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First-line combination therapy versus first-line monotherapy for primary hypertension

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ABSTRACT

Background

Starting with one drug and starting with a combination of two drugs are strategies suggested in clinical guidelines as initial treatment of hypertension. The recommendations are not based on evidence about clinically relevant outcomes. Some antihypertensive combinations have been shown to be harmful. The actual harm-to-benefit balance of each strategy is unknown.

Objectives

To determine if there are differences in clinical outcomes between monotherapy and combination therapy as initial treatment for primary hypertension.

Search methods

We searched the Hypertension Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL, 2016, Issue 2), Ovid MEDLINE, Ovid Embase, LILACS, ClinicalTrials.gov, Current Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) up to February 2016. We searched in clinical studies repositories of pharmaceutical companies, reviews of combination drugs in Food and Drug Administration and European Medicines Agency, and lists of references in reviews and clinical practice guidelines.

Selection criteria

Randomized, double-blind trials with at least 12 months' follow-up in adults with primary hypertension (systolic blood pressure/diastolic blood pressure 140/90 mmHg or higher, or 130/80 mmHg or higher if participants had diabetes), which compared combination of two first-line antihypertensive drug with monotherapy as initial treatment. Trials had to include at least 50 participants per group and report mortality, cardiovascular mortality, cardiovascular events or serious adverse events.

Data collection and analysis

Two authors independently selected trials for inclusion, evaluated the risk of bias and entered the data. Primary outcomes were mortality, serious adverse events, cardiovascular events and cardiovascular mortality. Secondary outcomes were withdrawals due to drug-related adverse effects, reaching blood pressure control (as defined in each trial) and blood pressure change from baseline. Analyses were based on the intention-to-treat principle. We summarized data on dichotomous outcomes as risk ratios with 95% confidence intervals.

Main results

We found three studies in which a subgroup of participants met our inclusion criteria. None of the studies focused solely on people initiating antihypertensive treatment so we asked investigators for data for this subgroup (monotherapy: 335 participants; combination therapy: 233 participants). They included outpatients, and mostly European and white people. Two trials included only people with type 2 diabetes, whereas the other trial excluded people treated with diabetes, hypocholesterolaemia or cardiovascular drugs. The follow-up was 12 months in two trials and 36 months in one trial. Certainty of evidence was very low due to the serious imprecision, and for using a subgroup not defined in advance. Confidence intervals were extremely wide for all important outcomes and included both appreciable harm and benefit.

Authors' conclusions

The numbers of included participants and, hence the number of events, were too small to draw any conclusion about the relative efficacy of monotherapy versus combination therapy as initial treatment for primary hypertension. There is a need for large clinical trials that address the question and report clinically relevant endpoints.

PLAIN LANGUAGE SUMMARY

Starting the treatment of hypertension with one medicine versus starting with a combination of two medicines

Background

Hypertension (high blood pressure) is a long-term condition that increases the risk of having health problems such as heart attack, stroke or kidney disease. There are several types of medicines that are used to treat hypertension. Over time, frequently a person needs more than one type of medicine to control their blood pressure. When a doctor prescribes medicines to reduce the blood pressure for the first time, he or she has two options, using only one medicine (called monotherapy) or using two medicines (called combination therapy). The combination therapy can be in the same tablet or in different tablets. The potential advantage of using combination therapy is that blood pressure could fall faster, but we do not know if this is better or worse for avoiding health problems.

Study characteristics

We looked for clinical studies that compared starting the treatment of hypertension in adults with monotherapy versus starting with combination therapy. Studies had to report results in terms of deaths, events due to diseases of the heart or the vessels (heart attack, stroke or heart failure); deaths due to diseases of the heart or the vessels, or any health-related serious side effects. We only selected studies with 50 or more people per group and that lasted at least 12 months. The evidence is current to February 2016.

Key results and certainty of the evidence

We found three studies that fit our criteria with 233 people were treated with combination therapy and 335 treated with monotherapy. However, we did not find enough data to answer our question. It is necessary to perform more and larger studies that compare monotherapy with combination therapy as initial treatment of hypertension.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Combination therapy versus monotherapy for primary hypertension						
Patient or population: people with primary hypertension Settings: outpatients mostly in Europe Intervention: combination therapy Comparison: monotherapy						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Monotherapy	Combination therapy				
Total mortality Follow-up: 12 to 36 months	3 per 1000	4 per 1000 (0 to 65)	RR 1.35 (0.08 to 21.72)	568 (3 studies)	⊕○○○ Very low ^{1,2,3}	-
Cardiovascular mortality Follow-up: 12 to 36 months	See footnote ⁴	See footnote ⁴	Not estimable	568 (3 studies)	⊕○○○ Very low ^{1,2,4}	-
Cardiovascular events Follow-up: 12 to 36 months	9 per 1000	9 per 1000 (2 to 39)	RR 0.98 (0.22 to 4.41)	568 (3 studies)	⊕○○○ Very low ^{1,2,3}	-
Serious adverse events Follow-up: 12 to 36 months	176 per 1000	136 per 1000 (55 to 338)	RR 0.77 (0.31 to 1.92)	568 (3 studies)	⊕○○○ Very low ^{1,2,5}	-
Withdrawals due to adverse effects Follow-up: 12 to 36 months	128 per 1000	109 per 1000 (68 to 173)	RR 0.85 (0.53 to 1.35)	568 (3 studies)	⊕○○○ Very low ^{1,2,5}	-

*The basis for the **assumed** is the mean monotherapy group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the combination group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: We are very uncertain about the estimate.

¹ All data come from subgroups of participants not predefined in the original studies. Outcomes of our review were not the primary outcome in any included trial.

² Two trials included only people with type 2 diabetes, whereas the other excluded participants treated with drugs for diabetes, hypocholesterolaemia or cardiovascular disease. So none of them was fully representative of the general hypertensive population.

³ There were very few events and confidence intervals were extremely wide.

⁴ There were no events for this outcome.

⁵ Confidence intervals were wide and included both appreciable harm and appreciable benefit.

BACKGROUND

Description of the condition

Elevated blood pressure (hypertension), arbitrarily defined as systolic blood pressure of 140 mmHg or greater or diastolic blood pressure of 90 mmHg or greater, is a risk factor for stroke, myocardial infarction, renal failure, congestive heart failure and peripheral artery disease. There is a graded relation between blood pressure and the risk of cardiovascular disease (NICE 2011; ESH-ESC 2013). In over 90% of cases, it is primary hypertension as there is no secondary cause that can be determined (NICE 2011). The main goal of attempts to lower the blood pressure is to prevent cardiovascular morbidity and death, without adversely affecting quality of life. Blood pressure reduction per se is one of the main approaches to cardiovascular risk reduction (Law 2009; Gradman 2010).

Description of the intervention

Stepped therapy constitutes the usual initial approach in most people with hypertension, increasing the dose of the first drug or adding other drugs if blood pressure targets are not reached. First-line low-dose thiazides have the best evidence for reducing mortality and morbidity (Wright 2009). Guidelines that are often based on lower levels of evidence have suggested other classes for first-line therapy in addition to thiazides including: beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) (ESH-ESC 2013; CHEP 2015). They also suggest that determination of the need for drug therapy is based on a combined assessment of the blood pressure level and the risk of cardiovascular disease. Available data suggest that at least 75% of people with hypertension will require combination therapy to achieve blood pressure targets (Gradman 2010).

Using a combination of two antihypertensive drugs as initial therapy has the aim of providing a faster reduction of blood pressure. The preferred drug combinations are ACEI or ARB with a thiazide-type diuretic or CCB, and thiazide-type diuretic with CCB (ESH-ESC 2013; CHEP 2015). In one large trial with high-risk participants, ACEI/CCB combination resulted in fewer cardiovascular events than ACEI/hydrochlorothiazide (ACCOMPLISH 2008). Guidelines have suggested that chlorthalidone and indapamide have better evidence of benefit on clinical outcomes than bendroflumethiazide or hydrochlorothiazide (NICE 2011), however, that is not supported by evidence from randomized controlled trials (Wright 2009). Furthermore, most single-pill combinations include hydrochlorothiazide. The combination of ACEI and ARB is not recommended (ESH-ESC 2013; JNC 8 2014; CHEP 2015).

How the intervention might work

Treatment of hypertension reduces the risk of stroke, coronary artery disease and congestive heart failure, as well as overall cardiovascular morbidity and mortality from cardiovascular causes. Stepped antihypertensive therapy starting with low-dose thiazides reduces mortality and cardiovascular morbidity (Wright 2009), and in head-to-head trials, first-line thiazides are better at reducing total cardiovascular events than first-line beta-blockers (Wiysonge 2012), first-line drugs inhibiting the renin-angiotensin system (Xue 2015), and first-line CCBs (Chen 2010).

The clinical practice guideline from the National Institute for Health and Care excellence (NICE) recommends monotherapy as the initial approach (NICE 2011). People with diabetes are excluded from its scope. For people with type 2 diabetes, the NICE guideline also recommends monotherapy as first-line therapy (NICE 2008). Exceptions to this are people of African-Caribbean descent for whom it recommends an ACEI plus either a diuretic or a CCB. Guidelines from the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) state that initial treatment can make use of monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed (ESH-ESC 2013). Monotherapy could be the initial treatment for a mild blood pressure elevation with low or moderate cardiovascular risk. A combination of two drugs at low doses should be preferred as first-step treatment when systolic blood pressure is greater than 160 mmHg and/or diastolic blood pressure is greater than 100 mmHg, or total cardiovascular risk is high or very high. Some current guidelines suggest that two drugs be used for initial therapy if there is an elevation in blood pressure of 20 mmHg systolic or 10 mmHg diastolic above goal (ESH-ESC 2013; JNC 8 2014; CHEP 2015). For people with past stroke CHEP 2015 recommends initiating treatment with an ACEI/thiazide-type diuretic combination.

Some advantages of initial combination treatment have been proposed: two drugs can be given at low doses so reducing the risk of adverse effects. Combination therapy provides more rapid control of blood pressure than monotherapy. Adherence may be improved, and subsequently blood pressure control, when the person perceives the treatment is effective and well tolerated (ESH-ESC 2013).

The disadvantages of initiating treatment with drug combinations are that one of the drugs may be ineffective or unnecessary, thus complicating the treatment (ESH-ESC 2013), and that a substantial decrease in blood pressure can be poorly tolerated in some people (e.g. older people) (CHEP 2015).

Why it is important to do this review

It is unknown whether the benefits of combination therapy as compared to monotherapy for initial treatment of hypertension exceed the harms.

One meta-analysis showed that combining drugs from different classes is more effective in lowering blood pressure than increasing the dose of one drug, but it did not provide information about morbidity or adverse effects. The authors recommended considering combination as routine initial therapy (Wald 2009). Although the value of routinely starting treatment with combination therapy, particularly with low doses, has been proposed, this has not been widely accepted. It is not known if beginning with two drugs results in improved cardiovascular outcomes or mortality compared with starting one drug (JNC 8 2014). The recommendation of using combinations when blood pressure is 20/10 mmHg above goal is not based on direct evidence from randomized controlled trials (JNC 8 2014; CHEP 2015).

Combinations of drugs acting on the renin-angiotensin system were proposed; however, these have been shown to be harmful (ONTARGET 2008; ALTITUDE 2012; Makani 2013).

One observational study, which included 1127 people older than 80 years living in nursing homes, found a significant increase in two-year mortality (adjusted hazard ratio 1.78, 95% CI 1.34 to 2.37) associated with combinations of antihypertensive drugs in people with systolic blood pressure less than 130 mmHg (PARTAGE 2015).

There is an increasing awareness about the problem of polypharmacy. The single most important predictor of risk of adverse drug events in older people is the number of prescribed drugs, so using the minimum number of drugs is a measure to improve patient safety (Scott 2015).

OBJECTIVES

To determine if there are differences in clinical outcomes between initial therapy with monotherapy or combination therapy for primary hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized double-blind controlled trials of at least one year of duration and containing 50 or more participants per group. The trials must have reported data for at least one of the primary outcomes. We excluded trials using non-randomized allocation methods such as alternate allocation, week of presentation or retrospective controls.

Types of participants

We included participants aged at least 18 years who's blood pressure was measured using a validated technique.

Trials were limited to those where participants had a baseline resting systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg (130/80 mmHg or greater in people with diabetes). We included the study if 70% or more of the participants met the above definitions, or individual participant data were available, or data of relevant participants were provided separately allowing specific inclusion of this population. We excluded people with confirmed secondary hypertension. Trials were not limited by any other factor or baseline risk.

Types of interventions

Intervention: combination therapy (i.e. participants treated initially with two antihypertensive drugs).

Control: monotherapy (i.e. participants treated initially with one antihypertensive drug).

Treatment should have been clearly defined as a specific class of first-line antihypertensive therapy in one of the following classes: thiazide type diuretics, loop diuretics, beta-blockers, CCBs, ACEIs, ARBs, renin inhibitors or α -adrenergic blockers (ATC codes: C03, C07, C08, C09, C02CA, C02LE). We excluded drug classes that have not been confirmed to lower blood pressure as monotherapy (e.g. potassium-sparing diuretics triamterene and amiloride (Heran 2012)). If a trial used combination of diuretics with those agents, we planned to analyze it separately.

Initial therapy is defined as the first-time participants were treated with antihypertensive drugs.

Both groups under study should have had the same blood pressure target, if any defined.

Drugs and doses were acceptable when the doses were within the manufacturer recommended dose range for hypertension.

Types of outcome measures

Primary outcomes

- Total mortality.
- Total serious adverse events, defined according to the International Conference on Harmonisation Guidelines (ICH 1995), as any event that leads to death, that was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, or was a congenital anomaly/birth defect.
- Total cardiovascular events including total myocardial infarction, stroke, sudden death, hospitalization or death from congestive heart failure, and other significant vascular events such as ruptured aneurysms (did not include angina, transient ischaemic attacks, surgical or other procedures, or accelerated hypertension).

- Cardiovascular mortality.

If a study used a different definition for serious adverse events, the review authors decided on inclusion of data by consensus; if needed we consulted another review author.

All primary outcomes were important outcomes to be included in the 'Summary of findings' table.

Secondary outcomes

- Withdrawals due to drug-related adverse effects (important outcome).
- Reaching blood pressure control, as defined in each trial.
- Systolic and diastolic blood pressure change from baseline.

Search methods for identification of studies

We searched the Cochrane Library, Ovid MEDLINE and Ovid Embase for related reviews.

We searched the following databases for primary studies:

- Hypertension Group Specialised Register (1946 to February 2016) ([Appendix 1](#));
- the Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 2) ([Appendix 2](#));
- Ovid MEDLINE (2005 to February 2016) ([Appendix 3](#))*;
- Ovid Embase (2010 to February 2016) ([Appendix 4](#))*;
- LILACS (1982 to March 2016);
- trial registries (ClinicalTrials.gov, Current Controlled Trials and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)).

*MEDLINE and Embase results were limited to recent years as the US Cochrane Center searched MEDLINE prior to 2005, the UK Cochrane Centre searched Embase prior to 2010, and the Cochrane Hypertension Specialised Register includes randomized trials from weekly searches of MEDLINE and Embase.

The Specialised Register also includes randomized trials from searches of Agricola, AMED, BIOSIS, CAB Abstracts, CINAHL, Food Science & Technology Abstracts, International Pharmaceutical Abstracts, LILACS, ProQuest Dissertations & Theses, PsycINFO, Scirus, Scopus and Web of Science.

Electronic searches

We searched electronic databases using a strategy combining the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision) with selected MeSH terms and free-text terms relating to hypertension. We translated the MEDLINE search strategy ([Appendix 3](#)) into the Cochrane Hypertension Specialised Register ([Appendix 1](#)), CENTRAL ([Appendix 2](#)) and Embase ([Appendix 4](#)) using the appropriate controlled vocabulary as applicable.

Searching other resources

We contacted relevant pharmaceutical companies and searched in their clinical studies repositories ([Appendix 6](#)).

We searched on web pages of the US Food and Drug Administration (FDA) (www.fda.gov) and the European Medicines Agency (EMA) (www.ema.europa.eu) for published and unpublished clinical trial data relevant to the review. We only considered FDA and EMA reports of authorized combination drugs. We looked in the Scientific Discussion of the European Public Assessment Reports and in the FDA's Medical Reviews.

We searched in TRIP Database (www.tripdatabase.com) for systematic reviews, guidelines and health technology assessment reports.

We searched for additional trials by checking the reference lists of included trials and reviews, guidelines and health technology assessment reports ([Appendix 7](#)).

Dealing with duplicate publications

When we identified more than one publication of an original trial, we assessed those articles together to maximize data collection.

References from published studies

We examined the references of the included and excluded studies for further potentially eligible randomized controlled trials.

Language

We applied no language restrictions.

Correspondence

We contacted with trial investigators to ask for data of subgroup participants without previous antihypertensive treatment, for missing data or to clarify study details.

Data collection and analysis

Two review authors independently reviewed the search results. One review author (LCS) checked all results. We used [EROS](#) software for screening and classifying references.

Selection of studies

In an initial phase, we excluded a record if the title or the abstract showed that was not a randomized double-blind controlled trial, participants were not naive to antihypertensive treatment, there were fewer than 50 participants per group, follow-up was less than 12 months, trial did not compare monotherapy with a combination therapy of the included classes, targets of blood pressure were different between groups or antihypertensive doses were not in the recommended range. We obtained the remaining articles in full

text and excluded them if they did not meet the inclusion criteria. If a study could have included a subgroup of participants that met our criteria (more than 50 people with hypertension without previous antihypertensive drugs per group), we provisionally included it and we contacted authors for data of the subgroup. Two authors independently reviewed the selected articles. We resolved disagreements by discussion and involved all authors if necessary.

Data extraction and management

Two authors independently extracted data from selected trials using a standard data extraction form including study design, randomization, allocation concealment, blinding, drugs, doses, duration of treatment, baseline characteristics, losses to follow-up, outcomes, analysis and reporting. We resolved differences between authors by discussion and involved all authors if necessary. We used Microsoft Access and Microsoft Excel for dealing with individual participant data. We use Review Manager 5 software for data synthesis and analyses (RevMan 2014). Quantitative analyses of outcomes were based on the intention-to-treat principle. We considered all publications of the trials, including protocols and FDA and EMA authorized drug reports.

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias in each trial with the Cochrane 'risk of bias' tool (Higgins 2011). We resolved any differences in opinion by discussion and, if necessary with the participation of a third author. We reported the overall risk of bias of each of the included studies according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met;
- unclear risk of bias (plausible bias that raised some doubt about the results) if one or more criteria were assessed as unclear;
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

We planned to perform sensitivity analyses excluding trials with high or high and unclear risk of bias.

Measures of treatment effect

We based quantitative analyses of outcomes on intention-to-treat results. We statistically summarized data on dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI). We planned to calculate the risk difference (RD) and number needed to treat for an additional beneficial outcome. We summarized continuous outcomes as mean differences (MD) with 95% CI.

We combined data for change in blood pressure using mean differences.

Unit of analysis issues

The unit of analysis was the individual participants.

Dealing with missing data

We contacted the investigators in case of missing data. We based the quantitative analyses of outcomes on intention-to-treat results.

Assessment of heterogeneity

We planned to examine heterogeneity with standard Chi^2 test, and the I^2 statistic.

Values of the I^2 statistic were graded as (Higgins 2011):

- 0% to 40%: heterogeneity might not be important;
- 30% to 60%: moderate heterogeneity;
- 50% to 90%: substantial heterogeneity;
- 75% to 100% considerable heterogeneity.

If data exhibited more than moderate heterogeneity (I^2 greater than 60%), we planned to investigate possible causes. If we had not been able to address heterogeneity causes, we would not have performed the meta-analysis.

Assessment of reporting biases

We planned to assess reporting bias following the recommendations on testing for funnel plot asymmetry as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

Two authors analyzed the data in Review Manager 5 (RevMan 2014), and reported them in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We planned to use a fixed-effect model to pool the data into a meta-analysis. In the presence of statistical heterogeneity (greater than 30% or $P < 0.05$ as estimated by the I^2 statistic), we used a random-effects model.

If meta-analysis had not been appropriated, we would have provided a narrative describing the results.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses:

- people aged less than 75 years versus people aged 75 years or over;
- men versus women;
- people with diabetes versus people without diabetes.

Sensitivity analysis

We planned to perform sensitivity analyses to assess the robustness of the results.

- According to baseline blood pressure levels:
 - less than 160 mmHg;
 - 160 mmHg and over to less than 180 mmHg;
 - 180 mmHg and over.
- Pharmaceutical sponsored versus independent trials. We considered a trial as pharmaceutical sponsored if this was noted in the publication, if any of the authors worked for a pharmaceutical company, or if the trial was sent to FDA or EMA for drug authorization.
- Excluding trials with high or high and unclear risk of bias.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#) tables.

Results of the search

Database searches identified 13,173 records with 48 records from additional sources. After removing duplicates, 7910 records remained. We screened the titles and abstracts and excluded 7682 records. We obtained the full-text articles of 228 records and assessed them for eligibility. We excluded 186 full-text articles. We provisionally accepted 12 studies (reported in 42 articles) for inclusion while we contacted authors for subgroup data. We subsequently included three studies, excluded four studies and listed five studies as awaiting classification. See [Figure 1](#) for the flow chart of the bibliographic search.

Figure 1. Study flow diagram.

We sought help for checking inclusion criteria in two full-text articles written in Chinese and in Russian.

We checked 100 clinical studies included in the FDA's Medical Reviews of 24 fixed-combination drugs, and 70 clinical studies included in the EMA's scientific discussion of the Public Assessment Reports of seven fixed-combination drugs. None of them meet our inclusion criteria, mostly because the follow-up was less than one year. We did not look whether studies included in FDA or EMA reviews also were in the bibliographic search.

Included studies

The three included studies involved 1867 participants with active treatment (monotherapy: 1077 participants; combination: 790 participants). None of the studies was limited to people who initiated antihypertensive treatment so we asked investigators for this subgroup that comprised 568 participants, 30% of the total (monotherapy: 335 participants; combination: 233 participants). [PREMIER 2003](#) and [BENEDICT-A 2004](#) included only people with type 2 diabetes. [PREMIER 2003](#) included only people with albuminuria whereas [BENEDICT-A 2004](#) excluded people with albuminuria. [REASON 2001](#) excluded people treated with antidiabetes, hypocholesterolaemia or cardiovascular drugs. The characteristics of participants included in our review are showed in [Table 1](#). Follow-up was 12 months in [PREMIER 2003](#) and [REASON 2001](#), and was 36 months in [BENEDICT-A 2004](#). The therapeutic groups compared were: ACEI/thiazide-type diuretic versus ACEI ([PREMIER 2003](#)); ACEI/thiazide-type diuretic versus beta-blocker ([REASON 2001](#)), and ACEI or CCB (non-dihydropyridine) versus ACEI/CCB (non-dihydropyridine) ([BENEDICT-A 2004](#)). The three trials were industry funded.

Excluded studies

As our objective was the first-line therapy of hypertension we discarded numerous studies that compared monotherapy with combination in the case of failure of monotherapy.

One large study included only people who were not taking antihypertensive drugs. [MRC-O 1992](#) was conducted in general practices in the UK. Participants aged 65 to 74 years, with systolic blood pressure of 160 mmHg to 209 mmHg and diastolic blood pressure less than 115 mmHg, were randomized to atenolol 50 mg daily (1102 participants) or hydrochlorothiazide 25 mg daily to 50 mg daily plus amiloride 2.5 mg daily to 5 mg daily (1081 participants). The regimens were adjusted to achieve target systolic blood pressures of 150 mmHg or less or 160 mmHg or less depending on baseline blood pressure. Mean follow-up was 5.8 years. The participants in the combination therapy group had fewer cardiovascular deaths and fewer cardiovascular events. There were no statistically significant differences in total mortality ([Wiysonge](#)

[2012](#)). We excluded this trial because doctors and nurses were not blinded to treatment.

[PICXEL 2005](#) included 556 participants with hypertension and left ventricular hypertrophy who were randomized to receive perindopril 2 mg plus indapamide 0.625 mg or enalapril 10 mg. Doses were increased depending on the response. Follow-up was 12 months. We sought data from participants without prior antihypertensive treatment from the study authors. However, we excluded this trial as there were fewer than 50 participants per group (perindopril/indapamide: 40 participants, enalapril: 46 participants).

[DEMAND 2011](#) included 380 participants aged 40 years or over with hypertension and known history of type 2 diabetes mellitus for less than 25 years, with urinary albumin excretion of less than 200 µg/minute and serum creatinine of 1.5 mg/dL or less. Participants were randomized to manidipine 10 mg daily plus delapril 30 mg daily, delapril 30 mg daily or placebo. Target blood pressure was 120/80 mmHg. Additional antihypertensive drugs were allowed to achieve target blood pressure. The mean follow-up was 47 months. The study authors provided individual participant data. However, there were fewer than 50 participants without prior antihypertensive treatment per group (delapril/manidipine: 38 participants, delapril: 33 participants).

[BENEDICT-B 2011](#) included 281 participants aged 40 years or over with hypertension (defined as an untreated systolic blood pressure of 130 mmHg or greater or a diastolic blood pressure of 85 mmHg or greater), history of type 2 diabetes mellitus not exceeding 25 years, urinary albumin excretion rate 20 µg/minute or greater and less than 200 µg/minute, and serum creatinine concentration 1.5 mg/dL or less. Two categories of participants entered the study: people who had developed microalbuminuria during the [BENEDICT-A 2004](#) study and people included after a new screening. Participants were randomized to trandolapril 2 mg daily or trandolapril 2 mg daily plus verapamil 180 mg daily. The target blood pressure was 120/80 mmHg. Additional antihypertensive drugs were allowed to achieve the target blood pressure. Median follow-up was 4.5 years. The authors provided individual participant data. However, there were fewer than 50 participants without prior antihypertensive treatment per group (trandolapril: 39 participants, trandolapril/verapamil: 40 participants).

[ONTARGET 2008](#) included 25,620 participants with coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage. Hypertension was not required for inclusion. Participants were randomized to ramipril 10 mg, telmisartan 80 mg or ramipril 10 mg plus telmisartan 80 mg. We excluded this trial because there was a three-week run-in period in which participants received ramipril plus telmisartan, so participants were not naive to antihypertensive treatment at randomization.

[Zhang 2010](#) included 124 participants, 112 without history of

using any antihypertensive medication, who were randomized to fosinopril/indapamide or fosinopril alone. The follow-up was 14 months. We excluded this trial because it was not stated as double blind and it did not provide any of the primary outcomes.

[ACCELERATE 2011](#) enrolled 1254 participants, of whom 521 were treatment-naïve, and were randomized to aliskiren 150 mg (a direct renin inhibitor), amlodipine 5 mg or aliskiren 150 mg plus amlodipine 5 mg. We excluded this trial because follow-up

was only 32 weeks.

Risk of bias in included studies

The assessment of risk of bias is based on both published and unpublished data. Study authors provided clarification of methods of [PREMIER 2003](#) and [REASON 2001](#) and the protocol of [BENEDICT-A 2004](#). [Figure 2](#) shows the 'Risk of bias' summary of included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
BENEDICT-A 2004	+	+	+	+	+	+	?
PREMIER 2003	+	+	+	+	?	+	?
REASON 2001	+	+	+	+	?	+	?

Allocation

All three included studies used a computer-generated randomization list. The allocation was performed centrally and study centres received blinded treatments and randomization numbers. We judged the risk of allocation bias to be low for all included studies.

Blinding

All three included studies were double-blind, and stated that capsules of identical appearance were used. [REASON 2001](#) and [BENEDICT-A 2004](#) stated that evaluators were blinded to treatment. We judge the risk of performance and detection bias to be low in all studies.

Incomplete outcome data

In [REASON 2001](#), there were 21 withdrawals for which reasons were not provided. In [PREMIER 2003](#), there were more withdrawals due to lack of efficacy in the monotherapy group (six with monotherapy versus zero with combination therapy). It is unclear if those circumstances can lead to differences in endpoints.

Selective reporting

We sent our protocol to investigators asking for outcomes of interest for this review in the subgroup of participants naive to antihypertensive drugs. Study authors provided data as aggregate data for [REASON 2001](#) and [PREMIER 2003](#); and as individual participant data for [BENEDICT-A 2004](#); so we judged selective reporting bias to be low.

Other potential sources of bias

In [BENEDICT-A 2004](#), inclusion criteria were changed during the trial (from untreated blood pressure 140/90 mmHg or greater to 130/85 mmHg or greater. Blood pressure targets were also changed during the trial from 130/85 mmHg to 120/80 mmHg (protocol amendment 3; 27 May 1999).

All data came from subgroups of participants not predefined in the original studies. Outcomes of our review were not the primary outcome in any included trial.

Effects of interventions

See: [Summary of findings for the main comparison Combination therapy versus monotherapy for primary hypertension](#)

The number of participants included in our review and hence the number of events was clearly insufficient to reach any conclusion

about the differential effect of initiating treatment with combination therapy versus monotherapy on important outcomes.

At the end of one year, there were no statistically significant differences in change of blood pressure between having started with monotherapy or with combination therapy. However, CIs included differences larger than 5 mmHg for systolic blood pressure. The large heterogeneity precluded aggregating results of 'Reaching target blood pressure'. Separating in subgroups by blood pressure target did not address it. Differences in how trials were conducted can provide some explanation. In [REASON 2001](#), the dose was doubled after three months if blood pressure remained above 160/90 mmHg, whereas in [PREMIER 2003](#), the dose was doubled after three months if blood pressure remained above 140/90 mmHg. Despite this, in data provided by investigators, target blood pressure was defined as less than 140/90 mmHg in both trials. Another factor may be that [REASON 2001](#) used atenolol as monotherapy but it was not included in the combination therapy.

Only [BENEDICT-A 2004](#) provided data for separate results in men and women. The scarcity of events for mortality, cardiovascular mortality, cardiovascular events and reaching blood pressure target precluded subgroup analysis for these outcomes. There was no indication of a differential effect in serious adverse events, withdrawals due to adverse effects or changes in blood pressure at one year. However, there were too few women to make any conclusions. [BENEDICT-A 2004](#) also provided individual data of the age of participants. But as it only included 17 people aged 75 years or older, there were not enough data to provide results of this subgroup.

DISCUSSION

Summary of main results

The number of participants and hence the number of events were too small to draw any conclusions.

Overall completeness and applicability of evidence

Despite the huge number of clinical trials with antihypertensive drug combinations, our search was almost fruitless. The reasons for excluding studies merit consideration.

- No naive participants: clinical trials are not addressing questions that doctors face in every-day practice. The inclusion of participants with and without previous antihypertensive treatment facilitates recruitment but it impairs the interpretation

and applicability of results. Clinical practice guidelines address the question but recommendations are based, at best, on indirect evidence.

- Follow-up less than 12 months: there are numerous trials of short duration (eight to 12 weeks) that mostly respond to regulatory requirements for pharmaceutical companies. Those follow-ups are not enough for having results of hard clinical outcomes in a chronic condition like hypertension.

The dangers of relying only on theoretical or pharmacological considerations are well illustrated with the case of combinations of drugs targeting the renin-angiotensin system. Some authors have recommended them because they act at different levels of the physiological pathway and could have synergic actions. However, when those combinations were compared with monotherapy in large clinical trials with hard endpoints, the results were more adverse effects (including hypotension, hyperkalaemia and renal failure), with no benefits in people without heart failure, despite greater reductions in blood pressure (ONTARGET 2008; ALTITUDE 2012; Makani 2013). Those results led regulatory agencies to amend product information to say that combined use of ACEIs, ARBs or aliskiren is not recommended (EMA/294911/2014; FDA 2014).

Quality of the evidence

Although included trials were of fair quality, overall certainty of evidence was very low due to the scarcity of data, and for using a subgroup that was not defined in advance.

Potential biases in the review process

As stated, one potential bias introduced is that we could not use the whole population of the trials but only a subgroup. We excluded MRC-O 1992 as it was not double blind. It is arguable that it can provide evidence that may be as uncertain as that from the small subgroups of participant of the included trials. In the discussions for designing the protocol, we decided to limit the inclusion criteria to double-blind trials because we believed there was a high risk of differential care or co-interventions if doctors judged that participants were receiving treatments of different intensity.

Agreements and disagreements with other studies or reviews

In one large clinical trial that focused on people who were not taking antihypertensive drugs (MRC-O 1992), there were better results in terms of cardiovascular morbidity and mortality with a combination therapy than with monotherapy. There were no statistically significant differences in all-cause mortality. Drugs compared in the trial were hydrochlorothiazide/amiloride versus a beta-

blocker (atenolol) (see Excluded studies). It is unclear if differences could have arisen from the different classes of drugs used. However, one systematic review did not find differences between diuretics and beta-blockers in those outcomes (Wiysonge 2012), so the utilization of a combination of two diuretics with different mechanisms of action could have influenced the results. We did not include this trial because it was not double blind.

One systematic review included 42 clinical trials of factorial designs with durations ranging between four and 12 weeks (Wald 2009). One review included 354 trials (50 studying combination therapy) (Law 2003a; Law 2003b). The median duration was four weeks (range two to 15 weeks). They did not find any trials of sufficient duration to meet our inclusion criteria. They concluded that combination therapy is the preferred initial strategy in the treatment of hypertension, but this statement was not based on results of hard clinical endpoints with combination therapy but on indirect evidence. They based their conclusions on the larger reduction of blood pressure obtained with combination therapy. However, we found no differences in blood pressure reductions attained after one year.

The JNC 8 2014 guideline supports both strategies: start with monotherapy, and begin with two drugs either as separate tablets or as a single tablet combination. The evidence review found no randomized controlled trials that compared monotherapy versus combination therapy and assessed important health outcomes. The guideline acknowledges that it is unknown if one of the strategies results in improved cardiovascular outcomes, cerebrovascular outcomes, kidney outcomes or mortality compared with the alternative strategy. Our review confirms the lack of evidence about this question. In addition, the possibility of increasing cost without evidence of benefit has to be considered, especially in low-income environments.

AUTHORS' CONCLUSIONS

Implications for practice

Doctors should be aware that recommendations about initiating antihypertensive therapy with drug combinations are not based on randomized controlled trial evidence. This review demonstrates that existing evidence is insufficient to distinguish between the two approaches: initiating therapy with a two-drug combination or initiating therapy with one drug.

Implications for research

There is a clear need for trials comparing monotherapy versus combination therapy as initial treatment for hypertension. These trials need to be of sufficient duration and size to assess mortality and morbidity. Trials including people with and without previous antihypertensive treatment should provide separate results for

these groups. People of particular interest are those with complicated hypertension and those whose blood pressure is more than 20/10 mmHg above their goal blood pressure. Older people and different ethnic groups should be well represented, due to possible differences in response to drugs. The most obvious approach that should be studied is a combination thiazide-type diuretic plus angiotensin-converting enzyme inhibitor versus thiazide-type diuretic alone.

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

BENEDICT-A 2004

Methods	Multicentre, randomized, double-blind trial Follow-up: 36 months
Participants	Inclusion criteria: aged ≥ 40 years with hypertension (defined as an untreated systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 85 mmHg), history of type 2 diabetes mellitus not exceeding 25 years, urinary albumin excretion rate $< 20 \mu\text{g}/\text{min}$ and serum creatinine concentration $\leq 1.5 \text{ mg}/\text{dL}$ Exclusion criteria: HbA1c $> 11\%$, non-diabetic renal disease, heart failure or specific indications or contraindications to ACEI or CCB therapy Country: Italy
Interventions	Monotherapy 1: verapamil SR 240 mg daily Monotherapy 2: trandolapril 2 mg daily Combination therapy: verapamil 180 mg + trandolapril 2 mg daily Target blood pressure 120/80 mmHg. Additional antihypertensive drugs were allowed to achieve the target blood pressure in the following steps: step 1, hydrochlorothiazide or furosemide; step 2, doxazosin, prazosin, clonidine, methyldopa or beta-blockers (allowed based on of specific indications) and step 3, minoxidil or long-acting dihydropyridine CCB. Potassium-sparing diuretics, inhibitors of the renin-angiotensin system and non-dihydropyridine CCBs different from the study drugs were not allowed
Outcomes	Primary endpoint: development of persistent microalbuminuria (urinary albumin excretion $\geq 20 \mu\text{g}/\text{min}$ at 2 consecutive visits) Other outcomes: urinary albumin excretion, blood pressure after 1 month, major cardiovascular events, overall and cardiovascular mortality, HbA1c, retinal changes, adverse effects and safety laboratory parameters
Funding sources	Abbott GmbH & Co
Declarations of interest	Not reported.
Notes	Trial started March 1997. We used data of participants without previous antihypertensive treatment (verapamil + trandolapril: 115 participants, verapamil: 106 participants, trandolapril: 109 participants)

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to each therapy with a 1:1 ratio according to a computer-generated randomization list created by the Biometric Unit of Abbott

BENEDICT-A 2004 (Continued)

Allocation concealment (selection bias)	Low risk	The participant randomization number was requested by telephone or fax and was assigned by the Treatment Assignment Secretariat at the Mario Negri Institute (Ranica, Italy) by an independent investigator unaware of treatments' allocation schemes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study treatments were externally non-distinguishable pink-ivory two-coloured capsules. Investigators, participants, care providers, endpoint evaluators, monitors and data analysts were masked throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators, participants, care providers, endpoint evaluators, monitors and data analysts were masked throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Schematic diagram of the trial.
Selective reporting (reporting bias)	Low risk	Protocol available. Individual participant data provided.
Other bias	Unclear risk	Inclusion criteria were changed during the trial (from untreated blood pressure $\geq 140/90$ mmHg to $\geq 130/85$ mmHg). Blood pressure targets were also changed from 130/85 mmHg to 120/80 mmHg (protocol amendment 3; 27 May 1999) Subgroup of participants naive to antihypertensives not predefined. Study not designed for our objectives

PREMIER 2003

Methods	Multicentre, randomized, double-blind trial Follow-up: 52 weeks
Participants	Inclusion criteria: aged 40 to 75 years with type 2 diabetes, hypertension defined as supine systolic blood pressure ≥ 140 mmHg and < 180 mmHg and supine diastolic blood pressure < 110 mmHg, and albumin excretion rate ≥ 20 $\mu\text{g}/\text{min}$ and < 500 $\mu\text{g}/\text{min}$ in at least 2 of 3 assays Exclusion criteria: HbA1c $\geq 9\%$ within the 3 months before the study, with presumed non-diabetic kidney disease, serum creatinine ≥ 140 $\mu\text{mol}/\text{L}$, known contraindications to ACEI therapy, or indapamide or other severe disease Countries: Argentina, Austria, Belgium, Brazil, Czech Republic, France, Germany, Hun-

	gary, Ireland, Mexico, Morocco, the Netherlands, Poland, Slovakia, South Africa, Spain, Switzerland, Tunisia, Turkey, UK
Interventions	Both groups: open 4-week prerandomization run-in period of placebo once daily Monotherapy: Enalapril 10 mg daily Combination therapy: perindopril 2 mg + indapamide 0.625 mg once daily Target blood pressure was < 140/90 mmHg. Dose adjustment was permitted after week 12 in double-blind steps: perindopril 4 mg + indapamide 1.25 mg or enalapril 20 mg then perindopril 8 mg + indapamide 2.5 mg or enalapril 40 mg. Non-study antihypertensive drugs were not permitted
Outcomes	Primary outcome: change in the albumin excretion rate after 1 year Secondary outcomes: albumin/creatinine ratio, supine blood pressure and blood pressure response defined as a reduction in systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg or reduction of systolic blood pressure $\geq$ 20 mmHg or reduction of diastolic blood pressure $\geq$ 10 mmHg, or a combination of these. Serious adverse events were predefined as those that were fatal or required prolonged hospitalization
Funding sources	Institut de Recherches Internationales Servier
Declarations of interest	Not reported
Notes	Trial conducted between March 1997 and January 2001. The trial recruited 481 participants and we used data of 109 participants without previous antihypertensive treatment (perindopril + indapamide: 55 participants; enalapril: 54 participants)

Risk of bias

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized block randomization method used to assign treatments (personal communication)
Allocation concealment (selection bias)	Low risk	At the beginning of the study, investigators received randomized permutation blocks and the corresponding sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study products were supplied in the form of capsules of identical appearance Prior to the study, the investigator received the therapeutic units and the corresponding coded envelopes Blister packs and boxes were identified with a unique drug code number for each participant. A 2-part tear-off label was affixed to each blister pack and box. When the medi-

PREMIER 2003 (Continued)

		cation was delivered to the participant, the investigator removed the tear-off portion of the label and attach it to the participant's case report form
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators provided description of blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In our subgroup, in monotherapy group there were more withdrawals due to lack of efficacy (6 with monotherapy versus 0 with combination therapy)
Selective reporting (reporting bias)	Low risk	Investigators provided results data as requested.
Other bias	Unclear risk	Subgroup of participants naive to antihypertensives not predefined. Study not designed for our objectives

REASON 2001

Methods	Multicentre, randomized, double-blind trial Follow-up: 12 months
Participants	Inclusion criteria: aged 18 to 84 years with essential hypertension defined as a supine systolic blood pressure ≥ 160 mmHg and < 210 mmHg, or a supine diastolic blood pressure ≥ 95 mmHg and < 110 mmHg, or both. In all cases, hypertension was uncomplicated Exclusion criteria: people receiving medication for diabetes, hypocholesteraemia or cardiovascular disease Countries: Australia, Austria, Belgium, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, Switzerland and UK
Interventions	Both groups: 4-week placebo period Monotherapy: atenolol 50 mg Combination therapy: perindopril 2 mg + indapamide 0.625 mg In both groups, the medication was taken orally in the morning as a single dose. The dosage was then adapted to the blood pressure, and the dose was doubled (2 capsules once daily) after 3 months if systolic blood pressure remained > 160 mmHg or diastolic blood pressure > 90 mmHg, or both. At the end of the procedure, drug dosage was progressively decreased over 8 to 15 days to avoid any complication caused by atenolol withdrawal
Outcomes	Brachial systolic blood pressure, diastolic blood pressure, pulse pressure, aortic pulse wave velocity, carotid and aortic blood pressures, heart rate, adverse effects Target blood pressure defined as $< 140/90$ mmHg

REASON 2001 (Continued)

Funding sources	INSERM, Association Claude Bernard, GPH-CV, and Laboratoires Servier
Declarations of interest	Not reported
Notes	Study dates not reported. Trial recruited 471 participants. We used data of 129 participants without previous antihypertensive treatment (perindopril/indapamide: 63 participants; atenolol: 66 participants)

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	Computerized block randomization method used to assign treatments (personal communication)	
Allocation concealment (selection bias)	Low risk	Prior to the study, the investigator received the therapeutic units and the corresponding coded envelopes	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study products were supplied in the form of capsules of identical appearance	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All measurements were analyzed by 2 physicians blinded to treatment, clinical data and physical examination	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In the whole study, 471 participants were randomized, 354 completed active treatment period but only reasons for 96 withdrawals were provided. There lacked information on 7 participants in the perindopril + indapamide group and 12 participants in the atenolol group	
Selective reporting (reporting bias)	Low risk	Investigators provided results data as requested.	
Other bias	Unclear risk	Subgroup of participants naive to antihypertensives not predefined. Study not designed for our objectives	

ACEI: angiotensin-converting enzyme inhibitor; CCB: calcium channel blocker; HbA1c: glycated haemoglobin; min: minute; SR: slow release.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACCELERATE 2011	Follow-up only 32 weeks
BENEDICT-B 2011	We requested data of participants naïve to antihypertensive drugs. Authors provided individual participant data, but there were fewer than 50 participants per group (trandolapril: 39 participants, trandolapril + verapamil: 40 participants)
DEMAND 2011	We requested data of participants naïve to antihypertensive drugs. Authors provided individual participant data, but there were fewer than 50 participants per group (delapril: 33 participants, delapril + manidipine participants: 38)
MRC-O 1992	Single-blind trial.
ONTARGET 2008	Participants entered a run-in period in which they received ramipril 2.5 mg once daily for 3 days, followed by telmisartan 40 mg + ramipril 2.5 mg once daily for 7 days and then ramipril 5 mg + telmisartan 40 mg for 11 to 18 days; so participants were not naïve to antihypertensive treatment at randomization
PICXEL 2005	We requested data of participants naïve to antihypertensive drugs. Authors provided aggregate data, but there were fewer than 50 participants per group (enalapril: 46 participants, perindopril + indapamide: 40 participants)
Zhang 2010	Not stated that it was a double-blind trial. No data of any of our primary outcomes

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Derosa 2013](#)

Methods	Multicentre, randomized, double-blind, clinical trial Follow-up: 12 months
Participants	Inclusion criteria: aged ≥ 18 with stage I essential hypertension (defined as sitting systolic blood pressure ≥ 140 mmHg and < 160 mmHg and sitting diastolic blood pressure ≥ 90 mmHg and < 100 mmHg after a 2-week washout placebo period) Exclusion criteria: type 2 diabetes mellitus, impaired liver or kidney function, anaemia, unstable cardiovascular conditions (e.g. NYHA class I to IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months of study enrolment Country: Italy
Interventions	Monotherapy 1: olmesartan 20 mg, Monotherapy 2: amlodipine 10 mg Combination therapy: olmesartan 20 mg + amlodipine 5 mg in single tablet
Outcomes	Body weight, body mass index, systolic and diastolic blood pressures, fasting plasma glucose, fasting plasma insulin, lipid profile, tumour necrosis factor- α , retinol binding protein-4, and interleukins 6 and 7 At baseline, and after 6 and 12 months, participants underwent an euglycaemic, hyperinsulinaemic clamp

Derosa 2013 (Continued)

Notes	We requested data of outcomes of interest in the subgroup of participants naive to antihypertensive treatment but received no response. There are 6 publications of the trial with the same data, as of February 2016, 5 of them have been retracted
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Derosa 2014

Methods	Multicentre, randomized, double-blind, clinical trial Follow-up: 24 months
Participants	Inclusion criteria: outpatients aged < 65 years, with a first diagnosed essential hypertension (diastolic blood pressure > 90 mmHg and < 110 mmHg or systolic blood pressure > 140 mmHg and < 180 mmHg, or both), and naive to antihypertensive treatment Exclusion criteria: hypertrophic cardiomyopathies due to aetiologies other than hypertension; history of heart failure, left ventricular ejection fraction $\leq$ 50%, angina, stroke, transient Ischaemic cerebral attack, coronary artery bypass surgery or myocardial infarction any time prior to first visit; concurrent symptomatic arrhythmia; liver dysfunction; creatinine > 1.5 mg/dL; endocrine, infective or inflammatory disorders; use of anti-inflammatory medications Country: Italy
Interventions	Monotherapy 1: enalapril 20 mg once a day Monotherapy 2: lercanidipine 10 mg once a day Combination therapy: enalapril 20 mg + lercanidipine 10 mg once a day
Outcomes	Body mass index, systolic and diastolic blood pressure, fasting plasma glucose, lipid profile, lipoprotein a, soluble receptor for advanced glycation end products, soluble CD40 ligand, serum myeloperoxidase, high sensitivity C-reactive protein and tumour necrosis factor- α
Notes	We requested data of outcomes of interest but received no response. There are 2 publications of the trial with the same data, as of February 2016, 1 of them has been retracted

INSIGHT 2000

Methods	Multicentre, randomized, double-blind, clinical trial Mean follow-up: 3.5 years
Participants	Inclusion criteria: aged 55 to 80 years with hypertension (blood pressure $\geq$ 150/95 mmHg or $\geq$ 160 mmHg systolic) and at least 1 additional cardiovascular risk factor: hypercholesterolaemia; smoker (10 cigarettes per day currently or up to 1 year before entry); family history of myocardial infarction in parent or sibling before age 50 years; current left-ventricular hypertrophy, coronary heart disease; left-ventricular strain; peripheral vascular disease Countries: Denmark, France, Israel, Italy, the Netherlands, Norway, Spain, Sweden, UK
Interventions	Monotherapy: initially nifedipine 30 mg daily Combination therapy: hydrochlorothiazide 25 mg + amiloride 2.5 mg daily Dose titration was by dose doubling, and addition of atenolol 25 to 50 mg or enalapril 5 to 10 mg in people whose blood pressure fell by < 20/10 mmHg or was > 140/90 mmHg

INSIGHT 2000 (Continued)

Outcomes	Primary: cardiovascular death, myocardial infarction, heart failure or stroke Secondary: total mortality; death from a vascular cause; and non-fatal vascular events including transient ischaemic attacks, angina (new or worsening) and renal failure; serious adverse events
Notes	We requested data of outcomes of interest in the subgroup of participants without previous antihypertensive treatment but received no response

PREVER-treatment 2016

Methods	Multicentre, randomized, double-blind, clinical trial
Participants	Aged 40 to 70 years, stage 1 hypertension (140 mmHg to 159 mmHg/90 mmHg to 99 mmHg; > 130 mmHg in people with diabetes); no more than 1 antihypertensive, no previous coronary heart disease and severe chronic disease Country: Brazil
Interventions	Monotherapy: losartan starting dose 50 mg, up to 100 mg daily Combination therapy: chlorthalidone 12.5 mg + amiloride 2.5 mg starting dose up to chlorthalidone 25 mg + amiloride 5 mg daily Amlodipine up to 10 mg daily and propranolol up to 160 mg daily, in an open fashion, will be added if blood pressure is not controlled
Outcomes	Primary: blood pressure variation and proportion of use of add-on drugs, adverse events, development or worsening of microalbuminuria and left ventricular hypertrophy on electrocardiogram Secondary: fatal or major cardiovascular events: myocardial infarction, stroke, coronary interventions, heart failure, duplication of creatinine Time frame: 18 months.
Notes	Number of participants naïve to antihypertensive drugs not reported

VALIANT 2003

Methods	Multicentre, randomized, double-blind, event-driven, clinical trial Median follow-up: 24.7 months
Participants	Inclusion criteria: aged ≥ 18 years who had had acute myocardial infarction (0.5 to 10 days previously) that was complicated by clinical or radiological signs of heart failure or evidence of left ventricular systolic dysfunction Countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Italy, the Netherlands, New Zealand, Norway, Poland, Russia, Slovakia, South Africa, Spain, Sweden, UK, US
Interventions	Monotherapy 1: valsartan 20 mg twice daily Monotherapy 2: captopril 6.25 mg 3 times daily Combination therapy: valsartan 20 mg twice daily + captopril 6.25 mg 3 times daily Doses were gradually increased with the goal of reaching valsartan 160 mg, captopril 50 mg or valsartan 80 mg + captopril 50 mg at 3 months. Investigators increased or decreased the doses of the study drugs at their discretion according to the participant's clinical status

VALIANT 2003 (Continued)

Outcomes	Primary: all-cause mortality Secondary: cardiovascular death, acute coronary syndromes, cardiovascular morbidity, revascularization procedures, cardiovascular procedures, hospitalizations, adverse events
Notes	Participants were candidates to receive also beta-blockers. Guidelines discourage the studied combination. We requested data of outcomes of interest for the subgroup of people with hypertension without previous treatment and without additional antihypertensive drugs but received no response

DATA AND ANALYSES

Comparison 1. Combination therapy versus monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	3	568	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.08, 21.72]
1.1 People with diabetes	2	439	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.08, 21.72]
1.2 People without diabetes	1	129	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Cardiovascular mortality	3	568	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 People with diabetes	2	439	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 People without diabetes	1	129	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Cardiovascular events	3	568	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.22, 4.41]
3.1 People with diabetes	2	439	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.10, 3.95]
3.2 People without diabetes	1	129	Risk Ratio (M-H, Fixed, 95% CI)	3.14 [0.13, 75.69]
4 Serious adverse events	3	568	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.31, 1.92]
4.1 People with diabetes	2	439	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.24, 1.64]
4.2 People without diabetes	1	129	Risk Ratio (M-H, Random, 95% CI)	3.14 [0.34, 29.42]
5 Withdrawals due to adverse effects	3	568	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.53, 1.35]
5.1 People with diabetes	2	439	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.49, 1.35]
5.2 People without diabetes	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.32, 3.45]
6 Reaching target blood pressure at 1 year	3	548	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.52, 2.54]
6.1 People with diabetes, target $\leq$ 120/80 mmHg	1	314	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.18]
6.2 People with diabetes, target $\leq$ 140/90 mmHg	1	105	Risk Ratio (M-H, Random, 95% CI)	2.0 [1.24, 3.22]
6.3 People without diabetes, target $\leq$ 140/90 mmHg	1	129	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.62, 1.28]
7 Systolic blood pressure change from baseline at end of 1 year	3	548	Mean Difference (IV, Random, 95% CI)	-2.06 [-5.39, 1.27]
7.1 People with diabetes	2	419	Mean Difference (IV, Random, 95% CI)	-2.54 [-8.27, 3.19]
7.2 People without diabetes	1	129	Mean Difference (IV, Random, 95% CI)	-2.33 [-7.28, 2.62]
8 Diastolic blood pressure change from baseline at end of 1 year	2	443	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-1.21, 0.96]
8.1 People with diabetes	1	314	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.56, 0.78]
8.2 People without diabetes	1	129	Mean Difference (IV, Fixed, 95% CI)	1.45 [-1.40, 4.30]

Comparison 2. Combination therapy versus monotherapy (men versus women)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Women	1	103	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.52, 3.00]
1.2 Men	1	227	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.45, 1.24]
2 Withdrawals due to adverse effects	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Women	1	103	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.43, 3.73]
2.2 Men	1	227	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.42, 1.66]
3 Systolic blood pressure change from baseline at end of 1 year	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Women	1	97	Mean Difference (IV, Fixed, 95% CI)	1.74 [-2.10, 5.58]
3.2 Men	1	217	Mean Difference (IV, Fixed, 95% CI)	-1.03 [-3.25, 1.19]
4 Diastolic blood pressure change from baseline at end of 1 year	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Women	1	97	Mean Difference (IV, Fixed, 95% CI)	0.47 [-1.96, 2.90]
4.2 Men	1	217	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-2.08, 0.54]

Analysis 1.1. Comparison 1 Combination therapy versus monotherapy, Outcome 1 Total mortality.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 1 Total mortality

(Continued ...)

Analysis 1.2. Comparison 1 Combination therapy versus monotherapy, Outcome 2 Cardiovascular mortality.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 2 Cardiovascular mortality

(Continued ...)

Analysis 1.3. Comparison 1 Combination therapy versus monotherapy, Outcome 3 Cardiovascular events.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 3 Cardiovascular events

Analysis 1.4. Comparison 1 Combination therapy versus monotherapy, Outcome 4 Serious adverse events.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 4 Serious adverse events

Analysis 1.5. Comparison 1 Combination therapy versus monotherapy, Outcome 5 Withdrawals due to adverse effects.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 5 Withdrawals due to adverse effects

Analysis 1.6. Comparison 1 Combination therapy versus monotherapy, Outcome 6 Reaching target blood pressure at 1 year.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 6 Reaching target blood pressure at 1 year

Analysis 1.7. Comparison 1 Combination therapy versus monotherapy, Outcome 7 Systolic blood pressure change from baseline at end of 1 year.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 7 Systolic blood pressure change from baseline at end of 1 year

Analysis 1.8. Comparison 1 Combination therapy versus monotherapy, Outcome 8 Diastolic blood pressure change from baseline at end of 1 year.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 1 Combination therapy versus monotherapy

Outcome: 8 Diastolic blood pressure change from baseline at end of 1 year

Analysis 2.1. Comparison 2 Combination therapy versus monotherapy (men versus women), Outcome 1 Serious adverse events.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 2 Combination therapy versus monotherapy (men versus women)

Outcome: 1 Serious adverse events

Analysis 2.2. Comparison 2 Combination therapy versus monotherapy (men versus women), Outcome 2 Withdrawals due to adverse effects.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 2 Combination therapy versus monotherapy (men versus women)

Outcome: 2 Withdrawals due to adverse effects

Analysis 2.3. Comparison 2 Combination therapy versus monotherapy (men versus women), Outcome 3 Systolic blood pressure change from baseline at end of 1 year.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 2 Combination therapy versus monotherapy (men versus women)

Outcome: 3 Systolic blood pressure change from baseline at end of 1 year

Analysis 2.4. Comparison 2 Combination therapy versus monotherapy (men versus women), Outcome 4 Diastolic blood pressure change from baseline at end of 1 year.

Review: First-line combination therapy versus first-line monotherapy for primary hypertension

Comparison: 2 Combination therapy versus monotherapy (men versus women)

Outcome: 4 Diastolic blood pressure change from baseline at end of 1 year

ADDITIONAL TABLES

Table 1. Baseline characteristics of included participants (without previous antihypertensive treatment)

Characteristic	Treatment	Mean (standard deviation)		
		BENEDICT-A 2004	PREMIER 2003	REASON 2001
Number of participants	Combination	115	55	63
	Monotherapy	215	54	66
Total participants included in the trial (%)	Combination	38.08%	22.78%	28.09%
	Monotherapy	35.54%	22.54%	25.82%
Age (years)	Combination	60.98 (7.62)	57.27 (8.53)	52.49 (12.68)
	Monotherapy	60.62 (8.36)	59.93 (8.75)	50.38 (10.57)
Sex (% men)	Combination	67.83%	74.55%	71.43%

Table 1. Baseline characteristics of included participants (without previous antihypertensive treatment) (Continued)

	Monotherapy	69.30%	77.78%	62.12%
Ethnicity (% white people)	Combination	100.00%	96.36%	98.41%
	Monotherapy	100.00%	88.89%	93.94%
Body mass index (kg/m ²)	Combination	28.68 (5.19)	28.23 (3.18)	26.85 (3.11)
	Monotherapy	28.34 (4.42)	29.22 (3.51)	26.99 (2.38)
Systolic blood pressure (mm Hg)	Combination	151.61 (9.70)	154.56 (9.86)	162.56 (11.24)
	Monotherapy	152.11 (11.57)	154.04 (11.67)	158.74 (12.84)
Diastolic blood pressure (mm Hg)	Combination	88.72 (7.17)	90.98 (8.43)	97.65 (6.89)
	Monotherapy	89.54 (6.32)	91.00 (8.26)	98.94 (5.07)

APPENDICES

Appendix 1. Hypertension Group Specialised Register search strategy

Database: Hypertension Group Specialised Register

Search Date: 18 February 2016

 #1 ((combination* or combined or dual or polytherap* or versus or vs)) AND ((monotherap* or single)) (3824)
 #2 hypertens* (30884)
 #3 RCT:DE (22196)
 #4 (Review OR Meta-Analysis):MISC2 (1073)
 #5 (#3 OR #4) (23269)
 #6 #1 AND #2 AND #5 (2073)
 #7 (#6) AND ('>15/1/2015:CRSCREATED) (54)

Appendix 2. CENTRAL search strategy

Database: Cochrane Central Register of Controlled Trials on Wiley <Issue 2, 2016>

Search Date: 24 February 2016

 #1 MESH DESCRIPTOR Thiazides EXPLODE ALL TREES 2247
 #2 MESH DESCRIPTOR Sodium Chloride Symporter Inhibitors EXPLODE ALL TREES 2703
 #3 MESH DESCRIPTOR Sodium Potassium Chloride Symporter Inhibitors EXPLODE ALL TREES 967
 #4 (loop or ceiling) next diuretic* 430
 #5 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*) 5995

#6 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide) 1047

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 7024

#8 MESH DESCRIPTOR Angiotensin-Converting Enzyme Inhibitors EXPLODE ALL TREES 5527

#9 angiotensin converting enzyme inhibitor* 5257

#10 ace near3 inhibitor* 2876

#11 acei 527

#12 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril* or perindopril* or pivopril or quinapril* or ramipril* or rentiapril or saralasin or s nitrosocaptopril or spirapril* or temocapril* or teprotide or trandolapril* or utibapril* or zabicipril* or zofenopril*) 8166

#13 #8 OR #10 OR #11 OR #12 9839

#14 MESH DESCRIPTOR Renin EXPLODE ALL TREES WITH QUALIFIERS AI 117

#15 (aliskiren or ciprokiren or ditekiren or enalkiren or remikiren or rasilez or tekturna or terlakiren or zankiren) 402

#16 renin inhibitor* 233

#17 #14 OR #15 OR #16 484

#18 MESH DESCRIPTOR Angiotensin Receptor Antagonists EXPLODE ALL TREES 2422

#19 angiotensin near3 (receptor antagon* or receptor block*) 2999

#20 arb* 4936

#21 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan) 4796

#22 #18 OR #19 OR #20 OR #21 10295

#23 MESH DESCRIPTOR Calcium Channel Blockers EXPLODE ALL TREES 7947

#24 (amlodipine or amrinone or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil) 11977

#25 calcium near2 (antagonist* or block* or inhibitor*) 6289

#26 #23 OR #24 OR #25 14839

#27 MESH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES 9426

#28 (acebutolol or adimolol or afurolol or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlorthalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthioproprianolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol) 14878

#29 beta near2 (adrenergic* or antagonist* or block* or receptor*) 12586

#30 #27 OR #28 OR #29 20454

#31 MESH DESCRIPTOR Adrenergic alpha-Antagonists EXPLODE ALL TREES 2967

#32 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin) 2151

#33 adrenergic near2 (alpha or antagonist*) 6322

#34 (adrenergic or alpha or receptor*) near2 block* 9598

#35 #31 OR #32 OR #33 OR #34 16896

#36 (#7 and #13) or (#7 and #17) or (#7 and #22) or (#7 and #26) or (#7 and #30) or (#7 and #35) or (#13 and #17) or (#13 and #22) or (#13 and #26) or (#13 and #30) or (#13 and #35) or (#17 and #22) or (#17 and #26) or (#17 and #30) or (#17 and #35) or (#22 and #26) or (#22 and #30) or (#22 and #35) or (#26 and #30) or (#26 and #35) or (#30 and #35) 18270

#37 MESH DESCRIPTOR Drug Therapy, Combination EXPLODE ALL TREES 37231
 #38 (add* or combin* or multipl* or plus or polytherap* or versus) 340456
 #39 #37 OR #38 340830
 #40 hypertens* 38052
 #41 (elevat* blood pressure) OR (high blood pressure) 1237
 #42 #40 OR #41 38384
 #43 #36 AND #39 AND #42 5921

Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
 Search Date: 17 February 2016

 1 exp thiazides/ (14707)
 2 exp sodium chloride symporter inhibitors/ (13491)
 3 exp sodium potassium chloride symporter inhibitors/ (12903)
 4 ((loop or ceiling) adj diuretic?).tw. (2260)
 5 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide? or torasemide or torsemide).tw. (31142)
 6 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (2104)
 7 or/1-6 [Diur] (45728)
 8 exp angiotensin-converting enzyme inhibitors/ (39581)
 9 angiotensin converting enzyme inhibit\$.tw. (16370)
 10 (ace adj2 inhibit\$).tw. (16651)
 11 acei.tw. (2456)
 12 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril\$ or perindopril\$ or pivopril or quinapril\$ or ramipril\$ or rentiapril or saralasin or s nitrosocaptopril or spirapril\$ or temocapril\$ or teprotide ortrandolapril\$ or utibapril\$ or zabicipril\$ or zofenopril\$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (24274)
 13 or/8-12 [ACEI] (53483)
 14 renin/ai (1792)
 15 (aliskiren or ciprokiren or ditekiren or enalkiren or remikiren or rasilez or tekturna or terlakiren or zankiren).mp. (1050)
 16 renin inhibit\$.tw. (1579)
 17 or/14-16 [RI] (2521)
 18 exp Angiotensin Receptor Antagonists/ (19071)
 19 (angiotensin adj3 (receptor antagon\$ or receptor block\$)).tw. (10291)
 20 arb?.tw. (4369)
 21 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan).tw. (13495)
 22 or/18-21 [ARB] (26662)
 23 exp calcium channel blockers/ (75276)
 24 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw. (56584)
 25 (calcium adj2 (antagonist? or block\$ or inhibit\$)).tw. (35051)

26 or/23-25 [CCB] (100261)

27 exp adrenergic beta-antagonists/ (78362)

28 (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthiopropiranolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebiolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw. (57503)

29 (beta adj2 (adrenergic? or antagonist? or block\$ or receptor?)).tw. (88743)

30 or/27-29 [BB] (143122)

31 exp adrenergic alpha antagonists/ (47646)

32 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (12950)

33 (adrenergic adj2 (alpha or antagonist?)).tw. (18615)

34 ((adrenergic or alpha or receptor?) adj2 block\$).tw. (51746)

35 or/31-34 [AB] (104786)

36 (7 and 13) or (7 and 17) or (7 and 22) or (7 and 26) or (7 and 30) or (7 and 35) or (13 and 17) or (13 and 22) or (13 and 26) or (13 and 30) or (13 and 35) or (17 and 22) or (17 and 26) or (17 and 30) or (17 and 35) or (22 and 26) or (22 and 30) or (22 and 35) or (26 and 30) or (26 and 35) or (30 and 35) (72944)

37 drug therapy, combination/ (145056)

38 (add\$ or combin\$ or multipl\$ or plus or polytherap\$ or versus).tw. (4293782)

39 or/37-38 (4359134)

40 hypertension/ (206653)

41 hypertens\$.tw. (322164)

42 (elevat\$ blood pressure or high blood pressure).tw. (15326)

43 or/40-42 (377727)

44 randomized controlled trial.pt. (406353)

45 controlled clinical trial.pt. (90060)

46 randomized.ab. (303578)

47 placebo.ab. (155055)

48 clinical trials as topic/ (174893)

49 randomly.ab. (214986)

50 trial.ti. (131809)

51 or/44-50 (928118)

52 animals/ not (humans/ and animals/) (4155531)

53 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (812029)

54 (pregnancy-induced or ocular hypertens\$ or preeclampsia or pre-eclampsia).ti. (12640)

55 51 not (52 or 53 or 54) (818364)

56 36 and 39 and 43 and 55 (5067)

Appendix 4. Embase search strategy

Database: Embase <1980 to 2016 February 17>

Search Date: 17 February 2016

-
- 1 exp thiazide diuretic agent/ (46226)
 - 2 exp loop diuretic agent/ (56565)
 - 3 ((loop or ceiling) adj diuretic?).tw. (3459)
 - 4 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw. (37810)
 - 5 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (3263)
 - 6 or/1-5 [Diur] (106881)
 - 7 exp dipeptidyl carboxypeptidase inhibitor/ (146186)
 - 8 angiotensin converting enzyme inhibit\$.tw. (21331)
 - 9 (ace adj2 inhibit\$).tw. (25520)
 - 10 acei.tw. (5240)
 - 11 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril\$ or perindopril\$ or pivopril or quinapril\$ or ramipril\$ or rentiapril or saralasin or s nitrosocaptopril or spirapril\$ or temocapril\$ or teprotide ortrandolapril\$ or utibapril\$ or zabicipril\$ or zofenopril\$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (33968)
 - 12 or/7-11 [ACEI] (154071)
 - 13 exp renin inhibitor/ (4859)
 - 14 (aliskiren or ciprokiren or ditekiren or enalkiren or remikiren or rasilez or tekturna or terlakiren or zankiren).tw. (1813)
 - 15 renin inhibit\$.tw. (2287)
 - 16 or/13-15 [RI] (5298)
 - 17 exp angiotensin receptor antagonist/ (69189)
 - 18 (angiotensin adj3 (receptor antagon\$ or receptor block\$)).tw. (16085)
 - 19 arb?.tw. (9548)
 - 20 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan).tw. (21598)
 - 21 or/17-20 [ARB] (74927)
 - 22 calcium channel blocking agent/ (52169)
 - 23 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw. (73579)
 - 24 (calcium adj2 (antagonist? or block\$ or inhibit\$)).tw. (44698)
 - 25 or/22-24 [CCB] (131470)
 - 26 exp beta adrenergic receptor blocking agent/ (236463)
 - 27 (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or flestolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthioproprianolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or nebivolol or nifenalol or nipradilol or oxprenolol or pafenolol or pamatolol or penbutolol or pindolol or practolol or

primidolol or prizidilol or procinolol or pronetalol or propranolol or proxodolol or ridazolol or salcardolol or soquinolol or sotalol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol).tw. (68222)

28 (beta adj2 (adrenergic? or antagonist? or block\$ or receptor?)).tw. (103274)

29 or/26-28 [BBs] (287177)

30 exp alpha adrenergic receptor blocking agent/ (115277)

31 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (15697)

32 (adrenergic adj2 (alpha or antagonist?)).tw. (6)

33 ((adrenergic or alpha or receptor?) adj2 block\$).tw. (55368)

34 or/30-33 [ABs] (162951)

35 (6 and 12) or (6 and 16) or (6 and 21) or (6 and 25) or (6 and 29) or (6 and 34) or (12 and 16) or (12 and 21) or (12 and 25) or (12 and 29) or (12 and 34) or (16 and 21) or (16 and 25) or (16 and 29) or (16 and 34) or (21 and 25) or (21 and 29) or (21 and 34) or (25 and 29) or (25 and 34) or (29 and 34) (174303)

36 drug combination/ (54909)

37 (add\$ or combin\$ or multipl\$ or plus or polytherap\$ or versus).tw. (5913215)

38 or/36-37 (5945339)

39 exp hypertension/ (542792)

40 (hypertens\$ or antihypertens\$).tw. (491524)

41 (elevat\$ blood pressure or high blood pressure).tw. (22308)

42 or/39-41 (707892)

43 randomized controlled trial/ (392740)

44 crossover procedure/ (46085)

45 double-blind procedure/ (126172)

46 (randomi\$ed or randomly).tw. (308240)

47 (crossover\$ or cross-over\$).tw. (77955)

48 placebo.ab. (219015)

49 (doubl\$ adj blind\$).tw. (158957)

50 assign\$.ab. (270427)

51 allocat\$.ab. (97040)

52 or/43-51 (1023296)

53 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5434986)

54 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (581628)

55 (pregnancy-induced or ocular hypertens\$ or preeclampsia or pre-eclampsia).ti. (18196)

56 52 not (53 or 54 or 55) (865566)

57 35 and 38 and 42 and 56 (6223)

Appendix 5. Search strategies for other databases

Database: ClinicalTrials.gov

Search Date: 18 February 2016

Search terms: combination AND randomized AND (versus OR vs)

Study type: Interventional Studies

Conditions: hypertension

Outcome: blood pressure (81)

Database: WHO International Clinical Trials Registry Platform

Search Date: 18 February 2016

#1 hypertens* AND combination AND randomized AND versus (46)

#2 hypertens* AND combination AND randomized AND vs (20)

#3 #1 OR #2 (60)

Database: LILACS

Search Date: 03 March 2016

(tw:(monoter* OR combinac*)) AND (tw:(hypertens*)) AND (instance:"regional") AND (db:("LILACS") AND type of study:(“clinical trials” OR “systematic reviews”))

Appendix 6. Pharmaceutical companies checked

Company	Website
Abbot	www.abbott.com/citizenship/disclosures/clinical-study-results.htm
Abbvie	www.abbvie.com/research-innovation/clinical-trials-conduct-transparency/clinical-study-results.html#VIL4lF2h1V
AstraZeneca	www.astrazenecaclinicaltrials.com/
Bayer	pharma.bayer.com/en/research-and-development/clinical-trials/trial-finder/index.php
Boehringer Ingelheim	trials.boehringer-ingelheim.com/trial-results.html
Bristol-Myers Squibb	www.bms.com/clinical-trials/Pages/home.aspx
Daiichi Sankyo	www.daiichisankyo.com/rd/our-approach/clinical-studies/index.html
GlaxoSmithKline	www.gsk-clinicalstudyregister.com/
Menarini	www.menarini.com/clinical-studies/clinical-trial-results
Merck	www.merck.com/research/home.html
Mylan	www.mylanpharms.com/
Novartis	www.novctrd.com/ctrdWebApp/clinicaltrialrepository/public/login.jsp
Pfizer	www.pfizer.com/research/research-clinical-trials/trial-results-research-progress
Recordati	www.recordati.com/activities/randd.aspx?sc_lang=en
Sanofi Aventis	en.sanofi.com/rd/clinical-trials/our-commitments/clinical-study-results.aspx
Servier	www.servier.com
Takeda	www.takeda.com/research/ct/

(Continued)

Teva	www.tevapharm.com/Pages/Default.aspx
UCB	www.ucb.com/rd/clinical-trials

Appendix 7. Reviews and guidelines checked

Hilleman 1999; Ruzicka 2001; Law 2003a; Law 2009; Wald 2009; Sood 2010; Gradman 2010; Lv 2010; NICE 2011; ESH-ESC 2013; Liu 2013; Makani 2013; Pova 2014; Bakris 2014; CHEP 2015; JNC 8 2014.

HISTORY

Protocol first published: Issue 1, 2013

Review first published: Issue 1, 2017

Date	Event	Description
8 November 2013	Amended	Adding the following text to 'Types of interventions' to clarify the clinical sense of the potential results: 'Combination therapy includes the combinations of diuretics with the potassium-sparing agents triamterene or amiloride, but in any case we will analyse their data also separately because they are not used as antihypertensives in monotherapy.'

CONTRIBUTIONS OF AUTHORS

JG is the lead author, entered text of the review into Review Manager 5, assisted with searches appraised inclusion criteria and quality, and extracted and analyzed data.

LCS co-ordinated the review, conducted the external correspondence, appraised inclusion criteria and quality, and extracted and analyzed data.

AA appraised inclusion criteria and quality of studies, and drafted the final review.

JJE appraised inclusion criteria and quality of studies, and drafted the final review.

IG appraised inclusion criteria and quality of studies, and interpreted the analysis from a methodological and policy perspective.

MJA appraised inclusion criteria and quality of studies, and interpreted the analysis from a clinical perspective.

JE appraised inclusion criteria and quality of studies, and drafted the final review.

All authors participated in the writing of discussion and conclusions.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Navarre Health Service and Health Department of the Government of Navarre, Spain.
Working time of authors (employees of the Government of Navarre). Facilities. Library services.

External sources

- University of British Columbia, Vancouver, Canada.
Bibliographic searches. Methodological support.
- European Social Fund Operational Programme 2007 to 2013, Other.
50% of the full research project, as salary for the Pharmacotherapy Research Coordinator in the Navarre Health Service (LCS).

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have improved the wording of the title of the review from “Monotherapy versus combination therapy used as first-line therapy for primary hypertension” to “First-line combination therapy versus first-line monotherapy for primary hypertension”.

We have corrected the unit of analysis from ‘individual trials’ to ‘individual participants’.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [adverse effects; *therapeutic use]; Cardiovascular Diseases [mortality]; Diastole; Drug Therapy, Combination [adverse effects]; Hypertension [*drug therapy]; Randomized Controlled Trials as Topic; Selection Bias; Systole

MeSH check words

Adult; Aged; Humans