

Hypertension in adults: diagnosis and management

E. Evidence review for step 1 treatment

NICE guideline

Intervention evidence review

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Draft for Consultation

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

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1 Step 1 treatment

1.1 Review question: Is monotherapy or combination antihypertensive therapy more clinically and cost effective for step 1 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. When 1 pathway is modified by a medication, the other pathways may compensate to keep the blood pressure elevated. It may therefore be more clinically and cost-effective to start more than 1 antihypertensive medication at the same time, thus potentially achieving the target blood pressure quicker and with fewer visits to the healthcare provider. In this chapter, the evidence for this approach is compared to that for starting with monotherapy.

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 are not on current pharmacological treatment for hypertension (minimum wash-out 4 weeks)
Intervention	Combination antihypertensive therapy – adjunct or non-adjunct (definition: 2 antihypertensive medications prescribed simultaneously – may be in 1 pill or 2). Examples include: <ul style="list-style-type: none"> • Angiotensin-converting enzyme (ACE) inhibitor and calcium channel blocker (CCB) • Angiotensin-II receptor blocker (ARB) and CCB • ACE inhibitor and diuretic (thiazide like or conventional) • ARB and diuretic (thiazide like or conventional) • ACE inhibitor and CCB (Trandolapril and verapamil; TARKA) • Beta blocker and CCB (atenolol and nifedipine) • Beta blocker and thiazides (atenolol and chlorthalidone; timolol and bendroflumethiazide) • Non-thiazide and thiazide diuretic (amiloride and hydrochlorothiazide)
Comparison	Antihypertensive Monotherapy. Examples include: <ul style="list-style-type: none"> • ACE inhibitor or low-cost ARB) • Thiazide-like diuretic (such as chlorthalidone or indapamide) • Conventional thiazide diuretic (such as bendroflumethiazide or hydrochlorothiazide) • CCB • Beta-blockers • Aliskiren (direct renin inhibitors) • Doxazosin, prazosin, terazosin, (alpha blockers) • Clonidine, moxonidine, methyl dopa (centrally acting anti-HTN)
Outcomes	Assessed 12 months or more (using final endpoint) Critical <ul style="list-style-type: none"> • All-cause mortality

	<ul style="list-style-type: none"> • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) <p>Important</p> <ul style="list-style-type: none"> • Heart failure needing hospitalisation • Vascular procedures (including both 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: Changes in eGFR or creatinine • 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)

1.4 1 Methods and process

2 This evidence review was developed using the methods and process described in
3 Developing NICE guidelines: the manual.¹⁵⁵ Methods specific to this review question are
4 described in the review protocol in appendix A.

5 Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 6 Clinical evidence

1.5.1 7 Included studies

8 Three studies were included in the review^{13, 14, 47, 52, 133, 139, 148}; these are summarised in Table
9 2 below. Evidence from these studies is summarised in the clinical evidence summary below
10 (Table 3).

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

1.5.2 3 Excluded studies

14 Cochrane reviews relevant to this review question were identified. Li 2014¹³² was excluded
15 due to an incorrect population. Garjon 2017⁸⁹ was excluded due to no relevant outcomes.

16 See the excluded studies list in appendix I.

1.5.3 7 Summary of clinical studies included in the evidence review

18 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Asmar 2003 (REASON trial) 14,13,133,139,52	Combination: Perindopril 2 mg plus indapamide 0.625 mg (n=235)	Hypertension (Systolic BP 160-210; Diastolic BP 95-110 mmHg) without type 2 diabetes (n=471)	At 12 months: <ul style="list-style-type: none"> • Discontinuation due to adverse events • Change in creatinine 	Mixed population; 65% had received previous medication

Study	Intervention and comparison	Population	Outcomes	Comments
	Monotherapy: Atenolol 50 mg (n=234)			
Dahlof 2005 (PIXCEL trial)⁴⁷	Combination: Perindopril 2 mg plus indapamide 0.625 mg (n=341) Monotherapy: Enalapril 10 mg (n=338)	Hypertension with or without type 2 diabetes (n=679)	At 12 months: <ul style="list-style-type: none"> Discontinuation due to adverse events 	Number of participants with type 2 diabetes not specified
Mogensen 2003 (PREMIER trial)¹⁴⁸	Combination: Perindopril 2 mg plus indapamide 0.625 mg (n=237) Monotherapy: Enalapril 10 mg (n=244)	Hypertension with type 2 diabetes (n=481)	At 12 months <ul style="list-style-type: none"> Serious cardiovascular events Change in creatinine clearance Discontinuation due to adverse events Hypotension 	

1 See appendix D for full evidence tables.

2

1.5.4 1 Quality assessment of clinical studies included in the evidence review

2 Table 3: Clinical evidence summary: monotherapy versus combination (adults with hypertension and type 2 diabetes strata)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Combination versus monotherapy (95% CI)
Serious cardiovascular events	481 (1 study) 12 months	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 0.39 (0.15 to 0.98)	63 per 1,000	39 fewer per 1,000 (from 1 fewer to 54 fewer)
Change in creatinine clearance (ml/min)	481 (1 study) 12 months	LOW ¹ due to risk of bias		The mean change in creatinine in the control group was -4.8	The mean change in creatinine in the intervention groups was 0.7 higher (1.19 lower to 2.59 higher)
Discontinuation due to adverse events	481 (1 study) 12 months	VERY LOW ^{1,3} due to risk of bias, imprecision	RR 0.88 (0.49 to 1.59)	89 per 1,000	11 fewer per 1,000 (from 47 fewer to 50 more)
Discontinuation due to adverse events ⁶	538 (1 study) 12 months	VERY LOW ^{1,3,4} due to risk of bias, imprecision, indirectness	RR 1.21 (0.41 to 3.56)	22 per 1,000	5 more per 1,000 (from 13 fewer to 54 more)
Dizziness (hypotension)	481 (1 study) 12 months	VERY LOW ^{1,3,5} due to risk of bias, imprecision, indirectness	RR 0.58 (0.14 to 2.41)	21 per 1,000	9 fewer per 1,000 (from 18 fewer to 30 more)

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

² Downgraded by 1 increment because the majority of the evidence had indirect outcomes

³ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

⁴ Downgraded by 1 increment because the majority of the evidence had an indirect population

⁵ Downgraded by 1 increment because the majority of the evidence had indirect outcomes; unclear if dizziness related to hypotension

⁶ Mixed population (including people with type 2 diabetes)

1 **Table 4: Clinical evidence summary: monotherapy versus combination (adults with hypertension and without type 2 diabetes strata)**
2

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Combination versus monotherapy (95% CI)
Change in creatinine ($\mu\text{mol/L}$)	457 (1 study) 12 months	HIGH		The mean change in creatinine in the control group was 1.7	The mean change in creatinine in the intervention groups was 2.3 higher (0.7 to 3.9 higher)
Discontinuation due to adverse events	418 (1 study) 12 months	VERY LOW ^{1,2} due to risk of bias, imprecision	RR 0.89 (0.49 to 1.62)	99 per 1,000	11 fewer per 1,000 (from 52 fewer to 58 more)

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
² Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

3 See appendix F for full GRADE tables.

4

1.6 1 Economic evidence

1.6.1 2 Included studies

3 No relevant health economic studies were identified.

1.6.2 4 Excluded studies

5 Five economic studies relating to this review question were identified but were excluded due
6 to limited applicability or methodological limitations.^{119,146,215,192,204} This includes 1 study
7 included in the previous guideline that was not applicable because it compared treatment to
8 no treatment as opposed to combination therapy versus monotherapy.

9 These are listed in appendix I with the reasons for exclusion given.

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

1.6.3 Resource costs

Some illustrative costs are demonstrated below of monotherapies and combination therapies, based on the drugs that were used in the clinical evidence identified.

Table 5: UK costs of anti-hypertensives (monotherapies or combinations)

Drug	Detail	Daily dose	Cost/ month (£)	Cost/year (£)
Monotherapies				
Perindopril erbumine (ACE inhibitor)	2 mg tablets, pack of 30 = £6.12	2 mg	£6.21	£74.46
Enalapril maleate (ACE inhibitor)	10 mg tablets, pack of 28 = £2.31	10 mg (a)	£2.51	£30.11
Atenolol (Beta blocker)	50 mg tablets, pack of 28 = £0.55	50 mg	£0.60	£7.17
Losartan (ARB)	50 mg tablets, pack of 28 = £0.85	50 mg (b)	£0.92	£11.08
Combination				
Perindopril erbumine (ACE inhibitor) and Indapamide (thiazide) <i>Separate pills</i>	2 mg tablets, pack of 30 = £6.12 1.5 mg tablets, pack of 30 = £3.40	2 mg 1.5 mg (c)	£6.21 £3.45	£74.46 <u>£41.37</u> £115.83
Losartan and hydrochlorothiazide <i>single pill</i>	50 mg Losartan, 12.5 mg thiazide, pack of 28 = £1.49	50 mg Losartan, 12.5 mg thiazide (b)	£1.62	£19.42

Source: BNF (Drug Tariff price)²⁷, DATE: 8 November 2018.

(a) Dose from clinical review

(b) Clinical review 100 mg but used 50 mg here as combination was 50 mg so comparing the same dose in monotherapy and combination.

(c) Clinical review used 2 mg perindopril and 0.625 mg indapamide but these doses weren't available in the BNF.

1 Also illustrated below are costs of cardiovascular events to demonstrate costs that might be
2 avoided from avoiding events. It is important to note that these are from NHS reference costs
3 and are therefore the costs related to initial hospitalisation ONLY.

4 **Table 6: Costs of hospitalisation from cardiovascular events**

HRG code	HRG code description	Weighted average cost
EB10A to EB10E	Actual or Suspected Myocardial Infarction, with CC Score 13+	£1,518
Myocardial infarction	Actual or Suspected Myocardial Infarction, with CC Score 10-12	
	Actual or Suspected Myocardial Infarction, with CC Score 7-9	
	Actual or Suspected Myocardial Infarction, with CC Score 4-6	
	Actual or Suspected Myocardial Infarction, with CC Score 0-3	
AA35A to AA35F	Stroke with CC Score 16+	£3,279
Stroke	Stroke with CC Score 13-15	
	Stroke with CC Score 10-12	
	Stroke with CC Score 7-9	
	Stroke with CC Score 4-6	
EB13A to EB13D	Stroke with CC Score 0-3	
Angina	Angina with CC Score 12+	£713
	Angina with CC Score 8-11	
	Angina with CC Score 4-7	
	Angina with CC Score 0-3	

5 (a) From NHS reference costs 2016/17, total Healthcare resource group (HRG) schedule. ⁵⁵

6

7 **Example costings:**

8 Assumptions:

- 9 • The medications are those used in the trials in the clinical review: monotherapy is
10 Enalapril 10 mg per day, and dual therapy is perindopril erbumine plus indapamide in
11 separate pills of dose 2 mg and 1.5 mg per day respectively.

12 This may not necessarily be the most common drugs that would be used in UK practice.

13 **Table 7: Cost trade-off illustration**

Intervention	Drug cost (per 1000) (a)	Cardiovascular events (per 1000) (b)	Cardiovascular event cost	Total cost
CV event = MI				
Monotherapy	£30,113	63	£95,634	£125,747
Dual therapy	£115,827	25	£37,297	£153,124
CV event = Stroke				
Monotherapy	£30,113	63	£206,564	£236,676
Dual therapy	£115,827	25	£80,560	£196,386

14 (a) 12 month cost as clinical studies were over a 12 month period.

15 (b) Data taken from the clinical review

16

1.7 1 Evidence statements

1.7.1 2 Clinical evidence statements

3 **Monotherapy versus combination (adults with hypertension and type 2 diabetes** 4 **strata)**

5 Very low quality evidence from 1 study with 481 participants showed a clinically important
6 benefit of combination therapy compared to monotherapy for serious cardiovascular events
7 in people with type 2 diabetes.

8 Very low to low quality evidence from 1 study with 481 participants showed no clinically
9 important difference for change in creatinine clearance, discontinuation due to adverse
10 events and dizziness. Very low quality evidence from 1 study with 538 participants showed
11 no clinically important difference for discontinuation due to adverse events.

12 **Monotherapy versus combination (adults with hypertension and without type 2** 13 **diabetes strata)**

14 High quality evidence from 1 study with a total of 457 participants showed no clinically
15 important difference between monotherapy or combination therapy for change in creatinine.
16 Very low quality evidence from 1 study with 418 participants showed no clinically important
17 difference for discontinuation due to adverse events.

1.7.2 8 Health economic evidence statements

19 No relevant economic evaluations were identified.

1.8 20 Recommendations

21 The recommendations in this section apply to people with hypertension with or without type 2
22 diabetes. They will replace the recommendations on blood pressure management in the
23 NICE guideline on type 2 diabetes in adults.

1.8. 24 Step 1 treatment

25 E1. Offer an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor
26 blocker (ARB)^a to adults starting step 1 antihypertensive treatment who:

27

- 28 • have type 2 diabetes (of any age or family origin) or
- 29 • are aged under 55 but not of African or Caribbean family origin. **[2019]**

30 E2. Offer a calcium-channel blocker (CCB) to adults starting step 1 antihypertensive
31 treatment who:

- 32 • are aged 55 or over and do not have type 2 diabetes **or**
- 33 • are of African or Caribbean family origin and do not have type 2 diabetes (of any
34 age). **[2019]**

^a In 2007, the MHRA issued a drug safety update on ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy that states 'Use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed'. There is also a 2009 MHRA safety update for ACE inhibitors and angiotensin II receptor antagonists: use during breastfeeding and related clarification: ACE inhibitors and angiotensin II receptor antagonists.

- 1 E3. If an ACE inhibitor is not tolerated for example, because of cough, offer an ARB^b to treat
2 hypertension. [2019]
- 3 E4. Do not combine an ACE inhibitor with an ARB to treat hypertension. [2019]
- 4 E5. If a CCB is not tolerated, for example because of oedema, offer a thiazide-like diuretic to
5 treat hypertension. [2019]
- 6 E6. If there is evidence of heart failure, offer a thiazide-like diuretic and follow the NICE
7 guideline on chronic heart failure. [2019]
- 8 E7. If starting or changing diuretic treatment for hypertension, offer a thiazide-like diuretic,
9 such as indapamide or chlorthalidone in preference to a conventional thiazide diuretic
10 such as bendroflumethiazide or hydrochlorothiazide. [2019]
- 11 E8. For adults with hypertension already having treatment with bendroflumethiazide or
12 hydrochlorothiazide, who have stable, well-controlled blood pressure, continue with their
13 current treatment. [2019]
- 14 E9. Discuss with the person if they are taking their medicine as prescribed and support
15 adherence in line with NICE's guideline on medicines adherence. [2019]

1.8.26 Research recommendations

- 17 RR1. Are there subgroups of people with hypertension who should start on dual therapy?
18 See also the rationale in appendix J.

1.9 19 The committee's discussion of the evidence

1.9.20 Interpreting the evidence

1.9.1.21 The outcomes that matter most

22 The committee considered all-cause mortality, quality of life, stroke and myocardial infarction
23 (MI) to be critical outcomes for decision-making. Heart failure, angina, vascular procedures,
24 and discontinuation due to adverse events as well as specific adverse events and resource
25 use were considered important outcomes for decision-making. In the population without type
26 2 diabetes, evidence was identified for adverse events only (discontinuation due to adverse
27 events, change in creatinine levels). In people with type 2 diabetes, the only evidence
28 identified was an indirect outcome of major cardiovascular events and adverse event
29 outcomes (change in creatinine clearance, dizziness and discontinuation due to adverse
30 events).

1.9.1.21 The quality of the evidence

32 The committee discussed that the evidence was limited; from 3 studies, only 1 of which
33 reported a critical outcome (serious cardiovascular events), albeit an indirect composite
34 measure of the individual outcomes the committee were interested in. All of the evidence for
35 people with hypertension and type 2 diabetes was low or very low quality due mainly to risk
36 of bias, indirectness and imprecision. Risk of bias was rated as high because of high attrition
37 rates due to participants dropping out of trials or being lost to follow up. The evidence was

^b In 2007, the MHRA issued a drug safety update on ACE inhibitors and angiotensin II receptor antagonists: not for use in pregnancy that states 'Use in women who are planning pregnancy should be avoided unless absolutely necessary, in which case the potential risks and benefits should be discussed'. There is also a 2009 MHRA safety update for ACE inhibitors and angiotensin II receptor antagonists: use during breast feeding and related clarification: ACE inhibitors and angiotensin II receptor antagonists.

1 also downgraded due to population indirectness. Some participants included within the
2 evidence were outside of the scope of this review question, such as those with moderate to
3 severe chronic kidney disease (CKD). The population included within the evidence was
4 based on studies with small sample sizes.

5 The only high quality evidence available was for change in creatinine for adults with
6 hypertension and without type 2 diabetes. However, this was also only from a single,
7 relatively small study.

1.9.1.3 8 **Benefits and harms**

9 The committee discussed that there was an indication that initiating dual therapy may be
10 better than monotherapy as the step 1 treatment option, in terms of reducing cardiovascular
11 events in a diabetes population, albeit from very low quality evidence. The evidence for
12 people without type 2 diabetes was more limited, with evidence available for the outcomes of
13 change in creatinine and discontinuation due to adverse events, neither of which were
14 cardiovascular events so determining the benefit of treatment was not possible.

15 It was noted that there was conflicting evidence from 2 separate studies in terms of
16 discontinuation due to adverse events; however, the committee agreed it was more intuitive
17 to see more discontinuation in people with dual therapy. Although this was also low quality
18 evidence and a relatively small numbers of events, the committee considered that this did not
19 demonstrate any substantial increase in harm from dual therapy.

20 In considering the body of evidence, the committee discussed that it was disappointing that
21 there was not more evidence on patient important outcomes available to demonstrate a
22 benefit of dual therapy as a step 1 treatment option. The committee was aware of
23 epidemiological and observational evidence suggesting that many people do start on 2 drugs
24 and have good outcomes as a result such as quicker reductions in blood pressure, which
25 result in mortality benefit; furthermore, observational evidence suggests that not optimising
26 management for people with hypertension early can have a substantial impact on
27 subsequent quality of life. However, the committee agreed that the level of available
28 evidence identified in this review was insufficient to change the recommendations from
29 CG127.

30 The committee discussed the evidence identified in 2011 in CG127¹⁵⁴ related to step 1
31 treatment. The recommendations were stratified by age and family origin reflecting data from
32 clinical trials showing differential effects of the different classes of blood pressure lowering
33 drugs on blood pressure lowering and clinical outcomes in younger (less than 55 years old)
34 versus older people and in black people of African and Caribbean descent. Three studies
35 and an age-stratified analysis from a fourth study also compared blood pressure response
36 across various drug classes and identified ACE inhibitors and beta-blockers as more
37 effective at lowering blood pressure in younger people, when compared to calcium channel-
38 blockers or thiazide-type diuretics. The evidence for ACE inhibitor and ARBs were closely
39 correlated (although lacked head-to-head evidence) and the previous guideline
40 recommended that these treatments should be treated as equal in terms of efficacy;
41 however, due to cost differences, it was considered that ACE inhibitors should be initiated
42 first and an ARB considered an alternative for when an ACE inhibitor was poorly tolerated.
43 The 2011 guideline did not identify evidence to show any consistent trend favouring 1 drug
44 class over the other. The committee agreed it was appropriate to retain these
45 recommendations but to keep in mind that ACE inhibitors and ARBs are now equal in terms
46 of both cost and efficacy.

47 The committee also discussed step 1 treatment in people with type 2 diabetes, and noted
48 that NG28 recommended ACE inhibitors as step 1 treatment rather than ARBs. The
49 committee noted that this was based both on differences in costs and on limited evidence of
50 a difference in reno-protective benefits between the two treatments. The committee agreed

1 that from their current clinical experience ARBs and ACE inhibitors were similarly effective
2 are were not aware of evidence to contradict this.

3

4 However, the committee agreed that beta-blockers are not often used as antihypertensive
5 treatment in current practice and recent meta-analysis (not relevant to this review protocol)
6 have demonstrated this class to be low efficacy for the treatment of hypertension in terms of
7 improving cardiovascular outcomes. The committee discussed whether these drugs are ever
8 an appropriate choice for people with hypertension. They discussed people with evidence of
9 a high sympathetic drive and noted that the primary cause should be addressed rather than
10 treating the hypertension primarily and that in these cases, beta-blockers would not be the
11 most appropriate choice of drug. The committee therefore agreed not to retain the
12 recommendations related to the use of beta-blockers in people under 55 years.

13 For people of African or Caribbean family origin with type 2 diabetes, the previous
14 recommendation from the type 2 diabetes guideline (NG28) was to offer an ACE inhibitor and
15 either a diuretic or a calcium-channel blocker as step 1 dual therapy. This was based on
16 evidence of improved cardiovascular outcomes for diuretics or calcium-channel blockers
17 (CCBs) when compared to ACE inhibitors in this subgroup. No evidence was identified in this
18 review to suggest that step 1 dual therapy should be recommended for this population, and
19 so the recommendation for step 1 dual therapy was not retained for this group in NG28. The
20 committee noted that considerations may apply in the presence of target organ damage such
21 as microalbuminuria as these patients are at higher CVD risk.

1.9.22 Cost effectiveness and resource use

23 Five studies were identified that may be relevant for this question but were selectively
24 excluded due to methodological limitations. One of these was a study included in the
25 previous guideline comparing treatment versus no treatment based on resource use from the
26 HYVET study in an elderly population. A no treatment comparison is not of interest in this
27 question but that study fell under the question of step 1 treatment in people aged over 80 in
28 the previous guideline and has therefore been selectively excluded because the comparison
29 is not relevant to this update of the review.

30 The committee was presented with some examples of unit costs of monotherapy and dual
31 therapy based on the drugs used in the clinical studies, as well as some illustrative
32 hospitalisation costs for cardiovascular events.

33 Dual therapy treatments are likely to have higher costs. In theory, 2 medications instead of 1
34 may also lead to more adverse events, which also needs to be traded off against benefit.
35 This was not clear from the clinical review, which found no difference in discontinuation rates.
36 The major impact on effectiveness that would be traded-off against the additional drug use is
37 the impact on cardiovascular events or mortality. The clinical review showed that there were
38 39 fewer serious cardiovascular events with the dual therapy treatment than with the
39 monotherapy, in a population with hypertension and type 2 diabetes. Cardiovascular events
40 are likely to be events like myocardial infarction or stroke, which are very costly to treat and
41 can have a long-term impact on quality of life. Therefore, any events avoided could be
42 argued as being significant. This evidence was of very low quality, however, and was from
43 only 1 study and therefore may not be sufficient evidence to change practice, as the
44 committee cannot be confident that these outcomes are likely to represent the true outcomes
45 in the general population with such little evidence.

46 As an example of some costing illustrations, a cohort of 1000 people taking monotherapy or
47 dual therapy for 12 months would lead to higher intervention costs for the dual therapy arm
48 (£30,113 versus £115,827 respectively) (based on the drugs that were used in the included
49 trial). Trading this off against the cardiovascular event outcomes from the clinical review,
50 shows that when the CV event is assumed to be an MI, monotherapy is overall less costly

1 than dual therapy (£125,747 versus £153,124) because even though there are more CV
2 events – the cheaper intervention cost is outweighing the additional cost of CV events. If the
3 CV events are assumed to be strokes, then monotherapy is overall more expensive than
4 dual therapy (£236,676 versus £196,386) as strokes are more expensive. This is a very
5 simplified example, and there are a number of factors that haven't been captured.
6 Cardiovascular event costs are likely to be higher than just initial hospitalisation costs such
7 as including follow-ups and rehabilitation perhaps. There is no quality of life captured, but
8 events would have a detriment to quality of life. These factors are likely to favour dual
9 therapy. However, different drugs also have different costs, and dual therapy in a single pill
10 may be more expensive because of the ease of having to take only 1 pill but have the benefit
11 of 2 drugs. There are no adverse events included or other costs associated with treatment
12 like monitoring, which might be higher in a dual therapy strategy. Therefore, even if dual
13 therapy was overall a more expensive strategy, it is uncertain if this would be cost effective.

14 It is also uncertain in what timeframe people might be reviewed, in which case some people
15 on monotherapy would go on to other lines of treatment anyway. This argument is implying
16 that if people do not stay on monotherapy for very long (with uncontrolled hypertension), then
17 the difference in intervention will only apply for a short duration. Effectively, what is being
18 compared is bringing forward step 2 treatment versus starting on step 1 treatment. Some
19 data from UK GP practices on the proportion of hypertensives on different numbers of drugs
20 showed (depending on age and sex) that around 40–60% of people are on 1 drug, 30–40%
21 of people are on 2 drugs, and 10–20% are on 3 drugs. Therefore, most people tend to stay
22 on 1 drug, implying it would be a big change to start on 2 drugs. However, it is unclear if their
23 hypertension is controlled or uncontrolled on 1 drug. Those who remain controlled on 1 drug
24 would have lower medication costs for the same outcome although 2 drugs are known to get
25 a person to a target more quickly. If monitoring following initiation of monotherapy occurred in
26 a timely way, then those uncontrolled on 1 drug would be stepped up to step 2 drugs more
27 quickly. However, being on step 2 treatment from the beginning may avoid some events that
28 would have happened in that space of time. In summary, there are many factors to consider
29 that make it uncertain if starting on dual therapy is cost effective.

30 The committee were not able to make a recommendation about starting on dual therapy
31 (whether that is 2 drugs in 1 pill or separately) because of the limited clinical evidence, and
32 there was no robust cost effectiveness evidence. The committee discussed the potential for
33 treatment inertia and the factors related to that such as people being asymptomatic and the
34 discussion that happens about benefits and risks of taking, changing or adding treatments.
35 The frequency of monitoring to assess the effectiveness of treatment can also be variable.
36 As the committee couldn't make a recommendation favouring starting with dual therapy, a
37 research recommendation was made to identify in which groups dual therapy should be
38 initiated.

39 Some of the recommendations from the previous hypertension guideline were edited,
40 including removing a recommendation on when to use beta-blockers, as these are not used
41 very much in practice, and removing references to low cost ARBs, as ACE inhibitors and
42 ARBs are similarly low cost now. In general, the previous recommendations were agreed to
43 still be appropriate and represent good practice. These were based on a combination of
44 clinical evidence and cost effectiveness evidence, as a model in the 2004 guideline
45 comparing monotherapies for step 1 treatment (for which costs were updated in the 2011
46 guideline) showed that CCBs were generally the most cost effective. In higher risk people,
47 thiazides were shown to be the most cost effective for people at high risk of heart failure. A
48 sensitivity analysis on age showed that ACE inhibitors or ARBs were likely to be the most
49 cost effective.

50 The recommendations for people with hypertension and type 2 diabetes from the current
51 type 2 diabetes guideline (NG28) were also discussed. Step 1 antihypertensive treatment in
52 the type 2 diabetes guideline is an ACE inhibitor for everyone of any age except black people
53 of African or Caribbean family origin: where dual therapy of an ACE inhibitor plus a diuretic or

1 CCB was step 1. The committee discussed what had informed those recommendations, and
2 noted they were based on physiological information rather than a clinical evidence base.
3 Although there was some evidence identified for this question on people with hypertension
4 and diabetes, it was only from a single small study, and the committee did not consider this
5 strong enough to base a recommendation on. People with hypertension but no diabetes are
6 offered a CCB in the hypertension guideline, but an ACE inhibitor or ARB is more suitable for
7 those with diabetes because these drugs are better at improving renal outcomes compared
8 to other blood pressure lowering agents. It was discussed how in practice the step 1 dual
9 therapy recommendation for people of African or Caribbean family origin is not generally
10 current practice. Black people often show inadequate response to ACE inhibitors and
11 therefore require additional drugs. What tends to happen is an ACE inhibitor is given for step
12 1 instead of the more appropriate ARB and hence treatment may be escalated more quickly
13 to dual therapy for this group.

14 The committee's view was that a monotherapy of an ACE inhibitor could be offered to
15 anyone with diabetes of any age or family origin, as the dual therapy recommendation for the
16 black people of African or Caribbean family origin population is not generally followed in
17 practice and was not based on evidence. Given that current practice generally already offers
18 an ACE inhibitor to people with diabetes regardless of age or family origin with an ARB as an
19 alternative, this is unlikely to have a large impact on practice.

1.9.30 Other factors the committee took into account

21 The committee reviewed the wording of the recommendations in CG127 and highlighted that
22 if a thiazide like diuretic was being offered, indapamide is likely to be the drug that is used.
23 The previous wording of the recommendation may have implied chlorthalidone should be first
24 choice, by the nature of it being listed first; however, chlorthalidone hasn't become more
25 widely available to European market as was hoped. Indapamide is widely available and well
26 used in the UK; therefore, the committee suggested reordering the wording of the
27 recommendation to place indapamide first in this recommendation.

28 The committee further noted that there were safety concerns regarding the use of ACE
29 inhibitors and ARBs in pregnant women. A footnote has been added to this recommendation
30 to alert to MHRA safety updates.

31 It was noted that it was important to highlight that medicines should be taken as prescribed in
32 order to be most effective, a recommendation was included to highlight that this should be
33 discussed with the person and that adherence should be supported.

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1 Appendices

2 Appendix A: Review protocols

3 Table 8: Review protocol: Step 1 antihypertensive treatment

Field	Content
Review question	Is monotherapy or combination antihypertensive therapy more clinically and cost effective for step 1 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 whether monotherapy or combination therapy is most clinically and cost effective as a step 1 treatment for primary hypertension
Eligibility criteria – population / disease / condition / issue / domain	Population: Adults (over 18 years) with primary hypertension who are not on current pharmacological treatment for hypertension (minimum wash-out 4 weeks) Stratify by presence or absence of type 2 diabetes
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Antihypertensive pharmacological combination therapy received for a minimum of 1 year (either adjunct or non-adjunct, defined as 2 antihypertensive medications prescribed simultaneously – may be in 1 pill or 2). Examples include: <ul style="list-style-type: none"> • ACE inhibitor and CCB • ARB and CCB • ACE inhibitor and diuretic (thiazide-like or conventional) • ARB and diuretic (thiazide-like or conventional) • ACE inhibitor and CCB (Trandolapril and verapamil; TARKA) • Beta blocker and CCB (atenolol and nifedipine) • Beta blocker and thiazides (atenolol and chlorthalidone; timolol and bendroflumethiazide) • Non-thiazide and thiazide (amiloride and hydrochlorothiazide)
Eligibility criteria – comparator(s) / control or reference (gold) standard	Antihypertensive pharmacological monotherapy received for a minimum of 1 year. Examples include: <ul style="list-style-type: none"> • ACE inhibitor • Low-cost ARB • Thiazide-like diuretic (such as chlorthalidone or indapamide) • Conventional thiazide diuretic (such as bendroflumethiazide or hydrochlorothiazide) • CCB • Beta-blockers • Aliskiren (direct renin inhibitors) • Doxazosin, prazosin, terazosin, (alpha blockers) • Clonidine, moxonidine, methyldopa (centrally acting antihypertensive)
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. <ul style="list-style-type: none"> • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • MI

	<p>Important</p> <ul style="list-style-type: none"> • Heart failure needing hospitalisation • (including lower limb, coronary and carotid artery procedures)Angina needing hospitalisation • 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) • Discontinuation or dose reduction due to side effects • [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	<p>Minimum follow up time: 1 year</p> <p>Exclusions:</p> <ul style="list-style-type: none"> • Studies including participants with type 1 diabetes or chronic kidney disease (A3 or above [heavy proteinuria]); for type 2 diabetes strata studies including participants with 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 • Crossover trials (unless washout is ≥ 4 weeks) • Children (younger than 18 years)
Proposed sensitivity / subgroup analysis, or meta-regression	<p>Subgroups for analysis of heterogeneity:</p> <ul style="list-style-type: none"> • Age (75 as a cut off)* • Family origin (African and Caribbean, White, South Asian) • Severity (moderate [stage 1 BP 140-59/90-99] versus high [stage 2 BP 160/100]) <p>*To note that we will also extract evidence in those aged over 80 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:</p> <p>Cochrane review (2017): http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010316.pub2/full</p>
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 critically individual studies. 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

1 Table 9: 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 criteria	<ul style="list-style-type: none"> Populations, interventions and comparators must be as specified in the clinical review protocol above.

	<ul style="list-style-type: none"> • 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.
<p>Search strategy</p>	<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>
<p>Review strategy</p>	<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).¹⁵⁵</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • 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. <p>Where there is discretion</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"> • 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.

1

1 Appendix B: Literature search strategies

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

4 For more detailed information, please see the Methodology Review.

B.1.5 Clinical search literature search strategy

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

11 **Table 10: 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

12 **Table 11: 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.	Drug Combinations/
41.	Drug Therapy, Combination/ or *Drug Therapy/
42.	drug therap*.ti,ab.
43.	((combination* or combined or multiple or single) adj (therap* or agent* or drug* or treatment*)).ti,ab.
44.	(monotherap* or mono therap*).ti,ab.
45.	or/40-44
46.	39 and 45
47.	exp Angiotensin-Converting Enzyme Inhibitors/
48.	Angiotensin-converting enzyme inhibitor*.ti,ab.
49.	(ACE inhibitor* or ACEI).ti,ab.
50.	(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.
51.	exp Calcium Channel Blockers/
52.	Calcium channel blocker*.ti,ab.
53.	CCB.ti,ab.
54.	(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.
55.	exp Angiotensin Receptor Antagonists/
56.	(Angiotensin II adj3 (antagonist* or blocker*).ti,ab.

57.	ARB.ti,ab.
58.	(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.
59.	Diuretics/
60.	Diuretics, Thiazide/
61.	((thiazide or thiazide-like or non-thiazide or conventional or potassium sparing) adj3 diuretic*).ti,ab.
62.	(Amiloride or Cyclopenthiiazide or Spironolactone or Bendroflumethiazide or Hydrochlorothiazide or Co-amilozone 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 Sevikaar 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.
63.	Adrenergic beta-Antagonists/
64.	(adrenergic beta antagonist* or beta blocker* or b blocker*).ti,ab.
65.	(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.
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.	Antihypertensive Agents/
70.	centrally acting antihypertensive*.ti,ab.
71.	(Clonidine or Moxonidine or Methyldopa or Catapres or Dixarit or Aldomet or Physiotens).ti,ab.
72.	renin inhibitor*.ti,ab.
73.	(Aliskiren or Rasilez).ti,ab.
74.	((trandolapril and verapamil) or TARKA).ti,ab.
75.	or/47-74
76.	46 and 75
77.	randomized controlled trial.pt.
78.	controlled clinical trial.pt.
79.	randomi#ed.ti,ab.
80.	placebo.ab.
81.	randomly.ti,ab.
82.	Clinical Trials as topic.sh.
83.	trial.ti.
84.	or/77-83
85.	Meta-Analysis/
86.	exp Meta-Analysis as Topic/
87.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
88.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
89.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
90.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

91.	(search* adj4 literature).ab.
92.	(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.
93.	cochrane.jw.
94.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
95.	or/85-94
96.	76 and (84 or 95)

1 Table 12: Embase (Ovid) search terms

1.	exp Hypertension/
2.	hypertens*.ti,ab.
3.	(essential adj hypertension).ti,ab.
4.	(isolat* adj hypertension).ti,ab.
5.	(elevat* adj2 blood adj pressur*).ti,ab.
6.	(high adj blood adj pressur*).ti,ab.
7.	(increase* adj2 blood pressur*).ti,ab.
8.	((systolic or diastolic or arterial) adj2 pressur*).ti,ab.
9.	or/1-8
10.	exp pregnancy/
11.	exp Maternal Hypertension/
12.	(pre eclampsia or pre-eclampsia or preeclampsia).ti,ab.
13.	exp Hypertension, Portal/ not exp Hypertension/
14.	exp Hypertension, Pulmonary/ not exp Hypertension/
15.	exp Intracranial Hypertension/
16.	exp Ocular Hypertension/ not exp Hypertension/
17.	exp Diabetes Mellitus, Type 1/ not exp Diabetes Mellitus, Type 2/
18.	or/10-17
19.	9 not 18
20.	letter.pt. or letter/
21.	note.pt.
22.	editorial.pt.
23.	case report/ or case study/
24.	(letter or comment*).ti.
25.	or/20-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animal/ not human/
29.	nonhuman/
30.	exp Animal Experiment/
31.	exp Experimental Animal/
32.	animal model/
33.	exp Rodent/
34.	(rat or rats or mouse or mice).ti.
35.	or/27-34
36.	19 not 35
37.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
38.	36 not 37

39.	limit 38 to English language
40.	Drug Combinations/
41.	*Therapy/ or *Drug Therapy/
42.	drug therap*.ti,ab.
43.	((combination* or combined or multiple or single) adj (therap* or agent* or drug* or treatment*)).ti,ab.
44.	(monotherap* or mono therap*).ti,ab.
45.	or/40-44
46.	39 and 45
47.	exp *Angiotensin-Converting Enzyme Inhibitors/
48.	Angiotensin-converting enzyme inhibitor*.ti,ab.
49.	(ACE inhibitor* or ACEI).ti,ab.
50.	(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.
51.	exp *Calcium Channel Blockers/
52.	Calcium channel blocker*.ti,ab.
53.	CCB.ti,ab.
54.	(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.
55.	exp *Angiotensin Receptor Antagonists/
56.	(Angiotensin II adj3 (antagonist* or blocker*)).ti,ab.
57.	ARB.ti,ab.
58.	(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.
59.	Diuretics/
60.	Diuretics, Thiazide/
61.	((thiazide or thiazide-like or non-thiazide or conventional or potassium sparing) adj3 diuretic*).ti,ab.
62.	(Amiloride or Cyclopenthiiazide or Spironolactone 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.
63.	*Adrenergic beta-Antagonists/
64.	(adrenergic beta antagonist* or beta blocker* or b blocker*).ti,ab.
65.	(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.
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.	*Antihypertensive Agents/
70.	centrally acting antihypertensive*.ti,ab.
71.	(Clonidine or Moxonidine or Methyldopa or Catapres or Dixarit or Aldomet or Physiotens).ti,ab.
72.	renin inhibitor*.ti,ab.
73.	(Aliskiren or Rasilez).ti,ab.
74.	((trandolapril and verapamil) or TARKA).ti,ab.
75.	or/47-74
76.	46 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)

1 Table 13: 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: [Calcium Channel Blockers] explode all trees
#13.	Calcium channel blocker*:ti,ab
#14.	CCB:ti,ab
#15.	(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 Zanicidip 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
#16.	MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#17.	(AngiotensinII near/3 (antagonist* or blocker*)):ti,ab
#18.	ARB:ti,ab
#19.	(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
#20.	MeSH descriptor: [Diuretics] this term only
#21.	MeSH descriptor: [Sodium Chloride Symporter Inhibitors] this term only
#22.	((thiazide or thiazide-like or non-thiazide or conventional or potassium sparing) near/3 diuretic*):ti,ab
#23.	(Amiloride or Cyclopentthiazide or Spironolactone 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
#24.	MeSH descriptor: [Adrenergic beta-Antagonists] this term only
#25.	(adrenergic beta antagonist* or beta blocker* or b blocker*):ti,ab
#26.	(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
#27.	MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#28.	(adrenergic alpha antagonist* or alpha adrenoceptor blocker* or alpha blocker*):ti,ab
#29.	(Doxazosin or Prazosin or Terazosin or Cardura or Doxadura or Raporsin or Slocinx or Doxzogen or Larbex or Hypovase or Hytrin):ti,ab
#30.	MeSH descriptor: [Antihypertensive Agents] this term only
#31.	centrally acting antihypertensive*:ti,ab
#32.	(Clonidine or Moxonidine or Methyldopa or Catapres or Dixarit or Aldomet or Physiotens):ti,ab
#33.	renin inhibitor*:ti,ab
#34.	(Aliskiren or Rasilez):ti,ab
#35.	((trandolapril and verapamil) or TARKA):ti,ab
#36.	(or #8-#35)
#37.	#7 and #36
#38.	MeSH descriptor: [Drug Combinations] this term only
#39.	MeSH descriptor: [Drug Therapy, Combination] this term only

#40.	MeSH descriptor: [Drug Therapy] this term only
#41.	drug therap*:ti,ab
#42.	((combination* or combined or multiple or single) near/1 (therap* or agent* or drug* or treatment*)):ti,ab
#43.	(monotherap* or mono therap*):ti,ab
#44.	(or #38-#43)
#45.	#37 and #44

B.2.1 Health Economics literature search strategy

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

8 **Table 14: 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

9 **Table 15: 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

1 Table 16: 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

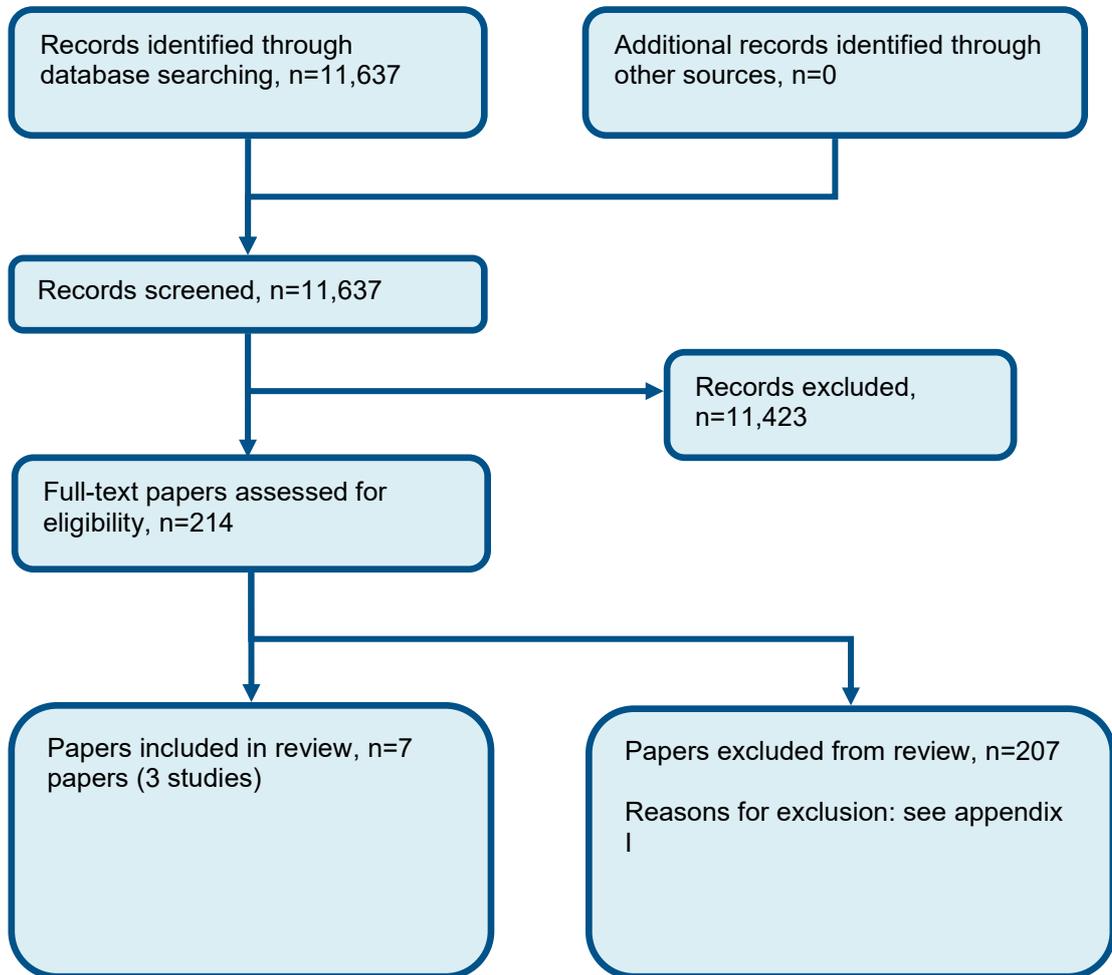
1 Table 17: NHS EED and HTA (CRD) search terms

#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

2

1 Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of step 1 antihypertensive treatment



2

1 Appendix D: Clinical evidence tables

2

Study (subsidiary papers)	Asmar 2001 ¹⁴ (Asmar 2001 ¹³ , de Luca 2004 ⁵²)
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=471)
Countries and setting	Conducted in Multiple countries; Setting: Australia, Austria, Belgium, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, Switzerland and UK
Line of therapy	First line
Duration of study	12 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Hypertensive according to ABPM
Stratum	Hypertension without type 2 diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	Uncomplicated hypertension 160-210 mmHg SBP, 95-110 DBP, measured in the supine position. 4-week washout of current medication.
Exclusion criteria	(1) taking anti-diabetic, cardiovascular or cholesterol lowering drugs
Recruitment/selection of participants	Not specified
Age, sex and family origin	Age – Mean (SD): 54(12.1). Sex (M:F): Define. Family origin: Not specified
Further population details	1. Age: Not stated / Unclear 2. Family origin: Not stated / Unclear 3. Hypertension severity: Severe (Stage 2: 160/100 mmHg)
Indirectness of population	No indirectness
Interventions	(n=235) Intervention 1: Angiotensin-converting enzyme (ACE) inhibitor and diuretic (thiazide-like or conventional). After a 4-week washout, people received perindopril 2 mg plus indapamide 0.625 mg for 1 year. Medication was taken orally each morning and dosage could be adjusted after 3, 6 or 9 months of treatment according to the conventional BP. In the event of SBP above 160 mmHg or DBP above 90 mmHg, the dose was increased to 2 tablets each morning. Other drugs were not allowed during the follow up. Duration 12 months. Concurrent medication/care: Washout period; no concomitant treatment. Indirectness: No indirectness (n=234) Intervention 2: Beta-blockers – Atenolol. After a 4-week washout, people received atenolol 50 mg for

Study (subsidiary papers)	Asmar 2001¹⁴ (Asmar 2001¹³, de Luca 2004⁵²)
	1 year. Medication was taken orally each morning and dosage could be adjusted after 3, 6 or 9 months of treatment, according to the conventional BP. In the event of SBP above 160 mmHg or DBP above 90 mmHg, the dose was increased to 2 tablets each morning. Other drugs were not allowed during the follow up. Duration 12 months. Concurrent medication or care: washout; none allowed. Indirectness: No indirectness
Funding	Academic or government funding (INSERM, the association Claude Benard, the Groupe de Pharmacologie et d'Hemodynamique Cardiovasculaire, Laboratoires Servier.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERINDOPRIL AND INDAPAMIDE COMBINATION versus ATENOLOL	
<p>Protocol outcome 1: Discontinuation or dose reduction due to side effects at 12 months or longer - Actual outcome for Hypertension without type 2 diabetes: Discontinuation due to adverse events at 12 months; Group 1: 19/216, Group 2: 20/202 Risk of bias: All domain – High, Selection – Low, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 19; Group 2 Number missing: 32</p> <p>Protocol outcome 2: Side effect 2: Change in eGFR at ≥12 months - Actual outcome for Hypertension without type 2 diabetes: Creatinine levels (mmol/L) at 12 months; Group 1: mean 4 (SD 9.7); n=232, Group 2: mean 1.7 (SD 7.7); n=225 Risk of bias: All domain – Low, Selection – Low, Blinding – Low, Incomplete outcome data – Low, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 9</p> <p>Protocol outcomes not reported by the study</p>	
	Health-related quality of life at ≥12 months; All-cause mortality at ≥12 months; Myocardial infarction at ≥12 months; Heart failure needing hospitalisation at ≥12 months; Vascular procedures (including both coronary and carotid artery procedures) at ≥12 months; Angina needing hospitalisation at ≥12 months; Side effect 1: hypotension (dizziness) at ≥12 months; Stroke (ischaemic or haemorrhagic) at ≥12 months

1

Study	Dahlof 2005⁴⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=679)
Countries and setting	Conducted in Multiple countries; Setting: Not specified
Line of therapy	First line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Defined by sitting SBP between 140-210 mmHg.
Stratum	Overall

Study	Dahlof 2005 ⁴⁷
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) aged 18 or above (2) Left ventricular hypertrophy (LVH) has to be confirmed by the Central Echocardiography Committee prior to inclusion on the W-4 echocardiography.
Exclusion criteria	Severe, secondary, or complicated hypertension, previously known electrocardiogram (ECG) abnormalities (atrioventricular block second-or-third degree, ventricular arrhythmia, rhythm disturbance such as atrial flutter or atrial fibrillation), poor echogenicity, asymmetric septal hypertrophy defined as an interventricular septal wall thickness (IVSWT)/posterior wall thickness (PWT) >1.5, dilated left ventricle defined as an end-diastolic left ventricular internal diameter (LVIDd) >60 mm, left ventricular fractional shortening <25%, segmental or global kinetic abnormality, vascular disease, concomitant liver or renal disease, significant abnormalities in laboratory parameters. Contraindication to study treatments, obesity, alcohol or drug abuse, pregnancy or possibility of pregnancy are also criteria for non-selection.
Recruitment/selection of participants	Not specified
Age, sex and family origin	Age – Mean (SD): 55(9.5) years. Sex (M:F): 262:294. Family origin: 98% White, the remaining not specified
Further population details	1. Age: Mixed population 2. Family origin: White 3. Hypertension severity: Not stated / Unclear
Extra comments	Comorbid left ventricular hypertrophy defined as LVMI >120 (men) or >100 (women) g/m squared
Indirectness of population	No indirectness
Interventions	(n=338) Intervention 1: ACE inhibitors – Enalapril. 10 mg/day. Dosage could be doubled twice if hypertension was inadequately controlled. Duration 12 months. Concurrent medication/care: None allowed. Indirectness: No indirectness (n=341) Intervention 2: ACE inhibitor and diuretic (thiazide-like or conventional). 2 mg perindopril per day, 0.625 mg indapamide per day. Dosage could be doubled twice if hypertension was inadequately controlled. Duration 12 months. Concurrent medication/care: None allowed. Indirectness: No indirectness
Funding	Study funded by industry (SERVIER)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PERINDOPRIL/ INDAPAMIDE	
Protocol outcome 1: Discontinuation or dose reduction due to side effects at ≥12 months - Actual outcome: Discontinuation due to adverse events at 12 months; Group 1: 7/264, Group 2: 6/274 Risk of bias: All domain – High, Selection – Low, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 61; Group 2 Number missing: 77	
Protocol outcomes not reported by the study	Health-related quality of life at ≥12 months; All-cause mortality at ≥12 months; Myocardial infarction at ≥12 months; Heart failure needing hospitalisation at ≥12 months; Vascular procedures (including both coronary and carotid artery procedures) at ≥12 months; Angina needing hospitalisation at ≥12 months; Side effect 1:

Study	Dahlof 2005⁴⁷
	hypotension (dizziness) at ≥12 months; Side effect 2: Acute kidney injury at ≥12 months; Stroke (ischaemic or haemorrhagic) at ≥12 months

1

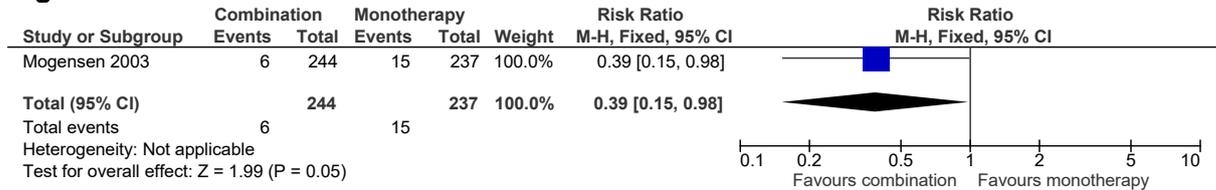
Study	Mogensen 2003¹⁴⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=481)
Countries and setting	Conducted in Multiple countries; Setting: 104 centres in 20 countries (including the UK)
Line of therapy	First line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Supine systolic BP between 140–180 mmHg, supine diastolic BP less than 110 mmHg
Stratum	Hypertension with type 2 diabetes
Subgroup analysis within study	Not applicable
Inclusion criteria	(1) Type 2 diabetes (2) AER rate of 20 or less ug/min
Exclusion criteria	(10 HbA1c 9% or above (2) nondiabetic kidney disease (3) serum creatinine 140 or above (4) contraindications to trial medications (5) other severe diseases
Age, sex and family origin	Age – Range: 40–75 years. Sex (M:F): Define. Family origin: 92% White, 4% Black, 1% Asian, 3% other
Further population details	1. Age: Mixed population 2. Family origin: Mixed population 3. Hypertension severity: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=244) Intervention 1: ACE inhibitors – Enalapril. After a 4-week run in period of placebo, participants took 10 mg/day enalapril, which was adjusted after week 12 (doubling the dosage in 2 steps at 12-week intervals). Duration 12 months. Concurrent medication or care: The choice of antidiabetic medication was left to the investigator. Indirectness: No indirectness (n=237) Intervention 2: ACE inhibitor and diuretic (thiazide-like or conventional). After a 4-week run in period of placebo, participants took 2 mg/day perindopril and 0.625 mg/day indapamide, which was adjusted after week 12 (doubling the dosage in 2 steps at 12-week intervals if BP remained high. Duration 12 months. Concurrent medication/care: The choice of antidiabetic medication was left to the investigator. Indirectness: No indirectness

Study	Mogensen 2003 ¹⁴⁸
Funding	Academic or government funding (Institut de Recherches Internationales SERVIER.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PERINDOPRIL AND INDAPAMIDE	
<p>Protocol outcome 1: Myocardial infarction at ≥12 months - Actual outcome for Hypertension with type 2 diabetes: Serious cardiovascular events at 12 months; Risk of bias: All domain – High, Selection – Low, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 38; Group 2 Number missing: 44</p> <p>Protocol outcome 2: Discontinuation or dose reduction due to side effects at ≥12 months - Actual outcome for Hypertension with type 2 diabetes: Discontinuation due to adverse events at 12 months; Group 1: 21/237, Group 2: 19/244 Risk of bias: All domain – High, Selection – Low, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 38; Group 2 Number missing: 44</p> <p>Protocol outcome 3: Side effect 1: hypotension (dizziness) at ≥12 months - Actual outcome for Hypertension with type 2 diabetes: Dizziness (unclear if related to hypotension) at 12 months; Risk of bias: All domain – High, Selection – Low, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: Serious indirectness; Group 1 Number missing: 38; Group 2 Number missing: 44</p> <p>Protocol outcome 4: Side effect 2: Change in eGFR at ≥12 months - Actual outcome for Hypertension with type 2 diabetes: Creatinine clearance (ml/min) at 12 months; Group 1: mean -4.1 (SD 11.4); n=237 Group 2: mean -4.8 (SD 9.7) n=244; Risk of bias: All domain – Very high, Selection – High, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: no indirectness; Baseline details: Difference in outcome at baseline; Group 1 Number missing: 38; Group 2 Number missing: 44</p>	
Protocol outcomes not reported by the study	Health-related quality of life at ≥12 months; All-cause mortality at ≥12 months; Heart failure needing hospitalisation at ≥12 months; Vascular procedures (including both coronary and carotid artery procedures) at ≥12 months; Angina needing hospitalisation at ≥12 months; Stroke (ischaemic or haemorrhagic) at ≥12 months

1 Appendix E: Forest plots

E.1 2 Combination versus monotherapy in adults with primary hypertension and type 2 diabetes

Figure 2: Serious cardiovascular events at 12 months



4

Figure 3: Change in creatinine at 12 months

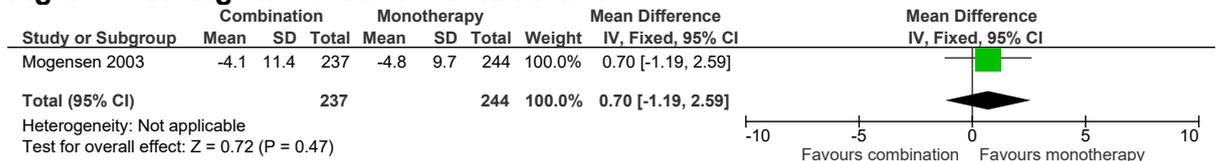
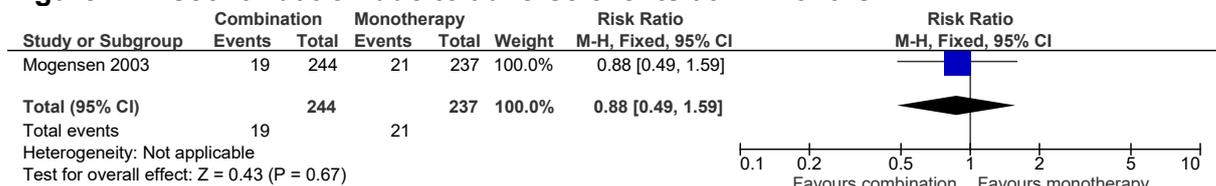


Figure 4: Discontinuation due to adverse events at 12 months



5

Figure 5: Discontinuation due to adverse events at 12 months (including type 2 diabetes)

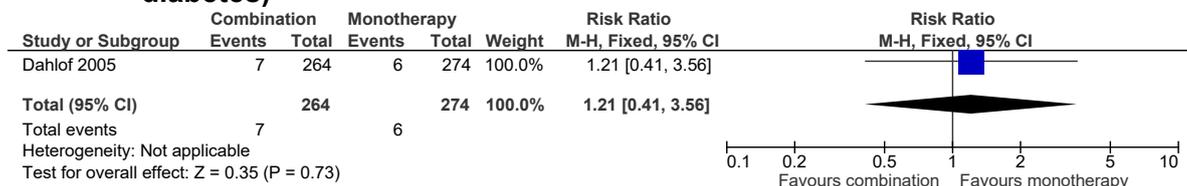
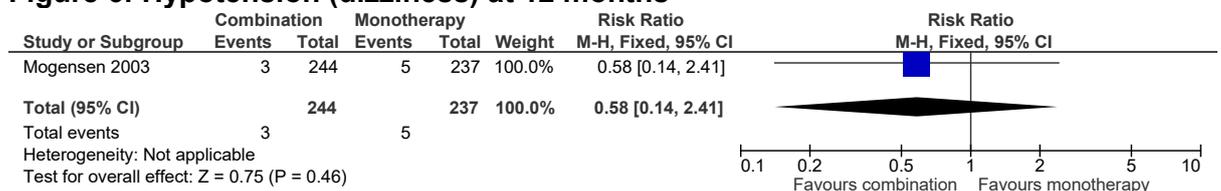
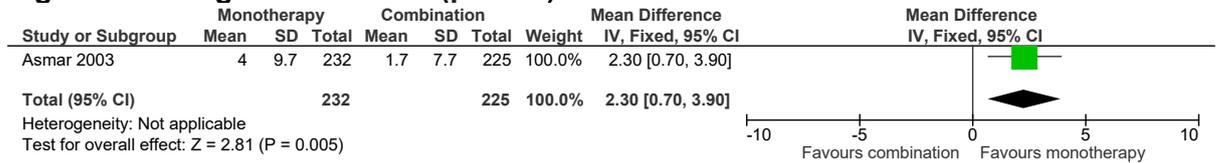


Figure 6: Hypotension (dizziness) at 12 months



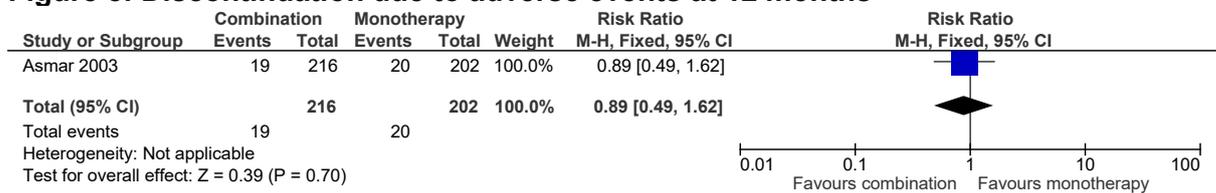
E.2.1 Combination versus monotherapy in adults with primary hypertension without type 2 diabetes

Figure 7: Change in creatinine ($\mu\text{mol/L}$) at 12 months



3

Figure 8: Discontinuation due to adverse events at 12 months



4

1 Appendix F: GRADE tables

2 Table 18: Clinical evidence profile: combination versus monotherapy in adults with primary hypertension and type 2 diabetes

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination versus monotherapy	Control	Relative (95% CI)	Absolute		
Serious cardiovascular events (follow-up 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	serious ²	serious ³	none	6/244 (2.5%)	15/237 (6.3%)	RR 0.39 (0.15 to 0.98)	39 fewer per 1000 (from 1 fewer to 54 fewer)	⊕○○○ VERY LOW	CRITICAL
Change in creatinine (ml/min; follow-up 12 months; Better indicated by lower values)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	237	244	-	MD 0.7 higher (1.19 lower to 2.59 higher)	⊕⊕○○ LOW	IMPORTANT
Discontinuation due to adverse events (follow-up 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ³	none	19/244 (7.8%)	21/237 (8.9%)	RR 0.88 (0.49 to 1.59)	11 fewer per 1000 (from 47 fewer to 50 more)	⊕○○○ VERY LOW	IMPORTANT
Discontinuation due to adverse events – overall strata (follow-up 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	Serious ⁴	very serious ³	none	7/264 (2.7%)	6/274 (2.2%)	RR 1.21 (0.41 to 3.56)	5 more per 1000 (from 13 fewer to 54 more)	⊕○○○ VERY LOW	IMPORTANT
Dizziness (hypotension; follow-up 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	Serious ⁵	very serious ³	none	3/244 (1.2%)	5/237 (2.1%)	RR 0.58 (0.14 to 2.41)	9 fewer per 1000 (from 18 fewer to 30 more)	⊕○○○ VERY LOW	IMPORTANT

- 1 ¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
 2 ² Downgraded by 1 increment because the majority of the evidence had indirect outcomes
 3 ³ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
 4 ⁴ Downgraded by 1 increment because the majority of the evidence had an indirect population
 5 ⁵ Downgraded by 1 increment because the majority of the evidence had indirect outcomes; unclear if dizziness related to hypotension

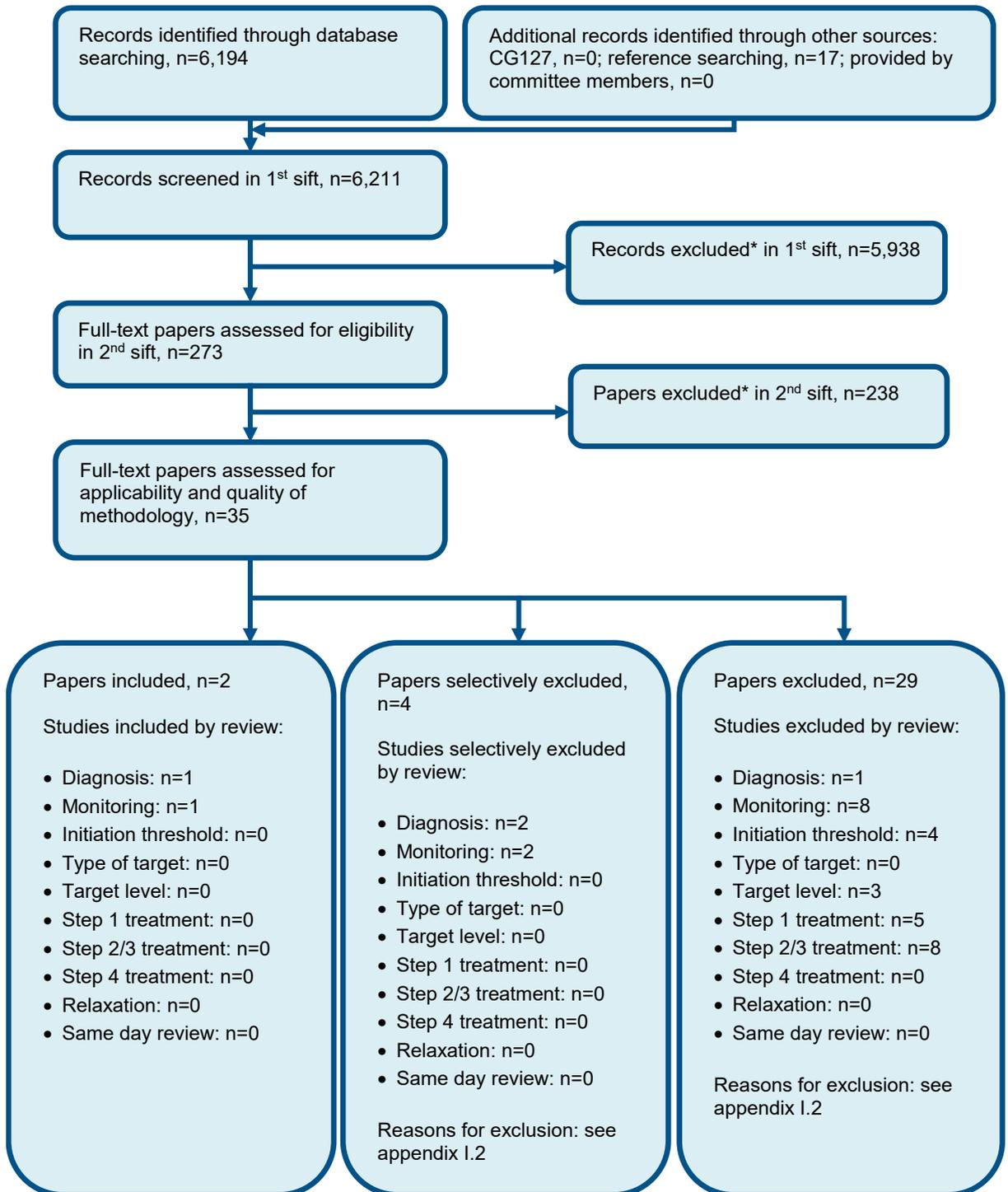
6 **Table 19: Clinical evidence profile: combination versus monotherapy in adults with primary hypertension and without type 2**
 7 **diabetes**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination versus monotherapy	Control	Relative (95% CI)	Absolute		
Change in creatinine (mmol/L; follow-up 12 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	232	225	-	MD 2.3 higher (0.7 to 3.9 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Discontinuation due to adverse events (follow-up 12 months)												
1	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	very serious ²	none	19/216 (8.8%)	20/202 (9.9%)	RR 0.89 (0.49 to 1.62)	11 fewer per 1000 (from 52 fewer to 58 more)	⊕○○○ VERY LOW	IMPORTANT

- 8 ¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
 9 ² Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

1 Appendix G: Health economic evidence selection

Figure 9: Flow chart of health economic study selection for the guideline



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

1 Appendix H: Health economic evidence tables

3 None.

4 Appendix I: Excluded studies

I.1.5 Excluded clinical studies

6 Table 20: Studies excluded from the clinical review

Reference	Reason for exclusion
Aalbers 2010 ¹	Incorrect study design
Abate 1998 ²	Less than minimum duration
Amir 1994 ³	Incorrect study design
Anan 2005 ⁴	Less than minimum duration
Andersson 1999 ⁵	Less than minimum duration
Anderton 1988 ⁶	No washout period
Andreadis 2010 ⁷	Less than minimum duration
Andreadis 2005 ⁸	Less than minimum duration
Anonymous 1988 ¹⁰	Less than minimum duration
Anonymous (Veterans Administration cooperative study group) 1983 ⁹	Less than minimum duration
Aoki 1977 ¹¹	Less than minimum duration
Applegate 1997 ¹²	Inappropriate washout period
Bakris 2013 ¹⁵	No washout period
Basile 2011 ¹⁶	Less than minimum duration
Bays 2014 ¹⁷	Systematic review; references checked
Benedict group 2003 ¹⁸	Incorrect study design
Benjamin 1988 ¹⁹	Incorrect study design
Bennett 2017 ²⁰	Systematic review; references checked
Beretta-Piccoli 1987 ²¹	Less than minimum duration
Bielmann 1991 ²²	Less than minimum duration
Black 2008 ²³	Incorrect interventions
Black 2002 ²⁴	Incorrect study design
Black 2003 ²⁵	Incorrect interventions
Black 1998 ²⁶	Study protocol
Bohm 2017 ²⁸	Incorrect population
Bomback 2012 ²⁹	Less than minimum duration
Bradley 1975 ³⁰	Incorrect study design
Breithaupt-Grogler 1998 ³¹	Less than minimum duration
Bremner 1997 ³²	Wrong comparison
Bremner 1997 ³³	Wrong comparison
Brown 2015 ³⁸	Less than minimum duration
Brown 2000 ³⁴	Less than minimum duration

Reference	Reason for exclusion
Brown 2001 ³⁵	Less than minimum duration
Brown 1985 ³⁶	No relevant outcomes
Brown 2008 ³⁷	Incorrect study design
Chalmers 1999 ³⁹	Less than minimum duration
Chaugai 2018 ⁴⁰	Wrong comparison
Chung 2009 ⁴¹	Less than minimum duration
Ciulla 2009 ⁴²	Incorrect study design
Ciulla 2004 ⁴³	Less than minimum duration
Cushman 1998 ⁴⁴	No useable outcomes
Dafgard 1981 ⁴⁵	No useable outcomes
Dahlof 2005 ⁴⁸	Incorrect study design
Dahlof 1987 ⁴⁶	Incorrect study design
Damian 2016 ⁴⁹	Wrong population
De Galan 2009 ⁵¹	Wrong comparison
Degl'Innocenti 2004 ⁵³	Wrong comparison
Delea 2009 ⁵⁴	Not article
DeQuattro 1997 ⁵⁶	Less than minimum duration
DeQuattro 1997 ⁵⁷	Less than minimum duration
Derosa 2016 ⁶⁵	Inappropriate washout period
Derosa 2015 ⁶⁴	No relevant outcomes
Derosa 2014 ⁵⁸	No useable outcomes
Derosa 2013 ⁵⁹	Incorrect study design
Derosa 2013 ⁶⁰	Inappropriate washout period
Derosa 2014 ⁶²	Inappropriate washout period
Derosa 2013 ⁶¹	Article retracted
Derosa 2014 ⁶³	Article retracted
Destro 2008 ⁶⁶	Inappropriate washout period
Dickson 2008 ⁶⁷	Incorrect study design
Divitiis 1984 ⁵⁰	Inappropriate washout period
Drayer 1995 ⁶⁸	Less than minimum duration
Duckett 1990 ⁶⁹	Incorrect study design
Dzurik 1990 ⁷⁰	Less than minimum duration
Elliot 1987 ⁷²	Less than minimum duration
El-Mehairy 1979 ⁷¹	No useable outcomes
Family Physicians Hypertension Study Group 1984 ⁷³	Less than minimum duration
Fang 2014 ⁷⁴	No useable outcomes
Feldman 2009 ⁷⁵	Less than minimum duration
Fell 1990 ⁷⁶	Incorrect study design
Ferrari 2008 ⁷⁷	Systematic review; references checked
Fogari 2008 ⁸⁰	Incorrect washout period
Fogari 2007 ⁷⁸	Incorrect comparison
Fogari 2002 ⁷⁹	Wrong population/inappropriate washout
Forette 2002 ⁸¹	Wrong comparison
Franklin 1996 ⁸²	Less than minimum duration

Reference	Reason for exclusion
Franz 1990 ⁸³	Not in English
Freytag 2002 ⁸⁴	Incorrect study design
Frishman 1995 ⁸⁵	Less than minimum duration
Fu 2017 ⁸⁶	Systematic review; references checked
Fujisaki 2014 ⁸⁷	Incorrect study design
Garcia de Vinuesa 2001 ⁸⁸	Wrong population
Garjon 2017 ⁸⁹	Systematic review; no relevant outcomes
Girerd 1998 ⁹⁰	Less than minimum duration
Goodman 1985 ⁹¹	Incorrect study design
Goyal 2014 ⁹²	Less than minimum duration
Grassi 2010 ⁹³	Systematic review; references checked
Grimm 1996 ⁹⁴	Incorrect study design
Gupta 2008 ⁹⁵	Incorrect study design
Guyot 1990 ⁹⁶	Not in English
Hall 1998 ⁹⁸	Less than minimum duration
Hall 1998 ⁹⁷	Incorrect study design
Harmankaya 2003 ⁹⁹	No useable outcomes, less than minimum duration
Hasegawa 2004 ¹⁰⁰	Wrong population
He 2017 ¹⁰¹	Systematic review; references checked
Heidbreder 1992 ¹⁰³	Inappropriate washout period, less than minimum duration
Heidbreder 1991 ¹⁰²	Wrong population
Helmer 2018 ¹⁰⁴	Systematic review; references checked
Herlitz 2001 ¹⁰⁵	Wrong comparison
Hersh 1995 ¹⁰⁶	Incorrect study design
Hill 1985 ¹⁰⁷	Less than minimum duration, incorrect study design
Hilleman 1999 ¹⁰⁸	Systematic review; references checked
Hofling 1991 ¹⁰⁹	Not in English
Holzgreve 1989 ¹¹¹	Wrong population
Holzgreve 2003 ¹¹⁰	Not article
Home 2009 ¹¹²	Wrong population/interventions
Ihm 2016 ¹¹³	Less than minimum duration
Ishimitsu 1997 ¹¹⁴	Incorrect study design
Jang 2015 ¹¹⁵	Less than minimum duration
Jicheng 2009 ¹³⁵	Wrong interventions
Johnson 1994 ¹¹⁷	Incorrect study design; no relevant outcomes
Johnson 2005 ¹¹⁶	Wrong study design, wrong population
Katayama 2006 ¹¹⁸	Incorrect study design
Kim 2011 ¹²²	Less than minimum duration
Kim 2014 ¹²⁰	Wrong population
Kim 2016 ¹²¹	Wrong population, less than minimum duration
Kinouchi 2011 ¹²³	No useable outcomes
Kjeldsen 2016 ¹²⁴	Less than minimum duration
Kjeldsen 2008 ¹²⁶	Wrong comparison
Kjeldsen 2002 ¹²⁵	Incorrect study design
Kostis 2004 ¹²⁸	Abstract

Reference	Reason for exclusion
Kostis 1997 ¹²⁷	Wrong population
Kuschnir 2004 ¹²⁹	Less than minimum duration, inappropriate washout
Lassila 2000 ¹³⁰	Wrong population/ wrong interventions
Laurent 2001 ¹³¹	Literature review
Li 2014 ¹³²	Incorrect population
Lucas 1985 ¹³⁴	Less than minimum duration
MacDonald 2015 ¹³⁶	Incorrect study design
MacKay 1996 ¹³⁷	Less than minimum duration
Malacco 2008 ¹³⁸	Less than minimum duration
Mancia 2017 ¹⁴⁰	Subgroup analysis
Mancia 2012 ¹⁴¹	Wrong population
Marques da Silva 2015 ¹⁴²	Incorrect comparison
Masao 1994 ¹⁴³	Not in English
Matsuzaki 2011 ¹⁴⁴	Wrong comparison
Mayaudon 1995 ¹⁴⁵	Not in English
Miyoshi 2017 ¹⁴⁷	Less than minimum duration
Morgan 2002 ¹⁴⁹	Inappropriate washout period
Morgan 2004 ¹⁵⁰	Less than minimum duration
MRC Working Party 1992 ¹⁵¹	Incorrect study design
Nakao 2004 ¹⁵²	Incorrect study design
Nalbantgil 2003 ¹⁵³	Less than minimum duration
Nedogoda 2005 ¹⁵⁶	Not in English
Neldam 2012 ¹⁵⁷	Systematic review; references checked
Neldam 2012 ¹⁵⁸	Systematic review; references checked
Nelson 1982 ¹⁵⁹	Incorrect study design
Neutel 2000 ¹⁶²	Less than minimum duration
Neutel 1999 ¹⁶¹	Less than minimum duration. Wrong population
Neutel 2014 ¹⁶⁰	Incorrect study design
Obel 1990 ¹⁶³	Less than minimum duration
Olivan Martinez 1993 ¹⁶⁴	Not in English
Packer 2013 ¹⁶⁵	Wrong population
Pannier 2002 ¹⁶⁶	Not in English
Papademetriou 2009 ¹⁶⁷	Incorrect study design
Papademetriou 1998 ¹⁶⁸	Incorrect study design
Park 2016 ¹⁷¹	Less than minimum duration
Park 2016 ¹⁶⁹	Wrong population, less than minimum duration
Park 2016 ¹⁷⁰	Incorrect population
Patel 2007 ¹⁷²	Incorrect study design, less than minimum duration
Paz 2016 ¹⁷³	Systematic review; references checked
Perez-Maraver 2005 ¹⁷⁴	Wrong population
Persson 1976 ¹⁷⁵	Less than minimum duration
Pessina 2006 ¹⁷⁶	Incorrect study design
Petelina 2005 ¹⁷⁷	Not in English
Petersen 2001 ¹⁷⁸	Wrong population
Petrie 1975 ¹⁷⁹	Inappropriate washout period, less than minimum duration

Reference	Reason for exclusion
Pool 2009 ¹⁸⁰	Less than minimum duration
Prisant 1998 ¹⁸¹	Less than minimum duration
Radevski 2000 ¹⁸³	Wrong population
Radevski 1999 ¹⁸²	Wrong comparison
Rakesh 2017 ¹⁸⁴	No useable outcomes
Ratnasabapathy 2003 ¹⁸⁵	Wrong comparison
Redon 2012 ¹⁸⁶	Wrong comparison
Roca-Cusachs 2001 ¹⁸⁷	Less than minimum duration
Rosenfeld 1989 ¹⁸⁸	Incorrect study design
Ruggenenti 2011 ¹⁹¹	Incorrect study design
Ruggenenti 2004 ¹⁹⁰	Wrong population
Ruggenenti 2011 ¹⁸⁹	Incorrect study design
Saruta 2015 ¹⁹³	Wrong comparison
Sassano 1989 ¹⁹⁴	Less than minimum duration
Seedat 1984 ¹⁹⁶	Less than minimum duration
Seedat 1983 ¹⁹⁵	Incorrect study design
Shaifali 2014 ¹⁹⁷	No useable outcomes
Shi 2017 ¹⁹⁸	No relevant outcomes
Shimamoto 2015 ¹⁹⁹	Inappropriate washout period
Smith 2007 ²⁰⁰	Less than minimum duration
Sohn 2017 ²⁰¹	Less than minimum duration
Soucek 2007 ²⁰²	Not in English
Sung 2016 ²⁰³	Less than minimum duration
Thijs 2010 ²⁰⁵	Incorrect study design
Timofeeva 2006 ²⁰⁶	Not in English
Umemoto 2017 ²⁰⁸	Subgroup analysis
Umemoto 2016 ²⁰⁷	Subgroup analysis
Uzui 2014 ²⁰⁹	Wrong comparison
Wang 2017 ²¹⁰	Less than minimum duration
Weinberger 1982 ²¹¹	Less than minimum duration
Weir 2001 ²¹²	Less than minimum duration
White 1995 ²¹³	Incorrect study design
Wilhelmsen 1987 ²¹⁴	Incorrect study design
Yip 2008 ²¹⁶	Incorrect study design
Yu 2011 ²¹⁷	Not in English
Yusuf 2016 ²¹⁸	Wrong comparison
Yusuf 2008 ²¹⁹	Wrong population
Zanchetti 2006 ²²⁰	Literature review
Zhang 2010 ²²¹	Inappropriate washout
Zhu 2013 ²²²	Less than minimum duration

1

2

I.2.1 Excluded health economic studies

2 **Table 21: Studies excluded from the health economic review**

Reference	Reason for exclusion
Kato 2015 ¹¹⁹	This study was assessed as partially applicable with very serious limitations because it was a before-and-after study comparing whether switching from monotherapy to combination therapy is cost effective. Clinical data does not meet the requirements of clinical review.
Mazza 2017 ¹⁴⁶	This study was assessed as partially applicable with very serious limitations because it is based on retrospective data, and blood pressure lowering is used for effect rather than clinical endpoints. Therefore, clinical data does not meet the requirements of clinical review.
Saito 2008 ¹⁹²	This study was assessed as partially applicable with very serious limitations because the effectiveness of the combination treatment is based on an assumption (assumption of on-treatment blood pressure) rather than being based on a clinical trial. This also seems to have been put through a risk calculator, which should ideally be used for baseline risks rather than risks post treatment. Therefore, clinical data does not meet the requirements of clinical review.
Wisloff 2012 ²¹⁵	This study was assessed as partially applicable with very serious limitations because the effectiveness of the combination treatment is multiplicative rather than being based on a clinical trial. Therefore, clinical data does not meet the requirements of clinical review.
Szucs 2010 ²⁰⁴	This was a study included in the previous guideline. This study was assessed as not applicable because treatment is being compared to no treatment.

3

1 Appendix J: Research recommendations

J.1.2 Dual therapy

3 **Research question: Are there subgroups of people with hypertension who should start**
 4 **on dual therapy?**

5 **Why this is important:**

6 The physiological control of blood pressure results from the interaction of multiple biological
 7 pathways, including those acting on the kidneys and blood vessels. Most antihypertensive
 8 medication act on a single component of these pathways and so are intrinsically limited in
 9 their ability to lower blood pressure. This is the principle reason that many people prescribed
 10 antihypertensive medication require more than 1 type of medication to achieve their target
 11 blood pressure.

12 In the evidence review for step 1 treatment, the committee considered whether individuals
 13 with hypertension should be commenced on single or dual therapy. Only limited evidence
 14 was available from a single study, and this was felt to be insufficient to determine confidently
 15 whether dual therapy may be beneficial. The theoretical benefit of starting dual therapy is
 16 that more rapid achievement of target blood pressure may lead to a reduction in
 17 cardiovascular events. It is unknown whether dual therapy may be of benefit to all individuals
 18 commencing antihypertensive medication or just certain subgroups such as those with type 2
 19 diabetes, established cardiovascular disease or chronic kidney disease.

20 **Criteria for selecting high-priority research recommendations:**

PICO question	Population: Adults (over the age of 18) who meet the criteria for medication to be initiated for the treatment of hypertension, split into subgroups including type 2 diabetes, history of stroke, history of cardiovascular disease, or pre-existing CKD. Intervention(s): Dual therapy as an initial treatment strategy in the treatment of hypertension. Comparison: Single agent therapy. Outcome(s): Critical: All-cause mortality, stroke (ischaemic or haemorrhagic), myocardial infarction, health related quality of life, and development or progression of chronic kidney disease (CKD). Important: Time to reach blood pressure target,
Importance to patients or the population	Impact would be delay in the development of or slowing the progression of adverse outcomes without an increase in adverse events as a result of the treatment regimen.
Relevance to NICE guidance	This would impact the recommendations within the NICE clinical guideline for hypertension as to whether staged treatment (as per current guideline) is retained or whether dual therapy would be recommended for any specific subgroups of people.
Relevance to the NHS	If blood pressure targets are attained in a more timely fashion without additional adverse effects, this may be cost effective in terms of number of clinic appointments or consultations required. If improved cardiovascular outcomes, this would be cost effective and would reduce the QALY associated with treatment of hypertension.
National priorities	N/A
Current evidence base	Although there was some evidence identified for using dual therapy, this was not in hard clinical outcomes and therefore further evidence with these outcomes could inform future updates of the guideline.
Equality	There are no expected equality issues.

Study design	This question would be best answered by an RCT although the duration of follow up required means that a long-term (at least 5 years) study would be required.
Feasibility	The study would need a 5-year follow-up. Technically, it should be straight forward, but funding could be an issue.
Other comments	As the medications used for the treatment of hypertension are generic, it is unlikely that any funding would be forthcoming from the pharmaceutical industry, so the research would need to be funded by a central body.
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

1