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Pharmacotherapy for hypertension in adults aged 18 to 59 years (Review)

Musini VM, Gueyffier F, Puil L, Salzwedel DM, Wright JM

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[Intervention Review]

Pharmacotherapy for hypertension in adults aged 18 to 59 years

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ABSTRACT

Background

Hypertension is an important risk factor for adverse cardiovascular events including stroke, myocardial infarction, heart failure and renal failure. The main goal of treatment is to reduce these events. Systematic reviews have shown proven benefit of antihypertensive drug therapy in reducing cardiovascular morbidity and mortality but most of the evidence is in people 60 years of age and older. We wanted to know what the effects of therapy are in people 18 to 59 years of age.

Objectives

To quantify antihypertensive drug effects on all-cause mortality in adults aged 18 to 59 years with mild to moderate primary hypertension. To quantify effects on cardiovascular mortality plus morbidity (including cerebrovascular and coronary heart disease mortality plus morbidity), withdrawal due adverse events and estimate magnitude of systolic blood pressure (SBP) and diastolic blood pressure (DBP) lowering at one year.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for randomized controlled trials up to January 2017: the Cochrane Hypertension Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (from 1946), Embase (from 1974), the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov. We contacted authors of relevant papers regarding further published and unpublished work.

Selection criteria

Randomized trials of at least one year' duration comparing antihypertensive pharmacotherapy with a placebo or no treatment in adults aged 18 to 59 years with mild to moderate primary hypertension defined as SBP 140 mmHg or greater or DBP 90 mmHg or greater at baseline, or both.

Data collection and analysis

The outcomes assessed were all-cause mortality, total cardiovascular (CVS) mortality plus morbidity, withdrawals due to adverse events, and decrease in SBP and DBP. For dichotomous outcomes, we used risk ratio (RR) with 95% confidence interval (CI) and a fixed-effect model to combine outcomes across trials. For continuous outcomes, we used mean difference (MD) with 95% CI and a random-effects model as there was significant heterogeneity.

Main results

The population in the seven included studies (17,327 participants) were predominantly healthy adults with mild to moderate primary hypertension. The Medical Research Council Trial of Mild Hypertension contributed 14,541 (84%) of total randomized participants, with mean age of 50 years and mean baseline blood pressure of 160/98 mmHg and a mean duration of follow-up of five years. Treatments used in this study were bendrofluazide 10 mg daily or propranolol 80 mg to 240 mg daily with addition of methyldopa if required. The risk of bias in the studies was high or unclear for a number of domains and led us to downgrade the quality of evidence for all outcomes.

Based on five studies, antihypertensive drug therapy as compared to placebo or untreated control may have little or no effect on all-cause mortality (2.4% with control vs 2.3% with treatment; low quality evidence; RR 0.94, 95% CI 0.77 to 1.13). Based on 4 studies, the effects on coronary heart disease were uncertain due to low quality evidence (RR 0.99, 95% CI 0.82 to 1.19). Low quality evidence from six studies showed that drug therapy may reduce total cardiovascular mortality and morbidity from 4.1% to 3.2% over five years (RR 0.78, 95% CI 0.67 to 0.91) due to reduction in cerebrovascular mortality and morbidity (1.3% with control vs 0.6% with treatment; RR 0.46, 95% CI 0.34 to 0.64). Very low quality evidence from three studies showed that withdrawals due to adverse events were higher with drug therapy from 0.7% to 3.0% (RR 4.82, 95% CI 1.67 to 13.92). The effects on blood pressure varied between the studies and we are uncertain as to how much of a difference treatment makes on average.

Authors' conclusions

Antihypertensive drugs used to treat predominantly healthy adults aged 18 to 59 years with mild to moderate primary hypertension have a small absolute effect to reduce cardiovascular mortality and morbidity primarily due to reduction in cerebrovascular mortality and morbidity. All-cause mortality and coronary heart disease were not reduced. There is lack of good evidence on withdrawal due to adverse events. Future trials in this age group should be at least 10 years in duration and should compare different first-line drug classes and strategies.

PLAIN LANGUAGE SUMMARY

Treatment for hypertension in adults aged 18 to 59 years

Review question

We wanted to study the benefits and harms of using blood pressure lowering (antihypertensive) medicines in adults aged 18 to 59 years with raised blood pressure (hypertension).

We searched the available medical literature to find all the trials that had assessed this question. The data included in this review is up to date as of January 2017.

Background

Hypertension increases the risk of stroke, heart attacks and heart failure; therefore, the main goal of treatment with antihypertensive medicines is to reduce this risk. There is substantial evidence mostly in people older than 60 years that antihypertensive therapy reduces these outcomes.

Study characteristics

We found seven studies that randomly assigned 17,327 people aged 18 to 59 years with hypertension to either antihypertensive medicines or placebo (pretend treatment)/no treatment**.** The average duration of treatment was five years. Medicine classes studied in most people included medicines called thiazide diuretics or beta-blockers.

Key results

Treatment may have little or no effect on death from any cause compared with placebo or no treatment (2.4% with placebo/no treatment versus 2.3% with treatment; low quality evidence) and it may reduce the number of people experiencing heart disease or death from heart disease from 4.1% to 3.2% (low quality evidence). It may reduce stroke by a small amount from 1.3% to 0.6% (low quality evidence). We are not certain about the effects of treatment on the number of people who had blocked arteries (low quality evidence). Withdrawal due to side effects increased from 0.7% to 3.0% although the quality of evidence for this result was very low. The effects of treatment on blood pressure varied between the studies and we are uncertain as to how much of a difference treatment makes on average.

Conclusions

Antihypertensive medicines for adults aged 18 to 59 years with raised blood pressure have a small beneficial effect to reduce stroke. However, death due to all-causes and heart attack were not reduced and withdrawals due to side effects were increased.

Quality of evidence

The overall evidence was graded as low or very low quality.

Summary of findings for the main comparison. Antihypertensive drug therapy compared to control for hypertension in adults aged 18 to 59 years

Antihypertensive drug therapy compared to control for hypertension in adults aged 18 to 59 years

Patient or population: adults aged 18-59 years with primary hypertension (mild to moderate systolic or diastolic hypertension)
Setting: outpatient
Intervention: antihypertensive drug therapy (mean duration: 5 years)
Comparison: control (placebo or untreated)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with antihypertensive drug therapy				
All-cause mortality	24 per 1000	23 per 1000 (19 to 28)	RR 0.94 (0.77 to 1.13)	16,776 (5 RCTs)	⊕⊕⊖⊖ **Low** [1,2]	-
Total cardiovascular mortality + morbidity	41 per 1000	32 per 1000 (27 to 37)	RR 0.78 (0.67 to 0.91)	17,278 (6 RCTs)	⊕⊕⊖⊖ **Low** [1,3]	ARR 0.9%, NNTB = 112
Cerebrovascular mortality + morbidity	13 per 1000	6 per 1000 (5 to 9)	RR 0.46 (0.34 to 0.64)	17,278 (6 RCTs)	⊕⊕⊖⊖ **Low** [1,3]	ARR 0.7%, NNTB 143
Coronary heart disease mortality + morbidity	26 per 1000	26 per 1000 (21 to 31)	RR 0.99 (0.82 to 1.19)	16,241 (4 RCTs)	⊕⊕⊖⊖ **Low** [1,3]	-
Withdrawal due to adverse events	7 per 1000	32 per 1000 (11 to 93)	RR 4.82 (1.67 to 13.92)	1,223 (3 RCTs)	⊕⊖⊖⊖ **Very low** [1,2,4]	ARI 3.8%, NNTH 27
Decrease in SBP [5] at end of 1 year	The mean SBP was 0	MD 14.98 lower (20.44 lower to 9.52 lower)	-	14,845 (3 studies)	⊕⊖⊖⊖ **Very low** [1,3,7]	-
Decrease in DBP [6] at end of 1 year	The mean DBP was 0	MD 7.62 lower (10.55 blower to 4.69 lower)	-	15,857 (4 studies)	⊕⊖⊖⊖ **Very low** [1,3,7]	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ARI: absolute risk increase; **ARR:** absolute risk reduction; **CI:** confidence interval; **DBP:** diastolic blood pressure; **MD:** mean difference; **NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat to for an additional harmful outcome; **RCT:** randomized controlled trial; **RR:** risk ratio; **SBP:** systolic blood pressure.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Several additional trials met the inclusion criteria but did not report data in the 18- to 59-year-old subgroup of participants (which are listed under Characteristics of excluded studies table).
[2]Imprecision due to wide confidence interval.
[3]High risk of bias due to lack of blinding of physician and participants as well as incomplete outcome data reporting in the MRC-TMH trial.
[4]Only 3 out of 7 included trials reported this outcome. The data from MRC-TMH 1985 for this subgroup were not available. High risk of attrition bias and unclear risk of reporting bias of the USPHSHCSG 1977 study which contributes 100% weight to the effect size.
[5]The range of change in SBP in the control group ranged from increase by 1.5 mmHg to decrease from 9 to 14 mmHg.
[6]The range of decrease in DBP in the control group ranged from 0.6 mmHg to 7 mmHg.
[7]Significant heterogeneity (I^2 > 95%).

BACKGROUND

Description of the condition

Elevated blood pressure (BP), commonly called hypertension, is an important healthcare problem internationally. Hypertension has been defined as a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic blood pressure (DBP) of at least 90 mmHg, or both. The worldwide prevalence of elevated BP is about 26% of the adult population, and the prevalence increases with age (Kearney 2005). Elevated blood pressure is a major contributor to adverse cardiovascular events (cardiovascular disease; CVD) and has been estimated to contribute 4.5% to the global disease burden (WHO 2003). People of younger age (less than 60 years) have a lower prevalence of hypertension than older people.

The main goal of antihypertensive treatment is to reduce strokes, myocardial infarctions (MI) and heart failure. Several systematic reviews have shown benefit of antihypertensive drug therapy in reducing cardiovascular mortality and morbidity primarily in people over 60 years of age (Collins 1990; Thijs 1992; Psaty 1997; Gueyffier 1999; Psaty 2003; Musini 2009; Wright 2009).

Does benefit due to antihypertensive therapy differ in different age groups? There are various claims made in the literature regarding the benefits of antihypertensive therapy in different age groups. One meta-analysis of 31 trials with 190,606 participants by the Blood Pressure Lowering Treatment Trialists' Collaboration concluded that reduction of BP produces benefits in younger (aged less than 65 years) and older (aged greater than 65 years) adults, with no strong evidence that protection against major vascular events afforded by different drug classes varies substantially with age (BPLTTC 2008). In contrast, the results from the Prospective Studies Collaboration meta-analysis by analyzing individual data of one million adults from 61 prospective observational studies of BP and mortality showed that at ages 40 to 69 years, each difference of 20 mmHg usual SBP (approximately 10 mmHg usual DBP) was associated with more than a two-fold difference in the stroke death rate, and with two-fold differences in the death rates from ischaemic heart disease (IHD) and other vascular causes. The annual absolute estimated differences in risk are greater in old age (Prospective Studies Collaboration 2002).

Although reduction in BP is believed to result in reduction in clinically important outcomes such as stroke or MIs, it a poor surrogate outcome measure for all-cause mortality and morbidity. Similar or greater reduction in BP by different classes of antihypertensive drugs may not necessarily result in similar or greater magnitude of reduction in clinically relevant outcomes (Wright 2009).

Description of the intervention

High BP should be managed first by changing life style (eating a healthy diet with less salt, exercising regularly, quitting smoking and maintaining a healthy weight). When these lifestyle changes are not sufficient, treatment with antihypertensive drugs is recommended. Several different classes of medications are available to reduce BP (thiazide diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers and alpha-blockers) (NICE 2016).

How the intervention might work

Different classes of antihypertensive drugs have different mechanisms of action. The mechanism of action by which thiazide diuretics lower BP in the long term is not fully understood. After chronic use, thiazides lower peripheral resistance. The mechanism of these effects is uncertain as it may involve effects on 'whole body,' renal autoregulation or direct vasodilator actions (Hughes 2004; Longo 2012). Thiazides act on the kidney to inhibit reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter (Duarte 2010). They also increase calcium reabsorption at the distal tubule and increase the reabsorption of calcium ions (Ca^{2+}) by a mechanism involving the reabsorption of sodium and calcium in the proximal tubule in response to sodium depletion.

Alpha-blockers (α_1 adrenergic receptor blockers) inhibit the binding of norepinephrine (noradrenaline) to the α_1 receptors causing vasodilation.

Beta-blockers are competitive antagonists that block the receptor sites for epinephrine (adrenaline) and norepinephrine on adrenergic beta-receptors. Some block activation of all types of beta-adrenergic receptors (β_1, β_2 and β_3) and others are selective for one of the three types of beta receptors (Frishman 2005).

Calcium channel blockers reduce BP through various mechanisms: by vasodilation, reduction in the force of contraction of the heart, by slowing the heart beat and by directly reducing aldosterone production.

ACE inhibitors block the conversion of angiotensin I (AI) to angiotensin II (AII). They thereby lower arteriolar resistance and increase venous capacity. They decrease cardiac output, cardiac index, stroke work and volume, and lower resistance in blood vessels in the kidneys. As a result of negative feedback of conversion of AI to AII, renin and AI increase in concentration in the blood. Bradykinin increases because of less inactivation by ACE.

ARBs block the activation of angiotensin II AT_1 receptors. Blockage of AT_1 receptors directly causes vasodilation, reduces secretion of vasopressin, and reduces production and secretion of aldosterone.

Why it is important to do this review

Clinical trials in adults with mild to moderate hypertension have included people over a wide age range from 18 to 104 years of age. There are two Cochrane Reviews evaluating the effectiveness of antihypertensive drug therapy in people with primary hypertension compared to placebo or no treatment: "First line drugs for hypertension" in adults aged 18 years or older (Wright 2009) and an updated review "Pharmacotherapy of hypertension in the elderly" (aged 60 years or older) with a subgroup meta-analysis in very elderly people (aged 80 years or older) (Musini 2009).

Wright 2009 found that despite a similar magnitude of reduction in BP, a surrogate outcome measure, the clinical effectiveness in terms of all-cause mortality and cardiovascular mortality and morbidity was different for different drug classes. First-line low-dose thiazides reduced all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may have been similarly effective but the evidence was less robust. First-line high-

dose thiazides and first-line beta-blockers were inferior for some outcomes to first-line low-dose thiazides. However, the review did not provide data on clinical effectiveness of antihypertensive drug therapy in different age groups.

Musini 2009 concluded that all-cause mortality as well as cardiovascular mortality and morbidity were modestly reduced in elderly people (aged 60 years or older). However, the decrease in all-cause mortality was limited to people 60 to 79 years of age.

Therefore, it is important to know the relative and absolute magnitude of the effect of antihypertensive drugs in different age groups of people with primary hypertension. This systematic review aimed to find the relative and absolute magnitude of the reduction in all-cause mortality as well as cardiovascular mortality and morbidity in adults aged 18 to 59 years with primary hypertension (mild to moderate systolic or diastolic hypertension).

OBJECTIVES

To quantify antihypertensive drug effects on all-cause mortality in adults aged 18 to 59 years with mild to moderate primary hypertension. To quantify effects on cardiovascular mortality plus morbidity (including cerebrovascular and coronary heart disease mortality plus morbidity), withdrawal due adverse events and estimate magnitude of systolic and diastolic blood pressure lowering at one year.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCT) of at least one year' duration. Trials must have included a control group that either received a placebo or received no antihypertensive therapy.

We excluded trials using non-randomized allocation methods such as alternate allocation, week of presentation or retrospective controls. Trials that compared two specific antihypertensive first-line therapies without a placebo or untreated control were also excluded.

Types of participants

Trials included only people aged 18 to 59 years or separately report outcomes for people in this age group. To maximize data inclusion, if trials included at least 90% of participants in the specified age group (18 to 59 years) but did not report outcomes data separately for this specific age group, we included the overall data in all randomized participants provided in these trials.

Participants must have had primary hypertension with a SBP of at least 140 mmHg or a DBP of at least 90 mmHg, or both at baseline.

Types of interventions

Acceptable antihypertensive drug therapies included: diuretics, ACE inhibitors, ARBs, beta-blockers, combined alpha- and beta-blockers, calcium-channel blockers, alpha-blockers, central sympatholytics, direct vasodilators or peripheral adrenergic antagonists. Drugs could have been administered alone or in combination, and in fixed or stepped care regimens. The control group must have received a placebo or no anti-hypertensive therapy.

Types of outcome measures

Primary outcomes

- All-cause mortality (death from all causes).

Secondary outcomes

- Cardiovascular mortality plus morbidity (included fatal and non-fatal stroke, fatal and non-fatal MI, sudden death, hospitalization or death from congestive heart failure and other significant vascular deaths such as ruptured aneurysms). It did not include angina, transient ischaemic attacks, surgical or other procedures, or accelerated hypertension.
- Cerebrovascular mortality plus morbidity including fatal and non-fatal stroke.
- Coronary heart disease mortality plus morbidity including fatal and non-fatal MI, and sudden or rapid cardiac death.
- Withdrawal due to adverse events.
- Decrease in SBP and DBP.

When the primary trial did not report on outcomes that fitted the above definitions, decisions were made based on maximizing the inclusion of the data as defined in each included study and maintaining concordance with how the data were classified in previous reviews (Musini 2009; Wright 2009).

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist (DS) conducted systematic searches in the following databases for RCTs without language, publication year or publication status restrictions:

- the Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 23 January 2017);
- the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) (searched 23 January 2017);
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 23 January 2017);
- Embase Ovid (searched 23 January 2017);
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 23 January 2017);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) (searched 23 January 2017).

The search strategy used in this review was identical to the Cochrane Review on "First line drugs for hypertension" (Wright 2009) and "Pharmacotherapy for hypertension in elderly patients" (Musini 2009). The Cochrane Hypertension Information Specialist (DS) modelled subject strategies for databases on the search strategy designed for MEDLINE. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomized controlled (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Box 6.4.b; Higgins 2011a). Search strategies for major databases are provided in Appendix 1.

Search was not done for regulatory documents from the Food and Drug Administration (FDA) or European Medicine Agency (EMA).

There were no language restrictions.

Searching other resources

We carefully checked the bibliographies of previously published meta-analyses on the treatment of hypertension to help identify references to trials (Collins 1990; Thijs 1992; MacMahon 1993; Insua 1994; Mulrow 1994; Pearce 1995; Gueyffier 1996; Psaty 1997; Mulrow 1998; Gueyffier 1999; Quan 1999; Nikolaus 2000; Psaty 2003; Turnbull 2003; Kang 2004; BBLTTC 2005; BPLTTC 2008; Law 2009; Musini 2009; Wright 2009; Thomopoulos 2014; Sundström 2015; Zanchetti 2015; Parsons 2016; Tan 2016; Thomopoulos 2016; Kızılırmak 2017; Wiysonge 2017).

We contacted experts in the field to identify any other trials missed in our search. We checked reference lists of included studies and contacted relevant trialists for information about unpublished or ongoing studies.

Data collection and analysis

Selection of studies

One review author (VM or LP or DS) screened the titles and abstracts of citations from the search. Articles were rejected on initial screen if they were not reports of an RCT or there was no possibility that the trial could fit the requirements of this review. Of the articles selected for further review, at least two review authors (VM, LP or JMW) independently assessed whether they met the inclusion criteria.

Data extraction and management

Two review authors (VM and JMW) independently performed data abstraction, cross-checked and compared whenever possible to data from previously published meta-analyses. The data abstraction form included details of study design, randomization, blinding, duration of treatment, baseline characteristics, number of participants lost to follow-up, outcomes, intervention, statistical analysis and reporting. Trial characteristics are detailed in the Characteristics of included studies table. One review author (FG) provided data in the 18- to 59-year-old subgroup from the INDANA (Gueyffier 1995) database for the MRC-TMH 1985 trial.

Assessment of risk of bias in included studies

Two review authors (VM and JMW) independently assessed risk of bias of each included trial and resolved any disagreements by adjudication or discussion with a third review author (AT or LP or FG). Risk of bias assessment was done according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We assessed seven domains: randomization and allocation concealment to assess selection bias; blinding of the participants and physicians to assess performance bias; blinding of outcome assessor to assess detection bias; incomplete outcome reporting to assess attrition bias; selective reporting of outcomes to assess selective reporting bias and other bias to assess whether the study was funded by a drug manufacturer (in which case it was assessed as high risk of bias).

'Summary of findings' table

We used GRADEpro software to present the 'Summary of findings' table (GRADEpro). We decided to include all clinically relevant primary and secondary outcomes such as all-cause mortality, total cardiovascular mortality and morbidity, cerebrovascular mortality and morbidity, coronary heart disease mortality and morbidity, withdrawal due to adverse events and magnitude of reduction in SBP and DBP.

The five factors considered in grading overall quality of evidence were: limitations in study design and implementation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision in results and high probability of publication bias. This approach specifies four levels of quality: high, moderate, low and very low quality evidence. The highest quality rating is for randomized trial evidence. Quality rating is downgraded by one level for each factor, up to a maximum of three levels for all factors. If there are severe problems for any one factor (when assessing limitations in study design and implementation, in concealment of allocation, loss of blinding or attrition over 50% of participants during follow-up), randomized trial evidence may fall by two levels due to that factor alone.

Measures of treatment effect

We used Review Manager 5 for data synthesis and analyses (RevMan 2014). Quantitative analyses of outcomes were based on intention-to-treat results. We used risk ratios (RR) with 95% confidence intervals (CI) to combine outcomes across trials. If there was a significant difference in any outcome measure, we presented an absolute risk reduction (ARR) and number needed to treat for an additional beneficial (NNTB) or harmful (NNTH) outcome in the 'Summary of findings' table. For continuous outcomes (SBP and DBP), we calculated the mean difference (MD) with 95% CI to combine outcomes across studies.

Unit of analysis issues

For all outcomes measures reported, we used data from each trial at the end of the follow-up period mentioned in each trial, which varied from two to 10 years.

Dealing with missing data

When participants were lost to follow-up, we used data as reported for participants who were followed until end of the study in the analyses. Refer to how data was accounted for and included in each study under assessment of attrition bias in the Risk of bias in included studies section.

For example, in the MRC-TMH 1985 study, events such as non-fatal stroke or MI terminated participation in the study and follow-up of such participants to the end of the study was not done. In such instances, data available up to the time point during which participants were followed were included in the analyses.

Assessment of heterogeneity

We tested heterogeneity of treatment effect between the trials using a standard Chi^2 statistic for heterogeneity. We used the fixed-effect model to obtain summary statistics of pooled trials, unless there was significant between-study heterogeneity, in which case we used the random-effects model to test statistical significance.

When heterogeneity was estimated to be significant (I^2 greater than 50%), we explored the factors contributing to heterogeneity.

Assessment of reporting biases

We planned to assess publication bias if at least 10 studies met the inclusion criteria using a funnel plot. However, in this review, only seven studies met the inclusion criteria and provided data for quantitative analyses, so funnel plot analyses were not performed.

Data synthesis

We used Review Manager 5 to perform data synthesis and analyses (RevMan 2014). We presented dichotomous outcomes as RR with 95% CI using a fixed-effect model and continuous outcomes (SBP and DBP) as MD with 95% CI.

Subgroup analysis and investigation of heterogeneity

Since most participants included in this review were subgroups of participants from four of the seven trials in adults aged 18 years or older, further dividing participants into various other subgroup and analysing outcomes would lead to an increase in alpha error. Multiple comparisons within further subgroups would increase the chances of finding significant differences and therefore was not done.

When heterogeneity was significant (I^2 greater than 50%), we attempted to identify trials that would contribute to heterogeneity and explore their population characteristics, baseline BP, blinded or open-label study design, use of antihypertensive drugs as fixed dose or stepped up therapy or response to placebo that would possibly explain the reason for heterogeneity. As the decrease in SBP and DBP showed significant heterogeneity, we presented results as MD with 95% CI using a random-effects model instead of a fixed-effect model.

Sensitivity analysis

To test for robustness of results, we conducted the following sensitivity analyses:

- placebo controlled trials versus untreated trials;
- double blind trials versus open-label or single-blind trials;
- trials using combined starting drugs as stepped up therapy versus fixed-dose therapy.

RESULTS

Description of studies

Results of the search

Since the search strategy used in this review was identical to the Cochrane Review "First line drugs for hypertension" (Wright 2009) and "Pharmacotherapy for hypertension in elderly patients" (Musini 2009), we included search findings to 2008 from these reviews. The PRISMA diagram for search to 2008 is not shown.

The Wright 2009 review search from 1946 to 2008 resulted the identification of 6232 citations. Of these, 5985 articles were rejected on initial screen as they were not reports of an RCT or there was no possibility that the trial could fit the requirements of this review. A total of 247 citations were retrieved for detailed evaluation by two review authors (JMW and VM) of which 13 were review articles. Of the remaining 234 citations, 59 were excluded upon detailed reading as they did not meet minimum inclusion criteria. A total of 175 reports of 57 potentially first-line trials were evaluated. Forty-eight reports of 33 trials were excluded and were listed in the 'Characteristics of excluded studies' table in the Wright 2009 review. Finally, 127 reports of 24 trials were included in the Wright 2009 review. Not all trials included in the Wright 2009 review pertained to the age group 18 to 59 years old therefore we excluded 17 of the 24 studies included in the Wright 2009 review. These are listed in the Characteristics of excluded studies table.

The search strategy from 2008 to January 2017 resulted in 11,855 citations after removing duplicates. We screened the titles and abstracts and excluded 11,500 citations. Articles were rejected on this initial screen if the article was not a report of a RCT or there was no possibility that the trial could fit the requirements of this review. At leat two review authors (LP, VM or JMW) assessed the remaining articles to determine if they met the inclusion criteria. Three hundred and fifty-five full-text articles were retrieved of which all 355 articles were excluded on detailed reading as they did not meet the minimum inclusion criteria (Figure 1).

Figure 1. This is a partial study flow diagram and shows search findings from 2008 until 2017. The search done from 1946 to 2008 was identical to the "First line drugs for hypertension" review in which 24 trials met the inclusion

criteria of which 17 had to be excluded and only seven studies provided data for quantitative synthesis in 18- to 59-year-old participants.

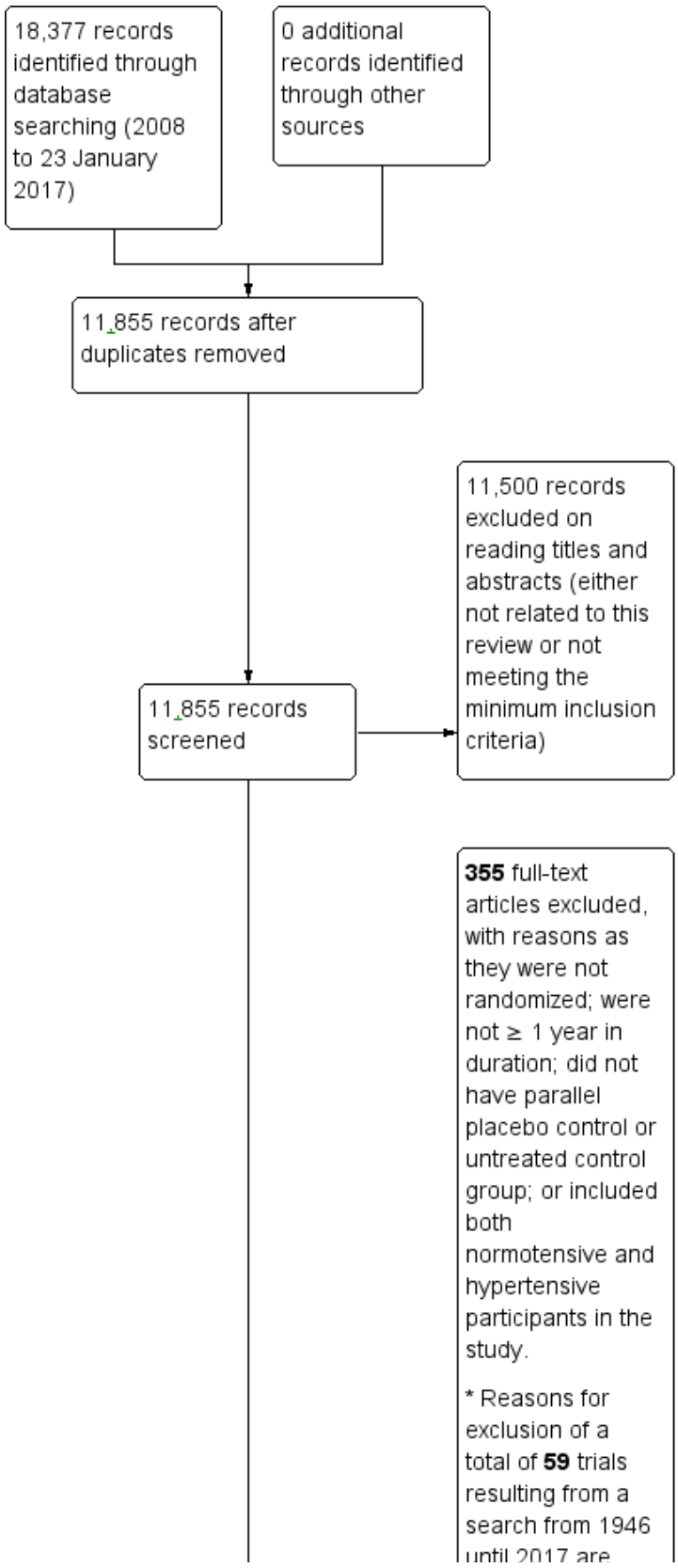
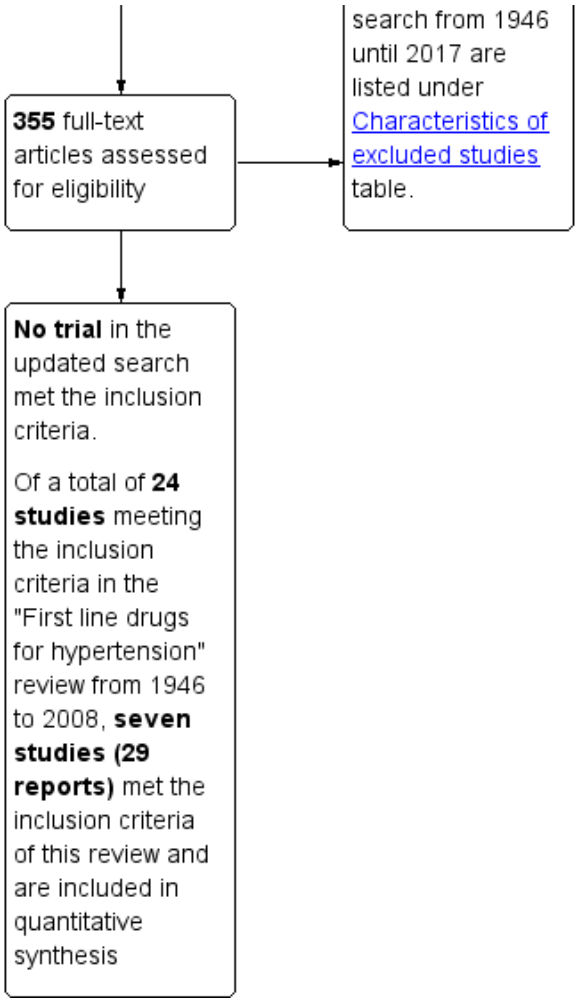


Figure 1. (Continued)



A total of seven studies (in 27 reports) identified previously in the "First line drugs for hypertension" review (Wright 2009) met the inclusion criteria and provide information in 18- to 59-year-old participants and were therefore included in the quantitative analyses.

Please note that 59 trials including 17 trials from the "First line drugs for hypertension" review (Wright 2009) resulting from literature search from 1946 until 2017 were excluded and reasons for exclusion were listed under the Characteristics of excluded studies table.

Included studies

Seven trials met the inclusion criteria (Carter 1970; VA-II 1970; HSCSG 1974; USPHSHCSG 1977; VA-NHLBI 1977; MRC-TMH 1985; Oslo 1986).

This review included 17,327 (88%) participants aged 18 to 59 years from a total of 19,684 randomized participants from the seven included studies in adults with hypertension. In the MRC-TMH 1985 trial, we were able to include only the people aged 18 to 59 years. The MRC-TMH study contributed 14,541 (84%) of the total randomized participants with a mean age of 50 years and mean baseline BP of 160/98 mmHg and a mean duration of follow-up of five years. Treatment used in this study was bendrofluazide 10 mg daily or propranolol 80 mg to 240 mg daily and with methyldopa added if required.

Refer to the Characteristics of included studies table and Table 1 for details regarding baseline characteristics for all included participants. No data regarding baseline characteristics was available for the specific 18- to 59-year-old subgroup of participants in four trials (Carter 1970; VA-II 1970; HSCSG 1974; MRC-TMH 1985). Three trials included only 18- to 59-year-old participants (USPHSHCSG 1977; VA-NHLBI 1977; Oslo 1986). VA-II 1970 did not provide the age range of included participants. The mean age of participants included in these four trials was 41.3 years.

All seven trials used first-line high-dose thiazide drugs for lowering BP. Two trials evaluated beta-blockers versus placebo (MRC-TMH 1985; Oslo 1986). Three of the seven trials used methyldopa (Carter 1970; MRC-TMH 1985; Oslo 1986). Two trials used reserpine (VA-II 1970; VA-NHLBI 1977). Five trials used a stepped approach to antihypertensive drug administration (Carter 1970; VA-II 1970; VA-NHLBI 1977; MRC-TMH 1985; Oslo 1986). The remaining two trials used a standard fixed dose of drug in the intervention arm.

Two trials included only men (Oslo 1986; VA-II 1970; Oslo 1986). Three trials did not report ethnicity (Carter 1970; MRC-TMH 1985; Oslo 1986). The four remaining trials reported ethnicity for all included participants. African-Americans comprised the following percentages in these trials: HSCSG 1974 80%; VA-II 1970 42%; VA-NHLBI 1977 25%; and USPHSHCSG 1977 28%. Three trials based entry on DBP (VA-II 1970; USPHSHCSG 1977; VA-NHLBI 1977). Four trials based entry on either SBP or DBP (Carter 1970; HSCSG 1974; MRC-TMH 1985; Oslo 1986).

Definition of stroke differed across trials. In more recent trials, it was defined as the presence of neurological deficit lasting more than 24 hours. Older trials (such as HSCSG 1974) defined stroke as a neurological deficit lasting more than 24 hours or a marked increase in transient ischaemic attacks (twice the weekly prerandomization level of occurrence, more than four per week or deterioration of more than 8 points in neurological score). VA-NHLBI 1977 defined stroke as typical weakness or paralysis. Some trials did not define stroke. In our opinion combining all strokes (including reversible ischaemic neurological deficit (RIND)), into one outcome is not optimal. More clinically relevant interpretations could be made if strokes were subdivided into three groups: strokes with no disability, strokes with mild disability and strokes with severe disability. The definition of MI and sudden death was consistent across most trials. MI was defined as typical chest pain with ECG changes or increased cardiac enzymes; sudden death was defined as death within 24 hours of first evidence of acute CVD or unrelated to other known pre-existing diseases.

It was possible in most trials to determine which participants were treated for primary or secondary prevention. All trials excluded people with angina and congestive heart failure, as these conditions would require use of antihypertensive drugs for reasons independent of their antihypertensive action. Some trials allowed people with prior MI or stroke if they were not recent (e.g. within the previous three months). Thus, by determining the baseline prevalence of stroke and MI it was possible to calculate the percentage that represented secondary prevention. In six trials, the study population consisted of predominantly ambulatory participants recruited from the community, primary care centres or hospital-based clinics (VA-II 1970; HSCSG 1974; USPHSHCSG 1977; VA-NHLBI 1977; MRC-TMH 1985; Oslo 1986). Two trials were secondary prevention and included stroke survivors who were ambulatory and contributed 301 (0.02%) of total randomized participants(Carter 1970; HSCSG 1974). One trial did not report prevalence of stroke or MI (VA-II 1970). Three trials were 100% primary prevention (USPHSHCSG 1977; VA-NHLBI 1977; Oslo 1986).

One trial reported baseline prevalence of diabetes as 0% (USPHSHCSG 1977). Three trials reported baseline prevalence of smoking (USPHSHCSG 1977 46.7%; MRC-TMH 1985 29.7%; Oslo 1986 41.7%;).

Mean baseline BP for all the trials ranged from 147 mmHg to 176 mmHg for SBP and from 99 mmHg to 103 mmHg for DBP. One trial did not report baseline SBP level (VA-NHLBI 1977). For complete description of the BP inclusion criteria for each study see the Characteristics of included studies table. One trial that contributed the most weight to effect size in this review included mostly people receiving primary prevention followed up for a mean duration of five years with mean baseline BP of 160/98 mmHg (MRC-TMH 1985). The mean duration of follow-up across the seven included studies ranged from two to 10 years.

Excluded studies

Fifty-nine trials resulting from the search from 1946 to 2017 were excluded from this review and reasons for exclusion are provided in the Characteristics of excluded studies table. Twenty-four trials met the inclusion criteria in the "First line drugs for hypertension" review by Wright 2009 and "Pharmacotherapy for hypertension in the elderly review" by Musini 2009, but 17 were excluded from this review. The reasons for excluding them were mostly because they did not report outcomes separately for the 18 to 59 years age group or were conducted in people 60 years or older.

Risk of bias in included studies

We assessed risk of bias for each included study using the Cochrane 'Risk of bias' tool for RCTs as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Potential parameters of methodological quality listed in the 'Risk of bias' table include: method used to randomize participants, whether randomization was completed in an appropriate and blinded manner; whether participants, providers, outcome assessors, or a combination of these were blinded to assigned therapy; whether the control group received a placebo or no treatment; percent of participants who did not complete follow-up (dropouts); percent of participants not on assigned active or placebo therapy at study completion; selective reporting of outcomes and other bias in terms of funding of the trial by the manufacturer.

Refer to Figure 2 for the 'Risk of bias' graph which provides review authors' judgements about each risk of bias item presented as percentages across all included studies. Refer to Figure 3 for the 'Risk of bias' summary which provides review authors' judgements about each risk of bias item for each included study.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

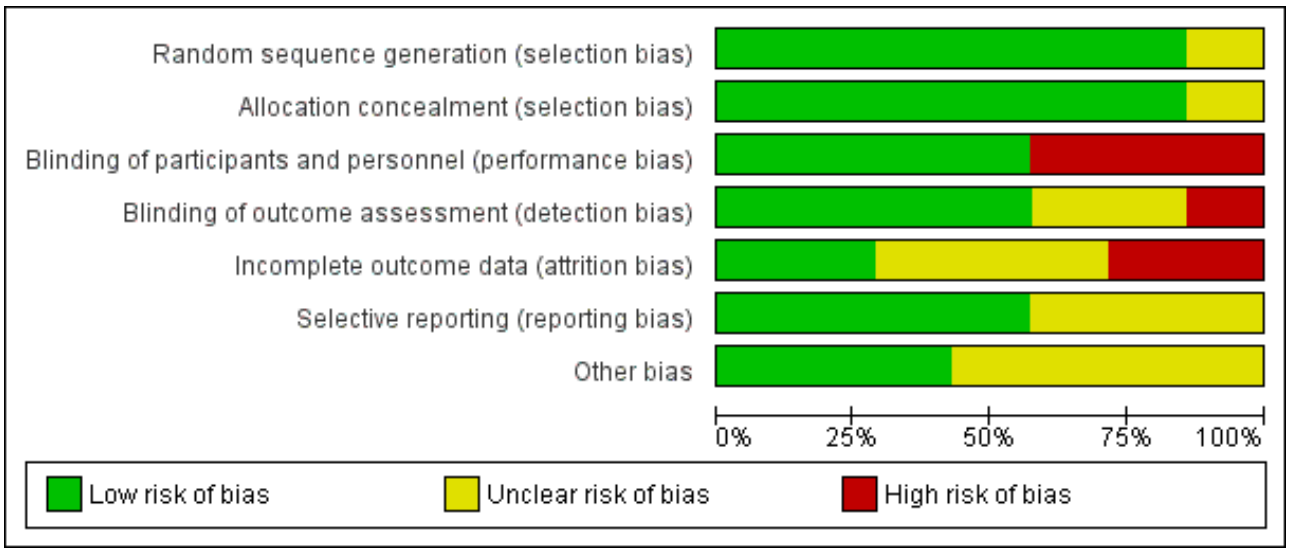
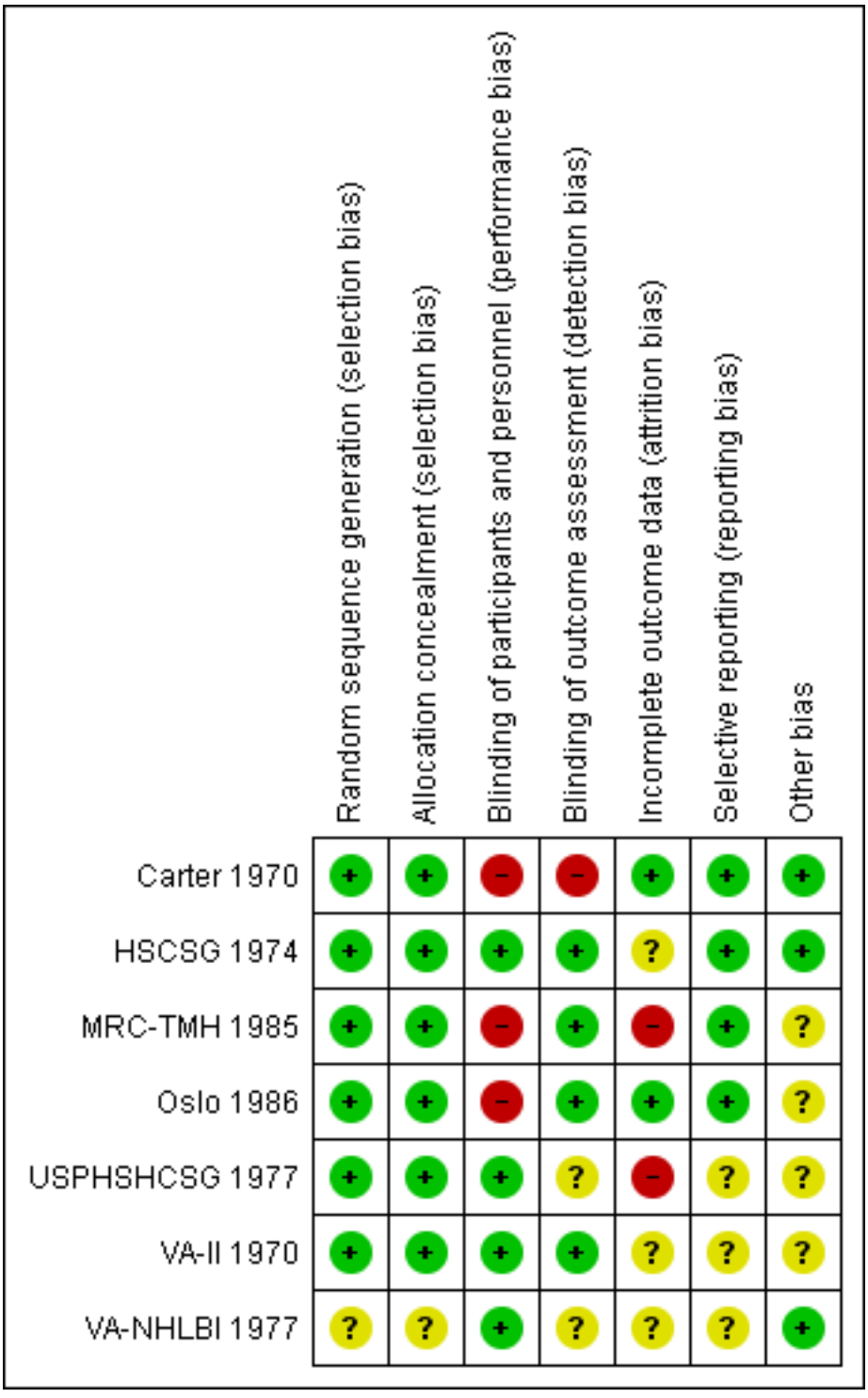


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomization was at low risk of bias in six trials (Carter 1970; VA-II 1970; HSCSG 1974; USPHSHCSG 1977; MRC-TMH 1985; Oslo 1986). It was judged as unclear in VA-NHLBI 1977.

Allocation concealment was at low risk of bias in six trials (Carter 1970; VA-II 1970; HSCSG 1974; USPHSHCSG 1977; MRC-TMH 1985; Oslo 1986), and unclear in VA-NHLBI 1977.

Blinding

Blinding of participant and personnel was at low risk of bias in four trials (VA-II 1970; HSCSG 1974; USPHSHCSG 1977; VA-NHLBI 1977).

It was at high risk of bias in three trials; two as treating physicians were aware of the treatment being prescribed (Carter 1970; MRC-TMH 1985), and one as both participants and treating physicians were aware of the treatment being prescribed (Oslo 1986).

Blinding of outcome assessors was at low risk of bias in four trials (VA-II 1970; HSCSG 1974; MRC-TMH 1985; Oslo 1986). It was at unclear risk of bias in two trials (USPHSHCSG 1977; VA-NHLBI 1977), and at high risk of bias in one trial as study did not mention blinding of physician or outcome assessor (Carter 1970).

Incomplete outcome data

Incomplete outcome data was at low risk of bias in two trials (Carter 1970; Oslo 1986), at unclear risk of bias in three trials (VA-II 1970; HSCSG 1974; VA-NHLBI 1977), and at high risk of bias in two trials (USPHSHCSG 1977; MRC-TMH 1985). In the MRC-TMH 1985 trial, participant participation was terminated in the event of non-fatal stroke or MI. In the USPHSHCSG 1977 trial, attrition rate was high due to dropouts or occurrence of morbid events. Vital statistics information was unknown in 26 participants who dropped out.

Selective reporting

Selective reporting was at low risk of bias in four trials (Carter 1970; HSCSG 1974; MRC-TMH 1985; Oslo 1986), and at unclear risk of bias in three trials (VA-II 1970; USPHSHCSG 1977; VA-NHLBI 1977).

Other potential sources of bias

Other potential bias in terms of funding by the manufacturer was at low risk of bias in three trials (Carter 1970; HSCSG 1974; VA-NHLBI 1977), and at unclear risk of bias in four trials (VA-II 1970; USPHSHCSG 1977; MRC-TMH 1985; Oslo 1986).

Effects of interventions

See: **Summary of findings for the main comparison** Antihypertensive drug therapy compared to control for hypertension in adults aged 18 to 59 years

See Summary of findings for the main comparison.

All-cause mortality

Antihypertensive drug therapy as compared to placebo or untreated control had no effect on all-cause mortality (RR 0.94, 95% CI 0.77 to 1.13; participants = 16,776; studies = 5; I^2 = 43% Analysis 1.1).

Data from two studies (VA-II 1970; HSCSG 1974) were not provided in the original Mulrow 1998 review for the 18- to 59-year-old subgroup. These two studies contributed 551 (3.2%) of total randomized participants included.

Cardiovascular mortality plus morbidity

Antihypertensive drug therapy as compared to placebo or untreated control reduced cardiovascular mortality plus morbidity (RR 0.78, 95% CI 0.67 to 0.91; participants = 17,278; studies = 6; I^2 = 13%; Analysis 1.2).

The original Mulrow 1998 review and the Carter 1970 study did not provide total cardiovascular mortality plus morbidity data in 29 (0.2%) of total randomized participants.

Cerebrovascular mortality plus morbidity

Antihypertensive drug therapy as compared to placebo or untreated control reduced stroke (RR 0.46, 95% CI 0.34 to 0.64; participants = 17,278; studies = 6; I^2 = 40%; Analysis 1.3).

Coronary heart disease mortality plus morbidity

Antihypertensive drug therapy as compared to placebo or untreated control did not reduce coronary heart disease (RR 0.99, 95% CI 0.82 to 1.19; participants = 16,241; studies = 4; I^2 = 0%; Analysis 1.4).

Withdrawal due to adverse events

Data for withdrawal due to adverse events in the 18- to 59-year-old subgroup were not available in four trials (VA-II 1970; HSCSG 1974; VA-NHLBI 1977; MRC-TMH 1985). Three trials report this outcome (Carter 1970; USPHSHCSG 1977; Oslo 1986). However, two trials reported no adverse events in either the treatment and the control groups (Carter 1970; Oslo 1986). The RR was based on one study (RR 4.82, 95% CI 1.67 to 13.92; participants = 1223; study = 1; Analysis 1.5) (USPHSHCSG 1977).

Withdrawal due to adverse events was not available in the 18- to 59-year-old subgroup in one trial (MRC-TMH 1985).

Decrease in systolic and diastolic blood pressure

Four trials reported data for DBP in 18- to 59-year-old subgroup of participants at end of 1 year (USPHSHCSG 1977; VA-NHLBI 1977; MRC-TMH 1985; Oslo 1986), and three studies reported data for SBP (USPHSHCSG 1977; MRC-TMH 1985; Oslo 1986). Therefore, we added this outcome to the list of secondary outcomes in the review.

Antihypertensive drug therapy significantly lowered both SBP and DBP as compared to the control group. Since heterogeneity was significant for BP data results were presented using a random-effects model (SBP: MD -14.98, 95% CI -20.44 to -9.52; participants = 14,845; studies = 3; I^2 = 95%; Analysis 1.6; DBP: MD -7.62, 95% CI -10.55 to -4.69; participants = 15,857; studies = 4; I^2 = 96%; Analysis 1.7).

Sensitivity analysis

In a sensitivity analyses to test the robustness of the overall treatment effect size, we deselected trials based on placebo controlled versus untreated group; double-blind versus open-label or single-blind trials; trials using combined starting drugs as stepped up therapy versus fixed dose therapy; and secondary prevention versus mostly primary prevention. In all these instances, there were no clinically important changes in the treatment effect.

DISCUSSION

Summary of main results

This review summarizes the effects of antihypertensive drug therapy for elevated BP in adults aged 18 to 59 years. The pooled data showed that using antihypertensive drug therapy (mostly high-dose thiazide diuretics) reduced cardiovascular mortality and morbidity primarily due to a reduction in cerebrovascular mortality and morbidity, but had no effect on all-cause mortality or coronary heart disease. Withdrawals due to adverse events were increased

with drug therapy. The mean decrease in SBP/DBP at end of 1 year was 15/8 mmHg.

Overall completeness and applicability of evidence

The subgroup of people 18 to 59 years of age from the MRC-TMH 1985 study represented 84% of total randomized participants and thus contributed the most to the treatment effect size for all mortality and morbidity outcomes. Therefore, the evidence from this review is most applicable to people who were eligible for this study. The mean age of participants was 50 years and the mean baseline BP was 160/98 mmHg. This means that about half of the participants would be in the mild hypertension range and half would be in the moderate hypertension range. Most of the participants (97.8%) were being treated for primary prevention. The mean duration of follow-up was five years. Treatment used in this study was first-line bendrofluazide 10 mg daily or first-line propranolol 80 mg to 240 mg daily and methyldopa was added if required.

In this review, in five trials, about 40% of the participants did not achieve the DBP goal of less than 90 mmHg although three trials used stepped care therapy (VA-II 1970; MRC-TMH 1985; Oslo 1986), and two trials used fixed-dose combination therapy (HSCSG 1974; USPHSHCSG 1977). This observation is important to note because it implies that in routine practice a substantial proportion of people with elevated BP are unlikely to be able to achieve BP targets. This does not mean these people will not benefit as BP reduction is only partly responsible for the risk reduction of antihypertensive treatment (Boissel 2005).

The data on withdrawals due to adverse events was incomplete as only three out of seven trials reported this outcome, with two trials (total participants = 834) reporting zero events in both arms. MRC-TMH 1985 was not included in the withdrawals due to adverse events outcome as that outcome was not available separately for the 18- to 59-year age group. However, withdrawals due to adverse events were increased by drug treatment in the full MRC-TMH 1985 trial (RR 4.81, 95% CI 4.15 to 5.58; absolute risk increase 8.9%). This is very similar to the estimate from the present review (RR 4.82; absolute risk increase 3.8%), which primarily represents the results of the USPHSHCSG 1977 trial (participants = 389). Even though we have graded this outcome as very low quality evidence, it is likely a reasonably robust estimate.

The thiazide arm of the MRC-TMH 1985 trial was classified as high-dose thiazide in the "First line drugs for hypertension" review (Wright 2009). That review concluded that using low-dose thiazide was beneficial in terms of reducing all-cause mortality, total cardiovascular events, coronary heart disease and stroke. This benefit for coronary heart disease and all-cause mortality was not observed in first-line high-dose thiazide trials. Thus, first-line low-dose thiazides are preferred, even though we do not have any evidence for low-dose thiazides in the age group studied here.

We calculated the absolute risk reduction (ARR) and NNTB for clinical outcomes that were significantly reduced with antihypertensive therapy compared to placebo or untreated control groups. For cardiovascular mortality plus morbidity, the relative risk reduction was 22%, ARR was 0.9% and NNTB was 112. For cerebrovascular events (fatal and non-fatal stroke) the relative risk reduction was 64%, ARR was 0.7%, and NNTB was 143. This means that approximately 112 people need to be treated for about five years to prevent one adverse cardiovascular event and most of this benefit comes from a reduction in stroke (cerebrovascular mortality and morbidity).

Sensitivity analyses did not show any clinically important changes in the treatment effect.

MRC-TMH 1985 also contributed more than 90% of the weight to the estimate of BP reduction in this review. Therefore, the mean BP reduction found in this review was close to that seen in the MRC-TMH 1985 trial. The BP lowering effect was greater in the other trials, which resulted in high heterogeneity. This is likely because the design and number of drugs used in the trials differed.

Quality of the evidence

The overall quality of the evidence was graded using online GRADEpro software (GRADEpro). The 'Summary of findings' table provided the grading of the quality of evidence for each clinically important outcome. All-cause mortality, cardiovascular mortality plus morbidity, cerebrovascular mortality plus morbidity and coronary heart disease mortality plus morbidity were downgraded to low quality evidence because of high risk of performance and attrition bias as well as lack of reporting of data from several trials that had to be excluded (Summary of findings for the main comparison). Low quality evidence means our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Withdrawal due to adverse events was downgraded to very low quality evidence as it was only reported in three of the seven trials meeting the inclusion criteria. Very low quality evidence means we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Since one study with high risk of performance and attrition bias provided most of the data to the estimated effect size, it is likely to be an overestimate of the true effect (MRC-TMH 1985).

Potential biases in the review process

Reporting bias is possible as eight studies (met the inclusion criteria but did not report data in the 18- to 59-year-old subgroup of participants separately and thus were excluded from this review (HOPE HYP 2000; TEST 1995; UKPDS 1998; VA-I 1962; Wolff 1966; Anon 1973; ATTMH 1984; PATS 1995). Availability of data for all clinically relevant outcomes from all randomized studies meeting the inclusion criteria in this age group is needed.

Three trials combined a reserpine derivative with thiazide as first-line drug therapy (VA-II 1970; HSCSG 1974; USPHSHCSG 1977). The MRC-TMH 1985 trial, which contributed the most weight in this review, added methyldopa if needed to first-line high-dose thiazide or beta-blocker therapy. Therefore, results of this review are mostly applicable to those treatment approaches.

Since all seven included studies used high-dose thiazides, at present we do not have evidence for low-dose antihypertensive drug therapy as compared to placebo or untreated control in adults aged 18- to 59-years with primary hypertension. Given the findings and conclusions of the first-line drug review regarding all-cause mortality and morbidity benefits of using low-dose thiazide (Wright 2009), we recommend future RCTs compare first-line low-dose

thiazide with other first-line classes of antihypertensive drugs in young adults aged 18 to 59 years.

Agreements and disagreements with other studies or reviews

This is the first systematic review of drug therapy in adults aged 18 to 59 years with elevated BP. The ARR in adults aged 18- to 59-years in this review for cardiovascular mortality and morbidity was small (0.9%) with an NNTB of 112 over five years. It is important for clinicians and participants to know the approximate magnitude of benefit in this setting. For people aged 60- to 79-years the absolute reductions over five years were greater, total cardiovascular events, ARR 3.8% with an NNTB 26 over five years (Musini 2009).

Several guidelines to treat people with hypertension have been published. The eighth revision of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) mainly based their recommendations on evidence from RCTs. However, five out of 10 recommendations are based on expert opinion (James 2014).

They recommended the following:

- thiazide-type diuretics, ACE inhibitors, ARBs and calcium channel blockers as the initial therapy of choice. Although all these drug classes have comparable outcome benefits they concluded that thiazide-type diuretics are superior to the other three classes in terms of heart failure;
- specific recommendation in people aged less than 60 years, treatment goal is SBP less than 140 mmHg (expert opinion - grade E evidence);
- in the general population aged less than 60 years, the target should be DBP less than 90 mmHg and treatment should be initiated above this value (for ages 30 to 59 years, strong recommendation grade A; for ages 18 to 29 years, expert opinion - grade E);
- in the general population excluding black people (including people with diabetes), initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, ACE inhibitor or ARB (general population moderate recommendation - grade B and for black people with diabetes weak recommendation - grade C);
- beta blockers are no longer considered as an initial therapy option.

The European Society of hypertension (ESH) 2013 guidelines recommend diuretics, beta-blockers, calcium channel blockers, ACE inhibitors and ARBs are included as viable options for initial hypertension therapy. Goal BP in people with diabetes mellitus is less than 140/85 mmHg. Recommendation for specific age group less than 60 years is SBP/DBP less than 140/90 mmHg (Mancia 2013).

The American Society of Hypertension/International Society of Hypertension (ASH/ISH) recommend ACE inhibitors or ARB as initial therapy in non-black people under 60 years of age; a calcium channel blocker or thiazide diuretic is recommended for black people (Weber 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Antihypertensive drugs used to treat predominantly healthy adults aged 18 to 59 years with mild to moderate primary hypertension have a small absolute effect to reduce cardiovascular mortality and morbidity (0.9% over a five-year period) primarily due to reduction in cerebrovascular mortality and morbidity (0.7%). All-cause mortality and coronary heart disease were not reduced. There is lack of good evidence on withdrawal due to adverse events.

Implications for research

Long-term randomized controlled trials of at least 10 years' duration are needed to investigate which first-line drug is best in people in this age group as they will potentially be taking these drugs over a long duration. Future randomized controlled head to head studies should compare first-line low-dose thiazides versus other first-line classes and measure all-cause mortality, total serious adverse events and total cardiovascular serious adverse events. Long-term high-quality observational studies may also provide valuable additional information.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Carter 1970

Methods	Randomized, single site study conducted in UK. Participants were stroke survivors admitted to hospital and followed in clinics.
Participants	99 participants of which 71 were aged 18 to 59 years; 54% men; age range: 40-79; mean: 69 years; race/ethnicity: not reported. Mean BP at entry: not reported. **Pre-existing factors:** stroke: 100%; BP entry criteria: SBP > 160 mmHg and DBP < 110 mmHg) or DBP ≥ 110 mmHg irrespective of SBP. **Exclusion criteria:** cerebral haemorrhage; embolism; tumour; accelerated hypertension; "those with an obvious need for hypotensive therapy;" left ventricular failure; congestive cardiac failure; gross radiological cardiac enlargement; various cardiac arrhythmias or evidence of renal failure. **Mean follow-up:** 4.0 years.
Interventions	**Treatment:** first choice: thiazide diuretic (dose or type of thiazide not specified; assumed to be high-dose thiazide); second choice: methyldopa; third choice: bethanidine, debrisoquine or guanethidine. **Control:** observation without placebo.
Outcomes	All-cause mortality; stroke; CHD; CHF not reported for 18- to 59-year-old subgroup.
Notes	Definition of total cardiovascular outcomes: not reported. Dropouts due to adverse events: not reported. Quality of life or functional status outcomes: not reported. Percentage of participants not on assigned therapy at study end: not reported. Difference in BP at study end: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Placed at random into treated (50) or control (49) groups. The two groups matched reasonably closely with regard to numbers, age, sex, and severity of hypertension." Comment: method of randomization not described. Probably randomization achieved as groups matched at baseline.
Allocation concealment (selection bias)	Low risk	Method for allocation concealment not mentioned. Probably achieved as groups matched well at baseline.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Did not state blinding of participants or personnel. Treating physicians aware of treatment being prescribed.

Carter 1970 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	No mention blinding of outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "2 out of 99 patients (2%) have been lost to follow-up, a treated man aged 65 and untreated women of 70 - so results are available for 49 treated and 48 untreated patients." Comment: attrition rate was low and although reason for loss to follow-up not mentioned, it could not have affected the outcome analysis.
Selective reporting (reporting bias)	Low risk	Protocol not available to confirm reporting bias. Mortality rate and recurrence rate of strokes mentioned as study objectives were reported in results section. Quote: "Figures for minor strokes or transient cerebral ischaemic attacks are not available."
Other bias	Low risk	"Part of the expenses of this research project was covered by a grant from the clinical research subcommittee of the North West Metropolitan Regional Hospital Board."

HSCSG 1974

Methods	Randomized, double-blind, placebo-controlled trial conducted in USA with a 6-week drug run-in phase.
Participants	Ambulatory stroke survivors with mild to moderate hypertension, 80% African-Americans, mean age 59 years, range < 75 years, 60% men. Baseline SBP/DBP 167/100 mmHg, pulse pressure 67 mmHg. 80% of participants had completed stroke in year before randomization. 16% had mixtures of completed stroke and TIA, and 4% had only TIAs. **Inclusion criteria:** SBP ≥ 140-220 mmHg and DBP 90-115 mmHg and stroke or TIA or both in previous year. Ambulatory, capable of long-term attendance at treatment clinic, < 75 years of age and no concomitant disease that might be influenced adversely by prolonged treatment with drug or placebo. **Follow-up:** 3 years.
Interventions	Treatment: deserpidine 1 mg + methyclothiazide 10 mg. Control: no treatment.
Outcomes	All-cause mortality, stroke, CHD, CHF, SBP and DBP.
Notes	Stroke endpoint defined by same criteria for entry into study. Also confirmed by a majority of a committee consisting of 2 members outside of the study and the Central Registry neurologist. Marked increase in frequency of TIAs (twice the weekly prerandomization level of occurrence and > 4 per week), or a deterioration of more than 8 points in the neurological score also qualified as a stroke endpoint. Scoring system of residual deficits by neurologist was based on total of 100 points, allowed a maximum of 35 points for level of consciousness and mentation, 9 points for cranial nerve function, 30 points for motor system, 3 points for reflexes, 3 points for sensory function and 20 points for "health and performance" function. Quote: "The study was terminated earlier than planned when it became evident that further follow-up would not significantly affect the results. All patients without endpoints were under observation for at least one year; the mean follow-up period for all individuals including those with end points was 27.4 months, and for those not having endpoints, it was 38.6 months."

HSCSG 1974 *(Continued)*

Mulrow 1998 provided data for cardiovascular mortality and morbidity and cerebrovascular mortality and morbidity in people aged ≥ 60 years for this study which is referenced as **HTN COOP 1974**. Data on all-cause mortality not provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "A prospective double blind cooperative study was undertaken to determine the influence of treatment on the prognosis in stroke survivors with mild to moderate hypertension. If no intolerable side effects occurred, the patient was placed on a regimen of two tablets daily of randomized medication." "To ensure that drug and placebo were balanced among groups with characteristics of possible prognostic importance, patients were divided into cells based on these characteristics, and drug or placebo was prescribed to maintain a balance within these cells. The characteristics for which this randomization was conducted were sex, race, diastolic blood pressure above or below 100 mm Hg, and the four stroke categories." "Although no effort was made to assure an equal distribution of drug-treated and placebo-treated patients within each clinic, the drug-placebo ratio differed appreciably in only two of the ten clinics." "No statistically significant differences were noted in the frequency of abnormalities in the laboratory findings, ECGs, and chest X ray films between the drug and placebo groups." Comment: randomization probably done. However, method for random sequence generation not mentioned. However, baseline characteristics well matched.
Allocation concealment (selection bias)	Low risk	Quotes: "The bio-statistical section was responsible for assignment of patients to drug or placebo regimens, distribution of medication by mail to the individual clinics, data preparation, coding, and analysis." "For use in an emergency, a sealed envelope held by a disinterested person at the local clinic identified the type of medication the patient was receiving" (page 410). Comment: method of allocation concealment not reported; however, baseline characteristics well matched.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "A prospective double blind cooperative study." "Neither the doctor nor the patient was aware of whether placebo or drug had been supplied. For use in an emergency, a sealed envelope held by a disinterested person at the local clinic identified the type of medication the patient was receiving." Comment: participants and treating physicians blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "the report of the stroke event and the neurological findings were submitted to Central Registry for confirmation. A stroke endpoint was defined by the same criteria for entry into the study. It also was confirmed by a majority of a committee consisting of two members outside of the study and the Central Registry neurologist." "Similarly, any medical event justifying removal of the patient from the study was carefully reviewed and classified into cardiovascular and non-cardiovascular categories. The events of a cardiovascular nature were confirmed by an outside cardiologist."

HSCSG 1974 *(Continued)*

		"Patient records without information concerning blood pressure or type of medication were given to both cerebrovascular and cardiovascular reviewers" (page 410). Comment: outcome assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Five-hundred one patients were exposed to pre randomization drug trial. Forty-nine who entered the drug trial were not subsequently randomized." Comment: of the 452 participants randomized, total withdrawals not reported. Quote: "The study was terminated earlier than planned (3 years follow up) when it became evident that further follow-up would not significantly affect the results. All patients without endpoints were under observation for at least one year; the mean follow-up period for all individuals including those with endpoints was 27.4 months, and for those not having endpoints, it was 38.6 months." Comment: attrition rate not mentioned and how data were analyzed in these participants not reported.
Selective reporting (reporting bias)	Low risk	Comment: protocol not available. Cerebrovascular and cardiovascular outcomes, BP measurements, drug intolerance and laboratory measurements were reported.
Other bias	Low risk	Investigation supported by grants from the National Institute of Neurological Diseases and Stroke.

MRC-TMH 1985

Methods	Randomized, single-blind trial comparing 2 treatments and placebo in ambulatory people in England, Scotland and Wales.
Participants	**Overall randomized participants:** 17,354 (treatment 8700; control 8654); 8306 men and 9048 women; mean age 52 years, range 35-64 years. Ethnicity not reported. Men (49%). Baseline mean SBP/DBP 161.4/98.2 mmHg, pulse pressure 63 mmHg. **Subgroup 18- to 59-year age group:** 14,541 (83.8%) participants (bendrofluazide 3611; propranolol 3674; placebo 7256); men 7863 (54.1%); SBP 160 ± 16.9 mmHg; DBP 94.5 ± 5.8 mmHg; smokers 4321 (29.7%). **Inclusion criteria:** SBP < 200 mmHg and DBP 90-109 mmHg. **Exclusion criteria:** secondary hypertension; taking antihypertensive treatment; normally accepted indications for antihypertensive treatment (such as congestive cardiac failure) present; myocardial infarction or stroke within the previous 3 months; presence of angina, intermittent claudication, diabetes, gout, bronchial asthma, serious intercurrent disease or pregnancy. **Follow-up:** 5 years.
Interventions	**Treatment:** bendrofluazide 10 mg daily, propranolol 80-240 mg daily, + methyldopa if required. **Control:** placebo. Note: 288 participants were randomly assigned to observation only taking no tablets and were merged with placebo.
Outcomes	All-cause mortality, stroke, CHD, total cardiovascular events, SBP and DBP.

MRC-TMH 1985 *(Continued)*

Notes	For age group 18 to 59 years in this trial, data were provided by author FG from the INDANA database. CHF and withdrawal due to adverse event data not available. Note that CHF data were not included in total cardiovascular outcomes in 18- to 59-year-old subgroup.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated at entry... Randomisation was in stratified blocks of eight within each sex, 10 year age group, and clinic." Comment: no information provided for sequence generation. Random sequence generation achieved properly and baseline characteristics were matching.
Allocation concealment (selection bias)	Low risk	No description of method for allocation concealment provided; however, baseline characteristics well matched.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "four treatments: the thiazide diuretic bendrofluazide; placebo tablets that looked like bendrofluazide; the beta blocker propranolol; and placebo tablets that looked like propranolol. The two placebo groups were treated as one in all analyses." Quote: "When the protocol was written, it was judged unreasonable to ask general practitioners to undertake such adjustments in a double blind study, and the trial was therefore single blind only." Comment: participants blinded but not the physicians.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The evidence on which the diagnosis of each terminating event was based was assessed by an arbitrator ignorant of the treatment regimen... The arbitrator used WHO [World Health Organization] criteria for classification." "All events were assessed by an independent arbiter who was blind to the treatment regimen." "Each electrocardiogram tracing was read by two observers who were blind to the treatment regimen; the second reader was also blind to the first reader's coding. If these two readers disagreed, a third reader was used." Comment: adjudication was independent and blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quotes: "All analyses presented here are based on randomised treatment ("intention to treat") categories. Thus data for all participants are presented as if the individual was still in the treatment group to which he was originally randomised, although substantial percentages of patients (see below) were in fact withdrawn from their randomly allocated regimen during follow up." "The total five and a half year cumulative percentages of men who stopped taking their randomised treatment, including both those withdrawn from their randomly allocated regimen but continuing on follow up and those lapsing from the trial, were 43% of the bendrofluazide group, 42% of the propranolol group, and 47% of the placebo group. For women the figures were 33%, 40%, and 40% respectively. The cumulative percentages of people not taking either primary active drug by five and a half years were smaller: 33% of men originally randomised to bendrofluazide and 34% of men randomised to propranolol and 28% and 31% respectively of women."

MRC-TMH 1985 *(Continued)*

		"Events terminating a patient's participation were: stroke, whether fatal or non-fatal; coronary events, including sudden death thought to be due to a coronary cause, death known to be due to myocardial infarction, and non-fatal myocardial infarction; other cardiovascular events, including deaths due to hypertension (ICD [International Classification of Diseases] 400-404) and to rupture or dissection of an aortic aneurysm; and death from any other cause. Clinic staff reported these events to the coordinating centre. The records of all patients who suffered non-fatal terminating events and of any others who lapsed from the trial, whatever the reason, were "flagged" at the Southport NHS [National Health Service] central register to ensure notification of death). Comment: myocardial infarction and stroke were reasons for terminating the study follow-up, except for death flagging. This induces a censoring attrition bias, limited to the occurrence non-fatal events myocardial infarction or stroke.
Selective reporting (reporting bias)	Low risk	No information about prespecified outcomes available on which to make this assessment. However, aim was to study mortality and morbidity, which were reported.
Other bias	Unclear risk	Conflict of interest was not reported. "The working party thanks the general practitioners and nurses collaborating in the trial; the staff at the coordinating centre; the staff of the Wolfson Research Laboratories, Queen Elizabeth Medical Centre, Birmingham, for carrying out the biochemical analyses; Duncan, Flockhart and Co Ltd for tablets of bendrofluazide and placebo; Imperial Chemical Industries Ltd for financial support and for tablets of propranolol and placebo; Ciba Laboratories for supplies of guanethidine; and Merck Sharp and Dohme Ltd for a mobile screening unit, funds for its staffing, and supplies of methyldopa."

Oslo 1986

Methods	Open, randomized trial conducted in ambulatory young men randomized to treatment or no treatment in Norway.
Participants	785 men, mean age 45.3 years, range 40-49 years. Ethnicity not reported. Baseline mean SBP/DBP 156.2/97 mmHg, pulse pressure 59 mmHg. **Inclusion criteria:** SBP 150-179 mmHg and DBP < 110 mmHg. Followed for 5-6 years. Target BP < 140/90 mmHg. **Exclusion criteria:** new or previous CHD; cardiovascular disease; intermittent claudication; CHF or valvular heart disease; drug-treated hypertension during the last year; diabetes mellitus (fasting blood sugar ≥ 8.3 mmol/L); retinopathy (Keith-Wagener grade 3 and 4); renal disease (proteinuria, haematuria, creatinine ≥ 123.8 mmol/L, chronic nephritis); hepatic disease; psychosis; severe neurosis; people regularly treated with psychopharmacological drugs; malignant disease; chronic disease such as rheumatoid arthritis; endocrine disorders; obvious alcohol abuse and social maladjustment; secondary hypertension; electrocardiographic changes at rest: left bundle branch block, atrial fibrillation, S-T segment depressions; marked left ventricular hypertrophy; $R_{max} + S_{max}$ in precordial leads ≥ 45 mm and simultaneous ST-T changes (Minnesota code 4-l) S-T segment depression and T-wave flattening or inversion. **Mean follow-up:** 5 years.
Interventions	**Treatment:** hydrochlorothiazide (95%), methyldopa, and propranolol (26%). At 5-year follow-up, 36.7% were taking hydrochlorothiazide alone, 26% were taking hydrochlorothiazide + propranolol, 20% were taking hydrochlorothiazide + methyldopa and 18% were taking other drugs.

Oslo 1986 *(Continued)*

	Control: no treatment.
Outcomes	Stroke, CHD, all-cause mortality, CHF, SBP and DBP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "During 1973, 785 men, aged 40 to 49, with mild, symptom-free hypertension were randomly assigned for a five-year controlled drug treatment study, 406 men in the treatment group and 379 in the control group." "The randomization was performed by a "random number table"." Comment: participants were randomly allocated using random number tables and the baseline characteristics were similar.
Allocation concealment (selection bias)	Low risk	Method used for allocation concealment not mentioned. Participants and physicians aware of treatment given; however, baseline characteristics were similar.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Drug treatment was started with hydrochlorothiazide. If SBP remained above 140 mm Hg and/or DBP above 90 mm Hg, alpha methyldopa was added. If there were side effects, methyldopa was replaced with propranolol. The control group was not given a placebo." Comment: no mention of blinding, both participants and physicians aware of treatment provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Possible and definite coronary events and other cardiac complications were also evaluated by a "blind" diagnostic board of two independent cardiologists." Comment: blinding of outcome assessors probably done, though it was not clearly stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quotes: "In this study the patients have seen the same physicians and the same paramedical staff during 4 years and the drop-out rate has been small, 0.6 per cent and the same in both groups." "Three men refused the drugs, and 13 (1.7%) dropped out of the study, three in the treatment group and 10 in the control group." "The mean observation time was 66 months (range: 60 to 76). Only 13 (1.7%) men failed to report for regular examinations. However, these men were followed for possible cardiovascular events at the end of the study." Comment: number of dropouts was low and participants were followed until end of study to account for all outcomes.
Selective reporting (reporting bias)	Low risk	Quote: "Each patient with cardiovascular events has been counted once, i.e., the number of events is identical with the number of patients with events. If a patient had more than one event, the most serious was counted. Nobody had both coronary heart disease and a cerebrovascular event." Comment: all outcomes (coronary, cerebrovascular and other events) properly reported and accounted for in results section.

Oslo 1986 *(Continued)*

Other bias	Unclear risk	Conflict of interest not reported. Source of funding not stated.

USPHSHCSG 1977

Methods	Randomized, double-blind, placebo-controlled trial conducted in ambulatory young people in USA.
Participants	389 participants. Mean age 44.3 years, range 21-55 years. 28% African-Americans. 80% men. Baseline mean SBP/DBP 146.9/99 mmHg and pulse pressure 48 mmHg. **Inclusion criterion:** DBP 90-115 mmHg. Target: none (medication was not titrated). **Exclusion criteria:** diabetes mellitus, renal insufficiency, or hypercholesterolaemia; abnormal ECG including single or double Master test; radiographic cardiomegaly; grade III or IV retinopathy; clinical history or findings of previous arterial thrombosis or vascular insufficiency, whether coronary, cerebral or peripheral; CHF; angina pectoris; valvular heart disease; or secondary or correctable hypertension; and known sensitivities to the intervention agents. **Follow-up:** 10 years.
Interventions	**Treatment:** chlorothiazide 500 mg twice daily + rauwolfia serpentina 100 mg twice daily. **Control:** placebo.
Outcomes	All-cause mortality, CHD, stroke, CHF, SBP and DBP.
Notes	Study carried out in middle-aged population with mild hypertension which is itself a low-risk factor for studying mortality and morbidity data in such a population. Study terminated if participant had a stroke.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "Subjects were randomly assigned to treatment or placebo and then matched by race and sex for two broad age groups (under 46 and 46-55). The randomization was carried out within each of the six participating clinics" (page 100). "The distribution of all pre-treatment characteristics into the active drug and placebo groups was uniform." Comment: randomization carried out, but method used for generation of random numbers not specified.
Allocation concealment (selection bias)	Low risk	Quote: "At the conclusion of the trial period, subjects were randomly assigned either active or placebo treatment, and this medication was substituted for the identical placebo of the trial period and administered in double-blind fashion. Active therapy consisted of chlorothiazide, 500 mg, plus rauwolfia serpentina, 100 mg, in one tablet taken twice daily. There was no intervention on diet or smoking or other behavioral factors." Comment: allocation carried out randomly but methodology used to conceal allocation not mentioned; however, baseline characteristics well matched.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "At the conclusion of the trial period, subjects were randomly assigned either active or placebo treatment, and this medication was substituted for the identical placebo of the trial period and administered in double-blind fashion."

USPHSHCSG 1977 *(Continued)*

		"The complications were also classified in terms of those events considered likely to be the consequence of elevated pressure per se and those which are predominantly associated with vascular sclerosis (Table 2). All such events were reviewed by two consultants otherwise unassociated with the trial, who were provided with all pertinent information except knowledge of the treatment regimen." Comment: participants and treating physicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quotes: "administered in double-blind fashion." "Follow-up continued for another 4 months, the last 2 weeks of which included home blood pressures again. At that point the annual examination procedures were repeated. Thereafter, the regimens were unblinded and investigators were at liberty to treat as clinically indicated." "Of the complications observed, only stroke required termination from the regimen to which they were randomized. For myocardial infarction it was elective, depending on the clinical circumstances. Thus, by design, most subjects continued on the same double-blind follow-up after their first morbid event and were at risk for additional subsequent events. Others were followed on known medication." Comment: blinding of outcome assessor not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quotes: "Of importance in considering the morbidity and side effects data in this report is the fact that there was no differential dropout rate between the treatment and control groups (33.2% vs. 34.7%). This applies to those who simply failed to return ("Lost to Follow-up") as well as those who voluntarily "withdrew" from assigned therapy but remained under follow-up. The number for whom vital status is unknown is also similar in the two groups (14 vs.12)." "During that time, 206 (52.9%) were terminated from their assigned regimen (Table 5). Dropouts accounted for 132 (33.9%), of whom 75 have been lost to regular follow-up. The vital status of 26 of the dropouts is unknown. Drug intolerance necessitated terminations in 23 cases and major morbid events in 27, four of which were deaths. The remainder of those terminated have continued under regular follow-up on known medications, including 24 who were terminated as treatment failures on the basis of progressive elevation of blood pressure to above a predetermined level." "The dropout rate of 33.9% overall is within that allowed for in the calculation of sample size (5% per year of follow-up). At the beginning of closeout, one-half remained on their assigned coded medication." Comment: attrition rate high. Attrition rates per year not mentioned as cut-off was kept at 5% lost to follow-up, and if > 5% the outcome measures will be affected.
Selective reporting (reporting bias)	Unclear risk	Comment: secondary and tertiary outcomes as mentioned in the objectives not mentioned in results section.
Other bias	Unclear risk	Comment: conflict of interest not reported. Source of funding not stated.

VA-II 1970

Methods	Randomized, double-blind, placebo-controlled study conducted in ambulatory men in USA.

VA-II 1970 *(Continued)*

Participants	380 men, mean age 52 years, range not reported. 42% participants were African-Americans. 100% men. Baseline mean SBP/DBP 162/104 mmHg and pulse pressure 58 mmHg. **Inclusion criterion:** DBP 90-114 mmHg. **Exclusion criteria:** history of severe hypertensive complication such as a cerebral or subarachnoid haemorrhage, hypertensive neuroretinopathy, dissecting aneurysm or renal failure, but did not include atherosclerotic complications such as coronary artery disease or cerebrovascular thrombosis; people with surgically curable hypertension, unrelated fatal diseases such as malignant tumours, people unwilling or unable to return to clinic and poorly motivated or otherwise unco-operative or unreliable people. **Follow-up:** 3.7 years.
Interventions	**Treatment:** step 1: hydrochlorothiazide 100 mg + reserpine 0.2 mg; step 2: hydralazine 75-150 mg. **Control:** placebo.
Outcomes	All-cause mortality, CHD, stroke, CHF, SBP and DBP.
Notes	Study is referenced as **VA COOP** in Mulrow 1998 review. The review provides data on total cardiovascular mortality + morbidity, cerebrovascular mortality + morbidity, and CHD mortality + morbidity in people aged ≥ 60 years. However, data on all-cause mortality were not provided in Mulrow 1998 review. Quotes: "The study was terminated in the subgroup of 143 patients whose diastolic blood pressures averaged 115 through 129 mm Hg prior to randomization." "Many uncooperative and unreliable patients were identified and eliminated from the trial on the basis of pill counts, urine fluorescence test results, and irregularity of clinic attendance during a pre randomization observation period. Treatment obviously would not have been as effective in a group of patients less carefully selected with regard to their desire to cooperate. The population was further limited in that it excluded female patients and patients with labile hypertension whose diastolic blood pressures averaged lower than 90 mm Hg during the fourth through the sixth day of hospitalization."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Three hundred and eighty male hypertensive patients with diastolic blood pressures averaging 90 to 114 mm Hg were randomly assigned to either active antihypertensive agents or placebos." Comment: although method used for random sequence generation not stated it was probably done. Tables 1 and 2 indicated that the two groups were comparable according to the indicated variables.
Allocation concealment (selection bias)	Low risk	Quote: "Accepted patients were then randomly assigned double-blind to either active drugs or placebos." Comment: method used for allocation concealment not reported; however, baseline characteristics well matched.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "Accepted patients were then randomly assigned double-blind to either active drugs or placebos." "Active drugs consisted of two types of tablets, one being a combination tablet containing 50 mg hydrochlorothiazide and 0.1 mg reserpine which was given twice daily. The other was 25 mg of hydralazine hydrochloride given three times daily. The latter medication was raised to 50 mg three times daily if the diastolic blood pressure remained at 90 mm Hg or higher. Obviously, practical-

VA-II 1970 *(Continued)*

		ly all of the patients in the placebo group had their "doses" raised to this level." "Patients in the control group received placebos identical in taste and appearance to the active drugs." "In order to avoid losses to protocol because of side effects presumably caused by one or the other of the two agents, provision was made to permit substitution of a tablet which contained either reserpine or hydrochlorothiazide alone and omitted the offending medication. These special tablets were made available on request of a participating physician. Similar appearing placebo tablets were made available for the control patients and the physician did not know whether the substitution represented active drugs or placebos." Comment: trial was double-blind where participants and physicians were not aware of treatment allocated to either group.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "The records of the patients reported as having assessable morbid events were reviewed by two consulting physicians who had not participated in the trial." "All available data pertaining to each organic complication, except the type of protocol treatment and the level of blood pressure, were presented to the reviewers and their decisions regarding the occurrence and classification of an event according to the definitions given in the protocol (see list of assessable events at the end of the communication) were accepted as final." Comment: outcome assessors probably blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quotes: "Fifty-six or 15% of the 380 randomized patients were classified as drop-outs during the course of the trial. Of this number 27 had been randomized to receive placebos and 29 to receive active drugs. The average period of follow up prior to dropping out was 17.6 months with a range from less than 1 month to 49 months." "Thus, the earliest entrants were observed for 5.5 years and the latest entrants for a minimum of 1 year. The average potential duration of observation, disregarding losses and terminations, was 3.9 years for the control group and 3.7 years for the treated patients. However, because of the losses and terminations due to elevated diastolic blood pressure described below, the actual duration of post randomization observation was 3.3 years for the control group and 3.2 years for the treated patients." Comment: reasons for dropouts mentioned; though reasons were not given separately for the 2 groups. How data were analyzed in these participants not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: protocol not available. Mortality (various causes of death) and morbidity (various terminating morbid events other than death) data reported.
Other bias	Unclear risk	Conflicts of interest not reported.

VA-NHLBI 1977

Methods	Randomized, double-blind, placebo-controlled trial conducted in ambulatory people in USA.

VA-NHLBI 1977 *(Continued)*

Participants	Mean age 37.5 years, range 21-50 years. 74% white and 25% African-American and 1% other. 81% men. Baseline mean DBP 93.3 mmHg with 66% having mean DBP 85-95 mmHg at time of randomization. **Inclusion criterion:** DBP 85-105 mmHg. Target < 85 mmHg. **Exclusion criteria:** significant cardiovascular renal abnormalities, insulin-requiring diabetes, treatment with vasoactive drugs, concomitant "fatal" disease, history of depression or of recent (within last 2 years) gout or peptic ulcer, and any conditions felt to make non-compliance likely. **Follow-up:** 2 years.
Interventions	**Treatment:** step 1: chlorthalidone 50 mg, step 2 100 mg (53% chlorthalidone alone), step 3: chlorthalidone 100 mg + reserpine 0.25 mg. **Control:** placebo.
Outcomes	All-cause mortality, stroke, CHD, CHF and DBP.
Notes	No intervention on diet or smoking or other behavioural factors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the conclusion of the trial period, subjects were randomly assigned either active or placebo treatment, and this medication was substituted for the identical placebo of the trial period and administered in double-blind fashion." Comment: method for random sequence generation not specified. Table for baseline characteristics of the 2 groups not provided.
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not mentioned. Baseline characteristics of the 2 groups could not be assessed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The Cooperative Studies Program Central Research Pharmacy was responsible for distribution of coded double-blind study drug to each clinical center and for assuring proper handling of these drugs when they were distributed to the individual subjects." "The blinded active and placebo drugs were both designated by small letters in parentheses; whereas the known drugs were designated by underlined capital letters: C, 2C, 1/2C and R. The protocol defined three standard successive therapeutic steps: (c), (2c), and (2c)+(r). Each subject began (c) when he was randomized." "The study biostatistician supervised data management and reporting. The data center supplied each clinical center with instruction manuals, data forms, randomization numbers, and individual subject identification labels for all forms, drug bottles, sample containers, electrocardiograms, and x-rays." Comment: trial stated as double-blind and probably participants and physicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessor not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "By preliminary count there were 98 losses to study in the active group and 104 in the placebo group, making the total cumulative dropout rate equal

VA-NHLBI 1977 *(Continued)*

		to 20% with a “dropout” being defined as a subject with an appointment overdue for more than 60 days." Comment: dropout rates 19.3% (98/508 participants) in treatment group and 20.6% (104/504 participants) in placebo group. Reasons for loss to follow-up not stated separately for teach group.
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Comment: major and minor morbid events reported with adverse events for each group.
Other bias	Low risk	Quotes: "This project was jointly supported by the Cooperative Studies Program of the Medical Research Service of the Veterans Administration and by an Interagency Agreement (2 Y01-HV-40012-04) awarded by the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health, Education, and Welfare." "A feasibility trial to investigate the practicality of determining the advantages and disadvantages of prompt pharmacologic treatment for mild hypertension was jointly funded by the Veterans Administration and the National Heart, Lung and Blood Institute" (page 286).

BP: blood pressure; CHD: coronary heart disease; CHF: congestive heart failure; DBP: diastolic blood pressure; ECG: electrocardiogram; SBP: systolic blood pressure; TIA: transient ischaemic attack.

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

Study	Reason for exclusion
ADVANCE 2007	Randomi zed controlled trial; 215 collaborating centres in 20 countries from Asia, Australasia, Europe and North America. After 6-week active run-in period, 11,140 pa rticipants with type 2 diabetes aged ≥ 55 years were randomi zed to treatment with fixed combination of perindopril + indapamide or matching placebo, in addition to current therapy. No BP criteria for inclusion. All other treatments continued at discretion of responsible physician, with exception of ACE inhibitors. Participants taking ACE inhibitor other than perindopril had this treatment withdrawn and were offered substitution with open-label perindopril at 2 mg or 4 mg a day. Control group included nonspecific antihypertensive therapy.
ALLHAT 1996	Prospective, randomiz ed, double-blind, active-controlled clinical trial. Drug-drug comparison of different drug classes with no placebo or untreated control group.
Anon 1973	Single -blind, randomi zed, placebo- controlled trial conducted in the UK in 116 men and women aged 45 -69 years with 2 casual, sitting DBP of 100 -120 mmHg on each of 2 occasions separated by an interval of ≥ 2 weeks. Untreated control group received calcium lactate tablets. Treatment group received any combination of bendrofluazide with potassium supplement, methyldopa or debrisoquine ; choice of treatment at discretion of physician. However, data in 45- to 59 -year -old pa rticipants not reported separately.
ATTMH 1984	Australian National Blood Pressure Study, a controlled therapeutic trial of antihypertensive drug treatment in 3427 men and women with mild hypertension. Pa rticipants were aged 30 -69 years and randomi zed to active treatment or placebo. Active group had chlorothiazide 500 mg daily as first-order drug. Thereafter, if blood pressure control was not achieved, dose was increased to 500 mg twice daily or second-order drug (methyldopa, propranolol or pindolol) was added (or both). Subsequently, third-order drugs (hydralazine or clonidine) were given if necessary. Initial objective was to reduce DBP to ≤ 90 mmHg but after 2 years the goal was lowered to 80 mmHg. Of 1721 pa rticipants randomi zed to treatment, 1428 were aged 30 -59 years and of 1706 randomi zed to placebo, 1417 were aged 30 to 59 years.

Study	Reason for exclusion
	Data in the age group 30- to 59 -years were not reported separately.
Berglund 1981	Drug-drug comparison of bendrofluazide 2.5 mg vs propranolol 160 mg with no placebo or untreated control group.
CASTEL 1994	Drug-drug comparison with no placebo or untreated control group. Control group included nonspecific antihypertensive therapy.
Coope 1986	Randomized multisite study comparing antihypertensive treatment to control (observation without placebo) in p eople aged 60- to 79- years.
Dutch TIA 1993	Randomiz ed, double-blind, placebo-controlled trial in 1473 pa rticipants aged > 65 years with TIA or disabling stroke were randomized to atenolol or placebo. Only p eople aged ≥ 65 years were included in this trial.
EWPHBPE 1988	Randomi zed, placebo -controlled, double-blind trial conducted in Europe. Only pa rticipants aged ≥ 60 years were included in this trial.
Fuchs 2011	Randomized, double-blind, clinical trial, controlled by placebo in pa rticipants aged 30-70 years with prehypertension.
GENERIC 2010	Single-centre, randomiz ed, double-blind, placebo-controlled, cross-over trial comparing effects of moexipril and placebo on insulin sensitivity and 24-hour BP control in postmenopausal women with essential hypertension. Only an 8- week trial.
GLANT 1995	Employed alternate allocation (i.e . not random allocation). Drug-drug comparison of delapril 30-120 mg vs several dihydropyridine calcium channel blockers with no placebo or untreated control group.
HANE 1997	Morbidity and mortality outcomes not reported.
HAPPHY 1987	6569 men aged 40-64 years with mild to moderate hypertension randomized to diuretic or beta -blocker therapy. No placebo control group.
HDFP 1982	Treated group included various lifestyle measures in addition to antihypertensive drug therapy. Control group was usual care and participants were not necessarily untreated controls.
HOPE HYP 2000	Double-blind, randomized trial in pa rticipants aged ≥ 55 years with previous coronary artery disease, cerebrovascular disease, peripheral vascular disease or diabetes + 1 additional risk factor (high BP > 160 mmHg or > 90 mmHg, total cholesterol > 5.2 mmol/L, high-density lipoprotein cholesterol < 0.9 mmol/L, current cigarette smoking or known microalbuminuria). Pa rticipants randomized to ramipril 2.5 mg titrating to 10 mg or placebo. Other factor was v itamin E 400 IU/day. Data in 55- to 59 -year- old pa rticipants were not reported separately.
HOT 1995	Evaluated the effects of achieving prespecified levels of DBP control with all pa rticipants receiving antihypertensive treatment. No placebo control group.
HYVET 2003	Randomized, open -label trial conducted in Europe. Only included participa nts aged ≥ 80 years.
HYVET 2008	Randomiz ed, double-blind, placebo -controlled trial. Only included participa nts aged ≥ 80 years.
IDM 2001	Multinational, randomized, double-blind, placebo-controlled study . 590 participants aged 30-70 years with hypertension with type 2 diabetes and microalbuminuria . Participants randomized to irbesartan 150 mg daily or 300 mg daily, and followed for 2 years. Other antihypertensive drugs were prescribed to 56% of the placebo group.

Study	Reason for exclusion
INSIGHT 1996	Prospective, randomiz ed, double-blind trial in Europe and Israel with 6321 participa nts aged 55-80 years with hypertension (BP 150/95 mmHg, or SBP 160 mmHg). Participa nts had ≥ 1 additional cardiovascular risk factor. Participa nts randomly assigned to nifedipine 30 mg in a long-acting gastrointestinal-transport system formulation (3157 participa nts), or co-amilozide hydrochlorothiazide 25 g + amiloride 2 .5 mg (3164 participants). Dose titration by dose doubling, and addition of atenolol 25- 50 mg or enalapril 5- 10 mg. No placebo or untreated control group.
IPPPSH 1985	Randomized, double -blind study in 6357 men and women aged 40-64 years with uncomplicated hypertension. All participa nts received beta -blocker oxprenolol. Participa nts then randomized to either continuing treatment with oxprenolol or receiving placebo. Study medications could be increased or other non -beta-blocker antihypertensive drugs could be added as necessary in both groups with aim of reducing DBP to ≤ 95 mmHg.
Jikei 2007	Did not truly randomiz e participants to treatment arms and control group included non-specific antihypertensive therapy.
Kuramoto 1981	Randomi zed, double-blind, placebo -controlled trial conducted in Japan. Included participa nts aged 60-90 years.
Kuramoto 1994	Head-to-h ead comparison of different drug therapies (nicardipine vs trichlormethiazide) without placebo or untreated control group.
Lewis 2001	Prospective, randomiz ed, double-blind clinical trial. Included participa nts aged 30 -70 years, a documented diagnosis of type 2 diabetes mellitus, hypertension or documented treatment with antihypertensive agents, and proteinuria, with urinary protein excretion ≥ 900 mg per 24 hours. 1715 hypertensive participa nts randomly assigned by a central office to 1 of 3 treatment regimens: irbesartan, amlodipine or placebo. Control group also received antihypertensive medications.
MAPHY 1988	3234 white men aged 40 -64 years randomized to metoprolol or thiazide diuretic. No placebo control group.
Materson 1993	Randomized, double -blind study of 1292 men aged ≥ 18 years with hypertension (DBP 95 -109 mmHg). M ean age 58 ± 10 years. Participa nts randomized to placebo or 1 of 6 drugs: hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem sustained release or prazosin. 546 participa nts were age d < 60 years but results not reported separately .
MIDAS 1996	Drug-drug comparison of hydrochlorothiazide 25 mg vs isradipine 5 mg with no placebo or untreated control group.
Morgan 1980	Allocation to groups not random, based on week of presentation at clinic.
MRCO 1992	Prospective, randomi zed, placebo-controlled, single-blind trial. 4396 participa nts in the UK aged 65-74 years with hypertension (SBP 160-209 mmHg; DBP < 115 mmHg). Trial only included participa nts aged 65-74 years.
NORDIL 2000	Prospective, randomiz ed, open, blinded endpoint study. E nrolled 10,881 participa nts, aged 50- 74 years, at health centres in Norway and Sweden, who had DBP ≥ 100 mmHg. Participa nts randomly assigned to diltiazem or diuretics or both. No placebo or untreated control group.
PATS 1995	Randomi zed, double-blind, placebo -controlled trial conducted in China. 5665 Chinese men (72%) and women (28%) with history of TIA, minor stroke or major stroke without severe disability. Mean age 60 ± 8 years. Baseline BP 154/93 mmHg. 16% of participa nts were not hypertensive with BP < 140/90 mmHg. Mean follow-up 2 years. After single- blind run-in phase on placebo, eligible participa nts were randomi zed to indapamide 2.5 mg treatment or placebo. Data o n 18- to 59- year- old participa nts not reported separately.

Study	Reason for exclusion
PROGRESS 2001	< 50% of participa nts had elevated BP and about 50% of participa nts were receiving other antihypertensive therapy at baseline and throughout trial.
QUIET 2001	Most participa nts did not have elevated BP. 25% of participa nts receiv ed a beta-blocker.
SCAT 2000	> 60% did not have hypertension and about 50% received beta-blockers at baseline and throughout.
Schmieder 2009	Randomized, double-blind, multicentre, placebo- controlled study. After 2- to 4-week placebo run-in, 1124 participa nts were randomized to aliskiren 150 mg, hydrochlorothiazide 12.5 mg or placebo once daily. Forced titration (to aliskiren 300 mg or hydrochlorothiazide 25 mg) occurred at week 3; at week 6, participa nts receiving placebo were reassigned (1:1 ratio) to aliskiren 300 mg or hydrochlorothiazide 25 mg. From week 12, amlodipine 5 mg was added and titrated to 10 mg from week 18 for participa nts whose BP remained uncontrolled. Not a placebo- controlled study of 52 weeks' duration.
SCOPE 2003	4964 participa nts aged 70 -89 years, with SBP 160 -179 mmHg or DBP 90- 99 mmHg, and a Mini Mental State Examination test score > 24. Participa nts randomly assigned to receive the angiotensin receptor blocker candesartan or placebo, with open-label active antihypertensive therapy added as needed. As a consequence, active antihypertensive therapy was extensively used in control group (84% of participa nts). Mean follow-up 3.7 years. No true placebo control group. Both groups allowed some participa nts to take hydrochlorothiazide at baseline and most of control group received antihypertensive therapy.
SHELL 1994	Head-to-head comparison of different drug therapies with no placebo or untreated control group.
SHEP - Pilot 1985	Randomi zed, double-blind, placebo -controlled trial conducted in USA. Participa nts aged > 60 years.
SHEP 1991	Randomi zed, double-blind, placebo -controlled trial conducted in USA. Participa nts aged > 60 years.
Sprackling 1981	Randomi zed, open -label study in welfare home for elderly people. Age range not reported. Mean age 80.7 years. Participa nts randomized to methyldopa 250 mg twice daily or observation without placebo. Data in 18- to 59- year old participants not reported separately.
STONE 1996	Employed alternate allocation (i.e . not random allocation). 4 weeks after group assignment, attending physicians reallocated participants from placebo group to treatment group if their DBP was ≥ 110 mmHg.
STOP 1991	Randomi zed, double -blind, placebo -controlled multisite study in Sweden. Participa nts aged 70-84 years.
STOP-2 1993	Prospective, randomiz ed, double-blind, intervention study compar ing effects of active antihypertensive therapy and placebo on frequency of fatal and non-fatal stroke and myocardial infarction and other cardiovascular death in hypertensive Swedish men and women aged 70-84 years.
Strandberg 1991	5- year long, multifactorial, randomized, controlled primary prevention trial in 1222 middle- aged healthy men. Age range not reported. Mean age 48 years. Treatment group had multiple interventions. Drug treatment (mainly the beta-blockers, propranolol hydrochloride or pindolol, or diuretics, hydrochlorothiazide alone or combined with amiloride hydrochloride for hypertension, or both; probucol mainly for type IIA and clofibrate for type IIB and IV hyperlipidaemias) used if target levels were not reached by advice alone. Control group was usual treatment not untreated control.
Syst China 1993	Allocation to treatment and control groups not randomized (alternate allocation employed).

Study	Reason for exclusion
Syst-Eur 1991	Randomized, double-blind, placebo- controlled trial conducted in Europe. Participa nts aged > 60 years.
TEST 1995	Randomiz ed, double-blind, placebo- controlled trial conducted in Sweden. 720 Swedish participa nts aged > 40 years, within 3 weeks of a stroke or TIA with SBP > 140 mmHg. Participa nts randomized to atenolol or placebo. Data in 40- to 59- year- old pa rti cipants not reported separately.
TOMHS 1995	4- year, multicentre, randomized, double -blind study of 902 men and women aged 45 -69 years. All participants took part in a lifestyle intervention programme to reduce weight, decrease sodium and alcohol intake, and increase leisure physical activity. Participa nts randomized to placebo or 1 of 5 antihypertensive medications. However, data in 45- to 59 -year- old participa nts not reported separately.
UKPDS 1998	Randomiz ed, controlled, open -label trial conducted in the UK. Newly diagnosed participa nts aged 25 -65 years with type 2 diabetes mellitus and hypertension (SBP ≥ 160 or DBP ≥ 90 mmHg (or both) in participa nts not on antihypertensive therapy and SBP ≥ 150 or ≥ 85 mmHg in participa nts on antihypertensive therapy). Tight BP group received captopril 25-50 mg twice daily or atenolol 50-100 mg once daily . Supplemental drugs added were frusemide 20-40 mg twice daily, slow- release nifedipine 10-40 mg twice daily, methyldopa 250-500 mg twice daily, prazosin 1-5 mg 3 times daily given sequentially to achieve target BP. Control group were given treatment if SBP ≥ 200 or DBP ≥ 105 mmHg (or both) (e.g. frusemide, long- acting nifedipine, methyldopa, prazosin given sequentially to control BP). If possible ACE inhibitor s and beta-blockers avoided. Data in 25- to 59- year- old participa nts not reported separately.
VA Coop 1960	425 participa nts (255 participa nts aged < 60 years) with mild, moderately severe or severe hypertension randomized to treatment with placebo or reserpine both alone and in combination with hydralazine in mild cases; in severe cases to 3 blocking agents, pentolinium tartrate, mecamylamine hydrochloride and chlorisondamine chloride each in combination with reserpine. In moderately severe group, both series of therapeutic regimens were utilized to compare ganglionic blocking agents with the less drastic forms of antihypertensive drug therapy. Data in 18- to 59- year- old participa nts not reported separately.
VA-I 1962	Randomiz ed, double-blind, placebo- controlled trial conducted in USA. Participa nts were 30- to 70- year -old men. Participa nts were randomized to treatment: step 1 : hydrochlorothiazide 100 mg + reserpine 0.2 mg + hydralazine 75 mg; step 2: hydralazine 150 mg. Data in 18- to 59- year- old participa nts not reported separately.
VACS 1982	Prospective, multicentre, randomiz ed, double-blind trial. 394 m en aged 21-65 years with hypertension (DBP 95-114 mmHg). Propranolol 80-640 mg daily vs hydrochlorothiazide 50-200 mg daily for 12 months. No placebo control group.
VHAS 1997	Prospective, multicentre, randomiz ed, parallel-group trial. 1414 participa nts in Italy aged 40-65 years with hypertension (mean seated SBP ≥ 160 mmHg and mean seated DBP ≥ 95 mmHg). Drug-drug comparison of chlorthalidone 25 mg vs verapamil 240 mg with no placebo or untreated control group.
White 1995	Not a randomiz ed controlled study. No placebo group and participa nts not randomly allocated to moexipril or moexipril + hydrochlorothiazide.
Wolff 1966	Double -blind randomized study of 87 outpatients aged 21-70 years . Randomized to antihypertensive drug therapy (reserpine 0.25 mg 3 times daily, chlorothiazide 0.5 g twice daily or hydrochlorothiazide 25 mg 4 times daily, and guanethidine by titration given, as needed, on successive visits until standing DBP fell < 90 mmHg or placebo. Data in 21- to 59- year- old participa nts not reported separately.

ACE: angiotensin-converting enzyme ; BP: blood pressure ; DBP: diastolic blood pressure ; SBP: systolic blood pressure ; T IA : transient isch a emic attack .

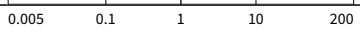
DATA AND ANALYSES

Comparison 1. Antihypertensive drug therapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	16776	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.77, 1.13]
2 Cardiovascular mortality plus morbidity overall	6	17278	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.67, 0.91]
3 Cerebrovascular mortality plus morbidity	6	17278	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.34, 0.64]
4 Coronary heart disease mortality plus morbidity	4	16241	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.19]
5 Withdrawal due to adverse events	3	1223	Risk Ratio (M-H, Fixed, 95% CI)	4.82 [1.67, 13.92]
6 Decrease in systolic blood pressure	3	14845	Mean Difference (IV, Random, 95% CI)	-14.98 [-20.44, -9.52]
7 Decrease in diastolic blood pressure	4	15857	Mean Difference (IV, Random, 95% CI)	-7.62 [-10.55, -4.69]

Analysis 1.1. Comparison 1 Antihypertensive drug therapy versus control, Outcome 1 All-cause mortality.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Carter 1970	6/27	13/22		6.94%	0.38[0.17,0.83]
MRC-TMH 1985	174/7285	178/7256		86.39%	0.97[0.79,1.2]
Oslo 1986	10/406	9/379		4.51%	1.04[0.43,2.52]
USPHSHCSG 1977	2/193	4/196		1.92%	0.51[0.09,2.74]
VA-NHLBI 1977	2/508	0/504		0.24%	4.96[0.24,103.07]
Total (95% CI)	**8419**	**8357**		**100%**	**0.94[0.77,1.13]**
Total events: 194 (Treatment), 204 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.02, df=4(P=0.13); I^2=43%					
Test for overall effect: Z=0.68(P=0.5)					

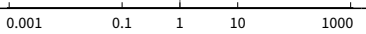


Analysis 1.2. Comparison 1 Antihypertensive drug therapy versus control, Outcome 2 Cardiovascular mortality plus morbidity overall.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
HSCSG 1974	16/132	23/120		6.83%	0.63[0.35,1.14]
MRC-TMH 1985	215/7285	260/7256		73.83%	0.82[0.69,0.98]
Oslo 1986	14/406	18/379		5.28%	0.73[0.37,1.44]
USPHSHCSG 1977	16/193	24/196		6.75%	0.68[0.37,1.23]
VA-II 1970	8/148	21/151		5.89%	0.39[0.18,0.85]
VA-NHLBI 1977	8/508	5/504		1.42%	1.59[0.52,4.82]
Total (95% CI)	**8672**	**8606**		**100%**	**0.78[0.67,0.91]**
Total events: 277 (Treatment), 351 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.72, df=5(P=0.33); I^2=12.65%					
Test for overall effect: Z=3.15(P=0)					

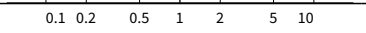
Analysis 1.3. Comparison 1 Antihypertensive drug therapy versus control, Outcome 3 Cerebrovascular mortality plus morbidity.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
HSCSG 1974	17/132	19/120		16.93%	0.81[0.44,1.49]
MRC-TMH 1985	35/7285	76/7256		64.76%	0.46[0.31,0.68]
Oslo 1986	0/406	5/379		4.84%	0.08[0,1.53]
USPHSHCSG 1977	1/193	6/196		5.06%	0.17[0.02,1.39]
VA-II 1970	2/148	10/151		8.42%	0.2[0.05,0.92]
VA-NHLBI 1977	0/508	0/504			Not estimable
Total (95% CI)	**8672**	**8606**		**100%**	**0.46[0.34,0.64]**
Total events: 55 (Treatment), 116 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.65, df=4(P=0.16); I^2=39.85%					
Test for overall effect: Z=4.77(P<0.0001)					



Analysis 1.4. Comparison 1 Antihypertensive drug therapy versus control, Outcome 4 Coronary heart disease mortality plus morbidity.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
MRC-TMH 1985	179/7285	181/7256		86.29%	0.99[0.8,1.21]
USPHSHCSG 1977	15/193	16/196		7.55%	0.95[0.48,1.87]
VA-II 1970	6/148	8/151		3.77%	0.77[0.27,2.15]
VA-NHLBI 1977	8/508	5/504		2.39%	1.59[0.52,4.82]
Total (95% CI)	**8134**	**8107**		**100%**	**0.99[0.82,1.19]**
Total events: 208 (Treatment), 210 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.95, df=3(P=0.81); I^2=0%					



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.12(P=0.91)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.5. Comparison 1 Antihypertensive drug therapy versus control, Outcome 5 Withdrawal due to adverse events.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Carter 1970	0/27	0/22			Not estimable
Oslo 1986	0/406	0/379			Not estimable
USPHSHCSG 1977	19/193	4/196		100%	4.82[1.67,13.92]
Total (95% CI)	**626**	**597**		**100%**	**4.82[1.67,13.92]**
Total events: 19 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.91(P=0)					

Favours treatment 0.01 0.1 1 10 100 Favours control

Analysis 1.6. Comparison 1 Antihypertensive drug therapy versus control, Outcome 6 Decrease in systolic blood pressure.

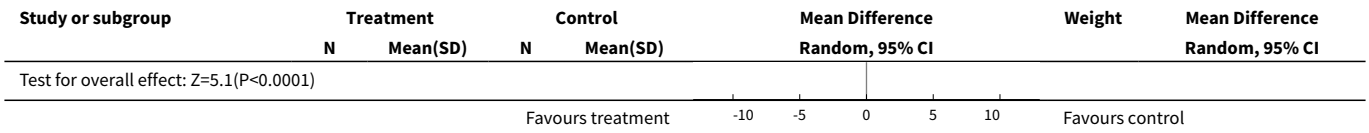
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
MRC-TMH 1985	6824	136.5 (16.9)	6883	147 (17.2)		35.76%	-10.5[-11.07,-9.93]
Oslo 1986	406	130 (16.1)	379	147 (17.9)		33.6%	-17[-19.39,-14.61]
USPHSHCSG 1977	175	-16.5 (19.4)	178	1.5 (16.7)		30.64%	-18[-21.78,-14.22]
Total ***	**7405**		**7440**			**100%**	**-14.98[-20.44,-9.52]**
Heterogeneity: Tau^2=21.63; Chi^2=40.39, df=2(P<0.0001); I^2=95.05%							
Test for overall effect: Z=5.38(P<0.0001)							

Favours treatment -20 -10 0 10 20 Favours control

Analysis 1.7. Comparison 1 Antihypertensive drug therapy versus control, Outcome 7 Decrease in diastolic blood pressure.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
MRC-TMH 1985	6824	86.5 (8.5)	6883	91 (9.2)		26.78%	-4.5[-4.8,-4.2]
Oslo 1986	406	85 (9.9)	379	95 (12)		24.99%	-10[-11.54,-8.46]
USPHSHCSG 1977	175	-10.4 (11.4)	178	-0.6 (11.3)		22.84%	-9.8[-12.17,-7.43]
VA-NHLBI 1977	508	-11.8 (9.9)	504	-5.2 (12)		25.39%	-6.6[-7.96,-5.24]
Total ***	**7913**		**7944**			**100%**	**-7.62[-10.55,-4.69]**
Heterogeneity: Tau^2=8.31; Chi^2=71.22, df=3(P<0.0001); I^2=95.79%							

Favours treatment -10 -5 0 5 10 Favours control



ADDITIONAL TABLES

Table 1. Baseline characteristics of included studies in all randomized participants aged 18 years or older

Study Study design	Number of 18- to 59-year-old participants/total randomized participants (%) Characteristics of all randomized participants in each study	Mean baseline SBP/DBP (mmHg)	Mean age (range)	Control group	Treatment used	Outcomes reported in 18- to 59-year-old participants
Carter 1970 Open label	49/97 (50.5%); included all hypertensive survivors aged < 80 years of ischaemic type major strokes admitted to Ashford Hospital. Men: 57%	165/101	Not reported (40 to 79 years)	Untreated	Stepped-up therapy Bendrofluazide (93%), methyldopa and debrisoquine FU 4.0 years	All-cause mortality
HSCSG 1974 Double blind	252/452 (55.7%). 80% of participants had completed stroke in year before randomization; 16% completed stroke + TIA and 4% TIA only. Severe neurological disability in 9.9% of treated group and 5% of control group. Black: 80% Men: 60%	167/100 77% of the drug treated and 74% of the placebo treated participants had SBP < 180 mmHg	59 years (< 75 years)	Placebo	Fixed-dose therapy Deserpidine 1 mg + methyclothiazide 10 mg FU 3.0 years	Cardiovascular mortality + morbidity Cerebrovascular mortality + morbidity CHD mortality + morbidity
MRC-TMH 1985 Single blind	14,541/17,354 (83.8%). Men: 52%. Primary prevention participants. Refer to exclusion criteria listed in Characteristics of included studies table.	161/98.	52 years (35-64 years)	Placebo 288/12,375 (0.02%) participants randomly assigned to observation taking no tablets and merged with placebo	Stepped-up therapy Bendrofluazide 10 mg daily (71% monotherapy), propranolol 80-240 mg daily (78% monotherapy), methyldopa added if required FU 4.9 years	All-cause mortality Cardiovascular mortality + morbidity Cerebrovascular mortality + morbidity CHD mortality + morbidity SBP DBP

Table 1. Baseline characteristics of included studies in all randomized participants aged 18 years or older *(Continued)*

Oslo 1986 Open label	785/785 (100%) Men: 100% Primary prevention participants. Refer to exclusion criteria listed in Characteristics of included studies table	156/97	45 years (40-49 years)	Untreated	Stepped-up therapy Hydrochlorothiazide (95%), methyldopa and propranolol (26%). At 5-year follow-up, 36.7% were on hydrochlorothiazide alone, 26% were on hydrochlorothiazide + propranolol, 20% were on hydrochlorothiazide + methyldopa and 18% participants were on other drugs. FU 5.5 years	All-cause mortality Cardiovascular mortality + morbidity Cerebrovascular mortality + morbidity CHD mortality + morbidity SBP DBP
USPHSHCSG 1977 Double blind	389/389 (100%) Men: 80% Primary prevention participants. Refer to exclusion criteria listed in Characteristics of included studies table	147/99	44 years (21-55 years)	Placebo	Fixed-dose therapy Chlorothiazide 500 mg twice daily + Rauwolfia serpentina 100 mg twice daily FU 7.0 years	All-cause mortality Cardiovascular mortality + morbidity Cerebrovascular mortality + morbidity CHD mortality + morbidity SBP DBP
VA-II 1970 Double blind	299/380 (78.7%) Men: 100% Primary prevention participants. Refer to exclusion criteria listed in Characteristics of included studies table	176/103	51 years (range not reported)	Placebo	Stepped-up therapy First line: hydrochlorothiazide 100 mg + reserpine 0.2 mg Second line: hydralazine 75-150 mg FU 3.3 years	Cardiovascular mortality + morbidity Cerebrovascular mortality + morbidity CHD mortality + morbidity
VA-NHLBI 1977 Double blind	1012/1012 (100%) Men: 100% Primary prevention participants. Refer to exclusion criteria listed in Characteristics of included studies table	SBP not reported/93	38 years (range 21-50 years)	Placebo	Stepped-up therapy Chlorthalidone 50 mg, 100 mg (53% chlorthalidone alone) Reserpine 0.25 mg FU 1.5 years	All-cause mortality Cardiovascular mortality + morbidity Cerebrovascular mortality + morbidity

Table 1. Baseline characteristics of included studies in all randomized participants aged 18 years or older *(Continued)*

						CHD mortality + morbidity DBP
Total of 7 studies published from 1970 to 1986	**17,327/19,684 (88% of total randomized participants in the 7 studies were 18-59 years of age) of which only 301/1,7327 (0.02%) participants were secondary prevention**	**SBP 147-176/ DBP 99-103 mmHg**	**Mean age 37.5-45 years**	**5 RCTs were placebo controlled and 2 RCTS had untreated group as control**	**Mostly high-dose thiazide and beta-blockers Mean follow-up 1.5-7 years.**	**5/7 RCTs report on all clinically important outcomes**

CHD: coronary heart disease; DBP: diastolic blood pressure; FU: follow-up; SBP: systolic blood pressure; TIA: transient ischaemic attack.

APPENDICES

Appendix 1. Search strategy used in various databases

1 MEDLINE search strategy

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 23 January 2017
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1 exp thiazides/ (15913)
2 exp sodium chloride symporter inhibitors/ (14603)
3 exp sodium potassium chloride symporter inhibitors/ (14205)
4 ((ceiling or loop) adj diuretic?).tw. (2564)
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?).tw. (34947)
6 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (2353)
7 or/1-6 [THZ] (50922)
8 exp angiotensin-converting enzyme inhibitors/ (44001)
9 angiotensin converting enzyme inhibit$.tw. (18514)
10 (ace adj2 inhibit$).tw. (18317)
11 acei.tw. (2857)
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 enalaprilat 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$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (27811)
13 or/8-12 [ACEI] (59794)
14 exp Angiotensin Receptor Antagonists/ (22055)
15 (angiotensin adj3 (receptor antagon$ or receptor block$)).tw. (11889)
16 arb?.tw. (5159)
17 (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 or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw. (15972)
18 or/14-17 [ARB] (31152)
19 exp calcium channel blockers/ (83029)
20 (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. (62158)
21 (calcium adj2 (antagonist? or block$ or inhibit$)).tw. (39065)
22 or/19-21 [CCB] (111557)
23 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp. (16154)
24 (reserpine or serpentina or rauwolfia or serpasil).mp. (20757)
25 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (19858)
26 exp hydralazine/ (4964)
27 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw. (4648)
28 or/23-27 [CNS] (59745)
29 exp adrenergic beta-antagonists/ (84772)
30 (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 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 methylthiopropranolol 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. (62363)
31 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (101145)
32 or/29-31 [BB] (159886)
33 exp adrenergic alpha antagonists/ (51279)
34 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (14099)
35 (adrenergic adj2 (alpha or antagonist?)).tw. (20625)
36 ((adrenergic or alpha or receptor?) adj2 block$).tw. (58854)
37 or/33-36 [AB] (116499)
38 hypertension/ (236571)
39 hypertens$.tw. (375255)
40 ((high or elevat$ or rais$) adj2 blood pressure).tw. (26803)
41 or/38-40 (441992)
42 randomized controlled trial.pt. (484850)
43 controlled clinical trial.pt. (97360)
44 randomized.ab. (371359)
45 placebo.ab. (182081)
46 clinical trials as topic/ (194591)
47 randomly.ab. (255305)
48 trial.ti. (167150)
49 or/42-48 (1091343)
50 animals/ not (humans/ and animals/) (4782114)
51 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (908496)
52 (pregnancy-induced or ocular hypertens$ or preeclampsia or pre-eclampsia).ti. (14675)
53 49 not (50 or 51 or 52) (963798)
54 (7 or 13 or 18 or 22 or 28 or 32 or 37) and 41 and 53 (16902)
55 54 and (2016$ or 2017$).ed. (350)
56 remove duplicates from 55 (262)

Database: Cochrane Hypertension Register Segment via Cochrane Register of Studies (CRS-Web)
Search Date: 23 January 2017

#1 hypertension AND antihypertensive* AND (Meta-analysis OR Review):MISC2 AND INSEGMENT (481)

Database: Cochrane Central Register of Controlled Trials on Wiley <2017, Issue 1> via Cochrane Register of Studies Online
Search Date: 23 January 2017

#1MeSH descriptor Thiazides explode all trees2264
#2MeSH descriptor Sodium Chloride Symporter Inhibitors explode all trees2727
#3MeSH descriptor Sodium Potassium Chloride Symporter Inhibitors explode all trees978
#4(loop or ceiling) next diuretic*:ti,ab352
#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*):ti,ab4989
#6(chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide):ti,ab922
#7#1 OR #2 OR #3 OR #4 OR #5 OR #66548
#8MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees5579
#9"angiotensin converting enzyme" next inhibit*:ti,ab2953
#10ace near3 inhibit*:ti,ab2920
#11acei:ti,ab594
#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*):ti,ab7539
#13#8 OR #9 OR #10 OR #11 OR #1210315
#14MeSH descriptor Angiotensin Receptor Antagonists explode all trees2489
#15angiotensin near3 (receptor next antagon* or receptor next block*):ti,ab2114
#16arbs:ti,ab367
#17(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):ti,ab4793
#18#14 OR #15 OR #16 OR #175695
#19MeSH descriptor Calcium Channel Blockers explode all trees8037
#20(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):ti,ab11368
#21calcium near2 (antagonist* or block* or inhibit*):ti,ab4225
#22#19 OR #20 OR #2113977
#23(methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa):ti,ab,kw572
#24(reserpine or serpentina or rauwolfia or serpasil):ti,ab,kw236
#25(clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets):ti,ab,kw2740
#26MeSH descriptor Hydralazine explode all trees300
#27(hydralazin* or hydrallazin* or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat):ti,ab,kw435
#28#23 OR #24 OR #25 OR #26 OR #273942
#29MeSH descriptor Adrenergic beta-Antagonists explode all trees9495
#30(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 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 methylthiopropranolol 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):ti,ab13874
#31beta near2 (adrenergic* or antagonist* or block* or receptor*):ti,ab8680
#32#29 OR #30 OR #3118044
#33MeSH descriptor Adrenergic alpha-Antagonists explode all trees2990
#34(alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin):ti,ab2066
#35adrenergic near2 (alpha or antagonist*):ti,ab417
#36(adrenergic or alpha or receptor*) near2 block*:ti,ab5740
#37#33 OR #34 OR #35 OR #369205
#38MeSH descriptor Hypertension13998
#39hypertens*:ti,ab33338
#40(elevat* or high* or raise*) near2 blood pressure:ti,ab2119
#41#38 OR #39 OR #4035759
#42#7 OR #13 OR #18 OR #22 OR #28 OR #32 OR #3748936
#43#41 AND #4216773
#4415/07/2016 TO 23/01/2017:CD48785
#45#43 AND #44282

Database: Embase <1974 to 2017 January 20>
Search Date: 23 January 2017
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1 exp thiazide diuretic agent/ (51659)
2 exp loop diuretic agent/ (65822)
3 ((loop or ceiling) adj diuretic?).tw. (3851)
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. (41498)
5 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (3678)
6 or/1-5 [THZ] (119840)
7 exp dipeptidyl carboxypeptidase inhibitor/ (156912)
8 angiotensin converting enzyme inhibit$.tw. (22618)
9 (ace adj2 inhibit$).tw. (26647)
10 acei.tw. (5851)
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 enalaprilat 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$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (36182)
12 or/7-11 [ACEI] (164401)
13 exp angiotensin receptor antagonist/ (76376)
14 (angiotensin adj3 (receptor antagon$ or receptor block$)).tw. (17419)
15 arb?.tw. (10600)
16 (abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan or Atacand or Avapro or Benicar or Cozaar or Diovan or Micardis or Teveten).tw. (24341)
17 or/13-16 [ARB] (82029)
18 calcium channel blocking agent/ (56888)
19 (amlodipine or aranidipine or barnidipine or bencyclane or benidipine or bepridil or cilnidipine or cinnarizine or clentiazem or darodipine or diltiazem or efonidipine or elgodipine or etafenone or fantofarone or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidipine or lercanidipine or lidoflazine or lomerizine or manidipine or mibefradil or nicardipine or nifedipine or niguldipine or nilvadipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or semotiadil or terodiline or tiapamil or verapamil or Cardizem CD or Dilacor XR or Tiazac or Cardizem Calan or Isoptin or Calan SR or Isoptin SR Coer or Covera HS or Verelan PM).tw. (77978)
20 (calcium adj2 (antagonist? or block$ or inhibit$)).tw. (46895)
21 or/18-20 [CCB] (139374)

22 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp. (28804)
23 (reserpine or serpentina or rauwolfia or serpasil).mp. (29001)
24 (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (45436)
25 hydralazine/ (18117)
26 (hydralazin$ or hydrallazin$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw. (6288)
27 or/22-26 [CNS] (106569)
28 exp beta adrenergic receptor blocking agent/ (269004)
29 (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 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 methylthiopropranolol 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. (79345)
30 (beta adj2 (adrenergic? or antagonist? or block$ or receptor?)).tw. (116005)
31 or/28-30 [BB] (322790)
32 exp alpha adrenergic receptor blocking agent/ (130668)
33 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (16607)
34 (adrenergic adj2 (alpha or antagonist?)).tw. (18171)
35 ((adrenergic or alpha or receptor?) adj2 block$).tw. (71101)
36 or/32-35 [AB] (197581)
37 exp hypertension/ (630228)
38 (hypertens$ or antihypertens$).tw. (545187)
39 ((high or elevat$ or rais$) adj2 blood pressure).tw. (35380)
40 or/37-39 (797400)
41 double blind$.mp. (218473)
42 placebo$.tw. (252570)
43 blind$.tw. (339409)
44 or/41-43 (491232)
45 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5877496)
46 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (699940)
47 (pregnancy-induced or ocular hypertens$ or preeclampsia or pre-eclampsia).ti. (19926)
48 44 not (45 or 46 or 47) (456527)
49 (6 or 12 or 17 or 21 or 27 or 31 or 36) and 40 and 48 (13447)
50 49 and (2016$ or 2017$).dc. (346)
51 remove duplicates from 50 (342)

Database: ClinicalTrials.gov
Search Date: 23 January 2017

Search terms: randomized
Study type: Interventional Studies
Conditions: hypertension
Interventions: antihypertensives
First Received: From 07/15/2016 to 01/23/2017 (40)

Database: WHO International Clinical Trials Registry Platform (ICTRP)

Search Date: 23 January 2017

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antihypertensive AND hypertension AND randomized (92)
antihypertensive AND high blood pressure AND randomized (32)

CONTRIBUTIONS OF AUTHORS

VM and JMW were responsible for the design of the protocol.

VM, LP, and DS screened titles and abstracts, and assessed all retrieved trials for inclusion or exclusion.

VM, JMW and FG extracted data independently and verified data entry.

VM and JMW assessed risk of bias, performed data analysis and graded evidence overall.

All authors contributed to the final draft of the review.

DECLARATIONS OF INTEREST

VM: none.

FG: none.

LP: none.

DS: none.

JMW: none.

SOURCES OF SUPPORT

Internal sources

- Department of Anesthesiology, Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, Canada.

  Office space.

External sources

- CIHR grant to the Hypertension Review group, Vancouver, Canada.

  Infrastructure.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review from "Pharmacotherapy for hypertension in non-elderly adults" to define the age group of eligible participants (Musini 2010).

Although the protocol stated in the objectives "To quantify antihypertensive drug effect on all-cause mortality in people 18 to 59 years with mild to moderate systolic or diastolic hypertension" we have now further clarified that it included only participants with primary hypertension similar to the systematic review "First line drugs for hypertension" in which participants with secondary hypertension were excluded.

The protocol was revised to include an additional outcome measure Decrease in systolic and diastolic blood pressure. Since there was significant heterogeneity (I^2 greater than 90%) in the mean difference in both systolic and diastolic blood pressure we used a random-effects model to present the overall effect size instead of the fixed-effect model.

Total cardiovascular mortality plus morbidity was identified as a secondary outcome under objectives in the protocol. Since total cardiovascular mortality plus morbidity includes cerebrovascular mortality plus morbidity and coronary heart disease mortality plus morbidity, we decided to show data for these two outcomes separately in addition to total cardiovascular mortality plus morbidity outcome.

Following the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), we presented a 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [adverse effects] [*therapeutic use]; Bendroflumethiazide [therapeutic use]; Blood Pressure [drug effects]; Cause of Death; Coronary Disease [mortality] [prevention & control]; Hypertension [*drug therapy] [mortality]; Methyldopa [therapeutic use]; Myocardial Infarction [mortality] [prevention & control]; Patient Dropouts [statistics & numerical data]; Propranolol [therapeutic use]; Randomized Controlled Trials as Topic; Stroke [mortality] [prevention & control]

MeSH check words

Adult; Humans; Middle Aged; Young Adult