National Institute for Health and Care Excellence

Final

Hypertension in adults: diagnosis and management

[F] Evidence review for step 2 and step 3 treatment

NICE guideline NG136

Intervention evidence review underpinning recommendations 1.4.38 to 1.4.43 in the guideline

August 2019

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

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1.1 Review question: What is the most clinically and cost-effective sequence for step 2 and step 3 treatment for hypertension?

1.2 Introduction

Most individuals on treatment for hypertension are prescribed more than 1 medication to achieve their target blood pressure. One of the reasons for this is that different medications act on different pathways of blood pressure regulation, and when 1 pathway is blocked by a medication, the other pathways may compensate to keep the blood pressure elevated.

It is plausible that there is an ideal sequence in which to add additional antihypertensive medications, whereby if the step 1 medication doesn't have the desired effect the choice of step 2 and step 3 medications are selected based on highest chance of success in achieving the blood pressure target. Various biologically plausible approaches to medication sequencing have been suggested over the years, and in this chapter, we review the clinical and economic evidence for selecting step 2 and step 3 medications.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (over 18 years) with primary hypertension who have previously received medication for hypertension to which they have had an inadequate response.
Intervention	Step 2 or step 3 antihypertensive pharmacological treatment received for a minimum of 1 year. Examples include: • Angiotensin-converting enzyme (ACE) inhibitor • Angiotensin-II receptor blocker (ARB) • Thiazide-like diuretic (such as chlortalidone or indapamide) • Conventional thiazide diuretic (such as bendroflumethiazide or hydrochlorothiazide) • Calcium channel blockers (CCB) • Beta-blockers • Aliskiren (direct renin inhibitors) • Alpha blockers (doxazosin, prazosin, terazosin) • Centrally acting antihypertensives (clonidine, moxonidine, methyldopa) • Combinations including 2 or 3 antihypertensive medications (including where a medication is added to the previous medication[s]).
Comparison	Compared against each other (class comparisons)
Outcomes	All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted. **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI)

	Important • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Change in creatinine or eGFR • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [Coronary heart disease outcome in the absence of MI data]
Study design	Randomised control trials (RCT) and systematic reviews (SR)

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[229] Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

1.4 Clinical evidence

1.4.1 Included studies

No relevant clinical studies for step 2 or step 3 antihypertensive pharmacological therapy received for a minimum of 1 year were identified.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

Two Cochrane reviews relevant to this review question were identified. Chen 2010[62] and Garjon 2017[63] were both excluded due to having less than the minimum duration of follow up defined in the protocol for this review; participants were on therapy for 3 to 12 weeks.

See the excluded studies list in appendix I. Table 14 outlines the full excluded studies list, and Table 13 provides additional detail of studies that were included in the previous guideline iteration (CG127) but excluded from this update.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

Eight economic studies relating to this review question were identified but were excluded due to limited applicability.[45, 112, 170, 85, 207, 260, 258, 259] The interventions did not fit the protocol because they were either comparing within class comparisons, for example, different ARBs plus a thiazide or comparing treatments being titrated up versus adding another drug. These are listed in appendix I, including the reasons for exclusion.

See also the health economic study selection flow chart in appendix G.

1.5.3 Resource costs

The costs of drugs from each of the 3 main classes are demonstrated below. The drug representing each class was selected based on committee opinion.

Table 2: UK costs of main classes of antihypertensive drugs

Drug	Detail	Daily dose	Cost/month (£)	Cost/year (£)
ACE inhibitor (Ramipril)	10 mg capsules, pack of 28 = £0.88	10 mg	£0.96	£11.47
ARB (Losartan)	50 mg tablets, pack of 28 = £0.82	50 mg	£0.89	£10.69
CCB (Amlodipine)	10 mg tablet, pack of 28 = £0.67	10 mg	£0.73	£8.73
Diuretic (Indapamide)	2.5 mg tablet, pack of 28 = £0.90	2.5 mg	£0.98	£11.73

Source: BNF, drug tariff price, May 2019[50]

1.6 Evidence statements

1.6.1 Clinical evidence statements

No relevant published evidence was identified.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee considered all-cause mortality, quality of life, stroke and myocardial infarction to be critical outcomes for decision-making. Heart failure, vascular procedures, angina, reduction in medication, acute kidney injury, new onset diabetes, change in creatinine and

hypotension were also considered important for decision-making. However, no available evidence was identified for any of these outcomes.

1.7.1.2 The quality of the evidence

No studies relevant to the review protocol were identified.

1.7.1.3 Benefits and harms

Although several recognised trials were identified in the literature search, they were not fully applicable to the review question and were excluded due to not meeting the protocol for this review. In general, trial designs were mainly titration studies, designed to test how good treatments are at getting people to a target. The trials were not designed to test different combinations of treatments from the outset and did not recruit individuals whose blood pressure had been uncontrolled on monotherapy, which was required to inform this review question. Although trials with a titration design were not excluded from the review, the methodology undertaken and presentation of results often resulted in unuseable data for the purpose of this review.The committee discussed the LIFE and VALUE trials, but it agreed that the aim of these studies related more to inform step 1 treatment. The ALLHAT trial was excluded, as the intervention used a fixed regimen of dose escalation that doesn't reflect clinical practice. Additionally, drugs not available in the UK were used in the treatment regimen and therefore this evidence would not be generalisable to UK practice. Furthermore, it was agreed that it did not meet this review protocol, as it was a step 1 treatment comparison. The ACCOMPLISH trial was excluded because the trial related to step 1 treatment choices; people were randomised to 2 different combination therapies, rather than the population having an inadequate response to monotherapy and being randomised to a second drug. Although this evidence was used to inform recommendations in the previous guideline, the committee agreed that this was indirect evidence due to the study design and because 1 of the medication (benazepril) was not licensed in the UK. The committee discussed the generalisability of this drug to the UK setting and agreed that there is emerging evidence to suggest that some drugs within the antihypertensive classes may have different treatment effects and mechanisms of action. Therefore, the committee agreed that evidence from an unlicensed medication was no longer applicable. The committee identified the ANBP2 trial to be a step 1 treatment comparison; thus, it did not meet this review protocol and was excluded.

The committee considered the ASCOT trial to be most relevant to this review protocol. However, on further exploration of the trial design, the committee agreed the comparison would not have informed recommendations on step 2 and step 3 treatment as it compared a calcium-channel blocker (CCB) and angiotensin-converting enzyme (ACE) inhibitor combination to a beta-blocker and diuretic combination. The underlying treatment effects of each combination and how each drug influences this would be difficult to determine across combinations of treatments without any adjunct drugs across the groups. The trial also involved the use of a beta-blocker as step 1 comparison, which have been proven to be less effective and the use of beta-blockers for hypertension is not routine clinical practice in the UK.

The committee agreed that given the lack of evidence to inform choice of step 2 or step 3 treatments, it would not recommend a rigid pathway, but instead it recommended a more individualised approach to choice of treatment. It was agreed that the choice of drug should be discussed and agreed with the person according to the risks and benefits and the step 1 treatment that had been used. In order to help inform this discussion, it was agreed that a patient decision aid should be developed to accompany the recommendation to enable healthcare professionals to discuss with the person with hypertension informing that person's choice. This could be used during consultations to enhance knowledge on the risks and benefits of each drug. This would also likely aid adherence, which is a significant issue for asymptomatic long-term conditions such as hypertension.

1.7.2 Cost effectiveness and resource use

No economic evidence was included for this question. Eight studies were excluded for limited applicability, as they did not have the right interventions or clinical study design. Some economic evaluations were based on studies comparing combinations of drugs within the same class, and some were based on studies comparing different starting drugs (that is, different monotherapies) and then either adding the same step 2 drug or adding on the drug that was used as the step 1 drug in the other arm of the study. These are not direct comparisons of different combinations of drugs and are therefore not designed to answer what the most cost-effective sequence is in a population who have not had their blood pressure controlled with step 1 treatment.

Although all the drugs that could be used sequentially for hypertension (ACE inhibitor, angiotensin II receptor blocker [ARB], CCB, a diuretic/thiazide-like diuretic) are available as generics, there are small differences between each of the drugs that can lead to cost burdens when taking into account the size of the population.

Given that there was no clinical evidence identified, the committee opted for a recommendation taking more of an individualised approach to deciding step 2 and step 3 treatments in discussion with the person with hypertension. This recommendation will replace the previous recommendations on step 2 and step 3 treatments. The committee discussed how an individualised approach to treatment is what already happens in practice; for example, an individual on an ACE inhibitor or an ARB may prefer a diuretic to a CCB as a step 2 drug because of swollen ankles.

This recommendation is not anticipated to have a resource impact.

1.7.3 Other factors the committee took into account

The committee discussed whether in the absence of available evidence, there was value of a research recommendation in this area. However, they agreed that these medications are all well established with known efficacy and it was unlikely this research would be funded or seen as a priority area. In practice, the decision should be based on a more individualised approach according to the risks and benefits and the step 1 treatment that had been used and a patient decision aid would be of more value that a research recommendation.

The side-effect profile and patient acceptability of different drugs were considered when discussing the order in which different classes of antihypertensive medications should be started. Diuretics are associated with a higher rate of kidney injury, electrolyte abnormalities and hospitalisation that the other classes of medication. Additionally, increased urinary frequency may be difficult for many patients and lead to reduced medication adherence. These potential harms from diuretics are not offset by increased reduction in cardiovascular disease events when compared to the other medication classes. It is for these reasons that calcium-channel blockers are recommended as a step 1 medication (depending on subgroup and not in those at risk of heart failure) and diuretics are recommended as add-on therapy for step 2 or step 3.

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Appendices

Appendix A: Review protocols

Table 3: Review protocol: Step 2 and step 3 treatment

Field	Content
Review question	What is the most clinically and cost-effective sequence for step 2 and step 3 treatment for hypertension in adults?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	To identify the most clinically and cost-effective sequence of pharmacological treatment for adults with hypertension
Eligibility criteria – population / disease / condition / issue / domain	Adults (over 18 years) with primary hypertension who have previously received medication for hypertension to which they have had an inadequate responsive. Stratify by: • Presence or absence of type 2 diabetes • The drug class previously received
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Step 2 or step 3 antihypertensive pharmacological treatment received for a minimum of 1 year. Examples include: • ACE inhibitor • ARB • Thiazide-like diuretic (such as chlortalidone or indapamide) • Conventional thiazide diuretic (such as bendroflumethiazide or hydrochlorothiazide) • CCB • Beta-blockers • Aliskiren (direct renin inhibitors) • Alpha blockers (doxazosin, prazosin, terazosin) • Centrally acting antihypertensives (clonidine, moxonidine, methyldopa) • Combinations including 2 or 3 antihypertensive medications (including where a medication is added to the previous medication[s]).
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Compared against each other (class comparisons)
Outcomes and prioritisation	All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted. **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • MI **Important** • Heart failure needing hospitalisation

	• Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Side effect 1: Acute kidney injury • Side effect 2: New onset diabetes • Side effect 3: Change in creatinine or eGFR • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [coronary heart disease outcome in the absence of MI data]
Eligibility criteria – study design	RCTs and SRs
Other inclusion exclusion criteria	Minimum follow up time: 1 year Exclusions: • Studies designed based on intolerance to prior antihypertensive treatment • Studies including participants with type 1 diabetes or chronic kidney disease (A3 or above [heavy proteinuria]). For the type 2 diabetes strata, studies including participants with chronic kidney disease (A2 or above [heavy proteinuria]) • Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (Conn's adenoma, phaeochromocytoma, renovascular hypertension) • Pregnant women • Children (aged under18 years) • Crossover trials (unless washout is 4 weeks or more) • Reserpine (withdrawn from UK market) – exclude studies using this treatment.
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups to explore heterogeneity: • Age (under 55, 55–74 and 75 and over)* • Family origin (African and Caribbean, White, South Asian) • Severity (moderate [stage 1 BP 140–59/90–99] versus high [stage 2 BP 160/100]) *To note that evidence in those >80 years will be sub-grouped separately if this evidence is reported separately.
Selection process – duplicate screening / selection / analysis	A senior research fellow will undertake quality assurance prior to completion.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome. Endnote will be used for bibliography, citations, sifting and reference management.
Information sources – databases and dates	Medline, Embase, the Cochrane Library Language: Restrict to English only
Identify if an update	Yes, 2011
Author contacts	https://www.nice.org.uk/guidance/cg127
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.

Search strategy – for 1 database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details, please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome 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/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Anthony Wierzbicki in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 4: Health economic review protocol

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.
Search	• Populations, interventions and comparators must be as specified in the clinical

criteria	review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. No date cut-off from the previous guideline was used.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the US will also be excluded. Studies published after 2002 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[229] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude selectively the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the US will be excluded before being

	assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later (including any such studies included in the previous guideline[s]) but that depend on unit costs and resource data entirely or predominantly before 2002 will be rated as 'Not applicable'. • Studies published before 2002 (including any such studies included in the previous guideline[s]) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review, the more useful the analysis will be for decision-making in the guideline. • Generally, economic evaluations based on excludes from the clinical review will be excluded.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017.

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946–02 October 2018	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974–02 October 2018	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to Issue 8 of 12, August 2018 CENTRAL to Issue 7 of 12, July 2018 DARE and NHS EED to Issue 2 of 4, April 2015 HTA to Issue 4 of 4, October 2016	None

Table 6: Medline (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	exp pregnancy/
9.	exp Hypertension, Pregnancy-Induced/ not exp Hypertension/
10.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
11.	exp Hypertension, Portal/ not exp Hypertension/
12.	exp Hypertension, Pulmonary/ not exp Hypertension/
13.	exp Intracranial Hypertension/ not exp Hypertension/
14.	exp Ocular Hypertension/ not exp Hypertension/
15.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
16.	or/9-15
17.	7 not 16

18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
38.	36 not 37
39.	limit 38 to English language
40.	exp Angiotensin-Converting Enzyme Inhibitors/
41.	Angiotensin-converting enzyme inhibitor*.ti,ab.
42.	(ACE inhibitor* or ACEI).ti,ab.
43.	(Captopril or Enalapril or Fosinopril or Imidapril or Lisinopril or Moexipril or Perindopril or Quinapril or Ramipril or Trandolapril or Capoten or Ecopace or Noyada or Innovace or Tanatril or Zestril or Perdix or Coversil or Accupro or Tritace).ti,ab.
44.	Captopril/ or Enalapril/ or Fosinopril/ or Lisinopril/ or Perindopril/ or Ramipril/
45.	exp Angiotensin Receptor Antagonists/
46.	(Angiotensin II adj3 (antagonist* or blocker*)).ti,ab.
47.	ARB.ti,ab.
48.	(Azilsartan or Candesartan or Eprosartan or Irbesartan or Losartan or Olmesartan or Telmisartan or Valsartan or Edarbi or Amias or Teveten or Aprovel or Ifirmasta or Sabervel or Cozaar or Olmetec or Tolura or Micardis or Diovan).ti,ab.
49.	Losartan/ or Valsartan/ or Olmesartan Medoxomil/
50.	exp Calcium Channel Blockers/
51.	Calcium channel blocker*.ti,ab.
52.	CCB.ti,ab.
53.	(Amlodipine or Clevidipine or Diltiazem or Felodipine or Isradipine or Lacidipine or Lercanidipine or Nicardipine or Nifedipine or Verapamil or Amlostin or Istin or Adizem or Angitil or Dilcardia or Dilzem or Slozem or Tildiem or Viazem or Zemtard or Kenzem or Cardioplen or Felendil or Neofel or Parmid or Plendil or Pinefeld or Vascalpha or Molap or Motens or Zanidip or Cardene or Adalat or Adipine or Coracten or Fortipine or Nifedipress or Tensipine or Valni or Securon or Verapress or Vertab or Univer or Zolvera or Cleviprex).ti,ab.
54.	Amlodipine/ or Diltiazem/ or Felodipine/ or Isradipine/ or Nicardipine/ or Nifedipine/ or Verapamil/
55.	Diuretics/

56.	Diuretics, Thiazide/
57.	((thiazide or thiazide-like or non-thiazide or conventional or potassium sparing) adj3 diuretic*).ti,ab.
58.	Mineralocorticoid Receptor Antagonists/
59.	((mineralocorticoid or aldosterone) adj3 antagonist*).ti,ab.
60.	(Amiloride or Cyclopenthiazide or Spironolactone or Eplerenone or Bendroflumethiazide or Hydrochlorothiazide or Co-amilozide or Co-triamterzide or Co-zidocapt or Chlortalidone or Indapamide or Metolazone or Xipamide or Carace or Zestoretic or Coversyl or Accuretic or Cozaar or Sevikar or Olmetec or Actelsar or Tolucombi or Co-Diovan or Hygroton or Co-tenidone or Kalspare or Natrilix or Cardide or Indipam or Rawel or Tensaid or Alkapamid or Zaroxolyn or Diurexan or Aprinox or Neo-Naclex or CoAprovel or Lisoretic or Dyazide or Navispare or Lasilactone).ti,ab.
61.	Amiloride/ or Cyclopenthiazide/ or Spironolactone/ or Bendroflumethiazide/ or Hydrochlorothiazide/ or Chlortalidone/ or Indapamide/ or Metolazone/ or Xipamide/ or Chlortalidone/ or Metolazone/
62.	Adrenergic beta-Antagonists/
63.	(adrenergic beta antagonist* or beta blocker* or b blocker*).ti,ab.
64.	(Carvedilol or Labetalol or Atenolol or Nadolol or Oxprenolol or Pindolol or Propranolol or Timolol or Acebutolol or Bisoprolol or Celiprolol or Esmolol or Metoprolol or Nebivolol or Tenormin or Tenif or Corgard or Slow-Trasicor or Visken or Viskladix or Bedranol or Beta-Prograne or Syprol or Betim or Sectral or Cardicor or Congescor or Celectol or Breviblock or Betaloc or Lopresor or Nebilet).ti,ab.
65.	Labetalol/ or Nadolol/ or Oxprenolol/ or Pindolol/ or Propranolol/ or Timolol/ or Acebutolol/ or Bisoprolol/ or Celiprolol/ or Metoprolol/ or Nebivolol/
66.	exp Adrenergic alpha-Antagonists/
67.	(adrenergic alpha antagonist* or alpha adrenoreceptor blocker* or alpha blocker*).ti,ab.
68.	(Doxazosin or Prazosin or Terazosin or Cardura or Doxadura or Raporsin or Slocinx or Doxzogen or Larbex or Hypovase or Hytrin).ti,ab.
69.	Doxazosin/ or Prazosin/
70.	Antihypertensive Agents/
71.	centrally acting antihypertensive*.ti,ab.
72.	(Clonidine or Moxonidine or Minoxidil or Methyldopa or Catapres or Dixarit or Aldomet or Physiotens).ti,ab.
73.	Clonidine/ or Minoxidil/ or Methyldopa/
74.	renin inhibitor*.ti,ab.
75.	(Aliskiren or Rasilez).ti,ab.
76.	or/40-75
77.	39 and 76
78.	randomized controlled trial.pt.
79.	controlled clinical trial.pt.
80.	randomi#ed.ti,ab.
81.	placebo.ab.
82.	randomly.ti,ab.
83.	Clinical Trials as topic.sh.
84.	trial.ti.
85.	or/78-84
86.	Meta-Analysis/
87.	exp Meta-Analysis as Topic/
88.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
89.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
90.	(reference list* or bibliograph* or hand search* or manual search* or relevant

	journals).ab.
91.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
92.	(search* adj4 literature).ab.
93.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
94.	cochrane.jw.
95.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
96.	or/86-95
97.	77 and (85 or 96)

Table 7: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	exp pregnancy/
9.	exp Maternal Hypertension/
10.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
11.	exp Hypertension, Portal/ not exp Hypertension/
12.	exp Hypertension, Pulmonary/ not exp Hypertension/
13.	exp Intracranial Hypertension/
14.	exp Ocular Hypertension/ not exp Hypertension/
15.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
16.	or/8-15
17.	7 not 16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	case report/ or case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental Animal/
30.	animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
36.	34 not 35

37.	limit 36 to English language
38.	exp *Angiotensin-Converting Enzyme Inhibitors/
39.	Angiotensin-converting enzyme inhibitor*.ti,ab.
40.	(ACE inhibitor* or ACEI).ti,ab.
41.	(Captopril or Enalapril or Fosinopril or Imidapril or Lisinopril or Moexipril or Perindopril or Quinapril or Ramipril or Trandolapril or Capoten or Ecopace or Noyada or Innovace or Tanatril or Zestril or Perdix or Coversil or Accupro or Tritace).ti,ab.
42.	*Captopril/ or *Enalapril/ or *Fosinopril/ or *Imidapril/ or *Lisinopril/ or *Moexipril/ or *Perindopril/ or *Quinapril/ or *Ramipril/ or *Trandolapril/ or *enalapril maleate/
43.	*angiotensin receptor antagonist/
44.	(Angiotensin II adj3 (antagonist* or blocker*)).ti,ab.
45.	ARB.ti,ab.
46.	(Azilsartan or Candesartan or Eprosartan or Irbesartan or Losartan or Olmesartan or Telmisartan or Valsartan or Edarbi or Amias or Teveten or Aprovel or Ifirmasta or Sabervel or Cozaar or Olmetec or Tolura or Micardis or Diovan).ti,ab.
47.	*Azilsartan/ or *Candesartan/ or *Eprosartan/ or *Irbesartan/ or *Losartan/ or *Valsartan/ or *Olmesartan Medoxomil/ or *Telmisartan/
48.	exp *Calcium Channel Blockers/
49.	Calcium channel blocker*.ti,ab.
50.	CCB.ti,ab.
51.	(Amlodipine or Clevidipine or Diltiazem or Felodipine or Isradipine or Lacidipine or Lercanidipine or Nicardipine or Nifedipine or Verapamil or Amlostin or Istin or Adizem or Angitil or Dilcardia or Dilzem or Slozem or Tildiem or Viazem or Zemtard or Kenzem or Cardioplen or Felendil or Neofel or Parmid or Plendil or Pinefeld or Vascalpha or Molap or Motens or Zanidip or Cardene or Adalat or Adipine or Coracten or Fortipine or Nifedipress or Tensipine or Valni or Securon or Verapress or Vertab or Univer or Zolvera or Cleviprex).ti,ab.
52.	*Amlodipine/ or *Diltiazem/ or *Felodipine/ or *Isradipine/ or *Nicardipine/ or *Nifedipine/ or *Verapamil/
53.	*Diuretics/
54.	*thiazide diuretic agent/
55.	((thiazide or thiazide-like or non-thiazide or conventional or potassium sparing) adj3 diuretic*).ti,ab.
56.	*mineralocorticoid antagonist/
57.	((mineralocorticoid or aldosterone) adj3 antagonist*).ti,ab.
58.	(Amiloride or Cyclopenthiazide or Spironolactone or Eplerenone or Bendroflumethiazide or Hydrochlorothiazide or Co-amilozide or Co-triamterzide or Co-zidocapt or Chlortalidone or Indapamide or Metolazone or Xipamide or Carace or Zestoretic or Coversyl or Accuretic or Cozaar or Sevikar or Olmetec or Actelsar or Tolucombi or Co-Diovan or Hygroton or Co-tenidone or Kalspare or Natrilix or Cardide or Indipam or Rawel or Tensaid or Alkapamid or Zaroxolyn or Diurexan or Aprinox or Neo-Naclex or CoAprovel or Lisoretic or Dyazide or Navispare or Lasilactone).ti,ab.
59.	*Amiloride/ or *Cyclopenthiazide/ or *Spironolactone/ or *Bendroflumethiazide/ or *Hydrochlorothiazide/ or *Chlortalidone/ or *Indapamide/ or *Metolazone/ or *Xipamide/
60.	*Adrenergic beta-Antagonists/
61.	(adrenergic beta antagonist* or beta blocker* or b blocker*).ti,ab.
62.	(Carvedilol or Labetalol or Atenolol or Nadolol or Oxprenolol or Pindolol or Propranolol or Timolol or Acebutolol or Bisoprolol or Celiprolol or Esmolol or Metoprolol or Nebivolol or Carvedilol or Tenormin or Tenif or Corgard or Slow-Trasicor or Visken or Viskladix or Bedranol or Beta-Prograne or Syprol or Betim or Sectral or Cardicor or Congescor or Celectol or Breviblock or Betaloc or Lopresor or Nebilet).ti,ab.
63.	*Carvedilol/ or *Labetalol/ or *Nadolol/ or *Oxprenolol/ or *Pindolol/ or *Propranolol/ or *Timolol/ or *Acebutolol/ or *Bisoprolol/ or *Celiprolol/ or *Metoprolol/ or *Nebivolol/

64.	exp *Adrenergic alpha-Antagonists/
65.	(adrenergic alpha antagonist* or alpha adrenoreceptor blocker* or alpha blocker*).ti,ab.
66.	(Doxazosin or Prazosin or Terazosin or Cardura or Doxadura or Raporsin or Slocinx or Doxzogen or Larbex or Hypovase or Hytrin).ti,ab.
67.	*doxazosin/ or *Prazosin/ or *Terazosin/
68.	*Antihypertensive Agents/
69.	centrally acting antihypertensive*.ti,ab.
70.	(Clonidine or Moxonidine or Methyldopa or Catapres or Dixarit or Aldomet or Physiotens).ti,ab.
71.	*clonidine/ or *moxonidine/ or *Methyldopa/
72.	renin inhibitor*.ti,ab.
73.	(Aliskiren or Rasilez).ti,ab.
74.	*Aliskiren/
75.	or/38-74
76.	37 and 75
77.	random*.ti,ab.
78.	factorial*.ti,ab.
79.	(crossover* or cross over*).ti,ab.
80.	((doubl* or singl*) adj blind*).ti,ab.
81.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
82.	crossover procedure/
83.	single blind procedure/
84.	randomized controlled trial/
85.	double blind procedure/
86.	or/77-85
87.	systematic review/
88.	meta-analysis/
89.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
90.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
91.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
92.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
93.	(search* adj4 literature).ab.
94.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
95.	cochrane.jw.
96.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
97.	or/87-96
98.	76 and (86 or 97)

Table 8: Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hypertension] explode all trees
#2.	hypertens*:ti,ab
#3.	(elevat* near/2 blood next pressur*):ti,ab
#4.	(high near/1 blood near/1 pressur*):ti,ab
#5.	(increase* near/2 blood pressur*):ti,ab
#6.	((systolic or diastolic or arterial) near/2 pressur*):ti,ab

#7.	(or #1-#6)
#8.	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#9.	Angiotensin-converting enzyme inhibitor*:ti,ab
#10.	(ACE inhibitor* or ACEI):ti,ab
#11.	(Captopril or Enalapril or Fosinopril or Imidapril or Lisinopril or Moexipril or Perindopril or Quinapril or Ramipril or Trandolapril or Capoten or Ecopace or Noyada or Innovace or Tanatril or Zestril or Perdix or Coversil or Accupro or Tritace):ti,ab
#12.	MeSH descriptor: [Captopril] explode all trees
#13.	MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#14.	(AngiotensinII near/3 (antagonist* or blocker*)):ti,ab
#15.	ARB:ti,ab
#16.	(Azilsartan or Candesartan or Eprosartan or Irbesartan or Losartan or Olmesartan or Telmisartan or Valsartan or Edarbi or Amias or Teveten or Aprovel or Ifirmasta or Sabervel or Cozaar or Olmetec or Tolura or Micardis or Diovan):ti,ab
#17.	MeSH descriptor: [Losartan] explode all trees
#18.	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#19.	Calcium channel blocker*:ti,ab
#20.	CCB:ti,ab
#21.	(Amlodipine or Clevidipine or Diltiazem or Felodipine or Isradipine or Lacidipine or Lercanidipine or Nicardipine or Nifedipine or Verapamil or Amlostin or Istin or Adizem or Angitil or Dilcardia or Dilzem or Slozem or Tildiem or Viazem or Zemtard or Kenzem or Cardioplen or Felendil or Neofel or Parmid or Plendil or Pinefeld or Vascalpha or Molap or Motens or Zanidip or Cardene or Adalat or Adipine or Coracten or Fortipine or Nifedipress or Tensipine or Valni or Securon or Verapress or Vertab or Univer or Zolvera or Cleviprex):ti,ab
#22.	MeSH descriptor: [Amlodipine] explode all trees
#23.	MeSH descriptor: [Diuretics] this term only
#24.	MeSH descriptor: [Sodium Chloride Symporter Inhibitors] this term only
#25.	((thiazide* or thiazide-like or non-thiazide or conventional or potassium sparing) near/3 diuretic*):ti,ab
#26.	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#27.	((mineralocorticoid or aldosterone) near/3 antagonist*):ti,ab
#28.	(Amiloride or Cyclopenthiazide or Spironolactone or Eplenerone or Bendroflumethiazide or Hydrochlorothiazide or Co-amilozide or Co-triamterzide or Co-zidocapt or Chlortalidone or Indapamide or Metolazone or Xipamide or Carace or Zestoretic or Coversyl or Accuretic or Cozaar or Sevikar or Olmetec or Actelsar or Tolucombi or Co-Diovan or Hygroton or Co-tenidone or Kalspare or Natrilix or Cardide or Indipam or Rawel or Tensaid or Alkapamid or Zaroxolyn or Diurexan or Aprinox or Neo-Naclex or CoAprovel or Lisoretic or Dyazide or Navispare or Lasilactone):ti,ab
#29.	MeSH descriptor: [Amiloride] explode all trees
#30.	MeSH descriptor: [Adrenergic beta-Antagonists] this term only
#31.	(adrenergic beta antagonist* or beta blocker* or b blocker*):ti,ab
#32.	(Carvedilol or Labetalol or Atenolol or Nadolol or Oxprenolol or Pindolol or Propranolol or Timolol or Acebutolol or Bisoprolol or Celiprolol or Esmolol or Metoprolol or Nebivolol or Carvedilol or Tenormin or Tenif or Corgard or Slow-Trasicor or Visken or Viskladix or Bedranol or Beta-Prograne or Syprol or Betim or Sectral or Cardicor or Congescor or Celectol or Breviblock or Betaloc or Lopresor or Nebilet):ti,ab
#33.	MeSH descriptor: [Labetalol] explode all trees
#34.	MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#35.	(adrenergic alpha antagonist* or alpha adrenoreceptor blocker* or alpha blocker*):ti,ab
#36.	(Doxazosin or Prazosin or Terazosin or Cardura or Doxadura or Raporsin or Slocinx or Doxzogen or Larbex or Hypovase or Hytrin):ti,ab

#37.	MeSH descriptor: [Doxazosin] explode all trees
#38.	MeSH descriptor: [Antihypertensive Agents] this term only
#39.	centrally acting antihypertensive*:ti,ab
#40.	(Clonidine or Moxonidine or Methyldopa or Catapres or Dixarit or Aldomet or Physiotens):ti,ab
#41.	MeSH descriptor: [Clonidine] explode all trees
#42.	renin inhibitor*:ti,ab
#43.	(Aliskiren or Rasilez):ti,ab
#44.	(or #8-#43)
#45.	#7 and #44

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017.

For more detailed information, please see the Methodology Review.

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to hypertension in adults population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 9: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014–28 August 2018	Exclusions Health economics studies
Embase	2014–28 August 2018	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception–28 August 2018 NHS EED - Inception to March 2015	None

Table 10: Medline (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/

14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	Economics/
29.	Value of life/
30.	exp "Costs and Cost Analysis"/
31.	exp Economics, Hospital/
32.	exp Economics, Medical/
33.	Economics, Nursing/
34.	Economics, Pharmaceutical/
35.	exp "Fees and Charges"/
36.	exp Budgets/
37.	budget*.ti,ab.
38.	cost*.ti.
39.	(economic* or pharmaco?economic*).ti.
40.	(price* or pricing*).ti,ab.
41.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
42.	(financ* or fee or fees).ti,ab.
43.	(value adj2 (money or monetary)).ti,ab.
44.	or/28-43
45.	27 and 44

Table 11: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(elevat* adj2 blood adj pressur*).ti,ab.
4.	(high adj blood adj pressur*).ti,ab.
5.	(increase* adj2 blood pressur*).ti,ab.
6.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.

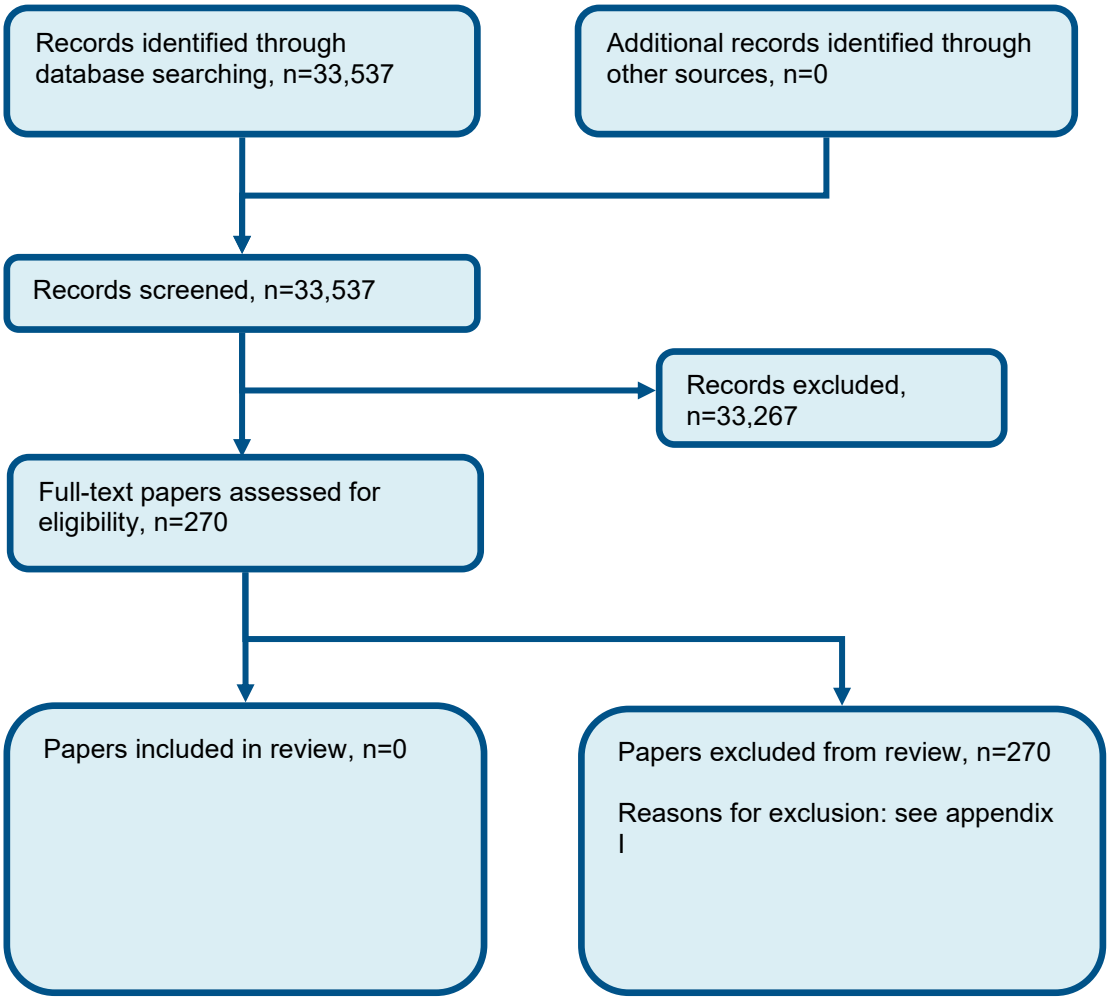
13.	or/8-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
35.	(price* or pricing*).ti,ab.
36.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
37.	(financ* or fee or fees).ti,ab.
38.	(value adj2 (money or monetary)).ti,ab.
39.	or/26-38
40.	25 and 39

Table 12: NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hypertension EXPLODE ALL TREES IN NHSEED,HTA
#2.	(Hypertens*) IN NHSEED, HTA
#3.	(elevat* adj2 blood adj pressur*) IN NHSEED, HTA
#4.	(high adj blood adj pressur*) IN NHSEED, HTA
#5.	(increase* adj2 blood pressur*) IN NHSEED, HTA
#6.	((systolic or diastolic or arterial) adj2 pressur*) IN NHSEED, HTA
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of step 2 or step 3 treatment



Appendix D: Clinical evidence tables

None.

Appendix E: Forest plots

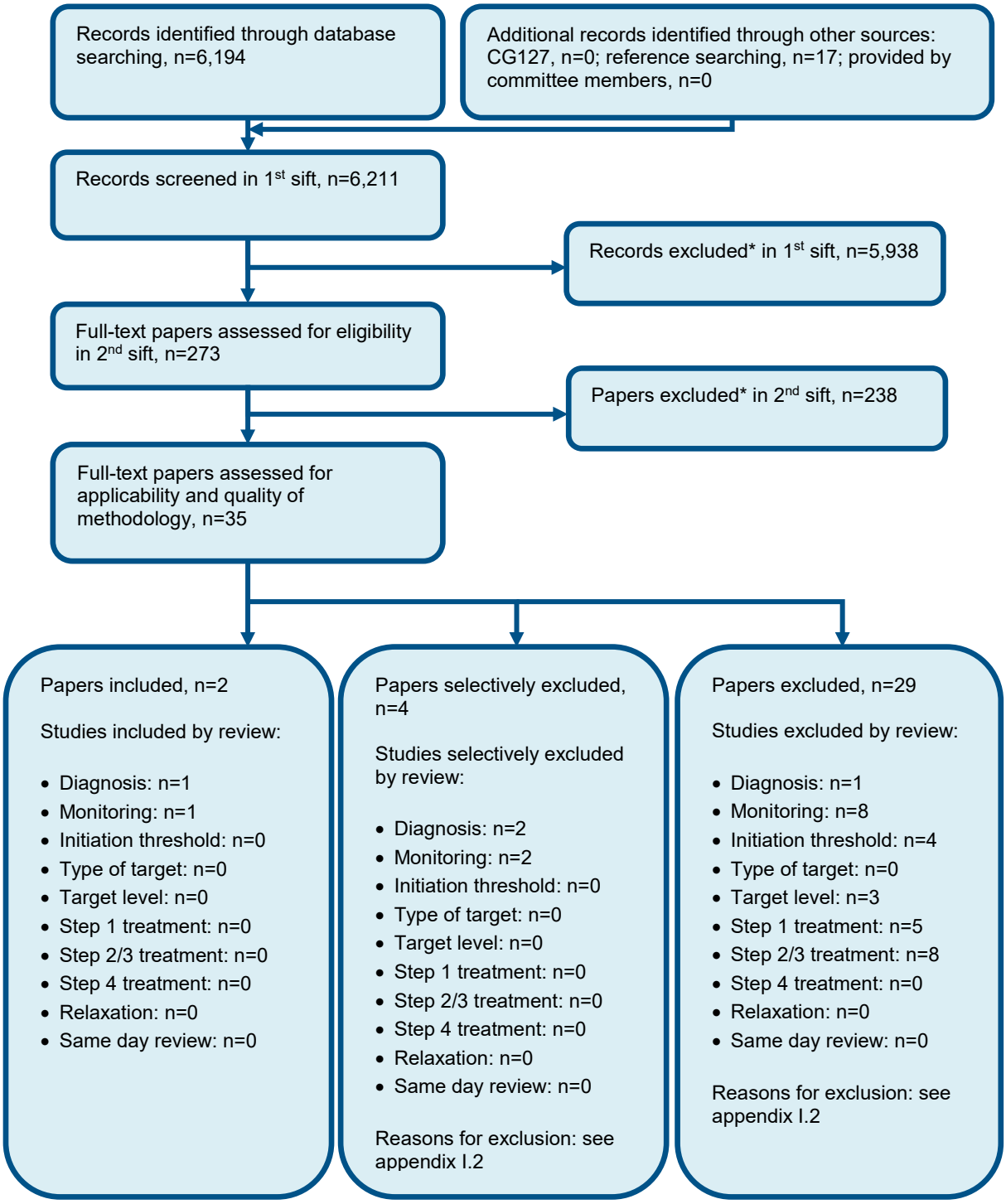
None.

Appendix F: GRADE tables

None.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table13: Studies excluded from the clinical review that were included in the previous guideline (CG127)

Study	Exclusion reason
Jamerson 2008 (ACCOMPLISH trial)	Incorrect study design and incorrect interventions. Study compared initial combination therapy versus combination therapy at step 1 rather than the population having an inadequate response to monotherapy and being randomised to a second drug. The medication used (benazepril) was also not licensed in the UK.

Table 14: Studies excluded from the clinical review

Study	Exclusion reason
Abarquez 1993[1]	Less than minimum duration
Abascal 1998[2]	Incorrect study design
Abe 2007[3]	Not review population
Abe 2009[4]	Less than minimum duration
Abetel 1984[5]	Not in English
Adir 1987[6]	Inappropriate comparison
Adolphe 1993[7]	Less than minimum duration
Agabiti-rosei 1992[8]	Less than minimum duration. Inappropriate comparison
Agabiti-rosei 2005[9]	No relevant outcomes
Agarwal 2013[10]	Less than minimum duration
Ahola 2012[11]	Incorrect study design
Ahrens 2010[12]	Incorrect study design
Akanabe 1985[13]	Less than minimum duration
Akioyamen 2016[14]	Systematic review, references checked
Akram 2007[15]	Less than minimum duration
Alderman 1989[16]	Inappropriate comparison
Alici 2009[17]	Less than minimum duration. Inappropriate comparison
ALLHAT collaborators 2000[18]	Inappropriate comparison
ALLHAT officers 2002[19]	Inappropriate comparison
Alviar 2013[20]	Inappropriate comparison
Amar 1999[21]	Article not in English
Ames 1992[22]	Less than minimum duration
Amir 1994[23]	No relevant outcomes
Andersen 1986[24]	Inappropriate comparison

Study	Exclusion reason
Andersen 2003[25]	Inappropriate comparison
Andersen 2005[26]	Inappropriate comparison
Ando 2014[27]	Incorrect population
Andreadis 2005[28]	Less than minimum duration
Andren 1983[29]	Less than minimum duration
Andreucci 1983[30]	Incorrect study design. Incorrect interventions
Angeli 2004[31]	Not review population
Anonymous 1999[34]	Inappropriate comparison
Anonymous 2018[35]	Article not in English
Anonymous 1993[32]	Inappropriate comparison
Anonymous 1996[33]	Less than minimum duration
Applegate 1991[36]	No relevant outcomes. Incorrect study design
Arima 2014[37]	Not review population
Arriaga-gracia 1993[38]	Less than minimum duration
Bakris 2007[40]	Not review population
Bakris 2013[39]	Not review population
Balamuthusamy 2009[41]	Systematic review - references checked
Baldwin 1987[42]	Inappropriate comparison
Bang 2017[43]	Incorrect interventions
Bangalore 2008[44]	Systematic review, references checked. Inappropriate comparison
Benjamin 1988[46]	Incorrect study design
Berger 1992[47]	Less than minimum duration
Black 2003[48]	Inappropriate comparison
Blumenthal 1990[49]	Less than minimum duration
Boissel 1995[51]	Inappropriate comparison
Borgmastars 1987[52]	No relevant outcomes
Bremner 1997[53]	Incorrect interventions
Brenner 2001[54]	Not review population
Brown 2001[55]	Less than minimum duration
Byrd 2011[56]	Not review population
Byyny 1996[57]	Less than minimum duration. Inappropriate comparison
Castano 2004[58]	Inappropriate comparison
Celis 1996[59]	Inappropriate comparison
Cesaris 1986[60]	Article not in English
Chatellier 1987[61]	Less than minimum duration
Chi 2016[64]	Systematic review, references checked. Less than minimum duration
Chrysant 1997[65]	Incorrect study design. Inappropriate comparison
Circelli 2012[66]	Less than minimum duration
Coope 1986[67]	Inappropriate comparison
Correa 2018[68]	Incorrect study design
Cowley 1987[69]	Less than minimum duration
Cranston 1962[70]	Incorrect study design
Curb 1996[71]	Inappropriate comparison
Daae 1998[72]	Incorrect interventions
Dahlof 2002[74]	Less than minimum duration

Study	Exclusion reason
Dahlöf 2005[73]	Incorrect study design
Daien 2012[75]	Systematic review, references checked
De rosa 2002[76]	Inappropriate comparison
Degl'innocenti 2004[77]	Inappropriate comparison
Destro 2010[78]	Incorrect study design
Devereux 2007[79]	Inappropriate comparison
Dews 2001[80]	Incorrect study design
Diao 2012[81]	Inappropriate comparison
Du 2018[82]	Incorrect study design
Ekbom 1992[83]	Incorrect study design
Ekbom 2004[84]	Incorrect interventions. Incorrect study design
Estacio 1998[86]	Not review population
Family Physicians Hypertension Study Group 1984[87]	Less than minimum duration
Fariello 1990[88]	Less than minimum duration
Farsang 2003[89]	Incorrect study design
Fasano 1989[90]	Incorrect study design. Incorrect interventions
Faust 1993[92]	Article not in English
Faust 1993[91]	Article not in English
Ferdinand 2001[93]	Incorrect study design
Fernandes 2016[94]	Less than minimum duration
Fernandez 2001[95]	Less than minimum duration
Ferrara 1984[96]	No relevant outcomes
Finnerty 1979[97]	Incorrect interventions
Fogari 1991[103]	No relevant outcomes
Fogari 1996[101]	Incorrect study design. Incorrect interventions
Fogari 1999[100]	Inappropriate comparison
Fogari 2006[99]	Less than minimum duration
Fogari 2012[102]	Less than minimum duration
Fogari 2014[98]	Less than minimum duration
Forette 2002[104]	Inappropriate comparison
Forrest 1983[105]	Less than minimum duration
Fossum 2004[106]	No relevant outcomes. Inappropriate comparison
Franco 1992[107]	Article not in English
Franse 2000[108]	Incorrect interventions. Inappropriate comparison
Frewin 1991[109]	Incorrect study design. Incorrect interventions
Frick 1986[111]	Inappropriate comparison
Frick 1987[110]	No relevant outcomes. Inappropriate comparison
Gao 2011[113]	Systematic review, references checked
Gasowski 1999[114]	Incorrect study design. Incorrect interventions
Gazdick 1994[115]	Incorrect study design
George 1990[116]	Less than minimum duration
Ghiadoni 2017[117]	Less than minimum duration
Giles 1992[118]	Inappropriate comparison. No relevant outcomes
Gillespie 2005[119]	Systematic review, references checked

Study	Exclusion reason
Girerd 2010[120]	Incorrect study design
Gitt 2013[121]	Incorrect study design
Glorioso 2007[122]	Incorrect study design. Less than minimum duration
Goicolea 2002[123]	Article not in English
Gosse 2002[124]	Inappropriate comparison
Grimm 1996[125]	Incorrect study design
Guo 2005[127]	Article not in English
Guo 2011[126]	Article not in English
Gupta 2018[128]	Incorrect interventions
Gyntelberg 1977[129]	Article not in English
Hall 1998[130]	Inappropriate comparison
Hamada 2010[132]	No relevant outcomes
Hamada 2014[131]	No relevant outcomes
Hamed 2014[133]	Less than minimum duration. Incorrect study design
Hanon 2015[134]	Inappropriate comparison
Hanon 2017[135]	Inappropriate comparison
Hansson 1999[138]	Inappropriate comparison
Hansson 1999[137]	Inappropriate comparison
Hansson 1999[139]	Inappropriate comparison
Hansson 2000[136]	Inappropriate comparison
Hasegawa 2011[140]	Inappropriate comparison
Helgeland 1980[141]	Inappropriate comparison
Helgeland 1983[142]	Less than minimum duration
Himmelmann 1995[143]	Inappropriate comparison
Hosie 1983[144]	Inappropriate comparison
Hradec 2013[145]	Inappropriate comparison
Hughes 2008[146]	Incorrect interventions. No relevant outcomes
Hulley 1985[147]	Inappropriate comparison
Ibsen 1990[149]	Incorrect interventions
Ibsen 2003[148]	Article not in English
Ichihara 2006[150]	Inappropriate comparison
J. Elan investigators 2006[151]	Inappropriate comparison
Jamerson 2008[152]	Incorrect study design
Johnson 2009[153]	No relevant outcomes
Johnston 1991[154]	Inappropriate comparison
Julius 2004[155]	Not review population
Kaku 2011[156]	Inappropriate comparison
Katayama 2008[157]	Inappropriate comparison
Kawalec 2018[158]	Incorrect study design
Kereiakes 2012[159]	Less than minimum duration
Kerfoot 2014[160]	Incorrect study design. Incorrect interventions. Inappropriate comparison
Kim 2012[162]	Incorrect interventions
Kim 2013[161]	No relevant outcomes
Kjeldsen 2002[163]	Inappropriate comparison
Kjeldsen 2006[166]	Incorrect interventions

Study	Exclusion reason
Kjeldsen 2008[165]	Incorrect population
Kjeldsen 2016[164]	Incorrect interventions
Ko 2001[167]	Not review population
Kohlmann 2009[168]	Inappropriate comparison
Kostis 2005[169]	Inappropriate comparison
Kuwajima 2001[171]	Not review population
Lacourciere 2000[172]	Incorrect study design
Laufer 1998[173]	Incorrect interventions. No relevant outcomes
Laurent 2014[174]	Inappropriate comparison
Lavenius 1982[175]	Less than minimum duration
Leonetti 2002[176]	Inappropriate comparison
Levine 2001[177]	Incorrect study design
Licata 1994[178]	Less than minimum duration
Lim 2000[179]	Less than minimum duration
Lin 1991[180]	Incorrect interventions
Lin 1993[181]	Less than minimum duration
Lin 1995[182]	Incorrect interventions
Lind 1994[183]	No relevant outcomes
Lindholm 1996[185]	Incorrect interventions
Lindholm 2000[186]	Incorrect interventions
Lindholm 2001[184]	Not review population
Lindholm 2002[188]	Inappropriate comparison
Lindholm 2002[187]	Incorrect interventions. Incorrect study design
Lindner 1984[189]	Article not in English
Lindroos 1984[190]	Less than minimum duration
Littlejohn 2009[191]	Less than minimum duration
Liu 1999[193]	Inappropriate comparison
Liu 2000[192]	Not in English
Lombardo 1997[194]	Inappropriate comparison
López 1997[195]	Article not in English
Lu 2017[196]	Systematic review, references checked
Ludwig 2002[197]	Inappropriate comparison
Luno 2017[198]	Not review population
Lynch 2008[199]	Inappropriate comparison
Lynch 2012[200]	Inappropriate comparison
Maclean 1986[202]	Not review population
Maclean 1986[203]	Less than minimum duration
Malacco 2003[204]	Incorrect interventions. Incorrect study design
Malminiemi 2000[205]	Inappropriate comparison. No relevant outcomes
Mancia 2007[206]	Incorrect study design. Incorrect interventions
Mann 1998[208]	Incorrect study design
Marfatia 2012[209]	Less than minimum duration
Marre 2004[210]	Incorrect interventions
Martinez-martin 2011[211]	Inappropriate comparison
Mason 2005[212]	Systematic review - references checked

Study	Exclusion reason
Matsuno 2011[213]	Not review population. No relevant outcomes
Matsushita 2010[214]	Incorrect study design. Inappropriate comparison
Matsuzaki 2011[215]	Inappropriate comparison
Mazza 2016[216]	No relevant outcomes
M'Buyamba-kabangu 1987[201]	Less than minimum duration
Mcareavey 1983[217]	No relevant outcomes
Mende 2017[218]	Less than minimum duration
Metelitsa 1991[219]	Incorrect interventions
Metelitsa 1991[220]	Article not in English
Middeke 1990[221]	No relevant outcomes
Middeke 1997[222]	Inappropriate comparison
Misson 1984[223]	No relevant outcomes
Mizuno 2017[224]	Less than minimum duration
Morgan 1989[225]	Less than minimum duration
Mroczek 1984[226]	Inappropriate comparison
Muller 1986[227]	no relevant outcomes
Nakae 2006[228]	Article not in English
Nct[230]	Citation only
Neutel 1999[232]	Incorrect study design. Incorrect interventions
Neutel 2017[231]	Not review population
Oberman 1983[233]	Less than minimum duration
Ocón 1985[234]	Not in English
Ogawa 2012[235]	Incorrect interventions
Ogihara 2000[236]	Inappropriate comparison
Ogihara 2012[237]	Inappropriate comparison
Ogihara 2014[238]	Inappropriate comparison
Ogihara 2015[239]	Inappropriate comparison
Ohnishi 2001[240]	No relevant outcomes
Okin 2012[241]	Incorrect study design. Inappropriate comparison
Oshikawa 2014[242]	Not review population
Ostergren 2008[243]	Not review population
Park 2017[244]	No relevant outcomes
Patay 2010[245]	Incorrect study design
Persson 1986[246]	Incorrect study design
Philip 1987[247]	Less than minimum duration
Pierini 2013[248]	Less than minimum duration. Inappropriate comparison
Piller 2006[249]	Inappropriate comparison. No relevant outcomes
Remonti 2016[250]	NMA, references checked
Ritter 2013[251]	Incorrect study design
Roush 2018[252]	Inappropriate comparison
Ruoff 1986[253]	Inappropriate comparison
Russell 1985[254]	Inappropriate comparison
Safar 1994[255]	Incorrect study design
Saha 2005[256]	Less than minimum duration. Not review population
Saini 1998[257]	Inappropriate comparison

Study	Exclusion reason
Saku 1996[261]	Inappropriate comparison
Sano 1994[262]	Inappropriate comparison
Saruta 2015[263]	Inappropriate comparison
Sato 2002[264]	Inappropriate comparison. No relevant outcomes
Sato 2009[265]	Citation only
Sato 2012[266]	Incorrect study design
Sato 2013[267]	Not review population
Seedat 1992[268]	Less than minimum duration
Seedat 1998[269]	Incorrect interventions
Soucek 2007[270]	Article not in English
Spoelstra-de Man 2006[271]	Inappropriate comparison
Stamler 1986[272]	Incorrect interventions
Swales 1982[273]	Incorrect study design
Thomopoulos 2017[274]	Incorrect study design
Trimarco 2015[275]	Incorrect study design
Umemoto 2017[276]	Inappropriate comparison
Wallin 1983[277]	Inappropriate comparison
White 2008[278]	Inappropriate comparison

I.2 Excluded health economic studies

Table 15: Studies excluded from the health economic review

Reference	Reason for exclusion
Belsey 2011[45]	This study was assessed as not applicable as it was comparing different monotherapies of the same class (different ARB's) with the addition of the same second drug in all arms. This design of study is not applicable because the focus of the review is to compare different add on drugs as second line to the same monotherapies to determine the best sequence of drugs.
Ekman 2008[85]	This study was assessed as not applicable as it was comparing combinations of different types of ARB's with the addition of a thiazide. The focus of the review is not to compare within class drugs, or which is the best monotherapy, but to compare different add on drugs as second line to the same monotherapies to determine the best sequence of drugs.
Fujikawa 2005[112]	This study was assessed as not applicable as it was comparing increasing the dose of monotherapy versus combination therapy. The outcomes were also cost per patient achieving BP target which is less applicable than a cost utility analysis.
Kourlaba 2013[170]	This study was assessed as not applicable as it was comparing combinations of different types of ARB's with the addition of a thiazide. The focus of the review is not to compare within class drugs, or which is the best monotherapy, but to compare different add on drugs as second line to the same monotherapies to determine the best sequence of drugs.
Maniadakis 2011[207]	This study was assessed as not applicable as it was comparing combinations of different types of ARB's with the addition of a thiazide. The focus of the review is not to compare within class drugs, or which is the best monotherapy, but to compare different add on drugs as second line to the same monotherapies to determine the best sequence of drugs.

Reference	Reason for exclusion
Saito 2005[260]	This study was assessed as not applicable as people begin on monotherapy but only go onto combination if they do not meet their targets. Therefore it is not comparing different combinations from the outset.
Saito 2006[258]	This study was assessed as not applicable as it was comparing different stepwise approaches of increasing doses or adding other drugs if targets are note met. Therefore it is not comparing different combinations from the outset. The outcome is also cost per lowering one unit of BP which is less applicable than a cost utility analysis.
Saito 2007[259]	This study was assessed as not applicable as it was comparing different stepwise approaches of increasing doses or adding other drugs if targets are note met. Therefore it is not comparing different combinations from the outset. The outcome is also cost per patient achieving BP target which is less applicable than a cost utility analysis.