National Institute for Health and Care Excellence

Draft for Consultation

Hypertension in adults: diagnosis and management

G. Evidence review for step 4 treatment

NICE guideline

Intervention evidence review

March 2019

Draft for Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

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

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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

1.2 Introduction

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

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

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	Adults (aged 18 years and older) with primary hypertension are taking the maximally tolerated doses of at least 3 drugs (including a diuretic) and their blood pressure is still not controlled.
Intervention	Step 4 antihypertensive pharmacological treatment received for a minimum of 1 year. Examples include: • Alpha-blockers • Beta-blockers • Other or further diuretics such as amiloride and spironolactone • Aliskiren (direct renin inhibitors) • Clonidine, minoxidil, methyldopa, moxonidine (centrally acting antihypertensive)
Comparison	Compared against each other (class comparisons) Compared to placebo (class compared to placebo)
Outcomes	All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted. **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • Myocardial infarction (MI) **Important**

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

1.4 Clinical evidence

1.4.1 Included studies

No relevant clinical studies comparing step 4 antihypertensive pharmacological treatment received for a minimum of 1 year were identified.

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

1.4.2 Excluded studies

One Cochrane review relevant to this review question was identified.[44] This was excluded because it included crossover studies without the minimum washout period of 4 weeks. The references were checked for any relevant studies.

See the excluded studies list in appendix I.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

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

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

1.5.3 Resource costs

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

Table 2: UK costs of step 4 drugs

Drug	Detail	Daily dose	Cost/ month (£)	Cost/ year (£)
Alpha blockers				
Doxazosin	4 mg tablets, 28 pack = £0.86	4 mg per day	£0.93	£11.21
Beta blockers				
Bisoprolol fumarate	5 mg tablets, 28 pack = £0.57	5 mg per day	£0.62	£7.43
Further diuretics				
Amiloride	5 mg tablets, 28 pack = £4.60	5 mg per day	£5.00	£59.96
Spironolactone	25 mg tablets, 28 pack = £1.09	25 mg per day	£1.18	£14.21
Direct renin inhibitors				
Aliskiren	150 mg tablets, 28 pack = £28.51	150 mg per day	£30.97	£371.65
Centrally acting anti-hypertensives				
Moxonidine	0.2 mg tablets, 28 pack = £1.15	0.4 mg per day	£2.50	£29.98

(a) Costs are from the BNF drug tariff price. Accessed on 8 November 2018. [49]

1.6 Evidence statements

1.6.1 Clinical evidence statements

No relevant published evidence was identified.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 Recommendations

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

G1. If hypertension is not controlled in adults taking the optimal tolerated doses of an ACE inhibitor or an ARB plus a CCB and a thiazide-like diuretic, regard them as having resistant hypertension. **[2019]**

G2. Before considering further treatment for a person with resistant hypertension:

- Confirm elevated clinic blood pressure measurements using ambulatory or home blood pressure recordings.
- Assess for postural hypotension.
- Discuss adherence (see recommendation 1.4.28). **[2019]**

G3. For people with confirmed resistant hypertension, consider adding a fourth antihypertensive drug as step 4 treatment (see recommendations 1.4.46 to 1.4.48) or seeking expert advice.[a] **[2019]**

G4. Consider further diuretic therapy with low-dose spironolactone[b] for adults with resistant hypertension starting step 4 treatment who have a blood potassium level of 4.5 mmol/l or less. Use particular caution in people with a reduced estimated glomerular filtration rate because they have an increased risk of hyperkalaemia. **[2019]**

G5. When using further diuretic therapy for step 4 treatment of resistant hypertension, monitor blood sodium and potassium and renal function within 1 month of starting treatment and repeat as needed thereafter. **[2019]**

G6. Consider an alpha-blocker or beta-blocker for adults with resistant hypertension starting step 4 treatment who have a blood potassium level of more than 4.5 mmol/l. **[2019]**

G7. If blood pressure remains uncontrolled in people with resistant hypertension taking the optimal tolerated doses of 4 drugs, seek expert advice. **[2019]**

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 to be critical outcomes for decision-making. Heart failure, vascular procedures, angina and discontinuation or dose reduction due to side effects were also considered important for decision-making.

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

1.8.1.2 The quality of the evidence

No clinical studies relevant to the review question were identified.

1.8.1.3 Benefits and harms

No clinical studies relevant to this review protocol were identified.

The committee discussed the use of different step 4 antihypertensive treatments. It agreed that there was very little evidence within this area, so the committee formed consensus recommendations based on their clinical experience. The committee discussed the findings of the PATHWAY-2 trial. It agreed that this study did not meet the inclusion criteria for this review due to having a short follow-up and no outcomes relevant to the agreed protocol. Nevertheless, it suggested that adding spironolactone could be effective at reducing blood pressure as a step 4 treatment. It was noted that higher doses of spironolactone were used (25 mg–50 mg), and the 50 mg dose was noted to lower blood pressure more. However, it

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

[b] At the time of consultation (March 2019), spironolactone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

was unclear what proportion of people were receiving the 50 mg dose. The study also suggested that amiloride could be as effective as spironolactone in lowering blood pressure. However, the committee noted that amiloride is more expensive, and it is taken twice a day, whereas spironolactone is taken only once daily making it a more convenient option for people who are already taking multiple medications. The committee agreed that changes in blood pressure alone, without information on cardiovascular events was not very informative to patient important outcomes, however it agreed that there was no evidence to suggest a better treatment option was available than spironolactone, which was now part of common clinical practice, and so it should still be recommended as step 4 treatment for those who had an inadequate response to 3 previous treatments. The need for further research to inform choice of step 4 treatment was discussed; however, the committee considered this would be unlikely to be funded, as the PATHWAY-2 trial had addressed this question previously, despite not including the hard cardiovascular outcomes this committee considered necessary to make a strong recommendation on the topic.

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

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

The committee discussed the long-term implications of spironolactone treatment. Although there was no evidence identified for this within the review, including a lack of information on adverse events, the committee agreed that the multiple known harms of consistently high blood pressure outweighed this uncertainty. It did agree, however, that further evidence was required in order for healthcare professionals and people with hypertension to understand the choice of drugs available and the benefit and harms associated with each of these.

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

1.8.2 Cost effectiveness and resource use

No economic evidence was identified for this question.

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

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

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

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

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

References

1. Abarquez RF, Jr., Sy RG, Castillo RR. Efficacy of slow-release oral isradipine in moderate-to-severe hypertension with add-on spirapril. American Journal of Hypertension. 1993; 6(3 Pt 2):77S-79S

2. Abascal VM, Larson MG, Evans JC, Blohm AT, Poli K, Levy D. Calcium antagonists and mortality risk in men and women with hypertension in the Framingham Heart Study. Archives of Internal Medicine. 1998; 158(17):1882-6

3. Abe H, Minatoguchi S, Ohashi H, Murata I, Minagawa T, Okuma T et al. Renoprotective effect of the addition of losartan to ongoing treatment with an angiotensin converting enzyme inhibitor in type-2 diabetic patients with nephropathy. Hypertension Research. 2007; 30(10):929-35

4. Abe M, Okada K, Matsumoto K. Clinical experience in treating hypertension with fixed-dose combination therapy: Angiotensin II receptor blocker losartan plus hydrochlorothiazide. Expert Opinion on Drug Metabolism & Toxicology. 2009; 5(10):1285-303

5. Abetel G, Mérier G, Karly M, Genoud A, Bousquet JC. Value of a blood pressure profile in evaluating 2 antihypertensive agents. Schweizerische Medizinische Wochenschrift. 1984; 114(48):1746-9

6. Adir J, Janda SM, Curry CL, Taylor RE, Poku CD, Rotenberg KS. Comparative efficacy and safety of immediate-release and controlled-release hydralazine in black hypertensive patients. Clinical Therapeutics. 1987; 9(6):640-50

7. Adolphe AB, Vlachakis ND, Rofman BA, Brescia D, Zellner SR. Long-term open evaluation of amlodipine vs hydrochlorothiazide in patients with essential hypertension. International Journal of Clinical Pharmacology Research. 1993; 13(4):203-10

8. Agabiti-Rosei E, Ambrosioni E, Finardi G, Folino P, Gambassi G, Malini P et al. Perindopril versus captopril: Efficacy and acceptability in an Italian multicenter trial. American Journal of Medicine. 1992; 92(4B):79S-83S

9. Agabiti-Rosei E, Trimarco B, Muiesan ML, Reid J, Salvetti A, Tang R et al. Cardiac structural and functional changes during long-term antihypertensive treatment with lacidipine and atenolol in the European Lacidipine Study on Atherosclerosis (ELSA). Journal of Hypertension. 2005; 23(5):1091-8

10. Agarwal R, Weir MR. Blood pressure response with fixed-dose combination therapy: Comparing hydrochlorothiazide with amlodipine through individual-level meta-analysis. Journal of Hypertension. 2013; 31(8):1692-701

11. Ahola TL, Kantola IM, Maki J, Reunanen A, Jula AM. Adding a low-dose antihypertensive regimen would substantially improve the control of hypertension and reduce cardiovascular morbidity among uncomplicated hypertensive patients. European Journal of Preventive Cardiology. 2012; 19(4):712-22

12. Ahrens K, Bramlage P. Importance of a fixed combination of telmisartan and amlodipine for the treatment of hypertension. Drugs of Today. 2010; 46(5):339-50

13. Akanabe H, Ishiguro M, Yagi Y, Ohshima S, Ohmae M, Mori H et al. Effect of diltiazem hydrochloride in essential hypertension. International Journal of Clinical Pharmacology, Therapy, and Toxicology. 1985; 23(2):63-9

14. Akioyamen L, Levine M, Sherifali D, O'Reilly D, Frankfurter C, Pullenayegum E et al. Cardiovascular and cerebrovascular outcomes of long-term angiotensin receptor blockade: Meta-analyses of trials in essential hypertension. Journal of the American Society of Hypertension. 2016; 10(1):55-69

15. Akram J, Sheikh UE, Mahmood M, Donnelly R. Antihypertensive efficacy of indapamide SR in hypertensive patients uncontrolled with a background therapy: The NATIVE study. Current Medical Research and Opinion. 2007; 23(12):2929-36

16. Alderman MH. Evaluation of the efficacy of prazosin versus propranolol as initial antihypertensive therapy. American Journal of Medicine. 1989; 86(1B):45-9

17. Alici G, Aliyev F, Bellur G, Okcun B, Turkoglu C, Karpuz H. Effect of seven different modalities of antihypertensive therapy on pulse pressure in patients with newly diagnosed stage I hypertension. Cardiovascular Therapeutics. 2009; 27(1):4-9

18. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA. 2000; 283(15):1967-1975

19. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288(23):2981-97

20. Alviar CL, Devarapally S, Nadkarni GN, Romero J, Benjo AM, Javed F et al. Efficacy and safety of dual calcium channel blockade for the treatment of hypertension: A meta-analysis. American Journal of Hypertension. 2013; 26(2):287-97

21. Amar J, Joire JE, Salvador M. Study of the efficacity and tolerance of diltiazem LP 300 mg in 2000 hypertensive patients (alone or combined with an angiotensin converting enzyme inhibitor). Annales de Cardiologie et d'Angeiologie. 1999; 48(1):69-75

22. Ames R, Griffing G, Marbury T, Miller E, Schoenberger J, Glenn B et al. Effectiveness of indapamide versus enalapril as second-step therapy of systemic hypertension. American Journal of Cardiology. 1992; 69(3):267-70

23. 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

24. Andersen H, Botta G, Galasse R, Hill JF. Efficacy of captopril and hydrochlorothiazide administered once a day. Postgraduate Medical Journal. 1986; 62(Suppl 1):146-9

25. Andersen NH, Knudsen ST, Poulsen PL, Poulsen SH, Helleberg K, Eiskjaer H et al. Dual blockade with candesartan cilexetil and lisinopril in hypertensive patients with diabetes mellitus: Rationale and design. Journal of the Renin-Angiotensin-Aldosterone System. 2003; 4(2):96-9

26. Andersen NH, Poulsen PL, Knudsen ST, Poulsen SH, Eiskjaer H, Hansen KW et al. Long-term dual blockade with candesartan and lisinopril in hypertensive patients with diabetes: The CALM II study. Diabetes Care. 2005; 28(2):273-7

27. Ando K, Ohtsu H, Uchida S, Kaname S, Arakawa Y, Fujita T et al. Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: A double-blind, randomised, placebo-controlled trial. The Lancet Diabetes & Endocrinology. 2014; 2(12):944-53

28. 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

29. Andren L, Svensson A, Hansson L. Captopril or atenolol in essential hypertension. Acta Medica Scandinavica Supplementum. 1983; 677:115-8

30. Andreucci VE, Usberti M, Federico S, Pecoraro C, Balletta M, Meccariello S. Long-term follow-up of minoxidil therapy in refractory hypertension. A prospective trial in patients with various degrees of renal insufficiency. Clinical Nephrology. 1983; 19(2):55-60

31. Angeli F, Verdecchia P, Reboldi GP, Gattobigio R, Bentivoglio M, Staessen JA et al. Calcium channel blockade to prevent stroke in hypertension: A meta-analysis of 13 studies with 103,793 subjects. American Journal of Hypertension. 2004; 17(9):817-22

32. Anonymous. The Nordic Diltiazem Study (NORDIL): A prospective intervention trial of calcium antagonist therapy in hypertension. Blood Pressure. 1993; 2(4):312-21

33. Anonymous. Efficacy and tolerability of losartan versus enalapril alone or in combination with hydrochlorothiazide in patients with essential hypertension. Cardiovascular Reviews and Reports. 1996; 17(1):57-58

34. Anonymous. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Hypertension. 1999; 34(5):1129-33

35. Applegate WB, Byington RP. MIDAS, the Multicenter Isradipine/Diuretic Atherosclerosis Study. Design features and baseline data. American Journal of Hypertension. 1991; 4(2 Pt 2):114S-117S

36. Arima H, Anderson C, Omae T, Woodward M, MacMahon S, Mancia G et al. Degree of blood pressure reduction and recurrent stroke: The PROGRESS trial. Journal of Neurology, Neurosurgery and Psychiatry. 2014; 85(11):1284-5

37. Arriaga-Gracia J, Sanchez-Garcia JL, Gonzalez-Garcia CA. Nicardipine or propranolol combined with hydrochlorothiazide in patients with essential hypertension. Proceedings of the Western Pharmacology Society. 1993; 36:39-43

38. 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

39. Bakris GL, Cooper-Dehoff RM, Zhou Q, Kupfer S, Champion A, Pepine CJ et al. Dual therapy in hypertensive patients with coronary artery disease: The role of calcium channel blockers and beta-blockers. American Journal of Cardiovascular Drugs. 2007; 7(Suppl 1):25-9

40. Balamuthusamy S, Molnar J, Adigopula S, Arora R. Comparative analysis of beta-blockers with other antihypertensive agents on cardiovascular outcomes in hypertensive patients with diabetes mellitus: A systematic review and meta-analysis. American Journal of Therapeutics. 2009; 16(2):133-42

41. Baldwin SP, Harless WT, Lacy CA, Motley JF, Rietbrock MJ, Sehy JT. A comparative study of the efficacy and side effects of metolazone 1/2 mg tablets (Microx) vs triamterene 50 mg plus hydrochlorothiazide 25 mg in the treatment of mild hypertension. Advances in Therapy. 1987; 4(6):265-278

42. Bang CN, Soliman EZ, Simpson LM, Davis BR, Devereux RB, Okin PM et al. Electrocardiographic left ventricular hypertrophy predicts cardiovascular morbidity and mortality in hypertensive patients: The ALLHAT study. American Journal of Hypertension. 2017; 30(9):914-922

43. Bangalore S, Wild D, Parkar S, Kukin M, Messerli FH. Beta-blockers for primary prevention of heart failure in patients with hypertension insights from a meta-analysis. Journal of the American College of Cardiology. 2008; 52(13):1062-72

44. Batterink J, Stabler SN, Tejani AM, Fowkes CT. Spironolactone for hypertension. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD008169. DOI: https://dx.doi.org/10.1002/14651858.CD008169.pub2.

45. 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

46. Berger A, Chima P, Dawes M, Davey NB, Grundy PF, Lee PS et al. A fixed combination of felodipine 5 mg and metoprolol 50 mg compared with double doses of the individual components as antihypertensive therapy. Journal of Drug Development. 1992; 4(4):199-206

47. 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

48. Blumenthal JA, Ekelund LG, Emery CF. Quality of life among hypertensive patients with a diuretic background who are taking atenolol and enalapril. Clinical Pharmacology and Therapeutics. 1990; 48(4):447-54

49. 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

50. Boissel JP, Collet JP, Lion L, Ducruet T, Moleur P, Luciani J et al. A randomized comparison of the effect of four antihypertensive monotherapies on the subjective quality of life in previously untreated asymptomatic patients: Field trial in general practice. Journal of Hypertension. 1995; 13(9):1059-67

51. Borgmastars H, Forsen B, Tuomilehto J, Hellebo R, Walle PO, Nielsen HM et al. Felodipine versus hydrochlorothiazide as an addition to a beta-blocker in the treatment of hypertension. Drugs. 1987; 34(Suppl 3):136-8

52. 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

53. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. New England Journal of Medicine. 2001; 345(12):861-9

54. 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

55. Byrd JB, Zeng C, Tavel HM, Magid DJ, O'Connor PJ, Margolis KL et al. Combination therapy as initial treatment for newly diagnosed hypertension. American Heart Journal. 2011; 162(2):340-6

56. Byyny RL. Antihypertensive efficacy of the angiotensin II AT1-receptor antagonist losartan: Results of a randomized, double-blind, placebo-controlled, parallel-group trial using 24-hour blood pressure monitoring. Blood Pressure Supplement. 1996; 5:71-7

57. Castano G, Mas R, Gamez R, Fernandez J, Illnait J, Fernandez L et al. Concomitant use of policosanol and beta-blockers in older patients. International Journal of Clinical Pharmacology Research. 2004; 24(2-3):65-77

58. Celis H, Yodfat Y, Thijs L, Clement D, Cozic J, De Cort P et al. Antihypertensive therapy in older patients with isolated systolic hypertension: The Syst-Eur experience in general practice. Family Practice. 1996; 13(2):138-43

59. Cesaris R, Ranieri G, Chiarappa R. Nadolol vs. chlortalidone in hypertensive patients unresponsive to treatment with captopril alone. Clinica Terapeutica. 1986; 116(6):465-471

60. Chatellier G, Sassano P, Amiot AM, Corvol P, Menard J. Efficacy and influence on quality of life of enalapril as a first step treatment of hypertension. Clinical and Experimental Hypertension Part A: Theory and Practice. 1987; 9(2-3):513-9

61. Chi C, Tai C, Bai B, Yu S, Karamanou M, Wang J et al. Angiotensin system blockade combined with calcium channel blockers is superior to other combinations in cardiovascular protection with similar blood pressure reduction: A meta-analysis in 20,451 hypertensive patients. Journal of Clinical Hypertension. 2016; 18(8):801-8

62. Chrysant SG, Cohen M. Long-term antihypertensve effects with chronic administration of isradipine controlled release. Current Therapeutic Research, Clinical and Experimental. 1997; 58(1):1-9

63. Circelli M, Nicolini G, Egan CG, Cremonesi G. Efficacy and safety of delapril/indapamide compared to different ACE-inhibitor/hydrochlorothiazide combinations: A meta-analysis. International Journal of General Medicine. 2012; 5:725-34

64. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. BMJ. 1986; 293(6555):1145-51

65. Correa A, Rochlani Y, Khan MH, Aronow WS. Pharmacological management of hypertension in the elderly and frail populations. Expert Review of Clinical Pharmacology. 2018; 11(8):805-817

66. Cowley AJ, Wynne RD, Hampton JR. Flosequinan as a third agent for the treatment of hypertension: A placebo controlled, double-blind study. European Journal of Clinical Pharmacology. 1987; 33(2):203-4

67. Cranston WI, Juel-Jensen BE. The effects of spironolactone and chlorthalidone on arterial pressure. The Lancet. 1962; 1(7240):1161-1164

68. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA. 1996; 276(23):1886-92

69. Daae LN, Westlie L. A 5-year comparison of doxazosin and atenolol in patients with mild-to-moderate hypertension: Effects on blood pressure, serum lipids, and coronary heart disease risk. Blood Pressure. 1998; 7(1):39-45

70. 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

71. Dahlof B, Zanchetti A, Diez J, Nicholls MG, Yu CM, Barrios V et al. Effects of losartan and atenolol on left ventricular mass and neurohormonal profile in patients with essential hypertension and left ventricular hypertrophy. Journal of Hypertension. 2002; 20(9):1855-64

72. Daien V, Duny Y, Ribstein J, du Cailar G, Mimran A, Villain M et al. Treatment of hypertension with renin-angiotensin system inhibitors and renal dysfunction: A systematic review and meta-analysis. American Journal of Hypertension. 2012; 25(1):126-32

73. De Rosa ML, Cardace P, Rossi M, Baiano A, De Cristofaro A. Evaluation of long-term efficacy and tolerability of irbesartan in elderly hypertensive patients with renal impairment in an open-label study. Current Therapeutic Research, Clinical and Experimental. 2002; 63(3):201-215

74. 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

75. Destro M, Cagnoni F, D'Ospina A, Ricci AR, Demichele E, Peros E et al. Role of valsartan, amlodipine and hydrochlorothiazide fixed combination in blood pressure control: an update. Vascular Health and Risk Management. 2010; 6:253-60

76. Devereux RB, de Faire U, Fyhrquist F, Harris KE, Ibsen H, Kjeldsen SE et al. Blood pressure reduction and antihypertensive medication use in the losartan intervention for endpoint reduction in hypertension (LIFE) study in patients with hypertension and left ventricular hypertrophy. Current Medical Research and Opinion. 2007; 23(2):259-70

77. Dews I, VandenBurg M. A 52-week, open-label, dose-titration safety study of imidapril in the treatment of mild to moderate hypertension. Current Therapeutic Research - Clinical and Experimental. 2001; 62(2):167-176

78. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD006742. DOI: https://dx.doi.org/10.1002/14651858.CD006742.pub2.

79. Du LP, Cheng ZW, Zhang YX, Li Y, Mei D. The impact of fixed-dose combination versus free-equivalent combination therapies on adherence for hypertension: A meta-analysis. Journal of Clinical Hypertension. 2018; 20(5):902-907

80. Ekbom T, Dahlof B, Hansson L, Lindholm LH, Schersten B, Wester PO. Antihypertensive efficacy and side effects of three beta-blockers and a diuretic in elderly hypertensives: A report from the STOP-Hypertension study. Journal of Hypertension. 1992; 10(12):1525-30

81. Ekbom T, Linjer E, Hedner T, Lanke J, De Faire U, Wester PO et al. Cardiovascular events in elderly patients with isolated systolic hypertension. A subgroup analysis of treatment strategies in STOP-Hypertension-2. Blood Pressure. 2004; 13(3):137-41

82. Estacio RO, Schrier RW. Antihypertensive therapy in type 2 diabetes: Implications of the appropriate blood pressure control in diabetes (ABCD) trial. American Journal of Cardiology. 1998; 82(9 Suppl 1):9-14

83. 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 chlorthalidone given alone and in combination. Current Therapeutic Research, Clinical and Experimental. 1984; 35(1):31-39

84. Fariello R, Dal Palu C, Pessina A, Semplicini A, Pirrelli A, Vulpis V et al. Antihypertensive efficacy of urapidil versus hydrochlorothiazide alone in patients with mild to moderate essential hypertension and of their combination in nonresponders to monotherapy. Drugs. 1990; 40(Suppl 4):60-2

85. Farsang C, Lengyel M, Borbas S, Zorandi A, Szoradi Dienes B. Value of rilmenidine therapy and its combination with perindopril on blood pressure and left ventricular hypertrophy in patients with essential hypertension (VERITAS). Current Medical Research and Opinion. 2003; 19(3):205-217

86. Fasano ML, Soro S, Ferrara LA. Long-term antihypertensive efficacy of ketanserin plus chlorthalidone. Drugs Under Experimental and Clinical Research. 1989; 15(11-12):587-90

87. Faust G. One-year study of nilvadipine administered once a day. Efficacy and long-term tolerability in hypertensives. Fortschritte der Medizin. 1993; 111(11):46-50

88. Faust G. A one year study of single administration of nilvadipine. Results of the effectiveness and long-term tolerance in hypertension. Fortschritte der Medizin. 1993; 111(11):188-192

89. Ferdinand KC. Advances in antihypertensive combination therapy: benefits of low-dose thiazide diuretics in conjunction with omapatrilat, a vasopeptidase inhibitor. Journal of Clinical Hypertension. 2001; 3(5):307-12

90. Fernandes LA, Cestario ED, Cosenso-Martin LN, Vilela-Martin JF, Yugar-Toledo JC, Fuchs FD. Chlorthalidone plus amiloride reduces the central systolic blood pressure in stage 1 hypertension patients. Cardiology Research. 2016; 7(6):196-201

91. Fernandez R, Puig JG, Rodriguez-Perez JC, Garrido J, Redon J, Group TS. Effect of two antihypertensive combinations on metabolic control in type-2 diabetic hypertensive patients with albuminuria: A randomised, double-blind study. Journal of Human Hypertension. 2001; 15(12):849-56

92. Ferrara LA, de Simone G, Mancini M, Fasano ML, Pasanisi F, Vallone G. Changes in left ventricular mass during a double-blind study with chlorthalidone and slow-release nifedipine. European Journal of Clinical Pharmacology. 1984; 27(5):525-8

93. Finnerty FA, Jr., Gyftopoulos A, Berry C, McKenney A. Step 2 regimens in hypertension. An assessment. JAMA. 1979; 241(6):579-81

94. Fogari R, Derosa G, Zoppi A, Lazzari P, D'Angelo A, Mugellini A. Comparative effect of canrenone or hydrochlorothiazide addition to valsartan/amlodipine combination on urinary albumin excretion in well-controlled type 2 diabetic hypertensive patients with microalbuminuria. Expert Opinion on Pharmacotherapy. 2014; 15(4):453-9

95. Fogari R, Mugellini A, Zoppi A, Lazzari P, Destro M, Rinaldi A et al. Effect of telmisartan/hydrochlorothiazide vs lisinopril/hydrochlorothiazide combination on ambulatory blood pressure and cognitive function in elderly hypertensive patients. Journal of Human Hypertension. 2006; 20(3):177-85

96. Fogari R, Zoppi A, Corradi L, Mugellini A, Lazzari P, Preti P et al. Long-term effects of ramipril and nitrendipine on albuminuria in hypertensive patients with type II diabetes and impaired renal function. Journal of Human Hypertension. 1999; 13(1):47-53

97. Fogari R, Zoppi A, Lusardi P, Mugellini A. Efficacy and tolerability of manidipine hydrochloride in the long-term treatment of mild-moderate hypertension. Manidipine Efficacy in Long-Term Treatment Group. Blood Pressure Supplement. 1996; 5:24-8

98. Fogari R, Zoppi A, Mugellini A, Maffioli P, Preti P, Derosa G. Effects of valsartan or ramipril addition to amlodipine/hydrochlorothiazide combination on left ventricular mass in diabetic hypertensive patients with left ventricular hypertrophy. Expert Opinion on Pharmacotherapy. 2012; 13(8):1091-9

99. Fogari R, Zoppi A, Tettamanti F, Malamani G, Pasotti C. The effect of celiprolol on the blood lipid profile in hypertensive patients with high cholesterol levels. Cardiovascular Drugs and Therapy. 1991; 4(Suppl 6):1287-90

100. 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

101. Forrest WA, Bridgman KM, Ebbutt AF. "24-hour blood pressure control" with sustained release oxprenolol 160mg plus cyclopenthiazide 0.25mg (Trasidrex) in general practice. British Journal of Clinical Practice. 1983; 37(11-12):385-8

102. Fossum E, Olsen MH, Hoieggen A, Wachtell K, Reims HM, Ibsen H et al. Long-term plasma catecholamines in patients with hypertension and left ventricular hypertrophy treated with losartan or atenolol: ICARUS, a LIFE substudy. Journal of Human Hypertension. 2004; 18(6):375-80

103. Franco RJ, Sampaio M, Balbi AL, Martin LC, Luna RL. An open comparative study of captopril + hydrochlorothiazide versus chlorthalidone for the treatment of mild and moderate primary hypertension. Arquivos Brasileiros de Cardiologia. 1992; 59(5):423-427

104. Franse LV, Pahor M, Di Bari M, Somes GW, Cushman WC, Applegate WB. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension. 2000; 35(5):1025-30

105. Frewin DB, Aldons P, Wilson LL, O'Sullivan EF, Wyndham RN, Karrasch J et al. Felodipine in combination with a beta-adrenoceptor blocker as an effective substitute for triple therapy in severe hypertension. The Australian Felodipine Multicentre Study Group. European Journal of Clinical Pharmacology. 1991; 41(5):393-6

106. Frick MH, Cox DA, Himanen P, Huttunen M, Pitkajarvi T, Porsti P et al. Serum lipid changes in a one-year, multicenter, double-blind comparison of doxazosin and atenolol for mild to moderate essential hypertension. American Journal of Cardiology. 1987; 59(14):61G-67G

107. Frick MH, Halttunen P, Himanen P, Huttunen M, Porsti P, Pitkajarvi T et al. A long-term double-blind comparison of doxazosin and atenolol in patients with mild to moderate essential hypertension. British Journal of Clinical Pharmacology. 1986; 21(Suppl 1):55S-62S

108. Gao D, Ning N, Niu X, Wei J, Sun P, Hao G. Aliskiren vs. angiotensin receptor blockers in hypertension: meta-analysis of randomized controlled trials. American Journal of Hypertension. 2011; 24(5):613-21

109. Gasowski J, Staessen JA, Celis H, Fagard RH, Thijs L, Birkenhager WH et al. Systolic Hypertension in Europe (Syst-Eur) trial phase 2: Objectives, protocol, and initial progress. Systolic Hypertension in Europe Investigators. Journal of Human Hypertension. 1999; 13(2):135-45

110. Gazdick LP, Maxwell M, Ruff D, Goldberg AI, Nelson EB, Berman R et al. A double-blind, randomized, parallel, active-controlled study to evaluate the antihypertensive efficacy and safety of losartan in patients with severe hypertension. American Journal of Hypertension. 1994; 7(4 Pt 2):100A

111. George C, Grippat J, Safar M. Second line treatment of essential hypertension after beta-blockade. A randomised trial in 558 patients initially treated with bisoprolol 10mg. Drug Investigation. 1990; 2(3):150-154

112. Ghiadoni L, Bruno RM, Cartoni G, Stea F, Magagna A, Virdis A et al. Combination therapy with lercanidipine and enalapril reduced central blood pressure augmentation in hypertensive patients with metabolic syndrome. Vascular Pharmacology. 2017; 92:16-21

113. Giles TD, Sander GE, Roffidal LE, Quiroz AC, Mazzu AL. Comparative effects of nitrendipine and hydrochlorothiazide on calciotropic hormones and bone density in hypertensive patients. American Journal of Hypertension. 1992; 5(12 Pt 1):875-9

114. Gillespie EL, White CM, Kardas M, Lindberg M, Coleman CI. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. Diabetes Care. 2005; 28(9):2261-6

115. Girerd X, Genes N. Comparison of an early or a late drug titration on the efficacy and safety of Irbesartan/HCTZ combination in uncontrolled hypertensive patients: Results of the actual study. Journal of Hypertension. 2010; 28(Suppl A):e18-9

116. Gitt AK, Baumgart P, Bramlage P, Mahfoud F, Potthoff SA, Senges J et al. EARLY Treatment with azilsartan compared to ACE-inhibitors in anti-hypertensive therapy--rationale and design of the EARLY hypertension registry. BMC Cardiovascular Disorders. 2013; 13:46

117. Glorioso N, Argiolas G, Filigheddu F, Troffa C, Cocco F, Bulla E et al. Conceptual basis and methodology of the SOPHIA study. Pharmacogenomics. 2007; 8(11):1497-509

118. Goicolea I, Fernández González R, Piniés J, Garrido J, Martínez JM, Armenteros S et al. Effect of antihypertensive combinations on arterial pressure, albuminuria, and glycemic control in patients with type II diabetic nephropathy: A randomized study. Nefrologia. 2002; 22(2):170-178

119. Gosse P, Dubourg O, Gueret P, De Simone G, Schmieder R, De Leeuw PW et al. Efficacy of very low dose perindopril 2 mg/indapamide 0.625 mg combination on left ventricular hypertrophy in hypertensive patients: The P.I.C.X.E.L. study rationale and design. Journal of Human Hypertension. 2002; 16(9):653-9

120. 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

121. Guo JH, Lu YH, Shi GP, Guo ZP, Xu Q, Shen JH et al. Protective effect of spironolactone on myocardium during perioperation period of percataneous coronary intervention. Academic Journal of Second Military Medical University. 2011; 32(8):889-892

122. Guo JZ, Gong YC, Zhang JL, Qing YW, Dai QY, Wang YC et al. A clinical intervention study among 463 essential hypertensive patients with metabolic syndrome. Chinese Journal of Cardiovascular Diseases. 2005; 33(2):132-136

123. Gupta A, Mackay J, Whitehouse A, Godec T, Collier T, Pocock S et al. Long-term mortality after blood pressure-lowering and lipid-lowering treatment in patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study: 16-year follow-up results of a randomised factorial trial. Lancet. 2018; 392(10153):1127-1137

124. Gyntelberg F, Jacobsen K, Martlev A, Backer P. 2 antihypertensive therapeutic regimes compared in a controlled clinical trial in general practice. Cyclopenthiazide + KC1/methyldopa versus oxprenolol/hydralazine. Ugeskrift for Laeger. 1977; 139(11):641-646

125. 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

126. Hamada T, Kuwabara M, Watanabe A, Mizuta E, Ohtahara A, Omodani H et al. A comparative study on the effectiveness of losartan/hydrochlorothiazide and telmisartan/hydrochlorothiazide in patients with hypertension. Clinical and Experimental Hypertension. 2014; 36(4):251-7

127. Hamada T, Mizuta E, Kondo T, Hirai M, Yamada K, Kato M et al. Effects of a low-dose antihypertensive diuretic in combination with losartan, telmisartan, or candesartan on serum urate levels in hypertensive patients. Arzneimittel-Forschung. 2010; 60(2):71-5

128. Hamed AT, Taha MM. Comparative study on renoprotective effect of aliskiren-pentoxifylline combination, valsartan and enalapril among patients with hypertension, type 2 diabetes mellitus and diabetic nephropathy. Jordan journal of pharmaceutical sciences. 2014; 7(1):1-14

129. Hanon O, Boully C, Caillard L, Labouree F, Cochiello S, Chaussade E. Treatment of hypertensive patients with diabetes and microalbuminuria with combination indapamide sr/amlodipine: Retrospective analysis of NESTOR. American Journal of Hypertension. 2015; 28(8):1064-71

130. Hanon O, Caillard L, Chaussade E, Hernandorena I, Boully C. Blood pressure-lowering efficacy of indapamide SR/amlodipine combination in older patients with hypertension: A post hoc analysis of the NESTOR trial (Natrilix SR vs Enalapril in Hypertensive Type 2 Diabetics With Microalbuminuria). Journal of Clinical Hypertension. 2017; 19(10):965-972

131. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. The Lancet. 2000; 356(9227):359-65

132. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B et al. Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. The Lancet. 1999; 354(9192):1751-6

133. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. The Lancet. 1999; 353(9153):611-6

134. Hansson L, Lithell H, Skoog I, Baro F, Banki CM, Breteler M et al. Study on COgnition and Prognosis in the Elderly (SCOPE). Blood Pressure. 1999; 8(3):177-83

135. Hasegawa H, Takano H, Narumi H, Ohtsuka M, Mizuguchi T, Namiki T et al. Effects of telmisartan and losartan on cardiovascular protection in Japanese hypertensive patients. Hypertension Research. 2011; 34(11):1179-84

136. Helgeland A. Treatment of mild hypertension: A five year controlled drug trial. The Oslo study. American Journal of Medicine. 1980; 69(5):725-32

137. Helgeland A. Double-blind comparison of trimazosin and propranolol in essential hypertension. American Heart Journal. 1983; 106(5 Pt 2):1253-8

138. Himmelmann A, Hansson L, Hansson BG, Hedstrand H, Skogstrom K, Ohrvik J et al. ACE inhibition preserves renal function better than beta-blockade in the treatment of essential hypertension. Blood Pressure. 1995; 4(2):85-90

139. Hosie J, Jones JC, Clifford PD. Long term usage of Prestim (timolol/bendrofluazide) in the management of mild to moderate hypertension in general practice. British Journal of Clinical Practice. 1983; 37(11-12):393-6

140. Hradec J, Zamorano J, Sutradhar S. Post hoc analysis of the Cluster Randomized Usual Care versus Caduet Investigation Assessing Long-term risk (CRUCIAL) trial. Current Medical Research and Opinion. 2013; 29(6):589-96

141. Hughes AD, Stanton AV, Jabbar AS, Chapman N, Martinez-Perez ME, Mc GTSA. Effect of antihypertensive treatment on retinal microvascular changes in hypertension. Journal of Hypertension. 2008; 26(8):1703-7

142. Hulley SB, Furberg CD, Gurland B, McDonald R, Perry HM, Schnaper HW et al. Systolic Hypertension in the Elderly Program (SHEP): Antihypertensive efficacy of chlorthalidone. American Journal of Cardiology. 1985; 56(15):913-20

143. Ibsen H, Lindholm LH, Pedersen OL, Dahlöf B, Kjeldsen S. The effect of losartan versus atenolol on cardiovascular morbidity and mortality in patients with diabetes mellitus in the LIFE-study. Ugeskrift for Laeger. 2003; 165(5):459-462

144. Ibsen H, Westberg B. The efficacy and tolerability of long-term felodipine treatment in hypertension. The Scandinavian Multicenter Group. Cardiovascular Drugs and Therapy. 1990; 4(3):641-7

145. Ichihara A, Kaneshiro Y, Takemitsu T, Sakoda M. Effects of amlodipine and valsartan on vascular damage and ambulatory blood pressure in untreated hypertensive patients. Journal of Human Hypertension. 2006; 20(10):787-94

146. J. Elan Investigators. Effect of losartan and amlodipine on left ventricular diastolic function in patients with mild-to-moderate hypertension (J-ELAN): Rationale and design. Circulation Journal. 2006; 70(1):124-8

147. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. New England Journal of Medicine. 2008; 359(23):2417-28

148. Johnson JA, Gong Y, Bailey KR, Cooper-DeHoff RM, Chapman AB, Turner ST et al. Hydrochlorothiazide and atenolol combination antihypertensive therapy: Effects of drug initiation order. Clinical Pharmacology and Therapeutics. 2009; 86(5):533-9

149. Johnston GD, Wilson R, McDermott BJ, McVeigh GE, Duffin D, Logan J. Low-dose cyclopenthiazide in the treatment of hypertension: A one-year community-based study. Quarterly Journal of Medicine. 1991; 78(286):135-43

150. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on

valsartan or amlodipine: The VALUE randomised trial. The Lancet. 2004; 363(9426):2022-31

151. Kaku K, Enya K, Sugiura K, Totsuka N. Efficacy and safety of combination therapy with candesartan cilexetil and pioglitazone hydrochloride in patients with hypertension and type 2 diabetes mellitus. Current Medical Research and Opinion. 2011; 27(Suppl 3):73-84

152. Katayama S, Kawamori R, Iwamoto Y, Saito I, Kuramoto K, Group AS. In half of hypertensive diabetics, co-administration of a calcium channel blocker and an angiotensin-converting enzyme inhibitor achieved a target blood pressure of <130/80 mmHg: The azelnidipine and temocapril in hypertensive patients with type 2 diabetes (ATTEST) study. Hypertension Research. 2008; 31(8):1499-508

153. Kawalec P, Holko P, Gawin M, Pilc A. Effectiveness of fixed-dose combination therapy in hypertension: Systematic review and meta-analysis. Archives of Medical Science. 2018; 14(5):1125-1136

154. Kereiakes DJ, Chrysant SG, Izzo JL, Littlejohn T, Oparil S, Melino M et al. Long-term efficacy and safety of triple-combination therapy with olmesartan medoxomil and amlodipine besylate and hydrochlorothiazide for hypertension. Journal of Clinical Hypertension. 2012; 14(3):149-57

155. Kerfoot BP, Turchin A, Breydo E, Gagnon D, Conlin PR. An online spaced-education game among clinicians improves their patients' time to blood pressure control: A randomized controlled trial. Circulation: Cardiovascular Quality and Outcomes. 2014; 7(3):468-74

156. Kim JH, Zamorano J, Erdine S, Pavia A, Al-Khadra A, Sutradhar S et al. Reduction in cardiovascular risk using proactive multifactorial intervention versus usual care in younger (< 65 years) and older (>= 65 years) patients in the CRUCIAL trial. Current Medical Research and Opinion. 2013; 29(5):453-63

157. Kim JH, Zamorano J, Erdine S, Pavia A, Al-Khadra A, Sutradhar S et al. Proactive cardiovascular risk management versus usual care in patients with and without diabetes mellitus: CRUCIAL trial subanalysis. Postgraduate Medicine. 2012; 124(4):41-53

158. Kjeldsen SE, Dahlof B, Devereux RB, Julius S, Aurup P, Edelman J et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: A Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA. 2002; 288(12):1491-8

159. Kjeldsen SE, Dzongowski P, Li N, Wang L, Radlmaier A. Fixed-dose combination of nifedipine gastrointestinal therapeutic system and candesartan cilexetil in patients with moderate-to-severe essential hypertension: An open-label, long-term safety and efficacy study. Journal of Clinical Pharmacy and Therapeutics. 2016; 41(6):695-702

160. 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

161. Kjeldsen SE, Julius S, Mancia G, McInnes GT, Hua T, Weber MA et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: The VALUE trial. Journal of Hypertension. 2006; 24(7):1405-12

162. Ko GT, Chan HC, Chan CH. Blood pressure reduction and tolerability of amlodipine versus nifedipine retard in Chinese patients with type 2 diabetes mellitus and

hypertension: A randomized 1-year clinical trial. International Journal of Clinical Pharmacology and Therapeutics. 2001; 39(8):331-5

163. Kohlmann O, Jr., Roca-Cusachs A, Laurent S, Schmieder RE, Wenzel RR, Fogari R. Fixed-dose manidipine/delapril versus losartan/hydrochlorothiazide in hypertensive patients with type 2 diabetes and microalbuminuria. Advances in Therapy. 2009; 26(3):313-24

164. Kostis JB, Wilson AC, Freudenberger RS, Cosgrove NM, Pressel SL, Davis BR et al. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. American Journal of Cardiology. 2005; 95(1):29-35

165. Kuwajima I, Kuramoto K, Ogihara T, Iimura O, Abe K, Saruta T et al. Tolerability and safety of a calcium channel blocker in comparison with a diuretic in the treatment of elderly patients with hypertension: secondary analysis of the NICS-EH. Hypertension Research. 2001; 24(5):475-80

166. Lacourciere Y, Belanger A, Godin C, Halle JP, Ross S, Wright N et al. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. Kidney International. 2000; 58(2):762-9

167. Laufer E, Reid C, Qi XL, Jennings GL. Absence of detectable regression of human hypertensive left ventricular hypertrophy following drug treatment for 1 year. Clinical and Experimental Pharmacology and Physiology. 1998; 25(3-4):208-15

168. Laurent S, Boutouyrie P, Vascular Mechanism Collaboration. Dose-dependent arterial destiffening and inward remodeling after olmesartan in hypertensives with metabolic syndrome. Hypertension. 2014; 64(4):709-16

169. Lavenius B, Hansson L. A double-blind comparison of spironolactone and hydrochlorothiazide in hypertensive patients treated with metoprolol. International Journal of Clinical Pharmacology, Therapy, and Toxicology. 1982; 20(6):291-5

170. Leonetti G, Magnani B, Pessina AC, Rappelli A, Trimarco B, Zanchetti A et al. Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. American Journal of Hypertension. 2002; 15(11):932-40

171. Levine B. Eprosartan provides safe and effective long-term maintenance of blood pressure control in patients with mild to moderate essential hypertension. Current Medical Research and Opinion. 2001; 17(1):8-17

172. Licata G, Ganguzza A, Corrao S, Merlino G, Chiara T, D'Aubert MD et al. Effects of cilazapril on renal haemodynamics in mild to moderate hypertensive subject: randomized controlled trial vs. hydrochlorothiazide. American Journal of Hypertension. 1994; 7(4 Pt 2):49A

173. Lim PO, Donnan PT, MacDonald TM. Does the Dundee Step Test predict outcome in treated hypertension? A sub-study protocol for the ASCOT trial. Anglo-Scandinavian Cardiac Outcome Trial. Journal of Human Hypertension. 2000; 14(1):75-8

174. Lin M, Chiang HT, Chen CY. Comparisons of long-term effects between converting enzyme inhibitors and conventional therapy in treating mild to moderate hypertension. Chinese Medical Journal. 1991; 48(5):339-50

175. Lin M, chiang HT, Yang YF, Lin SL, Chen CY, Kong CW et al. Long-term beneficial effects of converting enzyme inhibitors in patients with moderate hypertension and left ventricular hypertrophy. Acta Cardiologica Sinica. 1993; 9(4):254-263

176. Lin M, Yang YF, Chiang HT, Lee D, Wang SP, Chang MS et al. Beneficial effects of angiotensin-converting enzyme inhibitors on cardiovascular and renal functions in patients with hypertension and diabetes. Acta Cardiologica Sinica. 1995; 11(1):30-38

177. Lind L, Pollare T, Berne C, Lithell H. Long-term metabolic effects of antihypertensive drugs. American Heart Journal. 1994; 128(6 Pt 1):1177-83

178. Lindholm LH, Anderson H, Ekbom T, Hansson L, Lanke J, Dahlof B et al. Relation between drug treatment and cancer in hypertensives in the Swedish Trial in Old Patients with Hypertension 2: A 5-year, prospective, randomised, controlled trial. The Lancet. 2001; 358(9281):539-44

179. Lindholm LH, Hansson L, Dahlof B, Ekbom T, Hedner T, De Faire U et al. The Swedish Trial in old patients with hypertension-2 (STOP-hypertension-2): A progress report. Blood Pressure. 1996; 5(5):300-4

180. Lindholm LH, Hansson L, Ekbom T, Dahlof B, Lanke J, Linjer E et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. Journal of Hypertension. 2000; 18(11):1671-5

181. Lindholm LH, Ibsen H, Borch-Johnsen K, Olsen MH, Wachtell K, Dahlof B et al. Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. Journal of Hypertension. 2002; 20(9):1879-86

182. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. The Lancet. 2002; 359(9311):1004-10

183. Lindner UK. Ergometric diagnosis and therapy control of hypertension in out-patients. Medizinische Klinik. 1984; 79(11):326-328

184. Lindroos M, Lehtonen A. Timolol and a hydrochlorothiazide-amiloride combination in the treatment of essential hypertension in young and middle-aged patients: A comparative study with once-daily administration. International Journal of Clinical Pharmacology, Therapy, and Toxicology. 1984; 22(12):643-5

185. Littlejohn T, Punzi H, Webster D, Majul CR, Oigman W, Olvera R. Telmisartan plus amlodipine combination is effective in both treatment-nave and previously treated hypertensive patients: Sub-analysis from a factorial design study. Journal of Clinical Hypertension. 2009; 11(Suppl A):A36

186. Liu JC, Zhou DX, Li ZS. A comparison of amlodipine with benazepril in treatment of elderly primary hypertension. Journal of Railway Medical University. 2000; 21(9):28-30

187. Liu L, Wang JG, Celis H, Staessen JA. Implications of the Systolic Hypertension in China trial. Clinical and Experimental Hypertension. 1999; 21(5-6):499-505

188. Lombardo M, Alli C, Broccolino M, Ferrari S, Montemurro L, Zaini G et al. Long-term effects of angiotensin-converting enzyme inhibitors and calcium antagonists on the right and left ventricles in essential hypertension. American Heart Journal. 1997; 134(3):557-64

189. López NC, Corral JL, Perozo M, García P, Bustillo N, Arreaza MR et al. Nifedipine in the treatment of moderate and severe arterial hypertension. Long-term effect on arterial pressure and on the left ventricle. Revista Española de Cardiología. 1997; 50(8):567-572

190. Lu Z, Chen Y, Li L, Wang G, Xue H, Tang W. Combination therapy of renin-angiotensin system inhibitors plus calcium channel blockers versus other two-drug combinations for hypertension: A systematic review and meta-analysis. Journal of Human Hypertension. 2017; 31(1):1-13

191. Ludwig M, Stapff M, Ribeiro A, Fritschka E, Tholl U, Smith RD et al. Comparison of the effects of losartan and atenolol on common carotid artery intima-media thickness in patients with hypertension: Results of a 2-year, double-blind, randomized, controlled study. Clinical Therapeutics. 2002; 24(7):1175-93

192. Luno J, Varas J, Ramos R, Merello I, Aljama P, MartinMalo A et al. The combination of beta blockers and renin-angiotensin system blockers improves survival in incident hemodialysis patients: A propensity-matched study. KI Reports. 2017; 2(4):665-675

193. Lynch AI, Boerwinkle E, Davis BR, Ford CE, Eckfeldt JH, Leiendecker-Foster C et al. Pharmacogenetic association of the NPPA T2238C genetic variant with cardiovascular disease outcomes in patients with hypertension. JAMA. 2008; 299(3):296-307

194. Lynch AI, Eckfeldt JH, Davis BR, Ford CE, Boerwinkle E, Leiendecker-Foster C et al. Gene panels to help identify subgroups at high and low risk of coronary heart disease among those randomized to antihypertensive treatment: The GenHAT study. Pharmacogenetics and Genomics. 2012; 22(5):355-66

195. M'Buyamba-Kabangu JR, Fagard R, Lijnen P, Staessen J, Lissens W, Ditu M et al. Calcium entry blockade or beta-blockade in long-term management of hypertension in blacks. Clinical Pharmacology and Therapeutics. 1987; 41(1):45-54

196. Maclean D, Elton RA, Muir AL, Readman AS, Vallance BD, Wilcox RG. Felodipine compared with hydralazine as third line therapy in hypertension. British Journal of Clinical Pharmacology. 1986; 21:577P-8P

197. Maclean D, Vallance BD, Wilcox RG. Felodipine vs hydralazine: A controlled trial as third line therapy in hypertension. British Journal of Clinical Pharmacology. 1986; 21(6):621-626

198. Malacco E, Mancia G, Rappelli A, Menotti A, Zuccaro MS, Coppini A et al. Treatment of isolated systolic hypertension: The SHELL study results. Blood Pressure. 2003; 12(3):160-7

199. Malminiemi K. Long-term celiprolol therapy lowers fasting plasma leptin levels. Cardiovascular Drugs and Therapy. 2000; 14(1):67-75

200. Mancia G, Parati G, Bilo G, Maronati A, Omboni S, Baurecht H et al. Assessment of long-term antihypertensive treatment by clinic and ambulatory blood pressure: data from the European Lacidipine Study on Atherosclerosis. Journal of Hypertension. 2007; 25(5):1087-94

201. Mann J, Julius S. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of cardiovascular events in hypertension. Rationale and design. Blood Pressure. 1998; 7(3):176-83

202. Marfatia R, White WB, Schumacher H. Effects of telmisartan with hydrochlorothiazide versus valsartan with hydrochlorothiazide in patients with moderate-to-severe hypertension. International Journal of Hypertension. 2012; 2012:976828

203. Marre M, Puig JG, Kokot F, Fernandez M, Jermendy G, Opie L et al. Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: the NESTOR Study. Journal of Hypertension. 2004; 22(8):1613-22

204. Martinez-Martin FJ, Rodriguez-Rosas H, Peiro-Martinez I, Soriano-Perera P, Pedrianes-Martin P, Comi-Diaz C. Olmesartan/amlodipine vs olmesartan/hydrochlorothiazide in hypertensive patients with metabolic syndrome: The OLAS study. Journal of Human Hypertension. 2011; 25(6):346-53

205. Mason JM, Dickinson HO, Nicolson DJ, Campbell F, Ford GA, Williams B. The diabetogenic potential of thiazide-type diuretic and beta-blocker combinations in patients with hypertension. Journal of Hypertension. 2005; 23(10):1777-81

206. Matsuno Y, Minatoguchi S, Fujiwara H, Gifu Substudy Group of The Case-J Trial. Effects of candesartan versus amlodipine on home-measured blood pressure, QT dispersion and left ventricular hypertrophy in high-risk hypertensive patients. Blood Pressure Supplement. 2011; 1:12-9

207. Matsushita K, Muramatsu T, Kondo T, Maeda K, Shintani S, Murohara T et al. Rationale and design of the NAGOYA HEART Study: Comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance. Journal of Cardiology. 2010; 56(1):111-7

208. 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

209. Mazza A, Schiavon L, Zuin M, Lenti S, Ramazzina E, Rubello D et al. Effects of the antihypertensive fixed-dose combinations on an early marker of hypertensive cardiac damage in subjects at low cardiovascular risk. American Journal of Hypertension. 2016; 29(8):969-75

210. McAreavey D, Ramsay LE, Latham L, Lorimer AR, McLaren D, Reid JL et al. The 'third drug' trial: a comparative study of anti-hypertensive agents added to treatment when blood pressure is uncontrolled by a beta-blocker plus thiazide diuretic. Journal of Hypertension Supplement. 1983; 1(2):S116-S9

211. Mende CW, Giles TD, Bharucha DB, Ferguson WG, Mallick M, Patel MD. Efficacy of nebivolol-valsartan single-pill combination in obese and nonobese patients with hypertension. Journal of Clinical Hypertension. 2017; 19(6):632-639

212. Metelitsa VI, Filatova NP. Comparative trial of nadolol, propranolol, prazosin and hydrochlorothiazide in patients with arterial hypertension after 12 months of treatment using the stepwise protocol. Cooperative study in the USSR: II. Results of the combined treatment, side effects, factors affecting drop-out rate and conclusion. Journal of Drug Development. 1991; 4(1):15-23

213. Metelitsa VI, Filatova NP. The results of the comparative study of nadolol, propranolol, prazosin and hydrochlorothiazide in patients with arterial hypertension in a 12-month stepped-plan treatment (cooperative research). The Working Group of the Cooperative Program to Study New Preparations in the Prevention of Arterial Hypertension. I. The research protocol and results of monotherapy. Terapevticheskii Arkhiv. 1991; 63(8):30-34

214. Middeke M, Richter WO, Schwandt P, Beck B, Holzgreve H. Normalization of lipid metabolism after withdrawal from antihypertensive long-term therapy with beta blockers and diuretics. Arteriosclerosis. 1990; 10(1):145-7

215. Middeke M, Richter WO, Schwandt P, Holzgreve H. The effects of antihypertensive combination therapy on lipid and glucose metabolism: Hydrochlorothiazide plus sotalol vs. hydrochlorothiazide plus captopril. International Journal of Clinical Pharmacology and Therapeutics. 1997; 35(6):231-4

216. Misson R, Merkel T, Cutler RE. Comparison of blood pressure, plasma lipid and cardiac performance responses to prazosin versus propranolol in thiazide-treated hypertensive patients. American Journal of Cardiology. 1984; 53(3):51A-54A

217. Mizuno H, Hoshide S, Tomitani N, Kario K. Comparison of ambulatory blood pressure-lowering effects of higher doses of different calcium antagonists in uncontrolled hypertension: The Calcium Antagonist Controlled-Release High-Dose Therapy in Uncontrolled Refractory Hypertensive Patients (CARILLON) Study. Blood Pressure. 2017; 26(5):284-293

218. Morgan TO. Efficacy of cilazapril compared with hydrochlorothiazide in the treatment of mild-to-moderate essential hypertension. Multicentre Study Group. American Journal of Medicine. 1989; 87(6B):37S-41S

219. Mroczek WJ, Burris JF, DeQuattro V. A multicenter evaluation of guanadrel sulfate and methyldopa in hypertensive patients receiving a diuretic. Current Therapeutic Research, Clinical and Experimental. 1984; 36(5 I):1004-1015

220. Muller FB, Bolli P, Linder L, Kiowski W, Erne P, Buhler FR. Calcium antagonists and the second drug for hypertensive therapy. American Journal of Medicine. 1986; 81(6A):25-9

221. Nakae S, Taniguchi I, Suzuki K, Yoshida H, Kunou M, Saito Y. Comparison of an angiotensin II receptor blocker and an angiotensin converting enzyme inhibitor on the aldosterone breakthrough during antihypertensive treatment. Tokyo jikeikai medical journal. 2006; 121(4):165-176

222. 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

223. Nct. A Prospective Randomised Study to Compare a Fixed Dose Combination of Telmisartan 80 mg Plus Hydrochlorothiazide 25 mg With a Fixed Dose Combination of Telmisartan 80 mg Plus Hydrochlorothiazide 12.5 mg in Patients With Uncontrolled Hypertension Who Fail to Respond Adequately to Treatment With a Fix. Available from: https://clinicaltrials.gov/ct2/show/NCT00239369?cond=A+Prospective+Randomised+Study+to+Compare+a+Fixed+Dose+Combination+of+Telmisartan+80+mg+Plus+Hydrochlorothiazide+25+mg+With+a+Fixed+Dose+Combination+of+Telmisartan+80+mg+Plus+Hydrochlorothiazide+12.5+mg+in+Patients+With+Uncontrolled+Hypertension+Who&rank=1 Last accessed: 10/10/2018

224. Neutel JM, Cushman WC, Lloyd E, Barger B, Handley A. Comparison of long-term safety of fixed-dose combinations azilsartan medoxomil/chlorthalidone vs olmesartan medoxomil/hydrochlorothiazide. Journal of Clinical Hypertension. 2017; 19(9):874-883

225. Neutel JM, Frishman WH, Oparil S, Papademitriou V, Guthrie G. Comparison of telmisartan with lisinopril in patients with mild-to-moderate hypertension. American Journal of Therapeutics. 1999; 6(3):161-6

226. Oberman A, Pool PE. Trimazosin for the treatment of hypertensive patients failing to respond to thiazides. American Heart Journal. 1983; 106(5 Pt 2):1258-64

227. Ocón J, Oliván J, Garrido Peralta M, Ruilope L, Rodicio JL, Seco Vasco J et al. Multicenter study of the efficacy of 3 antihypertensive regimens: captopril + hydrochlorothiazide, oxprenolol + hydrochlorothiazide, and alphamethyldopa + hydrochlorothiazide. Medicina Clínica. 1985; 85(15):617-621

228. Ogawa H, Kim-Mitsuyama S, Matsui K, Jinnouchi T, Jinnouchi H, Arakawa K et al. Angiotensin II receptor blocker-based therapy in Japanese elderly, high-risk, hypertensive patients. American Journal of Medicine. 2012; 125(10):981-90

229. Ogihara T, Kuramoto K. Effect of long-term treatment with antihypertensive drugs on quality of life of elderly patients with hypertension: A double-blind comparative study between a calcium antagonist and a diuretic. NICS-EH Study Group. National Intervention Cooperative Study in Elderly Hypertensives. Hypertension Research. 2000; 23(1):33-7

230. Ogihara T, Matsuzaki M, Umemoto S, Rakugi H, Matsuoka H, Shimada K et al. Combination therapy for hypertension in the elderly: A sub-analysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial. Hypertension Research. 2012; 35(4):441-8

231. Ogihara T, Saruta T, Rakugi H, Saito I, Shimamoto K, Matsuoka H et al. Combinations of olmesartan and a calcium channel blocker or a diuretic in elderly hypertensive patients: A randomized, controlled trial. Journal of Hypertension. 2014; 32(10):2054-63

232. Ogihara T, Saruta T, Rakugi H, Saito I, Shimamoto K, Matsuoka H et al. Combination therapy of hypertension in the elderly: A subgroup analysis of the Combination of OLMesartan and a calcium channel blocker or diuretic in Japanese elderly hypertensive patients trial. Hypertension Research. 2015; 38(1):89-96

233. Ohnishi K, Kohno M, Yukiiri K, Masugata H, Wada Y, Takagi Y et al. Influence of the angiotensin II receptor antagonist losartan on diuretic-induced metabolic effects in elderly hypertensive patients: Comparison with a calcium channel blocker. International Journal of Clinical Pharmacology and Therapeutics. 2001; 39(10):417-22

234. Okin PM, Kjeldsen SE, Lindholm LH, Dahlof B, Devereux RB. The relationship of electrocardiographic left ventricular hypertrophy to decreased serum potassium. Blood Pressure. 2012; 21(3):146-52

235. Oshikawa J, Toya Y, Morita S, Taguri M, Hanaoka K, Hasegawa T et al. Angiotensin receptor blocker (ARB)-diuretic versus ARB-calcium channel blocker combination therapy for hypertension uncontrolled by ARB monotherapy. Clinical and Experimental Hypertension. 2014; 36(4):244-50

236. Ostergren J, Poulter NR, Sever PS, Dahlof B, Wedel H, Beevers G et al. The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. Journal of Hypertension. 2008; 26(11):2103-11

237. Park C, Wang G, Durthaler JM, Fang J. Cost-effectiveness analyses of antihypertensive medicines: A systematic review. American Journal of Preventive Medicine. 2017; 53(6 Suppl 2):S131-S142

238. Patay B. Series of single patient trials comparing the efficacy between the most commonly prescribed thiazide diuretic in the us, hydrochlorothiazide, and lisinopril for the treatment of stage 1 hypertension. 2010. Available from: https://clinicaltrials.gov/ct2/show/NCT01258764?term=Series+of+Single+Patient+Trials+Comparing+the+Efficacy+Between+the+Most+Commonly+Prescribed+Thiazide+Diuretic+in+the+US%2C+Hydrochlorothiazide%2C+and+Lisinopril+for+the+Treatment+of+Stage+1+Hypertension&rank=1 Last accessed: 11/10/2018

239. Persson B, Granerus G, Hedner T, Wysocki M, Andersson O. Systemic and renal hemodynamic effects of single oral doses of cadralazine and long term

antihypertensive effects of cadralazine in patients receiving therapy with beta-blockers and diuretics. Acta Medica Scandinavica Supplementum. 1986; 714:177-82

240. Philip IG, Qureshi SM, Richards HH, Sharma SK, Wright FG, Young PH et al. A comparison of a hydrochlorothiazide plus triamterene combination (Dyazide) and atenolol in the treatment of patients with mild hypertension: A multicentre study in general practice. British Journal of Clinical Practice. 1987; 41(10):947-53

241. Pierini D, Anderson KV. Azilsartan medoxomil/chlorthalidone: A new fixed-dose combination antihypertensive. Annals of Pharmacotherapy. 2013; 47(5):694-703

242. Piller LB, Ford CE, Davis BR, Nwachuku C, Black HR, Oparil S et al. Incidence and predictors of angioedema in elderly hypertensive patients at high risk for cardiovascular disease: A report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Journal of Clinical Hypertension. 2006; 8(9):649-56; quiz 657-8

243. Remonti LR, Dias S, Leitao CB, Kramer CK, Klassman LP, Welton NJ et al. Classes of antihypertensive agents and mortality in hypertensive patients with type 2 diabetes-Network meta-analysis of randomized trials. Journal of Diabetes and Its Complications. 2016; 30(6):1192-200

244. Ritter J. A phase I randomized, placebo-controlled, double-blind study in hypertensive patients of the blood pressure interaction between TC-5214 and anti-hypertensive medications (Calcium Channel Blockers, Beta Blockers, and ACE Inhibitors). 2013. Available from: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/to-investigate-interaction-of-tc-5214-with-antihypertensive-medication/ Last accessed: 10/10/2018

245. Roush GC, Abdelfattah R, Song S, Ernst ME, Sica DA, Kostis JB. Hydrochlorothiazide vs chlorthalidone, indapamide, and potassium-sparing/hydrochlorothiazide diuretics for reducing left ventricular hypertrophy: A systematic review and meta-analysis. Journal of Clinical Hypertension. 2018; 24:24

246. Ruoff G. Comparative trials of terazosin with other antihypertensive agents. American Journal of Medicine. 1986; 80(5 Suppl 2):42-8

247. Russell GI, Pohl JE, Baldwin J, Bing RF, Heagerty AM, Thurston H et al. Treatment of essential hypertension: Changes in blood pressure, echocardiography and electrocardiography on three therapeutic regimes. European Journal of Clinical Pharmacology. 1985; 28(2):119-24

248. Safar M, Zanchetti A, Sever PS. Perindopril and indapamide as a combination in the treatment of mild to moderate hypertension: A double-blind randomized placebo-controlled european multicenter study. American Journal of Hypertension. 1994; 7(4):43A

249. Saha C, Eckert GJ, Ambrosius WT, Chun TY, Wagner MA, Zhao Q et al. Improvement in blood pressure with inhibition of the epithelial sodium channel in blacks with hypertension. Hypertension. 2005; 46(3):481-7

250. Saini R, Romanini M, Mos L. Tolerability and efficacy of fosinopril and hydrochlorothiazide compared with amiloride and hydrochlorothiazide in patients with mild to moderate hypertension. Clinical Drug Investigation. 1998; 15(2):91-9

251. Saku K, Zhang B, Okamoto T, Takeda Y, Liu K, Jimi S et al. Medium-term effects of betaxolol monotherapy and combination therapy with nitrendipine on lipoprotein and apolipoprotein metabolism in patients with mild to moderate essential hypertension. Journal of Human Hypertension. 1996; 10(4):263-268

252. Sano T, Kawamura T, Matsumae H, Sasaki H, Nakayama M, Hara T et al. Effects of long-term enalapril treatment on persistent microalbuminuria in well-controlled hypertensive and normotensive NIDDM patients. Diabetes Care. 1994; 17(5):420-424

253. 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

254. Sato A, Hayashi M, Saruta T. Relative long-term effects of spironolactone in conjunction with an angiotensin-converting enzyme inhibitor on left ventricular mass and diastolic function in patients with essential hypertension. Hypertension Research. 2002; 25(6):837-42

255. Sato N. Combination of Antihypertensive therapy in the elderly, Multicenter Investigation Multi-center randomized controlled study on efficacy of ARB/Diuretic mixture versus ARB/Ca channel blocker combination therapy to blood pressure or cognitive function in the elderly patients who have insufficient controlled hypertension in ARB monotherapy. UMIN CTR [https://centeruminacjp]. 2009;

256. Sato N, Saijo Y, Hasebe N, Camui Investigators. Combination of antihypertensive therapy in the elderly, multicenter investigation (CAMUI) trial. International Heart Journal. 2012; 53(4):244-8

257. Sato N, Saijo Y, Sasagawa Y, Morimoto H, Takeuchi T, Sano H et al. Combination of antihypertensive therapy in the elderly, multicenter investigation (CAMUI) trial: Results after 1 year. Journal of Hypertension. 2013; 31(6):1245-55

258. Seedat YK, Parag KB. Comparison of fosinopril and propranolol combined with chlorthalidone in the treatment of moderately to severely hypertensive black and Indian patients. Current Therapeutic Research, Clinical and Experimental. 1992; 51(6):830-838

259. Seedat YK, Randeree IG. Antihypertensive effect and tolerability of perindopril in indian hypertensive and type 2 diabetic patients: 1-year randomised, double-blind, parallel study vs atenolol. Clinical Drug Investigation. 1998; 16(3):229-40

260. 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

261. Spoelstra-de Man AM, van Ittersum FJ, Schram MT, Kamp O, van Dijk RA, Ijzerman RG et al. Aggressive antihypertensive strategies based on hydrochlorothiazide, candesartan or lisinopril decrease left ventricular mass and improve arterial compliance in patients with type II diabetes mellitus and hypertension. Journal of Human Hypertension. 2006; 20(8):599-611

262. Stamler R, Stamler J, Gosch FC, Berkson DM, Dyer A, Hershinow P. Initial antihypertensive drug therapy: Alpha blocker or diuretic: Interim report of a randomized, controlled trial. American Journal of Medicine. 1986; 80(2 Suppl 1):90-3

263. Swales JD, Bing RF, Heagerty A, Pohl JE, Russell GI, Thurston H. Treatment of refractory hypertension. The Lancet. 1982; 1(8277):894-6

264. Thomopoulos C, Katsimagklis G, Archontakis S, Skalis G, Makris T. Optimizing the management of uncontrolled hypertension: What do triple fixed- dose drug combinations add? Current Vascular Pharmacology. 2017; 16(1):61-65

265. Trimarco V, Izzo R, Migliore T, Rozza F, Marino M, Manzi MV et al. Should thiazide diuretics be given as first line antihypertensive therapy or in addition to other medications? High Blood Pressure & Cardiovascular Prevention. 2015; 22(1):55-9

266. 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

267. Wallin JD, Wilson D, Winer N, Maronde RF, Michelson EL, Langford H et al. Treatment of severe hypertension with labetalol compared with methyldopa and furosemide. Results of a long-term, double-blind, multicenter trial. American Journal of Medicine. 1983; 75(4 Pt 1):87-94

268. White WB, Murwin D, Chrysant SG, Koval SE, Davidai G, Guthrie R. Effects of the angiotensin II receptor blockers telmisartan versus valsartan in combination with hydrochlorothiazide: A large, confirmatory trial. Blood Pressure Monitoring. 2008; 13(1):21-7

1 Appendices

2 Appendix A: Review protocols

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

Field	Content
Review question	What is the most clinically and cost-effective step 4 antihypertensive drug treatment for hypertension in adults?
Type of review question	Intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	To establish which step 4 treatment is most clinically and cost effective in adults with hypertension that remains uncontrolled following step 3 treatment.
Eligibility criteria – population / disease / condition / issue / domain	Population: Adults (over 18 years) with primary hypertension are taking the maximally tolerated doses of at least 3 drugs (including a diuretic) and their blood pressure is still uncontrolled. Stratify by: • Presence or absence of type 2 diabetes • The drug class(es) previously received
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Step 4 antihypertensive pharmacological treatment received for a minimum of 1 year. • Alpha-blockers • Beta-blockers • Other or further diuretics such as amiloride and spironolactone • Aliskiren (direct renin inhibitors) • Clonidine, minoxidil, methyldopa, moxonidine (centrally acting antihypertensive)
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Compared against each other (class comparisons) • Compared to placebo (class compared to placebo)
Outcomes and prioritisation	All outcomes to be measured at a minimum of 12 months. Where multiple time points are reported within each study, the longest time point only will be extracted. **Critical** • All-cause mortality • Health-related quality of life • Stroke (ischaemic or haemorrhagic) • MI **Important** • Heart failure needing hospitalisation • Vascular procedures (including lower limb, coronary and carotid artery procedures) • Angina needing hospitalisation • Discontinuation or dose reduction due to side effects • Side effect 1: Acute kidney injury

	• Side effect 2: New onset diabetes • Side effect 3: Change in creatinine or eGFR • Side effect 4: Hypotension (dizziness) • [Combined cardiovascular disease outcomes in the absence of MI and stroke data] • [coronary heart disease outcome in the absence of MI data]
Eligibility criteria – study design	RCTs and SRs
Other inclusion exclusion criteria	Minimum follow up time: 1 year Exclusions: • Studies including participants with type 1 diabetes or chronic kidney disease (A3 or above [heavy proteinuria]). For the type 2 diabetes strata studies including participants with or chronic kidney disease (A2 or above [heavy proteinuria]) • Indirect populations with secondary causes of hypertension such as tumours or structural vascular defects (Conn's adenoma, phaeochromocytoma, renovascular hypertension) • Pregnant women • Children (aged under 18 years) • Crossover trials (unless washout is 4 weeks or more) • Reserpine (withdrawn from UK market) – exclude studies using this treatment.
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups to explore heterogeneity: • Age (under 55, 55-74 and 75 or older)* • Family origin (African and Caribbean, White, South Asian) *To note that we will also extract evidence in those >80 years old 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: PATHWAY-2 trial (2015) http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00257-3/abstract
Identify if an update	Yes, 2011
Author contacts	https://www.nice.org.uk/guidance/cg127
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for 1 database	For details, please see appendix B

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

1 **Table 4: Health economic review protocol**

Review question	**All questions – health economic evidence**
Objectives	To identify health economic studies relevant to any of the review questions.

Search 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).[222] **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.

1

Appendix B: Literature search strategies

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

For more detailed information, please see the Methodology Review. [Add cross reference]

B.1 Clinical search literature search strategy

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

Table 5: Database date parameters and filters used

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

Table 6: Medline (Ovid) search terms

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

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

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

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

Table 7: Embase (Ovid) search terms

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

36.	34 not 35
37.	limit 36 to English language
38.	exp *Angiotensin-Converting Enzyme Inhibitors/
39.	Angiotensin-converting enzyme inhibitor*.ti,ab.
40.	(ACE inhibitor* or ACEI).ti,ab.
41.	(Captopril or Enalapril or Fosinopril or Imidapril or Lisinopril or Moexipril or Perindopril or Quinapril or Ramipril or Trandolapril or Capoten or Ecopace or Noyada or Innovace or Tanatril or Zestril or Perdix or Coversil or Accupro or Tritace).ti,ab.
42.	*Captopril/ or *Enalapril/ or *Fosinopril/ or *Imidapril/ or *Lisinopril/ or *Moexipril/ or *Perindopril/ or *Quinapril/ or *Ramipril/ or *Trandolapril/ or *enalapril maleate/
43.	*angiotensin receptor antagonist/
44.	(Angiotensin II adj3 (antagonist* or blocker*)).ti,ab.
45.	ARB.ti,ab.
46.	(Azilsartan or Candesartan or Eprosartan or Irbesartan or Losartan or Olmesartan or Telmisartan or Valsartan or Edarbi or Amias or Teveten or Aprovel or Ifirmasta or Sabervel or Cozaar or Olmetec or Tolura or Micardis or Diovan).ti,ab.
47.	*Azilsartan/ or *Candesartan/ or *Eprosartan/ or *Irbesartan/ or *Losartan/ or *Valsartan/ or *Olmesartan Medoxomil/ or *Telmisartan/
48.	exp *Calcium Channel Blockers/
49.	Calcium channel blocker*.ti,ab.
50.	CCB.ti,ab.
51.	(Amlodipine or Clevidipine or Diltiazem or Felodipine or Isradipine or Lacidipine or Lercanidipine or Nicardipine or Nifedipine or Verapamil or Amlostin or Istin or Adizem or Angitil or Dilcardia or Dilzem or Slozem or Tildiem or Viazem or Zemtard or Kenzem or Cardioplen or Felendil or Neofel or Parmid or Plendil or Pinefeld or Vascalpha or Molap or Motens or Zanidip or Cardene or Adalat or Adipine or Coracten or Fortipine or Nifedipress or Tensipine or Valni or Securon or Verapress or Vertab or Univer or Zolvera or Cleviprex).ti,ab.
52.	*Amlodipine/ or *Diltiazem/ or *Felodipine/ or *Isradipine/ or *Nicardipine/ or *Nifedipine/ or *Verapamil/
53.	*Diuretics/
54.	*thiazide diuretic agent/
55.	((thiazide or thiazide-like or non-thiazide or conventional or potassium sparing) adj3 diuretic*).ti,ab.
56.	*mineralocorticoid antagonist/
57.	((mineralocorticoid or aldosterone) adj3 antagonist*).ti,ab.
58.	(Amiloride or Cyclopenthiazide or Spironolactone or Eplerenone or Bendroflumethiazide or Hydrochlorothiazide or Co-amilozide or Co-triamterzide or Co-zidocapt or Chlortalidone or Indapamide or Metolazone or Xipamide or Carace or Zestoretic or Coversyl or Accuretic or Cozaar or Sevikar or Olmetec or Actelsar or Tolucombi or Co-Diovan or Hygroton or Co-tenidone or Kalspare or Natrilix or Cardide or Indipam or Rawel or Tensaid or Alkapamid or Zaroxolyn or Diurexan or Aprinox or Neo-Naclex or CoAprovel or Lisoretic or Dyazide or Navispare or Lasilactone).ti,ab.
59.	*Amiloride/ or *Cyclopenthiazide/ or *Spironolactone/ or *Bendroflumethiazide/ or *Hydrochlorothiazide/ or *Chlortalidone/ or *Indapamide/ or *Metolazone/ or *Xipamide/
60.	*Adrenergic beta-Antagonists/
61.	(adrenergic beta antagonist* or beta blocker* or b blocker*).ti,ab.
62.	(Carvedilol or Labetalol or Atenolol or Nadolol or Oxprenolol or Pindolol or Propranolol or Timolol or Acebutolol or Bisoprolol or Celiprolol or Esmolol or Metoprolol or Nebivolol or Carvedilol or Tenormin or Tenif or Corgard or Slow-Trasicor or Visken or Viskladix or Bedranol or Beta-Prograne or Syprol or Betim or Sectral or Cardicor or Congescor or Celectol or Breviblock or Betaloc or Lopresor or Nebilet).ti,ab.

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

Table 8: Cochrane Library (Wiley) search terms

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

#6.	((systolic or diastolic or arterial) near/2 pressur*):ti,ab
#7.	(or #1-#6)
#8.	MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#9.	Angiotensin-converting enzyme inhibitor*:ti,ab
#10.	(ACE inhibitor* or ACEI):ti,ab
#11.	(Captopril or Enalapril or Fosinopril or Imidapril or Lisinopril or Moexipril or Perindopril or Quinapril or Ramipril or Trandolapril or Capoten or Ecopace or Noyada or Innovace or Tanatril or Zestril or Perdix or Coversil or Accupro or Tritace):ti,ab
#12.	MeSH descriptor: [Captopril] explode all trees
#13.	MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#14.	(AngiotensinII near/3 (antagonist* or blocker*)):ti,ab
#15.	ARB:ti,ab
#16.	(Azilsartan or Candesartan or Eprosartan or Irbesartan or Losartan or Olmesartan or Telmisartan or Valsartan or Edarbi or Amias or Teveten or Aprovel or Ifirmasta or Sabervel or Cozaar or Olmetec or Tolura or Micardis or Diovan):ti,ab
#17.	MeSH descriptor: [Losartan] explode all trees
#18.	MeSH descriptor: [Calcium Channel Blockers] explode all trees
#19.	Calcium channel blocker*:ti,ab
#20.	CCB:ti,ab
#21.	(Amlodipine or Clevidipine or Diltiazem or Felodipine or Isradipine or Lacidipine or Lercanidipine or Nicardipine or Nifedipine or Verapamil or Amlostin or Istin or Adizem or Angitil or Dilcardia or Dilzem or Slozem or Tildiem or Viazem or Zemtard or Kenzem or Cardioplen or Felendil or Neofel or Parmid or Plendil or Pinefeld or Vascalpha or Molap or Motens or Zanidip or Cardene or Adalat or Adipine or Coracten or Fortipine or Nifedipress or Tensipine or Valni or Securon or Verapress or Vertab or Univer or Zolvera or Cleviprex):ti,ab
#22.	MeSH descriptor: [Amlodipine] explode all trees
#23.	MeSH descriptor: [Diuretics] this term only
#24.	MeSH descriptor: [Sodium Chloride Symporter Inhibitors] this term only
#25.	((thiazide* or thiazide-like or non-thiazide or conventional or potassium sparing) near/3 diuretic*):ti,ab
#26.	MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#27.	((mineralocorticoid or aldosterone) near/3 antagonist*):ti,ab
#28.	(Amiloride or Cyclopenthiazide or Spironolactone or Eplenerone or Bendroflumethiazide or Hydrochlorothiazide or Co-amilozide or Co-triamterzide or Co-zidocapt or Chlortalidone or Indapamide or Metolazone or Xipamide or Carace or Zestoretic or Coversyl or Accuretic or Cozaar or Sevikar or Olmetec or Actelsar or Tolucombi or Co-Diovan or Hygroton or Co-tenidone or Kalspare or Natrilix or Cardide or Indipam or Rawel or Tensaid or Alkapamid or Zaroxolyn or Diurexan or Aprinox or Neo-Naclex or CoAprovel or Lisoretic or Dyazide or Navispare or Lasilactone):ti,ab
#29.	MeSH descriptor: [Amiloride] explode all trees
#30.	MeSH descriptor: [Adrenergic beta-Antagonists] this term only
#31.	(adrenergic beta antagonist* or beta blocker* or b blocker*):ti,ab
#32.	(Carvedilol or Labetalol or Atenolol or Nadolol or Oxprenolol or Pindolol or Propranolol or Timolol or Acebutolol or Bisoprolol or Celiprolol or Esmolol or Metoprolol or Nebivolol or Carvedilol or Tenormin or Tenif or Corgard or Slow-Trasicor or Visken or Viskladix or Bedranol or Beta-Prograne or Syprol or Betim or Sectral or Cardicor or Congescor or Celectol or Breviblock or Betaloc or Lopresor or Nebilet):ti,ab
#33.	MeSH descriptor: [Labetalol] explode all trees
#34.	MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#35.	(adrenergic alpha antagonist* or alpha adrenoreceptor blocker* or alpha blocker*):ti,ab

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

B.2 Health Economics literature search strategy

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

Table 9: Database date parameters and filters used

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

Table 10: Medline (Ovid) search terms

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

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

Table 11: Embase (Ovid) search terms

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

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

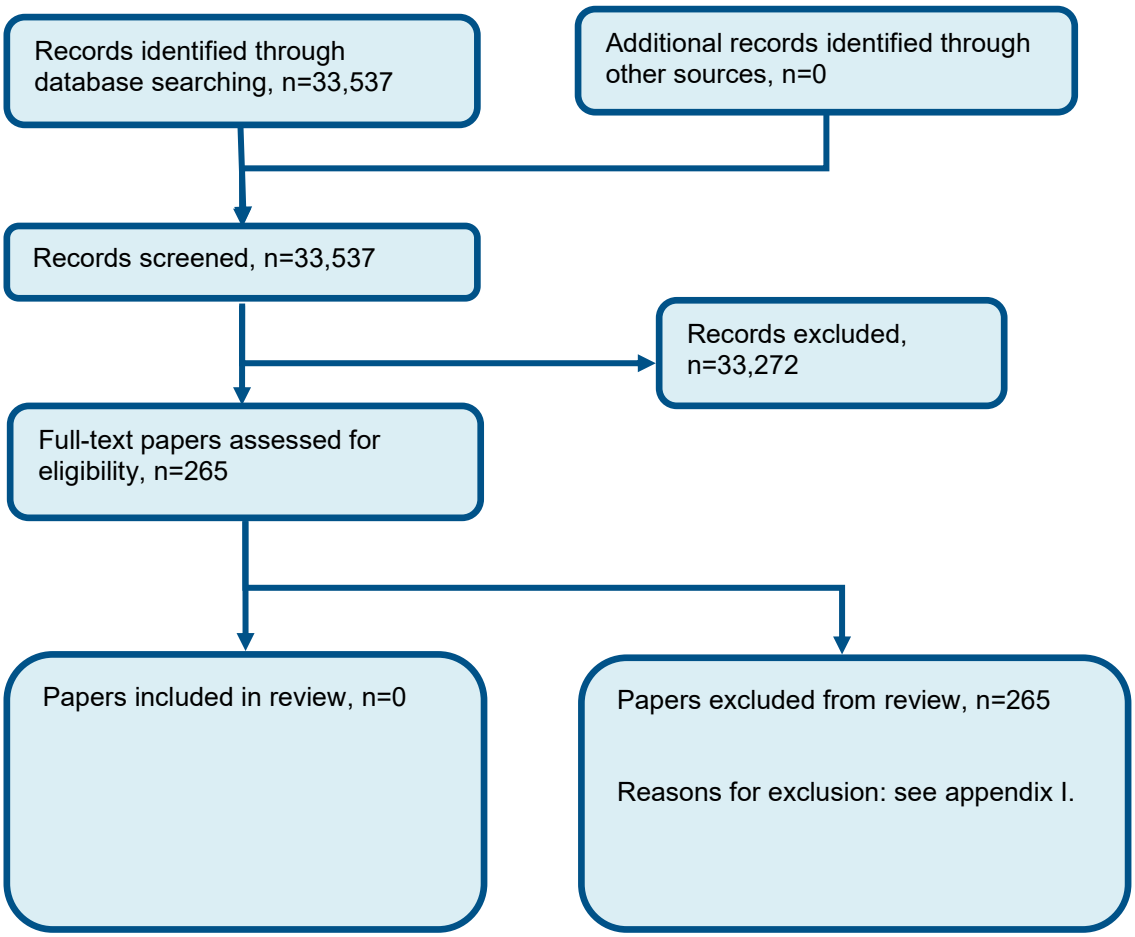
1 **Table 12: NHS EED and HTA (CRD) search terms**

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

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of step 4 treatment



Appendix D: Clinical evidence tables

None.

Appendix E: Forest plots

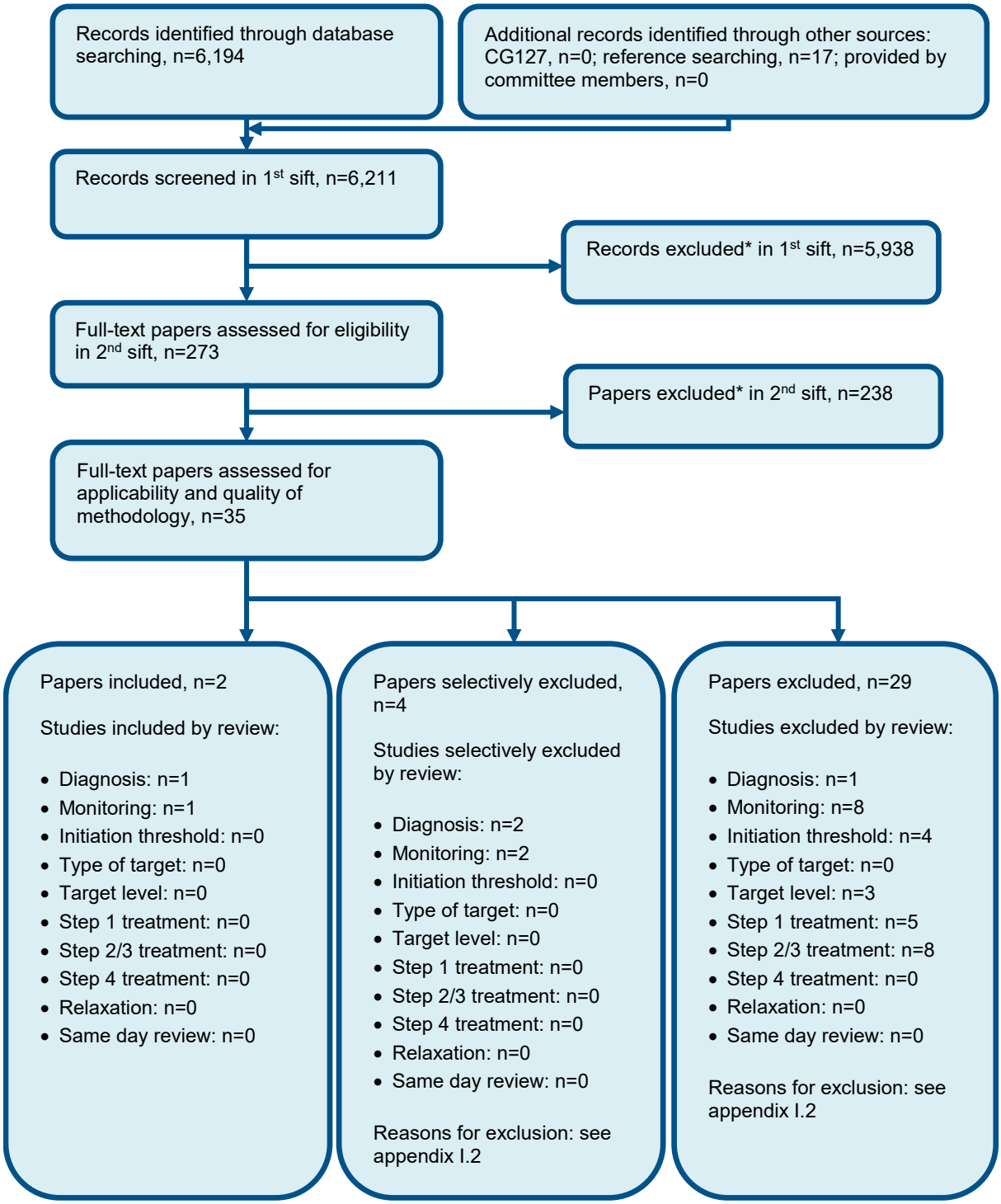
None.

Appendix F: GRADE tables

None.

Appendix G: Health economic evidence selection

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



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 13: Studies excluded from the clinical review

Study	Exclusion reason
Abarquez 1993[1]	Less than minimum duration
Abascal 1998[2]	Incorrect study design
Abe 2007[3]	Not review population
Abe 2009[4]	Less than minimum duration
Abetel 1984[5]	Not in English
Adir 1987[6]	Inappropriate comparison
Adolphe 1993[7]	Less than minimum duration
Agabiti-Rosei 1992[8]	Less than minimum duration. Inappropriate comparison
Agabiti-Rosei 2005[9]	No relevant outcomes
Agarwal 2013[10]	Less than minimum duration
Ahola 2012[11]	Incorrect study design
Ahrens 2010[12]	Incorrect study design
Akanabe 1985[13]	Less than minimum duration
Akioyamen 2016[14]	Systematic review, references checked
Akram 2007[15]	Less than minimum duration
Alderman 1989[16]	Inappropriate comparison
Alici 2009[17]	Less than minimum duration. Inappropriate comparison
ALLHAT officers 2002[19]	Inappropriate comparison
ALLHAT Collaborative Research Group 2000[18]	Inappropriate comparison
Alviar 2013[20]	Inappropriate comparison
Amar 1999[21]	Article not in English
Ames 1992[22]	Less than minimum duration
Amir 1994[23]	No relevant outcomes
Andersen 1986[24]	Inappropriate comparison
Andersen 2003[25]	Inappropriate comparison
Andersen 2005[26]	Inappropriate comparison
Ando 2014[27]	Incorrect population
Andreadis 2005[28]	Less than minimum duration
Andren 1983[29]	Less than minimum duration
Andreucci 1983[30]	Incorrect study design. Incorrect interventions
Angeli 2004[31]	Not review population
Anonymous 1999[34]	Inappropriate comparison
Anonymous 1993[32]	Inappropriate comparison

Study	Exclusion reason
Anonymous 1996[33]	Less than minimum duration
Applegate 1991[35]	No relevant outcomes. Incorrect study design
Arima 2014[36]	Not review population
Arriaga-gracia 1993[37]	Less than minimum duration
Bakris 2007[39]	Not review population
Bakris 2013[38]	Not review population
Balamuthusamy 2009[40]	Systematic review - references checked
Baldwin 1987[41]	Inappropriate comparison
Bang 2017[42]	Incorrect interventions
Bangalore 2008[43]	Systematic review, references checked. Inappropriate comparison
Batterink 2010[44]	Incorrect study design
Benjamin 1988[45]	Incorrect study design
Berger 1992[46]	Less than minimum duration
Black 2003[47]	Inappropriate comparison
Blumenthal 1990[48]	Less than minimum duration
Boissel 1995[50]	Inappropriate comparison
Borgmastars 1987[51]	No relevant outcomes
Bremner 1997[52]	Incorrect interventions
Brenner 2001[53]	Not review population
Brown 2001[54]	Less than minimum duration
Byrd 2011[55]	Not review population
Byyny 1996[56]	Less than minimum duration. Inappropriate comparison
Castano 2004[57]	Inappropriate comparison
Celis 1996[58]	Inappropriate comparison
Cesaris 1986[59]	Article not in English
Chatellier 1987[60]	Less than minimum duration
Chi 2016[61]	Systematic review, references checked. Less than minimum duration
Chrysant 1997[62]	Incorrect study design. Inappropriate comparison
Circelli 2012[63]	Less than minimum duration
Coope 1986[64]	Inappropriate comparison
Correa 2018[65]	Incorrect study design
Cowley 1987[66]	Less than minimum duration
Cranston 1962[67]	Incorrect study design
Curb 1996[68]	Inappropriate comparison
Daae 1998[69]	Incorrect interventions
Dahlof 2002[71]	Less than minimum duration
Dahlöf 2005[70]	Incorrect study design
Daien 2012[72]	Systematic review, references checked
De rosa 2002[73]	Inappropriate comparison
Degl'innocenti 2004[74]	Inappropriate comparison
Destro 2010[75]	Incorrect study design
Devereux 2007[76]	Inappropriate comparison
Dews 2001[77]	Incorrect study design
Diao 2012[78]	Inappropriate comparison
Du 2018[79]	Incorrect study design

Study	Exclusion reason
Ekbom 1992[80]	Incorrect study design
Ekbom 2004[81]	Incorrect interventions. Incorrect study design
Estacio 1998[82]	Not review population
Family Physicians Hypertension Study Group 1984[83]	Less than minimum duration
Fariello 1990[84]	Less than minimum duration
Farsang 2003[85]	Incorrect study design
Fasano 1989[86]	Incorrect study design. Incorrect interventions
Faust 1993[88]	Article not in English
Faust 1993[87]	Article not in English
Ferdinand 2001[89]	Incorrect study design
Fernandes 2016[90]	Less than minimum duration
Fernandez 2001[91]	Less than minimum duration
Ferrara 1984[92]	No relevant outcomes
Finnerty 1979[93]	Incorrect interventions
Fogari 1991[99]	No relevant outcomes
Fogari 1996[97]	Incorrect study design. Incorrect interventions
Fogari 1999[96]	Inappropriate comparison
Fogari 2006[95]	Less than minimum duration
Fogari 2012[98]	Less than minimum duration
Fogari 2014[94]	Less than minimum duration
Forette 2002[100]	Inappropriate comparison
Forrest 1983[101]	Less than minimum duration
Fossum 2004[102]	No relevant outcomes. Inappropriate comparison
Franco 1992[103]	Article not in English
Franse 2000[104]	Incorrect interventions. Inappropriate comparison
Frewin 1991[105]	Incorrect study design. Incorrect interventions
Frick 1986[107]	Inappropriate comparison
Frick 1987[106]	No relevant outcomes. Inappropriate comparison
Gao 2011[108]	Systematic review, references checked
Gasowski 1999[109]	Incorrect study design. Incorrect interventions
Gazdick 1994[110]	Incorrect study design
George 1990[111]	Less than minimum duration
Ghiadoni 2017[112]	Less than minimum duration
Giles 1992[113]	Inappropriate comparison. No relevant outcomes
Gillespie 2005[114]	Systematic review, references checked
Girerd 2010[115]	Incorrect study design
Gitt 2013[116]	Incorrect study design
Glorioso 2007[117]	Incorrect study design. Less than minimum duration
Goicolea 2002[118]	Article not in English
Gosse 2002[119]	Inappropriate comparison
Grimm 1996[120]	Incorrect study design
Guo 2005[122]	Article not in English
Guo 2011[121]	Article not in English
Gupta 2018[123]	Incorrect interventions

Study	Exclusion reason
Gyntelberg 1977[124]	Article not in English
Hall 1998[125]	Inappropriate comparison
Hamada 2010[127]	No relevant outcomes
Hamada 2014[126]	No relevant outcomes
Hamed 2014[128]	Less than minimum duration. Incorrect study design
Hanon 2015[129]	Inappropriate comparison
Hanon 2017[130]	Inappropriate comparison
Hansson 1999[133]	Inappropriate comparison
Hansson 1999[132]	Inappropriate comparison
Hansson 1999[134]	Inappropriate comparison
Hansson 2000[131]	Inappropriate comparison
Hasegawa 2011[135]	Inappropriate comparison
Helgeland 1980[136]	Inappropriate comparison
Helgeland 1983[137]	Less than minimum duration
Himmelmann 1995[138]	Inappropriate comparison
Hosie 1983[139]	Inappropriate comparison
Hradec 2013[140]	Inappropriate comparison
Hughes 2008[141]	Incorrect interventions. No relevant outcomes
Hulley 1985[142]	Inappropriate comparison
Ibsen 1990[144]	Incorrect interventions
Ibsen 2003[143]	Article not in English
Ichihara 2006[145]	Inappropriate comparison
J. Elan investigators 2006[146]	Inappropriate comparison
Jamerson 2008[147]	Incorrect study design
Johnson 2009[148]	No relevant outcomes
Johnston 1991[149]	Inappropriate comparison
Julius 2004[150]	Not review population
Kaku 2011[151]	Inappropriate comparison
Katayama 2008[152]	Inappropriate comparison
Kawalec 2018[153]	Incorrect study design
Kereiakes 2012[154]	Less than minimum duration
Kerfoot 2014[155]	Incorrect study design. Incorrect interventions. Inappropriate comparison
Kim 2012[157]	Incorrect interventions
Kim 2013[156]	No relevant outcomes
Kjeldsen 2002[158]	Inappropriate comparison
Kjeldsen 2006[161]	Incorrect interventions
Kjeldsen 2008[160]	Incorrect population
Kjeldsen 2016[159]	Incorrect interventions
Ko 2001[162]	Not review population
Kohlmann 2009[163]	Inappropriate comparison
Kostis 2005[164]	Inappropriate comparison
Kuwajima 2001[165]	Not review population
Lacourciere 2000[166]	Incorrect study design
Laufer 1998[167]	Incorrect interventions. No relevant outcomes
Laurent 2014[168]	Inappropriate comparison

Study	Exclusion reason
Lavenius 1982[169]	Less than minimum duration
Leonetti 2002[170]	Inappropriate comparison
Levine 2001[171]	Incorrect study design
Licata 1994[172]	Less than minimum duration
Lim 2000[173]	Less than minimum duration
Lin 1991[174]	Incorrect interventions
Lin 1993[175]	Less than minimum duration
Lin 1995[176]	Incorrect interventions
Lind 1994[177]	No relevant outcomes
Lindholm 1996[179]	Incorrect interventions
Lindholm 2000[180]	Incorrect interventions
Lindholm 2001[178]	Not review population
Lindholm 2002[182]	Inappropriate comparison
Lindholm 2002[181]	Incorrect interventions. Incorrect study design
Lindner 1984[183]	Article not in English
Lindroos 1984[184]	Less than minimum duration
Littlejohn 2009[185]	Less than minimum duration
Liu 1999[187]	Inappropriate comparison
Liu 2000[186]	Not in English
Lombardo 1997[188]	Inappropriate comparison
López 1997[189]	Article not in English
Lu 2017[190]	Systematic review, references checked
Ludwig 2002[191]	Inappropriate comparison
Luno 2017[192]	Not review population
Lynch 2008[193]	Inappropriate comparison
Lynch 2012[194]	Inappropriate comparison
Maclean 1986[196]	Not review population
Maclean 1986[197]	Less than minimum duration
Malacco 2003[198]	Incorrect interventions. Incorrect study design
Malminiemi 2000[199]	Inappropriate comparison. No relevant outcomes
Mancia 2007[200]	Incorrect study design. Incorrect interventions
Mann 1998[201]	Incorrect study design
Marfatia 2012[202]	Less than minimum duration
Marre 2004[203]	Incorrect interventions
Martinez-martin 2011[204]	Inappropriate comparison
Mason 2005[205]	Systematic review - references checked
Matsuno 2011[206]	Not review population. No relevant outcomes
Matsushita 2010[207]	Incorrect study design. Inappropriate comparison
Matsuzaki 2011[208]	Inappropriate comparison
Mazza 2016[209]	No relevant outcomes
M'Buyamba-Kabangu 1987[195]	Less than minimum duration
Mcareavey 1983[210]	No relevant outcomes
Mende 2017[211]	Less than minimum duration
Metelitsa 1991[212]	Incorrect interventions
Metelitsa 1991[213]	Article not in English

Study	Exclusion reason
Middeke 1990[214]	No relevant outcomes
Middeke 1997[215]	Inappropriate comparison
Misson 1984[216]	No relevant outcomes
Mizuno 2017[217]	Less than minimum duration
Morgan 1989[218]	Less than minimum duration
Mroczek 1984[219]	Inappropriate comparison
Muller 1986[220]	no relevant outcomes
Nakae 2006[221]	Article not in English
NCT[223]	Citation only
Neutel 1999[225]	Incorrect study design. Incorrect interventions
Neutel 2017[224]	Not review population
Oberman 1983[226]	Less than minimum duration
Ocón 1985[227]	Not in English
Ogawa 2012[228]	Incorrect interventions
Ogihara 2000[229]	Inappropriate comparison
Ogihara 2012[230]	Inappropriate comparison
Ogihara 2014[231]	Inappropriate comparison
Ogihara 2015[232]	Inappropriate comparison
Ohnishi 2001[233]	No relevant outcomes
Okin 2012[234]	Incorrect study design. Inappropriate comparison
Oshikawa 2014[235]	Not review population
Ostergren 2008[236]	Not review population
Park 2017[237]	No relevant outcomes
Patay 2010[238]	Incorrect study design
Persson 1986[239]	Incorrect study design
Philip 1987[240]	Less than minimum duration
Pierini 2013[241]	Less than minimum duration. Inappropriate comparison
Piller 2006[242]	Inappropriate comparison. No relevant outcomes
Remonti 2016[243]	NMA, references checked
Ritter 2013[244]	Incorrect study design
Roush 2018[245]	Inappropriate comparison
Ruoff 1986[246]	Inappropriate comparison
Russell 1985[247]	Inappropriate comparison
Safar 1994[248]	Incorrect study design
Saha 2005[249]	Less than minimum duration. Not review population
Saini 1998[250]	Inappropriate comparison
Saku 1996[251]	Inappropriate comparison
Sano 1994[252]	Inappropriate comparison
Saruta 2015[253]	Inappropriate comparison
Sato 2002[254]	Inappropriate comparison. No relevant outcomes
Sato 2009[255]	Citation only
Sato 2012[256]	Incorrect study design
Sato 2013[257]	Not review population
Seedat 1992[258]	Less than minimum duration
Seedat 1998[259]	Incorrect interventions

Study	Exclusion reason
Soucek 2007[260]	Article not in English
Spoelstra-de Man 2006[261]	Inappropriate comparison
Stamler 1986[262]	Incorrect interventions
Swales 1982[263]	Incorrect study design
Thomopoulos 2017[264]	Incorrect study design
Trimarco 2015[265]	Incorrect study design
Umemoto 2017[266]	Inappropriate comparison
Wallin 1983[267]	Inappropriate comparison
White 2008[268]	Inappropriate comparison

I.21 Excluded health economic studies

2 No health economic studies were found.