

# Hypertension in adults: diagnosis and management

[G] Evidence review for step 4 treatment

*NICE guideline NG136*

*Intervention evidence review underpinning recommendations  
1.4.44 to 1.4.50 in the guideline*

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*Final*

*This evidence review was developed by  
the National Guideline Centre*



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# 1 Step 4 treatment

## 1.1 Review question: What is the most clinically and cost-effective sequence for step 4 treatment for hypertension?

## 1.2 Introduction

Antihypertensive treatment is usually very effective in lowering blood pressure to within normal limits. However, in some individuals, blood pressure remains elevated despite being prescribed multiple antihypertensive medications, and these individuals remain at an elevated risk of cardiovascular events. The term 'resistant hypertension' is commonly applied to individuals who are prescribed 3 antihypertensive medications including a diuretic, but their blood pressure remains above the target. Those with resistant hypertension have double the risk of cardiovascular events than those without resistant hypertension, thus making them an important group to study. Estimates vary as to what proportion of those with hypertension have 'resistant hypertension', but it is generally thought to be around 5%.

Current clinical practice when selecting a step 4 treatment is to choose 1 of a number of medications based on the person's and the clinician's preference without robust evidence as to which might lower blood pressure the most effectively. During the guideline scoping process, a number of recently published clinical studies were highlighted that were designed to identify which medication(s) would be the optimal choice as step 4 treatment. In this chapter, the evidence for choosing a step 4 medication was reviewed.

## 1.3 PICO table

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

**Table 1: PICO characteristics of review question**

<b>Population</b>	Adults (aged 18 years and older) with primary hypertension who are taking the maximally tolerated doses of at least 3 drugs (including a diuretic) and their blood pressure is still not controlled.
<b>Intervention</b>	Step 4 antihypertensive pharmacological treatment received for a minimum of 1 year. Examples include: <ul style="list-style-type: none"> <li>• Alpha-blockers</li> <li>• Beta-blockers</li> <li>• Other or further diuretics such as amiloride and spironolactone</li> <li>• Aliskiren (direct renin inhibitors)</li> <li>• Clonidine, minoxidil, methyldopa, moxonidine (centrally acting antihypertensive)</li> </ul>
<b>Comparison</b>	Compared against each other (class comparisons) Compared to placebo (class compared to placebo)
<b>Outcomes</b>	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. <p><b>Critical</b></p> <ul style="list-style-type: none"> <li>• All-cause mortality</li> <li>• Health-related quality of life</li> <li>• Stroke (ischaemic or haemorrhagic)</li> <li>• Myocardial infarction (MI)</li> </ul> <p><b>Important</b></p>

	<ul style="list-style-type: none"><li>• Heart failure needing hospitalisation</li><li>• Vascular procedures (including lower limb, coronary and carotid artery procedures)</li><li>• Angina needing hospitalisation</li><li>• Discontinuation or dose reduction due to side effects</li><li>• Side effect 1: Acute kidney injury</li><li>• Side effect 2: New onset diabetes</li><li>• Side effect 3: Change in creatinine or eGFR</li><li>• Side effect 4: Hypotension (dizziness)</li><li>• [Combined cardiovascular disease outcomes in the absence of MI and stroke data]</li><li>• [Coronary heart disease outcome in the absence of MI data]</li></ul>
<b>Study design</b>	Randomised controlled trials (RCT) and systematic reviews (SR)

## 1.4 Clinical evidence

### 1.4.1 Included studies

No relevant clinical studies comparing step 4 antihypertensive pharmacological treatment 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

One Cochrane review relevant to this review question was identified.<sup>44</sup> This was excluded because it included crossover studies without the minimum washout period of 4 weeks as required for inclusion within this review. The references were checked for any relevant studies.

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.

See the excluded studies list in appendix I.

## 1.5 Economic evidence

### 1.5.1 Included studies

No relevant health economic studies were identified.

### 1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

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

### 1.5.3 Resource costs

Costs are illustrated below for average doses of the most commonly used drugs from each class listed on the review protocol, based on committee opinion.

**Table 2: UK costs of step 4 drugs**

Drug	Detail	Daily dose	Cost/ month (£)	Cost/ year (£)
<b>Alpha blockers</b>				
Doxazosin	4 mg tablets, 28 pack = £1	4 mg per day	£1.13	£13.56
<b>Beta blockers</b>				
Bisoprolol fumarate	5 mg tablets, 28 pack = £0.59	5 mg per day	£0.64	£7.69
<b>Further diuretics</b>				
Amiloride	5 mg tablets, 28 pack = £2.60	5 mg per day	£2.82	£33.89
Spironolactone	25 mg tablets, 28 pack = £1	25 mg per day	£1.09	£13.04
<b>Direct renin inhibitors</b>				
Aliskiren	150 mg tablets, 28 pack = £28.51	150 mg per day	£30.97	£371.65
<b>Centrally acting anti-hypertensives</b>				
Moxonidine	0.2 mg tablets, 28 pack = £1.02	0.4 mg per day	£2.22	£26.59

(a) Costs are from the BNF drug tariff price. Accessed in May 2019. <sup>49</sup>

## 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 and discontinuation or dose reduction due to side effects were also considered important for decision-making.

No relevant clinical studies were identified therefore no evidence was available for any of these outcomes.

### 1.7.1.2 The quality of the evidence

No clinical studies relevant to the review question were identified.

### 1.7.1.3 Benefits and harms

No clinical studies relevant to this review protocol were identified.

The committee discussed the use of different step 4 antihypertensive treatments. It agreed that there was very little evidence within this area, so the committee formed consensus recommendations based on their clinical experience. They were aware of a trial (PATHWAY-2) that assessed the step 4 treatment in resistant hypertension. After discussing the findings of the PATHWAY-2 trial, they agreed that this study did not meet the inclusion criteria for this review due to having a short follow-up and no outcomes relevant to the agreed protocol. Nevertheless, it suggested that adding spironolactone could be effective at reducing blood pressure as a step 4 treatment. It was noted that higher doses of spironolactone were used (25 mg–50 mg), and the 50 mg dose was noted to lower blood pressure more. However, it was unclear what proportion of people were receiving the 50 mg dose. The study also suggested that amiloride could be as effective as spironolactone in lowering blood pressure. However, the committee noted that amiloride is more expensive, and it is taken twice a day, whereas spironolactone is taken only once daily making it a more convenient option for people who are already taking multiple medications. The committee agreed that changes in blood pressure alone, without information on cardiovascular events was not very informative to patient important outcomes, however they agreed that there was no evidence to suggest a better treatment option was available than spironolactone, which was now part of common clinical practice, and so it should still be recommended as step 4 treatment for those who had an inadequate response to 3 previous treatments.

It was discussed that the previous spironolactone dose recommendation of 25 mg once daily was too specific given the limited evidence base; instead, the committee decided to leave this more open as a 'low-dose' if the potassium level was 4.5 mmol/l or lower. The committee suggested that they were aware of recent evidence, outside of the remit for this review, which suggested a smaller dose of 12.5 mg could be effective as a step 4 treatment. The committee also agreed that there was no evidence with hard outcomes data to warrant recommending a higher dose thiazide in people with higher potassium levels, and it was agreed that in this case alpha- or beta-blockers should be considered instead, as higher dose thiazide diuretics are not more effective than lower dose thiazide diuretics.

The need for further research to inform choice of step 4 treatment was discussed; however, the committee considered this would be unlikely to be funded, as the PATHWAY-2 trial had addressed this question previously, despite not including the hard cardiovascular outcomes this committee considered necessary to make a strong recommendation on the topic.

The committee discussed the need to seek specialist advice in order to investigate alternative reasons for a lack of response to treatment, such as adherence issues or secondary causes of hypertension to better manage treatment. The previous guideline recommendation stated that specialist advice should be sought regardless of whether a fourth antihypertensive drug was already added. The committee agreed that its clinical experience suggested the decision to seek specialist advice would be made on a case-by-case basis, but generally, it would either be appropriate to treat a person with resistant hypertension or to seek specialist advice. The committee highlighted the importance of taking the person's preference into account, particularly where people might be concerned that they are already on 3 drugs and hadn't responded well to these. The committee therefore agreed to reword the previous recommendation to clarify that either option should be considered.

The committee discussed the long-term implications of spironolactone treatment. Although there was no evidence identified for this within the review, including a lack of information on adverse events, the committee agreed that the multiple known harms of consistently high



blood pressure outweighed this uncertainty. They did agree, however, that further evidence was required in order for healthcare professionals and people with hypertension to understand the choice of drugs available and the benefit and harms associated with each of these.

The committee discussed the use of ambulatory or home blood pressure measurement to confirm elevated blood pressure levels based on their experience and current practice. It was agreed that this is generally the method used in current practice to confirm resistant hypertension. Although there could be some variation in current practice, the committee agreed that this is the best and most accurate method of identifying people with resistant hypertension. Screening for postural hypotension was also considered an important factor to include in a recommendation, as it could affect whether additional treatment could be harmful.

### 1.7.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

The drugs that could be used for resistant hypertension can vary in price; for example, amiloride hydrochloride is more expensive than spironolactone. The population affected with resistant hypertension, although being a small proportion of those with hypertension (around 6%), still results in a large amount of people given the size of the hypertensive population.

It was discussed how the measurement method to confirm resistant hypertension is important and best practice would be to confirm elevated measurements using ambulatory or home blood pressure recordings. This has been added as a recommendation and is generally already believed to be current practice. But where it is not, it will be of benefit because it will more accurately identify those with resistant hypertension. The committee considered that the population on 3 drugs who actually have resistant hypertension is likely to be smaller than those labelled as having resistant hypertension. This could mean a reduction in treatment as there might be some overtreatment of resistant hypertension in practice due to inappropriate measurement (overtreatment can however also be because people are not properly adhering to their medication, rather than their medication is not working – although this is more difficult to identify). There might be some additional diagnostic costs involved if some areas do not currently confirm resistant hypertension in this way, but this depends on the measurement method; for example, if someone is already using home monitoring with their own device then that person could use the same method to diagnose if the hypertension is resistant.

There was no clinical evidence identified; therefore, the committee agreed to carry forward previous recommendations with some minor amendments. These included deleting a recommendation on considering higher dose thiazide-like diuretic therapy for those with high blood potassium levels, as this was not considered to be current practice and people would generally go onto step 4 of alpha or beta-blockers.

It was also discussed how the recommendation around seeking specialist advice for those in whom blood pressure was uncontrolled on 3 drugs was unclear, as it stated specialist advice should be sought even if a step 4 treatment was already added. The committee's opinion was that not all clinicians would seek specialist advice, as some would be more comfortable trying a step 4 treatment and some would prefer to seek advice first. The recommendation was changed to make it clearer that step 4 treatment could be considered or specialist advice could be sought. As the previous recommendation was a consider recommendation, practice was variable as to whether people were seeking specialist advice; therefore, this wording change is unlikely to have an impact on practice. It was also discussed whether it should be specified if seeking advice means referring a person to a more specialist service, or if it should be stated who this individual might be. However, the committee agreed that asking for advice is more flexible because the advice may well be to refer the person, or it

may be more of an informal discussion between clinicians. Additionally, specifying whether the specialist should be a hypertension specialist was thought to be too restrictive because the specialist could also be another role such as a cardiologist, nephrologist or endocrinologist and would really depend on local services.

On balance, the recommendations are not expected to have a resource impact.

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## Appendices

### Appendix A: Review protocols

**Table 3: Review protocol: Step 4 treatment**

Field	Content
Review question	What is the most clinically and cost-effective step 4 antihypertensive drug 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 establish which step 4 treatment is most clinically and cost effective in adults with hypertension that remains uncontrolled following step 3 treatment.
Eligibility criteria – population / disease / condition / issue / domain	Population: Adults (over 18 years) with primary hypertension are taking the maximally tolerated doses of at least 3 drugs (including a diuretic) and their blood pressure is still uncontrolled.  Stratify by: <ul style="list-style-type: none"> <li>• Presence or absence of type 2 diabetes</li> <li>• The drug class(es) previously received</li> </ul>
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Step 4 antihypertensive pharmacological treatment received for a minimum of 1 year. <ul style="list-style-type: none"> <li>• Alpha-blockers</li> <li>• Beta-blockers</li> <li>• Other or further diuretics such as amiloride and spironolactone</li> <li>• Aliskiren (direct renin inhibitors)</li> <li>• Clonidine, minoxidil, methyldopa, moxonidine (centrally acting antihypertensive)</li> </ul>
Eligibility criteria – comparator(s) / control or reference (gold) standard	<ul style="list-style-type: none"> <li>• Compared against each other (class comparisons)</li> <li>• Compared to placebo (class compared to placebo)</li> </ul>
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.  <b>Critical</b> <ul style="list-style-type: none"> <li>• All-cause mortality</li> <li>• Health-related quality of life</li> <li>• Stroke (ischaemic or haemorrhagic)</li> <li>• MI</li> </ul> <b>Important</b> <ul style="list-style-type: none"> <li>• Heart failure needing hospitalisation</li> <li>• Vascular procedures (including lower limb, coronary and carotid artery procedures)</li> <li>• Angina needing hospitalisation</li> <li>• Discontinuation or dose reduction due to side effects</li> <li>• Side effect 1: Acute kidney injury</li> </ul>



	<ul style="list-style-type: none"> <li>• Side effect 2: New onset diabetes</li> <li>• Side effect 3: Change in creatinine or eGFR</li> <li>• Side effect 4: Hypotension (dizziness)</li> <li>• [Combined cardiovascular disease outcomes in the absence of MI and stroke data]</li> <li>• [coronary heart disease outcome in the absence of MI data]</li> </ul>
Eligibility criteria – study design	RCTs and SRs
Other inclusion exclusion criteria	<p>Minimum follow up time: 1 year</p> <p>Exclusions:</p> <ul style="list-style-type: none"> <li>• 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 or chronic kidney disease (A2 or above [heavy proteinuria])</li> <li>• Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (Conn’s adenoma, pheochromocytoma, renovascular hypertension)</li> <li>• Pregnant women</li> <li>• Children (aged under 18 years)</li> <li>• Crossover trials (unless washout is 4 weeks or more)</li> <li>• Reserpine (withdrawn from UK market) – exclude studies using this treatment.</li> </ul>
Proposed sensitivity / subgroup analysis, or meta-regression	<p>Subgroups to explore heterogeneity:</p> <ul style="list-style-type: none"> <li>• Age (under 55, 55-74 and 75 or older)*</li> <li>• Family origin (African and Caribbean, White, South Asian)</li> </ul> <p>*To note that we will also extract evidence in those &gt;80 years old if this evidence is reported separately.</p>
Selection process – duplicate screening / selection / analysis	A senior research fellow will undertake quality assurance prior to completion.
Data management (software)	<p>Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).</p> <p>GRADEpro will be used to assess the quality of evidence for each outcome.</p> <p>Endnote will be used for bibliography, citations, sifting and reference management.</p>
Information sources – databases and dates	<p>Medline, Embase, the Cochrane Library</p> <p>Language: Restrict to English only</p> <p>Key papers: PATHWAY-2 trial (2015)</p> <p><a href="http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00257-3/abstract">http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00257-3/abstract</a></p>
Identify if an update	Yes, 2011
Author contacts	<a href="https://www.nice.org.uk/guidance/cg127">https://www.nice.org.uk/guidance/cg127</a>
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	A standardised evidence table format will be used, and published as appendix

process – forms / duplicate	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 <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a>
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
<b>Objectives</b>	To identify health economic studies relevant to any of the review questions.
<b>Search criteria</b>	<ul style="list-style-type: none"> <li>Populations, interventions and comparators must be as specified in the clinical review protocol above.</li> </ul>

	<ul style="list-style-type: none"> <li>• 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).</li> <li>• 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.)</li> <li>• Unpublished reports will not be considered unless submitted as part of a call for evidence.</li> <li>• Studies must be in English.</li> </ul>
<b>Search strategy</b>	<p>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.</p>
<b>Review strategy</b>	<p>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.</p> <p>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.</p> <p>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).<sup>227</sup></p> <p><b>Inclusion and exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both, then there is discretion over whether it should be included.</li> </ul> <p><b>Where there is discretion</b></p> <p>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.</p> <p>The health economist will be guided by the following hierarchies.</p> <p><i>Setting:</i></p> <ul style="list-style-type: none"> <li>• UK NHS (most applicable).</li> <li>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).</li> <li>• OECD countries with predominantly private health insurance systems (for example, Switzerland).</li> <li>• Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations.</li> </ul>

*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. [\[Add cross reference\]](#)

### 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 NHSEED 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 Cyclopenthiiazide 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 Cyclopenthiiazide/ or Spironolactone/ or Bendroflumethiazide/ or Hydrochlorothiazide/ or Chlortalidone/ or Indapamide/ or Metolazone/ or Xipamide/ or Chlorthalidone/ 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 adrenoceptor 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 Cyclopenthiiazide 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 *Cyclopenthiiazide/ 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 Zandip 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 Cyclopenthiiazide 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 adrenoceptor 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

## 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 NHSEED - 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.

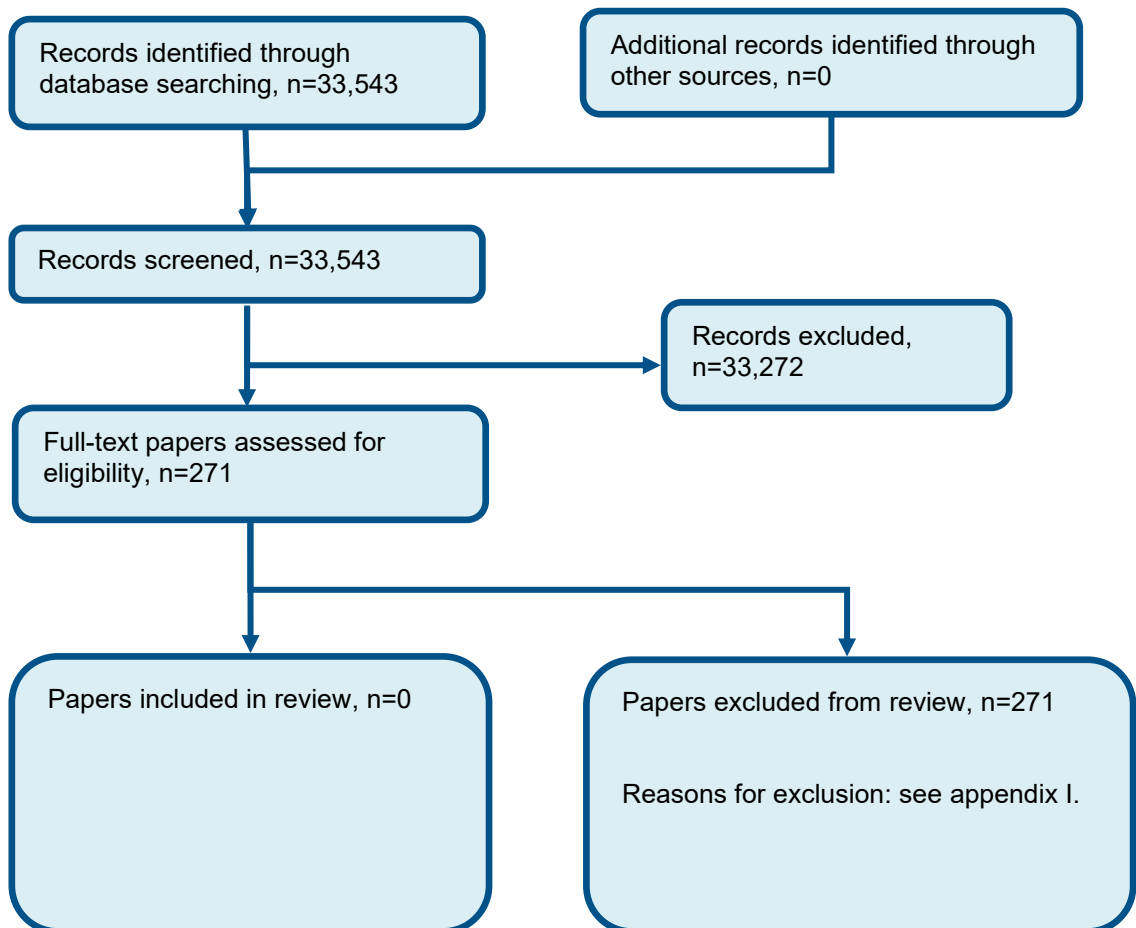
15.	13 not 14
16.	animal/ not human/
17.	nonhuman/
18.	exp Animal Experiment/
19.	exp Experimental Animal/
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	health economics/
27.	exp economic evaluation/
28.	exp health 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 4 treatment



## **Appendix D: Clinical evidence tables**

None.

## **Appendix E: Forest plots**

None.

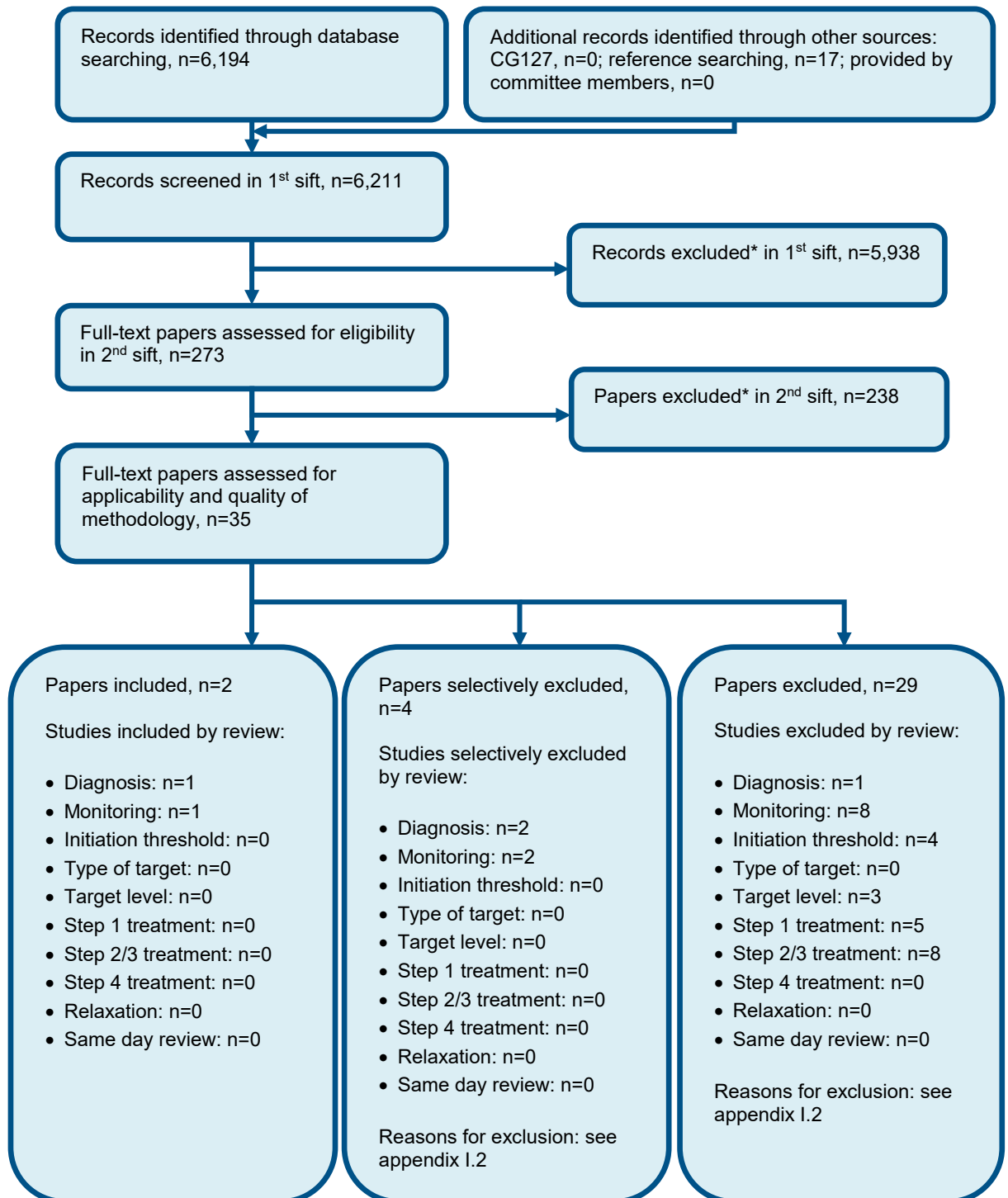
## **Appendix F: GRADE tables**

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

**Table 13: Studies excluded from the clinical review that were included in the previous guideline (CG127)**

Study	Exclusion details
Chapman 2007 <sup>60</sup>	Follow up from the ASCOT trial consisting of only 1,790 of the original 19,257 participants. Incorrect comparison; follow up of those who took spironolactone only.
de Souza 2010 <sup>75</sup>	Incorrect comparison; not a comparative study. The uncontrolled group received spironolactone and there were no details of the comparator.
Gaddam 2010 <sup>110</sup>	Less than minimum duration; 8 weeks follow up, less than the 12 month minimum follow up specified by the protocol.
Lane 2007 <sup>170</sup>	Less than minimum duration; 3-6 months follow up, less than the 12 month minimum follow up specified by the protocol.
Mahmud 2005 <sup>202</sup>	Incorrect intervention, incorrect population, less than minimum duration. One group consisted of people not having any previous antihypertensive treatment and were given either spironolactone or bendroflumethiazide as step 1 treatment. There was a 4 week follow up with a 4 week washout period and another 4 weeks of intervention. The second group were followed up 3 to 4 months later, less than the 12 month minimum follow up specified by the protocol.
Rodilla 2009 <sup>250</sup>	Less than minimum duration. The follow up was for a median of 3 months for the spironolactone group, and 5 months for the doxazosin group, not meeting the 12 month minimum follow up specified by the protocol.

**Table 14: Studies excluded from the clinical review**

Study	Exclusion reason
Abarquez 1993 <sup>1</sup>	Less than minimum duration
Abascal 1998 <sup>2</sup>	Incorrect study design
Abe 2007 <sup>3</sup>	Not review population
Abe 2009 <sup>4</sup>	Less than minimum duration
Abetel 1984 <sup>5</sup>	Not in English
Adir 1987 <sup>6</sup>	Inappropriate comparison
Adolphe 1993 <sup>7</sup>	Less than minimum duration
Agabiti-Rosei 1992 <sup>8</sup>	Less than minimum duration. Inappropriate comparison
Agabiti-Rosei 2005 <sup>9</sup>	No relevant outcomes
Agarwal 2013 <sup>10</sup>	Less than minimum duration

Study	Exclusion reason
Ahola 2012 <sup>11</sup>	Incorrect study design
Ahrens 2010 <sup>12</sup>	Incorrect study design
Akanabe 1985 <sup>13</sup>	Less than minimum duration
Akiyamen 2016 <sup>14</sup>	Systematic review, references checked
Akram 2007 <sup>15</sup>	Less than minimum duration
Alderman 1989 <sup>16</sup>	Inappropriate comparison
Alici 2009 <sup>17</sup>	Less than minimum duration. Inappropriate comparison
ALLHAT officers 2002 <sup>19</sup>	Inappropriate comparison
ALLHAT Collaborative Research Group 2000 <sup>18</sup>	Inappropriate comparison
Alviar 2013 <sup>20</sup>	Inappropriate comparison
Amar 1999 <sup>21</sup>	Article not in English
Ames 1992 <sup>22</sup>	Less than minimum duration
Amir 1994 <sup>23</sup>	No relevant outcomes
Andersen 1986 <sup>24</sup>	Inappropriate comparison
Andersen 2003 <sup>25</sup>	Inappropriate comparison
Andersen 2005 <sup>26</sup>	Inappropriate comparison
Ando 2014 <sup>27</sup>	Incorrect population
Andreadis 2005 <sup>28</sup>	Less than minimum duration
Andren 1983 <sup>29</sup>	Less than minimum duration
Andreucci 1983 <sup>30</sup>	Incorrect study design. Incorrect interventions
Angeli 2004 <sup>31</sup>	Not review population
Anonymous 1999 <sup>34</sup>	Inappropriate comparison
Anonymous 1993 <sup>32</sup>	Inappropriate comparison
Anonymous 1996 <sup>33</sup>	Less than minimum duration
Applegate 1991 <sup>35</sup>	No relevant outcomes. Incorrect study design
Arima 2014 <sup>36</sup>	Not review population
Arriaga-gracia 1993 <sup>37</sup>	Less than minimum duration
Bakris 2007 <sup>39</sup>	Not review population
Bakris 2013 <sup>38</sup>	Not review population
Balamuthusamy 2009 <sup>40</sup>	Systematic review - references checked
Baldwin 1987 <sup>41</sup>	Inappropriate comparison
Bang 2017 <sup>42</sup>	Incorrect interventions
Bangalore 2008 <sup>43</sup>	Systematic review, references checked. Inappropriate comparison
Batterink 2010 <sup>44</sup>	Incorrect study design
Benjamin 1988 <sup>45</sup>	Incorrect study design
Berger 1992 <sup>46</sup>	Less than minimum duration
Black 2003 <sup>47</sup>	Inappropriate comparison
Blumenthal 1990 <sup>48</sup>	Less than minimum duration
Boissel 1995 <sup>50</sup>	Inappropriate comparison
Borgmastars 1987 <sup>51</sup>	No relevant outcomes
Bremner 1997 <sup>52</sup>	Incorrect interventions
Brenner 2001 <sup>53</sup>	Not review population
Brown 2001 <sup>54</sup>	Less than minimum duration
Byrd 2011 <sup>55</sup>	Not review population
Byyny 1996 <sup>56</sup>	Less than minimum duration. Inappropriate comparison

Study	Exclusion reason
Castano 2004 <sup>57</sup>	Inappropriate comparison
Celis 1996 <sup>58</sup>	Inappropriate comparison
Cesaris 1986 <sup>59</sup>	Article not in English
Chapman 2007 <sup>60</sup>	Incorrect study population, incorrect intervention
Chatellier 1987 <sup>61</sup>	Less than minimum duration
Chi 2016 <sup>62</sup>	Systematic review, references checked. Less than minimum duration
Chrysant 1997 <sup>63</sup>	Incorrect study design. Inappropriate comparison
Circelli 2012 <sup>64</sup>	Less than minimum duration
Coope 1986 <sup>65</sup>	Inappropriate comparison
Correa 2018 <sup>66</sup>	Incorrect study design
Cowley 1987 <sup>67</sup>	Less than minimum duration
Cranston 1962 <sup>68</sup>	Incorrect study design
Curb 1996 <sup>69</sup>	Inappropriate comparison
Daae 1998 <sup>70</sup>	Incorrect interventions
Dahlof 2002 <sup>72</sup>	Less than minimum duration
Dahlöf 2005 <sup>71</sup>	Incorrect study design
Daien 2012 <sup>73</sup>	Systematic review, references checked
De rosa 2002 <sup>74</sup>	Inappropriate comparison
de Souza 2010 <sup>75</sup>	Incorrect study design
Degl'innocenti 2004 <sup>76</sup>	Inappropriate comparison
Destro 2010 <sup>77</sup>	Incorrect study design
Devereux 2007 <sup>78</sup>	Inappropriate comparison
Dews 2001 <sup>79</sup>	Incorrect study design
Diao 2012 <sup>80</sup>	Inappropriate comparison
Du 2018 <sup>81</sup>	Incorrect study design
Ekbom 1992 <sup>82</sup>	Incorrect study design
Ekbom 2004 <sup>83</sup>	Incorrect interventions. Incorrect study design
Estacio 1998 <sup>84</sup>	Not review population
Family Physicians Hypertension Study Group 1984 <sup>85</sup>	Less than minimum duration
Fariello 1990 <sup>86</sup>	Less than minimum duration
Farsang 2003 <sup>87</sup>	Incorrect study design
Fasano 1989 <sup>88</sup>	Incorrect study design. Incorrect interventions
Faust 1993 <sup>90</sup>	Article not in English
Faust 1993 <sup>89</sup>	Article not in English
Ferdinand 2001 <sup>91</sup>	Incorrect study design
Fernandes 2016 <sup>92</sup>	Less than minimum duration
Fernandez 2001 <sup>93</sup>	Less than minimum duration
Ferrara 1984 <sup>94</sup>	No relevant outcomes
Finnerty 1979 <sup>95</sup>	Incorrect interventions
Fogari 1991 <sup>101</sup>	No relevant outcomes
Fogari 1996 <sup>99</sup>	Incorrect study design. Incorrect interventions
Fogari 1999 <sup>98</sup>	Inappropriate comparison
Fogari 2006 <sup>97</sup>	Less than minimum duration

Study	Exclusion reason
Fogari 2012 <sup>100</sup>	Less than minimum duration
Fogari 2014 <sup>96</sup>	Less than minimum duration
Forette 2002 <sup>102</sup>	Inappropriate comparison
Forrest 1983 <sup>103</sup>	Less than minimum duration
Fossum 2004 <sup>104</sup>	No relevant outcomes. Inappropriate comparison
Franco 1992 <sup>105</sup>	Article not in English
Franse 2000 <sup>106</sup>	Incorrect interventions. Inappropriate comparison
Frewin 1991 <sup>107</sup>	Incorrect study design. Incorrect interventions
Frick 1986 <sup>109</sup>	Inappropriate comparison
Frick 1987 <sup>108</sup>	No relevant outcomes. Inappropriate comparison
Gaddam 2010 <sup>110</sup>	Less than minimum duration
Gao 2011 <sup>111</sup>	Systematic review, references checked
Gasowski 1999 <sup>112</sup>	Incorrect study design. Incorrect interventions
Gazdick 1994 <sup>113</sup>	Incorrect study design
George 1990 <sup>114</sup>	Less than minimum duration
Ghiadoni 2017 <sup>115</sup>	Less than minimum duration
Giles 1992 <sup>116</sup>	Inappropriate comparison. No relevant outcomes
Gillespie 2005 <sup>117</sup>	Systematic review, references checked
Girerd 2010 <sup>118</sup>	Incorrect study design
Gitt 2013 <sup>119</sup>	Incorrect study design
Glorioso 2007 <sup>120</sup>	Incorrect study design. Less than minimum duration
Goicolea 2002 <sup>121</sup>	Article not in English
Gosse 2002 <sup>122</sup>	Inappropriate comparison
Grimm 1996 <sup>123</sup>	Incorrect study design
Guo 2005 <sup>125</sup>	Article not in English
Guo 2011 <sup>124</sup>	Article not in English
Gupta 2018 <sup>126</sup>	Incorrect interventions
Gyntelberg 1977 <sup>127</sup>	Article not in English
Hall 1998 <sup>128</sup>	Inappropriate comparison
Hamada 2010 <sup>130</sup>	No relevant outcomes
Hamada 2014 <sup>129</sup>	No relevant outcomes
Hamed 2014 <sup>131</sup>	Less than minimum duration. Incorrect study design
Hanon 2015 <sup>132</sup>	Inappropriate comparison
Hanon 2017 <sup>133</sup>	Inappropriate comparison
Hansson 1999 <sup>136</sup>	Inappropriate comparison
Hansson 1999 <sup>135</sup>	Inappropriate comparison
Hansson 1999 <sup>137</sup>	Inappropriate comparison
Hansson 2000 <sup>134</sup>	Inappropriate comparison
Hasegawa 2011 <sup>138</sup>	Inappropriate comparison
Helgeland 1980 <sup>139</sup>	Inappropriate comparison
Helgeland 1983 <sup>140</sup>	Less than minimum duration
Himmelman 1995 <sup>141</sup>	Inappropriate comparison
Hosie 1983 <sup>142</sup>	Inappropriate comparison
Hradec 2013 <sup>143</sup>	Inappropriate comparison
Hughes 2008 <sup>144</sup>	Incorrect interventions. No relevant outcomes

Study	Exclusion reason
Hulley 1985 <sup>145</sup>	Inappropriate comparison
Ibsen 1990 <sup>147</sup>	Incorrect interventions
Ibsen 2003 <sup>146</sup>	Article not in English
Ichihara 2006 <sup>148</sup>	Inappropriate comparison
J. Elan investigators 2006 <sup>149</sup>	Inappropriate comparison
Jamerson 2008 <sup>150</sup>	Incorrect study design
Johnson 2009 <sup>151</sup>	No relevant outcomes
Johnston 1991 <sup>152</sup>	Inappropriate comparison
Julius 2004 <sup>153</sup>	Not review population
Kaku 2011 <sup>154</sup>	Inappropriate comparison
Katayama 2008 <sup>155</sup>	Inappropriate comparison
Kawalec 2018 <sup>156</sup>	Incorrect study design
Kereiakes 2012 <sup>157</sup>	Less than minimum duration
Kerfoot 2014 <sup>158</sup>	Incorrect study design. Incorrect interventions. Inappropriate comparison
Kim 2012 <sup>160</sup>	Incorrect interventions
Kim 2013 <sup>159</sup>	No relevant outcomes
Kjeldsen 2002 <sup>161</sup>	Inappropriate comparison
Kjeldsen 2006 <sup>164</sup>	Incorrect interventions
Kjeldsen 2008 <sup>163</sup>	Incorrect population
Kjeldsen 2016 <sup>162</sup>	Incorrect interventions
Ko 2001 <sup>165</sup>	Not review population
Kohlmann 2009 <sup>166</sup>	Inappropriate comparison
Kostis 2005 <sup>167</sup>	Inappropriate comparison
Kuwajima 2001 <sup>168</sup>	Not review population
Lacourciere 2000 <sup>169</sup>	Incorrect study design
Lane 2007 <sup>170</sup>	Less than minimum duration, incorrect population
Laufer 1998 <sup>171</sup>	Incorrect interventions. No relevant outcomes
Laurent 2014 <sup>172</sup>	Inappropriate comparison
Lavenius 1982 <sup>173</sup>	Less than minimum duration
Leonetti 2002 <sup>174</sup>	Inappropriate comparison
Levine 2001 <sup>175</sup>	Incorrect study design
Licata 1994 <sup>176</sup>	Less than minimum duration
Lim 2000 <sup>177</sup>	Less than minimum duration
Lin 1991 <sup>178</sup>	Incorrect interventions
Lin 1993 <sup>179</sup>	Less than minimum duration
Lin 1995 <sup>180</sup>	Incorrect interventions
Lind 1994 <sup>181</sup>	No relevant outcomes
Lindholm 1996 <sup>183</sup>	Incorrect interventions
Lindholm 2000 <sup>184</sup>	Incorrect interventions
Lindholm 2001 <sup>182</sup>	Not review population
Lindholm 2002 <sup>186</sup>	Inappropriate comparison
Lindholm 2002 <sup>185</sup>	Incorrect interventions. Incorrect study design
Lindner 1984 <sup>187</sup>	Article not in English
Lindroos 1984 <sup>188</sup>	Less than minimum duration
Littlejohn 2009 <sup>189</sup>	Less than minimum duration

Study	Exclusion reason
Liu 1999 <sup>191</sup>	Inappropriate comparison
Liu 2000 <sup>190</sup>	Not in English
Lombardo 1997 <sup>192</sup>	Inappropriate comparison
López 1997 <sup>193</sup>	Article not in English
Lu 2017 <sup>194</sup>	Systematic review, references checked
Ludwig 2002 <sup>195</sup>	Inappropriate comparison
Luno 2017 <sup>196</sup>	Not review population
Lynch 2008 <sup>197</sup>	Inappropriate comparison
Lynch 2012 <sup>198</sup>	Inappropriate comparison
Maclea 1986 <sup>200</sup>	Not review population
Maclea 1986 <sup>201</sup>	Less than minimum duration
Mahmud 2005 <sup>202</sup>	Incorrect study population, incorrect intervention, less than minimum duration
Malacco 2003 <sup>203</sup>	Incorrect interventions. Incorrect study design
Malminiemi 2000 <sup>204</sup>	Inappropriate comparison. No relevant outcomes
Mancia 2007 <sup>205</sup>	Incorrect study design. Incorrect interventions
Mann 1998 <sup>206</sup>	Incorrect study design
Marfatia 2012 <sup>207</sup>	Less than minimum duration
Marre 2004 <sup>208</sup>	Incorrect interventions
Martinez-martin 2011 <sup>209</sup>	Inappropriate comparison
Mason 2005 <sup>210</sup>	Systematic review - references checked
Matsuno 2011 <sup>211</sup>	Not review population. No relevant outcomes
Matsushita 2010 <sup>212</sup>	Incorrect study design. Inappropriate comparison
Matsuzaki 2011 <sup>213</sup>	Inappropriate comparison
Mazza 2016 <sup>214</sup>	No relevant outcomes
M'Buyamba-Kabangu 1987 <sup>199</sup>	Less than minimum duration
Mcareavey 1983 <sup>215</sup>	No relevant outcomes
Mende 2017 <sup>216</sup>	Less than minimum duration
Metelitsa 1991 <sup>217</sup>	Incorrect interventions
Metelitsa 1991 <sup>218</sup>	Article not in English
Middeke 1990 <sup>219</sup>	No relevant outcomes
Middeke 1997 <sup>220</sup>	Inappropriate comparison
Misson 1984 <sup>221</sup>	No relevant outcomes
Mizuno 2017 <sup>222</sup>	Less than minimum duration
Morgan 1989 <sup>223</sup>	Less than minimum duration
Mroczek 1984 <sup>224</sup>	Inappropriate comparison
Muller 1986 <sup>225</sup>	no relevant outcomes
Nakae 2006 <sup>226</sup>	Article not in English
NCT <sup>228</sup>	Citation only
Neutel 1999 <sup>230</sup>	Incorrect study design. Incorrect interventions
Neutel 2017 <sup>229</sup>	Not review population
Oberman 1983 <sup>231</sup>	Less than minimum duration
Ocón 1985 <sup>232</sup>	Not in English
Ogawa 2012 <sup>233</sup>	Incorrect interventions
Ogihara 2000 <sup>234</sup>	Inappropriate comparison
Ogihara 2012 <sup>235</sup>	Inappropriate comparison

Study	Exclusion reason
Ogihara 2014 <sup>236</sup>	Inappropriate comparison
Ogihara 2015 <sup>237</sup>	Inappropriate comparison
Ohnishi 2001 <sup>238</sup>	No relevant outcomes
Okin 2012 <sup>239</sup>	Incorrect study design. Inappropriate comparison
Oshikawa 2014 <sup>240</sup>	Not review population
Ostergren 2008 <sup>241</sup>	Not review population
Park 2017 <sup>242</sup>	No relevant outcomes
Patay 2010 <sup>243</sup>	Incorrect study design
Persson 1986 <sup>244</sup>	Incorrect study design
Philip 1987 <sup>245</sup>	Less than minimum duration
Pierini 2013 <sup>246</sup>	Less than minimum duration. Inappropriate comparison
Piller 2006 <sup>247</sup>	Inappropriate comparison. No relevant outcomes
Remonti 2016 <sup>248</sup>	NMA, references checked
Ritter 2013 <sup>249</sup>	Incorrect study design
Rodilla, 2009 <sup>250</sup>	Less than minimum duration
Roush 2018 <sup>251</sup>	Inappropriate comparison
Ruoff 1986 <sup>252</sup>	Inappropriate comparison
Russell 1985 <sup>253</sup>	Inappropriate comparison
Safar 1994 <sup>254</sup>	Incorrect study design
Saha 2005 <sup>255</sup>	Less than minimum duration. Not review population
Saini 1998 <sup>256</sup>	Inappropriate comparison
Saku 1996 <sup>257</sup>	Inappropriate comparison
Sano 1994 <sup>258</sup>	Inappropriate comparison
Saruta 2015 <sup>259</sup>	Inappropriate comparison
Sato 2002 <sup>260</sup>	Inappropriate comparison. No relevant outcomes
Sato 2009 <sup>261</sup>	Citation only
Sato 2012 <sup>262</sup>	Incorrect study design
Sato 2013 <sup>263</sup>	Not review population
Seedat 1992 <sup>264</sup>	Less than minimum duration
Seedat 1998 <sup>265</sup>	Incorrect interventions
Soucek 2007 <sup>266</sup>	Article not in English
Spiegelstra-de Man 2006 <sup>267</sup>	Inappropriate comparison
Stamler 1986 <sup>268</sup>	Incorrect interventions
Swales 1982 <sup>269</sup>	Incorrect study design
Thomopoulos 2017 <sup>270</sup>	Incorrect study design
Trimarco 2015 <sup>271</sup>	Incorrect study design
Umemoto 2017 <sup>272</sup>	Inappropriate comparison
Wallin 1983 <sup>273</sup>	Inappropriate comparison
White 2008 <sup>274</sup>	Inappropriate comparison

## I.2 Excluded health economic studies

No health economic studies were found.