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[Intervention Review]

Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals

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ABSTRACT

Background

High blood pressure is an important public health problem because of associated risks of stroke and cardiovascular events. Antihypertensive drugs are often used in the belief that lowering blood pressure will prevent cardiac events, including myocardial infarction and sudden death (death of unknown cause within one hour of the onset of acute symptoms or within 24 hours of observation of the patient as alive and symptom free).

Objectives

To assess the effects of antihypertensive pharmacotherapy in preventing sudden death, non-fatal myocardial infarction and fatal myocardial infarction among hypertensive individuals.

Search methods

We searched the Cochrane Hypertension Specialised Register (all years to January 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (2016, Issue 1), Ovid MEDLINE (1946 to January 2016), Ovid EMBASE (1980 to January 2016) and ClinicalTrials.gov (all years to January 2016).

Selection criteria

All randomised trials evaluating any antihypertensive drug treatment for hypertension, defined, when possible, as baseline resting systolic blood pressure of at least 140 mmHg and/or resting diastolic blood pressure of at least 90 mmHg. Comparisons included one or more antihypertensive drugs versus placebo, or versus no treatment.

Data collection and analysis

Review authors independently extracted data. Outcomes assessed were sudden death, fatal and non-fatal myocardial infarction and change in blood pressure.

Main results

We included 15 trials (39,908 participants) that evaluated antihypertensive pharmacotherapy for a mean duration of follow-up of 4.2 years. This review provides moderate-quality evidence to show that antihypertensive drugs do not reduce sudden death (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.81 to 1.15) but do reduce both non-fatal myocardial infarction (RR 0.85, 95% CI 0.74, 0.98; absolute risk reduction (ARR) 0.3% over 4.2 years) and fatal myocardial infarction (RR 0.75, 95% CI 0.62 to 0.90; ARR 0.3% over 4.2 years). Withdrawals due to adverse effects were increased in the drug treatment group to 12.8%, as compared with 6.2% in the no treatment group.

Authors' conclusions

Although antihypertensive drugs reduce the incidence of fatal and non-fatal myocardial infarction, they do not appear to reduce the incidence of sudden death. This suggests that sudden cardiac death may not be caused primarily by acute myocardial infarction. Continued research is needed to determine the causes of sudden cardiac death.

PLAIN LANGUAGE SUMMARY

Drugs used to lower blood pressure do not reduce sudden death

High blood pressure increases risks of stroke and heart attack. In people with moderate elevations of blood pressure, drugs that lower blood pressure reduce the incidence of stroke and heart attack. It is not known whether blood pressure-lowering drugs reduce sudden death (death of unknown cause within one hour of the onset of acute symptoms or within 24 hours of observation of the patient as alive and symptom free). We found 15 trials including 39,908 people that investigated whether blood pressure-lowering drugs reduce sudden death. This review presents moderate-quality evidence to show that blood pressure-lowering drugs reduce heart attacks but do not appear to reduce sudden cardiac death. This suggests that sudden cardiac death may not be caused primarily by heart attack. Continued research is needed to determine the causes of sudden cardiac death.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Antihypertensive pharmacotherapy versus control for prevention of sudden cardiac death in hypertensive individuals

Antihypertensive pharmacotherapy versus control for prevention of sudden cardiac death in hypertensive individuals

Patient or population: people with hypertension (defined as baseline systolic resting blood pressure \geq 140 mmHg and/or resting diastolic blood pressure \geq 90 mmHg)

Setting: primary care outpatient

Intervention: antihypertensive pharmacotherapy (first-line thiazide, angiotensin-converting enzyme inhibitor, calcium channel blocker or beta-blocker)

Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with antihypertensive pharmacotherapy				
Sudden cardiac death (mean follow-up: 4.2 years)	Study population		RR 0.96 (0.81 to 1.15)	39908 (15 RCTs)	⊕⊕⊕⊖ moderate ^a	
	13 per 1000	12 per 1000 (10 to 14)				
Non-fatal myocardial infarction (mean follow-up: 4.2 years)	Study population		RR 0.85 (0.74 to 0.98)	39908 (15 RCTs)	⊕⊕⊕⊖ moderate ^a	
	20 per 1000	17 per 1000 (15 to 20)				
Fatal myocardial infarction (mean follow-up: 4.2 years)	Study population		RR 0.75 (0.62 to 0.90)	39908 (15 RCTs)	⊕⊕⊕⊖ moderate ^a	
	12 per 1000	9 per 1000 (7 to 11)				

*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)

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

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of 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

^aDowngraded 1 level for imprecision (wide confidence intervals)

BACKGROUND

Description of the condition

High blood pressure is an important public health problem because of associated risks of stroke and cardiovascular events. It is most often of unknown origin, is relatively easy to detect and can be lowered with antihypertensive drugs. Extensive epidemiological data support the well-known relationship between blood pressure and risk of cardiovascular disease, particularly the importance of systolic blood pressure as a determinant of risk (Glynn 2010).

Major coronary heart disease manifests as and is captured in trials by three different outcomes: non-fatal myocardial infarction, fatal myocardial infarction and sudden cardiac death. Antihypertensive therapy could have different effects on different outcomes, and some study authors suspect that it could increase the incidence of sudden cardiac death (Hoes 1994), which is defined as sudden unexpected death within one hour of the onset of acute symptoms or within 24 hours of observation of the patient as alive and symptom free (Chugh 2004).

Most reviews have focused on the effects of blood pressure-lowering drugs on total fatal and non-fatal myocardial infarction, but not specifically on sudden cardiac death. Instead, sudden cardiac death is included with total myocardial infarction because it is assumed that it is totally or most often caused by acute myocardial infarction. In fact, sudden cardiac death could have several causes not related to acute myocardial infarction (see below) (Zheng 2001).

Description of the intervention

The intervention of interest in this systematic review is any antihypertensive drug used alone or in combination with other antihypertensive drugs as part of stepped-care therapy. The control in this review is placebo or no treatment.

How the intervention might work

Antihypertensive drugs lower blood pressure through a variety of mechanisms. Major classes of antihypertensive drugs include thiazide diuretics, beta-blockers, drugs inhibiting the renin-angiotensin system, calcium channel blockers, direct vasodilators, centrally active drugs and others. Several systematic reviews have shown the benefits of antihypertensive drug therapy in reducing cardiovascular morbidity and mortality in patients of all ages with moderate to severe hypertension (Gueyffier 1999; Musini 2009). At the present time, it is not known whether the benefits of antihypertensive therapy outweigh the harms in individuals with uncomplicated mild (grade 1) hypertension (Diao 2012; Sundström 2015).

It has been hypothesised, but not proven, that the benefits of antihypertensive drugs in reducing the incidence of stroke, myocardial infarction and heart failure are mediated through blood pressure reduction. If this is so, all drugs that lower blood pressure to the same degree should be similarly effective in reducing cardiovascular events. Some evidence suggests that this is not the case, and that different classes of antihypertensive drugs have differential effects on different outcomes (Chen 2010; Wiysonge 2012; Wright 2009; Xue 2015).

Effects of antihypertensive drugs on sudden cardiac death are potentially more complicated, as sudden cardiac death could be caused by acute myocardial infarction, but also could result from spontaneous fatal arrhythmia (ventricular fibrillation, torsade de pointes, asystole) or another sudden fatal event (e.g. ruptured aortic aneurysm, intracerebral haemorrhage). A particular class of antihypertensive drugs could be beneficial for one cause and deleterious for another. Other causes of sudden death cannot be ruled out because autopsies are not systematically done even in the event of sudden death in a randomised trial.

Why it is important to do this review

No published systematic review has compared the effects of antihypertensive drugs versus placebo or no treatment on the incidence of sudden cardiac death. If antihypertensive pharmacotherapy or a specific class of antihypertensive therapy increases sudden cardiac death, it is important to establish this, as it raises important questions: Is it appropriate to classify sudden cardiac death under total myocardial infarction? Are approaches available to prevent the increase in sudden cardiac death associated with use of antihypertensive drugs? Should patients with a particularly increased risk of sudden cardiac death be identified and treated differently?

OBJECTIVES

To assess the effects of antihypertensive pharmacotherapy in preventing sudden cardiac death, non-fatal myocardial infarction and fatal myocardial infarction among hypertensive individuals.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials of antihypertensive drugs in predominantly hypertensive patients (> 50%) with duration of follow-up of at least one year. Trials must include a comparative control group given placebo or no treatment.

We excluded trials that compared two specific antihypertensive therapies without placebo or with no treatment control, trials of blood pressure-lowering devices and trials providing multi-factorial interventions.

Trials had to provide data on the incidence of sudden cardiac death among participants in treated and control groups.

Types of participants

Most participants must have had high blood pressure (> 50%) at baseline. High blood pressure is defined as baseline resting systolic blood pressure (SBP) of at least 140 mmHg and/or resting diastolic blood pressure (DBP) of at least 90 mmHg.

Trials were not limited by any other factor nor by baseline risk. We excluded trials that recruited participants in the first month following an acute cardiovascular event.

Types of interventions

Treatment interventions

Antihypertensive drug classes, including angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, renin inhibitors, beta-adrenergic blockers, combined alpha- and beta-blockers, calcium channel blockers, diuretics, alpha-adrenergic blockers, central sympatholytics, direct vasodilators and antihypertensive drugs with unknown mechanisms of action.

Control interventions

Placebo and no treatment.

Types of outcome measures

Primary outcomes

- Sudden cardiac death.

Secondary outcomes

- Fatal myocardial infarction.
- Non-fatal myocardial infarction.
- Withdrawals due to adverse effects.

Search methods for identification of studies

Electronic searches

We searched the Database of Abstracts of Reviews of Effectiveness (DARE) for related reviews.

This review falls within the scope of the search strategies developed for [Wright 2009](#), for which we searched the following databases: the Hypertension Group Specialised Register (all years to January 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (2016, Issue 1), Ovid MEDLINE (1946 to January 2016), Ovid EMBASE (1980 to January 2016), the WHO International Clinical Trials Registry Platform (all years to January 2016), and ClinicalTrials.gov (all years to January 2016).

The Hypertension Group Specialised Register includes controlled trials from searches of CAB Abstracts, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Food Science and Technology Abstracts (FSTA), Global Health, the Latin American Caribbean Health Sciences Literature (LILACS), MEDLINE, ProQuest Dissertations & Theses, PsycINFO, Web of Science and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

We searched electronic databases using a strategy that combined the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE (sensitivity-maximising version (2008 revision)) with selected Medical Subject Heading (MeSH) terms and free text terms. We applied no language restrictions. We translated the MEDLINE search strategy ([Appendix 1](#)) for use with EMBASE, CENTRAL, the Hypertension Group Specialised Register and ClinicalTrials.gov, using the appropriate controlled vocabulary as applicable.

Searching other resources

We searched the reference lists of all relevant studies and systematic reviews for additional studies. We contacted authors of included studies to request information about any other relevant unpublished or ongoing studies.

We examined other sources to retrieve potential studies for the review:

- Food and Drug Administration (FDA), to ask whether this group had related clinical trial information in its possession.

Data collection and analysis

Selection of studies

One review author (GT) screened citations/abstracts obtained as a result of the search strategies. We rejected articles on the initial screen if we determined from the title or from the abstract that the article was not a report of a randomised clinical trial. We also rejected articles that were irrelevant to the review, or that clearly did not meet the inclusion criteria. We obtained in full text trials that might be of relevance and citations of uncertain relevance. Two review authors (GT, YM) independently assessed full-text articles for inclusion, using predetermined inclusion criteria. We recorded reasons for exclusion of trials. We provided a full accounting of search results in the form of a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram ([Liberati 2009](#)).

Data extraction and management

We extracted and managed data using the Cochrane Review Manager software, RevMan 5.3. Review authors (GT, YM, AL, LT and JMW) extracted data independently, using a piloted, standard form, then cross-checked data. We resolved discrepancies by discussion and by consensus, or we sought adjudication by a third review author if we could not reach consensus.

Assessment of risk of bias in included studies

Review authors used the 'Risk of bias' tool to assess each trial according to guidelines provided in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Potential parameters of methodological quality listed in the 'Risk of bias' table include method used to randomise participants; whether randomisation was completed in an appropriate and blinded manner; whether participants, providers and/or outcome assessors were blinded to assigned therapy; whether the control group received placebo or no treatment; the proportion of participants who did not complete follow-up; selective reporting of outcomes; and any other biases, including whether or not funding was provided by the drug industry.

Two review authors independently assessed risk of bias within each included study on the basis of these domains, assigning ratings of 'low risk of bias', 'high risk of bias' and 'unclear risk of bias' (uncertain risk of bias). Review authors resolved disagreements by discussion or by obtaining a third party opinion. When published articles did not include sufficient detail to permit full assessment, we contacted study authors to ask for clarification of methods used.

We presented the risk of bias assessment in a table for each study.

Measures of treatment effect

We measured most of our outcomes as the proportion of participants suffering an event, including sudden cardiac death, fatal myocardial infarction, non-fatal myocardial infarction and withdrawal due to adverse effects. When performing a meta-analysis, we used risk ratios.

Unit of analysis issues

For the subgroup analysis of the two-arm Medical Research Council (MRC) trial (MRC-TMH 1985), we halved the placebo group to prevent double counting.

Dealing with missing data

When information was missing from the included studies, we contacted investigators (using email, letter and/or fax) to request the missing information, and we explored the INDANA (Individual Data Analysis of Antihypertensive Drug Intervention Trials) database.

'Summary of findings' table

We presented data on the following outcomes: sudden cardiac death, non-fatal myocardial infarction, fatal myocardial infarction and proportion of participants who experienced at least one withdrawal due to an adverse event. We presented dichotomous outcomes as risk ratios and 95% confidence intervals. We presented data regarding numbers of participants and studies for each outcome. We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach ([Grade working group 2004](#)) to determine the quality of the evidence and downgraded the quality if (1) most (> 50%) included studies had high risk of bias; (2) the outcome had significant statistical heterogeneity ($I^2 > 50%$); and (3) the outcome had wide 95% CIs, indicating that the intervention effect was highly variable.

Assessment of heterogeneity

We tested for heterogeneity of treatment effects between trials by using a standard χ^2 statistic for heterogeneity and an alpha of 0.05 for statistical significance, and we estimated heterogeneity using the I^2 test. I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

We applied the fixed-effect model to obtain summary statistics of pooled trials, unless significant between-study heterogeneity

was present, in which case we used the random-effects model. If significant heterogeneity was present, and if I^2 was greater than 50%, we explored reasons for heterogeneity (variation in trial methods, interventions and study population characteristics) in an attempt to find potential explanations for the observed variation.

Assessment of reporting biases

Positive results are consistently more likely to be published than negative results, leading to publication bias, which can result in overestimation of the effect size of studies. If we identified sufficient trials (≥ 10 studies), we visually inspected funnel plots for small-study effects, and we considered the causes of funnel plot asymmetry, including publication bias. We considered use of additional statistical tests such as Egger's test when appropriate (*Cochrane Handbook for Systematic Reviews of Interventions*).

Data synthesis

We performed data synthesis and analyses using the most current version of the Cochrane Review Manager software, RevMan 5.3.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to look for variation in treatment effect among classes of first-line antihypertensive drugs, namely, first-line diuretics versus other first-line antihypertensive drugs.

Sensitivity analysis

We performed sensitivity analyses to test for robustness of results on trial quality. We did this by restricting analyses to trials with placebo and those judged to have low risk of bias. We also performed sensitivity analyses to see whether recruiting only patients with diabetes affected trial results.

RESULTS

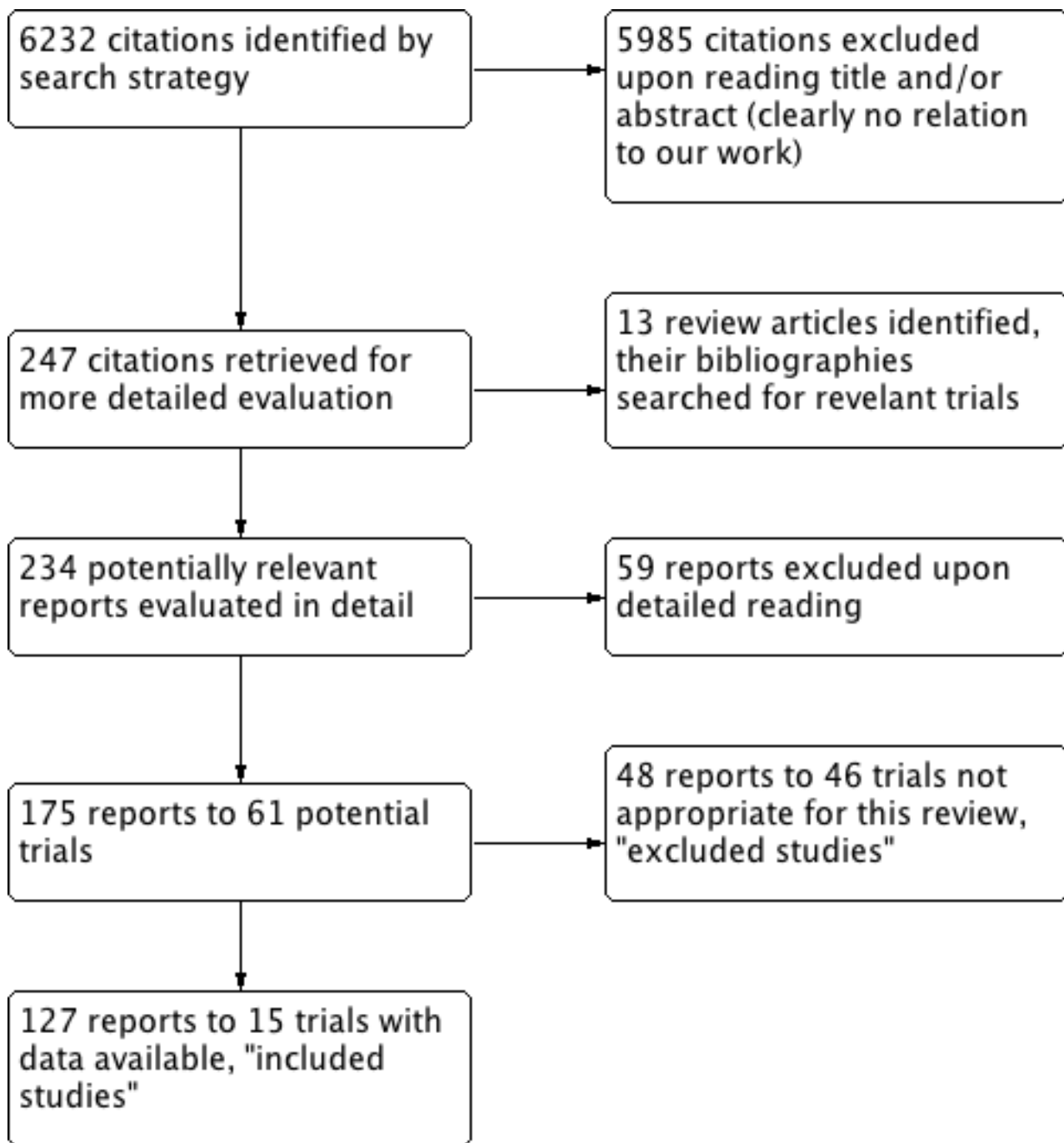
Description of studies

Details for the included trials can be found in the [Characteristics of included studies](#) table. Reasons for exclusion of excluded trials can be found in the [Characteristics of excluded studies](#) table.

Results of the search

We identified 61 trials, included 15 trials (39,908 participants) and excluded 46 trials. We have summarised the study selection process in the PRISMA flow diagram shown in [Figure 1](#).

Figure 1. PRISMA study flow diagram.



Included studies

We have provided details of included trials in the [Characteristics of included studies](#) table.

Studies recruited patients with high blood pressure, defined as baseline resting SBP of at least 140 mmHg and/or resting DBP of at least 90 mmHg. The average age of participants across all included trials was 63 years. Mean follow-up of studies ranged from 1.5 to 8.3 years. Most participants were recruited from industrialised countries, including the USA (57%) and European multi-sites (43%).

Most trials evaluated first-line diuretics (EWPBPE 1985; HSCGS 1974; MRC-TMH 1985 Diuretic arm; OSLO 1986; SHEP 1991; SHEP-Pilot 1989; USPHSHCSG 1977; VA-I 1967; VA-II 1970; VA-NHLBI 1978), except for DIABHYCAR 2004 and UKPDS38 1998, both of which evaluated an angiotensin-converting enzyme inhibitor, and SYST-EUR 1997, which evaluated a first-line calcium channel blocker. Five trials evaluated first-line beta-blockers (Coope 1986; MRC-TMH 1985 Betablocker arm; OSLO 1986; STOP 1991; UKPDS38 1998).

Females represented 38% of the population studied. Four trials (OSLO 1986; VA-I 1967; VA-II 1970; VA-NHLBI 1978) included only

men (2320 participants). Eight trials reported ethnicity. African Americans accounted for the following percentages in these trials: [HSCGS 1974](#) 80%; [SHEP 1991](#) 13.8%; [SHEP-Pilot 1989](#) 18%; [USPHSHCSG 1977](#) 28%; [VA-I 1967](#) 53.8%; [VA-II 1970](#) 42%; [VA-NHLBI 1978](#) 25%; and [UKPDS38 1998](#) 8%. Seven trials did not report ethnicity ([Coope 1986](#); [DIABHYCAR 2004](#); [EWPHBPE 1985](#); [MRC-TMH 1985](#); [OSLO 1986](#); [STOP 1991](#); [SYST-EUR 1997](#)).

Twelve trials reported initial mean SBP of participants ranging from 145 mmHg to 196 mmHg and DBP ranging from 75 mmHg to 102 mmHg. The final mean SBP ranged from 127 mmHg to 180 mmHg and DBP from 44 mmHg to 92 mmHg. Two studies ([VA-I 1967](#); [VA-NHLBI 1978](#)) reported initial and final mean DBP: respectively, [VA-I 1967](#) 121 mmHg and 91 mmHg, and [VA-NHLBI 1978](#) 93 mmHg and 83 mmHg. [VA-II 1970](#) reported only the initial mean SBP/DBP: 164/104 mmHg.

Ten trials reported baseline prevalence of diabetes as follows: [Coope 1986](#) 0%; [DIABHYCAR 2004](#) 100%; [EWPHBPE 1985](#) 0%; [MRC-TMH 1985](#) 0%; [SHEP 1991](#) 10.1%; [SYST-EUR 1997](#) 10.5%; [UKPDS38 1998](#) 100%; [USPHSHCSG 1977](#) 0%; [VA-I 1967](#) 9.1%; and [VA-NHLBI 1978](#) 0%.

Three trials ([SHEP 1991](#); [SHEP-Pilot 1989](#); [SYST-EUR 1997](#)) restricted recruitment to persons with systolic hypertension, defined as SBP 160 to 219 mmHg and DBP < 90 mmHg ([SHEP 1991](#); [SHEP-Pilot 1989](#)), DBP < 95 mmHg ([SYST-EUR 1997](#)) or simply systolic > 140 mmHg ([DIABHYCAR 2004](#)). Five trials based entry on diastolic hypertension ([USPHSHCSG 1977](#); [VA-I 1967](#); [VA-II 1970](#); [VA-NHLBI 1978](#); [UKPDS38 1998](#)); six trials based entry on either systolic or diastolic hypertension ([Coope 1986](#); [EWPHBPE 1985](#); [HSCGS 1974](#); [MRC-TMH 1985](#); [OSLO 1986](#); [STOP 1991](#)).

Excluded studies

We excluded 46 trials and have provided reasons for exclusion in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

We assessed risk of bias from six domains for each of the included studies.

Allocation

We judged most of the trials as having low risk of bias for sequence generation and allocation concealment. For trials with insufficient reporting, we judged risk of bias as unclear.

Blinding

Twelve of the 15 trials blinded participants to therapy ([DIABHYCAR 2004](#); [EWPHBPE 1985](#); [HSCGS 1974](#); [MRC-TMH 1985](#); [SHEP 1991](#); [SHEP-Pilot 1989](#); [STOP 1991](#); [SYST-EUR 1997](#); [USPHSHCSG 1977](#); [VA-I 1967](#); [VA-II 1970](#); [VA-NHLBI 1978](#)) and of these all but [MRC-TMH 1985](#) also blinded providers to therapy. Eight trials specifically reported blinding of outcome assessors ([Coope 1986](#); [EWPHBPE 1985](#); [SHEP 1991](#); [SHEP-Pilot 1989](#); [STOP 1991](#); [SYST-EUR 1997](#); [UKPDS38 1998](#); [VA-II 1970](#)).

Incomplete outcome data

Participants who were lost to follow-up or who dropped out prematurely were usually included in the clinical outcome or safety analysis of each trial. Most trials used intention-to-treat analysis; we therefore judged them to have low risk of attrition bias.

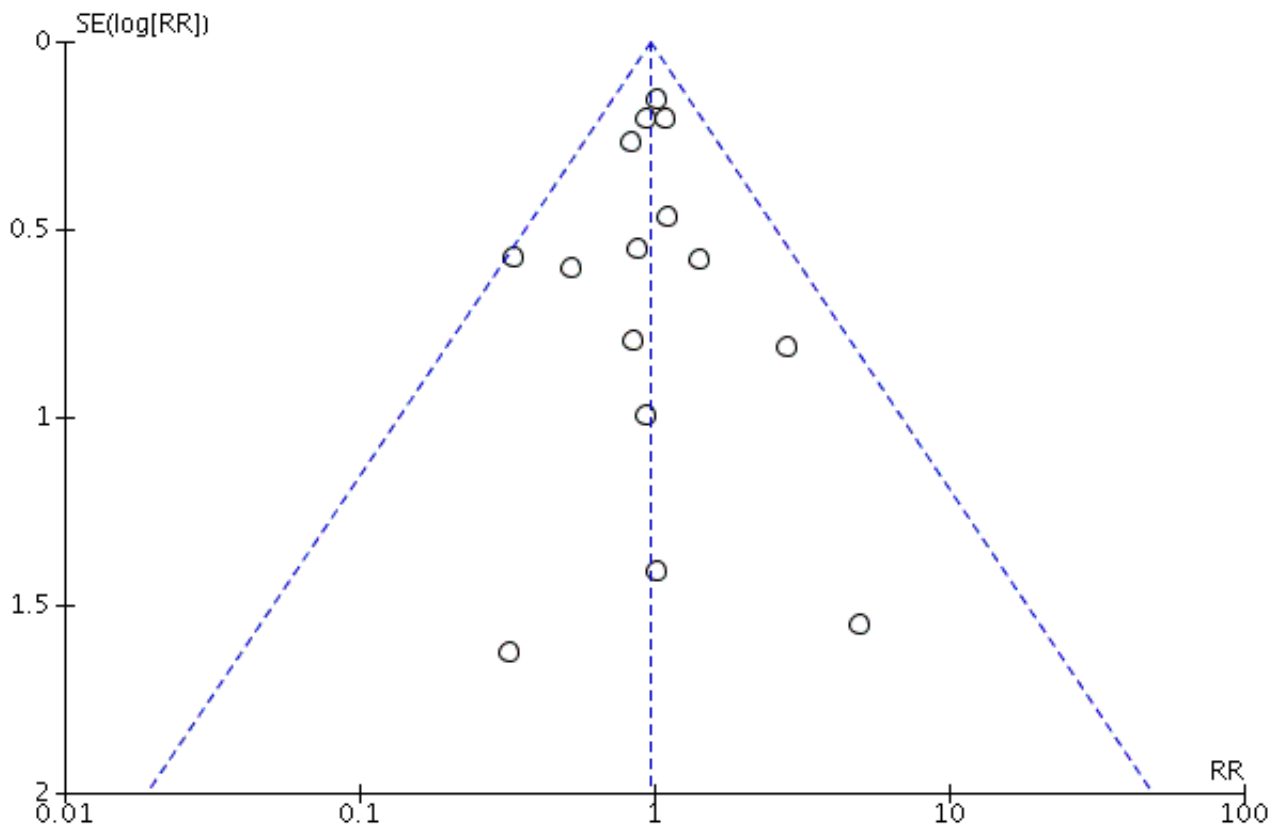
Selective reporting

All studies reported sudden cardiac death and myocardial infarction numbers; therefore, we can consider them as having low risk of reporting bias.

Other potential sources of bias

We defined publication bias as selective publication of studies with positive results; this is another source of bias that may have skewed the results of this review. The most common way to investigate whether an effect estimate is subject to publication bias is to examine for funnel plot asymmetry. Examining the funnel plot for sudden cardiac death in this review revealed no asymmetry to suggest high risk of publication bias ([Figure 2](#)).

Figure 2. Funnel plot of comparison: 1 Antihypertensive drug therapy vs control, outcome: 1.1 Sudden cardiac death.



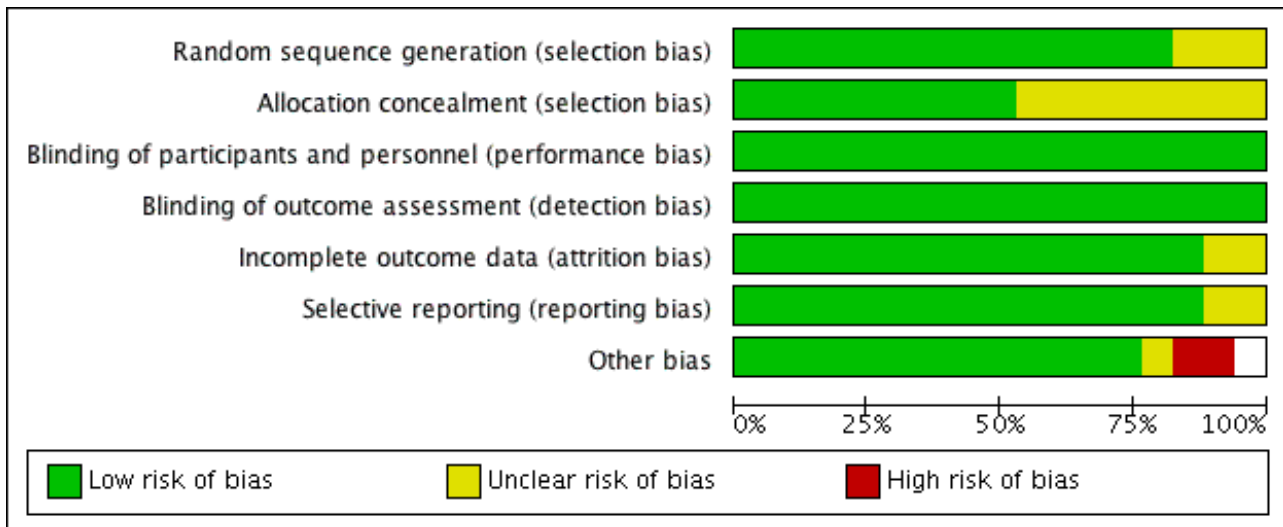
Thirteen of the 15 trials were funded by government agencies, not by industry, and thus were judged to have low risk of other bias.

We have summarised our judgements about each risk of bias item for each included study and about each risk of bias item presented as percentages across all included studies in [Figure 3](#) and [Figure 4](#), respectively.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Coope 1986	+	?	+	+	+	+	+
DIABHYCAR 2004	+	+	+	+	+	+	-
EWPBPE 1985	?	?	+	+	+	+	+
HSCGS 1974	?	+	+	+	?	+	+
MRC-TMH 1985	+	?	+	+	+	+	+
MRC-TMH 1985 Betablocker arm	+	?	+	+	+	+	+
MRC-TMH 1985 Diuretic arm	+	?	+	+	+	+	+
OSLO 1986	+	?	+	+	?	?	
SHEP 1991	+	+	+	+	+	+	+
SHEP-Pilot 1989	+	+	+	+	+	+	+
STOP 1991	+	?	+	+	+	+	+
SYST-EUR 1997	+	+	+	+	+	+	-
UKPDS38 1998	?	?	+	+	+	?	?
USPHSHCSG 1977	+	+	+	+	+	+	+
VA-I 1967	+	+	+	+	+	+	+
VA-II 1970	+	+	+	+	+	+	+
VA-NHLBI 1978	+	+	+	+	+	+	+

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

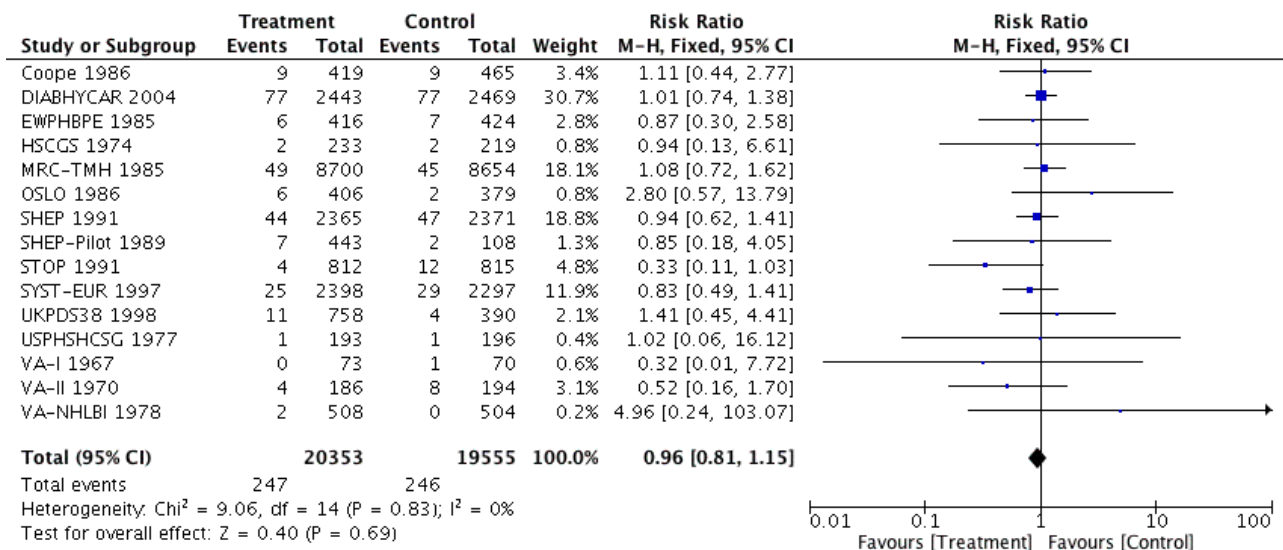
See: [Summary of findings for the main comparison Antihypertensive pharmacotherapy versus control for prevention of sudden cardiac death in hypertensive individuals](#)

See [Summary of findings for the main comparison](#). We performed analyses on the combined results of all 15 studies.

Sudden cardiac death

For the 39,908 participants included in this review, treatment with antihypertensive drugs as compared with no treatment or placebo did not affect sudden cardiac death (RR 0.96, 95% CI 0.81 to 1.1) ([Analysis 1.1, Figure 5](#)).

Figure 5. Forest plot of comparison: 1 Antihypertensive drug therapy vs control, outcome: 1.1 Sudden cardiac death.



Non-fatal myocardial infarction and fatal myocardial infarction

Antihypertensive pharmacotherapy resulted in a significant reduction in non-fatal myocardial infarction (RR 0.85, 95% CI 0.74

to 0.98, ARR 0.3% over 4.2 years) ([Analysis 1.2, Figure 6](#)) and fatal myocardial infarction (RR 0.75, 95% CI 0.62 to 0.90, ARR 0.3% over 4.2 years) ([Analysis 1.3, Figure 7](#)). We found no evidence of heterogeneity among included trials.

Figure 6. Forest plot of comparison: 1 Antihypertensive drug therapy vs control, outcome: 1.2 Non-fatal myocardial infarction.

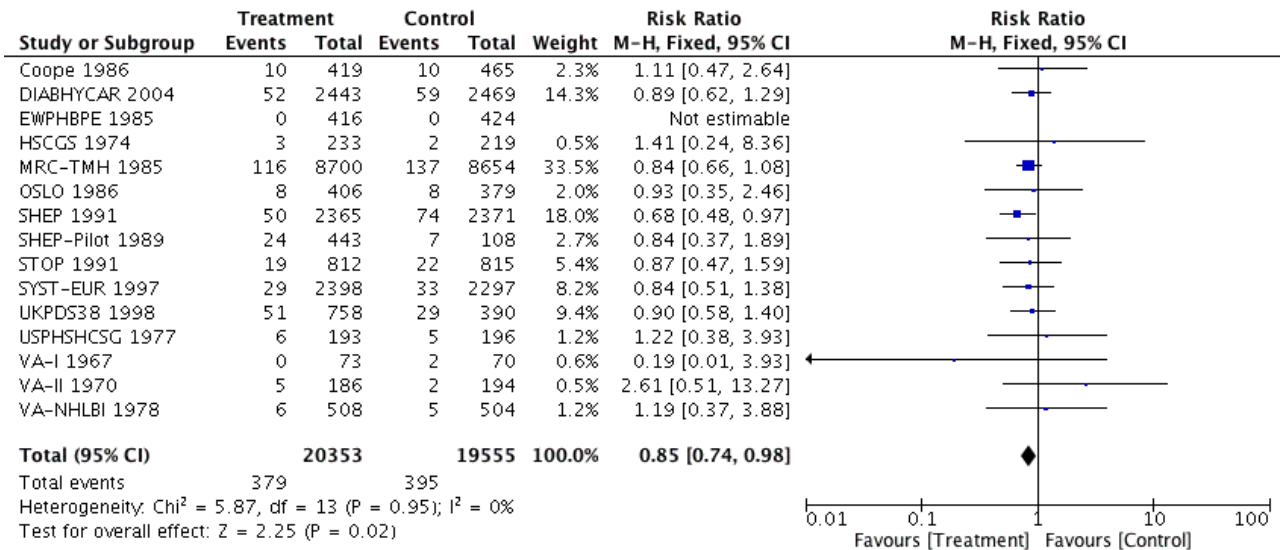
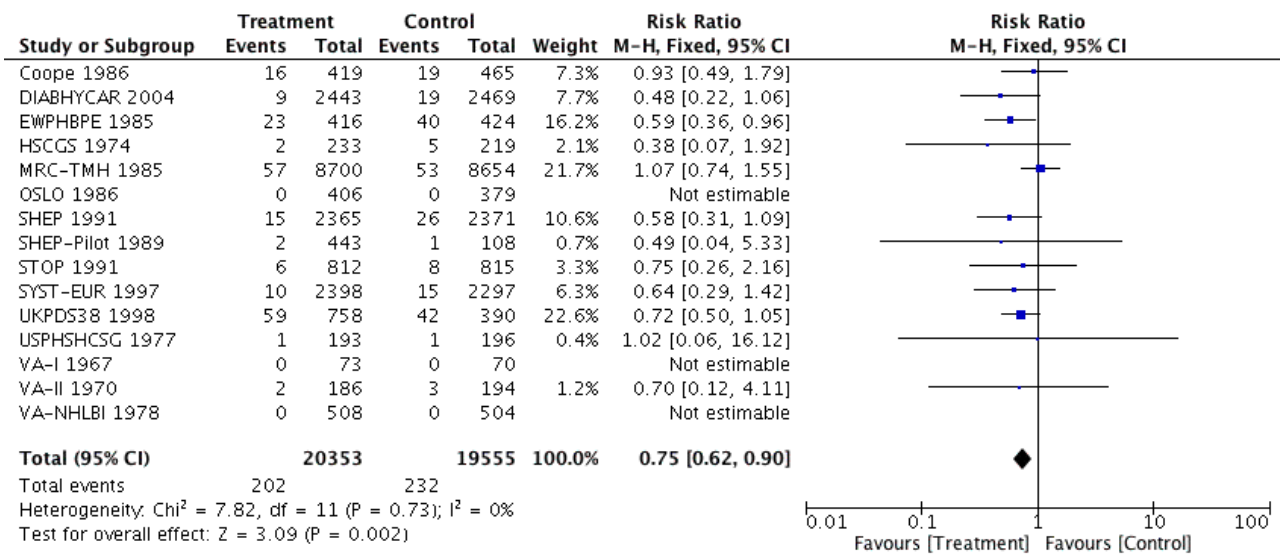


Figure 7. Forest plot of comparison: 1 Antihypertensive drug therapy vs control, outcome: 1.3 Fatal myocardial infarction.

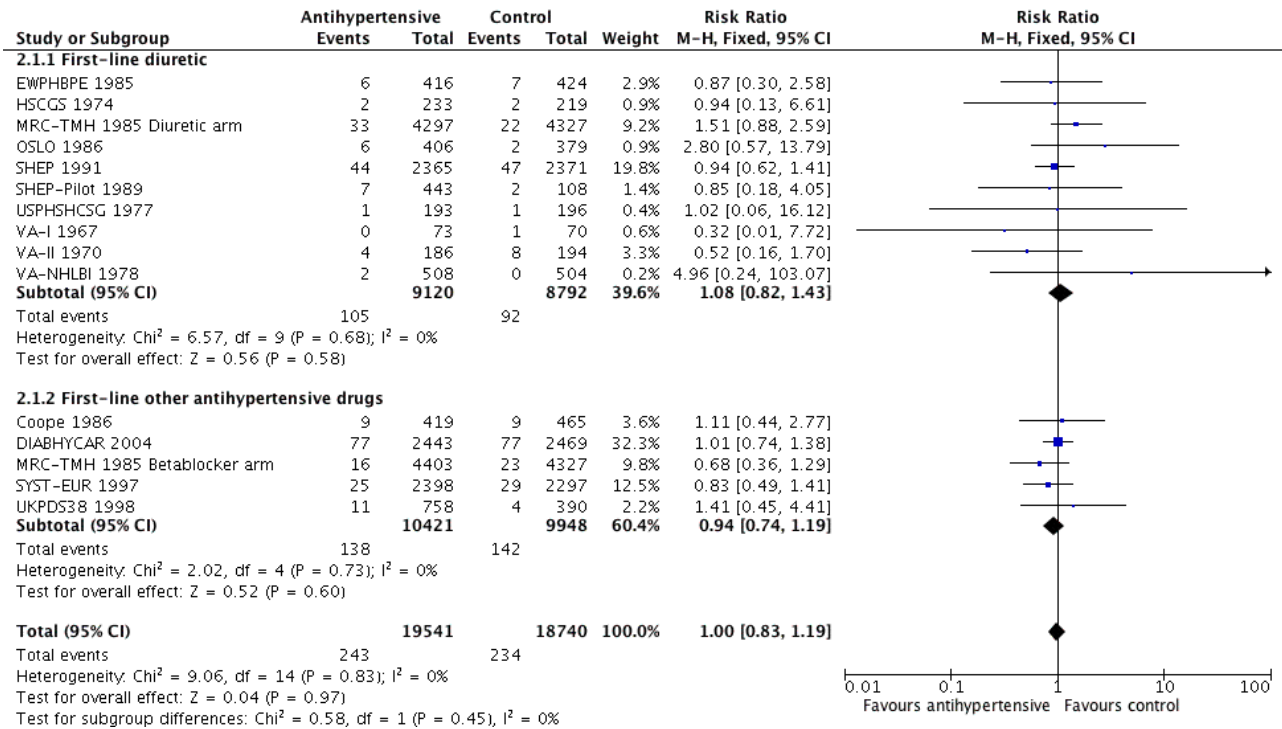


Subgroup analysis

To analyse whether a class effect of drugs was evident, we performed a subgroup analysis of first-line diuretics versus other antihypertensive drugs. In clinical trials, medications given to treat hypertension are often added to achieve the goal of lowering blood pressure. For this reason, we analysed data related to first-line treatment only.

The risk ratio for sudden cardiac death was 1.08 (95% CI 0.82 to 1.43) when diuretics were used as first-line agents, and 0.94 (0.74 to 1.19) for other antihypertensive treatments (Analysis 2.1, Figure 8). We noted no significant heterogeneity between subgroups based on use of first-line drugs.

Figure 8. Forest plot of comparison: 3 Subgroup analysis, first-line diuretic versus others, outcome: 3.1 Sudden cardiac death.



Withdrawals due to adverse effects (WDAEs)

Ten of 15 trials reported the numbers of participants who dropped out of trials because of adverse drug effects. WDAEs occurred in 6.2% of the no treatment group, and this percentage increased to 12.8% in the drug treatment group (RR 2.06, 95% CI 1.11 to 3.83, absolute risk increase 6.6%). Heterogeneity was high for this outcome (I² = 98%).

DISCUSSION

Summary of main results

Fifteen trials evaluated antihypertensive pharmacotherapy of various drug classes in a total of 39,908 hypertensive individuals, with periods of follow-up ranging from 1.5 to nine years (mean 4.2 years).

This systematic review demonstrates that antihypertensive pharmacotherapy used in the treatment of hypertensive patients has not been proven to significantly reduce sudden cardiac death (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.81 to 1.15). In contrast, in the same trials, antihypertensive therapy reduced both non-fatal myocardial infarction (RR 0.85, 95% CI 0.74 to 0.98) and fatal myocardial infarction (RR 0.75, 95% CI 0.62 to 0.90).

These findings suggest that sudden cardiac death is not totally or mostly caused by acute myocardial infarction, as if this were the case, it would have been reduced by antihypertensive therapy to a similar degree (e.g. RR 0.72 to 0.82). Therefore, sudden cardiac death could most often result from a condition unaffected by antihypertensive therapy, or more likely is caused in part by acute myocardial infarction and is reduced by antihypertensive therapy and is caused in part as well by another mechanism (e.g.

ventricular arrhythmias), which is increased by antihypertensive therapy, resulting in an overall null effect.

High blood pressure is a well-known risk factor for cardiac hypertrophy. Increased left ventricular mass detected by echocardiography is associated with increased risk for sudden cardiac death after other known coronary disease risk factors were accounted for (Haider A). It is unclear, however, whether antihypertensive therapies that promote the regression of left ventricular hypertrophy would reduce the risk of sudden death (Messerli 1999).

These facts make the lack of risk reduction of sudden death difficult to explain, unless we assume that at least some antihypertensive drugs may increase the incidence of sudden death. Diuretics have long been suspected to potentially induce sudden death by causing hypokalaemia and subsequent ventricular arrhythmia (Hoes 1995). On the other hand, beta-blockers are supposed to prevent sudden death due to arrhythmia (Hjalmarson 1997; Kaplan 1997), at least for secondary prevention of myocardial infarction.

In this review, we tested this possibility by performing a subgroup analysis of diuretics versus control for sudden cardiac death; we found that the pooled risk ratio of 1.08 (95% CI 0.82 to 1.43) did not affirm a differential effect for diuretics, and the pooled effect for other drugs was not different (RR 0.94, 95% CI 0.74 to 1.19). However, so few trials used other first-line antihypertensive drugs that the subgroup analysis was not a good test of that possibility. Sudden death represents 19.4% of total deaths and is more frequent than fatal myocardial infarction (13.4% of total deaths). It has been estimated that 40.7% of sudden deaths are due to coronary causes (Loire 1996), providing the rationale for including them within major coronary events. In North America and Europe, their annual incidence ranges from 50 to 100 per 100,000 in the

general population (Byrne 2008; Chugh 2004; Vreede-Swagemakers 1997; Vaillancourt 2004).

The fact that antihypertensive pharmacotherapy does not prevent this frequent cause of death is a matter of public health concern. One important improvement in coronary death prevention seen during the past two decades results from coronary angioplasty in acute coronary syndrome. These results, however, do not call into question the prescription of antihypertensive drugs, which remain associated with a significant reduction in coronary and cerebrovascular events. This shows that additional research is needed to determine the causes of sudden death. It also suggests that sudden cardiac death may be a misnomer, and that until we have attained a good estimate of its different causes, this might be better labelled 'sudden death'.

Overall completeness and applicability of evidence

This comprehensive review provides the most up-to-date evidence from available randomised controlled trials. We have done our best to contact study authors to collect data on sudden cardiac death from the more recent studies (HOPE 2000; HYVET 2008; HYVET-Pilot 2003), which did not report it. We applied no language restrictions when selecting studies.

Quality of the evidence

Overall, we judged the risk of bias of studies included in this review as moderate to low. However, only six of the 15 trials (53%) described the method of concealment of allocation. Most trials with unclear concealment of allocation were described as 'randomised', and study authors provided no other details. Some study authors stated that these trials were double-blind but offered no information about how this was achieved.

Potential biases in the review process

One potential bias that deserves attention is the fact that most trials used a combination of antihypertensive medications as stepped-care therapy. As a result, the drugs used and the amount of blood pressure reduction achieved were heterogeneous.

For most long-term and large-scale studies, it is impossible to maintain single first-line drug treatment because a single drug frequently does not lower blood pressure to a level considered low enough. In most cases, physicians in the included studies added other antihypertensive drugs (e.g. reserpine) to reach the target blood pressure.

We excluded many studies because they did not report the incidence of sudden cardiac death. This lack of completeness could have biased the analysis, but as most of these eligible studies were

published before 1991, it is unlikely that their data will become available.

Agreements and disagreements with other studies or reviews

This is the first systematic review undertaken to specifically assess the effects of antihypertensive therapy on sudden cardiac death. Estimates of effects of risk reduction on fatal and non-fatal myocardial infarction provided here are similar to those reported by other reviews (Musini 2009; Wright 2009).

AUTHORS' CONCLUSIONS

Implications for practice

We found moderate-quality evidence suggesting that antihypertensive drugs lead to a small reduction in the incidence of fatal and non-fatal myocardial infarction but do not reduce the incidence of sudden cardiac death. This suggests that sudden cardiac death in people with hypertension may be attributable to causes other than acute myocardial infarction. Withdrawals due to adverse effects were increased in the drug treatment group to 12.8%, as compared with 6.2% in the no treatment group.

Implications for research

Sudden death should not be included as part of a composite outcome of major coronary events in future trials. Autopsies should be performed to establish the cause of death when people die suddenly during a clinical trial. More research is needed to determine the causes of sudden death.

Future clinical trials of cardiovascular prevention should systematically and separately explore the impact of treatment on sudden death and should identify treatments that could have a preventive effect on this outcome.

Specific risk scores for sudden death should be developed so they can be used to check whether sudden death shares the same capacity for prognosis as coronary events, fatal or not, and to help identify subgroups of individuals at particularly high risk for sudden death. Sudden death risk scores might prove useful once effective preventive treatments have been identified, as is the case for beta-blockers and aldosterone antagonists for congestive heart failure with reduced left ventricular ejection fraction.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Coope 1986

Methods	Randomised controlled group Trial conducted in Europe
Participants	Patients 60 to 79 years of age who were registered in 13 general practices in England and Wales
Interventions	Atenolol 100 mg (\pm bendrofluzide 5 mg \pm alpha-methyldopa 500 mg) Control: no treatment
Outcomes	Total mortality Systolic BP and diastolic BP Stroke, myocardial infarction, sudden death
Notes	

Coope 1986 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the patient was randomised into the treatment or control group" Quote: "These had been prepared from random number tables"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "a double-blind protocol" SCD not likely affected
Blinding of outcome assessment (detection bias) All outcomes	Low risk	SCD not likely affected
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Analysis has been on the 'intention to treat' basis"
Selective reporting (reporting bias)	Low risk	Quote: "All deaths and major recordable events were entered with full details on special forms"
Other bias	Low risk	Not industry funded

DIABHYCAR 2004

Methods	Multi-centre randomised double-blind parallel-group Trial conducted in Europe and North Africa
Participants	Patients with type 2 diabetes > 50 years of age who use oral antidiabetic drugs and have persistent microalbuminuria or proteinuria and serum creatinine < 150 µmol/L
Interventions	Ramipril (1.25 mg/d) vs placebo (on top of usual treatment)
Outcomes	Total mortality Cardiovascular death Myocardial infarction, stroke, heart failure leading to hospital admission, end-stage renal failure, sudden death Systolic BP and diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
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DIABHYCAR 2004 (Continued)

Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias) All outcomes	Low risk	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	SCD unlikely affected
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	

EWPBPE 1985

Methods	Double-blind randomised placebo-controlled Trial conducted in Europe
Participants	Elderly patients (mean age 72 years, range > 60 years) Male 30%. Ethnicity not reported Baseline SBP/DBP 183/101 mmHg; pulse pressure 82 mmHg Inclusion criteria: SBP 160 to 239 mmHg and DBP 90 to 119 mmHg. Participants followed for 7 years
Interventions	HCTZ/triamterene 25/50 mg 1 to 2 tabs methyldopa 0.5 to 2 g Control: matching placebo
Outcomes	Total mortality: death from any cause Fatal myocardial infarction and ischaemic heart disease, sudden death, heart failure, stroke Systolic blood pressure and diastolic blood pressure
Notes	Only intention-to-treat data included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to an active treatment or

EWPHBPE 1985 (Continued)

		placebo treatment group"
		Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients remained in the double-blind part of the trial until the summer of 1984" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Data were sent to the coordinating office every three months on specially designed forms, and deaths and other terminating events were classified independently by two investigators into previously agreed categories. These investigators were not aware of the treatment group to which patients had been assigned" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two analyses: per-protocol analysis and Intention-to-treat analysis. "After leaving the double-blind part of the trial, the surviving patients were followed up until July 1984, but only date and cause of death were recorded"
Selective reporting (reporting bias)	Low risk	SCD reported
Other bias	Low risk	Not industry funded

HSCGS 1974

Methods	Prospective double-blind randomised placebo-controlled Trial conducted in USA
Participants	Ambulatory patients, stroke survivors, 80% African Americans, mean age 59 years (range < 75 years). Male 60% Baseline SBP/DBP 167/100 mmHg; pulse pressure 67 mmHg Inclusion criteria: SBP \geq 140 to 220 mmHg, DBP 90 to 115 mmHg Participants followed for 3 years
Interventions	Methyclothiazide 10 mg + deserpidine 1 mg. Control placebo
Outcomes	Total mortality Stroke, sudden death, myocardial infarction, congestive heart failure, pulmonary embolism Systolic BP and diastolic BP
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement

HSCGS 1974 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Quote: "The biostatistical 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"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not described but low risk for SCD
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not described but low risk for SCD
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Low risk	Sudden cardiac death reported
Other bias	Low risk	Not industry funded

MRC-TMH 1985

Methods	Randomised single-blind comparison of 2 treatments and placebo Trial conducted in UK
Participants	Ambulatory young patients. Mean age 52 years (range 35 to 64 years). Ethnicity not reported. Male 52%. Baseline mean SBP/DBP 161.4/98.2 mmHg. Pulse pressure 63 mmHg Inclusion criteria: SBP < 200 mmHg and DBP 90 to 109 mmHg Participants followed for 5 years
Interventions	Bendrofluazide 10 mg daily (71% mono), propranolol 80 to 240 mg daily (78% mono), methyldopa added if required
Outcomes	Total mortality Stroke, myocardial infarction Systolic BP and diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated at entry" Comment: probably done

MRC-TMH 1985 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "single-blind" Comment: low risk for SCD
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" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All analyses presented here are based on randomised treatment ('intention to treat') categories"
Selective reporting (reporting bias)	Low risk	SCD reported
Other bias	Low risk	Not industry funded

MRC-TMH 1985 Betablocker arm

Methods	See above
Participants	See above
Interventions	See above
Outcomes	See above
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See above
Allocation concealment (selection bias)	Unclear risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias)	Low risk	See above

MRC-TMH 1985 Betablocker arm (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	See above
Other bias	Low risk	See above

MRC-TMH 1985 Diuretic arm

Methods	See above
Participants	See above
Interventions	See above
Outcomes	See above
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See above
Allocation concealment (selection bias)	Unclear risk	See above
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	See above
Selective reporting (reporting bias)	Low risk	See above
Other bias	Low risk	See above

OSLO 1986

Methods	Randomized controlled group Trial conducted in Norway
Participants	Ambulatory young male patients. Mean age 45.3 years (range 40 to 49 years). Ethnicity not reported

Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals (Review)

OSLO 1986 (Continued)

Baseline mean SBP/DBP 156.2/97 mmHg; pulse pressure 59 mmHg

Inclusion criteria: SBP 150 to 179 mmHg and DBP < 110 mmHg

Participants followed for 5 to 6 years

Interventions	Hydrochlorothiazide (95%), methyldopa and propranolol (26%) At 5-year follow-up, 36.7% were taking HCTZ alone, 26% HCTZ + propranolol, 20% HCTZ + methyldopa and 18% other drugs
Outcomes	Total mortality Sudden death, myocardial infarction, stroke Systolic BP and diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The drugs were administered in a randomised manner" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Low risk for SCD
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for SCD
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Unclear

SHEP 1991

Methods	Multi-centre randomised double-blind placebo-controlled Trial conducted in USA
Participants	Ambulatory patients. Mean age 72 years (range > 60 years) 13.9% of participants were African Americans. Male 43% Baseline mean SBP/DBP 170/77 mmHg; pulse pressure 93 mmHg Inclusion criteria: SBP 160 to 219 mmHg and DBP < 90 mmHg

SHEP 1991 (Continued)

	Participants followed for 4.5 years
Interventions	Chlorthalidone 12.5 to 25 mg (69%) Step 2: atenolol 25 to 50 mg (23%) or reserpine 0.05 to 0.1 mg Identical placebo
Outcomes	Total mortality Stroke, myocardial infarction, sudden death Quality of life measures Systolic BP and diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Screenees were randomly allocated by the coordination center to one of two treatment group[s]" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was stratified by clinical center and by anti-hypertensive medication status at initial contact" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants were randomized in a double-blind manner" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Information related to study end points was collected by clinic staff... Occurrence of study events listed above was confirmed by a coding panel of three physicians blind to randomization allocation" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk for SCD
Selective reporting (reporting bias)	Low risk	Low risk for SCD
Other bias	Low risk	Not Industry funded

SHEP-Pilot 1989

Methods	Randomised double-blind placebo-controlled Trial conducted in USA
Participants	Ambulatory patients. Mean age 72 years (range > 60 years)

SHEP-Pilot 1989 (Continued)

18% of participants were non-white. Male 37%

Baseline mean SBP/DBP 170/77 mmHg; pulse pressure 93 mmHg

Inclusion criteria: SBP 160 to 219 mmHg and DBP < 90 mmHg

Participants followed for 3 years

Interventions	Chlorthalidone 25 to 50 mg daily (87%) Step II randomised to hydralazine, reserpine or metoprolol (13%) Control: placebo
Outcomes	Total mortality Stroke, myocardial infarction, sudden death Systolic BP and diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned in a double-blind [fashion]" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "The ratio of assignment was 4:1 to permit the expected comparison among Step II medications" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Working independently and without knowledge of the participant's treatment group assignment, each member made a diagnosis based on the criteria table"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Analysis was by intention to treat"
Selective reporting (reporting bias)	Low risk	Quote: "The diagnosis of "no event" was also acceptable and was the final diagnosis for five suspected morbid events"
Other bias	Low risk	Not industry funded

STOP 1991

Methods	Prospective randomised double-blind placebo-controlled intervention study Trial conducted in Sweden
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STOP 1991 (Continued)

Participants	Hypertensive men and women 70 to 84 years of age
Interventions	Treatment consisted of atenolol 50 mg, hydrochlorothiazide 25 mg + amiloride 2.5 mg, metoprolol 100 mg or pindolol 5 mg. Control placebo
Outcomes	Total mortality Stroke, myocardial infarction, sudden death Systolic BP and diastolic BP
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind administration of active hypertension therapy or placebo" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Endpoints were evaluated by an independent endpoint committee, unaware of treatment given or blood pressure" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "77% of the placebo group and 84% of the actively treated group were still taking the study medication." In the analysis, the intention-to-treat principle was used"
Selective reporting (reporting bias)	Low risk	Low risk for SCD
Other bias	Low risk	Not industry funded

SYST-EUR 1997

Methods	Randomised double-blind placebo-controlled Trial conducted in Europe
Participants	Ambulatory patients, with mean age 70.2 (range > 60) years Male 31%. Ethnicity not reported Baseline mean SBP/DBP 174/85.5 mmHg; pulse pressure 89 mmHg Inclusion criteria: SBP 160 to 219 mmHg and DBP < 95 mmHg

SYST-EUR 1997 (Continued)

Participants followed for 2.5 years

Interventions	Nitrendipine 10 mg daily, 10 mg BID, 20 mg BID; enalapril 5 mg, 10 mg, 20 mg daily in the evening; HCTZ 12.5 mg, 25 mg daily in the morning Matched placebos
Outcomes	Total mortality Myocardial infarction, stroke, sudden death Systolic BP and diastolic BP

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After stratification by centre, sex, and previous cardiovascular complications, we randomly assigned" Comment: probably done
Allocation concealment (selection bias)	Low risk	Adequate Quote: "by means of computerised random function"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The endpoint committee, which was unaware of the patients' treatment status, identified all major endpoints by reviewing the patients' files and other source documents"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The data were analysed by intention to treat with two-sided test"
Selective reporting (reporting bias)	Low risk	Adequate
Other bias	High risk	Industry funding

UKPDS38 1998

Methods	Randomised controlled open-label Trial conducted in UK
Participants	Newly diagnosed patients with type 2 diabetes mellitus and hypertension (BP > or = 160 and/or > or = 90 mmHg in patients not receiving antihypertensive therapy and > or = 150 and/or > or = 85 mmHg in patients receiving antihypertensive therapy). Mean age 56 years. Male 55%, white 86%. Baseline SBP/DBP 160/94 mmHg; pulse pressure 66 mmHg. Participants followed for 8.4 years

UKPDS38 1998 (Continued)

Interventions	Tight BP control group (captopril 25 mg to 50 mg BID or atenolol 50 mg OD to 100 mg/d. Supplemental drugs added frusemide 20 to 40 mg BID, slow-release nifedipine 10 to 40 mg BID, methyldopa 250 to 500 mg BID, prazosin 1 to 5 mg TID, given sequentially to achieve target BP). Control group was given treatment if BP > or = 200 and /or 105 mmHg (frusemide, long-acting nifedipine, methyldopa, prazosin, given sequentially to control BP. If possible, ACEI and beta-blockers were avoided)
Outcomes	Mortality, stroke, CHD and CHF, systolic BP and diastolic BP
Notes	The less tight control group received no treatment unless BP rose to > or = 200/105 mmHg before 1992, or > or = 180/105 mmHg after 1992. In the control group at 1 year, 50% of participants were treated for BP > or = 180 mmHg and/or 105 mmHg with specified drug therapy (14% were taking ACE Inhibitors or beta-blockers)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Low risk for SCD
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for SCD
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Primary analysis was on an intention to treat basis"
Selective reporting (reporting bias)	Unclear risk	Unclear
Other bias	Unclear risk	Not industry funded

USPHSHCSG 1977

Methods	Randomised double-blind placebo-controlled Trial conducted in USA
Participants	Ambulatory young patients, with mean age 44.3 (range 21 to 55) years. 28% were African American. 80% were male Baseline mean SBP/DBP 146.9/99 mmHg; pulse pressure 48 mmHg Inclusion criterion: DBP 90 to 115 mmHg Participants followed for 10 years
Interventions	Chlorothiazide 500 mg BID plus rauwolfia serpentina 100 mg BID vs placebo

USPHSHCSG 1977 (Continued)

Outcomes	Total mortality Myocardial infarction, sudden death and stroke Systolic BP and diastolic BP
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly assigned either active or placebo treatment" Comment: probably done
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "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"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk for SCD
Selective reporting (reporting bias)	Low risk	Low risk for SCD
Other bias	Low risk	Not industry funded

VA-I 1967

Methods	Randomised double-blind placebo-controlled Trial conducted in USA
Participants	Ambulatory patients, with mean age 51 years (range not reported). 53.8% were African American. 100% were male Baseline mean SBP/DBP 186/121 mmHg; pulse pressure 65 mmHg Inclusion criterion: DBP < 115 to 129 mmHg Participants followed for 1.5 years
Interventions	Step 1. HCTZ 100 mg + reserpine 0.2 mg + hydralazine 75 mg Step 2. Hydralazine 150 mg Control: placebo
Outcomes	Total mortality

VA-I 1967 (Continued)

Myocardial infarction, sudden death
 Systolic BP and diastolic BP

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned to either active or placebo treatment" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "A table of random numbers was utilized by the statistician in determining the assignments" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The double-blind technique was employed by utilizing a series of complex code numbers" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for SCD
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk for SCD
Selective reporting (reporting bias)	Low risk	Low risk for SCD
Other bias	Low risk	Not industry funded

VA-II 1970

Methods	Prospective randomised placebo-controlled single-blind Trial conducted in Australia
Participants	Ambulatory patients, with mean age 52 years (range not reported). 42% were African American. 100% were male. Baseline mean SBP/DBP was 162/104 mmHg; pulse pressure was 58 mmHg Inclusion criterion: DBP < 90 to 114 mmHg. Participants followed for 3.7 years
Interventions	Step 1. HCTZ 100 mg + reserpine 0.2 mg Step 2. Hydralazine 75 to 150 mg Control: placebo
Outcomes	Total mortality, stroke, myocardial infarction, sudden death Systolic and diastolic blood pressure
Notes	

VA-II 1970 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization of patients" Comment: probably done
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blinded to either active drugs or placebos" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the records of the patients reported as having assessable morbid events were reviewed by two consulting physicians who had not participated in the trial" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk for SCD
Selective reporting (reporting bias)	Low risk	Low risk for SCD
Other bias	Low risk	Not industry funded

VA-NHLBI 1978

Methods	Randomised double-blind placebo-controlled Trial conducted in USA
Participants	Ambulatory patients, with mean age 37.5 (range 21 to 50) years 25% were African American. 100% were male Baseline mean DBP 93.3 mmHg Inclusion criterion: DBP 85 to 105 mmHg Participants followed for 2 years
Interventions	chlorthalidone 50 mg, 100 mg (53% chlorthalidone alone). Reserpine 0.25 mg
Outcomes	Total mortality Stroke, myocardial infarction, sudden death Systolic BP and diastolic BP
Notes	

VA-NHLBI 1978 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At that time each qualifying subject was randomized to active or placebo treatment" Comment: probably done
Allocation concealment (selection bias)	Low risk	Adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Low risk for SCD
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low risk for SCD
Selective reporting (reporting bias)	Low risk	Low risk for SCD
Other bias	Low risk	Not industry funded

Abbreviations:

ACE: angiotensin-converting enzyme.

ACEI: angiotensin-converting enzyme inhibitor.

BP: blood pressure.

CHD: congestive heart disease.

CHF: congestive heart failure.

DBP: diastolic blood pressure.

HCTZ: hydrochlorothiazide.

SCD: sudden cardiac death.

SBP: systolic blood pressure.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
ADVANCE 2007	Control group included non-specific antihypertensive therapy
ALLHAT 2000	Active controlled trial Drug-drug comparison of different drug classes with no placebo or untreated control group.
ANBP 1981	All components from the composite outcome were terminating events, without complementary mortality survey. All analyses regarding these separated components are subject to a censoring bias
Barracough 1973	Sudden cardiac death data could not be obtained

Study	Reason for exclusion
Berglund 1981	Active controlled trial Drug-drug comparison of bendrofluazide 2.5 mg vs propranolol 160 mg with no placebo or untreated control group
Carter 1970	Sudden cardiac death data could not be obtained
CASTEL 1994	Active controlled trial Drug-drug comparison with no placebo or untreated control group
GLANT 1995	Active controlled trial Drug-drug comparison of delapril 30 to 120 mg vs several dihydropyridine calcium channel blockers with no placebo or untreated control group
HANE 1997	Active controlled trial Morbidity and mortality outcomes not reported
HAPPHY 1987	Active controlled trial Drug-drug comparison of bendrofluazide 5 mg or HCTZ 50 mg vs atenolol 100 mg or metoprolol 200 mg with no placebo or untreated control group
HDFP 1984	Systematic antihypertensive treatment programme (Stepped Care [SC]) vs referral to community medical therapy (Referred Care [RC]) No placebo and no treatment arm Treated group included various lifestyle measures in addition to antihypertensive drug therapy. Control group was given usual care and did not necessarily include untreated controls
HOPE 2000	Sudden cardiac death data could not be obtained
HOT 1995	No placebo and no untreated control group Evaluates the effects of achieving pre-specified levels of diastolic blood pressure control with all patients receiving antihypertensive treatment
HOT 1998	Active controlled trial (less intensive treatment)
HYVET 2008	Sudden cardiac death data could not be obtained
HYVET-Pilot 2003	Sudden cardiac death data could not be obtained
IDM 2001	Other antihypertensive drugs were prescribed to 56% of the placebo group
INSIGHT 1996	Active controlled trial No placebo and no untreated control group
IPPPSH 1985	Thiazide was given to more than 67% of participants in both treated and control groups
Jikei 2007	Did not truly randomise participants to treatment arms, and control group included non-specific antihypertensive therapy
Kuramoto-2 1994	Head-to-head comparison of different drug therapies (nicardipine vs trichlormethiazide) without a placebo or untreated control group

Study	Reason for exclusion
Lewis 2001	Placebo group received an average of 3.3 antihypertensive drugs per patient during the study
MAPHY 1991	Active controlled trial Represents a subgroup of participants included in the HAPPHY trial. Excluded for the same reason as in the HAPPHY 1987 trial
Materson 1995	Morbidity and mortality outcomes not reported for different drug classes
MIDAS 1996	Active controlled trial Drug-drug comparison of HCTZ 25 mg vs isradipine 5 mg with no placebo or untreated control group
Morgan 1980	Not a randomised controlled trial Allocation to the 4 study groups (no treatment, reduced salt intake, thiazide diuretic, beta-blocker) was non-random
MRC-O 1992	Sudden cardiac death data could not be obtained
NORDIL 2000	Active controlled trial No placebo or untreated control group
PATS 1995	Sudden cardiac death data could not be obtained
PROGRESS 2001	< 50% of participants had elevated blood pressure, and about 50% were receiving other antihypertensive therapy at baseline and throughout the trial
QUIET 2001	Most participants did not have elevated blood pressure. 25% were receiving a beta-blocker
SCAT 2000	Mean initial blood pressure was less than 140/90 mmHg (SBP/DBP) More than 60% did not have hypertension, and about half were taking beta-blockers at baseline and throughout
SCOPE 2003	Both groups allowed some participants to take hydrochlorothiazide at baseline, while most of the control group received antihypertensive therapy
SHELL 1994	Active controlled trial Head-to-head comparison of different drug therapies without a non-drug control group
SHELL 1995	No placebo or untreated control group Evaluation based on 2 active controlled trials
Sprackling 1981	Sudden cardiac death data could not be obtained
STONE 1996	Allocation not randomised. Employed alternate allocation with no blinding to treatment allocation
STOP-2 1993	Active controlled trial Head-to-head comparison of different drug therapies without a placebo or untreated control group
Strandberg 1991	Treatment group had multiple interventions. Control group was given usual treatment and was not an untreated control

Study	Reason for exclusion
SYS-CHINA 1992	Allocation to treatment and control groups was not randomised (alternate allocation was employed)
TEST 1995	Sudden cardiac death data could not be obtained
TOMHS 1995	Multi-factorial interventions Morbidity and mortality events were not reported separately for the different drug treatments
VA Coop 1960	Did not report results separately
VACS 1982	Active controlled trial Drug-drug comparison of HCTZ 50 mg vs propranolol 80 mg with no placebo or untreated control group
VHAS 1997	Active controlled group Drug-drug comparison of chlorthalidone 25 mg vs verapamil 240 mg with no placebo or untreated control group
White WB 1995	Active controlled trial No placebo group, and participants were not randomly allocated to moexipril or moexipril + hydrochlorothiazide

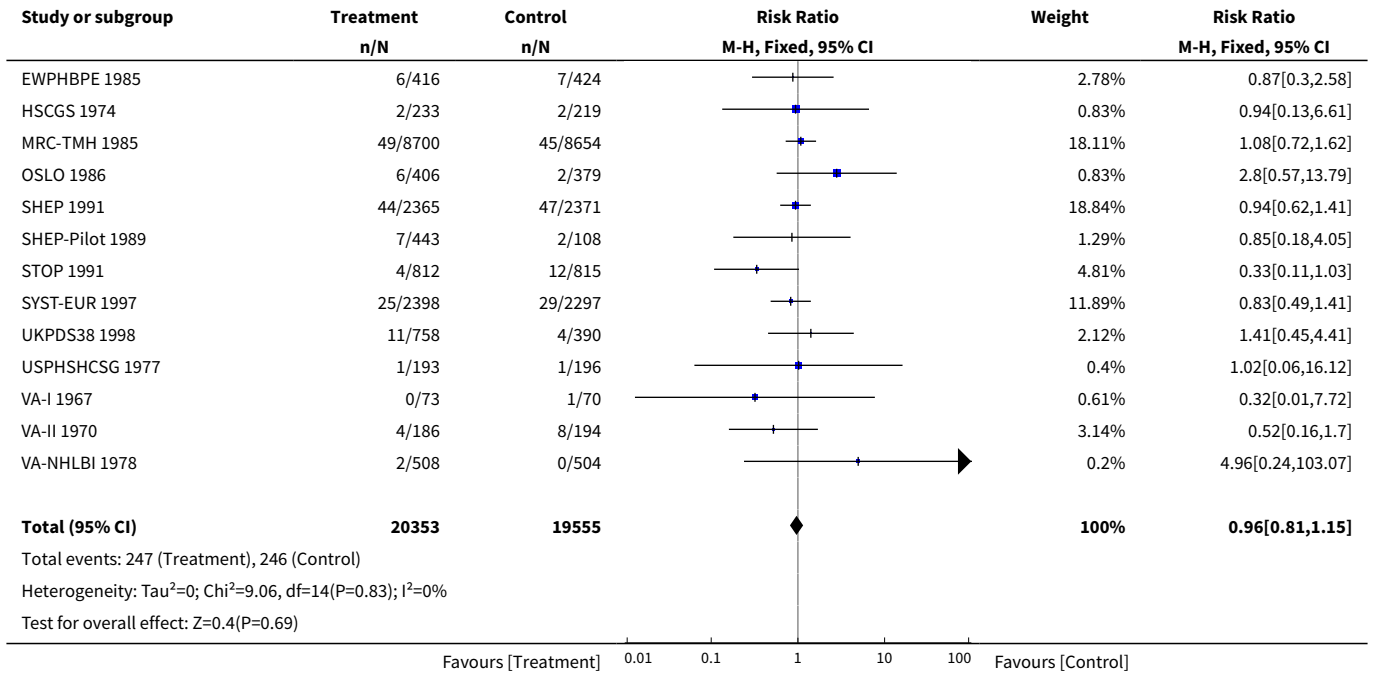
DATA AND ANALYSES

Comparison 1. Antihypertensive drug therapy versus control

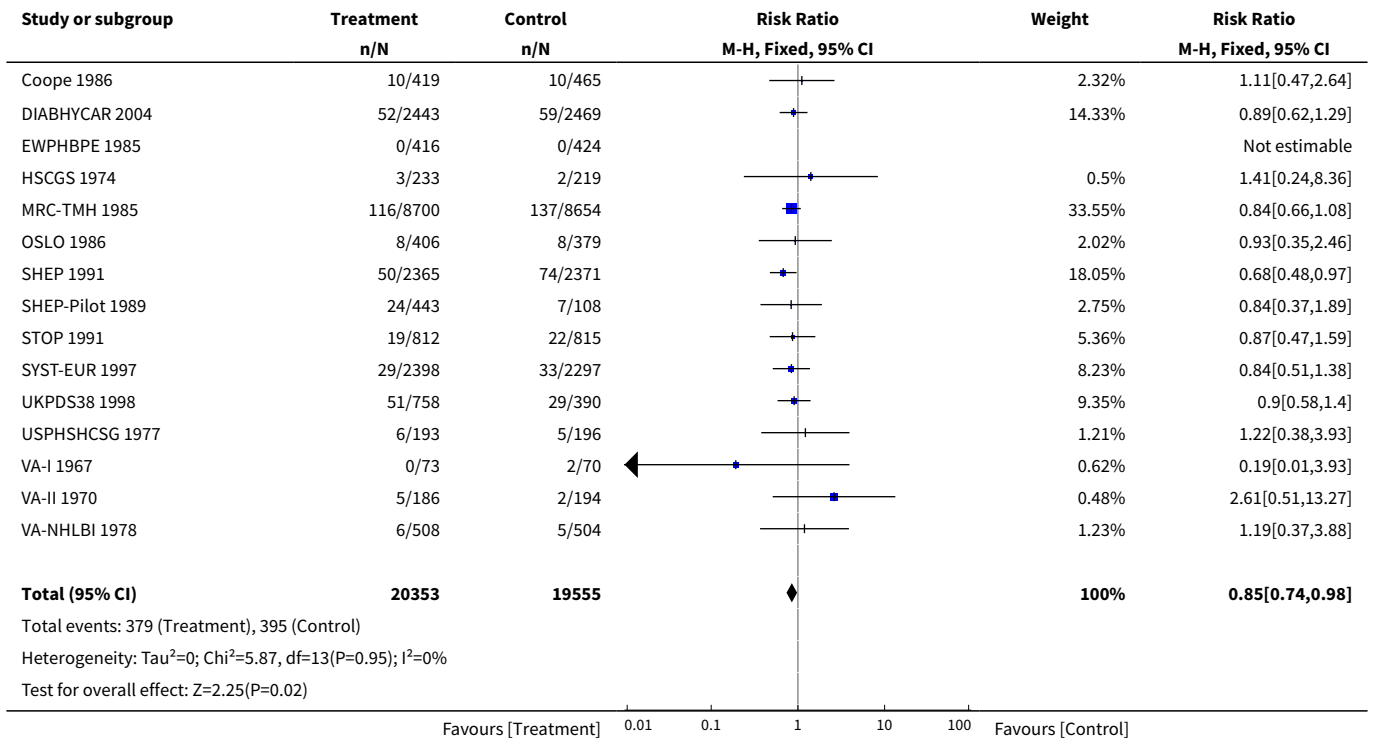
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	15	39908	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.15]
2 Non-fatal myocardial infarction	15	39908	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.98]
3 Fatal myocardial infarction	15	39908	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.62, 0.90]
4 Withdrawals due to adverse effects	10	32026	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.11, 3.83]

Analysis 1.1. Comparison 1 Antihypertensive drug therapy versus control, Outcome 1 Sudden cardiac death.

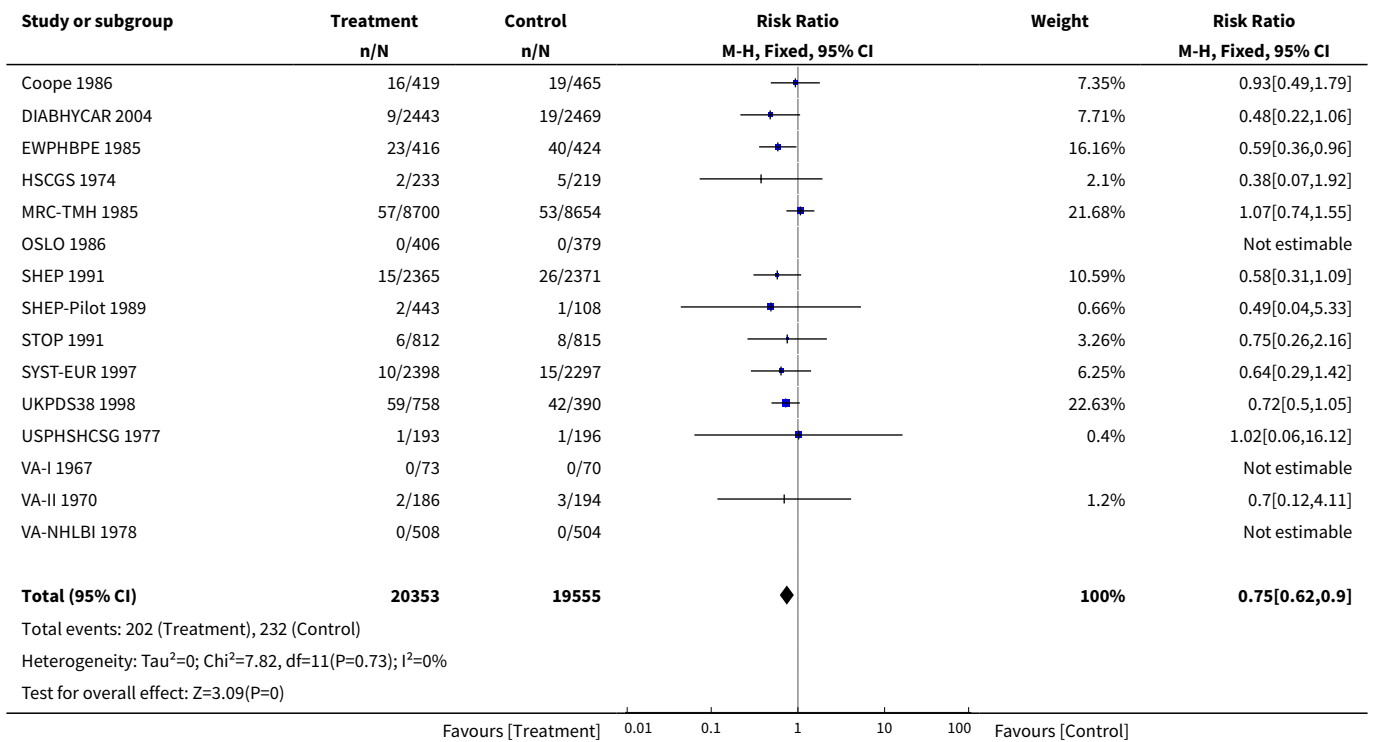
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Coope 1986	9/419	9/465		3.42%	1.11[0.44,2.77]
DIABHYCAR 2004	77/2443	77/2469		30.73%	1.01[0.74,1.38]
Favours [Treatment] 0.01 0.1 1 10 100 Favours [Control]					



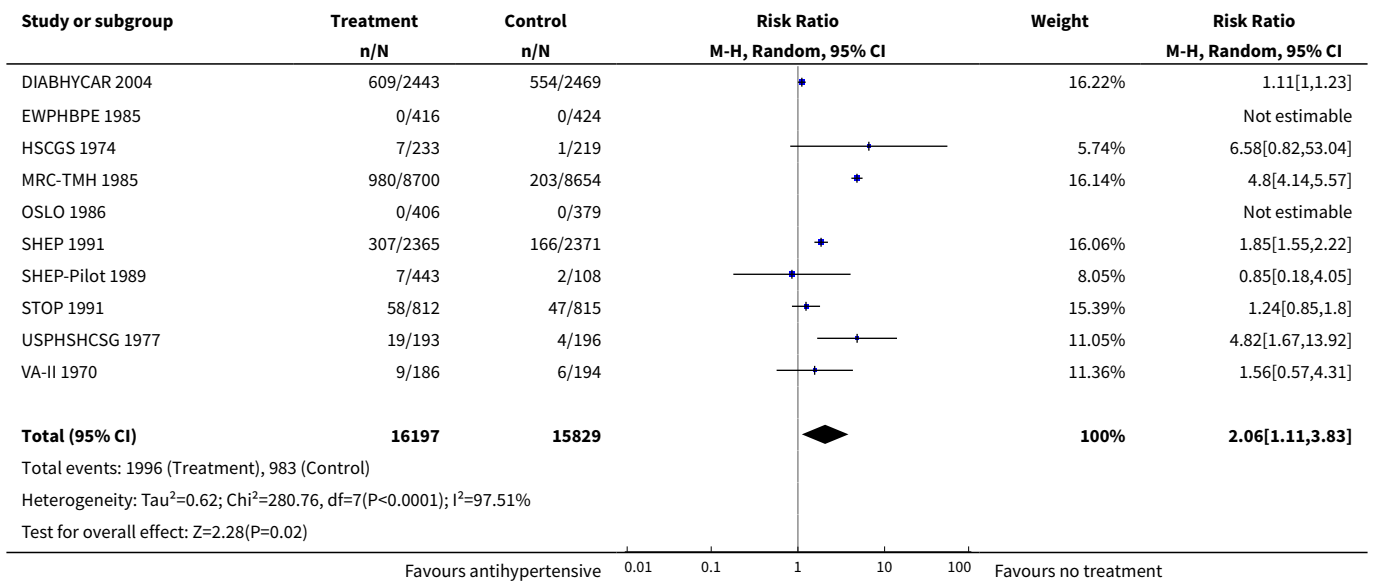
Analysis 1.2. Comparison 1 Antihypertensive drug therapy versus control, Outcome 2 Non-fatal myocardial infarction.



Analysis 1.3. Comparison 1 Antihypertensive drug therapy versus control, Outcome 3 Fatal myocardial infarction.



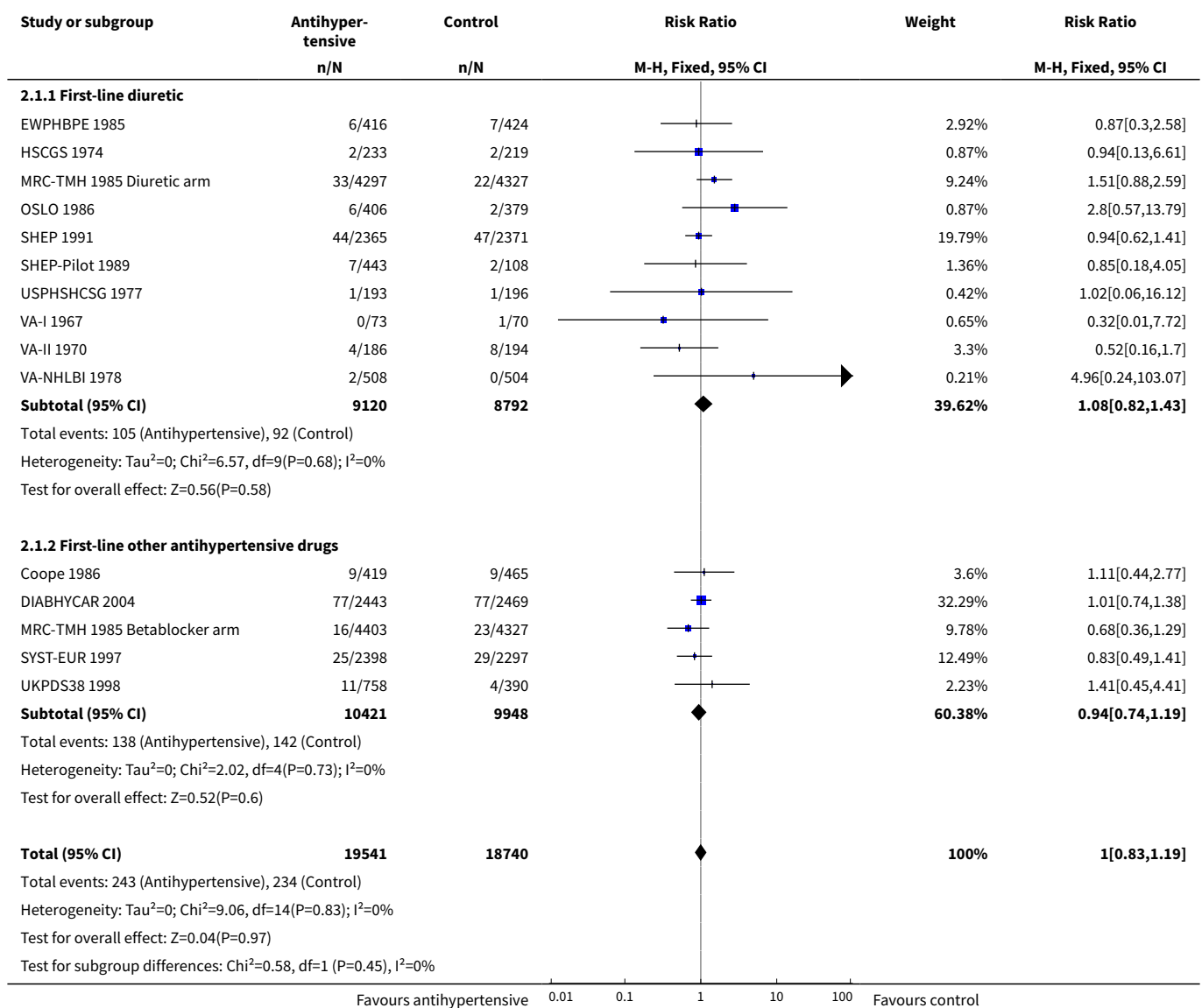
Analysis 1.4. Comparison 1 Antihypertensive drug therapy versus control, Outcome 4 Withdrawals due to adverse effects.



Comparison 2. Subgroup analysis, first-line diuretic versus others

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	15	38281	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.19]
1.1 First-line diuretic	10	17912	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.43]
1.2 First-line other antihypertensive drugs	5	20369	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.74, 1.19]

Analysis 2.1. Comparison 2 Subgroup analysis, first-line diuretic versus others, Outcome 1 Sudden cardiac death.



APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update

Search Date: 13 January 2016

1 exp thiazides/ (14683)

2 exp sodium chloride symporter inhibitors/ (13465)

3 exp sodium potassium chloride symporter inhibitors/ (12878)

4 ((ceiling or loop) adj diuretic?).tw. (2241)

5 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).tw. (30887)

6 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (2099)

7 or/1-6 [THZ] (45504)

8 exp angiotensin-converting enzyme inhibitors/ (39474)

9 angiotensin converting enzyme inhibit\$.tw. (16301)

10 (ace adj2 inhibit\$).tw. (16602)

11 acei.tw. (2437)

12 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril\$ or perindopril\$ or pivopril or quinapril\$ or ramipril\$ or rentiapril or saralasin or s nitrosocaptopril or spirapril\$ or temocapril\$ or teprotide ortrandolapril\$ or utibapril\$ or zabicipril\$ or zofenopril \$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (24224)

13 or/8-12 [ACEI] (53318)

14 exp Angiotensin Receptor Antagonists/ (18967)

15 (angiotensin adj3 (receptor antagon\$ or receptor block\$)).tw. (10209)

16 arb?.tw. (4325)

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. (13440)

18 or/14-17 [ARB] (26495)

19 exp calcium channel blockers/ (75134)

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 ncardipine 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. (56470)

21 (calcium adj2 (antagonist? or block\$ or inhibit\$)).tw. (34966)

22 or/19-21 [CCB] (100015)

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. (14779)

24 (reserpine or serpentina or rauwolfia or serpasil).mp. (19670)

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 isoglaucou or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (18463)

26 exp hydralazine/ (4535)

27 (hydralazin\$ or hydrallazin\$ or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophtalazine or idralazina or 1-hydrazinophtalazine or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat).tw. (4154)

28 or/23-27 [CNS] (55461)

29 exp adrenergic beta-antagonists/ (78226)

30 (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmepitranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthioproporanolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or neбивolol 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. (57382)

31 (beta adj2 (adrenergic? or antagonist? or block\$ or receptor?)).tw. (88421)

32 or/29-31 [BB] (142694)

33 exp adrenergic alpha antagonists/ (47587)

34 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (12922)

35 (adrenergic adj2 (alpha or antagonist?)).tw. (18584)

36 ((adrenergic or alpha or receptor?) adj2 block\$).tw. (51526)

37 or/33-36 [AB] (104492)

38 hypertension/ (205857)

39 hypertens\$.tw. (320460)

40 ((high or elevat\$ or rais\$) adj2 blood pressure).tw. (22415)

41 or/38-40 (378583)

42 randomized controlled trial.pt. (403223)

43 controlled clinical trial.pt. (89924)

- 44 randomized.ab. (300551)
- 45 placebo.ab. (154066)
- 46 clinical trials as topic/ (174243)
- 47 randomly.ab. (213007)
- 48 trial.ti. (130278)
- 49 or/42-48 (921351)
- 50 animals/ not (humans/ and animals/) (4139775)
- 51 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (808940)
- 52 (pregnancy-induced or ocular hypertens\$ or preeclampsia or pre-eclampsia).ti. (12542)
- 53 49 not (50 or 51 or 52) (812533)
- 54 (7 or 13 or 18 or 22 or 28 or 32 or 37) and 41 and 53 (15322)
- 55 54 and (2015\$ or 2016\$).ed. (284)
- 56 remove duplicates from 55 (276)

Database: Cochrane Central Register of Controlled Trials on Wiley <Issue 1, 2016> via Cochrane Register of Studies Online
Search Date: 14 January 2016

-
- #1MeSH descriptor Thiazides explode all trees2247
- #2MeSH descriptor Sodium Chloride Symporter Inhibitors explode all trees2703
- #3MeSH descriptor Sodium Potassium Chloride Symporter Inhibitors explode all trees967
- #4(loop or ceiling) next diuretic*:ti,ab324
- #5(amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopentiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*):ti,ab4836
- #6(chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide):ti,ab894
- #7#1 OR #2 OR #3 OR #4 OR #5 OR #66356
- #8MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees5527
- #9"angiotensin converting enzyme" next inhibit*:ti,ab2838
- #10ace near3 inhibit*:ti,ab2849
- #11acei:ti,ab525
- #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,ab7364

#13#8 OR #9 OR #10 OR #11 OR #1210002

#14MeSH descriptor Angiotensin Receptor Antagonists explode all trees2422

#15angiotensin near3 (receptor next antagon* or receptor next block*):ti,ab1960

#16arbs:ti,ab338

#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,ab4511

#18#14 OR #15 OR #16 OR #175317

#19MeSH descriptor Calcium Channel Blockers explode all trees7947

#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,ab11089

#21calcium near2 (antagonist* or block* or inhibit*):ti,ab4116

#22#19 OR #20 OR #2113599

#23(methyldopa or alphamethyldopa or amodopa or dopamet 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 aldometil or hydopa or methylidihydroxyphenylalanine 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,kw567

#24(reserpine or serpentina or rauwolfia or serpasil):ti,ab,kw231

#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 isoglaucan or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets):ti,ab,kw2648

#26MeSH descriptor Hydralazine explode all trees299

#27(hydralazin* or hydrallazin* or hydralazine or hydrazinophthalazine or hydrazinophthalazine or hydrazinophthalazine or dralazine or hydralacin or hydrolazine or hypophthalin or hypofthalin or hydrazinophthalazine or idralazina or 1-hydrazinophthalazine or apresin or nepresol or apresoline or apresoline or apresolin or alphapress or alazine or idralazina or loproress or plethorit or praeparat):ti,ab,kw431

#28#23 OR #24 OR #25 OR #26 OR #273837

#29MeSH descriptor Adrenergic beta-Antagonists explode all trees9425

#30(acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthioproprianolol or metipranolol or metoprolol or moprolol or nadolol or oxprenolol or penbutolol or pindolol or nadolol or neбивolol 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 sotolol or spirendolol or talinolol or tertatolol or tienoxolol or tilisolol or timolol or tolamolol or toliprolol or tribendilol or xibenolol):ti,ab13596

#31beta near2 (adrenergic* or antagonist* or block* or receptor*):ti,ab8436

#32#29 OR #30 OR #3117593

#33MeSH descriptor Adrenergic alpha-Antagonists explode all trees2966

#34(alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin):ti,ab1992

#35adrenergic near2 (alpha or antagonist*):ti,ab402

#36(adrenergic or alpha or receptor*) near2 block*:ti,ab5466

#37#33 OR #34 OR #35 OR #368851

#38MeSH descriptor Hypertension13751

#39hypertens*:ti,ab31186

#40(elevat* or high* or raise*) near2 blood pressure:ti,ab1976

#41#38 OR #39 OR #4033478

#42#7 OR #13 OR #18 OR #22 OR #28 OR #32 OR #3747478

#43#41 AND #4216338

Database: Embase <1974 to 2016 January 12>

Search Date: 13 January 2016

1 exp thiazide diuretic agent/ (49977)

2 exp loop diuretic agent/ (61804)

3 ((loop or ceiling) adj diuretic?).tw. (3467)

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. (40241)

5 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide).tw. (3621)

6 or/1-5 [THZ] (115178)

7 exp dipeptidyl carboxypeptidase inhibitor/ (146016)

8 angiotensin converting enzyme inhibit\$.tw. (21265)

9 (ace adj2 inhibit\$.tw. (25386)

10 acei.tw. (5169)

11 (alacepril or altiopril or ancovenin or benazepril or captopril or ceranapril or ceronapril or cilazapril or deacetylalacepril or delapril or derapril or enalapril or epicaptopril or fasidotril or fosinopril or foroxymithine or gemopatrilat or idapril or imidapril or indolapril or libenzapril or lisinopril or moexipril or moveltipril or omapatrilat or pentopril\$ or perindopril\$ or pivopril or quinapril\$ or ramipril\$ or rentiapril or saralasin or s nitrosocaptopril or spirapril\$ or temocapril\$ or teprotide ortrandolapril\$ or utibapril\$ or zabicipril\$ or zofenopril \$ or Aceon or Accupril or Altace or Capoten or Lotensin or Mavik or Monopril or Prinivil or Univas or Vasotec or Zestril).tw. (34232)

12 or/7-11 [ACEI] (154116)

13 exp angiotensin receptor antagonist/ (68667)

Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals (Review)

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14 (angiotensin adj3 (receptor antagon\$ or receptor block\$)).tw. (15952)

15 arb?.tw. (9450)

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. (22408)

17 or/13-16 [ARB] (74373)

18 calcium channel blocking agent/ (51954)

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. (75122)

20 (calcium adj2 (antagonist? or block\$ or inhibit\$)).tw. (45137)

21 or/18-20 [CCB] (133231)

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. (27831)

23 (reserpine or serpentina or rauwolfia or serpasil).mp. (30770)

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 isoglaucan or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp. (44044)

25 hydralazine/ (17592)

26 (hydralazin\$ or hydrallazin\$ or hydralizine or hydrazinophthalazine or hydrazinophthalazine or hydrazinophthalizine or dralazine 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. (6203)

27 or/22-26 [CNS] (105686)

28 exp beta adrenergic receptor blocking agent/ (253415)

29 (acebutolol or adimolol or afurolool or alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or bornaprolol or brefonalol or bucindolol or bucumolol or bufetolol or bufuralol or bunitrolol or bunolol or bupranolol or butofilolol or butoxamine or carazolol or carteolol or carvedilol or celiprolol or cetamolol or chlortalidone cloranolol or cyanoiodopindolol or cyanopindolol or deacetylmetipranolol or diacetolol or dihydroalprenolol or dilevalol or epanolol or esmolol or exaprolol or falintolol or fleistolol or flusoxolol or hydroxybenzylpinodolol or hydroxycarteolol or hydroxymetoprolol or indenolol or iodocyanopindolol or iodopindolol or iprocrolol or isoxaprolol or labetalol or landiolol or levobunolol or levomoprolol or medroxalol or mepindolol or methylthioproporanolol 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. (76208)

30 (beta adj2 (adrenergic? or antagonist? or block\$ or receptor?)).tw. (110070)

31 or/28-30 [BB] (306054)

32 exp alpha adrenergic receptor blocking agent/ (126208)

33 (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).tw. (15975)

34 (adrenergic adj2 (alpha or antagonist?)).tw. (17678)

35 ((adrenergic or alpha or receptor?) adj2 block\$).tw. (67235)

36 or/32-35 [AB] (190161)

37 exp hypertension/ (556409)

38 (hypertens\$ or antihypertens\$).tw. (508004)

39 ((high or elevat\$ or rais\$) adj2 blood pressure).tw. (32657)

40 or/37-39 (730540)

41 double blind\$.mp. (203065)

42 placebo\$.tw. (230914)

43 blind\$.tw. (310333)

44 or/41-43 (449503)

45 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5742913)

46 Pregnancy/ or Hypertension, Pregnancy-Induced/ or Pregnancy Complications, Cardiovascular/ or exp Ocular Hypertension/ (614605)

47 (pregnancy-induced or ocular hypertens\$ or preeclampsia or pre-eclampsia).ti. (18262)

48 44 not (45 or 46 or 47) (417356)

49 (6 or 12 or 17 or 21 or 27 or 31 or 36) and 40 and 48 (12964)

50 49 and (2015\$ or 2016\$).em. (421)

51 remove duplicates from 50 (402)

Database: ClinicalTrials.gov
Search Date: 13 January 2016

Search terms: randomized
Study type: Interventional Studies
Conditions: hypertension
Interventions: antihypertensive
Outcome Measures: blood pressure
First Received: First Received: From 01/01/2015 to 01/13/2016 (43)

CONTRIBUTIONS OF AUTHORS

Garry Taverny: drafted the protocol, obtained copies of studies, selected studies for inclusion, extracted data from reports, entered data into RevMan, carried out the analysis, interpreted the analysis, drafted the final review and will update the review.

Yanis Mimouni: selected studies for inclusion and extracted data from reports.

Anne LeDigarcher: selected studies for inclusion and extracted data from reports.

Pr. Philippe Chevalier: formulated the idea for the review.

Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals (Review)

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Lutgarde Thijs: extracted data from studies.

Pr. James M Wright: extracted data from studies, interpreted the analysis, drafted the final review and will update the review.

Pr. François Gueyffier: interpreted the analysis, drafted the final review, extracted data from the INDANA database for related trials and will update the review.

Pr. François Gueyffier formulated the idea for the review, and every review author contributed to the draft of the protocol.

DECLARATIONS OF INTEREST

Garry Taverny: nothing to declare.

Yanis Mimouni: nothing to declare.

Anne LeDigarcher: nothing to declare.

Pr. Philippe Chevalier: nothing to declare.

Lutgarde Thijs: nothing to declare.

Pr. James M Wright: nothing to declare.

Pr. François Gueyffier: nothing to declare.

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Internal sources

- University of British Columbia, Vancouver, Canada.
- Université Claude Bernard Lyon 1, France.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Anne LeDigarcher, Pr. Philippe Chevalier and Lutgarde Thijs joined the team of review authors and contributed to this review.

We have made the following changes to the inclusion criteria:

- Added the requirement that "> 50% [of] study participants had to have hypertension" (added to be more inclusive and more explicit).
- Added the requirement that trials report primary outcome in intervention and control groups (added so that irrelevant trials could be excluded).
- Deleted the primary outcome "specific cause of SCD when known" (changed because if cause of death were known, it would not be reported as SCD).
- Deleted secondary outcome "change in blood pressure at study end" (judged not relevant to the objective of this review).
- Added "withdrawals due to adverse effects" as secondary outcome (important to include harms data in all reviews if possible).

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*therapeutic use]; Death, Sudden, Cardiac [*prevention & control]; Hypertension [complications] [*drug therapy]; Myocardial Infarction [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans