National Institute for Health and Care Excellence

Final

Hypertension in adults: diagnosis and management

[E] Evidence review for step 1 treatment

NICE guideline NG136

Intervention evidence review underpinning recommendations 1.4.30 to 1.4.37 in the guideline

August 2019

Final

This evidence review was developed by the National Guideline Centre

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Contents

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: • 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 chlortalidone,chlortalidone; timolol and bendroflumethiazide) • Non-thiazide and thiazide diuretic (amiloride and hydrochlorothiazide)
Comparison	Antihypertensive Monotherapy. Examples include: • ACE inhibitor or low-cost ARB) • Thiazide-like diuretic (such as chlortalidone chlortalidoneor 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 anti-HTN)
Outcomes	Assessed 12 months or more (using final endpoint) **Critical** • All-cause mortality

	• Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) **Important** • 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 Methods and process

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

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

1.5 Clinical evidence

1.5.1 Included studies

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

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

1.5.2 Excluded studies

Cochrane reviews relevant to this review question were identified. Li 2014[132] was excluded due to an incorrect population. Garjon 2017[89] was excluded due to no relevant outcomes.

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

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: • 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: • 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 • Serious cardiovascular events • Change in creatinine clearance • Discontinuation due to adverse events • Hypotension	

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

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)

Table 4: Clinical evidence summary: monotherapy versus combination (adults with hypertension and without 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)
Change in creatinine (µmol/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.

See appendix F for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No relevant health economic studies were identified.

1.6.2 Excluded studies

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

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

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 = £1.86	2 mg	£1.89	£22.63
Enalapril maleate (ACE inhibitor)	10 mg tablets, pack of 28 = £1.53	10 mg (a)	£1.66	£19.94
Atenolol (Beta blocker)	50 mg tablets, pack of 28 = £0.54	50 mg	£0.59	£7.04
Losartan (ARB)	50 mg tablets, pack of 28 = £0.82	50 mg (b)	£0.89	£10.69
Combination				
Perindopril erbumine (ACE inhibitor) and Indapamide (thiazide) *Separate pills*	2 mg tablets, pack of 30 = £1.86 1.5 mg tablets, pack of 30 = £3.40	2 mg 1.5 mg (c)	£1.89 £3.45	£22.63 £41.37 £64.00
Losartan and hydrochlorothiazide *single pill*	50 mg Losartan, 12.5 mg thiazide, pack of 28 = £1.13	50 mg Losartan, 12.5 mg thiazide (b)	£1.23	£14.73

Source: BNF (Drug Tariff price)[27], DATE: 03 May 2019.
(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.

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

Table 6: Costs of hospitalisation from cardiovascular events

HRG code	HRG code description	Weighted average cost
EB10A to EB10E Myocardial infarction	Actual or Suspected Myocardial Infarction, with CC Score 13+ 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	£1,515
AA35A to AA35F Stroke	Stroke with CC Score 16+ Stroke with CC Score 13-15 Stroke with CC Score 10-12 Stroke with CC Score 7-9 Stroke with CC Score 4-6 Stroke with CC Score 0-3	£3,339
EB13A to EB13D Angina	Angina with CC Score 12+ Angina with CC Score 8-11 Angina with CC Score 4-7 Angina with CC Score 0-3	£716

(a) From NHS reference costs 2017/18, total Healthcare resource group (HRG) schedule. {NHS Improvement, 2018 #1855}

Example costings:

Assumptions:

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

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

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	£19,945	63	£95,436	£115,381
Dual therapy	£63,997	25	£37,220	£101,217
CV event = Stroke				
Monotherapy	£19,945	63	£210,382	£230,327
Dual therapy	£63,997	25	£82,049	£146,046

(a) 12 month cost as clinical studies were over a 12 month period.
(b) Data taken from the clinical review

1.7 Evidence statements

1.7.1 Clinical evidence statements

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

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

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

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

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

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

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

1.8.1.2 The quality of the evidence

The committee discussed that the evidence was limited; from 3 studies, only 1 of which reported a critical outcome (serious cardiovascular events), albeit an indirect composite measure of the individual outcomes the committee were interested in. All of the evidence for people with hypertension and type 2 diabetes was low or very low quality due mainly to risk of bias, indirectness and imprecision. Risk of bias was rated as high because of high attrition rates due to participants dropping out of trials or being lost to follow up. The evidence was also downgraded due to population indirectness. Some participants included within the evidence were outside of the scope of this review question, such as those with moderate to severe chronic kidney disease (CKD). The population included within the evidence was based on studies with small sample sizes.

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

1.8.1.3 Benefits and harms

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

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

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

The committee discussed the evidence identified in 2011 in CG127[154] related to step 1 treatment. The recommendations were stratified by age and family origin reflecting data from clinical trials showing differential effects of the different classes of blood pressure lowering drugs on blood pressure lowering and clinical outcomes in younger (less than 55 years old) versus older people and in black people of African or Caribbean descent. Three studies and an age-stratified analysis from a fourth study also compared blood pressure response across various drug classes and identified ACE inhibitors and beta-blockers as more effective at lowering blood pressure in younger people, when compared to calcium channel-blockers or thiazide-type diuretics. The evidence for ACE inhibitor and ARBs were closely correlated (although lacked head-to-head evidence) and the previous guideline recommended that these treatments should be treated as equal in terms of efficacy; however, due to cost differences, it was considered that ACE inhibitors should be initiated first and an ARB considered an alternative for when an ACE inhibitor was poorly tolerated. The 2011 guideline did not identify evidence to show any consistent trend favouring 1 drug class over the other. The committee agreed it was appropriate to retain these recommendations but to keep in mind that ACE inhibitors and ARBs are now equal in terms of both cost and efficacy.

The committee also discussed step 1 treatment in people with type 2 diabetes, and noted that NG28 recommended ACE inhibitors as step 1 treatment rather than ARBs. The committee noted that this was based both on differences in costs and on limited evidence of a difference in reno-protective benefits between the two treatments. The committee agreed that from their current clinical experience ARBs and ACE inhibitors were similarly effective are were not aware of evidence to contradict this.

However, the committee agreed that beta-blockers are not often used as antihypertensive treatment in current practice and recent meta-analysis (not relevant to this review protocol) have demonstrated this class to be low efficacy for the treatment of hypertension in terms of improving cardiovascular outcomes. The committee discussed whether these drugs are ever

an appropriate choice for people with hypertension. They discussed people with evidence of a high sympathetic drive and noted that the primary cause should be addressed rather than treating the hypertension primarily and that in these cases, beta-blockers would not be the most appropriate choice of drug. The committee therefore agreed not to retain the recommendations related to the use of beta-blockers in people under 55 years.

For people of black African or African Caribbean family origin with type 2 diabetes, the previous recommendation from the type 2 diabetes guideline (NG28) was to offer an ACE inhibitor and either a diuretic or a calcium-channel blocker as step 1 dual therapy. The committee discussed what had informed those recommendations. There were no trials looking at combination treatments in this group and so results from monotherapy studies were considered. There was evidence that CCBs provided better cardiovascular outcomes in black individuals with hypertension compared to ACEi, and that A drugs resulted in improved outcomes in all individuals with diabetes. Additionally, physiological studies suggested lower efficacy of A drugs in black and/or older individuals. Based on these observations it was decided by consensus that for black, hypertensive, diabetic individuals the first-line combination of A+C/D should be used. Although there was some evidence identified for this question on people with hypertension and diabetes, it was only from a single small study, and the committee did not consider this strong enough to base a recommendation on. People with hypertension but no diabetes are offered a CCB in the hypertension guideline, but an ACE inhibitor or ARB is more suitable for those with diabetes as mentioned above. It was discussed how in practice the step 1 dual therapy recommendation for people of black African or African Caribbean family origin is not generally current practice. Black people often show inadequate response to ACE inhibitors and therefore require additional drugs. What tends to happen is an ACE inhibitor is given for step 1 instead of the more appropriate ARB and hence treatment may be escalated more quickly to dual therapy for this group. In summary, the recommendation for step 1 dual therapy was not retained for this group in NG28. The committee noted that considerations may apply in the presence of target organ damage such as microalbuminuria as these patients are at higher CVD risk. The recommendation to offer an ARB in preference for an ACE inhibitor for people of black African or African Caribbean family origin either with or without type 2 diabetes was also retained. The previous guideline committee (CG127) considered that people of black African or Caribean family origin that take ACE inhibitors have an increased risk of developing angioedema which can be life threatening. Although the incidence of this adverse event is low, the previous committee suggested that an ARB in preference to an ACE inhibitor should be considered for such patients.

1.8.2 Cost effectiveness and resource use

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

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

Dual therapy treatments are likely to have higher costs. In theory, 2 medications instead of 1 may also lead to more adverse events, which also needs to be traded off against benefit. This was not clear from the clinical review, which found no difference in discontinuation rates. The major impact on effectiveness that would be traded-off against the additional drug use is

the impact on cardiovascular events or mortality. The clinical review showed that there were 39 fewer serious cardiovascular events with the dual therapy treatment than with the monotherapy, in a population with hypertension and type 2 diabetes. Cardiovascular events are likely to be events like myocardial infarction or stroke, which are very costly to treat and can have a long-term impact on quality of life. Therefore, any events avoided could be argued as being significant. This evidence was of very low quality, however, and was from only 1 study and therefore may not be sufficient evidence to change practice, as the committee cannot be confident that these outcomes are likely to represent the true outcomes in the general population with such little evidence.

As an example of some costing illustrations, a cohort of 1000 people taking monotherapy or dual therapy for 12 months would lead to higher intervention costs for the dual therapy arm (£19,945 versus £63,997 respectively) (based on the drugs that were used in the included trial). Trading this off against the cardiovascular event outcomes from the clinical review, shows that monotherapy is overall more expensive than dual therapy. This is a very simplified example, and there are a number of factors that haven't been captured. Cardiovascular event costs are likely to be higher than just initial hospitalisation costs such as including follow-ups and rehabilitation perhaps. There is no quality of life captured, but events would have a detriment to quality of life. These factors are likely to favour dual therapy. However, different drugs also have different costs, and dual therapy in a single pill may be more expensive because of the ease of having to take only 1 pill but have the benefit of 2 drugs. There are no adverse events included or other costs associated with treatment like monitoring, which might be higher in a dual therapy strategy. Therefore, even if dual therapy was overall a more expensive strategy, it is uncertain if this would be cost effective.

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

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

Some of the recommendations from the previous hypertension guideline were edited, including removing a recommendation on when to use beta-blockers, as these are not used very much in practice, and removing references to low cost ARBs, as ACE inhibitors and ARBs are similarly low cost now. In general, the previous recommendations were agreed to still be appropriate and represent good practice. These were based on a combination of

clinical evidence and cost effectiveness evidence, as a model in the 2004 guideline comparing monotherapies for step 1 treatment (for which costs were updated in the 2011 guideline) showed that CCBs were generally the most cost effective. In higher risk people, thiazides were shown to be the most cost effective for people at high risk of heart failure. A sensitivity analysis on age showed that ACE inhibitors or ARBs were likely to be the most cost effective.

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

1.8.3 Other factors the committee took into account

The committee reviewed the wording of the recommendations in the previous 2011 hypertension guideline (CG127) and highlighted that if a thiazide like diuretic was being offered, indapamide is likely to be the drug that is used. The previous wording of the recommendation may have implied chlortalidone should be first choice, by the nature of it being listed first; however, chlortalidone hasn't become more widely available to European market as was hoped, and therefore this has been removed from the recommendation.

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

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

References

1. Aalbers J. Reduced blood pressure variability in ASCOT-BPLA trial favours use of amlodipine/perindopril combination to reduce stroke risk. Cardiovascular Journal of Africa. 2010; 21(2):115

2. Abate G, Zito M, Carbonin PU, Cocchi A, Cucinotta D, Manopulo R et al. Pinacidil and hydrochlorothiazide alone or in combination in the treatment of hypertension in the elderly. Current Therapeutic Research, Clinical and Experimental. 1998; 59(1):62-71

3. Amir M, Cristal N, Bar-On D, Loidl A. Does the combination of ACE inhibitor and calcium antagonist control hypertension and improve quality of life? The LOMIR-MCT-IL study experience. Blood Pressure Supplement. 1994; 1:40-2

4. Anan F, Takahashi N, Ooie T, Yufu K, Hara M, Nakagawa M et al. Effects of valsartan and perindopril combination therapy on left ventricular hypertrophy and aortic arterial stiffness in patients with essential hypertension. European Journal of Clinical Pharmacology. 2005; 61(5-6):353-9

5. Andersson OK. Improved efficacy with maintained tolerability in the treatment of primary hypertension. Comparison between the felodipine-metoprolol combination tablet and monotherapy with enalapril. Swedish Multicentre Group. Journal of Human Hypertension. 1999; 13(1):55-60

6. Anderton JL, Vallance BD, Stanley NN, Crowe PF, Mittra B, Perks WH. Atenolol and sustained release nifedipine alone and in combination in hypertension. A randomised, double-blind, crossover study. Drugs. 1988; 35(Suppl 4):22-6

7. Andreadis EA, Sfakianakis ME, Tsourous GI, Georgiopoulos DX, Fragouli EG, Katsanou PM et al. Differential impact of angiotensin receptor blockers and calcium channel blockers on arterial stiffness. International Angiology. 2010; 29(3):266-72

8. Andreadis EA, Tsourous GI, Marakomichelakis GE, Katsanou PM, Fotia ME, Vassilopoulos CV et al. High-dose monotherapy vs low-dose combination therapy of calcium channel blockers and angiotensin receptor blockers in mild to moderate hypertension. Journal of Human Hypertension. 2005; 19(6):491-6

9. Anonymous. Low-dose captopril for the treatment of mild to moderate hypertension. Hypertension. 1983; 5(5 Suppl 3):III139-44

10. Anonymous. Nifedipine and atenolol singly and combined for treatment of essential hypertension: Comparative multicentre study in general practice in the United Kingdom. Nifedipine-Atenolol Study Review Committee. BMJ. 1988; 296(6620):468-72

11. Aoki K, Kondo S, Mochizuki A, Yoshida T, Kato S, Kato K et al. Antihypertensive effect of cardiovascular Ca^{2+}-antagonist in hypertensive patients in the absence and presence of beta-adrenergic blockade. American Heart Journal. 1978; 96(2):218-26

12. Applegate W, Cohen JD, Wolfson P, Davis A, Green S. Long-term effectiveness of enalapril plus extended-release diltiazem in essential hypertension. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1997; 17(1):107-12

13. Asmar RG, London GM, O'Rourke ME, Mallion JM, Romero R, Rahn KH et al. Amelioration of arterial properties with a perindopril-indapamide very-low-dose combination. Journal of Hypertension Supplement. 2001; 19(4):S15-20

14. Asmar RG, London GM, O'Rourke ME, Safar ME, Reason Project Coordinators and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: A comparison with atenolol. Hypertension. 2001; 38(4):922-6

15. Bakris G, Briasoulis A, Dahlof B, Jamerson K, Weber MA, Kelly RY et al. Comparison of benazepril plus amlodipine or hydrochlorothiazide in high-risk patients with hypertension and coronary artery disease. American Journal of Cardiology. 2013; 112(2):255-9

16. Basile J, Babazadeh S, Lillestol M, Botha J, Yurkovic C, Weitzman R. Comparison of aliskiren/hydrochlorothiazide combination therapy with hydrochlorothiazide monotherapy in older patients with stage 2 systolic hypertension: Results of the ACTION study. Journal of Clinical Hypertension. 2011; 13(3):162-9

17. Bays H, Zhu D, Schumacher H. Single-pill combination of telmisartan and hydrochlorothiazide: Studies and pooled analyses of earlier hypertension treatment. High Blood Pressure & Cardiovascular Prevention. 2014; 21(2):119-26

18. Benedict Group. The BErgamo NEphrologic DIabetes Complications Trial (BENEDICT): Design and baseline characteristics. Controlled Clinical Trials. 2003; 24(4):442-61

19. Benjamin N, Phillips RJ, Robinson BF. Verapamil and bendrofluazide in the treatment of hypertension: A controlled study of effectiveness alone and in combination. European Journal of Clinical Pharmacology. 1988; 34(3):249-53

20. Bennett A, Chow CK, Chou M, Dehbi HM, Webster R, Salam A et al. Efficacy and safety of quarter-dose blood pressure-lowering agents: A systematic review and meta-analysis of randomized controlled trials. Hypertension. 2017; 70(1):85-93

21. Beretta-Piccoli C, Amstein R, Bertel O, Brunner HR, Buhler FR, Follath F et al. Antihypertensive efficacy of ketanserin alone or in combination with a beta-blocker or a diuretic: The Swiss Ketanserin Study. Journal of Cardiovascular Pharmacology. 1987; 10(Suppl 3):S119-23

22. Bielmann P, Leduc G, Thibault G, Lepage J, Davignon J. Effects of chlortalidone and metoprolol alone or in combination (logroton) on blood pressure, lipids, lipoproteins and circulating plasma ANF levels in essential hypertension. International Journal of Clinical Pharmacology, Therapy, and Toxicology. 1991; 29(12):479-85

23. Black HR, Davis B, Barzilay J, Nwachuku C, Baimbridge C, Marginean H et al. Metabolic and clinical outcomes in nondiabetic individuals with the metabolic syndrome assigned to chlortalidone, amlodipine, or lisinopril as initial treatment for hypertension: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Diabetes Care. 2008; 31(2):353-60

24. Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, Neaton JD et al. Results of the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) trial by geographical region. Journal of Hypertension. 2005; 23(5):1099-106

25. Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA. 2003; 289(16):2073-2082

26. Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm RH et al. Rationale and design for the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Trial. Controlled Clinical Trials. 1998; 19(4):370-390

27. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from: https://www.evidence.nhs.uk/formulary/bnf/current Last accessed: 08 November 2018

28. Bohm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: Results from ONTARGET and TRANSCEND trials. Lancet. 2017; 389(10085):2226-2237

29. Bomback AS, Rekhtman Y, Klemmer PJ, Canetta PA, Radhakrishnan J, Appel GB. Aldosterone breakthrough during aliskiren, valsartan, and combination (aliskiren + valsartan) therapy. Journal of the American Society of Hypertension. 2012; 6(5):338-45

30. Bradley WF. A long-term clinical trial of prazosin. Postgraduate Medicine. 1975; Special:95-9

31. Breithaupt-Grogler K, Gerhardt G, Lehmann G, Notter T, Belz GG. Blood pressure and aortic elastic properties: Verapamil SR/trandolapril compared to a metoprolol/hydrochlorothiazide combination therapy. International Journal of Clinical Pharmacology and Therapeutics. 1998; 36(8):425-31

32. Bremner AD, Baur M, Oddou-Stock P, Bodin F. Valsartan: Long-term efficacy and tolerability compared to lisinopril in elderly patients with essential hypertension. Clinical and Experimental Hypertension. 1997; 19(8):1263-1285

33. Bremner AD, Mehring GH, Meilenbrock S. Long-term systemic tolerability of valsartan compared with lisinopril in elderly hypertensive patients. Advances in Therapy. 1997; 14(5):245-253

34. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). The Lancet. 2000; 356(9227):366-72

35. Brown MJ, Palmer CR, Castaigne A, De Leeuw PW, Mancia G, Rosenthal T et al. Principal results from the international nifedipine GITS Study: Intervention as a goal in hypertension treatment (INSIGHT). European Heart Journal, Supplement. 2001; 3(Suppl B):B20-B26

36. Brown MJ, Struthers AD, Di Silvio L. Metabolic and haemodynamic effects of alpha2-adrenoceptor stimulation and antagonism in man. Clinical Science. 1985; 68(Suppl 10):137S-139S

37. Brown MJ, Toal CB. Formulation of long-acting nifedipine tablets influences the heart rate and sympathetic nervous system response in hypertensive patients. British Journal of Clinical Pharmacology. 2008; 65(5):646-652

38. Brown MJ, Williams B, MacDonald TM, Caulfield M, Cruickshank JK, McInnes G et al. Comparison of single and combination diuretics on glucose tolerance (PATHWAY-3): Protocol for a randomised double-blind trial in patients with essential hypertension. BMJ Open. 2015; 5(8):e008086

39. Chalmers J. Efficacy and acceptability of the fixed low-dose perindopril-indapamide combination as first-line therapy in hypertension. European Heart Journal, Supplement. 1999; 1(Suppl L):L20-L25

40. Chaugai S, Sherpa LY, Sepehry AA, Kerman SRJ, Arima H. Effects of long- and intermediate-acting dihydropyridine calcium channel blockers in hypertension: A systematic review and meta-analysis of 18 prospective, randomized, actively

controlled trials. Journal of Cardiovascular Pharmacology and Therapeutics. 2018; 23(5):433-445

41. Chung JW, Lee HY, Kim CH, Seung IW, Shin YW, Jeong MH et al. Losartan/hydrochlorothiazide fixed combination versus amlodipine monotherapy in Korean patients with mild to moderate hypertension. Korean Circulation Journal. 2009; 39(4):151-6

42. Ciulla MM, Paliotti R, Esposito A, Cuspidi C, Muiesan ML, Rosei EA et al. Effects of antihypertensive treatment on ultrasound measures of myocardial fibrosis in hypertensive patients with left ventricular hypertrophy: Results of a randomized trial comparing the angiotensin receptor antagonist, candesartan and the angiotensin-converting enzyme inhibitor, enalapril. Journal of Hypertension. 2009; 27(3):626-32

43. Ciulla MM, Paliotti R, Esposito A, Dìez J, López B, Dahlöf B et al. Different effects of antihypertensive therapies based on losartan or atenolol on ultrasound and biochemical markers of myocardial fibrosis: Results of a randomized trial. Circulation. 2004; 110(5):552-557

44. Cushman WC, Cohen JD, Jones RP, Marbury TC, Rhoades RB, Smith LK. Comparison of the fixed combination of enalapril/diltiazem ER and their monotherapies in stage 1 to 3 essential hypertension. American Journal of Hypertension. 1998; 11(1 Pt 1):23-30

45. Dafgard T, Forsen B, Lindahl T. Comparative study of hydrochlorothiazide and a fixed combination of metoprolol and hydrochlorothiazide essential hypertension. Annals of Clinical Research. 1981; 13(Suppl 30):37-44

46. Dahlöf B, Andrén L, Eggertsen R, Jern S, Svensson A, Hansson L. The long-term effect of isradipine in pindolol-treated patients. Journal of Hypertension Supplement. 1987; 5(5):S567-70

47. Dahlof B, Gosse P, Gueret P, Dubourg O, de Simone G, Schmieder R et al. Perindopril/indapamide combination more effective than enalapril in reducing blood pressure and left ventricular mass: The PICXEL study. Journal of Hypertension. 2005; 23(11):2063-70

48. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. The Lancet. 2005; 366(9489):895-906

49. Damian DJ, McNamee R, Carr M. Changes in selected metabolic parameters in patients over 65 receiving hydrochlorothiazide plus amiloride, atenolol or placebo in the MRC elderly trial. BMC Cardiovascular Disorders. 2016; 16:188

50. de Divitiis O, Petitto M, Di Somma S, Fazio S, Galderisi M, Villari B et al. Acebutolol and nifedipine in the treatment of arterial hypertension: Efficacy and acceptability. Arzneimittel-Forschung. 1984; 34(6):710-5

51. de Galan BE, Perkovic V, Ninomiya T, Pillai A, Patel A, Cass A et al. Lowering blood pressure reduces renal events in type 2 diabetes. Journal of the American Society of Nephrology. 2009; 20(4):883-92

52. de Luca N, Asmar RG, London GM, O'Rourke MF, Safar ME, Reason Project Investigators. Selective reduction of cardiac mass and central blood pressure on low-

dose combination perindopril/indapamide in hypertensive subjects. Journal of Hypertension. 2004; 22(8):1623-30

53. Degl'Innocenti A, Elmfeldt D, Hofman A, Lithell H, Olofsson B, Skoog I et al. Health-related quality of life during treatment of elderly patients with hypertension: Results from the Study on COgnition and Prognosis in the Elderly (SCOPE). Journal of Human Hypertension. 2004; 18(4):239-245

54. Delea TE, Sofrygin O, Palmer JL, Lau H, Munk VC, Sung J et al. Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. Journal of the American Society of Nephrology. 2009; 20(10):2205-2213

55. Department of Health. NHS reference costs 2016-17. 2017. Available from: https://improvement.nhs.uk/resources/reference-costs/#archive Last accessed: 03/01/19

56. DeQuattro V, Lee D. Fixed-dose combination therapy with trandolapril and verapamil SR is effective in primary hypertension. Trandolapril Study Group. American Journal of Hypertension. 1997; 10(7 Pt 2):138S-145S

57. DeQuattro V, Lee D, Messerli F, The Trandolapril Study Group. Efficacy of combination therapy with trandolapril and verapamil sr in primary hypertension: A 4 x 4 trial design. Clinical and Experimental Hypertension. 1997; 19(3):373-87

58. Derosa G, Bonaventura A, Romano D, Bianchi L, Fogari E, D'Angelo A et al. Effects of enalapril/lercanidipine combination on some emerging biomarkers in cardiovascular risk stratification in hypertensive patients. Journal of Clinical Pharmacy and Therapeutics. 2014; 39(3):277-85

59. Derosa G, Cicero AF, Carbone A, Querci F, Fogari E, D'Angelo A et al. Effects of an olmesartan/amlodipine fixed dose on blood pressure control, some adipocytokines and interleukins levels compared with olmesartan or amlodipine monotherapies. Journal of Clinical Pharmacy and Therapeutics. 2013; 38(1):48-55

60. Derosa G, Cicero AF, Carbone A, Querci F, Fogari E, D'Angelo A et al. Olmesartan/amlodipine combination versus olmesartan or amlodipine monotherapies on blood pressure and insulin resistance in a sample of hypertensive patients. Clinical and Experimental Hypertension. 2013; 35(5):301-7

61. Derosa G, Cicero AF, Carbone A, Querci F, Fogari E, D'Angelo A et al. Variation of some inflammatory markers in hypertensive patients after 1 year of olmesartan/amlodipine single-pill combination compared with olmesartan or amlodipine monotherapies. Journal of the American Society of Hypertension. 2013; 7(1):32-9

62. Derosa G, Cicero AF, Carbone A, Querci F, Fogari E, D'Angelo A et al. Different aspects of sartan + calcium antagonist association compared to the single therapy on inflammation and metabolic parameters in hypertensive patients. Inflammation. 2014; 37(1):154-62

63. Derosa G, Cicero AF, Carbone A, Querci F, Fogari E, D'Angelo A et al. Results from a 12 months, randomized, clinical trial comparing an olmesartan/amlodipine single pill combination to olmesartan and amlodipine monotherapies on blood pressure and inflammation. European Journal of Pharmaceutical Sciences. 2014; 51:26-33

64. Derosa G, Mugellini A, Pesce RM, D'Angelo A, Maffioli P. Perindopril and barnidipine alone or combined with simvastatin on hepatic steatosis and inflammatory parameters in hypertensive patients. European Journal of Pharmacology. 2015; 766:31-6

65. Derosa G, Mugellini A, Pesce RM, D'Angelo A, Maffioli P. Olmesartan combined with amlodipine on oxidative stress parameters in type 2 diabetics, compared with single therapies: A randomized, controlled, clinical trial. Medicine. 2016; 95(13):e3084

66. Destro M, Luckow A, Samson M, Kandra A, Brunel P. Efficacy and safety of amlodipine/valsartan compared with amlodipine monotherapy in patients with stage 2 hypertension: A randomized, double-blind, multicenter study: The EX-EFFeCTS Study. Journal of the American Society of Hypertension. 2008; 2(4):294-302

67. Dickson M, Plauschinat CA. Compliance with antihypertensive therapy in the elderly: A comparison of fixed-dose combination amlodipine/benazepril versus component-based free-combination therapy. American Journal of Cardiovascular Drugs. 2008; 8(1):45-50

68. Drayer JI, Stimpel M, Fox A, Weber M. The antihypertensive properties of the angiotensin-converting enzyme inhibitor moexipril given alone or in combination with a low dose of a diuretic. American Journal of Therapeutics. 1995; 2(8):525-531

69. Duckett GK, Cheadle B. Hypertension in the elderly: A study of a combination of atenolol and nifedipine. British Journal of Clinical Practice. 1990; 44(2):52-4

70. Dzurik R, Fetkovska N, Dvorak I, Jonas P, Markuljak I, Petr P et al. Isradipine in monotherapy and in combination with bopindolol: Results of a 3-month multicentre study in hypertensives. Cor et Vasa. 1990; 32(2 Suppl 1):42-53

71. El-Mehairy MM, Shaker A, Ramadan M, Hamza S, Tadros SS. Long-term treatment of essential hypertension using nadolol and hydrochlorothiazide combined. British Journal of Clinical Pharmacology. 1979; 7(Suppl 2):199S-203S

72. Elliott HL, Meredith PA, Campbell L, Reid JL. The combination of prazosin and verapamil in the treatment of essential hypertension. Clinical Pharmacology and Therapeutics. 1988; 43(5):554-60

73. Family Physicians Hypertension Study Group, Cajochen C, Krauchi K, Von AMA, Mori D, Graw P et al. A multicenter comparison of the antihypertensive effects of atenolol and chlortalidone given alone and in combination. Current Therapeutic Research, Clinical and Experimental. 1984; 35(1):31-39

74. Fang H, Chen W, Liu X, Xu W. The efficacy and safety of arotinolol combined with a different calcium channel blocker in the treatment of Chinese patients with essential hypertension: A one-year follow-up study. Clinical and Experimental Hypertension. 2014; 36(8):590-5

75. Feldman RD, Zou GY, Vandervoort MK, Wong CJ, Nelson SA, Feagan BG. A simplified approach to the treatment of uncomplicated hypertension: A cluster randomized, controlled trial. Hypertension. 2009; 53(4):646-53

76. Fell PJ. Long-term treatment of hypertension in the elderly with a combination of atenolol and nifedipine. Current Medical Research and Opinion. 1990; 12(1):66-70

77. Ferrari R. Optimizing the treatment of hypertension and stable coronary artery disease: Clinical evidence for fixed-combination perindopril/amlodipine. Current Medical Research and Opinion. 2008; 24(12):3543-57

78. Fogari R, Derosa G, Zoppi A, Preti P, Lazzari P, Destro M et al. Effect of telmisartan-amlodipine combination at different doses on urinary albumin excretion in hypertensive diabetic patients with microalbuminuria. American Journal of Hypertension. 2007; 20(4):417-22

79. Fogari R, Preti P, Zoppi A, Rinaldi A, Corradi L, Pasotti C et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. American Journal of Hypertension. 2002; 15(12):1042-9

80. Fogari R, Zoppi A, Mugellini A, Preti P, Destro M, Rinaldi A et al. Effectiveness of hydrochlorothiazide in combination with telmisartan and olmesartan in adults with moderate hypertension not controlled with monotherapy: A prospective, randomized, open-label, blinded end point (PROBE), parallel-arm study. Current Therapeutic Research, Clinical and Experimental. 2008; 69(1):1-15

81. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S et al. The prevention of dementia with antihypertensive treatment: New evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Archives of Internal Medicine. 2002; 162(18):2046-2052

82. Franklin SS, Weir MR, Smith DH, Codispoti J, Stokes A, McNally C et al. Combination treatment with sustained-release verapamil and indapamide in the treatment of mild-to-moderate hypertension. American Journal of Therapeutics. 1996; 3(7):506-514

83. Franz IW, Tönnesmann U, Behr U, Ketelhut R. Regression of left ventricular hypertrophy in hypertensive patients under long-term therapy with antihypertensive agents. Deutsche Medizinische Wochenschrift. 1990; 115(16):603-609

84. Freytag F, Holwerda NJ, Karlberg BE, Meinicke TW, Schumacher H. Long-term exposure to telmisartan as monotherapy or combination therapy: Efficacy and safety. Blood Pressure. 2002; 11(3):173-81

85. Frishman WH, Burris JF, Mroczek WJ, Weir MR, Alemayehu D, Simon JS et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. Journal of Clinical Pharmacology. 1995; 35(2):182-8

86. Fu S, Wen X, Han F, Long Y, Xu G. Aliskiren therapy in hypertension and cardiovascular disease: a systematic review and a meta-analysis. Oncotarget. 2017; 8(51):89364-89374

87. Fujisaki K, Tsuruya K, Nakano T, Taniguchi M, Higashi H, Katafuchi R et al. Impact of combined losartan/hydrochlorothiazide on proteinuria in patients with chronic kidney disease and hypertension. Hypertension Research. 2014; 37(11):993-8

88. Garcia de Vinuesa S, Luno J, Gomez-Campdera F, Ridao N, Sanchez M, Dall'Anese C et al. Effect of strict blood pressure control on proteinuria in renal patients treated with different antihypertensive drugs. Nephrology Dialysis Transplantation. 2001; 16(Suppl 1):78-81

89. Garjon J, Saiz LC, Azparren A, Elizondo JJ, Gaminde I, Ariz MJ et al. First-line combination therapy versus first-line monotherapy for primary hypertension. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD010316. DOI: https://dx.doi.org/10.1002/14651858.CD010316.pub2.

90. Girerd X, Giannattasio C, Moulin C, Safar M, Mancia G, Laurent S. Regression of radial artery wall hypertrophy and improvement of carotid artery compliance after long-term antihypertensive treatment in elderly patients. Journal of the American College of Cardiology. 1998; 31(5):1064-73

91. Goodman C, Rosendorff C, Coull A. Comparison of the antihypertensive effect of enalapril and propranolol in black South Africans. South African Medical Journal. 1985; 67(17):672-6

92. Goyal J, Khan ZY, Upadhyaya P, Goyal B, Jain S. Comparative study of high dose mono-therapy of amlodipine or telmisartan, and their low dose combination in mild to moderate hypertension. Journal of Clinical and Diagnostic Research JCDR. 2014; 8(6):HC08-11

93. Grassi G, Mancia G. Olmesartan medoxomil: As monotherapy and in combination treatment in hypertension. High Blood Pressure & Cardiovascular Prevention. 2010; 17(1):1-14

94. Grimm RH, Jr., Flack JM, Schoenberger JA, Gonzalez NM, Liebson PR. Alpha-blockade and thiazide treatment of hypertension. A double-blind randomized trail comparing doxazosin and hydrochlorothiazide. American Journal of Hypertension. 1996; 9(5):445-54

95. Gupta AK, Dahlof B, Dobson J, Sever PS, Wedel H, Poulter NR et al. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. Diabetes Care. 2008; 31(5):982-8

96. Guyot D, Lemarié JC. Efficacy of Triatec in monotherapy and in combination with Lasilix in a French multicenter study. Revue du Praticien. 1990; 40(18 Suppl):27-30, 35-8

97. Hall J, Marbury T, Gray J, Chaudhery S, Chen S, James D et al. Long term safety, tolerability and efficacy of valsartan: Results from one and two year trials. Journal of Clinical Research. 1998; 1:147-159

98. Hall WD, Montoro R, Littlejohn T, Jain A, Feliciano N, Zheng H. Efficacy and tolerability of valsartan in combination with hydrochlorothiazide in essential hypertension. Clinical Drug Investigation. 1998; 16(3):203-10

99. Harmankaya O, Seber S, Yilmaz M. Combination of pentoxifylline with angiotensin converting enzyme inhibitors produces an additional reduction in microalbuminuria in hypertensive type 2 diabetic patients. Renal Failure. 2003; 25(3):465-70

100. Hasegawa Y, Yamaguchi T, Omae T, Woodward M, Chalmers J. Effects of perindopril-based blood pressure lowering and of patient characteristics on the progression of silent brain infarct: The Perindopril Protection against Recurrent Stroke Study (PROGRESS) CT Substudy in Japan. Hypertension Research. 2004; 27(3):147-156

101. He T, Liu X, Li Y, Liu XY, Wu QY, Liu ML et al. High-dose calcium channel blocker (CCB) monotherapy vs combination therapy of standard-dose CCBs and angiotensin receptor blockers for hypertension: A meta-analysis. Journal of Human Hypertension. 2017; 31(2):79-88

102. Heidbreder D, Froer KL, Bauer B, Cairns V, Breitstadt A. Efficacy and safety of ramipril in combination with hydrochlorothiazide: Results of a long-term study. Journal of Cardiovascular Pharmacology. 1991; 18(Suppl 2):S169-S173

103. Heidbreder D, Froer KL, Breitstadt A, Cairns V, Langley A, Bender N. Combination of ramipril and hydrochlorothiazide in the treatment of mild to moderate hypertension: Part 1--A double-blind, comparative, multicenter study in nonresponders to ramipril monotherapy. Clinical Cardiology. 1992; 15(12):904-10

104. Helmer A, Slater N, Smithgall S. A Review of ACE Inhibitors and ARBs in black patients with hypertension. Annals of Pharmacotherapy. 2018; 52(11):1143-1151

105. Herlitz H, Harris K, Risler T, Boner G, Bernheim J, Chanard J et al. The effects of an ACE inhibitor and a calcium antagonist on the progression of renal disease: The Nephros Study. Nephrology Dialysis Transplantation. 2001; 16(11):2158-65

106. Hersh AD, Kelly JG, Laher MS, Carmody M, Doyle GD. Effect of hydrochlorothiazide on the pharmacokinetics of enalapril in hypertensive patients with varying renal function. Journal of Cardiovascular Pharmacology. 1996; 27(1):7-11

107. Hill JF, Bulpitt CJ, Fletcher AE. Angiotensin converting enzyme inhibitors and quality of life: The European trial. Journal of Hypertension Supplement. 1985; 3(2):S91-4

108. Hilleman DE, Ryschon KL, Mohiuddin SM, Wurdeman RL. Fixed-dose combination vs monotherapy in hypertension: A meta-analysis evaluation. Journal of Human Hypertension. 1999; 13(7):477-83

109. Höfling B, Häringer E, Herrmann W, Pieske H, Pieske R, Philippi M. Therapy of mild to moderate hypertension. Efficacy and tolerance of Amlodipine in comparison with the combination nifedipine/mefruside. Fortschritte der Medizin. 1991; 109(15):327-330

110. Holzgreve H. Combination versus monotherapy as initial treatment in hypertension. Herz. 2003; 28(8):725-32

111. Holzgreve H, Distler A, Michaelis J, Philipp T, Wellek S. Verapamil versus hydrochlorothiazide in the treatment of hypertension: Results of long term double blind comparative trial. BMJ. 1989; 299:881-6

112. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. The Lancet. 2009; 373(9681):2125-2135

113. Ihm SH, Jeon HK, Cha TJ, Hong TJ, Kim SH, Lee NH et al. Efficacy and safety of two fixed-dose combinations of S-amlodipine and telmisartan (CKD-828) versus S-amlodipine monotherapy in patients with hypertension inadequately controlled using S-amlodipine monotherapy: An 8-week, multicenter, randomized, double-blind, phase III clinical study. Drug Design, Development and Therapy. 2016; 10:3817-3826

114. Ishimitsu T, Yagi S, Ebihara A, Doi Y, Domae A, Shibata A et al. Long-term evaluation of combined antihypertensive therapy with lisinopril and a thiazide diuretic in patients with essential hypertension. Japanese Heart Journal. 1997; 38(6):831-40

115. Jang JY, Lee SH, Kim BS, Seo HS, Kim WS, Ahn Y et al. Additive beneficial effects of valsartan combined with rosuvastatin in the treatment of hypercholesterolemic hypertensive patients. Korean Circulation Journal. 2015; 45(3):225-33

116. Johnson BA, Roache JD, Ait-Daoud N, Wallace C, Wells LT, Wang Y. Effects of isradipine on methamphetamine-induced changes in attentional and perceptual-motor skills of cognition. Psychopharmacology. 2005; 178(2-3):296-302

117. Johnson BF, Johnson J, Surve A, Smith H. The interaction of hydrochlorothiazide with spirapril: A novel ace inhibitor. American Journal of Therapeutics. 1994; 1(1):4-7

118. Katayama K, Nomura S, Ishikawa H, Murata T, Koyabu S, Nakano T. Comparison between valsartan and valsartan plus cilnidipine in type II diabetics with normo- and microalbuminuria. Kidney International. 2006; 70(1):151-156

119. Kato H, Shiraishi T, Ueda S, Kubo E, Shima T, Nagura M et al. Blood pressure control and satisfaction of hypertensive patients following a switch to combined drugs

of an angiotensin receptor blocker and a calcium channel blocker in clinical practice of nephrology. Clinical and Experimental Nephrology. 2015; 19(3):465-73

120. Kim JH, Kim JM, Cho YZ, Na JH, Kim HS, Kim HA et al. Effects of candesartan and propranolol combination therapy versus propranolol monotherapy in reducing portal hypertension. Clinical and molecular hepatology. 2014; 20(4):376-383

121. Kim KI, Shin MS, Ihm SH, Youn HJ, Sung KC, Chae SC et al. A randomized, double-blind, multicenter, phase III study to evaluate the efficacy and safety of fimasartan/amlodipine combined therapy versus fimasartan monotherapy in patients with essential hypertension unresponsive to fimasartan monotherapy. Clinical Therapeutics. 2016; 38(10):2159-2170

122. Kim SH, Ryu KH, Lee NH, Kang JH, Kim WS, Park SW et al. Efficacy of fixed-dose amlodipine and losartan combination compared with amlodipine monotherapy in stage 2 hypertension: A randomized, double blind, multicenter study. BMC Research Notes. 2011; 4:461

123. Kinouchi K, Ichihara A, Bokuda K, Kurosawa H, Itoh H. Differential effects in cardiovascular markers between high-dose angiotensin II receptor blocker monotherapy and combination therapy of arb with calcium channel blocker in hypertension (DEAR Trial). International Journal of Hypertension. 2011; 2011:284823

124. Kjeldsen SE, Cha G, Villa G, Mancia G, Investigators D. Nifedipine GITS/candesartan combination therapy lowers blood pressure across different baseline systolic and diastolic blood pressure categories: DISTINCT study subanalyses. Journal of Clinical Pharmacology. 2016; 56(9):1120-9

125. Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L, Lanke J et al. Influence of age, sex and blood pressure on the principal endpoints of the Nordic Diltiazem (NORDIL) Study. Journal of Hypertension. 2002; 20(6):1231-7

126. Kjeldsen SE, Jamerson KA, Bakris GL, Pitt B, Dahlof B, Velazquez EJ et al. Predictors of blood pressure response to intensified and fixed combination treatment of hypertension: The ACCOMPLISH study. Blood Pressure. 2008; 17(1):7-17

127. Kostis JB, Davis BR, Cutler J, Grimm RH, Jr., Berge KG, Cohen JD et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. JAMA. 1997; 278(3):212-6

128. Kostis JB, Silfani T. The combination of olmesartan medoxomil plus hydrochlorothiazide in subjects with stage 2 hypertension: Results of a randomized, double-blind, factorial-design study. American Journal of Hypertension. 2004; 17(5):114A

129. Kuschnir E, Bendersky M, Resk J, Panart MS, Guzman L, Plotquin Y et al. Effects of the combination of low-dose nifedipine GITS 20 mg and losartan 50 mg in patients with mild to moderate hypertension. Journal of Cardiovascular Pharmacology. 2004; 43(2):300-5

130. Lassila HC, Sutton-Tyrrell K, Schwartz F, Wildman RP, Kuller LH. Antihypertensive medication use 5 years following the systolic hypertension in the elderly program. CVD Prevention. 2000; 3(3):229-234

131. Laurent S. Clinical benefit of very-low-dose perindopril-indapamide combination in hypertension. Journal of Hypertension Supplement. 2001; 19(4):S9-14

132. Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database of

Systematic Reviews 2014, Issue 8. Art. No.: CD009096. DOI: https://dx.doi.org/10.1002/14651858.CD009096.pub2.

133. London GM, Asmar RG, O'Rourke MF, Safar ME, Reason Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: Comparison with atenolol. Journal of the American College of Cardiology. 2004; 43(1):92-9

134. Lucas CP, Morledge JH, Tessman DK. Comparison of hydrochlorothiazide and hydrochlorothiazide plus bevantolol in hypertension. Clinical Therapeutics. 1985; 8(1):49-60

135. Lv J, Zhang H, Chen Y, Li G, Jiang L, Singh AK et al. Combination therapy of prednisone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: A randomized controlled trial. American Journal of Kidney Diseases. 2009; 53(1):26-32

136. MacDonald TM, Williams B, Caulfield M, Cruickshank JK, McInnes G, Sever P et al. Monotherapy versus dual therapy for the initial treatment of hypertension (PATHWAY-1): A randomised double-blind controlled trial. BMJ Open. 2015; 5(8):e007645

137. MacKay JH, Arcuri KE, Goldberg AI, Snapinn SM, Sweet CS. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. A double-blind, placebo-controlled trial of concomitant administration compared with individual components. Archives of Internal Medicine. 1996; 156(3):278-85

138. Malacco E, Omboni S, Study Group. Antihypertensive effect of zofenopril plus hydrochlorothiazide versus zofenopril monotherapy in patients with essential hypertension according to their cardiovascular risk level: A post hoc analysis. Current Therapeutic Research, Clinical and Experimental. 2008; 69(3):232-42

139. Mallion JM, Chamontin B, Asmar R, De Leeuw PW, O'Brien E, Duprez D et al. Twenty-four-hour ambulatory blood pressure monitoring efficacy of perindopril/indapamide first-line combination in hypertensive patients: The REASON study. American Journal of Hypertension. 2004; 17(3):245-51

140. Mancia G, Cha G, Gil-Extremera B, Harvey P, Lewin AJ, Villa G et al. Blood pressure-lowering effects of nifedipine/candesartan combinations in high-risk individuals: Subgroup analysis of the DISTINCT randomised trial. Journal of Human Hypertension. 2017; 31(3):178-188

141. Mancia G, Parati G, Bilo G, Gao P, Fagard R, Redon J et al. Ambulatory blood pressure values in the ongoing telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET). Hypertension. 2012; 60(6):1400-6

142. Marques da Silva P, Haag U, Guest JF, Brazier JE, Soro M. Health-related quality of life impact of a triple combination of olmesartan medoxomil, amlodipine besylate and hydrochlorotiazide in subjects with hypertension. Health & Quality of Life Outcomes. 2015; 13(24):1-13

143. Masao I, Kaoru Y, Toshikazu Y, Tomohiro K, Yoshihiro K, Michitoshi I. Clinical study on long-term drug treatment of mild essential hypertension. Multicenter double-blind trial by group comparison of carteorol and hydrochlorothiazide. Rinsho hyoka. 1994; 22(1):61-104

144. Matsuzaki M, Ogihara T, Umemoto S, Rakugi H, Matsuoka H, Shimada K et al. Prevention of cardiovascular events with calcium channel blocker-based combination

therapies in patients with hypertension: A randomized controlled trial. Journal of Hypertension. 2011; 29(8):1649-59

145. Mayaudon H, Chanudet X, Janin G, Madonna O. Comparison of the efficacy of enalapril + hydrochlorothiazide and captopril + hydrochlorothiazide combinations on mild-to-moderate hypertension by ambulant blood pressure monitoring. Annales de Cardiologie et d'Angeiologie. 1995; 44(5):235-241

146. Mazza A, Sacco AP, Townsend DM, Bregola G, Contatto E, Cappello I et al. Cost-benefit effectiveness of angiotensin-II receptor blockers in patients with uncomplicated hypertension: A comparative analysis. Biomedicine and Pharmacotherapy. 2017; 90:665-669

147. Miyoshi T, Murakami T, Sakuragi S, Doi M, Nanba S, Mima A et al. Comparable effect of aliskiren or a diuretic added on an angiotensin II receptor blocker on augmentation index in hypertension: A multicentre, prospective, randomised study. Open Heart. 2017; 4(1):e000591

148. Mogensen CE, Viberti G, Halimi S, Ritz E, Ruilope L, Jermendy G et al. Effect of low-dose perindopril/indapamide on albuminuria in diabetes - Preterax in albuminuria regression: Premier. Hypertension. 2003; 41(5):1063-1071

149. Morgan T, Anderson A. A comparison of candesartan, felodipine, and their combination in the treatment of elderly patients with systolic hypertension. American Journal of Hypertension. 2002; 15(6):544-9

150. Morgan T, Anderson A, Bertram D, MacInnis RJ. Effect of candesartan and lisinopril alone and in combination on blood pressure and microalbuminuria. Journal of the Renin-Angiotensin-Aldosterone System. 2004; 5(2):64-71

151. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: Principal results. MRC Working Party. BMJ. 1992; 304(6824):405-12

152. Nakao N, Seno H, Kasuga H, Toriyama T, Kawahara H, Fukagawa M. Effects of combination treatment with losartan and trandolapril on office and ambulatory blood pressures in non-diabetic renal disease: A COOPERATE-ABP substudy. American Journal of Nephrology. 2004; 24(5):543-548

153. Nalbantgil S, Zoghi M, Ozerkan F, Boydak B, Nalbantgil I, Onder R et al. Comparison of candesartan and felodipine alone and combined in the treatment of hypertension: A single-center, double-blind, randomized, crossover trial. Current Therapeutic Research, Clinical and Experimental. 2003; 64(7):380-8

154. National Clinical Guideline Centre. Hypertension: the clinical managment of primary hypertension in adults: update of clinical guidelines 18 and 34. NICE clinical guideline 127. London. National Clinical Guideline Centre, 2011. Available from: http://guidance.nice.org.uk/CG127

155. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

156. Nedogoda SV, Marchenko IV, Chaliabi TA, Tsoma VV, Brel UA, Prokhorova EA. Comparative efficacy of fixed dose combinations of perindopril with indapamide and captopril with hydrochlorothiazide in patients with high risk hypertension. Kardiologiia. 2005; 45(11):24-26

157. Neldam S, Edwards C, Lang M, Jones R, Teamsta Investigators. Long-term tolerability and efficacy of single-pill combinations of telmisartan 40-80 mg Plus

amlodipine 5 or 10 mg in patients whose blood pressure was not initially controlled by amlodipine 5-10 mg: Open-label, long-term follow-ups of the TEAMSTA-5 and TEAMSTA-10 studies. Current Therapeutic Research, Clinical and Experimental. 2012; 73(1-2):65-84

158. Neldam S, Schumacher H, Guthrie R. Telmisartan 80 mg/hydrochlorothiazide 25 mg provides clinically relevant blood pressure reductions across baseline blood pressures. Advances in Therapy. 2012; 29(4):327-38

159. Nelson GI, Donnelly GL, Hunyor SN. Haemodynamic effects of sustained treatment with prazosin and metoprolol, alone and in combination, in borderline hypertensive heart failure. Journal of Cardiovascular Pharmacology. 1982; 4(2):240-245

160. Neutel JM, Giles TD, Punzi H, Weiss RJ, Li H, Finck A. Long-term safety of nebivolol and valsartan combination therapy in patients with hypertension: An open-label, single-arm, multicenter study. Journal of the American Society of Hypertension. 2014; 8(12):915-20

161. Neutel JM, Smith DH, Weber MA. Low dose combination therapy vs. high dose monotherapy in the management of hypertension. Journal of Clinical Hypertension. 1999; 1(3):79-86

162. Neutel JM, Weir MR, Moser M, Harris S, Edwards D, Michelson EL et al. The effects of candesartan cilexetil in isolated systolic hypertension: A clinical experience trial. Journal of Clinical Hypertension. 2000; 2(3):181-186

163. Obel AO. Efficacy and tolerability of long term oxprenolol and chlortalidone singly and in combination in hypertensive blacks. Japanese Heart Journal. 1990; 31(2):183-92

164. Oliván Martínez J, Hoyos Jiménez M, Miranda García MJ, Justo Alpañés E, Pérez Cano R. Double blind comparative randomized study of the efficacy of celiprolol versus amiloride-hydrochlorothiazide in mild to moderate AHT. Anales de Medicina Interna. 1993; 10(5):221-227

165. Packer M, Carson P, Elkayam U, Konstam MA, Moe G, O'Connor C et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: Results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). JACC Heart failure. 2013; 1(4):308-314

166. Pannier B, Guerin A, London G, Asmar R, Safar M. Combination of low dose perindopril/indapamide versus atenolol in the hypertensive patient: Effects on systolic blood pressure and arterial haemodynamics. Archives des Maladies du Coeur et des Vaisseaux. 2002; 95(Special 6):11-16

167. Papademetriou V. Comparison of Nebivolol monotherapy versus Nebivolol in combination with other antihypertensive therapies for the treatment of hypertension. American Journal of Cardiology. 2009; 103(2):273-8

168. Papademetriou V, Prisant LM, Neutel JM, Weir MR. Efficacy of low-dose combination of bisoprolol/hydrochlorothiazide compared with amlodipine and enalapril in men and women with essential hypertension. American Journal of Cardiology. 1998; 81(11):1363-5

169. Park CG, Ahn TH, Cho EJ, Kim W, Kim HS, Yang JY et al. Comparison of the efficacy and safety of fixed-dose s-amlodipine/telmisartan and telmisartan in hypertensive patients inadequately controlled with telmisartan: A randomized, double-blind, multicenter study. Clinical Therapeutics. 2016; 38(10):2185-2194

170. Park JB, Shin JH, Kim DS, Youn HJ, Park SW, Shim WJ et al. Safety of the up-titration of nifedipine GITS and valsartan or low-dose combination in uncontrolled hypertension: The FOCUS Study. Clinical Therapeutics. 2016; 38(4):832-42

171. Park JS, Shin JH, Hong TJ, Seo HS, Shim WJ, Baek SH et al. Efficacy and safety of fixed-dose combination therapy with olmesartan medoxomil and rosuvastatin in Korean patients with mild to moderate hypertension and dyslipidemia: An 8-week, multicenter, randomized, double-blind, factorial-design study (OLSTA-D RCT: OLmesartan rosuvaSTAtin from Daewoong). Drug Design, Development and Therapy. 2016; 10:2599-609

172. Patel A, Advance Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. The Lancet. 2007; 370(9590):829-40

173. Paz MA, de-La-Sierra A, Saez M, Barcelo MA, Rodriguez JJ, Castro S et al. Treatment efficacy of anti-hypertensive drugs in monotherapy or combination: ATOM systematic review and meta-analysis of randomized clinical trials according to PRISMA statement. Medicine. 2016; 95(30):e4071

174. Perez-Maraver M, Carrera MJ, Micalo T, Sahun M, Vinzia C, Soler J et al. Renoprotective effect of diltiazem in hypertensive type 2 diabetic patients with persistent microalbuminuria despite ACE inhibitor treatment. Diabetes Research and Clinical Practice. 2005; 70(1):13-9

175. Persson I. Combination therapy of essential hypertension with pindolol (Visken) and hydralazine. Advances in Clinical Pharmacology. 1976; 11:1114-8

176. Pessina AC, Ciccariello L, Perrone F, Stoico V, Gussoni G, Scotti A et al. Clinical efficacy and tolerability of alpha-blocker doxazosin as add-on therapy in patients with hypertension and impaired glucose metabolism. Nutrition, Metabolism, and Cardiovascular Diseases. 2006; 16(2):137-47

177. Petelina TI, Gapon LI, Bakhmatova Iu A, Zhevagina IA. Clinical efficacy of combined therapy with enalapril + trimetazidine in patients with hypertension comorbid with ischemic heart disease and metabolic disturbances. Terapevticheskii Arkhiv. 2005; 77(8):19-23

178. Petersen LJ, Petersen JR, Talleruphuus U, Moller ML, Ladefoged SD, Mehlsen J et al. A randomized and double-blind comparison of isradipine and spirapril as monotherapy and in combination on the decline in renal function in patients with chronic renal failure and hypertension. Clinical Nephrology. 2001; 55(5):375-83

179. Petrie JC, Galloway DB, Webster J, Simpson WT, Lewis JA. Atenolol and bendrofluazide in hypertension. British Medical Journal. 1975; 4(5989):133-5

180. Pool JL, Glazer R, Crikelair N, Levy D. The role of baseline blood pressure in guiding treatment choice: A secondary analysis of the use of valsartan/hydrochlorothiazide as initial therapy in hypertensive adults in a randomized, double-blind, placebo-controlled trial. Clinical Drug Investigation. 2009; 29(12):791-802

181. Prisant LM, Neutel JM, Papademetriou V, DeQuattro V, Hall WD, Weir MR. Low-dose combination treatment for hypertension versus single-drug treatment-bisoprolol/hydrochlorothiazide versus amlodipine, enalapril, and placebo: Combined analysis of comparative studies. American Journal of Therapeutics. 1998; 5(5):313-21

182. Radevski IV, Valtchanova SP, Candy GP, Tshele EF, Sareli P. Comparison of acebutolol with and without hydrochlorothiazide versus carvedilol with and without hydrochlorothiazide in black patients with mild to moderate systemic hypertension. American Journal of Cardiology. 1999; 84(1):70-5

183. Radevski IV, Valtchanova ZP, Candy GP, Hlatswayo MN, Sareli P. Antihypertensive effect of low-dose hydrochlorothiazide alone or in combination with quinapril in black patients with mild to moderate hypertension. Journal of Clinical Pharmacology. 2000; 40(7):713-21

184. Rakesh O, Pranesh K, Bhavin V. A randomized active controlled clinical study to evaluate efficacy and safety of resveratrol as an adjuvant therapy in patients with hypertension. Asian Journal of Pharmaceutical and Clinical Research. 2017; 10(1):376-379

185. Ratnasabapathy Y, Lawes CM, Anderson CS. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS): Clinical implications for older patients with cerebrovascular disease. Drugs and Aging. 2003; 20(4):241-51

186. Redon J, Mancia G, Sleight P, Schumacher H, Gao P, Pogue J et al. Safety and efficacy of low blood pressures among patients with diabetes: Subgroup analyses from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). Journal of the American College of Cardiology. 2012; 59(1):74-83

187. Roca-Cusachs A, Torres F, Horas M, Rios J, Calvo G, Delgadillo J et al. Nitrendipine and enalapril combination therapy in mild to moderate hypertension: Assessment of dose-response relationship by a clinical trial of factorial design. Journal of Cardiovascular Pharmacology. 2001; 38(6):840-9

188. Rosenfeld JB, Zabludowski J. The efficacy and tolerability of nifedipine (NIF) and nisoldipine (NIS) both alone and combined with a beta-blocker in patients with essential hypertension: A multicenter, parallel-group study. Journal of Clinical Pharmacology. 1989; 29(11):1013-6

189. Ruggenenti P, Fassi A, Ilieva A, Iliev IP, Chiurchiu C, Rubis N et al. Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: The BENEDICT-B randomized trial. Journal of Hypertension. 2011; 29(2):207-216

190. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V et al. Preventing microalbuminuria in type 2 diabetes. New England Journal of Medicine. 2004; 351(19):1941-51

191. Ruggenenti P, Lauria G, Iliev IP, Fassi A, Ilieva AP, Rota S et al. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: The delapril and manidipine for nephroprotection in diabetes (DEMAND) randomized clinical trial. Hypertension. 2011; 58(5):776-83

192. Saito I, Kobayashi M, Matsushita Y, Mori A, Kawasugi K, Saruta T. Cost-utility analysis of antihypertensive combination therapy in Japan by a Monte Carlo simulation model. Hypertension Research. 2008; 31(7):1373-1383

193. Saruta T, Ogihara T, Saito I, Rakugi H, Shimamoto K, Matsuoka H et al. Comparison of olmesartan combined with a calcium channel blocker or a diuretic in elderly hypertensive patients (COLM Study): Safety and tolerability. Hypertension Research. 2015; 38(2):132-6

194. Sassano P, Chatellier G, Billaud E, Corvol P, Menard J. Comparison of increase in the enalapril dose and addition of hydrochlorothiazide as second-step treatment of hypertensive patients not controlled by enalapril alone. Journal of Cardiovascular Pharmacology. 1989; 13(2):314-9

195. Seedat YK. Guanfacine alone and in combination therapy in the treatment of moderate and severe hypertension. Chest. 1983; 83(Suppl 2):403-4

196. Seedat YK, Rawat R. An evaluation of the antihypertensive effect of enalapril with hydrochlorothiazide and methyldopa compared to propranolol with hydrochlorothiazide and hydralazine in patients with moderate to severe hypertension. Current Therapeutic Research, Clinical and Experimental. 1984; 35(5):851-859

197. Shaifali I, Kapoor AK, Singh HK, Patial RK. A comparative evaluation of Losartan/Hydrochlorothiazide (fixed combination) versus Amlodipine monotherapy in patients with hypertension in Rohilkhand region. Internet Journal of Medical Update. 2014; 9(2):9-16

198. Shi R, Liu K, Shi D, Liu Q, Chen X. Effects of amlodipine and valsartan on blood pressure variability and pulse wave velocity in hypertensive patients. American Journal of the Medical Sciences. 2017; 353(1):6-11

199. Shimamoto K, Kimoto M, Matsuda Y, Asano K, Kajikawa M. Long-term safety and efficacy of high-dose controlled-release nifedipine (80 mg per day) in Japanese patients with essential hypertension. Hypertension Research. 2015; 38(10):695-700

200. Smith TR, Philipp T, Vaisse B, Bakris GL, Wernsing M, Yen J et al. Amlodipine and valsartan combined and as monotherapy in stage 2, elderly, and black hypertensive patients: Subgroup analyses of 2 randomized, placebo-controlled studies. Journal of Clinical Hypertension. 2007; 9(5):355-64

201. Sohn IS, Kim CJ, Ahn T, Youn HJ, Jeon HK, Ihm SH et al. Efficacy and tolerability of combination therapy versus monotherapy with candesartan and/or amlodipine for dose finding in essential hypertension: A phase II multicenter, randomized, double-blind clinical trial. Clinical Therapeutics. 2017; 39(8):1628-1638

202. Soucek M, Plachý M. The FEVER (Felodipine EVEnt Reduction) trial; a randomised, double-blind, placebo-controlled trial in Chinese hypertensive patients. Vnitrni Lekarstvi. 2007; 53(1):63-70

203. Sung J, Jeong JO, Kwon SU, Won KH, Kim BJ, Cho BR et al. Valsartan 160 mg/Amlodipine 5 mg combination therapy versus Amlodipine 10 mg in hypertensive patients with inadequate response to Amlodipine 5 mg monotherapy. Korean Circulation Journal. 2016; 46(2):222-8

204. Szucs TD, Waeber B, Tomonaga Y. Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: an analysis of the HYVET study from a Swiss perspective. Journal of Human Hypertension. 2010; 24(2):117-123

205. Thijs L, Richart T, De Leeuw PW, Kuznetsova T, Grodzicki T, Kawecka-Jaszcz K et al. Morbidity and mortality on combination versus monotherapy: A posthoc analysis of the Systolic Hypertension in Europe trial. Journal of Hypertension. 2010; 28(4):865-874

206. Timofeeva LA, Alekhin MN, Ugriumov MO, Chumakova OS, Larina VN, Sidorenko BA. Effect of twelve-month combined therapy with perindopril and indapamide on the level of blood pressure and left ventricular hypertrophy in patients with hypertensive disease. Kardiologiia. 2006; 46(3):30-34

207. Umemoto S, Ogihara T, Matsuzaki M, Rakugi H, Ohashi Y, Saruta T et al. Effects of calcium channel blocker-based combinations on intra-individual blood pressure variability: Post hoc analysis of the COPE trial. Hypertension Research. 2016; 39(1):46-53

208. Umemoto S, Ogihara T, Matsuzaki M, Rakugi H, Shimada K, Kawana M et al. Effects of calcium-channel blocker benidipine-based combination therapy on cardiac events-subanalysis of the COPE trial. Circulation Journal. 2017; 82(2):457-463

209. Uzui H, Morishita T, Nakano A, Amaya N, Fukuoka Y, Ishida K et al. Effects of combination therapy with olmesartan and azelnidipine on serum osteoprotegerin in patients with hypertension. Journal of Cardiovascular Pharmacology and Therapeutics. 2014; 19(3):304-9

210. Wang JG, Yukisada K, Sibulo A, Jr., Hafeez K, Jia Y, Zhang J. Efficacy and safety of sacubitril/valsartan (LCZ696) add-on to amlodipine in Asian patients with systolic hypertension uncontrolled with amlodipine monotherapy. Journal of Hypertension. 2017; 35(4):877-885

211. Weinberger MH. Comparison of captopril and hydrochlorothiazide alone and in combination in mild to moderate essential hypertension. British Journal of Clinical Pharmacology. 1982; 14(Suppl 2):127S-131S

212. Weir MR, Wang RY. Use of angiotensin II receptor blockers alone and in combination with other drugs: A large clinical experience trial. Journal of the Renin-Angiotensin-Aldosterone System. 2001; 2(Suppl 1):S217-S222

213. White WB, Stimpel M. Long-term safety and efficacy of moexipril alone and in combination with hydrochlorothiazide in elderly patients with hypertension. Journal of Human Hypertension. 1995; 9(11):879-84

214. Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J et al. Beta-blockers versus diuretics in hypertensive men: Main results from the HAPPHY trial. Journal of Hypertension. 1987; 5(5):561-72

215. Wisloff T, Selmer RM, Halvorsen S, Fretheim A, Norheim OF, Kristiansen IS. Choice of generic antihypertensive drugs for the primary prevention of cardiovascular disease: a cost-effectiveness analysis. BMC Cardiovascular Disorders. 2012; 12:26

216. Yip GW, Wang M, Wang T, Chan S, Fung JW, Yeung L et al. The Hong Kong diastolic heart failure study: A randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. Heart. 2008; 94(5):573-80

217. Yu LT, Zhu J, Tan HQ, Wang GG, Teo KK, Liu LS. Telmisartan, ramipril, or both in high-risk Chinese patients: Analysis of ONTARGET China data. Chinese Medical Journal. 2011; 124(12):1763-8

218. Yusuf S, Lonn E, Pais P, Bosch J, Lopez-Jaramillo P, Zhu J et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. New England Journal of Medicine. 2016; 374(21):2032-43

219. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. New England Journal of Medicine. 2008; 358(15):1547-1559

220. Zanchetti A, Parati G, Malacco E. Zofenopril plus hydrochlorothiazide: Combination therapy for the treatment of mild to moderate hypertension. Drugs. 2006; 66(8):1107-15

221. Zhang JL, Qin YW, Zheng X, Qiu JL, Zhao XX, Zou DJ. Combination therapy with angiotensin-converting enzyme inhibitors and indapamide impairs glucose tolerance in Chinese hypertensive patients. Blood Pressure. 2010; 19(2):110-8

222. Zhu D, Bays H, Gao P, Mattheus M, Voelker B, Ruilope LM. Efficacy and tolerability of a single-pill combination of telmisartan 80 mg and hydrochlorothiazide 25 mg according to age, gender, race, hypertension severity, and previous antihypertensive use: planned analyses of a randomized trial. Integrated Blood Pressure Control. 2013; 6:1-14

Appendices

Appendix A: Review protocols

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: • 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 chlortalidone; 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: • ACE inhibitor • Low-cost ARB • Thiazide-like diuretic (such as chlortalidone 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. • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • MI

	Important • 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	Minimum follow up time: 1 year Exclusions: • 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	Subgroups for analysis of heterogeneity: • 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]) *To note that we will also extract evidence in those aged over 80 if this evidence is reported separately.
Selection process – duplicate screening / selection / analysis	A senior research fellow will undertake quality assurance prior to completion.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome. Endnote will be used for bibliography, citations, sifting and reference management.
Information sources – databases and dates	Medline, Embase, the Cochrane Library Language: Restrict to English only Key papers: Cochrane review (2017): http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010316.pub2/full
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

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	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis,

	comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. No date cut-off from the previous guideline was used.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the US will also be excluded. Studies published after 2002 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[155] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude selectively the remaining studies. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:*

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

Appendix B: Literature search strategies

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

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 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

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 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 Cyclopenthiazide 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.	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)

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 Cyclopenthiazide 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)

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 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
#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 Cyclopenthiazide 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 adrenoreceptor 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 Health Economics literature search strategy

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

Table 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

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

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/

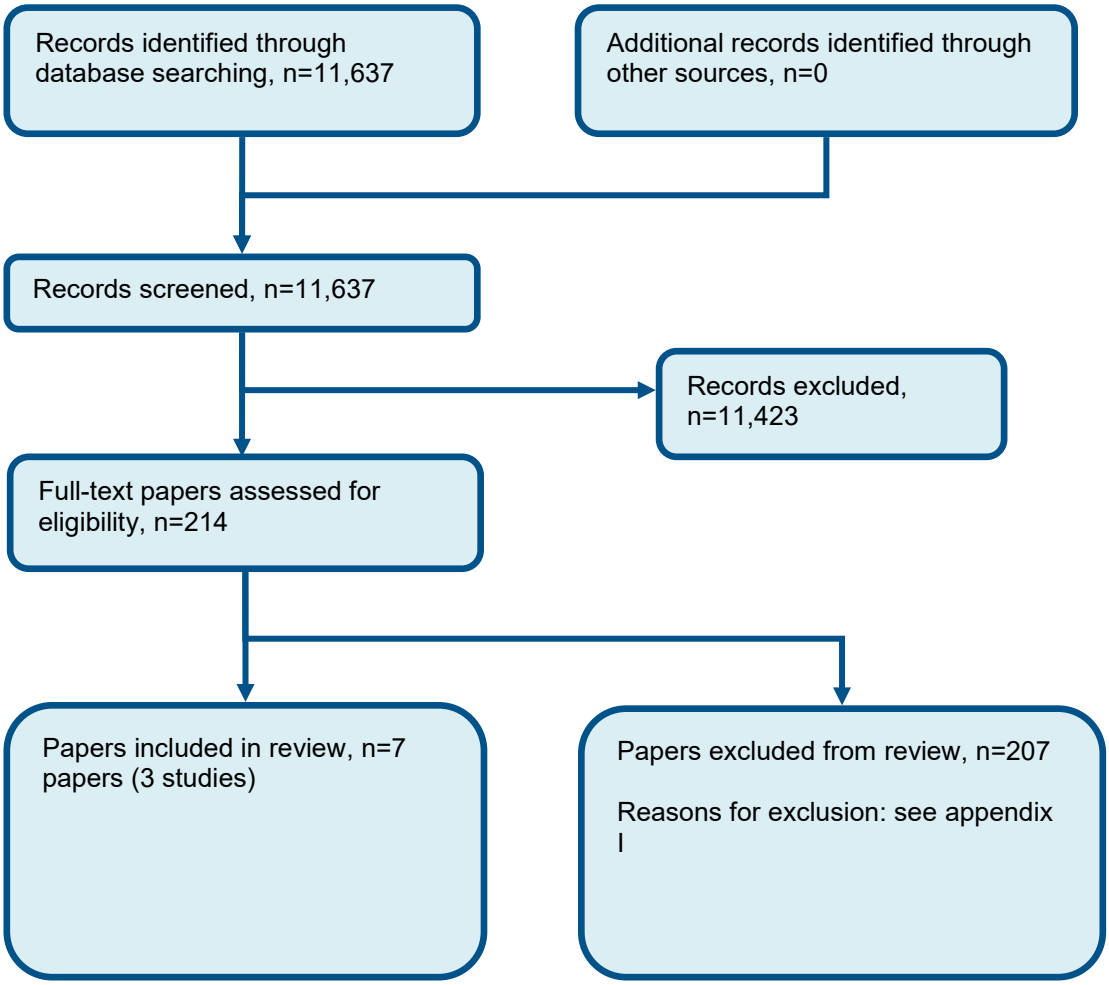
20.	animal model/
21.	exp Rodent/
22.	(rat or rats or mouse or mice).ti.
23.	or/15-22
24.	7 not 23
25.	limit 24 to English language
26.	health economics/
27.	exp economic evaluation/
28.	exp health care cost/
29.	exp fee/
30.	budget/
31.	funding/
32.	budget*.ti,ab.
33.	cost*.ti.
34.	(economic* or pharmaco?economic*).ti.
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

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

Appendix C: Clinical evidence selection

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



Appendix D: Clinical evidence tables

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 2001[14] (Asmar 2001[13], de Luca 2004[52])
	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 Cardiovsculaire, Laboratoires Servier.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PERINDOPRIL AND INDAPAMIDE COMBINATION versus ATENOLOL 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 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	
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: hypotension (dizziness) at ≥12 months; Stroke (ischaemic or haemorrhagic) at ≥12 months

Study	Dahlof 2005[47]
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 2005[47]
	hypotension (dizziness) at ≥12 months; Side effect 2: Acute kidney injury at ≥12 months; Stroke (ischaemic or haemorrhagic) at ≥12 months

Study	Mogensen 2003[148]
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
Funding	Academic or government funding (Institut de Recherches Internationales

Study	Mogensen 2003[148]
	SERVIER.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENALAPRIL versus PERINDOPRIL AND INDAPAMIDE 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 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 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 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	
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

Appendix E: Forest plots

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

Figure 2: Serious cardiovascular events at 12 months

Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mogensen 2003	6	244	15	237	100.0%	0.39 [0.15, 0.98]
Total (95% CI)		**244**		**237**	**100.0%**	**0.39 [0.15, 0.98]**
Total events	6		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)

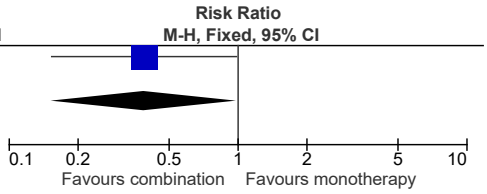


Figure 3: Change in creatinine at 12 months

Study or Subgroup	Combination Mean	Combination SD	Combination Total	Monotherapy Mean	Monotherapy SD	Monotherapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Mogensen 2003	-4.1	11.4	237	-4.8	9.7	244	100.0%	0.70 [-1.19, 2.59]
Total (95% CI)			**237**			**244**	**100.0%**	**0.70 [-1.19, 2.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)

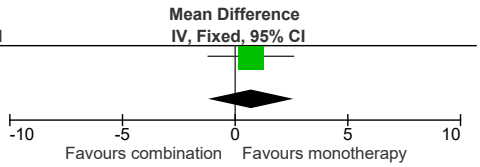


Figure 4: Discontinuation due to adverse events at 12 months

Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mogensen 2003	19	244	21	237	100.0%	0.88 [0.49, 1.59]
Total (95% CI)		**244**		**237**	**100.0%**	**0.88 [0.49, 1.59]**
Total events	19		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)

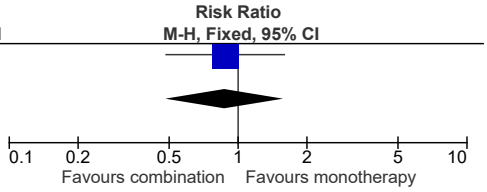


Figure 5: Discontinuation due to adverse events at 12 months (including type 2 diabetes)

Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahlof 2005	7	264	6	274	100.0%	1.21 [0.41, 3.56]
Total (95% CI)		**264**		**274**	**100.0%**	**1.21 [0.41, 3.56]**
Total events	7		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)

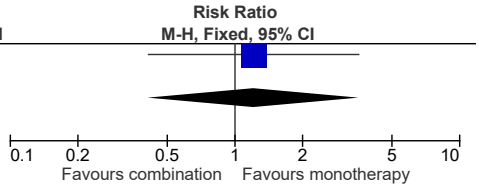
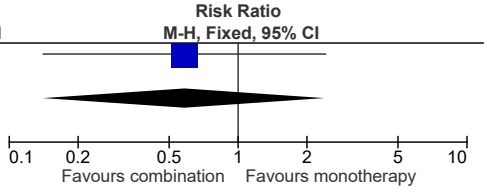


Figure 6: Hypotension (dizziness) at 12 months

Study or Subgroup	Combination Events	Combination Total	Monotherapy Events	Monotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Mogensen 2003	3	244	5	237	100.0%	0.58 [0.14, 2.41]
Total (95% CI)		**244**		**237**	**100.0%**	**0.58 [0.14, 2.41]**
Total events	3		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.46)



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

Figure 7: Change in creatinine (µmol/L) at 12 months

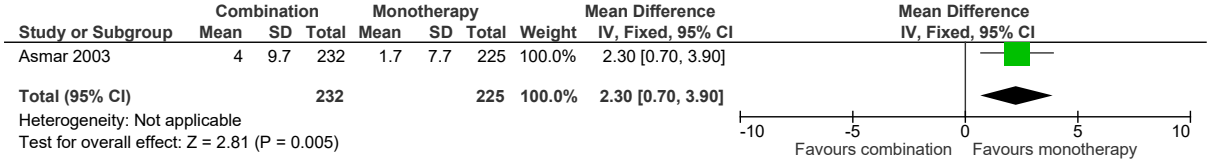
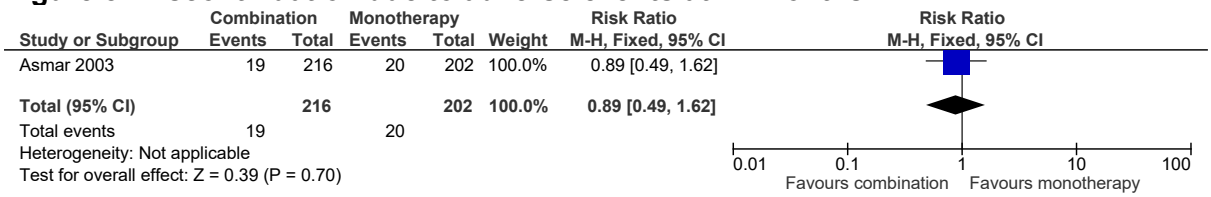


Figure 8: Discontinuation due to adverse events at 12 months



Appendix F: GRADE tables

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)	⊕OOO 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)	⊕⊕OO 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)	⊕OOO 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)	⊕OOO 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)	⊕OOO VERY LOW	IMPORTANT

[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

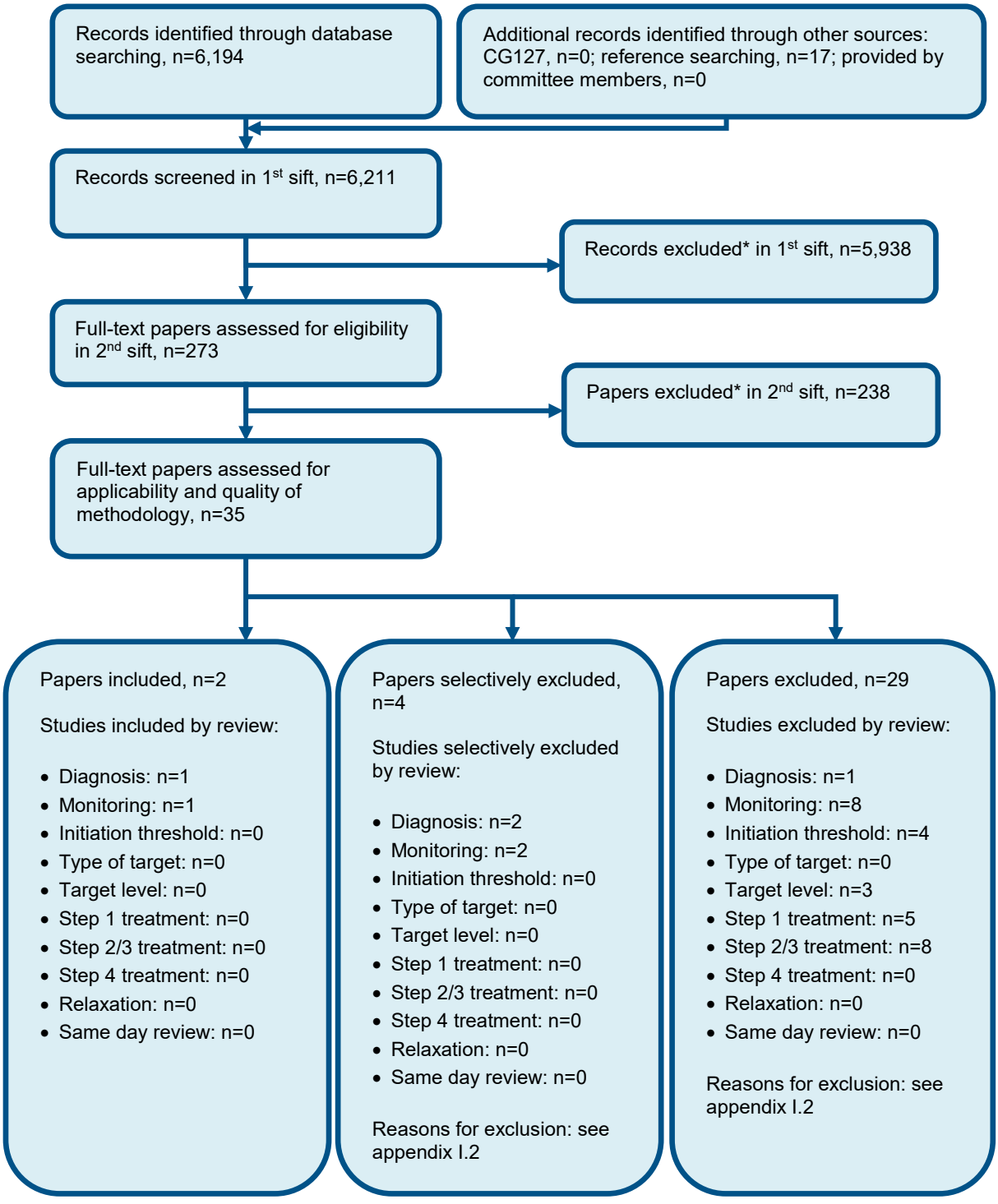
Table 19: Clinical evidence profile: combination versus monotherapy in adults with primary hypertension and without type 2 diabetes

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		
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)	⊕OOO VERY LOW	IMPORTANT

[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.

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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

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

I.2 Excluded health economic studies

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.

Appendix J: Research recommendations

J.1 Dual therapy

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

Why this is important:

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

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

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.