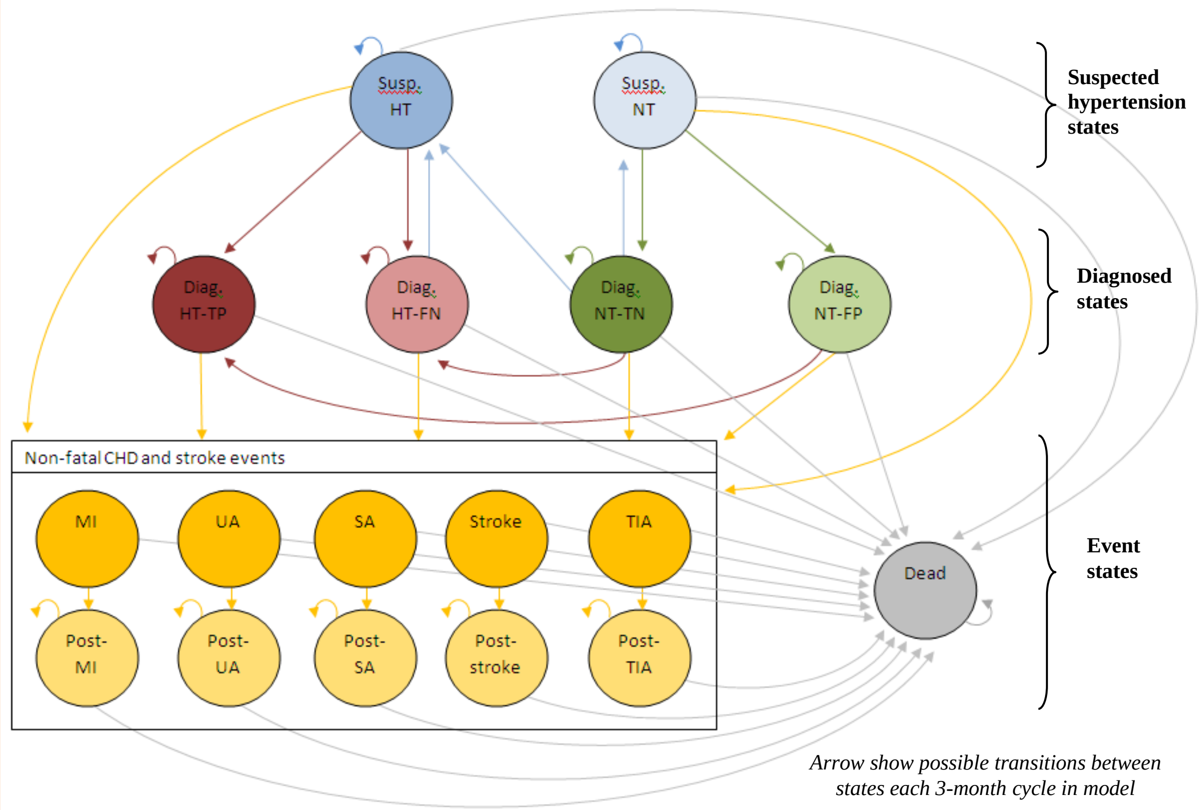
Figure 122 illustrates the key health states in the model and possible transitions between them each cycle. Note that this is a simplified illustration; in the model each comparator (CBPM, HBPM and ABPM) has its own set of suspected hypertension and diagnosed states to allow implementation of a failure rate for ABPM and HBPM. A 3-month cycle duration was used in this model to reflect the typical diagnosis duration for CBPM. The population entering the model is one of people suspected of having hypertension and so people are initially distributed between the two suspected hypertension health states.

The model was run for repeated cycles, and the time spent in each health state is calculated. By attributing costs and quality of life weights to each health state total costs and QALYs can be calculated for the population. This model was run for 240 cycles (60 years) in order to calculate lifetime costs and QALYs (people entering the model had a minimum age of 40 years).

Each comparator in the model (CBPM, HBPM and ABPM) had its own set up transition probabilities therefore each will have different total costs and QALYs. Comparing these results allows us to identify which is the most cost-effective.

Update 2011

Figure 122: Markov model – simplified transition state diagram



Susp. HT	*Suspected of having hypertension with true raise blood pressure (truly hypertensive)*
Susp. NT	*Suspected of having hypertension with falsely raised blood pressure (truly normotensive)*
Diag. HT-TP	*Diagnosed as hypertensive – true positive (truly hypertensive)*
Diag. HT-FN	*Diagnosed as normotensive – false negative (truly hypertensive)*
Diag. NT-TN	*Diagnosed as normotensive – true negative (truly normotensive)*
Diag. NT-FP	*Diagnosed as hypertensive – false positive (truly normotensive)*
CHD	*Coronary heart disease*
MI	*Myocardial infarction*
SA	*Stable angina*
TIA	*Transient ischemic attack*
UA	*Unstable angina*

Transition probabilities: suspected hypertension health states

Whilst individuals in the model are *suspected* of having hypertension without a confirmed diagnosis (as when the population enters the model) they can be in one of two health states:

- Suspected of having hypertension with *true* raised blood pressure
- Suspected of having hypertension with *false* raised blood pressure

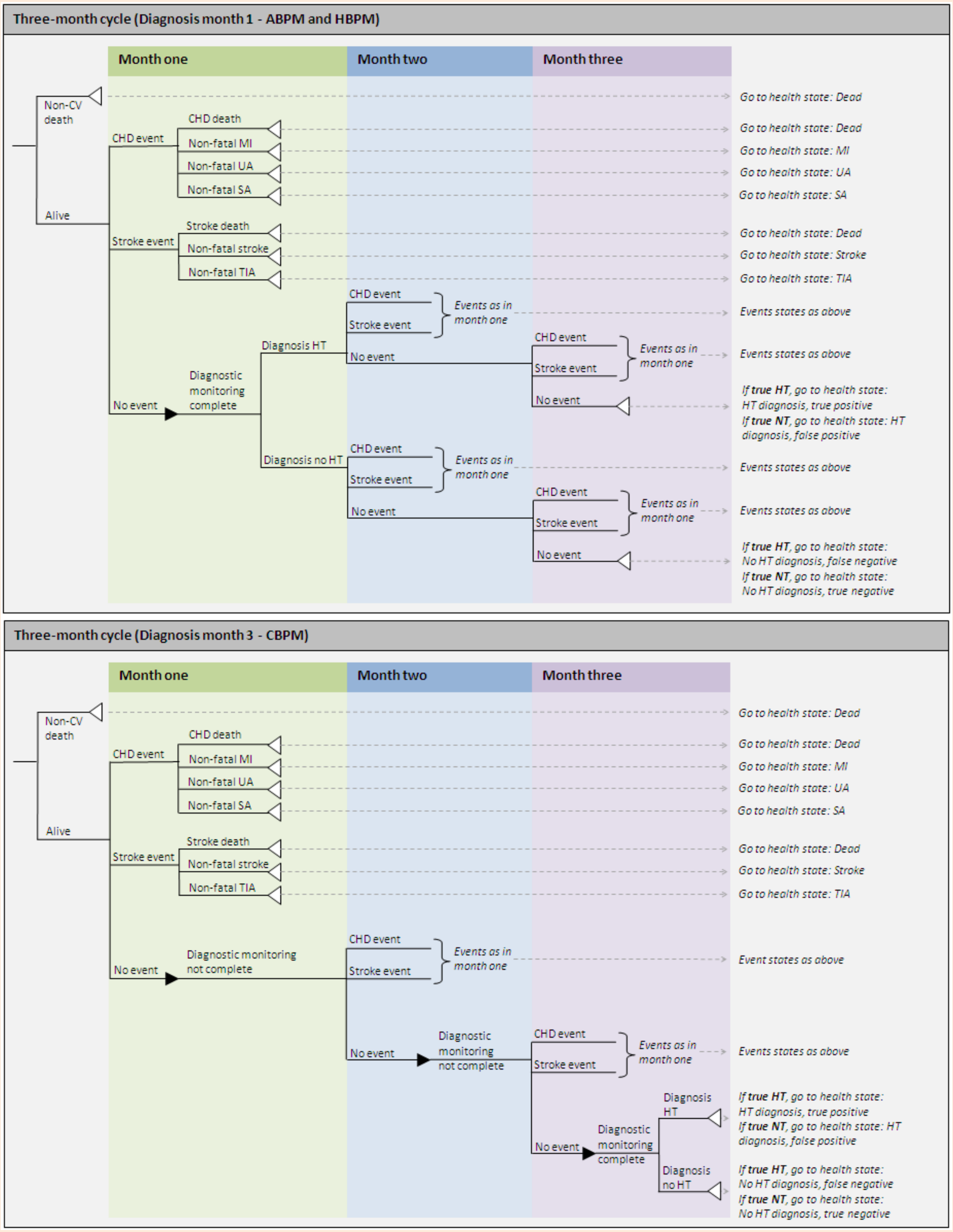
From these two states people in the model can move to a diagnosed state, a non-fatal CV event state or the dead state. The method used for calculation of transition probabilities is illustrated in Figure 123. This accounts for different durations until diagnosis is complete with the different monitoring methods. Transition probabilities from these states will depend on the method used to confirm diagnosis (CBPM, HBPM or ABPM).

The probability of moving to a cardiovascular event state (including death from cardiovascular causes) from the suspected hypertension states depends on the underlying cardiovascular risk of an individual which in turn depends on which suspected hypertension state that individual is in; it is higher in the health state with true raised blood pressure. It also depends on the monitoring method being used to confirm diagnosis and the duration until

Update 2011

diagnosis is complete. This is because once a diagnosis is complete people diagnosed as having hypertension receive antihypertensive treatment, and if they are truly hypertensive (true positives) they will get a reduction in their risk of having a cardiovascular event.
The probability of diagnosis being complete is either 0 or 1 each month – it is 1 the month diagnosis is complete and 0 in the other months.
In the health state ‘suspected hypertension with true raised blood pressure’, the probability of receiving a diagnosis of hypertension or not depends on the sensitivity of the monitoring method used to confirm diagnosis; in the health state ‘suspected hypertension with false raised blood pressure’ it depended on the specificity.
For simplicity, it was assumed that in people who are truly normotensive, blood pressure cannot become raised (that is they become hypertensive) in the suspected hypertension health states during which diagnosis occurs, although once they have moved to one of the diagnosed heath states they can become hypertensive over time.
The probability of non-CV death is not dependant on the health state or monitoring method.
In the model, failure of ABPM (and HBPM in sensitivity analysis) was incorporated by assuming that those that failed were diagnosed by CBPM instead. These people were assumed to have transition probabilities as for CBPM (NB. this aspect of the model is not represented in Figure 123).

Figure 123: Decision tree illustrating how transition probabilities from suspected hypertension states (truly hypertensive and truly normotensive) were calculated



CHD = coronary heart disease; CV = cardiovascular; HT = hypertension; MI = myocardial infarction; NT = normotensive; SA = stable angina; TIA = transient ischemic attack; UA = unstable angina.
Note that incorporation of failure rate with ABPM or HBPM is not represented in diagram – see text for details.

Update 2011

Transition probabilities: diagnosed health states

Once diagnosis has been confirmed people can be in one of four health states if they haven't experienced a cardiovascular event or died:

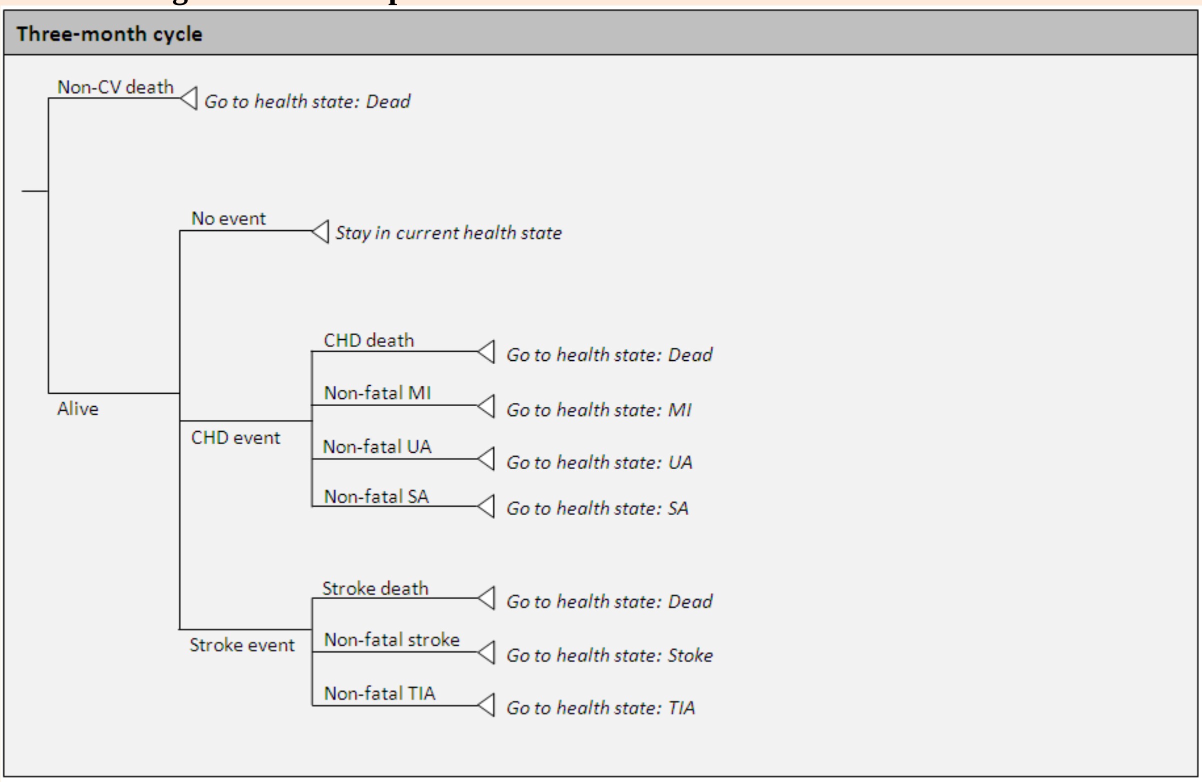
- True positive – diagnosed with hypertension and truly hypertensive (raised CV risk, receive treatment)
- False positive – diagnosed with hypertension but truly normotensive (no raised CV risk, receive treatment)
- False negative – diagnosed without hypertension but truly hypertensive (raised CV risk, no treatment)
- True negative – diagnosed without hypertension and truly normotensive (no raised CV risk, no treatment)

Probabilities in these states do not depend on the method of confirming diagnosis.

In all of the above states people are at risk of cardiovascular events and this is risk is calculated using Framingham equations and population norms for the various individual risk factors (age, sex, blood pressure, cholesterol, smoking and diabetes status). The probability varies between states depending on whether people are truly hypertensive (in which case risk is increased compared with those that are truly normotensive because blood pressure is higher) and whether they are treated (if treated and truly hypertensive people receive risk reduction, but no risk reduction is applied in the case of those falsely labelled as hypertensive). The probability of non-CV death is not dependant on the health state.

The method used to calculate transition probabilities for the true positive health state is illustrated in Figure 124.

Figure 124: Decision tree illustrating how probabilities of movement from state HT diagnosis and true positive were calculated

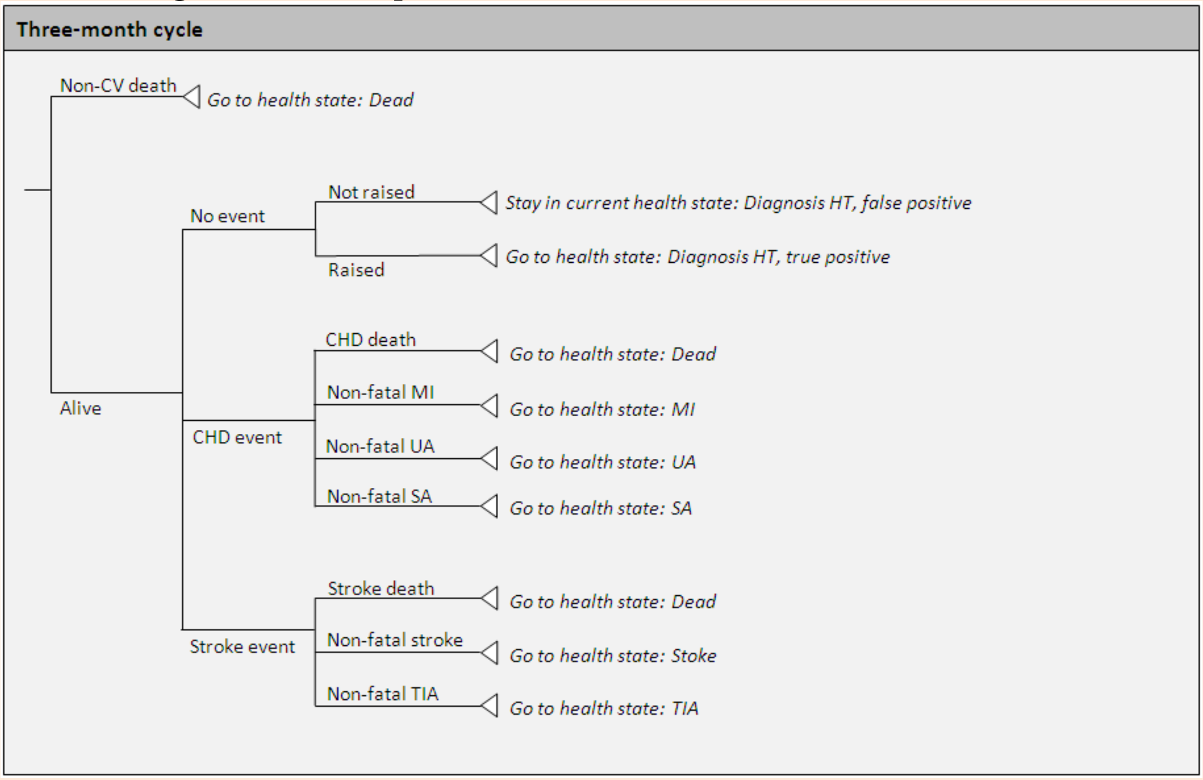


CHD = coronary heart disease; CV = cardiovascular; HT = hypertension; MI = myocardial infarction; NT = normotensive; SA = stable angina; TIA = transient ischemic attack; UA = unstable angina

Update 2011

In the false positive state, there is also a probability that people's blood pressure will rise over time and they will become truly hypertensive and so move to being a true positive. The method used to calculate transition probabilities for the false positive health state is illustrated in Figure 125.

Figure 125: Decision tree illustrating how transition probabilities from state HT diagnosis and false positive were calculated



CHD = coronary heart disease; CV = cardiovascular; HT = hypertension; MI = myocardial infarction; NT = normotensive; SA = stable angina; TIA = transient ischemic attack; UA = unstable angina

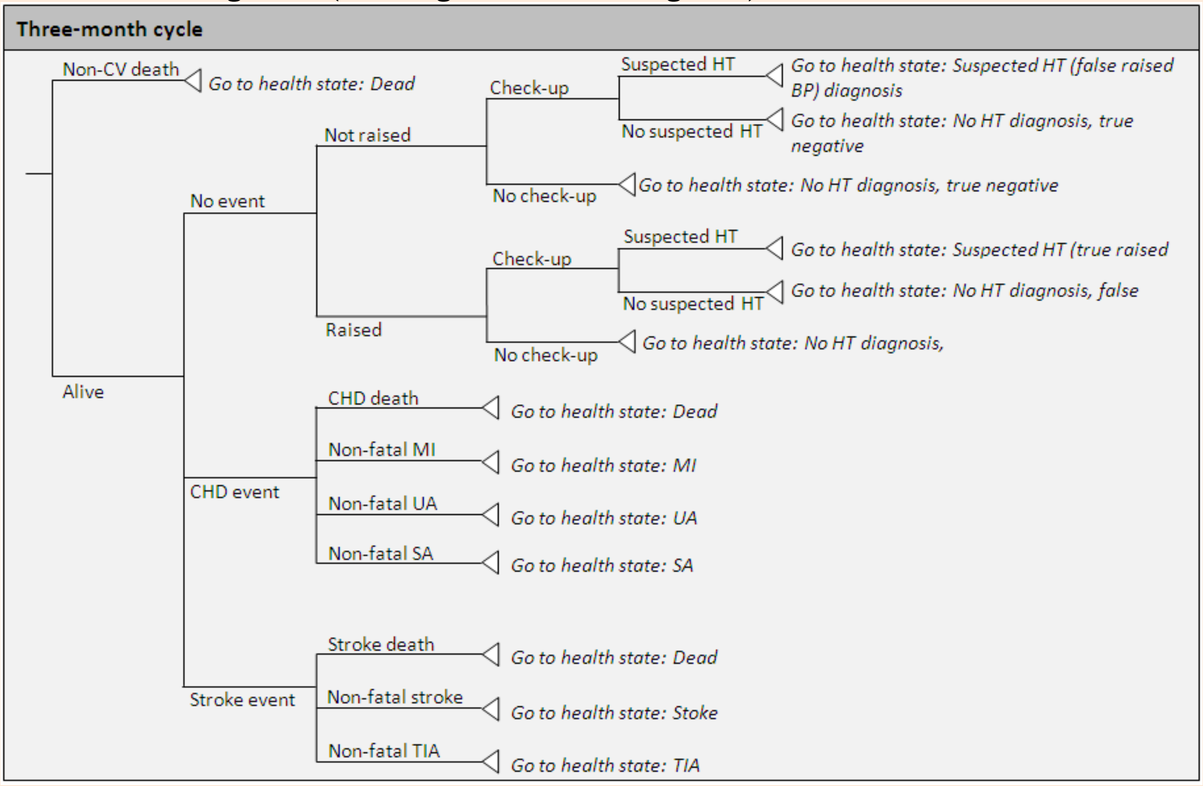
Update 2011

In the heath states where people are diagnosed as not having hypertension (true negative and false negative), there is the additional possibility in a cycle that they will have a blood pressure check-up and move back to one of the suspected hypertension states.

In the false negative state the probability of having truly raised blood pressure will always be 1 (as these people are already hypertensive). In the true negative state this will reflect the probability of becoming hypertensive over time (as in the false positive state described previously).

The method used to calculate transition probabilities for the heath states where people are diagnosed as not having hypertension (true negative and false negative) is illustrated in Figure 126.

Figure 126: Decision tree illustrating how transition probabilities from health state no HT diagnosed (true negative or false negative) were calculated



CHD = coronary heart disease; CV = cardiovascular; HT = hypertension; MI = myocardial infarction; NT = normotensive; SA = stable angina; TIA = transient ischemic attack; UA = unstable angina

Transition probabilities: event health states

In the model it was assumed that once a person has moved to a non-fatal event state (MI, UA, SA, stroke or TIA) they stay there unless they die; that is repeat events are not explicitly modelled. This was considered a reasonable simplification for modelling purposes and also reflects what happens in many trials where an individual is censured at their first event.

In the model the non-fatal CHD and stroke events are each implemented as two states; event and post-event. This is so that a different cost can be applied in the first cycle reflecting acute management and/or diagnostic costs. The event state is a tunnel state where patients move automatically to the post-event state in the next cycle (unless they die).

The probability of death is increased in the CVD states and varied by type of event.

Once people have moved to the dead state in the model they cannot of course move elsewhere; this is known as an absorbing state. If you run the model long enough, everyone will eventually be in this state. This model was run for 240 cycles (60 years) by which time

Update 2011

most people in the population will have died as people entering the model had a minimum age of 40 years.

J.2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected from its respective probability distribution simultaneously; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 1000 times – and results were summarised. Probability distributions in the analysis were based on error estimates from data sources, for example confidence intervals around relative risk estimates. The number of simulations used was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using methods as described by Koehler and colleagues[330]. It was set to ensure that the Monte Carlo error was not more than 5% of the standard error for these parameters.

In addition, various sensitivity analyses were undertaken to test the robustness of model assumptions and data sources. In these, one or more inputs were changed and the analysis rerun to see the impact on results.

J.2.3 Model inputs

J.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence included in the guideline (the systematic review and meta analysis of sensitivity and specificity under taken by the research group[275]), supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG and research group. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 1 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table. Details of the probability distributions used for the probabilistic analysis are also included in subsequent sections.

Table 113: Summary of base-case model inputs

Input	Data	Sources	Probability distribution
Comparators	• CBPM • HBPM • ABPM		n/a
Population	People with suspected hypertension (screening CBPM ≥140/90 mmHg)		n/a
Perspective	UK NHS & PSS	NICE reference case[430]	n/a
Time horizon	Lifetime		n/a
Discount rate	Costs: 3.5% Outcomes: 3.5%	NICE reference case[430]	n/a
Cohort settings			
Subgroups	10 stratified by: • Age: 40, 50, 60, 70, 75 • Gender: male, female		n/a
Prevalence of true HT in population suspected of having	16%-68% (age and gender dependant)	Estimated using HSE 2006 and Hodgkinson et al. meta analysis[28,275]	Derived from estimates of: prevalence of true hypertension: fixed

Input	Data	Sources	Probability distribution
hypertension			estimates of sens and spec of screening test: beta
Diagnosis inputs			
Sensitivity	CBPM: 85.6% (95% CI: 81.0, 89.2) HBPM: 85.7% (95% CI: 78.0, 91.0) ABPM: 100%	Hodgkinson et al. meta analysis sensitivity analysis (excluding populations with low mean blood pressure)[275]; ABPM is assumed to be reference standard with 100% sensitivity and specificity.	CBPM and HBPM: beta ABPM: fixed
Specificity	CBPM: 45.9% (95% CI: 33.0, 59.3) HBPM: 62.4% (95% CI: 48.0, 75.0) ABPM: 100%		CBPM and HBPM: beta ABPM: fixed
Time until diagnosis complete	CBPM: 3 months HBPM: 1 month ABPM: 1 month	Assumption based on guideline recommendations	n/a
Failure rate	HBPM: 0% ABPM: 5%	Expert opinion Based on review of rates in studies and expert opinion[178,223,253,372]	Fixed
Mortality and CVD risk			
Probability non-CV death	Age and gender dependant	England and Wales 2007-09 lifetables with circulatory-death excluded[459,460]	Fixed
Probability CHD event if truly normotensive (10-yr)	0.9%-17.5% (age and gender dependant)	Calculated using Framingham CHD and stroke risk equations and risk factor profile based on HSE 2006[28,44,422,480]	Framingham CHD and stroke risk equations: fixed Blood pressure: normal Total cholesterol: normal HDL cholesterol: normal % diabetes: beta % smoker: beta
Probability CHD event if truly hypertensive (10-yr)	1.7%-23.6% (age and gender dependant)		
Probability stroke event if truly normotensive (10-yr)	0.3%-4.7% (age and gender dependant)		
Probability stroke event if truly hypertensive (10-yr)	0.7%-11.3% (age and gender dependant)		
CHD event distribution	MI: 14.3%-37.8% UA: 10.4%-20.9% SA: 37.7%-62.9% CHD death: 6.6%-17.8% (age and gender dependant)	Ward et al.[626]	Fixed
Stroke event distribution	Stroke: 51.7%-70.1% TIA: 13.4%-36.1% Stroke death: 12.2%-16.5% (age and gender dependant)	Ward et al.[626]	Fixed
RR CHD events on treatment - true positives	0.633-0.717 (age and gender dependant)	Calculated using Law et al. meta analysis[351] results and HSE distribution of people	Relative risks: lognormal % on 1, 2, 3 drugs: Dirichlet

Input	Data	Sources	Probability distribution
		on one, two or three drugs[28]	
RR CHD events on treatment - false positives	1	Assumption that people without raised BP get no benefit of treatment in base case	n/a
RR stroke events on treatment - true positives	0.526-0.717 (age and gender dependant)	Calculated using Law et al. meta analysis[351] results and HSE distribution of people on one, two or three drugs[28]	Relative risks: lognormal % on 1, 2, 3 drugs: Dirichlet
RR stroke events on treatment - false positives	1	Assume that people without raised BP get no benefit of treatment in base case	n/a
SMR post-MI	2.68 (95% CI: 2.48, 2.91)	Bronnum-Hansen et al.[103]	Lognormal
SMR post-UA	2.19 (95% CI: 2.05, 2.33)	UA/NSTEMI NICE guideline[423]	Lognormal
SMR post-SA	1.95 (95% CI: 1.65, 2.31)	Rosengren et al.[515]	Lognormal
SMR post-stroke	2.72 (95% CI: 2.59, 2.85)	Bronnum-Hansen et al.[102]	Lognormal
SMR post-TIA	1.4 (95% CI: 1.1, 1.8)	Oxfordshire Community Stroke Project[169]	Lognormal
BP over time and ongoing monitoring			
Probability of BP raised (true negative and false positive)	15%-38% (age and gender dependant)	Calculated based on HSE 2006[28]	Beta
Check-up frequency if diagnosed not hypertensive	Every 5 years	Assumption based on current practice	n/a
Diagnosis method following check-up	Same as initial diagnosis method		n/a
Quality of life (utilities)			
No CV event utility	0.704-0.909 (age and gender dependant)	General population utilities from analysis of EQ5D from HSE 2006[422]	Beta
Stroke utility	0.629	Ward et al.[626] Applied multiplicatively to general population age and gender dependant utilities	Beta
TIA utility	1		Fixed
MI utility	0.760		Beta
UA utility	0.770		Beta
SA utility	0.808		Beta
Death utility	0	By definition.	n/a
Disutility of being on hypertension treatment	0	Assumption that no quality of life loss due to treatment in base case	n/a
Costs			
Cost of diagnosis CBPM	£38.00	Calculated based on GDG recommendations, expert opinion and UK unit costs[30,486]	Fixed
Cost of diagnosis HBPM	£39.13		
Cost of diagnosis ABPM	£53.40		
Annual hypertension	£57.20-£61.64 (age and	Calculated based on GDG	% on 1, 2, 3 drugs:

Input	Data	Sources	Probability distribution
treatment cost	gender dependant)	recommendations and UK unit costs[28,306,593,486]	Dirichlet Unit costs: Fixed
Initial stroke costs (3-months)	£9630	Youman et al.[649] inflated to 2009/10[486]	Fixed
Post-stroke costs (3-months)	£559	Youman et al.[649] inflated to 2009/10[486]	
Initial TIA cost (3-months)	£992	Diagnostic tests and procedures: Ward et al.[626] inflated to 2009/10[486]; drug costs: relevant NICE guidance[428,432] and BNF 60[306]	
Post-TIA costs (3-months)	£26	Relevant NICE guidance[428,432] & BNF 60[306]	
Initial MI costs (3-months)	£4792	Palmer et al.[474] inflated to 2009/10[486]	
Post-MI costs (3-months)	£141	Assumption from NICE hypertension guideline update 2006[425] inflated to 2009/10[486]	
Initial UA costs (3-months)	£2875	Assumed to be 60% of initial MI costs	
Post-UA costs (3-months)	£85	Assumed to be 60% of post-MI costs	
Initial SA cost (3-months)	£400	Assumption based on review of range of costs of diagnosis[174,486]	
Post-SA costs (3-months)	£6	Relevant NICE guidance[424] and BNF 60[306]	
Cost of check-up in those diagnosed as not hypertensive	£28	PSSRU unit costs[486]	

J.2.3.2 Cohort settings

Update 2011

Subgroups

The analysis was run separately for ten age and gender stratified groups:

- Male and female
- 40, 50, 60, 70 and 75 years of age

Prevalence of true hypertension

When entering the model the population (people suspected of having hypertension due to a screening reading greater than or equal to 140/90 mmHg) were distributed between the health states ‘suspected hypertension – true high blood pressure’ and ‘Suspected hypertension – false high blood pressure’. This is the prevalence of true hypertension among the population that screened positive. As the population entering the model is always the same, this value will not vary between the comparators in the model (confirmation of diagnosis with further CBPM, ABPM or HBPM).

The prevalence of true hypertension among those screening positive for hypertension is the positive predictive value of the screening test (the percentage of people who are true positive out of all positives). This is dependent on the prevalence of hypertension in the population of interest (that is the prevalence of true hypertension in the population that was screened) and the sensitivity and specificity of the screening test.

It is well known that the prevalence of hypertension in the general population increases with age. It would therefore be expected that the prevalence of true hypertension among those that have a positive screening results (the positive predictive value) would vary with age.

In addition however, the sensitivity and specificity of the screening test will also vary with prevalence and so age – 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 this is not the case[98]. This tends to in part counteract the impact of the disease prevalence on the positive predictive value meaning that it varies less than would be expected if sensitivity and specificity were independent of disease prevalence[98].

No study was identified that looked at the sensitivity and specificity or positive predictive value of a screening CBPM by prevalence or age to inform this input in the model. The following approach was therefore used to provide an approximation for each age group. This used an approximation of the prevalence of true hypertension that varied by age, and a constant estimate for the sensitivity and specificity for the CBPM screening test. The resulting model inputs are shown in Table 114.

The prevalence of true hypertension by age was approximated using the reported prevalence of hypertension by 10-year age bands from on the Health Survey for England (HSE) 2006 data[28]. In HSE 2006 hypertension was determined based on the mean of two of three measurements taken by a nurse at a single visit. It is therefore likely to overestimate the prevalence of 'true' hypertension as determined by ABPM. It will however reflect the appropriate trend in the prevalence of hypertension with age. The prevalence of untreated hypertension was used in order to exclude those already diagnosed with hypertension as those already diagnosed will not be screened. As some patients will be diagnosed during the age period this may somewhat underestimate the prevalence in the screening population. Over all this approach was considered likely to give a reasonable estimate for the model that appropriately reflected the varying prevalence with age.

The sensitivity and specificity applied for the CBPM screening test was that from the systematic review reported by Hodgkinson and colleagues[275] included in the clinical review of CBPM (using ABPM as the reference standard). This did not differentiate between CBPM screening and CBPM to confirm diagnosis but was considered to be the best estimate available. There was insufficient information available to vary this input with age (to reflect the variation in prevalence as discussed above).

The ideal way to incorporate sensitivity and specificity in a probabilistic analysis is using bivariate distributions since sensitivity and specificity are linked. However this requires information about the covariance of sensitivity and specificity which was not available in this instance and so these parameters were incorporated independently using beta distributions. These were parameterised by manually adjusting n until the confidence interval was close to that reported. This was done instead of using the total study n to parameterise the distribution as this would underestimate uncertainty as uncertainty due to heterogeneity between studies in the meta analysis would not be accounted for.

In sensitivity analysis the prevalence of true hypertension input in the model was varied through a wide range to explore the uncertainty in this input (see Section J.2.4).

Update 2011

Update 2011

Table 114: Estimated prevalence of true HT in population with suspected hypertension (those with a screening reading ≥140/90 mmHg) by age and gender

	35-44				45-54				55-64				65-74				75+			
	Male		Female		Male		Female		Male		Female		Male		Female		Male		Female	
	uHT	NT	uHT	NT	uHT	NT	uHT	NT	uHT	NT	uHT	NT	uHT	NT	uHT	NT	uHT	NT	uHT	NT
General population split(a)	14%	86%	6%	94%	25%	75%	19%	81%	33%	67%	24%	76%	37%	63%	42%	58%	43%	57%	42%	58%
Test positive rates(b)	75%	25%	75%	25%	75%	25%	75%	25%	75%	25%	75%	25%	75%	25%	75%	25%	75%	25%	75%	25%
% population positive test(c)	11%	22%	5%	24%	19%	19%	14%	21%	25%	17%	18%	19%	27%	16%	32%	15%	32%	14%	31%	15%
Prevalence of true HT among those with suspected HT(d)	33%		16%		49%		40%		59%		48%		63%		68%		69%		68%	

a) *estimated based on HSE 2006[28]; uHT = untreated hypertension (≥140/90 mmHg); NT = normotensive (<140/90 mmHg and untreated for hypertension).*

b) *Positive test among those with hypertension = sensitivity of screening reading; Positive test among those without hypertension = 1-specificity of screening reading; estimated based on meta analysis of CBPM sensitivity and specificity across all populations[275]*

c) *Calculated by multiplying general population % by test positive rate. For example, for 'Male, 35-44 years) = 14% x 75% = 11%.*

d) *Calculated by dividing % population positive test and uHT by total % population positive test. For example, for 'Male, 35-44 years' = 11%/(11%+22%) = 33%.*

J.2.3.3 Diagnosis inputs

Sensitivity and specificity of CBPM, HBPM and ABPM to confirm the diagnosis of hypertension

The sensitivity and specificity of CBPM, HBPM and ABPM are based on the meta analysis reported by Hodgkinson and colleagues[275] included in the systematic review of the clinical literature for the guideline. In this analysis a diagnostic threshold of 135/85 mmHg was used of ABPM and HBPM and 140/90 mmHg for CBPM which fits with international standards for hypertension diagnosis. It was recognised that the threshold for treatment of hypertension (as opposed to diagnosis) used in the previous and current NICE guidelines took account of cardiovascular risk between blood pressures 140-159/90-99 mmHg and that this was not taken account of in the model.

In line with the meta analysis, that assumed ABPM to be the reference standard test for hypertension, the sensitivity and specificity of ABPM were both assumed to be 100% in the base case for the cost-effectiveness analysis. The sensitivity and specificity of CBPM and HBPM (compared to ABPM) were based on the sensitivity analysis from the meta analysis that excluded studies with low mean blood pressure(i.e. that included a high proportion of normotensives)[275]; this analysis was considered to be most relevant for the population entering the model who have suspected hypertension. Data used is summarised in Table 115.

Table 115: Sensitivity and specificity of CBPM, HBPM and ABPM to confirm the diagnosis of hypertension

Method	Sensitivity	Specificity
CBPM	85.6% (95% CI 81.0 to 89.2)	45.9% (95% CI 33.0 to 59.3)
HBPM	85.7% (95% CI 78.0 to 91.0)	62.4% (95% CI 48.0 to 75.0)
ABPM	100%	100%

Source: Hodgkinson et al. meta analysis (sensitivity analysis excluding studies with low mean blood pressure)[275]; ABPM is assumed to be reference standard with 100% sensitivity and specificity

These sensitivity and specificity values were incorporated in the probabilistic analysis using the same method as described in the previous section.

As discussed in Section J.2.3.2 above, the sensitivity and specificity of HBPM and CBPM will vary with prevalence (and so age). However, there was considered insufficient information available to vary this input with age in the base-case analysis. An exploratory sensitivity analysis was however undertaken to examine this issue (see Section J.2.4). Other sensitivity analyses undertaken where sensitivities and specificities were varied are also described in Section J.2.4.

Failure rate with HBPM and ABPM

It was assumed in the analysis that HBPM would always provide a successful assessment of blood pressure. This was based on expert clinical opinion that the failure rate with HBPM was negligible.

It was assumed that ABPM would have a 5% failure rate in the base-case analysis. This was based on expert clinical opinion following consideration of failure rates observed in a number of clinical studies that ranged between 3% and 15%[178,223,253,372]. If ABPM failed it was assumed that people went on to have their diagnosis confirmed by CBPM instead.

These inputs were not varied probabilistically in the analysis as they were based on an informed assumption rather than a study there was no estimate of uncertainty around the mean estimate with which to parameterise a distribution and so instead. Varying the failures rates for ABPM and HBPM was examined in sensitivity analyses (see Section J.2.4).

Update 2011

Time until diagnosis is complete

In the model it was assumed that a diagnosis would take 3 months to be completed if CBPM was used, and 1 month if either ABPM or HBPM were used. This was on the basis that CBPM would take 2 further visits a month apart, ABPM would require 24hr monitoring, HBPM would require 1 week of monitoring and taking into consideration allowance for scheduling of appointments.

These inputs were not varied probabilistically in the analysis. Varying the time until diagnosis is complete for ABPM and HBPM was examined in sensitivity analysis (see Section J.2.4).

J.2.3.4 Cardiovascular risk and mortality

Cardiovascular risk with and without hypertension

Average cardiovascular risk was calculated by age group and gender for those with hypertension (≥140/90 mmHg) and without hypertension (<140/90 mmHg). Framingham risk equations were used. The JBS/BNF definition of cardiovascular disease was used, that is non-fatal myocardial infarction and stroke, coronary and stroke death and new angina pectoris. This was calculated using the Framingham CHD risk equation and the Framingham stroke risk equation using a risk calculator spreadsheet developed by the University of Edinburgh[44,480]. Resulting risk estimates used in the model are shown in Table 118 and Table 119, and displayed graphically in Figure 127 and Figure 128.

Risk factor inputs for each age group, by gender, were obtained from the HSE 2006[28,422]. The mid-point of each age range was used. Average total cholesterol and HDL cholesterol were available from the HSE 2006 report[28]. The proportion of people who smoked and had diabetes was also available from the same report[28]. Data of LVH was not available and was assumed to be 0% for the purposes of calculations. These inputs are summarised in Table 116.

The total cholesterol and HDL cholesterol inputs were incorporated into the probabilistic analysis. A gamma distribution was used initially to reflect the feasible range (bounded by zero) but as the standard errors were small relative to the means the software often returned an error (a programming issue with Excel). Therefore a normal distribution was used instead – a normal distribution is not bounded by 0 but as the standard error of the estimate is small the distribution will be tight and not vary far from the point estimate, and therefore will not go below zero. This was parameterised using the mean and standard error.

The percentages of people who had diabetes and who were smokers were also incorporated in the probabilistic analysis. Beta distributions were used to reflect the feasible range for a proportion (bounded by zero and one). These were parameterised using alpha (calculated as the proportion multiplied by the n number) and beta (calculated as n number minus alpha). The HSE analysis incorporated a weighting that attempted to reduce non-response bias. The results from the weighted analysis were used for the proportion; however the unweighted n numbers were used when calculating alpha and beta as these were judged to more appropriately reflect the uncertainty in the estimates.

Ideally, the uncertainty in the coefficients in the Framingham risk equations would also be incorporated into the model; however, this was not possible as the appropriate covariance matrices were not available to do so.

Update 2011

Update 2011

Table 116: Cardiovascular risk factors by age and gender

	35-44		45-54		55-64		65-74		75+	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Age(a)	40	40	50	50	60	60	70	70	75	75
Total cholesterol(b)	5.6 (0.04)	5.2 (0.03)	5.7 (0.05)	5.7 (0.04)	5.6 (0.04)	6.1 (0.04)	5.2 (0.06)	5.9 (0.05)	4.9 (0.07)	5.6 (0.07)
HDL cholesterol(c)	1.3 (0.01)	1.6 (0.01)	1.4 (0.02)	1.7 (0.02)	1.4 (0.02)	1.7 (0.02)	1.3 (0.02)	1.6 (0.02)	1.3 (0.02)	1.7 (0.02)
Smoker(d)	28% (1178)	23% (1490)	24% (1046)	24% (1278)	19% (1123)	20% (1269)	14% (852)	13% (933)	9% (600)	8% (895)
Diabetes(e)	2.4% (1183)	1.2% (1494)	6.0% (1050)	3.6% (1279)	8.5% (1126)	6.0% (1268)	15.7% (437)	10.4% (470)	13.5% (317)	10.6% (470)
LVH(f)	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

a) *Mid-point of range (except 75+ - as risk tables are technically not valid over 75 years will conservatively use an age of 75 for this group)*
b) *HSE 2006 Table 10.3 Total cholesterol, by age and sex. Mean (standard error) (including those taking lipid lowering drugs) (mmol/l)*
c) *HSE 2006 Table 10.8 HDL-cholesterol, by age and sex. Mean (standard error) (including those taking lipid lowering drugs) (mmol/l)*
d) *HSE 2006 Table 8.1 Cigarette smoking status, by age and sex. Current cigarette smoker. Proportion (unweighted n number).*
e) *HSE 2006 Table 4.1 Prevalence of doctor-diagnosed diabetes (type 1 and 2), by age and sex. Types 1 and 2 combined. Proportion (unweighted n number).*
f) *LVH not reported in HSE 2006. Assumed 0% for risk calculations.*

The remaining risk factor required for the risk estimation equations was blood pressure. Average blood pressure for each age group, by sex, for those with hypertension (BP ≥140/90 mmHg) and without hypertension (BP <140/90 mmHg) was calculated using HSE 2006 individual level data as the published report did not report this information. Untreated people were used for calculations. Definitions used were as described in the HSE 2006 report. In HSE, blood pressure was measured three times in a single nurse visit. The blood pressure variables used in this analysis was the same as those used in the main HSE 2006 report; that is, the means of the second and third measurements obtained from the informants in whom three readings were successfully obtained, excluding those that had eaten, drunk alcohol, or smoked in the 30 minutes before the measurement was taken. The HSE analysis incorporated a weighting that attempted to reduce non-response bias; this was also incorporated in this analysis. The results are shown in Table 117.

Table 117: Average systolic blood pressure for untreated hypertensive and normotensive individuals by age and gender

		Normotensive untreated				Hypertensive untreated			
Sex	**Age**	**Mean**	**N(a)**	**SD**	**SE**	**Mean**	**N**	**SD**	**SE**
Men	**35-44**	123	670	8.3	0.32	144	113	7.8	0.74
	45-54	124	457	8.8	0.41	150	150	12.1	0.99
	55-64	125	332	9.3	0.51	151	164	10.9	0.85
	65-74	125	181	10.2	0.76	154	104	13.5	1.32
	75+	123	110	10.7	1.02	157	83	15.3	1.67
Women	**35-44**	115	769	10.2	0.37	147	55	11.8	1.59
	45-54	118	518	11.1	0.49	149	117	14.4	1.33
	55-64	121	411	10.7	0.53	153	127	12.5	1.11
	65-74	124	185	10.7	0.78	156	135	13.3	1.15
	75+	126	164	11.6	0.91	156	120	13.0	1.19

(a) Weighted based (study n following weighting to account for non-response bias)

Source: Analysis of HSE 2006 dataset[422]; normotensive = <140/90 mmHg (untreated); hypertensive = ≥140/90 mmHg (untreated)

Systolic blood pressure inputs were incorporated into the probabilistic analysis. A gamma distribution was used initially to reflect the feasible range (bounded by zero) but as the standard errors were small relative to the means the software often returned an error (a programming issue with Excel). Therefore a normal distribution was used instead – a normal distribution is not bounded by 0 but as the standard error of the estimate is small the distribution will be tight and not vary far from the point estimate, and therefore will not go below zero. This was parameterised using the mean and standard error.

Uncertainty in the CHD and stroke risk equations was not incorporated into the probabilistic analysis. The appropriate covariance matrices for the regression coefficients were not available to allow this to be done appropriately.

10-year CHD and stroke risk was generated by the equations (see Table 118 and Table 119). This was converted to monthly or 3-monthly probabilities for application in the model using the standard formula.

Instantaneous rate = -(LN[1-'10-year probability'])/120

Probability over X months = 1-EXP(-rate*'X months')

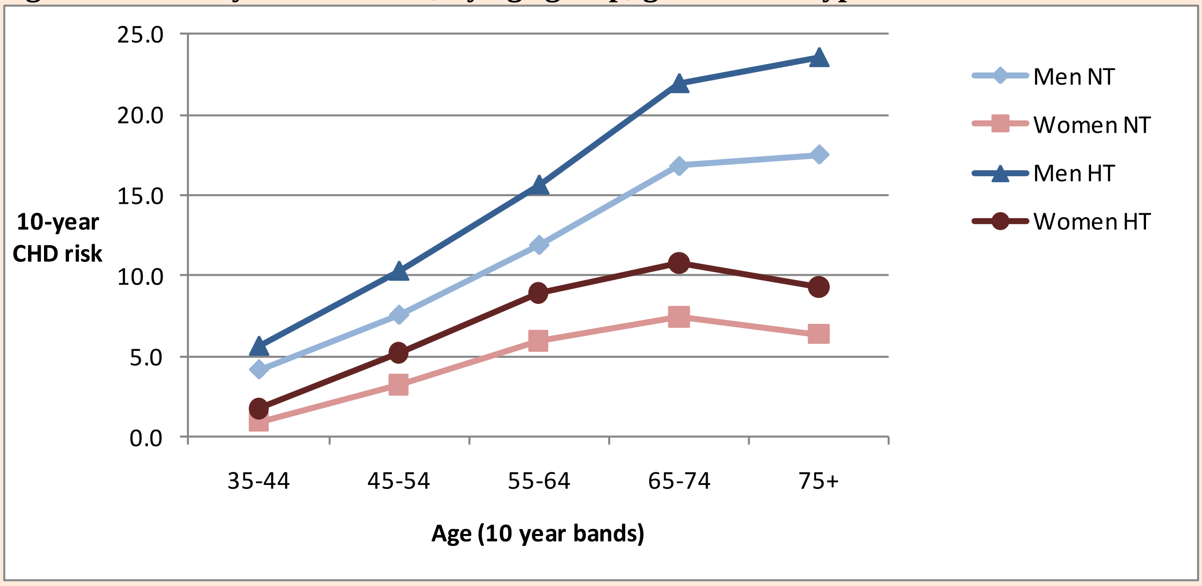
Update 2011

Table 118: 10-year CHD risk, by age group, gender and hypertension status

Normotensive		Smoker		Non-smoker		Overall
Sex	**Age**	**Diabetes**	**No Diabetes**	**Diabetes**	**No Diabetes**	
Men	**35-44**	8.6	6.1	4.9	3.3	**4.1**
	45-54	14.3	10.7	8.9	6.3	**7.5**
	55-64	21.0	16.4	14.0	10.4	**11.9**
	65-74	27.6	22.3	19.5	15.1	**16.8**
	75+	29.1	23.7	20.8	16.2	**17.5**
Women	**35-44**	4.0	1.6	2.0	0.7	**0.9**
	45-54	10.1	4.8	6.0	2.5	**3.2**
	55-64	16.0	8.5	10.2	4.9	**5.9**
	65-74	18.9	10.5	12.4	6.2	**7.4**
	75+	17.3	9.3	11.1	5.4	**6.4**
Hypertensive		**Smoker**		**Non-smoker**		**Overall**
Sex	**Age**	**Diabetes**	**No Diabetes**	**Diabetes**	**No Diabetes**	
Men	**35-44**	11.1	8.1	6.6	4.6	**5.6**
	45-54	18.4	14.1	12.0	8.8	**10.3**
	55-64	26.0	20.9	18.2	13.9	**15.6**
	65-74	33.9	28.2	25.1	20.0	**21.9**
	75+	36.5	30.6	27.4	22.1	**23.6**
Women	**35-44**	6.5	2.8	3.6	1.4	**1.7**
	45-54	14.5	7.5	9.1	4.2	**5.2**
	55-64	21.6	12.4	14.5	7.5	**8.9**
	65-74	24.8	14.7	17.1	9.2	**10.8**
	75+	22.7	13.2	15.4	8.1	**9.3**

Update 2011

Figure 127: 10-year CHD risk, by age group, gender and hypertension status



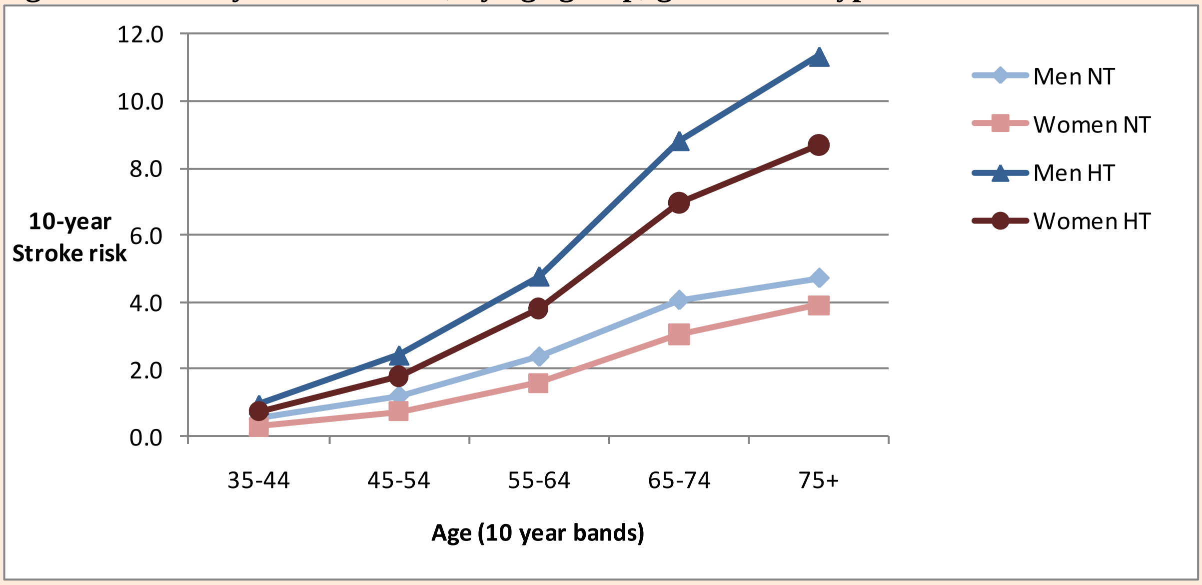
CHD = coronary heart disease; HT = hypertensive; NT = normotensive

Table 119: 10-year stroke risk, by age group, gender and hypertension status

Normotensive		Smoker		Non-smoker		Overall
Sex	**Age**	**Diabetes**	**No Diabetes**	**Diabetes**	**No Diabetes**	
Men	**35-44**	1.24	0.77	0.68	0.42	**0.5**
	45-54	2.84	1.77	1.56	0.97	**1.2**
	55-64	5.62	3.53	3.12	1.95	**2.4**
	65-74	9.47	6.00	5.30	3.33	**4.0**
	75+	11.47	7.30	6.46	4.06	**4.7**
Women	**35-44**	1.02	0.42	0.56	0.23	**0.3**
	45-54	2.53	1.06	1.39	0.58	**0.7**
	55-64	5.43	2.29	3.01	1.26	**1.6**
	65-74	10.13	4.34	5.68	2.40	**3.0**
	75+	13.40	5.80	7.57	3.22	**3.9**
Hypertensive		**Smoker**		**Non-smoker**		**Overall**
Sex	**Age**	**Diabetes**	**No Diabetes**	**Diabetes**	**No Diabetes**	
Men	**35-44**	2.22	1.39	1.22	0.76	**1.0**
	45-54	5.65	3.55	3.13	1.96	**2.4**
	55-64	11.18	7.11	6.29	3.96	**4.8**
	65-74	20.00	12.96	11.50	7.31	**8.8**
	75+	26.33	17.31	15.41	9.88	**11.3**
Women	**35-44**	2.61	1.09	1.44	0.60	**0.7**
	45-54	6.11	2.58	3.39	1.42	**1.8**
	55-64	12.69	5.48	7.16	3.04	**3.8**
	65-74	22.29	9.94	12.90	5.57	**7.0**
	75+	28.04	12.76	16.48	7.20	**8.7**

Update 2011

Figure 128: 10-year stroke risk, by age group, gender and hypertension status



HT = hypertensive; NT = normotensive

In the model different cardiovascular events were each associated with different quality of life, costs and subsequent increased risk of mortality. CHD events were split into non-fatal MI, unstable angina (UA) and stable angina (SA) and CHD death. Stroke events were split into non-fatal stroke and TIA, and stroke death. The distribution of events used were based on those used for the NICE statins HTA model; these were estimated based using UK incidence data supplemented by expert opinion where necessary[59,170,574,626]. A distribution was not reported for the age band 35-44 and so this was assumed to be the same as in the 45-54 age band. These inputs were not varied probabilistically in the model. Uncertainty in the estimates were not reported by Ward et al.; going back to the original data sources may have allowed some estimation of this, although this was also supplemented by assumptions. However, these inputs were considered unlikely to have a significant impact on results and so it was not judged warranted to try to implement them probabilistically.

Table 120: Distribution of CHD events and stroke events

Gender	Age	CHD events				Stroke events		
		SA	UA	MI	CHD death	TIA	Stroke	Stroke death
Men	35-44	39.4%	13.7%	37.8%	9.1%	27.4%	58.9%	13.7%
	45-54	39.4%	13.7%	37.8%	9.1%	27.4%	58.9%	13.7%
	55-64	49.9%	10.8%	26.2%	13.1%	25.9%	60.1%	14.0%
	65-74	37.7%	14.6%	30.5%	17.1%	23.1%	62.4%	14.5%
	75+	38.5%	16.3%	32.5%	12.7%	15.9%	68.2%	15.9%
Women	35-44	58.1%	20.9%	14.3%	6.6%	36.1%	51.7%	12.2%
	45-54	58.1%	20.9%	14.3%	6.6%	36.1%	51.7%	12.2%
	55-64	62.9%	13.3%	16.7%	7.1%	21.1%	64.0%	14.9%
	65-74	44.3%	11.4%	26.5%	17.8%	13.4%	70.1%	16.5%
	75+	45.4%	10.4%	31.1%	13.1%	14.6%	69.2%	16.2%

Source: Ward et al. (NICE statins HTA mode)l[626]
CHD events: SA + UA + MI + CHD death = 100%. Stroke events: TIA + stroke + stroke death = 100%
CHD = coronary heart disease; MI = myocardial infarction; SA = stable angina; TIA = transient ischemic attack; UA = unstable angina.

Sensitivity analyses were used to examine the impact of higher CV risk in the population (see Section J.2.4).

Cardiovascular risk reduction with treatment

In the base-case analysis, people who are hypertensive and receiving treatment (that is true positive diagnoses) get cardiovascular risk reduction from being on treatment.

The risk reduction used in the model was based on the meta analysis reported by Law and colleagues[351] that presented relative risks for CHD events and stroke stratified by pretreatment systolic blood pressure (120-180 in 10mmHg increments) or pretreatment diastolic blood pressure (75-110 in 5mmHg increments), age (40-90 in 10 year increments), and number and dose of drugs (1-3 drugs, at half or standard dose).

Average risk reductions were calculated for use in the model for each age and gender stratified subgroup based on the average untreated systolic blood pressure in each group and the split between usage of one, two and three drugs. In the base case it was assumed that standard doses were used. Average untreated blood pressure for each subgroup was based on the analysis of the HSE 2006 dataset described above (Table 117)[422]. The split between usage of one, two and three drugs was based on that reported in the HSE 2006 as summarised in Table 130[28].

CHD events in the meta analysis were defined as “fatal or non-fatal myocardial infarction or sudden cardiac death but excluding ‘silent’ infarcts”. In the model this risk reduction was

Update 2011

applied to all CHD events (MI, UA, SA and CHD death). Stroke was defined in the meta analysis as “one or more strokes”. In the model this risk reduction was applied to all stroke events (stroke, TIA, stroke death).

Table 121: Relative risk of CHD and stroke events with antihypertensive treatment applied in model if hypertensive

	Relative risk for CHD events		Relative risk for stroke events	
	M	**F**	**M**	**F**
35-44	0.668	0.633	0.565	0.526
45-54	0.643	0.641	0.543	0.543
55-64	0.654	0.648	0.564	0.556
65-74	0.685	0.661	0.601	0.573
75+	0.717	0.700	0.717	0.700

Source: *Average risk reductions calculated based on Law et al. meta analysis[351], and systolic blood pressure and drug usage data from HSE 2006[28,422]*

In the model the risk reduction was implemented by applying the relative risk to the instantaneous rates and recalculating the probabilities as described above.
Relative risk inputs were incorporated into the probabilistic analysis using lognormal distributions. These were parameterised using the confidence intervals for the relative risk reductions[352]. The percentages of people on one, two or three drugs was also varied in the probabilistic analysis. These were incorporated into the probabilistic analysis for each age group using Dirichlet distributions using the unweighted study participant total multiplied by the proportion from the weighted analysis. The HSE analysis incorporated a weighting that attempted to reduce non-response bias. The results from the weighted analysis were used for the proportion; however the unweighted n numbers were used as these were judged to more appropriately reflect the uncertainty in the estimates.
In addition, two sensitivity analyses were undertaken to explore the impact of calculating risk reductions based on the meta analysis results for half standard doses and of applying a risk reduction to those who are not hypertensive (normotensive) and receiving treatment (see Section J.2.4).

Non-cardiovascular mortality

Age-dependant mortality in the model was based on rates from interim life tables for England and Wales[459]. Rates were adjusted by multiplying by the percentage of non-circulatory deaths based on national mortality data by cause, as shown in Table 122[460]. These inputs were not varied probabilistically in the analysis as rates are based on national data the level of uncertainty in the model input was considered to be very low and did not warrant incorporation.

Table 122: Non-cardiovascular mortality as a percentage of all mortality

Deaths by age		35-44	45-54	55-64	65-74	75+
All cause	M	6419	12269	27093	47862	79799
	F	3811	8291	18187	33883	77827
Circulatory (ICD10: 100-199)	M	1286	3627	8128	15356	28831
	F	514	1307	3220	8557	27334
Non-circulatory death as % of all deaths	M	80%	70%	70%	68%	63%
	F	87%	84%	82%	75%	63%

Source: *Office for National Statistics, 2008[460]*

Mortality post-cardiovascular event

Once people had experienced a non-fatal cardiovascular event and so entered one of the cardiovascular event health states they were attributed a higher mortality rate. This higher rate was implemented by applying relevant standardised mortality ratios (all cause mortality) to age-dependant general population mortality rates from England and Wales life tables. Standardised mortality rates were identified from the literature and those used are summarised in Table 123.

Table 123: Standardised mortality ratios for cardiovascular events

Event	SMR (95% CI)	Source
MI	2.68 (2.48-2.91)*	Average of SMRs for men and women. All cause mortality after first non-fatal MI compared to that expected in general population. Danish population[103].
UA	2.19 (2.05-2.33)*	Weighted average of SMRs for UA/NSTEMI with and without new MI at 6 months. UA/NSTEMI NICE guideline[423]. Validated using Fox et al. age adjusted HR for mortality with UA compared to SA was 1.1.
SA	1.95 (1.65-2.31)	Age-adjusted relative risk for death from any cause in men with angina (compared to men free from clinical CHD). 16-year follow-up Swedish general population sample. Rosengren[515]
Stroke	2.72 (2.59-2.85)*	Average of SMRs for men and women. All cause mortality after first non-fatal stroke compared to that expected in general population. Danish population.[102]
TIA	1.4 (1.1-1.8)	Risk ratio for mortality in people with TIA compared to that expected in those without TIA (age and sex matched). UK population. Oxfordshire Community Stroke Project[169]

**CI from Monte Carlo simulation*

Where more than one estimate was identified the decision about which estimate to use took into account the size of the study, the country the study was carried out in, how long the follow-up was and when the study was carried out.

These inputs were incorporated into the probabilistic analysis using lognormal distributions parameterised using the confidence intervals [352].

J.2.3.5 Becoming hypertensive over time

In the model people could become hypertensive over time. The probability of becoming hypertensive in a cycle was calculated by 10-year age bands based on the HSE 2006 data on the prevalence of hypertension[28]. These are summarised in Table 124.

The probability of becoming hypertensive in a particular 10-year age band was calculated taking the percentage increase in hypertension from the current age band to the next age band, and dividing it by the percentage of normotensive people in the current age band. This 10-year probability was then converted to a 3-month probability using the standard formula. As 75+ was the highest age band reported in the HSE 2006 it was not possible to calculate the probability of becoming hypertensive in this age band and it was assumed to be the same as in the 65-74 age band.

Table 124: Probability of becoming hypertensive in a 10-year age band if normotensive

Gender	Age band	10-year probability (n)	Per cycle (3-month) probability
Male	35-44	21% (715)	0.60%
	45-54	20% (663)	0.55%
	55-64	25% (739)	0.70%
	65-74	15% (592)	0.41%

Update 2011

Gender	Age band	10-year probability (n)	Per cycle (3-month) probability
	75+	Assumed equal to 65-74	0.41%
Female	35-44	18% (965)	0.11%
	45-54	19% (810)	0.12%
	55-64	38% (870)	0.28%
	65-74	16% (638)	0.10%
	75+	Assumed equal to 65-74	0.10%

Source: Calculated based on prevalence of hypertension data from HSE 2006[28]

These inputs were incorporated into the probabilistic analysis using beta distributions. Beta distributions were used to reflect the feasible range for a proportion (bounded by zero and one). These were parameterised using alpha (calculated as the proportion multiplied by the n number) and beta (calculated as n number minus alpha). The HSE analysis incorporated a weighting that attempted to reduce non-response bias. The results from the weighted analysis were used for the proportion; however the unweighted n numbers were used when calculating alpha and beta as these were judged to more appropriately reflect the uncertainty in the estimates.

J.2.3.6 Re-diagnosis over time

It was assumed in the model that people who are diagnosed as not having hypertension have their blood pressure rechecked every 5 years. It is assumed that all people in the population will be suspected of having hypertension again at this check-up and will be re-diagnosed using the same method as previously - either repeated CBPM, HBPM or ABPM. If ABPM or HBPM failed initially and so the patient was diagnosed using CBPM, it is assumed that CBPM is used again at re-diagnosis. Sensitivity and specificity of diagnosis were assumed to be the same.

This input was not varied probabilistically in the analysis. Varying the frequency of blood pressure check-ups was examined in sensitivity analysis (see Section J.2.4).

J.2.3.7 Quality of life (utilities)

General population quality of life (utilities)

Quality of life weights (utilities) were applied to patients in the model based on general population estimates stratified by age and gender (Table 125). This was obtained by analysing the HSE 2006 dataset[422]. It was assumed that having hypertension does not reduce quality of life in itself as it is generally asymptomatic; reductions in quality of life were however applied once a patient had experienced a cardiovascular event (see 'Quality of life following a cardiovascular event' below).

Update 2011

Table 125: General population quality of life (EQ5D utility)

Sex	Age in ten year bands	Mean EQ5D	SEM
Men	35-44	0.909	0.005
	45-54	0.869	0.007
	55-64	0.832	0.008
	65-74	0.804	0.011
	75+	0.751	0.013
Women	35-44	0.897	0.005
	45-54	0.848	0.007
	55-64	0.812	0.008

Sex	Age in ten year bands	Mean EQ5D	SEM
	65-74	0.780	0.010
	75+	0.704	0.011

Source: Analysis of HSE 2006 dataset[422]

General population utilities were incorporated into the probabilistic analysis using beta distributions. This is bounded by 0 and 1 – although utility can technically go below 0 the values being used here are far from 0 and so this was considered reasonable.

On-treatment quality of life

In the base-case analysis it was assumed that there was no impact on utility of being on anti-hypertensive therapy. This was because side effects of treatment are generally fairly mild, and those that do experience side effects can often change to a different drug that is better tolerated, and also because no utility data was identified to quantify any loss.
A series of sensitivity analyses were undertaken where a range of utility decrements was applied when patients were treated (see Section J.2.4).

Quality of life following a cardiovascular event

Quality of life weights (utilities) were applied multiplicatively to the general populations weights once people had experienced an event in the model. The values used were from the NICE statins HTA model – these were identified by a comprehensive literature search[626]. These are summarised in Table 126 including the original data sources that were cited.

Table 126: Quality of life (utilities) following cardiovascular events

Event	Utility (SE)	Source
MI	0.760 (0.018)	Goodacre[234]
UA	0.770 (0.038)	Goodacre[234]
SA	0.808 (0.038)(a)	Melsop[403]
Stroke	0.629 (0.04)	Tengs[588]
TIA	1	Assumed no difference to population norms
Dead	0	By definition

a) SE assumed to be equal to UA

Source: Ward et al. NICE Statins HTA assessment report[626]

Update 2011

Cardiovascular event utilities (except TIA and dead) were incorporated into the probabilistic analysis using beta distributions. This is bounded by 0 and 1 – although utility can technically go below 0 the values being used here are far from 0 and so this was considered reasonable.

J.2.3.8 Resource use and costs

Cost of diagnosis

The costs per person of confirming a diagnosis with CBPM, HBPM and ABPM used in the base-case analysis were £38.00, £39.13 and £53.40 respectively. The basis for these costs is described below with summaries of resource use in Table 127, and unit costs in Table 128 (healthcare visits) and Table 129 (device costs per use). Where costs included VAT this was removed in line with NICE methodological guidelines for cost-effectiveness analysis[427].
Probabilistic analysis aims to take account in uncertainty about the true mean estimate and not variability in the input. These inputs were not incorporated probabilistically into the analysis as they were based on standard national cost sources and estimated typical resource use. However, as these costs may be variable depending on the method of implementation of ABPM a series of sensitivity analyses were undertaken around the assumption made

regarding the costs of CBPM, HBPM and ABPM; these are described in Section Section J.2.4.

It was assumed that all patients will have an initial set of CBPM readings that identified them as potentially having hypertension and so eligible to enter the model. As this is common to all three comparators in the model this cost is not included in the analysis.

The cost of confirming a diagnosis with CBPM was based on the recommendation in this guideline that 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 is 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.

The cost of confirming a diagnosis with HBPM was based on the recommendation that measurements should ideally be taken for 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.

The cost of confirming a diagnosis with ABPM was based on the recommendation that measurement should be taken for 24hrs. 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.

Table 127: Resource use for diagnosis confirmation by CBPM, HBPM and ABPM

Cost element	Associated resource use	Cost per diagnosis
Diagnosis confirmation based on CBPM‡	Consultation 1 (CBPM)† • Practice nurse appointment Consultation 2 (CPBM +/- treatment consultation)† • GP appointment	£38.00
Diagnosis confirmation based on HBPM	Consultation 1 (train patient in HBPM) • Practice nurse appointment 7 days HBPM • HBPM monitor use Consultation 2 (review results +/- treatment consultation) • GP appointment	£39.13
Diagnosis confirmation based on ABPM	Consultation 1 (fit ABPM monitor) • Practice nurse appointment 24hrs ABPM • ABPM monitor use Download data • Practice nurse appointment Consultation 2 (review results +/- treatment consultation) • GP appointment (review results +/- treatment consultation)	£53.40

†It is recommend that following an initial high BP reading CBPM is done at least twice more at monthly intervals to confirm diagnosis.

‡The cost of the CBPM monitor is not included 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.

The unit costs applied for healthcare visits are summarised in Table 128 below.

Table 128: Healthcare visits unit costs

Item	Unit cost	Source
Practice nurse appointment	£10	Nurse (GP practice), per surgery consultation (15.5 mins). PSSRU 2010 unit costs[486]
GP appointment	£28	GP, per surgery consultation (11.7 mins) (Cost excluding direct care staff costs). PSSRU 2010 unit costs[486].

The HBPM and ABPM device costs per use were estimated taking into account the cost of the devices, estimated typical usage per year, calibration/servicing costs, battery costs and cuff costs. Inputs used to calculate costs are summarised in Table 129 below. Device costs were based on prices listed in the NHS supply chain catalogue[30]. Uses per year were estimated by the clinical members of the GDG taking into account the time HBPM and ABPM takes (7 days and 24hrs respectively) and allowing for some time lapse between uses. It was acknowledges that in individual settings uses may be higher or lower depending on demand and this input was varied in sensitivity analyses (see Section J.2.4). Other inputs were also varied as deemed useful.

Table 129: HBPM and ABPM device costs per use

Monitor costs	HBPM	ABPM	Source(a)
Purchase cost per device	£42	£1,016	Median from NHS supply chain catalogue; for HBPM only monitors also on the BHS list of validated devices suitable for home use were used[30,100].
Device lifetime (years)	5	5	Assumption.
Resale value	£0.00	£0.00	Assumption.
Discount (interest rate)	3.5%	3.5%	
Annuitisation factor	467.3%	467.3%	Calculated based on above rate[183].
Equivalent annual cost	£8.99	£217.42	
Uses per year	40	125	Expert opinion.
Cost per use	**£0.22**	**£1.74**	
Calibration/servicing costs	**HBPM**	**ABPM**	**Source**
Calibration/service	£9.17	£380.00	HBPM: Personal communication South Birmingham PCT ABPM: Calibration, servicing and insurance covering parts. Average of two estimates (£460 and £300).
Frequency (years)	1	1	Expert opinion.
Annual cost	£9.17	£380.00	
Cost per use	**£0.23**	**£3.04**	
Battery costs	**HBPM**	**ABPM**	**Source**
No. batteries per monitor	4	3	Expert opinion.
Uses from batteries	7	6	Expert opinion.
Cost of batteries	£0.27	£0.27	1.5 volt size AA / LR6 battery high power alkaline. NHS supply chain catalogue (£2.68 per pack of 10, if purchasing 10+ packs)[30].
Annual cost	£6.13	£16.75	
Cost per use	**£0.15**	**£0.13**	
Cuff costs	**HBPM**	**ABPM**	**Source**
Cost of cuff	£16	£16	Median cost of adult cuff with or without hose/connector. NHS supply chain catalogue[30].
No. regular cuffs per year	1	2	Expert opinion.
No. large cuffs per year	0.5	2	Expert opinion.
Annual cost	£20.80	£60.80	Averaged across device lifetime allowing for one

			regular cuff included with monitor.
Cost per use	**£0.52**	**£0.49**	
Total costs	**HBPM**	**ABPM**	**Source**
Total annual cost	£45.08	£674.97	
Total cost per use	**£1.13**	**£5.40**	

a) VAT excluded

Cost of hypertension treatment

The annual cost of hypertension treatment was assumed to consist of antihypertensive drug therapy and an annual check up with the GP (as recommended in the guideline). The cost of hypertension treatment was applied to all alive patients (that is those who had and had not experienced a CV event). Typical average antihypertensive drug costs were calculated taking into account the percentage of people on one, two or three-plus drugs by 10-year age band and gender based on the HSE 2006 report[28]. For each age-band, typical drug classes (ACEi/ARB, CCB and diuretic) were assigned when on one, two or three drugs based on the guideline recommended treatment algorithm. Costs for each class were based on BNF 60 costs for the most commonly used drug in each class with optimal doses provided by clinical GDG members; ramipril 10mg (ACEi/RB), amlopidpine 10mg (CCB), bendroflumethiazide 2.5mg (diuretic)[306,593]. Drug costs are summarised in Table 130. An annual check-up was estimated to cost £28 based on the average UK cost of a GP appointment[486]. The percentages of people on one, two or three drugs was varied in the probabilistic analysis; drug costs and check-up units costs were not as these were taken from standard national sources. These were incorporated into the probabilistic analysis for each age group using Dirichlet distributions using the unweighted study participant total multiplied by the proportion from the weighted analysis. The HSE analysis incorporated a weighting that attempted to reduce non-response bias. The results from the weighted analysis were used for the proportion; however the unweighted n numbers were used as these were judged to more appropriately reflect the uncertainty in the estimates.

Update 2011

Table 130: Cost of antihypertensive drug treatment, by 10-year age band and gender

		Men				**Women**			
	Number of drugs	**1**	**2**	**3+**	**Average**	**1**	**2**	**3+**	**Average**
35-54	**No. drugs (%)**	52%	38%	12%		53%	37%	10%	
	A	*100%*	*100%*	*100%*		*100%*	*100%*	*100%*	
	C	*0%*	*50%*	*100%*		*0%*	*50%*	*100%*	
	D	*0%*	*50%*	*100%*		*0%*	*50%*	*100%*	
	Cost/pat/year	£20.73	£35.98	£51.23	**£30.06**	£20.73	£35.98	£51.23	**£29.20**
55-64	**No. drugs (%)**	48%	32%	20%		42%	39%	19%	
	A	*0%*	*100%*	*100%*		*0%*	*100%*	*100%*	
	C	*50%*	*50%*	*100%*		*50%*	*50%*	*100%*	
	D	*50%*	*50%*	*100%*		*50%*	*50%*	*100%*	
	Cost/pat/year	£15.25	£35.98	£51.23	**£28.75**	£15.25	£35.98	£51.23	**£30.06**
65-74	**No. drugs (%)**	37%	40%	23%		38%	41%	20%	
	A	*0%*	*100%*	*100%*		*0%*	*100%*	*100%*	
	C	*50%*	*50%*	*100%*		*50%*	*50%*	*100%*	
	D	*50%*	*50%*	*100%*		*50%*	*50%*	*100%*	
	Cost/pat/year	£15.25	£35.98	£51.23	**£31.74**	£15.25	£35.98	£51.23	**£31.20**
75+	**No. drugs (%)**	32%	49%	19%		28%	48%	24%	

		Men				Women			
	A	*0%*	*100%*	*100%*		*0%*	*100%*	*100%*	
	C	*50%*	*50%*	*100%*		*50%*	*50%*	*100%*	
	D	*50%*	*50%*	*100%*		*50%*	*50%*	*100%*	
	Cost/pat/year	£15.25	£35.98	£51.23	**£32.56**	£15.25	£35.98	£51.23	**£33.64**

A = ACEi/ARB; C = calcium channel blocker; D = diuretic

Source: Percentage of patients on 1, 2 or 3 drugs based on HSE 2006[28]; Drug type used based on guideline recommended treatment algorithm; Costs based on ramapril 10mg (A), amlopidpine 10mg (C), bendroflumethiazide 2.5mg (D) and BNF 60 costs[306].

Cost of cardiovascular events

When people in the model experienced a cardiovascular event they were assigned an initial cost in the first cycle representing the acute management and/or diagnosis cost. In subsequent post-event cycles they were assigned an ongoing cost representing the average costs following an event. The costs used are summarised in Table 131 and the basis for them described in more detail following the table. The cost of hypertension treatment described above was also applied for alive patients.

Table 131: Cost of cardiovascular events per 3 month cycle

Event	Initial event cost (first cycle)	Post-event costs (subsequent cycles)	Source
MI	£4792	£141	Palmer et al.[474] inflated to 2009/10[486];assumption from hypertension guideline 2006 Pharmcological update[425] inflated to 2009/10[486]
UA	£2875	£85	Assumed to be 60% of MI costs
SA	£400	£6	Assumption & BNF 60[306]
Stroke	£9630	£559	Youman et al.[649] inflated to 2009/10[486]
TIA	£992	£26	Lipids HTA[626] inflated to 2009/10[486] & BNF 60[306]

Cost data was sought from national cost sources and published studies by non-systematic searches. The lipids HTA undertook a systematic search for data for these health states and so this was taken as a starting point[626]. The sources and assumptions made for the drugs model undertaken as part of the 2006 pharmacological update of this guideline were also reviewed. Few studies were identified providing suitable data.

The initial cost of stroke and post-event costs applied in the model was based on a study by Youman and colleagues, inflated to 2009/10 costs[486,649]. Youman and colleagues modelled the cost of stroke over 5 years. This was based on data from a UK study that collected hospital, other health service and social services use and discharge setting up to 1 year. Their model incorporated recurrent events. The initial cost of stroke was based on a weighted average of the acute cost of mild, moderate and severe stroke from this analysis weighted by the severity distribution. This was calculated over 3 months in the analysis which matched the cycle length in the model. Post-stroke costs per 3-month cycle were calculated by subtracting the acute costs from the total 5-year costs and dividing by 19 (in 5 years there would be twenty 3-month cycles, but the first is the acute period and so is removed). Using this study was considered better than trying to estimate costs using more recent NHS reference costs as it would be difficult to appropriately incorporate all the relevant costs for stroke such as rehabilitation and social care. As described above, the Youman costing study extrapolated one-year UK data – a 2009 review of stoke costing studies based on patient-level data suggested that no longer terms, more recent UK studies were available to inform a cost estimate[375].

The initial cost of TIA covers clinical assessment, diagnostic tests and procedures in those that require them plus pharmacological management for secondary prevention. Some patients

Update 2011

will be admitted to hospital due to the acute event but many will not and will undergo assessment in outpatient clinics. The cost applied in the model was based on the tests and procedures cost estimated by expert opinion as part of the Lipids HTA inflated to 2009/10 costs (£966)[626] plus drug costs calculated based on recommended treatments based on relevant NICE guidelines[428,432] and current drug prices from BNF 60(£26 per 3 months – modified-release dipyridamole, low dose aspirin and simvastatin 40mg[306,428,432]). The cost of assessment, tests and procedures above was similar to the current average UK cost of a hospitalisation for TIA (£854)[174]. Post-TIA only the cost of drugs was applied. Note that the cost of hypertension management was also still applied in all alive patients (drug costs and 1 GP visit per year). It is noted that this approach potentially underestimated post-TIA costs as it does not incorporate recurrent events.

The initial cost of MI applied in the model was based on an estimate reported by Palmer and colleagues, inflated to 2009/10 costs[474,486]. The post-MI cost applied in the model was based on the assumption made in the 2006 analysis for pharmacological update to the guideline that the costs post-MI were £500 per year, inflated to 2009/10 costs[425,486]. Palmer and colleagues estimated the cost of MI up to 1 year based on data from the Nottingham Heart Attack Register. This recorded hospital resource use (cardiac and non-cardiac stays and angiography, PCI and CABG interventions). The initial MI cost for the 3 month cycle was calculated by assuming that costs post 3 months were constant and any excess costs occurred in the first 3 months; as such 9 months post-MI costs were subtracted from the 1 year MI costs from Palmer et al to give the initial MI cost. Using this study was considered better than trying to estimate costs using more recent NHS reference costs as it would be difficult to appropriately incorporate all the relevant costs for MI that occur post-discharge such as planned coronary intervention and cardiac rehabilitation.

Limited information was available about the cost of managing an unstable angina event and subsequent costs post-event. The cost of an unstable angina (UA) event and costs post-event were assumed to be 60% of the costs of MI. The justification for this was that unstable angina is an acute coronary syndrome that requires emergency medical attention and is managed in the same way as a non-ST elevation MI[423]. Patients are however likely to be at the lower end of the disease severity spectrum and therefore it is likely that a lower proportion will undergo invasive procedures such as angiography, PCI and CABG hence the cost will be lower.

Limited information was available about the initial cost of diagnosing stable angina and the subsequent costs. The NICE chest pain guideline describes how a diagnosis of stable angina would be reached[431]; this might be clinical assessment alone, a CT scan, non-invasive functional imaging or coronary angiography. These have varying cost with a standard GP consultation being as low as £28 and elective coronary angiography costing nearly £2000[174,486]. An outpatient cardiology appointment costs £163[174]. Outpatient imaging is typically in the range of £100-£300. In the model an average cost of £400 per patient was assumed for the initial costs of stable angina taking into account an outpatient assessment plus non-invasive imaging as a typical package of care. Ongoing management comprised drugs to ease symptoms and reduce CV risk. After the initial stable angina cycle only drug costs were applied (as for TIA). Drug costs were estimated based on relevant NICE guidance[424,428] and BNF 60 costs[306] (£6 per 3 months – glyceryl trinitrate spray, low dose aspirin, simvastatin 40mg). Note that the cost of hypertension management is also still applied in all alive patients (drug costs and 1 GP visit per year). It is noted that this potentially underestimates ongoing costs as this does not incorporate further complications of CVD.

These costs were not incorporated probabilistically into the analysis. The majority were derived from estimated typical resource use and standard national cost sources and so uncertainty information was not available; these inputs were considered unlikely to have a significant impact on results and so were judged not to warrant implementation

Update 2011

probabilistically. They were varied in sensitivity analyses to look at the impact of higher and lower costs being used (see Section J.2.4).

Cost of follow-up in those diagnosed as not having hypertension

The cost of checkups for those not diagnosed as having hypertension applied in the model was £28 based on the average UK cost of a GP appointment[486]. This cost was not incorporated probabilistically into the analysis as it was taken from standard national cost sources.

J.2.4 Sensitivity analyses

Sensitivity analyses were performed for the subgroup 'Male, aged 60 years' using the deterministic analysis unless otherwise specified. Below is a summary of the sensitivity analyses that were performed.

Diagnostic costs

The cost of diagnosis with the different comparators was a key input in the model (see Section J.2.3.8 for full details of how this cost was calculated). In the base case the GDG aimed to estimate typical costs. However, it was acknowledged that there were uncertainties in this estimate and variations that would depend on how or where ABPM or HBPM were implemented. For this reason a wide range of sensitivity analyses were carried out to explore the impact of these uncertainties. These are summarised in Table 132 along with the revised cost per diagnosis that resulted. Additional unit costs employed to calculate the cost per diagnosis are presented in Table 133.

Table 132: Sensitivity analysis inputs – cost per diagnosis

ID	Sensitivity analysis description	CBPM	HBPM	ABPM
Base case (for comparison)				
BC	Base case	£38.00	£39.13	£53.40
Device cost per use sensitivity analyses				
SA1	Lower (half) ABPM and HBPM monitor acquisition cost	£38.00	£39.01	£52.53
SA2	Lower (half) ABPM and HBPM servicing costs	£38.00	£39.01	£50.88
SA3	Maximum uses per year: ABPM (156 = 3/week)); HBPM (52 = 1/week)	£38.00	£38.90	£52.35
SA4	Same uses per year for ABPM as HBPM (40/year)	£38.00	£39.13	£64.59
SA5	SA1, SA2 and SA3 combined	£38.00	£37.73	£50.44
SA6	Low usage per year (10 per year in both) and cuffs required reduced accordingly (1 regular and 1 large over 5 years in both)	£38.00	£40.29	£108.20
SA7	ABPM lifetime longer (10 years) (HBPM not changing – 5 years)	£38.00	£39.13	£52.62
SA8	Training costs added in for ABPM	£38.00	£39.13	£53.72
SA9	Training costs added in for ABPM and HBPM	£38.00	£40.13	£54.36
Healthcare visits sensitivity analyses				
SA10	All appointments with GP	£56.00	£57.13	£89.40
SA11	All appointments with nurses (last with nurse prescriber)	£24.00	£25.13	£39.40
SA12	Three appointments required to confirm diagnosis with CBPM	£48.00	£39.13	£53.40
SA13	Four appointments required to confirm diagnosis with CBPM	£58.00	£39.13	£53.40
SA1	Five appointments required to confirm diagnosis with CBPM	£68.00	£39.13	£53.40

Update 2011

ID	Sensitivity analysis description	CBPM	HBPM	ABPM
4				
Other sensitivity analyses				
SA15	ABPM via direct access at hospital (replaces appointment 1 and practice nurse part of appointment 2; appointment 3 with GP still required to review results and have treatment consultation if required)	£38.00	£39.13	£84.00

Table 133: Sensitivity analysis inputs – additional diagnosis unit costs

Item	Unit cost	Source
Nurse practitioner appointment	£14	Nurse advanced (includes lead specialist, clinical nurse specialist, senior specialist), per consultation (15 mins). PSSRU 2010 unit costs[486].
ABPM at hospital (direct access)	£56	Direct Access: Diagnostic Services: DA09 24 Hour ECG/BP Monitoring. NHS reference costs[174].
Total training costs per year with HBPM or ABPM	£120	Based on assumption that if see 125 cases of suspected hypertension per year then would have 4 nurses requiring training, 3hrs training per year, £10/hr time. Assume training provided by device manufacturer. Assumed spread across 1 ABPM or 3 HPBM devices.

Failure rates for ABPM and HBPM

There was limited data to inform the estimates of failure rates for ABPM and HBPM. This was therefore varied in a series of sensitivity analyses as described in Table 134.

Table 134: Sensitivity analysis inputs – failures rates

Heading	Base case	SA16	SA17	SA18
HBPM	0%	0%	5%	0%
ABPM	5%	10%	5%	0%

Time until diagnosis complete

In the model base-case analysis it was assumed that if a diagnosis was made using CBPM it would take 3 months to complete but if made using HBPM or ABPM it would take only 1 month to complete. This meant that patients diagnosed with HBPM or ABPM in the model received treatment quicker and thus also received the costs and risk reductions from treatment sooner. However, there was concern from some clinicians as to whether the delay to diagnosis would in reality translate to a difference in CV events and so a sensitivity analysis was undertaken where time to diagnosis was set to 3 months for all comparators (SA19).

Prevalence true hypertension among population entering model (suspected hypertension)

As described in the model inputs section J.2.3.2, due to a lack of data there was considerable uncertainty in the model inputs around the prevalence of true hypertension among the population entering the model with suspected hypertension. On this basis a series of sensitivity analyses were run where the prevalence was varied between 10% and 80%. This sensitivity analysis was run for all subgroups using the deterministic analysis (SA41–90).

Sensitivity and specificity

ABPM set same as HBPM (SA20):

The underlying assumption in the meta analysis used to inform sensitivity and specificity and in the model was that ABPM is the reference standard test for confirming a diagnosis of hypertension with 100% sensitivity and specificity. To test this assumption an extreme case

Update 2011

sensitivity analysis was undertaken where the sensitivity and specificity of ABPM was set equal to HBPM – thus modelling no difference in accuracy between them.

Sensitivity set to 100% for all three options (SA21):

A sensitivity analysis was run where the sensitivity model input for all three comparators was set at 100%. Specificity was as in the base-case analysis. This effectively models a scenario where all options are equally effective at accurately identifying those with hypertension as having hypertension and they only vary in terms of being able to accurately diagnose those without hypertension as not having hypertension.

Varying HBPM sensitivity and specificity (SA22-29):

A series of analyses was undertaken where the sensitivity and specificity of HBPM where varied between the base-case inputs and 100% to see if there was a level of sensitivity and specificity at which HBPM became more cost effective than ABPM. Specificity was varied to 70%, 80%, 90% and 100% (base-case input 62.4%). Sensitivity was varied to 90%, 95% and 100% (base-case input 85.7%).

Sensitivity and specificity varied by age (SA91-100):

As discussed in the model inputs section J.2.3.3, the sensitivity and specificity of HBPM and CBPM compared to the reference standard ABPM will vary with prevalence (and so age). However, there was considered insufficient information available to vary this input with age in the base-case analysis. An exploratory sensitivity analysis was run where the sensitivity and specificity valued were altered in order to simulate a scenario where sensitivity and specificity vary with age (to reflect the variation in prevalence of true hypertension with age). The deterministic analysis was used.

In the base-case analysis the sensitivity and specificity of CBPM, HBPM and ABPM were based on a sensitivity analysis from the meta analysis reported by Hodgkinson and colleagues[275] (see section J.2.3.3 for details). In this sensitivity analysis, these values were retained for the middle age group in the model (55-65 years). For the lower age groups (35-44 and 45-54 years), that most likely have a lower prevalence of true hypertension, the sensitivity for CBPM and HBPM was reduced by 5% and the corresponding specificity was estimated from the Roc curves reported by Hodgkinson and colleagues. For the higher age groups (65-74 and 75+ years), that most likely have a higher prevalence of true hypertension, the sensitivity for CBPM and HBPM was increased by 5% and the corresponding specificity was estimated from the Roc curves reported by Hodgkinson and colleagues. The sensitivity and specificity of ABPM were assumed to be 100%. The values used are summarised in Table 135.

Update 2011

Table 135: Sensitivity analysis inputs – Sensitivity and specificity of CBPM, HBPM and ABPM to confirm the diagnosis of hypertension varying with age

Age groups	Method	Sensitivity	Specificity
35-44 years **45-54 years**	**CBPM**	81%	58%
	HBPM	81%	70%
	ABPM	100%	100%
55-64 years *(sensitivity and specificity as in base case)*	**CBPM**	85.6%	44.9%
	HBPM	85.7%	62.4%
	ABPM	100%	100%
65-74 years **75+ years**	**CBPM**	91%	20%
	HBPM	91%	48%
	ABPM	100%	100%

Sensitivity and specificity varied by age and prevalence of true hypertension adjusted (SA101-110):

A second exploratory sensitivity analysis was undertaken where sensitivity and specificity were varied by age as described above and in addition the prevalence of hypertension was varied from the base case.

The prevalence true hypertension among the population entering model (suspected hypertension) was varied from the base case by decreasing it by 20% in the lower age groups (35-44 and 45-54 years) and increasing it by 20% in the higher age groups (65-74 and 75+ years). The middle age group was not changed from the base case.

Table 136: Sensitivity analysis inputs – adjusted prevalence true hypertension among population entering model (suspected hypertension)

Age group	Gender	Base case value	% change	New value
35-44 years	Male	33%	-20%	26%
	Female	16%		13%
45-54 years	Male	49%		40%
	Female	40%		32%
55-64 years	Male	59%	0%	59%
	Female	48%		48%
65-74 years	Male	63%	+20%	75%
	Female	68%		82%
75+ years	Male	69%		83%
	Female	68%		81%

Treatment effect

Risk reductions based on half standard dose (instead of based on standard dose; from Law et al meta analysis) (SA29):

As described in Section J.2.3.4, the risk reductions used in the model were based on the meta analysis reported by Law and colleagues[351] that presented relative risks for CHD events and stroke stratified by pretreatment systolic blood pressure (120-180 in 10mmHg increments) or pretreatment diastolic blood pressure (75-110 in 5mmHg increments), age (40-90 in 10 year increments), and number and dose of drugs (1-3 drugs, at half or standard dose). In the base-case analysis, CV risk reductions were calculated using the standard dose results. A sensitivity analysis was undertaken with risk reductions calculated using the half-standard dose results instead.

Risk reduction applied for those not hypertensive as well as those hypertensive (SA30):

A key assumption of the model was that only patients with hypertension obtained a risk reduction from being treated – that is people who were normotensive but treated (due to being misdiagnosed) did not get any benefit from treatment. In a sensitivity analysis, a cardiovascular risk reduction was also applied to people who normotensive and who were receiving treatment (that is false positive diagnoses). The relative risks were calculated in the same way as for people with hypertension (see model input section J.2.3.4) except that the systolic blood pressures used were those for people who were normotensive. This resulted in a lower risk reduction for this group of people. The values used are summarised in Table 137.

Update 2011

Table 137: Sensitivity analysis inputs: relative risk of CHD and stroke events with antihypertensive treatment

	Relative risk for CHD events				Relative risk for stroke events			
	Hypertensive		Normotensive(a)		Hypertensive		Normotensive(a)	
	M	F	M	F	M	F	M	F
35-44	0.668	0.633	0.740	0.737	0.565	0.526	0.650	0.65
45-54	0.643	0.641	0.748	0.743	0.543	0.543	0.667	0.665
55-64	0.654	0.648	0.718	0.75	0.564	0.556	0.640	0.68
65-74	0.685	0.661	0.779	0.782	0.601	0.573	0.714	0.717
75+	0.717	0.700	0.823	0.779	0.717	0.700	0.823	0.779

a) Normotensive risk reduction only applied in sensitivity analysis

Source: *Average risk reductions calculated based on Law et al. meta analysis[351], and systolic blood pressure and drug usage data from HSE 2006[28,422]*

CV risk

CV risk increased by multiple of 1.4 in all people (SA31)

In certain patient groups it is recommended that risk estimates from the Frammingham risk are increased. For example a multiplication of 1.4 is recommended for people of Asian background[428]. On this basis a sensitivity analysis was undertaken where risk estimates for both hypertensive and normotensive people in the model were increased by a multiple of 1.4.

CV risk increased by multiple of 2 in people with hypertension only (SA32)

Risk was estimated in the model using average population characteristics for all risk factors apart from blood pressure. It is possible however that people with hypertension may be more likely to have other risk factors than those without hypertension and so the method used potentially underestimates CV risk. On this basis, a sensitivity analysis was undertaken where risk estimates for people with hypertension were doubled. Risk estimates for people without hypertension were not changed.

Update 2011

Check-up frequency for those diagnosed as not hypertensive

In the base-case analysis it was assumed that patients who were diagnosed without hypertension would have a check-up every 5 years. However, some patients may be followed up more frequently and so a sensitivity analysis was undertaken where these patients were followed up every year (SA33).

Quality of life (utility) impact of treatment

In the base-case analysis it was assumed that there was no detrimental impact on quality of life (utility) of being on anti-hypertensive therapy. However, this was considered a potentially conservative assumption and so a series of sensitivity analyses was undertaken where a utility decrement of 1% (SA34), 2% (SA35), 5% (SA36) and 10% SA37) was applied to all patients on treatment.

HT treatment costs

In the base case, drug costs were potentially conservative as they were estimated based on the non-proprietary cost of the most commonly used drug in the recommended drug classes (Section A.2.3.8 for full details). Healthcare visits were based on the recommended follow-up of once a year which may also be conservative in terms of what happens in the real world, for example in the control groups of a recent trial, consultation rates for hypertension were higher[401]. A sensitivity analysis was therefore run with higher treatment costs. This incorporated a 30% increase in drug costs and four GP visits per year (SA38) – the revised costs used are summarised in Table 138.

Table 138: Sensitivity analysis inputs – higher cost of hypertension treatment per year (drug costs and healthcare visits)

	Base case(a)		Sensitivity analysis(b)	
	Men	**Women**	**Men**	**Women**
35-44	£58.06	£57.20	£151.08	£149.97
45-54	£58.06	£57.20	£151.08	£149.97
55-64	£56.75	£58.06	£149.38	£151.08
65-74	£59.74	£59.20	£153.26	£152.56
75+	£60.56	£62.64	£154.33	£155.73

a) Incorporating drug costs based on ramipril 10mg, amlopidpine 10mg, bendroflumethiazide 2.5mg and one GP visit per year (see Section J.2.3.8 for full details).
b) Incorporating a 30% increase in drug costs and four GP visits per year.

CVD costs

As described in Section J.2.3.8, there was limited data to inform CVD costs in the model. Two sensitivity analyses were therefore undertaken where these costs were adjusted. In one costs were increased by 30% (SA39) and one where they were reduced by 30% (SA40).

J.2.5 Computations

The model was constructed in Microsoft Excel and was evaluated by cohort simulation. People started in cycle 0 distributed between the two suspected hypertension states as described above. During cycle 1, patients were redistributed as follows. A set of five transition matrices (35-44, 45-54, 55-64, 65-74, 75+) were computed for each of the three comparators that contained transition probabilities for all movements within the model except age-dependant mortality (non-cardiovascular death from suspected hypertension and diagnosed states, and all-cause mortality from cardiovascular disease states). Each cycle, the age-dependant death rates were applied to all those alive in the model and then the relevant transition matrix (as determined by the cohorts starting age and the current cycle) was applied in order to recalculate the number of people in each state.

Total QALYs for each comparator were calculated from the above information as follows. Each cycle, the time spent (i.e. 3 months) in each state of the model was weighted by the quality of life weight (utility) for that state. This gives the QALYs for each state for the cycle. These were summed to give the total QALYs per cycle and discounted to reflect time preference (formula below). The total discounted QALYs was the sum of the discounted QALYs per cycle. The same process was used to calculate costs using state dependant costs.

$\text{Discounted total} = \dfrac{\text{Total}}{(1+r)^n}$	Where: r = discount rate per annum n = time (years)

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with two alternatives by the difference in QALYs (formula below). The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$\text{ICER} = \dfrac{\text{Costs(B)} - \text{Costs(A)}}{\text{QALYs(B)} - \text{QALYs(A)}}$ Where: Costs/QALYs(X) = total discounted costs/QALYs for option X	• Cost-effective if: ICER < Threshold

When there are more than two comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NMB was used to identify the optimal strategy in the probabilistic analysis simulations.

$$\text{Net monetary benefit}(X) = (\text{QALYs}(X) \times D) - \text{Costs}(X)$$ *Where: Costs/QALYs(X) = total discounted costs/QALYs for option X; D = threshold*	• Cost-effective if: highest net monetary benefit

The probabilistic analysis was run for 1000 simulations. Each simulation, total discounted costs and total discounted QALYs were calculated for each diagnosis option. Net benefit was also calculated and the most cost-effective option identified (that is, the one with the highest net benefit), at a threshold of £20,000 per QALY gained. The results of the probabilistic analysis were summarised in terms of mean costs, mean QALYs and mean net benefit for each treatment option, where each was the average of the 1000 simulated estimates. The option with the highest mean net benefit (averaged across the 1000 simulations) was the most cost-effective at the specified threshold. The percentage of simulations where each strategy was the most cost-effective gives an indication of the strength of evidence in favour of that strategy being cost-effective.

J.2.6 Interpreting results

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[429,429].

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

c) 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

d) The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

J.2.7 Validation

The model was developed in consultation with the GDG and the Birmingham research group; model structure, inputs and results were presented to and discussed with the GDG and research group for clinical and technical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model methods and results were peer reviewed by the lead economist in the research group. The model was also peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of many of the model calculations.

Update 2011

J.3 Results

J.3.1 Base-case analysis

In the base-case analysis, confirming a diagnosis of hypertension with ABPM following an initial raised screening blood pressure was the most cost-effective option in all age/gender subgroups. Results are summarised in Table 19, and shown graphically in Figure 129. Breakdowns of clinical events and costs are presented in Table 140 and Table 141. A summary of the number of people initially misdiagnosed is presented in Table 142, and how misdiagnosis changes over time is illustrated in Figure 130 and Figure 131.

In most subgroups ABPM was associated with higher QALYs and 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 had lower costs but was associated with a small reduction in QALYs; however, ABPM was still the most cost effective option. In these subgroups QALYs were similar between the comparators and the small QALYs gain associated with CBPM/HBPM did not justify the additional cost; the cost-effectiveness ratios for CBPM compared to ABPM were above the threshold typically considered cost effective of £20,000-£30,000 per QALY gained.

As can be seen by looking at the breakdown of costs in Table 141, the savings with ABPM compared with CBPM and HBPM were primarily due to the hypertensive treatment costs that are avoided due to the higher specificity of ABPM; that is the ability of ABPM to correctly diagnose those without hypertension as not having hypertension. These savings offset the additional diagnostic costs associated with ABPM in all subgroups. The differences in magnitude of cost savings is primarily dependent on the prevalence of true hypertension input for the subgroup, which varies with age (this can be seen by looking at the sensitivity analysis results in Table 136 where the prevalence is varied through a wide range). The lower the prevalence of true hypertension in the subgroup the higher the cost savings will be. This is because the lower the prevalence of true hypertension in the subgroup the higher the number of people without hypertension – and this is the group effected by the specificity of the monitoring method. In the model base-case analysis the prevalence of true hypertension in the population of people suspected of having hypertension generally increases with age.

QALY differences also vary between subgroups. QALYs are driven by the number the cardiovascular events experienced by the population (this can be seen in Table 140). These are influenced by a number of inputs in the model the most straightforward being the sensitivity of the monitoring method; that is the ability of it to correctly diagnose those with hypertension as having hypertension. The more people with hypertension that are correctly diagnosed, the more that receive treatment and the associated cardiovascular risk reduction that will lead to a reduction in cardiovascular events. In the model ABPM has the highest sensitivity and so more people are correctly diagnosed and get the risk reduction they need. With ABPM and HBPM risk reduction is also received sooner than with CPBM as diagnosis is quicker. However, in addition because many people become hypertensive over time, many people will eventually need treatment. If people are treated (albeit unnecessarily) before they are hypertensive, it means that they may avoid being hypertensive and untreated in the period before they next have their blood pressure check-up. This means that less-specific tests have the unexpected advantage in the model of some people getting treatment, and so CV risk reduction, sooner. Due to the high rate of development of hypertension over time this effect is not insignificant. As ABPM is the most specific test as well as the most sensitive, this effect works to counteract some of the benefits of accurately diagnosing people with hypertension. The relative balance of these effects depends on the prevalence of true hypertension in the population entering the model and this varies by subgroup (in general it increases with age). When the prevalence of true hypertension is high, the effects related to test sensitivity will have a greater influence, and when prevalence is low the effects related to test specificity will

Update 2011

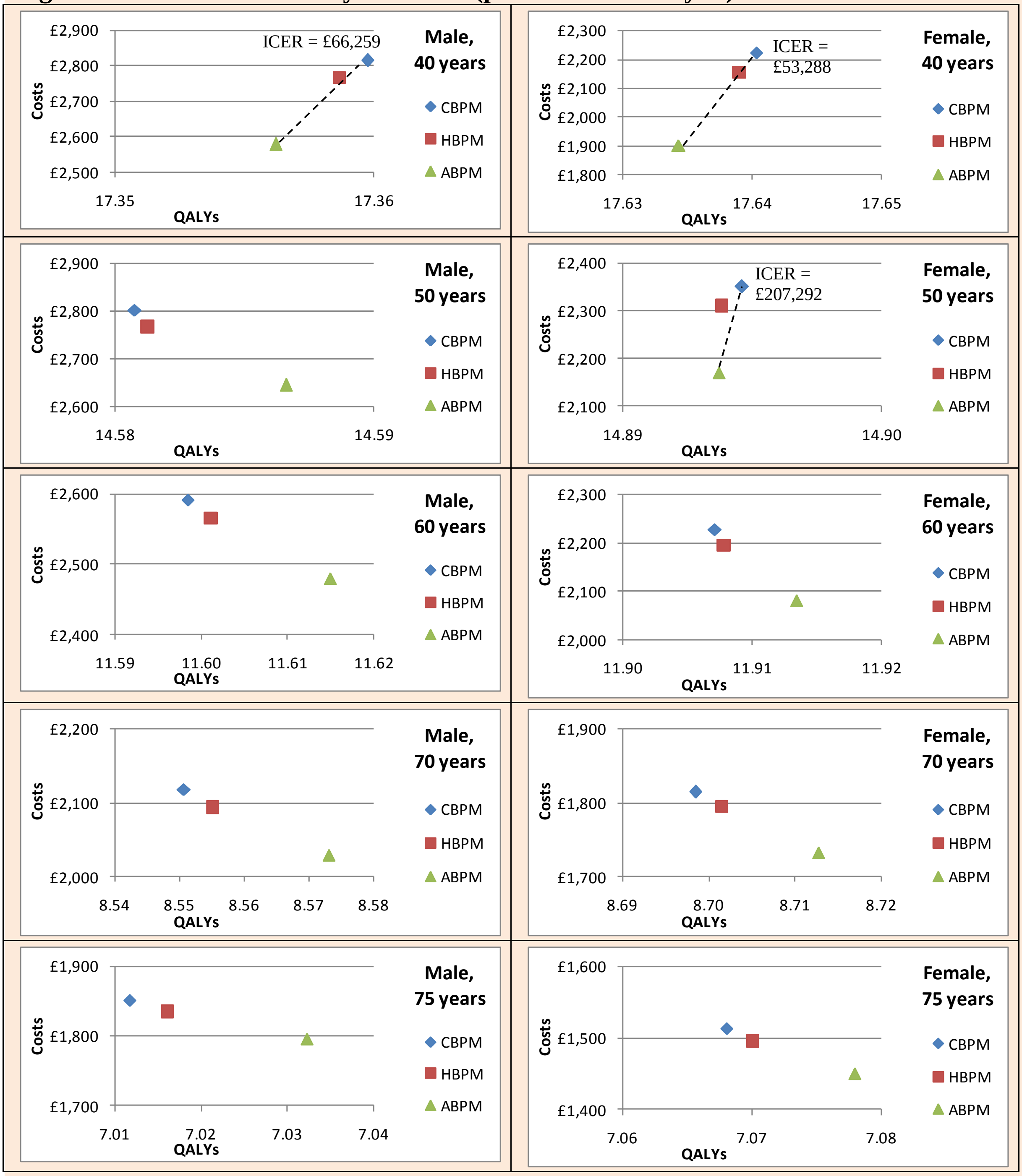
play a greater role. Note that the analysis does not take incorporate any quality of life reduction for patients of being on treatment in the base case.

Table 139: Base-case 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.

Figure 129: Base-case analysis results (probabilistic analysis) – cost effectiveness



ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.
Where a line is shown this represents the cost-effectiveness frontier and the ICER displayed is for the higher cost intervention (CBPM) compared to the lower cost intervention (ABPM). In all other scenarios ABPM dominates (higher QALYs and lower costs).

Update 2011

Table 140: Base-case analysis results (probabilistic analysis) – clinical outcome breakdown

	Cardiovascular events per 1000					Mean per person		
	MI	UA	SA	Stroke	TIA	Life years	QALYs	Disc. QALYs
Male, 40 years								
CBPM	124.8	55.2	162.5	69.3	23.3	39.17	31.55	17.36
HBPM	124.9	55.2	162.6	69.3	23.3	39.16	31.55	17.36
ABPM	125.1	55.3	163.0	69.4	23.3	39.15	31.54	17.36
Male, 50 years								
CBPM	113.5	52.0	153.7	70.5	22.9	30.45	23.91	14.58
HBPM	113.5	52.0	153.7	70.5	22.9	30.45	23.91	14.58
ABPM	113.4	52.0	153.8	70.5	22.9	30.46	23.92	14.59
Male, 60 years								
CBPM	99.9	48.0	131.2	69.2	21.0	22.36	17.16	11.60
HBPM	99.9	48.0	131.1	69.1	21.0	22.37	17.16	11.60
ABPM	99.7	47.9	130.5	68.9	20.9	22.39	17.18	11.62
Male, 70 years								
CBPM	82.1	40.7	98.6	62.0	16.5	15.30	11.48	8.55
HBPM	82.0	40.7	98.4	61.8	16.4	15.31	11.49	8.56
ABPM	81.4	40.4	97.7	61.2	16.2	15.34	11.52	8.57
Male, 75 years								
CBPM	70.5	35.5	83.7	58.6	13.7	12.28	9.04	7.01
HBPM	70.4	35.4	83.5	58.5	13.6	12.29	9.04	7.02
ABPM	69.7	35.0	82.6	57.8	13.5	12.32	9.06	7.03
Female, 40 years								
CBPM	45.8	26.7	104.1	66.4	17.3	42.00	32.98	17.64
HBPM	45.8	26.8	104.3	66.5	17.3	42.00	32.98	17.64
ABPM	46.0	27.0	105.1	66.7	17.4	41.99	32.96	17.63
Female, 50 years								
CBPM	44.9	23.4	96.5	68.1	16.4	32.95	25.09	14.89
HBPM	45.0	23.5	96.6	68.1	16.4	32.95	25.09	14.89
ABPM	45.1	23.5	96.8	68.2	16.4	32.95	25.08	14.89
Female, 60 years								
CBPM	41.6	17.8	75.8	65.1	14.0	24.34	18.01	11.91
HBPM	41.6	17.8	75.7	65.1	14.0	24.34	18.02	11.91
ABPM	41.6	17.7	75.4	64.9	14.0	24.35	18.03	11.91
Female, 70 years								
CBPM	32.9	11.9	50.1	57.6	11.9	16.61	11.89	8.70
HBPM	32.9	11.9	50.0	57.4	11.9	16.61	11.89	8.70
ABPM	32.5	11.7	49.4	56.7	11.7	16.63	11.91	8.71
Female, 75 years								
CBPM	26.9	9.0	39.3	50.7	10.7	13.30	9.26	7.07
HBPM	26.8	8.9	39.2	50.6	10.7	13.30	9.26	7.07
ABPM	26.5	8.8	38.7	49.9	10.5	13.32	9.27	7.08

Update 2011

Disc. QALYs = discounted quality-adjusted life years (3.5% per annum); MI = myocardial infarction; QALYs = quality-adjusted life years; SA = stable angina; TIA = transient ischemic attack; UA = unstable angina.

Table 141: Base-case analysis results (probabilistic analysis) – cost breakdown (mean per person)

	Diag-nosis	Treat-ment	No HT FU	MI	UA	SA	Stroke	TIA	Total cost	Disc. Cost
Male, 40 years										
CBPM	£58	£2,119	£15	£1,450	£386	£119	£2,171	£58	£6,378	£2,815
HBPM	£74	£2,023	£25	£1,451	£387	£119	£2,173	£58	£6,309	£2,767
ABPM	£184	£1,524	£69	£1,453	£387	£119	£2,177	£59	£5,973	£2,580
Male, 50 years										
CBPM	£54	£1,647	£12	£1,147	£322	£104	£1,996	£53	£5,335	£2,801
HBPM	£65	£1,583	£18	£1,146	£322	£104	£1,996	£53	£5,288	£2,768
ABPM	£137	£1,285	£44	£1,143	£322	£104	£1,991	£53	£5,078	£2,645
Male, 60 years										
CBPM	£51	£1,208	£9	£860	£259	£80	£1,679	£43	£4,189	£2,591
HBPM	£59	£1,164	£14	£859	£258	£80	£1,677	£43	£4,154	£2,566
ABPM	£108	£982	£29	£855	£257	£79	£1,663	£42	£4,016	£2,479
Male, 70 years										
CBPM	£49	£811	£8	£599	£187	£53	£1,216	£28	£2,950	£2,117
HBPM	£55	£778	£11	£597	£187	£52	£1,211	£28	£2,920	£2,094
ABPM	£90	£665	£20	£592	£185	£52	£1,194	£28	£2,825	£2,029
Male, 75 years										
CBPM	£47	£646	£6	£472	£149	£42	£1,031	£21	£2,414	£1,851
HBPM	£51	£625	£9	£470	£149	£42	£1,027	£21	£2,394	£1,835
ABPM	£78	£559	£13	£465	£147	£41	£1,011	£21	£2,336	£1,795
Female, 40 years										
CBPM	£63	£2,265	£19	£509	£227	£82	£2,161	£46	£5,372	£2,224
HBPM	£85	£2,128	£33	£509	£228	£82	£2,165	£46	£5,276	£2,156
ABPM	£232	£1,442	£95	£512	£229	£83	£2,181	£47	£4,822	£1,901
Female, 50 years										
CBPM	£56	£1,800	£13	£468	£178	£72	£2,077	£40	£4,704	£2,352
HBPM	£70	£1,719	£22	£468	£178	£72	£2,080	£40	£4,648	£2,312
ABPM	£154	£1,355	£54	£469	£178	£72	£2,083	£40	£4,403	£2,170
Female, 60 years										
CBPM	£54	£1,322	£11	£387	£112	£50	£1,755	£29	£3,721	£2,227
HBPM	£63	£1,263	£17	£387	£112	£50	£1,754	£29	£3,676	£2,195
ABPM	£126	£1,007	£38	£385	£111	£50	£1,743	£29	£3,489	£2,081
Female, 70 years										
CBPM	£49	£906	£8	£259	£60	£28	£1,255	£21	£2,586	£1,815
HBPM	£55	£877	£11	£258	£60	£28	£1,249	£21	£2,558	£1,795
ABPM	£89	£768	£19	£254	£59	£28	£1,225	£21	£2,464	£1,733
Female, 75 years										
CBPM	£48	£716	£7	£190	£40	£20	£973	£18	£2,013	£1,513
HBPM	£53	£691	£10	£190	£40	£20	£969	£18	£1,990	£1,496
ABPM	£83	£607	£16	£187	£39	£20	£953	£17	£1,923	£1,450

Update 2011

Disc. cost = discounted total cost (3.5% per annum); MI = myocardial infarction; No HT FU = follow-up in those diagnosed as not hypertensive; SA = stable angina; TIA = transient ischemic attack; UA = unstable angina.

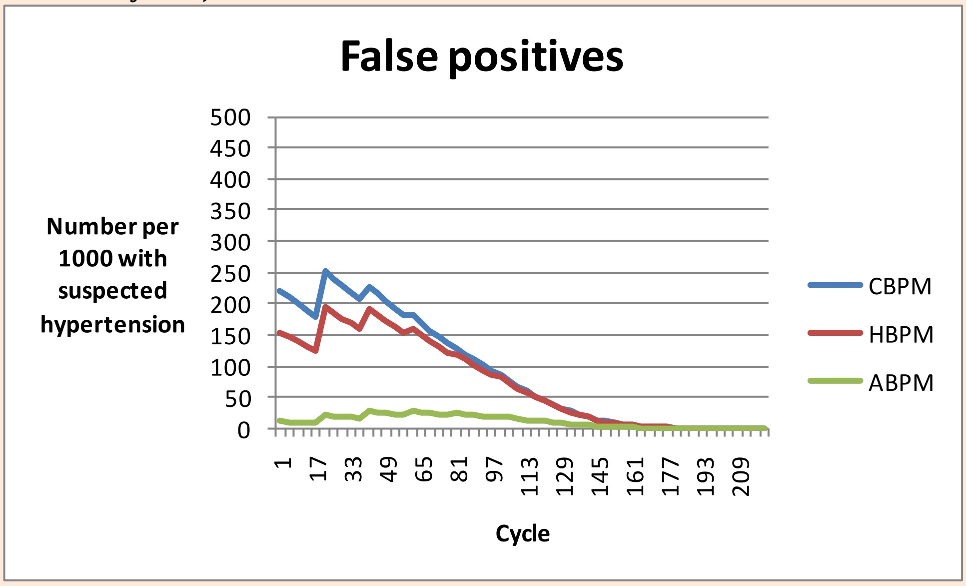
Table 142: Initial misdiagnosis per 1000 people with suspected hypertension (deterministic)

	False positives	False negatives	Total misdiagnosed per 1000 with suspected hypertension	False positives	False negatives	Total misdiagnosed per 1000 with suspected hypertension
40 years	**Male**			**Female**		
CBPM	363	47	410	452	24	476
HBPM	252	47	299	314	23	338
ABPM	18	2	20	23	1	24
50 years	**Male**			**Female**		
CBPM	273	71	344	323	58	380
HBPM	189	70	260	224	57	282
ABPM	14	4	17	16	3	19
60 years	**Male**			**Female**		
CBPM	221	84	305	279	69	349
HBPM	153	84	237	194	69	263
ABPM	11	4	15	14	3	17
70 years	**Male**			**Female**		
CBPM	200	89	289	171	97	269
HBPM	139	89	227	119	97	216
ABPM	10	4	14	9	5	13
75 years	**Male**			**Female**		
CBPM	165	98	263	174	96	270
HBPM	114	97	212	121	96	216
ABPM	8	5	13	9	5	14

Table shows the number of people misdiagnosed (false positives and false negatives) at the end of the initial diagnosis period; that is after 1 cycle in the model.

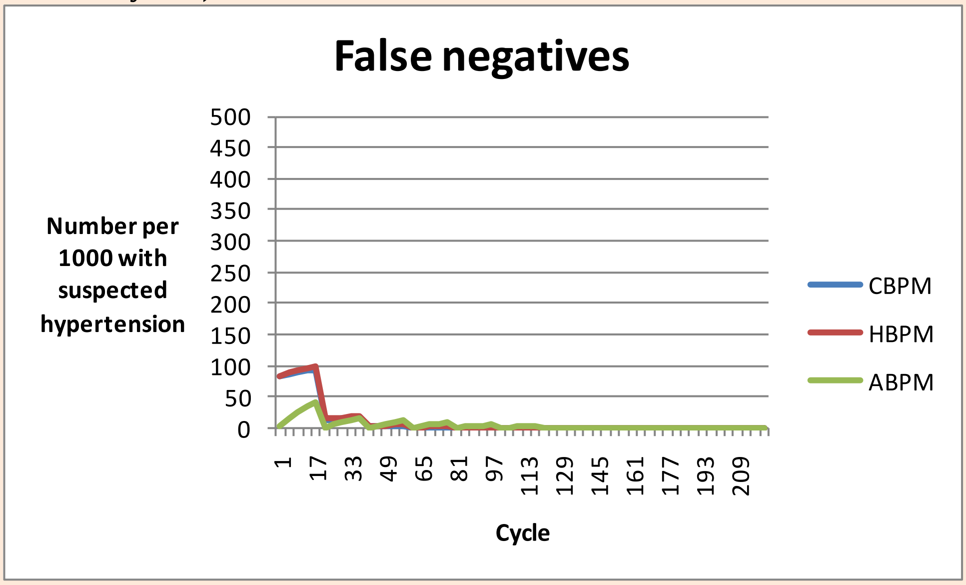
Update 2011

Figure 130: Misdiagnosis over time - false positives (deterministic, male, aged 60 years)



Graph shows how the number of people in the model who have a false positive diagnosis changes over time. Overall false positives reduce over time because people develop true hypertension and so become true positives. Peaks occur every 5 years when those who were diagnosed as not having hypertension have a blood pressure check-up – a certain proportion of these will have a false positive diagnosis and hence the number of false positives increases.This effect dimishes over time as the number of people without a hypertension diagnosis in the model diminishes.

Figure 131: Misdiagnosis over time - false negatives (deterministic, male, aged 60 years)



Graph shows how the number of people in the model who have a false negative diagnosis changes over time. Between blood pressure checkups (every 5 years) over time the number of false negatives increases as people who were initially true negatives develop hypertension and so become false negatives. However, at each 5-year check-up a certain proportion of these are correctly identified as true positives when rediagnosed and the graph sharply dips down.

J.3.2 Sensitivity analyses

A description of the sensitivity analyses undertaken is provided in the Methods, Section J.2.4. Table 143, Table 144, Table 145 and Table 146 summarise the results of these analyses. Sensitivity analyses were run using the deterministic analysis for a male aged 60 years unless otherwise specified.

In most sensitivity analyses, ABPM remained the most cost effective option. This included a wide range of sensitivity analyses testing the impact of different cost assumptions regarding diagnostic costs.

Three sensitivity analyses resulted in a different option becoming the most cost effective: when the sensitivity and specificity of ABPM was set equal to that of HBPM; when the sensitivity of HBPM was set at 100% (that is equal to ABPM); and when the model was changed so that people who were normotensive (<140/90 mmHg) and being treated (that is, people who were incorrectly diagnosed as having hypertension and thus receiving ‘unnecessary’ treatment) also received cardiovascular risk reduction from treatment.

In all scenarios ABPM, and HBPM, remained cost saving compared to CBPM except for when the frequency of check-ups was increased from every 5 years to annually. Here ABPM resulted in somewhat higher overall costs than CBPM and HBPM; however, QALYs were also higher with ABPM and it was still found to be the most cost-effective option (male, 60 years subgroup).

Incorporating a quality of life reduction for people on treatment had a large effect on the magnitude of QALYs gained with ABPM compared to CBPM (Table 143). Even a 1% reduction in quality of life increased the QALYs gained from 0.16 in the base case male, 60 years analysis to 0.37. The same reduction would also change the QALY losses seen in the base-case results seen in the younger subgroups to QALY gains (not shown in table).

Update 2011

The prevalence of true hypertension in the population of people with suspected hypertension entering the model also had an effect of note (Table 144). The conclusion that ABPM was the most cost-effective option was maintained across all analyses. The magnitude of cost and QALY differences was impacted. QALY differences between ABPM and CBPM became more favourable as prevalence increased. Cost savings were greatest with low prevalence.

Table 143: Sensitivity analyses results (SA1-SA40) (deterministic, male, aged 60 years)

Analysis	Incr. QALYs vs CBPM		Incr. costs vs CBPM		Optimal strategy
	HBPM	ABPM	HBPM	ABPM	
Base case					
Base case (probabilistic)	0.003	0.017	-£26	-£112	ABPM
Base case (deterministic)	0.003	0.016	-£26	-£117	ABPM
Sensitivity analyses (deterministic)					
Diagnostic costs					
SA1: ABPM/HBPM device acquisition cost halved	0.003	0.016	-£27	-£119	ABPM
SA2: ABPM/HBPM servicing costs halved	0.003	0.016	-£27	-£120	ABPM
SA3: Max. uses per year: ABPM (156); HBPM (52)	0.003	0.016	-£27	-£119	ABPM
SA4: ABPM = HBPM uses per year (40)	0.003	0.016	-£26	-£99	ABPM
SA5: SA1, SA2 and SA3 combined	0.003	0.016	-£27	-£122	ABPM
SA6: Low usage per year (ABPM/HBPM = 10)	0.003	0.016	-£25	-£25	ABPM
SA7: ABPM lifetime longer (10 years)	0.003	0.016	-£26	-£119	ABPM
SA8: ABPM training costs added	0.003	0.016	-£26	-£117	ABPM
SA9: ABPM and HBPM training costs added	0.003	0.016	-£25	-£116	ABPM
SA10: All appointments with GP	0.003	0.016	-£24	-£79	ABPM
SA11: All appointments with nurses	0.003	0.016	-£28	-£124	ABPM
SA12: 3x CBPM required to confirm diagnosis	0.003	0.016	-£39	-£130	ABPM
SA13: 4x CBPM required to confirm diagnosis	0.003	0.016	-£52	-£142	ABPM
SA14: 5x CBPM required to confirm diagnosis	0.003	0.016	-£65	-£155	ABPM
SA15: ABPM via direct access at hospital	0.003	0.016	-£26	-£66	ABPM
Failure rates					
SA16: Failure rates HBPM 0% and ABPM 10%	0.003	0.015	-£26	-£103	ABPM
SA17: Failure rates HBPM 5% and ABPM 5%	0.003	0.016	-£24	-£117	ABPM
SA18: Failure rates HBPM 0% and ABPM 0%	0.003	0.017	-£26	-£134	ABPM
Time until diagnosis complete					
SA19: Time until diagnosis complete all 3 months	-0.002	0.011	-£29	-£118	ABPM
Sensitivity and specificity					
SA20: Sensitivity and specificity ABPM = HBPM	0.003	0.003	-£26	-£5	HBPM
SA21: Sensitivity set to 100% for all 3 options	0.003	-0.001	-£26	-£115	ABPM
SA22: HBPM specificity set to 70%	0.002	0.016	-£45	-£117	ABPM
SA23: HBPM specificity set to 80%	0.000	0.016	-£74	-£117	ABPM
SA24: HBPM specificity set to 90%	-0.001	0.016	-£110	-£117	ABPM
SA25: HBPM specificity set to 100%	-0.003	0.016	-£157	-£117	ABPM
SA26: HBPM sensitivity set to 90%	0.009	0.016	-£27	-£117	ABPM
SA27: HBPM sensitivity set to 95%	0.015	0.016	-£28	-£117	ABPM

Update 2011

Analysis	Incr. QALYs vs CBPM		Incr. costs vs CBPM		Optimal strategy
SA28: HBPM sensitivity set to 100%	0.021	0.016	-£29	-£117	HBPM
Treatment effects					
SA29: Risk reduction based on half doses	0.002	0.013	-£26	-£114	ABPM
SA30: Risk reduction applied to all treated people	-0.010	-0.041	-£14	-£59	CBPM
CV risk					
SA31: CV risk increased by x1.4 (NT & HT)	0.004	0.020	-£26	-£112	ABPM
SA32: CV risk doubled in HT only	0.006	0.029	-£29	-£125	ABPM
Check up frequency in those diagnosed as not hypertensive					
SA33: Check-up every year	0.004	0.008	£8	£69	ABPM
Quality of life (utility) impact of being on treatment					
SA234: 1% utility decrement on treatment	0.008	0.037	-£26	-£117	ABPM
SA35: 2% utility decrement on treatment	0.014	0.058	-£26	-£117	ABPM
SA36: 5% utility decrement on treatment	0.030	0.121	-£26	-£117	ABPM
SA37: 10% utility decrement on treatment	0.058	0.226	-£26	-£117	ABPM
Cost of hypertension treatment					
SA38: Higher hypertension treatment costs	0.003	0.016	-£77	-£357	ABPM
Cost of cardiovascular events					
SA39: CVD event costs increased by 30%	0.003	0.016	-£28	-£123	ABPM
SA40: CVD event costs decreased by 30%	0.003	0.016	-£25	-£111	ABPM

CVD = cardiovascular disease; FP = false positive (incorrectly diagnosed as having hypertension); Incr. = incremental; QALYs = quality-adjusted life years; SA = sensitivity analysis; TP = true positive (correctly diagnosed as having hypertension).

Update 2011

Table 144: Sensitivity analysis – prevalence of true hypertension in population entering model (SA41-SA90) (deterministic, all subgroups)

Analysis	Incr. QALYs vs CBPM		Incr. costs vs CBPM		Optimal strategy
	HBPM	ABPM	HBPM	ABPM	
10%					
SA41: Male, 40 years	-0.003	-0.011	-£70	-£347	ABPM
SA42: Male, 50 years	-0.003	-0.011	-£64	-£306	ABPM
SA43: Male, 60 years	-0.003	-0.007	-£60	-£273	ABPM
SA44: Male, 70 years	-0.001	-0.002	-£56	-£232	ABPM
SA45: Male, 75 years	-0.001	-0.001	-£51	-£199	ABPM
SA46: Female, 40 years	-0.002	-0.008	-£73	-£365	ABPM
SA47: Female, 50 years	-0.003	-0.009	-£64	-£306	ABPM
SA48: Female, 60 years	-0.002	-0.005	-£60	-£282	ABPM
SA49: Female, 70 years	-0.001	-0.002	-£61	-£260	ABPM
SA50: Female, 75 years	0.000	-0.001	-£56	-£224	ABPM
20%					
SA51: Male, 40 years	-0.002	-0.008	-£61	-£305	ABPM
SA52: Male, 50 years	-0.002	-0.007	-£57	-£270	ABPM
SA53: Male, 60 years	-0.001	-0.002	-£53	-£241	ABPM
SA54: Male, 70 years	0.000	0.002	-£50	-£205	ABPM
SA55: Male, 75 years	0.000	0.002	-£45	-£175	ABPM
SA56: Female, 40 years	-0.001	-0.006	-£64	-£320	ABPM
SA57: Female, 50 years	-0.002	-0.007	-£57	-£268	ABPM
SA58: Female, 60 years	-0.002	-0.002	-£53	-£249	ABPM
SA59: Female, 70 years	0.000	0.001	-£54	-£230	ABPM
SA60: Female, 75 years	0.000	0.001	-£49	-£197	ABPM
40%					
SA61: Male, 40 years	-0.001	-0.003	-£44	-£220	ABPM
SA62: Male, 50 years	0.000	0.001	-£42	-£198	ABPM
SA63: Male, 60 years	0.001	0.007	-£40	-£178	ABPM
SA64: Male, 70 years	0.002	0.011	-£37	-£152	ABPM
SA65: Male, 75 years	0.002	0.010	-£33	-£128	ABPM
SA66: Female, 40 years	-0.001	-0.003	-£46	-£229	ABPM
SA67: Female, 50 years	-0.001	-0.002	-£41	-£193	ABPM
SA68: Female, 60 years	0.000	0.003	-£39	-£182	ABPM
SA69: Female, 70 years	0.001	0.007	-£41	-£171	ABPM
SA70: Female, 75 years	0.001	0.005	-£36	-£142	ABPM
60%					
SA71: Male, 40 years	0.000	0.003	-£27	-£135	ABPM
SA72: Male, 50 years	0.001	0.009	-£27	-£125	ABPM
SA73: Male, 60 years	0.003	0.016	-£26	-£114	ABPM
SA74: Male, 70 years	0.004	0.020	-£25	-£99	ABPM
SA75: Male, 75 years	0.004	0.017	-£21	-£80	ABPM
SA76: Female, 40 years	0.000	0.000	-£28	-£138	ABPM
SA77: Female, 50 years	0.000	0.003	-£25	-£118	ABPM
SA78: Female, 60 years	0.001	0.009	-£25	-£116	ABPM
SA79: Female, 70 years	0.002	0.012	-£27	-£111	ABPM

Update 2011

Analysis	Incr. QALYs vs CBPM		Incr. costs vs CBPM		Optimal
SA80: Female, 75 years	0.002	0.008	-£23	-£87	ABPM
80%					
SA81: Male, 40 years	0.002	0.008	-£10	-£50	ABPM
SA82: Male, 50 years	0.003	0.017	-£12	-£53	ABPM
SA83: Male, 60 years	0.005	0.026	-£12	-£51	ABPM
SA84: Male, 70 years	0.006	0.029	-£12	-£45	ABPM
SA85: Male, 75 years	0.005	0.024	-£10	-£33	ABPM
SA86: Female, 40 years	0.001	0.003	-£10	-£47	ABPM
SA87: Female, 50 years	0.001	0.008	-£10	-£43	ABPM
SA88: Female, 60 years	0.003	0.015	-£11	-£50	ABPM
SA89: Female, 70 years	0.004	0.017	-£13	-£51	ABPM
SA90: Female, 75 years	0.003	0.012	-£10	-£32	ABPM

QALYs = quality-adjusted life years.

Table 145: Sensitivity analysis results – sensitivity and specificity varied by age (SA91-SA100) (deterministic, all subgroups)

Analysis	Incr. QALYs vs CBPM		Incr. costs vs CBPM		Optimal strategy
	HBPM	ABPM	HBPM	ABPM	
SA91: Male, 40 years(a)	-0.001	-0.001	-£46	-£213	ABPM
SA92: Male, 50 years(a)	0.000	0.011	-£31	-£139	ABPM
SA93: Male, 60 years(b)	0.003	0.016	-£26	-£117	ABPM
SA94: Male, 70 years(c)	0.004	0.013	-£29	-£116	ABPM
SA95: Male, 75 years(c)	0.004	0.013	-£22	-£79	ABPM
SA96: Female, 40 years(a)	-0.002	-0.005	-£61	-£289	ABPM
SA97: Female, 50 years(a)	-0.001	0.002	-£36	-£161	ABPM
SA98: Female, 60 years(b)	0.000	0.005	-£34	-£155	ABPM
SA99: Female, 70 years(c)	0.003	0.009	-£26	-£109	ABPM
SA100: Female, 75 years(c)	0.002	0.006	-£24	-£92	ABPM

a) CBPM: sensitivity = 81%, specificity = 58%. HBPM: sensitivity = 81%, specificity = 70%. ABPM: sensitivity = 100%, specificity = 100%.
b) CBPM: sensitivity = 86%, specificity = 46%. HBPM: sensitivity = 86%, specificity = 62%. ABPM: sensitivity = 100%, specificity = 100%.
c) CBPM: sensitivity = 91%, specificity = 20%. HBPM: sensitivity = 91%, specificity = 48%. ABPM: sensitivity = 100%, specificity = 100%.

Table 146: Sensitivity analysis results – sensitivity and specificity varied by age and initial prevalence of true hypertension adjusted by age (SA101-110) (deterministic, all subgroups)

Analysis	Incr. QALYs vs CBPM		Incr. costs vs CBPM		Optimal strategy
	HBPM	ABPM	HBPM	ABPM	
SA101: Male, 40 years	-0.002	-0.003	-£51	-£238	ABPM
SA102: Male, 50 years	0.000	0.006	-£37	-£170	ABPM
SA103: Male, 60 years	0.003	0.016	-£26	-£117	ABPM
SA104: Male, 70 years	0.006	0.018	-£19	-£73	ABPM
SA105: Male, 75 years	0.006	0.017	-£11	-£37	ABPM
SA106: Female, 40 years	-0.002	-0.006	-£64	-£303	ABPM
SA107: Female, 50 years	-0.001	0.000	-£42	-£188	ABPM
SA108: Female, 60 years	0.000	0.005	-£34	-£155	ABPM

SA109: Female, 70 years	0.004	0.012	-£15	-£58	ABPM
SA110: Female, 75 years	0.003	0.008	-£12	-£45	ABPM

J.3.2.1 Selected further exploration using probabilistic analysis

Selected sensitivity analyses were run using the probabilistic analysis for all male subgroups in order to explore effects in more detail.

In the deterministic analysis above, in the male 60 years subgroup HBPM became the most cost effective option when the sensitivity and specificity of ABPM was set to be the same as HBPM for a male aged 60 years using the deterministic analysis. This is because diagnostic costs are lower with HBPM. This conclusion was maintained across all age groups with fairly low uncertainty in the probabilistic analysis (Table 147).

Table 147: Sensitivity analysis results– sensitivity and specificity of ABPM set equal to HBPM (probabilistic analysis, male subgroups)

Subgroup	Incremental QALYs vs CBPM		Incremental costs vs CBPM		Optimal strategy	Probability CE
	HBPM	ABPM	HBPM	ABPM		
Male, 40 years	-0.001 (CI: -0.006, 0.004)	-0.001 (CI: -0.005, 0.004)	-£48 (CI: -£124, £16)	-£21 (CI: -£85, £37)	HBPM	78%
Male, 50 years	0.001 (CI: -0.009, 0.009)	0.001 (CI: -0.008, 0.009)	-£34 (CI: -£88, £10)	-£10 (CI: -£57, £29)	HBPM	72%
Male, 60 years	0.003 (CI: -0.010, 0.015)	0.003 (CI: -0.010, 0.014)	-£26 (CI: -£68, £6)	-£5 (CI: -£40, £24)	HBPM	78%
Male, 70 years	0.005 (CI: -0.008, 0.018)	0.004 (CI: -0.008, 0.017)	-£23 (CI: -£62, £8)	-£3 (CI: -£37, £25)	HBPM	81%
Male, 75 years	0.005 (CI: -0.007, 0.016)	0.004 (CI: -0.006, 0.015)	-£16 (CI: -£43, £6)	£3 (CI: -£22, £23)	HBPM	83%

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

Note: Failure rates remained set at 0% and 5% for HBPM and ABPM respectively.

As sensitivity and specificity are the key differentiator between comparators in the model, the probabilistic analysis across all male subgroups was used to examine in more detail the sensitivity analysis where the sensitivity of all three comparators was set to 100% and only specificity varied between them (Table 148). This found that the most cost-effective option varied across age groups with HBPM becoming cost-effective in the 50 year old subgroup. In addition uncertainty in the conclusions was increased. In the male, 60 years subgroup the probability of being the most cost effective option was essentially equal for ABPM and HBPM. In the age 70 and 75 subgroups the probability of ABPM being the most cost-effective option was reduced from 100% in the base case to about 65%.

Table 148: Sensitivity analysis results – sensitivity set to 100% for CBPM, HBPM, ABPM (probabilistic analysis, male subgroups)

Subgroup	Incremental QALYs vs CBPM		Incremental costs vs CBPM		Optimal strategy	Probability CE
	HBPM	ABPM	HBPM	ABPM		
Male, 40 years	-0.001 (CI: -0.003, 0.001)	-0.008 (CI: -0.012, -0.004)	-£49 (CI: -£125, £14)	-£241 (CI: -£321, -£129)	ABPM	98%
Male, 50 years	0.001 (CI: -0.002,	-0.005 (CI: -0.010, 0.000)	-£33 (CI: -£89, £11)	-£156 (CI: -£231, -£64)	HBPM	64%(a)

	0.003)					
Male, 60 years	0.003 (CI: 0.000, 0.006)	-0.001 (CI: -0.006, 0.004)	-£26 (CI: -£70, £9)	-£109 (CI: -£179, -£33)	ABPM	49%(b)
Male, 70 years	0.005 (CI: 0.003, 0.008)	0.003 (CI: -0.002, 0.007)	-£22 (CI: -£58, £4)	-£82 (CI: -£141, -£24)	ABPM	63%(c)
Male, 75 years	0.005 (CI: 0.003, 0.007)	0.003 (CI: 0.000, 0.006)	-£16 (CI: -£45, £7)	-£55 (CI: -£102, -£8)	ABPM	64%(d)

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

Note: Failure rates remained set at 0% and 5% for HBPM and ABPM respectively.

(a) CBPM = 0%; ABPM = 36%
(b) CBPM = 0%; HBPM = 51%
(c) CBPM = 0%; HBPM = 37%
(d) CBPM = 0%; HBPM = 36%

CBPM became the most cost effective option when the model was changed so that people who were normotensive (<140/90 mmHg) and being treated (that is, people who were incorrectly diagnosed as having hypertension) also received cardiovascular risk reduction from treatment. Note that the risk reduction they received was lower than that received by people with hypertension. This conclusion was maintained across all age groups (Table 149) although the probabilistic analysis indicated that uncertainty increased with age. There was particularly high uncertainty about the most cost-effective option in the oldest subgroup.

Table 149: Sensitivity analysis results – CVD risk reduction applied to all treated people (including those not hypertensive) (probabilistic analysis, male subgroups)

Subgroup	Incremental QALYs vs CBPM		Incremental costs vs CBPM		Optimal strategy	Probability CE
	HBPM	ABPM	HBPM	ABPM		
Male, 40 years	-0.017 (CI: -0.043, 0.005)	-0.099 (CI: -0.133, -0.054)	-£29 (CI: -£77, £11)	-£121 (CI: -£171, -£57)	CBPM	94%(a)
Male, 50 years	-0.016 (CI: -0.046, 0.008)	-0.078 (CI: -0.124, -0.022)	-£16 (CI: -£47, £7)	-£64 (CI: -£105, -£21)	CBPM	89%(b)
Male, 60 years	-0.011 (CI: -0.040, 0.013)	-0.048 (CI: -0.094, 0.001)	-£11 (CI: -£33, £5)	-£46 (CI: -£82, -£12)	CBPM	78%(c)
Male, 70 years	-0.005 (CI: -0.026, 0.014)	-0.017 (CI: -0.051, 0.019)	-£13 (CI: -£36, £5)	-£47 (CI: -£83, -£14)	CBPM	59%(d)
Male, 75 years	-0.001 (CI: -0.016, 0.012)	-0.002 (CI: -0.024, 0.020)	-£10 (CI: -£30, £4)	-£32 (CI: -£61, -£3)	CBPM	34%(e)

CE= cost effective at a £20,000 threshold; CI = 95% confidence interval; QALYs = quality-adjusted life years.
(a) HBPM = 6%, ABPM = 0%
(b) HBPM = 11%, ABPM = 0%
(c) HBPM = 20%, ABPM = 2%
(d) HBPM = 26%, ABPM = 15%
(e) HBPM = 26%, ABPM = 39%

In the deterministic sensitivity analysis above (in the male 60 years subgroup only), where the check-up frequency in people diagnosed as not hypertensive was changed from every 5-years to every year, ABPM was no longer cost saving (although was still cost effective). This is because diagnostic costs were increased in this sensitivity analysis because in the model every time a person is checked-up they are suspected of having hypertension again and are rediagnosed using the same method as in the first instance (CBPM, HBPM or ABPM). These high additional diagnostic costs are no longer offset by cost savings (mainly avoided treatment costs). The probabilistic analysis across all male subgroups was used to examine this sensitivity analysis in more detail (Table 150).

Update 2011

In this analysis HBPM became the most cost-effective option in the lower two subgroups (age 40 and 50 years). In the very lowest subgroup (age 40 years) the probability of HBPM and CPBM being the most cost effective option was essentially equal. In other subgroups, ABPM remained the most cost-effective option although uncertainty was increased compared to the base-case analysis where there was a 100% probability that ABPM was cost effective; uncertainty was still however very low in the two highest subgroups. This is because the additional costs associated with HBPM or ABPM compared to CBPM reduced with age and the QALYs gained generally increased with age.

Table 150: Sensitivity analysis results – check-up frequency in those diagnosed without hypertension (probabilistic analysis, male subgroups)

Subgroup	Incremental QALYs vs CBPM		Incremental costs vs CBPM		Optimal strategy	Probability CE
	HBPM	ABPM	HBPM	ABPM		
Male, 40 years	0.001 (CI: 0.000, 0.002)	0.000 (CI: -0.001, 0.002)	£13 (CI: £9, £19)	£133 (CI: £78, £167)	HBPM	49%(a)
Male, 50 years	0.002 (CI: 0.000, 0.005)	0.004 (CI: 0.001, 0.007)	£10 (CI: £5, £15)	£93 (CI: £49, £129)	HBPM	89%(b)
Male, 60 years	0.004 (CI: 0.001, 0.008)	0.008 (CI: 0.005, 0.011)	£8 (CI: £2, £13)	£66 (CI: £32, £96)	ABPM	62%(c)
Male, 70 years	0.006 (CI: 0.002, 0.011)	0.011 (CI: 0.008, 0.015)	£5 (CI: -£1, £11)	£49 (CI: £22, £73)	ABPM	96%(d)
Male, 75 years	0.005 (CI: 0.002, 0.008)	0.010 (CI: 0.007, 0.013)	£5 (CI: £1, £10)	£39 (CI: £19, £58)	ABPM	98%(e)

CE= cost effective at a £20,000 threshold; CI = 95% confidence interval; QALYs = quality-adjusted life years.
(a) CBPM = 51%, ABPM = 0%
(b) CBPM = 3%, ABPM = 8%
(c) CBPM = 0%, HBPM = 38%
(d) CBPM = 0%; HBPM = 5%
(e) CBPM = 0%; HBPM = 2%

Update 2011

J.4 Discussion

J.4.1 Summary of results

ABPM was considered by the GDG the most accurate method of confirming a diagnosis of hypertension based on the clinical review when compared with CBPM and HBPM. ABPM monitors are however the most expensive to purchase.

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).

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. QALY differences were driven by differences in cardiovascular events.

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.

Update 2011

J.4.2 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 ≥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 is noted that the analysis is most probably conservative in terms of ABPM in a number of places. For example, ABPM reduced treatment costs compared to CBPM and HBPM and the cost of these used in the base-case analysis was most likely on the low side as they were based on the most commonly used generic drug costs and a single clinic visit per year. In addition, the base case did 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 base-case analysis because side effects of antihypertensive drugs are generally fairly mild 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 unnecessary 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 a single ABPM probably does not have 100% sensitivity and specificity. However, prognostic studies indicated that ABPM was most predictive of prognosis and so this was considered a reasonable assumption for the analysis; without making this assumption it would not be possible to undertake the analysis given the available studies.

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 reference 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 were not available to allow this to be incorporated into the base-case 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 base case 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.

The base case 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

Update 2011

be. 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 base-case analysis reflects the GDG’s interpretation of the clinical data relating to treatment thresholds and as such is 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 ≥160/100mmHg (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 base-case 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%.

Check-up frequency

In the base-case 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 diagnostic costs.

Model input uncertainty

Throughout this report issues with model input uncertainty have been highlighted. 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 base-case analysis and these were varied in sensitivity analyses.

J.4.3 Comparisons with published studies

No published cost effectiveness studies were indentified that compared CBPM, HBPM and ABPM for confirmation of a diagnosis of hypertension. One partially applicable study with potentially serious limitations was identified that compared ABPM with CBPM which found that ABPM was cost-saving[338].

The analysis presented in this report compared all three options for confirming a diagnosis of hypertension from a UK NHS perspective taking into account a wide range of considerations with extensive sensitivity analysis. As such it is directly applicable to the guideline and the current UK NHS. The results of this analysis are broadly in agreement with the published analysis comparing ABPM and CBPM.

Update 2011

J.4.4 Conclusion = Evidence statements

This analysis that compared CBPM, HBPM and ABPM for confirming a diagnosis of 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.

J.4.5 Implications for future research

Further research that would improve the model would include further studies of the relative sensitivity and specificity of CBPM, HBPM and ABPM and in particular how this varies with disease prevalence / age. In addition, information about the prevalence of true hypertension among those with a positive screening reading including stratification by age would improve the specification of the base-case analysis; this may become quite readily available if ABPM to confirm diagnosis following a screening reading suggesting hypertension is implemented. Limited published data was available to inform the estimates of cardiovascular disease related costs; while this was not a great driver of cost in this analysis published assessment of UK cardiovascular event acute and/or diagnostic costs and post-event costs would improve the accuracy of this and future economic analyses in the field.

Appendix K: Research recommendations (2011)

K.1 Out of office monitoring

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

Why this is important

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 is however very little data regarding the utility of HBPM or ABPM for monitoring the quality of blood pressure control on treatment or as indicators of clinical outcome on treatment when compared to clinic blood pressure monitoring. The recommendation is for studies incorporating HBPM and/or ABPM to monitor blood pressure responses to treatment and their relationship to clinical outcomes.

K.2 Intervention thresholds below 40 years of age

In adults with hypertension below the age of 40, what are the appropriate intervention thresholds?

Why is this important

Outcomes: Progression of hypertension, intermediate risk markers of CV damage/structure (for example, LVH and vascular structure, renal damage, cerebral damage or cognitive changes)

There is genuine uncertainty about how to assess the impact of blood pressure treatment in younger people (aged <40years) with stage 1 hypertension and in particular, whether, if left untreated, younger people with untreated stage 1 hypertension without overt TOD or CVD, are disadvantaged by delaying treatment with regard to the likelihood of developing TOD. Also, whether any TOD that does develop is reversible. Such surrogate or intermediate disease markers are the only indicators that are likely to be feasible in younger people as traditional clinical outcomes are unlikely to occur is sufficient number over the time scale of a typical clinical trial. The data will be important to inform treatment decisions reading younger people with stage 1 hypertension who do not have overt TOD.

Update 2011

K.3 Methods for assessing lifetime CV risk

In adults with hypertension below the age of 40 years what is the most accurate method for assessing the lifetime risk of cardiovascular events and impact of therapeutic intervention on this risk?

Why is this important

Current short term risk estimates (i.e. over 10 years) are likely to substantially underestimate the lifetime cardiovascular risk of younger people with hypertension, because short-term risk assessment is powerfully influenced by age. Nevertheless, the lifetime risk associated with untreated stage 1 hypertension in young people with stage 1 hypertension 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.

K.4 Optimal systolic blood pressure

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

Why is this important

There is inadequate data about the optimal blood pressure treatment targets, particularly for systolic blood pressure. Current guidance is largely based on the blood pressure targets adopted in clinical trials but there have been no large trials that have randomised hypertensive people to different systolic BP targets with sufficient power to examine clinical outcomes.

K.5 Step 4 treatment – resistant hypertension

In adults with hypertension, which drug treatment (diuretic therapy versus step 4 treatments) is the most clinically and cost effective for step 4 treatment?

Why is this important

Although this guideline gives a steer towards the use of further diuretic therapy for treatment at step 4, i.e. resistant hypertension, this is largely based on post-hoc observational data from clinical trials and further data is needed to compare further diuretic therapy (and which diuretic – i.e. potassium sparing or higher dose thiazide-like?) with alternative treatment options at step 4 to define whether further diuretic therapy is the best option.

K.6 Blood pressure equipment

In people with hypertension, which is automated blood pressure monitors are suitable for use in people with atrial fibrillation?

Why is this important

Atrial fibrillation may prevent accurate blood pressure measurement with automated devices. It would be valuable to know if this can be overcome.

Appendix L: CG18 Essential Hypertension: managing adult patients in primary care, 2004

Appendix M: CG34 Hypertension: management in adults in primary care: pharmacological update, 2006